Leitlinienprogramm Onkologie

Evidenztabellen

zur S3-Leitlinie Diagnostik, Therapie und Nachsorge des Melanoms

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Evidenztabellen

DKG Krebsgesellschaft · Deutsche Krebshilfe Helfen. Forschen. Informieren. · AWMF

Inhaltsverzeichnis

1. Informationen zum Dokument

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1.2. Herausgeber

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF), Deutschen Krebsgesellschaft e.V. (DKG) und Deutschen Krebshilfe (DKH).

1.3. Kontakt

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1.4. Finanzierung der Leitlinie

Die Entwicklung der Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Onkologischen Leitlinienprogramms gefördert.

1.5. Federführende Fachgesellschaften

Deutsche Dermatologische Gesellschaft (DDG)

Deutschen Krebsgesellschaft (DKG) vertreten durch die Arbeitsgemeinschaft Dermatologische Onkologie (ADO) von DKG und DGG

1.6. Zitierweise

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Diagnostik, Therapie und Nachsorge des Melanoms, Evidenztabellen 3.0, 2018, AWMF Registernummer: 032/024OL, http://www.leitlinienprogramm-onkologie.de/leitlinien/melanom/ (abgerufen am TT.MM.JJJJ)

2. AG Diagnostik

2.1. Frage I.2. und I.3. Apparative Verfahren zur klinischen Diagnostik des malignen Melanoms - Adaptation

Frage I.2. Welche diagnostischen Verfahren sind geeignet, die klinische Diagnose des MM zu verbessern?
Frage I.3. Welche Hilfsmittel oder apparativen Verfahren können die klinische Diagnostik des MM ggf. weiter verbessern?

2.1.1. Synopse Quelleitlinien (kurz)

Thema/Fragestellung	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)	LL Kanada Cancer Care Ontario 2007
2. Welche diagnostischen Verfahren/Hilfsmittel können helfen, die klinische Diagnose des MM zu sichern?	Klinische Untersuchung, Anamnese mit Konzentration auf Veränderungen von Hautläsionen; Dermatoskopie wird empfohlen (A); Beobachtungsperiode möglich; Einsatz von „Sequential digital dermoscopy imaging“ und/oder „Total body photography“ kann in Zweifelsfällen in Erwägung gezogen werden (B)	Klinische Untersuchung, Dermatoskopie	Klinische Untersuchung, Dermatoskopie	(nur relevant für medikamentöse Therapien)
3. Erhöht der Einsatz der Dermatoskopie (mit/ohne Schulung der anwendenden Ärzte) die diagnostische Genauigkeit?	Training in Dermatoskopie wird empfohlen für Ärzte, die regelmäßig pigmentierte HV untersuchen (A)	Empfohlen	Keine Erwähnung	

2.1.2. Empfehlung, Hintergrundstext und Literatur Australische Quell-Leitlinie

(mit Seitenangaben der Quellleitlinie)

	LL Australien **New Zealand Guidelines Group 2008**	**LL GB** **NICE 2006**	**LL Frankreich** **French National Authority for Health 2005)**
Schlüsselempfehlungen	S. 31 1. Training and utilisation of dermoscopy is recommended for clinicians routinely examining pigmented skin lesions Grade of Recommendation: A 2. Consider the use of sequential digital dermoscopy imaging to detect melanomas that lack dermoscopic features of melanoma Grade of Recommendation: B 3. Consider the use of baseline total body photography as a tool for the early detection of melanoma in patients who are at high risk for developing primary melanoma Grade of Recommendation: C	S. 84 A. Recommendations Investigation and diagnosis GPs should receive training as recommended in the NICE *Referral guidelines for suspected cancer* [44] on the diagnosis of precancerous and cancerous lesions, and should receive feedback through audit on their diagnostic accuracy. GPs should refer certain groups of skin lesions as described in Box 1 and Figure 14 directly to an LSMDT without biopsy. This practice should be subject to audit. All excised skin specimens should be sent for histopathological examination as recommended in the NICE *Referral guidelines for suspected cancer*. [45] Dermatoscopy should be available in all MDTs, but its use requires training. There should be equity of access so that	Die französische LL gibt keine Empfehlungen zur klinischen Erstdiagnose eines Melanoms; die Dermatoskopie wird jedoch im Abschnitt über Untersuchung und Nachsorge von R0-resezierten Patienten (N0, M0) kurz besprochen sowie auf Gutachten der Haute Autorité de Santé (HAS) und der Agency for Healthcare Research and Quality (AHRQ) verwiesen:

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
		all tissue samples are reviewed in high-quality histopathology services. Accurate diagnosis in dermatopathology depends on clinicopathological correlation, involving input from both clinician and pathologist. Although this can be achieved in difficult cases by interspecialist discussion or seeing the patient records, in some instances (such as cutaneous lymphoma) it may be essential for the patient to be seen jointly. Accordingly, for good clinical governance, it is recommended that the histopathology reporting of any specimens likely to be considered by a skin cancer MDT should be undertaken in a laboratory having easy access to relevant clinicians, patient records and the attending patient.	
Hintergrundtexte	S. 29 - 30 5.6 Evidence-based assessment of aids to the clinical diagnosis of melanoma 5.6.1 Dermoscopy Dermoscopy (surface microscopy, oil epiluminescence microscopy, dermatoscopy) is a technique that uses a	S. 90 E. Evidence Dermatoscopy One RCT found that, following a brief training intervention for GPs in the use of dermatoscopy, there was a significant improvement in the accuracy of clinical diagnosis of melanoma and in the	S. 44 EXAMEN CLINIQUE, DERMOSCOPIE Les performances diagnostiques de l'examen clinique et de la dermoscopie dans le diagnostic des tumeurs cutanées font actuellement l'objet d'une expertise par la Haute Autorité de Santé (HAS) et ne seront donc ici

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	hand-held magnifying device combined with either the application of a liquid between the transparent plate of the device and the skin, or the use of cross-polarised light. This technique allows the visualisation of diagnostic features of pigmented skin lesions that are not seen with the naked eye. [15–18] Meta-analyses performed on studies in a variety of clinical and experimental settings have shown that using dermoscopy improves diagnostic accuracy for melanoma.[19,20] From a meta-analysis of nine level II diagnostic studies subject to varying degrees of verification bias performed prospectively in a clinical setting [21–31] the diagnostic accuracy for melanoma, as expressed by the relative diagnostic odds ratio, was 15.6 (95% CI 2.9–83.7) times higher for dermoscopy compared with naked eye examination. Importantly the meta-analysis was restricted to studies that directly compared the two methods within each study. Sensitivity of dermoscopy was 18% (95% CI 9%–27%; P=0.002) higher than for eye examination, but there was no evidence of an effect on specificity [31] (see Appendix 4). Specificity can also be	diagnosis of melanoma using dermatoscopy. The improvement was significantly greater for the use of dermatoscopy than for clinical diagnosis. Three systematic reviews and one case series provide evidence that hand-held dermatoscopy improves diagnostic accuracy as compared with unaided examination. There is evidence from one systematic review that the diagnostic accuracy of dermatoscopy depends on the degree of experience of the examiner. Teledermatology One RCT compared teledermatology with face-to-face consultation as a method of examining patients with skin lesions at a dermatology department. All patients received a further, independent face-to-face skin examination with a consultant dermatologist. For each randomised group, concordance between the two consultations for each patient was measured, primarily for management plan and secondarily for diagnosis. There was significantly greater concordance between consultations for management plan and for diagnosis in patients	qu'évoquées. Ces performances ont surtout été étudiées pour le diagnostic initial du mélanome, et non dans la situation spécifique du patient ayant déjà eu un mélanome. Pour ces derniers, la probabilité de survenue d'un autre mélanome est beaucoup plus élevée que dans la population générale. Une revue systématique publiée par l'*Agency for healthcare research and quality* (AHRQ) a récemment revu les performances de l'examen clinique pour établir une éventuelle stratégie de dépistage systématique des cancers de la peau et a montré que les performances diagnostiques (en termes de sensibilité et de spécificité) des dermatologues étaient supérieures à celles des non-dermatologues [17]. À noter cependant que cette revue systématique a été faite avant que la dermoscopie, une technique initialement mise au point en Europe et en Australie, soit largement diffusée aux États-

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	examined by its effect on excision rates of benign lesions, which was not addressed in the meta-analysis. Two such studies suggest reduced rates of excision of benign lesions using dermoscopy (reduced benign to malignant ratio of excised lesions and reduction of patients referred to biopsy) and provide indirect evidence for improved specificity in a specialist setting. [22,23] While there are fewer studies on dermoscopy in general practice, all three that were undertaken in this context (one study with both general practitioners and inexperienced specialists or trainees) [32] show a consistently improved sensitivity for the diagnosis of melanoma or the identification of suspicious lesions requiring biopsy. [21,32,33] It should be noted that all the studies cited were undertaken by clinicians with some training in dermoscopy (restricted to lectures or reading material in some studies). For this reason, and based on other evidence [34], some formal training in dermoscopy is required to achieve improvement in diagnostic accuracy.	randomised to face-to-face skin examination than in those randomised to teledermatology. No difference was detected between randomised groups for patient satisfaction. One RCT compared two types of teledermatology (by live videoconference and by sending still photographic images) with traditional outpatient consultation, as methods for GPs to refer patients to dermatologists. The dermatologist requested a subsequent hospital appointment for 69% of patients examined by the still image method, compared to 46% of patients examined by videoconferencing and 45% of patients examined in person. One RCT compared teledermatology with standard referral and found that patients in the teledermatology group received definitive treatment significantly more quickly than patients in the standard referral group. Teledermatology patients were significantly more likely to avoid the need for a further clinic visit compared with control patients. One RCT compared teledermatology	Unis. Deux méta-analyses récentes ont montré que pour les dermatologues expérimentés, la dermoscopie améliorait les performances diagnostiques [160, 161]. Dans l'étude de Bafounta *et al.*, le rapport de vraisemblance positif estimé de la dermoscopie et de l'examen clinique ont été respectivement de 9,0 [IC95 : 5,9-19,0] et 3,7 [IC95 : 2,8-5,3] [160]. La méta-analyse de Kittler *et al.* a confirmé ces données, montrant clairement que seuls les opérateurs expérimentés amélioraient leurs performances diagnostiques [161]. *KLINISCHE UNTERSUCHUNG, DERMATOSKOPIE* *Die diagnostische Leistungsfähigkeit der klinischen Untersuchung und der Dermatoskopie in der Diagnostik von Hauttumoren ist zur Zeit Gegenstand eines Gutachtens der Haute Autorité de Santé (HAS) und wird hier daher nur erwähnt.*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	5.6.2 Sequential digital imaging Sequential digital dermoscopy imaging (SDDI) involves the capture and assessment of successive dermoscopic images, separated by an interval of time, of one or many melanocytic lesions to detect suspicious change. This is performed in two settings: short-term digital monitoring (over a period of 1.5–4.5 months) for suspicious melanocytic lesions, and long-term monitoring for surveillance (usually at intervals of 6–12 months). [35] Four level II studies that were conducted in a specialist setting show consistently that SDDI allows the detection of melanoma that lack dermoscopic evidence of malignancy. [35–38] In one prospective study of melanomas diagnosed by a variety of clinical means, 34% were detected using the changes detected by SDDI exclusively and were without dermoscopic features of melanoma. [36] Long-term digital monitoring is generally used in the surveillance of high-risk patients, usually with multiple dysplastic naevi. In contrast, short-term digital monitoring of individual suspicious naevi can be used in any patient setting. At this time	consultation using a videolink with outpatient consultation and found no difference between the groups in the reported clinical diagnoses. One RCT of teledermatology compared to traditional consultation found no significant difference between groups for patient satisfaction with either their care or the management of their skin problems, and 85% of the telemedicine patients reported that they would use the system again. Two systematic reviews suggest that there is no consensus from primary studies on whether teledermatology is more cost-effective than traditional management of dermatology patients. Audit data from the UK indicates that GPs report quicker referral of dermatology patients through teledermatology. S. 99 E. Resource implications	*Die Wirksamkeit dieser Verfahren ist vor allem für die Primärdiagnostik des Melanoms untersucht worden, nicht für die spezielle Situation der Patienten, die bereits ein Melanom gehabt haben. Für letztere ist die Wahrscheinlichkeit, ein weiteres Melanom zu überleben, sehr viel höher als in der Allgemeinbevölkerung.* *Ein systematisches Review der Agency for Healthcare Research and Quality (AHRQ) hat unlängst die Wirksamkeit der klinischen Untersuchung untersucht, um möglicherweise eine Strategie zum systematischen Screening von Hauttumoren zu etablieren und um zu zeigen, dass die diagnostische Wirksamkeit der klinischen Untersuchung (Sensitivität und Spezifität) bei Dermatologen der von Nicht-Dermatologen überlegen ist. [17]* *Es ist allerdings zu bemerken, dass dieses systematische Review durchgeführt wurde, bevor die Dermatoskopie, eine Technik, die zuerst in Europa und Australien*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	diagnostic accuracy of the technique was not able to be assessed. 5.6.3 Automated instruments for the diagnosis of primary melanoma An automated diagnostic instrument is defined as one that requires minimal or no input from the clinician to achieve a diagnosis. Each automated instrument offers different technology with differing diagnostic ability. Guidelines for assessing such instruments have been published. [39] To date, only three instruments have had their diagnostic accuracy compared with a human diagnosis in the clinical field with a sample size that could allow some assessment of their application to the wider clinical arena. [25,40,41] The instruments showed a significantly inferior [25,41] or equivalent [40] specificity for the diagnosis of melanoma compared with specialists. In all studies sample sizes were not large enough to be able to detect potential differences in the sensitivity for melanoma. Further studies are required to assess the impact of automated instruments against human performance in the clinical field.	Investigation and diagnosis The main resource implication of the recommendations concerning the investigation and diagnosis concerns the additional role for histopathologists. The increased workload has been calculated taking account of LSMDT and SSMDT working, implementation of the minimum dataset, doubling the reporting of severely atypical naevi, and MM and SSMDT mandatory review. Approximately two-thirds of the additional workload relates to SSMDT and tertiary review. It is estimated that approximately 1.75 additional consultant histopathologists/dermatopathologists would be required per network to support the guidance. In addition, there would be an additional requirement for laboratory staff, not calculated here. The additional annual employment costs of the histopathologists will be around £171,991 per network. (This cost has been included in the total cost for additional staff required as a result of the guidance, reported in the 'Organisation of skin cancer services' chapter.)	*entwickelt wurde, größere Verbreitung in den USA fand. Zwei aktuelle Meta-Analysen haben gezeigt, dass die Dermatoskopie bei erfahrenen Dermatologen die diagnostische Leistung verbessert [160, 161]. In der Studie von Bafounta et al. ist der geschätzte positive prädiktive Wert der Dermatoskopie und der klinischen Untersuchung 9,0 [IC95 : 5,9-19,0] bzw. 3,7 [IC95 : 2,8-5,3] [160]. Die Meta-Analyse von Kittler et al. hat diese Daten bestätigt und klar gezeigt, dass nur erfahrene Anwender der Dermatoskopie ihre diagnostische Leistung damit verbessern [161].*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	5.7 Total body photography for early melanoma diagnosis in high-risk subjects Total body photography (TBP) is widely used in the follow-up of high-risk patients [42], particularly those with large numbers of melanocytic naevi or dysplastic naevi. TBP has been recommended for the detection of new or changing pigmented lesions. Use of TBP is advocated in the follow-up of high-risk patients by the authors of most studies. [43–50] The technique has been said to reduce the need for unnecessary removal of benign lesions to exclude melanoma [45,46] and to increase the sensitivity and specificity of clinical examination for the detection of melanoma. [46,47] Several authors point out that TBP was the key factor in the detection of most melanomas in their high-risk populations. [44–46,48] Two authors referred to the role of TBP in enabling the detection of clinically subtle or undiagnosable melanoma. [46,47] No appropriately controlled or randomised study has been undertaken to confirm these observations in a high-		

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	risk population. Almost all melanomas are new or changing lesions and baseline images are helpful in identifying a new or changing lesion. Evidence summary From a meta-analysis of nine level II studies prospectively performed in a clinical setting, the diagnostic accuracy for melanoma, as expressed by the relative diagnostic odds ratio, was 15.6 times higher for dermoscopy compared with naked eye examination. Sensitivity of dermoscopy was 18% (95% CI 9%–27%; P=0.002) higher than for eye examination, but there was no evidence of an effect on specificity. LoE: I, References: 21, 22, 24–31 Dermoscopy has been shown to reduce the benign:malignant ratio of excised melanocytic lesions and reduce the number of patients referred for biopsy in a specialist setting LoE: II, References: 22, 23 Four level II studies show consistently that sequential digital dermoscopic imaging allows the detection of suspicious dermoscopic change in		

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	melanomas that lack dermoscopic evidence of melanoma at a particular time LoE: II, References: 35–38 To date only three automated instruments for the diagnosis of primary melanoma have been assessed against clinicians with a reasonable sample size in the clinical field. Here, instrument specificity was either inferior or equivalent to specialist diagnosis, and sample sizes were inadequate to assess differences in sensitivity LoE: II, References: 25, 40, 41 Eight level IV studies and one level III-3 study examined surveillance of high-risk subjects with total body photography but only one included a comparison arm (of lower-risk subjects). All studies on high-risk patients showed early melanoma detection and/or high melanoma incidence. All studies were designed to assess the outcomes of surveillance in high-risk groups rather than the value of TBP. LoE: IV		

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)
	References: 43-51		
Bemerkungen		Diese Leitlinie bezieht sich auf MM und auf NMSC. Referenzen und ausführliche Evidenztabellen dieser Leitlinie werden wegen ihres Umfangs als separates Dokument zur Verfügung gestellt: GB NICE Guideline Evidence Review, S. 174 bis 211.	Das Gutachten der HAS, der Artikel der AHRQ, auf den die Leitlinie sich bezieht, sowie dessen Aktualisierung aus dem Jahr 2009 werden als Zusatzmaterial zu dieser Tabelle zur Verfügung gestellt.

Literatur:

LL Australien New Zealand Guidelines Group 2008

21. Agenziano G, Puig S, Zalaudek I, et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. J Clin Oncol 2006;24:1877-1882
20. Bafounta ML, Beauchet A, Aegerter P, et al. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? Results of a meta-analysis using techniques adapted to the evaluation of diagnostic tests. Arch Dermatol 2001;137:1343-1350
51. Banky JP, Kelly JW, English DR, et al. Incidence of new and changed nevi and melanomas detected using baseline images and dermoscopy in patients at high risk for melanoma. Arch Dermatol 2005;141:998-1006
40. Bauer P, Cristofolini P, Boi S, et al. Digital epiluminescence microscopy: usefulness in the differential diagnosis of cutaneous pigmentary lesions. A statistical comparison between visual and computer inspection. Melanoma Res 2000;10:345-349
27. Benelli C, Roscetti E, Pozzo VD, et al. The dermoscopic versus the clinical diagnosis of melanoma. Eur J Dermatol 1999;9:470-476
34. Binder M, Puespoeck-Schwarz M, Steiner A, et al. Epiluminescence microscopy of small pigmented skin lesions: short-term formal training improves the diagnostic performance of dermatologists. J Am Acad Dermatol 1997;36:197-202
25. Bono A, Bartoli C, Cascinelli N, et al. Melanoma detection. A prospective study comparing diagnosis with the naked eye, dermatoscopy and telespectrophotometry. Dermatology 2002;205:362-366
26. Bono A, Tolomio E, Trincone S, et al. Micro-melanoma detection: a clinical study on 206 consecutive cases of pigmented skin lesions with a diameter < or = 3 mm. Br J Dermatol 2006;155:570-573
17. Bowling J, Argenziano G, Azenha A, et al. Dermoscopy key points: recommendations from the international dermoscopy society. Dermatology 2007;214:3-5
22 .Carli P, de Giorgi V, Chiarugi A, et al. Addition of dermoscopy to conventional naked-eye examination in melanoma screening: a randomized study. J Am Acad Dermatol 2004;50:683-689
23. Carli P, De Giorgi V, Crocetti E, et al. Improvement of malignant/benign ratio in excised melanocytic lesions in the 'dermoscopy era': a retrospective study 1997-2001. Br J Dermatol 2004;150:687-692
24. Carli P, Mannone F, De Giorgi V, et al. The problem of false-positive diagnosis in melanoma screening: the impact of dermoscopy. Melanoma Res 2003;13:179-182
28. Cristofolini M, Zumiani G, Bauer P, et al. Dermatoscopy: usefulness in the differential diagnosis of cutaneous pigmentary lesions. Melanoma Res 1994;4:391-394
32. Dolianitis C, Kelly J, Wolfe R, et al. Comparative performance of 4 dermoscopic algorithms by nonexperts for the diagnosis of melanocytic lesions. Arch Dermatol 2005;141:1008-1014
29. Dummer W, Doehnel KA, Remy W. Videomicroscopy in differential diagnosis of skin tumors and secondary prevention of malignant melanoma. Hautarzt 1993;44:772-776
46. Feit NE, Dusza SW, Marghoob AA. Melanomas detected with the aid of total cutaneous photography. Br J Dermatol 2004;150:706-714
36. Haenssle HA, Krueger U, Vente C, et al. Results from an observational trial: digital epiluminescence microscopy follow-up of atypical nevi increases the sensitivity and the chance of success of conventional dermoscopy in detecting melanoma. J Invest Dermatol 2006;126:980-985
41. Har-Shai Y, Glickman YA, Siller G, et al. Electrical impedance scanning for melanoma diagnosis: a validation study. Plast Reconstr Surg 2005;116:782-790
45. Kelly JW, Yeatman JM, Regalia C, et al. A high incidence of melanoma found in patients with multiple dysplastic naevi by photographic surveillance. Med J Aust 1997;167:191-194
35. Kittler H, Guitera P, Riedl E, et al. Identification of clinically featureless incipient melanoma using sequential dermoscopy imaging. Arch Dermatol 2006;142:1113-1119
19. Kittler H, Pehamberger H, Wolff K, et al. Diagnostic accuracy of dermoscopy. Lancet Oncol 2002;3:159-165
48. MacKie RM, McHenry P, Hole D. Accelerated detection with prospective surveillance for cutaneous malignant melanoma in high-risk groups. Lancet 1993;341:1618-1620
18. Malvehy J, Puig S, Argenziano G, et al. Dermoscopy report: proposal for standardization. Results of a consensus meeting of the International Dermoscopy Society. J Am Acad Dermatol 2007;57:84-95
43. Marghoob AA, Kopf AW, Rigel DS, et al. Risk of cutaneous malignant melanoma in patients with 'classic' atypical-mole syndrome. A case-control study. Arch Dermatol 1994;130:993-998
47. Masri GD, Clark WH,Jr, Guerry D,4th, et al. Screening and surveillance of patients at high risk for malignant melanoma result in detection of earlier disease. J Am Acad Dermatol 1990;22:1042-1048
15. Menzies S, Crotty KA, Ingvar C, McCarthy WH. An Atlas of Surface Microscopy of Pigmented Skin Lesions: Dermoscopy. 2nd ed. Sydney: McGraw-Hill, 2003.
37. Menzies SW, Gutenev A, Avramidis M, et al. Short-term digital surface microscopic monitoring of atypical or changing melanocytic lesions. Arch Dermatol 2001;137:1583-1589
16. Menzies SW, Zalaudek I. Why perform dermoscopy? The evidence for its role in the routine management of pigmented skin lesions. Arch Dermatol 2006;142:1211-1212
44. Rivers JK, Kopf AW, Vinokur AF, et al. Clinical characteristics of malignant melanomas developing in persons with dysplastic nevi. Cancer 1990;65:1232-1236
38. Robinson JK, Nickoloff BJ. Digital epiluminescence microscopy monitoring of high-risk patients. Arch Dermatol 2004;140:49-56
39. Rosado B, Menzies S, Harbauer A, et al. Accuracy of computer diagnosis of melanoma: a quantitative meta-analysis. Arch Dermatol 2003;139:361-7; discussion 366
42. Shriner DL, Wagner RF,Jr. Photographic utilization in dermatology clinics in the United States: a survey of university-based dermatology residency programs. J Am Acad Dermatol 1992;27:565-567
30. Stanganelli I, Serafini M, Bucch L. A cancer-registry-assisted evaluation of the accuracy of digital epiluminescence microscopy associated with clinical examination of pigmented skin lesions. Dermatology 2000;200:11-16
50. Tiersten AD, Grin CM, Kopf AW, et al. Prospective follow-up for malignant melanoma in patients with atypical-mole (dysplastic-nevus) syndrome. J Dermatol Surg Oncol 1991;17:44-48
31. Vestergaard ME, Macaskill P, Holt PE, et al. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. Br J Dermatol 2008;159:669-676

49. Wang SQ, Kopf AW, Koenig K, et al. Detection of melanomas in patients followed up with total cutaneous examinations, total cutaneous photography, and dermoscopy. J Am Acad Dermatol 2004;50:15-20
33. Westerhoff K, McCarthy WH, Menzies SW. Increase in the sensitivity for melanoma diagnosis by primary care physicians using skin surface microscopy. Br J De

LL Frankreich French National Authority for Health 2005)

17. AHRQ, Agency for Healthcare Research and Quality. Screening for Skin Cancer. File Inventory, Systematic Evidence Review Number 2 [online]. AHRQ Publication 2001. Available: URL: http://www.ahrq.gov/clinic/prev/skncainv.htm
160. Bafounta ML, Beauchet A, Aegerter P, et al. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? Results of a meta-analysis using techniques adapted to the evaluation of diagnostic tests. Arch Dermatol 2001;137:1343-1350
161. Kittler H, Pehamberger H, Wolff K, et al. Diagnostic accuracy of dermoscopy. Lancet Oncol 2002;3:159-165

2.2. Frage I.3. Konfokale Laserscan-Mikroskopie und optische Kohärenztomographie - De-novo-Recherche

Frage I.3. Welche Hilfsmittel oder apparativen Verfahren können die klinische Diagnostik des MM ggf. weiter verbessern

Beantwortung durch Adaptation (s.o. I.2.)

Ergänzende Recherche zu:

- Konfokale Laserscan-Mikroskopie (CLSM)
- Optische Kohärenztomographie (OCT)

2.2.1. PICO, Suchwörter

Suchwörter		
Stichwort	melanoma	Confocal, laserscan microscopy
Synonyme	melanoma	Clsm
Ober-/Unterbegriffe, MESH-Term	s. Suchstrategie	

2.2.2. Datenbanken, Suchstrategien, Trefferzahlen

2.2.2.1. Primärrecherche 2012

Datenbank	**Suchstrategie**	**Datum**	**Treffer**
1. Suche			
Medline	"melanoma"[tiab] AND ("confocal"[tiab] OR "laserscan microscopy"[tiab] OR	26.01.2012	275

	“clsm”[tiab]) NOT "uveal"[tiab] NOT "models, animal"[Mesh] "melanoma"[tiab] AND ("oct"[tiab] OR "optical coherence tomography"[tiab] OR “optical coherence tomographic”[tiab] OR “multiphoton"[tiab]) NOT "uveal"[tiab] NOT "models, animal"[Mesh]		92
Cochrane Library	melanoma and (confocal or "laserscan microscopy" or clsm).ti,ab. melanoma and (oct or "optical coherence tomography" or “optical coherence tomographic” or “multiphoton").ti,ab.	26.01.2012 26.01.2012	1 4
Bemerkungen: Datum der Erst-Recherche für Medline und Cochrane war der 21.09.2010. Eine letzte Update-Recherche erfolgte am 26.01.2012 für Medline bzw. am 19.01.2012 für Cochrane. In den Tabellen angegeben sind die Zahlen der letzten Update-Recherche. 31.08.2012: Aufgrund der eingegangenen Kommentare im Rahmen der Konsultationsphase in Bezug auf die Literaturauswahl zur konfokalen Laserscanmikroskopie wurde die Literatur, die bei der systematischen Recherche gefunden wurden, reevaluiert. Die Tabelle wurde daraufhin ergänzt entsprechend der angegeben Ein- und Ausschlußkriterien. Abschluß Konsultationsphase, Stand 09/2012: Das Statement zur konfokalen Laserscanmikroskopie wurde aus der Leitlinie herausgenommen (Details: s. „Kommentare zur Konsulationsfassung“). Eine Überarbeitung der Evidenztabelle nach erneuter sytematischer Literaturrecherche ist für das Update der Leitlinie geplant.			

2.2.2.2. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	"melanoma"[tiab] AND ("confocal"[tiab] OR "laserscan microscopy"[tiab] OR “clsm”[tiab]) NOT "uveal"[tiab] NOT "models, animal"[Mesh] "melanoma"[tiab] AND ("oct"[tiab] OR "optical coherence tomography"[tiab] OR “optical coherence tomographic”[tiab] OR “multiphoton"[tiab]) NOT "uveal"[tiab] NOT "models, animal"[Mesh]	12.09.2016	240 106
Cochrane Library	melanoma and (confocal or "laserscan microscopy" or clsm).ti,ab.	12.09.2016	2

	melanoma and (oct or "optical coherence tomography" or “optical coherence tomographic” or “multiphoton").ti,ab.	12.09.2016	5

2.2.3. Auswahlkriterien

2.2.3.1. Primärrecherche 2012

Auswahl der Literatur		
Gesamttreffer		372
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt	
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research CLSM: nur Artikel, bei Sensitivität und Spezifität bestimmt wurden	
Anzahl nach Abstractscreening		29
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung		9

2.2.3.2. Aktualisierungsrecherche 2016

Auswahl der Literatur		
Gesamttreffer		346
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt	
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research	

	CLSM: nur Artikel, bei Sensitivität und Spezifität bestimmt wurden
Anzahl nach Abstractscreening	59
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	27

2.2.4. Evidenztabelle

2.2.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic: Optical coherence tomography (OCT), Multiphoton laser tomography (MLT)							
Dimitrow et al. (2009)	To examine the clinical applicability of multiphoton laser tomography with regard to statistical evaluation of sensitivity, specificity, accuracy, and reliability.	Diagnostic study	83 patients	Sensitivity and specificity in and ex vivo Accuracy Interobserver reliability	Overall sensitivity 75% in vivo, 93% ex vivo Specificity 80% in vivo, 74% ex vivo Diagnostic accuracy 85% in vivo, 97% ex vivo Interobserver agreement: kappa values for different	Specificity and sensitivity for single criteria: see full-text of publication	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					criteria ranging from 0.6 to 0.8		
Gambichler et al. (2007)	To visualize and characterize melanocytic skin lesions (MSL) by using OCT in vivo, compare OCT features of benign nevi (BN) and MM, and histologically validate the OCT findings.	Diagnostic study	75 patients with 92 MSL	Frequency of several characteristics of lesions	See full-text for frequency of all investigated characteristics of lesions.	The diagnostic performance of OCT in the diagnosis of MSL could not be fully determined. Sensitivity and specificity studies also including other skin tumors have not been performed	3b
Subtopic: Confocal laser scan microscopy (CLSM)							
Gerger et al. (2007)	To validate diagnostic confocal examination of melanocytic skin tumours using unselected tumour images.	A total of 3709 unselected CLSM tumour images obtained from 20 malignant melanomas and 50 benign naevi	60 patients	Sensitivity and specificity Positive and negative predictive value (PPV, NPV) Diagnostic accuracy	Sensitivity 97.5% Specificity 99% PPV 97.5% NPV 99% Diagnostic accuracy 92.4% for benign naevi and	High risk of verification bias (no histology if diagnosed “on unequivocal clinical and conventional dermoscopic criteria as benign nevi“)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					97.6% for melanoma images	Computerized images were provided, a loss in sensitivity or specificity through acquisition of the images by an unexperienced examiner could therefore not be observed	
Gerger et al. (2005)	To systematically validate CLSM in diagnosing melanocytic skin tumors in an observer-blinded manner, and to evaluate morphologic features determined by CLSM for their presence or absence, diagnostic performance, and reliability.	Diagnostic study	88 patients with 117 lesions (90 benign nevi, 27 melanomas)	Sensitivity, specificity Positive and negative predictive value (PPV, NPV)	5 independent observers without previous experience in CLSM 2 Residents: sensitivity 96.3%, specificity 100% and 99%, PPV 100% and 96.3%, NPV 99% Senior physician without dermatopathologic qualification: sensitivity 92.6% and specificity 99%, PPV 96.2%, NPV 98%	High risk of verification bias (selective histopathological confirmation of diagnosis)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					2 Dermatopathologists: sensitivity 96.3% and 59.3%, specificity 94% and 96%, PPV 81.3% and 80%, NPV 99% and 89.7% Overall sensitivity 88.2%, specificity 97.6%, PPV 90.7%, NPV 96.9%.		
Gerger et al. (2006)	To systematically investigate the diagnostic impact and reliability of well described morphologic features in a large series of melanocytic and nonmelanocytic skin tumors.	Diagnostic study	119 patients with 117 melanocytic and 45 non-melanocytic skin lesions	Sensitivity, specificity Positive and negative predictive value (PPV, NPV)	Diagnostic differentiation of MM from BCC, BN, and SK reached sensitivity and specificity values of 85.19% and 98.52% (Observer 1), 92.59% and 98.52% (Observer 2), and 92.59% and 99.26% (Observers 3 and 4), respectively with the following overall	High risk of verification bias (see above)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					performance: sensitivity, 90.74%; specificity, 98.89%; PPV, 94.22%; and NPV, 98.17%.		
Gerger et al. (2008)	To assess the applicability of image analysis and a machine learning algorithm on diagnostic discrimination of benign and malignant melanocytic skin tumours in in vivo confocal laser-scanning microscopy (CLSM).	Diagnostic study	60 patients (total of 857 CLSM tumour images including 408 benign nevi and 449 melanoma images)	Sensitivity, specificity	Correct classification by CART analysis in 97.55% and 96.32% of melanoma and nevi images, overall performance 96.97% Human observer: sensitivity 85.52%, specificity 80.15%, overall performance 82.84%, positive predictive value 82.58%, negative predictive value 83.42%	Use of pre-selected CLSM images (high risk of selection bias)	3b
Koller et al. (2010)	To investigate the applicability of an automated image analysis system using a machine	Diagnostic study	178 patients with 16269 RCM tumor images	Diagnostic accuracy	Classification tree analysis: correct classification in 93.60% of	Risk of verification bias (verification by histopathology dependent on clinical	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	learning algorithm on diagnostic discrimination of benign and malignant melanocytic skin tumours in reflectance confocal microscopy (RCM)				melanoma and 90.40% of nevi images of the learning set When applied to the independent test set 46.71 ± 19.97% (range 7.81–83.87%) of the tumour images in benign melanocytic skin lesions were classified as 'malignant', in contrast to 55.68 ± 14.58% (range 30.65–83.59%; t-test: P < 0.036) in malignant melanocytic skin lesions 78.95% of melanocytic skin tumours (62.50% of the melanoma and 84.50% of the nevi) correctly classified by independent	examination) ROC curve: see full-text	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					clinical dermatologist		
Langley et al. (2007)	The aim of this study was to evaluate the diagnostic accuracy of CSLM compared to dermoscopy in a prospective examination of benign and malignant melanocytic lesions.	Diagnostic study .	125 patients	Sensitivity, specificity Positive and negative predictive value (PPV, NPV)	Dermoscopy: sensitivity 89.2%, specificity 84.1%, PPV 70.2%, NPV 94.9% CSLM: sensitivity 97.3%, specificity 83.0%, PPV 70.6%, NPV 98.6% No melanomas misidentified when both techniques were used together	No verification bias (all diagnoses were confirmed histologically) Clinical, dermatoscopic and confocal imaging were performed sequentially by a single observer; result of clinical examination and dermatoscopy may lead to bias in confocal examination	2b
Lorber et al. (2009)	To examine the correlation between objectively reproducible image-analysis features und visual morphology in melanocytic skin tumours using CLSM.	Diagnostic study	60 patients with 70 melanocytic skin lesions	Diagnostic accuracy	CART analysis of the whole set of CLSM tumour images correctly classified 97.55% of melanoma images and 96.32% of nevi images.	High risk of verification bias (selective histopathological confirmation of diagnosis).	3b

2.2.4.1.1. Literatur

Dimitrow E, Ziemer M, Koehler MJ, et al. Sensitivity and specificity of multiphoton laser tomography for in vivo and ex vivo diagnosis of malignant melanoma. J Invest Dermatol 2009;129:1752-1758
Gambichler T, Regeniter P, Bechara FG, et al. Characterization of benign and malignant melanocytic skin lesions using optical coherence tomography in vivo. J Am Acad Dermatol 2007;57:629-637
Gerger A, Hofmann-Wellenhof R, Langsenlehner U, et al. In vivo confocal laser scanning microscopy of melanocytic skin tumours: diagnostic applicability using unselected tumour images. Br J Dermatol 2008;158:329-333
Gerger A, Koller S, Kern T, et al. Diagnostic applicability of in vivo confocal laser scanning microscopy in melanocytic skin tumors. J Invest Dermatol 2005;124:493-498
Gerger A, Koller S, Weger W, et al. Sensitivity and specificity of confocal laser-scanning microscopy for in vivo diagnosis of malignant skin tumors. Cancer 2006;107:193-200
Gerger A, Wiltgen M, Langsenlehner U, et al. Diagnostic image analysis of malignant melanoma in in vivo confocal laser-scanning microscopy: a preliminary study. Skin Res Technol 2008;14:359-363
Koller S, Wiltgen M, Ahlgrimm-Siess V, et al. In vivo reflectance confocal microscopy: automated diagnostic image analysis of melanocytic skin tumours. J Eur Acad Dermatol Venereol 2010
Langley RG, Walsh N, Sutherland AE, et al. The diagnostic accuracy of in vivo confocal scanning laser microscopy compared to dermoscopy of benign and malignant melanocytic lesions: a prospective study. Dermatology 2007;215:365-372
Lorber A, Wiltgen M, Hofmann-Wellenhof R, et al. Correlation of image analysis features and visual morphology in melanocytic skin tumours using in vivo confocal laser scanning microscopy. Skin Res Technol 2009;15:237-241

2.2.4.2. Aktualisierungsrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic: Reflectance confocal microscopy (RCM) or Confocal laser scan microscopy (CLSM)							
Alarcon et al. (2014)	To assess the impact of RCM analysis on the number of equivocal lesions, assumed to be melanocytic, excised for every melanoma.	Diagnostic study 3 arms (dermatoscopy, dermatoscopy+RCM, RCM)	343 Patients with doubtful lesions	Number needed to treat (NNT) Secondary outcomes included sensitivity, specificity, positive predictive value and negative predictive value	NNT Group 1: 3-73 Group 2: 2-87 Group 3: 1-12 Sensitivity ? Specificity ?	RCM is not to replace but to complement dermoscopy QUADAS: 7x yes Funding source: The research at the Melanoma Unit in Barcelona was partially funded by grants 06/0265	2a

						and 09/01393 from Fondo de Investigaciones Sanita- rias, Spain; by the CIBER de Enfermedades Raras of the Instituto de Salud Carlos III, Spain; by the AGAUR 2009 SGR 1337 of the Catalan Govern- ment, Spain; by the European Commission under the 6th Framework Programme, contract no. LSHC-CT-2006-018702 (GenoMEL) and by the National Cancer Institute of the US National Institutes of Health (CA83115).	
Benati et al. (2015)	To investigate the likelihood of diagnosing melanoma according to dis- tinct dermoscopic and confocal	Diagnostic study	83 excised melanocytic lesions dermoscopically showing globules were analysed.	Odds Ratio	Univariate analysis showed that regular distribution of globules on dermoscopy is associated with a ninefold lower risk	A combined approach using dermoscopy and RCM is useful for the in vivo characterization of melanocytic	3b

	aspects. To determine the best critical value of these optical properties for melanoma diagnosis.				for melanoma, whereas an irregular distribution is associated with an almost 10-fold increased risk for melanoma Concerning confocal features, dense nests are associated with a fivefold lower risk for melanoma, whereas loosely arranged nests are associated with an almost sixfold risk for melanoma; moreover, the presence of round cells is associated with a 17-fold lower risk for melanoma, whereas pleomorphic cells are associated with an almost 16-fold risk for melanoma	lesions displaying a globular pattern. QUADAS: 6x yes Funding source: none	
Borsari et al. (2016)	To identify lesions on which RCM	Cohort- study: Prospectively	1147 patients	Sensitivity and Specificity	Sensitivity: 95,3% Specificity: 83,9%	Funding source: none	2a

	performs better in terms of diagnostic accuracy and consequently to outline the best indications for use of RCM.	acquired and evaluated RCM images from consecutive patients with at least 1 clinically and/or dermoscopically equivocal skin lesion.			RCM showed a high diagnostic accuracy for lesions located on sun-damaged skin	QUADAS: 9x yes	
Calin et al. (2013)	To provide an overview of the most investigated optical diagnostic techniques: optical coherence tomography, fluorescence spectrometry, reflectance spectrometry, Raman spectroscopy, and confocal microscopy	Retrospective cohort study	Search in 3 databases	Sensitivity, Specificity	Specificity and sensitivity of this method are ranging between 72–92 % and 64–92 %	Funding source: This work was financed by the Ministry of Education, Research, Youth and Sport by means of the Research Program no. PN II PCCA 184/2012. QUADAS: 7x yes	3b
Coco et al. (2016)	To calculate the percentage of false-negative melanomas upon reflectance confocal microscopy	Retrospective cohort study of 201 casas	201 patients with biopsy-proven melanoma	False-negative confocal cases	7 of 201 lesions were judged as negative on confocal examination: Confocal and dermoscopic	Funding source: This work was partially funded by Research Project NET-2011-02347213, Italian Ministry of Health.	2b

	examination in a large series of cases.				examination, along with patient-related information and clinical history, can lead to an optimal patient management.	QUADAS: 10x yes	
Farnetani et al. (2015)	To test interobserver reproducibility of recognition of previously published RCM descriptors and accuracy of RCM-based skin cancer diagnosis.	Observational retrospective cohort web-based study	100 patients with biopsy-proven lesions	Fair to good interrater agreement (κ statistic, 0.3) and independent correlation with malignant vs benign diagnosis on discriminant analysis. Sensitivity and specificity for diagnosis of malignant vs benign for each evaluator, for majority diagnosis (rendered by 5 of 9 evaluators), and for experienced vs recent RCM users.	Sensitivity for the group of evaluators was 88.9% (range, 82.9%-100%), and the mean specificity was 79.3% (range, 69.2%-90.8%). Majority diagnosis showed sensitivity of 100% and specificity of 80.0%. Sensitivity was higher for experienced vs recent RCM users (91.0% vs 84.8%), but specificity was similar (80.0% vs 77.9%).	Funding source: none QUADAS: 8x yes	3a
Ferrari et al. (2015)	To detect the most relevant Reflectance	Diagnostic study	322 lesions	Sensitivity, Specificity	RCM represents a rapid non-invasive technique that can	Unclear result Funding source:	3a

	confocal microscopy (RCM) features for the detection of dermoscopic difficult melanomas.				aid early diagnosis of dermoscopic difficult melanomas. Use of RCM on lesions with clinical and/or dermoscopic suspect of malignancy may reduce the number of unnecessary excision increasing the rate of accurate diagnoses.	none QUADAS: 6x yes	
Figueroa-Silva et al. (2016) [7]	To evaluate diagnostic RCM features of pigmented lesions typified by the presence of DI and calculate RCM diagnostic accuracy for MM diagnosis.	Diagnostic study of 1964 cases	1964 lesions with dermoscopic islands (DI) from a database	Sensitivity and specificity of RCM for the diagnosis of MM	Sixty-three (3.2%) out of 1964 lesions presented DI. Among them, 30.2% were in situ MMs and 12.7% invasive MMs. Sensitivity and specificity of RCM for the diagnosis of MM in case of DI was 88.9%. DI could be a sign of early MMs and underlined that RCM could be a good tool to discriminate MMs and naevi in the	Funding source: Dr. Cinotti was supported by the grant 'bourse d'aide a la mobilite ' from the 'Colle ge des Enseignants de Dermatologie de France (CEDEF)' QUADAS: 9x yes	3a

					presence of DI because it can identify the presence of cytological atypia		
Guida et al. (2016)	To define RCM criteria that can differentiate 'false twins', namely Spitz naevi and melanomas sharing similar dermoscopic appearance.	Retrospective cohort study	34 cases were included histopathologically verified Spitz naevi and melanomas excised between 2010 and 2014 from the databases of two tertiary skin cancer centres	???	p-value < 0,05?	Unclear focus and results Funding source: none QUADAS: 8x yes	4
Guitera et al. (2016)	To find and test best diagnosis methods with dermoscopy and reflectance confocal microscopy (RCM) tools	Retrospective cohort study	Study population contained 191 lesions consecutive, difficult-to-diagnose, light-colored and amelanotic skin lesions from three centers	Sensitivity, specificity, OR 4 categories: benign with high confidence, benign with low confidence; malignant with low confidence; malignant with high confidence	Thus, in our series, no melanoma would have been missed (not biopsied) when confocal and dermoscopy assessment were combined suggesting that these techniques are indeed complimentary/synergistic for the evaluation of amelanotic/lightly pigmented skin	Funding source: none QUADAS: 13x yes	3b

					lesions that are notoriously difficult to diagnose.		
Longo et al. (2013)	To assess whether the diagnostic accuracy of RCM was comparable to histopathology for the diagnosis of nodular lesions, and to identify possible limitations of this technique.	Retrospective blinded cohort study of 140 cases	140 nodular lesions	Sensitivity, specificity	96 5% sensitivity 94 1% specificity	Funding source: none QUADAS: 13x yes	3a
Menge et al. (2016)	To determine concordance rate between RCM and histopathology in the evaluation of suspected LM and to identify factors that may obscure diagnosis.	Prospective cohort study involving 17 participants	17 patients	Sensitivity, specificity, NPV, PPV	Sensitivity 100%, Specificity 71%, Positive predictive value 85%, Negative predictive value 100%)	Low sample size Founding source: none QUADAS: 9x yes	2b

Pellacani et al. (2014)	To analyze cell morphology of consecutive melanomas as they appear on RCM and to correlate morphology with tumor and patient characteristics.	Retrospective cohort study	100 Patients: retrospectively evaluated a consecutive series of 100 melanomas for which a complete set of information	Absolute and relative frequencies were calculated for all parameters associated with the different tumor categories.	Mean, standard deviation (SD), median and interquartile ranges were calculated for continuous parameters	Funding source: Study supported in part by the Italian Ministry of University and Research PRIN (Project of Relevant National Interest), call 2012 (Prot-2012-JJX494).	3a
Pellacani et al. (2014)	To determine prospectively the potential impact of confocal microscopy when implemented in a routine melanoma diagnosis workflow.	Prospective cohort study	1005 patients were screened: 423 consecutive patients with 493 lesions	NNE (Number Needed to Excise)	NNE: 6,8 with RCM examination compared with a hypothetical 14 6 without RCM evaluation.	Funding source: none QUADAS: 5x yes	2a
Pellacani et al. (2014)	To describe the characteristic RCM features of common melanocytic nevi and to correlate them with histo-pathology.	Cohort study	A total of 180 biopsy-proven nevi were imaged with RCM prior to excision.	Correlation between clinical pattern and histopathological characteristics of nevi	RCM offers nowadays the unique opportunity to systematically evaluate the histo-morphology of melanocytic neoplasms.	Funding source: Supported in part by a grant of the Istituto Superiore di Sanita , Rome, Italy (project no. 527/B/3A/4) and in part by the European Commission Marie Curie FP7 Reintegration Grant (PIRG07-GA-	3a

						2010-268359). QUADAS: 5x yes	
Pellacani et al. (2016)	To estimate the influence of RCM on number of benign lesions needed to excise (NNE) a melanoma, in term of clinical outcomes and costs per patient.	Cohort study	Two unrelated databases	NNE	NNE: 6.25 for University Hospital, compared to 19.41 for Territorial Dermatology. The systematic use of RCM was dramatically affecting the number of benign lesions excised, and this can be translated in a significant cost-benefit advantage.	Funding source: The study has been partially co-funded by the European Union CIP-ICT PSP PROGRAMME GA N. 621066 DIAGNOPTICS and by the Italian Minister of Health NET-2011-02347213.	3a

Pupelli et al. (2013)	To analyse the confocal features of small-diameter lesions (naevi and melanomas with diameter >5 mm) to determine whether they show specific morphological criteria.	Cohort study	24 Patients with malignant melanoma and 72 Patients with naevi	OR and CI	OR: CI: 95% The combination of dermoscopy and RCM can lead to a cor- rect diagnosis of a number of naevi that share some morphological aspects with melanomas.	Funding source: none QUADAS: 7x yes	3b
Rao et al. (2013)	To assess RCM diagnostic accuracy in a support teleconsultation setting.	Cohort study	334 lesions	Sensitivity, specificity	Sensitivity: >90% Specificity: >60% RCM is a tool in the clinical diagnosis of skin lesions, providing a high diagnostic accuracy in teleconsultation use.	Funding source: none QUADAS: 11x yes	3a
Stanganelli et al. (2015)	To determine whether combining sequential dermoscopy imaging with reflectance confocal microscopy (RCM) can improve melanoma	Retrospective cohort study	70 lesions from 70 patients	seven-point checklist score at baseline, changes in structure and/or colour, and development of new melanoma-specific criteria at follow-up	A correct mela- noma diagnosis was achieved with RCM in almost all cases (11 of 12, 92%). Referring for excision only those lesions with RCM-positive features and/or pre- senting	Funding source: no external source QUADAS: 7x yes	3b

	detection and reduce the burden of unnecessary excisions.				major changes at digital dermoscopy follow-up, theoretically 27 of 58 naevi could be saved from surgery.		

Stevenson et al. (2013)	To determine the diagnostic accuracy of reflectance confocal microscopy (RCM), for melanoma diagnosis, as an add-on test to clinical examination and dermoscopy in the diagnosis of equivocal pigmented skin lesions using histopathology as the reference standard.	Review	Five studies comprising 909 lesions	Sensitivity, specificity, CI	Sensitivity of 93% [95% CI 89-96] and a specificity of 76% [95% CI 68-83]. The utility of reflectance confocal microscopy (RCM) as an add-on test for the diagnosis of melanoma depends on the trade off between over-excising benign lesions and misdiagnosing melanoma as benign. This becomes important when considering lesions on surgically difficult or cosmetically important areas of the body.	Founding source: none	2b

Vaisnoriene et al. (2014)	To evaluate the significance of in vivo RCM features of melanocytic atypia for the diagnosis of melanocytic nevi, dysplastic nevi and cutaneous melanoma.	Cohort study	138 lesions	Sensitivity, specificity	Separately and all together taken the in vivo RCM features of melanocytic atypia were significant in differential diagnosis of benign and malignant melanocytic skin lesions, though none of the features was significant in discriminating nevi without cytologic atypia of dysplastic nevi. In vivo RCM feature of dense cell clusters corresponded with melanin containing nevomelanocytes on histopathology though exact correspondence of non-homogeneous and atypical sparse cell clusters remained questionable.	Funding source: This study was partially supported by two grants from the Research Council of Lithuania (grant numbers LIG-10044, VP1- 3.1-SMM-01-V-02-003). No financial support was provided by companies involved with ownership of the in vivo RCM device. QUADAS: 9x yes	3b

Xiang et al. (2015)	To investigate the characteristics of melanin-containing cells by in vivo CLSM.	Cohort study	130 lesions in patients with fitzpatrick's skin phototype (SPT) III to IV (55 male and 75 female) between 7 and 75 years of age were recruited from the clinic	Characteristics of melanin containing cells: Shape Size Arrangement Density Borders Brightness	Our study presents the CLSM characteristics of melanin-containing cells. These characteristics may facilitate in vivo diagnosis based on shape, size, arrangement, density, borders, and brightness.	Funding source: none QUADAS: 6x yes	3a
Subtopic: High-definition optical coherence tomography (HD-OCT)							
Boone et al. (2016) [22]	To quantify in vivo optical properties such as light attenuation in melanocytic lesions by HD-OCT. To determine the best critical value of these optical properties for melanoma diagnosis.	Retrospective Study	45 cases	Sensitivity, specificity, NPV, PPV	The diagnostic performance of HD-OCT in discrimi- nating MM from non-melanoma has been found to be moderate with an NPV (Negative Predictive Value) of 89.7%.	Funding source: none QUADAS: 9x yes	3b
Gambichler et al. (2015)	To review recent (January 2009–October 2014) advances in the clinical application	Review	25 papers were selected with at least 20 patients as minimum sample size.	OCT of epidermal thickness, skin appendages, wound healing, extracellular	Combining OCT with other imaging techniques, such as Raman, Doppler,	Funding source: none	3a

	of OCT of the human skin, focusing on studies that included a reasonable sample size and statistical analysis.			matrix and skin brosis, vascular malformations, and skin tumors such as basal cell carcinoma, actinic keratoses, and malignant melanoma.	fluorescence, and ultrasound, may further improve the diagnostic performance of OCT in skin research as well as future dermatology practice.		
Gambichler et al. (2015)	To assess the diagnostic performance of HD-OCT in the differentiation of benign melanocytic skin lesions (MSL) and cutaneous melanoma (CM)	Multicentre pilot study	93 Patients with benign MSL and CM	Sensitivity, specificity, ppv, npv	Sensitivity of HD-OCT was 74.1% (95% CI 53.7–88.8%), specificity was 92.4% (95% CI 83.2–97.5%). Ppv: 80% (95% CI 59.3–93.1%) NPV: 89.7% (95% CI 79.9–95.7%)	Funding source: Agfa Healthcare Agfa Healthcare who has transiently provided the Skintell" device for this study. QUADAS: 8x yes	2a
Gambichler et al. (2015)	To assess whether micromorphological HD-OCT correlate with benign naevi (BN) and malignant melanoma (MM).	Cohort study	48 lesions (BN, MM)	Architectural and cellular alterations of melanocytic skin lesions	Using HD-OCT it is possible to visualize architectural and cellular alterations of melanocytic skin lesions. The overlap of HD-OCT features seen in BN and MM and the absence of suspicious HD-OCT features in some	Funding source: Agfa Healthcare has transiently provided the Skintell® device for this study QUADAS: 6x yes	3a

					MM represents an important limitation of HD-OCT affecting the sensitivity of HD-OCT in diagnosing MM.		
Gambichler et al. (2015)	To assess the diagnostic performance of HD-OCT in the differentiation of benign melanocytic skin lesions (MSL) and cutaneous melanoma (CM).	Multicentric prospective pilot study	93 MSL: 66 benign MSL and 27 CM	Sensitivity, specificity, CI, PPV, NPV	Sensitivity 74.1% [95% confidence interval (CI) 53.7–88.8%)], specificity 92.4% (95% CI 83.2–97.5%) PPN: 80 % NPV: 89,7 %	Funding source: Agfa Healthcare QUADAS: 6 x yes	3a
Meyer et al. (2014)	To validate the accuracy and reliability of high-frequency ultrasonography (HFUS) and optical coherence tomography for assessing melanoma thickness in vivo.	Prospective study	131 patients with at least one equivocal melanocytic lesion	Intra- class correlation coefficient confidence interval inter-rater reproducibility.	ICC 0.807 CI 95% (0 703– 0 877) IRR G = 0 97 HFUS is a reliable and reproducible noninvasive method for assessing melanoma thickness	Funding source: This work was funded by the French Interministry Unified Fund (Fonds Interministeriel Unifi e), the Midi-Pyrenees Region (Region Midi-Pyrenees) and the Pierre Fabre Research Institute (Institute de Recherche Pierre Fabre).	3a

						QUADAS: 9x yes	
Wessels et al. (2015)	We hypothesize that OCT images of nevi will differ qualitatively and quantitatively from melanomas.	Cohort study	40 lesions from 33 consecutive patients	Morphologic characteristics	Morphologically, absence of the lower border of the lesion was characteristic for melanoma	Funding source: none declared QUADAS: 5x yes	3b

Anmerkung: Bei Studien, die für zwei oder mehrere Teilfragen relevant sind, ist nur der Ergebnisteil und LoE erneut angegeben, für die übrigen Felder wird auf die erste Erwähnung der Studie in der Evidenztabelle verwiesen.

2.2.4.2.1. Literatur

Alarcon I, Carrera C, Palou J et al. Impact of in vivo reflectance confocal microscopy on the number needed to treat melanoma in doubtful lesions. Br J Dermatol 2014; 170: 802-808.
Benati E, Argenziano G, Kyrgidis A et al. Melanoma and naevi with a globular pattern: confocal microscopy as an aid for diagnostic differentiation. Br J Dermatol 2015; 173: 1232-1238.
Borsari S, Pampena R, Lallas A et al. Clinical Indications for Use of Reflectance Confocal Microscopy for Skin Cancer Diagnosis. JAMA Dermatol 2016; 152: 1093-1098.
Calin MA, Parasca SV, Savastru R et al. Optical techniques for the noninvasive diagnosis of skin cancer. J Cancer Res Clin Oncol 2013; 139: 1083-1104.
Coco V, Farnetani F, Cesinaro AM et al. False-Negative Cases on Confocal Microscopy Examination: A Retrospective Evaluation and Critical Reappraisal. Dermatology 2016; 232: 189-197.
Farnetani F, Scope A, Braun RP et al. Skin Cancer Diagnosis With Reflectance Confocal Microscopy: Reproducibility of Feature Recognition and Accuracy of Diagnosis. JAMA Dermatol 2015; 151: 1075-1080.
Ferrari B, Pupelli G, Farnetani F et al. Dermoscopic difficult lesions: an objective evaluation of reflectance confocal microscopy impact for accurate diagnosis. J Eur Acad Dermatol Venereol 2015; 29: 1135-1140.
Guida S, Pellacani G, Cesinaro AM et al. Spitz naevi and melanomas with similar dermoscopic patterns: can confocal microscopy differentiate? Br J Dermatol 2016; 174: 610-616.
Guitera P, Menzies SW, Argenziano G et al. Dermoscopy and in vivo confocal microscopy are complementary techniques for diagnosis of difficult amelanotic and light-coloured skin lesions. Br J Dermatol 2016; 175: 1311-1319.
Longo C, Farnetani F, Ciardo S et al. Is confocal microscopy a valuable tool in diagnosing nodular lesions? A study of 140 cases. Br J Dermatol 2013; 169: 58-67.
Menge TD, Hibler BP, Cordova MA et al. Concordance of handheld reflectance confocal microscopy (RCM) with histopathology in the diagnosis of lentigo maligna (LM): A prospective study. J Am Acad Dermatol 2016; 74: 1114-1120.
Pellacani G, De Pace B, Reggiani C et al. Distinct melanoma types based on reflectance confocal microscopy. Exp Dermatol 2014; 23: 414-418.
Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. Br J Dermatol 2014; 171: 1044-1051.
Pellacani G, Scope A, Farnetani F et al. Towards an in vivo morphologic classification of melanocytic nevi. J Eur Acad Dermatol Venereol 2014; 28: 864-872.
Pellacani G, Witkowski A, Cesinaro AM et al. Cost-benefit of reflectance confocal microscopy in the diagnostic performance of melanoma. J Eur Acad Dermatol Venereol 2016; 30: 413-419.
Pupelli G, Longo C, Veneziano L et al. Small-diameter melanocytic lesions: morphological analysis by means of in vivo confocal microscopy. Br J Dermatol 2013; 168: 1027-1033.
Rao BK, Mateus R, Wassef C, Pellacani G. In vivo confocal microscopy in clinical practice: comparison of bedside diagnostic accuracy of a trained physician and distant diagnosis of an expert reader. J Am Acad Dermatol 2013; 69: e295-300.
Stanganelli I, Longo C, Mazzoni L et al. Integration of reflectance confocal microscopy in sequential dermoscopy follow-up improves melanoma detection accuracy. Br J Dermatol 2015; 172: 365-371.
Stevenson AD, Mickan S, Mallett S, Ayya M. Systematic review of diagnostic accuracy of reflectance confocal microscopy for melanoma diagnosis in patients with clinically equivocal skin lesions. Dermatol Pract Concept 2013; 3: 19-27.
Vaisnoriene I, Rotomskis R, Kulvietis V et al. Nevomelanocytic atypia detection by in vivo reflectance confocal microscopy. Medicina (Kaunas) 2014; 50: 209-215.
Xiang W, Song X, Peng J et al. Real-time in vivo confocal laser scanning microscopy of melanin-containing cells: A promising diagnostic intervention. Microsc Res Tech 2015; 78: 1121-1127.

Boone MA, Suppa M, Dhaenens F et al. In vivo assessment of optical properties of melanocytic skin lesions and differentiation of melanoma from non-malignant lesions by high-definition optical coherence tomography. Arch Dermatol Res 2016; 308: 7-20.
Gambichler T, Pljakic A, Schmitz L. Recent advances in clinical application of optical coherence tomography of human skin. Clin Cosmet Investig Dermatol 2015; 8: 345-354.
Gambichler T, Schmid-Wendtner MH, Plura I et al. A multicentre pilot study investigating high-definition optical coherence tomography in the differentiation of cutaneous melanoma and melanocytic naevi. J Eur Acad Dermatol Venereol 2015; 29: 537-541.
Gambichler T, Plura I, Schmid-Wendtner M et al. High-definition optical coherence tomography of melanocytic skin lesions. J Biophotonics 2015; 8: 681-686.
Meyer N, Lauwers-Cances V, Lourari S et al. High-frequency ultrasonography but not 930-nm optical coherence tomography reliably evaluates melanoma thickness in vivo: a prospective validation study. Br J Dermatol 2014; 171: 799-805.
Wessels R, de Bruin DM, Relyveld GN et al. Functional optical coherence tomography of pigmented lesions. J Eur Acad Dermatol Venereol 2015; 29: 738-744.

2.3. Frage I.6., I.7., I.8., VII.6. Ausbreitungsdiagnostik bei Patienten mit malignem Melanom – De-novo-Recherche

Frage I.6. Welche Ausbreitungsdiagnostik ist bei asymptomatischen Patientien bei Diagnose des Primärtumors bis Stadium IIA/ab Stadium IIB indiziert?

Frage I.7. Welche Ausbreitungsdiagnostik ist bei Patientien mit Verdacht auf bzw. Nachweis von lokoregionaler Metastasierung indiziert?

Frage I.8. Welche Ausbreitungsdiagnostik ist bei Patientien mit Verdacht auf bzw. Nachweis von Fernmetastasen indiziert?

Frage IX.6. Welche Untersuchungen sind im Rahmen der Nachsorge bei asymptomatischen Patienten indiziert?

2.3.1. PICO, Suchwörter

Verfahren:

- LK-Sono
- Röntgen-Thorax
- Abdomen-Sono
- MRT
- CT
- PET
- PET/CT
- Szintigraphie
- Labor

PICO-Unterfragen:

- Wie ist die Sensitivität und Spezifität des Verfahrens zur Diagnose von Metastasen des MM bei Primärdiagnose?
- Ändert die Durchführung des Verfahrens bei Patienten mit Primärdiagnose des MM das Krankheitsstadium?
- Ändert die Durchführung des Verfahrens bei Patienten mit Primärdiagnose des MM die Therapie?
- Ändert die Durchführung des Verfahrens bei Patienten mit Primärdiagnose des MM das Überleben?
- Wie hoch sind die zusätzlichen Kosten bei Durchführung des Verfahrens bei Patienten mit Primärdiagnose des MM?

2.3.2. Datenbanken, Suchstrategie, Trefferzahlen

2.3.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche		Der letzten Update-Recherche:	Insgesamt (Update-Recherche)
Medline	"melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR ("lymph nodes"[all fields] OR ("lymph"[all fields] AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymph node"[all fields]))	26.01.2012	3153
	"melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND ("chest X-ray"[all fields] OR "chest radiography"[all fields] OR "Radiography, Thoracic"[Mesh])		83
	"melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR "abdomen"[all fields] OR “abdominal"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		588
	"melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND ("Magnetic Resonance Imaging"[Mesh] OR “Magnetic Resonance Imaging”[all fields] OR “mri”[all fields] OR “magnetic resonance”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		595
	"melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (“Tomography, X-Ray Computed"[Mesh] OR “computer tomography”[all fields] OR “ct”[all fields] OR "Tomography, Spiral Computed"[Mesh] OR		936

Datenbank	Suchstrategie	Datum	Treffer
	"Tomography Scanners, X-Ray Computed"[Mesh] OR "Positron-Emission Tomography"[Mesh] OR “positron-emission tomography”[all fields] OR “pet”[all fields] OR "Tomography, Emission-Computed, Single-Photon"[Mesh] OR “single-photon emission computed tomography”[all fields] OR “spect”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh]) "melanoma"[tiab] AND (“staging”[tiab] OR "diagnosis"[tiab]) AND ("scintigraphy”[tiab] OR “scinti*”[tiab]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh]) "melanoma"[tiab] AND ("LDH"[all fields] OR “lactate dehydrogenase” OR "S100"[all fields] OR "MIA"[tiab] OR "melanoma-inhibiting activity"[tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		 66 594
Cochrane Library	(melanoma and (staging or diagnosis) and ("chest x-ray" or "chest radiography")).ti,ab. (melanoma and (staging or diagnosis) and ("ultrasonography" or "sonography" or "ultrasound" or sonogr*)).ti,ab. (melanoma and (staging or diagnosis) and ("magnetic resonance" or mri)).ti,ab. (melanoma and (staging or diagnosis) and (“computer tomography” or ct or “positron emission tomography” or pet or spect or “single-photon emission computed tomography” or “spect ct” or “pet ct”)).ti,ab. (melanoma and (staging or diagnosis) and (scintigraphy or scinti*)).ti,ab.	19.01.2012	7 7 5 9 4

Datenbank	Suchstrategie	Datum	Treffer
	(melanoma and (staging or diagnosis) and (ldh or "lactate dehydrogenase" or s100* or mia or "melanoma inhibiting activity")).ti,ab.		10
Embase	(melanoma and (staging or diagnosis) and ("chest x-ray" or "chest radiography")).ti,ab. (melanoma and (staging or diagnosis) and ("ultrasonography" or "sonography" or "ultrasound" or sonogr*)).ti,ab. (melanoma and (staging or diagnosis) and ("magnetic resonance" or mri)).ti,ab. (melanoma and (staging or diagnosis) and (“computer tomography” or ct or “positron emission tomography” or pet or spect or “single-photon emission computed tomography” or “spect ct” or “pet ct”)).ti,ab. (melanoma and (staging or diagnosis) and (scintigraphy or scinti*)).ti,ab. (melanoma and (staging or diagnosis) and (ldh or "lactate dehydrogenase" or s100* or mia or "melanoma inhibiting activity")).ti,ab.	23.01.2012	79 546 431 777 142 317
Bemerkungen: Datum der Erst-Recherche für Medline und Cochrane war der 17.08.2010. Die erste EMBASE-Recherche erfolgte am 11.05.2011. Eine letzte Update-Recherche (initiale Suche, Ergänzungsrecherche) erfolgte am 23.01.2012 für EMBASE, am 26.01.2012 für Medline bzw. am 19.01.2012 für Cochrane. In den Tabellen angegeben sind die Zahlen der letzten Update-Recherche. Bezüglich Tumor-Marker: da eine Meta-Analyse (Mocellin et al. 2008) vorliegt, wurden lediglich Studien eingeschlossen, die nicht in der Meta-Analse enthalten waren, die nach der Metaanalyse erschienen sind oder die bestimmte Teilaspekte abdecken, die in der Meta-analyse nicht berücksichtigt wurden. Bezüglich PET und PET/CT: Die erste systematische Recherche zeigte zwei Meta-Analysen (Krug und Jimenez-Requena). Einzelne Studien wurden nur mit aufgenommen, sofern sie noch nicht in diesen beiden Meta-analysen enthalten waren oder Aspekte beinhalteten, die aus den Meta-analysen nicht hervorgingen. Da die Meta-Analyse von Xing erst im Rahmen einer Update-Recherche identifiziert wurde, sind einzelne Studien, die in der Meta-analyse enthalten sind, auch in		

Datenbank	Suchstrategie	Datum	Treffer
dieser Tabelle aufgeführt. Die Studien sind jedoch gekennzeichnet und haben einen dementsprechend schlechteren Evidenzgrad. Bei gleicher Suchstrategie zu den Fragen I.6, I.7, I.8 und VII.6 und teils Überschneidungen der Studien sind alle relevanten Recherche-Ergebnisse in dieser Tabelle zusammengefasst. Eine Übersicht über die Zuteilung der Studien zu den verschiedenen Fragestellungen befindet sich am Ende der Tabelle.			

2.3.2.2. Aktualisierungsrecherche 2015 für I.7. und I.8

Datenbank	Suchstrategie	Datum	Treffer
Medline	((((("melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND(("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR"sonography"[all fields]) OR ("lymph nodes"[all fields] OR ("lymph"[all fields] AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymph node"[all fields]))))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication]))) (("melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND("chest X-ray"[all fields] OR "chest radiography"[all fields] OR "Radiography,Thoracic"[Mesh]))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication]) (("melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND(("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR"sonography"[all fields]) OR "abdomen"[all fields] OR “abdominal"[all fields])NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh]))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication]) (("melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND ("Magnetic Resonance Imaging"[Mesh] OR “Magnetic Resonance Imaging”[all fields] OR “mri”[all fields] OR “magnetic resonance”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh]))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication]) (("melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (“Tomography, X-Ray Computed"[Mesh] OR “computer tomography”[all fields] OR “ct”[all fields] OR "Tomography, Spiral Computed"[Mesh] OR "Tomography Scanners, X-Ray Computed"[Mesh] OR "Positron-EmissionTomography"[Mesh] OR “positron-emission tomography”[all fields] OR“pet”[all fields] OR	16.09.2015	716 14 170 192 386

	"Tomography, Emission-Computed, Single-Photon"[Mesh] OR “single-photon emission computed tomography”[all fields] OR “spect”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication]) (("melanoma"[tiab] AND ("LDH"[all fields] OR “lactate dehydrogenase” OR"S100"[all fields] OR "MIA"[tiab] OR "melanoma-inhibiting activity"[tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) NOT ("ophthalmology"[Mesh]OR "eye"[Mesh] OR "eye neoplasms"[Mesh])))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication])		3
Cochrane Library	(melanoma and (staging or diagnosis) and ("chest x-ray" or "chest radiography")).ti,ab. (melanoma and (staging or diagnosis) and ("ultrasonography" or "sonography" or "ultrasound" or sonogr*)).ti,ab. (melanoma and (staging or diagnosis) and ("magnetic resonance" or mri)).ti,ab. (melanoma and (staging or diagnosis) and (“computer tomography” or ct or “positron emission tomography” or pet or spect or “single-photon emission computed tomography” or “spect ct” or “pet ct”)).ti,ab. (melanoma and (staging or diagnosis) and (scintigraphy or scinti*)).ti,ab. (melanoma and (staging or diagnosis) and (ldh or "lactate dehydrogenase" or s100* or mia or "melanoma inhibiting activity")).ti,ab.	16.09.2015	7 18 14 20 4 11
Die Update-Literatur-Recherche erfolgte am 16.09.2015 und schloss alle Studien mit ein, die ab dem 26.01.2012 auf Medline bzw. ab 2012 auf Cochrane erschienen sind. Es wurden nur Studien aufgenommen, die einen hohen Evidenzlevel besitzen. Da in Hinblick auf die apparative Diagnostik keine randomisiert kontrollierten Studien vorliegen, wurde in diesem Fall ein „hohes Evidenzlevel“ bis LoE von 2b definiert.			

2.3.2.3. Aktualisierungsrecherche 2016 für I.6, I.7/8, VII.6

Datenbank	Suchstrategie	Datum	Treffer

1. Suche		Der letzten Update-Recherche:	Insgesamt (Update-Recherche)
Medline	**I.6** melanoma[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR ("lymph nodes"[all fields] OR ("lymph"[all fields] AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymph node"[all fields]))	12.09.2016	1000
	melanoma[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND ("chest X-ray"[all fields] OR "chest radiography"[all fields] OR "Radiography, Thoracic"[Mesh])		15
	melanoma[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR "abdomen"[all fields] OR “abdominal"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		223
	melanoma[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND ("Magnetic Resonance Imaging"[Mesh] OR “Magnetic Resonance Imaging”[all fields] OR “mri”[all fields] OR “magnetic resonance”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		253
	melanoma[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (“Tomography, X-Ray Computed"[Mesh] OR “computer tomography”[allfields] OR “ct”[all fields] OR "Tomography, Spiral Computed"[Mesh] OR "Tomography Scanners, X-Ray Computed"[Mesh] OR "Positron-Emission Tomography"[Mesh] OR “positron-emission tomography”[all fields] OR “pet”[all fields] OR "Tomography, Emission-Computed, Single-Photon"[Mesh] OR “single-photon emission computed tomography”[all fields] OR “spect”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		478

	melanoma[tiab] AND (“staging”[tiab] OR "diagnosis"[tiab]) AND ("scintigraphy”[tiab] OR “scinti*”[tiab]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		3
	"melanoma"[tiab] AND ("LDH"[all fields] OR “lactate dehydrogenase” OR "S100"[all fields] OR "MIA"[tiab] OR "melanoma-inhibiting activity"[tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		198
	I.7/8, VII.6 ((((("melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND(("ultrasonography"[Mesh] OR"ultrasonography"[all fields] OR"sonography"[all fields]) OR ("lymph nodes"[all fields] OR ("lymph"[all fields]AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymphnode"[all fields]))))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication]))) (("melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND("chest X-ray"[all fields] OR "chest radiography"[all fields] OR "Radiography,Thoracic"[Mesh]))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication]) Publication]) (("melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND(("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR"sonography"[all fields]) OR "abdomen"[all fields] OR “abdominal"[all fie lds])NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh]))) AND ("2012.01.27"[Date -Publication] : "3000"[Date - Publication]) ((("melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND ("Magnetic Resonance Imaging"[Mesh] OR “Magnetic Resonance Imaging”[all fields] OR “mri”[all fields] OR “magnetic resonance”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh]))) AND ("2012.01.27"[Date -fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh]		192 15 41 44

	OR "eye neoplasms"[Mesh])))) AND ("2012.01.27"[Date -Publication] : "3000"[Date - Publication]) ((("melanoma"[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (“Tomography, X-Ray Computed"[Mesh] OR “computer tomography”[all fields] OR “ct”[all fields] OR "Tomography, Spiral Computed"[Mesh] OR "Tomography Scanners, X-Ray Computed"[Mesh] OR "Positron-EmissionTomography"[Mesh] OR “positron-emission tomography”[all fields] OR“pet”[all fields] OR "Tomography, Emission-Computed, Single-Photon"[Mesh] OR “single-photon emission computed tomography”[all fields] OR “spect”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication]) ((("melanoma"[tiab AND ("LDH"[all fields] OR “lactate dehydrogenase” OR"S100"[all fields] OR "MIA"[tiab] OR"melanoma-inhibiting activity"[tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) NOT ("ophthalmology"[Mesh]OR "eye"[Mesh] OR "eye neoplasms"[Mesh]))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication])		73 31
Cochrane Library	(melanoma and (staging or diagnosis) and ("chest x-ray" or "chest radiography")).ti,ab. (melanoma and (staging or diagnosis) and ("ultrasonography" or "sonography" or "ultrasound" or sonogr*)).ti,ab. (melanoma and (staging or diagnosis) and ("magnetic resonance" or mri)).ti,ab. (melanoma and (staging or diagnosis) and (“computer tomography” or ct or “positron emission tomography” or pet or spect or “single-photon emission computed tomography” or “spect ct” or “pet ct”)).ti,ab. (melanoma and (staging or diagnosis) and (scintigraphy or scinti*)).ti,ab.	21.09.2016	7 7 5 9 4

	(melanoma and (staging or diagnosis) and (ldh or "lactate dehydrogenase" or s100* or mia or "melanoma inhibiting activity")).ti,ab.		10

2.3.3. Auswahlkriterien

2.3.3.1. Primärrecherche 2012

Auswahl der Literatur		
Gesamttreffer		8349
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt	
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research	
Anzahl nach Abstractscreening		296
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung		114

2.3.3.2. Aktualisierungsrecherche 2015

Auswahl der Literatur		
Gesamttreffer		1555
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt	
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research	

Anzahl nach Abstractscreening	1202
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	3

2.3.3.3. Aktualisierungsrecherche 2016

Auswahl der Literatur	
Gesamttreffer	1328
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research
Anzahl nach Abstractscreening	203
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	24

2.3.4. Evidenztabelle (zusammengefaßt für I.6., I.7., I.8., VII.6.)

2.3.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic LYMPH NODE ULTRASOUND							
Xing et al. (2011)	To examine the utility of ultrasonography, computed tomography (CT), positron emission tomography (PET), and a combination of both (PET-CT) for the staging and surveillance of melanoma patients.	Systematic review and meta-analysis	10 528 patients with cutaneous melanoma at primary diagnosis or under surveillance (follow-up)	Sensitivity, specificity Diagnostic odds' ratio (OR)	Data for initial staging of regional nodes: Sensitivity 60% Specificity 97% Diagnostic OR 42	Very large patient cohort, but patients under follow-up included	1a
Bafounta et al. (2004)	To investigate whether lymph-node ultrasonography improves detection of nodal invasion during the initial staging and follow-up of	Systematic review and meta-analysis of 12 published diagnostic studies until December 2003	6642 patients Predominantly stage I and II, six studies also stage III, very few (1.9% in one study) stage IV	Sensitivity and specificity Odds' ratios Positive and negative likelihood ratios	Odds ratio of sonography: 1755 (95% CI 726–4238) Odds' ratio of palpation 21 (4–111) Sonography: Positive likelihood ratio 41.9,	Variations in the definition of false negatives and verification bias in included studies	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with melanoma.				negative likelihood ratio 0.024 Palpation: Positive likelihood ratio 4.55, negative likelihood ratio 0.22		
Voit et al. (2010)	The aim of this study was to evaluate a number of specifically defined morphology US patterns and to correlate this with tumor involvement of the SN.	Prognostic and diagnostic study	400 patients with CM before SLNE	Sensitivity, specificity Positive predictive value, negative predictive value Overall and distant-metastasis-free survival	Highest sensitivity and PPV in following combination: presence of peripheral perfusion, loss of central echoes, and balloon-shaped lymph nodes Sensitivity 82% Specificity 80% PPV 52% NPV 94% 5-year OS according to peripheral perfusion 81% and 92% for present and absent 5-year OS for the loss of central echoes 49% vs.	Preliminary report (400 of 650 patients)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					92% when echoes still present 5-year OS rates for the presence and absence of a balloon-shaped lymph node 48% and 92%		
Sibon et al. (2007)	To evaluate the ability of high-resolution ultrasonography (hrUS) to detect sentinel-node (SN) melanoma metastases preoperatively before sentinel-node biopsy (SNB), to define hrUS resolution, and to evaluate which US criteria should be used.	Diagnostic study	131 consecutive patients with 132 ≥1-mm thick or ulcerated CM	Sensitivity and specificity Positive and negative predictive value Positive and negative likelihood ratios	Targeted high-resolution sonography for the detection of SLN: Stringent criteria: Sensitivity 8.8% Specificity 95.9% PPV 42.9% NPV 75.2% Non-stringent criteria: Sensitivity 20.6% Specificity 89.8% PPV 41.2% NPV 76.5%	Patients with mucosal melanoma included	1b
Saiag et al. (2005)	(1) to compare the respective ability of ultrasonography and palpation to detect nodal metastasis during	Diagnostic study	160 consecutive patients with stage I to stage III CM	Sensitivity, Specificity	Sonography: Sensitivity 76.9% Specificity 98.4% Palpation: Sensitivity 41.5% Specificity 95.7%	Patients with mucosal melanoma included	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	initial staging and follow-up in patients having melanomas (2) to assess which ultrasound criteria should be used to define metastasis in cases of cutaneous or mucosal melanoma (3), because scar tissue can modify ultrasonographic images, to evaluate whether ultrasonography remains useful once patients have undergone radical LD						
Stoffels et al. (2011)	To clarify the reliability of preoperative ultrasonography (US) in direct comparison to the result of SLNE and seeks to identify potential	Diagnostic study	221 patients with primary malignant melanoma with a Breslow index of >= 1.0 mm	Sensitivity Specificity PPV NPV	US: Sensitivity: 13.6% Specificity: 96.9% PPV: 97.2% NPV: 12,6% SLNE alone: Sensitivity: 94% Specificity: 98.6%	Reference standard for SLNE not described	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	advantages of preoperative ultrasound if performed in conjunction with lymphoscintigraphy in detecting malignant melanoma metastases in sentinel lymph node (SLN).				PPV 100% NPV 98,3% Preoperative US in conjunction with dynamic lymphoscintigraphy, followed by SLNE: detecting ratio: 100% (n = 28) for micrometastases, 98.6% (n = 42⁄43) for macro-metastases		
Hinz et a. (2011)	To evaluate whether high-resolution ultrasound combined with power Doppler sonography (PDS) is an appropriate tool for preoperative identification and characterization of sentinel lymph nodes (SLNs) in patients with	Diagnostic study	81 consecutive patients with CM in whom dissection of SLNs was indicated underwent ultrasound examinations before and after the preoperative lymphoscintigraphy.	sensitivity, specifity, PPV, NPV positive likelihood ratio negative likelihood ratio	A total of 170 SLNs (mean 2.1 per patient) were removed and examined by histopathology. sensitivity, specifity, PPV, NPV of ultrasound: 22.2% (95% CI = 2.8–60.0), 100% (95% CI = 97.7–100.0), 100.0% (95% CI = 15.8–100.0), and	patient cohort with only 9 positive SLNs in total No information about follow-up	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cutaneous melanoma.				95.8% (95% CI = 91.6–98.3), respectively. positive likelihood ratio: 0 negative likelihood ratio: 0.78.		
Chai et al. 2011	To assess feasibility and staging results of clinically targeted ultrasound (before lymphoscintigraphy) compared to SLNB.	Diagnostic study	325 patients with melanoma underwent ultrasound before SLNB without palpable lymphadenopathy in regional nodal basins	Sensitivity, specificity, PPV, NPV	sensitivity of ultrasound: 33.8%, specificity: 85.7%, PPV: 36.5%, NPV: 84.2%	No information about time interval between US and SLNB Confidence interval not given	2b
Sanki et al. (2009)	To reassess traditional ultrasound descriptors of sentinel lymph node (SLN) metastases, to determine the minimum cross-sectional area (CSA) of an SLN metastasis	Diagnostic study	716 CM patients	Sensitivity and specificity Positive and negative predictive value Positive and negative likelihood ratios Diagnostic accuracy	Targeted high-resolution sonography for the detection of SLN: Sensitivity 24.3% Specificity 96.8% PPV 60.3% NPV 86.2% Diagnostic accuracy 86.7%	Design (retrospective vs. prospective) not described	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	detectable by ultrasound (US), and to establish whether targeted, high-resolution US of SLNs identified by lympho-scintigraphy before initial melanoma surgery can be used as a substitute for excisional SLN biopsy.						
Testori et al. (2005)	(1) To obtain, using US, a pre-operative indication of the presence or absence of metastatic deposits in the sentinel node (SN); (2) to obtain, using US, the precise pre-operative location of superficial or deep, or peculiarly sited, SNs; and (3) to evaluate the	Diagnostic study	Of 300 melanoma patients who underwent SNB, 88 received sonography of the lymph nodes preoperatively	Sensitivity, specificity Positive and negative predictive value	Sensitivity 94.1% Specificity 89.8% PPV 64% NPV 98.7%	Inclusion criteria for patients who received pre-operative sonography unclear	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	role of US in the early diagnosis of falsenegative SNs (i.e. recurrences in the lymph node basin) during follow-up.						
Hocevar et al. (2004)	The aim of this study was to evaluate the ability of a combination of US and US-FNAB to stage the regional lymph node basins in patients with MM.	Diagnostic study	57 patients with CM, in whom SLN biopsy was planned	Sensitivity and specificity Positive and negative predictive value	Sensitivity 71% Specificity 84% PPV 59% NPV 90%	Risk of verification bias Design of study not described (retrospective versus prospective)	2b
Hafner et al. (2004)	To evaluate the sensitivity and specificity of baseline staging in the early detection of regional lymph node metastases or distant metastases in patients with MM.	Diagnostic study	100 consecutive patients with CM > 1.0 mm	Sensitivity, specificity Positive and negative predictive value	Sensitivity 8% Specificity 88% PPV 18% NPV 73%	Risk of verification bias	2b
Kunte et al. (2009)	The aim of this	Prospective	25 consecutive	Sensitivity,	Sensitivity 33.3%	Risk of verification	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	study was to evaluate the ability of high resolution B-mode ultrasonography (US) for pre-operative identification and characterization of sentinel lymph nodes (SLN) in patients with cutaneous melanoma.	diagnostic study	patients before SLN for CM	specificity Positive and negative predictive value	Specificity 100.0% PPV 100.0% NPV 87.9%	bias Small patient cohort	
Schmid-Wendtner et al. (2004)	to evaluate whether signal enhanced color Doppler sonography (CDS) is superior to native CDS in detection of characteristic vascularity patterns that are important for the differentiation between benign and malignant lymphadenopathy in patients with	Diagnostic study	22 melanoma patients	Sensitivity Secificity	signal-enhanced sonography : sensitivity = 92.3%, specificity=100.0% . For melanoma metastases, a sensitivity of 90.0% and a specificity of 85.7% was calculated. For both P-values <0.05	Prospective two-center study lack of histopathologic correlation in all presumptive sonographic diagnoses small study group sensitivity and specifity of native CDS not given study inclinded in	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cutaneous melanomas.					Xing et al. 2011	
Uren (1999)	to determine if high-resolution ultrasound could identify metastases in newly palpable lymph nodes found during clinical follow-up for melanoma, and to define the ultrasound features that were associated with this diagnosis	Diagnostic study	52 patients (61 individual node fields)	Ultrasound features in metastatic lymph nodes Sensitivity specifity	specifity = 87% sensitivity = 94% accuracy = 89% If presence of 2 US-features (=node thicker greater than two-third of the length and low-level internal echos) were present: Sensitivity = 94%, specifity = 100%, accuray 98%	No information about the time interval between ultrasound and FNAB/excision biopsy Small population Different examined fields: axilla, groin, supraclaviculaire, submental, cervical study inclinded in Xing et al. 2011	3b-
Subtopic CHEST X-RAY							
Wang et al. (2004)	To examine the yield of a chest radiograph and serum lactate dehydrogenase (LDH) in the work-up for newly	Diagnostic study	210 CM patients without clinical evidence of metastasis	False positives Alteration of surgical management	False positives 15/210 (7%) Alteration of surgical management in 0%		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	diagnosed localized melanoma, and to investigate how often the results of chest radiograph and LDH alter the initial surgical management.						
Hafner et al. (2004)	See above	Diagnostic study	100 consecutive patients with CM > 1.0 mm	Sensitivity, specificity Positive and negative predictive value	Sensitivity - Specificity 96% PPV 0% NPV 100%	study inclinded in Xing et al. 2011	2b
Vermeerenet et al. (2011)	to evaluate therapeutic consequences of preoperative staging with Chest X-ray (CXR) in patients with a primary melanoma planned for sentinel node biopsy (SNB).	diagnostic study	248 medical records of patients treated for primary melanoma CXR in 227 patients CXRs were made prior to SNB	False positives	Preoperative CXR did not identify pulmonary metastasis and did not change planned treatment strategies. In 5%, the CXR was inconclusive → false positives	Reference standard: complementary radiodiagnostic imaging and/or follow-up.	3b
Panagiotou et al. (2001)	To determine which imaging modalities should be performed	Retrospective study	158 asymptomatic patients submitted to at least a chest X-ray, an	true-positive and false-positive rate	TP: 26.6% FP: 7.6% In 12% CT was the only imaging		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	during the evaluation of patients with local-regional malignant melanoma		abdominal US and a CT of the chest, abdomen and pelvis		modality depicting metastases highest positive yield During the surveillance period, 118 asymptomatic patients relapsed. Detection of relapse: .- in 33.1% by physical examination - in 38.1% by chest X-ray - in 16,9% by abdominal CT		
Yancovitz et al. (2007)	To investigate whether initial imaging led to a change in stage or treatment plan	Diagnostic study	158 patients, 135 with stage I/II disease and 23 with stage III disease	True and false positives and negatives	True positives 0/7 (0.0%), False-positives 5/7 (71.4%) True negatives 112/126 (88.9%) 2/126 lost to follow-up	study included in Xing et al. 2011	3b
Tsao et al. (2004)	To determine if	Case-control study	994 CM patients in	Overall survival	28/1938 chest x-	Cohort consisting	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	earlier detection of pulmonary metastasis by routine chest radiography (CR) is associated with a prolonged survival.		stages I – IV		rays leading to first diagnosis of CM stage IV (1.4%) Overall survival according to Kaplan-Meier curve: no difference between patients with known stage IV at the time of diagnosis and initial diagnosis of stage IV by x-ray False positives (of all x-rays): 3.5%	of stage I – IV patients	
Hofmann et al. (2002)	Assessment of the performance, costs and survival benefits of staging methods (history and physical examination; chest X-ray; ultrasonography of the abdomen; high resolution sonography of the peripheral lymph nodes) at initial staging and during	Diagnostic study with historical cohort; economical evaluation	661 patients (stage I/II: 630 patients, stage III: 27 patients, stage IV: 4 patients)	True and false positives and negatives Detection rate Cost-efficiency of imaging procedures Survival	524 total chest x-rays 1 true positive (0.2%) 23 false positives (4.4%) Detection rate 3.2% Cost of chest x-ray at initial staging: 11761 EUR (1887 EUR due to false positive results)	Diagnostic standard procedures varied over time; no defined gold standard of diagnosis	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	follow-up of stage I/II+III disease.						
Terhune et al. (1998)	To evaluate the use of an initial staging chest x-ray film in asymptomatic patients who present with localized primary cutaneous melanoma.	Diagnostic study	876 CM patients at initial staging	True and false positives .	130/876 (15%) patients with suspicious findings Additional workup led to 1/876 true positives (0.1%) 129/876 false positives (14.7%)	X-rays not obtained from all patients “Initial” chest x-ray up to 6 months after diagnosis	3b
Iscoe et al. (1986)	The description of predictive value of clinical, laboratory and radiologic investigations in the staging of patients with clinical stage I melanoma.	Diagnostic study	393 consecutive CM patients	True and false positives Positive and negative predictive value	Number of chest x-rays: 345 True positives: 0 False positives: 8 Positive predictive value: 0% Negative predictive value: 97.6%	Index tests not carried out on all patients	3b
Khansur et al. (1989)	To evaluate the role of staging workup in primary and recurrent malignant melanoma.	Diagnostic study	115 patients with primary CM (72 in localized stage) and 28 patients with recurrent disease	True and false positives	0/72 true positives 2/72 false positives (3%)	Criteria for selecting staging examinations unclear	3b-
Ardizzoni et al.	To evaluate the	Diagnostic study	116 patients;	True and false	Positive results: 0	Design	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(1987)	yield, in terms of cost-benefit-ratio, of a multimodal staging procedure consisting of multiple nuclear scans, chest X-ray and abdominal ultrasonography to detect silent metastases in asymptomatic melanoma patients		clinically 93 in stage I and 23 in stage II	positives and negatives	of 116 chest x-rays 0% true positives 0% false positives 2 patients with lung metastases later in follow-up => 2% false negatives, 98% true negatives	(prospective vs. retrospective) not clear Follow-up time not given	
Meyer and Stolbach (1978)	To evaluate radiographic evaluation for the recognition of occult sites of metastatic disease beyond the regional nodes in malignant melanoma.	Diagnostic study	53 CM patients without symptoms to suggest distant metastasis	True and false positives	4/53 true positives (8%) 0 false positives	Cohort probably included patients with lymph node metastases	3b-
Zartman et al. (1987)	To answer the question whether extensive diagnostic staging procedures are justified for patients with	Cohort study	90 CM patients with level III and IV lesions	Positive results	No positive results for chest x-ray	Patients with complete staging included; indications for different staging examinations unclear	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	primary diagnosis of melanoma						
Goerz et al. (1986)	To investigate which staging and follow-up examinations are necessary for patients with malignant melanoma.	Diagnostic study	378 patients with histologically confirmed CM (stage not given)	True and false positives	0% positive results for chest x-ray at initial staging During follow-up examinations, distant metastasis was proven in 34/378 patients, in 32 of them by physical examination, in 2 by chest x-ray.		3b-
Kersey et al. (1985)	To determine the value of staging and serial follow-up investigations in newly diagnosed patients with completely excised primary cutaneous malignant melanoma	Diagnostic study	393 patients at primary diagnosis of CM	True and false positives	True positives 0 False positives 8/345 (2%)	Extent of staging examinations and extent/ length of follow-up depended on center and tumor site	3b-
Collins et al. (1993)	To determine whether the detection of	Diagnostic study	follow-up of 227 consecutive patients.	number of suspect lesions in PA and lateral radiographs	In 1 case was an abnormality	Sensitivity and specifity not given	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastatic disease would be reduced if the lateral projection were not obtained.				evident on the lateral radiograph which was not previously detected on the PA films Normal PA and lateral radiograph: 60,8%. Abnormality equally visible on PA and lateral radiograph: 16,7%. Abnormality more easily visualized on PA than on lateral radiograph: 11%. Abnormality more easily visualized on lateral than on PA radiograph: 4,4%. Abnormality on PA radiograph not visualized on lateral projection 6,6%. Abnormality on lateral radiograph not visualized on PA	No reference test Population not described in detail No information about the study design No information about selection criteria Sensitivity or specificity not given	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					projection: 0,44%		
Webb (1977)	To describe the frequency of radiographic patterns of thoracic metastasis in patients with melanoma, and to correlate these patterns with the symptoms, clinical course, and survival of the patients.	diagnostic study	65 patients with malignant melanoma metastatic to the thorax	radiographic patterns of thoracic metastasis Survival rates	Abnormalities in chest x-ray in 42/62 patients Survival: see full-text	11 patients received x-ray and tomogram Tissue specimen in only 31 Small population, asymptomatic patients included	4
Subtopic ABDOMINAL ULTRASOUND							
Hafner et al. (2004)	See above	See above	100 consecutive patients with CM > 1.0 mm	Sensitivity, specificity Positive and negative predictive value	Sensitivity - Specificity 97% PPV 0% NPV 100%		2b
Panagiotou et al. (2001)	See above	See above	See above	See above	See above	See above	3b
Hofmann et al. (2002)	See above	See above	661 patients (stage I/II: 630	True and false positives and	487 total abdominal	Diagnostic standard	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			patients, stage III: 27 patients, stage IV: 4 patients)	negatives Detection rate Cost-efficiency of imaging procedures Survival	sonographies 2 true positive (0.4%) 25 false positives (5.1%) Detection rate 6.5% Cost of chest x-ray at initial staging: 16618 EUR (6421 EUR due to false positive results)	procedures varied over time; no defined gold standard of diagnosis	
Pandalai et al. (2010)	To evaluate the clinical utility of standardized radiographic staging.	Diagnostic stuy	58 consecutive asymptomatic patients with stage III AJCC melanoma .	True- positive (TP) rate false-positive (FP) rate	Initial staging examinations: 9% TP, 91% FP All examinations: 3% TP; 23% FP. Analyzed per patient, in 37 (64%) of 58 patients, >=1 examination was initially reported as positive. 3 patients (5%) had a TP and 34 (59%) had ≥1 FP report. The positive	Small sample size Sensitivity and specificity not given Small number of MRI/CT of the head, PET and bone scan No routine standardized staging procedure was followed	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					reports of the staging scans generated 45 additional examinations (0.78 per patient). analyzed by type of radiograph, the 5 TP findings were found in 3 (13%) of 23 suspicious chest CT scans, 1 (5%) of 20 suspicious abdomen and pelvis CT scans, and in 1 (100%) of 1 PET scans. Of the 5 brain MRIs, 2 head CT scans, and 1 bone scan that were initially reported as ‘‘suspicious,’’ none was proven to be TP. ratio of FP:TP: 34:3		
Kuan et al. (1988)	To emphasize the sensitivity and	Retrospective cohort study	88 patients with pathologically	Sensitivity	In patients who had all 3	Poor information about selection	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	specificity of the examinations both for the detection of space-occupying lesions and for the assessment of extent of metastatic disease		proven cutaneous melanoma in various clinical stages	specificity	examinations (n=24): Sensitivity in detecting intra-abdominal metastasis:CT: 94% vs. US: 62% (P< 0.05) CT vs. LS: 38% (P< 0.01) In patients with only US and LS (n=64): Sensitivity US: 88% vs. LS 54% (P< 0.01). CT detected metastases significantly earlier than US (P=0.03)	criteria and population Poor data about patients` follow-up Small population	
Ardizzoni et al. (1987)	See above	See above	116 patients; clinically 93 in stage I and 23 in stage II	True and false positives and negatives	0/66 positives for liver involvement 1/66 true positives for iliac lymph node involvement (2%) 1/66 false positives for iliac lymph node	Design (prospective vs. retrospective) not clear from description Follow-up time not given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					involvement (2%)		
Goerz et al. (1986):	See above	See above	378 patients with histologically confirmed CM	True and false positives	0% positive results	Stage of patients not given	3b-
Holloway et al. (1997)	To determine the frequency of gallbladder pathology, other than gallstones in this group o patients.	diagnostic study	464 patients with cutaneaous melanoma except one which arose on the nasal mucosa.	Detection rate of metatasis	Ultrasound appearances typical of gallbladder metastases in 4,1%	No further information about the population.	4
Stutte (1989)	To describe ultrasonographic findings and to evaluate the significance of upper abdominal ultrasonography in assessing the spread of metastasizing malignant melanome during follow up.	Prognostic study Retrospective study	42 patients with distant metastases of CM	Mean overall survival	Mean survival time: - for patients with ≤ 3 liver metastases ≤ 3 cm diameter: 8,4 months - for patients with numerous metastases or metastases > 3cm diameter: 4,3 months - for patients with isoechoic metastases: 2,6 months.	No information about inclusion criterias Small patient cohort	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Zartman et al. (1987)	See above	See above	90 CM patients with level III and IV lesions	Positive results	No positive results for abdominal sonography	Patients with complete staging included; indications for different staging examinations unclear	4
Doiron et al. (1981)	To discusses which of these imaging modalities yields the most information in patients with intraabdominal metastatic melanoma	Diagnostic study	163 patients with malignant melanoma in clinical stage III examined by RN liver scan, US, and CT in various combinations over a 2-years-period. Patients were divided into 3 groups according to the examinations: (1) RN liver scan, US, and CT (38 patients) (2) RN liver scans and CT (10 patients) (3) US and RN liver scan.(115 patients)	False negatives (FN) False positives (FP)	Group 1: CT, US and RN demonstrated 20, 22 and 23 normal results respectively and 18, 17 and 15 abnormal results respectively 1 FN (CT) 1 FN (US) 8 FP and 1 FN (RN) Group 2: CT, RN demonstrated both 7 normal results and both 3 negative results. 2FP and 1 FN (RN) Group 3: US and RN demonstated 52	Sensitivity and specificity not given No information about follow-up	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					and 75 normal results respectively and 43 and 40 abnormal results respectively 2 FP (US) 10 FP (RN)		
Subtopic MRI							
Hausmann et al. (2011)	To compare the diagnostic accuracy of whole-body MRI with the standard diagnostic algorithm (whole-body CT and brain MRI) in patients with stage III/IV MM.	Diagnostic study	33 consecutively admitted patients with histologically confirmed diagnosis of stage III or IV MM	Sensitivity specificity	The sensitivity of whole-body MRI was observerdependent. Sensitivity: MRI vs. CT: 73.4 % vs. 78.2 %, p = 0.0744. Sensitivity in the detection of small (1–5 mm) pulmonary nodules: MRI vs. CT: 2.9 % vs. 66.9 %, p < 0.0001 Overall specificity:	Data interpretation by two blinded examiners	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					MRI vs. CT: 83.4 % vs. 50.4 %, p < 0.0001		
Pfannenberg et al. (2007)	To compare the overall and site-based accuracy and impact on patient management of positron emission tomography/computed tomography (PET/CT) and whole-body (wb) magnetic resonance imaging (MRI) in staging of advanced melanoma.	Diagnostic study	64 patients: 25 patients stage III, 39 patients stage IV	Sensitivity Specificity positive predictive value (PPV) negative predictive value (NPV) accuracy	The overall accuracy: PET/CT: 86.7% wbMRI: 78.8% CT: 75.0% PET: 74.3% PET vs. wbMRI: P = 0.0007 PET vs. PET/CT: P < 0.0001 . Sensitivity, specifity, TN, FN, TP, FP: see full text/table 2	Cerebral lesions in wbMRI were recorded, but excluded from the analysis because of the lack of comparable PET data. The selection of inclusion criteria led to underestimated calculated specificity, because only the lesions suspicious of malignancy in one of the different methods were included in the study and compared by different methods. Study included in Xing et al. 2011 and Krug et al.	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						2008	
Dellestable et al. (2011)	To assess the Se and specificity (Sp) of wb-MRI with a diffusion sequence for detecting melanoma metastasis compared to PET/CT.	Diagnostic study	40 patients were included and a total of 72 metastases were noted	Sensitivity specificity	CT: sensitivity: 80%, specificity: 95% PET/CT sensitivity: 74% specificity: 89% Wb-MRI sensitivity: 83% specificity: 96% The sensitivity of MRI was distinctly superior to PET/CT for both hepatic and pulmonary lesions.	no detailed information about patient cohort small patient cohort	2b-
Laurent et al. (2011)	To compare whole-body MRI with a multi-contrast protocol including a DW (Diffusion Weighted) sequence to PET-CT using (18)FDG for staging	Diagnostic study	35 patients	Sensitivity specificity	sensitivity and specificity for whole-body MRI: 82% and 97% PET-CT: 72.8% and 92.7%. DW sequence	prospective blinded study small patient cohort	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	advanced melanoma.				allowed the detection of 14 supplementary malignant lesions (20%) in comparison with standard MRI protocol. DW sequence has been shown to be the most accurate for detecting metastases in the liver, bone, subcutaneous and intra-peritoneal sites.		
Mueller-Horvat (2005)	To compare contrast-enhanced whole-body magnetic resonance imaging (wbMRI) and whole-body computed tomography (wbCT) to detect distant metastases for staging.	Diagnostic study	43 patients AJJC stage III–IV malignant melanoma	Metastasis detection rate	wbCT vs. wbMRI: detection of 522 vs. 730 metastases wbCT vs. wbMRI: -pulmonary metastases: 188 vs. 143 - metastases in kidneys, adrenal glands and lymph nodes: same number of	4 patients had choroid malignant melanoma specifity and sensitivity not given no follow-up small population uninterpretable results not	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					detected lesions - liver: 122 vs. 199. - spleen 26 vs. 54 - subcutaneous tissue 39 vs. 61 - muscle 4 vs. 11 - bone marrow 23 vs. 132 Brain 15 vs. 25 Therapy was modified as a consequence of wbMRI findings in 10/41 (24%) patients.	described	
Schlamann et al. (2008)	To investigate the incidence of cerebral metastasis in asymptomatic melanoma patients in relation to the stage of disease to estimate the reasonability of this examination.	Diagnostic study	120 CM patients without other malignancy or neurological disease	Incidence of cerebral metastasis	Stage I: 0/27 positive results Stage II: 1/29 positive results (3%); patient in stage IIC Stage III/IV: 14/64 positive results (22%)	Criteria for patient selection unclear	3b-
Fogarty et al. (2006)	To retrospectively evaluate the use of	Diagnostic study	100 of 193 consecutive CM	Detection rate Upstaging by MRI	Patients in stages I – III: 0% positive	Patients in stages I – IV included	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	brain magnetic resonance imaging (MRI) in the initial staging of patients with cutaneous melanoma		patients without neurological symptoms		results No patients upstaged by staging MRI		
Subtopic PET							
Xing et al. (2011)	To examine the utility of ultrasonography, computed tomography (CT), positron emission tomography (PET), and a combination of both (PET-CT) for the staging and surveillance of melanoma patients.	Systematic review and meta-analysis	10 528 patients with cutaneous melanoma at primary diagnosis or under surveillance (follow-up)	Sensitivity, specificity Diagnostic odds' ratio (OR)	Data for initial staging of regional nodes: Sensitivity 30% Specificity 96% Diagnostic OR 9.45	Very large patient cohort, but patients under follow-up included	1a
Krug et al. (2008)	To calculate summary estimates of the diagnostic performance of fluorine 18 fluorodeoxyglucose (FDG) positron	Systematic review with meta-analysis	2905 CM patients in 28 studies of which 2096 underwent PET alone and 809 underwent PET/CT	Pooled sensitivity and specificity Positive and negative likelihood ratio (LR+, LR-) Diagnostic odds' ratio (OR) Changes in	Pooled sensitivity: 83% Pooled specificity: 85% LR+: 4.56 LR-: 0.27 Overall diagnostic OR: 19.8	In 17 studies, patients enrolled exclusively for initial staging; in 11 studies, proportion of initial staging patients 18 – 97%	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	emission tomographic (PET) imaging in the initial staging of cutaneous malignant melanoma (CMM)			disease management	Early-stage subgroup (10 studies, 755 patients): Pooled diagnostic OR 4.3 (95% CI: 1, 18) Mean sensitivity 60% 8 studies suggested that FDG PET was associated with 33% (range, 15%–64%) disease management changes	Overall, many low-quality studies resp. small patients cohorts	
Jimenez-Requena et al. (2010)	To perform a systematic review of the literature to evaluate the accuracy of FDG-PET in staging and restaging of cutaneous melanoma.	Systematic review with meta-analysis	444 CM patients (group I = regional staging), stages I – III, in 7 studies	Pooled specificity and sensitivity Positive and negative likelihood ratio (LR+, LR-) Summary receiver-operating curve (ROC)	Group I (regional staging): Pooled specificity: 0.99 No global homogeneity for sensitivity, LR+ or LR- ROC curves grouped in the left margin, indicating global high specificity	Overall, many low-quality studies resp. small patients cohorts	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Schwimmer et al. (2000)						Data included in Jimenez-Requena et al. (2010): Meta-analysis of the performance of (18)F-FDG PET in cutaneous melanoma	
Bastiaannet et al. (2009	to perform a head-to-head-comparison of FDG-PET and CT in staging of patients with melanoma with palpable lymph node metastases (AJCC stage III) in terms of diagnostic accuracy and impact on treatment.	Prospective multicenter study	In total 251 Patients with palpable and histologically or cytologically proven lymph node metastases (after negative sentinel lymph node)	False negatives (FN) true positives (TP) false positives (FP) true negatives (TN) sensitivity	FDG-PET detected more metastatic sites (133 v 112, P = .03), detecting significantly more bone and subcutaneous metastases. CT had more FN results (n=17) than PET (n=11). Numbers of FN, TP, FP and TN: see full Sensitivity to detect distant metastases CT scan 78% PET scan 86%	study included in Xing et al. 2011 and Jimenez-Requena 2008	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Pfannenberg et al. (2007)	See above	See above	See above	See above	See above	See above	2b
Laurent et al. (2011)	See above	See above	See above	See above	See above	See above	2b-
Koskivuo et al. (2007)	To determine the clinical impact of whole body positron emission tomography (FDG PET) To detect clinically silent metastases in the follow-up of patients with high risk melanoma.	Prospective study	30 asymptomatic melanoma patients (AJCC stage IIB-IIIC) 7-24 months after the primary surgery and sentinel node biopsy.	Sensitivity Specificity PPV NPV Clinical impact	sensitivity and specificity for melanoma recurrence: 86% and 96%, respectively. PPV: 86% NPV: 96% positive PET finding had an impact on treatment decisions in every case: 3 patients underwent surgical resection, 4patients received chemotherapy or interferon.	Small patient cohort Study included in Xing et al. 2011	2b-
Maubec et al. (2007)	To determine the value of F-18 fluorodeoxy-D-glucose positron	Diagnostic study	25 CM patients with lesions > 4 mm	Sensitivity, specificity	Initial tumor site: 14/19 true negatives (74%) 5/19 false	Prospective design small number of patients	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	emission tomography scanning in the detection of regional and/or distant metastasis				positives (26%) Sensitivity 17%, specificity 74% Microscopic lymph node disease: 12/19 true negatives (63%) 7/19 false negatives (37%) Sensitivity 0%	Study included in Xing et al. 2011	
El-Maraghi and Kielar (2008)	To evaluate PET and PET/computed tomography (CT) compared with SLNB for staging local lymph nodes in patients with intermediate-risk melanoma.	Systematic review without meta-analysis	20 studies; number of patients unclear because some included studies did not report cohort size	True and false negatives and positives Sensitivity and specificity Positive and negative predictive value	Ranges (no meta-analysis): TP 0 – 10% FP 0 – 18% TN 60 – 74% FN 3 – 40% Sensitivity 0 – 92% Specificity 7 – 100% PPV 0 – 100% NPV 20 – 85%	Levels of evidence according to authors: 7 studies 2b, 1 review 3a, 3 review 3b, 3 studies 3b, 3 studies 4, 2 letters/opinion articles 5 Overall, many low-quality studies resp. small patients cohorts	3a
Pleiss et al. (2007)	to assess the potential of fluor-18-FDGPET in order to evaluate the	Prognostic and diagnostic study	95 Patients with maligant melanoma who had received a PET	overall 5-year survival sensitivity	Sensitivity, specificity, and accuracy of FDG-PET were 91%, 86%, and 89%,	No information about the final assessment of findings (e.g. histology and/or	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	survival prognosis in melanoma			specifity	respectively, and of CT 58%, 91%, and 73%, respectively. survival in patients with - both studies (CT and PET) being negative: 5-year survival, 83% - both studies (CT and PET) being positive: 5-year survival, 61%; p < 0.02 - PET being positive but CT still negative: 5-year survival, 73%	clinical follow-up) Number of TP and FP etc. missing. Data for the calculation of sensitivity/specificity not given No information about the time-period between PET and CT	
Clark et al. (2006)	To investigate the utility of whole-body PET imaging in 64 patients with T2 to T4 melanomas prior to sentinel lymph node dissection without clinically suspected metastases	diagnostic study	64 CM patients without clinical evidence of metastasis	True and false positives and negatives Change in management	PET scans normal in 60 of 64 patients (94%) 2/64 (3%) false positives 2/64 true positives 19/64 false negatives (regarding sentinel node status)	22/64 patients with T4 lesions Study included in Xing et al. 2011	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					No change in management by PET results		
Vereecken et al. (2005)	The purpose of this study was to evaluate the impact of extensive initial staging on the management of melanoma patients.	Diagnostic study	43 patients with intermediate/high risk melanoma (Breslow thickness ≥ 1 mm or regression/ ulceration)	Evidence of metastasis	Paraclinical investigation (CT scan of the chest, CT of the abdomen, CT or NMR of the brain and whole body FDG PET scan) failed to reveal any sign of evidence of disseminated disease in the series of 43 patients. Positivity:67% Sensitivity: 40% PPV: 9,3%	Results concerning PET already considered in Jimenez-Requena et al. 2010, in Krug et al. 2008 and in Xing et al. 2011 No distinction between results for MRI and CT of the brain. Imaging results validated by 6 months follow-up.	3b
Stas et al. (2002)	To evaluate (1) the sensitivity and specificity of PET scan at a single lesion level compared with conventional screening procedures (CSP) –	Retrospective diagnostic study CSP= chest X-ray, blood analysis, ultrasonography, (US), computed tomography (CT),	100 PET scans on 84 melanoma patients with regional or distant recurrences according to CSP	Sensitivity Specifity Accuracy Therapeutic impact	At the single lesion level: Sensitivity: PET: 85% CSP: 81% Specificity: PET: 90% CSP: 87% Accuracy:	Comparison of PET scan and CSP results at a lesion-based level→ see full-text Therapeutic impact of PET scan results → see full	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	both of these accompanied by clinical examination; and (2) the additional value of the PET scan at the level of the individual patient and its therapeutic impact for different types of melanoma recurrence.	magnetic resonance imaging (MRI) and nuclear bone scans			PET 88% CSP: 84% The overall therapeutic impact (PET): 26%	text Study included in Jimenez-Requena et al. 2010 and Xing et al. 2011	
Wagner et al. (2011)	To assess the rate of distant metastases in patients with a positive SLN biopsy (SLNB).	Diagnostic study	46 consecutive patients with a positive SLNB underwent PET or PET–computed tomography within 6 weeks of the SLNB procedure and without any clinical sign of nodal involvement or of distant metastasis.	FN	Positive PET-scan: 0% Nonconclusive PET scan 13% Negative PET in 87%, among them 12% presented with distant metastasis within 12 months.	46 PET procedures were performed: In 22 patients: stand-alone PET and aCT scan with a contrast medium. In 24 patients: PET–CT scan without injection of contrast medium. Results: no differentiation between PET and PET/CT Images were	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						interpreted by a specialist aware of all the clinical findings → not blinded	
Constantinidou et al. (2008)	To evaluate the role of PET or PET/ computed tomography (CT) as a routine procedure in patients with positive sentinel node biopsy (SNB).	Diagnostic study	30 patients with Breslow thickness of at least 1mm and who had a positive sentinel node biopsy.	Positive rate	Positive PET in 2 patients (6%) LN dissection positive in 5 cases (16%) With a median follow-up of 24 months, 21 patients remained disease free.alteration of melanoma management in none of the 30	Follow-up methods not described in detail Small patient number	3b-
Horn et al. (2005)	To investigate the clinical value of implementing whole-body FDG-PET as a routine investigation in stage III melanoma patients with sub-clinical regional	Diagnostic study	33 patients with cutaneous malignant melanoma and subclinical lymph node metastases diagnosed by sentinel node biopsy (SNB)	sensitivity specificity NPV	Sensitivity and a specificity for melanoma metastases: 80% and 88%, respectively. NPV: 96%.	Small patient cohort Only cases with positive PET findings received verification via CT scan, MRI, ultrasonography	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	lymph node metastases diagnosed by SNB.					or biopsy Small population Study included in Krug et al. 2008 and in Xing et al. 2011	
Loffler et al. (2003)	To disclose the diagnostic benefit of scanning the legs and to evaluate the therapeutic benefit resulting.	Diagnostic study	213 consecutive PET studies in 153 patients with suspected or recent melanoma	Detection rate	Suspicious findings at the legs in 53 patients on 76 occasions. 38/53 showed pathologic uptake in the torso as well. In 15/53 patients it was restricted to the legs. 11 of those 15 patients had a previous history in that location. In 1 patient the finding was a new and clinically relevant metastasis, in 3 other patients the leg manifestations were already known.	Sensitivity and specificity not given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					In 6 other patients a validation of the positive PET findings was not possible		
Krug et al. (2000)	To assess the diagnostic value of fluor-18-Fluorodeoxy-glucose positron emission tomography (FDG-PET) in screening for melanoma metastases	Diagnostic study	94 melanoma patients who had been examined by whole-body FDG-PET. 40 patients showed evidence of lymphogenous, 42 of hematogenous metastasis.	Metastases-detection rate	In no case did PET change the staging. In 13 patients, PET agreed with morphological diagnosis in the number of metastatically invaded organs. This included 3 patients without metastases. The estimated number of organs invaded by metastases was higher with PET in 5 patients and higher with morphological imaging techniques in 6 patients. Among the PET findings with higher or	Different reference tests Sensitivity and specifity not given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					equivocal counts of organs with metastases there were 2 confirmed false-positive findings. (Results for the different organs (lungs, liver…): see full text)		
Dietlein et al. (1999)	To examine if - FDG-PET can improve staging of patients with melanoma when compared with combinations of standard radiological examinations currently used in routine practice? - if the setting of indications for PET can be opimized?	Diagnostic study	91 FDG-PET examinations perfomed on 68 patients with advanced melanoma.	True positives False positives	FDG-PET detected more lymph node and bone metastases High proportion of non-verifiable PET findings Comparision of ultrasonographic and radiological methods with FDG-PET for examining the lungs, abdominal organs, LN and skeleton: see full-text.	FDG-PET images from various institutes Different staging examinations Sensitivity /specificity not given No data concerning follow-up Study included in Jimenez-Requena et al. 2010	3b-
Subtopic							

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
CT							
Xing et al. (2011)	See above	Systematic review and meta-analysis	10 528 patients with cutaneous melanoma at primary diagnosis or under surveillance (follow-up)	Sensitivity, specificity Diagnostic odds' ratio (OR)	Data for initial staging of regional lymph nodes: Sensitivity 9% Specificity 92% Diagnostic OR 1.13	Very large patient cohort, but patients under follow-up included	1a
Bastiaannet et al. (2009)	See above	See above	See above	See above	See above	study included in Xing et al. 2011 and Jimenez-Requena 2008	2b
Pfannenberg et al. (2007)	See above	See above	See above	See above	See above	See above	2b
Dellestable et al. (2011)	See above	See above	See above	See above	See above	See above	2b-
Hausmann et al. (2011)	See above	See above	See above	See above	See above	See above	2b
Panagiotou et al. (2001)	See above	See above	See above	See above	See above	See above	3b
Sawyer et al. (2009)	To determine whether CT changes management in AJCC IIB disease or	Diagnostic study	132 CM patients in stages IIB/C (42 IIB, 90 IIC)	True and false positives Change in clinical management	Region – number of scans with metastases – change in management in %	No homogenous reference standard Values for true and false positive based on initial	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	worse with regard to initial staging scans and subsequent follow up scans. A second objective was to determine whether CT of the head and neck should be performed.				Chest – 3 – 0% Abdomen – 2 – 0% Pelvis – 0 – 0% Head – 3 – 0.7% Neck – 0 – 0% True and false positives of regional CT scans: Chest True positives: 9 (81%) False positives: 2 (19.0%) Abdomen True positives: 7 (53%) False positive: 6 (47%) Pelvis True positives: 3 (38%) False positives: 5 (62%) Head True positives: 6 (100%) False positives: 0	and follow-up scans; probably lower if only initial scans were considered	
Yancovitz et al. (2007)	See above	Diagnostic study	158 patients, 135 with stage I/II disease and 23 with stage III	True and false positives and negatives	Number of CT studies: 57 chest, 57 abdomen/ pelvis, 57 head	study included in Xing et al. 2011	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			disease		Positives: Chest CT 24 of 57 Abdomen/ pelvis 11 Cranial CT 2 True positives: Chest CT 0 of 57 (0.0%) Abdomen/ pelvis CT 0 of 57 (0.0%) Cranial CT 0 of 57 (0.0%) False positives: Chest CT 21 of 57 (37%) Abdomen/ pelvis CT 10 of 11 (18%) Cranial CT 2 of 57 (4.0%) True negatives: Chest CT 50 of 57 (88%) Abdomen/ pelvis CT 46 of 57 (81%) Cranial CT 53 of 57 (93%) (Rest lost to follow-up) No false negatives		
Van den Brekel et al. (1998)	To assess the value of CT	Diagnostic study	26 CM patients with neck CT	Sensitivity and specificity	CT scans of the neck:	Different reference standards	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	scanning in detecting lymph node metastases in the neck from malignant melanoma and to look at possible CT characteristics of such metastases.		before neck dissection, 8 of them negative for palpation	True and false positives and negatives	2/26 (8%) false negatives (slices of 8 mm instead of 5 mm) Sensitivity of both palpation and CT scanning 86%, specificity 100%	(comprehensive and selective neck dissection) Inclusion criteria unclear Only 8 asymptomatic patients	
Iscoe et al. (1986):	See above	Diagnostic study	393 consecutive CM patients	True and false positives Positive and negative predictive value (PPV, NPV)	Chest CT: Number of exams: 59 True positives: 0 False positives: 9 PPV: 0% NPV: 98.0% Cranial CT: Number of exams: 52 True positives: 0 False positives: 9 PPV: / NPV: 98.1%	Index tests not done on all patients	3b
Heaston et al. (1983)	First, to determine prospectively the sensitivity and specificity of conventional chest radiography,	Diagnostic study	42 CM patients in stages I – III (11 in stages I – II)	Sensitivity, specificity False-positive and false-negative rate Overall accuracy	Chest CT: Sensitivity 100% Specificity 95% False positives 2% False negatives 0% Overall accuracy	Sensitivity and specificity calculated for a cohort including stage III melanoma patients; not	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	tomography, and computed tomography in a selected group of patients with high propensity for pulmonary melanoma metastases; second, to evaluate the impact of the discovery of pulmonary nodules on the clinical therapy of melanoma.				98%	enough data given to calculate for stage I and II alone	
Aloia et al. (2006)	To analyse the efficacy of routine radiologic staging in asymptomatic patients with microscopic nodal involvement before completion of lymphadenectomy.	Diagnostic retrospective Cohort study	270 staged patients with positive SLNB melanoma	True positive and False negative rate	TP detection rate of occult distant metastases: 1,9% FP: 12%.	Calculation of sensitivity and specificity not possible False and true negatives not given	3b-
Miranda et al. (2004)	To determine the rate of detectable	Diagnostic study	185 patients with pathologic	Diagnostic yield of imaging studies:	142 patients underwent chest	Not in every case of indeterminate	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	systemic metastasis at the time of SSL in asymptomatic patients with melanoma in North America		evidence of metastasis to at least 1 SLN		CT: - 1 positive finding - 114 negative - 27 indeterminate 146 patients underwent CT of the abdomen and pelvis: - 1 positive finding, - - 123 negative - 22 indeterminate. 96 underwent MRI imaging (brain), 16 underwent CT (brain): - no positive findings - 105 negative - 7 were indeterminate. CT of the chest and abdomen/pelvis/brain: indeterminate rates were 19%, 15% and 6,3%	findings additional diagnostic was performed Sensitivity/specificity not given	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					respectively.		
Johnson (1997)	To evaluate the yield and clinical impact of computed tomography (CT) imaging in otherwise asymptomatic patients with stage III melanoma metastatic to the regional nodes	Diagnostic study	127 asymptomatic patients stage III (28 patients: microscopic disease at ELND. 99 patients with palpable disease diagnosed by fine needle aspirate, open biopsy, or TLND)	True (TP) and false positives (FP)	20 patients: TP CT scan revealing unsuspected metastases. 15 patients: abnormal CT scans subsequently shown to be a benign process or second malignancy. No difference in the incidence of TP CT between the groups of patients with clinically apparent vs. occult nodal disease. significantly higher incidence of abdominal and pelvic metastatic sites identified by CT scan in patients with inguinal nodal disease vs. patients with	TP and FP rates: see full text FP and FN not given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					axillary or head and neck nodal disease.		
Buzaid et al. (1995)	To determine the value of CT scans in the staging of asymptomatic melanoma patients who presented with or developed localregional disease as the first site of recurrence and had both a normal chest radiograph and serum lactate dehydrogenase (LDH) level.	Diagnostic study	89 patients who either presented with or developed localregional disease as the first site of recurrence	TP-rate TN-rate	Findings on CT scan were TP for six patients (7%), FP for 20 (22%), and TN for 63 (71%).	No detailed data about the follow-up regime/time of follow up Sensitivity and specificity not given Study included in Xing et al. 2011	3b-
Khansur et al. (1989)	See above	Diagnostic study	115 patients with primary CM (72 in localized stage) and 28 patients with recurrent disease	True and false positives	Cranial CT: 0 true positives and 0 false positives in patients with localized disease	Criteria for selecting staging examinations unclear	3b-
Kuan et al. (1988)	See above	See above	See above	See above	See above	See above	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Goerz et al. (1986):	See above	Diagnostic study	378 patients with histologically confirmed CM	True and false positives	Whole-body CT: 2/378 true positives (distant metastasis)	Stages not given	3b-
Kersey et al. (1985)	See above	Diagnostic study	393 patients at primary diagnosis of CM	True and false positives	CT chest: 0/59 true positives 9/59 false positives (15%) Cranial CT: 0/51 true positives 0/51 false positives	Extent of staging examinations and extent/ length of follow-up depended on center and tumor site	3b-
Patten et al. (1990)	To determine whether the frequency of CT detection of axial skeletal metastases was greater than that reported for plain film radiology and to determine if the thickness and depth of penetration of the primary melanoma (according to the Breslow and Clark classifications) can	Cross-sectional study	125 CM patients	Prevalence of bone metastasis	Examinations: CT abdomen (41%), chest (27%), pelvis (25%), and neck (7%) 98/125 patients (78%) with CT evidence of metastatic melanoma 17/98 (17%) skeletal metastases 2/17 only evidence of metastatic disease	Not enough data given to differentiate between prevalence of bone metastasis in early stage and advanced stage melanoma	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	be used to predict the occurrence of skeletal metastases.						
Zartman et al. (1987)	See above	Cohort study	90 CM patients with level III and IV lesions	Positive results	No positive results in cranial CT	Patients with complete staging included; indications for different staging examinations unclear	4
Silverman et al. (1984)	To assess the value of computed tomography in the detection of abdominal spread of malignant melanoma.	Cross-sectional study	70 CM patients	Prevalence of abdominal metastases	52 scans of abdomen and pelvis, 5 of abdomen, 2 of pelvis, 11 limited to the liver Nodal enlargement in abdomen or pelvis in 30% Liver metastases in 17% Adrenal metastases in 11% Nodular masses in the subcutaneous fat in 8,6% Splenic metastases in 2% Mesenteric	Most patients symptomatic at time of CT scan (abdominal pain, abnormal liver function tests or liver imaging)	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastases in 4%		
Ginaldi et al. (1981)	To investigate the value of CT as a staging procedure in neurologically asymptomatic melanoma patients, and to describe the neurological features of metastases and their incidence in melanoma patients.	Diagnostic study	179 CM patients; 74 of them with no neurological findings	Detection rate	Cranial CT: Positive results in 9/74 patients (11%) 2/9 had known single metastases in the liver and lung, 2/9 others recurrent local disease, 5/9 other systemic metastases	No clear distinction between patients of different stages	4
Doiron et al. (1981)	See above	See above	See above	See above	See above	See above	4
Subtopic PET/CT							
Xing et al. (2011)	See above	Systematic review and meta-analysis	10 528 patients with cutaneous melanoma at primary diagnosis or under surveillance (follow-up)	Sensitivity, specificity Diagnostic odds' ratio (OR)	Data for initial staging of regional nodes: Sensitivity 11% Specificity 97% Diagnostic OR 4.39	Very large patient cohort, but patients under follow-up included	1a
Krug et al. (2008)	See above	Systematic review with meta-analysis	2905 CM patients in 28 studies of	Positive and negative likelihood	LR+ 9.68 LR- 0.10	4 eligible studies about PET/CT	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			which 2096 underwent PET alone and 809 underwent PET/CT (4 studies)	ratio (LR+, LR-) Diagnostic odds' ratio (OR)	Diagnostic OR 37.6		
Essler et al. (2011)	To assess the prognostic value of FDG PET/CT compared to the tumor markers S100B and melanoma inhibitory activity (MIA) in patients with high risk melanoma.	diagnostic and prognostic study	125 consecutive patients Patients who had a Breslow tumor thickness .2.0 mm, elevated S100B or MIA level	specificities sensitivities NPV PPV	Overall specificity for FDG PET/CT: 96.8% (95% CI, 89.1% to 99.1%) corresponding sensitivity: 96.8% (89.0% to 99.1%) NPV for PET/CT 96.8% (89.1% to 99.1%), PPV: 96.7% (89.0% to 99.1%), Patients with elevated S100B- or MIA values or PET/CT positive findings showed a significantly (p,0.001 each, univariate Cox regression models) higher risk of melanoma associated death which was		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					increased 4.2-, 6.5- or 17.2-fold, respectively.		
Etchebehere et al. (2010)	To assess the impact of [F-18] FDG-PET/CT on the restaging and changing management of patients with malignant melanoma.	Diagnostic study	78 patients (Initial restaging/before PET/CT): local recurrence in 11 patients, locoregional recurrence in 23 patients and distant recurrence in 44 of 78 patients.	Impact on patient management Sensitivity Specificity	In 27% of the patients the management was changed after the [F-18] FDG-PET/CT studies. Upstaging in 5 of 23 (22%) patients. sensitivity, specificity, PPV, NPV for lesion detection: 95% accuracy: 94.9%. 2FP, 2 FP	AJCC 2001 staging System was used	2b
Klode et al. (2010)	Comparison of SLNE and PET-CT in patients with early-stage malignant melanoma	Diagnostic study	61 CM patients in stages I and II before sentinel biopsy	Sensitivity and specificity Positive and negative predictive value (PPV, NPV)	Sensitivity 5.9% Specificity 100% PPV 100% NPV 78%	50% of eligible patients declined PET-CT	2b
Veit-Haibach et al. (2009)	To evaluate the diagnostic	Diagnostic study	56 CM patients after surgical	Sensitivity and specificity	Sensitivity and specificity	Insufficient data for 24% of patients	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	accuracy of contrastenhanced FDG-PET/CT (ce-PET/CT), PET-only, and CT-only in patients with newly diagnosed and resected cutaneous malignant melanoma.		resection who underwent combined PET/CT imaging and had sufficient follow-up; 18 of them in stage III or IV	Positive and negative predictive value (PPV, NPV)	regarding N-stage: 38.5% and 100% PPV and NPV regarding N-stage: PET-CT 100% and 84.3% Sensitivity and specificity regarding M-stage: PET-CT 38.5% and 100% PPV and NPV regarding M-stage: PET-CT 41.7% and 93.2%	Study included in Xing et al. 2011	
Singh et al. (2008)	To evaluate the role of preoperative 18F-fluorodeoxyglucose-positron emission tomography/ computed tomography scanning, preoperative lymphoscintigraphy (LS), and sentinel lymph node biopsy in patients with malignant	Diagnostic study	52 CM patients initially classified as stage I or II, before sentinel biopsy	Sensitivity and specificity Positive and negative predictive value (PPV, NPV) Overall diagnostic accuracy	18F-FDG PET imaging for the detection of regional lymph node metastases: Sensitivity 14.3% Specificity 94.7% PPV 50% NPV75% Diagnostic accuracy 73%	Study included in Xing et al. 2011	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma.						
Lagaru et al. (2007)	To analyse sensitivity and specificity of PET/CT for the detection of metastases of malignant melanoma.	Diagnostic study	106 CM patients who had whole-body FDG-PET/CT, 30 of them with stages IIIC and IV	Sensitivity and specificity	Per patient: Sensitivity 89.3% Specificity 88.0% True positives 50 False positives 6 False negatives 6 True negatives 44 Per lesion: Sensitivity 89.6% Specificity 84.6% True positives 78 False positives 8 False negatives 9 True negatives 44	Studies were done for disease re-staging in all patients; time interval from initial diagnosis not given Studie included in Xing et al. 2011	2b
Pfannenberg et al. (2007)	See above	See above	See above	See above	See above	See above	2b
Strobel et al. (2007)	To prospectively determine the accuracy of positron emission tomography (PET)/computed tomography (CT) with added CT morphologic information for depiction of metastases in	Diagnostic study	124 CM patients with tumor thickness > 4 mm; Clark level, III or IV; or known metastases	True and false positives and negatives Sensitivity and specificity Diagnostic accuracy	Without dedicated CT readout: 45/124 true positives (36%) 3/124 false positives (2%) 68/124 true negatives (55%) 8/124 false negatives (6%) Sensitivity 85% Specificity 96%	Cohort includes patients with already known metastasis Study included in Xing et al. 2011	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with high-risk melanoma and negative findings for metastases at PET, by using histologic findings or additional imaging and/or follow-up findings as reference standard.				Diagnostic accuracy 91% With dedicated CT readout: 52/124 true positives (34%) 4/124 false positives (3%) 67/124 true negatives (54%) 1/124 false negatives (1%) Sensitivity 98% Specificity 94% Diagnostic accuracy 96%		
Dellestable et al. (2011)	See above	Diagnostic study	See above	See above	See above	See above	2b-
Wagner et al. (2011)	To assess the role of routine staging with FDG PET-CT in melanoma patients with localized high risk melanoma.	Diagnostic study	48 consecutive patients with 1 < BT < 4 mm with ulceration and with BT >= 4 mm were staged with PET-CT (initial staging) prior to SLNB.	sensitivity, specificity, PPV, NPV	For regional nodal assessment: sensitivity, specificity, PPV, NPV of PET: 43%, 100%, 100% and 78%, respectively. For distant metastases: positive PET in 0%, negative PET in	Images were interpreted by a specialist, aware of all clinical findings/not blinded Small patient cohort, not described in detail	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					13% and indeterminate PET in 13% of patients		
Mansour et al. (2010)	(1) to determine the anatomic scatter plot of false-positive and true-positive FDG-avid sites; (2) to describe and determine the characteristics of false-positive FDG-avid sites; and (3) to identify patterns that are useful in predicting false-positive findings for patient management and counseling.	Diagnostic study	342 CM patients with PET/CT	True and false positives	True positives: Breslow 0 – 2 mm: 46.9% Breslow 2.01 – 4 mm: 18.8% Breslow > 4 mm: 34.4% Stage II: 3.2% Stage III: 33% Stage IV: 63.8% False positives: Breslow 0 – 2 mm: 30% Breslow 2.01 – 4 mm: 30% Breslow > 4 mm: 40% Stage II: 27.3% Stage III: 45.4% Stage IV: 27.3%	Limited purpose of the study (musculo-skeletal findings in PET/CT) No fixed indications for PET/CT	3b
Revel et al. (2010)	To assess the utility of PET-CT 18FDG in a group of N patients with cutaneous head and neck melanoma,	Diagnostic study	22 patients with N0 cutaneous head and neck melanoma with PET/CT before sentinel biopsy	Sensitivity and specificity	Sensitivity 18% Specificity 84%		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	combined with SLNB.						
Yancovitz et al. (2007)	See above	Diagnostic study	158 patients, 135 with stage I/II disease and 23 with stage III disease	True and false positives and negatives	Number of PET/CT studies: 42 Positives: 5/42 (12%) True positives 1/42 (2%) False positives: 3/42 (7%) True negatives: 37/42 (88%) False negatives: 0 Lost to follow-up: 1/42	study included in Xing et al. 2011	3b
Wagner et al. (2011)	See above	See above	See above	See above	See above	See above	3b-
Abbott et al. (2011)	to evaluate the role of [18F] fluorodeoxyglucose PET/CT as a surveillance tool in asymptomatic patients with primary cutaneous melanoma	Diagnostic study	34 patients with primary cutaneous malignant melanoma with AJCC stage III	Metastases detection	In 20 patients with microscopic stage 3 disease at diagnosis: PET/CT detected 2 of 3 recurrences and 1 incidental breast carcinoma.	No reference standard	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					In 14 patients with macroscopic stage 3 disease at, or subsequent to, their initial diagnosis: PET/CT detected 4 of 4 recurrences, metastases in 1 patient who remains asymptomatic and 1 incidental thyroid carcinoma.		
Subtopic SPECT/CT							
Van der Ploeg (2009)	To explore whether hybrid SPECT/CT leads to better anatomical localization of sentinel nodes or to the depiction of extra sentinel nodes in patients with melanoma when conventional imaging is inconclusive, and	Cohort study	85 CM patients who underwent both conventional lymphoscintigraphy and subsequent SPECT/CT	Additional diagnostic value of SPECT/CT (change of surgical approach)	Additional diagnostic value of SPECT/CT in 35% (30 patients)	Only patients with questionable results in lympho-scintigraphy or unusual drainage pattern included	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	whether this influences the surgical approach.						
Subtopic BONE SCINTIGRAPHY							
Au et al. (1984)	To evaluate the yield and accuracy of preoperative radionuclide scans in patients with primary melanoma for the detection of occult metastasis to brain, liver and bone.	Diagnostic study	192 CM patients; 171 in stage I (localized) and 21 in stage II (lymph node metastasis according to old AJCC staging)	True and false positives, false negatives	107/112 (96%) true negatives 5/112 (4%) false positives 0 true positinves	No information about false negatives (follow-up of patients with negative results unclear)	3b
Hofmann et al. (2002)	See above	Diagnostic study with historical cohort; economical evaluation	661 patients (stage I/II: 630 patients, stage III: 27 patients, stage IV: 4 patients)	True and false positives and negatives Cost-efficiency of imaging procedures	325 total bone scintigraphies 0 true positives 62 false positives (19%) Detection rate / Cost of bone scintigraphy at initial staging: 80654 EUR (4099 EUR due to false positive results)	Diagnostic standard procedures varied over time; no defined gold standard of diagnosis	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Khansur et al. (1989)	See above	Diagnostic study	115 patients with primary CM (72 in localized stage) and 28 patients with recurrent disease	True and false positives	0/141 true positives 3/141 false positives (2%)	Criteria for selecting staging examinations unclear	3b-
Ardizzoni et al. (1987)	See above	Diagnostic study	116 patients; clinically 93 in stage I and 23 in stage II	True and false positives and negatives	68/73 (93%) true negatives 5/73 (7%) false positives 0 true positives	Design (prospective vs. retrospective) not clear Follow-up time not given	3b-
Kersey et al. (1985)	See above	Diagnostic study	393 patients at primary diagnosis of CM	True and false positives	True positives 0 False positives 7/116 (6%)	Extent of staging examinations and extent/ length of follow-up depended on center and tumor site	3b-
Zartman et al. (1987)	See above	Cohort study	90 CM patients with level III and IV lesions	Positive results	No positive results for bone scintigraphy	Patients with complete staging included; indications for different staging examinations unclear	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic TUMOR MARKERS							
Mocellin et al. (2008)	Analysis of the prognostic value of S100B serum levels in patients with melanoma, with special regard to stages I – III (AJCC)	Meta-analysis of 20 prognostic studies containing 22 series of 3393 patients 5 series considered patients in stages I – IV 8 series considered patients in stage IV only 6 series considered patients in stages I – III only Other combinations in the remaining 3 series	3393 patients with melanoma, stages I – IV	Summary hazard ratio for survival	Summary hazard ratio for survival 2.23 (95% CI 1.92 – 2.58) Summary hazard ratio considering only patients in stages I – III: 2.28 (95% CI 1.8–2.89)	High degree of heterogeneity, which is not present when only studies of stages I – III are included Publication bias present (shown with a funnel plot), but after correction, Hazard Ratio still significantly higher for patients with elevated S100B Publication bias not present when only studies of stages I – III included	1a
Balch et al. (2009)	To revise the staging system for cutaneous melanoma on the basis of data from an expanded	Prognostic study	30,946 patients with stages I, II, and III melanoma and 7,972 patients with stage IV melanoma	Survival rate	Elevated serum LDH: The updated AJCC Melanoma Staging Database demonstrated that	Study included just for reference here; no data about LDH in earlier stages than IV	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	American Joint Committee on Cancer (AJCC) Melanoma Staging Database.				an elevated serum LDH is an independent and highly significant predictor of survival outcome among patients with stage IV disease. Thus 1- and 2-year overall survival rates for those stage IV patients in the 2008 AJCC Melanoma Staging Database with a normal serum LDH were 65% and 40%, respectively, compared with 32% and 18%, respectively, when the serum LDH was elevated at the time of staging (P < .0001). Therefore, serum LDH should be measured at the time stage IV disease is documented, and		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					if the LDH level is elevated, those patients are assigned to M1c regardless of the site of their distant metastases.		
Nowecki et al. (2008)	to assess the prognostic value of multimarker reverse transcriptase-polymerase chain reaction (RT-PCR) assay in lymphatic drainage (LY) after lymph node dissection (LND) and of preoperative serum lactate dehydrogenase (LDH) levels in AJCC stage III melanoma patients.	Prognostic study	255 consecutive patients with histological diagnosis of CM and regional (inguinal or axillary) LN involvement who underwent radical LND	Overall survival Disease-free survival Recurrence rate	estimated 3-year OS rate for patients with increased preoperative serum LDH level: 41.3% (95% CI: 28.4–54.6%), vs. 55.3% (95% CI: 45.8–64.9%) for patients with a normal baseline serum LDH level (P = 0.007). disease recurrence in 70% of patients with an increased preoperative serum LDH level compared with 53% patients with a normal serum LDH level (P =	Results for RT-PCR: see full-text	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.01). Negative impact of increased pre-lymphadenectomy serum LDH level on OS of melanoma patients with macrometastases after TLND. Serum LDH level does not differentiate the prognostic groups in patients with micrometastases		
Vereecken et al. (2009)	To investigate the prognostic significance of galectin-3 in comparison to S100B, LDH and CRP	Prognostic study	83 patients in stage III and IV	Overall survival	3 groups of patients were defined according to Gal-3 levels: <8 ng/ml (group 1), 8–10 ng/ml (group 2), >10 ng/ml (group 3). Group 1 and 2: similar overall survival, group 3: worst outcome. median survival was 4.1	LDH was omitted from the analysis because only 8 patients showed elevated LDH serum levels	1b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months. multivariate Cox proportional hazards model: AJCC stage and CRP serum levels =most important independent prognostic factors [HR =9.60, P=0.0002 and HR=2.75, P=0.002, respectively]. At a cut-off value of 10 ng/ml for Gal-3, (on quatrivariate analysis) serum Gal-3: strong independent prognostic value, superior to the other markers (HR=4.64, P=0.0001).		
Essler et al. (2011)	To assess the prognostic value of FDG PET/CT compared to the	Retrospective diagnostic and prognostic study	125 consecutive patients Patients who had a	specificities sensitivities NPV PPV	S100B: Overall specificity 85.7% (75.0% to 92.3%) corresponding		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	tumor markers S100B and melanoma inhibitory activity (MIA) in patients with high risk melanoma.		Breslow tumor thickness .2.0 mm, elevated S100B or MIA level		sensitivity:45.2% (33.4% to 55.5%), NPV 61.4% (50.9% to 70.9%). PPV: 75.7% (59.9% to 86.6%) MIA: Overall specificity 95.2% (86.9% to 98.4%). corresponding sensitivity 36.1% (25.2% to 48.6%), respectively. NPV: 60.6% (50.8% to 69.7%), PPV: 88.0% (70.0% to 95.8%). Patients with elevated S100B- or MIA values or PET/CT positive findings showed a significantly (p<0.001 each, univariate Cox regression models) higher risk of melanoma associated death which was increased 4.2-,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					6.5- or 17.2-fold, respectively.		
Kruijff et al. (2011)	Aim was to assess the correlation and the prognostic value of S-100B and Standardized Uptake Values (SUV) of Fluorodeoxyglucose (FDG)	Retrospective cohort study	62 patients with palpable nodal metastases, without distant metastases	DFS and DSS	No relation was found between S-100B and SUV. DFS for patients with an elevated vs. normal S-100B: 31% vs. 44,6% (HR = 3.1; p = 0.02) DFS for patients with normal vs. elevated SUV: 42% vs. 29% (HR = 1.1; p = 0.8). DSS for patients with normal vs. elevated S100B: 60.7% va. 44.7% (HR = 2.2; p = 0.07). DSS for patients with normal vs. elevated SUV: 59.1% vs. 43.5% (HR = 1.1; p = 0.8).		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					S-100B is associated with tumor load and a strong predictor for DFS in stage III melanoma		
Neuss et al. (2011)	To evaluate the correlation to clinical and pathological data.of the following preoperative serum tumour markers: S100, NSE, Albumin, LDH and CRP	Prognostic study	patients in tumour stage III before radical lymph node dissection	Serum levels	The serum level of CRP correlated with increasing number of LN node metastases. Significant elevated serum levels of S100 in patients with more than one positive SLN		2b
Bouwhuis et al. (2011)	To determine the prognostic value of S100B based on updated information using serial determinations in stage IIb/III melanoma patients.	Prognostic study	918 serum samples of 211 Patients who participated in the EORTC 18952 trial, evaluating efficacy of adjuvant intermediate doses of interferon a2b (IFN) versus observation	distant metastasis-free interval (DMFI) distant metastasis-free survival (DMFS) OS HR	Multivariate analyses: DMFS: HR of S100B >= 0.2 versus S100B < 0.2 was 5.57 (95% CI 3.81–8.16), P < 0.0001, after adjustment for stage, number of lymph nodes and sex.		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			Serum S100B levels were measured during treatment and follow-up		In stage IIb patients: HR adjusted for sex=2.14 (95% CI 0.71, 6.42) In stage III patients: the HR adjusted for stage, number of LN and sex=6.76 (95% CI 4.50–10.16). OS: HR: 4.73 (95% CI 3.14–7.12), P < 0.0001. In stage IIb patients: HR 2.73 (95% CI 0.79–9.44; P = 0.11). In stage III patients: 5.46 (95% CI 3.52–8.45; P < 0.0001). Serial determination of S100B in stage IIb–III melanoma is a strong independent		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					prognostic Marker, the prognostic impact of S100B >= 0.2 lg/l is more pronounced in stage III disease than in stage IIb.		
Paschen et al. (2009)	To investigate the correlation between sULBP2, sMICA and S100B levels and the prognostic value of sULBP2 levels	Prognostic study	208 patients (25 in stage I/II, 54 in stage III, 129 stage IV) 50 healthy controls	Clinical stage Tumor load Overall survival	S100B serum concentrations significantly correlated with stage of disease Patients with measurable tumor significantly higher serum concentrations of S100 than patients with clinically non-apparent tumor		2b
Andrés et al. (2008)	To compare the value of tyrosinase mRNA by reverse transcription polymerase chain reaction (RT-PCR) in peripheral blood and of serum S-100 protein in	Prospective diagnostic and prognostic study	90 CM patients in stages I – IV	Sensitivity Progression-free survival Overall survival	Sensitivity of S100: 22.2% for stage I 10.5% for stage II 7.4% for stage III 94.1% for stage IV Median follow-up: 312 days or to death Median	Very small control group for S100 (2 healthy subjects, 3 patients with breast cancer, Hodgkin lymphoma and Ewing's sarcoma, respectively)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with melanoma at different stages of disease.				progression-free survival 213 days for elevated serum S100; not reached for patients with normal S100 Median overall survival 282 days for elevated serum S100; not reached for patients with normal S100 level	Also contains data on tyrosinase Patients in stage I – IV	
Kruijff et al. (2009)	To investigate whether the perioperative measurement of the tumor markers S-100B has prognostic value in FDG-PET and spiral CT staged patients with stage III melanoma who are selected for therapeutic lymph node dissection	Prognostic study	56 patients with clinically and cytologically proven regional nodal metastases of melanoma	Disease-free survival Prognostic factors	2-year DFS in patients with - elevated vs. non-elevated preoperative S-100B concentrations: 34% vs. 61% (HR:2.6, P=0.03) - elevated vs. non-elevated postoperative S-100B concentrations: 30% vs. 51% (HR:2.0, P =0.1). In multivariate analysis:	Follow-up diagnostic procedures and follow-up intervals not stated in article Design not descirbed (prospective/retrospective)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					extranodal growth (HR 0.4, P = .05), and elevated preoperative S-100B concentrations (HR 2.6, P = .03) were significantly associated with decreased DFS.		
Wang et al. (2004)	See above	Diagnostic study	210 CM patients without clinical evidence of metastasis	True and false positives and negatives	LDH results available in 96 patients with melanoma > 1 mm 82/96 (85%) within institutional normal range 14/96 patients with elevated LDH, but no detection of systemic disease or alteration in surgical management (15% false positives) No true positives		2b
Kaskel et al. (1999)	To evaluate the clinical and prognostic value	Diagnostic study	1396 samples of 570 patients with melanoma and 53	Sensitivity, specifity, positive predictive value	For a cut-off of 0.114 µ/L	Part of the data on S-100 levels obtained in	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of S-100 in peripheral blood of patients with melanoma as a marker for metastasis.		control subjects (397: melanoma in situ or stage I or II, 104: stage III, 69: stage IV)	(PPV), negative predictive value (NPV), determination of optimal threshold (ROC).	Sensitivity: 94% specificity: 91%. For a cut-off of 0,2µg/L: sensitivity and specifity both 92% PPV value (cut-off 0,114 µg/L) for newly occurring metastases: 65%, NPV (no metastases): 99%. FN results included patients with unknown primary melanoma and those with amelanotic melanoma metastases.	Munich have also been evaluated in a different study by Berking et al. follow-up performed in 197 patients only ROC: see full text	
Hofmann et al. (2009)	To determine the value of MIA testing in early-stage melanoma	Diagnostic study	1079 CM patients in stages I and II Reference group: 313 dermato-logical patients without history of melanoma or other malignancy	Mean values Sensitivity Specificity	Mean MIA value did not increase based on stage Sensitivity of MIA for metastasis: 67.6% in stage I and 65.6% in stage II	Different reference standard for patients with abnormal laboratory values	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Specificity: 76.9% for stage I and 66.7% for stage II More frequent false-positive values in elderly women and in men with an increased Breslow thickness		
Garbe et al. (2003)	To evaluate the diagnostic accuracy of protein S-100B, melanoma-inhibitory activity (MIA), LDH, AP, and tyrosinase/MART-1 reverse transcription-polymerase chain reaction (RT-PCR).	Diagnostic and prognostic study	296 consecutive AJCC Stage II or III clinically disease-free melanoma patients 120 healthy controls without melanoma or other known malignancies.	Sensitivity Specificity Diagnostic accuracy	Cutoff levels: S100: 0.12 µg/L MIA: 10.49 ng/mL Sensitivity: S- 100: 29%, PCR: 24%, MIA: 22%, AP: 17%, LDH: 2% Specificity: S-100: 93%, PCR : 80% MIA: 97%, AP: 89% LDH: 90% Diagnostic accuracy: MIA: 86%, S100: 84%, AP: 79%, LDH: 77% RT-PCR: 72% ROC analysis:	Different reference standard (CT) for patients with abnormal laboratory values (may lead to a higher sensitivity of the tumor markers than in reality) Detailed description of follow up; no drop-outs	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					diagnostic accuracy: S-100: 66%, MIA: 62%, LDH: 53%, AP: 51% Significant P values for S-100 (0.001) and MIA (0.011), but not for LDH (0.571), AP (0.807), and PCR (0.519). Somer's Dxy : S-100 had the highest predictive value Kaplan–Meier survival curves: highly significant difference in recurrence-free survival time in the time period after the follow-up examinations between patients with normal and pathologic values for both MIA and		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					S-100.		
Agarwala et al. (2009)	To assess each of the three stratification factors in this study (performance status, metastatic site and LDH) for an interaction with treatment on survival.	Prognostic study	760 patients (in study 301) and 760 (in study 18951)	Overall survival	LDH was within the upper range of normal for a large number of patients. highly ordered and monotonic relationship between LDH and survival: survival worsened as LDH became more elevated, even when LDH remained within normal range. LDH and tumour size poorly correlated; elevated LDH was not associated with any one disease site. LDH was highly predictive of oblimersen effect.	Post-hoc analysis of two randomised trials (Oblimersen GM301 and EORTC 18951)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Kaplan–Meier survival curves: see full-text		
Deichmann et al. (2004)	LDH was compared to CRP to evaluate, if LDH is of value in discriminating melanoma patients entering AJCC stage IV from patients staying in AJCC stages I, II or III.	Diagnostic study	91 patients with histologically proven melanoma progressing into stage IV, 125 patients stage I, II or III in follow-up examinations	Sensitivity specificity	LDH not significantly elevated in patients entering stage IV melanoma (P=0.785), whereas CRP was (P<0.001). LDH did not discriminate between the defined groups of patients (AUC=0.491; 95% CI, 0.410, 0.581), whereas CRP did (AUC=0.933; 95% CI, 0.900, 0.966; P<0.001). CRP in diagnosing AJCC stage IV entry: cutoff =2,1 or 2,2mg/dl: specificity=80%, sensitivitie=83,5%.	Sensitivity and specificity for LDH not given Small population No information on blinding	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					cutoff 2,4 or 2,5mg/dl: specificity = 83,2% and 85,66, respectively. sensitivity of 81,3%. Cutoff=2.9mg/dl: Specificity=89,6% sensitivity=79,1 cutoff point=3.0mg/dl: specificity=90,4 sensitivity=76,9		
Deichmann (2001)						Same data as in: Deichmann et al. (1999): S100-Beta, melanoma inhibiting activity, and lactate dehydrogenase discriminate progressive from non-progressive amercan joint committee on cancer stage IV melanoma	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Stoitchkov et al. (2003)	To define the potential use of this new marker for the follow-up of melanoma patients by means of serial measurement (before and after treatments, and during follow-up)	Diagnostic study	60 melanoma patients (24: stage I–II, 18 stage III, 18 stage IV)	Overall survival Change in serum concentrations by therapeutic interventions	In stage III patients with elevated marker concentration, LN dissection decreased the S100B level (from 0.27 to < 0.13 g/l, P= 0.008), but not the L-dopa/L-tyrosine ratio. Chemotherapy decreased the ratio by 38% (P 0.04) and the S100B level by 45% (P 0.02) in stage IV responders. increase in one or both markers during follow-up in patients with progressive disease: shorter survival in stage IV patients with high vs.	Small patient numbers divided into many subgroups Study included here in addition to S100 meta-analysis because of results about L-dopa/L-tyrosine ratio	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					normal L-Dopa/L-Tyrosine ratio at inclusion (3 vs. 15 months).Levels of S100B had no impact on survival, in stage IV patients. No correlation between L-dopa/L-tyrosine ratio and S100B.		
Stoitchkov et al. (2002)	Prospective evaluation of the potential of the serum L-dopa/L-tyrosine ratio in the management of melanoma, with an emphasis on staging, tumour burden and prognosis (the predictive value for disease progression in metastatic patients and survival).	Diagnostic study	89 melanoma patients with histologically proven primary and/or metastatic melanoma or measurable metastatic disease (by imaging). (9 stage I, 33 stage II, 19 stage III, 28 stage IV).	Sensitivity and specificity	overall sensitivity for melanoma: 51% for the ratio and 66% for S100B. (range: 33% (stage I) to 71% (stage IV) for the ratio, 56–89% for S100B) no statistical difference between stages I, II and III patients for both markers. Significant higher median ratio in stage IV.	Precursor study to Stoitchkov et al., 2003 Patients lost to follow-up are not included in analysis (risk of bias)	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					In stage III–IV patients, both markers were significantly higher in evolutive patients than in stable ones. The ability (sensitivity/specificity) of markers to predict disease progression in metastatic patients: 78%/67% for the ratio, 74%/83% for S100B (select cut-off) and 87%/33% using the manufacturer's reference values.		
Krahn et al. (2001)	To evaluate tumor markers S100, MIA, LDH and albumin in peripheral blood of melanoma patients	Diagnostic study	373 melanoma patients (284 with melanoma in situ or stage I/II and 89 with melanoma stage III/IV; 54 of these tumor free and 29 with newly	Sensitivity Specificity	Presence of lymph node, visceral and brain metastases: Sensitivity (for newly occurred metastases) for LDH 48%, for MIA 80%, for S100 86%	No follow-up as reference standard (cross-sectional design)	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			occurred metastases) 10 control subjects		Specificity for LDH 98%, for S100 91%, for MIA 62% No false positive results in the control group		
Deichmann et al. (1999)	Serum levels of S100-beta (S100b) and melanoma-inhibiting activity (MIA) were assessed for the ability to discriminate progressive from nonprogressive disease.	Diagnostic study	71 consecutive patients with stage IV melanoma Control group: 38 healthy adult	Sensitivities and specificities discrimination ability	Cut-offs: S100b 0.12 µg/L, MIA 6.50 ng/mL All tested serum parameters were significantly elevated in patients with progressive disease. Sensitivity: S100b=91% MIA=88% LDH=79% Specificity: S100b=76% MIA=73 LDH=92% In calculating Somers' Dxy and ROC-AUC values, S100b, MIA, and	Patients received different therapies Small population No information about follow-up	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					LDH showed high discrimination ability. Multiple logistic regression: LDH was the only statistically significant marker for progressive disease.		
Hofmann et al. (2011)	To assess the utility of melanoma inhibitory activity (MIA) serum marker in the follow up and primary diagnosis of stage III melanoma patients	Diagnostic study	138 melanoma patients in stage III at time of primary diagnosis and during periodical routine follow up	Sensitivity Specificity 5-year survival rate	MIA cut-off value of 12 ng⁄mL: sensitivity: 69.2%, specificity: 69.9%. PPV for relapsing disease: 67.2%, NPV: 72.0% 5-year survival rate: 78.1% (MIA <12 ng⁄mL) vs. 72.7% (MIA >=12 ng⁄mL). (P = 0.230).	No information about time interval between blood sample and staging/restaging examinations “relapse” not described in detail, staging results not given.	3b
Garnier et al. (2007)	L-DOPA/tyrosine ratio (an index of tyrosinase activity), melanoma antigens S100B and MIA, lactate	Diagnostic study	170 CM patients (stage I–II: 57, III: 54, IV: 59)	Sensitivity Specificity Increase with disease progression Overall survival	At inclusion: Sensitivity/ specificity of L-DOPA/tyrosine ratio with S100: 73%/70% L-DOPA/ tyrosine		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	deshydrogenase (LDH) and their combinations were evaluated for clinical value as tumour markers in melanoma.				ratio with LDH: 69%/69% L-DOPA/ tyrosine ratio with MIA: L-DOPA/ tyrosine ratio with MIA and LDH: 74%/68% During follow-up: Disease progression (11 stage I–II, 7 stage III patients) increased the L-DOPA/ tyrosine ratio by +35.7%, but not other marker levels (MIA: +18%, S100B: -20%, LDH: -9.7%) Cox regression model: survival predictors were S100B and MIA		
Tas et al. (2004)	To investigate the clinical value of S100 and MIA as tumor markers for malignant melanoma.	Diagnostic and prognostic study	48 CM (5 in stage I and II, 22 stage III, 21 in stage IV) Control group: 15 healthy subjects	Sensitivity, specificity Overall survival	Only 5 patients in stages I and II included; none of them had increased MIA, 2 had increased S100	Small patient sample in stage I Small patient sample, especially in stage I	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Only sensitivity of serum MIA statistically significantly correlated in Cox analysis, the prognostic significance of MIA level was lost	Small control group of healthy people, no details given Details of staging and follow-up (e.g. time intervals, examinations at follow-up) not reported	
Banfalvi et al. (2002)	To compare the prognostic values of serum 5-S-Cysteinyldopa, S-100B and LDH concentrations in Stage III-IV melanoma patients	Retrospective diagnostic and prognostic study	Data from 179 patients Stage III-IV melanoma patients at diagnosis: (37 in Stage III,142 in Stage IV). The age of patients ranged from 22 to 88 years (mean 59.8). Median follow up time was 15 months. 63 patients (with other skin diseases) were	Specificity Sensitivity PPV Overall Survival	Stage III: 5-S-CD was 60 % sensitivity, 91.6 % specificity, 93.8 % PPV Stage IV: LDH: Sensitivity=48.5 %, Specificity =83.3, PPV= 98.5. S 100B: Sensitivity=70.5, Specificity = 100, PPV= 100. 5-S-CD Sensitivity=69.1 Specificity =50, PPV= 96,9	In stage III data for sensitivity and specificity for S100B and LDH not given No further information about staging (reference standard)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			enrolled as control group.		calculated median survival: 4.6 months. Kaplan-Meyer analysis of the survival of patients with elevated vs. normal marker levels indicated significant differences in case of all the 3 markers, with the shortest survival of patients with elevated S 100B or LDH levels ($p<0.05$).		
Meral et al. (2001)	To investigate the hypothesis that the decline in serum melanoma-inhibiting acitivity (MIA) levels following initiation of treatment might have prognostic value	Prognostic study	35 patients with advanced stage melanoma (11 stage III, 24 stage IV) mean age 52.2 years Control group consisting of 20 adults without	Overall survival	The mean serum LDH, S100 and MIA levels of the patients with MM before treatment were significantly higher than in the control group. Patients with visceral dissemination vs.	See original article for overall survival curves (Kaplan-Meier) Survival analysis were not perfomed with serum S100 levels Analysis of LDH kinetics revealed	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			degenerative diseases of cartilage or joint pain		patients with nodal spread: MIA-levels 30.1 ng/ml vs.14.5 ng/ml. mean serum MIA level in the control group: 12.4 ± 3.2 ng/ml. (cut-off level: 8.7 ng/ml (mean + 2SD). 1-year OS rates: no change according to the site of the primary tumour, the type of surgical or radiation treatment or the chemotherapy regimen. Advanced stage MM patients in whom serum MIA levels did not decrease during systemic treatment had a less favourable prognosis.	no useful information.`	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Brouard et al. (2000)	To determine if serial PS100B is a marker for metastatic evolution by observation of its level/variation/evaluation in patients in complete remission and patients receiving chemotherapy	Diagnostic study	239 blood samples were taken in 122 patients with cutaneous melanoma (56 patients in complete remission, 56 patients with melanoma in progression	Sensitivity and specifictiy	The threshold to separate patients with metastases from those in complete remission was 0,09µg/L (Specificity 92%, sensitivity 70%). PPV (Stage III/IV): 77%, NPV 89%	Only results of 90 patients are presented. Drop outs are not commented.	3b
Schmitz et al. (2000)	To analyse the serum levels of S100B and MIA in non-melanoma control patients and melanoma patients to report on the sensitivity and specificity of both tumor markers	Diagnostic study	87 CM patients	Specificity Positive results	Specificity for S100 regarding the diagnosis of melanoma: 85.8% with a cut-off value of 0.12 µg/l 94.6% with a cut-off value of 0.20 µg/l Specificity for MIA: 89.9% with a cut-off of 6.5 µg/l 97.4% with a cut-off of 8.5 µg/l Values > 6.5 µg/l for MIA prior to treatment: 0% for stage I/ II	No follow-up (cross-sectional design)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					53.8% for stage III 68.3% for stage IV Values > 6.5 µg/l for MIA post treatment: 11.7% for stage I/II 9.7% for stage III 6.9% for stage IV Values > 0.12 µg/l for S100 prior to treatment: 50% for stage III 80% for stage IV Values > 0.12 µg/l for S100 post treatment: 16.1% for stage I/II 18% for stage III 14.3% for stage IV		
Stahlecker et al. (2000)	To evaluate whether MIA is a reliable tumor marker in terms of course of disease, therapy-monitoring and prognostic value	Diagnostic study	326 melanoma patients: 250 stage I, 52 stage II, 5 stage III and 19 stage IV Control group of 100 healthy blood donors	Positive results Sensitivity Specificity	Increased MIA levels: 4.4% in stage I (n = 250) 11.5% in stage II (n = 52) 60.0% in stage III (n = 5) 89.5% in stage IV (n = 19). Elevated MIA 22 patients with no		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					clinical evidence of disease (stage I, II or stage III, IV after metastatic surgery) 8 of them had detection of metastases at the same time, 5 of them 2 – 6 months later 9 stayed free of clinically detectable disease (false positives = 3%)		
Bosserhoff et al. (1997)	To investigate whether MIA provides a clinically useful parameter in patients with malignant melanomas, and to compare this with the diagnostic value of S100.	Diagnostic study	112 CM patients (38 stage I, 13 stage II, 6 stage III, and 44 stage IV) 350 clinically tumor-free patients during a follow-up period after removal of a primary stage I or II melanoma Controls: 72 healthy blood donors	Positive rates TP FN	Positivity of MIA: - 100% of sera from 50 patients with stage III and IV - 13% of sera from stage I - 23% of sera from stage II patients - 9% of clinically tumor-free patients; 15 (4%) of these patients developed metastases	Sample of stage II and III patients small 5 patients during chemotherapy of stage IV melanoma Sensitivity/specificity not given	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			Additional controls: 50 patients with sepsis, 23 patients with brain tumors, 243 patients with advanced epithelial and mesenchymal tumors		MIA-levels in patients with other malignancies: see full-text S100-positivity, cut-off: 0.15 ng/ml - 30/49 (61%) sera from stage III and IV patients - 0% of stage I and II sera - 4% of sera from healthy donors - 20% from septic patients, 16% from patients with gliomas, and 5% from patients with advanced carcinomas positive		
Bosserhoff et al. (1999)						Same patient cohort as Bosserhoff et al. (1997), less data	
Henze et al. (1997)	To examine serum S100	Diagnostic study	Blood samples from 73 patients	sensitivity	1/25 stage I/II patients, 3/14	Small population	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	concentrations of patients with different stages of malignant melanoma and to determine the value of serum S100 in the follow-up of melanoma patients during treatment		with malignant melanoma (25 patients: stage I/II, 14: stage III, 34: stage IV) Control group: 130 healthy patients.		stage III patients (sensitivity 21,4%) and 27/34 stage IV patients (sensitivity 79,4%) showed detectable S100 levels. For metastastic melanoma (stage III/IV): sensitivity 62,5%. Correlation between serum S100 and clinical stage (p=0,0899 stage I/II versus p<0,0001 stage III/IV)	Choroid melanoma included (n=1) No information about staging given	
Dumitrascu et al. (2009)	To investigate S-100B and MIA in relation to disease development	Diagnostic study	51 patients with skin melanoma (34% stage I, 40% stage II, 15% stage III and 11% stage IV) and 72 healthy volunteers	True and false positives	Mean serum level of S100 in healthy volunteers: 0.172 µg/l 5.55% FP Mean serum level of MIA in healthy volunteers: 7.28 µg/l No false positives S-100B significantly	Low patient numbers for each stage Selection critera for patients and healthy volunteers not given	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					elevated only in stage IV patients (p = 0.02) MIA significantly elevated both stage II, III and IV MIA levels decreased after surgical removal of tumors and/or after good response to specific therapy; increase followed tumor progression and poor clinical response to treatment		
Vucetic et al. (2008)	To investigate whether MIA serum level will be elevated in patients with metastases or local spreading of the disease before any symptom of such progression is clinically apparent	Diagnostic study	140 patients: (50 with positive SN, 50 with negative SN, 20 controls with dysplastic nevi 20 controls with basal cell carcinoma Exclusion criterion: palpable lymph nodes	Mean values Sensitivity Specificity	Mean MIA value in patients with positive sentinel nodes: 14.53 ng/ml Mean MIA value in patients with negative sentinel nodes: 7.32 ng/ml At a cutoff value of 8.5 ng/ml, 82% sensitivity and 82%	No follow-up as reference standard (cross-sectional design)	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					specificity of MIA		
Arenberger (2007)	quantification of the following five melanoma markers by establishing a quantitative multimarker real-time RT-PCR assay: melanoma antigen recognized by T cells (Melan-A/MART-1), melanosomal matrix protein (gp100), melanoma antigen-A3 family (MAGE-3), melanoma inhibitory protein (MIA), and tyrosinase. Additionally human telomerase reverse transcriptase (hTERT) was focused on The final aim is	Prospective study	65 patients with resected cutaneous melanoma stage IIB–III 33.9% stage IIA, 24.6% stage IIB, 12.3% stage IIC, 15.4% IIIA, 9.2% stage IIIB and 4.6% stage IIIC. Control group: 23 healthy donors	Detection rate	Tumour marker mean levels in patients with progression: MIA, 4.272±2.183 (statistically significant difference compared with cut-off value, P<0.01); Melan-A, 0.026±0.016 (P>0.05); MAGE 3332.927±196.239 (P<0.01); gp100, 0.953 ±0.827 (P<0.05). MAGE-3 was the most frequent positive marker (17x), than gp100 (10x), MIA (9x) and tyrosinase (1x). Melan-A did not show any significant elevation compared with cut-off. In patients with	Small population Elevation of tumour markers varies strongly (e.g. patient 35: MAGE-3= 36.4, in patient 2: MAGE-3=40 580). poor information about the patients` follow-up after the study.	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	the routine usage of this method for rapid screening of early metastasis and treatment response in high-risk melanoma patients.				progression, in 39% three markers were concomitantly positive, in 28% two markers and in 33% one marker were positive.		
Arenberger (2007)	See above	See above	See above	See above	See above	Same population / same results as in the previously described study (Arenberger P (2007): Multimarker real-time reverse transcription-PCR for quantitative detection of melanoma-associated antigens: a novel possible staging method)	
Smit et al. (2008)	To evaluate S-100B for monitoring response to chemoimmunother	Prognostic study.	44 patients with locoregional-lymph node or intransit	Overall survival Renissionrate	Correlations between the pattern and intensity of S-	Small population	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	apy followed by surgery and its predictive value for relapse and overall survival in patients with clinically detectable localized disease. To analyze the expression of S-100B in the lymph nodes and in-transit metastases of the included patients and to compare these findings with the values of S-100B in the serum.		metastases (cytologically proven, clinically detectable regional metastases of melanoma without evidence of distant metastases.		100B expression in the tumor specimen and the value of serum the S-100B did not reach statistical significance		
Lugovic et al. (2007)	To determine and compare levels of S100, MIA, LDH and tyrosinase in the serum of patients with MM in different disease stages, and to conclude whether these	Diagnostic study	50 melanoma patients (30% in stage I, 52% in stage II, 16% in stage III and 8% in stage IV)	Positive results	Increased MIA in 26% of stage I patients, 26% of stage II patients, 0% of stage III patients and 50% of stage IV patients Increased S100 in of stage I patients,	No follow-up as reference standard	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	might be useful prognostic tools for MM progression				9% of stage II patients, 0% of stage III patients and 50% of stage IV patients Increased LDH in 26% of stage I patients, 4% of stage II patients, 13% of stage III patients and 25% of stage IV patients		
Auge et al. (2005)	To compare the sensitivity and specificity of S-100 and MIA and their combination in advanced melanoma, and the relationship with prognostic factors such as growth patterns and site of metastases.	Diagnostic study	182 CM patients: 96 patients with no evidence of disease (NED, stages I and II) and 86 patients with stages III, IV	Sensitivity	Sensitivity of S100 (cutoff > 0.2 µg/l): 53.8% for SSM, 40% for ALM, 75% for NM Sensitivity of MIA (cutoff > 14 ng/l): 61.5% for SSM, 40% for ALM, 65% for NM Slightly elevated levels of S100 (< 0.24 µg/l) and MIA (< 16.4 ng/ml) in 1.2% and 3.2% of NED patients, respectively Sensitivity of S100	No data given for specificity Reference test not described in detail	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					for LN metastasis 58.3%, for multiple metastases 58.3%, for multiple with liver metastasis 70%, for brain metastasis 77% and for lung metastasis 30% Sensitivity of MIA for LN metastasis 54.1%, for multiple metastases 62.5%, for multiple with liver metastasis 70%, for brain metastasis 66.6% and for lung metastasis 23%		
Guba et al. (2002)	To evaluate the association between pre- and posttreatment levels of MIA and survival in 70 patients with advanced melanoma.	Diagnostic and prognostic study	70 patients with histologically confirmed metastastic melanoma. (50 stage III, 17 stage IV)	Overall-survival Specificity	Mia positivity concentrations: >8,8ng/l.: - stage III: 46% - stage IV: 65% Median OS in MIA positive patients (stage III/IV): 13 vs. 28 months in patients with negative pre-	No data for sensitivity given Small population	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					treatment MIA levels. staging-related analysis: stage III: median OS: 14 months in MIA positive patients vs. 28 months in negative patients. stage IV: 12 vs. 19 months respectively. Specifitiy (cut-off>8,8ng/l) = 95%		
Klimek et al. (2002)	To evaluate the sensitivity of serum MIA levels in predicting the risk of relapse in patients with AJCC stage II, III and IV melanoma	Diagnostic study	39 patients with stage II, III and IV melanoma 14 patients with clinically advanced melanoma (IV or unresectable III) as positive controls Serum from 20 patients with prostate or small cell lung cancer to establish a background	Sensitivity False positives	MIA: 17% sensitivity for recurrence 6% false positives No significant difference in the proportion of patients with elevated MIA levels between the group of patients who relapsed (17%) and those who did not relapse (6%)	MIA values taken at different intervals after diagnosis and treatment of melanoma	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			reference range				
Matsushita et al. (2002)	To compare the usefulness of the serum markers 5-S-cysteinyldopa (5-S-CD) and melanoma inhibitory activity (MIA) in the monitoring of postsurgical melanoma patients	Diagnostic study	45 CM patients (7 in stage I, 20 in stage II, 18 in stage III) 30 age-matched healthy volunteers	Sensitivity False positives	Sensitivity for detection of relapse: 64% for MIA False positives (non-progressive patients) for MIA 8.3% (6/72)	No selection criteria for the included patients given Evaluation per sample, not per patient No description of follow-up	3b-
Dreau et al. (1999)	To measure plasma MIA concentration in patients with metastatic melanoma or patients at high risk for recurrence treated with various immunotherapy regimens	Diagnostic study	84 CM patients (16 in stage II, 29 in stage III and 39 in stage IV) under treatment Most of stage II and III patients (36/45) were treated with polyvalent melanoma vaccine after surgical resection; all patients treated with IL-2 were stage IV	Sensitivity and specificity	At a threshold of 4.5 ng/ml values for discrimination between progression and no progression were: Sensitivity of 82% and specificity of 71% before treatment Sensitivity of 67% and specificity of 79% after treatment	Low patient numbers for each treatment modality Method of assigning patients to treatment regimens not described	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Tofani et al. (1997)	To assess the reliability of NSE and S100 as indexes of disease activity.	Diagnostic and cross-sectional study	53 consecutive patients with melanoma 24 patients presented with local disease (stage I or 11), 29 had metastases (stage III or IV). Twenty healthy volunteers were used as a control group.	Prevalence of increased NSE and S100 levels Sensitivity and specificity	In the whole group, elevation of S-100 in 30% of patients. No elevated levels in the subgroup of 24 patients stage I and II. Inceased levels in 55% of patients stage III and IV Serum NSE: elevated in 26%. 4/24 patients (16%) with melanoma in stages I and II had increased NSE values. Inceased levels in 34% of patients stage III and IV. For the whole group: sensitivity of S100 and NSE: 30 and 26%, respectively For patients I and	Small patient samples Study included in addition to S100 meta-analysis because of results about NSE No details about reference standard for the calculation of sensitivity and specificity	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					II: Poor sensitivity for NSE, S-100 values were normal in all patients. For patients stage III and IV: sensitivity for S-100 and NSE: 55% and 34% respectively ($p < 0.5$).		

2.3.4.2. Literatur

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Abbott et al. (2011)	x	x		x
Agarwala et al. (2009)			x	
Aloia et al. (2006)		x		
Andrés et al. (2008)	x	x	x	
Ardizzoni et al. (1987)	x			

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Arenberger (2007)	x	x		
Au et al. (1984)	x			
Auge et al. (2005)	x	x	x	
Bafounta et al. (2004)	x	x	x	x
Balch et al. (2009)	(x)	(x)	(x)	x
Bastiaannet et al. (2009)		x		x
Bastiaannet et al. (2012)		x	x	
Bosserhoff et al. (1997)	x	x	x	x
Bouwhuis et al. (2011)	x	x		x
Bronstein et al. (2012)		x	x	
Brouard et al. (2000)	x	x	x	x
Buzaid et al. (1995)		x		
Chai et al. (2011)	x			
Clark et al. (2006)	x			

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Collins et al. (1993)				x
Constantinidou et al. (2008)		x		
Deichmann et al. (2004)	x	x	x	x
Dellestable et al. (2011)			x	
Dietlein et al. (1999)		x	x	x
Doiron et al. (1981)			x	
Dreau et al. (1999)	x	x	x	
Dumitrascu et al. (2009)	x	x	x	
Etchebehere et al. (2010)		x	x	
El-Maraghi and Kielar (2008)	x			
Essler et al. (2011)	x	x	x	x
Fogarty et al. (2006)	x	x	x	x
Garbe et al. (2003)				x
Garnier et al. (2007)	x	x	x	

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Ginaldi et al. (1981)	x		x	x
Goerz et al. (1986)	x	x	x	x
Guba et al. (2002)		x	x	
Hafner et al. (2004)	x			
Hausmann et al. (2011)		x	x	x
Heaston et al. (1983)	x	x		
Henze et al. (1997)				x
Hinz et al. (2011)	x			
Hocevar et al. (2004)	x			
Hofmann et al. (2002)	x			x
Hofmann et al. (2009)				x
Hofmann et al. (2011)		x		x
Holloway et al. (1997)		x	x	x
Horn et al. (2005)		x		

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Lagaru et al. (2007)m	x	x	x	x
Iscoe et al. (1986)	x			
Johnson (1997)		x		
Kaskel et al. (1999)	x	x	x	x
Kersey et al. (1985)	x			x
Khansur et al. (1989)	x	x	x	x
Klode et al. (2010)	x			
Koskivuo et al. (2007)	x	x		x
Krahn et al. (2001)	x	x	x	x
Krug et al. (2000)		x	x	x
Krug et al. (2008)	x	x	x	x
Kruijff et al. (2009)		x		
Kruijff et al. (2011)		x		
Kuan et al. (1988)	x	x	x	

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Kunte et al. (2009)	x			
Laurent et al. (2011)			x	
Löffler et al. (2003)		x	x	x
Lugovic et al. (2007)	x	x	x	
Mansour et al. (2010)	x	x	x	x
Matsushita et al. (2002)	x	x	x	
Maubec et al. (2007)	x			
Meyer and Stolbach (1978)	x			
Miranda et al. (2004)		x		
Mocellin et al. (2008)	x	x	x	x
Mueller-Horvat (2005)		x	x	x
Neuss et al. (2011)		x		
Panagiotou et al. (2001)	x			x
Pandalai et al. (2010)		x		

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Paschen et al. (2009)	x	x	x	x
Patten et al. (1990)	x	x	x	x
Pfannenberg et al. (2007)		x	x	x
Pleiss et al.(2007)	x	x	x	x
Revel et al. (2010)	x			
Rodriguez et al. (2014)		x	x	
Saiag et al. (2005)	x	x		x
Sanki et al. (2009)	x			
Sawyer et al. (2009)	x			x
Schlamann et al. (2008)	x	x	x	x
Schmid-Wendtner et al. (2004)	x	x		
Schmitz et al. (2000)	x	x	x	
Sibon et al. (2007)	x			
Silverman et al. (1984)	x		x	x

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Singh et al. (2008)	x			
Smit et al. (2008)		x		x
Stahlecker et al. (2000)	x	x	x	x
Stas M et al. (2002)		x	x	
Stoffels et al. (2011)	x	x		
Stoitchkov et al. (2003)	x	x	x	
Strobel et al. (2007)	x	x	x	x
Stucky et al. (2010)	x	x		
Stutte (1989)		x	x	x
Tas et al. (2004)	x	x	x	x
Terhune et al. (1998)	x			
Testori et al. (2005)	x			x
Tofani et al. (1997)	x	x	x	x
Tsao et al. (2004)	x			x

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Uren (1999)		x		
Van den Brekel et al. (1998)	x	x		x
Van der Ploeg (2009)	x			
Veit-Haibach et al. (2009)	x	x	x	
Vereecken et al. (2005)	x			
Vereecken et al. (2009)		x	x	
Vermeerenet al. (2011)	x			
Vucetic et al. (2008)	x			
Wagner et al. (2011)		x		
Wang et al. (2004)	x			
Webb (1977)	x	x	x	x
Xing et al. (2011)	x	x	x	x
Yancovitz et al. (2007)	x	x		
Zartman et al. (1987)	x			

Abbott RA, Acland KM, Harries M, et al. The role of positron emission tomography with computed tomography in the follow-up of asymptomatic cutaneous malignant melanoma patients with a high risk of disease recurrence. Melanoma Res 2011;21:446-449
Agarwala SS, Keilholz U, Gilles E, et al. LDH correlation with survival in advanced melanoma from two large, randomised trials (Oblimersen GM301 and EORTC 18951). Eur J Cancer 2009;45:1807-1814
Aloia TA, Gershenwald JE, Andtbacka RH, et al. Utility of computed tomography and magnetic resonance imaging staging before completion lymphadenectomy in patients with sentinel lymph node-positive melanoma. J Clin Oncol 2006;24:2858-2865
Andres R, Mayordomo JI, Visus C, et al. Prognostic significance and diagnostic value of protein S-100 and tyrosinase in patients with malignant melanoma. Am J Clin Oncol 2008;31:335-339
Ardizzoni A, Grimaldi A, Repetto L, et al. Stage I-II melanoma: the value of metastatic work-up. Oncology 1987;44:87-89
Arenberger P, Arenbergerova M, Gkalpakiotis S, et al. Multimarker real-time reverse transcription-PCR for quantitative detection of melanoma-associated antigens: a novel possible staging method. J Eur Acad Dermatol Venereol 2008;22:56-64
Arenberger P, Arenbergerova M, Vohradnikova O, et al. Early detection of melanoma progression by quantitative real-time RT-PCR analysis for multiple melanoma markers. Keio J Med 2008;57:57-64
Au FC, Maier WP, Malmud LS, et al. Preoperative nuclear scans in patients with melanoma. Cancer 1984;53:2095-2097
Auge JM, Molina R, Filella X, et al. S-100beta and MIA in advanced melanoma in relation to prognostic factors. Anticancer Res 2005;25:1779-1782
Bafounta ML, Beauchet A, Chagnon S, et al. Ultrasonography or palpation for detection of melanoma nodal invasion: a meta-analysis. Lancet Oncol 2004;5:673-680
Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199-6206
Banfalvi T, Boldizsar M, Gergye M, et al. Comparison of prognostic significance of serum 5-S-Cysteinyldopa, LDH and S-100B protein in Stage III-IV malignant melanoma. Pathol Oncol Res 2002;8:183-187
Bastiaannet E, Wobbes T, Hoekstra OS, et al. Prospective comparison of [18F]fluorodeoxyglucose positron emission tomography and computed tomography in patients with melanoma with palpable lymph node metastases: diagnostic accuracy and impact on treatment. J Clin Oncol 2009;27:4774-4780
Bastiaannet E, Uyl-de Groot CA, Brouwers AH, et al. Cost-effectiveness of adding FDG-PET or CT to the diagnostic work-up of patients with stage III melanoma. Ann Surg. 2012;255(4):771-776.
Bosserhoff AK, Kaufmann M, Kaluza B, et al. Melanoma-inhibiting activity, a novel serum marker for progression of malignant melanoma. Cancer Res 1997;57:3149-3153
Bosserhoff AK, Lederer M, Kaufmann M, et al. MIA, a novel serum marker for progression of malignant melanoma. Anticancer Res 1999;19:2691-2693
Bouwhuis MG, Suciu S, Kruit W, et al. Prognostic value of serial blood S100B determinations in stage IIB-III melanoma patients: a corollary study to EORTC trial 18952. European journal of cancer (Oxford, England : 1990) 2011;47:361-368
Bronstein Y, Ng CS, Rohren E, et al. PET/CT in the management of patients with stage IIIC and IV metastatic melanoma considered candidates for surgery: evaluation of the additive value after conventional imaging. AJR Am J Roentgenol. 2012;198(4):902-908.Brouard M, Quillien V, Ollivier I, et al. Serum S100B protein and stage of cutaneous melanoma: a prospective study. Ann Dermatol Venereol 2000;127:56-59
Buzaid AC, Tinoco L, Ross MI, et al. Role of computed tomography in the staging of patients with local-regional metastases of melanoma. J Clin Oncol 1995;13:2104-2108
Chai CY, Zager JS, Szabunio MM, et al. Preoperative Ultrasound is Not Useful for Identifying Nodal Metastasis in Melanoma Patients Undergoing Sentinel Node Biopsy: Preoperative Ultrasound in Clinically Node-Negative Melanoma. Ann Surg Oncol 2011
Clark PB, Soo V, Kraas J, et al. Futility of fluorodeoxyglucose F 18 positron emission tomography in initial evaluation of patients with T2 to T4 melanoma. Arch Surg 2006;141:284-288
Collins CD, Padley SP, Greenwell F, et al. The efficacy of a single posteroanterior radiograph in the assessment of metastatic pulmonary melanoma. Br J Radiol 1993;66:117-119
Constantinidou A, Hofman M, O'Doherty M, et al. Routine positron emission tomography and positron emission tomography/computed tomography in melanoma staging with positive sentinel node biopsy is of limited benefit. Melanoma Res 2008;18:56-60
Deichmann M, Benner A, Bock M, et al. S100-Beta, melanoma-inhibiting activity, and lactate dehydrogenase discriminate progressive from nonprogressive American Joint Committee on Cancer stage IV melanoma. J Clin Oncol 1999;17:1891-1896
Deichmann M, Benner A, Kuner N, et al. Are responses to therapy of metastasized malignant melanoma reflected by decreasing serum values of S100beta or melanoma inhibitory activity (MIA)? Melanoma Res 2001;11:291-296
Deichmann M, Kahle B, Moser K, et al. Diagnosing melanoma patients entering American Joint Committee on Cancer stage IV, C-reactive protein in serum is superior to lactate dehydrogenase. Br J Cancer 2004;91:699-702
Dellestable P, Granel-Brocard F, Rat AC, et al. Impact of whole body magnetic resonance imaging (MRI) in the management of melanoma patients, in comparison with positron emission tomography/computed tomography (TEP/CT) and CT. Annales de dermatologie et de vénéréologie 2011;138:377-383
Dietlein M, Krug B, Groth W, et al. Positron emission tomography using 18F-fluorodeoxyglucose in advanced stages of malignant melanoma: a comparison of ultrasonographic and radiological methods of diagnosis. Nucl Med Commun 1999;20:255-261
Doiron MJ, Bernardino ME. A comparison of noninvasive imaging modalities in the melanoma patient. Cancer 1981;47:2581-2584
Dreau D, Bosserhoff AK, White RL, et al. Melanoma-inhibitory activity protein concentrations in blood of melanoma patients treated with immunotherapy. Oncol Res 1999;11:55-61
Dumitrascu G, Constantin C, Manda G, et al. Serum markers in skin melanoma--preliminary study. Roum Arch Microbiol Immunol 2009;68:125-135
El-Maraghi RH, Kielar AZ. PET vs sentinel lymph node biopsy for staging melanoma: a patient intervention, comparison, outcome analysis. J Am Coll Radiol 2008;5:924-931
Essler M, Link A, Belloni B, et al. Prognostic value of [18F]-fluoro-deoxy-glucose PET/CT, S100 or MIA for assessment of cancer-associated mortality in patients with high risk melanoma. PLoS One 2011;6:e24632
Etchebehere EC, Romanato JS, Santos AO, et al. Impact of [F-18] FDG-PET/CT in the restaging and management of patients with malignant melanoma. Nucl Med Commun 2010;31:925-930
Fogarty GB, Tartaguia C. The utility of magnetic resonance imaging in the detection of brain metastases in the staging of cutaneous melanoma. Clin Oncol (R Coll Radiol) 2006;18:360-362

Garbe C, Leiter U, Ellwanger U, et al. Diagnostic value and prognostic significance of protein S-100beta, melanoma-inhibitory activity, and tyrosinase/MART-1 reverse transcription-polymerase chain reaction in the follow-up of high-risk melanoma patients. Cancer 2003;97:1737-1745
Garnier JP, Letellier S, Cassinat B, et al. Clinical value of combined determination of plasma L-DOPA/tyrosine ratio, S100B, MIA and LDH in melanoma. Eur J Cancer 2007;43:816-821
Ginaldi S, Wallace S, Shalen P, et al. Cranial computed tomography of malignant melanoma. AJR Am J Roentgenol 1981;136:145-149
Goerz G, Schulte-Beerbuhl R, Roder K, et al. Malignant melanoma: which examinations are useful in staging and follow-up? Dtsch Med Wochenschr 1986;111:1230-1233
Guba M, Steinbauer M, Ruhland V, et al. Elevated MIA serum levels are predictors of poor prognosis after surgical resection of metastatic malignant melanoma. Oncol Rep 2002;9:981-984
Hafner J, Schmid MH, Kempf W, et al. Baseline staging in cutaneous malignant melanoma. Br J Dermatol 2004;150:677-686
Hausmann D, Jochum S, Utikal J, et al. Comparison of the diagnostic accuracy of whole-body MRI and whole-body CT in stage III/IV malignant melanoma. JDDG - Journal of the German Society of Dermatology 2011;9:212-222
Heaston DK, Putman CE, Rodan BA, et al. Solitary pulmonary metastases in high-risk melanoma patients: a prospective comparison of conventional and computed tomography. AJR Am J Roentgenol 1983;141:169-174
Henze G, Dummer R, Joller-Jemelka HI, et al. Serum S100--a marker for disease monitoring in metastatic melanoma. Dermatology 1997;194:208-212
Hinz T, Wilsmann-Theis D, Buchner A, et al. High-resolution ultrasound combined with power Doppler sonography can reduce the number of sentinel lymph node biopsies in cutaneous melanoma. Dermatology 2011;222:180-188
Hocevar M, Bracko M, Pogacnik A, et al. The role of preoperative ultrasonography in reducing the number of sentinel lymph node procedures in melanoma. Melanoma Res 2004;14:533-536
Hofmann MA, Gussmann F, Fritsche A, et al. Diagnostic value of melanoma inhibitory activity serum marker in the follow-up of patients with stage I or II cutaneous melanoma. Melanoma Res 2009;19:17-23
Hofmann MA, Schicke B, Fritsch A, et al. Impact of lymph node metastases on serum level of melanoma inhibitory activity in stage III melanoma patients. J Dermatol 2011;38:880-886
Hofmann U, Szedlak M, Rittgen W, et al. Primary staging and follow-up in melanoma patients--monocenter evaluation of methods, costs and patient survival. Br J Cancer 2002;87:151-157
Holloway BJ, King DM. Ultrasound diagnosis of metastatic melanoma of the gallbladder. Br J Radiol 1997;70:1122-1125
Horn J, Lock-Andersen J, Sjostrand H, et al. Routine use of FDG-PET scans in melanoma patients with positive sentinel node biopsy. Eur J Nucl Med Mol Imaging 2006;33:887-892
Iagaru A, Quon A, Johnson D, et al. 2-Deoxy-2-[F-18]fluoro-D-glucose positron emission tomography/computed tomography in the management of melanoma. Mol Imaging Biol 2007;9:50-57
Iscoe N, Kersey P, Gapski J, et al. Predictive value of staging investigations in patients with clinical stage I malignant melanoma. Plast Reconstr Surg 1987;80:233-239
Jimenez-Requena F, Delgado-Bolton RC, Fernandez-Perez C, et al. Meta-analysis of the performance of (18)F-FDG PET in cutaneous melanoma. Eur J Nucl Med Mol Imaging 2010;37:284-300
Johnson TM, Fader DJ, Chang AE, et al. Computed tomography in staging of patients with melanoma metastatic to the regional nodes. Ann Surg Oncol 1997;4:396-402
Kaskel P, Berking C, Sander S, et al. S-100 protein in peripheral blood: a marker for melanoma metastases: a prospective 2-center study of 570 patients with melanoma. J Am Acad Dermatol 1999;41:962-969
Kersey PA, Iscoe NA, Gapski JA, et al. The value of staging and serial follow-up investigations in patients with completely resected, primary, cutaneous malignant melanoma. Br J Surg 1985;72:614-617
Khansur T, Sanders J, Das SK. Evaluation of staging workup in malignant melanoma. Arch Surg 1989;124:847-849
Klimek VM, Williams L, Chapman PB. Serum levels of melanoma-inhibiting activity do not predict relapse in melanoma patients. Cytokines Cell Mol Ther 2002;7:71-74
Klode J, Dissemond J, Grabbe S, et al. Sentinel lymph node excision and PET-CT in the initial stage of malignant melanoma: a retrospective analysis of 61 patients with malignant melanoma in American Joint Committee on Cancer stages I and II. Dermatol Surg 2010;36:439-445
Koskivuo IO, Seppanen MP, Suominen EA, et al. Whole body positron emission tomography in follow-up of high risk melanoma. Acta Oncol 2007;46:685-690
Krahn G, Kaskel P, Sander S, et al. S100 beta is a more reliable tumor marker in peripheral blood for patients with newly occurred melanoma metastases compared with MIA, albumin and lactate-dehydrogenase. Anticancer Res 2001;21:1311-1316
Krug B, Crott R, Lonneux M, et al. Role of PET in the initial staging of cutaneous malignant melanoma: systematic review. Radiology 2008;249:836-844
Krug B, Dietlein M, Groth W, et al. Fluor-18-fluorodeoxyglucose positron emission tomography (FDG-PET) in malignant melanoma. Diagnostic comparison with conventional imaging methods. Acta Radiol 2000;41:446-452
Kruijff S, Bastiaannet E, Kobold AC, et al. S-100B concentrations predict disease-free survival in stage III melanoma patients. Ann Surg Oncol 2009;16:3455-3462
Kruijff S, Bastiaannet E, Speijers MJ, et al. The value of pre operative S-100B and SUV in clinically stage III melanoma patients undergoing therapeutic lymph node dissection. Eur J Surg Oncol 2011;37:225-232
Kuan AK, Jackson FI, Hanson J. Multimodality detection of metastatic melanoma. J R Soc Med 1988;81:579-582
Kunte C, Schuh T, Eberle JY, et al. The use of high-resolution ultrasonography for preoperative detection of metastases in sentinel lymph nodes of patients with cutaneous melanoma. Dermatol Surg 2009;35:1757-1765
Laurent V, Trausch G, Bruot O, et al. Comparative study of two whole-body imaging techniques in the case of melanoma metastases: advantages of multi-contrast MRI examination including a diffusion-weighted sequence in comparison with PET-CT. Eur J Radiol 2010;75:376-383
Loffler M, Weckesser M, Franzius C, et al. Malignant melanoma and (18)F-FDG-PET: Should the whole body scan include the legs? Nuklearmedizin 2003;42:167-172
Lugovic L, Situm M, Buljan M, et al. Results of the determination of serum markers in patients with malignant melanoma. Coll Antropol 2007;31 Suppl 1:7-11
Mansour AA,3rd, Kelley MC, Hatmaker AR, et al. Verification of musculoskeletal FDG-PET-CT findings performed for melanoma staging. Ann Surg Oncol 2010;17:1144-1151
Matsushita Y, Hatta N, Wakamatsu K, et al. Melanoma inhibitory activity (MIA) as a serum marker for early detection of post-surgical relapse in melanoma patients: comparison with 5-S-cysteinyldopa. Melanoma Res 2002;12:319-323
Maubec E, Lumbroso J, Masson F, et al. F-18 fluorodeoxy-D-glucose positron emission tomography scan in the initial evaluation of patients with a primary melanoma thicker than 4 mm. Melanoma Res 2007;17:147-154

Mays MP, Martin RC, Burton A, et al. Should all patients with melanoma between 1 and 2 mm Breslow thickness undergo sentinel lymph node biopsy? Cancer 2010;116:1535-1544
Meral R, Duranyildiz D, Tas F, et al. Prognostic significance of melanoma inhibiting activity levels in malignant melanoma. Melanoma Res 2001;11:627-632
Meyer JE, Stolbach L. Pretreatment radiographic evaluation of patients with malignant melanoma. Cancer 1978;42:125-126
Miranda EP, Gertner M, Wall J, et al. Routine imaging of asymptomatic melanoma patients with metastasis to sentinel lymph nodes rarely identifies systemic disease. Arch Surg 2004;139:831-6; discussion 836-7
Mocellin S, Zavagno G, Nitti D. The prognostic value of serum S100B in patients with cutaneous melanoma: a meta-analysis. Int J Cancer 2008;123:2370-2376
Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 2006;355:1307-1317
Muller-Horvat C, Radny P, Eigentler TK, et al. Prospective comparison of the impact on treatment decisions of whole-body magnetic resonance imaging and computed tomography in patients with metastatic malignant melanoma. Eur J Cancer 2006;42:342-350
Neuss H, Koplin G, Raue W, et al. Analysing the serum levels of tumour markers and primary tumour data in stage III melanoma patients in correlation to the extent of lymph node metastases--a prospective study in 231 patients. Acta Chir Belg 2011;111:214-218
Nowecki ZI, Rutkowski P, Kulik J, et al. Molecular and biochemical testing in stage III melanoma: multimarker reverse transcriptase-polymerase chain reaction assay of lymph fluid after lymph node dissection and preoperative serum lactate dehydrogenase level. Br J Dermatol 2008;159:597-605
Panagiotou IE, Brountzos EN, Bafaloukos D, et al. Evaluation of imaging studies at the initial staging and during follow-up of patients with local-regional malignant melanoma. Journal of B.U.ON 2001;6:411-414
Pandalai PK, Dominguez FJ, Michaelson J, et al. Clinical Value of Radiographic Staging in Patients Diagnosed With AJCC Stage III Melanoma. Ann Surg Oncol 2010
Paschen A, Sucker A, Hill B, et al. Differential clinical significance of individual NKG2D ligands in melanoma: soluble ULBP2 as an indicator of poor prognosis superior to S100B. Clin Cancer Res 2009;15:5208-5215
Patten RM, Shuman WP, Teefey S. Metastases from malignant melanoma to the axial skeleton: a CT study of frequency and appearance. AJR Am J Roentgenol 1990;155:109-112
Pfannenberg C, Aschoff P, Schanz S, et al. Prospective comparison of 18F-fluorodeoxyglucose positron emission tomography/computed tomography and whole-body magnetic resonance imaging in staging of advanced malignant melanoma. Eur J Cancer 2007;43:557-564
Pleiss C, Risse JH, Biersack HJ, et al. Role of FDG-PET in the assessment of survival prognosis in melanoma. Cancer Biother Radiopharm 2007;22:740-747
Revel A, Revel C, Dolivet G, et al. La TEP-TDM au 18FDG a-t-elle un intérêt dans la stadification ganglionnaire des mélanomes malins cutanés cervicofaciaux bénéficiant de la technique du ganglion sentinelle ? À propos de 22 cas. Médecine Nucléaire 2010;34:528-539
Rodriguez Rivera AM, Alabbas H, Ramjaun A, Meguerditchian AN. Value of positron emission tomography scan in stage III cutaneous melanoma: a systematic review and meta-analysis. Surg Oncol. 2014;23(1):11-16.
Saiag P, Bernard M, Beauchet A, et al. Ultrasonography using simple diagnostic criteria vs palpation for the detection of regional lymph node metastases of melanoma. Arch Dermatol 2005;141:183-189
Sanki A, Uren RF, Moncrieff M, et al. Targeted high-resolution ultrasound is not an effective substitute for sentinel lymph node biopsy in patients with primary cutaneous melanoma. J Clin Oncol 2009;27:5614-5619
Sawyer A, McGoldrick RB, Mackey SP, et al. Does staging computered tomography change management in thick malignant melanoma? J Plast Reconstr Aesthet Surg 2009;62:453-456
Schlamann M, Loquai C, Goericke S, et al. Cerebral MRI in neurological asymptomatic patients with malignant melanoma. Rofo 2008;180:143-147
Schmid-Wendtner MH, Dill-Muller D, Baumert J, et al. Lymph node metastases in patients with cutaneous melanoma: improvements in diagnosis by signal-enhanced color Doppler sonography. Melanoma Res 2004;14:269-276
Schmitz C, Brenner W, Henze E, et al. Comparative study on the clinical use of protein S-100B and MIA (melanoma inhibitory activity) in melanoma patients. Anticancer Res 2000;20:5059-5063
Schwimmer J, Essner R, Patel A, et al. A review of the literature for whole-body FDG PET in the management of patients with melanoma. Q J Nucl Med 2000;44:153-167
Sibon C, Chagnon S, Tchakerian A, et al. The contribution of high-resolution ultrasonography in preoperatively detecting sentinel-node metastases in melanoma patients. Melanoma Res 2007;17:233-237
Silverman PM, Heaston DK, Korobkin M, et al. Computed tomography in the detection of abdominal metastases from malignant melanoma. Invest Radiol 1984;19:309-312
Singh B, Ezziddin S, Palmedo H, et al. Preoperative 18F-FDG-PET/CT imaging and sentinel node biopsy in the detection of regional lymph node metastases in malignant melanoma. Melanoma Res 2008;18:346-352
Smit LH, Nieweg OE, Mooi WJ, et al. Value of serum S-100B for prediction of distant relapse and survival in stage III B/C melanoma. Anticancer Res 2008;28:2297-2302
Stahlecker J, Gauger A, Bosserhoff A, et al. MIA as a reliable tumor marker in the serum of patients with malignant melanoma. Anticancer Res 2000;20:5041-5044
Stas M, Stroobants S, Dupont P, et al. 18-FDG PET scan in the staging of recurrent melanoma: additional value and therapeutic impact. Melanoma Res 2002;12:479-490
Stoffels I, Dissemond J, Poeppel T, et al. Advantages of preoperative ultrasound in conjunction with lymphoscintigraphy in detecting malignant melanoma metastases in sentinel lymph nodes: A retrospective analysis in 221 patients with malignant melanoma AJCC Stages i and II. Journal of the European Academy of Dermatology and Venereology 2012;26:79-85
Stoitchkov K, Letellier S, Garnier JP, et al. Evaluation of the serum L-dopa/L-tyrosine ratio as a melanoma marker. Melanoma Res 2003;13:587-593
Stoitchkov K, Letellier S, Garnier JP, et al. Melanoma progression and serum L-dopa/L-tyrosine ratio: a comparison with S100B. Melanoma Res 2002;12:255-262
Strobel K, Dummer R, Husarik DB, et al. High-risk melanoma: accuracy of FDG PET/CT with added CT morphologic information for detection of metastases. Radiology 2007;244:566-574
Stutte H, Muller PH, d'Hoedt B, et al. Ultrasonographic diagnosis of melanoma metastases in liver, gallbladder, and spleen. J Ultrasound Med 1989;8:541-547
Tas F, Yasasever V, Duranyildiz D, et al. Clinical value of protein S100 and melanoma-inhibitory activity (MIA) in malignant melanoma. Am J Clin Oncol 2004;27:225-228
Terhune MH, Swanson N, Johnson TM. Use of chest radiography in the initial evaluation of patients with localized melanoma. Arch Dermatol 1998;134:569-572
Testori A, Lazzaro G, Baldini F, et al. The role of ultrasound of sentinel nodes in the pre- and post-operative evaluation of stage I melanoma patients. Melanoma Res 2005;15:191-198
Tofani A, Cioffi RP, Sciuto R, et al. S-100 and NSE as serum markers in melanoma. Acta Oncol 1997;36:761-764

Tsao H, Feldman M, Fullerton JE, et al. Early detection of asymptomatic pulmonary melanoma metastases by routine chest radiographs is not associated with improved survival. Arch Dermatol 2004;140:67-70
Uren RF, Howman-Giles R, Thompson JF, et al. High-resolution ultrasound to diagnose melanoma metastases in patients with clinically palpable lymph nodes. Australas Radiol 1999;43:148-152
van den Brekel MW, Pameijer FA, Koops W, et al. Computed tomography for the detection of neck node metastases in melanoma patients. Eur J Surg Oncol 1998;24:51-54
van der Ploeg IM, Valdes Olmos RA, Kroon BB, et al. The yield of SPECT/CT for anatomical lymphatic mapping in patients with melanoma. Ann Surg Oncol 2009;16:1537-1542
Veit-Haibach P, Vogt FM, Jablonka R, et al. Diagnostic accuracy of contrast-enhanced FDG-PET/CT in primary staging of cutaneous malignant melanoma. Eur J Nucl Med Mol Imaging 2009;36:910-918
Vereecken P, Awada A, Suciu S, et al. Evaluation of the prognostic significance of serum galectin-3 in American Joint Committee on Cancer stage III and stage IV melanoma patients. Melanoma Res 2009;19:316-320
Vereecken P, Laporte M, Petein M, et al. Evaluation of extensive initial staging procedure in intermediate/high-risk melanoma patients. J Eur Acad Dermatol Venereol 2005;19:66-73
Vermeeren L, Van Der Ent FW, Hulsewe KW. Is there an indication for routine chest x-ray in initial staging of melanoma?. J Surg Res 2011;166:114-119
Voit C, Van Akkooi AC, Schafer-Hesterberg G, et al. Ultrasound morphology criteria predict metastatic disease of the sentinel nodes in patients with melanoma. J Clin Oncol 2010;28:847-852
Vucetic B, Rogan SA, Hrabac P, et al. Biological value of melanoma inhibitory activity serum concentration in patients with primary skin melanoma. Melanoma Res 2008;18:201-207
Wagner T, Chevreau C, Meyer N, et al. Routine FDG PET-CT in patients with a high-risk localized melanoma has a high predictive positive value for nodal disease and high negative predictive value for the presence of distant metastases. J Eur Acad Dermatol Venereol 2011
Wagner T, Meyer N, Zerdoud S, et al. Fluorodeoxyglucose positron emission tomography fails to detect distant metastases at initial staging of melanoma patients with metastatic involvement of sentinel lymph node. Br J Dermatol 2011;164:1235-1240
Wang TS, Johnson TM, Cascade PN, et al. Evaluation of staging chest radiographs and serum lactate dehydrogenase for localized melanoma. J Am Acad Dermatol 2004;51:399-405
Webb WR, Gamsu G. Thoracic metastasis in malignant melanoma. A radiographic survey of 65 patients. Chest 1977;71:176-181
Xing Y, Bronstein Y, Ross MI, et al. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. J Natl Cancer Inst 2011;103:129-142
Yancovitz M, Finelt N, Warycha MA, et al. Role of radiologic imaging at the time of initial diagnosis of stage T1b-T3b melanoma. Cancer 2007;110:1107-1114
Zartman GM, Thomas MR, Robinson WA. Metastatic disease in patients with newly diagnosed malignant melanoma. J Surg Oncol 1987;35:163-164

2.3.4.3. Aktualisierungsrecherche 2015

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Rodriguez Rivera et al. (2014)	To review the collective experience and utility of FDG-PET scans in the detection of systemic metastases in patients with stage III melanoma	Systematic review and meta-analysis	A total of 623 patients with stage III melanoma	Sensitivity Specificty Positive and negative likelihood ratios	Sensitivity of FDG-PET: 89.42% (95% CI: 65.07 - 97.46) Specificity: 88.78% (95% CI: 77.04 - 94.91). Pooled positive likelihood ratio: 7.97 (95% CI: 3.58 - 17.71) Negative	Small sample size, 9 studies included Confirmation bias possible: adequate reference test was not applied properly (biopsy, further radiological studies and/or follow-up) 67% of the	IIa

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				SROC DOR Change of management	likelihood ratio: 0.12 (95% CI: 0.03 - 0.47). Area under the summary receiver operating curve (SROC): 0.94 (95% CI: 0.92 - 0.96) Diagnostic odds ratio (DOR): 66.84 (95% CI: 10.66 - 418.89). Change in stage and/or management was noted in 22% (126/573) of patients when FDG-PET was utilized.	patients had clinically evident stage III disease → findings possibly more relevant for patients stage IIIb/c disease	
Bastiaannet et al. (2012)	- to assess predictive value of FDG-PET and CT - to analyze their cost-effectiveness in several	Cohort study	253 melanoma patients with palpable, proven lymph node metastases	Sensitivity Specificity	FDG-PET: Sensitivity: 86,1% (CI: 78.4–93.7) Specificity: 93,1% (CI: 89.3–96.9)	True-positive upstaging in 61 patients (CT) respectively in 68 patients (FDG-PET)	IIb

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	diagnosis–treatment combinations.			Accuracy PPV NPV Cost-consequence analysis	CT Sensitiviy: 78,2% (CI: 69.0–87.4) Specificity: 93,7% (CI: 90.1–97.3) PPV, NPV, accuracy: see table 2/full-text Cost of diagnostic work-up: With CT: -5,5% With FDG-PET: +7,2% With both: +15,1%		
Bronstein et al. (2012)	To determine how often unexpected FDG PET-CT findings result in change of management of stage IV and clinically evident stage III melanoma patients with resectable disease based on conventional imaging	Cohort study	patients with stage IV and clinically evident stage III melanoma	Metastases detection rate change in surgical management	unexpected melanoma metastases in 12 % of scans As a result the surgery was cancelled in two patients, and the planned approach was altered in another two patients to address the	Small population	IIb

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					unexpected sites		

2.3.4.4. Aktualisierungsrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ultrasound, X-Ray, Clinical features							
Chai et al. (2012)	To assess feasibility of preoperative nodal ultrasound without lymphoscintigraphy localization of draining nodal basins as a screening tool in melanoma patients prior to SLNB and To compare the sensitivity and specificity of preoperative ultrasound in the detection of nodal metastases when compared to SLNB.	Retrospective cohort study	325 patients, 471 basins were examined with ultrasound	Sensitivity, Specificity Positive predictive value Negative predictive value	Sensitivity was 33.8%, specificity 85.7% Positive predictive value 36.5%, and negative predictive value 84.2%. Sensitivity and specificity improved somewhat with increasing Breslow depth. 65 patients (20.4%) had 69 SLNB positive nodal basins; 17 nodal basins from 15 patients with	QUADAS: 10 x yes	3a

					positive ultrasounds were considered truly positive. 45 SLNB positive basins had negative ultrasounds (falsely negative). Seven node-positive basins did not undergo ultrasound because of unpredicted drainage. A total of 253 patients with negative SLNBs had negative ultrasounds in 240 nodal basins (truly negative) but falsely positive ultrasounds occurred in 40 basins.		

Gonzalez-Alvarez et al. (2015)	To evaluate the correlation between dermoscopic structures and the positivity of sentinel lymph node. To develop an algorithm for the better selection of patients to be subjected to sentinel lymph node biopsy (SLNB) with lower number needed to treat.	Retrospective, single center, cohort study	123 consecutive melanomas with Breslow thickness >0.75 mm	Sensitivity Specificity	The presence of ulceration and blotch and the absence of a pigmented network in dermoscopy correlated with positive SLNB. Histological ulceration also correlated with positive SLNB. A dermoscopy SCORE predicted SLN status with a sensitivity of 96.3% and a specificity of 30.2%. When sex and Breslow thickness were added (SCOREBRESEX).	Funding source: Supported in part by grants from Fondo de Investigaciones Sanitarias P.I. 09/ 01393 and P.I. 12/00840, Spain; by the CI- BER de Enfermedades Raras of the Instituto de Sa- lud Carlos III, Spain, co- funded by 'Fondo Europeo de Desarrollo Regional (FEDER), Uni on Europea, Una manera de hacer Europa'; by the AGAUR 2014 SGR 603 of the Catalan Government, Spain and a grant from 'Fundaci o La Marat o de TV3,	3a

						201331-300, Catalonia, Spain.	
Haddad et al. (2013)	We characterized factors associated with use of imaging studies for the staging of patients with newly diagnosed clinical stage I/II cutaneous melanoma at our institution. Our goals were to look at our compliance with recommendations, our detection rate of distant metastases, and predictors of preoperative imaging.	Retrospective, cohort study	409 patients in which imaging was performed between first diagnosis and surgery for sentinel node	ORR	Chest x-rays was performed in 70% and advanced imaging in 14% (CT imaging, MRT imaging, ultrasound, and PET imaging). No metastatic lesions were identified. A Breslow thickness greater than 4 mm (ORR = 6.46 vs <1 mm; 95% CI, 2.07 to 20.15) and male sex (ORR = 2.62 vs female; 95% confidence interval, 1.26 to 5.46) were associated with an increased likelihood of	QUADAS: 7x yes	3a

					advanced imaging.		

Marone et al. (2012)	To define the diagnostic accuracy of high-resolution ultrasound (US) in detecting nodal involvement before sentinel lymph node biopsy (SLNB) in patients with cutaneous melanoma To define the sonographic criteria used to assess nodal metastases, and to establish if high-resolution US can directly select patients to radical lymphadenectomy, sparing selective lymphadenectomy.	Retrospective, single center, cohort study	623 patients	Sensitivity Specificity Positive Predictive Values Negative Positive Predictive Values	In 14.7% out of 122 excised lymph nodes, high-resolution ultrasound showed sonographic features consistent with malignant involvement before the surgical step. Ultrasound scan sensitivity and specificity were 15 and 100%, respectively, since positive and negative predictive values were 100 and 87% respectively.	QUADAS: 9x yes	3a
Meyer et al. (2014)	To validate the accuracy and reliability of high-frequency	Prospective cohort study	131 patients with at least one equivocal melanocytic lesion.	Repeatability Inter-reproducibility	Ultrasonography showed a good level of agreement with histology	Funding source: This work was funded by the French	2b

	ultrasonography (HFUS) and optical coherence tomography for assessing melanoma thickness in vivo.		Each lesion underwent optical coherence tomography and high-resolution ultrasound assessment, followed by excision and pathological examination.	Intrarater-reproducibility Reliability	[intraclass correlation coefficient (ICC) 0·807; 95% CI 0·703–0·877] and excellent inter-rater reproducibility (G = 0·97), resulting in reliable *in vivo* assessment of melanoma thickness. The 930-nm optical coherence tomography showed a poor level of agreement with histopathology (ICC 0·0; 95% CI −0·2–0·2) and the inter-rater reproducibility was null (G = 0·00).	Interministry Unified Fund (Fonds Interministeriel Unifi e), the Midi-Pyrenees Region (Region Midi-Pyrenees) and the Pierre Fabre Research Institute (Institut de Recherche Pierre Fabre). QUADAS: 9x yes	

Ogata et al. (2014)	To investigate the diagnostic ability of real-time elastography to differentiate between reactive and metastatic lymph nodes in cutaneous malignant melanoma (CMM) patients To determine the optimum cut-off value for elastography scores (1-5) for diagnosis CMM.	Prospective, single center cohort study	20 lymph nodes (metastatic, n = 13; reactive, n = 7) from 12 patients with melanoma	Sensitivity Specificity Accuracy	Sensitivity, specificity, and accuracy of elastography were 100, 71, and 90 % with an elastography score cut-off value of 3. Sensitivity, specificity, and accuracy of elastography were 92, 100, and 95 % for elastography with an elastography score cut-off value of 4; Sensitivity, specificity, and accuracy were 77, 57, and 70 % for B-mode ultrasound.	Funding source: This work was partly supported by the National Cancer Center Research and Development Fund (23-A-22). QUADAS: 7x yes Small sample size.	3a

Solivetti et al. (2014)	To compare ultrasound with 18-FDG PET-CT and telethermography in the detection of melanoma metastases in a subgroup of patients with advanced stage melanoma eligible for electro-chemotherapy.	Prospective single-centre, open-label study	15 patients with 52 lesions	number of detected lesions	All the 52 lesions were detected by high-frequency ultrasound (100%), 24/52 were detected by PET-CT (42,6%) and 15/52 were detected by TT (27,7%). PET-CT reported 3.7% false positives, while no false positive were reported by telethermography.	QUADAS: 9x yes	2b
CT/MRI							
Jouvet et al. (2014)	To compare the diagnostic performances of non-radiating whole-body magnetic resonance imaging (wbMRI), either volumetric, with	Prospective, single center study	37 patients with AJCC stage IV malignant melanoma	Sensitivity Specificity Intra-observer agreement Inter-observer	The number of visceral or lymph node metastases spotted was 218, with 125 metastases for wbMRI, 191/103 for PET-CT, 209/115 for CT	QUADAS: 9x yes	2b

	Volumetric interpolated breath-hold examination (VIBE) or metabolic, with diffusion-weighted sequences (wbMRI), with classical irradiating techniques such as PET-CT, CT and with lymph node ultrasonography (US) for the staging of advanced melanoma.			agreement	and 33/13 for lymph node ultrasound. No statistically significant difference (P<0.05) of overall diagnostic performances between wbMRI (Se 84%, Sp 87.1%, PPV 89.8%, NPV 80.2%) and PET-CT (Se 79.8%, Sp 93.1%, PPV 93.2%, NPV 79.4%) was observed. No statistically significant difference was found between wbMRI and PET-CT with two channels for CT with respect to different metastatic sites. Compared with the CT, wbMRI had significantly better overall specificity (P=0.0011) and		

					PPV (P=0.02). For lung exploration, sensitivity of wbMRI (51.6%) was inferior to CT (71.4%). To detect superficial metastatic lymph nodes, wbMRI and ultrasound both showed high diagnostic accuracy with no statistically significant difference. Intra-observer agreement was almost perfect for all imaging modalities considering the overall staging. Inter-observer agreement for wbMRI and diffusion alone was almost perfect		

					except for bone and lymphatic sites. Overall diagnostic performance of diffusion alone was significantly inferior to those of combined VIBE and diffusion sequences.		
Mosavi et al. (2013)	To assess the value of whole-body-MRI including diffusion-weighted imaging (DWI) compared to computed tomography for staging of malignant melanoma. To assess the value of diffusion-weighted imaging in addition to conventional MR	Prospective, single center study	23 patients with histologically confirmed malignant melanoma.	Detection rate Sensitivity	WB MRI and WB DWI detected 345 and 302 lesions, compared to 397 lesions with CT. The sensitivity of WB MRI and WB DWI varied considerably in different regions of the body. In the lungs, WB MRI and WB DWI showed 63% and 47% true-positive lesions. WB MRI and WB	Funding source: The study has been supported by the Research Foundation Stiftelsen Onkologiska Kliniken in Uppsala For-skningsfond, and by grants to Professor H. Ahlström from the Swedish Cancer Society, Uppsala University and	2b

	sequences for the detection of lesions.				DWI detected 56 bone lesions in 12 patients compared to 42 lesions in 8 patients with CT. WB MRI and WB DWI could detect 68 lesions outside the field of view of CT in six patients.	Hospital (ALF). Stage of disease of the melanoma patients not provided, probably mainly metastatic (Stage IV)	
Orfaniotis et al. (2012)	To investigate regional CT findings in patients diagnosed with AJCC IIB and IIC disease and establish whether the findings affirmed new UK guidelines.	Retrospective review of patient notes	172 patients of which 130 underwent CT scans (269 scans)	Metastasis detection rate	One hundred and four initial staging CT scans were performed on 75 patients and detected one (1.3%) occult melanoma metastasis. At follow-up, 165 scans were performed in 82 patients and detected 56 metastasis in 32(39%) patients leading to a	QUADAS: 9x yes	3a

					change in management in 29 (35%). Two of these 32 patients had occult melanoma metastasis. Symptomatic patients had statistically significant more metastatic disease diagnosed at follow-up CT scanning than asymptomatic patients p < .0001. Head CT detected 15/56 (27%) of all metastasis.		
Petralia et al. (2013)	To investigate whether whole-body diffusion-weighted imaging (WB-DWI) alone is adequate for detecting	Prospective, single center study	19 patients with advanced melanoma	Diagnostic accuracy / agreement	With almost perfect agreement between techniques (κ=85%, 95% CI 70–100%) for detection of examinations with	Funding source: Guarniflon S.p.A. for the financial support of Dr. Alessi. Funding sources had no	3a

	metastases in melanoma patients, or if standard WB contrast-enhanced magnetic resonance imaging (WB-ceMRI) is required.				metastatic findings, and complete agreement in extracranial metastasis detection, 10 metastases were detected using WB-DWI and 13 using WB-DWI + WB-ceMRI. WB-DWI and WB-DWI + WB-MRI had equivalent per patient DA (79%).	influence in acquisition, analysis, or interpretation of the data. Small sample size leading to large 95% CIs	
Podlipnik et al. (2016)	To analyse the performance of the follow-up components and identify procedures that detect melanoma metastasis earlier	Prospective cohort study	290 patients (Stage IIB, IIC, and III) which were followed up with an intensive protocol based on imaging studies (computed tomography of the chest, abdomen, and pelvis, and brain magnetic resonance imaging), periodic	Number of recurrences Method of detection of metastases	17.8% of recurrences were detected by the patient, 23.7% by the physician, and 56.7% by imaging tests.	QUADAS: 6x yes	2b

			laboratory tests, regular physical examinations, and patient self-examinations.				
Sofue et al. (2012)	To evaluate the magnetic resonance (MR) imaging feature of suspected hepatic metastasis in patients with malignant melanoma which showed intermediate findings on screened contrast-enhanced computed tomography (CECT).	Retrospective, single center study	38 patients	Sensitivity Specificity Accuracy Positive predictive value Negative predictive value	The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) to detect hepatic metastasis using MRI were 100%, 86.7%, 94.7%, 92.0%, and 100%, respectively.	Funding source: This work was supported in part by grants from Scientific Research Expenses for Health and Welfare Programs and the Grant- in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare. QUADAS: 10x	3b

						yes	
Zukauskaite et al. (2013)	To examine the frequency of asymptomatic brain metastases, detected by contrast-enhanced CT scans in the patient population admitted for IL-2-based treatment for metastatic melanoma.	Retrospective, single center study	697 patients screened before the start of IL-2-based immunotherapy.	Rate of asymptomatic brain metastasis	697 patients, 80 had asymptomatic brain metastases (12%)	QUADAS: 11x yes	3b
PET							
Bastiaannet et al. (2012)	To assess predictive value of fludeoxyglucose–positron emission tomography (FDG-PET) and computed tomography (CT) and to analyze their cost-effectiveness in several diagnosis–	Prospective, single center study	253 patients with melanoma with palpable, proven lymph node metastases	Sensitivity Specificity Positive predictive value (PPV) Negative predictive value (NPV)	FDG-PET showed a higher sensitivity than CT: 86.1% compared with 78.2%. Specificity was higher for CT (93.7%) compared with FDG-PET (93.1%). Overall, FDG-PET	funding source: none QUADAS: 9x yes	2b

	treatment combinations.				showed a higher PPV and NPV.		
McIvor et al. (2014)	To determine the clinical utility of FDG PET in this patient group.	Retrospective, single center study	322 melanoma patients AJCC stage I/II	Frequency of detected metastases Positive Predictive Value	322 patients were included in the study, of which 74 had initial positive FDG PET scans (23%). Adequate follow-up was available in 51 patients with the PET result confirmed as true positive in 37 (positive predictive value 73%). 108/248 patients initially negative had follow-up scans during the follow-up period, of which 48 became positive. The 73% of recurrences were over 12 months	QUADAS: 5x yes	3a

					post-diagnosis. No correlation with Breslow thickness was demonstrated.		
MRI							
Gramsch et al. (2013)	To find out how often isolated cerebral susceptibility artefacts in patients with malignant melanoma truly develop into metastases satisfying the criteria of contrast	Retrospective, single center study	408 patients with malignant melanoma but without cerebral metastases in the initial staging by MRI were reviewed 18 patients with malignant melanoma and signal intensity loss on T2*/SWI	Rate of hypointense lesions on T2*/SWI developing into metastases	None of these lesions developed into metastasis. Focal areas of susceptibility artefacts in the brain parenchyma without corresponding abnormalities in contrast-enhanced	QUADAS: 6x yes	3a

	enhancement and signal alteration on unenhanced T1- and T2-weighted images and FLAIR sequences. To examine the imaging characteristics of contrast-enhancing melanoma metastases on T2* and SWI sequences.		were included.		T1 weighted images are unlikely to represent brain metastases.		
PET/CT							
Gellén et al. (2015)	To investigate the diagnostic accuracy of PET/CT in early- and late-stage patients with high-risk cutaneous malignant melanoma.	Retrospective, single center study	97 patients in 3 groups: Stage I/II, resected stage III and unresectable stage III/stage IV.	Diagnostic accuracy	High diagnostic accuracy in all stages (91.3%, 92.5% and 96.2%). PET/CT was informative in 14 of 19 cases wherein another imaging	Funding source: Supported by the European Social Fund TA MOP-4.2.2.A-11/1/KONV-2012-0031, Hungarian Scientific	3a

					examination provided inconclusive results regarding lesion dignity. PET/CT was less suitable for properly evaluating the dignity of a lung lesion. A true positive scan was twice as likely in clinically negative patients with resected stage III disease than in patients with stage I/II disease (35.9% and 14.5%, P=0.007)	Research Fund OTKA NK101680 and OTKA K105872. QUADAS:11 x yes	
Schüle et al. (2016)	To evaluate the influence of 18F-FDG PET/CT in comparison to CT alone on treatment decisions in	Retrospective, single center study	64 consecutive patients with stage III/IV melanoma	Sensitivity Specificity	Of the 297 metastatic lesions according to the reference standard, 229 were detected on	QUADAS: 11x yes	3a

	patients with advanced melanoma To analyze the 5-year survival data in comparison to literature data.				CT as true-positive lesions (sensitivity 77.1 %, specificity 69.9 %), and 269 were detected on FDG PET/CT (sensitivity 90.6 %, specificity 77.2 %).		
Singnurkar et al. (2016)	To assess the impact of PET on staging and management of patients with high-risk or advanced melanoma.	Prospectively collected data of a PET-Registry	319 consecutive patients with potentially resectable localized high-risk melanoma	Change in stage of disease Change in therapeutic procedures after knowledge of PET findings	Significant increase in stage to M1 status after PET in 56 of 319 patients (17.6%) (P<0.0001). No significant relationship between upstaging with PET and the proportion of patients receiving radiation therapy (P=0.066) or systemic therapy (P=0.072). Significant relationship between upstaging	QUADAS: 7x yes	2b

					with PET and the proportion of patients undergoing surgical resection of metastases distant to the primary melanoma site (P=0.034).		
Scintigraphy							
Cachin et al. (2014)	To report the results of a phase III clinical trial comparing ^{123}I-BZA2 with ^{18}F-FDG PET efficacy for staging or restaging cutaneous or ocular melanoma.	Prospective, phase III trial	87 of the 186 patients were included because of premature study closure. Of the 87 patients, 75 (86.2%) underwent ^{18}F-FDG PET, 69 (79.3%) ^{123}I-BZA2 scintigraphy, and 69 (79.3%) both	Sensitivity Specificity	Sensitivity of ^{18}F-FDG for diagnosis of melanoma metastases was higher than that of ^{123}I-BZA2, at 87% and 39%, respectively (P=0.05). For specificity, ^{18}F-FDG and ^{123}I-BZA2 were not statistically different, at 78% and 94%.	Funding source: The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC	1b

						section 1734. This clinical trial was financially supported by the French National Cancer Institute and the French Dermatology Society. Cyclopharma Laboratory provided 18F-FDG and 123I-BZA2 radiopharmaceuticals. No other potential conflict of interest relevant to this article was reported. QUADAS: 9x yes	
Tumor markers							

Damude et al. (2016)	To investigate if the biomarkers S-100B and Lactate Dehydrogenase (LDH) are associated with non-sentinel nodes (NSN) positivity. To identify patients in whom complete lymph node dissection (CLND) could safely be omitted.	Retrospective, single center study	107 patients	Association with Non-sentinel nodes positivity	NSN positivity was found in 20.6% of the 107 patients undergoing CLND. Univariate analysis revealed S-100B value (p = 0.01) to be associated with NSN positivity. LDH level was not significantly associated with positive NSNs (p = 0.39). In multivariable analysis, S-100B showed to have the strongest association with NSN positivity, within its reference interval of 0.20 µg/l (p=0.02, odds ratio 5.71, 95% CI 1.37-23.87).	QUADAS: 9x yes	3a

Egberts et al. (2012)	To assess the prognostic value of YKL-40 in stage IV melanoma patients regarding treatment outcome and survival compared to the established markers LDH and serum S-100B and to evaluate their ability to discriminate between different stages of the disease.	Prospectively collected data of a single center study	50 patients with stage I/II melanoma and 61 patients with metastatic melanoma	Prognostic value regarding response	In stage IV melanoma patients, only the baseline serum levels of S-100B were significantly associated with treatment response (p=0.031), but not those of LDH (p=0.193) or YKL-40 (p = 0.186). Strong correlation between treatment response and unchanged or declining S-100B levels over time (p=0.003, OR: 9.52, 95%-CI: 1.87–47.62), but no significant correlation between treatment response and serum changes for LDH (p=0.534) and YKL-40 (p=0.306).	Funding source: 'Hiege Foundation against Skin Cancer', Hamburg, Germany. The sponsor was not involved in the study designs, collection, analysis and interpretation of data or in the writing of the manuscript. QUADAS: 9x yes	2a

Henry et al. (2013)	To compare the diagnostic and prognostic values of p-proteasome S100B protein, melanoma inhibitory activity protein (MIA) and lactate dehydrogenase (LDH) in the plasma of melanoma patients.	Prospectively collected data of a single center study	121 patients with malignant melanoma, classified according to the 2001 AJCC stages, 40 healthy as control group	Sensitivity Specificity	p-proteasome and S100B were the most sensitive (58.1% both) and p-proteasome and MIA the most specific (98.7 and 100%) in detecting metastatic disease.	Funding source: Societe Française de Dermatologie and the Ministére de la Sante (Programme Hospitalier de Recherche Clinique), The Ligue contre le Cancer (Comite du Gard) QUADAS: 10x yes	2a
Weide et al. (2012)	To clarify the prognostic impact of the serum markers LDH and S100B, adjusting for all potential and established prognostic factors like the number of distant sites and the organ	Retrospective, single center study	855 melanoma patients with distant disease	Overall survival	Serum lactate dehydrogenases (LDH), S100B, the interval between initial diagnosis and occurrence of distant metastasis, the site of distant metastases, and the number of involved distant sites were	Funding source: This work was supported by Deutsche Forschungsge-meinschaft grant SFB685. QUADAS: 7x yes	3a

	involvement. To examine the impact of complete metastasectomy and its interaction with the other significant prognostic factors.				significant independent prognostic factors in both bivariate and multivariate analyses. Visceral metastases other than lung (hazard ratio (HR) 1.8), elevated S100B (HR 1.7) and elevated LDH (HR 1.6) had the highest negative impact on survival. Complete metastasectomy was likewise an independent prognostic factor in multivariate analysis. This treatment was associated with favourable survival for patients with normal LDH and S100B values (5-year survival,		

					37.2%).		
Weide et al. (2013)	To analyse the impact of S100B, lactate dehydrogenase (LDH) and the type of treatment on survival in advanced patients receiving systemic treatment.	Retrospective, single center study	499 patients with unresectable melanoma at the time point of initiation of first-line systemic therapy.	Overall survival	IIn multivariate analysis LDH (Hazard ratio [HR] 1.6 [1.3-2.1]; p<0.001), S100B (HR 1.6 [1.2-2.1]; p<0.001) and the presence of brain metastases (HR 1.5 [1.1-1.9]; p=0.009), but not the type of treatment had significant independent impact.	QUADAS: 6x yes	3a
Wevers et al. (2013)	To assess and compare the prognostic impact of biomarkers S-100B and LDH and to determine the best timing of their measurement in stage IIIB–C	Retrospective, single center study	119 patients	Disease free survival Disease specific survival (DSS)	S-100B levels at all time points were associated with DFS. LDH measurements showed a significant association with	QUADAS: 8x yes	3a

	melanoma.				DSS in univariate analysis only when measured preoperatively		

2.3.4.4.1. Literatur

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Chai et al. (2012)		x		
Gonzalez-Alvarez et al. (2015)		x		
Haddad et al. (2013)	X	X		
Marone et al (2012)		X		
Meyer et al (2014)		X		
Ogata et al (2014)		x		
Solivetti et al (2014)		X	X	
Jouvet et al (2014)			X	X
Mosavi et al. (2013)				X

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Orfaniotis et al. (2012)				X
Petralia et al. (2013)			X	X
Podlipnik et al. (2016)				X
Sofue et al. (2012)			X	
Zukauskaite et al. (2013)				X
Bastiaannet et al. (2012)		X		
McIvor et al. (2014)				X
Gramsch et al. (2013)				X
Gellén et al. (2015)				X
Schüle et al. (2016)				X
Singnurkar et al. (2016)			X	
Cachin et al. (2014)				X
Damude et al. (2016)		X		
Egberts et al. (2012)				X

Literatur :	Zuteilung zu Fragestellung:			
	I.6	I.7	I.8	VII.6
Henry et al. (2013)	X			X
Weide et al. (2012)			X	X
Weide et al. (2013)			X	X
Wevers et al. (2013)		X		X

Chai, C.Y., et al., Preoperative ultrasound is not useful for identifying nodal metastasis in melanoma patients undergoing sentinel node biopsy: preoperative ultrasound in clinically node-negative melanoma. Ann Surg Oncol, 2012. 19(4): p. 1100-6.
Gonzalez-Alvarez, T., et al., Dermoscopy structures as predictors of sentinel lymph node positivity in cutaneous melanoma. Br J Dermatol, 2015. 172(5): p. 1269-77.
Haddad, D., et al., Preoperative imaging for early-stage cutaneous melanoma: predictors, usage, and utility at a single institution. Am J Surg, 2013. 206(6): p. 979-85; discussion 985-6.
Marone, U., et al., Can high-resolution ultrasound avoid the sentinel lymph-node biopsy procedure in the staging process of patients with stage I-II cutaneous melanoma? Ultraschall Med, 2012. 33(7): p. E179-85.
Meyer, N., et al., High-frequency ultrasonography but not 930-nm optical coherence tomography reliably evaluates melanoma thickness in vivo: a prospective validation study. Br J Dermatol, 2014. 171(4): p. 799-805.
Ogata, D., et al., Accuracy of real-time ultrasound elastography in the differential diagnosis of lymph nodes in cutaneous malignant melanoma (CMM): a pilot study. Int J Clin Oncol, 2014. 19(4): p. 716-21.
Solivetti, F.M., et al., HF ultrasound vs PET-CT and telethermography in the diagnosis of In-transit metastases from melanoma: a prospective study and review of the literature. J Exp Clin Cancer Res, 2014. 33: p. 96.
Jouvet, J.C., et al., Whole-body MRI with diffusion-weighted sequences compared with 18 FDG PET-CT, CT and superficial lymph node ultrasonography in the staging of advanced cutaneous melanoma: a prospective study. J Eur Acad Dermatol Venereol, 2014. 28(2): p. 176-85.
Mosavi, F., G. Ullenhag, and H. Ahlstrom, Whole-body MRI including diffusion-weighted imaging compared to CT for staging of malignant melanoma. Ups J Med Sci, 2013. 118(2): p. 91-7.
Orfaniotis, G., et al., Findings of computed tomography in stage IIB and IIC melanoma: a six-year retrospective study in the South-East of Scotland. J Plast Reconstr Aesthet Surg, 2012. 65(9): p. 1216-9.
Petralia, G., et al., Whole-body diffusion-weighted imaging: is it all we need for detecting metastases in melanoma patients? Eur Radiol, 2013. 23(12): p. 3466-76.
Podlipnik, S., et al., Performance of diagnostic tests in an intensive follow-up protocol for patients with American Joint Committee on Cancer (AJCC) stage IIB, IIC, and III localized primary melanoma: A prospective cohort study. J Am Acad Dermatol, 2016. 75(3): p. 516-524.
Sofue, K., et al., MR imaging of hepatic metastasis in patients with malignant melanoma: evaluation of suspected lesions screened at contrast-enhanced CT. Eur J Radiol, 2012. 81(4): p. 714-8.
Zukauskaite, R., et al., Asymptomatic brain metastases in patients with cutaneous metastatic malignant melanoma. Melanoma Res, 2013. 23(1): p. 21-6.
Bastiaannet, E., et al., Cost-effectiveness of adding FDG-PET or CT to the diagnostic work-up of patients with stage III melanoma. Ann Surg, 2012. 255(4): p. 771-6.
McIvor, J., et al., FDG PET in early stage cutaneous malignant melanoma. J Med Imaging Radiat Oncol, 2014. 58(2): p. 149-54; quiz 266.
Gramsch, C., et al., Isolated cerebral susceptibility artefacts in patients with malignant melanoma: metastasis or not? Eur Radiol, 2013. 23(9): p. 2622-7.
Gellen, E., et al., Diagnostic accuracy of (18)F-FDG-PET/CT in early and late stages of high-risk cutaneous malignant melanoma. J Eur Acad Dermatol Venereol, 2015. 29(10): p. 1938-44.
Schule, S.C., et al., Influence of (18)F-FDG PET/CT on therapy management in patients with stage III/IV malignant melanoma. Eur J Nucl Med Mol Imaging, 2016. 43(3): p. 482-8.
Cachin, F., et al., (123)I-BZA2 as a melanin-targeted radiotracer for the identification of melanoma metastases: results and perspectives of a multicenter phase III clinical trial. J Nucl Med, 2014. 55(1): p. 15-22.
Damude, S., et al., The predictive power of serum S-100B for non-sentinel node positivity in melanoma patients. Eur J Surg Oncol, 2016. 42(4): p. 545-51.

Egberts, F., et al., Comparative study of YKL-40, S-100B and LDH as monitoring tools for Stage IV melanoma. Eur J Cancer, 2012. 48(5): p. 695-702.
Henry, L., et al., Clinical use of p-proteasome in discriminating metastatic melanoma patients: comparative study with LDH, MIA and S100B protein. Int J Cancer, 2013. 133(1): p. 142-8.
Weide, B., et al., Serum markers lactate dehydrogenase and S100B predict independently disease outcome in melanoma patients with distant metastasis. Br J Cancer, 2012. 107(3): p. 422-8.
Weide, B., et al., Serum S100B, lactate dehydrogenase and brain metastasis are prognostic factors in patients with distant melanoma metastasis and systemic therapy. PLoS One, 2013. 8(11): p. e81624.
Wevers, K.P., et al., S-100B: a stronger prognostic biomarker than LDH in stage IIIB-C melanoma. Ann Surg Oncol, 2013. 20(8): p. 2772-9.

2.3.5. Frage I.9. Ausbreitungsdiagnostik beim metastasierten okkulten Melanom - Adaptation

Frage I.9. Welche Untersuchungen sind beim metastasierten okkulten Melanom zur Primärtumorsuche und Ausbreitungsdiagnostik indiziert?

Die Frage wurde letztendlich Konsens-basiert beantwortet.

2.3.5.1. Synopse Quellleitlinien (kurz)

Thema/Fragestellung	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
14. Welche Untersuchungen sind bei metastasiertem okkultem Melanom zur Primärtumorsuche und Ausbreitungsdiagnostik indiziert?	Klinische Untersuchung: Augen, Gehörgang, Kopfhaut, evtl. Koloskopie (IV); PET zur weiteren Ausbreitungsdiagnostik (IV)	Keine Angaben	Keine Angabe	nur relevant für medikamentöse Therapien

2.3.5.2. Empfehlung, Hintergrundstext und Literatur Australische Quell-Leitlinie

(mit Seitenangaben der Quellleitlinie)

	LL Australien New Zealand Guidelines Group 2008
Schlüsselempfehlungen	Recommendation Patients with metastases and no obvious primary tumour be examined for primary melanomas in obscure sites. If none are found, assume that the primary melanoma has completely regressed. Recommendation grade: D

	LL Australien **New Zealand Guidelines Group 2008**
Evidenzgrundlage	Evidence summary Patients with occult primary melanoma usually present with lymph node disease, a soft tissue metastasis, or widespread systemic disease, in the absence of a primary tumour and the diagnosis is made by pathological examination of the lymph node, or metastasis which shows the characteristics of melanoma. Such patients should be examined carefully to exclude the possibility of a hidden primary by examination of the eyes, inner ears and scalp, and possibly colonoscopy. The presenting lymph nodes or metastases should be treated appropriately regardless of the inability to detect the primary tumour and a PET scan should be performed Level IV , Referenz 1, 2
Hintergrundtext	Melanoma is among a number of cancers in humans where the primary tumour cannot always be found. In some patients the primary may be in an obscure site such as the eye, ear or the intestine, but in the majority it is likely that the primary tumour has been destroyed by the host's immune system via lymphocyte activation.1,2 It is likely that total regression occurs in 10–20% of melanomas, though only those where there have been metastases are diagnosable (about 5% of melanomas). Partial regression of primary tumours is more common and is often reported on pathology reports (30–50%). Two recent studies have shown that those patients with metastases and an occult primary melanoma have a better prognosis than those with metastases and a known primary melanoma.3,4 This suggests an intrinsically superior host tumour interaction in those with occult primary melanoma.
Referenzen	1. Tefany FJ, Barnetson RS, Halliday GM, McCarthy SW, McCarthy WH. Immunocytochemical analysis of the cellular infiltrate in primary regressing and non-regressing malignant melanoma. J Invest Dermatol 1991; 97(2):197–202. 2. Lowes MA, Bishop GA, Crotty K, Barnetson RS, Halliday GM. T helper 1 cytokine mRNA is increased in spontaneously regressing primary melanomas. J Invest Dermatol 1997; 108(6):914–919. 3. Vijuk G, Coates AS. Survival of patients with visceral metastatic melanoma from an occult primary lesion: a retrospective matched cohort study. Ann Oncol 1998; 9(4):419–422.

	LL Australien New Zealand Guidelines Group 2008
	4. Lee CC, Faries MB, Wanek LA, Morton DL. Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. J Clin Oncol 2008; 26(4):535–541.

Literatur :
1. Lee CC, Faries MB, Wanek LA, et al. Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. J Clin Oncol 2008;26:535-541
2. Lowes MA, Bishop GA, Crotty K, et al. T helper 1 cytokine mRNA is increased in spontaneously regressing primary melanomas. J Invest Dermatol 1997;108:914-919
3. Tefany FJ, Barnetson RS, Halliday GM, et al. Immunocytochemical analysis of the cellular infiltrate in primary regressing and non-regressing malignant melanoma. J Invest Dermatol 1991;97:197-202
4. Vijuk G, Coates AS. Survival of patients with visceral metastatic melanoma from an occult primary lesion: a retrospective matched cohort study. Ann Oncol 1998;9:419-422

2.3.5.3. Ergänzende Recherche, Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("occult melanoma"[tiab] or “melanoma” AND “unknown primary” [tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR ("lymph nodes"[all fields] OR ("lymph"[all fields] AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymph node"[all fields]))	26.01.2012	9
	("occult melanoma"[tiab] or “melanoma” AND “unknown primary” [tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR ("lymph nodes"[all fields] OR ("lymph"[all fields] AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymph node"[all fields]))		9
	("occult melanoma"[tiab] or “melanoma” AND “unknown primary” [tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) AND ("chest X-ray"[all fields] OR "chest radiography"[all fields] OR "Radiography, Thoracic"[Mesh])		0

Datenbank	Suchstrategie	Datum	Treffer
	("occult melanoma"[tiab] or “melanoma” AND “unknown primary” [tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR "abdomen"[all fields] OR “abdominal"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		0
	("occult melanoma"[tiab] or “melanoma” AND “unknown primary” [tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) AND ("Magnetic Resonance Imaging"[Mesh] OR “Magnetic Resonance Imaging”[all fields] OR “mri”[all fields] OR “magnetic resonance”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		3
	("occult melanoma"[tiab] or “melanoma” AND “unknown primary” [tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (“Tomography, X-Ray Computed"[Mesh] OR “computer tomography”[all fields] OR “ct”[all fields] OR "Tomography, Spiral Computed"[Mesh] OR "Tomography Scanners, X-Ray Computed"[Mesh] OR "Positron-Emission Tomography"[Mesh] OR “positron-emission tomography”[all fields] OR “pet”[all fields] OR "Tomography, Emission-Computed, Single-Photon"[Mesh] OR “single-photon emission computed tomography”[all fields] OR “spect”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		8
	("occult melanoma"[tiab] or “melanoma” AND “unknown primary” [tiab]) AND (“staging”[tiab] OR "diagnosis"[tiab]) AND ("scintigraphy”[tiab] OR “scinti*”[tiab]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		0
	("occult melanoma"[tiab] or “melanoma” AND “unknown primary” [tiab]) AND ("LDH"[all fields] OR “lactate dehydrogenase” OR "S100"[all fields] OR "MIA"[tiab] OR "melanoma-inhibiting activity"[tiab]) AND (“staging”[all fields] OR "diagnosis"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])		3

Auswahl der Literatur	
Gesamttreffer	25
Gesamttreffer nach Dublettenelimination	
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research
Anzahl nach Abstractscreening	1
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	1
Bemerkungen: Eine Ergänzungsrecherche für den Zeitraum nach 2008 wurde am 26.10.2011 auf Medline durchgeführt, die Update-Recherche erfolgte am 26.01.2012. Oben aufgeführt sind die Trefferzahlen der letzten Recherche. Hierbei wurde eine weitere relevante Studie identifiziert.	

2.3.5.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Tos T et al. (2011): Extensive Screening for Primary Tumor is Redundant in Melanoma of Unknown Primary	this article questions whether extensive physical examinations (opthalmoscopy, otoscopy, rhino-pharygoscopy, laryngoscopy, sigmoideoscopy, and in women,	retrospective study	103 patients diagnosed with unknown primary tumor during the period 1986–2006	Metastases detection rate	39 (38%) presented primarily with a cutaneous or a subcutaneous Metastasis, 63 (61%) with a lymph node metastasis. 1 patient presented with a bone metastasis (1%). 87		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	gynecological examination) are necessary.				patients (84%) were examined by an ophthalmologist. A choroidal melanoma was suspected as the primary tumor in 1 patient. 84 patients (82%) were examined by an oto-rhino-laryngologist, whereby no primary tumor was found. 95 patients (92%) were examined by sigmoideoscopy/ rectoscopy. No primary tumor was found. Of the 36 women, 32 had a gynecological examination (89%), revealing no primary tumor.		

2.3.5.5. Literatur:

Tos T, Klyver H, Drzewiecki KT. Extensive screening for primary tumor is redundant in melanoma of unknown primary. J Surg Oncol 2011;104:724-727

3. AG Sentinel Node Biopsie

3.1. Frage II.1. Sentinel-Node-Biopsie – De-novo-Recherche

Frage II.1. In welchen Fällen ist die Sentinel-Biopsie indiziert?

3.1.1. PICO, Suchwörter

PICO-Unterfragen:

- Senkt die Durchführung einer Sentinel-Biopsie die Rezidzivrate
- Senkt die Durchführung einer Sentinel-Biopsie die Mortalität
- Wie ist die Sensitivität und Spezifität einer Sentinel-Biopsie zum Nachweis einer lokoregionären Lymphknotenmetastasierung?

Suchwörter: s. hierfür auch Suchstrategie			
Ober-/Unterbegriffe, Mesh Term	melanoma	survival, mortality, relapse, recurrence, sensitivity, specificity, accuracy, outcome, prognos*, predict*, assoc*	s. Suchstrategie

3.1.2. Datenbanken, Suchstrategien, Trefferzahlen

3.1.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	“melanoma“[tiab] AND (“sentinel“[tiab] OR “Sentinel Lymph Node Biopsy”[MeSH])	26.01.2012	1039

Datenbank	Suchstrategie	Datum	Treffer
	AND (“survival”[tiab] OR “mortality”[tiab] OR “relapse”[tiab] OR “recurrence”[tiab] OR “sensitivity”[tiab] OR “specificity”[tiab] OR “accuracy” OR “outcome”[tiab] OR “prognos*”[tiab] OR “predict*”[tiab] OR “assoc*”[tiab])		
Cochrane Library	(melanoma and (sentinel or "sentinel lymph node biopsy" or snb or slne or sln) and (survival or mortality or relapse or recurrence or sensitivity or specificity or accuracy or outcome or predict* or prognosis or assoc*)).ti,ab.	26.01.2012	43
Embase	(melanoma and (sentinel or "sentinel lymph node biopsy" or snb or slne or sln) and (survival or mortality or relapse or recurrence or sensitivity or specificity or accuracy or outcome or predict* or prognosis or assoc*)).ti,ab.	23.01.2012	1751
2. Suche/Ergänzungen			
Medline	(sentinel[title] OR "snb"[title] OR "slne"[title] OR "sln"[title]) predict* melanoma[title]	26.01.2012	1176

Bemerkungen:
Eine erste Literaturrecherche in Medline und und Cochrane erfolgte am 07.10.2010 bzw. für Embase am 11.05.2011. Die zweite Recherche (Ergänzungsrecherche) wurde am 18.04.2011 durchgeführt. Die Update-Recherche wurde am 23.01.2012 für Embase bzw. am 26.01.2012 für Medline und am 19.01.2012 für Cochrane durchgeführt. In der Tabelle angegeben sind die Trefferzahlen der letzten Recherche.

Die Beantwortung der Frage stützt sich in erster Linie auf die Meta-Analysen. Weitere Studien wurden hinzugezogen, wenn sie Aspekte abdecken, die in der Meta-Analyse nicht berücksichtigt wurden bzw. die nach der letzten Meta-Analyse veröffentlicht wurden. Im Rahmen der Update-Recherche wurde, neben einzelnen Studien, weitere Systematische Reviews bzw. Meta-Analyse identifiziert. Einzelne relevante Studien wurden mit aufgenommen, da nur spezielle Melanompopulationen in der Metaanalyse bzw. im Review eingeschlossen wurden (Patienten mit Melanomen >4mm bzw. SNB im Kopf/Hals-Bereich)

3.1.2.2. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			

Medline	“melanoma“ [tiab] AND (“sentinel“[tiab] OR “Sentinel Lymph Node Biopsy”[MeSH]) AND (“survival”[tiab] OR “mortality”[tiab] OR “relapse”[tiab] OR “recurrence”[tiab] OR “sensitivity”[tiab] OR “specificity”[tiab] OR “accuracy” OR “outcome”[tiab] OR “prognos*”[tiab] OR “predict*”[tiab] OR “assoc*”[tiab])	12.09.2016	500

3.1.3. Auswahlkriterien

3.1.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	2970
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews
Anzahl nach Abstractscreening	77
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	48

3.1.3.2. Aktualisierungsrecherche 2016

Auswahl der Literatur	
Gesamttreffer	500
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews

Anzahl nach Abstractscreening	75
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	28

3.1.4. Evidenztabelle

3.1.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Valsecchi et al. (2011)	To perform a meta-analysis of all published studies of sentinel lymph node (SLN) biopsy for staging patients with melanoma.	Systematic review with meta-analysis	Melanoma patients; 53.4% male, median age 54 years	Proportion of successfully mapped (PSM) False-negative rate (FNR), post-test probability negative (PTPN) and positive predictive value (PVP) in the same nodal basin recurrence and for distant/all recurrences	Weighted PSM: 98.1% (improved in more recent studies and in articles with better quality scores) Distribution of FNR among studies ranged from 0.0% to 34%, weighted summary estimate 12.5% PTPN for same nodal basin recurrence ranged from 0.0% to 10.4%, summary estimate across studies 3.4% Weighted summary	Very large number of patients (25240). No significant differences in results were seen when data from three large clinical trials or from certain geographic regions were excluded, or in other subgroup analyses. No statement possible about proportion of patients with positive SNB experiencing subsequent nodal	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					estimate of PVP for nodal recurrence 7.5% Weighted estimate for FNR for distant recurrence 17.4%, for total recurrences 29.9% Weighted estimate for PTPN for distant recurrence 4.4%, for total recurrence 10.5% Probability of additional nodal involvement in CLND for patients with positive SNB: 20.1% PVP for distant and any recurrence 21.0% and 35.9%	recurrence despite CLND.	
Warycha et al. (2009)	To estimate the risk, potential predictors, and outcome of SLN positivity in	Systematic review with meta-analysis	Patients with thin (≤1 mm) primary melanoma Total number of	SLN positivity rate Heterogeneity Melanoma-related	Pooled SLN positivity rate 5.6% Significant heterogeneity	Unclear source of heterogeneity in this meta-analysis (may hint to unknown	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with thin melanomas.		patients: 3651	deaths	among studies; remained significant in subgroups of studies with high vs. low quality scores, indicating other covariates or patient selection criteria that are responsible for heterogeneity No statistical evidence of publication bias 4 melanoma-related deaths were reported	prognostic factors in patients with thin melanoma which need further investigation) Ulceration and Clark level > III have been correlated with a worse prognosis in patients with thin melanoma, but might not be associated with positive SLN	
Kunte et al. (2010)	To assess which factors predict the occurrence of micrometastasis and overall prognosis and whether SLNB should also be performed in patients with thin primary tumors.	Prognostic study	854 patients with malignant melanoma (56.8% male, 43.2% female), mean age 52.9 years	SLN status Disease-free survival (DFS) Overall survival (OS)	Rate of positive SLNs: 24.9% Probability of finding a positive SLN 5.7% in patients with tumor thickness ≤ 0.75 mm, 57.3% in patients with tumor thickness >	Prospective design For detailed p values according to tumor thickness etc. see original file. Prospective design and large patient numbers	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					4 mm SLN positive in 36.8% of patients with nodular melanoma (NM), 27.1% of patients with secondary nodular superficial spreading melanoma, 26.1% in acral lentiginous melanoma, 13.4% in superficial spreading melanoma, 8.8% Spitzoid melanoma and 38.3% of ulcerated melanomas In multivariate analysis, tumor thickness and histological tumor type significantly associated with SLN status Melanoma with tumor > 4 mm revealed 11.68-	Patients lost to follow-up not described for key characteristics (potential source of selection/attrition bias)	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					fold risk for a positive SLN in comparison with tumors < 1 mm 9.8% (63/641) of SLN negative patients had a recurrence of the disease, 8.4% (54/641) died of the disease (5-year survival rate: 90.1%, mean DFS 117.9 months, OS 119.8 months) Of SLN positive patients, 39.4% had a recurrence, 28.6% died of the disease (mean DFS 80.75 months, OS 94.91 months, 5-year survival rate: 58.1%		
Mays et al. (2010)	To evaluate prognostic factors in the subset of patients with a melanoma Breslow	Prognostic study	1110 patients with cutaneous melanoma between 1 mm and 2 mm in thickness	Rate of positive and negative SLNs Overall survival	Group A: melanoma from 1 mm to 1.59 mm in thickness	Post-hoc analysis of the multi-center, randomized Sunbelt Melanoma Trial	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	thickness between 1 and 2 mm and to determine whether all such patients require SLN biopsy.			Disease-free survival	Group B: melanoma from 1.60 mm to 2.0 mm in thickness (n = 348) On multivariate analysis, Breslow thickness, age and lymphovascular invasion were predictive of positive SLN	See full text (p. 1539) for complete partition tree	
Testori et al. (2009)	To investigate the relationship between primary tumor characteristics, SLN findings, and the clinical outcome	Observational study	1313 consecutive patients	Overall survival Predictors of SLN positivity and survival	Overall SLN identification rate 99.3% Patients were categorized into four different subgroups: (1) patients with negative SLN after pathological examination who never developed regional lymph node metastases during follow-up; (2) patients with	Large patient cohort Long median follow-up	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					pathological diagnosis of metastasis in the SLN without any positive NSLNs; (3) patients with positive SLNs and secondary deposits in NSLNs at CLND; and (4) patients with negative SLNs who developed clinically detectable regional metastases in the SNB lymphatic basin during follow-up. 5-year OS rates were 93%, 71.3%, 50.4% and 49.8% for groups A, B, C, and D, respectively		
Morton et al. (2006)	Same study as Morton et al. (2005)	Same study as Morton et al. (2005)	Same study as Morton et al. (2005)	Relapse rate Disease-free survival Melanoma-specific mortality and	Frequency of relapse at any site: 26.8% in the observation group and 20.7% in the biopsy group	Here, an intention-to-treat analysis was performed (missing in Morton et al., 2005)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				survival	Disease-free survival rate at 5 years: in the biopsy group 78.3%; in the observation group 73.1% Melanoma-specific death: 13.8% in the observation group and 12.5% in the biopsy group Melanoma-specific survival rate: 90.1% and 93.2%, respectively, at 3 years, and 86.6% and 87.1%, respectively, at 5 years Melanoma-specific mortality rate in the biopsy group: 9.7% when sentinel tumor-free and 26.2% if sentinel positive Estimated disease-		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					free survival rate at 5 years: 53.4% for positive and 83.2% for negative sentinel; corresponding values for melanoma-specific survival 72.3% and 90.2%, respectively		
McMasters et al. (2001)	To identify prognostic factors that are predictive of sentinel lymph node (SLN) metastasis in melanoma.	Prognostic study	Total of 1058 patients evaluated; 961 patients had complete data and were included in the statistical analysis	Positive sentinel node	SLN identification rate 99.7% SLN positivity 22% Independent predictors of SLN metastasis, in order of importance: Breslow thickness, Clark level, ulceration, and patient age	Prospective design Subgroup analysis of Melanoma Sunbelt Trial (multi-center, randomized trial); therefore patients partially identical with patients in Mays et al. (2010)	1b
Rondelli et al. (2011)	to assess the prognostic role of SLN in thick melanoma in terms of disease-free survival (DFS)	Systematic review with meta-analysis	9 studies included with a total of 1261 patients	DFS OS IRR	Overall, DFS: 71% in patients with a negative SLN, 39% in patients with a positive SLN after a median follow-up	Only retrospective studies included in meta-analysis	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	and overall survival (OS).			incidence rate ratios (IRD) incidence rate difference (IRD)	of 33 months (IRR 1.83, 95% CI = 1.56–2.14). OS: 71% in patients with a negative SLN, 49% in patients with a positive SLN (IRR 1.44, 95% CI = 1.25–1.65).		
Smith et al. (2012)	to compare melanoma-specific survival among patients with head and neck desmoplastic melanoma based on SLN status	Prognostic study	244 patients with desmoplastic melanoma of the head and neck who underwent SLNB	5-year disease-specific survival (DSS)	On univariable and multivariable analysis, SLN positivity did not significantly affect DSS in head and neck desmoplastic melanoma (P =.19 and P =.48, respectively).		2b
Burton et al. (2011)	to determine whether regression predicts nodal metastasis, disease-free survival (DFS), or overall survival (OS).	Prognostic study	2220 patients who underwent SLN biopsy; those with tumor-positive SLN underwent completion lymphadenectomy (261 with	DFS OS Prognostic factors	On multivariate analysis, factors independently predictive of DFS included Breslow thickness, ulceration, and SLN status (P < 0.05 in all cases);	Post hoc analysis of a multicenter prospective randomized trial	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			regression; 1959 without regression)		the same factors along with age, gender, and anatomic tumor location were significantly associated with OS (P < 0.05 in all cases). Regression was not significantly associated with DFS (risk ratio [RR], 0.94; 95% confidence interval [CI], 0.67-1.27; P = 0.68) or OS (RR, 1.01; 95% CI, 0.76-1.32; P = 0.93).		
De Vries et al. (2011)	To assess the long-term outcome after sentinel lymph node biopsy (SLNB) in melanoma patients.	Prognostic study	450 melanoma patients who underwent SLNB (Survival and prognostic factors were analyzed for 429 patients)	Relapse rate FN-rate Prognostic factors	In 29% relapse during follow-up; 46% in the SLN-positive group who underwent CLND and 22% in the SLN-negative group (p < 0.001). FN- rate 11%. On multivariate	CLND was performed in 119 patients and these patients were analyzed for recurrence and survival.	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					analysis strongest prognostic factors for DFS: primary melanoma ulceration and SLN positivity (HR: 2.2 and 2.3; p < 0.001). For DSS the same was found, HR of 2.1 for ulceration and 2.0 for SLN positivity (p=0.001 and p=0.002 respectively). 10-Year DFS was 71% for SN-negative patients compared with 48% for SLN-positive patients (p < 0.001). 10-Year DSS was 77% for node-negative patients compared to 60% for SLN-positive patients (p < 0.001).		
Murali et al (2011)	To investigate in detail the influence	Prognostic study	409 patients with primary cutaneous	DFS	Primary tumor features (presence	Same patient cohort as Murali et	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of SN tumor characteristics and clinical and primary tumor parameters on regional lymph node recurrence, distant metastasis, and survival.		melanoma who underwent SNB	melanoma-specific survival (MSS)	of ulceration and satellites) and presence of ENS in SNs were independent predictors of DFS, DMFS, and MSS. In addition, poorer DFS was independently associated with primary tumor site (head/neck and limbs vs. trunk), SN tumor features (MaxSize >2 mm, presence of PLI) and positive NSN in CLND; other factors independently predictive of DMFS were male sex, primary tumor features (absence of TILs), and SN tumor MaxSize >10 mm; and age ≥50 years was an additional independent	al. (2010): Non-Sentinel Node Risk Score (N-SNORE): A Scoring System for Accurately Stratifying Risk of Non-Sentinel Node Positivity in Patients With Cutaneous Melanoma With Positive Sentinel Lymph Nodes	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					predictor of MSS. CLND status was not an independent predictor of DMFS or MSS.		
Göppner et al. (2011)	To investigate the prognostic relevance of SLNB and other risk factors in the subgroup of melanomas > 4.0 mm and to compared it to previously published results.	Prognostic study	87 patients with thick melanomas 1 4.0 mm (T4).	Recurrence-Free Survival Overall survival	Multivariate analysis: SLN and ulceration, analyzed as separate risk factors as well as their combination, predicted a highly reduced life expectancy in terms of recurrence-free survival (RFS). SLN, but not ulceration, also predicted overall survival (OS)		2b
Koskivuo et al. (2011)	to evaluate the accuracy and prognostic value of the routine use of SNB in elderly patients with cutaneous	Prognostic study	423 consecutive patients >= 70 years with CM AJCC stage I–II	FN-rate Sensitivity Diagnostic accuracy	Recurrence in 18.9% of patients (median follow-up: 2·5 years) FN-rate: 8·3% Sensitivity: 91.7%		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma.			Relapse-free survival rate Cancer specific survival rate Prognostic factors	overall diagnostic accuracy: 98·0 % at 5 years: relapse-free survival rate: 80·0% in SN-negative patients and 39% in SN-positive patients cancer-specific survival rates: 88·6% and 46% respectively (P < 0·001). multivariable analysis: SN metastasis (P < 0·001), a Breslow thickness of >= 2·0 mm (P = 0·007) and presence of ulceration (P = 0·012) were independent prognostic factors for cancer-specific survival.		
Tejera-Vaquerizo et al. (2012)	To determine whether growth	Prognostic study	698 patients with invasive primary	Growth rate	Multivariate logistic regression	surrogate measure for GR in primary	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	rate (GR) of cutaneous melanoma predicts the histological sentinel lymph node (SLN) positivity		cutaneous melanoma in whom the SLN was identified	Prognostic factors	analysis: GR, Breslow thickness, and the presence of microscopic satellitosis independently associated with SLN positivity. probability of SLN positivity: 8.2% for slow growth melanomas (<0.10 mm/mo) compared with 19.8% for intermediate-growth melanomas (0.10-0.50 mm/mo) and 37.7% for fast-growth melanomas (>0.50 mm/mo). SLN positivity was the most important prognostic factor for DFS (HR, 2.13; 95% CI, 1.20-3.76) and for OS (HR, 3.99; 95% CI, 1.67-	invasive melanoma was calculated as the ratio of Breslow thickness to time to melanoma development.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					9.53).		
White et al. 2011	Prognostic study	undergoing sentinel lymph node (SLN) biopsy for primary melanoma	3463 patients (561 (16.3%) had a positive SLN biopsy)	Predictive factors	multivariate analysis: increasing Breslow thickness, lymphovascular invasion, ulceration, younger age, the absence of regression, and tumor location on the trunk were statistically significant predictors of a positive SLN	retrospective and prospective data multivariate analysis performed with data of 1526 patients (with complete records)	2b
Yonick et al. (2011)	To elucidate pathologic factors that are predictive of SLN positivity	Prognostic study	1199 patients	Correlation between histopathological features and SLN positivity	Thin melanomas in 39%; of these, 31% underwent SLNB Positive SLNs found in 11% Multiple logistic regression: ulceration and thickness associated with SLN positivity	Retrospective study No defined inclusion criteria for SNB	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					For scoring system, see full article		
Cadili and Dabbs (2010)	To identify the predictors of SLN melanoma metastasis.	Prognostic study	348 patients with malignant melanoma	Relative risk	73% negative and 27% positive SLN Breslow thickness and nodular type significantly correlated with positive SLN; head and neck tumour location significantly correlated with negative SLN	Retrospective design Correlation of head and neck tumour and negative SLN result may be caused by insufficient experience in head and neck SLNEs in this institution.	2b
Kretschmer et al. (2010)	To investigate the impact of the constitutional factor age on the clinical courses of melanoma patients with sentinel lymph node (SLN) biopsy.	Prognostic study	2,268 consecutive patients	Correlation between histological parameters/SNB status and age Melanoma-specific overall survival Adjusted relative risk	According to multivariate analysis, factors predictive for poor overall survival: age, micrometastasis to SLN, Breslow thickness and epidermal ulceration In multivariate	Retrospective design Large patient sample	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					logistic regression analysis, age of < 40 years was significantly related to a 2-fold probability of SLN-positivity		
Roach et al. (2010)	To investigate the significance of mitotic rate (MR) in melanoma	Prognostic study	551 patients had MR data reported	Overall survival Disease-free survival Odds' ratio (OR) for SLN positivity	High MR: thicker tumors, higher rate of ulceration, twice as many positive SLNs (31.3% vs. 14.7%) Tumor thickness and ulceration significant survival predictors upon multivariate analysis For SLN-negative and nonulcerated patients, MR groups were not significant for OS	Retrospective design	2b
Mandala et al. (2009)	To investigate if the tumour infiltrating lymphocytes (TILs)	Prognostic study	1251 consecutive patients with CM	Overall survival Disease-free survival	TIL status of lesion correlated with the Breslow thickness, Clark level and	Retrospective analysis (though of prospective database)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	are able to predict the sentinel lymph node (SLN) positivity, the disease-free survival (DFS) and overall survival (OS) in clinical stages I-II AJCC primary cutaneous melanoma (PCM).			Correlation between TIL status and SLN status	regression No difference in other variables evaluated, including SLN status or the presence of ulceration, among patients with brisk, non-brisk and absent TILs SLN identified in 394 patients (97.5%) 18.8% positive SLNs In multivariate analysis, increasing Breslow thickness, anatomical site and absence of TILs independently associated with positive SLN 5-year DFS 75.9% in negative SLNs,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					35.2% in positive SLNs 5-year OS 88.7% versus 42.9%, respectively		
Socrier et al. (2009)	To determine if regression in melanoma is associated with an increased risk of sentinel lymph node (SLN) metastasis.	Prognostic study	397 consecutive melanoma patients	Odds' ratio (OR)	SLN positive in 16% of melanomas with regression and 29% without regression Adjusted OR for regressive melanoma: 0.9	Retro- or prospective design unclear	2b
Gutzmer et al. (2008)	To investigate the value of the status of the sentinel lymph node (SLN) in patients with thick melanomas (Breslow thickness ≥ 4 mm)	Prognostic study	152 patients	Recurrence-free survival Overall survival Correlation between histological properties of primary tumour and SLN positivity Relative risk (RR) for SLN positivity	Probability of recurrence-free 5-year-survival: 42.5 ± 5% overall, 26.3 ± 6.6 % for SLN+ and 58.7 ± 7.1 % for SLN- In multivariate analysis the pathological status of the SLN had a highly significant prognostic value (p = 0.000009);	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					relative risk (RR) 3.3 The 5-year overall survival 53.2 ± 5.4 % (37.5 ± 8.1 % with positive SLN and 67.6 ± 6.7 % with negative SLN)		
Roulin et al. (2008)	To confirm the accuracy of sentinel node biopsy (SNB) and its morbidity, and to investigate predictive factors for SN status, disease-free survival (DFS) and disease-specific survival (DSS).	Prospective prognostic study	327 consecutive patients with primary melanoma	Recurrence rate Sensitivity and false-negative rate of SNB 5-year disease-free survival (DFS) 5-year disease-specific survival (DSS)	Success rate of SNB 99.1% Overall SNB + WE morbidity 7.6% SNB positivity rate 22.6% Mean Breslow thickness of primary melanoma 1.95 mm for SN-negative cases and 3.22 mm for SN-positive cases Breslow thickness only statistically significant predictor for metastases	Follow-up presumably too short to discover all recurrences (median follow-up 33 months; median time of recurrence 30 months, mean 34 months) No control group	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					46% of positive and 11% of negative SN patients recurred False-negative rate 8.6%, sensitivity 91.4%. 5-year DFS 43% for patients with positive SN and 83.5% for patients with negative SN 5-year DSS 49.1% for SN-positive patients and 87.4% for SN-negative patients		
Cecchi et al. (2007)	To report the experience with lymphatic mapping (LM) and sentinel lymph node biopsy (SLNB) in a selected group of patients with thin primary cutaneous melanomas.	Prospective cohort study	50 patients with thin melanomas	Prevalence of SLN-positivity in thin melanomas	SLN positivity rate 4%	CLND only performed on SLN-positive patients (risk of verification bias)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kaur et al. (2008)	To understand the significance of regression in melanoma and provide further information on whether patients should be subjected to sentinel lymph node biopsy (SLNB) on the basis of regression.	Prognostic study	146 consecutive melanoma patients	Correlation between histopathologic parameters and SLN positivity	Statistically significant greater proportion of individuals without regression showed sentinel lymph node (SLN) positivity (p=0.028) compared with patients without regression Correlation of age, sex, site and presence of tumour infiltrating lymphocytes (TIL) with regression and sentinel node status not statistically significant	Retrospective design, but 1 – 6 years prospective follow-up in 79% of the patients (recording survival and metastasis)	2b
Morris et al. (2008)	To assess whether the presence of RG was associated with a higher probability of a positive SLN or an increased risk of local or distant	Prognostic study	1349 patients with cutaneous melanoma	Correlation between regression and SLN positivity Overall survival Disease-free	10% of patients with RG and 18% of patients with NRG who underwent SLN biopsy had a positive SLN	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	recurrence.			survival	When stratified by Breslow depth category, there was no evidence of an increased risk of a positive SLN in those with RG OS not significantly different between the two groups DFS significantly longer for those with RG		
Paek et al. (2007)	To verify previous results in which increasing mitotic rate and decreasing age predicted sentinel lymph node (SLN) metastases in patients with melanoma, and to create a prediction model for the better selection of which patients with melanoma	Prognostic/ diagnostic study	910 patients with cutaneous melanoma	Correlation between histological features and SLN positivity OR for SLN positivity	≥1 positive SLNs identified in 26.7% of patients The best multivariate model included the following single variables: patient age, Breslow depth, the presence of angiolymphatic invasion, the number of	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	should undergo SLN biopsy.				mitoses, and body site location of the melanoma		
Taylor et al. (2007)	To evaluate the prognostic implications of tumor-infiltrating lymphocytes (TILs)	Prognostic study	887 patients who underwent SLN mapping for cutaneous melanoma	Correlation of histopathologic features with SLN positivity Overall survival Disease-free survival	SLN identification rate 98.6% SLN positivity rate 17.6% By multivariate logistic regression analysis, male sex, thickness, presence of ulceration, and absence of TILs were independently associated with positive SLN When brisk and nonbrisk TILs were analyzed separately, both levels were significant predictors of a negative SLN compared with absent TILs, by		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					univariate and multivariate analysis Histologic status of SLN was the most significant predictor of DFS and OS Negative SLN: 5-year DFS 80.0% Positive SLN: 5-year DFS 32.8% When stratified by SLN status, no survival advantage present with TILs		
Morton et al. (2005)	The objective of this study was to evaluate, in an international multicenter phase III trial, the accuracy, use, and morbidity of intraoperative lymphatic mapping and sentinel node	Randomized controlled clinical multi-center trial .	2001 patients with invasive primary cutaneous melanoma	Accuracy of sentinel node identification Dissected-basin recurrence in patients with negative sentinel node Surgical morbidity	Overall rate of SN identification: 95.3% 6.3% of patients with tumor-negative SNs developed regional nodal recurrence at a median followup of 54	Method of randomization described in Morton et al. (2006) No intention to treat analysis (ITT); instead an as-treated analysis was performed	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	biopsy (LM/SNB) for staging the regional nodal basin of patients with early-stage melanoma.				months Incidence of at least one local wound complication: 13.9% in the WEO arm and 13.8% in the LM/SNB arm Surgical morbidity: 37.2% for LM/SNB with immediate CLND vs 10.1% for LM/SNB without CLND		
Roka et al. (2005)	To investigate the accuracy of SLNB and the clinical outcome of patients.	Prognostic study	309 patients with malignant melanoma	Disease-free survival Overall survival	SNB success rate: 96.8% SLN positivity rate: 23% False-negative SLNB rate: 9.2% Among patients with one or more metastatic SLN, 21% had further metastases in non-SLNs in the	Prospective design Relatively short mean follow-up time	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					dissected basin Micrometastasis in SLN in 68%, macrometastasis in 32% 3-year DFSl for negative and positive SLN patients: 82 and 55%, respectively 3-year overall survival for negative and positive SLN: patients 93% and 83%, respectively By multivariate analysis, Breslow thickness the only statistically significant prognostic factor with respect to overall survival		
Cuéllar et al. (2004)	To describe independent prognostic factors	Prognostic study	94 MM patients	Correlation between potential prognostic factors	SLN positivity rate 20.2%	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	other than tumour thickness useful in SLN candidate selection.			and SLN positivity	No positive SLN in MM ≤ 1.0 mm and in patients with regression > 50% Small cell and ulceration were significant prognostic factors in multivariate analysis SLN positivity rate for small cell: 56.9% SLN positivity rate for ulceration: 35.5% SLN positivity rate for small cell and ulceration: 86.3%		
Macripo et al. (2004)	To analyse the parameters associated with a higher risk of occult nodal metastases, to evaluate the clinical outcome of	Prognostic study	274 melanoma patients with melanoma ≥ 1 mm or ulceration, regression or Clark level IV/V	Status of SLN (negative, micrometastasis or macrometastasis) Disease-free survival	SLN positivity rate 16.8% Subsequent radical node dissection revealed further melanoma metastases in 33%	Prospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma patients who underwent SLN procedure, and to identify by means of multivariate analysis the prognostic parameters with independent predictive value on disease-free survival (DFS) in node-positive and negative patients.				of patients with macrometastases and 10% of patients with micrometastases Relapse rate of SLN-positive patients: 54.3% Relapse rate of SLN-negative patients: 10.9% 5-year DFS and OS 42% for SLN+ and 69% for SLN- SLN status (micrometastases/ macrometastases) and thickness were independent prognostic factors in the SLN-positive group Low-risk group: micrometastases and Breslow thickness ≤ 2 mm; 2-year DFS 100%		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Intermediate-risk group: macrometastases or Breslow thickness >2 mm; 2-year DFS 71% High-risk group: macrometastases and Breslow thickness >2 mm; 2-year DFS 28%		
Stitzenberg et al. (2004)	To investigate if lymphatic mapping and sentinel lymphadenectomy (LM/SL) with a focused examination of the sentinel node (SN) will detect a significant number of SN metastases in patients with thin melanoma and which clinical or histopathologic factors may serve as predictors of SN tumor	Prognostic study	146 patients with a melanoma tumor thickness of ≤ 1.0 mm	Correlation of histopathological factors and SLN positivity	SLN positivity rate 4% On multivariate analysis, none of the clinical or histopathologic factors examined significantly associated with SN tumor involvement in patients with thin melanoma None of the patients had non-SN tumor involvement	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	involvement.						
Mraz-Gernhard et al. (1998)	To develop a prognostic model, based on clinical and pathological data, to estimate the probability of micrometastasis in the sentinel lymph node in patients with malignant melanoma.	Prognostic study	215 patients with AJCC stages I and II cutaneous malignant melanoma	Incidence of SLN positivity depending on histological features	SLN positivity rate 21.4% Only tumor thickness significantly correlated with SLN positivity Incidence of positive SLN according to number of high risk features (HRFs): 14% with no HRF 31% with 1 HRF 47% with 2 HRFs 75% with 3 or more HRFs	Retrospective design Similar rate of SLN positivity in melanomas between 1.0 and 2.9 and > 5 mm may be due to selection bias (exclusion of patients with evidence of regional lymph node metastasis) => may also be true for other studies	2b
Satzger et al. (2011)	To analyze the possible effect of SLND on the prognosis of melanoma patients.	Prognostic study	673 consecutive melanoma patients	Overall survival Recurrence-free survival	Pre-SLN group: 25.7% melanoma related deaths SLN group: 17.6% 5-year melanoma-specific survival rates: 80.3% in pre-	Retrospective design Historical control group	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					SLN patients, 84.8% in SLN patients 5-year survival rates: 72.8% in SLN positive patients, 89.9% in SLN negative patients 89.9% Relapse rate 39.0% in pre-SLN patients, 23.6% in SLN patients		
Ellis et al. (2010)	To clarify indications, predictive factors, and outcomes of sentinel node biopsy.	Prognostic and diagnostic study	397 patients with melanomas	Correlation between histological properties and SLN positivity Sensitivity and specificity, NPV and PPV	Breslow thickness > 2 mm, upper extremity primaries, and ulceration were predictive for SLN+ status SLN positivity rate 12%; for lesions > 1 mm 16% False-negative rate 4.0% Sensitivity of SLNB	Retrospective design Difficult definition of “false-positives” (here declared as 0, but not defined)	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					75.4%, with a negative predictive value of 95.4% and accuracy of 96.0%; specificity and positive predictive value 100%		
Kretschmer et al. (2008)	To determine surgical morbidity in melanoma patients with sentinel lymphnodectomy and complete regional lymph node dissection	Cohort study	315 melanoma patients	Complication rate	Mortality 0% Morbidity rate related to general anaesthesia 0% Complication rates: 65.5% after CLND, 13.8% after SLNE 19.5% in inguinal dissection, 9.2% in axillary dissection	Most data prospectively recorded (325 vs. 40 nodal basins) Surgical morbidity not recorded for all patients who underwent SLNE or CLND (possible source of bias)	2b-
de Rosa et al. (2011)	to examine the test performance of sentinel node biopsy in head and neck melanoma, including the identification rate and false-negative rate	Systematic review without meta-analysis (32 studies eligible for analysis)	3442 patients	predictive value positive (PPV) and negative (PVN) for nodal recurrence posttest probability FN-negative rate	Positive sentinel node biopsy: in 15% of patients. Subsequent completion neck dissection revealed additional	Distinct portions of the included studies were used to determine PVP, PTPN… 32 studies clinically heterogeneous	3a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					positive nodes in 13.67%. predictive value positive for nodal recurrence: 13.1%, posttest probability negative: 5%. Median FN-negative rate for nodal recurrence was 20.4%.		
Doeden et al. (2009)	We directly compared the relative contribution of lymphatic and hematogenous pathways in a cohort of patients with primary cutaneous melanoma with 3 years of clinical follow up.	Prognostic study	94 patients with primary cutaneous melanoma, 57 of which had a known SLN status	Overall survival Disease-free survival Correlation between lymphatic invasion (LI) resp. vascular invasion (VI) and SLN positivity	SLN positivity rate 75% in LI-positive patients, 39% in LI-negative patients Presence of LI was independent of tumor thickness and not associated with distant metastasis Kaplan-Meier analyses did not detect a significant difference in the overall or disease-	Small sample size (57 with known SLN status) Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					free survival in LI-positive or LI-negative patients By multivariate analysis, LI was not a significant risk factor for SLN metastasis		
Leiter et al. (2010)	To investigate the potential survival benefit of sentinel lymph node dissection (SLND).	Prognostic study	879 patients with primary cutaneous melanoma	Incidence of metastasis Overall survival Recurrence-free survival	Rate of regional lymph node metastasis: 16.5% in non-SLND collective, 7.3% in SLND collective; no difference in satellite/in-transit metastases and distant metastases Disease-free survival improved in the SLND collective	Retrospective design Historical control group without consistent reporting of ulceration	3b
Massi et al. (2006)	To evaluate whether tumour lymphangiogenesis and the expression of vascular endothelial growth	Case-control study	15 patients affected by primary cutaneous melanoma with metastasis to SLN were matched with	Correlation between LV and SLN positivity Overall survival	Number and area of peritumorous and intratumorous lymphatics was significantly higher in melanomas	Retrospective design Small patient sample	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	factor C (VEGF-C) is related to the risk of SLN metastasis and to clinical outcome in a case–control series of patients with melanoma.		a group of 30 patients without SLN metastasis.		associated with SLN metastasis than in non-metastatic melanomas No significant difference in VEGF-C expression by neoplastic cells between metastatic and non-metastatic melanomas In multivariate analysis, peritumorous LV density was an independent variable affecting overall survival		
Dadras et al. (2005)	To investigate whether the extent of tumor lymphangiogenesis can predict melanoma metastasis to sentinel lymph nodes.	Prognostic study	45 consecutive patients with nonmetastatic (n = 27) or metastatic (n = 18) primary cutaneous melanoma to the SLN.	Odds' ratio	Mean tumor thickness in SLN-positive patients 3.01 ± 0.52mm, in SLN-negative patients 1.70 ± 0.31mm Additional	Small patient sample Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					prognostic parameters such as tumor ulceration, mitotic activity, regression and number of tumor infiltrating lymphocytes did not differ between groups Frequency of intratumoral lymphatics in SLN-positive patients 83.3 ± 0.09%, in SLN-negative patients 59.3 ± 0.09%		
Roaten et al. (2005)	To investigate the assumption that SLNB has fewer complications than elective regional lymph node dissection (RLND).	Cohort study	339 consecutive patients undergoing SLNB for melanoma	Complication rates	SLN positivity rate 19.6% Complication rate 5.9% for SNB, 19.5% for RLND	Retrospective design No clear inclusion criteria and different characteristics (thicker tumors, more men, longer follow-up) in control group who received RLND	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Role of closed suction to be investigated further	
Leong et al. (2003)	To examine the role of sentinel lymph node biopsy (SLNB) in patients with a previous wide local excision (WLE).	Prospective case-control study	168 patients with clinically nodenegative truncal or extremity melanoma and Breslow thickness of ≥ 1 mm. A total of 103 of the 168 patients were referred after their WLE.	Number of positive SLNB False-negatives Disease-free survival Overall survival	SLN positivity rate 32.3% both for cases and controls No significant difference in relapse-free survival: 72.3% for cases, 81.7% for controls at 2 years; No significant difference in overall survival: 94.7% incases, 96.8% in controls at 2 years	Follow-up time span too short for reliable assessment of survival	3b
McCready et al. (2001)	To document experience with sentinel lymph-node biopsy in patients who have already undergone a wide local excision for	Prospective cohort study	100 patients with cutaneous melanoma	Accuracy of biopsy False-negative rates	SLN positivity rate 31% At completion lymphadenectomy, 29% rate of other positive nodes in the dissected basin	Only a historical control group available Small patient numbers, especially in the false-negative	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma because in many centres previous wide excision has been a contraindication for sentinel lymph node biopsy.					group	
Nguyen et al. (2001)	To determine whether primary melanoma histopathologic features could be applied to predict sentinel node status.	Prognostic study	112 consecutive melanoma patients	Correlation between histological features and SLN positivity	SLN positivity rate 20% False-negative rate 2.4% In multivariate analysis, the most significant cutoff for prediction of node positivity was a thickness of 1.5 mm Additional histologic features significantly predictive of occult micrometastases: ulceration and lymphovascular invasion	Retrospective design No explicit information about inclusion criteria for SLNE	3b
Pasquali et al.	To test the	Diagnostic study	543 patients		positive SN in 147		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2011)	discrimination, the calibration and the NPV of MSKCC nomogram in 543 patients				patients (27%). Mean predicted probability: 17.8% (95%CI: 16.8-18.8%). Nomogram discrimination was significant (area under the curve = 0.68; P < 0.0001) (R(2) = 0.99). Cut-off values between 4% and 9% led to a NPV, SNB reduction and overall error rates ranging between 100 and 91.2%, 2.2 and 27.2%, and 0 and 2.3%, respectively. incidence of SN metastasis was higher than that observed in the MSKCC series (27% vs 16%).		

3.1.4.1.1. Literatur

Burton AL, Gilbert J, Farmer RW, et al. Regression does not predict nodal metastasis or survival in patients with cutaneous melanoma. Am Surg 2011;77:1009-1013

Cadili A, Dabbs K. Predictors of sentinel lymph node metastasis in melanoma. Can J Surg 2010;53:32-36
Cecchi R, Buralli L, Innocenti S, et al. Sentinel lymph node biopsy in patients with thin melanomas. J Dermatol 2007;34:512-515
Cuellar FA, Vilalta A, Rull R, et al. Small cell melanoma and ulceration as predictors of positive sentinel lymph node in malignant melanoma patients. Melanoma Res 2004;14:277-282
Dadras SS, Lange-Asschenfeldt B, Velasco P, et al. Tumor lymphangiogenesis predicts melanoma metastasis to sentinel lymph nodes. Mod Pathol 2005;18:1232-1242
de Rosa N, Lyman GH, Silbermins D, et al. Sentinel node biopsy for head and neck melanoma: a systematic review. Otolaryngol Head Neck Surg 2011;145:375-382
de Vries M, Speijers MJ, Bastiaannet E, et al. Long-term follow-up reveals that ulceration and sentinel lymph node status are the strongest predictors for survival in patients with primary cutaneous melanoma. Eur J Surg Oncol 2011;37:681-687
Doeden K, Ma Z, Narasimhan B, et al. Lymphatic invasion in cutaneous melanoma is associated with sentinel lymph node metastasis. J Cutan Pathol 2009;36:772-780
Ellis MC, Weerasinghe R, Corless CL, et al. Sentinel lymph node staging of cutaneous melanoma: predictors and outcomes. Am J Surg 2010;199:663-668
Goppner D, Ulrich J, Pokrywka A, et al. Sentinel lymph node biopsy status is a key parameter to stratify the prognostic heterogeneity of malignant melanoma in high-risk tumors >4.0 mm. Dermatology 2011;222:59-66
Gutzmer R, Satzger I, Thoms KM, et al. Sentinel lymph node status is the most important prognostic factor for thick (> or = 4 mm) melanomas. J Dtsch Dermatol Ges 2008;6:198-203
Kaur C, Thomas RJ, Desai N, et al. The correlation of regression in primary melanoma with sentinel lymph node status. J Clin Pathol 2008;61:297-300
Koskivuo I, Hernberg M, Vihinen P, et al. Sentinel lymph node biopsy and survival in elderly patients with cutaneous melanoma. Br J Surg 2011;98:1400-1407
Kretschmer L, Starz H, Thoms KM, et al. Age as a key factor influencing metastasizing patterns and disease-specific survival after sentinel lymph node biopsy for cutaneous melanoma. Int J Cancer 2010
Kretschmer L, Thoms KM, Peeters S, et al. Postoperative morbidity of lymph node excision for cutaneous melanoma-sentinel lymphonodectomy versus complete regional lymph node dissection. Melanoma Res 2008;18:16-21
Kunte C, Geimer T, Baumert J, et al. Prognostic factors associated with sentinel lymph node positivity and effect of sentinel status on survival: an analysis of 1049 patients with cutaneous melanoma. Melanoma Res 2010;20:330-337
Leiter U, Buettner PG, Bohnenberger K, et al. Sentinel lymph node dissection in primary melanoma reduces subsequent regional lymph node metastasis as well as distant metastasis after nodal involvement. Ann Surg Oncol 2010;17:129-137
Leong WL, Ghazarian DM, McCready DR. Previous wide local excision of primary melanoma is not a contraindication for sentinel lymph node biopsy of the trunk and extremity. J Surg Oncol 2003;82:143-146
Macripo G, Quaglino P, Caliendo V, et al. Sentinel lymph node dissection in stage I/II melanoma patients: surgical management and clinical follow-up study. Melanoma Res 2004;14:S9-12
Mandala M, Imberti GL, Piazzalunga D, et al. Clinical and histopathological risk factors to predict sentinel lymph node positivity, disease-free and overall survival in clinical stages I-II AJCC skin melanoma: outcome analysis from a single-institution prospectively collected database. Eur J Cancer 2009;45:2537-2545
Massi D, Puig S, Franchi A, et al. Tumour lymphangiogenesis is a possible predictor of sentinel lymph node status in cutaneous melanoma: a case-control study. J Clin Pathol 2006;59:166-173
Mays MP, Martin RC, Burton A, et al. Should all patients with melanoma between 1 and 2 mm Breslow thickness undergo sentinel lymph node biopsy? Cancer 2010;116:1535-1544
McCready DR, Ghazarian DM, Hershkop MS, et al. Sentinel lymph-node biopsy after previous wide local excision for melanoma. Can J Surg 2001;44:432-434
McMasters KM, Wong SL, Edwards MJ, et al. Factors that predict the presence of sentinel lymph node metastasis in patients with melanoma. Surgery 2001;130:151-156
Morris KT, Busam KJ, Bero S, et al. Primary cutaneous melanoma with regression does not require a lower threshold for sentinel lymph node biopsy. Ann Surg Oncol 2008;15:316-322
Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. Ann Surg 2005;242:302-11; discussion 311-3
Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 2006;355:1307-1317
Mraz-Gernhard S, Sagebiel RW, Kashani-Sabet M, et al. Prediction of sentinel lymph node micrometastasis by histological features in primary cutaneous malignant melanoma. Arch Dermatol 1998;134:983-987
Murali R, Desilva C, Thompson JF, et al. Factors predicting recurrence and survival in sentinel lymph node-positive melanoma patients. Ann Surg 2011;253:1155-1164
Nguyen CL, McClay EF, Cole DJ, et al. Melanoma thickness and histology predict sentinel lymph node status. Am J Surg 2001;181:8-11
Paek SC, Griffith KA, Johnson TM, et al. The impact of factors beyond Breslow depth on predicting sentinel lymph node positivity in melanoma. Cancer 2007;109:100-108
Pasquali S, Mocellin S, Campana LG, et al. Maximizing the clinical usefulness of a nomogram to select patients candidate to sentinel node biopsy for cutaneous melanoma. Eur J Surg Oncol 2011;37:675-680
Roach BA, Burton AL, Mays MP, et al. Does mitotic rate predict sentinel lymph node metastasis or survival in patients with intermediate and thick melanoma? Am J Surg 2010;200:759-63; discussion 763-4
Roaten JB, Pearlman N, Gonzalez R, et al. Identifying risk factors for complications following sentinel lymph node biopsy for melanoma. Arch Surg 2005;140:85-89
Roka F, Kittler H, Cauzig P, et al. Sentinel node status in melanoma patients is not predictive for overall survival upon multivariate analysis. Br J Cancer 2005;92:662-667
Rondelli F, Vedovati M, Becattini C, et al. Prognostic role of sentinel node biopsy in patients with thick melanoma: a meta-analysis. J Eur Acad Dermatol Venereol 2011
Roulin D, Matter M, Bady P, et al. Prognostic value of sentinel node biopsy in 327 prospective melanoma patients from a single institution. Eur J Surg Oncol 2008;34:673-679
Satzger I, Meier A, Hoy L, et al. Sentinel node dissection delays recurrence and prolongs melanoma-related survival: an analysis of 673 patients from a single center with long-term follow-up. Ann Surg Oncol 2011;18:514-520
Smith VA, Lentsch EJ. Sentinel node biopsy in head and neck desmoplastic melanoma: An analysis of 244 cases. Laryngoscope 2012;122:116-120
Socrier Y, Lauwers-Cances V, Lamant L, et al. Histological regression in primary melanoma: not a predictor of sentinel lymph node metastasis in a cohort of 397 patients. Br J Dermatol 2010;162:830-834

Stitzenberg KB, Groben PA, Stern SL, et al. Indications for lymphatic mapping and sentinel lymphadenectomy in patients with thin melanoma (Breslow thickness < or =1.0 mm). Ann Surg Oncol 2004;11:900-906
Taylor RC, Patel A, Panageas KS, et al. Tumor-infiltrating lymphocytes predict sentinel lymph node positivity in patients with cutaneous melanoma. J Clin Oncol 2007;25:869-875
Tejera-Vaquerizo A, Nagore E, Herrera-Acosta E, et al. Prediction of Sentinel Lymph Node Positivity by Growth Rate of Cutaneous Melanoma. Arch Dermatol 2012
Testori A, De Salvo GL, Montesco MC, et al. Clinical considerations on sentinel node biopsy in melanoma from an Italian multicentric study on 1,313 patients (SOLISM-IMI). Ann Surg Oncol 2009;16:2018-2027
Valsecchi ME, Silbermins D, de Rosa N, et al. Lymphatic Mapping and Sentinel Lymph Node Biopsy in Patients With Melanoma: A Meta-Analysis. J Clin Oncol 2011
Warycha MA, Zakrzewski J, Ni Q, et al. Meta-analysis of sentinel lymph node positivity in thin melanoma (<or=1 mm). Cancer 2009;115:869-879
White J, R.L.R, Ayers GD, et al. Factors predictive of the status of sentinel lymph nodes in melanoma patients from a large multicenter database. Annals of Surgical Oncology 2011;18:3593-3600
Yonick DV, Ballo RM, Kahn E, et al. Predictors of positive sentinel lymph node in thin melanoma. Am J Surg 2011;201:324-7; discussion 327-8

3.1.4.2. Aktualisierungsrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bamboat et al. (2014)	To characterize the populations undergoing nodal observation (no CLND) and CLND To determine the pattern of initial recurrence between the no-CLND and CLND groups To determine melanoma-specific survival of both patient groups To characterize the outcome of no-CLND patients who experience a subsequent isolated nodal	Retrospective diagnostic study	4,310 patients undergoing SLN biopsy (SLNB)	Median time to recurrence Local/intransit recurrence rates Systemic recurrences RFS OS	Median time to recurrence was similar at 9 and 12 months, respectively (p=0.48). There was no difference in local and in transit recurrence rates between groups (16%, no CLND, and 18%, CLND; p=0.48). Nodal disease as a site of first recurrence occurred in 15% of patients in the no-CLND group and 6% of CLND patients (p=0.002). In contrast,	funding source: none	3a

	recurrence.				systemic recurrences occurred in 8 % of no-CLND patients compared with 27 % of CLND patients (p<0.001). While median recurrence-free survival was higher after CLND (34.5 vs. 20.9 months; p=0.02), melanoma-specific survival was similar (not reached, no CLND vs. 110 months, CLND; p=0.09).		
Beger et al. (2013)	To report a 10-year analysis of patients with cutaneous melanoma treated at the Academic Teaching Hospital Dresden-Friedrichstadt.	Diagnostic study, single center, retrospective	364 patients	Relapse rate Death rate Melanoma-related death	Patients undergoing SLNB had a lower relapse rate (10.6% vs. 33.3%; p<0.001). The most important finding is an almost 50% lower total death rate and melanoma-related death rate in the SLNB subgroup	funding source: none	3a

					(p<0.001 for both)		
Cooper et al. (2013)	To examine the association between multiple clinicopathologic features and SLNB result, and clinical outcome.	Diagnostic study, single center, retrospective	189 cases	Disease progression Distant metastasis OS	A total of 189 cases yielded 3 positive SLNBs (1.6%). Disease progression occurred in 6 cases (3.2%). Positive SLNB predicted distant metastasis and death from disease (P=0.0017). Mitotic rate was not associated with a positive SLNB result.	funding source: none	3a
Cordeiro et al. (2016)	To quantify the pro- portion of SN metastases in patients with thin melanoma. To determine the pooled effect of high-risk features of the primary	Systematic review and meta-analysis	Sixty studies (10,928 patients) met the criteria for inclusion (patients with a tumor thickness of <=1.0mm)	Proportion of SN metastases in patients with thin cutaneous melanoma. Effect of high-risk pathological features of the primary lesion on	Pooled SN positivity was 4.5 % [95 % CI 3.8-5.2 %]. Predictors of a positive SN were: thickness >/=0.75	funding source: Supported in part by the Al Hertz Melanoma Research Grant.	2a

	lesion on SN positivity.			the proportion of SN metastases.	mm [adjusted odds ratio (AOR) 1.90 (95 % CI 1.08-3.34); with a likelihood of SN metastases of 8.8 % (95 % CI 6.4-11.2 %)]; Clark level IV/V [AOR 2.24 (95 % CI 1.23-4.08); with a likelihood of 7.3 % (95 % CI 6.2-8.4 %)]; >/=1 mitoses/mm(2) [AOR 6.64 (95 % CI 2.77-15.88); pooled likelihood 8.8 % (95 % CI 6.2-11.4 %)]; and the presence of microsatellites [unadjusted OR 6.94 (95 % CI 2.13-22.60); likelihood 26.6 % (95 % CI 4.3-48.9 %)]		
Egger et al. (2013)	To determine if the LNR (ratio of positive nodes divided through number of all nodes) is an independent predictor of survival in patients	Post-hoc Analysis	345 patients who underwent SLN biopsy and subsequent completion of lymphadenectomy	DFS, OS	LNR of 0.10 was a significant cutoff point for determining DFS and OS. On multivariate analysis, LNR >0.10 was an independent		3a

	with stage III melanoma in a large multi-institutional study.				predictor of DFS and OS without other measures of lymph node disease burden. Patients with LNR >0.10 had worse DFS and OS.		
Fortes et al. (2016)	To investigate if the timing of SLNB influences long-term melanoma mortality	Retrospective cohort study	748 cutaneous melanoma patients	HR of early SLNB vs delayed SLNB	After adjusting for sex, age, Breslow thickness, mitotic rate, ulceration, and histologic type, patients who underwent early SLNB (≤30 days) and resulted positive on final pathology had a 3 times decreased risk of melanoma mortality (HR = .29; 95% CI = .11 to .77) in comparison to patients who underwent delayed SLNB (≥31 days) and resulted positive on final pathology.	funding source: This work was supported by the Italian Ministry of Health within the project of Epidemiology of melanoma (RC15-5.1).	3a
Geimer et al.	To compare	Retrospective,	596 patients who	OS	Mean overall		4

(2016)	survival data of a large cohort of melanoma patients who were treated by wide local excision only (WLE) and nodal observation (WLE group) to a group of patients treated with WLE plus SLND group to investigate the potential therapeutic benefit of SLND in the treatment of patients with melanoma.	historic cohort comparison	had undergone WLE plus SLND + 596 patients of a historical cohort who had undergone WLE only	DFS, Time to lymph node progression	tumour-specific survival (OS) was 102.7 months in the SLND group vs. 97.0 months in the WLE group respectively (P-value: 0.024). Disease-free survival (log-rank test: 0.003) and time to lymph node progression (P-value: <0.01) also differed significantly between the two groups.		
Gyorki et al. (2016)	To present a large single-center experience of SLNB in thick primary cutaneous melanoma.	Retrospective cohort study, meta-analysis	217 patients with primary T4 melanoma who underwent WLE and SLNB 10 manuscripts that satisfied the inclusion criteria.	OS	The 5-year OS for SLNB negative and positive patients was 68 and 45 %, respectively [HR 2.82; 95 % CI 1.76–4.51; P = .001]. On multivariate analysis, the only predictors of OS were the status of the SLN (HR 2.88; 95 % CI 1.75–4.73)		2a

					and the presence of satellitosis (HR 2.59; 95 % CI 1.30–5.76). Meta-analysis detected significant difference in OS according to sentinel lymph node status; the pooled analysis of 2104 patients demonstrated an overall HR for OS according to SLNB status of 2.3 (95 % CI 1.95–2.71).		
Ipenburg et al. (2016)	To gather information on patients in which a planned SNB was canceled after preoperative lymphoscintigraphyand to determine whether this is an acceptable management strategy.	Retrospective cohort study	Of the 3148 patients in whom the procedure had been planned, 203 patients (6.4 %) did not have a SNB.	Recurrence free survival Regional node disease-free survival Melanoma specific survival	Patients whose SNB was cancelled had significantly worse recurrence-free survival and regional node disease-free survival, but melanoma-specific survival was similar.		3a
Kachare et al. (2014)	To determine the impact of SNB on	Retrospective, 2 matched-cohorts	3955 patients	5-year-MSS	Improved 5-year MSS was		3a

	melanoma-specific survival (MSS) in a larger patient cohort.	study			associated with SNB (85.7 vs. 84.0 %), female gender (88.3 vs. 82.7 %), absence of ulceration (87.5 vs. 75.7 %), extremity location (87.4 %), T2 disease (88.6 vs. 77.9 %), and a negative SNB (88.9 vs. 64.8 %). The relationships between observation [hazard ratio (HR) 1.18], male gender (HR 1.33), ulceration (HR 1.77), head-and-neck location (HR 1.34), and T3 disease (HR 1.82) persisted on multi-variate analysis.		
Kachare et al. (2015)	To better understand the clinical utility of SNB in thick melanoma observation.	Retrospective cohort study	4571 (SNB, n=2,746; Observation, n=1,825), patients with clinically node-negative, thick melanoma.	5-year disease-specific survival (DSS).	Univariate analysis demonstrated SNB was associated with younger age (64 vs 75 years; *p*<.001) and extremity		3a

					primaries (*P*<.0001). On log-rank analysis, improved 5-DSS was associated with SNB (65 vs 62%; P=.008), location in the extremity versus head and neck or trunk (67 vs 61.5 and 60.3%; P=.004), female sex (69 vs 61%; P<.001), and no ulceration (74 vs 54%; P<.001). On Cox regression analysis, advanced age (P<.001), male sex (P=.01), trunk location (P=.0001), and ulceration (P<.001) continued to be associated with DSS.		
Kretschmer et al. (2015)	To analyze different types of nodal basin recurrence after sentinel lymph node biopsy (SLNB)	Retrospective, multicenter cohort study	2653 patients with successfully performed SLNB	5-year-false-negative-rate	The estimated 5-year negative predictive value of SLNB was 96.4%. The estimated false-negative (FN)		3a

	for melanoma.				rates after 1, 2, 3, 5, and 10 years were 2.5%, 4.6%, 6.4%, 8.7%, and 12.6%, respectively. False-negativity after SLNB increases over time, indicating that this parameter should be estimated by the Kaplan–Meier method.		
Mitteldorf et al. (2014)	To analyze the clinical relevance of SLNB in a selected group of 210 patients with thin primary melanomas who received SLNB due to the presence of at least one of the additional risk factors mentioned above.	Retrospective, single-center cohort study	210 patients with thin primary melanomas (<1 mm) and at least one of the following additional risk factors: ulceration, Clark level IV, age ≤40 years, mitosis ≥1, regression, and primary nodular or secondary nodular superficial spreading melanoma.	Melanoma-specific overall survival (MSS)	MSS significantly depended on SLN status. Data suggest that SLNB should be offered to patients with thin melanomas, if ulceration, nodular growth pattern, mitoses, or regression are present, or if the patient is younger than 40 years of age.		3a

Mosquera et al. (2016)	To better understand practice patterns across the U.S population and the survival impact of complete lymphadenectomy.	Retrospective cohort study	2172 patients out of the SEER database with patients with tumors 1–4 mm thick with positive SLNB.	Odd Ratio (OR) Hazard ratio (HR)	In the multivariate analysis, male gender [OR 1.27] and geographic area (Michigan OR, 2.31; Iowa OR, 1.69) were associated with CLND ($p < 0.05$). In the survival analysis, male gender, primary site, ulceration, Clark level, and depth and number of positive nodes were associated with survival ($p < 0.05$), but CLND was not ($p = 0.83$). In the Cox regression analysis, the relationship between male gender [HR, 1.14], primary site trunk versus extremity (HR, 1.3), ulceration (HR, 1.79), Clark level (2 vs. 4 HR, 3.51; 2 vs. 5 HR, 6.48), depth (HR, 1.43)		3a

					and number of nodes (1 vs. 2: HR, 1.23; 1 vs. ≥3: HR, 2.52) persisted ($p < 0.05$). However, when CLND was included in this model, it was not associated with improved survival.		
Mozzillo et al. (2013)	To evaluate the effect of combined superficial and deep groin dissection on disease-free and melanoma-specific survival To identify the most important factors for predicting the involvement of deep nodes according to clinically or microscopically detected nodal metastases.	Retrospective, single-center cohort study	133 patients with groin lymph node metastases.	5-year-disease free survival (DFS) 5-year-melanoma specific survival (MSS)	5-year DFS was significantly better for patients with superficial lymph node metastases than for patients with involvement of both superficial and deep lymph nodes (34.9% vs. 19.0%; P = 0.001). 5-year MSS was significantly better for patients with superficial node metastases only (55.6% vs. 33.3%; P = 0.001).		3a
Mozzillo et al. (2013)	To determine the rate of positive	Retrospective, two-center cohort	492 patients with thin (≤1 mm)	Factors associated with positivity of	In thin melanoma, sentinel node was	3a	

	sentinel nodes and associated factors and the correlation between sentinel node status and outcomes in patients with thin and thick melanoma.	study	melanoma who had undergone local wide excision of the primary tumor and sentinel node biopsy 298 patients with thick (≥4 mm) melanoma	SLN 5-year-OS	positive for metastatic melanoma in 24 (4.9 %) patients. No sentinel node positivity was detected in patients with primary tumor thickness <0.3 mm. Mitotic rate was the only factor significantly associated with sentinel node positivity (p=0.0001). Five-year OS was 81% for patients with positive sentinel node and 93% for negative sentinel node (p = 0.001). In patients with thick melanoma, 39% of patients had positive sentinel lymph nodes (median Breslow thickness 5 mm). In patients with positive sentinel node, 93%		

					had mitotic rate >1/mm2. Five-year OS was 49% for patients with positive sentinel lymph nodes and 56% for patients with negative sentinel nodes (p = 0.005).		
Oude Ophuis et al. (2016)	To investigate if time interval between primary diagnosis and WLE plus SNB is associated with survival differences in a SN positive melanoma population.	Retrospective cohort study	1015 patients with known date of primary melanoma excision.	Melanoma specific survival (MSS). Disease free survival (DFS) Overall survival (OS) SN tumor burden	5-year estimated MSS is not significantly different for short versus longer time intervals. Results were like the MSS data, namely that time interval was not a prognostic factor.		3a
Patuzzo et al. (2014)	To assess the accuracy and prognostic value of sentinel lymph node biopsy in the head and region.	Retrospective, single-center cohort study	331 patients	Detection rate 5-Year-overall survival False-negative-rate Relapse-free-survival (RFS)	SLN) was identified in all patients. The 5-y OS was 91.2% for SLN-negative patients and 48.7% for SLN-positive patients ($P < 0.0001$). Patients with scalp melanoma had thicker lesions and	funding source: none	3a

					an elevated risk of SLN positivity, recurrence, and death compared with those with other sites. Among the 272 SLN-negative patients, four patients developed regional nodal disease in the same basin and had undergone a previous SLNB procedure for a false-omission rate of 1.45%. Risks for false-negative SLN occurrences included thick and scalp melanomas. Multivariate analysis on prognostic factors affecting RFS showed positive SLNB status to be the most prognostic clinicopathologic predictor of recurrence (HR, 20.56;		

					P < 0.0001).		
Reintgen et al. (2013)	To analyze whether patients with stage III metastatic melanoma confined to their sentinel lymph nodes (SLNs) had a more favorable prognosis than patients who had SLN and non-SLN (NSLN) metastases.	Retrospective, cohort study	331 patients	Disease-free survival (DFS) Overall survival (OS)	As the regional metastatic disease involves NSLNs, DFS and OS decreases. For patients with a total of 2 nodes positive, those with disease confined to the SLNs had a significant better prognosis (DFS and OS: P <.00001) than those in whom 1 SLN and 1 non-SLN was involved.	funding source: none	3a
Ribero et al. (2015)	To evaluate the pattern and time of progression comparing patients with T4 (>4mm) melanoma who underwent SLNB to patients who did not.	Retrospective, single-center cohort study	350 patients	Disease-specific survival (DSS) Disease-Free Interval (DFI)	Multivariate analyses confirmed a better prognosis for SLN-negative patients compared with patients in the observation group (DSS hazard ratio [HR] 0.62, p=0.03; DFI HR 0.47, p<0.001).	funding source: This study was supported by the Lanza- vecchia-Lastretti Foundation for ‘‘Progetto Melanoma’’ (Rebecca Senetta).	3a
Rughani et al.	To determine the	Retrospective,	136 patients with	5-Y-OS	5-year OS for SLNB	funding source:	3a

(2012)	prognostic value of SLNB in patients with thick melanoma in terms of overall survival (OS) and recurrence-free survival (RFS).	single-center cohort study	primary tumors (Breslow thickness >4.0 mm) underwent SLNB	5-Y-RFS	positive patients was 32%, compared to 78% for negative patients. Significant predictors of poorer OS were increasing age (p=0.03), increasing Breslow thickness (p= 0.03) and SLNB positivity (p<0.0001). 5-Y-RFS was significantly worse in the SLNB positive population compared to the negative patients (p<0.0001); 27% vs. 66% respectively.	none	
Sabel et al. (2015)	To examine the use and benefit of SLN biopsy in elderly patients (>75 years)	Prospectively collected, database driven, single-center cohort study	952 patients	Disease-free (DFS) Melanoma-specific survival (MSS) Overall survival (OS)	Without adjusting for age or other confounders, OS, DFS, and distant DFS was higher among patients who underwent a SLN biopsy versus those who did not (p<0.001) and	funding source: none	3a

					among patients who had a negative SLN compared with those who had a positive SLN (p<0.001). For MSS, the SLN results were similarly prognostic, but the difference in MSS between patients undergoing SLN biopsy and those having WLE alone did not reach statistical significance (p=0.17).		
Satzger et al. (2014)	To evaluate the clinical outcome of sentinel positive patients receiving either a complete lymph node dissection or watchful waiting.	Retrospective, single-center cohort study	305 SLN-positive patients (247 received CLND) 58/305 (17%) patients did not undergo CLND. These were compared with a matched selection of 58 comparable patients who underwent CLND	Melanoma specific overall survival (MSS) Recurrence-free survival (RFS)	No significant differences in MSS (P=0.844) and RFS (P = 0.765) of non-CLND patients compared with CLND patients. Comparing the clinical outcome of 72 CLND patients with 34 non-CLND patients with minimal tumor	funding source: none	3a

					burden in SLN, there was no OS difference (P=0.610) nor RFS difference (P = 0.346).		
Teixeira et al. (2013)	To identify predictive factors associated with a positive SLNB and overall survival.	Retrospective, single-center cohort study	221 patients	SNLB positivity 5-year-survival-rate	Male gender, increasing Breslow thickness, tumor type, and absence of tumor-infiltrating lymphocytes were significantly associated with a positive SLNB. 5-year survival rates were 53.1% for SLN positive patients and 88.2% for SLN negative patients	funding source: none	3a
Tejera-Vaquerizo et al. (2015)	To evaluate in a large series of patients the effect on survival of the delay between excision of a primary melanoma and performance of sentinel-node	Multicenter, observational, retrospective, cohort study	1963 patients	Disease-free survival (DFS) Melanoma-specific survival (MSS)	A delay time of 40 days or less (HR 1.7 [1.2– 2.5]) increased Breslow thickness >2mm (HR 3.7 [1.4–10.7]), ulceration (HR, 1.6 [1.1–2.3]), sentinel-node	funding source: This work was supported by partially (Grants 03/0019, 05/0302, 06/0265, 09/1393 and 12/00840) from Fondo de	3a

	biopsy.				metastasis (HR 2.9 [1.9–4.2]), and primary melanoma localized in the head or neck were independently associated with worse melanoma-specific survival (all P < 0.03) Author claimed overrepresentation of high risk pts. in the early group for worse outcome of early SNB procedure.	Investigaciones Sanitarias, Spain; by the CIBER de Enfermedades Raras of the Instituto de Salud Carlos III, Spain; by the AGAUR 2009 SGR 1337 of the Catalan Government, Spain; by the European Commission under the 6th Framework Programme, Contract n°: LSHC-CT-2006-018702 (GenoMEL); and by the National Cancer Institute (NCI) of the US National Institute of Health (NIH) (CA83115).	
van der Ploeg et al. (2014)	To assess the therapeutic benefit of SNB in a large, nonrandomized patient cohort.	Retrospective, single-center cohort study	5840 patients receiving wide local excision (WLE) and SLB (n=2909) or WLE alone (observation group, OBS, n=2931).	Melanoma-specific survival (MSS) Disease-free survival (DFS) Regional recurrence-free survival Distant metastasis-	MSS was not significantly different for patients in the SNB and OBS groups. Stratified univariate analysis of MSS for	funding source: none	3a

				free survival (DMFS)	different thickness subgroups indicated a significantly better MSS for SNB patients with T2 and T3 melanomas (>1.0-4.0mm thick) (P=0.011), but this was not independently significant in multivariate analysis. Compared with OBS patients, SNB patients demonstrated improved DFS (P<0.001) and regional recurrence-free survival (P<0.001). There was also an improvement in DMFS for SNB patients with T2 and T3 melanomas (P=0.041).		
Venna et al. (2013)	To evaluate a cohort of patients with thin melanoma who	Retrospective, single-center cohort study	484 patients with T1 melanoma	Factors predicting SLN positivity Overall survival	34 patients had a positive SLNB finding. Four factors predicted a	funding source: none	3a

	have undergone SLNB to determine the factors that predict a higher risk of SLN metastasis, and to determine the prognostic impact of a positive SLNB result in patients with thin melanomas.				higher risk of SLN positivity: age 43 years or younger, Breslow depth 0.8 mm or greater, tumors on the lower extremity and trunk, and tumor-infiltrating lymphocyte level. By multivariate analysis, low tumor-infiltrating lymphocytes (P=.0015) and decreasing age (P=.0058) independently predicted SLN positivity. If 0 to 2 of these factors were present, the rate of a positive SLNB result was 3%; this increased to 15% with 3 factors present and to 30% if all 4 factors were present (P<.002). SLN-positive patients had significantly decreased survival		

					(P=.003), and SLN status was the most powerful predictor of survival (P=.009).		
White et al. (2014)	To determine the prognostic value of SLNs in thick (>4mm) melanoma.	Retrospective, single-center cohort study	120 patients (clinically node-negative)	Factor predicting positive SLN 5-Y-Disease-free survival (DFS) 5-Y-Overall survival (OS)	Factors predictive of positive SLN included male sex, ulceration, and high mitoses. 5-Y-DFS (positive SLN vs. negative SLN): 18% vs. 51% (p=0.018); positive SLN: HR: 2.85(1.2–3.69), p=0.01 5-Y-OS (positive SLN vs. negative SLN): 58% vs. 62% (p=0.04); positive SLN: HR: 2.91(1.02–4.0), p=0.02	funding source: none	
Wong et al. (2012)	To provide an evidence-based guideline on the use of lymphatic mapping and sentinel lymph node (SLN) biopsy in staging patients with newly	An Expert Panel was convened to develop clinical practice guideline recommendations based on a review of evidence from a systematic review of the medical	73 studies included	Recommendations for SLN biopsy and CLND	Intermediate-thickness melanomas: SLN biopsy is recommended for patients with cutaneous melanomas with Breslow thickness	funding source: none Guidelines provided by The American Society of Clinical Oncology (ASCO) and Society of	2a

	diagnosed melanoma.	literature.			of 1 to 4 mm at any anatomic site Thick melanomas: SLN biopsy may be recommended for staging purposes and to facilitate regional disease control for patients with melanomas that are T4 or > 4 mm in Breslow thickness Thin melanomas: There is insufficient evidence to support routine SLN biopsy for patients with melanomas that are T1 or < 1 mm in Breslow thickness, although it may be considered in selected high-risk patients Completion lymph node dissection is recommended for all patients with a positive SLN biopsy	Surgical Oncology (SSO)	

Yamamoto et al. (2015)	To evaluate SLNB in patients with thick (≥4mm tumor thickness), clinically lymph node-negative melanoma to provide additional insight into the indications for and relative value of SLNB in this setting.	Retrospective, single-center cohort study	571 patients	Frequency of positive SLNs False-negative-rate Disease-specific survival (DSS) Overall survival (OS) Recurrence free survival (RFS)	SLNB was performed in 412 pts (72%) whereas 46 pts (8.1%) presented with clinically lymph node-positive disease and 113 pts (20%) didnt undergo SLNB. A positive SLN was found in 161/412 pts (39.1%). 14 pts with a negative SLNB developed disease recurrence in the mapped lymph node basin (false-negative rate, 12.3%). DSS and OS for pts with a negative SLNB were 82.4 months and 53.4 months, respectively; 41.2 months and 34.7 months for pts with positive SLNB; and 26.8 months and 22 months, respectively, for pts with clinically	funding source: none	

					lymph node-positive disease (p<.0001). The median RFS was 32.4 months for pts who were SLNB negative, 14.3 months for pts who were SLNB positive, and 6.8 months for pts with clinically lymph node-positive disease (p<.0001).		

3.1.4.2.1. Literatur

Bamboat, Z.M., et al., Observation after a positive sentinel lymph node biopsy in patients with melanoma. Ann Surg Oncol, 2014. 21(9): p. 3117-23.
Beger, J., et al., A 10-year analysis of primary cutaneous malignant melanoma with sentinel lymph node biopsy and long-term follow-up. Int J Dermatol, 2013. 52(2): p. 220-30.
Cooper, C., et al., A 10-year, single-institution analysis of clinicopathologic features and sentinel lymph node biopsy in thin melanomas. J Am Acad Dermatol, 2013. 69(5): p. 693-9.
Cordeiro, E., et al., Sentinel Lymph Node Biopsy in Thin Cutaneous Melanoma: A Systematic Review and Meta-Analysis. Ann Surg Oncol, 2016. 23(13): p. 4178-4188.
Egger, M.E., et al., The lymph node ratio has limited prognostic significance in melanoma. J Surg Res, 2013. 179(1): p. 10-7.
Fortes, C., et al., The effect of time to sentinel lymph node biopsy on cutaneous melanoma survival. Am J Surg, 2016. 212(5): p. 935-940.
Geimer, T., et al., The impact of sentinel node dissection on disease-free and overall tumour-specific survival in melanoma patients: a single centre group-matched analysis of 1192 patients. J Eur Acad Dermatol Venereol, 2017. 31(4): p. 629-635.
Gyorki, D.E., et al., Sentinel Lymph Node Biopsy in T4 Melanoma: An Important Risk-Stratification Tool. Ann Surg Oncol, 2016. 23(2): p. 579-84.
Ipenburg, N.A., et al., Outcome of Melanoma Patients Who Did Not Proceed to Sentinel Node Biopsy After Preoperative Lymphoscintigraphy. Ann Surg Oncol, 2017. 24(1): p. 117-126.
Kachare, S.D., et al., The influence of sentinel lymph node biopsy on survival for intermediate-thickness melanoma. Ann Surg Oncol, 2014. 21(11): p. 3377-85.
Kachare, S.D., et al., Sentinel lymph node biopsy is prognostic but not therapeutic for thick melanoma. Surgery, 2015. 158(3): p. 662-8.
Kretschmer, L., et al., Nodal Basin Recurrence After Sentinel Lymph Node Biopsy for Melanoma: A Retrospective Multicenter Study in 2653 Patients. Medicine (Baltimore), 2015. 94(36): p. e1433.
Mitteldorf, C., et al., Sentinel node biopsy improves prognostic stratification in patients with thin (pT1) melanomas and an additional risk factor. Ann Surg Oncol, 2014. 21(7): p. 2252-8.
Mosquera, C., et al., Population-Based Analysis of Completion Lymphadenectomy in Intermediate-Thickness Melanoma. Ann Surg Oncol, 2017. 24(1): p. 127-134.
Mozzillo, N., et al., Superficial and deep lymph node dissection for stage III cutaneous melanoma: clinical outcome and prognostic factors. World J Surg Oncol, 2013. 11: p. 36.
Mozzillo, N., et al., Sentinel node biopsy in thin and thick melanoma. Ann Surg Oncol, 2013. 20(8): p. 2780-6.
Oude Ophuis, C.M., et al., The interval between primary melanoma excision and sentinel node biopsy is not associated with survival in sentinel node positive patients - An EORTC Melanoma Group study. Eur J Surg Oncol, 2016. 42(12): p. 1906-1913.
Patuzzo, R., et al., Accuracy and prognostic value of sentinel lymph node biopsy in head and neck melanomas. J Surg Res, 2014. 187(2): p. 518-24.
Reintgen, M., et al., Evidence for a better nodal staging system for melanoma: the clinical relevance of metastatic disease confined to the sentinel lymph nodes. Ann Surg Oncol, 2013. 20(2): p. 668-74.
Ribero, S., et al., Sentinel Lymph Node Biopsy in Thick-Melanoma Patients (N=350): What is Its Prognostic Role? Ann Surg Oncol, 2015. 22(6): p. 1967-73.
Rughani, M.G., et al., Sentinel node status predicts survival in thick melanomas: the Oxford perspective. Eur J Surg Oncol, 2012. 38(10): p. 936-42.
Sabel, M.S., et al., Sentinel Lymph Node Biopsy Use Among Melanoma Patients 75 Years of Age and Older. Ann Surg Oncol, 2015. 22(7): p. 2112-9.

Satzger, I., et al., Is there a therapeutic benefit of complete lymph node dissection in melanoma patients with low tumor burden in the sentinel node? Melanoma Res, 2014. 24(5): p. 454-61.
Teixeira, V., et al., Prediction of sentinel node status and clinical outcome in a melanoma centre. J Skin Cancer, 2013. 2013: p. 904701.
Tejera-Vaquerizo, A., et al., Effect of time to sentinel-node biopsy on the prognosis of cutaneous melanoma. Eur J Cancer, 2015. 51(13): p. 1780-93.
van der Ploeg, A.P., et al., Outcome following sentinel node biopsy plus wide local excision versus wide local excision only for primary cutaneous melanoma: analysis of 5840 patients treated at a single institution. Ann Surg, 2014. 260(1): p. 149-57.
Venna, S.S., et al., Analysis of sentinel lymph node positivity in patients with thin primary melanoma. J Am Acad Dermatol, 2013. 68(4): p. 560-7.
White, I., et al., Clinical impact of sentinel lymph node biopsy in patients with thick (>4 mm) melanomas. Am J Surg, 2014. 207(5): p. 702-7; discussion 707.
Wong, S.L., et al., Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. J Clin Oncol, 2012. 30(23): p. 2912-8.
Yamamoto, M., et al., Sentinel lymph node biopsy is indicated for patients with thick clinically lymph node-negative melanoma. Cancer, 2015. 121(10): p. 1628-36.

3.2. Frage II.5. und III.4. Tumorlast am Sentinel-Node und komplettierende Lymphadenektomie – De-novo-Recherche

Frage II.5. Hat die Tumorlast am Sentinel-Node eine prognostische Bedeutung?

Frage III.4. Ist eine komplettierende LAD bei Mikrometastasen am SLN indiziert?

3.2.1. Datenbanken, Suchstrategien, Trefferzahlen

3.2.1.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
Medline	melanoma[title] AND (("sentinel"[tiab] OR "sentinel lymph node"[tiab] OR sln[tiab] OR slne[tiab]) AND (("tumor load"[tiab] OR "tumor burden"[tiab]) OR (prognosis[tiab] OR survival[tiab])) OR starz OR dewar OR rotterdam OR s-classification)	26.01.2012	747
Cochrane Library	(melanoma and (sentinel or "sentinel lymph node" or sln or slne) and ("tumor load" or "tumor burden" or prognosis or survival or starz or dewar or rotterdam or "s classification")).ti,ab.	19.01.2012	27
Embase	(melanoma and (sentinel or "sentinel lymph node" or sln or slne) and ("tumor load" or "tumor burden" or prognosis or survival or starz or dewar or rotterdam or "s classification")).ti,ab.	23.01.2012	872

Bemerkungen: Eine erste Literaturrecherche in Medline und und Cochrane erfolgte am 01.02.2011 bzw. für Embase am 11.05.2011. Die Update-Recherche wurde am 23.01.2012 (Embase) bzw. am 26.01.2012 (Medline) und am 19.01.2012 (Cochrane) durchgeführt. In der Tabelle angegeben sind die Trefferzahlen der letzten Recherche.

Da die Literaturbasis für die Fragen II.5 und III.4 die gleiche ist (bei gleicher Suchstrategie), diente die Tabelle sowohl der AG chirurgische Therapie als auch der AG Sentinel als Grundlage zur Beantwortung der Fragen III.4 bzw. II.5.

3.2.1.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
Medline	“melanoma“[tiab] AND (“sentinel“[tiab] OR “Sentinel Lymph Node Biopsy”[MeSH]) AND (“survival”[tiab] OR “mortality”[tiab] OR “relapse”[tiab] OR “recurrence”[tiab] OR “sensitivity”[tiab] OR “specificity”[tiab] OR “accuracy” OR “outcome”[tiab] OR “prognos*”[tiab] OR “predict*”[tiab] OR “assoc*”[tiab]) AND ("2011.01.11"[Date - Publication] : "2015.09.16"[Date - Publication])	16.09.2015	499
Cochrane Library	(melanoma and (sentinel or "sentinel lymph node" or sln or slne) and ("tumor load" or "tumor burden" or prognosis or survival or starz or dewar or rotterdam or "s classification")).ti,ab.	16.09.2015	51

Bemerkungen: Die bisherige Empfehlung aus der S3-Leitlinie Melanom zu der Schlüsselfrage „Hat die Tumorlast am Sentinel-Node eine prognostische Bedeutung?“ (AG Sentinel) basiert auf Studien mit einem Evidenzlevel von 2b. Da es nur wenige Studien gibt mit einem höheren Evidenzlevel, wurden auch diesmal Studien in die Evidenztabelle aufgenommen, die ein Evidenzlevel bis schlechtestens 2b haben.

Da die Literaturbasis für die Fragen II.5 und III.4 die gleiche ist (bei gleicher Suchstrategie), diente die Tabelle sowohl der AG chirurgische Therapie als auch der AG Sentinel als Grundlage zur Beantwortung der Fragen III.4 bzw. II.5.

Die Suche in Cochrane erbrachte ein relevantes Review, was wiederrum nur eine Studie inkludierte.

3.2.1.3. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
Medline	“melanoma“[tiab] AND (“sentinel“[tiab] OR “Sentinel Lymph Node Biopsy”[MeSH]) AND (“survival”[tiab] OR “mortality”[tiab] OR “relapse”[tiab] OR “recurrence”[tiab] OR “sensitivity”[tiab] OR “specificity”[tiab] OR “accuracy” OR “outcome”[tiab] OR “prognos*”[tiab] OR “predict*”[tiab] OR “assoc*”[tiab]) AND ("2015.09.16"[Date - Publication] : "2016.09.20"[Date - Publication])	20.09.2016	119
Cochrane Library	(melanoma and (sentinel or "sentinel lymph node" or sln or slne) and ("tumor load" or	20.09.2015	51

	"tumor burden" or prognosis or survival or starz or dewar or rotterdam or "s classification")).ti,ab.		

3.2.2. Auswahlkriterien

3.2.2.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer (inkl. Dupletten)	1646
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews
Anzahl nach Abstractscreening	79
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	*25*

3.2.2.2. Aktualisierungsrecherche 2015

Auswahl der Literatur	
Gesamttreffer (inkl. Dubletten)	550
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews
Anzahl nach Abstractscreening	408

Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	11

3.2.2.3. Aktualisierungsrecherche 2016

Auswahl der Literatur	
Gesamttreffer (inkl. Dubletten)	119
Einschlusskriterien	Systematische Reviews, Meta-Analysen Prospective Studien Sprachen: e,dt
Ausschlusskriterien	Case Reports, narrative Reviews
Anzahl nach Abstractscreening	40
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	

3.2.3. Evidenztabelle

3.2.3.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Mocellin et al. (2007)	To investigate the prognostic value of PCR status of SLN.	Systematic review and meta-analysis	4019 patients who underwent SLN biopsy for clinical stage I to II cutaneous melanoma	Recurrence rate Overall survival Sensitivity, specificity, positive and negative predictive value (PPV, NPV)	Pooled positivity rate: 20.3% pathology-based In patients with pathology-negative SLN: PCR positive in 42.3%	Funnel plot did not show publication bias	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					In patients with pathology-positive SLN: PCR negative (false negative) in 49% PCR positivity in patients with pathology-positive SLN: 95.1% In patients with pathology-negative SLN: 46.6% Disease recurrence rate: 16.8% among PCR-positive patients; 8.7% in PCR negative patients PCR sensitivity 57.4%, specificity 61.1%, accuracy 60.6%, PPV 16.8%, NPV 91.3%		
Elsaesser et al. (2012)	investigated survival probabilities and prognostic factors in sentinel lymph	Cohort study	1909 SLNB staged patients with primary CM	5-year-OS Prognostic factors	5-year OS in SLNB negative patients: 90.3% (IB 96.2%, IIA 87.0%, IIB 78.1%, IIC 72.6%).		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	node biopsy (SLNB) staged patients with cutaneous melanoma (CM) with the aim of defining subgroups of patients who are at higher risk for recurrences and who should be considered for adjuvant clinical trials.				5-year OS in patients with micrometastases (stage IIIA/B): 70.9% which was clearly less favorable than for stages I-II. Multivariate analysis revealed tumor thickness, ulceration, body site, histopathologic subtype and SLNB status as independent significant prognostic factors.		
Quaglino et al. (2011)	to evaluate which prognostic variables could predict NSLN invasion in SLN-positive patients and their impact on the overall survival (OS).	Cohort study	603 patients who had undergone SLNB for melanoma	OS prognostic variables on CLND results and disease course.	Breslow thickness, ulceration and micro/macrometastatic pattern of SLN invasion carried a significantly independent higher likelihood of NSLN involvement; Starz classification did	Retrospective chart review	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					not maintain a statistical significance in multivariate analysis. NSLN involvement, was found in 33.3% of patients with one and 55.9% with ≥adverse parameters (p = 0.0001).		
Van der Ploeg et al. (2011)	To determine the role of tumor load and tumor site in the SN as prognostic factors for survival and as predictive factors for NSN positivity.	Cohort study	1080 patients with positive SLN	NSN status Overall survival	Significant factors regarding NSN status: age, study center, histology and location of the primary, Clark level, Breslow thickness, Rotterdam criteria, Rotterdam criteria II, III, and IV, Dewar criteria, Dewar criteria II, and RDC criteria Rate of additional positive lymph	Retrospective design Large patient cohort For detailed survival rates see original article	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					nodes in the group of patients with submicrometastases (≤ 0.1 mm, Rotterdam criteria): 9% Patients with 0.1 to 1.0 mm: 16%		
Murali et al (2011)	To investigate in detail the influence of SN tumor characteristics and clinical and primary tumor parameters on regional lymph node recurrence, distant metastasis, and survival.	Cohort study	409 patients with primary cutaneous melanoma who underwent SNB	DFS melanoma-specific survival (MSS)	Primary tumor features (presence of ulceration and satellites) and presence of ENS in SNs were independent predictors of DFS, DMFS, and MSS. In addition, poorer DFS was independently associated with primary tumor site (head/neck and limbs vs. trunk), SN tumor features (MaxSize >2 mm, presence of PLI) and positive NSN in CLND; other factors	Same patient cohort as Murali et al. (2010): Non-Sentinel Node Risk Score (N-SNORE): A Scoring System for Accurately Stratifying Risk of Non-Sentinel Node Positivity in Patients With Cutaneous Melanoma With Positive Sentinel Lymph Nodes	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					independently predictive of DMFS were male sex, primary tumor features (absence of TILs), and SN tumor MaxSize >10 mm; and age ≥50 years was an additional independent predictor of MSS. CLND status was not an independent predictor of DMFS or MSS.		
Balch et al. (2010)	To determine the survival rates and independent predictors of survival using a contemporary international cohort of patients with stage III melanoma.	Cohort study	2313 patients with stage III disease	Overall survival	5-year survival for patients with micrometastases: 67% When stratified by tumor thickness, ulceration, and number of involved nodes, 5-year-suvival rates were: 87% for a single nodal micrometastasis	Patient cohort partially identical with Balch et al. 2004 and 2009 For survival curves see original article	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					arising from a nonulcerated primary melanoma ≤ 2.0 mm in thickness, 23% for patients with four or more nodal macrometastases from an ulcerated primary melanoma greater than 6.0 mm in thickness For patients with nodal micrometastases independent predictors of survival were patient age, sex, tumor thickness, ulceration, primary anatomic site, and number of tumor-bearing lymph nodes For patients with nodal macrometastases, age, ulceration, anatomic site, and		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					number of tumor-bearing lymph nodes independently predicted survival		
Meier et al. (2010)	To compare the RFS and OS of 697 melanoma patients as predicted by various classification systems.	Cohort study	697 consecutive patients with primary cutaneous melanoma (Breslow tumor thickness ≥ 1 mm)	Recurrence-free survival Overall survival	CLND positivity rate 15.4% 21% recurrence rate 14% mortality rate (causes related to melanoma) In multivariate analysis, independent predictors for RFS were greatest dimension of the largest tumor cell deposit (cutoff point, <0.1 mm vs ≥ 0.1 mm), TPD (cutoff point, ≤ 2 mm vs >2 mm), and capsular involvement; TPD and capsular involvement also	Suggestion of new classification system Hannover II	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					for OS		
Balch et al. (2009)	To revise the staging system for cutaneous melanoma on the basis of data from an expanded American Joint Committee on Cancer (AJCC) Melanoma Staging Database.	Cohort study	3,307 stage III patients.	Overall survival	Independent predictors for survival: number of tumor-bearing nodes, tumor burden at the time of staging (ie, microscopic v macroscopic), presence or absence of primary tumor ulceration, and thickness of the primary melanoma 5-year survival rates: 70% for patients with T1-4N1M0 melanomas, 39% for patients with T1-4N3M0 melanomas	For stage III survival curves, see Fig. 1 in the publication. Patient cohort partially identical with Balch et al. 2004	2b
van Akkooi et al. (2008)	to evaluate the survival rate of minimal SN tumor burden	Cohort study	388 SN positive patients	overall survival (OS)	SN tumor burden increased significantly with tumor thickness.	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					estimated 5-year overall survival: - for SUB-micrometastases <0.1 mm SN tumor burden: 91% - for 0.1- to 1.0-mm SN tumor burden: 61% - for >1 mm SN tumor burden: 51% - for </=0.2 mm: 89%. Independent prongostic factors in OS (multivariate analysisi): - SN tumor burden - T4 primary tumors		
Satzger et al. (2008)	To compare different parameters of the SLN and to identify the parameters that are most important for the prediction of non-sentinel lymph node (NSLN)	Cohort study	180 patients with primary cutaneous melanoma	NSLN involvement	NSLN involvement in the CLND specimen in 16.0% of patients Primary melanomas significantly thicker, more often ulcerated, and	Patient population subgroup of Meier et al. (2010)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	involvement.				regressive in patients with NSLN involvement compared with patients without NSLN involvement Upon multivariate analysis, the three significant parameters were positivity by H&E (versus immunohistochemistry alone), relative tumor area > 10%, and presence of perinodal intralymphatic tumor		
Debarbieux et al. (2007)	To confirm the prognostic value of SLN biopsy (SLNB); to correlate patient prognosis to the micromorphometric features of SLN metastasis in SLN-positive patients; and to correlate these	Cohort study	455 patients	Overall survival Disease-specific survival	SLN positivity rate 22% Survival significantly shorter in SLN-positive than in SLN-negative patients Prognostic factor	10 patients lost to follow-up	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	micromorphometric features to the likelihood of positive completion lymph node dissection (CLND).				of disease-free survival: extracapsular invasion Prognostic factors of disease-specific survival: ulceration, maximum diameter of largest metastasis		
Satzger et al. (2007a)	To determine the prognostic relevance of histopathological characteristics of micrometastases in the SLN.	Cohort study	169 patients with primary cutaneous melanoma (Breslow's tumour thickness ≥ 1 mm) and positive SLN diagnosed from April 2000 to December 2004.	Overall survival (OS) Relapse-free survival (RFS)	Relapse rate 30% Mortality rate 20% (15% melanoma-related, 5% unrelated) Independent prognostic factors in multivariate analysis: invasion of capsule (present versus absent), tumor penetrative depth (TPD) with a cut-off of 2 mm (< 2 mm versus ≥ 2 mm) and deposit size (<	Patient population subgroup of Meier et al. (2010)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					30 cells versus ≥ 30 cells)		
van Akkooi et al. (2006)	to identify a SN positive patient group, which can be spared CLND	Cohort study	77 SN-positive patients	Disease-free survival Estimated 5-year survival Non-SN-positivity	Estimated 5-year OS rates: <0.1 mm SN tumor burden: 100% 0.1–1.0 mm SN tumor burden: 63% >1.0 mm SN tumor burden: 35% Distant metastases in <0,1 mm SN-positive patients: 1/16 = 6.3% Distant metastasis-free survival in <0,1 mm SN positive patients: 91% (identical to the 5-yr OS of SN negative patients) no additional non-SN positivity for SN-micro-metastases <0.1 mm.	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					multivariate analysis: SN tumor burden was the most important prognostic factor for DFS (P = 0.005) and OS (P = 0.03).		
Shivers et al. (2007)	To determine the relevance of low-volume disease of the sentinel lymph node detected only by RT-PCR-based assays.	Cohort study	311 Patients with melanoma	Overall survival Relapse-free survival Sensitivity and specificity of histology and PCR regarding the prediction of recurrence/death	SLN positivity rate: 19% in histology, 67% by PCR Recurrence rate: 42% of histologically and PCR positive patients 22% of histologically negative, but PCR positive patients 6.6% for histologically and PCR negative patients Prediction of death: Sensitivity of histology 47%, specificity 87%	Very long follow-up time (up to 15 years) Change in technique during the course of time	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Sensitivity of PCR 88%, specificity 38%		
Baehner et al. (2012)	To (1) quantitate tumor burden in sentinel lymph nodes (SLNs), and (2) assess the independent contributions of SLN tumor burden and primary melanoma thickness (PMT) with respect to progression-free survival (PFS) and overall survival (OS).	Cohort study	63 patients with one or more positive SLNs were available	Progression-free survival (PFS) OS	Cox proportional-hazard regression model: After adjusting for age and gender, both MMS maximum metastasis size (MMS)and PMT primary melanoma thickness were highly significant and provided independent prognostic information.		2b-
Fink et al. (2011)	to predict the likelihood of further non-SN metastases on the basis of earlier published micromorphometric classifications of SN metastases	Cohort study	Specimens of 124 positive-SN basins and subsequent complete lymph node dissection (121 patients)	NSN-positivity	metastases in non-SNs were found in 30 lymph node basins (24.2%). Classification according to Dewar: Significant correlation between the	Retrospective study	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					microanatomic location of the metastases and non-SN involvement (P=0.004). Classification according to Starz: Significant correlation between S.classification of SN and non-SN status (P<0.001) Classification of the size of the SN metastases according to the Rotterdam criteria for SN tumor burden: significant correlation with additional non-SN involvement (P=0.007) no statistically significant difference between		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					the three classifications (P=0.6).		
Murali et al. (2010)	To investigate clinicopathologic factors that predict NSN positivity in an attempt to identify patients who may be safely spared completion lymph node dissection (CLND).	Cohort study	409 patients	NSN positivity	Predictive of NSN status in muultivariate analysis: clinical characteristics (sex), primary tumor characteristics (ulceration and regression), and %PosSN	Retrospective design For details of the score, see original article	2b-
Riber-Hansen et al. (2009)	To use objective stereological techniques to correlate accurately total SLN tumour burden with recurrence and patient survival.	Cohort study	335 consecutive melanoma patients	Recurrence rate Overall survival	SLN positivity rate 30.3% Benign naevus inclusions in 36.1% of SLN patients Recurrence rate 10.4% (25.3% for patients positive in histology, 3.9% for negative patients) Mortality rate from metastatic disease	Description of study drop-outs described in another publication	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					6.7% (14.1% for patients positive in histology, 3.5% for negative patients)		
Van der Ploeg et al. (2009)	To evaluate the micromorphometric Starz classification in melanoma patients.	Cohort study	70 patients with a cutaneous melanoma	Disease-free survival (DFS)	Lymph node recurrence rate: 0% in S-I, S-II 12% in S-III Overall 3-year survival: 100% in S-I, S-II 80% in S-III 3-year disease-free survival rates: were 83% in S-I, S-II 60% in S-III	Small patient cohort	2b-
Frankel et al. (2008)	To examine whether the size and location of the metastases within the SLN may help further stratify the risk of additional positive NSLN.	Cohort study	144 melanoma patients	Presence of metastatic non-sentinel nodes	Independent predictors of additional disease in CLND: primary location on the head and neck or lower extremity, Breslow thickness > 4 mm, the presence of angiolymphatic invasion,	Design not consequently prospective	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					satellitosis, extranodal extension, three or more positive SLN and tumor burden within the SLN>1% surface area		
Satzger et al. (2007b)	To determine the prognostic significance of isolated HMB45 and/or Melan A positive cells (immunhistochemically positive cells, IPC) in melanoma SLN.	Cohort study	477 patients with primary cutaneous melanoma	Overall survival (OS) Relapse-free survival (RFS)	3 groups were differentiated according to the findings in the SLN: Group 1 included 308 patients with histologically and immunohistochemically negative SLN, group 2 included 47 patients with IPC, and group 3 included 122 patients with micrometastases. Relapse rate: 11.7% of SLN negative patients, 12.8% of IPC+ patients, 37.7% of histology+ patients	Patient population subgroup of Meier et al. (2010)	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Mortality rate: 5.5% of SLN negative patients, 6.4% of IPC+ patients, 23.8% of histology+ patients		
Namikawa et al. (2012)	to re-evaluate microscopic classifications of metastatic sentinel lymph nodes (SLN) in the Japanese population	Cohort study	450 patients, including the 149 cases with SLN metastasis,	LN positivity-rate	additional LN positivity rate of 0% only in patients with a maximum diameter category of less than 0.1 mm. As compared with that in the SLN metastasis-negative cases, the prognosis was poorer in cases with SLN metastasis, even those with lesions falling under the maximum diameter category of less than 0.1 mm, invasion depth category of SI (</=0.3 mm) and microanatomic	retrospective study	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					location category of subcapsular.		
Starz et al. (2004)	to identify the relevant predictors for the presence versus absence of nonsentinel lymph node metastases in CLND specimens	Cohort study	SLNE cohort: 324 patients pre-SLNE cohort:274 consecutive melanoma patients	Overall survival survival without distant metastases	S-classification was the most significant independent predictor of the presence/absence of NSN-metastases in binary logistic regression: (P = .010; adjusted relative risk = 3.31). survival without distant metastases: Highly significant divergence of the Kaplan-Meier curves of the pre-SLNE- and SLNE-cohort (P = .0057 by log rank test). Overall survival: Kaplan-Meier curves diverge after about 4 years of follow-up (P-=	Patients who underwent SLNE → same population as in Starz et al. 2001 (see above)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					.03). Cox regressions: S-classification is a significant independent predictor for distant metastasis (P = .014) and overall survival (P = .009)		
Bogenrieder et al. (2011)	to predict the absence of non-SN metastases in a multicentre study of patients with a positive SN based on primary melanoma features and SN tumour load.	Cohort study	70 SN positive patients	NSN-positivity	18/70 patients had non-SN metastases. No non-SN-metastases in patients with: - a Breslow thickness <2.0 mm and an SN tumour load <0.2 mm2 - a Breslow thickness <2.0 mm and SN penetrative depth <600 lm - a Breslow thickness <2.0 mm and a diameter of the largest SN	Differences in survival between different microanatomic locations of sentinel node metastases not investigated No follow-up	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					deposit <500 lm logistic regression: the SN metastatic area was the only independent factor predicting the presence of non-SN metastases		
Dewar et al. (2004)	to identify criteria that might be used in selecting patients who should undergo CLND	Cohort study	146 SN-positive patients	NSN-positivity	evidence of melanoma metastases in NSN in 24 of CLND specimens (16.4%) significant correlation between the microanatomic location and NSN involvement (subcapsular metastatic deposits in 26%: no NSN-involvement. SN-metastases with different microanatomic location: NSN-involvement in	Retrospective study differences in survival between different microanatomic locations of sentinel node metastases not investigated No follow-up	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					22,2%) strong correlation between depth of metastatic deposit from the capsule of the SN and NSN involvement (3/24 patients (12.5%) with positive NSNs had deposits less than 1mmin depth.)		
Starz et al. (2001)	predictive capacity of S-classification	Cohort study	342 patients with primary melanoma and SLNE (389 lymph node Regions) 62 patients with positive SLNs: 42 received RCLND	Presence of metastases survival	325 SLNs: S0 24 SLNs: S1 22 SLNs: S2 18 SLNs: S3. Correlation of the S categories with the T categories (of the pTNM classification) (Spearman correlation; P = 0.0001), occurrence of melanoma-positive non-SLN	Short follow-up Ulceration of the primary melanoma not included in this analysis (multivariate analysis directly using the T and S classifications as variables was not possible)	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					significantly increased from 0 of 12 in S1 SLNs to 2 of 13 in S2 SLNs and 9 of 15 in S3 SLNs (P = 0.001; chi-square test). The risk of developing distant metastases was dependent on the T classification (P < 0.0001; log rank test) and S-classification (P < 0.0001) T classification of the primary melanoma and S-classification= highly significant predictor for distant metastasis (P < 0.001). It turned out to be an independent factor of influence on distant metastasis and		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival in multivariate Cox analyses, which included tumor thickness, primary tumor site, patient gender, and patient age as covariates.		

3.2.3.1.1. Literatur

Baehner FL, Li R, Jenkins T, et al. The Impact of Primary Melanoma Thickness and Microscopic Tumor Burden in Sentinel Lymph Nodes on Melanoma Patient Survival. Ann Surg Oncol 2011

Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199-6206

Balch CM, Gershenwald JE, Soong SJ, et al. Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. J Clin Oncol 2010;28:2452-2459

Bamboat ZM, Konstantinidis IT, Kuk D, Ariyan CE, Brady MS, Coit DG. Observation after a positive sentinel lymph node biopsy in patients with melanoma. Ann Surg Oncol. 2014;21(9):3117-3123.

Bogenrieder T, van Dijk MR, Blokx WA, et al. No non-sentinel node involvement in melanoma patients with limited Breslow thickness and low sentinel node tumour load. Histopathology 2011;59:318-326

Debarbieux S, Duru G, Dalle S, et al. Sentinel lymph node biopsy in melanoma: a micromorphometric study relating to prognosis and completion lymph node dissection. Br J Dermatol 2007;157:58-67

Dewar DJ, Newell B, Green MA, et al. The microanatomic location of metastatic melanoma in sentinel lymph nodes predicts nonsentinel lymph node involvement. J Clin Oncol 2004;22:3345-3349

Egger ME, Bower MR, Czyszczon IA, et al. Comparison of sentinel lymph node micrometastatic tumor burden measurements in melanoma. J Am Coll Surg. 2014;218(4):519-528.

Elsaesser O, Leiter U, Buettner PG, et al. Prognosis of Sentinel Node Staged Patients with Primary Cutaneous Melanoma. PLoS One 2012;7:e29791

Feldmann R, Fink AM, Jurecka W, Rappersberger K, Steiner A. Accuracy of the non-sentinel node risk score (N-SNORE) in patients with cutaneous melanoma and positive sentinel lymph nodes: a retrospective study. Eur J Surg Oncol. 2014;40(1):73-76.

Fink AM, Weihsengruber F, Duschek N, et al. Value of micromorphometric criteria of sentinel lymph node metastases in predicting further nonsentinel lymph node metastases in patients with melanoma. Melanoma Res 2011;21:139-143

Frankel TL, Griffith KA, Lowe L, et al. Do micromorphometric features of metastatic deposits within sentinel nodes predict nonsentinel lymph node involvement in melanoma? Ann Surg Oncol 2008;15:2403-2411

Kibrite A, Milot H, Douville P, et al. Predictive factors for sentinel lymph nodes and non-sentinel lymph nodes metastatic involvement: a database study of 1,041 melanoma patients. Am J Surg. 2015.

Kim C, Economou S, Amatruda TT, Martin JC, Dudek AZ. Prognostic significance of microscopic tumor burden in sentinel lymph node in patients with cutaneous melanoma. Anticancer Res. 2015;35(1):301-309.

Meier A, Satzger I, Volker B, et al. Comparison of classification systems in melanoma sentinel lymph nodes--an analysis of 697 patients from a single center. Cancer 2010;116:3178-3188

Mocellin S, Hoon DS, Pilati P, et al. Sentinel lymph node molecular ultrastaging in patients with melanoma: a systematic review and meta-analysis of prognosis. J Clin Oncol 2007;25:1588-1595

Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014;370(7):599-609.

Murali R, Desilva C, Thompson JF, et al. Factors predicting recurrence and survival in sentinel lymph node-positive melanoma patients. Ann Surg 2011;253:1155-1164

Murali R, Desilva C, Thompson JF, et al. Non-Sentinel Node Risk Score (N-SNORE): a scoring system for accurately stratifying risk of non-sentinel node positivity in patients with cutaneous melanoma with positive sentinel lymph nodes. J Clin Oncol 2010;28:4441-4449

Nagaraja V, Eslick GD. Is complete lymph node dissection after a positive sentinel lymph node biopsy for cutaneous melanoma always necessary? A meta-analysis. Eur J Surg Oncol. 2013;39(7):669-680.

Namikawa K, Yamazaki N, Nakai Y, et al. Prediction of additional lymph node positivity and clinical outcome of micrometastases in sentinel lymph nodes in cutaneous melanoma: A multi-institutional study of 450 patients in Japan. J Dermatol 2012;39:130-137

Quaglino P, Ribero S, Osella-Abate S, et al. Clinico-pathologic features of primary melanoma and sentinel lymph node predictive for non-sentinel lymph node involvement and overall survival in melanoma patients: A single centre observational cohort study. Surg Oncol 2011;20:259-264

Riber-Hansen R, Nyengaard JR, Hamilton-Dutoit SJ, et al. Metastatic melanoma volume in sentinel nodes: objective stereology-based measurement predicts disease recurrence and survival. Histopathology 2009;54:796-803

Satzger I, Meier A, Zapf A, Niebuhr M, Kapp A, Gutzmer R. Is there a therapeutic benefit of complete lymph node dissection in melanoma patients with low tumor burden in the sentinel node? Melanoma Res. 2014;24(5):454-461.

Satzger I, Volker B, Al Ghazal M, et al. Prognostic significance of histopathological parameters in sentinel nodes of melanoma patients. Histopathology 2007;50:764-772

Satzger I, Volker B, Meier A, et al. Criteria in sentinel lymph nodes of melanoma patients that predict involvement of nonsentinel lymph nodes. Ann Surg Oncol 2008;15:1723-1732

Shivers S, Jakub J, Pendas S, et al. Molecular staging for patients with malignant melanoma. Expert Rev Anticancer Ther 2007;7:1665-1674

Starz H, Balda BR, Kramer KU, et al. A micromorphometry-based concept for routine classification of sentinel lymph node metastases and its clinical relevance for patients with melanoma. Cancer 2001;91:2110-2121

Starz H, Siedlecki K, Balda BR. Sentinel lymphonodectomy and s-classification: a successful strategy for better prediction and improvement of outcome of melanoma. Ann Surg Oncol 2004;11:162S-8S

van Akkooi AC, de Wilt JH, Verhoef C, et al. Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? Ann Oncol 2006;17:1578-1585

van Akkooi AC, Nowecki ZI, Voit C, et al. Sentinel node tumor burden according to the Rotterdam criteria is the most important prognostic factor for survival in melanoma patients: a multicenter study in 388 patients with positive sentinel nodes. Ann Surg 2008;248:949-955

van der Ploeg AP, van Akkooi AC, Haydu LE, et al. The prognostic significance of sentinel node tumour burden in melanoma patients: an international, multicenter study of 1539 sentinel node-positive melanoma patients. Eur J Cancer. 2014;50(1):111-120.

van der Ploeg AP, van Akkooi AC, Rutkowski P, et al. Prognosis in Patients With Sentinel Node-Positive Melanoma Is Accurately Defined by the Combined Rotterdam Tumor Load and Dewar Topography Criteria. J Clin Oncol 2011

van der Ploeg AP, van Akkooi AC, Rutkowski P, et al. Prognosis in patients with sentinel node-positive melanoma without immediate completion lymph node dissection. Br J Surg. 2012;99(10):1396-1405.

van der Ploeg IM, Kroon BB, Antonini N, et al. Is completion lymph node dissection needed in case of minimal melanoma metastasis in the sentinel node? Ann Surg 2009;249:1003-1007

Wevers KP, Murali R, Bastiaannet E, et al. Assessment of a new scoring system for predicting non-sentinel node positivity in sentinel node-positive melanoma patients. Eur J Surg Oncol. 2013;39(2):179-184.

3.2.3.2. Aktualisierungsrecherche 2015

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Morton et al. 2014	To evaluate the outcomes in melanoma patients (SNB vs. nodal observation)	RCT	Melanoma patients (CL III and a Breslow thickness >/= 1 mm and CL >/= IV and any Breslow thickness) 1661 patients underwent randomization: Observation group: wide excision and nodal observation with lymphadenectomy for nodal relapse biopsy group : wide excision and SNB with immediate lymphadenectomy for nodal metastases detected on biopsy	5- and 10-year-Melanoma specific survival 5- and 10-year disease-free survival Survival with tumor-positive and tumor-negative SN Incidence of SN-metastases and incidence of clinically detected nodal metastases	Melanoma specific survival rate: 20.8% with and 79.2% without nodal metastases intermediate-thickness melanomas: - 10-year disease-free survival rates: biopsy group 71,3 +/- 1,8% vs. observation group 64,7+/- 2,3% - distant disease-free survival: significantly improved when patients with nodal metastases received immediate rather than delayed lymphadenectomy	10-year follow-up/ 215 patients were lost to follow-up Different sentinel mapping procedures Different follow-up procedures in participating sites High rate of false negative biopsy results Ascertainment bias For further details and survival curves: see full-text and appendix	1b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- 10-year melanoma-specific survival rates: biopsy group 81.4±1.5% vs. observation group 78.3±2.0% - 10-year melanoma-specific survival rate: 62.1±4.8% for patients with metastasis vs. 85.1±1.5% for patients without metastasis thick melanomas: - 10-year disease-free survival rates: biopsy group 50,7 +/- 4,0% vs. observation group 40,5+/- 4,7% - 10-year melanoma-specific survival rates: no significant treatment-		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					related difference between the biopsy and the observation group (data see full-text) - 10-year melanoma-specific survival rate: 48.0±7.0% for patients with metastases vs. 64.6±4.9% for patients without metastases Similar rates of nodal metastases in biopsy and observation group		
Nagaraja et al. 2013	to determine which of the clinicopathologic prognostic factors could be used to predict the presence of positive non-SLNs.	Systematic research with meta-analysis	54 studies included with a total number of patients of 8388		The pooled estimates significantly associated with the high likelihood of NSN metastases were: ulceration (OR: 1.88, 95% CI: 1.53-2.31),	differences in sample size, populations studied, protocols for pathologic processing and examination of primary tumors and SNs, and	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					satellitosis (OR: 3.25, 95% CI: 1.86-5.66), neurotropism (OR: 2.51, 95% CI: 1.39-4.53), >1 positive SLN (OR: 1.77, 95% CI: 1.2-2.62), Starz 3 (old) (OR: 1.83, 95% CI: 0.89-3.76), angiolymphatic invasion (OR: 2.46, 95% CI: 1.34-4.54), extensive location (OR: 2.22, 95% CI: 1.74-2.81), macrometastases >2 mm (OR: 1.95, 95% CI: 1.61-2.35), extranodal extension (OR: 3.38, 95% CI: 1.79-6.40) and capsular involvement (OR: 3.16, 95% CI: 1.37-7.27). Characteristics associated with low risk of NSN	methods of data analysis, as well as the effects of interobserver variation in pathologic interpretation. Retrospective studies included	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastases: subcapsular location (OR: 0.51, 95% CI: 0.38-0.67), Rotterdam Criteria <0.1 mm (OR: 0.29, 95% CI: 0.17-0.50) and Starz I (new) (OR: 0.44, 95% CI: 0.22-0.91).		
Egger et al. 2014	to determine the classification scheme that best predicts nonsentinel node (NSN) metastasis, disease-free survival (DFS), and overall survival (OS).	Retrospective study	157 patients with melanoma >=1.0 mm Breslow thickness who underwent SLN biopsy	N-SN metastases after CLND Overall survival Disease free survival	independent predictors of a positive NSN: maximum diameter, maximum area, nonsubcapsular location according to Dewar's, and the SIII class according to Starz (significant for cut-off of 1mm) multivariate analysis: maximum diameter (cut-off of 3 mm) was the only classification	This study reviewed pathologic slides of tumorpositive SLNs from the Sunbelt Melanoma Trial and the University of Louisville Melanoma Database	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					system that was an independent risk factor predicting DFS (hazard ratio 2.31, p = 0.0181) and OS (hazard ratio 3.53, p = 0.0005).		
Satzger et al. 2014	to determine the therapeutic impact of CLND	Retrospective study	305 SLN-positive patients Matched-pair analysis between groups : - 58/305 did not undergo CLND - 58/305 underwent CLND Subgroup analysis in patients with SLN micrometastases < 0,1mm : - 72/106 patients underwent CLND - 34/106 did not undergo CLND	Recurrence-free survival Overall survival Recurrence rates	Matched-pair-analysis: CLND vs. non-CLND: Recurrence-free survival (P= 0.765) Overall survival (P = 0.844) Recurrence rates 17/58 (29%) vs.15/58 (26%) (P=1.000). Subgroup analysis: CLND vs. non-CLND: Overall survival P=0.610	Small patients number	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Recurrence-free-survival: P=0.346 Recurrence rates: 5/72 (7%) vs. 4/34 (9%) Multivariate analysis: independent prognostic factors: - ulceration of the primary melanoma (absent versus present) - the largest dimension of tumor cell deposit (</=0.1 versus >0.1 mm) - age of patients (</=60 versus >60 years),		
Van der Ploeg et al. 2012	to evaluate the impact of immediate CLND on the outcome of patients with SN-positive melanoma	Retrospective study	1174 Patients with SLN metastases, 1113 underwent CLND, 61 did not	Disease-free-survival	Matched pair analysis: CLND did not significantly influence disease-specific survival (HR 0·86, 0·46 to 1·61; P = 0·640).	Selection bias: patients who did not undergo CLND had more favourable prognostic factors Small number of	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Multivariate analysis: DSS: - SN tumour burden characteristic was significant prognostic factor, - CLND had no significant influence on prognosis 3- and 5-year DSS rates: Non-CLND: 74% and 66% CLND: 76,9% and 66,9% (HR 0.89, 0.58-1.37; P=0.600) Matched-pair-analyses CLND: 79% and 69% (HR 0.86, 0.46-1.61; P =0・640)	patients without CLND	
Van der Ploeg et al. 2014	To evaluate indices of SN tumour burden (intranodal	Retrospective study	11 melanoma centers : 1539 patients with	Disease-free survival	Breslow thickness, ulceration, Clark level of invasion,	Heterogeneity in SN biopsy protocols and	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	location, tumour penetrative depth (TPD) and maximum size of SN tumour deposits)		positive SLN, CLND in 1381 patients	Melanoma-specific survival N-SLN metastases-rate	number of SNs removed and all micromorpho-metric parameters were significant predictors of NSN status ($p < 0.05$) As continuous variables measured in millimetres, maximum SN metastasis size (odds ratio (OR) = 1.11, 95% confidence interval (CI): 1.07–1.15, $p < 0.001$) and tumour penetrative depth (OR = 1.26, 95% CI: 1.15–1.38, $p < 0.001$) were significant predictors of NSN status in the overall cohort Patients with	clinicopathologic features of the patient cohorts Not all patients with micrometastases <0,1mm in the SLN underwent CLND 11 melanoma centers used various classification systems ➔ Variation in the prediction of N-SLN-positivity ➔ 4 differents multivariate regression models for MSS Further details: see full-text	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					subcapsular micrometastases <0.1 mm in maximum dimension had the lowest frequency of NSN metastasis (5.5%). Significant prognostic factors for poorer MSS in the multivariate models included the presence of nonsubcapsular metastases, TPD > 1 mm and maximum SN tumour size > 1 mm A maximum SN tumour size > 1 mm was the most consistent independent predictor of NSN-positivity and		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					poorer DFS and MSS in individual centres, and in the combined cohort.		
Bamboat et al. 2014	To- determine the pattern of initial recurrence between the no-CLND and CLND Groups To determine melanoma-specific survival of both patient groups	Retrospective study	495 patients with positive SLN 167 patients (34%) underwent nodal observation 328 (66%) underwent CLND	Recurrence rates survival	Recurrences in 81 patients (49 %), no-CLND, with a median time to recurrence of 9 months, and in 179 patients (55 %), CLND, with a median time of 12 months (p = 0.46) regional recurrence rates: 16 %, no CLND, vs. 18 %, CLND; p = 0.58 - nodal only: (15 %, no CLND, vs. 6 %, CLND; p = 0.002) - systemic only (8 %, no CLND, vs. 27 %,	Patient selection bias (e.g. patients in the no-CLND group were significantly older than those undergoing CLND (66 vs. 56 years; p<0.001) patient, tumor and SLN characteristics see tables/full text big differences in median follow-up time between groups: 23 and 80 months for the no-CLND and CLND groups, respectively	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					CLND; p<0.001) median recurrence-free survival: 34.5 , CLND, vs. 20.9 months, no CLND; p = 0.02 melanoma-specific survival: not reached, no CLND vs. 110 months, CLND; p = 0.09.		
Feldmann et al. 2013	To validate the accuracy of N-SNORE in melanoma patients with positive SLN	Retrospective study	106 melanoma patients with positive SLN, who had undergone complete lymph node dissection (CLND) subsequently,	Non-sentinel-lymph-node-positivity rate	13 patients: score 0 63 patients: score 1-3 19 patients: score 4-5 6 patients: score 6-7 5 patients: score >8. NSLN positivity rates for these 5 risk groups were: 7.7%, 18.2%,	Small patient cohort	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					21.1%, 33.3%, and 80%, respectively. contingency coefficient: 0.322; p-value: 0.025		
Kibrité et al. 2015	to evaluate the significant factors associated with positive sentinel and subsequent lymph nodes status.	Retrospective study	957 patients who underwent SLNB Subsequent lymphadenectomy in 171 patients	Factors for predicting SLN positivity	multivariate analysis: 3 factors demonstrate a significant effect (P <0.05) for predicting SLN positivity : Breslow thickness, LVI, tumor location. Breslow thickness >/= 2 mm or SLN with macroscopic burden >/=2mm are the only statistically significant variables predicting the completion lymphadenectomy lymph nodes status (multivariate analysis):	Bias: not all patients with positive SN underwent lymphadenectomy	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Subsequent positive lymph nodes in - 9/100 (9%) patients with tumor load <2mm - 24/71 (33,8%) patients with tumor load >/= 2mm		
Kim et al. 2015	To examine the prognostic role of tumor burden in SLN on overall survival (OS) and diseasefree survival (DFS) in patients with cutaneous melanoma using different microscopic classifications and to assess clinical and histological predictors of additional NSLN metastases.	retrospective study	138 patients with positive SLN status 111 patients underwent CLND	Overall survival disease-free survival	Most significant cut-off point for both OS (p<0.0001) and DFS (p=0.0064): 1mm Estimated 5-year-OS: 75.6% in patients with SLN tumor burden ≤1mm vs. 34.6% in patients with SLN tumor burden >1mm. only statistically significant predictor of	Different pathological protocols used to examine SLN Small patient cohort	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastatic disease in NSLNs (by multivariate analysis): the number of positive SLN (OR=4.27; 95% CI=1.15-15.82; p=0.03)		
Wevers et al. 2013	To identify factors predicting NSN positivity and to assess the validity of the N-SNORE in an independent patient cohort.	Retrospective study	130 patients who underwent CLND after a positive SNLB		Presence of regression was associated with a positive NSN in multivariable logistic regression (OR 6.3; 95%CI 1.1-36.1; p = 0.04). The N-SLN positivity rates for the N-SNORE rsik groups were 5.9%, 19.8%, 24.5%, and 47.6%, respectively (p= 0.04) (after adjustment because of missing data on perinodal lymphatic invasion:	missing data were imputed to enable multivariate analysis ➔ Risk of bias	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					p = 0.003)		

3.2.3.3. Aktualisierungsrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Burke et al. 2016	To determine whether melanoma patients with sentinel node metastases should undergo complete lymphnode adenectomia	Prognostic study using a Markov model	Outcomes of melanoma patients with SNB and immediate CLND published in previous observations	5-year overall survival (OS) Life expectancy (LE) Quality-adjusted life expectancy (QALE).	The projected 5-year OS for 50-year-old patients with SLN metastases who underwent immediate CLND was 67.2 % compared with 63.1 % for the observation group. The LE gained by undergoing immediate CLND ranged from 2.19 years for patients aged 30 to 0.64 years for patients aged 70 years. The QALE gained by undergoing immediate CLND ranged from 1.39	Modelling of different outcome on the basis of retrospectively gathered data.	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					quality-adjusted life years for patients aged 30 to 0.36 for patients aged 70 years. In sensitivity analysis over a clinically plausible range of values for each input parameter, immediate CLND was no longer beneficial when the rate of long-term complications increased and the quality-of-life weight for long-term complications decreased.		
Cordeiro et al. 2016	To quantify the proportion of sentinel node metastases in patients with thin melanoma and to determine the pooled effect of high-risk features of the primary	Systematic review of sixty studies (10,928 patients)	Patients with thin melanomas underwent Sentinel node biopsy	Proportion of SN metastases in patients with thin cutaneous melanoma Effect of high-risk pathological features of the primary lesion	Pooled SN positivity was 4.5 % [95 % CI 3.8–5.2 %]. Predictors of a positive SN were: thickness ≥0.75 mm [adjusted odds	Systematic review of non-randomized observations	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	lesion on sentinel node positivity				ratio (AOR) 1.90 (95 % CI 1.08-3.34); with a likelihood of SN metastases of 8.8% (95 % CI 6.4–11.2%)]; Clark level IV/V [AOR 2.24 (95% CI 1.23–4.08); with a likelihood of 7.3% (95% CI 6.2–8.4 %)]; ≥1 mitoses/mm^2 [AOR 6.64 (95% CI 2.77–15.88); pooled likelihood 8.8 % (95% CI 6.2–11.4 %)]; and the presence of microsatellites [unadjusted OR 6.94 (95% CI 2.13–22.60); likelihood 26.6 % (95% CI 4.3–48.9 %)].		
Egger et al. 2016	To identify risk factors predictive of prognosis in patients with a tumor-negative	Post-hoc analysis of data from a multicenter prospective randomized trial	1,998 patients with tumor-negative SLN and ≥1.0 mm Breslow thickness	Risk factors for a worse prognosis Disease free survival	Ulceration, Breslow thickness, nonextremity tumor location, and age ≥45 years	Post-hoc analysis	3a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	SLN biopsy for cutaneous melanoma			Overall survival Local- or intransit metastasis free survival	were independent risk factors for worse disease-free survival and OS. Breslow thickness and ulceration were the only factors on multivariate analysis that predicted local and in-transit recurrence-free survival. Estimated 5-year OS rates ranged from 55.5 to 95.4% on the basis of the defined risk factors.		
Leiter et al, 2016	To assess whether complete lymph node dissection resulted in increased survival compared with observation in sentinel node positive patients	Randomised controlled trail	5547 patients were screened with sentinel lymph node biopsy and 1269 (23%) patients were positive for micrometastasis. Of these, 483	Distant metastasis-free survival	Distant metastasis-free survival at 3 years was 77.0% (90% CI 71.9-82.1; 55 events) in the observation group and 74.9% (69.5-80.3; 54 events) in the complete	Most patients had only minimal tumor infiltrated in the SN, 90% CI used. Underpowered trial due to missing events.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			(39%) agreed to randomisation (1:1) into the clinical trial: 241 patients were randomly assigned to the observation group and 242 to the complete lymph node dissection group. Ten patients did not meet the inclusion criteria, so 233 patients were analysed in the observation group and 240 patients were analysed in the complete lymph node dissection group,		lymph node dissection group.		
Mosquera et al 2017	To better understand practice patterns across the U.S population and the survival impact of complete lymphadenectomy	Cohort study of "The Surveillance Epidemiology and End Results Program (SEER)" registry	Patients undergoing SLN biopsy with positive nodes and intermediate-thickness tumors ([1–4 mm) were Included.	Practice patterns of CLND Overall survival	CLND was associated with lower mean age, male gender, primary site, number of positive nodes, and geographic region		3a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			Time frame of patients data: 2003-2012 2172 patients included		(p\0.05). In the multivariate analysis, male gender [odds ratio (OR), 1.27] and geographic area (Michigan OR, 2.31; Iowa OR, 1.69) were associated with CLND (p<0.05). In the survival analysis, male gender, primary site, ulceration, Clark level, and depth and number of positive nodes were associated with survival (p<0.05), but CLND was not (p = 0.83). In the Cox regression analysis, the relationship between male gender [hazard ratio (HR), 1.14],		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					primary site trunk versus extremity (HR, 1.3), ulceration (HR, 1.79), Clark level (2 vs. 4 HR, 3.51; 2 vs. 5 HR, 6.48), depth (HR, 1.43) and number of nodes (1 vs. 2: HR, 1.23; 1 vs. C3: HR, 2.52) persisted ($p<0.05$). However, when CLND was included in this model, it was not associated with improved survival.		
Oude Ophuis et al 2016	To determine melanoma specific survival (MSS) for time intervals between excisional biopsy and sentinel node biopsy in sentinel node biopsy positive patients	Cohort study	1080 patients were diagnosed with a positive SNB in nine Melanoma Group centers. 1015 patients (94%) were selected in which excisional biopsy date was known.	Melanoam specific survival	Sentinel node tumor burden was significantly higher in patients operated ≥47 days ($p=0.005$). Univariate survival was not significantly different for median time interval. Multivariable		3a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					analysis confirmed that time interval was no independent prognostic factor for MSS.		
Santos-Juanes et al 2017	To determine whether there is an association between performance of sentinel lymphnode biopsy and patient prognosis.	Systematic review and meta analysis	A total of six studies with 8764 patients who had undergone SLNB and 11054 patients who had undergone wide location excision alone (WLEA) were identified for the analysis.	Melanoma specific survival	The pooled MSS hazard risk from fixed effects analysis was determined to be 0.88 (95% CI=0.80-0.96). Although no significant survival difference was observed in four of the six series, the pooling summary data from all the studies that deal with this issue suggested that SLNB is associated with a significantly better outcome compared with WLEA for localized melanoma.	Evidence for publication bias was not found (Egger's test P=0.4654).	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Serra-Arbeloa et al 2016	To assess the cost-effectiveness of the sentinel node biopsy with lymphadenectomy for nodal metastases (SNB) in patients with primary cutaneous melanoma (CM) of different Breslow thickness (intermediate, thick, thin).	Decision-tree based analyses Decision tree models use hypothetical patients that move from one health state to another (transition probabilities) in a simulated natural evolution of a disease, predicting patient numbers in those health states. This type of model was performed for patients with different Breslow thickness CM: thin (≤1 mm), intermediate (1-4 mm), and thick (>4 mm), considering each one as a base case. This segmentation in three thickness classes was done	A hypothetical population of 10,000 patients over 18 years old with primary CM was included in every strategy and for every thickness.	Mean and total direct healthcare costs, Life years saved (LYSs) Quality-adjusted life years (QALYs) Cost effectiveness ratio (CER) Incremental cost effectiveness ratio (ICER) were estimated	Base case analyses showed that the best results were obtained for intermediate CM over 10-year time horizon. In this case, ICER for SNB was 130,508V / QALY, well over the threshold of acceptance (30,000V/QALY). In patients with intermediate CM over 1 and 5 years, and for those with thick and thin CM at any time horizon, negative ICER values were estimated since SNB was proved to be more expensive and less effective than WE. Sensitivity analyses confirmed the robustness of our results.		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		since it is considered to be an important prognostic factor, being worse as it increases. The decision trees were used to compare two strategies of management: (i) wide excision of the primary lesion followed by SNB and lymph-adenectomy for nodal metastases (SNB strategy), and (ii) wide excision of the primary melanoma followed by observation (WE strategy). Two different initial health state patients were observed, SN positive and SN negative in the SNB strategy. If SN was positive, complete lymph node					

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		dissection (CLND) followed the SNB, and mere observation if it was negative. The final variables, evaluated depending on the health state, disease free, nodal relapse, distant relapse and death, were estimated as life years saved (LYSs) and qualityeadjusted life years (QALYs), over 1, 5 and 10-year time horizons					
Svedman et al 2016	To provide an up-to-date summary of stage-specific survival and recurrence-free survival patterns in patients with CMM in Europe	Systematic literature review	Of the 8,749 studies identified, 26 studies were included, representing nine countries. 152,422 patients and included data from 1978 to 2011	Survival	Studies reporting survival by sentinel node (SN) status reported 5-year overall survival as 80%-95% for negative SN (stage I/II) and 35%-75% for positive SN (stage III) status; recurrence-free	Very mixed selection criteria for study inclusion	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival at 5 years: 76%-90% for negative and 35%-58% for positive SN status.		

3.2.3.3.1. Literatur

Burke EE, Portschy PR, Tuttle TM, et al. . Completion Lymph Node Dissection or Observation for Melanoma Sentinel Lymph Node Metastases: A Decision Analysis. Ann Surg Oncol. 2016 Sep;23(9):2772-8. doi: 10.1245/s10434-016-5273-5. Epub 2016 May 18

Cordeiro E, Gervais MK, Shah PS, at al. Sentinel Lymph Node Biopsy in Thin Cutaneous Melanoma: A Systematic Review and Meta-Analysis. Ann Surg Oncol. 2016 Dec;23(13):4178-4188. Epub 2016 Mar 1.

Egger ME, Bhutiani N, Farmer RW et al.. Prognostic factors in melanoma patients with tumor-negative sentinel lymph nodes. Surgery. 2016 May;159(5):1412-21. doi: 10.1016/j.surg.2015.12.002. Epub 2016 Jan 8.

Leiter U, Stadler R, Mauch C, Hohenberger W et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2016 Jun;17(6):757-767. doi: 10.1016/S1470-2045(16)00141-8. Epub 2016 May 5.

Mosquera C, Vora HS, Vohra N, et al. Population-Based Analysis of Completion Lymphadenectomy in Intermediate-Thickness Melanoma. Ann Surg Oncol. 2017 Jan;24(1):127-134. doi: 10.1245/s10434-016-5460-4. Epub 2016 Jul 27.

Oude Ophuis CM, Verhoef C, Rutkowski P et al.. The interval between primary melanoma excision and sentinel node biopsy is not associated with survival in sentinel node positive patients - An EORTC Melanoma Group study. Eur J Surg Oncol. 2016 Dec;42(12):1906-1913. doi: 10.1016/j.ejso.2016.05.012. Epub 2016 May 27.

Santos-Juanes J, Fernández-Vega I, Galache Osuna C et al.. Sentinel lymph node biopsy plus wide local excision vs. wide location excision alone for primary cutaneous melanoma: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2017 Feb;31(2):241-246. doi: 10.1111/jdv.13824. Epub 2016 Sep 5.

Serra-Arbeloa P, Rabines-Juárez ÁO, Álvarez-Ruiz MS et al. Sentinel node biopsy in patients with primary cutaneous melanoma of any thickness: A cost-effectiveness analysis. Surg Oncol. 2016 Sep;25(3):205-11. doi: 10.1016/j.suronc.2016.05.020. Epub 2016 May 20.

Svedman FC, Pillas D, Taylor A, et al Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe - a systematic review of the literature. Clin Epidemiol. 2016 May 26;8:109-22. doi: 10.2147/CLEP.S99021. eCollection 2016. Review.

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4. AG Chirurgische Therapie

4.1. Frage III.1. Sicherheitsabstände bei Primärexzision – De-novo-Recherche

Frage III.1. Welche Sicherheitsabstände sollen bei radikaler Exzision des Primärtumors eingehalten werden?

4.1.1. PICO, Suchwörter

Suchwörter		
Stichwort	melanoma	therapy, treatment, management, surgery, surgical procedures, excision
Synonyme	melanoma	safety margin, excision margin, surgical margin, narrow, wide
Ober-/Unterbegriffe, Mesh Term	s. Suchsstrategie	

4.1.2. Datenbanken, Suchstrategien, Trefferzahlen

4.1.2.1. Primärrecherche 2012

Datenbank	**Suchstrategie**	**Datum**	**Treffer**
1. Suche			
Medline	"melanoma"[tiab] AND (“therapy”[all fields] OR “treatment”[all fields] OR “management”[all fields] OR "surgery"[all fields] OR “surgical”[all fields] OR “surgical procedures, operative”[mesh] OR "excision"[all fields]) AND (“safety margin”[all fields] OR “excision margin”[all fields] OR “surgical margin”[all fields] OR “narrow”[all fields] OR “wide”[all fields])	26.01.2012	1235

Datenbank	Suchstrategie	Datum	Treffer
Cochrane Library	(melanoma and (therapy or treatment or management or surgery or surgical or excision) and ("safety margin" or "excision margin" or "surgical margin" or narrow or wide)).ti,ab.	19.01.2012	51
Embase	(melanoma and (therapy or treatment or management or surgery or surgical or excision) and ("safety margin" or "excision margin" or "surgical margin" or narrow or wide)).ti,ab.	23.01.2012	1642
Bemerkungen: Eine erste Literaturrecherche in Medline und und Cochrane erfolgte am 06.09.2010 bzw. für Embase am 11.05.2011. Die Update-Recherche wurde am 23.01.2012 (Embase) bzw. am 26.01.2012 für Medline und am 19.01.2012 für Cochrane durchgeführt. In der Tabelle angegeben sind die Trefferzahlen der letzten Recherche.			

4.1.2.2. Aktualisierungrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	melanoma[tiab] AND (“therapy”[all fields] OR “treatment”[all fields] OR “management”[all fields] OR "surgery"[all fields] OR “surgical”[all fields] OR “surgical procedures, operative”[mesh] OR "excision"[all fields]) AND (“safety margin”[all fields] OR “excision margin”[all fields] OR “surgical margin”[all fields] OR “narrow”[all fields] OR “wide”[all fields]) AND ("2012.01.24"[Date - Publication] : "3000"[Date - Publication])	12.09.2016	642
Cochrane Library	(melanoma and (therapy or treatment or management or surgery or surgical or excision) and ("safety margin" or "excision margin" or "surgical margin" or narrow or wide)).ti,ab.	12.09.2016	75

4.1.3. Auswahlkriterien

4.1.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	2928
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt Veröffentlichung ab 1970
Ausschlusskriterien	Case Reports (Case series included), narrative Reviews
Anzahl nach Abstractscreening	61
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	12

4.1.3.2. Aktualisierungrecherche 2016

Auswahl der Literatur	
Gesamttreffer	717
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt Veröffentlichung ab 25.01.2012
Ausschlusskriterien	Case Reports (Case series included), narrative Reviews
Anzahl nach Abstractscreening	40
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	12

4.1.4. Evidenztabelle

4.1.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Mocellin et al. (2011)	To quantify the impact of excision margins on disease-specific survival of patients with primary cutaneous melanoma	systematic review of RCT with Meta-analysis	5 eligible RCT A total of 3295 patients enrolled (1633 (49.5%) were allocated to narrow excision and 1662 (50.5%) to wide excision)	locoregional disease-free (LDFS) disease-free (DFS) disease-specific (DSS) overall survival .	Narrow margins: risk of both locoregional disease recurrence (HR: 1.30, CI: 1.07—1.57; P = 0.01) and death by disease (HR: 1.28, CI: 1.07—1.53, P = 0.01). As regards DFS, the borderline disadvantage (HR: 1.13, CI: 0.995—1.28; P = 0.06) becomes significant when considering RCT that enrolled patients with thicker melanoma (HR: 1.19, CI: 1.02—1.39, P = 0.03). When death by any cause (OS) was analyzed: narrow vs. wide excision margins (HR: 1.05, 95%CI:	The lack of DSS data from all the available RCT 4 of the 5 RCT included in systematic review of Sladden et al. 2010 (Cohn-Cedermark et al (2000), Balch et al (2001), Khayat et al (2003), Thomas et al (2004)	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.95– 1.16, P = 0.32		
Sladden et al. (2010)	To assess the effects of different excision margins for primary cutaneous melanoma.	Systematic review of 5 randomised controlled trials (RCTs) of surgical excision of melanoma comparing different width excision margins	1633 participants in the narrow excision margin group and 1664 in the wide excision margin group	Primary outcomes: 1. Time to death (any cause) 2. Time to combined endpoint of death (any cause) or recurrence (local, in transit, regional, distant) Secondary outcomes: 1. Quality of Life 2. Adverse events/outcomes	No significant difference in overall survival when comparing narrow with wide excision Overall survival wide excision: Hazard Ratio 1.04 compared with narrow excision; not significant Recurrence-free survival wide excision: Hazard Ratio 1.13 compared with narrow excision; not significant	Limited RCT data assessing treatment of thin melanomas < 1 mm and thick melanomas ≥ 4 mm. Melanomas in specific body sites not sufficiently investigated	1a
Gillgren et al. (2011)	to test whether survival was diff erent for a wide local excision margin of 2 cm compared with a 4-cm excision	randomised, multicentre trial	936 patients with cutaneous melanoma thicker than 2 mm, at clinical stage IIA–C (465 were	Overall survival	5-year overall survival was 65% (95% CI 60–69) in the 2-cm group and 65% (60–70) in the 4-cm group (p=0·69)		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	margin		randomly allocated to treatment with a 2-cm resection margin, 471 to receive treatment with a 4-cm resection margin)				
Subtopic: Margins in special localizations							
Jahn et al. (2006)	To define prognostic factors for melanoma of the ear and to evaluate surgical strategies for excision margins, histological evaluation and sentinel lymph node biopsy (SLNB) in order to achieve better cosmetic and functional results.	Prognostic study	161 patients with stage I and II melanoma of the external ear.	Recurrence-free and disease-specific survival	Recurrence-free survival rate 83% over 3 years and 79% over 5 years Tumour thickness and Clark invasion level were the only significant risk factors for disease-specific survival in Kaplan–Meier univariate analysis.	Prospective study design Patients not randomized between groups with different excision margins; recommendations for excision margins were reduced during the observation period (1976 – 2004); confounding by other historical factors possible. For details on recurrence-free	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						survival in relation to surgical margin, see Fig. 2 in full-text of the article.	
Hazan et al. (2008)	To review clinical and histologic features of lentigo maligna (LM) and lentigo maligna melanoma (LMM) and determine surgical margin necessary for complete excision.	Cross-sectional study	117 patients	Required surgical margin and number of stages for complete excision of LM and LMM	Mean total surgical margin required for excision of LM: 7.1 mm and 10.3 mm for LMM Mean number of stages required to completely excise a lesion: 1.67	Small number of invasive melanoma No data about recurrence rates	3b
Furukawa et al. (2007)	To evaluate how amputation level and cutaneous margin affects prognosis and reconstructive choice.	Prognostic study	15 patients (6 men, 9 women) with melanoma of the thumb between	Disease-free survival	Significant prognostic factors: stage and thickness Level of amputation and excision margin not significant	Small patient sample	3b
Mohrle et al. (2003)	To evaluate clinical parameters and surgical strategies influencing the prognosis of patients with facial	Prognostic study Survival and history of 3960 patients in stages I and II were	368 patients with facial melanoma	Overall survival (5 years) Recurrence-free survival (5 years)	Significant predictors for survival: tumour thickness, Clark level and ulceration, surgery	Patients not randomized between groups with different excision margins; recommendations	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma.	prospectively recorded between 1980 and 1999. Of these, 368 melanomas were localized in the face, 140 on the capillitium and 76 on the neck. Surgical margins were successively reduced during the observation period, starting from 5 cm in 1980. For functional and aesthetic reasons, recommendations for surgical margins could not always be followed in the head and neck regions.			with 3D histology and histological tumour subtype	for excision margins were reduced during the observation period (1976 – 2004); confounding by other historical factors possible.	
Pockaj et al. (2003)	To evaluate the prognostic variables and clinical ramifications of melanoma of the	Prognostic study, retrospective design	84 patients with invasive melanoma of the external ear	Lymph node involvement Local, regional and systemic recurrence	Local recurrence in 13% Recurrence of melanoma in the lymph nodes in	Retrospective design Patient numbers not sufficient for an evaluation of	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	ear.				12% Systemic metastases in 22% Type of resection did not influence systemic recurrence (P=0.41)	the influence of different surgical procedures on recurrences	
Tseng et al. (1997)	The purpose of the study was to investigate the surgical management of cutaneous melanomas of the hands and feet.	Prognostic study	116 patients with melanomas of the hands (n = 26) and feet (n = 90)	Recurrence rate	In melanomas <1.5 mm thickness, no local recurrences Metastases developed in 5% No local recurrence or metastasis in patients with < 1.5 mm acral-lentiginous melanoma Of 79 patients with melanoma ≥ 1.5 mm, 15 (19%) presented with regional node disease	No control groups Data on elective lymph node dissection biased (decision about ELND was left to the surgeon) and not sufficient (small numbers of patients)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					All 13 patients with subungual melanomas had lesions ≥1.5 mm in thickness; 6 (46%) of 13 had evidence of nodal disease at the time of presentation or at ELND or had regional node metastases develop within 1 year of initial diagnosis In patients with ALM, 71% presented with lesions ≥1.5-mm thick and were treated with wide excision or amputation; local recurrence in two (6%) of these patients, but nodal metastases or systemic disease or both in 19 (56%) of 34 patients		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hudson et Krige (1995)	To analyse the outcome of local treatment and patient survival using a 3 cm local excision margin and split skin grafting	Prognostic study	16 men and 3 women	Overall survival Time to progression	12 patients with stage I disease: mean Breslow depth 2.7 mm All 12 had local excision of the primary lesion with 3 cm margins and skin grafts applied to the galea; 6 developed regional lymph node metastases, 3 developed systemic metastases (all of whom died) One patient presented with stage II disease and developed local recurrence 5 patients in stage III disease were treated by wide local excision and therapeutic lymph node dissection; all died after a mean	Very small patient numbers No control group	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					of 9.6 months (range 3 – 22 months)		
Then et al. (2009)	To report early cure rates for periocular melanoma using Slow-Mohs surgery with en-face margin sectioning.	Retrospective, multicenter, noncomparative case series	14 patients with periocular MM	Number of stages needed for complete excision Recurrence rate	most common site: lower eyelid (8/14, 57.1%). Breslow thickness ranged from 0.27 to 1.70 mm, with four cases less than 0.76mm and one case greater than 1.5mm. Five cases were a Clark level II or greater. Complete excision was achieved with one level (6 cases) or two or three levels (8 cases), with 2- to 3-mm margins at each level in all but one case. With median follow-up of 36 months, there were two local recurrences (2/14, 14.3%).	Very low LoE (case series, retrospective design)	4
Subtopic: Vertical							

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
margins							
Kenady et al. (1982)	To determine whether the presence oor absence of muscle fasciae in patients with stages 0 and I malignant melanoma correlates with prognosis.	Retrospective prognostic study	202 patients with primary melanoma of the trunk and proximal limbs	Recurrence rate Survival rate	Sites of first recurrence or survival not significantly affected by the excision of fasciae	AJCC 1978 staging system used retrospectively Possible confounding by the fact that the control group is historical (other potential changes in melanoma management in the meantime)	2b

4.1.4.1.1. Literatur

Furukawa H, Tsutsumida A, Yamamoto Y, et al. Melanoma of thumb: retrospective study for amputation levels, surgical margin and reconstruction. J Plast Reconstr Aesthet Surg 2007;60:24-31
Gillgren P, Drzewiecki KT, Niin M, et al. 2-Cm Versus 4-Cm Surgical Excision Margins for Primary Cutaneous Melanoma Thicker than 2 Mm: a Randomised, Multicentre Trial. Lancet 2011;378:1635-1642
Hazan C, Dusza SW, Delgado R, et al. Staged excision for lentigo maligna and lentigo maligna melanoma: A retrospective analysis of 117 cases. J Am Acad Dermatol 2008;58:142-148
Hudson DA, Krige JE. Results of 3 cm excision margin for melanoma of the scalp. J R Coll Surg Edinb 1995;40:93-96
Jahn V, Breuninger H, Garbe C, et al. Melanoma of the ear: prognostic factors and surgical strategies. Br J Dermatol 2006;154:310-318
Kenady DE, Brown BW, McBride CM. Excision of underlying fascia with a primary malignant melanoma: effect on recurrence and survival rates. Surgery 1982;92:615-618
Mocellin S, Pasquali S, Nitti D. The impact of surgery on survival of patients with cutaneous melanoma: revisiting the role of primary tumor excision margins. Ann Surg 2011;253:238-243
Mohrle M, Schippert W, Garbe C, et al. Prognostic parameters and surgical strategies for facial melanomas. J Dtsch Dermatol Ges 2003;1:457-463
Pockaj BA, Jaroszewski DE, DiCaudo DJ, et al. Changing surgical therapy for melanoma of the external ear. Ann Surg Oncol 2003;10:689-696
Sladden MJ, Balch C, Barzilai DA, et al. Surgical excision margins for primary cutaneous melanoma. Cochrane Database Syst Rev 2009;(4):CD004835
Then SY, Malhotra R, Barlow R, et al. Early cure rates with narrow-margin slow-Mohs surgery for periocular malignant melanoma. Dermatol Surg 2009;35:17-23
Tseng JF, Tanabe KK, Gadd MA, et al. Surgical management of primary cutaneous melanomas of the hands and feet. Ann Surg 1997;225:544-50; discussion 550-3

4.1.4.2. Aktualisierungrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE

Bolshinsky et al. (2016)	To better understand the role of wide local excision (WLE) in the treatment of cutaneous melanoma by analyzing residual or locally metastatic disease in WLE specimens of melanomas initially diagnosed with a complete excisional biopsy.	Retrospective, single center cohort study	807 consecutive WLEs of melanomas diagnosed after complete excisional biopsy.	Number of residual disease Association of factors with residual or locally metastatic disease	In the 807 WLE specimens, further melanoma was found in 34 cases (4.2%; 95% CI: 2.9-5.8) On univariate analysis, features associated with residual or locally metastatic disease were histologic subtype (OR 3.0; 95% CI 1.3-7.1, p=.01) and tumor location (OR 7.3; 95% CI 2.0-26.6, p<.01). On multivariate analysis, lentigo maligna was independently associated with melanoma remaining in WLE specimens (OR 2.7; 95% CI 1.0-7.3, p=.04).	funding source: none	3a

Haydu et al. (2016)	To assess whether pathologic excision margins influence the prognosis and survival of patients with primary melanomas 1.01–2.00 mm in thickness and to determine the minimum safe excision margin.	Retrospective, single center cohort study	2131 patients	Melanoma specific survival (MSS) Disease free survival (DFS) Local and in-transit recurrence-free survival (LITRFS)	Pathologic excision margin of <8 mm (=1cm in vivo) had poorer prognosis (DFS) compared with the 8–16-mm group (1–2 cm in vivo; p=0.044). Comparing 8-mm with 16-mm pathologic margins, no differences were observed in any survival outcomes. Deep margin proved to be an independent predictor of LITRFS (p=0.003) in all excision margin categories. Pathologic excision margins <8 mm were associated with worse	funding source: none	3a

					regional node recurrence-free survival and distant RFS compared with margins ≥8 mm (p=0.049 and p=0.045). No significant difference in melanoma-specific survival occurred.		
Hayes et al. (2016)	To report an extended follow-up of the survival endpoints of this trial (patients with high-risk malignant melanoma [Breslow thickness ≥2 mm] randomly assigned to excision margins of either 1 cm or 3cm) with a median follow-up of 8·8 years.	Randomized controlled trial	900 patients randomized to surgery with either a 1 cm excision margin (n=453) or a 3 cm excision margin (n=447)	Overall survival Rate of complications	At a median follow-up of 8.8 years, 494 patients had died, with 359 of these deaths attributed to melanoma. 194 deaths were attributed to melanoma in the 1 cm group compared with 165 in the 3 cm group (unadjusted HR 1.24 [95% CI 1.01–	Primary endpoints of the original trial were locoregional recurrence and disease-free survival. Because of the restricted ability to obtain recurrence data in later years, these endpoints were not reassessed in the present long-term analysis. Funding source:	1a

					1.53]; p=0·041). Although a higher number of deaths overall occurred in the 1 cm group compared with the 3 cm group (253 vs 241), the difference was not significant (unadjusted HR 1.14 [95% CI 0.96–1.36]; p=0.14). Surgical complications were reported in 35 (8%) patients in the 1 cm excision margin group and 65 (15%) patients in the 3 cm group.	Cancer Research UK, North Thames National Health Service Executive, Northern and Yorkshire National Health Service Executive, British United Provident Association Foundation, British Association of Plastic Surgeons, the Meirion Thomas Cancer Research Fund, and the National Institute for Health and Research Biomedical Research Centre at The Royal Marsden NHS Foundation Trust.	
Hieken et al. (2013)	To identify how frequently final tumor stage and treatment recommendations	Retrospective, single center cohort study	Comparison the histopathology of the dermatopath-ologist-reviewed diagnostic biopsy	Margin positivity T-stage changes	Most biopsies were margin positive regardless of technique, and 36% of patients had	funding source: none	3a

	changed from diagnostic biopsy to final histopathology after wide local excision (WLE)		and final WLE in 332 cutaneous melanoma patients		residual melanoma on WLE; T-stage changed in 8% of patients.		
Hunger et al. (2015)	To analyse over a period of 16 years whether 1-cm surgical excision margin has caused any disadvantages in important outcome parameters, in comparison with 2-cm margins.	Retrospective, single center cohort study	325 patients	Disease free survival (DFS) Overall survival (OS)	No differences for DFS (p=.800; HR 0.948; 95% CI 0.627-1.433) and OS (p=.951; HR 1.018; 95% CI 0.575-1.803).	funding source: Funded by the Swiss Cancer League (OCS-02262-08-2008)	3a
Hunger et al. (2014)	To evaluate the clinical effect of excision of the deep fascia in melanomas thicker than 2 mm on patient outcome.	Retrospective, single center cohort study	213 patients (n=103 fascia preserved; n=110 fascia excides) with melanomas thicker than 2mm.	Disease free survival (DFS) Overall survival (OS)	Death attributable to melanoma (p=0.72), local recurrence (p=0.71), and locoregional (p=0.87) and distant metastases (p=0.34) were not significantly	Funding source: This study was funded by the Swiss Cancer League (OCS-02262-08-2008).	3a

					different. Kaplan–Meier and Cox regression analysis of both groups showed no evidence of significant difference regarding DFS [p=0.35; HR 1.25; 95% CI 0.79-1.97] and OS (p=0.63; HR 1.18; 95% CI 0.61–2.27).		
Joyce et al. (2015)	To assess the relation of histological excision margins of melanoma-in-situ (MIS) to recurrence and progression to invasive disease.	Retrospective, single center cohort study	410 patients had MIS (79% of Lentigo maligna) excised.	Rate of recurrences	The rate of recurrence was 2.2% (9/410), with a median follow-up of 23 months. Lentigo maligna had a similar rate of recurrence to non-lentigo MIS (2.3% vs 1.2%) (P = 0.69). The mean excision margin of those		3a

					that recurred was 1.9 mm compared with an average of 3.8 mm in those that did not. The rate of recurrence of MIS with histological excision margin ≤3.00 mm was 3.8% compared with 0.5% in those with a histological margin >3.00 mm (p=0.03). One case of MIS recurred as invasive disease.		
Koskivuo et al. (2015)	To compare the clinical outcomes of 1-cm margins with 2-cm margins in patients with a tumor thickness of 1.1- to 4.0-mm.	Retrospective study, matched-pairs design	80:80 (160 overall) patients matched for gender, age, Breslow thickness, and the anatomic location of the primary lesion.	Rate of recurrences Recurrence free survival (RFS) Overall survival (OS)	There were recurrences in 14 patients (17.5%) in the 1-cm group and in 15 patients (18.8%) in the 2-cm group. There were no differences in RFS or OS (p=0.977;	funding source: none	3a

					p=0.203).		
Kunishige et al. (2012)	To develop guidelines for predetermined surgical margins for excision of melanoma in situ.	Retrospective, single center cohort study	1072 patients with 1120 melanoma in situs.	Clearence rate Recurrence rate	6-mm margins were adequate for complete clearance in 86% of all tumors 9-mm margins were adequate for complete clearance in 98.9% of all tumors A 1.2-cm margin yielded 99.4% clearance, 1.5-cm margin yielded 99.6% clearance, and 3-cm margin yielded 100% clearance 3 MIS reappeared within or adjacent to the scar, reflecting incomplete removal. Recurrence rate	funding source: none	3a

					was 0.3%. Cure rate was 99.7% at 5-years and 99.2% at 10 years.		
Lamboo et al. (2014)	To identify the minimum safe excision margin and optimal nodal management associated with the best prognosis for patients with primary cutaneous T3 melanomas.	Retrospective, single center cohort study	1587 patients with melanomas 2.01- to 4.00-mm thick	Local and In-Transit Recurrence-Free Survival (LITRFS)	The minimum peripheral excision margin, when analysed as a continuous variable, was found to be a prognostic factor on univariate analysis (p=0.009), but lost significance on multivariate analysis (p=0.312). When patients were categorized in 2 groups with a cut off point at 8 mm, the >= 8 mm group had a significantly better prognosis with 87.0% cumulative LITRFS at 5 years compared with 75.4% in the < 8 mm group (p<0.001). This difference was still		3a

				Disease-Free Survival (DFS)	significant after adjustment for other variables in the multivariate model (HR=0.54; 95% CI: 0.35–0.85; p=0.008). The minimum peripheral excision margin as a continuous variable did not influence DFS on univariate or multivariate analysis (p=0.890, p=0.156, respectively). However, when analyses were performed using the various excision margin categories, some significant effects were observed. In univariate analysis, the >= 8-mm category had a significantly superior DFS rate compared with the <8-mm category		

				Melanoma-Specific Survival (MSS)	(64.3% vs 56.1%; p=0.014) and this difference retained its influence in the multivariate model. In univariate and multivariate analyses, the minimum peripheral excision margin did not significantly influence MSS (p=0.147 and p=0.641, respectively) A subgroup analysis of 565 patients was performed to compare 1 cm in vivo (n=188) and 2 cm in vivo (n=377) surgical excision margins. The 5-year cumulative MSS was 80.3% and 77.0% for the 1 cm and 2 cm group, respectively (p=0.643). The proportion of		

					recurrence-free patients at 5 years was 62.8% in the 1 cm group and 64.6% in the 2 cm group (p=0.273). On multivariate analysis, there were no significant differences between the 1 cm and 2 cm groups in terms of LITRFS, DFS, MSS (p=0.250, p=0.297, and p=0.760, respectively)		
MacKenzie Ross et al. (2016)	To identify clinical and pathologic factors associated with local recurrence in patients with T1 melanomas that might guide primary tumor management.	Retrospective (prospectively collected), single institution database evaluation.	11,290 patients	Local recurrence (LR)	From 11,290 primary melanomas ≤1 mm thick, 176 (1.56 %) cases with LR were identified. LR occurred after a median time of 37 months (range 3–306 months) and was associated with narrower excision margins (HR = .95, 95 % CI	Funding source: The authors gratefully acknowledge funding support from the National Health and Medical Research Council, Cancer Institute New South Wales, The Melanoma Foundation of the University of Sydney, and MIA. A.D.M.R. was the	3a

					0.92–0.98, p=0.001), desmoplastic, acral, and lentigo maligna melanoma subtypes (p=0.008), and melanomas composed predominantly of spindle cells (p=0.005). However, Breslow thickness, Clark level, ulceration, mitotic rate, regression, and lymphovascular invasion were not.	recipient of a Poche Fellowship at MIA.	
Rawlani et al. (2015)	To determine the risk associated with reducing margins of wide local excision (WLE) in H&N melanoma and	Retrospective (prospectively collected), single institution database evaluation.	79 patients overall 42 patients with margins of 1cm for lesions<1.0 mm thick, 1–2 cm for lesions 1.01–2.0 mm thick, and 2 cm for lesions >2.0	Local recurrence rate (LRR)	Overall LRR was 8.9% over a mean follow-up period of 71.3 months and a minimum of 60 months. Reducing margins of WLE did not increase LRRs as demonstrated	Funding source: none	3

	To identify risk factors of recurrence.		mm thick. Reduced margins (0.5 cm for lesions ≤1.0 mm thick, 0.5–1.0 cm for lesions 1.01–2.0 mm thick, and 1.0 cm for lesion >2.0 mm thick) were utilized in 37 cases to preserve critical anatomical structures such as the eyelid, nose, mouth and auricle.		by local recurrence-free survival (90.4% vs. 91.9%, p=0.806).		

4.1.4.2.1. Literatur

Bolshinsky, V., et al., Frequency of residual melanoma in wide local excision (WLE) specimens after complete excisional biopsy. J Am Acad Dermatol, 2016. 74(1): p. 102-7.
Haydu, L.E., et al., Minimum Safe Pathologic Excision Margins for Primary Cutaneous Melanomas (1-2 mm in Thickness): Analysis of 2131 Patients Treated at a Single Center. Ann Surg Oncol, 2016. 23(4): p. 1071-81.
Hayes, A.J., et al., Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: long-term follow-up of survival in a randomised trial. Lancet Oncol, 2016. 17(2): p. 184-192.
Hieken, T.J., et al., Accuracy of diagnostic biopsy for cutaneous melanoma: implications for surgical oncologists. Int J Surg Oncol, 2013. 2013: p. 196493.
Hunger, R.E., et al., A retrospective study of 1- versus 2-cm excision margins for cutaneous malignant melanomas thicker than 2 mm. J Am Acad Dermatol, 2015. 72(6): p. 1054-9.
Hunger, R.E., et al., Excision of fascia in melanoma thicker than 2 mm: no evidence for improved clinical outcome. Br J Dermatol, 2014. 171(6): p. 1391-6.
Joyce, K.M., et al., An assessment of histological margins and recurrence of melanoma in situ. Plast Reconstr Surg Glob Open, 2015. 3(2): p. e301.
Koskivuo, I., et al., One-cm Versus 2-cm Excision Margins for Patients With Intermediate Thickness Melanoma: A Matched-Pair Analysis. Dermatol Surg, 2015. 41(10): p. 1130-6.
Kunishige, J.H., D.G. Brodland, and J.A. Zitelli, Surgical margins for melanoma in situ. J Am Acad Dermatol, 2012. 66(3): p. 438-44.
Lamboo, L.G., et al., The optimum excision margin and regional node management for primary cutaneous T3 melanomas (2-4 mm in Thickness): a retrospective study of 1587 patients treated at a single center. Ann Surg, 2014. 260(6): p. 1095-102.
MacKenzie Ross, A.D., et al., The Association Between Excision Margins and Local Recurrence in 11,290 Thin (T1) Primary Cutaneous Melanomas: A Case-Control Study. Ann Surg Oncol, 2016. 23(4): p. 1082-9.
Rawlani, R., et al., Reducing margins of wide local excision in head and neck melanoma for function and cosmesis: 5-year local recurrence-free survival. J Surg Oncol, 2015. 111(7): p. 795-9.

4.2. Frage III.2. Prophylaktische Lymphadenektomie - Adaptation

Frage III.2. In welchen Fällen ist eine elektive (prophylaktische) LAD indiziert?

4.2.1. Synopse Quellleitlinien (kurz)

Thema/Fragestellung	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
In welchen Fällen ist die adjuvante (prophylaktische) LAD indiziert?	Nicht empfohlen (I)	Keine Angaben	Prophylaktische LAD bringt keinen Vorteil (A)	(nur relevant für medikamentöse Therapien)

4.2.2. Empfehlung, Hintergrundstext und Literatur Australische Quell Leitlinie

(mit Seitenangaben der Quellleitlinie)

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
Schlüsselempfehlungen	keine	keine	S. 42 Standard Le curage prophylactique systématique est contre-indiqué. *Standard* *Die prophylaktische LAD ist kontraindiziert.*
Hintergrundtexte	S. 83 A systematic review of randomised	S. 93 Lymph node clearance	S. 30 – 31 Curage ganglionnaire

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	controlled trials comparing elective lymph node dissection with surgery delayed until the time of clinical recurrence showed no significant overall survival benefit for patients undergoing elective lymph node dissection. [12] Therefore, except in rare circumstances, elective lymph node dissection is not recommended for melanoma patients. S. 84 Evidence summary Elective lymph node dissection is not recommended, regardless of the Breslow thickness of the primary tumour LoE: I References: 7, 12	One systematic review found no statistically significant advantage in terms of overall mortality arising from elective lymph node dissection compared to delayed lymph node dissection at the onset of clinical symptoms. One RCT of elective versus delayed regional lymph node dissection in patients with melanoma found that the routine use of immediate node dissection had no significant impact on survival, while the status of regional nodes significantly predicted survival. S. 232 – 234 (NICE Guideline Evidence Review) Summary of the supporting evidence for the recommendations Observational study evidence suggests that the status of the regional node basin is a strong predictor of survival, along with primary tumour characteristics such as Breslow thickness and ulceration. Systematic review and RCT evidence does not demonstrate that elective lymph node dissection carries a survival benefit over a policy of observing patients with primary melanoma after wide excision. However	prophylactique systématique DESCRIPTION DES ÉTUDES La méta-analyse de Lens *et al.* a évalué l'impact sur la survie globale du curage ganglionnaire prophylactique chez les patients porteurs d'un mélanome sans métastases ganglionnaires cliniquement décelables [84]. Quatre essais randomisés ont été inclus, soit un total de 1 704 patients [84-89]. L'un de ces essais n'a pas pu être utilisé pour l'analyse quantitative, car les données disponibles dans la publication, et après vérification auprès des auteurs, étaient insuffisantes [87]. SURVIE GLOBALE Aucun des quatre essais randomisées n'a montré de bénéfice en faveur du curage [85-89] *(Tableau IX)*. La méta-analyse n'a retrouvé aucune différence de survie à 5 ans entre le curage ganglionnaire et l'absence de

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		the systematic review by Lens et al. (2002a) suggests that some patients will benefit from elective lymph node dissection. Evidence based clinical guidelines from the UK recommend that in patients with melanoma, the presence of disease in one node indicates radical lymph node dissection but that elective lymph node dissection in the absence of lymph node disease should not be performed. Observational study evidence suggests that the prevalence of lymphoedema amongst patients who have undergone complete level I-III axillary lymph node dissection for melanoma is 10%, and 53% after additional axillary radiotherapy. · The systematic review by Lens et al. (2002a), calculated a pooled odds ratio for overall mortality as 0.86 in favour of elective lymph node dissection over delayed lymph node dissection at the onset of clinical symptoms (95% CI 0.68-1.09). The authors concluded that although the result was not statistically significant and although the primary studies had flaws, the possibility exists	curage ganglionnaire (odd ratio = 0,86 [IC95 : 0,68-1,09]) [84] *(Tableau X)*. COMPLICATIONS Aucune information concernant les complications n'est disponible dans la méta-analyse. Ce type de curage a toujours une certaine morbidité, plus importante pour le membre inférieur que pour le membre supérieur. La fréquence des complications précoces est de 10 à 15 % dans les meilleures séries lors de curages inguinaux [90, 91]. Le taux de lymphoedèmes tardifs varie de 6 à 15 % au membre inférieur, 6 % au membre supérieur [90, 92]. COMMENTAIRES MÉTHODOLOGIQUES ET CLINIQUES La validité clinique des essais randomisés inclus dans la méta-analyse est critiquable, en raison de la réalisation du curage ganglionnaire sur la seule base

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		that some subgroups of patients with melanoma will benefit from elective lymph node dissection. · The RCT by Cascinelli et al. (1998) compared elective versus delayed regional lymph node dissection in patients with melanoma and found that the routine use of immediate node dissection had no impact on survival (hazard ratio 0.72, 95% CI 0.5-1.02), whilst the status of regional nodes affected survival significantly. The authors concluded that regional node dissection offers increased survival in patients with node metastases only. · The retrospective, case series study by Kretschmer et al. (2005) found that overall survival at 5 years in patients who underwent delayed lymph node dissection following initial wide excision of melanoma was 37.4%. Disease free survival in this group of patients was 11.6%. · Evidence based guidelines produced by Roberts et al. (2002) on behalf of the British Association of Dermatologists state that elective lymph node dissection is not indicated in patients with melanoma and clinically negative lymph	de l'examen clinique. L'intérêt du curage prophylactique reste controversé et le curage ganglionnaire ne peut s'envisager que dans les localisations où il existe une voie de drainage unique, soit essentiellement les lésions des membres. CONCLUSION DE LA LITTÉRATURE Aucun bénéfice du curage ganglionnaire prophylactique après exérèse de mélanome n'a été démontré. Le curage ganglionnaire prophylactique systématique n'améliore pas la survie globale par rapport au curage ganglionnaire retardé ou à l'absence de curage ganglionnaire chez les patients atteints d'un mélanome cutané cliniquement NO (niveau de preuve A). *S. 30 - 31* *Systematische prophylaktische Lymphadenektomie (LAD)*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		nodes. · Evidence based guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) recommend that in patients with melanoma, the presence of disease in one node indicates radical lymph node dissection but that elective lymph node dissection in the absence of lymph node disease should not be performed.	*BESCHREIBUNG DER STUDIEN* *Die Metaanalyse von Lens et al. hat den Einfluss der prophylaktischen LAD auf das Gesamtüberleben bei Patienten mit Melanom ohne klinisch nachweisbare Lymphknotenmetastasen ausgewertet [84].* *Vier randomisierte Studien mit einer Gesamtzahl von 1 704 Patienten sind dabei eingeschlossen worden [84-89].* *Eine dieser Studien konnte nicht für die quantitative Analyse verwendet werden, da die Daten in der Publikation auch nach Verifikation bei den Autoren insuffizient waren [87].* *GESAMTÜBERLEBEN* *Keine der vier randomisierten Studien konnte einen Vorteil der LAD zeigen [85-89] (Tabelle IX).* *Die Metaanalyse ergab keinen Unterschied in der 5-Jahres-Überlebensrate zwischen Durchführung und Nicht-Durchführung der elektiven LAD (Odds-Ratio = 0,86 [IC95 : 0,68-*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			1,09]) [84] (Tabelle X). *KOMPLIKATIONEN* *In der Metaanalyse sind keine Informationen über Komplikationen verfügbar.* *Diese Art der LAD geht immer mit einer gewissen Morbidität einher, an der unteren Extremität ausgeprägter als an der oberen Extremität.* *Die Häufigkeit der Frühkomplikationen reicht von 10 bis 15% in den besseren Serien der inguinalen Lymphadenektomien [90, 91].* *Die Rate der späten Lymphödeme reicht von 6 bis 15% an den unteren Extremitäten und beträgt ca. 6% an den oberen Extremitäten [90, 92].* *METHODOLOGISCHE UND KLINISCHE KOMMENTARE* *Die klinische Validität der in die Meta-Analyse eingeschlossenen randomisierten Studien ist fragwürdig, da die Durchführung der LAD allein mit*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			dem Ergebnis der klinischen Untersuchung begründet wurde. Die Frage der prophylaktischen LAD bleibt kontrovers. Sie kann zudem nur bei Tumorlokalisationen in Betracht gezogen werden, an denen nur ein lymphatischer Abflussweg existiert, d.h. im Wesentlichen bei Läsionen an den Extremitäten. *SCHLUSSFOLGERUNG AUS DER LITERATUR* *Es konnte nach Exzision des Melanoms kein Vorteil der prophylaktischen LAD gezeigt werden. Sie verbessert im Vergleich zur späten LAD oder zum Verzicht auf LAD nicht das Überleben bei Patienten mit malignem Melanom im klinischen Stadium N0 (Evidenzlevel A).*
Bemerkungen		Diese Leitlinie bezieht sich auf MM und auf NMSC. Referenzen und ausführliche Evidenztabellen dieser Leitlinie werden	Im Volltext der Leitlinie tabellarische Darstellung der einbezogenen Studien (S. 30).

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		wegen ihres Umfangs als separates Dokument zur Verfügung gestellt: GB NICE Guideline Evidence Review, S. 232 bis 238.	

4.2.3. Literatur

LL Australien New Zealand Guidelines Group 2008

7. National Comprehensive Cancer Network. Melanoma: Clinical Practice Guidelines in Oncology. version 2. 2007. National Comprehensive Cancer Network
12. Lens MB, Dawes M, Goodacre T, et al. Elective lymph node dissection in patients with melanoma: systematic review and meta-analysis of randomized controlled trials. Arch Surg 2002;137:458-461

LL GB NICE 2006

Cascinelli N, Morabito A, Santinami M, et al. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. Lancet 1998;351:793-796
Lens MB, Dawes M, Goodacre T, et al. Elective lymph node dissection in patients with melanoma: systematic review and meta-analysis of randomized controlled trials. Arch Surg 2002;137:458-461
Roberts DL, Anstey AV, Barlow RJ, et al. U.K. guidelines for the management of cutaneous melanoma. Br J Dermatol 2002;146:7-17
Scottish Intercollegiate Guidelines Network. Cutaneous melanoma. A national clinical guideline. 2003 http://www.sign.ac.uk/pdf/sign72.pdf
Starritt EC, Joseph D, McKinnon JG, et al. Lymphedema after complete axillary node dissection for melanoma: assessment using a new, objective definition. Ann Surg 2004;240:866-874
White RR, Stanley WE, Johnson JL, et al. Long-term survival in 2,505 patients with melanoma with regional lymph node metastasis. Ann Surg 2002;235:879-887

LL Frankreich French National Authority for Health 2005)

90. Baas PC, Schraffordt Koops H, Hoekstra HJ, et al. Groin dissection in the treatment of lower-extremity melanoma. Short-term and long-term morbidity. Arch Surg 1992;127:281-286
86. Balch CM, Soong SJ, Bartolucci AA, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. Ann Surg 1996;224:255-63; discussion 263-6
91. Beitsch P, Balch C. Operative morbidity and risk factor assessment in melanoma patients undergoing inguinal lymph node dissection. Am J Surg 1992;164:462-5; discussion 465-6
85. Cascinelli N, Morabito A, Santinami M, et al. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. Lancet 1998;351:793-796
92. Karakousis CP, Heiser MA, Moore RH. Lymphedema after groin dissection. Am J Surg 1983;145:205-208
84. Lens MB, Dawes M, Goodacre T, et al. Elective lymph node dissection in patients with melanoma: systematic review and meta-analysis of randomized controlled trials. Arch Surg 2002;137:458-461
87. Sim FH, Taylor WF, Pritchard DJ, et al. Lymphadenectomy in the management of stage I malignant melanoma: a prospective randomized study. Mayo Clin Proc 1986;61:697-705
88. Veronesi U, Adamus J, Bandiera DC, et al. Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. N Engl J Med 1977;297:627-630
89. Veronesi U, Adamus J, Bandiera DC, et al. Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremities. Cancer 1982;49:2420-2430

4.3. Frage III.3. Therapeutische Lymphadenektomie – De-novo-Recherche

Frage III.3. In welchen Fällen ist die therapeutische LAD indiziert?

4.3.1. PICO-Unterfragen

- Hat die therapeutische LAD bei Patienten mit klinisch feststellbaren LK-Metastasen einen Einfluss auf das Überleben?
- Hat die therapeutische LAD bei Patienten mit klinisch feststellbaren LK-Metastasen einen Einfluss auf die rezidivfreie Zeit?
- Hat die therapeutische LAD bei Patienten mit klinisch feststellbaren LK-Metastasen einen Einfluss auf die Lebensqualität?

Suchwörter	
Stichwort, Synonyme, Ober-/Unterbegriffe, Mesh Term	s. Suchsstrategie

4.3.2. Datenbanken, Suchstrategien, Trefferzahlen

4.3.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	melanoma AND ("lymph node excision"[MeSH Terms] OR ("lymph"[All Fields] AND "node"[All Fields] AND "excision"[All Fields]) OR "lymph node excision"[All Fields] OR "lymphadenectomy"[All Fields] OR “lymph node dissection”[All Fields] OR “lymphonodectomy”[All Fields])	08.03.2011	3408

Datenbank	Suchstrategie	Datum	Treffer
Medline Update-Recherche	melanoma AND ("lymph node excision"[MeSH Terms] OR ("lymph"[All Fields] AND "node"[All Fields] AND "excision"[All Fields]) OR "lymph node excision"[All Fields] OR "lymphadenectomy"[All Fields] OR “lymph node dissection”[All Fields] OR “lymphonodectomy”[All Fields])	11.01.2011	3754
Cochrane Library	(melanoma and ((lymph and node and excision) or lymphadenectomy or "lymph node dissection" or lymphonodectomy)).ti,ab.	08.03.2011	93
Embase	(melanoma and ((lymph and node and excision) or lymphadenectomy or "lymph node dissection" or lymphonodectomy)).ti,ab.	11.05.2011	2148
2. Suche/Ergänzungen			

Bemerkungen: Eine erste Literaturrecherche in Medline und und Cochrane erfolgte am 08.03.2010 bzw. für Embase am 11.05.2011. Zweite Medline-Recherche (Update-Recherche) erfolgte am 11.01.2011. Da die Frage III.3. letztendlich konsensbasiert beantwortet wurde (s.3.3.3.), wurde auf eine Update-Recherche Anfang 2012 verzichtet.

4.3.3. Auswahlkriterien

Auswahl der Literatur

Gesamttreffer		5995
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt	
Ausschlusskriterien	Case Reports, narrative Reviews	
Anzahl nach Abstractscreening		61
Anzahl ausgewählter und bewerteter Volltexte, vorgesehen für Bewertung		27
Bemerkungen: Aufgrund des Fehlens von Studien, die das Outcome von Patienten, die eine therapeutische LAD erhalten haben, mit dem von Patienten vergleicht, die diese LAD trotz bestehender LK-Metastasen nicht erhalten haben, entschieden sich die Experten der AG chirurgische Therapie für eine konsensbasierte statt evidenzbasierte Beantwortung der Frage.		

4.3.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Pilko et al. (2011)	To compare the overall survival of different groups of stage III cutaneous melanoma patients	Prognostic study Cohort study	325 patients with stage III melanoma	Overall survival (OS) Disease-free survival (DFS)	The mean follow-up was 44 months (range 1 – 168 months). The 5-year DFS for the whole group was 36.6%, 5-year OS was 52.6%. On multivariate analysis, age, Breslow thickness, presence of	Retrospective design (prospective database) Short follow-up in some patients No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					ulceration, number of involved lymph nodes, type of lymph node dissection and size of SN metastasis were independent prognostic factors for OS.		
Pasquali et al. (2010)	To investigate whether patients with melanoma who undergo lymphadenectomy after a positive sentinel lymph node (SN) biopsy (SNB) have a better prognosis compared with patients who are treated for clinically evident disease.	Systematic review	The included 6 studies encompassed 2633 patients who had AJCC stage III melanoma.	Overall survival	Hazard ratio for overall survival (TLND vs. CLND): Summary measure 1.602	Study included here for the data on therapeutic node dissection (not completion node dissection after SNB) Systematic review and original data, but different objective of the study (therapeutic vs. completion node dissection, not therapeutic vs. control group), therefore lower level of evidence concerning the question of indication for	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						therapeutic node dissection	
Rutkowski et al. (2010)	To compare outcomes of patients with clinical nodal melanoma metastases without a detectable primary tumor (MUP) with those with a known primary site (KPM).	Prognostic study Cohort study	459 consecutive melanoma patients, stages IIIB and IIIC	Overall survival Disease-free survival Recurrence rates	3-year and 5-year OS rates: 48.0% and 41.4%, respectively, for the MUP group (median 36.2 months) and 42.0% and 36.0%, respectively, for the KPM group (median 25.7 months). 3-year and 5-year DFS rates: 47.0% and 44.0%, respectively, for the MUP group (median 14.9 months) and 31.1% and 28.3%, respectively, for the KPM group (median 11.7 months). Disease recurrences:in the MUP group 31	Retrospective design No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients; 52.5%, in the KPM group 299 cases; 74.8%		
Allan et al. (2008)	To review the experience of routine ilioinguinal dissection for all patients presenting with palpable metastatic melanoma in the groin.	prognostic and diagnostic study Cohort study	72 patients	Disease-free interval Disease-free survival Overall survival Pelvic lymph node status Diagnostic value of preoperative CT Complication rate (lymphoedema)	22 (30.6%) of 72 patients with histologically involved pelvic lymph nodes. Preoperative CT accuracy for pelvic lymph node involvement: sensitivity 60.0% specificity 100.0%, PPV 100.0% NPV 86.2%. Median time to first recurrence: 8.7 months (0.8–69.7 months). Regional recurrence in 6 (8.3%) of 72 patients (at a median of 4.9 months (0.9–32.0 months). Extranodal spread	Retrospective design Small patient cohort No control group (comparison of lymph node dissection vs. no lymph node dissection not possible) Confounder: adjuvant therapy	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					adversely associated with disease-free survival. 5-year DFS: 38% (95% CI 26–50), OS 47% (95% CI 33–60). Lymphoedema was reported in 32 (44.4%) of 72 patients.		
Lee et al. (2008)	Clinical outcomes of patients with MUP and known primary melanoma (MKP) with regional nodal metastases were compared to investigate the prognostic significance of MUP.	Prognostic study Cohort study	1,571 patients who underwent therapeutic regional lymphadenectomy (262: MUP, 1,309: MKP)	Overall survival Disease-free survival	significant factors on multivariate analysis: age, sex, nodal tumor burden, decade of diagnosis, status of primary. Greater risk was associated with age ≥ 60 years, male sex, increased number of tumor-involved nodes (>1), and MKP. The risk of death was 40%	Retrospective design No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					lower in the MUP group than the MKP group (HR = 1.507). 5-year and 10-year rates of OS for patients with MUP versus patients with MKP were 58% ± 7% versus 40% ± 7%, respectively, and 52% ± 7% versus 36% ± 7%, respectively. Median OS was also significantly longer in the MUP group than the MKP group (165 months vs. 34 months).		
Van Akkooi et al. (2007)	To evaluate morbidity and mortality following TLND, and disease-free (DFS) and overall survival (OS) following TLND.	Prognostic study Cohort study	236 melanoma patients who underwent TLND	Overall survival Disease-free survival Regional control rate	mean follow-up after TLND: 29 months (range 0 – 280 months). estimated 5-year DFS and OS for the 236 patients after	Retrospective design No follow-up in some patients No control group (comparison of	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Complication rate	TLND: 19% and 26%. estimated 5-year regional control rate after TLND: 79%. Median time to disease progression: 7 months. estimated 5-year DFS according to site of tumor: 23% (extremities) and 9% (central tumors) estimated 5-year DFS for different categories of nodal status (N1, N2, N3): 31%, 15% and 10%, respectively. significant different estimated 5-year OS rate for different intervals of diagnosis until TLND.	lymph node dissection vs. no lymph node dissection not possible) For data on complications, see original article	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Young et al. (2006)	To investigate rates of long-term survival for patients with regional (nodal) melanoma.	Prognostic study Cohort study	1422 patients with stage III melanoma who received complete lymphadenectomy	Overall survival Melanoma-specific survival	maximum follow-up: 386 months (32 years) rates of 15-, 20- and 25-year melanoma-specific survival: 36% ± 1%, 35% ± 1%, and 35% ± 1%, respectively. Median melanoma-specific OS: 28.1 months in the palpable and 90 months in the non-palpable group. When stratified by clinical status of regional nodes, survival rates were significantly lower if nodes were palpable.	Retrospective design Long follow-up No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b
Pienkowski et al. (2005)	to perform a single-institution analysis of factors influencing the clinical outcomes of cutaneous	Cohort study	353 consecutive melanoma patients with metastases to regional lymph nodes	Overall survival Disease-free surfvival	Estimated 5-year overall survival ratio:44% 5-year disease free survival rate: 35%	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma (CM) patients undergoing therapeutic lymphadenectomy (LND).				independent predictors of poor OS (multivariate analysis): - extracapsular melanoma invasion (p 3mm (p = 0.007) - male sex (p=0.011) - CM site in head/neck region (p = 0.05) negative factors for DFS: - nodal extracapsular melanoma extension (p < 0.0001) - male sex (p < 0.0001).		
Serpell et al. (2003)	To review regional disease control and morbidity in a series of lymphadenectomies	Cohort study	64 melanoma patients have undergone 73 RLND for metastatic regional melanoma	Overall survival Recurrence rate Complication rate	median time to diagnosis of regional lymph node disease: 11.2 (interquartile range 2–48) months.	Retrospective design Small patient cohort No control group	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					regional control: 92% local recurrences (LR): 8% LR all occurred within 12 months of lymphadenectomy, all but 1 patient with LR have died within 12 months. rate of LR local recurrence was similar with or without postoperative radiotherapy. 34/64 patients died, median time to death=12 months (range 2–35 months).	(comparison of lymph node dissection vs. no lymph node dissection not possible) For data on complications, see original article	
Fisher (2002)	To evaluate the effects on survival, disease-free interval, and recurrence patterns for	Cohort study	1444 melanoma patients: - 219 patients with ELND, histologically proven negative	Disease-free survival Overall survival	overall rate of nodal recurrence for all patients: 129/1045 patients 12%.	Retrospective design Study included here for data on delayed lymph	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients undergoing elective, therapeutic, and delayed lymph node dissection for malignant melanoma of the head and neck.		lymph nodes - 27 patients with ELND, histologically proven positive lymph nodes - 106 patients with DLND for regional lymph node recurrence - 112 patients with TLND for clinically positive lymph nodes		significant improvement in survival for DLND when compared with patients undergoing ELNDQ or TLND (P=0.01). Five-year survival after DLND and TLND was 56% and 36%, respectively.	node dissection (DLND); for further data on ELND and TLND see original article No control group for DLND (comparison of lymph node dissection vs. no lymph node dissection not possible)	
Pathak et al. (2002)	To determine the rates of regional recurrence for node-positive melanoma after neck dissection alone.	Cohort study	31 patients who underwent neck dissection for node-positive melanoma	Recurrence rate Mean time to recurrence Overall survival	mean follow-up: 45.3 months with a SD of 35.3 months and a range of 1 to 108 months. regional recurrence rate at 5 years for melanoma: 31%. mean time to recurrence: 78 months (95% CI: 63 to 93 months). mean survival for	Small patient cohort Very short follow-up in some patients (recurrence rate may be underestimated) No control group (comparison of lymph node dissection vs. no lymph node dissection not	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients undergoing neck dissection: 61 months.	possible)	
White et al. (2002)	To examine the long-term outcomes of patients with melanoma metastatic to regional lymph nodes.	Cohort study	2,505 patients	Overall survival Recurrence-free survival	For regional lymph node metastases: median overall survival: 3.4 years, median recurrence-free survival: 1.5 years. Estimated overall survival rates(95% CI) at 5, 10, 15, 20, and 25 years: 43% (41–45%), 35% (33– 37%), 28% (25–30%), 23% (20–26%), and 19% (13–24%), respectively. Estimated recurrence-free survival rates at 5, 10, 15, and 20 years: 33% (31–35%), 28% (26–30%), 25% (23–27%), and 22% (18–	Retrospective design Missing data led to exclusion of patients No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					26%) respectively, Both curves appeared to plateau at approximately 20%, no first recurrences after 21 years.		
Hughes et al. (2000)	to identify disease- and treatment-related factors that influence the outcome of patients undergoing therapeutic groin dissection for clinically detectable melanoma lymph node metastases	132 patients With clinically detectable LN-metastases 60 patients: superficial inguinal lymph node dissection (SLND) 72 patients: combined superficial inguinal and pelvic lymph node dissection (CLND)		Morbidity Overall survival Recurrence rate	no difference in postoperative morbidity or major lymphoedema between SLND and CLND overall 5-year-survival-rate: - 34% 5-year-survival-rate: -pelvic lymph node metastases (CLND): 19% - no pelvis lymph node metastases (CLND): 17% (P = 0.015)	Retrospective study	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Factors with significant impact on survival (univariate analysis): - age (P = 0.003) - number of involved superficial lymph nodes (P = 0.001) - presence of extracapsular spread (P = 0.003) Systemic recurrence rate: 62% Median time to systemic recurrence: 9 months .		
Cascinelli et al. (1998)	To evaluate the efficacy of immediate node dissection in patients with melanoma of the trunk and without clinical evidence of	Randomized controlled trial	Of 240 patients 122: wide excision and immediate node dissection 118: wide excision and dissection	Time to first recurrence Overall survival	36/118 patients (30.5%) developed regional node metastases median lag between excision of primary tumour	Study included here for the data on delayed node dissection (not immediate node dissection) Prospective,	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	regional node and distant metastases.		delayed until the time of appearance of clinically detectable node metastases.		and the diagnosis of regional node metastases: 8.3 months (interquartile range 3.7–16.2). minimum delay: 0.43 months, maximum 55.0 months “Delayed” patients had a survival rate at 5 years of 51.3% (95% CI 41.7–60.1).	randomized design, but different objective of the study (elective vs. therapeutic node dissection, not therapeutic vs. control group), therefore lower level of evidence concerning the question of indication for therapeutic node dissection	
Jonk et al. (1998)	To identify prognostic factors determining overall survival in patients with surgically treated neck node metastases of cutaneous melanoma	Cohort study	70 surgically treated with curative intent for cervical lymph node metastasis - radical neck dissection: 64 patient - - modified radical neck dissection: 4 patients - postero-lateral neck dissection:2 patients.	Overall survival	overall survivals after 5 and 10 years: 23% and 20%, respectively. Median survival: 22 months. Following a therapeutic neck dissection, 5-year survival rate: 22% following elective dissection, 5-year survival rate: 29%	Retrospective design Small patient cohort Patients predominantly male No control group (comparison of lymph node dissection vs. no lymph node	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(difference not significant).	dissection not possible)	
Karakousis and Driscoll (1996)	To report the experience with groin dissection for melanoma	Cohort study	205 patients who underwent groin dissection	Overall survival Disease-free survival Complication rate	Estimated-overall 5-year survival and disease-free survival rates for patients with histologically proven negative nodes: 73% and 67% respectively, rates for those with positive nodes: 39% and 29%, respectively. 10-year survival rate for patients with negative nodes was 63% and for those with positive nodes 33%. median length of survival for patients with clinically positive nodes: 29 months, for the 40 with negative nodes: 52	Retrospective design No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months. 5- and 10-year survival rates: in the former group: 37% and 32% respectively, in the latter group: 43% and 35%. For patients with positive nodes only in the inguinal region: 5-year overall and disease-free survival rates were 43% and 35% respectively; for patients with positive nodes in both the inguinal and deep node groups: 34% and 21%. Estimated 10-year survival rate for the former group: 39%. for the latter group: 25% at 92 months.		
Karakousis et al. (1994)						Patient cohort is a subset of Karakousis and	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Driscoll (1994); see above	
Gadd and Coit (1992)	To analyze the patterns of initial recurrence and outcome of patients with recurrence of melanoma following axillary or inguinal lymphadenectomy	Cohort study	403 patients with recurrences after lymphadenectomy;	Disease-free interval survival	The median disease-free interval: 11.2 months, range from 1 to 157 months. Median survival of patients with: - single-site recurrence: 11 months, with a 5-year survival rate of 10% - multiple sites: 3 months, no 5-year survivors - nonvisceral single-site recurrence: 18.5 months with a 5-year-survival rate of 14% - single visceral recurrence: 6	Retrospective design Missing tumor characteristics for circa half of the patient population; also missing treatment information in some patients No separate analysis for elective and therapeutic dissections Comparison between surgical and nonsurgical therapy, but groups not randomized	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months with a 5-year-survival rate of 3% - surgical resection of single-site recurrences: 17 months with a 5-year survival rate of 14% (Complete resection: median survival: 19 months, partial resection: 6 months) - nonsurgical therapy: 5 months with a 5-year survival rate of 2% - surgical resection of multiple site recurrences: 7 months - nonsurgical therapy of multiple site recurrences: 3 months		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Morton et al. (1991)	To evaluate the importance of various prognostic features after lymphadenectomy.	Cohort study .	1134 patients with lymph node metastases 737 patients in whom complete information was available	Overall survival	5-, 10- and 15-year survival: 46%, 41%, and 38%, respectively. Multivariate analysis:the number of involved nodes (p = 0.001), the location on an extremity (p = 0.0059), the depth of the primary (p = 0.0334), the patient's sex (p = 0.0627), and clinical stage (p = 0.0942) were significantly correlated with survival.	Missing information in many patients, who were excluded from the analysis Retrospective design No control group (comparison of lymph node dissection vs. no lymph node dissection not possible) For mathematical model of prognosis, see original article	3b
Karakousis et al. (1990)	To report on results and complications of axillary node dissection in melanoma	Cohort study	133 melanoma patients who underwent axillary node dissection	Overall survival Disease-free survival Complication rate	estimated 5-year disease-free survival rate for patients with: - histologically negative nodes: 80% - histologically	For data on complications, see original article Retrospective design No control group (comparison of lymph node	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					positive nodes: 23%. - palpable nodes: 13% - clinically negative nodes: 60%. In patients with clinically & histologically involved nodes: the greater the number of involved nodes, the shorter was the disease-free survival time after node dissection. Considering all patients with elective and therapeutic node dissections: recurrence in 53 patients (40%), 74% of them within 2 years.	dissection vs. no lymph node dissection not possible)	
Karakousis et al. (1986)						Patient cohort is a subset of	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Karakousis and Driscoll (1994); see above	
Finck et al. (1982)	To review the results of ilioinguinal dissection and to compare results for patients with inguinal and iliac node involvement with those with only inguinal involvement.	Cohort study	82 melanoma patients with inguinal lymph node metastases.	Disease-free interval Overall survival	Significant difference in disease-free interval for patients with inguinal and iliac node metastases and patients who had only inguinal involvement. ($p < 0.01$). Disease recurrence: - 20/24 (83.3%) patients with positive iliac nodes - 32/58 (55.2%) patients with negative iliac nodes. Median disease-free interval: - 5.8 months for patients with iliac metastases - 25.6 months for	Retrospective design Small patient cohort Missing information on primary tumour characteristics in many patient files No control group (comparison of lymph node dissection vs. no lymph node dissection not possible)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients without iliac nodal involvement. Median survival: - for patients with iliac metastases: 20.0 months - for patients with negative iliac nodes:52,1 months		
Veronesi et al. (1982)	To investigate whether regional lymph nodes should or should not be removed in stage I melanoma patients (elective dissection).	Randomized controlled trial	553 stage I melanoma patients	Overall survival	The type of treatment given did not modify the chances of cure for the patients, even if adjusted by single significant factors or by all of them. 5-year overall survival rates for delayed dissection: 57.9% for males 76.5% for females 10-year overall survival rates for delayed dissection: 48.7% for males	Prospective design Study included here for the data on therapeutic node dissection (not elective dissection) Different objective of the study (therapeutic vs. completion node dissection, not therapeutic vs. control group), therefore lower level of evidence concerning the question of	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					62.0% for females	indication for therapeutic node dissection Predominantly women in study group	
Sandeman (1966)	To review the results of radical surgery and other methods in the treatment of regionally advanced melanoma	Cohort study	113 patients with malignant melanoma in stages I-III	Overall survival	5-year OS survival for patients who originally presented in stage I, depending on treatment method: Surgery 27% Irradiation 23% Combined 67% 5-year overall survival for patients who originally presented in stage II, depending on treatment method: Surgery 27% Irradiation 33% Combined 0/4 Stage III: 5-year survival for irradiation 33%	Retrospective design Insufficient control group of patients who did not receive treatment	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Insufficient data for “no treatment” group and stage III with other treatment modalities		
Price and Duval (1963)	To determine whether or not prognosis in malignant melanoma is affected by regional lymph node excision	Cohort study	50 patients with malignant melanoma arising on an extremity	Overall survival	27 of 50 patients had clinically positive nodes on presentation. Of these 2 refused treatment (0% survivors) and 27/25 patients with clinical positive nodes received regional lymph node dissection: 20% survivors 14/23 patients with had clinically negative nodes; received regional lymph node dissection: 43% survivors	Retrospective design Small patient cohort Very old patient cohort (1931 – 1956), questionable transferability to current situation Very small, probably biased control group (2 patients with clinically involved nodes who refused treatment)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bowsher et al. (1986)	To evaluate short and long term postoperative morbidity, mortality and local recurrence rate after regional node dissection for melanoma	Cohort study	86 patients who received regional node dissection for melanoma (28% prophylactic, 72% therapeutic)	Recurrence rate	Local recurrence after dissection: - cervical: 33% - axillary: 13% - inguinal: 9% - axillary for trunk lesions: 21% - axillary for arm lesions: 6%	Retrospective design Small patient cohort No control group (comparison of lymph node dissection vs. no lymph node dissection not possible) For data on prophylactic RND and complications, see original article	3b-
Fortner et al. (1964)	To present results of groin dissection in malignant melanoma	Cohort study	220 patients who had undergone a groin dissection for malignant melanoma	Overall survival Recurrence rate Complication rate	5-year-survival-rate of patients with dissection: - unilateral groin dissection: 33,5% - histologically positive nodes: 23,3 % - histological negative nodes: 78,8%	Very old patient cohort (1931 – 1956), questionable transferability to current situation No control group (comparison of lymph node dissection vs. no	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					-radical groin dissection: 31,6% - nodal involvement by metastatic cancer confined to the superficial groin: 41,6% - positive nodes in both superficial and deep groups: 8,7% Complication-rate - during operation: 3% - postoperative: Approximately 60% Mortality rate within 30 days after operation: <0,5% Morbidity rate (relative to other than wound problems: 19,4%) Recurrence rate total for first year: 55,8%	lymph node dissection not possible) For further prognostic data see original article	

4.3.4.1. Literatur

Allan CP, Hayes AJ, Thomas JM. Ilioinguinal lymph node dissection for palpable metastatic melanoma to the groin. ANZ J Surg 2008;78:982-986
Bowsher WG, Taylor BA, Hughes LE. Morbidity, mortality and local recurrence following regional node dissection for melanoma. Br J Surg 1986;73:906-908
Cascinelli N, Morabito A, Santinami M, et al. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. Lancet 1998;351:793-796
Finck SJ, Giuliano AE, Mann BD, et al. Results of ilioinguinal dissection for stage II melanoma. Ann Surg 1982;196:180-186
Fisher SR. Elective, therapeutic, and delayed lymph node dissection for malignant melanoma of the head and neck: analysis of 1444 patients from 1970 to 1998. Laryngoscope 2002;112:99-110
FORTNER JG, BOOHER RJ, PACK GT. Results of Groin Dissection for Malignant Melanoma in 220 Patients. Surgery 1964;55:485-494
Gadd MA, Coit DG. Recurrence patterns and outcome in 1019 patients undergoing axillary or inguinal lymphadenectomy for melanoma. Arch Surg 1992;127:1412-1416
Hughes TMD, A'Hern RP, Thomas JM. Prognosis and surgical mananagement of patients with palpable inguinal lymph node metastases from melanoma. Br J Surg 2000;87:892-901
Jonk A, Strobbe LJ, Kroon BB, et al. Cervical lymph-node metastasis from cutaneous melanoma of the head and neck: a search for prognostic factors. Eur J Surg Oncol 1998;24:298-302
Karakousis CP, Driscoll DL. Groin dissection in malignant melanoma. Br J Surg 1994;81:1771-1774
Karakousis CP, Driscoll DL, Rose B, et al. Groin dissection in malignant melanoma. Ann Surg Oncol 1994;1:271-277
Karakousis CP, Emrich LJ, Rao U. Groin dissection in malignant melanoma. Am J Surg 1986;152:491-495
Karakousis CP, Hena MA, Emrich LJ, et al. Axillary node dissection in malignant melanoma: results and complications. Surgery 1990;108:10-17
Lee CC, Faries MB, Wanek LA, et al. Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. J Clin Oncol 2008;26:535-541
Morton DL, Wanek L, Nizze JA, et al. Improved long-term survival after lymphadenectomy of melanoma metastatic to regional nodes. Analysis of prognostic factors in 1134 patients from the John Wayne Cancer Clinic. Ann Surg 1991;214:491-9; discussion 499-501
Pasquali S, Mocellin S, Campana LG, et al. Early (sentinel lymph node biopsy-guided) versus delayed lymphadenectomy in melanoma patients with lymph node metastases : personal experience and literature meta-analysis. Cancer 2010;116:1201-1209
Pathak I, Gilbert R, Yoo J, et al. Outcome of neck dissection for node-positive melanoma. J Otolaryngol 2002;31:147-149
Pienkowski A, Nowecki ZI, Rutkowski P, et al. Analysis of survival and prognostic factors in patients with cutaneous melanoma after therapeutic lymphadenectomy. Nowotwory 2005;55:207-212
Pilko G, Besic N, Zgajnar J, et al. Prognostic heterogeneity after the excision of lymph node metastases in patients with cutaneous melanoma. Surg Oncol 2011;20:26-34
PRICE WE, DUVAL MK,Jr. Regional Lymph Node Dissection and Malignant Melanoma. Effect of Survival. Arch Surg 1963;87:747-750
Rutkowski P, Nowecki ZI, Dziewirski W, et al. Melanoma without a detectable primary site with metastases to lymph nodes. Dermatol Surg 2010;36:868-876
Sandeman TF. The radical treatment of enlarged lymph nodes in malignant melanoma. Am J Roentgenol Radium Ther Nucl Med 1966;97:967-979
Serpell JW, Carne PW, Bailey M. Radical lymph node dissection for melanoma. ANZ J Surg 2003;73:294-299
van Akkooi AC, Bouwhuis MG, van Geel AN, et al. Morbidity and prognosis after therapeutic lymph node dissections for malignant melanoma. Eur J Surg Oncol 2007;33:102-108
Veronesi U, Adamus J, Bandiera DC, et al. Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremities. Cancer 1982;49:2420-2430
White RR, Stanley WE, Johnson JL, et al. Long-term survival in 2,505 patients with melanoma with regional lymph node metastasis. Ann Surg 2002;235:879-887
Young SE, Martinez SR, Faries MB, et al. Can surgical therapy alone achieve long-term cure of melanoma metastatic to regional nodes? Cancer J 2006;12:207-2

4.3.5. Aktualisierungsrecherche 2016

2016 wurde keine Aktualisierungsrecherche durchgeführt.
Die Lenksungsgruppe hat sich mit den Mandatsträgern entschlossen, die Schlüsselfrage mittels eines Konsensusverfahrens basierend auf der letzten Literraturrecherche zu beantworten.

4.4. Frage III.4. Komplettierende LAD bei Mikrometastasen im SLN – De-novo-Recherche

Frage III.4. Ist eine komplettierende LAD bei Mikrometastasen im SLN indiziert?

Die Frage wurde in Zusammenarbeit mit der AG Sentinel Node Biopsie (Absatz 3.2) bearbeitet. Die entsprechenden Referenzen sind in diesem Kapitel gelistet.

4.5. Frage III.7. Operative Therapie bei Fernmetastasen – De-novo-Recherche

Frage III.7. Wann ist bei Fernmetastasen eine operative Therapie indiziert?

4.5.1. Datenbanken, Suchstrategien, Trefferzahlen

4.5.1.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(“melanoma”[tiab] AND ("neoplasm metastasis"[MeSH Terms] OR ("metastasis"[tiab])) AND ("surgery"[All Fields] OR “metastasectomy”[All Fields])	26.01.2012	3878
2. Suche/Ergänzungsrecherche			
Medline	(“melanoma”[tiab] AND ("neoplasm metastases"[MeSH Terms] OR ("metastases"[tiab]) OR (“metastatic”[tiab])) AND ("surgery"[All Fields] OR “metastasectomy”[All Fields])	26.01.2012	4137
Cochrane Library	(melanoma and (metastasis or metastases) and (surgery or metastasectomy)).ti,ab.	19.01.2012	89
Embase	(melanoma and metastasis and (surgery or metastasectomy)).ti,ab. (melanoma and metastases and (surgery or metastasectomy)).ti,ab.	23.01.2012	806 1342
Bemerkungen: Eine erste Literaturrecherche in Medline und und Cochrane erfolgte am 26.04.2011 bzw. für Embase am 11.05.2011. Eine Ergänzungsrecherche			

in Medline erfolgte am 08.12.2011. Die Update-Recherche wurde am 23.01.2012 (Embase) bzw. am 26.01.2012 (Medline) und am 19.01.2012 (Cochrane) durchgeführt. In der Tabelle angegeben sind die Trefferzahlen der letzten Recherche.

4.5.1.2. Aktualisierungrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(“melanoma”[tiab] AND ("neoplasm metastasis"[MeSH Terms] OR ("metastasis"[tiab])) AND ("surgery"[All Fields] OR “metastasectomy”[All Fields] AND ("2012.01.24"[Date - Publication] : "3000"[Date - Publication]))	12.09.2016	1234
Cochrane Library	(melanoma and (metastasis or metastases) and (surgery or metastasectomy)).ti,ab.	12.09.2016	46

4.5.2. Auswahlkriterien

4.5.2.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer inkl. Dupletten	10252
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt, ab Erscheinungsjahr 1978 population ≥ 20 patients
Ausschlusskriterien	narrative Reviews, Case Reports, gemischte Kollektive mit anderen Krebsarten, Studien ausschließlich zu Gehirn-Metastasen (andere AG)
Anzahl nach Abstractscreening	93

Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	31

4.5.2.2. Aktualisierungrecherche 2016

Auswahl der Literatur	
Gesamttreffer inkl. Dupletten	1280
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt, ab Erscheinungsjahr 1978 Population ≥ 20 Patienten
Ausschlusskriterien	narrative Reviews, Case Reports, gemischte Kollektive mit anderen Krebsarten, Studien ausschließlich zu Gehirn-Metastasen (andere AG)
Anzahl nach Abstractscreening	54
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	5

4.5.3. Evidenztabelle

4.5.3.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic Pulmonary Metastases							
Petersen et al. (2007)	to discriminate predictors of survival for	Cohort study	1720 patients with metastatic pulmonary	Survival 1-, 2- and 5-year-	OS (n=1720) - 1 year: 34% - 2-year: 14%	Retrospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with pulmonary metastatic melanoma.		melanoma 318 patients underwent resection (with curative intent)	survival	- 5 years: 6%. median survival: 7.3 months. complete vs incomeplete pathologic resection: - median survival: 19 vs. 11 months - 5-year survival: 21 vs. 3% (P<0.0001). single vs. repeated metastasectomy: - median survival: 17 vs.15 months (P<0.9). Significant predictors of survival (multivariate model): - nodular histologic type (P=0.033) - disease-free interval (P<0.001) - number of	complete follow-up on all patients large sample data collection during a span of 35 years.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					pulmonary metastases (P=0.012) - presence of extrathoracic metastasis (P<0.001) - performance of pulmonary metastasectomy (P<0.001). disease-free interval after surgery > 5 years: Survival: 19 months (vs 7 months, P<0.01) Patients without extrathoracic metastasis: 18 (vs 8 months, P<0.01).		
Leo et al (2000)	To evaluate the long-term results of lung metastasectomy for melanoma and to define a subset of	Cohort study .	328 patients who underwent lung metastasectomy Surgical patients underwent	Overall survival Mortality Prognostic factors of survival	5-year-survival: 18% 10-year-survival: 14% median survival 17 months.	Retrospective design Old patient cohort (1945-1995)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with better prognosis.		resection with curative intent only		R0-resection: 5- and 10-year survival: 22% and 16%(median survival 19 months) R1/R2-resection: 5-year-survival: 0% (median survival 11 months). Long- term survival according to the radicality of metastasectomy (16% vs 0% at 10 years, $P < 0.01$) independent unfavourable prognostic factors: - time to pulmonary metastases (TPM) <36 months - presence of multiple metastases Patients without these risk factors:	/questionable transferability to current situation Bias: chemo-/radiotherapy	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5-year-survival rate:29% Patients with 1 risk factors: 5-year-survival rate:20% Patients with 2 risk factors or incomplete resection: 5-year-survival rate:7% - mortality rate 67% - in the R0 group: 65% - in the R1–2 group: 80%). 5-year-survival inpatients with intrathoracic recurrence and further surgery: 19%		
Harpole et al. (1992)	To analyse patients from a melanoma data base - overall risk of	Cohort study	945 patients withpulmonary metases.	1-, 3- and 5-year survival-rates survival	1-, 3- and 5-year survival-rates: 30%, 9% and 4%	Retrospective analysis No information	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	pulmonary metastastic disease? - pulmonary resection as a primary therapy for metastases? - multivariate risk factors for survival?				Multivariate predictors of improved survival (p<0,001): -complete resection of pulmonary disease - longer time for formation of metastases -treatment with chemotherapy -1 or 2 pulmonary nodules - lymph nodes negative for metastases (p<0,005) -histologic type (p<0,04) curative resection for a solitary nodule (n=84) vs. no operation (n=142): 2-year and 5-year survival: 42% versus 20% (p<0,001)	about follow up	
Neuman et al.	to evaluate the	Cohort study	122 patients with	factors pedicitive	Median survival:	Retrospective	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(2007)	natural history of stage-IV melanoma metastatic to the lung and identify factors predictive of survival.		stage-IV melanoma and pulmonary metastases	of survival survival time to recurrence 5-year-survival	14 months 5-year survival: 8% Factors independently predictive of survival: - solitary pulmonary metastasis (HR 2.7, CI 1.6–4.4, p<0.0005) - absence of extra-pulmonary disease (HR 1.9, CI 1.2–3.1, P=0.01). - metastasectomy (HR 0.42, CI 0.21–0.87, P = 0.02). median survival of patients with metastasectomy vs. no surgical treatment: - 40 vs. 13 months Median time to recurrence: 5 months estimated 5-year	design No information about staging Small number of patients who received metastasectomy (n=26) Patients with pulmonary metastases and concurrent skin/subcutaneous /distant nodal disease were included Bias: systemic therapy	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival of patients undergoing metastasectomy: 29%. Patient who were followed up 3 and/or 5 years: 3-year- survival: 50% 5-year- survival: 23%		
Andrew et al.(2006)	To describe the experience with pulmonary metastasectomy	cohort study	86 patients 1-4 pulmonary metastases. (10 patients with unknown primary site)	relapse-free survival overall-survival 5-year-survival	overall median time to relapse: 8.4 months median survival: 35 months. 5-year survival rate: 33% 48/86 patients died (median survival time = 24 months), 16% of patients were relapse-free at a median follow-up of 35 months.	Retrospective design Short follow-up Patients received different postsurgical therapies	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					median survival of patients with a solitary vs. multiple lesions: 41 vs. 25 months (P = .05)		
Schuhan et al. (2011)	to determine the clinical course, outcome and prognostic factors in a subset of patients recently treated by metastasectomy.	Cohort study	30 patients with pulmonary metastases from malignant melanoma who underwent pulmonary resection Complete pulmonary resection in 27 patients	5-year survival rate Median survival prognostic parameter for OS	Cumulative 5-year survival rate after pulmonary resection: 35.1%, median survival: 18.3 months. patients with complete pulmonary vs. patients with incomplete resection: median survival: 20.5 months vs. 13.0 months completeness of resection=no statistically prognostic factor for survival. Multivariate	Small patient cohort	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					analysis: only significant prognostic parameter for overall survival: gender (9.4 months vs. 25.0 months for the female and male group, respectively (P = 0.022).		
Delaunay et al. (1991)	to assess the value of surgery in terms of survival and to delimit its indications	cohort study	38 patients with pulmonary metastases of malignant melanoma	Overall-survival Disease-free survival 5-year survival rate	median survival: 15 months (range 2-144 months). 5-year-survival: 20% median disease-free-survival: 10,5 months. Statistical significance in survival (incomplete vs. radical surgery: p<0,0001)	Retrospective multicenter study No information about follow-up/recruitment period 10 patients received neo-adjuvant treatment	3b-
Pogrebniak et al.	To update and	Cohort study	49 patients with	survival	Benign disease	retrospective study	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(1988)	reexamine the efficacy of excision of pulmonary melanoma metastases		resection of presumed pulmonary metastases from malignant melanoma		(n=13), metastastic disease (n=32), lung cancer (n=1) Survival (benign vs. malignant disease): 169 vs. 22 months Median survival after thoracotomy (malignant disease): 13 months. No difference in survival after complete vs. incomplete resection. 2-year-survival for patients with 1 vs. >1 nodule resected: 30% vs. 10%	screening methods out of use, questionable transferability to current situation	
Mathisen et al (1979)	To determine the efficacy of resection of pulmonary metastases from	Cohort study	33 patients who underwent thoracotomy for resection of suspected	survival	11 patients: non-malignant disease 10 unresectable disease: median	Retrospective study Small population Population not	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant melanoma		pulmonary metastases from malignant melanoma		survival: 10,5 months (3-20) 12 were rendered disease-free, median survival: 12 months (3-35). 5-year survival: 0%	described Old patient cohort (1957-1978) questionable transferability to current data 10 patients received postoperative chemotherapy	
Subtopic Abdominal/ retroperitoneal metastases							
Sanki et al. (2009)	To assess survival, morbidity and mortality following therapeutic or palliative resection of gastrointestinal (GI) tract melanoma metastases	retrospective prognostic cohort study	117 patients who underwent operations for acute and/or sub-acute symptoms or for imminently symptomatic GI metastases detected radiologically	Mortality Postoperative complications survival	Mortality rate after GI resection: 1.4% post-operative complications-rate: 2,5% 1-, 2- and 5-year survival rates: - for all patients: 57%, 39% and 27% - for patients having palliative resections: 34%,		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					19% and 0%. The median survival: - after surgical resection: 16.4 mo. - after resection with curative intent: 22.6 mo. - following palliative resection: 7.7 mo. significant prognostic indicators of survival (on multivariate analysis): - presence of residual intraabdominal disease - presence of non-GI metastases at the time of surgery or after surgery were the		
Ollila et al. (1996)	To evaluate the role of surgery in	Retrospective prognostic cohort	124 patients with metastatic	Operative morbidity and	median DFI: 23.2 (range, 1-154)		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	the survival of patients with melanoma metastatic to the gastrointestinal (GI) tract	study	melanoma in the stomach, small intestine, colon, or rectum	mortality relief of symptoms median and 5-year survival	months. 1 operative death 1 major operative complication After surgery relief of symptoms in 97% median survival in patients with curative resection vs. palliative procedures and nonsurgical interventions: 48.9 vs 5.4 and 5.7 months, respectively prognostic factors for long-term survival (multivariate analysis): - complete resection of GI tract metastases - GI tract as the initial site of		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					distant metastases.		
Hodgson et al. (2007)	To determine the role of resectional surgery in metastastic melanoma of the abdomen	Cohort study	25 patients (5 patients had occult tumours)	Survival morbidity mortality	median survival after abdominal resection: 8.3 (range 0.4–41.1) months. 1-year survival: 36% 1-year-survival after surgery with curative vs. palliative intend: 89 vs 10%, P < 0.0001) Superior survival in patients with ≤2 metastases compared with ≥2 (P = 0.0001) Intent of surgery (curative vs palliative) was the only factor significant on multivariate analysis (P =	Retrospective study Small population No information about follow-up	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.001). Relief of preoperative symptoms: 87% Operative morbidity: 12% 30-day mortality: 4%.		
Mittendorf et al. (2008)	to determine the natural history of melanoma metastasis to the adrenal gland and the appropriate role for surgical intervention	Cohort study	154 patients with adrenal metastasis 22 patients underwent surgical resection	surgical treatment survival	median OS:6.4 months (range 0,2-97 months). median OS for patients with: - synchronous metastatic disease: 6.6 months - isolated adrenal metastasis: 18.7 months (p<0,0001) median OS for patients with a disease-free interval of: - <1 year: 7 months	Retrospective design Small population	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- >1 year: 11 months (*P=0,35*). After a median follow-up of 12.6 months, 9/22 (41%) Patients who underwent surgical resection were alive, incl. 7 without recurrence. Survival of patients who underwent surgery vs. those managed nonoperatively (p<0,0001).		
Pawlik et al. (2006)	To evaluated the efficacy of hepatic resection in patients with metastatic ocular and cutaneous melanoma and to assesse factors that could affect survival after resection	Cohort study	40 patients with metastatic melanoma involving the liver who were treated with hepatic resection with curative intent	Survival 5-year-survival Time to recurrence	median time to recurrence: 8.3 months median survival: 28.2 months (range,4.6–93 .7 months) 5-year survival rate: 10.9%.	Retrospective design Patients with ocular melanoma included Some patients had other metastatic sites (not only liver) which were	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					5-year survival rate for patients with a primary ocular melanoma: 20.5%. 5-year survival rate for patients with cutaneous melanoma (P=0.03). No clinicopathologic factors predictive of survival after hepatic resection	not operated Bias: 17 patients (70.8%) received some form of systemic therapy	
Ricaniadia et al. (1995)	to investigate the role of surgical intervention in patient with GI metastasis and to define the group of patients who would benefit surgical resection.	Cohort study	68 patients with clinical indications of involvement of the gastrointestinal (GI) tract with metastatic melanoma 47 patients underwent abdominal surgery	Complication rate Survival 5-year-survival	median survival for patients unsuitable for surgery: 2.9 months. Relief of preoperative symptoms after surgery: 73% Postoperative complications: 29% Death within 30	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					days of surgery: 11% median survival: - after surgery vs. no surgery: 5.66 vs. 2.9 months (P=0.0035) - after complete resection and no other disease vs. resection and other metastasis present: 27,6 vs. 5.1 months - after by-pass procedure: 1,9 months 5-year survival: - after complete resection and no other evidence of disease: 28.3% (the other groups had only 1-year survivors)		
Szynglarewicz et al. (2012)	To asses the role of colorectal surgery in the treatment of metastatic	Cohort study	34 consecutive patients with skin melanoma who underwent	Mortality Morbidity	postoperative mortality: 0% postoperative	Small patient cohort No information	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma and to identify patients who can most benefit from surgical resection.		surgical resection of large bowel metastasis 9 patients: emergency surgery for obstruction, 25 patients had an elective procedure. Intend of surgery: curative in 14 patients, palliative in 20 patients	Median survival 1-, 2-, and 5-year survival rates Prognostic factors	morbidity: 9%. Median survival following surgery: 11.5 (4-68) months. 1-, 2-, and 5-year survival rates: 50%, 32%, and 17% respectively. Median survival significantly increased in patients without extra-abdominal metastases, with no evidence of non-large bowel metastases, if the DFI >24 months and when curative resection was performed. most important prognostic factors on multivariate analysis: apparently complete or palliative resection	about R1-Status	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					and the absence or presence of extraabdominal metastases		
de Wilt et al. (2003)	To analyse indications for surgery, complications, and overall survival with the aim of clarifying the indications for surgical treatment in such patients	Cohort study	15 patients who underwent surgical treatment of metastases 98 patients were treated conservatively .	Postoperative morbidity Overall survival 1-year-survival rate 2-year-survival rate	patients with splenectomy: median OS: 11 months 1-year survival rate: 35%, 2-year-survival-rate 21% patients with single splenic lesion and splenectomy: median OS: 23 months. 1-year survival rate: 70%, 2-year-survival-rate: 50% conservatively treated patients: median OS: 4 months. 1-year survival rate: 13%, 2-year-survival-rate 3% survival of patients	retrospective design Small patient number Medical/conservative treatment not described in detail, 4 patients who underwent splenectomy were included in clinical trials. No information about follow-up	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					with splenic metastases treated surgically vs. conservatively: P=0.02 Survival after splenectomy with palliative vs. curative intent: P=0,07		
Berger et al. (1999)	To determine whether surgery influences outcomes	Retrospective cohort study	Fifty patients with melanoma metastatic to the GI tract	Mortality rate survival	operative mortality rate: 2.5% mean survival times for the unexplored and unresected groups: 4.1 months significantly increased survival: - in the partial-resection group (8.9 months) compared with the unresectable group (P<0. 001). - in the complete-resection group		3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(23.5 months) than in the less than complete resection-group (P<0.0001).		
Khadra et al. (1990)	To examine if a surgical approach of metatases in the GIT is justified.	Cohort study	56 patients with symptomatic melanoma of the gastrointestinal tract (GIT) treated surgically (13 occult primary)	complication rate postoperative survival overall survival time to recurrence	relief of symptoms in 44 patients post postoperatively. postoperative complications: 8/56 patients (2 died) mean postoperative OS after 1st vs. 2nd metastases: 11.7 (range 1-60) vs. 3,6 months (range 0-12 months) median time of recurrence: 12 months (range 3-47 months) mean OS for ulcerated vs. non-ulcerated tumor: 46,6 vs. 84,9	Retrospective design Methods of follow-up not described No information about metastases other than in GIT-tract Bias: Adjuvant therapy (chemotherapy in 26 patients, radiotherapy in 1 patients, immunotherapy in 4 patients)	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months. mean OS when primary tumor <1,5 mm vs. >1,5 mm: 11,7 vs. 9,5 months.		
Chua et al. (2010)	To evaluate the efficacy of surgical metastasectomy on survival outcomes.	Retrospective cohort study	23 patients with visceral metastases from melanoma (15 underwent surgical resection)	disease-free interval Overall survival	DFI: 49 (range, 5 to 559) months Median OS: 9 months. 1- and 3-year survival: 39% and 30%, respectively. Survival was influenced by - the number of metastases (P = 0.05) and the treatment received (P = 0.03). After metastasectomy: DFI and OS: 14 and 21 months, respectively. 1- and 3-year survival: 60% and	Small patient cohort	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					40%, respectively. Significant longer survival for patients with single site vs. >1 site of metastasis ($P = 0.005$)		
Branum et al. (1991)	To evaluate the role of resection in the management of melanoma metastatic to the adrenal gland	Retrospective cohort study	28 patients with melanoma metastatic to the adrenal gland	Survival 5-year-survival	Mean survival in the group that underwent resection for cure: 59 months (3 to 112 months) survival in the group with unresectable tumors: 15 months (1.5 to 132 months). 5-year-survival: - 4/8 patients who underwent resection for cure 1/14 patients with unresectable tumors		4
Subtopic different							

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
metastatic sites							
Wasif et. (2011)	to study the impact of metastasectomy on survival in these patients.	Prognostic factors	4229 patients with stage IV melanoma patients were subdivided into M1a disease (cutaneous metastases) and Mbc disease (visceral metastases).	Median survival 5-year-survival	median survival of the study population: 7 months. Patients who underwent metastasectomy (33.6%) vs. patients without metastasectomy: median OS: 12 months vs 5 months 5-yeas OS: 16% vs. 7% (P < 0.001). In patients with M1a disease (n = 1,994): median survival of 14 months vs. 6 months, 5-year OS: 20% vs. 9% (P < 0.001). Younger age and diagnosis from 2001 to 2006 were predictors of	Those who had metastasectomy performed were compared with patients that did not.	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastasectomy. Metastasectomy was an independent and significant predictor of survival for the entire cohort (HR 0.59, 95% CI 0.55–0.63).		
Essner et al (2004)	to evaluate the outcome of patients with advanced-stage melanoma treated by surgical resection with curative intent.	Cohort study	4426 patients stage IV melanoma, 1574 (35%) underwent surgical resection with curative intent;	5-year-survival rate predictive factors on survival	5-year survival rate: patients who underwent surgical resection vs. nonsurgical treatment: mean±SD, 23%±2% vs. 6%±5% (P<0.001) 5-year survival rate: patients with a solitary vs. >/=4 metastases: 29%± 2% vs. 11%±3% (P<0.001) median survival is slightly higher for patients with skin	retrospective study No information about adjuvant therapies	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					or subcutaneous sites (alone) than for LN, GIT or lung sites, no significant differences in the estimated 5-year survival rate (P=0.29) predictive factors on multivariate analyses: - earlier primary tumor stage (I vs II) (P<0.001) - absence of intervening stage III metastases (P=0.02) - solitary metastasis (P<0.001) - disease-free interval >36 months from AJCC stage I or II to stage IV (P=0.005)		
Brand et al. (1997)	to identify important prognostic factors	Retrospective prognostic cohort study	3258 melanoma patients	Overall survival Prognostic factors	median survival time: 7 months		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	associated with Stage IV melanoma.		442 melanoma patients with distant metastases		2-year, 5-year, and 10-year survival rates: 11.9%, 6.7%, and 4.7%, respectively. Of the modalities of therapy given, only surgery was associated with prolonged survival (P< 0.0001) Factors significantly related to short term survival: - primary metastasis to the skin (P = 0.006) - - the brain (P = 0.015) - >1 metastatic site (P = 0.002) - Karnofsky performance status <80 (P = 0.0035) - subsequent >/=2 new metastatic sites (P = 0.0025)		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Tauceri et al (2009)	to agree on the role of surgery in patients with metastatic melanoma	cohort study	84 consecutive patients operated on for stage IV melanoma	survival 1-, 3- and 5-year-survival rate Mortality morbidity	postoperative mortality: 0 overall morbidity: 15%. minimal and maximal survival: 1.5 and 142.5 months, respectively. mean OS: 56.7 months (1 year: 72.1%, 3 years: 46.5%, 5 years: 23.16%). survival of reiterative surgery vs. single surgery:62.7 vs 42.4 months, median 50.9 vs 16.0, p=0.03. Reiterative surgery was shown as an independent prognostic factor (p<0.05).	retrospective design bias: 90.5% underwent adjuvant therapies	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ollila et al. (1999)	To examine whether a 2nd metastasectomy could prolong the survival of patients with recurrent stage IV melanoma.	Retrospective cohort study	131 patients who developed recurrent stage IV diseas	DFI to recurrence Survival 5-year-survival	Median DFI: 8 (range 0.6–91.8) months. Median survival: 18.2 months after complete metastasectomy vs. 12.5 months or 5.9 months after palliative surgical procedure or nonsurgical management, respectively. 5-year survival: 20.0% after complete surgical metastasectomy vs. 7.0% and 2.1% after palliative surgical and nonsurgical intervention, respectively. prognostic factors for survival: - prolonged DFI (P=0,0001) - complete surgical	Possibly overlapping population/ Ollila et al. 1996 2 gynecologic tumor sites included	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					metastasectomy (P=0,0001)		
Gohl et al. (1996)	To examine the value of surgical treatment of distant metastases of malignant melanoma	Cohort study	In 174 cases surgery was perfomed, in 70 patients with curative intent. 15 patients with occult melanoma.	Survival	Median survival - after R0 (curative surgery): 13 months - R1/R2: 6 months. - Patients without treatment: 3 months statistically significant difference in 1-year-survival for patients who underwent curative surgery vs.palliative surgery. 5-year-survival and 10-year-survival after curative surgery: 24% and 7% respectively	Retrospective design No information about adjuvant therapy Staging of patients not described	3b
Karakousis CP et al. (1994)	To evaluate surgical treatment during the management of	Cohort study	114 with disseminated melanoma amenable to	Survival Estimated 5-year-survival	Median survival after metastasectomy: 19 months	Retrospective design bilateral nodal	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with a small number of resectable lesions in an effort to prolong their life		surgical resection	5-year-survival rate	estimated 5-year survival rate: 22%. 5-year survival rate for those with: -distant subcutaneous metastases: 33% - distant LN metastases: 22% - pulmonary metastases: 74% (P=0.72). 5-year survival rate for : - combined group of s.c. and nodal metastases: 28% - pulmonary and visceral sites: 17% Significant prognostic parameters: - thickness of the primary melanoma (p=0.05) - number of metastatic lesions (p=0.03)	metastasis or spread from one groin to the contralateral groin was considered likely to be regional spread and these patients were excluded 93% underwent chemotherapy, 27% radiotherapy, 5% no further therapy	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- prior disease-free interval (p=0.05) .		
Overett et al. (1985)	To review clinicopathologic factors that determine the successful resection of tumor, survival, and quality of life	Cohort study	176 patients who underwent surgical intervention for distant metastases of	Survival 2- and 5-year-survival-rate Mortality Relapse rate	estimated 2- and 5-year survival rate: 2 1 % and 13%, respectively median survival time: 8.5 months. Estimated 2-year and 5-year survival-rate after complete resection of single-site- vs. multiple-site lesions: 47% and 33% vs. 17% and 9%, respectively (P < 0.01). Operative mortality Rate:1.4% relapse-rate: 66% Median interval to relapse in case of incomplete vs. complete resection: 3 vs. 9	Retrospective design Old patient cohort (1965-1979), questionable transferability to current situation	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months (P = 0.07). 5-years survival after repeated resection: 20% median survival in case of repeated resection vs. incomplete resection of new disease: 26 vs. 8 months (P<0.0005)		
Garbe (1996)	to identify patients with prolonged survival in stage IV disease and to analyse the possible impact of therapy on the course of the disease.	Retrospective review	263 patients having stage IV melanoma 111 patients: surgery and/or radiation therapy. (17 surgery alone) 89 patients: systemic treatment 48 patients: both systemic and local therapy. 111 patients: no treatment.	Survival	22 patients treated with multimodality survived > 24 months (median Survival: 33 months) 16: both systemic treatment and surgery and/or radiation, 3: systemic drug therapy, 3:only local treatment. 12/22 patients became tumour free after initial	Confounder adjuvant therapy	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					surgery or radiation. 2-year-survival for patients without treatment:0%		
Karakousis et al. (1983)	to identify, or confirm, favorable characteristics that may improve palliation	Cohort study	79 consecutive patients with resectable, recurrent malignant melanoma were treated with surgical excision	Survival	significant survival difference between Stage IV survivors (36 months) and those who manifested disease progression (12 months) (P < 0.02). Characteristic of those patients who remain disease free: - initial presence </=3 metastatic lesions - long prior disease-free interval	Retrospective design Small population No information about staging Poor information about follow-up	3b-
Wornom et al. (1983)	To examine the efficacy of surgery as palliative treatment in 65 patients with	Cohort study	65 patients with distant metastatic melanoma amenable to surgical	Survival mortality	overall operative mortality: 11% Relief of symptoms after excision of:	Retrospective design Most patients received	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	distant metastatic melanoma amenable to surgical excision				- 77% of brain metastases, - 100% of lung metastases - 88% of distant LN and s.c. metastases - 100% of abdominal metastases Median survival after excision of: - brain metastases: 8 months - lung metastases: 9 months - abdominal metastases 8 months - distant s.c., LN metastases: 15 months. median survival of patients with - combined visceral and resected superficial metastases: 14 months, 5-year	chemotherapy No information about staging No detailed information about population	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					survival: 0% - resection of superficial metastases and no detectable evidence of visceral metastasis: 17 months. 5-year survival: 14% 2-year survival: 29% for both groups.		
Feun et al. (1982)	To discuss the natural history of Stage IVA melanoma and the role of adjuvant therapy	Cohort study	102 patients with malignant melanoma who had distant metastases surgically resected and were judged to be clinically free of disease	survival disease-free-survival	median survival: 18 months. survival depending on site of resected metastases: - brain: 15 months - lung: 16 months - intraabdominal 18 months - skin and/or LN 23 months Disease-free interval not influenced by site	Retrospective design 35 patients who had surgery vs. 67 patients who received adjuvant therapy	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Similar survival of patients who had metastases resected from several organs at the same time and patients with one resected site group treated with surgery only vs. adjuvant group: median disease-free interval and survival: 6 and 16 months vs. 6 and 21 months, respectively		

4.5.3.1.1. Literatur

Andrews S, Robinson L, Cantor A, et al. Survival after surgical resection of isolated pulmonary metastases from malignant melanoma. Cancer Control 2006;13:218-223
Berger AC, Buell JF, Venzon D, et al. Management of symptomatic malignant melanoma of the gastrointestinal tract. Ann Surg Oncol 1999;6:155-160
Brand CU, Ellwanger U, Stroebel W, et al. Prolonged survival of 2 years or longer for patients with disseminated melanoma. An analysis of related prognostic factors. Cancer 1997;79:2345-2353
Branum GD, Epstein RE, Leight GS, et al. The role of resection in the management of melanoma metastatic to the adrenal gland. Surgery 1991;109:127-131
Chua TC, Saxena A, Morris DL. Surgical metastasectomy in AJCC stage IV M1c melanoma patients with gastrointestinal and liver metastases. Ann Acad Med Singapore 2010;39:634-639
de Wilt JH, McCarthy WH, Thompson JF. Surgical treatment of splenic metastases in patients with melanoma. J Am Coll Surg 2003;197:38-43
Delaunay MM, Amici JM, Avril MF, et al. Surgery of pulmonary metastasis from malignant melanoma. Results and criteria of surgical excision]. Ann Dermatol Venereol 1991;118:287-295
Essner R, Lee JH, Wanek LA, et al. Contemporary surgical treatment of advanced-stage melanoma. Arch Surg 2004;139:961-6; discussion 966-7
Feun LG, Gutterman J, Burgess MA, et al. The natural history of resectable metastatic melanoma (Stage IVA melanoma). Cancer 1982;50:1656-1663
Garbe C. Increased survival in distant melanoma metastasis and the effect of treatments. Analysis of the disease course of patients with a survival of 2 years or more]. Hautarzt 1996;47:35-43
Gohl J, Meyer T, Haas C, et al. Is surgical therapy of distant metastases of malignant melanoma worthwhile?]. Langenbecks Arch Chir Suppl Kongressbd 1996;113:122-126
Harpole DH,Jr, Johnson CM, Wolfe WG, et al. Analysis of 945 cases of pulmonary metastatic melanoma. J Thorac Cardiovasc Surg 1992;103:743-8; discussion 748-50
Hodgson R, Fink MA, Jones RM. The role of abdominal resectional surgery in metastatic melanoma. ANZ J Surg 2007;77:855-859
Karakousis CP, Moore R, Holyoke ED. Surgery in recurrent malignant melanoma. Cancer 1983;52:1342-1345
Karakousis CP, Velez A, Driscoll DL, et al. Metastasectomy in malignant melanoma. Surgery 1994;115:295-302

Khadra MH, Thompson JF, Milton GW, et al. The justification for surgical treatment of metastatic melanoma of the gastrointestinal tract. Surg Gynecol Obstet 1990;171:413-416
Leo F, Cagini L, Rocmans P, et al. Lung metastases from melanoma: when is surgical treatment warranted? Br J Cancer 2000;83:569-572
Mathisen DJ, Flye MW, Peabody J. The role of thoracotomy in the management of pulmonary metastases from malignant melanoma. Ann Thorac Surg 1979;27:295-299
Mittendorf EA, Lim SJ, Schacherer CW, et al. Melanoma adrenal metastasis: natural history and surgical management. Am J Surg 2008;195:363-8; discussion 368-9
Neuman HB, Patel A, Hanlon C, et al. Stage-IV melanoma and pulmonary metastases: factors predictive of survival. Ann Surg Oncol 2007;14:2847-2853
Ollila DW, Essner R, Wanek LA, et al. Surgical resection for melanoma metastatic to the gastrointestinal tract. Arch Surg 1996;131:975-9; 979-80
Ollila DW, Hsueh EC, Stern SL, et al. Metastasectomy for recurrent stage IV melanoma. J Surg Oncol 1999;71:209-213
Overett TK, Shiu MH. Surgical treatment of distant metastatic melanoma. Indications and results. Cancer 1985;56:1222-1230
Pawlik TM, Zorzi D, Abdalla EK, et al. Hepatic resection for metastatic melanoma: distinct patterns of recurrence and prognosis for ocular versus cutaneous disease. Ann Surg Oncol 2006;13:712-720
Petersen RP, Hanish SI, Haney JC, et al. Improved survival with pulmonary metastasectomy: an analysis of 1720 patients with pulmonary metastatic melanoma. J Thorac Cardiovasc Surg 2007;133:104-110
Pogrebniak HW, Stovroff M, Roth JA, et al. Resection of pulmonary metastases from malignant melanoma: results of a 16-year experience. Ann Thorac Surg 1988;46:20-23
Ricaniadis N, Konstadoulakis MM, Walsh D, et al. Gastrointestinal metastases from malignant melanoma. Surg Oncol 1995;4:105-110
Sanki A, Scolyer RA, Thompson JF. Surgery for melanoma metastases of the gastrointestinal tract: indications and results. Eur J Surg Oncol 2009;35:313-319
Schuhan C, Muley T, Dienemann H, et al. Survival after pulmonary metastasectomy in patients with malignant melanoma. Thorac Cardiovasc Surg 2011;59:158-162
Szynglarewicz B, Ekiert M, Forgacz J, et al. The role of surgery in the treatment of colorectal metastases from primary skin melanoma. Colorectal Dis 2012
Tauceri F, Mura G, Roseano M, et al. Surgery and adjuvant therapies in the treatment of stage IV melanoma: our experience in 84 patients. Langenbecks Arch Surg 2009;394:1079-1084
Wasif N, Bagaria SP, Ray P, et al. Does metastasectomy improve survival in patients with Stage IV melanoma? A cancer registry analysis of outcomes. J Surg Oncol 2011;104:111-115
Wornom IL,3rd, Smith JW, Soong SJ, et al. Surgery as palliative treatment for distant metastases of melanoma. Ann Surg 1986;204:181-185

4.5.3.2. Aktualisierungrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Subtopic Pulmonary Metastases							
Chua et al. (2012)	To identify the clinicopathologic and predictors of outcome after surgical management of melanoma lung metastases in a large series of patients.	Retrospective, single center cohort study	292 patients	Progression-free survival (PFS) Overall survival (OS)	The median PFS time was 10 months. The median OS and 3- and 5-year survival were 23 months [95% confidence interval (CI) 17–30], 41 and 34%, respectively.		3a

Subtopic Abdominal/ retroperitoneal metastases							
Flaherty et al. (2015) [2]	We hypothesized that surgery remains an optimal first-line treatment approach for resectable adrenal metastases.	Retrospective (prospectively collected), single institution database evaluation.	91 study patients of which 24 had an adrenalectomy	Overall survival (OS)	Median OS from diagnosis of adrenal metastases was 29.2 months with adrenalectomy vs 9.4 months with nonoperative treatment. Of those having adrenal surgery, 14 (58%) underwent an operative procedure that rendered the patient free of disease.		3a
Subtopic different metastatic sites							
Colman et al. (2014) [3]	To ask whether a group who underwent	Retrospective, single center	130 patients with bone metastases	Overall survival (OS)	Median OS for the nonoperative (N=80),		3a

	complete metastasectomy for skeletal melanoma had a longer overall survival than those who underwent intralesional/debulking surgery or nonoperative treatment. To ask whether the overall survival in these three treatment groups conforms with, or diverges from, the overall survival predicted by over 2100 historical control patients who underwent systemic therapy alone, as outlined by the method of Korn et al.	cohort study			intralesional (N=32), and resection (N=18) groups was 4.8, 5.1, and 11.8 months, respectively. Cox regression survival analysis confirmed the OS benefit resulting from wide resection (hazard ratio [HR] 0.53) after correcting for independent predictors of worse survival, such as pathologic spinal compression fracture (HR 1.68). The observed 1-year OS rate in the resection group was nearly double that of matched historical controls		

					(50.0 vs. 24.8%).		
Krygier et al. (2014) [4]	To determine overall survival after surgery for bone metastasis in patients with MM and the rate of local relapse after surgery for bone metastasis, and whether certain patients might benefit from more extensive surgery to reduce the risk of local recurrence, and whether there is an effect of prior radiation on survival and local progression.	Retrospective, single center cohort study	37 patients	Overall survival Local recurrence rate Local progression free survival (LPFS)	The median OS from surgery was 9 months (range, 1–135 months), 1-Y-OS: 30%, 2-Y-OS: 17%. Local recurrence developed in seven of 41 lesions (17%). The LPFS was 87% at 12 months and 67% at 24 months. Patients for whom prior radiation failed and patients who did not have excision of osseous metastases had higher rates of local recurrence.		3a
Wevers et al.	To evaluate the extent of disease	Retrospective, single center	70 patients with	Rate of metastasectomy	55 patients (78.6 %) were ineligible		3a

(2013) [5]	and resectability of melanoma patients presenting with stage IV disease to establish the incidence of completely resectable stage IV melanoma and To gain insight in factors that impede complete resection.	cohort study	stage IV melanoma	Overall survival	for complete surgical resection. A total of 6 patients did receive complete surgery as initial stage IV treatment, and in 9 patients incomplete surgery was performed. Overall median survival was 14.6 months, and the estimated 1-year survival rate was 51.0 %. The 1-year survival rates were 75, 49, and 80 % for surgery, systemic medical therapy, and radiotherapy, respectively (p=.70).		

4.5.3.2.1. Literatur

Eggermont, A.M., et al., Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. J Clin Oncol, 2012. 30(31): p. 3810-8.
Patel, J.N. and C.M. Walko, Sylatron: a pegylated interferon for use in melanoma. Ann Pharmacother, 2012. 46(6): p. 830-8.
Ascierto, P.A., et al., Adjuvant interferon alfa in malignant melanoma: an interdisciplinary and multinational expert review. Crit Rev Oncol Hematol, 2013. 85(2): p. 149-61.

Grob, J.J., et al., Adjuvant therapy with pegylated interferon alfa-2b (36 months) versus low-dose interferon alfa-2b (18 months) in melanoma patients without macrometastatic nodes: an open-label, randomised, phase 3 European Association for Dermato-Oncology (EADO) study. Eur J Cancer, 2013. 49(1): p. 166-74.
Mocellin, S., et al., Interferon alpha for the adjuvant treatment of cutaneous melanoma. Cochrane Database Syst Rev, 2013(6): p. Cd008955.
Flaherty, L.E., et al., Southwest Oncology Group S0008: a phase III trial of high-dose interferon Alfa-2b versus cisplatin, vinblastine, and dacarbazine, plus interleukin-2 and interferon in patients with high-risk melanoma--an intergroup study of cancer and leukemia Group B, Children's Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. J Clin Oncol, 2014. 32(33): p. 3771-8.
Mohr, P., et al., Intermittent High-Dose Intravenous Interferon Alfa-2b for Adjuvant Treatment of Stage III Melanoma: Final Analysis of a Randomized Phase III Dermatologic Cooperative Oncology Group Trial. J Clin Oncol, 2015. 33(34): p. 4077-84.
Eggermont, A.M., et al., Long term follow up of the EORTC 18952 trial of adjuvant therapy in resected stage IIB-III cutaneous melanoma patients comparing intermediate doses of interferon-alpha-2b (IFN) with observation: Ulceration of primary is key determinant for IFN-sensitivity. Eur J Cancer, 2016. 55: p. 111-21.
Eigentler, T.K., et al., Adjuvant treatment with pegylated interferon alpha-2a versus low-dose interferon alpha-2a in patients with high-risk melanoma: a randomized phase III DeCOG trial. Ann Oncol, 2016. 27(8): p. 1625-32.
McMasters, K.M., et al., Final Results of the Sunbelt Melanoma Trial: A Multi-Institutional Prospective Randomized Phase III Study Evaluating the Role of Adjuvant High-Dose Interferon Alfa-2b and Completion Lymph Node Dissection for Patients Staged by Sentinel Lymph Node Biopsy. J Clin Oncol, 2016. 34(10): p. 1079-86.

5. AG Mukosale Melanome

5.1. Frage IV.5: Sicherheitsabstände bei mukosalen Melanomen – De Novo Recherche?

Frage IV.5: Wie sind die operativen Sicherheitsabstände bei mukosalen Melanomen zu definieren?

5.1.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients suffering from mucosal melanoma	Surgery	observation	Local recurrence free survival, DFS, OS

Suchwörter				
Stichwort	mucosal melanoma	surgery	excision margins	
Synonyme		operation		
Mesh Term	mucosal melanoma	Surgery		

5.1.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	mucosal melanoma[tiab] AND (“therapy”[all fields] OR “treatment”[all fields] OR “management”[all fields] OR "surgery"[all fields] OR “surgical”[all fields] OR “surgical procedures, operative”[mesh] OR "excision"[all fields]) AND (“safety margin”[all fields] OR “excision margin”[all fields] OR “surgical margin”[all fields] OR “narrow”[all fields] OR “wide”[all fields])	16.09.2016	27
Cochrane Library	"mucosal melanoma”	02.10.2016	0

5.1.3. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer		723
Einschlusskriterien	Reviews Intervention: Chirurgie Sprachen: e,dt	
Ausschlusskriterien	Case Reports Monozentrischen, kleine Kohortenstudien (Pat. Anzahl <25) Kollektive mit gemischten Tumorentitiäten	
Anzahl ausgewählter Studien		**5**

5.1.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Lazarev S, et al. 2014	To provide a comprehensive summary of findings as they pertain to the available therapies for malignat melanoma of the head and neck (MMHN)	Systematic review	Patients suffering from MMHN	Clinical outcome OS	Achievement of clear margins was related to better clinical outcome in several studies. Negative margins were a significant prognostic factor for survival	Clinical outcome not specified	2a
Lee G, et al. 2016	To investigate the prognostic impact of different, surgical approaches (external vs. endoscopic) on oncological outcomes, measured as treatment failure patterns, disease-free survival (DFS), and disease-specific survival (DSS)	Retrospective reviews of 31 patients	Patients suffering from MMHN	DFS, DSS	Among variables, age and T classification, not the surgical approach, were significant prognosticators for DFS and DSS	Low sample size for a multivariante analysis	3b
Matsuda A, et al. 2015	To determine whether the extent of	Meta-analysis; 31 articles; n= 1006 patients	Articles reporting on patients (>1)	OS, RFS	Total 5-year OS and 5-year RFS rates were OS, 19.2%;		2a

	surgery is associated with survival in anorectal malignant melanoma (ARMM)	until August 2013.	with ARMM who underwent APR (abdominal perineal ressection) or LE (local excision)	Local recurrence data	RFS, 17.2%. Overall survival (OR, 1.14; 95% CI, 0.74–1.76; P = 0.54) and relapse-free survival (OR, 0.95; 95% CI, 0.43–2.09; P = 0.89) did not differ significantly between the APR and LE groups. APR significantly reduced local recurrence compared with LE (OR, 0.18; 95% CI, 0.09–0.36; P< 0.00001)		

5.1.5. Literatur

Lazarev, S., et al., Mucosal melanoma of the head and neck: a systematic review of the literature. Int J Radiat Oncol Biol Phys, 2014. 90(5): p. 1108-18.
Lee, G., et al., The Prognostic Role of the Surgical Approach and Adjuvant Therapy in Operable Mucosal Melanoma of the Head and Neck. Clin Exp Otorhinolaryngol, 2017. 10(1): p. 97-103.
Matsuda, A., et al., Abdominoperineal resection provides better local control but equivalent overall survival to local excision of anorectal malignant melanoma: a systematic review. Ann Surg, 2015. 261(4): p. 670-7.

5.2. Frage IV.7: Initiale Ausbreitungsdiagnostik bei mukosalen Melanomen – De Novo Recherche?

Frage IV.7: Welche initiale Ausbreitungsdiagnostik sollte erfolgen?

5.2.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients suffering from mucosal melanoma	Complementary diagnosis exams (direct observation, US, CT)	Observation/no intervention	Sensitivity, Specificity

Suchwörter				
Stichwort	mucosal melanoma	Staging	Examinations	
Synonyme		Imaging		
Mesh Term	mucosal melanoma	Imaging		

5.2.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	Mucosal melanoma[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields]	16.09.2016	39

Datenbank	Suchstrategie	Datum	Treffer
	OR "sonography"[all fields]) OR ("lymph nodes"[all fields] OR ("lymph"[all fields] AND "nodes"[all fields]) OR "lymph nodes"[all fields] OR ("lymph"[all fields] AND "node"[all fields]) OR "lymph node"[all fields]))		
	Mucosal melanoma[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND ("chest X-ray"[all fields] OR "chest radiography"[all fields] OR "Radiography, Thoracic"[Mesh])	16.09.2016	39
	Mucosal melanoma[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (("ultrasonography"[Mesh] OR "ultrasonography"[all fields] OR "sonography"[all fields]) OR "abdomen"[all fields] OR “abdominal"[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])	16.09.2016	9
	Mucosal melanoma[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND ("Magnetic Resonance Imaging"[Mesh] OR “Magnetic Resonance Imaging”[all fields] OR “mri”[all fields] OR “magnetic resonance”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])	16.09.2016	14
	Mucosal melanoma[tiab] AND (“staging”[all fields] OR "diagnosis"[all fields]) AND (“Tomography, X-Ray Computed"[Mesh] OR “computer tomography”[allfields] OR “ct”[all fields] OR "Tomography, Spiral Computed"[Mesh] OR "Tomography Scanners, X-Ray Computed"[Mesh] OR "Positron-Emission Tomography"[Mesh] OR “positron-emission tomography”[all fields] OR “pet”[all fields] OR "Tomography, Emission-Computed, Single-Photon"[Mesh] OR “single-photon emission computed tomography”[all fields] OR “spect”[all fields]) NOT ("ophthalmology"[Mesh] OR "eye"[Mesh] OR "eye neoplasms"[Mesh])	16.09.2016	20
Cochrane Library	"mucosal melanoma”	02.10.2016	0

5.2.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	51
Einschlusskriterien	Sprachen: e,dt
Ausschlusskriterien	Case Reports Monozentrischen, kleine Kohortenstudien (Pat. Anzahl <25) Kollektive mit gemischten Tumorentitiäten
Anzahl ausgewählter Studien	0

5.2.4. Ergebnis

Es wurden keine Literaturstellen mit relevanten Informationen zum Ausbreitungsstaging bei mukosalen Melanomen gefunden.

5.3. Frage IV.8: Postoperative Strahlentherapie -De novo-Recherche

Frage IV.8: Wann und wie sollte eine postoperative Strahlentherapie erfolgen?

5.3.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients suffering from mucosal melanoma	Radiation	Observation, other systemic treatments	OS, PFS

Suchwörter				
Stichwort	mucosal melanoma	radiation		
Synonyme		radiotherapy		
Mesh Term	mucosal melanoma	radiotherapy	radiation	

5.3.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(mucosal melanoma[tiab] OR mucosal melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH]) AND (primary OR margin*OR resection OR R1 OR R2 OR inoperab* OR unresectab*) NOT (uvea*[ti]	16.09.2016	170

	AND cutaneous [ti] AND skin [ti])		
Medline	(mucosal melanoma[tiab] OR mucosal melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH] OR irradiation) AND (mucosal OR primary OR margin* OR resection OR R1 OR R2 OR postoperative OR inoperab* OR unresectab*) NOT (uvea*[ti] OR anorectal[ti] OR cutaneous [ti] OR skin [ti])	19.09.2016	283
Cochrane Library	"mucosal melanoma" and ("radiotherapy" or "radiation")	02.10.2016	3 (0 dazu)

5.3.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	453
Einschlusskriterien	Systematische Reviews, Meta-Analysen Intervention: Strahlentherapie, Chirurgie Sprachen: e,dt
Ausschlusskriterien	Case Reports Kleine Kohortenstudien (Pat. Anzahl <75) Kollektive mit gemischten Tumorentitiäten
Anzahl ausgewählter Studien	**6**

5.3.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Gal, T.J.,	To evaluate the population	Retrospective cohort study	Patients with mucosal	5-Y-OS	Overall, the 5-year survival rate was		3a

2011	characteristics of mucosal melanoma of the nasal cavity and paranasal sinuses and determine the impact of the new staging classification	was performed using data from the SEER tumor registry, number of patients n=304	melanoma of the nasal cavity and paranasal sinuses		24.2%. Significant differences in survival were observed for surgery with radiation (P = .005) and surgery alone (P = .04) compared with radiation alone.		
Gore MR, et al. 2013	To determine whether there is a statistically significant increase in survival with combined therapy versus single modality therapy.	Meta-analysis; 39 articles with case reports; n= 423 patients	Patients suffering from mucosal melanoma of the head and neck	OS	The average survival was 24.15 months for surgery alone, 30.12 months for surgery and radiotherapy, and 23.45 months for surgery and chemoradiation. The two-tailed p-value was not significant for any of these differences in survival.		2a
Li, W., et al., 2015	Evaluation of the prognostic impact of postoperative adjuvant radiotherapy on head and neck mucosal melanoma: a meta-analysis	Meta-analysis Twelve cohort studies involving 1593 patients.	Patients with mucosal melanoma receiving surgery or surgery + radiation.	Risk of death	In comparing surgery alone with postoperative radiotherapy, there was no significant difference regarding a decrease in the death risk in HNMM patients (HR, 1.07; 95 % CI, 0.95-1.2;		2a

				Risk of local recurrence	p = 0.903; low heterogeneity, I(2) = 0); this was also the case for sinonasal melanoma after subgroup meta-analysis (HR, 1.04; 95 % CI, 0.8-1.36; p = 0.983; low heterogeneity, I(2) = 0 %). A sensitivity analysis and subgroup meta-analysis showed that disease progression was the main source of the instability in the results. Surgery combined with postoperative radiotherapy reduced the risk of local recurrence (HR, 0.51; 95 % CI, 0.35-0.76; p = 0.155) but did not reduce the risk of distant metastasis (HR, 2.26; 95 % CI, 1.01-5.05; p = 0.006).		
Samstein, R.M., et	To report data of a large	Retrospective analysis was	Localized sinonasal	LRFS, OS	Radiotherapy was associated with		3a

al., 2016	retrospective analysis of patients treated at Memorial Sloan Kettering Cancer Center (MSKCC) with localized, nonmetastatic mucosal melanoma of the nasal cavity or paranasal sinuses at initial presentation from 1998 to 2013	conducted on 78 patients	mucosal melanoma treated at Memorial Sloan Kettering Cancer Center (MSKCC from 1998–2013).		significantly greater Local recurrence free survival (5-years; 35% vs 59%; p = .01), but no difference in OS.		
Wushou, A., et al., 2015	To investigate the role of postoperative adjuvant radiotherapy (PORT) in HNMM treatment	Systematic review and meta-analysis, number of included studies n=8 with 423 patients	Studies including patients with treatment outcomes of head and neck mucosal malignant melanoma;	Local recurrence OS	Surgery plus PORT was significantly associated with improved local recurrence compared to surgery alone (OR = 0.36, 95% CI = 0.22e0.60, P = 0.000). The pooled OR analysis of all eight studies showed that PORT was not associated with better 3-year OS (OR = 1.41, 95% CI		2a

					= 0.94-2.09, P = 0.093). A similar result was found for 5-year OS (OR = 1.06, 95% CI: 0.70-1.61 P = 0.161)		
Wushou, A., et al., 2015	To compare treatment options of primary oral mucosal malignant melanoma (POMM) and to identify oral cavity site-specific prognostic factors	Retrospective POMM, number of patients n= 151	Case analysis from peer-reviewed publications in the PubMed and Embase electronic database from January 1984 to December 2013	OS HR	The patients who had surgery-based multiple therapy have a significantly longer survival compared with those who had surgery alone and those who had no surgical treatment (P = 0.000). Nonsurgical treatment (HR, 12.838; P = 0.000), and surgery alone (HR, 1.517; P = 0.001) were independent adverse prognostic factors for overall survival.		2a

5.3.5. Literatur

Gal, T.J., N. Silver, and B. Huang, Demographics and treatment trends in sinonasal mucosal melanoma. Laryngoscope, 2011. 121(9): p. 2026-33.
Gore, M.R. and A.M. Zanation, Survival in Sinonasal Melanoma: A Meta-analysis. J Neurol Surg B Skull Base, 2012. 73(3): p. 157-62.
Li, W., et al., Evaluation of the prognostic impact of postoperative adjuvant radiotherapy on head and neck mucosal melanoma: a meta-analysis. BMC Cancer, 2015. 15: p. 758.
Samstein, R.M., et al., Localized sinonasal mucosal melanoma: Outcomes and associations with stage, radiotherapy, and positron emission tomography response. Head Neck, 2016. 38(9): p. 1310-7.
Wushou, A., et al., Postoperative adjuvant radiotherapy improves loco-regional recurrence of head and neck mucosal melanoma. J Craniomaxillofac Surg, 2015. 43(4): p. 553-8.
Wushou, A. and Y.J. Zhao, The management and site-specific prognostic factors of primary oral mucosal malignant melanoma. J Craniofac Surg, 2015. 26(2): p. 430-4.

5.4. Frage IV.10: Systemtherapie – De-novo-Recherche

Frage IV.10: Welche Systemtherapie sollte im inoperablen oder metastasierten Stadium erfolgen?

5.4.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients suffering from mucosal melanoma	Systemic Therapy	BSC, no intervention	PFS, OS, Quality of life

Suchwörter				
Stichwort	mucosal melanoma	Systemic therapy		
Synonyme		Chemotherapy	Immunotherapy	Targeted Therapy
Mesh Term	mucosal melanoma	Systemic Therapy		

5.4.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(((mucosal melanoma[tiab] OR mucosal melanoma[MeSH]) AND (Clinical Trial, Phase III [Publication Type] OR Randomized Controlled Trial [Publication Type] OR “phase 3”	07.11.2016	13

	OR "phase III"[tiab] OR random*[tiab]) AND (“systemic therapy”[tiab] OR chemotherapy[tiab] OR "drug therapy"[MeSH] OR disseminated[tiab] OR metastatic[tiab] OR palliative[tiab] OR advanced[tiab] OR "stage IV"[tiab] OR "stage 4"[tiab] OR salvage[tiab])))		
	(“mucosal melanoma”[tiab] OR “mucosal melanoma”[MeSH]) AND ((liver[tiab] AND metastas*[tiab]) OR (hepatic[tiab] AND metastas*[tiab])) AND (treatment[tiab] OR therapy[tiab] OR “chemoembolization“[tiab] OR TACE[tiab] OR immunoembolization[tiab] OR IHP[tiab] OR HAI[tiab] OR perfusion[tiab] OR resection[tiab] OR surgery[tiab] OR “radiofrequency ablation”[tiab] OR RFA[tiab] OR radioembolization[tiab] OR brachytherapy[tiab])	07.11.2016	7
Cochrane Library	"mucosal melanoma" and ("therapy" or "chemotherapy")	02.10.2016	3 (0 dazu)

5.4.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	20
Einschlusskriterien	Kontrollierte Studien, Systematische Reviews, Meta-Analysen Intervention: Systemtherapie Sprachen: e,dt
Ausschlusskriterien	Case Reports Kleine Kohortenstudien (Pat. Anzahl <75) Kollektive mit gemischten Tumorentitiäten

Anzahl ausgewählter Studien	**6**

5.4.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Carvajal RD, et al. 2015	To report the efficacy and activity of nilotinib in patients with mucosal melanoma and with c-kit mutation after progression to imatinib and with brain metastastases	Phase II trial; n =20	Patients with melanomas harboring KIT mutations or amplification that are refractory or intolerant to a prior KIT inhibiton (Cohort A) Patients with melanomas harboring KIT mutations or amplification with brain metastases (Cohort B)	4-month disease control rate Response rate Time to-progression (TTP) Overall survival (OS)	Three patients on Cohort A (27%; 95% CI, 8% – 56%) and 1 on Cohort B (12.5%; 90% CI, 0.6% – 47%) achieved the primary endpoint. Two partial responses were observed in cohort A (18.2%; 90% CI, 3%–47%); none were observed in cohort B. The median TTP and OS was 3.3 (90% CI, 2.1–3.9 months) and 9.1 months (90% CI, 4.3–14.2 months), respectively, in all treated patients. Median TTP was 3.4 months (90% CI, 0.9–5.5 months) and 2.6 months (90% CI, 1.8–3.9 months) in cohorts A and B, respectively. The		3a

					median OS in cohort A was 14.2 months (90% CI, 7.1 months–∞) and was longer than observed in cohort B (4.3 months; 90% CI, 3.5–11.9 months; P=0.05).		
D'Angelo SP, et al. 2016	To report the efficacy and safety of nivolumab alone or combined with ipilimumab in patients with mucosal melanoma	Pooled analysis; n= 889 (nivolumab monotherapy; nivolumab + ipilimumab and ipilimumab monotherapy) 121 had mucosal melanoma	Patients with advanced melanoma who had received nivolumab monotherapy (3 mg/kg every 2 weeks until progression or unacceptable toxicity) in one of five ongoing clinical trials: 1) CA209-003; 2) CA209-038; 3) CheckMate 066; 4) CheckMate 037; 5) CheckMate 067	PFS Objective response rate	Among patients who received nivolumab monotherapy, median progression-free survival was 3.0 months (95% CI, 2.2 to 5.4 months) Median progression-free survival in patients treated with nivolumab combined with ipilimumab was 5.9 months (95% CI, 2.8 months to not reached) Nivolumab Monotherapy : 23.3% (95% CI, 14.8% to 33.6%) Nivolumab+Ipilimumab : 37.1% (95% CI, 21.5% to 55.1%)		2a

Del Vecchio M, et al. 2014	To report the activity and safety of ipilimumab in patients with mucosal melanoma treated in an Expanded Access Programme (EAP)	Retrospective analysis; n=71	Patients with mucosal melanoma treated in the EAP in Italy.	PFS OS	Median PFS and OS were 4.3 and 6.4 months, respectively.		3a
Handolias D, et al; 2010	To describe the frequency of KIT mutations in a prospectively selected group of Australian melanoma patients	Prospective study; n=32	Patients with acral or mucosal melanoma from two melanoma centres in Australia diagnosed between	Response to treatment with imatinib and sorafenib	Three patients were treated with imatinib and one with sorafenib. Two patients treated with imatinib had PR and one had PD. The patient treated with sorafenib had SD.	Primary end point is frequency, treatment only reported as second endpoint	3b
Hodi FS, et al. 2013	To identify amplifications and mutations in the KIT proto-oncogene in subsets of melanomas that can be therapeutic targets.	Multicenter phase II trial; n=24	Patients with metastatic mucosal, acral, or chronically sun-damaged (CSD) melanoma with KIT amplifications and/or mutations	BOOR (best overall response rate) to imatinib	BORR was 29% (two-stage 95% CI, 13% to 51%). There was a highly statistically significant relationship between best overall response and mutational status (P=.003). BORR was statistically significantly different by	Mixed cohort	2a

					mutational status (7 [54%] of 13 had mutated KIT vs 0% with amplified KIT; P =.006). Twelve patients achieved partial response (PR) or stable disease (SD) resulting in a disease control rate (DCR) of 50% (two-stage 95% CI, 29% to 71%). The DCR was significantly related to KIT mutational status (77% mutated vs 18% amplified; P =.01).		
Postow MA, et al. 2013	To assess the efficacy and safety of ipilimumab in patients with mucosal melanoma	Retrospective analysis; n=33	Patients with mucosal melanoma treated with ipilimumab as a single agent in Memorial Sloan-Kettering Cancer Center, Dana-Farber Cancer Institute, and Massachusett	ORR (overall response rate) OS	ORR by irRC in evaluable patients was 6.7% (2 of 30 patients; 95% confidence interval [CI]: 0.8%–22.1%). ORR in evaluable patients by mWHO was also 6.7% (2 of 30 patients). Median OS was 6.4 months		3a

			s General Hospital.				
Shoushtari AN, et al. 2016	To describe the outcomes of patients with acral and mucosal melanoma, who received treatment with nivolumab and pembrolizumab	Retrospective analysis; n=60	Patients with acral or mucosal treated with nivolumab or pembrolizumab between January 1, 2010, and April 1, 2015 either as standard clinical practice after approval by the FDA, through an EAP.	Objective Response (RECIST 1.1) PFS OS	The objective response rate was 23% (95% confidence interval, 10%-40%) in pts with mucosal melanoma. PFS: 3.9 months, Given the median follow-up of 10.6 months in patients who had primary mucosal melanoma, OS data were not mature enough to report.	Mixed cohort	3b
Zimmer L, et al. 2015	To assess the efficacy and safety of ipilimumab in patients with different subtypes of metastatic melanoma.	Phase II, open label, multicenter, single arm trial; n =103	Patients with pretreated metastatic cutaneous, mucosal and occult melanoma who received up to four cycles of ipilimumab administered at a dose of 3 mg/kg in 3 week intervals	OS rate at 12 months Median OS and overal response rate	1-year OS rate for mucosal melanoma were 14 % respectively. Median OS was 9.6 months (95 % CI 1.6–11.1) for mucosal Overall response rate mucosal melanoma was 17 %.	Mixed cohort	3b

5.4.5. Literatur

Carvajal, R.D., et al., Phase II Study of Nilotinib in Melanoma Harboring KIT Alterations Following Progression to Prior KIT Inhibition. Clin Cancer Res, 2015. 21(10): p. 2289-96.
D'Angelo, S.P., et al., Efficacy and Safety of Nivolumab Alone or in Combination With Ipilimumab in Patients With Mucosal Melanoma: A Pooled Analysis. J Clin Oncol, 2017. 35(2): p. 226-235.
Del Vecchio, M., et al., Efficacy and safety of ipilimumab 3mg/kg in patients with pretreated, metastatic, mucosal melanoma. Eur J Cancer, 2014. 50(1): p. 121-7.
Handolias, D., et al., Clinical responses observed with imatinib or sorafenib in melanoma patients expressing mutations in KIT. Br J Cancer, 2010. 102(8): p. 1219-23.
Hodi, F.S., et al., Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol, 2013. 31(26): p. 3182-90.
Postow, M.A., et al., Ipilimumab for patients with advanced mucosal melanoma. Oncologist, 2013. 18(6): p. 726-32.
Zimmer, L., et al., Open-label, multicenter, single-arm phase II DeCOG-study of ipilimumab in pretreated patients with different subtypes of metastatic melanoma. J Transl Med, 2015. 13: p. 351.

6. AG Adjuvante Therapie

6.1. Frage V.1. Adjuvante Chemotherapie - Adaptation

6.1.1. Synopse Quellleitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Beeinflusst eine adjuvante Chemotherapie das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?	Nein Kein zytotoxisches Medikament hat eine Überlegenheit gegenüber Beobachtung gezeigt	Nein Keine Evidenz für adjuvante Chemotherapie nach erfolgter chirurgischer Therapie	Nein Dacarbazin verbessert nicht das Überleben in adjuvanter Situation	Nein Keine Verbesserung des Gesamtüberlebens durch adjuvante Chemotherapie
Zugrunde liegende Evidenz	S. 93, keine Verknüpfung mit zugrundeliegender Evidenz	Manual: S. 81, keine Verknüpfung mit zugrundeliegender Evidenz Evidenz Review: S. 537 („keine Rolle im adjuvanten Setting“) 10 Studien zitiert	Niveau A 5 randomisierte Studien wurden untersucht + Bezug auf Cancer Care Ontario 2002	Ergebnis aus 9 random. Studien

Update Recherche am 11.01.2011

Suchstrategie Medline: (melanoma[tiab] OR melanoma[MeSH]) AND (chemotherapy[tiab] OR vindesine[tiab] OR dacarbacine[tiab] AND adjuvant[tiab])

Treffer: 483, Auswahl: Eigentler et al. 2008, Retsas et al. 1994

Literatur:

Eigentler TK, Radny P, Hauschild A, et al. Adjuvant treatment with vindesine in comparison to observation alone in patients with metastasized melanoma after complete metastasectomy: a randomized multicenter trial of the German Dermatologic Cooperative Oncology Group. Melanoma Res 2008;18:353-358
Retsas S, Quigley M, Pectasides D, et al. Clinical and histologic involvement of regional lymph nodes in malignant melanoma. Adjuvant vindesine improves survival. Cancer 1994;73:2119-2130

6.1.2. Empfehlung und Hintergrundstext französische Quell Leitlinie

Quellleitlinie: Recommandations pour la Pratique Clinique : Standards, Options et Recommandations 2005

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.39)	Übersetzung
DESCRIPTION DES ÉTUDES Au total, 5 essais randomisés ont été retenus pour l'analyse critique. Aucun nouvel essai randomisé n'a été retrouvé dans le cadre de la mise à jour 2005. Deux essais ont comparé l'administration de dacarbazine versus observation *114, 130+, un essai a comparé la dacarbazine versus placebo [127] et 1 essai a évalué l'association de dacarbazine à d'autres substances versus observation *131+. Un seul essai a étudié le méthyl-CCNU [116]. Le CCOPGI a révisé en 2002 la synthèse méthodique avec analyse quantitative initialement publiée en 1997 [12].	Beschreibung der Studien Insgesamt wurden 5 randomisierte Studien für eine kritische Analyse ausgewählt. Im Rahmen des Update 2005 wurde keine neue randomisierte Studie gefunden. Zwei Studien haben Dacarbazin versus Beobachtung verglichen [114,130], eine Studie hat Dacarbazin gegen Placebo verglichen [127] und 1 Studie hat Dacarbazin in Kombination mit anderen Substanzen versus Beobachtung evaluiert. [131] Nur eine Studie untersuchte Methyl-CCNU [116]. Die CCOPGI hat 2002 ein systematisches Review von 1997mit Metaanalyse überarbeitet [12].
SURVIE GLOBALE Aucune des 4 études qui ont évalué la dacarbazine (DITC) n'a rapporté de différence significative en termes de survie globale [114, 117, 127, 130, 131]. L'analyse poolée des données réalisée par le CCOPGI sur 7 essais randomisés n'a pas retrouvé de différence significative sur la survie globale à 3 ans (odd ratio = 1,03 [IC95 : 0,74-1,43] [12]. L'étude de Fisher et al. qui a comparé méthyl-CCNU versus observation n'a pas retrouvé de différence significative entre les deux bras comparés [116].	Gesamtüberleben Keine der 4 Studien, die Dacarbazin untersucht haben, haben einen signifikanten Unterschied in Bezug auf das Gesamtüberleben gezeigt [114, 117, 127, 130, 131]. Die gepoolte Analyse der Daten, die durch die CCOPGI aus 7 randomisierten Studien durchgeführt wurde, fand keinen signifikanten Unterschied bezogen auf das Gesamtüberleben nach 3 Jahren (odds ratio = 1,03 [IC95: 0,74-1,43] [12]. Die Studie von Fisher et al., die Methyl-CCNU versus Beobachtung verglichen hat, fand keinen signifikanten Unterschied zwischen den Vergleichsarmen [116].
COMMENTAIRES MÉTHODOLOGIQUES ET CLINIQUES La dacarbazine est la molécule qui a été la plus étudiée, seule ou association avec le BCG. Un seul essai randomisé a étudié 'efficacité du méthyl-CCNU sur une population de 136 patients, ce qui limite la portée des conclusions qui pourront être établies concernant cette molécule.	Methodologische und Klinische Kommentare Dacarbazin ist die am meisten untersuchte Substanz, allein oder zusammen mit BCG. Nur eine randomisierte Sudie überprüfte die Wirksamkeit von Methyl-CCNU an einer Population von 136 Patienten, dies beschränkt die Aussagekraft dieser Substanz.
CONCLUSIONS DE LA LITTÉRATURE La dacarbazine en situation adjuvante n'améliore pas la survie des patients porteurs d'un mélanome cutané opéré (niveau de preuve A). Les données dispo-nibles sont insuffisantes pour conclure sur le bénéfice/risque du methyl- CCNU en situation adjuvante chez les patients porteurs d'un mélanome cutané.	Schlussfolgerungen aus der Literatur Dacarbazin verbessert nicht das Überleben von Patienten mit operiertem kutanem Melanom in adjuvanter Situation (Level A). Die Daten für Methyl-CCNU sind insuffizient um über Benefit/Risiko in adjuvanter Situation bei Patienten mit kutanem Melanom zu entscheiden.
Standards, Options et Recommandations Les traitements adjuvants systémiques à base de levamisole, BCG ou dacarbazine ne sont pas recommandés en dehors d'essais thérapeutiques.	Standard, Optionen und Empfehlungen Eine adjuvante systemische Therapie mit Levamisole, BCG oder Dacarbazin wird ausserhalb von Therapiestudien nicht empfohlen.

Literatur:

12.CCOPGI, (Cancer Care Ontario Practice Guidelines Initiative). Systemic adjuvant therapy for patients at high risk for recurrent melanoma. Practice Guideline Report No 8-1 [online]. 2002. Available: URL: http://www.cancercare.on.ca/index_practiceGuidelinesandEvidencesum maries.htm#list
131. Randomized controlled trial of adjuvant chemoimmunotherapy with DTIC and BCG after complete excision of primary melanoma with a poor prognosis or melanoma metastases. Can Med Assoc J 1983;128:929-933
116. Fisher RI, Terry WD, Hodes RJ, et al. Adjuvant immunotherapy or chemotherapy for malignant melanoma. Preliminary report of the National Cancer Institute randomized clinical trial. Surg Clin North Am 1981;61:1267-1277
130. Hill GJ,2nd, Moss SE, Golomb FM, et al. DTIC and combination therapy for melanoma: III. DTIC (NSC 45388) Surgical Adjuvant Study COG PROTOCOL 7040. Cancer 1981;47:2556-2562
127. Lejeune F, Macher E, Kleeberg UR, Rumke P, Prade M, Thomas D, *et al.* An assessment of DTIC *versus* levamisole or placebo in the treatment of high risk stage I patients after removal of a primary melanoma of the skin: a phase III adjuvant study (EORTC protocol 18761). Eur J Cancer 1988;24:S81-90.
114. Veronesi U, Adamus J, Aubert C, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. N Engl J Med 1982;307:913-916

6.1.3. Empfehlung und Hintergrundstext kanadische Quell Leitlinie

Quellleitlinie: Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Updated Guideline Recommendations (Cancer Care Ontario) 2009

KEY EVIDENCE Chemotherapy

Data from randomized controlled trials do not suggest an improvement in OS with adjuvant chemotherapy alone for patients with resected high-risk melanoma (10 trials).

OUTCOMES Chemotherapy

Ten trials of chemotherapy are summarized in Table 9 (33,41,45-52). None of the trials were limited to high-risk patients. Two trials compared dacarbazine with observation (45,46), one compared dacarbazine with placebo (33), and five trials evaluated dacarbazine in combination with other agents (including immunomodulatory agents such as BCG) that are not commonly used at present, against observation alone (47-51). There was also a trial of methyl lomustine (methyl-CCNU) versus control (41) and a trial of carmustine (BCNU) combined with actinomycin-D and vincristine versus control (52). In the largest study of chemotherapy (46), 47% of patients treated with dacarbazine were alive after three years compared with 42% of control (p=0.64). Only the study by Hansson et al (49) reported a statistically significant survival benefit for patients who received chemotherapy as adjuvant treatment (p<0.025). That was the smallest of the chemotherapy trials, with only 26 patients randomized to three treatment groups. Data from the two active-treatment arms (da-carbazine alone and dacarbazine in combination with CCNU and vincristine) were combined and compared with results for nine patients in the control group, but that trial is far too small to permit any conclusions. Three-year mortality rates, from the text or from survival curves in the published reports from seven studies, were pooled and are presented in Figure 3. Three studies were not included in the meta-analysis because the number of deaths at three years could not be ascertained (45,51) or because no survival data were reported (47). The mortality risk ratio from the pooled analysis (0.94; 95% CI, 0.84 to 1.06; p=0.3) does not demonstrate any difference between chemotherapy and control. No heterogeneity was found among the results from these studies (p=0.52). Because response rates to chemotherapy in advanced disease have been unsatisfactory, there is no current interest in pursuing chemotherapy alone in the adjuvant setting.

Literatur:

48. Randomized controlled trial of adjuvant chemoimmunotherapy with DTIC and BCG after complete excision of primary melanoma with a poor prognosis or melanoma metastases. Can Med Assoc J 1983;128:929-933
41. Fisher RI, Terry WD, Hodes RJ, et al. Adjuvant immunotherapy or chemotherapy for malignant melanoma. Preliminary report of the National Cancer Institute randomized clinical trial. Surg Clin North Am 1981;61:1267-1277
49. Hansson J, Ringborg U, Lagerlof B, et al. Adjuvant chemotherapy of malignant melanoma. A pilot study. Am J Clin Oncol 1985;8:47-50
45. Hill GJ,2nd, Moss SE, Golomb FM, et al. DTIC and combination therapy for melanoma: III. DTIC (NSC 45388) Surgical Adjuvant Study COG PROTOCOL 7040. Cancer 1981;47:2556-2562
47. Jacquillat C, Banzet P, Maral J. Clinical trials of chemotherapy and chemoimmunotherapy in primary malignant melanoma. Recent Results Cancer Res 1982;80:254-258
52. Karakousis C, Blumenson L. Adjuvant chemotherapy with a nitrosourea-based protocol in advanced malignant melanoma. Eur J Cancer 1993;29A:1831-1835
50. Karakousis CP, Emrich LJ. Adjuvant treatment of malignant melanoma with DTIC + estracyt or BCG. J Surg Oncol 1987;36:235-238
33. Lejeune FJ, Macher E, Kleeberg U, Rumke P, Prade M, Thomas D, et al. An assessment of DTIC versus levamisole or placebo in the treatment of high risk stage I patients after surgical removal of a primary melanoma of the skin. Eur J Cancer Clin Oncol. 1988;24 Suppl 2:S81-S90.
46. Veronesi U, Adamus J, Aubert C, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. N Engl J Med 1982;307:913-916

6.2. Frage V.2. Adjuvante Vakzinierung – Adaptation

6.2.1. Synopse Quellleitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Beeinflusst eine adjuvante Vakzinationstherapie das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?	Nein Keine Überlegenheit von Vakzinierungen gegenüber Beobachtung	Nein Verwendung von Impfstoffen ist experimentell	Nein Aucun des procédés de vaccination utilisés jusqu'à ce jour n'a mis en évidence une différence significative sur la survie sans récidive ou sur la survie globale des patients atteints d'un mélanome cutané réséqué avec ou sans envahissement ganglionnaire et dont	Nein

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
			l'épaisseur est supérieure à 1,5 mm (niveau de preuve B1). Keine Vakzinierung hat einen signifikanten Unterschied zwischen rezidivfreiem Überleben oder Gesamtüberleben zeigen können (Td >1,5 N0 und N+) Niveau BI Entspricht in etwa Level of Evidence nach Oxford 1b	
Schlüsselempfehlung	Zur Vakzinierung keine Schlüsselempfehlung	Zur Vakzinierung keine Schlüsselempfehlung	Les procédés de vaccination ne sont pas indiqués dans le traitement adjuvant des patients opérés d'un mélanome cutané en dehors d'essais thérapeutiques. Recommandation: Option Vakzinierungstherapien sind als adjuvante Behandlung bei Patienten nach Operation eines kutanen Melanoms ausserhalb von klinischen Studien nicht indiziert.	Zur Vakzinierung keine Schlüsselempfehlung

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Zugrunde liegende Evidenz	S. 93, keine Verknüpfung mit zugrundeliegender Evidenz	Manual: S. 81, keine Verknüpfung mit zugrundeliegender Evidenz Evidenz Review: S.538, kein verbessertes OS, manche zeigen verbessertes rezidivfreies Überleben, Vakzinierung wichtiges Forschungsfeld 7 Studien	Diskutiert werden Studien mit:BCG, GMK, Melanomzell-Lysat (VMCL), Melanom Oncolysat (VMO), allogenes Melanomvakzin, polyvalentes Melanomvakzin, GM2-KLH, TIL	9 randomisierte Studien wurden zusammengefasst (virales Oncolysat, Ganglioside, polyvalentes Vakzin, Melanomzell-Lysat, „whole-cell“Vakzin) aufgrund der Heterogenität der Studien wurden die Daten nicht gepoolt. Keine Studie konnte ein verbessertes Überleben zeigen. Eine Subgruppenanalyse SWOG 9035 zeigte einen Überlebensbenefit für HLA-A2 und/oder HLA-C3 positive Patienten der Vakzin-Gruppe, dazu wurde jedoch keine klinische Empfehlung abgeleitet Im Update 10 Studien: EORTC18961, signifikant schlechteres Gesamtüberleben für GM2-KLH21 Arm

6.2.2. Empfehlung und Hintergrundstext französische Quell Leitlinie

Quellleitlinie: Recommandations pour la Pratique Clinique : Standards, Options et Recommandations 2005

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.36)	Übersetzung
VACCINATION *BCG thérapie* · Description des études Deux essais randomisés ont été retenus et ont compare l'administration de BCG *versus* observation d'une part, et BCG *versus* l'association BCG et dacarbazine *(Tableau XV)* [114, 115]. L'étude de L'OMS a concerné 761 patients randomisés en 4 bras (observation *versus* BCG seul *versus* dacarbazine seule *versus* association BCG et dacarbazine) [114] L'étude de Agarwala *et al.* présente les résultats à long terme d'un essai sur 734 patients mené entre 1974 et 1978 [115]. Les patients ont été randomisés selon 4 bras constituant 2 cohortes. La première cohorte a comparé BCG *versus* observation et la seconde BCG et dacarbazine *versus* BCG seul. · Survie globale Aucun des 2 essais n'a mis en évidence une différence significative en termes de survie globale dans les différents bras comparés [114, 115]. Dans une analyse en sous-groupe, l'étude de l'OMS a observe une différence significative sur la survie globale en faveur du traitement par BCG pour les patients présentant 2 à 3 ganglions envahis (45 % *versus* 31,7 % à 3 ans ; p = 0,01). · Survie sans récidive Aucun des 3 essais n'a mis en évidence une différence significative en termes de survie globale dans les différents bras comparés [114-116]. · Toxicité Les résultats de toxicité ont été rapportés dans les 2 études [114, 115], mais seule l'étude de Agarwala *et al.* a présenté des résultats détaillés. Aucune toxicité létale n'a été rapportée. Des adénopathies régionales et des réactions systémiques corrélées au traitement par le BCG ont été observées dans 10 à 13 % des cas [115]. · Commentaires cliniques et méthodologiques Les résultats de l'analyse en sous-groupes réalisée dans l'étude de l'OMS sont méthodologiquement très critiquables [114]. D'une part, l'analyse en sous-groupe n'était pas prévue initialement dans le protocole et, d'autre part,	Vakzinierung *BCG Therapie* ·Beschreibung der Studien Zwei randomisierte Studien wurden ausgewählt und haben die Gabe von BCG versus Beobachtung einerseits und BCG versus gemeinsame Gabe von BCG und Dacarbazin verglichen (Tab. XV) [114, 115]. Die Studie der WHO betraf 761 randomisierte Patienten in 4 Armen (Beobachtung versus BCG allein versus DTIC allein versus BCG plus DTIC) [114]. Die Studie von Agarwala et al. präsentierte die Langzeitergebnisse einer Studie an 734 Patienten, die zwischen 1974 und 1978 durchgeführt wurde [115]. Die Patienten wurden in 4 Arme randomisiert die Teil zweier Kohorten waren. Die erste Kohorte verglich BCG versus Beobachtung, die zweite BCG plus DTIC versus BCG allein. ·Gesamtüberleben Keine der zwei Studien hat einen signifikanten Unterschied in Bezug auf das Gesamtüberleben in den Vergleichsarmen gezeigt[114, 115]. In einer Subgruppenanalyse fand sich in der Studie der WHO einen signifikanten Unterschied für das Gesamtüberleben zugunsten einer Behandlung mit BCG für Patienten mit 2-3 positiven Lymphknoten. (45 % *versus* 31,7 % nach 3 Jahren ; p = 0,01). ·Rezidivfreies Überleben Keine der drei Studie zeigte einen signifikanten Unterschied in Bezug auf das Gesamtüberleben in den unterschiedlichen Vergleichsarmen [114-116]. ·Toxizität Ergebnisse zur Toxizität wurden in beiden Studien berichtet [114, 115], aber nur die Studie von Agarwala et al. präsentiere detaillierte Ergebnisse. Keine letale Toxizität wurde berichtet. Regionale Adenopathien und Systemreaktionen wurden korellierten in 10 bis 13% mit einer Behandlung mit BCG [115]. ·Klinische und Methodische Kommentare Die Ergebnisse der Subgruppenanalyse die in der Studie der WHO durchgeführt wurde sind methodisch sehr kritisierbar [114]. Zum einen war die Subgruppenanalyse ursprünglich nicht im Protokoll vorgesehen und, zum

Originaltext (Evidenztabellen und Text siehe Quell LL ab S.36)	Übersetzung
l'existence de ce résultat isolé n'a pas de cohérence clinique, puisque la difference de survie n'est significative que pour le sous-groupe de patients avec 2 ou 3 ganglions envahis, ce qui rend ces résultats difficilement interprétables. Vaccins mélaniques · Description des études Quatre essais randomisés sont disponibles : – 2 essais ont comparé un vaccin mélanique versus observation [117-119] (Tableau XVI), – 2 essais ont comparé l'administration d'un vaccin mélanique versus placebo [120-122] (Tableau XVII). Au total, 1 677 patients ont été randomisés dont 1 230 évaluables. Aucune des 4 études n'a inclus de patients porteurs d'un mélanome dont l'épaisseur était inférieure à 1,5 mm. Les interventions évaluées dans les 4 essais randomisés ont été : – lysat cellulaire de vaccin mélanique (VMCL) [117], – lysat de cellules tumorales irradiées (Melacine®) provenant de deux lignées allogéniques + un adjuvant [118, 119], – vaccin issu de quatre lignées allogéniques + virus de la variole atténué [120, 121], – vaccin issu de trois lignées allogéniques et une lignée xénogénique + un adjuvant (aluminium) [122] · Survie globale Trois des 4 essais randomisés disponibles ont évalué l'impact sur la survie d'un vaccin mélanique versus placebo ou observation [117, 120-122]. La survie globale était le critère de jugement secondaire pour ces études. Aucune difference de survie globale n'a été mise en évidence après un suivi médian variable selon les études compris entre 2,5 ans et 8 ans. Dans le quatrième essai, le suivi n'a pas été suffisant pour permettre l'analyse de la survie globale	anderen hat dieses isolierte Ergebnis keinen klinischen Zusammenhang, da der Unterschied im Überleben nur für die Subgruppe mit 2 oder 3 positiven Lymphknoten signifikant war, wodurch diese Ergebnisse schwierig zu interpretieren sind. Melanom Impfstoffe ·Beschreibung der Studien Vier randomisierte Studien stehen zur Verfügung: -Zwei Studien haben einen Melanom Impfstoff versus Beobachtung verglichen observation [117-119] (Tab. XVI), -Zwei Studien haben die Gabe eines Melanom Impfstoffes versus Placebo verglichen [120-122] (Tab. XVII). Insgesamt wurden 1 677 Patienten randomisiert, von denen 1 230 auswertbar waren. Keine der vier Studien hat Melanompatienten mit einer Tumordicke von weniger als 1,5mm eingeschlossen. Die untersuchten Interventionen in den vier randomisierten Studien waren: Zelllysat Impfstoff (VMCL) [117] Lysat aus bestrahlten Tumorzellen (Melacine®) aus zwei allogenen Linien plus ein Adjuvant [118, 119], Impfstoff aus vier allogenen Linien plus abgeschwächtes Varizellen Virus [120,121], Impfstoff aus drei allogenen Linien und einer xenogenen Linie plus ein Adjuvant (Aluminium) [122] ·Gesamtüberleben Drei der vier randomisierten verfügbaren Studien haben den Einfluss auf das Überleben eines Melanom Impfstoffes versus Placebo oder Beobachtung untersucht [117, 120-122]. Das Gesamtüberleben war der sekundäre Endpunkt dieser Studien. Einen Unterschied im Gesamtüberleben konnte in keiner der Studien nachgewiesen werden, die ein medianes Follow up zwischen 2,5 und 8 Jahren hatten. In der vierten Studie war das Follow up für eine Analyse des Gesamtüberlebens nicht ausreichend. [118, 119].

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[118, 119]. · Survie sans récidive Les 4 essais randomisés disponibles ont évalué l'impact sur la survie sans rechute d'un vaccin mélanique versus placebo ou observation. La survie sans rechute était le critère de jugement principal pour 3 études ; le critère de jugement principal n'était pas précisé pour la quatrième étude. Aucune difference significative de survie sans rechute n'a été retrouvée. Des analyses en sous-groupes ont été proposées dans certaines études. L'étude SOGT-9035 a notamment évalué l'interaction entre antigènes HLA et la survie sans récidive [119]. La survie sans récidive a été augmentée dans le groupe vaccin chez les patients qui exprimaient 2 ou plus de 5 antigènes de classe I (97 patients traités par vaccin versus 78 patients dans le groupe observation ; p = 0,0002). Avec les antigènes HLA A2 et C3, la survie sans rechute a été de 77 % dans le groupe vaccin versus 64 % dans le groupe observation (p = 0,004). · Toxicité La toxicité a été évaluée dans les 4 études [117, 118, 121, 122]. Les données de toxicité sont clairement présentées dans 2 des 4 études. Globalement, peu d'effets indésirables ont été observés. Dans l'étude de Sondak et al., 9 % des patients ont présenté une toxicité de grade 3 (réactions locales sévères, malaises et fatigue, troubles visuels, fièvre, diarrhées, thrombopénies et éruptions cutanées), 64 % ont présenté des toxicities de grade 2 et 23 % ont présenté des toxicités de grade 1 [118]. L'équipe de Hersey *et al.* a essentiellement observé des toxicités de grade 2 (érythèmes et ulcération au site d'injection chez 47 % des patients ; lymphopénie pour 33 % d'entre eux) et de grade 1 (malaises et fièvre respectivement chez 35 % et 20 % des patients). · Commentaires méthodologiques et cliniques Toutes les études ont réalisé les analyses en intention de traiter. Trois des 4 études présentent clairement le calcul du nombre de patients *a priori* (sur la	·Rezidivfreies Überleben Die vier verfügbaren randomisierten Studien haben den Einfluss auf das rezidivfreie Überleben eines Melanom Impfstoffes versus Placebo oder Beobachtung untersucht. Das rezidivfreie Überleben war der primäre Endpunkt in Drei Studien, für die vierte Studie war der primäre Endpunkt nicht klar. Es wurde kein signifikanter Unterschied im rezidivfreien Überleben gefunden. In einigen Studien wurden Subgruppenanalysen vorgeschlagen. Die Studie SOGT-9035 beinhaltet eine Untersuchung der Interaktion zwischem HLA Antigenen und rezidivfreiem Überleben [119]. Ein verlängertes rezidivfreies Überleben wurde in der Impfstoff Gruppe unter den Patienten die 2 oder mehr als 5 Antigene der Klasse I exprimierten, beobachtet (97 mit Impfstoff behandelte Patienten versus 78 Patienten im Beobachtungsarm; p = 0,0002). Mit den Antigenen HLA A2 und C3 war das rezidivfreie Überleben 77% in der Impfstoff Gruppe veruss 64% im Beobachtungsarm (p = 0,004). ·Toxizität Die Toxizität wurde in allen vier Studien untersucht [117, 118, 121, 122]. Daten zur Toxizität sind in zwei der vier Studien klar dargestellt. Insgesamt wurden nur wenig Nebenwirkungen beobachtet. In der Studie von Sondak et al. zeigten 9% der Patienten eine Grad 3 Toxizität (schwere Lokalreaktion, Unwohlsein und Fatigue, visuelle Probleme, Fieber, Durchfälle, Thrombopenien und Hautausschläge), 64% zeigten eine Grad 2 Toxizität und 23% eine Grad 1 Toxizität [118]. Das Team von Hersey et al. beobachtete im Wesentlichen Grad 2 Toxizitäten (Erytheme und Ulzerationen am Injektionsortbei 47% der Patienten; Lymphopenie bei 33%) und Grad 1 Toxizitäten (Unwohlsein und Fieber bei 35% und 20% der Patienten) ·Klinische und Methodische Kommentare Alle Studien haben eine Intent to treat (ITT) Analyse durchgeführt. Drei der vier Studien präsentieren eine klare Fallzahlberechnung a priori für das rezidivfreie Überleben [117-119, 122]. Die Studie von Bystryn et al. wurde vorzeitig beendet und wurde nur an 38 statt der 210 ursprünglich geplanten Patienten durchgeführt. Aus diesem Grund war die Dauer der Nachbeobachtung nicht

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survie sans rechute) [117-119, 122]. L'étude de Bystryn *et al.* a été arrêtée prématurément et n'a porté que sur 38 patients au lieu des 210 patients initialement prévus. De ce fait, le suivi n'a pas été suffisant (inférieur à 2 ans pour la majorité des patients) et n'a pas permis l'analyse de la survie globale [122]. Pour 3 des 4 études, les populations étudiées peuvent être appliquées à la pratique courante [117-119, 122]. En revanche, dans l'étude de Wallack *et al.* la population traitée est un peu complexe et hétérogène par rapport à la pratique courante bien que correspondant à des types cliniques définis et reconnus par la classification AJCC. Toutes les variables pertinentes n'ont pas été prises en compte lors de la randomisation, puisque seul le nombre de ganglions envahis a été condidéré [120-121]. *IFN* alpha versus *GMK* · Description des études Une seule étude randomisée est disponible [123] *(Tableau XVIII)*. Cette étude a comparé l'IFN alpha 2b hautes doses *versus* vaccine GMK (ganglioside GM2 conjugué avec de l'hémocyanine (KLH) combinée à une molécule adjuvante QS-21). Cette étude a porté sur des patients atteints d'un mélanome de stades IIB ou III réséqués. · Survie globale La survie globale a été évaluée après un suivi médian de 16 mois. Une différence statistiquement significative a été mise en évidence en faveur des patients traités par l'IFN alpha 2b. La survie globale à 2 ans a été de 78 % dans le bras IFNα2b *versus* 73 % dans le bras GMK (p = 0,035) [123]. · Survie sans récidive La survie sans récidive a été évaluée après un suivi median de 16 mois. Une différence statistiquement significative a été mise en évidence en faveur des patients traités par l'IFN alpha 2b. La survie sans récidive à 2 ans a été de 62 % dans le bras IFN alpha 2b *versus* 49 % dans le bras GMK (p = 0,027) [123]. · Toxicité Les toxicités les plus fréquemment observées dans le bras IFN alpha 2b ont été	ausreichend (weniger als 2 Jahre für die Mehrheit der Patienten) und erlaubt keine Analyse des Gesamtüberlebens [122]. In drei der vier Studien wurden Populationen untersucht, die auf die derzeitige Praxis übertragen werden können [117-119, 122]. Demgegenüber ist die in der Studie von Wallack et al. behandelte Patientenpopulation recht komplex und heterogen im Vergleicht zur derzeitigen Praxis obwohl die klinischen Stadien durch die AJCC Klassifikation angegeben wurden. Für die Randomisierung wurden nicht alle Variablen sondern nur die Anzahl der beteiligten Lymphknoten berücksichtigt wurde [120-121]. *IFNα* versus *GMK* ·Beschreibung der Studien Eine einzige randomisierte Studie ist verfügbar [123]. Diese Studie hat Hochdosis IFNα2b versus GMK Vakzin (Ganglioside GM2 konjugiert mit KLH kombiniert mit einem adjuvanten Molekül QS-21) verglichen. Diese Studie wurde an Melanom Patienten im resezierten Stadium IIB oder III durchgeführt. ·Gesamtüberleben Das Gesamtüberleben wurde nach einer medianen Nachbeobachtung von 16 Monaten evaluiert. Ein statistisch signifikanter Unterschied wurde für die mit IFN alpha 2b behandelten Patienten gesehen. Das Gesamtüberleben nach 2 Jahren war 78% im IFN alpha 2b Arm versus 73% im GMK Arm (p = 0,035) [123]. · Rezidivfreies Überleben Das rezidivfreie Überleben wurde nach einer medianen Nachbeobachtung von 16 Monaten evaluiert. Ein statistisch signifikanter Unterschied wurde für die mit IFN alpha 2b behandelten Patienten gesehen. Das rezidivfreie Überleben nach 2 Jahren war 62% im IFNα2b Arm versus 49% im GMK Arm (p = 0,027) [123]. ·Toxizität Die am häufigsten beobachteten Toxizitäten im IFN alpha 2b Arm waren Grad 3 Toxizitäten vom Typ Fatigue, Zytopenie, Anstieg der Leberenzyme und neurologische Symptome. 45% der Patienten im IFN alpha 2b Arm haben die Therapie aufgrund von Nebenwirkungen gestoppt. Die Nebenwirkungen waren

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des toxicités de grade 3 de type fatigue, cytopénies, élévation du taux des enzymes du foie et symptoms neurologiques. Quarante-cinq pour cent des patients traits par l'IFN alpha 2b ont arrêté le traitement en raison des effets indésirables. Les toxicités ont été globalement moins fréquentes dans le bras GMK. La toxicité la plus rapportée chez les patients traités par GMK a été une réaction locale au niveau du site d'injection. Aucun décès toxique n'a été rapporté. · Commentaires méthodologiques et cliniques Les analyses ont toutes été réalisées en intention de traiter. Les auteurs se sont basés sur les résultats positifs de l'étude ECOG1684 pour définir le protocole de leur essai définissant ainsi l'interféron-alpha à haute dose comme contrôle [104], bien que ces résultats n'aient pas été confirmés par la suite. De ce fait, l'absence de vrai bras contrôle invalide considérablement les conclusions. La population étudiée est mixte (77 % de patients présentaient un envahissement ganglionnaire) et la stadification NO (23 %) est hétérogène (45 % des patients ont été évalués cliniquement et 46 % ont eu une évaluation histologique). L'interprétation des résultats est donc rendue plus complexe, puisque dans les autres études, la proportion de patients sans envahissement est généralement majoritaire. Par ailleurs, le suivi médian n'étant que de 16 mois, l'évaluation de la survie doit être interprétée avec précaution. *Tumor infiltrating lymphocytes (TIL)* · Description des études Une étude est disponible [124, 125] *(Tableau XIX)*. Il s'agitd'une étude prospective randomisée comparant un traitement par TIL+ IL-2 *versus* IL-2 seule chez 88 patients porteurs d'un mélanome de stade III (AJCC) après curage ganglionnaire. Le suivi médian a été de 46,9 mois. · Survie globale, survie sans récidive Aucune différence significative en termes de survie globale et de survie sans récidive n'a été mise en évidence entre les 2 groupes. Néanmoins, une différence significative a été observée entre les deux bras de traitement dans	insgesamt weniger häufig im GMK Arm. Die am häufigsten berichtete Nebenwirkung im GMK Arm waren Lokalreaktionen am Injektionsort. Es wurde keine tödliche Nebenwirkung berichtet. ·Klinische und Methodische Kommentare Alle Analysen wurden als Intent to treat Analyse durchgeführt. Die Autoren haben sich auf die positiven Ergebnisse der Studie ECO1684 gestützt, um die Hochdosis Interferon-alpha Therapie in ihrem Protokoll als Kontrollarm zu definieren [104], obwohl sich diese Ergebnisse nachträglich nicht bestätigt haben. Da dadurch ein echter Kontrollarm fehlt, ist es nicht möglich gültige Schlussfolgerungen zu ziehen. Die untersuchte Population ist gemischt (77% der Patienten haben eine Lymphknotenbeteiligung) und die Stadieneinteilung NO (23%) ist heterogen (45% der Patienten wurden klinisch klassifiziert und 46% der Patienten wurden histologisch klassifiziert). Die Interpretation der Ergebnisse ist daher komplex, da in anderen Studien die Mehrzahl der Patienten keine Lymphknotenbeteiligung hat. Da auch die Nachbeobachtungszeit nur 16 Monate betrug, müssen die Überlebenszeitanalysen mit Vorsicht interpretiert werden. *Tumor infiltrating lymphocytes (TIL)* ·Beschreibung der Studien Eine Studie steht zur Verfügung [124, 125]. Es ist eine prospektive randomisierte Studie die eine Therapie mit TIL+IL-2 versus IL-2 allein bei 88 Melanom Patienten im Stadium III (AJCC) nach einer Lymphknotenausräumung vergleicht. Die mediane Nachbeobachtungszeit betrug 46,9 Monate. ·Gesamtüberleben, Rezidivfreies Überleben In Bezug auf das Gesamtüberleben und das rezidivfreie Überleben wurde kein signifikanter Unterschied zwischen den 2 Gruppen beobachtet. Dennoch wurde bei einer Subgruppe (bei Beteiligung nur eines Lymphknoten aber ohne Angaben zur Kapselüberschreitung) zwischen den Behandlungsarmen ein signifikanter Unterschied bezogen auf Gesamt- und rezifivfreies Überleben gesehen. ·Toxizität

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un sous groupe de patients (avec un seul ganglion envahi, mais pas de précision sur la rupture capsulaire), notamment sur la survie globale et le taux de rechute. · Toxicité Globalement, le traitement par TIL a été très bien toléré. Aucune toxicité de grades 3 ou 4 n'a été observée. Les principaux effets indésirables ont été une inflammation au site de l'injection et une asthénie. · Commentaires méthodologiques et cliniques La méthode de randomisation n'est pas décrite dans les articles et l'absence de réel bras contrôle limite considérablement la portée des conclusions qui pourront être établies. Les analyses en sous-groupes conduites *a posteriori* (non prévues initialement lors de la randomisation) ne permettent pas d'extrapoler des conclusions sur les critères de jugement. Il est également important de relever les contraintes techniques liées à ce procédé dont le succès est conditionné, dans un premier temps, par la production de TIL chez les patients concernés. *Conclusions de la littérature* Aucun des procédés de vaccination utilisés jusqu'à ce jour n'a mis en évidence une différence significative sur la survie sans récidive ou sur la survie globale des patients attaints d'un mélanome cutané réséqué avec ou sans envahissement ganglionnaire et dont l'épaisseur est supérieure à 1,5 mm (niveau de preuve B1).	Insgesamt wurde die Behandlung mit TIL sehr gut toleriert. Keine Grad 3 oder 4 Toxizitäten wurden beobachtet. Die hauptsächlichen Nebenwirkungen waren Entzündungen am Injektionsort und Asthenie. ·Klinische und Methodische Kommentare Die Methode der Randomisation wurde im Artikel nicht berichtet und das Fehlen eines echten Kontrollarms machen es schwierig gültige Schlussfolgerungen zu ziehen. Nachträglich durchgeführte Subgruppenanalysen (die zum Zeitpunkt der Randomisierung nicht vorgesehen waren) machen Schlussfolgerungen aus den Ergebnissen nicht möglich. Es ist auch wichtig die technischen Zwänge zu bedenken, da in einem ersten Schritt die Produktion von TIL bei den betroffenen Patienten erfolgen muss. Schlussfolgerung aus der Literatur Keine der Impfverfahren die bis heute verwendet wurden haben einen signifikanten Unterschied für das Gesamtüberleben oder rezidivfreie überleben bei Patienten mit reseziertem Melanom, oder ohne Lymphknotenbeteiligung und mit einer Tumordicke grösser als 1,5mm erbracht (niveau de preuve B1). *Entspricht in etwa Level of Evidence nach Oxford 1b*

6.2.3. Empfehlung und Hintergrundstext kanadische Quell Leitlinie

Quellleitlinie: Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Updated Guideline Recommendations (Cancer Care Ontario) 2009

Nine randomized trials of vaccines are summarized in Table 8, one of a viral oncolysate, one of a ganglioside, one of a polyvalent vaccine, one of vaccinia melanoma cell lysate, and five of whole-cell vaccines. Six RCTs compared vaccine with observation, while three trials were double-blind. Seven of the nine trials were confined to patients with nodal involvement, and the majority of patients in one of the other trials were node positive. None of the reported trials have shown a statistically significant improvement in overall survival for patients treated with vaccines, an observation confirmed in a recent update of the SWOG 9035 trial. However, in that study, the subset analysis of patients who were positive for human leukemic antigen (HLA)-A2 and/or HLA-C3 demonstrated a significant five-year overall survival benefit of 93% for vaccine patients compared with 74% for patients in the observation group (p=0.009). This clearly hypothesis-generating observation cannot be used to direct clinical decisions. For obvious reasons attesting to heterogeneity of the studies and vaccines employed, we have elected not to pool those data in our analysis.

Literatur:

LL Frankreich French National Authority for Health 2005)

115. Agarwala SS, Neuberg D, Park Y, et al. Mature results of a phase III randomized trial of bacillus Calmette-Guerin (BCG) versus observation and BCG plus dacarbazine versus BCG in the adjuvant therapy of American Joint Committee on Cancer Stage I-III melanoma (E1673): a trial of the Eastern Oncology Group. Cancer 2004;100:1692-1698
122. Bystryn JC, Zeleniuch-Jacquotte A, Oratz R, et al. Double-blind trial of a polyvalent, shed-antigen, melanoma vaccine. Clin Cancer Res 2001;7:1882-1887
124. Dreno B, Nguyen JM, Khammari A, et al. Randomized trial of adoptive transfer of melanoma tumor-infiltrating lymphocytes as adjuvant therapy for stage III melanoma. Cancer Immunol Immunother 2002;51:539-546
116. Fisher RI, Terry WD, Hodes RJ, et al. Adjuvant immunotherapy or chemotherapy for malignant melanoma. Preliminary report of the National Cancer Institute randomized clinical trial. Surg Clin North Am 1981;61:1267-1277
117. Hersey P, Coates AS, McCarthy WH, et al. Adjuvant immunotherapy of patients with high-risk melanoma using vaccinia viral lysates of melanoma: results of a randomized trial. J Clin Oncol 2002;20:4181-4190
123. Kirkwood JM, Ibrahim JG, Sosman JA, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. J Clin Oncol 2001;19:2370-2380
125. Labarriere N, Pandolfino MC, Gervois N, et al. Therapeutic efficacy of melanoma-reactive TIL injected in stage III melanoma patients. Cancer Immunol Immunother 2002;51:532-538
118. Sondak VK, Liu PY, Tuthill RJ, et al. Adjuvant immunotherapy of resected, intermediate-thickness, node-negative melanoma with an allogeneic tumor vaccine: overall results of a randomized trial of the Southwest Oncology Group. J Clin Oncol 2002;20:2058-2066
119. Sosman JA, Unger JM, Liu PY, et al. Adjuvant immunotherapy of resected, intermediate-thickness, node-negative melanoma with an allogeneic tumor vaccine: impact of HLA class I antigen expression on outcome. J Clin Oncol 2002;20:2067-2075
114. Veronesi U, Adamus J, Aubert C, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. N Engl J Med 1982;307:913-916
120. Wallack MK, Sivanandham M, Ditaranto K, et al. Increased survival of patients treated with a vaccinia melanoma oncolysate vaccine: second interim analysis of data from a phase III, multi-institutional trial. Ann Surg 1997;226:198-206
121. Wallack MK, Sivanandham M, Whooley B, et al. Favorable clinical responses in subsets of patients from a randomized, multi-institutional melanoma vaccine trial. Ann Surg Oncol 1996;3:110-117

LL Kanada Cancer Care Ontario 2007

Eggermont AM, Suciu S, Ruka W, Marsden J, Testori A, Corrie P. EORTC 18961: Post-operative adjuvant ganglioside GM2-KLH21 vaccination treatment vs observation in stage II (T3-T4N0M0) melanoma: 2nd interim analysis led to an early disclosure of the results. J Clin Oncol. 2008;26(May 20 suppl):9004.

6.3. Frage V.3. Adjuvante Extremitätenperfusion - Adaptation

6.3.1. Synopse Quellleitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Beeinflusst eine adjuvante Extremitätenperfusion das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?	Adjuvant regional drug therapy improves disease free interval but does not improve overall survival Level II	-	La perfusion de melphalan sur membre isolé ne semble pas améliorer la survie globale des patients atteints d'un mélanome cutané Niveau de preuve C *Eine adjuvante Extremitätenperfusion mit Melphalan scheint das Gesamtüberleben von Melanompatienten nicht zu verbessern.* *Niveau C*	-
Schlüsselempfehlung	Prophylactic isolated limb perfusion (ILP) is not recommended Grade A	-	La perfusion de membre isolé n'est pas recommandée en dehors d'essais thérapeutiques et doit être réalisée par des équipes entraînées. Recommandation: Option *Eine Extremitätenperfusion wird ausserhalb klinischer Studien nicht empfohlen und soll durch erfahrene Teams durchgeführt werden.*	-
Zugrunde liegende Evidenz	1 Studie Koops, H.S. et al. 1998	-	2 Studien Koops, H.S. et al. 1998 Ghussen, F. et al. 1989	-

6.3.2. Empfehlung und Hintergrundstext französische Quell Leitlinie

Quellleitlinie: Recommandations pour la Pratique Clinique : Standards, Options et Recommandations 2005

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.40)	Übersetzung
Perfusion de melphalan sur membre isolé DESCRIPTION DES ÉTUDES Deux études randomisées ont étudié l'effet d'une perfusion sur membre isolé de melphalan après exérèse d'un melanoma primitif isolé [134, 135] (Tableau XXI). Les 2 essais ont évalué respectivement 107 et 832 patients dont l'épaisseur de la tumeur était supérieure à 1,5 mm. Dans l'étude de Ghussen et al. la perfusion de melphalan a été associée à une hyperthermie. SURVIE GLOBALE, SURVIE SANS RÉCIDIVE Seule une des deux études randomisées a montré un avantage en termes de contrôle local et de survie globale en faveur du traitement sur membre isolé par une association hyperthermie-melphalan après exérèse d'un melanoma primitif isolé [134]. L'étude de Koops et al. n'a pas montré de différence significative en termes de survie globale [135]. Une analyse en sous-groupe a cependant mis en évidence une survie sans récidive plus élevée chez les patients qui ont eu un curage ganglionnaire (RR = 0,75 [IC95 : 0,55-0,98]) et plus particulièrement chez les patients dont la tumeur était inférieure à 3 mm (RR = 0,56 [IC95 : 0,36-0,88]) [135]. Aucune différence en termes de survie globale n'a été observée dans les analyses en sousgroupes. TOXICITÉ Les toxicités ont été principalement de grade 1 et globalement plus importantes dans les groupes de patients perfusés [134, 135]. Les toxicités les plus fréquentes ont été la douleur et les infections du membre, souvent localisées au niveau du site de la perfusion. La plupart des complications ont cependant été réversibles. COMMENTAIRES MÉTHODOLOGIQUES ET CLINIQUES	Isolierte Extermitätenperfusion mit Melphalan ·Beschreibung der Studien Zwei randomisierte Studien haben den Effekt einer isolierten Extremitätenperfusion mit Melphalan nach Exizision des Primärmelanoms untersucht. Die beiden Studien haben 107 und 832 Patienten mit einer Tumordicke ab 1,5 mm eingeschlossen. In der Studie von Ghussen et al. war die Perfusion mit Melphalan mit Hyperthermie kombiniert. ·Gesamtüberleben, Rezidivfreies Überleben Nur eine der beiden Studien zeigte einen Vorteil in Bezug auf lokale Kontrolle und Gesamtüberleben zugunsten einer Therapie mit isolierter Extremitätenperfusion mit Hyperthermie-Melphalan nach Exzision eines Primärmelanoms. Die Studie von Koops et al. zeigte keinen signifikanten Unterschied in Bezug auf das Gesamtüberleben. Eine Subgruppenanalyse zeigte jedoch ein verlängertes rezidivfreies Überleben bei Patienten mit Lymphknotendissektion (RR = 0,75 [IC95 : 0,55-0,98]) *[Kommentar: in der Originalarbeit bezieht sich das verlängerte rezidivfreie Überleben auf Patienten OHNE Lymphknotendissektion: "…The difference was significant for patients who did not undergo elective lymph node dissection (ELND)."]* und besonders bei Patienten mit einem Tumordicke unter 3mm (RR = 0,56 [IC95 : 0,36-0,88]). Die Subruppenanalysen ergaben keine Unterschiede in Bezug auf das Gesamtüberleben. ·Toxizität Toxizitäten waren hauptsächlich Grad 1 und insgesamt am wichtigsten in den Gruppen der perfundierten Patienten. Die häufigsten Toxizitäten waren Schmerzen und Infektionen in der Extremität, häufig am Ort der Infusion. Die

Originaltext (Evidenztabelle und Text siehe Quell LL ab S.40)	Übersetzung
L'étude de Ghussen et al. a été arrêtée prématurément en raison d'une analyse intermédiaire qui a montré l'existence d'un bénéfice évident en termes de survie sans récidive en faveur des patients qui ont reçu une perfusion hyperthermique de melphalan (p < 0,001). Au total, 115 patients ont été inclus, dont 107 évaluables. Le calcul a priori du nombre de sujets nécessaires n'étant pas présenté, la puissance de l'étude ne peut être recalculée et la fiabilité des résultats est limitée. Les analyses en sous-groupes définies a posteriori ne permettent pas d'établir de conclusions fiables en regard de ces résultats. Les populations des 2 études ne sont pas comparables. À noter également que près de 10 ans séparent les 2 études et que les protocoles de traitement ont été différents (hyperthermie dans l'étude de Ghussen et al.). CONCLUSIONS DE LA LITTÉRATURE La perfusion de melphalan sur membre isolé ne semble pas améliorer la survie globale des patients atteints d'un melanoma cutané (niveau de preuve C).	meisten Komplikationen waren jedoch reversibel. ·Klinische und Methodische Kommentare Die Studie von Ghussen et al. wurde vorzeitig beendet, da eine Zwischenanalyse einen Benefit in Bezug auf das rezidivfreie Überleben zugunsten einer hyperthermen Perfusion mit Melphalan gezeigt hat (p < 0,001). Insgesamt wurden 115 Patienten eingeschlossen, davon waren 107 auswertbar. Die erforderliche Fallzahlberechnung wurde nicht dargestellt, die Power der Studie konnte nicht berechnet werden und die Verlässlichkeit der Daten ist limitiert. Die nachträglich definierten Subgruppenanalysen lassen keine verlässlichen Schlussfolgerungen aus den Ergebnissen zu. Die Populationen aus den beiden Studien sind nicht vergleichbar. Es ist zu beachten, dass fast 10 Jahre zwischen den beiden Studien lag und die Behandlungsprotokolle unterschiedlich waren (Hyperthermie in der Studie von Ghussen et al.) ·Schlussfolgerung aus der Literatur Eine adjuvante Extremitätenperfusion mit Melphalan scheint das Gesamtüberleben von Melanompatienten nicht zu verbessern. (Niveau de preuve C)

Literatur:

Ghussen F, Kruger I, Smalley RV, et al. Hyperthermic perfusion with chemotherapy for melanoma of the extremities. World J Surg 1989;13:598-602
Koops HS, Vaglini M, Suciu S, et al. Prophylactic isolated limb perfusion for localized, high-risk limb melanoma: results of a multicenter randomized phase III trial. European Organization for Research and Treatment of Cancer Malignant Melanoma Cooperative Group Protocol 18832, the World Health Organization Melanoma Program Trial 15, and the North American Perfusion Group Southwest Oncology Group-8593. J Clin Oncol 1998;16:2906-2912

6.4. Frage V.4. Adjuvante Immunstimulation - Adaptation

6.4.1. Synopse Quelleitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Beeinflusst eine unspezifische Immunstimulation (BCG, Levamisol) das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?	-	-	Le levamisole en situation adjuvante n'améliore pas la survie des patients porteurs d'un mélanome cutané opéré (niveau de preuve A). *Eine adjuvante Therapie mit Levamisole verbessert nicht das Überleben von Melanompatienten. (Niveau de preuve A)*	After the review of the available information with respect to levamisole, we have concluded that, if levamisole has an impact on the clinical course of malignant melanoma when given in the adjuvant setting, that effect is marginal (BCG wurde nicht in die Literatursuche eingschlossen)
Schlüsselempfehlung	-	-	Les traitements adjuvants systémiques à base de levamisole, BCG ou dacarbazine ne sont pas recommandés en dehors d'essais thérapeutiques. *Adjuvante systemische Therapien mit Levamisol, BCG oder Dacarbazine werden ausserhalb von klinischen Studien nicht empfohlen.*	Keine Empfehlung zu Levamisole enthalten

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Zugrunde liegende Evidenz	-	-	4 Studien, 1 Metaanalyse aus der kanadischen LL 2002 Loutfi et al 1987, Lejeune et al. 1988, Quirt et al 1991, Spitler et al. 1991, Cancer Care Ontario Practice Guidelines Initiative 2002	4 Studien Spitler et al 1980, Loutfi et al 1987, Lejeune et al. 1988, Quirt et al 1991, Spitler et al. 1991

Update Recherche am 07.03.2011

Suchstrategie Medline: melanoma [tiab] AND levamisole [tiab], Treffer: 50, Darunter seit 2005 keine neuen randomisierten Studien zu Levamisol

6.4.2. Empfehlung und Hintergrundstext französische Quell Leitlinie

Quellleitlinie: Recommandations pour la Pratique Clinique : Standards, Options et Recommandations 2005

Originaltext (Evidenztabelle siehe Quell LL ab S.38)	Übersetzung
LEVAMISOLE ·Description des études Quatre essais randomisés ont évalué l'efficacité du levamisole (immunomodulateur) en situation adjuvante chez les patients porteurs d'un mélanome cutané opéré [126-129]. Aucun nouvel essai randomisé n'a été retrouvé dans le cadre de la mise à jour 2005. Trois essais ont comparé levamisole versus placebo [126, 127, 129] et 1 essai a évalué levamisole versus observation [128]. ·Survie globale Aucun des 3 essais contre placebo n'a rapporté de différence significative en termes de survie globale [126, 127, 129]. L'étude du NCIC a observé une différence significative de la survie à 5 ans en faveur des patients traités par levamisole par rapport à l'absence de traitement (78 % versus 62 % ; p = 0,027) [128]. L'analyse poolée des données réalisée par le CCOPGI n'a pas retrouvé de différence significative (odd ratio = 0,90 [IC95 : 0,63-1,30]) [12]. ·Commentaires méthodologiques et cliniques Les doses de levamisole administrées dans les 4 études sont très hétérogènes, ce qui ne permet pas d'établir de conclusions concernant la relation effet-dose. La population incluse dans l'étude du NCIC est hétérogène (seuls 50 % des patients sont des patients à haut risque de récidive). ·Conclusions de la littérature	LEVAMISOLE ·Beschreibung der Studien Vier randomisierte Studien haben den Effekt von Levamisole (Immunmodulator) bei Patienten in der adjuvanten Situation nach Exzision eines kutanen Melanoms untersucht[126-129]. Keine neue randomisierte Studie wurde im Rahmen der Aktualisierung 2005 gefunden. Drei Studien haben Levamisole gegen Placebo verglichen [126, 127, 129] und eine Studie hat Levamisole gegen Beobachtung untersucht [128]. ·Gesamtüberleben Keine der drei Studien versus Placebo berichtete einen signifikanten Unterschied in Bezug auf das Gesamtüberleben [126, 127, 129]. Die Studie der NCIC (National Cancer Institute of Canada Clinical Trials Group) hat einen signifikanten Unterschied des Überlebens nach 5 Jahren für Pataienten die mit Levamisole behandelt wurden im Vergleich zu unbehandelten Patienten gezeigt. Die Metaanalyse durch die CCOPGI hat keinen signifikanten Unterschied gezeigt. (odd ratio = 0,90 [IC95 : 0,63-1,30]) [12]. ·Klinische und Methodische Kommentare Die in den vier Studien verabreichten Dosierungen von Levamisole waren sehr heterogen, daher lassen sich keine Schlussfolgerungen zur dosisabhängigen Wirkung ziehen. Die eingeschlossene Population in der NCIC Studien ist sehr heterogen (nur 50% der Patienten sind Hochrisikopatienten)

Originaltext (Evidenztabelle siehe Quell LL ab S.38)	Übersetzung
Le levamisole en situation adjuvante n'améliore pas la survie des patients porteurs d'un mélanome cutané opéré (niveau de preuve A).	·Schlussfolgerung aus der Literatur Eine adjuvante Therapie mit Levamisole verbessert nicht das Überleben von Melanompatienten. (Niveau de preuve A)

Literatur:

12. CCOPGI, (Cancer Care Ontario Practice Guidelines Initiative). Systemic adjuvant therapy for patients at high risk for recurrent melanoma. Practice Guideline Report No 8-1 [online]. 2002. Available: URL: http://www.cancercare.on.ca/index_practiceGuidelinesandEvidencesummaries.htm#list.
127. Lejeune F, Macher E, Kleeberg UR, Rumke P, Prade M, Thomas D, et al. An assessment of DTIC versus levamisole or placebo in the treatment of high risk stage I patients after removal of a primary melanoma of the skin: a phase III adjuvant study (EORTC protocol 18761). Eur J Cancer 1988;24:S81-90.
126. Loutfi A, Shakr A, Jerry M, et al. Double blind randomized prospective trial of levamisole/placebo in stage I cutaneous malignant melanoma. Clin Invest Med 1987;10:325-328
128. Quirt IC, Shelley WE, Pater JL, et al. Improved survival in patients with poor-prognosis malignant melanoma treated with adjuvant levamisole: a phase III study by the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1991;9:729-735
129. Spitler LE. A randomized trial of levamisole versus placebo as adjuvant therapy in malignant melanoma. J Clin Oncol 1991;9:736-740

6.4.3. Empfehlung und Hintergrundstext kanadische Quell Leitlinie

Quellleitlinie: Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Updated Guideline Recommendations (Cancer Care Ontario) 2009

Levamisole is an anti-helminthic with disputed immunostimulatory properties in vitro. On the basis of that activity, levamisole has been investigated as adjuvant therapy in a number of cancers. Apart from results as adjuvant therapy in colon cancer when combined with a cytotoxic agent, the trials in other cancers have been negative.

There are four randomized controlled trials of levamisole in melanoma, of which three are placebo-controlled (30-33). The (NCIC) study (34) enrolled a heterogeneous group of patients with 50% being at high risk of recurrence (personal communication, B. Zee). The total dose of levamisole used in this level I study was 800 mg over a two-week period for an 80 kg individual. Three smaller trials evaluated total doses of 450 mg (31,31), 600 mg (32), and 600 to 1000 mg (33) over a two-week period. Whether those differences in dose are substantive is difficult to know in the absence of any data that demonstrate a dose-response relationship for levamisole with any measure of activity.

Although the initial report by Spitler et al (31) described a survival trend in favour of levamisole compared with placebo in the subgroup of patients without lymph node disease (p=0.07, two-sided), there was no survival difference between treatments for the total study population. That lack of benefit was confirmed by a subsequent report of long-term follow-up (30). Loutfi et al (32) and Lejeune et al (33) concluded that there was no meaningful impact on survival with levamisole compared with placebo. The only study in which levamisole had an impact, albeit a marginal one, was the study from the NCIC (34) in which there was a statistically significant difference in the survival rate in favour of levamisole when the

five-year point estimates of overall survival were assessed (78% for levamisole versus 62% for control, p=0.027, 2-sided). However, when the whole survival experience was compared between the groups, the difference in survival was not significant (p=0.08, two-sided). That difference represented a risk reduction in mortality of 29% and was observed in all risk groups, including the group to which this systematic review is directed.

Without an intermediate marker of activity for levamisole, it is impossible to categorically state whether or not there are substantive differences in the regimens used in those four trials. This systematic review is directed at a specific segment of the population involved in those trials. While a meta-analysis restricted to data from the high-risk subgroup might help to reconcile the seemingly disparate findings, survival results are not reported separately for that patient subgroup, and data for individual cases are generally not available. However, it is our belief that the regimens evaluated are unlikely to be substantially different in their clinical activity and that the impact of levamisole does not differ across risk groups. A meta-analysis of five-year death rates (Figure 2), abstracted from survival curves in published reports, yields a risk ratio of 0.94 (95% CI, 0.75 to 1.20; p=0.6). No heterogeneity was found among the results from these studies (p=0.19).

After the review of the available information with respect to levamisole, we have concluded that, if levamisole has an impact on the clinical course of malignant melanoma when given in the adjuvant setting, that effect is marginal.

Adverse effects

Morbidity from levamisole is generally mild, although it was severe enough to result in discontinuation of therapy in 41% of patients in the NCIC study (34), 44% in the Loutfi et al study (compared with 16% in the placebo group) (32), and 17% in the Lejeune et al study (compared with no patients in the placebo group) (33). Data on toxicity was reported for two of the placebo-controlled trials (32,33). In the study by Loutfi et al, 22% of patients on levamisole reported a flu-like syndrome (compared with 3% on placebo), 14% reported nausea and vomiting (compared with 8% on placebo), and 14% reported musculoskeletal symptoms (compared with no patients on placebo) (32). The most commonly reported adverse events in the Lejeune et al study were nausea and vomiting (27% with levamisole versus 10% with placebo), weakness (27% versus 14%), and anorexia (22% versus 8%) (33). Hematologic abnormalities were noted for 7% of patients on levamisole and none of the placebo group in the Loutfi et al study (32), and for 16% and 5%, respectively, of those groups in the Lejeune et al study (33). No treatment-related mortality has been observed in the four levamisole studies summarized here.

Literatur:

33. Lejeune FJ, Macher E, Kleeberg U, Rumke P, Prade M, Thomas D, et al. An assessment of DTIC versus levamisole or placebo in the treatment of high risk stage I patients after surgical removal of a primary melanoma of the skin. Eur J Cancer Clin Oncol. 1988;24 Suppl 2:S81-S90.
32. Loutfi A, Shakr A, Jerry M, et al. Double blind randomized prospective trial of levamisole/placebo in stage I cutaneous malignant melanoma. Clin Invest Med 1987;10:325-328
34. Quirt IC, Shelley WE, Pater JL, et al. Improved survival in patients with poor-prognosis malignant melanoma treated with adjuvant levamisole: a phase III study by the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1991;9:729-735
30. Spitler LE. A randomized trial of levamisole versus placebo as adjuvant therapy in malignant melanoma. J Clin Oncol 1991;9:736-740
31. Spitler LE, Sagebiel R. A randomized trial of levamisole versus placebo as adjuvant therapy in malignant melanoma. N Engl J Med 1980;303:1143-1147

6.5. Frage V.5. Adjuvante Therapie mit Bevacizumab – De novo Recherche?

Frage V.5 Beeinflusst eine adjuvante Therapie mit Bevacizumab das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?

6.5.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients, clinical stage II and III	Bevacizumab treatment	Observation	OS, PFS

Suchwörter				
Stichwort	melanoma	Bevacizumab	adjuvant	
Mesh Term	melanoma	Bevacizumab, Avastin		

6.5.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (Bevacizumab [tiab] OR Bevacizumab [MeSH] OR Avastin[tiab] AND adjuvant[tiab])	26.09.2016	16
Cochrane Library	(melanoma and bevacizumab and adjuvant).mp.	26.09.2016	3

6.5.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	19
Einschlusskriterien	system. Reviews, klinische Studien zu adjuvanten Therapie mit Bevacizumab bei Patienten mit Rezidivrisiko, tumorfreies Stadium I-III Intervention: Bevazizumab Monotherapie, Vergleichsgruppe: Beobachtung Sprachen: e,dt
Ausschlusskriterien	Nicht systematische Reviews Kohorten Studien, Case Reports Kombinationstherapien Vergleichsgruppe Chemotherapie, andere Systemtherapien Therapiestudien mit Interferon alpha im Stadium IV Kollektive mit gemischten Tumorentitiäten
Anzahl ausgewählter Studien	**1**

6.5.4. Evidenztabelle

Referenz	Ziele	Design	Untersuchte Population	untersuchte Endpunkte	Ergebnisse	Bemerkungen	Evidenzklasse (level of evidence/Oxford)
Corrie et al., 2014	To establish whether angiogenesis inhibition would offer clinical benefit in patients at high risk of	RCT Arm A: Bevacizumab 7.5 mg/kg iv, every 3 weeks for 1 year n=671 pts. Arm B:	Patients were at least 16 years old, with histological confirmation of completely resected American Joint	Primary endpoint: OS Secondary endpoints: DFS, distant-metastasis-free interval, safety	OS: HR 0.97, 95% CI 0.78–1.22; p=0.76 DFS: HR 0.83, 95% CI 0.70–0.98, p=0·03 Distant-metastasis-free interval: HR 0.88, 95% CI 0.73–1.06, p=0.18	Jaded Score: 3 (High quality study) 1:1 randomization preplanned interim results	1b

	recurrence	Observation n=672 pts.	Committee on Cancer stage IIB (T3bN0M0 and T4aN0M0), IIC (T4bN0M0), or III (TxN1–3M0) cutaneous melanoma	and toxic effects, and health-related quality of life Tertiary endpoints were assessment of biological predictive and prognostic markers	Safety: not significantly different Health-related quality of life: not significantly different The interaction between treatment and BRAF status was not significant (p=0·10); however, in patients with BRAF mutant tumours, we noted an improvement in the disease-free interval in those given bevacizumab. Disease-free interval did not differ significantly between treatment groups in the wild-type BRAF population.		

6.5.5. Literatur

Corrie, P.G., et al., Adjuvant bevacizumab in patients with melanoma at high risk of recurrence (AVAST-M): preplanned interim results from a multicentre, open-label, randomised controlled phase 3 study. Lancet Oncol, 2014. 15(6): p. 620-30.

6.6. Frage V.6. Adjuvante Therapie mit Ipilimumab – De Novo Recherche

Frage V.6: Beeinflusst eine adjuvante mit Ipilimumab das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?

6.6.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients, clinical stage II and III	Ipilimumab treatment	Observation	OS, PFS

Suchwörter				
Stichwort	melanoma	Ipilimumab	Adjuvant	
Mesh Term	melanoma	Ipilimumab, Yervoy		

6.6.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (Ipilimumab [tiab] OR Ipilimumab [MeSH] OR Yervoy[tiab] AND adjuvant[tiab])	01.12.2016	80
Cochrane Library	(melanoma and Ipilimumab and adjuvant).mp.	01.12.2016	1

6.6.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	81

Einschlusskriterien	system. Reviews, klinische Studien zu adjuvanten Therapie mit Ipilimumab bei Patienten mit Rezidivrisiko, tumorfreies Stadium I-III Intervention: Ipilimumab Monotherapie, Vergleichsgruppe: Beobachtung Sprachen: e,dt
Ausschlusskriterien	Nicht systematische Reviews Kohorten Studien, Case Reports Kombinationstherapien Vergleichsgruppe Chemotherapie, andere Systemtherapien Therapiestudien mit Interferon alpha im Stadium IV Kollektive mit gemischten Tumorentitiäten
Anzahl ausgewählter Studien	**1**

6.6.4. Evidenztabelle

Referenz	Ziele	Design	Untersuchte Population	untersuchte Endpunkte	Ergebnisse	Bemerkungen	Evidenzklasse (level of evidence/Oxford)
Eggermont AM, et al. 2015 [1]	To assess ipilimumab as adjuvant therapy for patients with completely resected stage III melanoma at high risk of recurrence	Phase III RCT; n= 951	Patients with stage III cutaneous melanoma (excluding lymph node metastasis ≤1 mm or in-transit metastasis) with adequate resection of lymph nodes (ie, the primary	Recurrence-free survival (RFS), assessed by an independent review committee, and analysed by intention to treat. Distant-metastasis free survival (also assessed by the independent review committee), OS,	Median follow-up of 2.74 years. Median RFS was 26·1 months (95% CI 19·3–39·3) in the ipilimumab group versus 17.1 months (95% CI 13.4–21.6) in the placebo group (hazard ratio 0.75; 95% CI 0·64–0·90; p=0·0013); 3-year RFS was 46·5% (95% CI 41·5–51·3) in the ipilimumab group	JADAD score 4 (high quality study)	1b

			cutaneous melanoma must have been completely excised with adequate surgical margins) who had not received previous systemic therapy for melanoma.	adverse event profile, and health-related QOL (assessed with EORTC QLQ-C30 instrument).	versus 34·8% (30.1–39·5) in the placebo group. Ipilimumab group, 465 (99%) of 471 patients had an adverse event of any grade, with grade 3 or 4 adverse events in 254 (54%) patients; 432 (91%) of 474 patients in the placebo group had an adverse event of any grade, with grade 3 or 4 adverse events occurring in 118 (25%) patients. On-study immune-related adverse events were more frequently reported in the ipilimumab group than in the placebo group. The most common grade 3–4 immune-related adverse events in the ipilimumab group were gastro intestinal, hepatic, and endocrine in nature. For all		

					classes, most patients had only one episode of a grade 3–4 immune-related adverse event. Five (1%) participants died because of drug-related adverse events in the ipilimumab group		
Eggermont AM, et al. 2016 [2]	To evaluated ipilimumab at a dose of 10 mg per kilogram in patients who had undergone complete resection of stage III melanoma.	Phase III RCT; n= 951	Patients with stage III cutaneous melanoma (excluding lymph node metastasis ≤1 mm or in-transit metastasis) with adequate resection of lymph nodes (ie, the primary cutaneous melanoma must have been completely excised with adequate surgical margins) who	Recurrence-free survival (RFS), assessed by an independent review committee, and analysed by intention to treat. Distant-metastasis free survival (also assessed by the independent review committee), OS, adverse event profile, and health-related QOL (assessed with EORTC QLQ-C30 instrument).	5-year rate of recurrence-free survival was 40.8% in the ipilimumab group, as compared with 30.3% in the placebo group (hazard ratio for recurrence or death, 0.76; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). The rate of overall survival at 5 years was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group (hazard ratio for death, 0.72; 95.1% CI, 0.58 to 0.88; P = 0.001). The rate of	JADAD score 4 (high quality study) Update zu Eggermont et. al 2015	1b

			had not received previous systemic therapy for melanoma.		distant metastasis–free survival at 5 years was 48.3% in the ipilimumab group, as compared with 38.9% in the placebo group (hazard ratio for death or distant metastasis, 0.76; 95.8% CI, 0.64 to 0.92; P = 0.002). Adverse events of grade 3 or 4 occurred in 54.1% of the patients in the ipilimumab group and in 26.2% of those in the placebo group. Immunerelated adverse events of grade 3 or 4 occurred in 41.6% of the patients in the ipilimumab group and in 2.7% of those in the placebo group. In the ipilimumab group, 5 patients (1.1%) died owing to immune-related adverse events.		

6.6.5. Literatur

1. Eggermont, A.M., et al., *Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial.* Lancet Oncol, 2015. **16**(5): p. 522-30.
2. Eggermont, A.M., et al., *Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy.* N Engl J Med, 2016. **375**(19): p. 1845-1855.

6.7. Frage V.7. und V.8. Adjuvante Interferon alpha Therapie – De novo Recherche

Frage IV.7. Beeinflusst eine Therapie mit IFN-alpha das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?

Frage IV.8. Welche Patientengruppe profitiert von einer Interferon-alpha-Therapie?

6.7.1. PICO, Suchwörter

PICO - Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients, clinical stage II and III	IFN-alpha treatment	Observation	OS, PFS

Suchwörter				
Stichwort	melanoma	Interferon-alpha	adjuvant	
Synonyme		Interferon alpha, Interferon alpha, IFN-α, IFN-alpha		
Ober-/Unterbegriffe		interferon-alpha-2b, interferon-alpha-2a,		

		multiferon		
Mesh Term	melanoma	Interferon-alpha		

6.7.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (Interferon-alpha[tiab] OR Interferon-alpha[MeSH] OR "Interferon alpha"[tiab] OR IFN-alpha [tiab] OR IFN-alpha[tiab] OR interferon-alpha-2b[tiab] OR interferon-alpha-2a[tiab] OR multiferon[tiab]) AND (adjuvant[tiab])	12.04.11	404 (25)
Cochrane Library	(melanoma and interferon alpha and adjuvant).mp.	12.04.11	46 (8, davon 7 Dubletten, 1 Studie dazu Rudolf Z 1994)
Embase	(melanoma and (Interferon alpha or IFN alpha or interferon alpha 2b or interferon alpha 2a or multiferon) and (adjuvant)).ti,ab.	11.05.11	301 (nach Dublettenelimination 0 dazu)
Update Suche			
Medline	s.o.	30.01.12	**427** (2 dazu: Petrella, Eggermont)
Cochrane Library	s.o.	30.01.12	**47** (0 dazu)
Embase	s.o.	23.01.12	**308** (0 dazu)

6.7.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	782
Einschlusskriterien	system. Reviews, klinische Studien zu adjuvanter Therapie mit Interferon alpha bei Patienten mit Rezidivrisiko, tumorfreies Stadium I-III Intervention: IFN alpha Monotherapie, Vergleichsgruppe: Beobachtung Sprachen: e,dt
Ausschlusskriterien	Nicht systematische Reviews Kohorten Studien, Case Reports Kombinationstherapien Vergleichsgruppe Chemotherapie, andere Systemtherapien Therapiestudien mit Interferon alpha im Stadium IV Kollektive mit gemischten Tumorentitiäten
Anzahl ausgewählter Studien (8 Reviews, 16 RCTs, *davon 2 nur als Abstract vorliegend*)	**24**
Anzahl in Reviews zusätzlich berücksichtigter Studien (E2696+E1694 kein Obs Arm, Kokoschka, Rusciani mangelnde Qualität)	4
Anzahl der ausgeschlossenen Studien nach Bewertung (Rudolf)	1

6.7.4. Evidenztabelle - Kurzfassung

RCT	No. of patients	OS	p	RFS	p	LoE
Low Dose						
Pehamberger, AMCG, 1998	311	no benefit, HR n.r.	-	**benefit, HR n.r.**	**<0.2**	1b
Garbe, DeCOG, 2008	444	**HR = 0.62**	**0.0045**	**HR = 0.69**	**0.018**	1b
Kleeberg, EORTC 18871, 2004	484	HR = 0.96	0.72	HR = 1.04	0.71	1b
Hancock, UKCCCR, 2004	674	OR = 0.94	0.6	OR = 0.91	0.3	1b
Cascinelli, WHO, 2001	444	no benefit, HR n.r.	0.72	no benefit, HR n.r.	0.5	1b
Cameron, SMG, 2001	95	no benefit, HR n.r.	>0.2	no benefit, HR n.r.	-	1b
Kirkwood, E1690, 2000	642	HR = 1.04§	0.813	HR = 1.19§	0.171	1b
Grob, FCGM, 1998	489	no benefit, HR n.r.	0.059	**benefit, HR n.r.**	**0.035**	1b
Intermediate Dose						
Hansson, Nordic trial, 2011	855	HR = 0.91	0.642	**HR = 0.80**	**0.030**	1b
Eggermont, EORTC 18952, 2005	832 835	HR = 1.00* HR = 0.85*	0.96 0.11	HR = 0.95* HR = 0.83*	0.59 0.05	1b
High Dose						
Agarwala, E1697, 2011	*1150*	*no benefit, HR n.r.*	-	*no benefit, HR n.r.*	-	
McMasters, Sunbelt Trial, 2008	*218*	*HR = 1.07*	*0.79*	*HR = 0.82*	*0.46*	
Kirkwood, E1690, 2000	642	HR = 1.0§	0.995	HR = 1.28§	0.054	1b

RCT	No. of patients	OS	p	RFS	p	LoE
Kirkwood, E1684, 1996/2004	287	Upd.: HR = 1.22§ benefit, HR n.r.	0.18 0.0237	**Upd.: HR = 1.38§** benefit, HR n.r.	**0.02** 0.0023	1b
Creagan, NCCTG, 1995	262	HR = 0.9	0.53	HR = 0.83	0.37	1b
Pegylated						
Eggermont, EORTC 18991, 2008	1256	HR = 0.98	0.78	**HR = 0.82**	**0.01**	1b

*13 month, 25 month interferon; DMFS not RFS was calculated, § HR relates to proportion alive and proportion relapsfree (> 1 = Favour IFN)

Agarwala 2011, Mc Masters 2008: only abstract available

6.7.5. Hochdosis versus Niedrigdosis Interferon alpha

Randomisierte Studie HDI versus LDI versus Beobachtung: kein signifikanter Unterschied

RCT	No. of patients	OS	p	RFS	p	LoE
Kirkwood et al. 2000	HDI n=215, HDI vs. Obs LDI n=215, LDI vs. Obs HDI vs. LDI*	HR = 1.0§ HR = 1.04§ RR = 1.02*§ Favour LDI, n.s.	n.s. n.s. 0.92*	HR = 1.28§ HR = 1.19§ RR = 0.93*§, Favour HDI, n.s.	n.s. n.s. 0.50*	1b

* Data not reported, calculated based on event data RR=(events/group A)/(events group B), p value: Fisher's exact test; § HR relates to proportion alive and proportion relapsfree

Subgruppenvergleich Metaanalyse Mocellin et al. 2010: 6 HDI Studien versus 7 LDI und IDI Studien, kein signifikanter Unterschied

Study	No. of trials / patients	OS HR (95% CI)	No. of trials / patients	PFS HR (95% CI)	No. of trials / patients	OS HR (95% CI)	No. of trials / patients	PFS HR (95% CI)	Subgroup comparison	LoE
Mocellin et al. 2010	HDI				LDI or IDI				OS p=0.99 PFS p=0.05	2b
	5/3114	0.89 (0.77 – 1.02)	6/3221	**0.75** **(0.68 – 0.83)**	7/4590	**0.89** **(0.81 – 0.98)**	8/4901	**0.85** **(0.78 – 0.93)**		

Vergleich Hochdosis versus Niedrigdosis Interferon alpha Studien im Stadium der lokoregionären Metastasierung (AJCC 2009: St. III)

RCT Low Dose	Anteil Patienten mit lokoreg. Met.	OS	p	RFS	p	RCT High Dose	Anteil Patienten mit lokoreg. Met.	OS	p	RFS	p
Cascinelli, WHO, 2001	97%	no benefit, HR n.r.	0.72	no benefit, HR n.r.	0.5	**Kirkwood, E1684, 2004 (Update), 1996**	89%	Upd.: no benefit: HR = 1.22[§] **benefit, HR n.r.**	0.18 **0.0237**	**Upd.: HR = 1.38[§]** **benefit, HR n.r.**	**0.02** **0.0023**
Hancock, UKCCCR, 2004	81%	OR = 0.94	0.6	OR = 0.91	0.3	**Kirkwood, E1690, 2000**	74%	HR = 1.0[§]	0.995	HR = 1.28[§]	0.054
Kirkwood, E1690, 2000	74%	HR = 1.04[§]	0.813	HR = 1.19[§]	0.171	**Creagan, NCCTG, 1995**	61%	HR = 0.9	0.53	HR = 0.83	0.37
Garbe, DeCOG, 2008	61%	**HR = 0.62**	**0.0045**	**HR = 0.69**	**0.018**						
Kleeberg,	60%	HR =	0.72	HR =	0.71						

RCT Low Dose	Anteil Patienten mit lokoreg. Met.	OS	p	RFS	p	RCT High Dose	Anteil Patienten mit lokoreg. Met.	OS	p	RFS	p
EORTC 18871, 2004		0.96		1.04							
Cameron, SMG, 2001	St II + III Anteil n.r.	no benefit, HR n.r.	>0.2	no benefit, HR n.r.	-						
Pehamberger, AMCG, 1998	0%	no benefit, HR n.r.	-	**benefit, HR n.r.**	**<0.2**						
Grob, FCGM, 1998	0%	no benefit, HR n.r.	0.059	**benefit, HR n.r.**	**0.035**						

[§] HR relates to proportion alive and proportion relapsfree

6.7.6. Evidenztabellen – Langfassung

6.7.6.1. Evidenztabelle – Systematische Reviews and Metaanalysen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Petrella et al. 2012	To conduct another update of the evidence and recommendations. This report summarises the evidence published between July 2005 and June 2010 that informed the	Systematic review (Update) adjuvant treatment for stage AJCC stage IIB, IIC and III.	7 new RCTs: EORTC 18991 Sunbelt Trial Pectasides et al. 2009 EORTC 18952 Stadler et al. 2006 DeCOG 2008 DeCOG 2010	OS DFS	HDI vs. Obs: no sign. benefit Hazard Ratio: 0.93 [0.78,1.12] HDI vs. Obs: sign. Benefit Hazard Ratio: 0.77 [0.65, 0.92] P = 0.004; 9%	most LDI studies not included Conflict of Interest: The first author received consulting fees or honoraria greater than $5000 from Schering-Plough in	1a-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	development of revised recommendations for adjuvant interferon therapy by the Melanoma DSG.		Metaanalyses: Mocellin et al. Wheatley et al.		absolute risk reduction at 5 years	the past 2 years.	
Eggermont et al. 2011	To present a meta-analysis of the two largest adjuvant IFN/PEG-IFN randomised trials in a combined total of 2644 patients with high-risk melanoma (stage IIb/III)	Metaanalysis of 2 studies	EORTC 18991 EORTC 18952 2644 patients with high-risk melanoma stage IIb/III	OS RFS DMFS	IDI+peg IFN vs. Obs: no sign. benefit Hazard Ratio: 0.94 [0.80, 1.11] sign. benefit Hazard Ratio: 0.85 [0.76, 0.95] p=0.004 sign. benefit Hazard Ratio: 0.89 [0.79, 1.00] p=0.36	Conflict of Interest: Alexander M.M. Eggermont: Consultant in advisory boards for melanoma for Merck, BMS, Roche, GSK. Poulam Patel: Ad hoc advisory boards for Schering-Plough Research Institute – honoraria paid.	1a-
Garbe et al. 2011	to present the success of current treatments and the promise of those still in clinical development that may yield incremental	Systematic review adjuvant and palliative treatments	Interferon alpha: 11 RCTs NCCTG ECOG 1684 ECOG 1690 EORTC 18952 SMG	Metaanalysis Overall survival (OS)	12 RCTs Significant improvement odds ratio = 0.88, 95% CI = 0.79–0.99, p<0.03	Number needed to treat not reported No quality assessment of studies updated data of	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	improvements in the treatment of advanced, metastatic melanoma		WHO DeCOG FCGM UKCCCR AMCG EORTC 18991	Disease free survival (DFS)	Significant improvement odds ratio = 0.83, 95% CI = 0.75–0.92 p<0.0001	E1684 (Kirkwood 2004) and EORTC 18871 (Kleeberg 2004) not included Conflict of Interest: Claus Garbe: Consultant/advisory role: Roche Pharma, MSD, Bristol-Myers Squibb, Swedish Orphan, Genta, GlaxoSmithKline; Research funding/contracted research: Roche Pharma, MSD, Bristol-Myers Squibb, Swedish Orphan, Genta, GlaxoSmithKline; Axel Hauschild: Consultant/advisory role: Abraxis Oncology, Bayer Schering, Bristol-Myers Squibb, Essex Pharma/Schering-Plough; Honoraria: GlaxoSmithKline,	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Merck, Onyx Pharmaceuticals, Pfizer, Roche Pharma, Synta Pharmaceuticals Corp.; John M. Kirkwood: Consultant/advisory role: Schering (for FDA review of PegIFN), GlaxoSmithKline (for chairmanship of vaccine steering committee).	
Mocellin et al. 2010	to examine the effect of IFN-alpha on DFS and OS in patients with high-risk cutaneous melanoma	Systematic review Adjuvant treatment with interferon alpha	14 RCTs (published 1990 – 2008) 8122 patients NCCTG ECOG 1684 AMCG FCGM ECOG 1690 SMG WHO ECOG 1694 E2696 UKCCCR EORTC 18871	OS DFS	Significant improvement HR for death = 0.89, 95% CI = 0.83–0.96; P=.002 Number needed to treat 29 patients Significant improvement HR for disease recurrence = 0.82, 95% CI = 0.77–0.87; p<.001	absolute risk reduction not reported Reported hazard ratio were used for meta-analysis updated data of E1684 (Kirkwood 2004) not included Data of E1694 and E2696 (control vaccination arm with potentially	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			EORTC 18952 DeCOG EORTC 18991			worse outcome) were included OS benefit was observed only when trials that used low or intermediate IFN-a doses were considered Funding: no funds involved All authors declared no conflict of interest.	
Verma et al. 2006	To examine the role of systemic adjuvant therapy	Systematic review	Interferon alpha: 13 RCTs, published 1980 - 2004 Metaanalysis: E1684, E1690, E1694	OS	Metaanalysis E1684, E1690, E1694: significant Improvement RR (2 years) 0.85, 95% CI = 0.73–0.99; P=.03 not significant after exclusion of E1694: HR 0.87, 95% CI = 0.71–1.07; P=.18	Number needed to treat not reported No quality assessment of studies only 3 RCTs were included into metaanalysis other RCTs and published metaanalyses were reported	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						narratively Funding: Supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.	
Pirad et al. 2004	to evaluate the effect of IFN-alpha on the relapse rate (RR) and the overall survival (OS).	Systematic review	9 RCTs 2 880 patients ECOG 1684 NCCTG ECOG 1690 Rusciani FCGM AMCG SMG Kokoschka WHO	Metaanalysis OS RR	 no significant benefit OR = 0.87; 95% CI =0.74–1.02; p = 0.1029 Significant lower OR = 0.74; 95% CI = 0.64–0.86; p = 0.0001	Number needed to treat not reported No quality assessment of studies heterogeneity tests are non-significant (=homogeneous effects of studies), but studies were heterogeneous in regard to the schedules, the classification used and the median time of follow-up Funding/Conflict of interest: not mentioned	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Wheatley et al. 2003	To assess all the available evidence for adjuvant interferon-alpha	Metaanalysis	12 RCTs ECOG 1684 ECOG 1690 NCCTG E2696 EORTC 18952 WHO UKCCCR FCGM AMCG SMG Kleeberg (18871) Kleeberg (DKG-80)	Metaanalysis OS RFS	 no significant benefit HR = 0.93; 95% CI 0.85-1.02; p=0.1 significant benefit HR = 0.83; 95% CI 0.77-0.90; p=0.000003	Number needed to treat not reported few studies were used without existing publication, data of EORTC 18871 + DKG-80 were not reproducible within the later publication (Kleeberg et al. 2004) Funding/Conflict of interest: not mentioned	1a- (SR with heterogeneity)
Lens et al. 2002	to assess the benefit of IFN alpha therapy in malignant melanoma	Systematic review	9 RCTs, 8 RCTs included, 3 178 patients AMCG FCGM ECOG 1684 ECOG 1690 NCCTG SMG UKCCCR WHO	OS RFS	analysis on available data for 2 771 patients from 6 trials no study with benefit ECOG 1684: significant benefit, not confirmed analysis on	High quality SR Number needed to treat reported for each individual trial no metaanalysis due to heterogeneity of studies, the authors state that any	1a- (SR with heterogeneity)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					available data for 2 020 patients from 4 trials 1 study with benefit ECOG 1684 significant benefit, confirmed ECOG 1690: significant benefit, not confirmed	recommendation should be made on the basis of an evaluation of the individual studies. Funding: Center for Evidence-Based Medicine, University of Oxford	

6.7.6.2. Evidenztabelle – Niedrigdosis IFN alpha

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Garbe et al. 2008 DeCOG	to improve disease-free survival (DFS) and overall survival (OS) with interferon (IFN) a2a with or without dacarbazine (DTIC) compared with observation alone	RCT Treatment groups LDI (LDI plus DTIC) OBS	444 patients, resected Stage III n=148 (n=148) n=148	OS DFS	LDI vs OBS significant benefit HR 0.62; 97.5% CI: 0.42-0.89; p=0.0045; events: 65/148 vs 88/148 significant benefit HR 0.69; 97.5% CI:	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: German Cancer Aid (Deutsche Krebshilfe); German Cancer	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					0.49-0.96; p=0.018; events: 84/148 vs 102/148	Society (Frankfurt, Germany); Hoffmann-LaRoche AG (Grenzach-Whylen, Germany).	
Hancock et al. 2004 UKCCCR	To evaluate low-dose extended duration interferon alfa-2a	RCT Treatment groups LDI OBS	674 patients, resected stage IIB and stage III n=338 n=336	OS RFS	LDI vs OBS no benefit OR 0.94; 95% CI: 0.75-1.18; p=0.6; events: 151/338 vs 156/336 no benefit OR 0.91; 95% CI: 0.75-1.10; p=0.3; events: 211/338 vs 215/336	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: The study was supported by a grant from Roche Products Ltd	1b
Kleeberg et al. 2004 EORTC 18871	to evaluate the efficacy and toxicity of low dose recombinant interferon-alpha 2 b (rIFN-alpha2b) (1 MU) or recombinant interferon gamma in comparison with an untreated control group	RCT Treatment groups OBS very LDI alpha (very LDI gamma)	728 patients Stage II-III n=244 n=240 (n=244)	OS RFS	LDI vs. OBS no benefit HR 1.04; 95% CI: 0.84-1.30; events: 137/240 vs 148/244 no benefit HR 0.96; 95% CI: 0.76-1.21; events: 159/240 vs 158/244	Jadad Score 2 of 5 not placebo controlled, not blinded, randomization scheme not described Funding:Essex and Boeringer-Ingelheim, grant number 3U10-	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						CA11488-18S1 through 5U10-CA11488-33 from the National Cancer Institute	
Cascinelli et al. 2001 WHO	to see whether interferon alpha-2a increased survival prospects in stage III melanoma patients	RCT Treatment groups OBS LDI	444 patients with lymph node involvement n=219 n=225	OS RFS	LDI vs. OBS no benefit HR n.r., p=0.72 events: 146/225 vs 138/219 no benefit HR n.r., p=0.5; events: 162/225 vs 158/219	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: not mentioned	1b
Cameron et al. 2001 SMG	To test the possible disease-free and overall survival advantage of a short, 6-month course of low-dose IFN for patients with high-risk, surgically resected, malignant melanoma.	RCT Treatment groups OBS LDI	95 patients with at least 3mm Breslow thickness or lymph node involvement n=49 n=46	OS RFS	LDI vs. OBS no benefit HR n.r., p>0.2; events: 31/46 vs 36/49 no benefit HR n.r., p>0.1; events: 32/46 vs 35/49	Jadad Score 2 of 5 not placebo controlled, not blinded, randomization scheme not described Funding: not mentioned, IFN supplied by Schering-Plough	1b
Kirkwood et al. 2000	To evaluate the efficacy of high-	RCT	642 patients, 75% nodal involvement		LDI vs. OBS no benefit	Jadad Score 3 of 5 not placebo	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
E1690	dose IFNalpha2b (HDI) for 1 year and low-dose IFNalpha2b (LDI) for 2 years versus OBS	Treatment groups OBS (HDI) LDI	n=212 (n=215) n=215	OS RFS	HR 1.04§; 95% CI: 0.78-1.38; p=0.813; events: 96/215 vs 93/212 no benefit HR 1.19§; 95% CI: 0.93-1.53; p=0.171; events: 122/215 vs 127/212	controlled, not blinded Funding: not reported assistance of Schering-Plough Research Institute and Schering-Plough Oncology Biotech with posttrial data collection	
Grob et al. 1998 FCGM	To assess the efficacy of adjuvant low dose interferon alpha	RCT Treatment groups OBS LDI	489 patients, tumor thickness > 1.5mm without clinically detectable node metastases n=245 n=244	OS RFS	LDI vs. OBS no benefit HR n.r., p=0.059 events: 59/244 vs 76/245 significant benefit HR n.r., p=0.035 events: 100/244 vs 119/245	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: grant from Hoffman-La Roche Ltd, also provided the interferon -2a (Roferon-A).	1b
Pehamberger et al. 1998 AMCG	To investigate whether adjuvant IFNalpha2a diminishes the occurrence of metastases and	RCT Treatment groups OBS LDI	311 patients, tumor thickness > 1.5mm n=157 n=154	OS	LDI vs. OBS no benefit HR n.r., events: 17/154 vs 21/157	Jadad Score 2 of 5 not placebo controlled, not blinded, randomization scheme not	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	thus prolongs disease-free survival in melanoma patients			RFS	significant benefit HR n.r., p=<0.2 events: 37/154 vs 57/157	described Funding: in part by Hoffmann-La Roche, Vienna, Austria.	
Rusciani et al. 1997	*to study the use of recombinant interferon-alpha (IFN-alpha) as adjuvant therapy for patients with Stage I and Stage II melanoma*	*RCT* *Treatment groups* *Obs* *LDI*	*84+ 70 patients, stages I+II,* *n=70* *n=84*	*DFS*	*Significant benefit events LDI vs. OBS 11/84 vs 21/70*	*Jadad Score 0 of 5 matched controlls, no randomisation, not placebo controlled, not blinded, no description of dropouts* *Study excluded*	*2b* *low quality RCT* *study excluded*
Kokoschka et al. 1990	*To evaluate the efficacy of rIFN alpha 2b therapy in high-risk melanoma patients stage I and stage II*	*Cohort Study* *Treatment groups* *OBS* *LDI*	*135 patients, stages I+II* *n=82* *n=53*	*OS* *DFS*	*no significant benefit*	*Cohort Study* *Only included in SR by Pirad et al.*	*2b* *study excluded*

[§] HR relates to proportion alive and proportion relapsfree (> 1 = Favour IFN)

6.7.6.3. Evidenztabelle - Mittlere Dosis IFN alpha

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hansson et al. 2011 Nordic IFN trial	To investigate whether adjuvant therapy with intermediate-dose interferon alfa-2b for 1 or 2 years would improve outcomes in patients with stage IIB-IIC or III resected cutaneous melanoma	RCT Treatment groups OBS IDI 12 months IDI 24 months	855 patients stage IIB-IIC n=284 n=285 n=286	OS (12 months + 24 months) PFS (12 months + 24 months) 24 months alone	IDI vs. OBS no benefit HR 0.91; 95% CI: 0.74-1.10; p=0.642; events: 285/571 vs 148/284 significant benefit HR 0.80; 95% CI: 0.67-0.96; p=0.030; events: 338/571 vs 183/284 no benefit	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: Schering-Plough; the Radiumhemmet Research Funds, Stockholm; and the Stockholm County Council	1b
Eggermont et al. 2005 EORTC 18952	to assess the effect of two regimens of interferon of intermediate dose versus observation alone	RCT Treatment groups Intermediate IFN, 13 months Intermediate IFN, 25 months OBS	1388 patients n=553 n=556 n=279	OS 13 months 25 months DFS 13 months	IDI vs. OBS no benefit HR 1.00; 95% CI: 0.79-1.25; p=0.96; HR 0.85; 95% CI: 0.67-1.07; p=0.11; events: 535/1109 vs 146/279 no benefit HR 0.97; 95% CI: 0.78-1.20; p=0.72; HR 0.83; 95% CI:	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: not mentioned The authors declared that they have no conflict of interest.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				25 months	0.67-1.03; p=0.05; events: 679/1109 vs 183/279		

6.7.6.4. Evidenztabelle - Hochdosis IFN alpha

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kirkwood et al. 2004/1996 Update E 1684 Initial Data E1684	To update the analyses To evaluate Interferon alfa-2b as an adjuvant therapy	RCT Treatment groups OBS HDI	287patients, stages IIb and III n=137 n=143	OS RFS	HDI vs. OBS Update: no benefit HR 1.22; 95% CI: n.r.; p=0.18; Initial: significant benefit HR n.r., p=0.0237 events 81/143 vs 90/137 significant benefit Update: HR 1.38, p=0.02 Initial: HR n.r., p=0.0023 events HDI vs. OBS 90/143 vs 103/137	Jadad Score 3 of 5 not placebo controlled, not blinded Funding: grants from the National Institutes of Health, Bethesda, MD. Update: Grant CA-23318, awarded by the National Cancer Institute, United States Department of Health and Human Services.	1b
Kirkwood et al. 2000 E1690	To evaluate the efficacy of high-dose IFNalpha2b (HDI) for 1 year and low-dose	RCT Treatment groups OBS HDI	642 patients, 75% nodal involvement n=212 n=215	OS	HDI vs OBS no benefit HR 1.00; 95% CI: 0.75-1.33; p=0.995;	Jadad Score 3 of 5 not placebo controlled, not blinded	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	IFNalpha2b (LDI) for 2 years versus OBS	(LDI)	(n=215)	RFS	events HDI vs. OBS 98/215 vs 93/212 no benefit HR 1.28; 95% CI: 1.00-1.65; p=0.054; events HDI vs. OBS 114/215 vs 127/212 events LDI vs. OBS 122/215 vs 127/212	Impact on RFS only significant by Cox multivariable analysis Funding: not reported assistance of Schering-Plough Research Institute and Schering-Plough Oncology Biotech with posttrial data collection	
Creagan et al. 1995 NCCTG	To report a prospective randomized trial designed to determine the clinical efficacy in terms of recurrence rates, time to recurrence, and patient survival following IFN-a2a given as postsurgical adjuvant therapy to selected	RCT Treatment groups OBS HDI	262 patients, stages I and II n=131 n=131	OS RFS	HDI vs OBS no benefit HR 0.83; 95% CI: 0.61-1.13; p=0.24; events: 68/131 vs 72/131 no benefit HR 0.90; 95% CI: 0.64-1.25; p=0.53; events: 77/131 vs 85/131	Jadad Score 2 of 5 not placebo controlled, not blinded, randomization scheme not described Funding: supported in part by Public Health	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with high-risk stage I and II malignant melanoma						
Agarwala et al. 2011 *E1697*	*To assess the benefit of 4 weeks of HDI compared with Observation in relation to the RFS and OS of patients with resectable intermediate and high-risk melanoma*	*RCT* *Treatment groups* *OBS* *HDI 4 weeks*	*1150 patients T2N0, T3N0, T4N0, T1-4N1a-2a* *n=596* *n=581*	*5-year survival rate* *RFS*	*no benefit IFN vs OBS* *0.82 vs 0.85* *6.8 vs 7.3 years*	*only ASCO abstract available*	
McMasters et al. 2008 *Sunbelt Trial*	*To evaluate the role of high-dose interferon alfa-2b (IFN) or completion lymph node dissection (CLND) in patients with melanoma staged by sentinel lymph node (SLN) biopsy*	*RCT* *Treatment groups* *Observation* *HDI*	*218 patients, after SLN biopsy, 1 positive node* *n=106* *n=112*	*OS* *RFS*	*no benefit HR 1.07; CI: 0.65-1.78; p=0.79* *no benefit HR 0.82; 95% CI: 0.47-1.40; p=0.46*	*only ASCO abstract available*	
Kirkwood et al. 2001 *E 1694*	*To evaluate the efficacy of HDI for 1 year versus vaccination with*	*RCT* *Treatment groups* *HDI*	*874 patients, stages IIB/III* *n=385*	*OS*	*significant benefit events IFN vs. Vacc. 52/385 vs 81/389*	*Included in SR although no OBS Arm*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	GM2	*vacination*	*n=389*	*RFS*	*significant benefit events IFN vs. Vacc. 98/385 vs 151/389*	*Funding: Eastern Cooperative Oncology Group grant no. NIH CA 39229-16 and R03 grant no. CA75950-02.*	
Kirkwood et al. 2001 *E2696*	*To evaluate the toxicity and other effects of the established adjuvant high-dose IFNalpha2b regimen in relation to immune responses to GMK*	*RCT* *Treatment groups* *Vacc+HDI day 1* *Vacc+HDI day 28* *Vacc*	*107 patients, stages IIB, III, and IV* *n=36* *n=36* *n=35*	*RFS* *no OS analysis due to short follow up*	*significant benefit events IFN+Vacc vs. Vacc. 28/72 vs 19/35*	*Included in SR although no OBS Arm* *Funding: unrestricted grant from Dr Craig Tendler of Schering Plough Research Institute, provision of the vaccine by Drs Robert Israel and Paul Maddon of Progenics, Inc.*	

6.7.6.5. Evidenztabelle - Pegyliertes IFN alpha

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Eggermont et al. 2008/2011 Update EORTC	To present the long-term results at 7.6-years follow up	RCT Treatment groups Observation	1256 patients, resected Stage III n=629	OS	PegIFN vs. OBS no benefit Update: HR 0.96; 95% CI	Jadad Score 3 of 5 not placebo controlled, not blinded	1b

18991 Initial Data EORTC 18991	To determine whether pegylated interferon alfa-2b can facilitate prolonged exposure while maintaining tolerability	Peylated IFN alfa-2b	n=627	RFS	0.82-1.11; p=0.57 Events: 332/627 vs 336/629 Initial: HR 0.98; 95% CI 0.82-1.16.; p=0.78 events: 262/627 vs 263/629 significant benefit Update: HR 0.87; 95% CI 0.76-1.00, p=0.05 events: 384/627 vs 406/629 Initial: HR 0.82; 95% CI 0.71-0.96; p=0.01 events: 328/627 vs 368/629	Funding: Schering Plough Research International.	

6.7.7. Subgruppenanalysen

Subgruppenvergleich Metaanalyse Mocellin et al. 2010: Stadium II versus Stadium III, kein signifikanter Unterschied

Study	No. of trials / patients	OS HR (95% CI)	No. of trials / patients	PFS HR (95% CI)	No. of trials / patients	OS HR (95% CI)	No. of trials / patients	PFS HR (95% CI)	Subgroup comparison	LoE
Mocellin et al. 2010	Stadium II				Stadium III				OS p=0.36 PFS p=0.42	2a

	1/499	0.70 (0.50 – 0.98)	2/810	0.70 (0.55 – 0.88)	3/2144	0.87 (0.68 – 1.11)	3/2144	0.82 (0.72 – 0.93)		

Subgruppenanalysen der eingeschlossenen randomisierten Studien

Study	Subgroup / No. of patients	OS, HR	p	PFS, HR	p	LoE
Hansson et al. 2011	All patients / n=855	0.91	0.642	**0.80**	**0.030**	1b
(Intermediate Dose)	Stage IIB-IIC / n=166	n.r.	-	Favour IFN, n.s.	0.082	3b
	Stage III, palpable nodes / n=554	n.r.	-	**Favour IFN**	**0.015**	3b
	Stage III, 1 pos. node / n=374	n.r.	-	Favour IFN, n.s.	-	3b
	Stage III, 2-3 pos. node, n=201	n.r.	-	Favour IFN, n.s.	-	3b
	Stage III, >/= 4 pos. node / n=114	n.r.	-	**Favour IFN**	**0.038**	3b
	Ulzeration, n=238	1.05, Favour Obs, n.s.	0.809	1.04, Favour Obs, n.s.	0.829	3b
Eggermont et al. 2011	2 studies, all patients, n = 2644	0.94	0.36	**0.85**	**0.004**	1a-
(Intermediate Dose+ Pegylated Interferon alpha)	N1, n=1154	0·81	0.07	**0.78**	**0.01**	3b
	N2, n=1031	1·01	0.92	0.91	0.25	3b
	No Ulceration, n=1336	1·11	0·20	0.92	0.30	3b
	Ulceration, n=849	**0.72**	**0.001**	**0·75**	**0.001**	3b
	Ulceration + N1, n=484	**0.58**	**0.0003**	**0.69**	**0.003**	3b

Study	Subgroup / No. of patients	OS, HR	p	PFS, HR	p	LoE
	Ulceration + N2, n=365	0.89	0.41	0.83	0.15	3b
McMasters et al. 2010	SN-, Ulceration, n=127	n.s.		n.s.		3b
(High Dose)	SN+, Ulceration, n=75	n.s.			**0.0169**	3b
	SN+, no Ulceration, n=147	n.s.		n.s.		
Kleeberg et al. 2004	St. IIb vs. St. III	IFN benefit: similar				3b
(Low Dose)						
Hancock et al. 2004	stage, age, sex	IFN benefit: n.s. differences				3b
(Low Dose)						
Kirkwood et al. 2000	T4 N0 M0			1.46	0.20	3b
(Benefit of High Dose)	T1-4 N1 M0			1.16	0.74	3b
	T1-4 N1-2 M0			1.57	0.20	3b
	Recurrent N+			1.27	0.18	3b
	N0			1.46	0.19	3b
	N1			1.0	0.99	3b
	N2-3			**1.92**	**0.02**	3b
	N>=4			1.15	0.58	3b

Study	Subgroup / No. of patients	OS, HR	p	PFS, HR	p	LoE
Creagan et al. 1995	Stage I			n.s.	0.93	3b
(High Dose)	Stage II			Favour IFN, n.s.	0.09	3b

6.7.8. Toxizität

Study	**Treatment groups** (number of patients)	**Treatment related deaths**	**Discontinuation because of toxicity**	Number of patients with **Grade 3 or 4 Toxicities** (%)	**Fatigue** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Depression** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Neutropenia** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Hepatotoxicity** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)
Agarwala et al. 2011	OBS (n=596) HDI 4 weeks (n=581)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Eggermont et al. 2008	OBS (n=629) Peylated IFN alfa-2b (n=627)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Hansson et al. 2011 **Nordic IFN trial**	OBS (n=284) IDI 12 months (n=285) IDI 24 months	n=0	 n=72 (25%) n=72 (25%)	n.r.	n=106 (37%) / n=5 (2%) n=267 (94%) / n=28 (10%) n=266 (93%) /	n=108 (38%) / n=1 (<1%) n=210 (74%) / n=17 (6%) n=214 (75%)	n.r.	n=41 (14%) / n=2 (1%)* n=118 (41%) / n=2 (1%)* n=122 (43%) /

Study	**Treatment groups** (number of patients)	**Treatment related deaths**	**Discontinuation because of toxicity**	Number of patients with **Grade 3 or 4 Toxicities** (%)	**Fatigue** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Depression** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Neutropenia** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Hepatotoxicity** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)
	(n=286)				n=32 (11%)			n=6 (2%)* *ALAT
Kirkwood et al. 1996	OBS (n=140) HDI (n=146)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Eggermont et al. 2008 **EORTC 18991**	OBS (n=629, Tox. assessed n=613) Peylated IFN alfa-2b (n=627, Tox. assessed n=608)	n.r.	 n=191 (31%)	n=74 (12%) n=278 (46%)	n=252 (41%) / n=7 (1%) n=574 (94%) / n=97 (16%)	n=153 (25%) / n=3 (<1%) n=360 (59%) / n=39 (6%)	n.r.	n=221 (36%) / n=10 (2%)* n=479 (79%) / n=66 (11%)* *Liver function test
Garbe et al. 2008 DeCOG	LDI (n=148) (LDI plus DTIC) OBS (n=148)	n.r.	n=20 (14%)	n=13 (9%)	n.r.	n.r.	n.r.	n.r. / n=0
Eggermont et al. 2005 **EORTC 18952**	Intermediate IFN, 13 months (n=553, tox. assessed n= 521) Intermediate	n=0	n=87 (16%) (N=539) n=108 (20%)	n.r.	n.r. / 78 (15%) n.r. / n=67	n.r. / n=62 (12%) n.r. / n=56	n.r.	n.r. / n=16 (3%) n.r. / n=21 (4%)

Study	**Treatment groups** (number of patients)	**Treatment related deaths**	**Discontinuation because of toxicity**	Number of patients with **Grade 3 or 4 Toxicities** (%)	**Fatigue** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Depression** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Neutropenia** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Hepatotoxicity** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)
	IFN, 25 months (n=556, tox. assessed n= 532) OBS (n=279, tox. assessed n= 252)		(N=539)		(13%) n.r. / n=5 (2%)	(11%) n.r. / n=9 (4%)		n.r. / n=1 (<1%)
Hancock et al. 2004 **UKCCCR**	LDI (n=338, tox. assessed range 322-327)) OBS (n=336)	n=0	n=50 (15%)	n=56 (17%)	n=265 (78%) / n=22 (7%) n=116 (38%) / n=4 (1%)	n=179 (55%) / n=11 (3%) n=94 (31%) / n=5 (2%)	n.r.	n=113 (35%) / n=7 (2%) n=65 (22%) / n=1 (<1%)
Kleeberg et al. 2004 **EORTC 18871**	OBS (n=244) very LDI alpha (n=240) (very LDI gamma, n=244)	n.r.	n=11 (5%)	n.r.	n.r.	n.r.	n.r.	n.r.

Study	**Treatment groups** (number of patients)	**Treatment related deaths**	**Discontinuation because of toxicity**	Number of patients with **Grade 3 or 4 Toxicities** (%)	**Fatigue** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Depression** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Neutropenia** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Hepatotoxicity** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)
Cascinelli et al. 2001 **WHO**	OBS (n=219) LDI (n=225)	n.r.	n=0	n.r.	n.r.	n.r.	n.r.	n.r.
Cameron et al. 2001 **SMG**	OBS LDI	n=0	n=0	n.r.	n.r.	n.r.	n.r.	n.r.
Kirkwood et al. 2000 **E1690**	OBS (n=212) HDI (n=215) LDI (n=215)	n=0	n.r.	n.r.	n.r. / n=0 n.r. / n=51 (24%) n.r. / n=7 (3%)	n.r. / n=0 n.r. / n=20 (9%) n.r. / n=5 (2%)	n.r. / n=0 n.r. / n=94 (44%) n.r. / n=12 (6%)	n.r. / n=6 (3%) n.r. / n=61 (29%) n.r. / n=9 (4%)
Grob et al. 1998 **FCGM**	OBS (n=245) LDI (n=244)	n=0	n=35 (14%)	n.r. n=24 (10%)	n.r. n=118 (48%) / n=5 (2%)	n.r. n=40 (16%) / n=3 (1%)	n.r. n.r. / n=6 (2%)	n.r.
Pehamberger et al. 1998 **AMCG**	OBS (n=157) LDI (n=154)	n.r.	n=5 (3%)	n.r.	n.r.	n.r.	n.r.	n.r.

Study	**Treatment groups** (number of patients)	**Treatment related deaths**	**Discontinuation because of toxicity**	Number of patients with **Grade 3 or 4 Toxicities** (%)	**Fatigue** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Depression** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Neutropenia** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)	**Hepatotoxicity** Number of patients with any Grade Tox. (%) / with Grade 3 or 4 Tox. (%)
Kirkwood et al. 1996 **E 1684**	OBS (n=137) HDI (n=143)	n=2 (lethal hepatic toxicity)	26%	67%	n.r. n=140 (100%) / n=69 (48%)* *constitutional symptoms including fatigue	n.r. n=118 (83%) / n=40 (28%)* *neurologic	n.r.	n.r. n=89 (62%) / n=20 (14%)
Creagan et al. 1995 **NCCTG**	OBS (n=131) HDI (n=131)	n.r.	n.r.	n.r.	n.r. n=117 (89%) / n=26 (20%)	n.r.	n.r.	n.r.

6.7.9. Metaanalysen

Eine Metaanalyse wurde mit 13 Studien (14 Vergleiche) unter Einschluss der in bisherigen Metaanalysen nicht erfassten Studie von Hansson et al. 2011 wurden nach den definierten Ein- und Ausschlusskriterien durchgeführt (kein Einschluss bei fehlendem Beobachtungsarm, damit Ausschluss E1694 und E2696: Vergleichsarm jew. Vakzine).

Aufgrund der Heterogenität der Studien keine Metaanalyse über alle 14 Vergleiche, sondern getrennt nach verschiedenen Dosis Schemata:

- Hochdosis Interferon alpha
- Mittlere Dosis Interferon alpha
- Niedrigdosis Interferon alpha

Limitation: unterschiedliche Follow up Perioden innerhalb der Studien

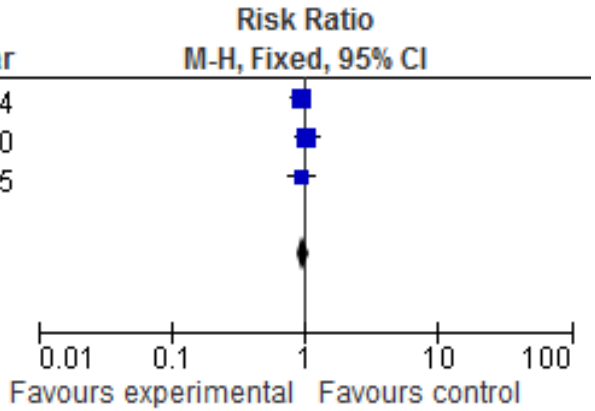
Auswertung durch Review Manager 5.1, The Cochrane Collaboration

Abbildung 1: Hochdosis Interferon alpha versus Beobachtung

Outcome: Mortalität Risk Ratio: 0.98 CI [0.87, 1.10] n.s

	IFN		OBS			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
E1684 Upd, Kirkwood	93	146	95	140	36.9%	0.94 [0.79, 1.11]	2004
E1690 HDI, Kirkwood	98	215	93	212	35.7%	1.04 [0.84, 1.28]	2000
NCCTG, Creagan	68	131	72	131	27.4%	0.94 [0.75, 1.18]	1995
Total (95% CI)		**492**		**483**	**100.0%**	**0.98 [0.87, 1.10]**	
Total events	259		260				

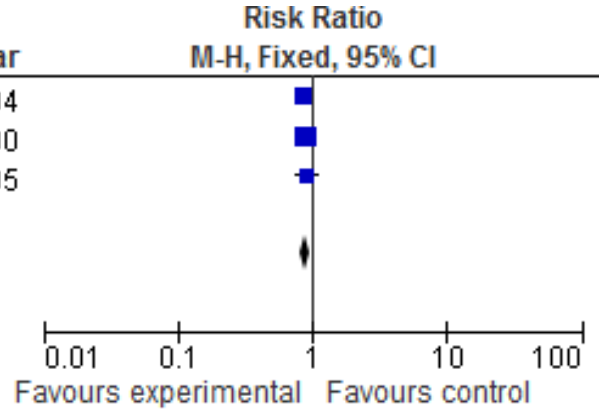
Heterogeneity: Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)



Outcome: Progression Risk Ratio: 0.88 CI [0.80, 0.97] **sign.**

	IFN		OBS			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
E1684 Upd, Kirkwood	95	146	106	140	33.7%	0.86 [0.74, 1.00]	2004
E1690 HDI, Kirkwood	114	215	127	212	39.8%	0.89 [0.75, 1.05]	2000
NCCTG, Creagan	77	131	85	131	26.5%	0.91 [0.75, 1.10]	1995
Total (95% CI)		**492**		**483**	**100.0%**	**0.88 [0.80, 0.97]**	
Total events	286		318				

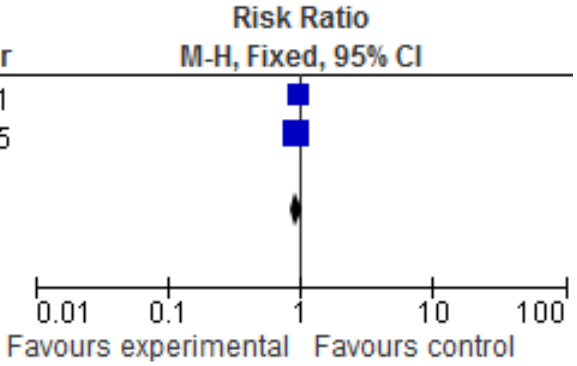
Heterogeneity: Chi² = 0.19, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.51 (P = 0.01)



Outcome: Mortalität Risk Ratio: 0.94 CI [0.85, 1.03] n.s

Study or Subgroup	IFN Events	IFN Total	OBS Events	OBS Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
NordicTrial, Hansson	285	571	148	284	45.9%	0.96 [0.83, 1.10]	2011
EORTC 18952, Eggermont	535	1109	146	279	54.1%	0.92 [0.81, 1.05]	2005
Total (95% CI)		**1680**		**563**	**100.0%**	**0.94 [0.85, 1.03]**	
Total events	820		294				

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)



Outcome: Progression Risk Ratio: 0.93 CI [0.86, 1.00] **sign.**

Study or Subgroup	IFN Events	IFN Total	OBS Events	OBS Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
NordicTrial, Hansson	338	571	183	284	45.5%	0.92 [0.82, 1.03]	2011
EORTC 18952, Eggermont	679	1109	183	279	54.5%	0.93 [0.85, 1.03]	2005
Total (95% CI)		**1680**		**563**	**100.0%**	**0.93 [0.86, 1.00]**	
Total events	1017		366				

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)

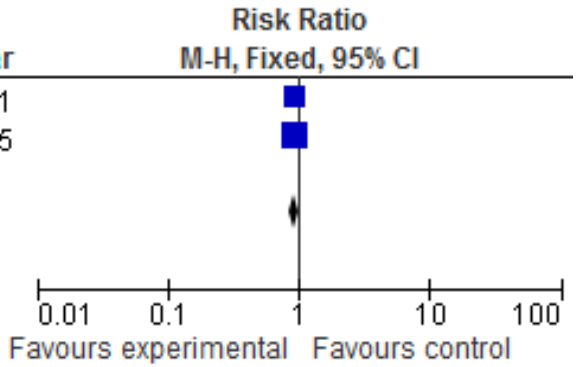
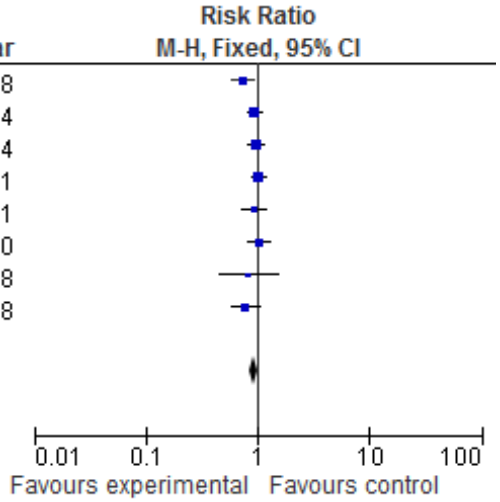


Abbildung 3: Niedrigdosis Interferon alpha versus Beobachtung

Outcome: Mortalität Risk Ratio: 0.93 CI [0.86, 1.00] **sign.**

	IFN		OBS			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
DeCOG, Garbe	65	148	88	148	11.6%	0.74 [0.59, 0.93]	2008
EORTC 11887, Kleeberg	137	240	148	244	19.4%	0.94 [0.81, 1.09]	2004
UKCCCR, Hancock	151	338	156	336	20.7%	0.96 [0.82, 1.13]	2004
WHO, Cascinellil	146	225	138	219	18.5%	1.03 [0.90, 1.18]	2001
SMG, Cameron	31	46	36	49	4.6%	0.92 [0.71, 1.19]	2001
E1690 LDI, Kirkwood	96	215	93	212	12.4%	1.02 [0.82, 1.26]	2000
AMCG, Pehamberger	17	154	21	157	2.8%	0.83 [0.45, 1.50]	1998
FCGM, Grob	59	244	76	245	10.0%	0.78 [0.58, 1.04]	1998
Total (95% CI)		**1610**		**1610**	**100.0%**	**0.93 [0.86, 1.00]**	
Total events	702		756				

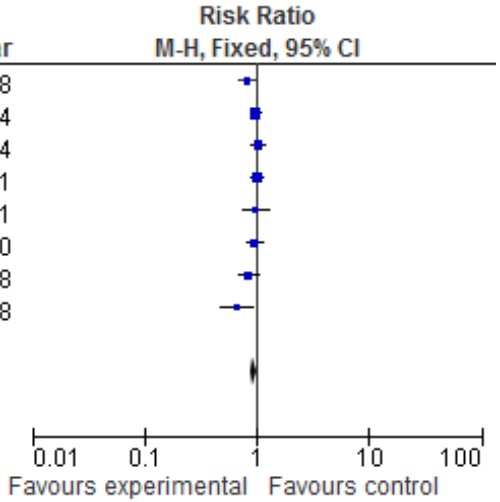
Heterogeneity: Chi² = 8.56, df = 7 (P = 0.29); I² = 18%
Test for overall effect: Z = 2.05 (P = 0.04)



Outcome:. Progression Risk Ratio: 0.93 CI [0.88, 0.99] **sign.**

	IFN		OBS			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
DeCOG, Garbe	84	148	102	148	10.5%	0.82 [0.69, 0.98]	2008
UKCCCR, Hancock	211	338	215	336	22.2%	0.98 [0.87, 1.09]	2004
EORTC 11887, Kleeberg	159	240	158	244	16.1%	1.02 [0.90, 1.16]	2004
WHO, Cascinellil	162	225	158	219	16.5%	1.00 [0.89, 1.12]	2001
SMG, Cameron	32	46	35	49	3.5%	0.97 [0.75, 1.26]	2001
E1690 LDI, Kirkwood	122	215	127	212	13.2%	0.95 [0.81, 1.11]	2000
FCGM, Grob	100	244	119	245	12.2%	0.84 [0.69, 1.03]	1998
AMCG, Pehamberger	37	154	57	157	5.8%	0.66 [0.47, 0.94]	1998
Total (95% CI)		**1610**		**1610**	**100.0%**	**0.93 [0.88, 0.99]**	
Total events	907		971				

Heterogeneity: Chi² = 10.58, df = 7 (P = 0.16); I² = 34%
Test for overall effect: Z = 2.40 (P = 0.02)



6.7.10. Literatur

Agarwala SS, Lee SJ, Flaherty LE, et al. Randomized phase III trial of high-dose interferon alfa-2b (HDI) for 4 weeks induction only in patients with intermediate- and high-risk melanoma (Intergroup trial E 1697) . ASCO Meeting Abstracts 2011;29:8505
Cameron DA, Cornbleet MC, Mackie RM, et al. Adjuvant interferon alpha 2b in high risk melanoma - the Scottish study. Br J Cancer 2001;84:1146-1149
Cascinelli N, Bufalino R, Morabito A, et al. Results of adjuvant interferon study in WHO melanoma programme. Lancet 1994;343:913-914
Creagan ET, Dalton RJ, Ahmann DL, et al. Randomized, surgical adjuvant clinical trial of recombinant interferon alfa-2a in selected patients with malignant melanoma. J Clin Oncol 1995;13:2776-2783
Eggermont AM, Suciu S, MacKie R, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomised controlled trial. Lancet 2005;366:1189-1196
Eggermont AM, Suciu S, Santinami M, et al. EORTC 18991 phase III trial: Long-term adjuvant pegylated interferon-{alpha}2b (PEG-IFN) versus observation in resected stage III melanoma: Long-term results at 7.6-years follow-up. ASCO Meeting Abstracts 2011;29:8506b
Eggermont AM, Suciu S, Santinami M, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. Lancet 2008;372:117-126
Eggermont AM, Suciu S, Testori A, et al. Ulceration and stage are predictive of interferon efficacy in melanoma: Results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. Eur J Cancer 2012;48:218-225
Garbe C, Eigentler TK, Keilholz U, et al. Systematic review of medical treatment in melanoma: current status and future prospects. Oncologist 2011;16:5-24
Garbe C, Radny P, Linse R, et al. Adjuvant low-dose interferon {alpha}2a with or without dacarbazine compared with surgery alone: a prospective-randomized phase III DeCOG trial in melanoma patients with regional lymph node metastasis. Ann Oncol 2008;19:1195-1201
Grob JJ, Dreno B, de la Salmoniere P, et al. Randomised trial of interferon alpha-2a as adjuvant therapy in resected primary melanoma thicker than 1.5 mm without clinically detectable node metastases. French Cooperative Group on Melanoma. Lancet 1998;351:1905-1910
Hancock BW, Wheatley K, Harris S, et al. Adjuvant interferon in high-risk melanoma: the AIM HIGH Study--United Kingdom Coordinating Committee on Cancer Research randomized study of adjuvant low-dose extended-duration interferon Alfa-2a in high-risk resected malignant melanoma. J Clin Oncol 2004;22:53-61
Hansson J, Aamdal S, Bastholt L, et al. Two different durations of adjuvant therapy with intermediate-dose interferon alfa-2b in patients with high-risk melanoma (Nordic IFN trial): a randomised phase 3 trial. Lancet Oncol 2011;12:144-152
Kirkwood JM, Ibrahim J, Lawson DH, et al. High-dose interferon alfa-2b does not diminish antibody response to GM2 vaccination in patients with resected melanoma: results of the Multicenter Eastern Cooperative Oncology Group Phase II Trial E2696. J Clin Oncol 2001;19:1430-1436
Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol 2000;18:2444-2458
Kirkwood JM, Ibrahim JG, Sosman JA, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. J Clin Oncol 2001;19:2370-2380
Kirkwood JM, Manola J, Ibrahim J, et al. A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma. Clin Cancer Res 2004;10:1670-1677
Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 1996;14:7-17
Kokoschka EM, Trautinger F, Knobler RM, et al. Long-term adjuvant therapy of high-risk malignant melanoma with interferon alpha 2b. J Invest Dermatol 1990;95:193S-197S
Lens MB, Dawes M. Interferon alfa therapy for malignant melanoma: a systematic review of randomized controlled trials. J Clin Oncol 2002;20:1818-1825
McMasters KM. The Sunbelt Melanoma Trial. Ann Surg Oncol 2001;8:41S-43S
Mocellin S, Pasquali S, Rossi CR, et al. Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis. J Natl Cancer Inst 2010;102:493-501
Pehamberger H, Soyer HP, Steiner A, et al. Adjuvant interferon alfa-2a treatment in resected primary stage II cutaneous melanoma. Austrian Malignant Melanoma Cooperative Group. J Clin Oncol 1998;16:1425-1429
Petrella T, Verma S, Spithoff K, et al. Adjuvant Interferon Therapy for Patients at High Risk for Recurrent Melanoma: An Updated Systematic Review and Practice Guideline. Clin Oncol (R Coll Radiol) 2012
Pirard D, Heenen M, Melot C, et al. Interferon alpha as adjuvant postsurgical treatment of melanoma: a meta-analysis. Dermatology 2004;208:43-48
Rudolf Z. Adjuvant treatment of malignant melanoma with interferon after radical surgery - Part II. Effect of recombinant alpha interferon. Radiology and Oncology 1994;28:183-187
Rusciani L, Petraglia S, Alotto M, et al. Postsurgical adjuvant therapy for melanoma. Evaluation of a 3-year randomized trial with recombinant interferon-alpha after 3 and 5 years of follow-up. Cancer 1997;79:2354-2360
Verma S, Quirt I, McCready D, et al. Systematic review of systemic adjuvant therapy for patients at high risk for recurrent melanoma. Cancer 2006;106:1431-1442
Wheatley K, Ives N, Hancock B, et al. Does adjuvant interferon-alpha for high-risk melanoma provide a worthwhile benefit? A meta-analysis of the randomised trials. Cancer Treat Rev 2003;29:241-252

6.7.11. Aktualisierungsrecherche 2016

6.7.11.1. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
Suche			
Medline	(melanoma[tiab] OR "melanoma"[MeSH Terms]) AND (Interferon-alpha[tiab] OR "interferon-alpha"[MeSH Terms] OR "Interferon alpha"[tiab] OR IFN-alpha[tiab] OR IFN-alpha[tiab] OR interferon-alpha-2b[tiab] OR interferon-alpha-2a[tiab] OR multiferon[tiab]) AND adjuvant[tiab] AND ("2011/04/13"[PDAT] : "2016/11/16"[PDAT])	16.11.2016	116 (11)
Cochrane Library	(melanoma and interferon alpha and adjuvant).mp.	16.11.2016	4 (1)

6.7.11.2. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	119
Einschlusskriterien	system. Reviews, klinische Studien zu adjuvanter Therapie mit Interferon alpha bei Patienten mit Rezidivrisiko, tumorfreies Stadium I-III Intervention: IFN alpha Monotherapie, Vergleichsgruppe: Beobachtung Sprachen: e,dt
Ausschlusskriterien	Nicht systematische Reviews Kohorten Studien, Case Reports Kombinationstherapien Vergleichsgruppe Chemotherapie, andere Systemtherapien Therapiestudien mit Interferon alpha im Stadium IV Kollektive mit gemischten Tumorentitiäten

Anzahl ausgewählter Studien	**12**

6.7.11.3. Evidenztabellen

Referenz	Ziele	Design	Untersuchte Population	untersuchte Endpunkte	Ergebnisse	Bemerkungen	Evidenzklasse (level of evidence/Oxford)
Eggermont et al, 2012	To determine whether the recurrence free survival benefit is maintained at this time point and to identify factors predictive of efficacy with adjuvant PEG-IFN-alpha-2b therapy.	Phase III, RCT, 1:1 randomization to: PEG-IFN-α-2b (8-week induction phase, 6μg/kg per week subcutaneously (SC), with 3μg/kg per week SC for the maintenance phase (intended treatment duration of up to 5 years) N=627 or Observation N=629	Patients age 18 to 70 years with histologically documented stage III melanoma (TxN1-2M0) after complete regional lymphadenectomy.	Recurrence-free survival (RFS; primary end point) Overall survival (OS) Distant metastasis-free survival (DMFS)	At 7.6 years median follow-up, 384 recurrences or deaths had occurred with PEG-IFN-α-2b vs 406 in the observation group (hazard ratio [HR], 0.87; 95%CI, 0.76 to 1.00; P = .055); 7-year RFS rate was 39.1% vs 34.6%. There was no difference in OS (P = .57). In stage III-N1 ulcerated melanoma, RFS (HR, 0.72; 99% CI, 0.46 to 1.13; P = .06), DMFS (HR, 0.65; 99%CI, 0.41 to 1.04; P = .02), and OS (HR, 0.59; 99% CI, 0.35 to 0.97; P = .006) were		1B Jaded-Score: 3 Supported by Schering-Plough Research Institute and Fonds Cancer (FOCA) in Belgium. Medical writing assistance was supported by Merck.

					prolonged with PEG-IFN-α-2b.		
Patel and Walko, 2012	To review the currently available literature on peginterferon alfa-2b (pegIFN [Sylatron]), including its role in therapy and toxicity for adjuvant treatment of locally advanced melanoma.	Systematic review (literature search was performed of PubMed and the American Society of Clinical Oncology abstracts from 1976 to February 2012, using the primary search terms peginterferon alfa-2b, interferon, Sylatron, and melanoma)	Patients with melanoma who remain at high risk for relapse following surgery	Not defined	Although the safety profile remains similar between the pegylated and non-pegylated forms, once weekly administration is feasible secondary to an extended serum half-life and may have improved convenience for the patient.	Deutliche methodische Mängel, so wird eine systematische Suche suggeriert, jedoch keine Trefferanzahl angegeben.	4
Ascierto et al, 2013	To review the recent evidence and make recommendations to European physicians regarding the adjuvant treatment of patients with	Systematic review (Relevant clinical trials of adjuvant therapy in melanoma were identified by searching PubMed using appropriate search terms;	Patients with resected melanoma at high risk of recurrence.	Not defined	Recent data largely confirm DFS and OS benefits, but optimal dose/duration is not clarified. The data suggest greater responses in patients with stage III micro-metastatic versus macro-metastatic	Methodische Mängel, so ist eine systematische Suche, wohl durchgeführt wordem, der Suchstring sowie die Trefferanzahl werden jedoch nicht angeben.	4 Editorial assistance was provided by Helen Varley, PhD, UBC-Envision Group, Horsham, UK, and was supported by Merck & Co. Inc.

	high-risk melanoma	relevant abstracts presented at the American Society of Clinical Oncology 2011 annual meeting were identified by searching the ASCO abstract database online.)			disease, and ulceration may also predict greater sensitivity to therapy, although further investigation is needed. Presently, IFN□ and PegIFN□2b remain valid adjuvant therapies following resection of high-risk melanoma; the most appropriate treatment regimen should be determined on an individual patient basis according to patient lifestyle and approach, potential for toxicity, and the available clinical evidence		
Grob et al, 2013	To compare the efficacy and safety of prolonged adjuvant low-dose Peg-IFN therapy (36 months) and standard European low-dose IFN	Phase III, RCT, 1:1 randomization to: Peg-IFN 100 μg once-weekly subcutaneously (SC) for 36 months N=443 or	Patients with resected melanoma ≥1.5 mm thick and without clinically detectable node metastases	Disease-free survival (DFS) Distant-metastasis free survival (DMFS) Overall Survival	There were no statistical differences between the two arms for the primary outcome of DFS (hazard ratio [HR 0.91, 95% confidence interval [CI] 0.73–1.15) or the secondary		1b Jaded-Score: 3 Sponsored by the University Hospital Bordeaux, France. Partial financial support was provided by Merck & Co. Inc. (formerly

	therapy (18 months) in an intermediate-risk melanoma population (Breslow tumour thickness ≥1.5 mm without clinically detectable nodes).	IFN 3 MU SC three times weekly for 18 months N=453			outcomes of DMFS (HR 1.02, 95% CI 0.80–1.32) and OS (HR 1.09, 95% CI 0.82–1.45).		Schering-Plough Corp.).
Mocellin et al., 2013	To assess the disease-free survival and overall survival effects of interferon alpha as adjuvant treatment for people with high-risk cutaneous melanoma	Systematic Review and Meta-Analysis of 17 RCTs Queried databases up to August 2012: the Cochrane Skin Group Specialised Register, CENTRAL in The Cochrane Library (2012, issue 8), MEDLINE (from 2005), EMBASE (from 2010), AMED (from 1985), and LILACS (from 1982). We also	People with regional lymph node metastasis (American Joint Committee on Cancer TNM stage III) undergoing radical lymph node dissection, or people without nodal disease but with primary tumour thickness greater than 1 mm (AJCC TNM stage II).	Disease free survival Overall Survival	Adjuvant interferon was associated with significantly improved disease free survival (HR (hazard ratio) = 0.83; 95% CI (confidence interval) 0.78-0.87, P< 0.00001 ; 17 RCTs evaluable) and overall survival (HR = 0.91; 95% CI 0.85-0.97; P=0.003, 15 RCTs evaluable).		IA

		searched trials databases in 2011, and proceedings of the ASCO annual meeting from 2000 to 2011. We checked the reference lists of selected articles for further references to relevant trials. Only randomised controlled trials (RCTs) comparing interferon alpha to observation (or any other treatment) for the postoperative (adjuvant) treatment of patients with high-risk skin melanoma.					
Flaherty et al, 2014	To determine whether a short course of biochemotherap	Phase III, RCT, 1:1 randomization to:	Patients with histologically proven melanoma of	Recurrence free survival Overall survival	Biochemotherapy improved RFS (hazard ratio [HR], 0.75; 95% CI, 0.58 to 0.97;		1b Jaded-Score : 3

	y would be more effective than high-dose interferon	Arm A: High-dose IFN alfa-2b (IFN-□-2b) 20MU/m2 per day intravenously (IV) 5 days per week for 4 weeks followed by 10MU/m2 subcutaneously three times per week for 48 weeks. N= 203 OR Arm B: Biochemotherapy consisting of cisplatin 20 mg/m2 administered as a 30-minute infusion on days 1 through 4, vinblastine 1.2 mg/m2 IV push immediately after cisplatin on days 1-4, dacarbazine 800	cutaneous origin or from an unknown primary (mucosal and uveal primaries were excluded) and were stage IIIA-N2a through stage IIIC-N3		P=.015), with a median RFS of 4.0 years (95% CI, 1.9 years to not reached [NR]) versus 1.9 years for HDI (95% CI, 1.2 to 2.8 years) and a 5-year RFS of 48% versus 39%. Median OS was not different (HR, 0.98; 95% CI, 0.74 to 1.31; P=.55), with a median OS of 9.9 years (95% CI, 4.62 years to NR) for biochemotherapy versus 6.7 years (95% CI, 4.5 years to NR) for HDI and a 5-year OS of 56% for both arms.		

		mg/m2 administered IV over 1 hour on day 1 only after vinblastine, IL-2 at 9MU/m2 administered as a 96-hour continuous IV infusion on days 1-4, and IFN-□-2b at 5 MU/m2 administered on days 1-5; the dosing regimen continued on an outpatient basis on days 8, 10, and 12. Treatment was repeated every 21 days for a total of three cycles. N= 199					
Mohr et al., 2015	To evaluate the efficacy, safety, tolerability, and quality of life (QoL) in patients receiving intravenous,	Phase III, RCT, 1:1 randomization to: IFN-α-2b 20MIU/m2 IV similar to	Patients with histologically proven cutaneous malignant melanoma in patients with resected	Distant metastases-free survival Overall Survival Relapse-free survival	No significant differences for distant metastasis-free survival (hazard ratio [HR], 1.21; P=.12) or overall survival (HR, 1.01; P=.85).		1b Jaded Score: 3

	intermittent high-dose interferon alfa-2b (IFN-α-2b [iHDI]) compared with standard high-dose IFN-α-2b (HDI)	standard HDI for the first 4 weeks. After this cycle of IV IFN-α-2b treatment, patients received no continuing IFN-α-2b therapy for 12 weeks. The second and third iHDI cycles, which were identical to the first cycle, took place from weeks 17-20, and weeks 33-36, respectively. N=311 OR IFN-□-2b 20 MIU/m2 IV from days 1 to 5, days 8 to 12, days 15 to 19, and days 22 to 26. Starting from day 29 in week 5, patients received IFN-α-2b 10 MIU/m2	micrometatasis or macrometastasis in stage IIIA, IIIB, or IIIC; complete R0 resection no more than 56 days before inclusion; age 18 to 70 years;	Quality of Life	In contrast, the difference for relapse-free survival was significant (HR, 1.27; P=.03), favoring standard HDI. Early termination of treatment because of adverse events or QoL occurred significantly more often with HDI than with iHDI (26.0% vs. 14.8%; P=.001).		

		SC 3 times per week for 48 weeks. N=316					
Eggermont et al., 2016	To report on the long-term outcome of the EORTC 18952 adjuvant interferon (IFN) and identify key predictive factors for outcome.	Phase III, RCT, 2:2:1 randomization to: IFN-α-2b 10 MU iv, 5 times/week for 4 weeks followed by 12 months IFN-α-2b at 10 MU sc, 3 times/week N=553 OR IFN-α-2b 10 MU iv, 5 times/week for 4 weeks followed by 24 months IFN-α-2b at 5 MU sc. 3 times/week N=556 OR versus IFN-α-2b 10 MU iv, 5	Patients 18-70 years of age with cutaneous melanoma stage IIB (T4N0M0) IIIA/B/C (anyTN1-2M0), with either microscopic involvement (N1) or palpable nodal involvement (N2) of regional lymph nodes, entered the study after adequate surgery of the primary tumour and complete lymph node dissection (stage III).	Relapse-free survival (RFS) Distant metastasis-free interval (DMFI) Distant metastasis-free survival (DMFS) Overall survival (OS)	RFS - 13-month IFN vs Obs : 0.94 (99%CI: 0.75-1.17), p=0.46 RFS - 25-month IFN vs Obs : 0.84 (99%CI: 0.67-1.06), p=0.06 RFS - 13-month IFN vs 25-month IFN: 0.94 vs 0.84, p=0.06 DMFI 0.95 vs 0.82, p=0.027 (13 vs. 25 month-IFN) DMFS - 13-month IFN vs Obs : 0.95 (99%CI: 0.75-1.20),p= 0.57 DMFS - 25-month IFN vs Obs : 0.84 (99%CI: 0.66-1.07), p=0.07 DMFS - 13-month IFN vs 25-month IFN: 0.94 vs 0.84, p=0.07 OS - 13-month IFN vs	Medianes Follow-up: 11 Jahre Prognostische Faktoren (Ulceration, Mikrometastasen) basieren auf Subgruppenanalysen	1b Jaded-Score: 3 Publication was supported by Fonds Cancer (FOCA) in Belgium. The trial was performed with the financial support of Schering Plough Research International that also provided the study drug at no cost.

		times/week for 4 weeks followed by observation N=279			Obs : 0.95 (99%CI: 0.75-1.21),p= 0.58 OS - 25-month IFN vs Obs : 0.84 (99%CI: 0.66-1.08), p=0.08 OS - 13-month IFN vs 25-month IFN: 0.95 vs 0.84, p=0.08 The impact of treatment was greatest in the ulceration group, whereas in patients with non-ulcerated primaries the impact was null (HR=1.0). In patients with ulcerated melanoma the HR for IFN 13 months versus 25 months versus observation were for: RFS 0.82 (p=0.16) vs 0.61 (p=0.0008); DMFS 0.76 (p=0.06) versus 0.57 (p=0.0003); OS 0.80 (p=0.13) versus 0.59 (p=0.0007). In stage IIB/III-N1 (microscopic nodal involvement		

					only) patients with ulcerated melanoma the HR estimates were for: RFS 0.85 vs 0.62; DMFS 0.80 vs 0.56; OS 0.77 vs 0.54.		
Eigentler et al, 2016	To examine whether pegylated IFN-α-2a (PEG-IFN) is superior to Interferon- α -2a (IFN) in high-risk melanoma patients with regard to distant metastasis-free survival (DMFS), disease-free survival and overall survival.	Phase III, RCT, 1 : 1 randomization to: Arm A : PEG-IFN 180 µg sc. once weekly for 24 months. N= 451 OR Arm B : IFN 3 MIU s.c. 3 times a week for 24 months N= 458	Patients were aged ≥18 and ≤75 years with a confirmed diagnosis of a cutaneous melanoma stage IIa (T3a)–stage IIIb according to the 6th edition of the American Joint Committee on Cancer classification. Lymph node staging was carried out either per sentinel lymph node biopsy or elective lymph node dissection.	DMFS DFS OS	5-year DMFS : PEG-IFN 61.0% vs IFN 67.3%; hazard ratio (HR) 1.16, P=0.21 5-year DFS : PEG-IFN 57.3% vs IFN 60.9%; HR 1.09, P=0.40 5-year OS : PEG-IFN 73.2% vs IFN 75.2%; HR 1.05, P=0.70		1B Jaded Score : 3 Funded by the University Hospital Tübingen with a grant from Hoffmann-La Roche AG, Germany

Malczewski et al., 2016	To assess whether a shorter duration of high-dose interferon (HDI) treatment was noninferior to longer treatment in terms of relapse-free survival, and To explore patient and tumor characteristics that might impact on outcome and interact with the effects of the drug.	Individual patient data random effects meta-analysis N=716 (stage IIB–IIIC patients out of 3 clinical trials)	All patients were randomized either to IFN-α-2b 15–20 MIU/m2 IV daily 5 days per week for 4 weeks (IV) or to the same regimen followed by IFN-α-2b 9–10 MIU/m2 administered three times per week for 48 weeks (IV and SC)	RFS Tumor and patient characteristics that impacted on outcomes	Non-inferiority of IV compared to IV and SC could not be conferred for RFS (hazard ratio [HR] 1.16, 95% Confidence interval [CI] 0.89–1.52; noninferior P=0.17). Stage (P<0.0001), site (acral vs. other, P<0.0001), and Breslow thickness (P=0.02) were significant predictors of RFS. The HR for death was 1.13 for IV compared to IV and SC, (95% CI 0.91–1.39). Stage (P<0.0001) and Breslow thickness (P=0.001) were significant independent predictors of OS.		IA
McMasters et al, 2016	To evaluate the role of high-dose interferon alfa-2b therapy (HDI) or	2 Cohort, phase III, RCT, 1:1 randomization to:	Patients aged 18 to 70 years with primary cutaneous melanoma ≥	Disease free survival (DFS) Overall survival(OS)	In cohort A, intention-to-treat analysis, there were no significant differences in DFS		1B Jaded-Score : 3

	completion lymph node dissection (CLND) for patients with melanoma staged by sentinel lymph node (SLN) biopsy.	Cohort A (Patients with a single tumor-positive lymph node after SLN biopsy underwent CLND) IFN-a-2b 20 MU/m2 iv per day, 5 days per week 3 4 weeks, followed by 10 MU/m2 SC three times per week for 48 weeks. N=106 OR Observation N=112 Cohort B (Patients with a tumor-positive lymph node detected by reverse transcriptase polymerase chain reaction only after SLN	1.0 mm Breslow thickness that underwent SLN biopsy.		(hazard ratio,0.82; P=.45) or OS (hazard ratio, 1.10; P=.68) for patients randomly assigned to HDI versus observation. In cohort B, intention-to-treat analysis, there were no significant differences in overall DFS (P=.069) or OS (P=.77) across the three randomized treatment arms. Similarly, efficacy analysis (excluding patients who did not receive the assigned treatment) did not demonstrate significant differences in DFS or OS in cohort A or cohort B.		

		biopsy) Observation N=180 OR CLND N=192 OR CLND followed by IFN-a-2b 20 MU/m2 iv per day, 5 days per week 3 4 weeks, followed by 10 MU/m2 SC three times per week for 48 weeks. N=184					

6.7.11.4. Literatur

Eggermont, A.M., et al., Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. J Clin Oncol, 2012. 30(31): p. 3810-8.
Patel, J.N. and C.M. Walko, Sylatron: a pegylated interferon for use in melanoma. Ann Pharmacother, 2012. 46(6): p. 830-8.
Ascierto, P.A., et al., Adjuvant interferon alfa in malignant melanoma: an interdisciplinary and multinational expert review. Crit Rev Oncol Hematol, 2013. 85(2): p. 149-61.
Grob, J.J., et al., Adjuvant therapy with pegylated interferon alfa-2b (36 months) versus low-dose interferon alfa-2b (18 months) in melanoma patients without macrometastatic nodes: n open-label, randomised, phase 3 European Association for Dermato-Oncology (EADO) study. Eur J Cancer, 2013. 49(1): p. 166-74.
Mocellin, S., et al., Interferon alpha for the adjuvant treatment of cutaneous melanoma. Cochrane Database Syst Rev, 2013(6): p. Cd008955.
Flaherty, L.E., et al., Southwest Oncology Group S0008: a phase III trial of high-dose interferon Alfa-2b versus cisplatin, vinblastine, and dacarbazine, plus interleukin-2 and interferon in patients with high-risk melanoma--an intergroup study of cancer and leukemia Group B, Children's Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. J Clin Oncol, 2014. 32(33): p. 3771-8.
Mohr, P., et al., Intermittent High-Dose Intravenous Interferon Alfa-2b for Adjuvant Treatment of Stage III Melanoma: Final Analysis of a Randomized Phase III Dermatologic Cooperative Oncology Group Trial. J Clin Oncol, 2015. 33(34): p. 4077-84.
Eggermont, A.M., et al., Long term follow up of the EORTC 18952 trial of adjuvant therapy in resected stage IIB-III cutaneous melanoma patients comparing intermediate doses of Interferon-alpha-2b (IFN) with observation: Ulceration of primary is key determinant for IFN-sensitivity. Eur J Cancer, 2016. 55: p. 111-21.
Eigentler, T.K., et al., Adjuvant treatment with pegylated interferon alpha-2a versus low-dose interferon alpha-2a in patients with high-risk melanoma: a randomized phase III DeCOG trial. Ann Oncol, 2016. 27(8): p. 1625-32.
McMasters, K.M., et al., Final Results of the Sunbelt Melanoma Trial: A Multi-Institutional Prospective Randomized Phase III Study Evaluating the Role of Adjuvant High-Dose Interferon Alfa-2b and Completion Lymph Node Dissection for Patients Staged by Sentinel Lymph Node Biopsy. J Clin Oncol, 2016. 34(10): p. 1079-86.

6.8. Frage V.9. Alleinige Nachsorge – De novo Recherche

Frage V.9. Ist Nachsorge allein eine akzeptable Strategie bei erhöhter Rezidivrate?

Informationen zu dieser Schlüsselfrage sind in den Evidentatbellen zur adjuvanten Therapie mit Interferon-α enthalten, da die meisetn Studien eine reine Nachsorge als Kontrollarm etabliert hatten.

7. AG Medikamentöse Therapie bei Metastasierung

7.1. Frage VI.1. Lokale medikamentöse Therapie Intransitmetastasen

Frage V.1. Welche therapeutischen (außer operativen) Maßnahmen sind bei Satelliten- und Intransit-Metastasen effektiv?

7.1.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients with locoregional metastases	Local therapies (except surgery, radiotherapy, extremity perfusion)	Standard of care	Efficacy

Suchwörter				
Stichwort	melanoma	Satellite Metastasis In-Transit Metastasis	therapy	interleukin-2, IL-2; rose bengal; imiquimod; DNCB, dinitrochlorobenzene; DPCP, diphencyprone; interferon beta, interferon-ß; electrochemotherapy
Synonyme		Local recurrence Locoregional spread	treatment	
Ober-/Unterbegriffe				

Mesh Term	melanoma	Neoplasm Recurrence, Local	therapeutics	

7.1.2. Datenbanken, Suchstrategien, Trefferzahlen

7.1.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("melanoma"[tiab] OR "melanoma"[MeSH]) AND ("Satellite metastases"[tiab] OR "Satellite metastasis"[tiab] OR "In-transit metastases"[tiab] OR "In-transit metastasis"[tiab] OR "Intransit metastases"[tiab] OR "Intransit metastasis"[tiab] OR "Local recurrence"[tiab] OR "Locoregional recurrence"[tiab] OR "Locoregional spread"[tiab] OR "Locoregional metastases"[tiab] OR "Locoregional metastasis"[tiab] OR intratumo*[tiab] OR "intralesional"[tiab] OR "Neoplasm Recurrence, Local"[MeSH]) AND ("therapy"[tiab] OR "treatment"[tiab] OR "therapeutics"[MeSH] OR "interleukin-2"[tiab] OR "IL-2"[tiab] OR "rose bengal"[tiab] OR "imiquimod"[tiab] OR "dinitrochlorobenzene"[tiab] OR „DNCB“[tiab] OR“diphencyprone“[tiab] OR "DPCP"[tiab] OR "interferon beta"[tiab] OR "interferon-ß“[tiab] OR "electrochemotherapy"[tiab])	16.12.10	2322
Embase	(melanoma and ("satellite metast*" or "In-transit metast*" or "Intransit metast*" or "local recurrence" or "locoregional recurrence" or "locoregional spread" or "locoregional metast*" or "locoregional metast*") and (therapy or treatment)).ti,ab.	12.10.10	579
Medline - Erweiterung der Suchstrategie	("melanoma"[tiab] OR "melanoma"[MeSH]) AND ("Satellite metastases"[tiab] OR "Satellite metastasis"[tiab] OR "In-transit metastases"[tiab] OR "In-transit metastasis"[tiab] OR "Intransit metastases"[tiab] OR "Intransit metastasis"[tiab]	06.04.11	2467

Datenbank	Suchstrategie	Datum	Treffer
	OR "Local recurrence"[tiab] OR "Locoregional recurrence"[tiab] OR "Locoregional spread"[tiab] OR "Locoregional metastases"[tiab] OR "Locoregional metastasis"[tiab] OR intratumo*[tiab] OR "intralesional"[tiab] OR "Neoplasm Recurrence, Local"[MeSH] OR "cutaneous metastases" OR "skin metastases" OR "cutaneous melanoma metastases" OR "skin melanoma metastases") AND ("therapy"[tiab] OR "treatment"[tiab] OR "therapeutics"[MeSH] OR "interleukin-2"[tiab] OR "IL-2"[tiab] OR "rose bengal"[tiab] OR "imiquimod"[tiab] OR "dinitrochlorobenzene"[tiab] OR „DNCB“[tiab] OR“diphencyprone“[tiab] OR "DPCP"[tiab] OR "interferon beta"[tiab] OR "interferon-ß“[tiab] OR "electrochemotherapy"[tiab])		
Update Suche			
Medline	s.o.	31.01.12	2586 (3 dazu: Boyd et al. 2011, Florin et al. 2011, Kis et al. 2011)
Cochrane Library	s.o.	31.01.12	13 (0 dazu)
Embase	s.o.	23.01.12	668 (0 dazu)

7.1.2.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	((("melanoma"[tiab] OR "melanoma"[MeSH])AND ("Satellite metastases"[tiab] OR "Satellite	16.09.15	572

Datenbank	Suchstrategie	Datum	Treffer
	metastasis"[tiab]OR "In-transit metastases"[tiab] OR "In-transit metastasis"[tiab]OR "Intransit metastases"[tiab] OR "Intransit metastasis"[tiab]OR "Local recurrence"[tiab] OR "Locoregional recurrence"[tiab]OR "Locoregional spread"[tiab] OR "Locoregional metastases"[tiab]OR "Locoregional metastasis"[tiab] OR intratumo*[tiab] OR "intralesional"[tiab] OR "Neoplasm Recurrence, Local"[MeSH] OR "cutaneous metastases"OR "skin metastases" OR "cutaneous melanoma metastases"OR "skin melanoma metastases")AND ("therapy"[tiab] OR "treatment"[tiab]OR "therapeutics"[MeSH] OR "interleukin-2"[tiab] OR "IL-2"[tiab]OR "rose bengal"[tiab] OR "imiquimod"[tiab] OR "dinitrochlorobenzene"[tiab]OR „DNCB“[tiab] OR“diphencyprone“[tiab] OR "DPCP"[tiab] OR "interferon beta"[tiab] OR "interferon-ß“[tiab] OR "electrochemotherapy"[tiab]))) AND ("2012.01.27"[Date - Publication] : "3000"[Date - Publication])		
Cochrane Library	(melanoma and (“Satellite metastasis” or “ In-transit metastases”)).ti,ab.	16.09.2015	2 (0 dazu)

7.1.2.3. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	((("melanoma"[tiab] OR "melanoma"[MeSH])AND ("Satellite metastases"[tiab] OR "Satellite metastasis"[tiab]OR "In-transit metastases"[tiab] OR "In-transit metastasis"[tiab]OR "Intransit metastases"[tiab] OR "Intransit metastasis"[tiab]OR "Local recurrence"[tiab] OR "Locoregional recurrence"[tiab]OR "Locoregional spread"[tiab] OR "Locoregional metastases"[tiab]OR "Locoregional metastasis"[tiab] OR intratumo*[tiab] OR "intralesional"[tiab] OR "Neoplasm Recurrence, Local"[MeSH] OR "cutaneous metastases"OR "skin metastases" OR "cutaneous melanoma metastases"OR "skin melanoma metastases")AND ("therapy"[tiab] OR "treatment"[tiab]OR "therapeutics"[MeSH] OR "interleukin-2"[tiab] OR "IL-2"[tiab]OR "rose bengal"[tiab] OR "imiquimod"[tiab] OR "dinitrochlorobenzene"[tiab]OR „DNCB“[tiab] OR“diphencyprone“[tiab] OR "DPCP"[tiab] OR "interferon beta"[tiab] OR "interferon-ß“[tiab] OR "electrochemotherapy"[tiab]))) AND ("2016.09.17"[Date -	17.09.16	166

	Publication] : "3000"[Date - Publication])		
Cochrane Library	(melanoma and (“Satellite metastasis” or “In-transit metastases”)).ti,ab.	17.09.2016	4 (0 dazu)

7.1.3. Auswahlkriterien

7.1.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	3267
Einschlusskriterien	Thematische Übereinstimmung (gemeinsame Berichte verschiedener Tumorentitäten wurden ausgeschlossen) Sprachen: e, dt Klinische Studien Bei nicht Vorhandensein von Studien Einschluss von Fallserien ab 3 Patienten
Ausschlusskriterien	Nicht systematische Reviews Case Reports Intratumorale Therapie als Systemtherapie
Anzahl nach Abstractscreening, vorgesehen für Bewertung	63
Anzahl ausgewählter Volltexte	36
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst: Immunmodulation (Interleukin-2, Imiquimod, BCG, Interferon beta, GM-CSF, Interferon gamma, Mycobacterium smegmatis) Ablative Therapien (Elektrochemotherapie, lokale Chemotherapie, Bengal Rosa, Carbon Laser) Contact Sensitizer (Dinitrochlorobenzene, Diphencyprone)	

7.1.3.2. Aktualisierungsrecherche 2015

Auswahl der Literatur	
Gesamttreffer	574
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e, dt Klinische Studien, Phase III Systematische Reviews
Ausschlusskriterien	Nicht systematische Reviews Case Reports Intratumorale Therapie als Systemtherapie
Anzahl ausgewählter Volltexte	5
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst: Immunmodulation (Interleukin-2, Imiquimod, BCG, Interferon beta, GM-CSF, Interferon gamma, Mycobacterium smegmatis) Ablative Therapien (Elektrochemotherapie, lokale Chemotherapie, Bengal Rosa, Carbon Laser) Contact Sensitizer (Dinitrochlorobenzene, Diphencyprone)	

7.1.3.3. Aktualisierungsrecherche 2016

Auswahl der Literatur	
Gesamttreffer	170
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e, dt Klinische Studien, Phase III Systematische Reviews

Ausschlusskriterien	Nicht systematische Reviews Case Reports Intratumorale Therapie als Systemtherapie
Anzahl ausgewählter Volltexte	4
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst: Immunmodulation (Interleukin-2, Imiquimod, BCG, Interferon beta, GM-CSF, Interferon gamma, Mycobacterium smegmatis) Ablative Therapien (Elektrochemotherapie, lokale Chemotherapie, Bengal Rosa, Carbon Laser) Contact Sensitizer (Dinitrochlorobenzene, Diphencyprone)	

7.1.4. Evidenztabelle

7.1.4.1. Primärrecherche 2012

Immunmodulation (Interleukin-2, Imiquimod, Interferon alpha, Interferon beta, Interferon gamma, BCG)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Boyd et al. 2011	To document the response of in-transit metastases to intra-lesional IL-2 injection	Case Series Treatment: IL-2 intralesional biweekly	39 patients with 629 intransit metastases	Response 5 year survival	Patients: CR 51% PR 31% No response 18% Lesions: Responserate 76% Complete responders versus partial responder 80% versus 33% (p= 0.012)	Response was evaluated for patients and for treated lesions separately. Limitations: Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Florin et al. 2011	To treat cutaneous metastases of malignant melanoma in a series of patients with imiquimod and 5-fluorouracil creams	Case Series Treatment: 5-fluorouracil cream in the morning and 5% imiquimod cream at night, 5 days per week, until response	5 patients with 45 intransit metastases	Response	CR = 19 lesions PR = 25 lesions SD = 1 lesion	Lack of control group	4
Weide et al. 2010	To confirm the previous results with intralesional Il-2 in a larger cohort and to identify relevant patient or regimen characteristics associated with response to treatment and with overall survival.	Phase II prospective open label study Treatment was initiated at 3 MIU IL-2 daily, dose escalation 1.5 MIU each treatment day. Schedule: 3 times weekly	51 patients enrolled, 48 patients evaluable with injectable dermal or subcutaneous metastases, Stage III (69%) or Stage IV (31%) no concomitant systemic chemotherapeutic 894 of 917 separately treated metastases (97.5%) were evaluable for local tumor response	Clinical Response Overall Survival Toxicity	Patients: Complete local response 33 patients (69%), (Stage III 82%, Stage IV 40%) Lesions: 78.7% CR rate, 0.7% PR rate, 16.3% stable metastases, and 4.3% progressive lesions. Overall Survival after 2 years: Stage III 77%, Stage IV 53%) Toxicity: only grad 1 and 2 toxicity, (injection site reaction, injection	Response was evaluated for patients and for treated lesions separately. Response for patients applied to local response. Limitations: Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					pain, fever, nausea, fatigue)		
Dehesa et al. 2009	To describe the experience over 2 years with the use of intralesional IL-2 to treat cutaneous metastases of malignant melanoma in 7 patients.	Case Series Treatment: twice weekly, starting with 3 MIU Il-2	7 melanoma patients with satellitosis an cutaneous metastases 244 lesions no other organs involved	Response Toxicity	Lesions: Complete remission 95.9% of treated lesions Partial remission: 3.7% of treated lesions Toxicitiy: few mild side effects (grade 1-2).	Limitations: Case Series, small sample size	4
Fujimura et al. 2009	To report 3 patients who were treated with peritumoral injection of interferon beta	Case Series Treatment: peritumoral interferon beta	3 melanoma patients Stage IV M1a	Reponse	Target lesion: 1 CR, 2 PR	Limitations: Case Series, small sample size	4
Green et al. 2006	To investigate the combination of topical imiquimod and intralesional IL-2, to treat a small cohort of patients with accessible melanoma metastases	Phase I/II prospective open label study Treatment: after 4 weeks of 5% imiquimod cream daily, start of IL-2 intralesional or subcutaneously in	13 patients, Stage III or IV with cutaneous and/or subcutaneous lesions 182 lesions	Response	Lesions: CR: 74 lesions (40,7%) PR: 18 lesions (9,9%) SD: 53 lesions (29,1%) PD: 33 lesions (18,1%) 4 lesions were not	Regressed lesions with remained pigmentation were classified as PR (possible explanation for low CR rates compared to other studies) Limitations: heterogenous	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	resistant to other treatments	addtion to imiquimod cream			assessable (2,2%)	treatment schedules	
Khorana et al. 2003	To determine the safety and tolerability of intratumoral injection with adeno-IFN-g, and to determine the maximum tolerated dose	Phase I single-center dose-escalation study Treatment: 4 successive dose levels: 107 infectious units (iu) (n=3), 108 iu (n=3), 109 iu (n=3), and 1010 iu (n=2) per injection per week for 3 weeks.	11 patients with histologically confirmed locally recurrent or metastatic malignant melanoma	Safety Toxicity Response	No treatment related death, no grade 4 or dose-limiting toxicities Most frequently observed toxicitiesgrade 1 pain and/or redness at the injected site in 8/11 (72%) patients, and grade 1 fatigue in 5/11 (45%) patients. Local response: 5 of 11 patients: minor decrease in size (<25%) of the injected lesion Distant response: SD: 1 of 11 patients PD: 10 of 11 patients	Limitations: Lack of control group	4
Paul et al. 2003	To examine the effect of	Case Series	20 patients with inoperable	Response	17 patients evaluable	Limitations: Lack of control	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	intralesional beta-interferon injections combined with radiotherapy in patients with metastatic malignant melanoma	Treatment: simultaneous external beam radiotherapy and intralesional injection of beta-interferon. 3–5 Mio IE / 3x/week	melanoma metastases		CR: 12 patients (70%) PR: 5 patients (30%)	group Combined treatment with radiotherapy	
Radny et al. 2003	To investigate the feasibility, efficacy, and safety of intralesionally injected IL-2 in 24 melanoma patients with skin and soft-tissue metastases	Phase II prospective open label study Treatment: 2-3 times weekly, 1-57 weeks, max. daily dose 12 MIU IL-2	24 melanoma patients with skin and soft-tissue metastases 16 patients Stage III 8 patients Stage IV 245 lesions	Response Safety	Lesions: CR: 209 lesions (85%) PR: 21 lesions (6%) PD: 7 lesions (3%) 8 lesions (3%) were not assessable Patients, local response: CR: 15 patients PR: 3 patients Main toxicities (grade I+II): Local reaction, Fever, Flu-like symptoms, Pain, Fatigue, Nausea/vomiting	Response was evaluated for patients and for treated lesions separately. Response for patients applied to local response. Limitations: single centre study, lack of control group	4
Bong et al. 2002	to study imiquimod as an	Case Series	3 melanoma patients with	Response	>90% regression in 2 patients, in one	Limitations: Small series	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	adjuvant for treating cutaneous metastases of malignant melanoma	Treatment: Twice daily application of imiquimod 5% cream, 21-28 weeks	multiple cutaneous in-transit metastases		patient complete response after addition of intralesional Il-2		
Si et al. 1996	To examine whether intralesional injections of GM-CSF induce regression of subcutanuous metastases in patients with melanoma and influence lymphoid infiltrates in and around the metastases	Phase I study Treatment: weekly injections of 15-50mg GM-CSF into two subcutaneous metastases up to 6 months	13 melanoma patients with at least 3 subcutaneous metastases Stage III or IV (6 patients)	Response	Local response: PR 1 patient SD 8 patients PD 4 patients	-	4
Tan et al. 1993	To determine the role of BCG immunotherapy in malignant melanoma	Systematic review *Stage I and II: RCTs of BCG (adjuvant therapy)* Stage III: RCTs (combination BCG-chemotherapy) + trials on	Stage III, intralesional therapy (local therapy): 15 non placebo controlled trials of intralesional BCG were identified	Response	Stage III, intralesional BCG trials: Pooled average complete response: 19%, PR 26%, extended survival 13% of patients. Threefold greater rate of	Selected intralesional BCG trials were not described in detail: number of treated lesions and lesions response not indicated, control groups not indicated	4*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		intralesional and oral BCG monotherapy			regression with intralesional BCG for intradermal metastases compared with subcutaneous and/or visceral metastases		
Fierlbeck et al. 1992	To compare the effect of intralesional beta-interferon at different dosages	Case Series Treatment: Group 1: $5x10^6$ I.E. rIFN-beta 3x/week Group 2: $5x10^6$ I.E. rIFN-beta 1x/week Group 3: $3x10^6$ I.E. rIFN-beta 1x/week	10 patients with cutaneous or subcutaneous melanoma metastases 19 lesions	Lesion Response	Group 1 (n=8) CR:2, PR:1, SD:3, PD:2 Group 2 (n=8) CR:3, PR:2, SD:2, PD:1 Group 3 (n=3) CR:0, PR:0, SD:1, PD:2	Limitations: Small sample size	4
Von Wussow et al. 1988	To study the effects of higher IFN concentrations on malignant melanoma metastases, patients were treated with intalesional IFN injections.	Retrospective evaluation Treatment: Systemic and intralesional Interferon alpha	51 patients	Lesion Response	Intralesional treatment (lesions n= 51) CR n=16 PR n=7 NC n=26 PD n=2	26 patients were treated with human interferon alpha and 25 patients with recombinant interferon alpha	4
Lokich et al. 1979	To describe the	Case Series	6 patients with	Lesion response	Complete	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treatment with intralesional methanol extraction residue of bacillus Calmette Guerin (MER-BCG)	Treatment: Single injection with MER-BCG	cutaneous or subcutaneous melanoma metastases 9 lesions		regression: 3 lesions Partial regression: 2 lesions Erythema/no regression: 4		
Vosika et al. 1979	To investigate the clinical pharmacology and efficacy of intralesional immonotherapy utilizing a vaccine composed of Mycobacterium smegmatis cell wall skeleton and the mycobacterial glypolipid fraction	Phase I study Treatment: every 1 or 2 weeks CWS/P3	15 melanoma patients Stage III and IV (8 patients)	Response injected and non-injected lesions	In 6 (40%) of the 15 patients, response (CR+PR) of at least one injected lesion was observed. In 4 of these 6 patients, noninjected disease also responded. 1 patient had PR of pulmonary metastasis in addition to CR of injected lesion.	Limitations: Small series, lack of control group	4
Nathanson et al. 1979	To compare the efficacy of treatment with BCG when it was alternatively administered either by	Randomised prospective study Treatment: IL-BCG Group: BCG intralesionally in the base of each	59 patients with histologically proven, surgically incurable melanoma, with measurable lesions in or associated	Response Rate Survival	IL-BCG vs. MPV-BCG (44 patients evaluable) 45% vs. 9% for	the study design does not cover the question of literature search (efficacy of local treatments compared to	4*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	intralesional injection, or intradermally in a nontumor bearing site, using the multipuncture (Tine) technique	lesion once a week for 6 weeks (up to 5 lesions) MPV-BCG: Multiple puncture BCG once a week for 6 weeks	with the skin	Toxicity	21.1 vs. 13.3 months More severe toxicity was observed in the IL-BCG group, but no deaths were seen due to toxicity in either group	standard treatment), the study is therefore downclassified as level 4 study Limitations: Imbalance of groups: more male patients in the IL-BCG group, randomization scheme not described	
Storm et al. 1979	To describe the treatment with intralesional bacille Calmette Guerin and hyperthermic perfusion	Case Series Treatment: Injection of lesions with Glaxo strain bacille Calmette Guerin every 2-3 weeks	27 melanoma patients with locally recurrent disease	Response	Complete or transient local disease control: 20 of 27 patients	number of treated lesions not indicated	4
Krown et al. 1978	To determine the optimal dose, schedule and toxicity of MER (methanol extraction residue of bacillus	Phase I study Treatment: 1-5 lesions were injected with 0.1 - 0.5 mg of MER on the first day, the	22 patients with skin and subcutaneous metastases without visceral metastases	Response	18 patients evaluable CR of all injected lesions: 8 patients PR: 4 patients 6 patients did not respond	number of treated lesions not indicated	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	Calmette-Guerin) given by the il route, and to compare it with BCG in terms of tumor regression and side effects.	dose was adjusted daily, depending upon the degree of local reaction and systemic effects		Toxicity	Fever (100%), Chills (45%), Malaise (50%), Headache (45%), Nausea and vomiting (18%), Hypotension (14%), Lethargy (14%), Cyanosis (9%), Confusion (5%)		

Ablative Therapien (Elektrochemotherapie, lokale Chemotherapie, Bengal Rosa, Carbon Laser)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kis et al. 2011	To investigate ECT treatment in melanoma patients	Case Series Treatment: ECT with i.v. bleomycin (15 mg/m2) under general sedation	9 patients with 158 cutaneous and subcutaneous metastases	Response	CR 23% PR 39% No change 30% PD 8%	-	4
Foote et al. 2009	To report three cases of intralesional rose bengal treatment followed by radiotherapy	Case Series	3 patients with cutaneous metastastes	Response	Local complete response in all 3 patients	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Thompson et al. 2008	To investigate the therapeutic potential of PV-10 (Rose Bengal) in patients with stage III metastatic melanoma.	Open label phase II study Treatment: One single IL injection of PV-10 in 1-3 target lesions	11 patients with locoregionally recurrent melanoma, Stage III 26 lesions treated 28 lesions untreated (to assess potential bystander effect)	lesion response overall response bystander effect toxicity	25 lesions evaluable: CR 36% (n=9) PR 12% (n=3) SD 28% (n=7) PD 24% (n=6) Patients: CR 27% (n=3) PR 27% (n=3) SD 27% (n=3) PD 18% (n=2) Apparent bystander effect in untreated tumours in 27% of patients Toxicity: transient mild to-moderate pain at the treatment site (n=8), local inflammation (n=4), treatment site pruritus (n=3), mild photosensitivity reaction (n=1), mild insomnia secondary to injection site pain (n=1)	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Quaglino et al. 2008	To prospectively evaluate clinical activity and tolerability of ECT with i.v. bleomycin	Prospective Phase II study Treatment: ECT with i.v. bleomycin	14 patients, Stage III	Response (8 weeks after ECT) Local tumor control rate	Patients(n=14): CR n=7 (50%) PR n= 6 (43%) PD n= 1 (7%) Lesions (n=160): CR 62% PR 33% 2 years local tumor control rate: 74.5%	-	4
Gaudy et al. 2006	To assess whether EP therapy improves the local control of skin metastases of melanoma by intralesional bleomycin	A prospective internally controlled study with randomization of melanoma skin metastases in each individual to intralesional injections of bleomycin alone or to intralesional injections of bleomycin with EP	12 patients Stage III (4 patients) and Stage IV (8 patients under chemotherapy) 54 lesions	Local response (lesions) Tolerance	Lesions treated with bleomycin + EP (n=30) versus bleomycin alone (n=24): CR 36% (11 of 30) vs. 8% (2 of 24) p = 0.016 All patients reported discomfort during the EP procedure, including local pain for 9 patients (75%) at the treatment site and muscle spasm with myoclonia in 3 cases (25%). No	the study design does not cover the question of literature search (efficacy of local treatments compared to standard treatment), the study is therefore downclassified as level 4 study Limitations: No comparison to standard treatments (e.g. surgery, radiotherapy)	4*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					clinical or biologic systemic toxicity.		
Byrne et al. 2005	to evaluate the effect of EPT after intratumoral injection of bleomycin, and to compare this with the effect of intratumoral injection of bleomycin alone	Phase II, randomized, open-label study comparing intralesional bleomycin + EPT with intralesional bleomycin alone. Treatment: Injectin of bleomycin followed by electrical pulses, possible retreatment at wek 4, 8 or 12	19 patients, stage III or IV with at least 2 cutaneous and/or subcutaneous metastases 36 evaluable lesions, lesions were randomized to treatment	lesion response	bleomycin only (19 Lesions) CR 26% (n=5) PR 5% (n=1) SD 15% (n=3) PD 53% (n=10) bleomycin plus EPT (17 lesions, plus 1 lesion crossed over) CR 72% (n=13) PR 5% (n=1) SD 18% (n=3) PD 5% (n=1) p=0.002	Response was evaluated for treated lesions. No data available for duration of response Limitations: No comparison to standard treatments (e.g. surgery, radiotherapy)	4*
Oratz et al. 2003	To evaluate the use of a novel intralesional chemotherapy – cisplatin / adrenaline injectable gel – for the treatment of refractory or recurrent	open-label, multicentre study Treatment: up to six weekly intratumoral injections of cisplatin/adrenaline gel within an 8 week period or	25 patients with 244 lesions were evaluable for efficacy	Response Toxicity	CR was achieved in 114 tumours (47%), PR in 16 tumours (7%). Median time to an individual tumour response was 62 days (range 1–534 days). Median duration of an		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cutaneous and soft tissue melanoma metastases	until complete response			individual tumour response (n = 124) was 347 days (range 30–783 days).		
Rols et al. 2000	To apply the electrochemotherapy method	Case Series Treatment: 10 mg/m2 dose of bleomycin i.v. followed by short, intense electric pulses	4 patients 55 metastases	Response	Objective responses of treated metastases: more than 90% Complete response rate 9%	Small series	4
Sersa et al. 2000	To evaluate the antitumor effectiveness of electrochemotherapy using intratumoral cisplatin administration on cutaneous tumor nodules in malignant melanoma patients	Phase II open-label Study Treatment: Intratumoral cisplatin followed by electrical pulses versus cisplatin alone versus electric pulses alone versus control	10 patients with cutaneous metastases, Stage III or IV ECT group: 82 lesions cisplatin group: 27 lesions electric pulses group: 2 lesions untreated controls: 22 lesions	Lesion response	ECT group (n=82): CR 68% (n=56), PR 10% (n=8), SD 15% (n=12), PD 7% (n=6) Cisplatin group (n=27): CR 19% (n=5), PR 19% (n=5), SD 30% (n=8), PD 33% (n=9) Electric pulses (n=2): SD 50% (n=1), PD 50% (n=1) Control group	No details given how lesions are allocated to different treatment groups Limitations: No comparison to standard treatments (e.g. surgery, radiotherapy) Small sample size	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(n=22): SD 36% (n=8), PD 64% (n=14)		
Glass et al. 1996	To report the effects of ECT in 5 patients with metastatic malignant melanoma	Case Series Treatment: Intralesional bleomycin followed by pulses of electricity delivered via needle electrodes or caliper	5 patients with cutaneous metastatic melanoma 23 lesions treated with ECT 3 lesions with electic pulses alone 9 lesions bleomycin alone	Lesion response	ECT: CR 78% (n=18) PR 17% (n=4) SD 4% (n=1) Electric pulses alone: No response Bleomycin alone: No response	-	4

Contact Sensitizer (Dinitrochlorobenzene, Diphencyprone)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Terheyden et al. 2006	To gain more insight to criteria of response to combined treatment with epifocal DNCB and intravenous DTIC, data were collected in this	retrospective study Treatment: epifocal DNCB and intravenous DTIC	72 evaluable patients with recurrent melanoma Stage III n=39 Stage IV n=33	Response Progression free survival	Stage III, patients n=39 Response CR n=15 (39%) PR n=9 (23%) SD n=9 (23%) PD n=6 (15%) Median PFS: 10 months (range 3 –	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	retrospective study			Overall survival	120 months) median OS 14 months (range 3 – 120 months)		
Damian et al. 2009	To report DPCP treatment of 7 patients with cutaneous metastastic melanoma	Case Series Treatment: 2 weeks after sensitization weekly applicatio of DPCP cream to all cutaneous metastases	7 patients with cutaneous metastastes	Response	CR 4 patients PR 3 patients	-	4
Trcka et al. 1998	To describe an immunochemother apy for metastatic melanoma	Case Series Treatment: epifocal DNCB and intravenous DTIC	15 evaluable melanoma patients	Response	n=15 CR n=4 PR n=3	-	4
Strobbe et al. 1997	To describe the experience with a combination of DNCB and DTIC in selected patients with regional cutaneous metastases	Case Series Treatment: Local DNCB 2% solution in acetone alone for 4 weeks, start of DTIC i.v. after 4 weeks	59 patients with the presence of locoregional metastases, Stage III 63% (n=37) or Stage IV 37% (n=22).	Response	Overall Response (patients) CR 25% (n=15) PR+SD 12% (n=7) PD 63% (n=37) Local Response (patients) CR+PR 68% (n=40)	No detailed data regarding local response available Limitations: Combination therapy	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Cohen et al. 1978	To compare efficacy and toxicity of intralesional BCG versus intralesional DNCB in patients with locoregional metastatic melanoma	Randomized prospective Study Treatment: BCG group: intralesional BCG injecitons every 4-6 weeks DNCB group: topical application until hypersensitivity occured (within 2 weeks) thereafter intralesional injections every 4-6 weeks	18 patients with intradermal or subcutaneous melanoma metastases, Stage III Randomisation in two treatment groups: 9 patients reveived BCG with 177 dermal and 22 subcutaneous lesions, 9 patients reveived DNCB with 504 dermal and 63 subcutaneous lesions	Response Survival Toxicity	Lesion response: BCG group Regression dermal lesions: 90% (n=157), subcutaneous lesions: 45% (n=10) DNCB group Regression dermal lesions: 90% (n=453), subcutaneous lesions: 43% (n=27) Overall Survival at 39 months: 33% in both groups. Toxicity BCG vs. DNCB Fever (88% vs. 0%), Chills (84% vs. 0%), Nausea 1(40% vs. 0%), Major ulceration (44% vs. 4%), Cellulitis (antibiotics) (16% vs. 2%), Distant infection (8% vs. 0%) Disseminated intravascular	the study design does not cover the question of literature search (efficacy of local treatments compared to standard treatment), the study is therefore downclassified as level 4 study	4*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					coagulation, including one near fatality. (12% vs. 0%)		

* the study design does not cover the question of literature search (efficacy of local treatments compared to standard treatment), the study is therefore downclassified as level 4 study

7.1.4.2. Aktualisierungsrecherche 2015

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Andtbacka et al. 2015	To evaluate whether treatment with T-VEC resulted in an improved durable response rate (DRR) compared with GM-CSF in patients with unresected stage IIIB to IV melanoma.	RCT Treatment: Group A: Talimogene Laherparepvec (n=295) Group B: GM-CSF (n=141)	Not surgically resectable, stage IIIB to IV melanoma suitable for direct or ultrasound-guided injection (at least one cutaneous, subcutaneous, or nodal lesion or aggregation of lesions 10 mm in diameter).	Durable Response Rate Overall Response Rate Overall Survival	DRR was higher with T-VEC (16.3%; 95% CI, 12.1% to 20.5%) than GM-CSF (2.1%; 95% CI, 0% to 4.5%]; odds ratio, 8.9; P <.001). Overall response rate was higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% v 5.7%; 95% CI, 1.9% to 9.5%). Median OS was 23.3 months (95% CI, 19.5 to 29.6	T-VEC efficacy was most pronounced in patients with stage IIIB, IIIC, or IVM1a disease and in patients with treatment-naive disease.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months) with T-VEC and 18.9 months (95% CI, 16.0 to 23.7 months) with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; P .051).		
Byers et al. 2014	To evaluate the current evidence regarding the efficacy and side effect profile of intra-lesional IL-2 therapy for treating in-transit melanoma	Systemic review Inclusion criteria: phase II or III studies that examined IL-2 injected directly into cutaneous/subcutaneous melanoma metastases and evaluated the clinical response. Exclusion criteria: Studies that were phase I, non-human, had fewer than five subjects, or had quality scores of less than three (of six)	140 patients with 2,182 lesions were treated in these six studies.	Response Rates by Lesion Response Rates by Subject Side Effects	Heterogeneity was seen in IL-2 dosage and treatment interval. Response rate was variable as well. Pooling the lesions, complete response was seen in 78%. Pooling subjects, 50% achieved a complete response. Treatment was generally well tolerated, with localized pain and swelling, and mild flu-like symptoms.	Problem with heterogeneity of includes studies regarding dosing of IL-2 described. However, IL-2 treatment intralesionally applied judged as sufficient and well tolerated	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		according to Newcastle-Ottawa Quality Assessment Scale for cohort studies. The literature search yielded 277 citations. 49 unique and potentially relevant studies were identified and their abstracts further evaluated. 28 articles did not address the research question, 2 were phase I studies and 4 were case reports with too few subjects. Four studies were found to be evaluating systemically delivered IL-2 (not intra-lesional). 2 studies used IL-2 indirectly administered					

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		through vectors. 2 studies were found to be long-term follow-up of previous studies and one study did not assess the clinical outcome. The remaining 6 articles matched our criteria and were subjected to quality assessment.					
Sisti et al. 2015	To critically assess the studies evaluating the monotherapy with Imiquimod cream in the treatment of cutaneous metastases from melanoma	Systemic review MEDLINE, EMBASE, Cochrane Library, and Google Scholar databases were searched with the purpose of study selection. The terms "melanoma" combined with "metastases" and "imiquimod" were used as database queries. The only inclusion criterion	17 patients treated in 11 studies	Not pre-specified in report Response rate and clinical outcome according to different dosing schedules reported	Response rate was variable. Pooling the lesions, complete regression of melanoma metastases was seen in 82.3% of the patients. There was no significant difference in terms of clinical outcome when comparing the frequency of Imiquimod application.	Review mainly included case reports, so baseline quality of selected papers was low. Whereas the search strategy is well described, outcomes objectives of the review are missing.	3a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		was: clinical human studies evaluating IMG monotherapy in metastatic melanoma. Any simultaneous combination therapy was excluded. 57 studies identified of which 46 did not meet inclusion criteria, leaving 11 case studies. A modified quality assessment tool for observational studies was used.					
Mali et al. 2012	To consolidate current experience with clinical electochemotherapy (ECT) of cutaneous or subcutaneous tumours from the effectiveness point	Systematic search of 16 bibliographic databases was performed to obtain articles regarding clinical ECT using search terms "electrochemother	431 patients and 1,894 tumours	Response of individual tumors: Complete response (CR), Partial response (PR),	CR 56.8% (for Melanoma) Specified for each study only	The search strategy is well described. More outcomes declared than reported	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of view and to provide a transparent and objective framework for discussion on differences in effectiveness of clinical ECT.	apy" and "clinical" and time range between 1st January 1991 and 18th October 2011. Results from initial search: 1181 references; 44 reports included in analysis The risk of bias of included studies was assessed independently by 2 out of 3 authors according to the recommendations of the Cochrane Collaboration.		No change (NC), Progressive disease (PD) , Objective response (OR; including CR and PR) No response (NR; including NC and PD)	 Specified for each study only OR 80.6% (for Melanoma) Specified for each study only		
Spratt et al. 2014	To perform the first meta-analysis of the efficacy of skin-directed therapies for cutaneous metastases.	Systematic literature searches were conducted in four databases (MEDLINE [via PubMed], EMBASE, The Cochrane	47 studies reporting on 915 patients with 4,313 cutaneous metastases of skin tumours (CMs) were included for	Complete Response (CR) Objective response rate (ORR)	1,890 (54.4%) of the 3,477 assessable patients had a CR. All 4,313 CMs were	Probably the most sufficient and comprehensive reviews including a meta-analysis of treatment of cutaneous	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Library, and ClinicalTrials.gov) for human-only studies. The search strategy contained two major components linked together with the AND operator: (1) skin-directed therapy: surgery, excision, topical, intralesional therapy, injection, photodynamic, photochemo-therapy, electrochemotherapy, radiation, radiotherapy, brachytherapy AND (2) skin metastasis: cutaneous metastasis/metastases, dermal metas-tasis/metastases.	analysis.		assessable for ORR analyses, of which 2,970 (68.9%) had ORRs. ORR was defined in 42 studies as the sum of CR plus PR. The ORR for all studies was 60.2% (95%CI, 50.6% to 69.0%).	metastases of skin tumors	

7.1.4.3. Literatur

Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. J Clin Oncol. 2015;33(25):2780-2788.
Bong AB, Bonnekoh B, Franke I, et al. Imiquimod, a topical immune response modifier, in the treatment of cutaneous metastases of malignant melanoma. Dermatology 2002;205:135-138
Boyd KU, Wehrli BM, Temple CL. Intra-lesional interleukin-2 for the treatment of in-transit melanoma. J Surg Oncol 2011;104:711-717
Byers BA, Temple-Oberle CF, Hurdle V, McKinnon JG. Treatment of in-transit melanoma with intra-lesional interleukin-2: a systematic review. J Surg Oncol. 2014;110(6):770-775.
Byrne CM, Thompson JF, Johnston H, et al. Treatment of metastatic melanoma using electroporation therapy with bleomycin (electrochemotherapy). Melanoma Res 2005;15:45-51
Cohen MH, Jessup JM, Felix EL, et al. Intralesional treatment of recurrent metastatic cutaneous malignant melanoma: a randomized prospective study of intralesional Bacillus Calmette-Guerin versus intralesional dinitrochlorobenzene. Cancer 1978;41:2456-2463
Damian DL, Shannon KF, Saw RP, et al. Topical diphencyprone immunotherapy for cutaneous metastatic melanoma. Australas J Dermatol 2009;50:266-271
Dehesa LA, Vilar-Alejo J, Valeron-Almazan P, et al. Experience in the treatment of cutaneous in-transit melanoma metastases and satellitosis with intralesional interleukin-2]. Actas Dermosifiliogr 2009;100:571-585
Fierlbeck G, d'Hoedt B, Stroebel W, et al. Intralesional therapy of melanoma metastases with recombinant interferon-beta]. Hautarzt 1992;43:16-21
Florin V, Desmedt E, Vercambre-Darras S, et al. Topical treatment of cutaneous metastases of malignant melanoma using combined imiquimod and 5-fluorouracil. Invest New Drugs 2011
Foote MC, Burmeister BH, Thomas J, et al. A novel treatment for metastatic melanoma with intralesional rose bengal and radiotherapy: a case series. Melanoma Res 2010;20:48-51
Fujimura T, Okuyama R, Ohtani T, et al. Perilesional treatment of metastatic melanoma with interferon-beta. Clin Exp Dermatol 2009;34:793-799
Garcia MS, Ono Y, Martinez SR, et al. Complete regression of subcutaneous and cutaneous metastatic melanoma with high-dose intralesional interleukin 2 in combination with topical imiquimod and retinoid cream. Melanoma Res 2011
Gaudy C, Richard MA, Folchetti G, et al. Randomized controlled study of electrochemotherapy in the local treatment of skin metastases of melanoma. J Cutan Med Surg 2006;10:115-121
Glass LF, Pepine ML, Fenske NA, et al. Bleomycin-mediated electrochemotherapy of metastatic melanoma. Arch Dermatol 1996;132:1353-1357
Green DS, Bodman-Smith MD, Dalgleish AG, et al. Phase I/II study of topical imiquimod and intralesional interleukin-2 in the treatment of accessible metastases in malignant melanoma. Br J Dermatol 2007;156:337-345
Khorana AA, Rosenblatt JD, Sahasrabudhe DM, et al. A phase I trial of immunotherapy with intratumoral adenovirus-interferon-gamma (TG1041) in patients with malignant melanoma. Cancer Gene Ther 2003;10:251-259
Kis E, Olah J, Ocsai H, et al. Electrochemotherapy of Cutaneous Metastases of Melanoma-A Case Series Study and Systematic Review of the Evidence. Dermatol Surg 2011
Krown SE, Hilal EY, Pinsky CM, et al. Intralesional injection of the methanol extraction residue of Bacillus Calmette-Guerin (MER) into cutaneous metastases of malignant melanoma. Cancer 1978;42:2648-2660
Lokich JJ, Garnick MB, Legg M. Intralesional immune therapy: methanol extraction residue of BCG or purified protein derivative. Oncology 1979;36:236-241
Mali B, Jarm T, Snoj M, Sersa G, Miklavcic D. Antitumor effectiveness of electrochemotherapy: a systematic review and meta-analysis. Eur J Surg Oncol. 2013;39(1):4-16.
Nathanson L, Schoenfeld D, Regelson W, et al. Prospective comparison of intralesional and multipuncture BCG in recurrent intradermal melanoma. Cancer 1979;43:1630-1635
Oratz R, Hauschild A, Sebastian G, et al. Intratumoral cisplatin/adrenaline injectable gel for the treatment of patients with cutaneous and soft tissue metastases of malignant melanoma. Melanoma Res 2003;13:59-66
Paul E, Muller I, Renner H, et al. Treatment of locoregional metastases of malignant melanomas with radiotherapy and intralesional beta-interferon injection. Melanoma Res 2003;13:611-617
Quaglino P, Mortera C, Osella-Abate S, et al. Electrochemotherapy with intravenous bleomycin in the local treatment of skin melanoma metastases. Ann Surg Oncol 2008;15:2215-2222
Radny P, Caroli UM, Bauer J, et al. Phase II trial of intralesional therapy with interleukin-2 in soft-tissue melanoma metastases. Br J Cancer 2003;89:1620-1626
Rols MP, Bachaud JM, Giraud P, et al. Electrochemotherapy of cutaneous metastases in malignant melanoma. Melanoma Res 2000;10:468-474
Sersa G, Stabuc B, Cemazar M, et al. Electrochemotherapy with cisplatin: clinical experience in malignant melanoma patients. Clin Cancer Res 2000;6:863-867
Si Z, Hersey P, Coates AS. Clinical responses and lymphoid infiltrates in metastatic melanoma following treatment with intralesional GM-CSF. Melanoma Res 1996;6:247-255
Sisti A, Sisti G, Oranges CM. Topical treatment of melanoma skin metastases with imiquimod: a review. Dermatol Online J. 2015;21(2).
Spratt DE, Gordon Spratt EA, Wu S, et al. Efficacy of skin-directed therapy for cutaneous metastases from advanced cancer: a meta-analysis. J Clin Oncol. 2014;32(28):3144-3155.
Storm FK, Sparks FC, Morton DL. Treatment for melanoma of the lower extremity with intralesional injection of bacille Calmette Guerin and hyperthermic perfusion. Surg Gynecol Obstet 1979;149:17-21
Strobbe LJ, Hart AA, Rumke P, et al. Topical dinitrochlorobenzene combined with systemic dacarbazine in the treatment of recurrent melanoma. Melanoma Res 1997;7:507-512
Tan JK, Ho VC. Pooled analysis of the efficacy of bacille Calmette-Guerin (BCG) immunotherapy in malignant melanoma. J Dermatol Surg Oncol 1993;19:985-990
Terheyden P, Kortum AK, Schulze HJ, et al. Chemoimmunotherapy for cutaneous melanoma with dacarbazine and epifocal contact sensitizers: results of a nationwide survey of the German Dermatologic Co-operative Oncology Group. J Cancer Res Clin Oncol 2007;133:437-444
Thompson JF, Hersey P, Wachter E. Chemoablation of metastatic melanoma using intralesional Rose Bengal. Melanoma Res 2008;18:405-411

Trcka J, Kampgen E, Becker JC, et al. Immunochemotherapy of malignant melanoma. Epifocal administration of dinitrochlorobenzene (DNCB) combined with systemic chemotherapy with dacarbazine (DTIC)]. Hautarzt 1998;49:17-22
von Wussow P, Block B, Hartmann F, et al. Intralesional interferon-alpha therapy in advanced malignant melanoma. Cancer 1988;61:1071-1074
Vosika GJ, Schmidtke JR, Goldman A, et al. Intralesional immunotherapy of malignant melanoma with mycobacterium smegmatis cell wall skeleton combined with trehalose dimycolate (P3). Cancer 1979;44:495-503
Weide B, Derhovanessian E, Pflugfelder A, et al. High response rate after intratumoral treatment with interleukin-2: results from a phase 2 study in 51 patients with metastasized melanoma. Cancer 2010;116:4139-4146
Weide B, Eigentler TK, Pflugfelder A, et al. Survival after intratumoral interleukin-2 treatment of 72 melanoma patients and response upon the first chemotherapy during follow-up. Cancer Immunol Immunother 2011;60:487-493

7.1.4.4. Evidenztabellen 2016

Referenz	Ziele	Design	Untersuchte Population	untersuchte Endpunkte	Ergebnisse	Bemerkungen	Evidenzklasse (level of evidence/Oxford)
Campana, L.G., et al., 2016	To describe ECT as treatment for cutaneous mlanoma	Prospective, multicenter, observational study n=376 patients	Patients with superficial metastases, who underwent ECT at 10 centers between 2008 and 2013	Procedure Response	Two hundred eighty-seven (76.3%) patients underwent a single ECT. The remaining 89 (23.7%) patients received from 2 up to 6 ECT courses on partially responding (n = 27) or newly occurred tumors (n=62). One-hundred seventy-seven (47.1%) subjects received further oncological		2a

					treatments after ECT, including cytotoxic chemotherapy, immunotherapy and radiation. Although not significant at statistical analysis, tumor response rate (and CR rate) at 60 days according to histotype was as follows: breast cancer, 89.5% (36.8%); BCC, 88.9% (66.7%); Kaposi sarcoma, 88.9 (44.4%); SCC, 85.2% (40.7%); soft tissue sarcoma, 83.3% (83.3%); melanoma, 83.1% (53.7%); other histotypes, 60% (30%). We did not observe any regression on untreated tumors, consistent with lack of an		

					abscopal effect.		
Deroose, J.P., et al. 2015	To report on repeated ILP in melanoma patients of the limb and compare the outcome results and local toxicity with those treated with a first ILP	Retrospective analysis of patients treated with Tumor necrosis factor-α and melphalan-based isolated limb perfusion (TM-ILP) number of patients n=32	Repeat TM-ILP for locoregional recurrence after isolated limb perfusion, between 1991 and 2013	Local reccurance rate Suvival	The local recurrence rate was 59% (n =22 out of 37). The estimated local recurrence rate after 1 and 2 years was 34 and 70%, respectively. The median time to local recurrence was 13 months. The 3- and 5-year survival rate after repeated ILP was 56 and 35%, respectively. The estimated median overall survival was 45 months		4
Hassan, S., et al., 2015	To validate the role of intralesional interleukin (IL)-2, to understand its mechanism of action,	Retrospectively collected the clinicopathological data of 31 consecutive patients	Melanoma patients with in-transit disease treated with intralesional IL-2 since 2009 -	Treatment response	Ten patients (10/31, 32 %) achieved a pathologic complete response (pCR), 17/21 (55 %) had a partial response, and		4

	and to better understand factors that may influence ist response		2012 at Sunnybrook Health Sciences Centre, Toronto, ON, Canada		4/21 (19 %) had progressive disease on treatment. pCR to IL-2 therapy was associated with overall survival (log-rank p = 0.004) and improved progression-free survival (PFS). A higher CD8+ T cell infiltrate was identified in in-transit lesions with a pCR compared with the other lesions (mean IHC score 3.78 vs. 2.61; p = 0.01). Patients with an elevated CD8+ infiltrate demonstrated an improved PFS.		
Quinn, C., et al., 2016	To examine the relative treatment effect of talimogene laherparepvec compared with	Systematic review, number of included trials n=4	Relevant trials were identified through a systematic review conducted in	Overall Survival	Median OS for ipilimumab and vemurafenib increased significantly when adjustment was applied, demonstrating		2a

	ipilimumab and vemurafenib		September 2015 of English-language studies, published since January 1990, on the efficacy and safety of treatments for metastatic melanoma		that variation in disease and patient characteristics was biasing OS estimates; adjusting for this made the survival data more comparable. For both ipilimumab and vemurafenib, the adjustments improved Kaplan–Meier OS curves; the observed talimogene laherparepvec OS curve remained above the adjusted OS curves for ipilimumab and vemurafenib, showing that long-term survival could differ from the observed medians.		

7.1.4.5. Literatur 2016

Campana, L.G., et al., Treatment efficacy with electrochemotherapy: A multi-institutional prospective observational study on 376 patients with superficial tumors. Eur J Surg Oncol, 2016. 42(12): p. 1914-1923.
Deroose, J.P., et al., Repeated isolated limb perfusion in melanoma patients with recurrent in-transit metastases. Melanoma Res, 2015. 25(5): p. 427-31.
Hassan, S., et al., Pathologic complete response to intralesional interleukin-2 therapy associated with improved survival in melanoma patients with in-transit disease. Ann Surg Oncol, 2015. 22(6): p. 1950-8.

Quinn, C., et al., Indirect Treatment Comparison of Talimogene Laherparepvec Compared with Ipilimumab and Vemurafenib for the Treatment of Patients with Metastatic Melanoma. Adv Ther, 2016. 33(4): p. 643-57.

7.2. Frage VI.2. und VI.3. Systemtherapie Einzelsubstanzen – De novo Recherche

Frage VI.2.: Für welche Substanzen konnten objektive Remissionen im metastasierten Stadium (First- und Secondline) gezeigt werden?

Frage VI.3.: Für welche Substanzen konnte eine Verbesserung des Gesamtüberlebens im metastasierten Stadium (First- und Secondline) gezeigt werden?

7.2.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Advanced melanoma patients stage IV, unresectable stage III	Systemic treatment	Standard of care/Placebo/Standard of care+Placebo	Overall Survival, Response, Duration of Response

Suchwörter				
Stichwort	melanoma	phase III phase 3	Chemotherapy	Stage IV Stage 4
Synonyme		random*		Palliative
Ober-/Unterbegriffe			Systemic therapy	Salvage metastatic Disseminated
Mesh Term	melanoma	Clinical Trial, Phase III Randomized Controlled Trial	Drug Therapy	

7.2.2. Datenbanken, Suchstrategien, Trefferzahlen

7.2.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (Clinical Trial, Phase III [Publication Type] OR Randomized Controlled Trial [Publication Type] OR “phase 3” OR "phase III"[tiab] OR random*[tiab]) AND (“systemic therapy”[tiab] OR chemotherapy[tiab] OR "drug therapy"[MeSH] OR metastatic[tiab] OR palliative[tiab] OR advanced[tiab] OR "stage IV"[tiab] OR "stage 4"[tiab] OR salvage[tiab])	26.07.11	1091 (Auswahl: 38)
Medline –erweiterte Suchstrategie	(melanoma[tiab] OR melanoma[MeSH]) AND (Clinical Trial, Phase III [Publication Type] OR Randomized Controlled Trial [Publication Type] OR “phase 3” OR "phase III"[tiab] OR random*[tiab]) AND (“systemic therapy”[tiab] OR chemotherapy[tiab] OR "drug therapy"[MeSH] OR **disseminated**[tiab] OR metastatic[tiab] OR palliative[tiab] OR advanced[tiab] OR "stage IV"[tiab] OR "stage 4"[tiab] OR salvage[tiab])	05.12.11	1142 (Avril et al. 2004 dazu)
Cochrane Library	(melanoma and (random* or phase 3) and (systemic therapy or chemotherapy or metastatic or palliative or advanced or salvage)).ti,ab.	17.10.11	385 (Auswahl: 25, abz. Dubletten: 2 dazu)
Embase	(melanoma and (random* or phase 3) and (systemic therapy or chemotherapy or metastatic or palliative or advanced or salvage)).ti,ab.	04.10.11	894 (Auswahl: 33, abz. Dubletten: 3 dazu)
Update Suche			
Medline	s.o.	30.01.12	1145 (2 dazu: Kim et al. 2012, Kirkwood et al. 2012)

Datenbank	Suchstrategie	Datum	Treffer
Medline	s.o.	01.08.12	**1221** (2 dazu: Flaherty et al. 2012, Hauschild et al. 2012)
Cochrane Library	s.o.	30.01.12	**389** (0 dazu)
Embase	s.o.	23.01.12	**937** (0 dazu)

7.2.2.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
Medline	(((melanoma[tiab] OR melanoma[MeSH]) AND (Clinical Trial, Phase III [Publication Type] OR Randomized Controlled Trial [Publication Type] OR “phase 3” OR "phase III"[tiab] OR random*[tiab]) AND (“systemic therapy”[tiab] OR chemotherapy[tiab] OR "drug therapy"[MeSH] OR disseminated[tiab] OR metastatic[tiab] OR palliative[tiab] OR advanced[tiab] OR "stage IV"[tiab] OR "stage 4"[tiab] OR salvage[tiab]))) AND ("2011.12.06"[Date - Publication] : "3000"[Date - Publication])	16.09.15	451
Cochrane Library	(melanoma and (random* or phase 3) and (systemic therapy or chemotherapy or metastatic or palliative or advanced or salvage)).ti,ab.	16.09.15	67

7.2.2.3. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (Clinical Trial, Phase III [Publication Type] OR	16.09.201	116 (Auswahl: 8); 1

Datenbank	Suchstrategie	Datum	Treffer
	Randomized Controlled Trial [Publication Type] OR “phase 3” OR "phase III"[tiab] OR random*[tiab]) AND (“systemic therapy”[tiab] OR chemotherapy[tiab] OR "drug therapy"[MeSH] OR metastatic[tiab] OR palliative[tiab] OR advanced[tiab] OR "stage IV"[tiab] OR "stage 4"[tiab] OR salvage[tiab]): Datumsfilter 2015/09/16 to 2016/12/31	6	Metaanalyse manuell hinzugeüfgt
Cochrane Library	Cochrane Database of Systematic Reviews: (melanoma and (random* or phase 3) and (systemic therapy or chemotherapy or metastatic or palliative or advanced or salvage))	17.09.2016	9 (0 dazu)

7.2.3. Auswahlkriterien

7.2.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	**2547**
Einschlusskriterien	RCTs zur medikamentösen Systemtherapie bei Melanompatienten im Stadium IV / nicht resektables Stadium III Interventionsarm: Monotherapie oder Monotherapie + Standardtherapie Beobachtungsarm: Placebo, Standardtherapie oder Placebo + Standardtherapie Publikationsjahr ab 1980
Ausschlusskriterien	Case Reports, Kohortenstudien Dosisfindungsstudie Kollektive mit gemischten Tumorentitäten
Anzahl nach Abstractscreening, vorgesehen für Bewertung	48
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	8
Anzahl ausgewählter Volltexte	40
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst: **Zielgerichtete Therapien /small molecules** (Trametinib, Dabrafenib, Selumetinib, Bevacizumab, Vemurafenib, Intetumumab, Bosentan, Sorafenib, Elesclomol, Tamoxifen) **Immuntherapien, Immunmodulation** (Ipilimumab, Vakzine, Lenalidomide, Thymosin, PF-3512676, Interferon alpha, Thalidomide, Histamine) **Chemotherapien/Chemosensitizer** (DHA-paclitaxel, Dacarbazine, Temozolomide, Lomeguatrib, Oblimersen, Cisplatin, Fotemustine, Vindesine, Detorubicin)	

7.2.3.2. Aktualisierungsrecherche 2015

Auswahl der Literatur	
Gesamttreffer	**518**
Einschlusskriterien	Systematische Reviews / Metaanalysen Phase III RCTs zur medikamentösen Systemtherapie bei Melanompatienten im Stadium IV / nicht resektables Stadium III Interventionsarm: Monotherapie oder Monotherapie + Standardtherapie Beobachtungsarm: Placebo, Standardtherapie oder Placebo + Standardtherapie Publikationsjahr ab 1980
Ausschlusskriterien	Phase I/II RCTs Case Reports, Kohortenstudien Dosisfindungsstudie Kollektive mit gemischten Tumorentitäten
Anzahl ausgewählter Volltexte Zielgerichtete Therapien /small molecules-RCTs Immuntherapien, Immunmodulation-RCTs Chemotherapien/Chemosensitizer-RCTs Reviews	N= 28 7 10 4 7

7.2.3.3. Aktualisierungsrecherche 2016

Auswahl der Literatur	
Gesamttreffer	**125**
Einschlusskriterien	Metaanalysen und systematische Reviews zu RCTs RCTs zur medikamentösen Systemtherapie bei Melanompatienten im Stadium IV / nicht resektables Stadium III Interventionsarm: Monotherapie oder Monotherapie + Standardtherapie

Auswahl der Literatur		
	Beobachtungsarm: Placebo, Standardtherapie oder Placebo + Standardtherapie Publikationsjahr ab 16.09.2015	
Ausschlusskriterien	Case Reports, Kohortenstudien Dosisfindungsstudie Kollektive mit gemischten Tumorentitäten	
Anzahl nach Abstractscreening, vorgesehen für Bewertung		8
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte		8
Anzahl ausgewählter Volltexte		8

7.2.4. Evidenztabelle

7.2.4.1. Primärrecherche 2012

Zielgerichtete Therapien / small molecules

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Flaherty et al. 2012	To compare trametinib (MEK Inhibitor) with dacarbazine or Taxol in patients with metastatic melanoma with the BRAF V600E or BRAF V600K mutation	RCT, open label Treatment: Group A trametinib (2 mg orally twice daily) Group B dacarbazine, 1000 mg/m² i.v. or paclitaxel 175mg/m² i.v. on day 1 every 3 weeks	322 patients with metastatic previously untreated or treated melanoma with the BRAF V600E or BRAF V600K mutation	**Overall Survival – 6 months** **Progression free survival** **Overall Response rate** Duration of Response	trametinib vs. chemotherapy 81% vs. 67% (HR 0.54; 95% CI, 0.32 to 0.92; p = 0.01) 4.8 vs. 1.5 months (HR 0.45; 95% CI, 0.33 to 0.63; P<0.001) 22% vs. 8% (p=0.01) 5.5 months vs. not yet reached	Jadad Score 4 Independent review of tumor assessment Funding: GlaxoSmithKline.	1b
Hauschild et al. 2012	To compare dabrafenib with dacarbazine chemotherapy in previously untreated mel	RCT, open label Treatment: Group A dabrafenib (150 mg orally twice	250 patients with previously untreated, metastatic melanoma with the BRAF V600E	**Overall Survival**	dabrafenib vs. dacarbazine HR 0,61 (95% CI, 0,25–1,48)	Jadad Score 4 Independent review of tumor assessment Funding:	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	anoma patients whose tumours harboured a BRAFV600E mutation.	daily) Group B dacarbazine, 1000 mg/m² i.v. on day 1 every 3 weeks	mutation	**Progression free survival** **Overall Response rate** Duration of Response	5,1 vs. 2,7 months (HR 0,30; 95% CI, 0,18–0,51; p<0·0001) 50% vs. 6% 5.5 months vs. not yet reached	GlaxoSmithKline.	
Chapman et al. 2011	To compare vemurafenib with dacarbazine in 675 patients with previously untreated, metastatic melanoma with the BRAF V600E mutation	RCT, open label Treatment: Group A vemurafenib (960 mg orally twice daily) Group B dacarbazine, 1000 mg/m² i.v. on day 1 every 3 weeks	675 patients with previously untreated, metastatic melanoma with the BRAF V600E	**Overall Survival – 6 months** **Overall Response rate** Duration of Response	Vemurafenib vs. DTIC 84% (95% CI, 78 to 89) vs. 64% (95% CI, 56 to 73), HR for death in the vemurafenib group 0.37 (95% CI, 0.26 to 0.55; P<0.001), sign. 48% vs. 5%, p<0.001, sign. not yet estimated	Jadad Score 2 no description of dropouts, tumor assessment not blinded, only 439 patients (65%) were evaluated for tumor response, 48 patients in the DTIC Group received no study treatment Funding: Hoffmann-La Roche	1b
O´day et al. 2011	To evaluate the safety and efficacy	RCT, double-blind (Group A+B)	129 chemotherapy-		DTIC vs. DTIC+ intetumumab vs.	Jadad Score 5	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of Intetumumab (CNTO 95), a fully human anti-alpha(v)-integrin monoclonal antibody	Treatment q3w: Group A 1000 mg/m² dacarbazine + placebo, (n=32) Group B 1000 mg/m² dacarbazine + 10 mg/kg intetumumab (n=32) Group C 10 mg/kg intetumumab (n=33) Group C 5 mg/kg intetumumab (n=32)	naive patients	Median Overall Survival Overall Response Rate Duration of Response	intetumumab 10mg vs. intetumumab 5mg 8 vs. 11 vs. 15 vs. 9.8 months, n.s. 10% (n=3) vs. 3% (n=1) vs. 6% (n=2) vs. 0%, n.s. 3.9, 7.3, and 10.3+ months vs. 7.0 months vs. 6.3 and 8.2+ months	Funding: Centocor Ortho Biotech, Inc., Malvern, PA, USA.	
Kefford et al. 2010	To evaluate the effects of bosentan - a dual endothelin receptor antagonist - in patients receiving	RCT, double-blind Treatment: Group A DTIC 1000 mg/m2	80 patients with previously untreated metastatic melanoma	Median Overall Survival	DTIC+Bosentan vs. DTIC+Placebo 13.0 months (95% CI, 7.8-16.6) vs. 10.6 months (95%	Jadad Score 4 tumor assessment not described as blinded Funding:	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	first-line dacarbazine therapy for stage IV metastatic cutaneous melanoma	every 3 weeks starting on Day 1 +Bosentan 500 mg twice a day (n=40) Group B DTIC 1000 mg/m2 every 3 weeks starting on Day 1+Placebo (n=40)		Overall Response Rate Duration of Response	CI, 6.9-14.7), n.s., (HR, 1.044; 95% CI, 0.584-1.865; p = 0.8841) not reported not reported	Actelion Pharmaceuticals Ltd., Allschwil, Switzerland.	
Hauschild et al. 2009	To evaluate the efficacy and safety of sorafenib with carboplatin and paclitaxel (CP) in patients with advanced melanoma	RCT, double-blind Treatment: Group A paclitaxel 225 mg/m2 plus carboplatin (AUC 6) + sorafenib 400mg (n=135) Group B paclitaxel 225 mg/m2 plus carboplatin (AUC 6) + placebo (n=135)	270 patients with advanced melanoma (unresectable stage III or stage IV) that had progressed during or after receiving at least one cycle of a regimen containing dacarbazine or temozolomide in the advanced setting	Median Overall Survival Overall Response Rate Duration of Response	C/P + Sorafenib vs. C/P + Placebo 42.0 weeks (9.7 months) vs. 42.0 (9.7 months), n.s., HR 1.01 (95% CI, 0.76 to 1.36; p=0.92) 12% (n=16) vs. 11% (n=15), n.s., p=1.0 not reported	Jadad Score 5 Funding: Bayer AG and Onyx Pharmaceuticals, Inc.	1b
O´Day et al. 2009	To evaluate	RCT, double-blind	81 metastatic		Elesclomol	Jadad Score 4	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	whether the addition of elesclomol to weekly paclitaxel could improve efficacy in patients with stage IV metastatic melanoma	Treatment: Group A elesclomol 213 mg/m² plus paclitaxel 80 mg/m(2) (E + P) (n= 53) Group B paclitaxel 80 mg/m² alone (n= 28)	melanoma patients with one or fewer prior standard chemotherapy regimens	Median Overall Survival **Progression Free Survival** Overall Response Rate Duration of Response	+Paclitaxel vs. Paclitaxel 11.9 vs. 7.8 months **3.7 months vs. 1.8 months, sign., p=0.035** 15.1% (n=8) vs. 3.6% (n=1) (p=0.153) ,n.s., p=0.153 range 58+ to 188+ days (censored patients), 107, 136 days vs. 115 days	Tumor assessment by investigators, Randomization without stratification, M1c patients unbalanced (25.8% vs. 75%) Funding: Synta Pharmaceuticals, Lexington, MA.	
McDermott et al. 2008	To evaluate the efficacy and safety of sorafenib plus dacarbazine in patients with advanced melanoma	RCT, double-blind Treatment: Group A sorafenib plus dacarbazine (n = 51) Group B	101 chemotherapy-naive patients with stage III (unresectable) or IV melanoma	Median Overall Survival Overall Response Rate	Sorafenib + DTIC vs. Placebo + DTIC 45.6 weeks vs. 51.3 weeks, n.s., p=0.927 24% (n=12) vs. 12% (n=6), n.s.,	Jadad Score 5 Funding: Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals Inc.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		placebo plus dacarbazine (n = 50)		Duration of Response	p=0.193 26.9 vs. 23.0 months, n.s., p=0.194		
Agarwala et al. 1999	To test the benefit of adding tamoxifen to dacarbazine and carboplatin chemotherapy for previously untreated patients with metastatic melanoma	RCT, open label Treatment: Group A carboplatin 300 mg/m² and dacarbazine 1g/m² plus tamoxifen 20 mg/day (D+C+T) Group B (D+C)	56 metastatic melanoma patients, without prior chemotherapy	Median Overall Survival Overall Response Rate Duration of Response	D+C+T vs. D+C 4.6 months vs. 7 months, n.s., p=0.1377 14.3% (n=4) vs. 10.7% (n=3), n.s., (p=1.0) 3, 3, 6, and 6 months vs. 2, 16 months + lost to follow up at 31 months	Jadad Score 2 unblinded tumor assessment, no description of dropouts and withdrawals, small sample size Funding: Not declared	1b

Immuntherapien, Immunmodulation

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hersh et al. 2011	To evaluate the safety and efficacy of **ipilimumab**	RCT, open label Treatment:	72 chemotherapy-naive patients		**Ipi** alone (n=32) vs. Ipi+DTIC (n=32)	Jadad Score 2 small sample size randomization	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	alone and in combination with dacarbazine (DTIC) in patients with unresectable, metastatic melanoma	Group A ipilimumab at 3 mg/kg every 4 weeks for four doses alone (n=37) Group B ipilimumab at 3 mg/kg every 4 weeks for four doses with up to six 5-day courses of DTIC at 250 mg/m²/day (n=35)		Median Overall Survival Overall Response Rate Durable Complete Response	11.4 months (95% CI, 6.1-15.6) vs. 14.3 months (95% CI, 10.2-18.8), n.s. 5.4% (95% CI, 0.7-18.2) vs. 14.3% (95% CI, 4.8-30.3), n.s. n=2 (1.6+/1.85+ years) vs. n=2 (1.73+/1.76+ years)	scheme not described, tumor assessment not blinded Funding: Bristol-Myers Squibb Co.	
Robert et al. 2011	To evaluate **ipilimumab** (10 mg per kilogram) plus dacarbazine in patients with previously untreated metastatic melanoma	RCT, double-blind Treatment: Group A Ipilimumab (10 mg per kilogram) plus dacarbazine (850 mg/m²) Group B dacarbazine (850 mg/m²) plus placebo	502 patients with previously untreated metastatic melanoma	**Median Overall Survival** Overall Survival 1 year 2 years 3 years	**Ipi**+DTIC vs. Placebo+DTIC **11.2 months (95% CI, 9.4 to 13.6) vs. 9.1 months (95% CI, 7.8 to 10.5) (hazard ratio for death with DITC+Ipi, 0.72; p<0.001)** 47.3% vs. 36.3% 28.5% vs. 17.9% 20.8% vs. 12.2%	Jadad Score 5 Funding: Bristol-Myers Squibb.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Overall Response Rate **Duration of Response**	15.2% vs. 10.3%, n.s. (p = 0.09) **19.3 months (95% CI, 12.1 to 26.1) vs. 8.1 months (95% CI, 5.19 to 19.8) (p=0.03)**		
Schwartzentruber et al. 2011	To investigate if the combination of a **melanoma vaccine** with interleukin-2, an immune activating agent, could improve outcomes	RCT, open label Treatment: Group A interleukin-2 alone (720,000 IU per kilogram of body weight per dose) Group B gp100: 209-217(210M) plus incomplete Freund's adjuvant (Montanide ISA-51) once per cycle, followed by interleukin-2	185 patients with stage IV or locally advanced stage III cutaneous melanoma, expression of HLA*A0201, an absence of brain metastases, and suitability for high-dose interleukin-2 therapy	Median Overall Survival **Overall Response Rate** Duration of Response	IL-2 vs. IL-2+**Vaccine** 11.1 months (95% CI, 8.7 to 16.3); vs. 17.8 months (95% CI, 11.9 to 25.8) n.s. (p=0.06) **6% vs. 16%, p=0.03** not reported	Jadad Score 4 tumor assessment blinded Funding: National Cancer Institute, Indiana University Health Goshen, Goshen Hospital and Health Care Foundation, Chiron, and Novartis	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hodi et al. 2010	To compare **ipilimumab**, administered with or without a glycoprotein 100 (gp100) peptide vaccine with gp100 alone in patients with previously treated metastatic melanoma	RCT, double-blind Treatment: Group A ipilimumab plus gp100 (n=403) Group B ipilimumab alone (n=137) Group C gp100 alone (n=136)	676 HLA-A*0201-positive patients with previously treated unresectable stage III or IV melanoma	**Median Overall Survival** **Overall Response Rate** Median Duration of Response Treatment related deaths	**ipilimumab** +gp100 vs. ipilimumab vs. gp100 **10.0 months vs. 10.1 months vs. 6.4 months, sign., (hazard ratio for death, 0.68; p<0.001).** **5.7% (n=23) vs. 11% (n=15) vs. 1.5% (n=2), sign., p=0.04** 11.5 (5.4–NR) vs. NR (28.1–NR) vs. NR (2.0–NR) months n=14	Jadad Score 5 tumor assessment by investigators Funding: Medarex and Bristol-Myers Squibb	1b
Eisen et al. 2010	To compare the treatment with **lenalidomide** to placebo in 306 patients with metastatic	RCT, double-blind Treatment: Group A lenalidomide (25	306 patients with previously treated metastatic malignant melanoma	Median Overall Survival	**lenalidomide** vs. placebo median 5.9 months (range 5.1-7.7) vs. 7.4	Jadad Score 5 Funding: Celgene Corporation, Summit, New	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant melanoma	mg/d on Days 1-21 of a 28-day cycle (n=154) Group B placebo (n=152)		 Overall Response Rate Duration of Response	months range 5.5-8.2); n.s., p=0.32 5.3% vs 5.8%; n.s., p=0.82 not reported	Jersey.	
Maio et al. 2010	To evaluate the efficacy and safety of combining **Thymosin alpha 1** with dacarbazine and interferon alfa in patients with metastatic melanoma	RCT, open label Treatment: Group A: DTIC+IFN alpha+ Thymosin alpha 1 (1.6mg) Group B: DTIC+IFN alpha+ Thymosin alpha 1 (3.2mg) Group C: DTIC+IFN alpha+ Thymosin alpha 1 (6.4mg) Group D: DTIC+Thymosin alpha 1 (3.2mg) Group D: DTIC+IFN alpha	571 chemotherapy-naive patients	 Median Overall Survival Overall Response Rate Median duration of Response **Clinical benefit**	DIT1.6 vs. DIT3.2 vs. DIT6.4 vs. DT3.2 vs. DI 9.3 vs. 8.6 vs. 10.3 vs. 9.3 vs. 6.6 months, n.s. **DTI+DT vs. DI, PP population: HR = 0.74; 95% CI, 0.57-0.95; p=0.02** 7.2% vs. 10.3% vs. 6.1% vs. 12.1% vs. 4.1%, n.s. 7.4 vs. 8.3 vs. 7.9 vs. 7.7 vs. 6.3 months **DT3.2 vs. DI:**	Jadad Score 4 tumor assessment blinded Funding: Sigma-Tau SpA, Pomezia, Italy	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				(CR+PR+SD)	**49.5% vs. 32.0% P=0.009**		
Weber et al. 2011	To assess the objective response rate of **PF-3512676**, a CpG oligodeoxynucleotide, alone in 2 doses or in combination with dacarbazine (DTIC) in patients with unresectable stage IIIB/C or stage IV malignant melanoma	RCT, open label Treatment: Group A PF-3512676 10 mg (n=46) Group B PF-3512676 40 mg (n=46) Group C PF-3512676 40 mg plus DTIC (850 mg/m²) (n=45) Group D DTIC (850 mg/m²) alone (n=39)	184 patients with previously untreated metastatic melanoma	Median Overall Survival Overall Response Rate Duration of Response	**PF-3512676** 10mg vs. PF-3512676 40mg vs. PF-3512676 40 mg + DTIC vs. DTIC 9.4 vs. 8.4 vs. 9.0 vs. 11.7 months, n.s. 2% vs. 0% vs. 16% vs. 8%, n.s. not estimated (number to small)	Jadad Score 3 Funding: not declared	1b
Schadendorf et al. 2006	To demonstrate the superiority of	RCT, open label	108 metastatic melanoma patients		**DC vaccination** vs. DTIC	Jadad Score 3	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	autologous peptide-loaded **dendritic cell (DC) vaccination** over standard dacarbazine (DTIC) chemotherapy in stage IV melanoma patients	Treatment: Group A DC vaccines loaded with MHC class I and II-restricted peptides (n=53) Group B DTIC 850 mg/m² (n=55)	with no prior systemic chemotherapy	Median Overall Survival Overall Response Rate	9.3 months vs. 11.6 months n.s. ITT: 3.8% (n=2) vs. 5.5% (n=3), n.s. (PP:4.9 vs. 4.8%)	Funding: German Cancer Aid	
Kaufmann et al. 2005	To compare TMZ alone and TMZ plus **IFN-alpha** in terms of objective response (OR), overall survival, and safety	RCT, open label Treatment: Group A TMZ alone (n=146) Group B TMZ + s.c. IFN-alpha (n=148)	294 patients with untreated stage IV metastatic melanoma	Median Overall Survival **Response Rate** Duration of Response	TMZ vs. TMZ + s.c. **IFN-alpha** 8.4 months (95% CI, 7.07 to 9.27) vs. 9.7 months (95% CI, 8.26 to 11.18), n.s., p=0.16 **13.4% (n=18 of 134 patients) vs. 24.1% (n=33 of 137 patients, sign., p=0.036** Longer in Group B	Jadad Score 3 unblinded tumor assessment by investigators Funding: Essex Pharma GmbH (Munich, Germany)	1b
Danson et al. 2003	To determine	RCT, open label	181 patients		TMZ vs. TMZ+IFN	Jadad Score 2	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	response rates, overall survival, and tolerability of the regimens temozolomide with interferon alfa-2b and, separately, with thalidomide in patients with advanced metastatic melanoma.	Treatment: Group A TMZ (n=59) Group B TMZ + Interferon alfa-2b (n=62) Group C TMZ + Thalidomide (n=60)		Median Overall Survival Overall Response Rate Response duration	vs. TMZ+Thalidomide 5.3 vs. 7.7 vs. 7.3 months 9% vs. 18% vs. 15% range 2.4 - 21.2 months	dropouts and withdrawals not described	
Agarwala et al. 2002	To determine whether the addition of **histamine** to a subcutaneousregimen of interleukin-2 (IL-2) would improve the survival of metastatic melanoma patients	RCT, open label Treatment: Group A IL-2 plus histamine (n=152) Group B IL-2 alone (n=153)	305 metastatic melanoma patients with or without previous systemic therapy except IL-2	Median Overall Survival Overall Response Rate	IL-2 + **histamine** vs. IL-2 alone 272 days (9.1 months) vs. 245 days (8.2 months), n.s., p=0.125 3% (n=5) vs. 3% (n=5), n.s.	Jadad Score 2 unblinded tumor assessment dropouts and withdrawals not described Funding: not declared	1b
Young et al. 2001	To evaluate DTIC +**IFN-alpha** in patients with metastatic melanoma	RCT, open label Treatment: Group A	61 advanced melanoma patients without previous DTIC or IFN	Median Overall Survival	DTIC +**IFN-alpha** Vs. DTIC 4.8 months (95% CI 2.0-8.0) vs. 7.2	Jadad Score 3 unblinded tumor assessment, small sample size	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		DTIC +IFN-alpha (n=30) Group B DTIC (n=31)		 Survival 6 months Overall Response Rate Duration of Response	months (95% CI 4.4-9.0), n.s., p=0.70 40% vs. 58% 18% (n=4) vs. 23% (n=6), n.s., p=0.59 median 212 days (95% CI 140–648) vs. median 180 days (95% CI 131–349)	Funding: Cancer Research Campaign and Roche Pharmaceuticals	
Falkson et al. 1998	To investigate the response rate, time to treatment failure (TTF), overall survival, and toxicity in patients with metastatic melanoma treated with dacarbazine alone, dacarbazine plus **interferon (IFN)**, dacarbazine plus tamoxifen (TMX), or dacarbazine plus	RCT, open label Treatment: Group A DTIC alone (n=69) Group B (n=68) DTIC + IFN Group C (n=66) DTIC + TMX Group D DTIC + IFN + TMX (n=68)	271 metastatic melanoma patients with no pnor chemotherapy except for adjuvant IFN	 Median Overall Survival Overall Response Rate	DTIC alone vs. DTIC + **IFN** vs. DTIC + TMX vs. DTIC + IFN + TMX pooled over the 4 Groups: 8.90 months (95% CI, 8.08 -10.8), n.s., p=0.85 15% vs. 21% vs. 18% vs. 19% (of 250 patients)	Jadad Score 3 unblinded tumor assessment Funding: in part by Public Health grants no. CA 21692, CA 23318, CA 07190, CA 18663, CA 16395, CA 66636, and CA 21115 from the National Cancer Institute, National Institutes	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	IFN plus TMX					of Health, and the Department of Health and Human Services, Bethesda. MD	
Sparano et al. 1993	To compare the response rate, survival, and toxicity of treatment with high-dose intravenous bolus interleukin-2 (IL-2) plus **interferon alfa-2a** (IFN-alpha) with high-dose IL-2 alone in patients with advanced melanoma	RCT, open label Treatment: Group A IL-2 + Interferon alfa-2a Group B IL-2 alone	85 patients	Median Overall Survival Response Rate Duration of Response	IL-2 + **IFN alpha** vs. IL-2 alone 9.7 months vs. 10.2 months, n.s. 10% (4 of 41 patients) vs. 5% (2 of 44 patients), n.s., p=0.30 11.5 months (range, 2.0 to 15.7+)	Jadad Score 3 unblinded but independently reviewed tumor assessment Funding: National Institutes of Health, Bethesda, MD, contracts no. NO1-CM73702, NO1-CM73703, N01-CM73704, NO1-CM73705, NO1-CM73706, and NO1-CM73707; National Institutes of Health Clinical Research Center grant no. MOI-RR00054 to Tufts University School ofMedicine; and by Hoffman La-Roche,	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Inc	
Thompson et al. 1993	To assess the combination of dacarbazine and **interferon-alpha 2a** versus dacarbazine alone as systemic therapy for metastatic malignant melanoma	RCT, open label Treatment: Group A DTIC plus IFN alpha 2a Group B DTIC alone	170 patients	 Median Overall Survival Response Rate Duration of Response	DTIC + **IFN alpha2a** vs. DTIC 229 vs. 269 days 21% (95% CI 13-31%) vs. 17% (95% CI 10-27%) 258 vs. 286 days		1b
Falkson et al. 1991	To assess if results with DTIC could be improved by using a combination of DTIC and **IFN alfa-2b** in metastatic malignant melanoma.	RCT, open label Treatment: Group A DTIC plus interferon alfa-2b (n=30) Group B DTIC alone (n=31)	64 metastatic melanoma patients	 **Median Overall Survival** **Overall Response Rate** Duration of Response	DTIC + **IFN alfa-2b** vs. DTIC **17.6 months vs. 9.6 months, sign., p < 0.01** **53% (n=16) vs. 20% (n=6), sign., p=0.007** Not reported	Jadad Score 2 Randomization scheme not described, unblinded tumor assessment, small sample size, imbalance of groups (more male patients in Group B) Funding: IFN alfa-2b was supplied by Scherag South Africa,	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Johannesburg.	

Chemotherapy/Chemosensitizer

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bedikian et al. 2011	To compare the efficacy and toxicity profiles of Docosahexaenoic acid (DHA)-paclitaxel with those of dacarbazine	RCT, open label Treatment: Group A DHA-paclitaxel, 900 mg/m² i.v. on day 1 every 3 weeks (n=194) Group B Dacarbazine, 1000 mg/m² i.v. on day 1 every 3 weeks (n=199)	393 chemonaive patients with metastatic melanoma	Median Overall Survival Overall Response rate Duration of Response	DHA-paclitaxel vs. DTIC 267 days (8.8 months) (95% CI 220–297) vs. 226 days (7.4months) (95% CI 192–263), n.s. 5.2% (n=10) vs. 5.5% (n=11), n.s. 134 days (4.4 months) (95% CI 77 to not estimated) vs. not estimated due to censoring pattern	Jadad Score 3 tumor assessment not described as blinded Funding: Luitpold Pharmaceuticals, Inc.	1b
Patel et al. 2011	To compare the efficacy of an extended schedule escalated dose of	RCT, open label Treatment:	859 chemotherapy-naive patients	Median Overall	TMZ vs. DTIC 9.1 months vs.	Jadad Score 3 tumor assessment was not blinded	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	temozolomide versus standard dose dacarbazine	Group A oral temozolomide 150mg/m²/day for seven consecutive days every 2weeks (n=429) Group B Dacarbazine, i.v. 1000mg/m²/day on day 1 every 3 weeks (n=430)		Survival Overall Response Rate Duration of Response	9.4months, n.s. (p=1.0) 14.5% (n=58) vs.9.8% (n=38), p=0.05 4.6 vs. 11.2 months, p=0.015, sign.	Funding: Schering Plough, UK National Cancer Research Network	
Ranson et al. 2007	To evaluate tumor response, pharmacodynamic effects, and safety of a combination of lomeguatrib (LM), an O6-methylguanine DNA-methyltransferase (MGMT) inactivator, and temozolomide (TMZ), TMZ alone, and LM/TMZ after disease progression on TMZ alone in	RCT, open label Treatment: Group A lomeguatrib 40mg/d, 2h later TMZ 125mg/m2/d, orally, 5 days every 4 weeks (n=52) Group B TMZ 125mg/m2/d, orally, 5 days every 4 weeks (n=52)	104 patients with unresectable stage III or IV cutaneous melanoma who had no prior systemic chemotherapy	Median Overall Survival Overall Response Rate	LM/TMZ vs. TMZ 7.6 months (95% CI, 6.9 - 10.3 months) vs. 7.7 months (95% CI, 6.3 - 10.7 months), n.s. 13.5% (n=7) vs. 17.3% (n=9), n.s.	Jadad Score 2 Randomization scheme not described, tumor assessment not blinded Funding: Kudos Pharmaceuticals, owned by AstraZeneca.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with advanced melanoma						
Bedikian et al. 2006	To evaluate whether targeting Bcl-2 using an antisense oligonucleotide (oblimersen sodium) could improve the efficacy of systemic chemotherapy in patients with advanced melanoma.	RCT, open label Treatment: Group A Oblimersen (7 mg/kg/d by continuous i.v.infusion for 5 days) + DTIC (n=386) Group B DTIC (n=385)	771 chemotherapy-naïve patients	Median Overall Survival PFS Overall Response Rate DurableResponse	Oblimersen + DTIC vs. DTIC 9.0 v 7.8 months; p=0.077 2.6 v 1.6 months; p=0.001 13.5% vs. 7.5% p=0.007 7.3 vs. 3.6% p=0.027	Jadad Score 4 Independent blinded tumor assessment Funding: Genta, Inc.	1b
Bafaloukos et al. 2005	To evaluate and compare the activity and safety profile of the combination Cisplatin + TMZ versus single-agent TMZ in patients with advanced melanoma	RCT, open label Treatment: Group A TMZ 200 mg/m²/day orally d1-5q28 (n=66) Group B TMZ + Cisplatin 200 mg/m² daily	132 metastatic melanoma patients with no previous chemotherapy	Median Overall Survival Overall Response Rate Duration of Response	TMZ vs. TMZ + Cisplatin 11.5 months vs. 12 months, n.s. 16 patients (26%) vs. 19 patients (29%), n.s. 5.7 months vs. 9.4 months, n.s.,	Jadad Score 2 Randomization scheme not described, tumor assessment not blinded Funding: Kudos Pharmaceuticals, owned by AstraZeneca.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		on days 1-5 and 75 mg/m² of cisplatin on day 1 (n=66)			p=0.35		
Avril et al. 2004	To compare fotemustine and dacarbazine (DTIC) in patients with disseminated cutaneous melanoma.	RCT, open label Treatment: Group A Fotemustine 100mg/m²; weekly, 3 weeks, (n = 112) Group B DTIC 250 mg/m²/d; 5d every 4 weeks, (n = 117)	229 patients	Median Overall Survival Response Rate Duration of Response	Fotemustine vs. DTIC 7.3 vs. 5.6 months, p = 0.067 13.4% vs. 6.0% (p= 0.057) n.s. difference	Jadad Score 3 Funding: Institut de Recherches Internationales Servier, Courbevoie, France	1b
Middleton et al. 2000	To compare temozolomide and dacarbazine (DTIC) in terms of overall survival, progression-free survival (PFS), objective response, and safety	RCT, open label Treatment: Group A Temozolomide (n=156) Group B DTIC (n=149)	305 advanced melanoma patients without previous treatment for metastatic disease	Median Overall Survival PFS	TMZ vs. DTIC 7.7 months vs. 6.4 months, n.s., HR 1.18 (95% CI, 0.92 to 1.52), p=0.20 (ITT population) 1.9 vs. 1.5 months; HR 1.37; sign., p=0.012	Jadad Score 3 unblinded tumor assessment, different time points for assessment between groups Funding: Not declared	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Overall Response Rate Duration of Response	13.5% (21 of 156) vs. 12.1% (18 of 149), n.s. longer in the TMZ group; 18 of the 21 TMZ responders survived longer than 12 months vs. 11 of the 18 DTIC responders		
Keilholz et al. 1997	To determine whether the addition of Cisplatin to a cytokine treatment regimen with IFN alpha and high-dose IL-2 influences survival of patients with metastatic melanoma	RCT, open label Treatment: Group A IFN alpha 10 x 106 U/m2 sc. on days 1 through 5 + IL-2 on days 3 through 8 (18 mIU/m2/6 h, 18 mIU/m2/12 h, 18 mIU/m2/24 h, and 4.5 mIU/m2/24 h x 3) Group B IFN alpha + IL-2 +	138 metastatic melanoma patients, no prior therapy with Cisplatin	Median Overall Survival Overall Response Rate Duration of Response	IFN alpha + IL-2 vs. IFN alpha + IL-2 + Cisplatin all patients: 9 months, n.s. between groups 18% vs. 33%, sign., p=0.04 17 vs. 6 months, n.s., p=0.057	Jadad Score 3 tumor assessment not blinded Funding: Chiron BV, Amsterdam, the Netherlands and Hoffmann-La Roche AG, Grenzach, Germany	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Cisplatin 100 mg/m2 on day 1					
Jungnelius et al. 1998	To investigate if the addition of Cisplatin to the combination DTIC and Vindesine could increase survival.	RCT, open label Treatment: Group A dacarbazine + vindesine + cisplatin (DVP) (n=161) Group B dacarbazine + vindesine (DV) (n=165)	326 metastatic melanoma patients, no prior chemotherapy	Median Overall Survival Overall Response Rate Duration of Response	DVP vs. DV 7.2 months vs. 5.9 months, n.s., p=0.22 31.4% vs. 21%, n.s. 6.0 months for the whole study population	Jadad Score 2 Randomization scheme not described, unblinded tumor assessment Funding: Not declared	1b
Ringborg et al. 1989	To evaluate treatment with dacarbazine alone or in combination with vindesine in patients with disseminated malignant melanoma	RCT, open label Treatment: Group A dacarbazine + vindesine (n=59) Group B dacarbazine alone (n=51)	119 patients (110 evaluable)	Median Overall Survival Overall Response Rate Duration of Response	dacarbazine + vindesine vs. dacarbazine alone 5.8 months vs. 4.7 months, n.s. 25% vs. 18%, n.s., p>0.20 171 days vs. 123 days, n.s.	Jadad Score 1 No description of dropouts, randomization scheme not described, unblinded tumor assessment Funding: Swedish Cancer Society and Eli Lilly Company	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Chauvergne et al. 1982	To evaluate the efficacy of detorubicin in combination with DTIC versus DTIC alone	RCT, open label Treatment: Group A DTIC (250 mg/m2, i.v., over 4 days every three weeks) + detorubicin (120 mg/m2, i.v. every three weeks) Group B DTIC alone	51 patient	 Median Overall Survival Overall Response Rate Duration of Response	DTIC + detorubicin vs. DTIC alone 8 months vs. 5 months, n.s. 36% (n=8 of 22 patients) vs. 15% (n=4 of 26), n.s. 6 months vs. 5 months,n.s.	Jadad Score 2 Randomization scheme not described, unblinded tumor assessment, small sample size Funding: Not declared	1b

7.2.4.2. Aktualisierungsrecherche 2015

7.2.4.2.1. RCTs- Chemotherapy/Chemosensitizer

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bedikian et al. 2014	To prospectively investigate whether Dacarbazine in combination with oblimersen was superior to Dacarbazine plus placebo in patients with advanced melanoma and low baseline LDH levels (r0.8ULN).	2-arm, phase III RCT Group A: Oblimersen 7mg/kg/day by continuous iv infusion for 5 days (120h), immediately followed by Dacarbazine 1000mg/m² iv (n=157) Group B: Placebo by continuous iv infusion for 5 days (120h), immediately followed by Dacarbazine 1000mg/m² iv (n=157)	Chemotherapy-naive patients with advanced melanoma and LDH at 0.8ULN	OS PFS Overall Response Rate (ORR) Durable Response Rate	13.5m vs 13.1m (HR: 1.04; p=0.73) 2.8m vs. 2.7m (HR: 0.85, p=0.23) 17.2% vs. 12.1% (p=0.19) 10.8% vs. 7.5% (p=0.32)	Jaded-Score: 5 Funding: Genta	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Daponte et al. 2013	To assess the effect of adding fotemustine and/or IFN to standard therapy with dacarbazine alone in patients with advanced malignant melanoma	4-arm, phase III RCT Group A: Fotemustin 100mg/m² d1 Dacarbazine 900mg/m² d2 q21 (n=64) Group B: Fotemustin 100mg/m² d1 Dacarbazine 900mg/m² d2 q21 Interferon-α2b 5UI 3x/week (n=68) Group C: Dacarbazine 900mg/m² d2 q21 (n=70) Group D: Dacarbazine 900mg/m² d2 q21	Patients with advanced melanoma	OS PFS	Median OS was 7.9 months (95% CI 6.6-10.2) for patients receiving fotemustine (groups A + B) compared with 8.6 months (95% CI 6.3-10.4) without fotemustine (groups C + D) (p=0.28). Median OS was 9.1 months (95% CI 6.3-11.1) with IFN-α2b (groups B + D) and 7.7 months (95% CI 6.3-9.7) without (groups A + C) (p=0.68). Median PFS was 2.7 months (95% CI 2.4-3.8) with fotemustine and 2.5 months (95% CI 2.3-3.7) (p=0.55) without. Median PFS was 2.8 months (95% CI 2.4-3.9) in IFN-	Jaded-Score: 3 Funding: National Cancer Institute, Naples	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Interferon-α2b 5UI 3x/week (n=58)		Response Toxicity	α2b-treated patients compared with 2.5 months (95% CI 2.3-2.9) without IFN-α2b (p=0.28). n (%) Group A: 32 (34%) Group B: 33 (26%) Group C: 34 (27%) Group D: 31 (23%) Provided as table only		
Flaherty et al. 2014	To determine whether carboplatin, paclitaxel, and sorafenib improve overall survival compared with carboplatin and paclitaxel in chemotherapy-naive patients with metastatic melanoma.	2-arm, phase III RCT Group A: Carboplatin AUC 6 q21 Paclitaxel 225mg/m² q21 Sorafenib 400mg po BID (n=410) Group B: Carboplatin AUC 6 q21	Cutaneous, mucosal, or unknown primary site melanoma, metastatic or unresectable disease.	OS PFS Objective Tumor Response (ORR)	11.1 months (95% CI, 10.3 to 12.3 months) for CPS and 11.3 months (95% CI, 9.8 to 12.2 months) for CP (p=.878) 4.9 months for CPS and 4.2 months for CP (p=.092) 20% for CPS and 18% for CP	Jaded-Score: 5 Funding: National Cancer Institute (NCI)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Paclitaxel 225mg/m² q21 (n=413)		Toxicity	(p=.427) More patients on the CPS arm had grade 3 or higher toxicities (84% v 78%; p=.027), with increased rash, hand-foot syndrome, and thrombocytopenia accounting for most of the difference.		
O'Day et al. 2013	To confirm the efficacy and tolerability of Elesclomol in combination with paclitaxel versus paclitaxel alone in patients with advanced melanoma	2-arm, phase III RCT Group A: Elesclomol 213 mg/m² and Paclitaxel 80 mg/m² weekly for 3 weeks followed by one week drug holiday Group B: Placebo + Paclitaxel 80 mg/m² weekly for 3 weeks followed	Patients with advanced (stage IV) melanoma of cutaneous origin and one or more measurable lesions	PFS	Median PFS was 3.4 months in the combination group and1.9 months in the paclitaxel group(HR,0.89;95% CI,0.73to1.08). A prospectively defined subgroup analysis revealed a statistically significant improvement in median PFS for the combination in patients with	Jaded-Score: 5 Funding: Synta Pharmaceuticals	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		by one week drug holiday Patients were stratified by prior systemic treatment, M1 subclass, and baseline lactate dehydrogenase (LDH) levels		OS	normal baseline LDH. The study was stopped when an early overall survival data analysis indicated an imbalance in total deaths favouring paclitaxel, predominantly in patients with high LDH levels. Median OS was 10.6 months in the combination group and 11.4 months in the paclitaxel group (HR, 1.10; 95% CI, 0.92 to 1.32;p=.18).		

7.2.4.2.2. RCTs- Immuntherapie/Immunmodulation

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Andtbacka et al.	To evaluate	2-arm, phase III	Not surgically	Durable Response	DRR was higher	Jadad-Score: 3	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2015	whether treatment with T-VEC resulted in an improved durable response rate (DRR) compared with GM-CSF in patients with unresected stage IIIB to IV melanoma.	RCT Treatment: Group A: Talimogene Laherparepvec (n=295) Group B: GM-CSF (n=141)	resectable, stage IIIB to IV melanoma suitable for direct or ultrasound-guided injection (at least one cutaneous, subcutaneous, or nodal lesion or aggregation of lesions 10 mm in diameter).	Rate Overall Response Rate Overall Survival	with T-VEC (16.3%; 95% CI, 12.1% to 20.5%) than GM-CSF (2.1%; 95% CI, 0% to 4.5%]; odds ratio, 8.9; P <.001). Overall response rate was higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% v 5.7%; 95% CI, 1.9% to 9.5%). Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) with T-VEC and 18.9 months (95% CI, 16.0 to 23.7 months) with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; P .051).	T-VEC efficacy was most pronounced in patients with stage IIIB, IIIC, or IVM1a disease and in patients with treatment-naive disease. Funded by: AMGEN	
Larkin et al. 2015	To confirm and extend [*findings of*	3-arm, phase III, RCT	Stage III (unresectable) or	Progression-free survival (PFS)	Median PFS: 11.5 months (95% CI,	Jadad-Score: 5	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	a phase 2 trial], we report one of the coprimary end points (progression-free survival) of a randomized, double-blind, multi-center, phase 3 trial (CheckMate 067) that was conducted to evaluate the safe-ty and efficacy of nivolumab alone or nivolumab comb-ined with ipilimu-mab in comparison with ipilimumab alone in patients with previously untreated meta-static melanoma.	Group A: Nivolumab alone (n=316) 3mg/kg q14 (plus Ipilimumab-matched placebo); Group B: Nivolumab comb-ined with Ipilimu-mab (n=314) Nivolumab 1mg/kg q21 plus Ipilimumab 3 mg/kg q21 for 4 doses, followed by Nivolumab 3mg/kg q14 Group C: Ipilimumab alone (n=315) 3mg/kg q21 for 4 doses (plus Nivolumab-matched placebo).	stage IV melanoma patients, no prior systemic treatment for advanced disease. Availability of tissue collected from metastatic or unresectable tumors (archival or recently biopsied samples) for the assessment of PD-L1 status; and known BRAF V600 mutation status.	Overall survival Objective Response Rate Tumor PD-L1 expression as a predictive biomarker for efficacy outcomes.	8.9 to 16.7) with nivolumab plus ipilimumab, vs. 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001), vs 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (HR for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001). Not reported on In patients with tumors positive for the PD-L1, median PFS was 14.0 months in the nivolumab-plus-	Overall survival data (coprimary end point) not available so far. Study not powered to confirm benefit of Nivo+Ipi vs Nivo alone. PD-L1 status of tumor tissue as stratification factor Funded by: Bristol-Myers Squibb	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Safety	ipilimumab group and in the nivolumab group, but in patients with PD-L1–negative tumors, progression-free survival was longer with the combination therapy than with nivolumab alone (11.2 months [95% CI, 8.0 to not reached] vs. 5.3 months [95% CI, 2.8 to 7.1]). Treatment-related adverse events of grade 3 or 4 occurred in 16.3% of the patients in the nivolumab group, 55.0% of those in the nivolumab-plus-ipilimumab group, and 27.3% of those in the ipilimumab group.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Maio et al. 2015	To conduct a milestone survival analysis of data from a randomized controlled phase III trial to confirm the survival benefit of ipilimumab in patients with advanced melanoma.	OS follow up from a RCT Group A: Ipilimumab 10mg/kg q21 + DTIC 850mg/m^2 (n=250) Group B: DTIC 850mg/m^2+ Placebo (n=252)	Untreated stage IIIc, N3 (unresectable) or stage IV melanoma	Overall survival 5-Y-OS	Median survival follow-up for the ipilimumab plus dacarbazine group was 11.0 months (range,0.4 to 71.9 months) and was 8.9 months (range, 0.1 to 73.2 months) for the placebo plus dacarbazine group. The updated median OS was 11.2months(95% CI, 9.5 to 13.8 months) in the ipilimumab plus dacarbazine group and was 9.1 months (95% CI, 7.8 to 10.5 months) in the placebo plus dacarbazine group (HR, 0.69; 95% CI, 0.57 to 0.84). OS rates in the ipilimumab plus	Jadad-Score: Not applicable Updated OS data from a previously published trial. Different dosing of Ipilimumab in contrast to the approved one in the EU Funded by: Bristol-Myers Squibb	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					dacarbazine group were consistently higher than those in the placebo plus dacarbazine group. At a minimum follow-up of 5 years, 18.2% of patients in the ipilimumab plus dacarbazine group were still alive compared with 8.8% of patients in the placebo plus dacarbazine group (P.002).		
McDermott et al. 2013	To describe the safety and long-term efficacy of ipilimumab among patients from the pivotal phase III MDX010-20 study who survived 2 years or longer	Updated data from a 3-arm phase III RCT Of 676 patients treated in MDX010-20, 474 were randomized at least 2 years before the study cut-off date and were eligible for this analysis.	Patients with unresectable stage III or IV melanoma who had been treated previously with chemotherapy or interleukin-2 (IL-2) were randomized 3:1:1.	Long term OS (2-3 Y OS rate)	≥2 years Ipi+gp100 54 of 284 (19%) Ipi 24 of 95 (25%) gp100 16 of 95 (17%) ≥3 years Ipi+gp100 24 of 156 (15%) Ipi 13 of 53 (25%)	Jadad-Score: Not applicable Subset analysis of the MDX010-20 study Funded by: Bristol-Myers Squibb	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Group A: Ipilimumab 3mg/kg q21 for 4 doses plus gp100 vaccine 2mL sc q21 for 4 doses (n=284) Group B: Ipilimumab 3mg/kg q21 for 4 doses (n=95) Group C: gp100 2mL sc q21 for 4 doses (n=95)		Safety	gp100 5 of 50 (10%) Safety in patients with ≥2 years' survival was comparable to that in the overall study population.		
Ribas et al. 2013	To evaluate overall survival (OS) and other safety and efficacy end points in patients with advanced melanoma treated with tremelimumab or standard-of-care chemotherapy.	2-arm RCT, phase III Group A: Tremelimumab 15 mg/kg once every 90 days (n=328) Group B: Physician's choice	Patients with treatment-naive, unresectable stage IIIc or IV melanoma	OS	Median OS by ITT was12.6months (95%CI, 10.8-14.3 months) in the tremelimumab arm and 10.7 months (95% CI, 9.4 to 12.0 months) in the chemotherapy arm (HR,0.88;P.127).	Jadad-Score: 3 Funded by: Pfizer	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		of standard-of-care chemotherapy (temozolomide or dacarbazine, n=327).			Survival at 2 and 3 years was 26.4% (95% CI, 22.0% to 31.7%) and 20.7% (95% CI, 16.7% to 25.6) in patients treated with tremelimumab and 22.7% (95% CI, 18.5% to 27.8%) and 17.0% (95% CI, 13.3% to 21.7%), in patients in the chemotherapy arm.		
				ORR	ORR based on investigator assessment were similar in both study arms:10.7% in the tremelimumab arm and 9.8% in the chemotherapy arm There were no significant differences between study arms in rate of		
				Response duration			

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					complete or partial response. Median response duration (defined as time from random assignment to progression or death resulting from disease progression for the objective responders) was significantly longer among tremelimumab responders compared with chemotherapy responders: 35.8 months (range, 5.6 to 44.3 months) versus 13.7 months (range, 4.0 to 44.3 months; P .0011).		
				Safety	Grade 3/4 AEs Tremelimumb: 52% Chemo: 37%		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Grade 5: Tremelimumab: 7% Chemo: 4%		
Robert el at. 2013	To describe the rationale for retreatment with ipilimumab and to provide resultant efficacy and safety outcomes	Subset of a 3-arm RCT Group A: Ipilimumab 3mg/kg q21 for 4 doses plus gp100 vaccine 2mL sc q21 for 4 doses (n=29) Group B: Ipilimumab 3mg/kg q21 for 4 doses (n=9) Group C: gp100 2mL sc q21 for 4 doses (n=2)	Patients with unresectable stage III or IV melanoma who had been treated previously with chemotherapy or interleukin-2 (IL-2) were randomized 3:1:1.	BOOR Safety	Best overall response rates (CR+PR) for 31 retreatment-eligible patients in the ipilimumab plus gp100 and ipilimumab plus placebo groups were 3 of 23 (13.0%) and 3 of 8 (37.5%), respectively, and disease control rates were 65.2% and 75.0%. Drug-related adverse events were reported in 25 patients (86.2%), 7 patients (77.8%), and 2 patients (100%) in the ipilimumab plus gp100, ipilimumab plus	Jadad-Score: not applicable Subset analysis of the MDX010-20 study Funded by: Bristol-Myers Squibb	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					placebo, and gp100 plus placebo arms, respectively. The most common adverse events were irAEs, occurring in 15patients (51.7%), 7 patients (77.8%), and 1 patient (50.0%) in the respective groups.		
Robert at al. 2015	To determine whether nivolumab, as compared with dacarbazine, improves overall survival among pre-viously untreated patients who have advanced melanoma without a BRAF mutation	2-arm RCT, phase III 1:1 randomisation Group A: Nivolumab 3mg/kg q14 plus a dacarbazine-matched placebo every 3 weeks Group B: Dacarbazine 1000mg/m^2 q21 plus a nivolumab-matched placebo	Unresectable, previously untreated stage III or IV melanoma without a BRAF mutation.	OS Investigator-assessed PFS	1 Y-OS rate of survival was 72.9% (95% confidence interval [CI], 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (HR for death, 0.42; 99.79% CI, 0.25 to 0.73; P<0.001). Median PFS was 5.1 months in the	Jadad-Score: 5 BRAF wt patients only PD-L1 status of tumor tissue as stratification factor Funded by: Bristol-Myers Squibb	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		every 2 weeks.		ORR PD-L1 expression in the tumor as a predictive biomarker of OS	nivolumab group vs 2.2 months in the dacarbazine group (HR for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; P<0.001). ORR was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group vs 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; P<0.001). Regardless of PD-L1 status, nivolumab-treated patients had improved OS, as compared with dacarbazine-treated patients (unad-justed HR for death among patients with		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					positive PD-L1 status, 0.30 [95% CI, 0.15 to 0.60]; unadjusted hazard ratio for death among those with PD-L1 negative or indeterminate PD-L1 status, 0.48 [95% CI, 0.32 to 0.71]). In the nivolumab group, the median OS was not reached in either PD-L1 subgroup. In the dacarbazine group, the median OS was slightly longer in the subgroup with positive PD-L1 status than in the subgroup with negative or indeterminate PD-L1 status (12.4 vs. 10.2 months)		
Robert et al. 2015	To compare PD-1 inhibition with	3-arm RCT, phase III	Patients had to had histologically	PFS	Estimated 6-month PFS rates were	Jadad-Score: 3	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	CTLA-4 blockade in a controlled, randomized trial involving patients with advanced melanoma	Group A: Pembrolizumab 10mg/kg q14 Group B: Pembrolizumab 10mg/kg q21 Group C: Ipilimumab 3mg/m^2 q21 for 4 cycles	confirmed, unresectable stage III or IV melanoma and had received no more than one previous systemic therapy for advanced disease. Known BRAF V600 mutational status was required.	OS	47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (HR for disease progression, 0.58; P<0.001 for both pembrolizumab regimens vs ipilimumab; 95% confidence intervals [CIs], 0.46 to 0.72 and 0.47 to 0.72). Estimated 12-month OS rates were 74.1%, 68.4%, and 58.2% (HR for death for pembrolizumab every 2 weeks, 0.63; 95% CI, 0.47 to 0.83; P = 0.0005; HR for pembrolizumab every 3 weeks,	PD-L1 status of tumor tissue as stratification factor Funded by: Merck Sharp & Dohme	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				ORR	0.69; 95% CI, 0.52 to 0.90; P=0.0036). ORR was improved with pembrolizumab administered every 2 weeks (33.7%) and every 3 weeks (32.9%), as compared with ipilimumab (11.9%) (P<0.001 for both comparisons).		
				Duration of response	Responses were ongoing in 89.4%, 96.7%, and 87.9% of patients, after a median follow-up of 7.9 months.		
Schadendorf et al. 2015	To provide a more precise estimate of long-term survival observed with ipilimumab therapy, we conducted a pooled analysis of	Primary analysis pooled OS data for 1,861 patients from 10 prospective and two retrospective studies of ipilimumab,	Patients with advanced melanoma	OS	Among 1,861 patients, median OS was 11.4 months (95% CI, 10.7 to 12.1 months). The survival curve	Jadad-Score: not applicable Mixed cohorts, maybe data from EAPs more valuable because it reflects the	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	OS data across multiple studies in advanced melanoma.	including two phase III trials. Patients were previously treated (n=1,257) or treatment naive (n=604), and the majority of patients received ipilimumab 3 mg/kg (n=965) or 10 mg/kg (n=706). Secondary analysis of OS data (n=4,846) with an additional 2,985 patients from an expanded access program.			began to plateau around year 3, with follow-up of up to 10 years. Three-year survival rates were 22%,plateau around year 3, with follow-up of up to 10 years. Three-year survival rates were 22%, 26%, and 20% for all patients, treatment-naive patients, and previously treated patients, respectively. Including data from the expanded access program, median OS was 9.5 months (95% CI, 9.0 to 10.0 months), with a plateau at 21% in the survival curve beginning around	standard of care more precisely. Funded by: Bristol-Myers Squibb	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					year 3.		
Weber et al. 2015	To assessed the efficacy and safety of nivolumab compared with investigator's choice of chemotherapy (ICC) as a second-line or later-line treatment in patients with advanced melanoma.	2-arm phase III RCT Randomisation schedule 2:1 Group A: Nivolumab 3 mg/kg q14 (n=272) Group B: Investigator's choice of chemotherapy (ICC) (dacarbazine 1000 mg/m² q21 or paclitaxel 175 mg/m² combined with carboplatin area under the curve 6 q21) (n=133)	Patients had unresectable or metastatic melanoma, and progressed after ipilimumab, or ipilimumab and a BRAF inhibitor if they were BRAFV600 mutation-positive.	ORR PFS Safety	38 (31.7%, 95% CI 23.5–40.8) of the 120 patients in the nivolumab group and in five (10.6%, 3.5–23.1) of the 47 patients in the ICC group archived an objective response. Median PFS was 4,7 months (95% CI 2,3–6,5) for the nivolumab group and 4,2 months (2,1–6,3) for the ICC group (HR 0.82; 99.99% CI 0·32–2·05) 6-month PFS was 48% (95% CI 38–56) in the nivolumab group and 34% (18–51) in the ICC group. Grade 3–4 treatment-related adverse events	Jadad-Score: 3 BRAF-Mutation status, PDL1-expression and best response to Ipilimumab used as stratification factors. ORR/PFS only reported for a subset of patients Funded by: Bristol-Myers Squibb	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					occurred in 24 (9%) of the 268 patients in the nivolumab group versus 32 (31%) of the 102 patients in the ICC group.		

7.2.4.2.3. Zielgerichtete Therapien /small molecules

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Flaherty et al. 2012	Not specified in report	Open-label, 2-armed Phase III RCT Group A: Trametinib (n=214) Group B: Chemotherapy (DTIC or Paclitaxel) (n=108)	Patients who had histologically confirmed, unre-sectable stage IIIC or IV cutaneous melanoma with a V600E or V600K BRAF mutation were eligible. Up to one previous chemotherapy schedules allowed.	Progression-free survival (PFS) Overall survival (OS)	4.8 months in the Trametinib group as compared with 1.5 months in the chemotherapy group (HR for progression, 0.45; 95% CI, 0.33-0.63; P<0.001) 6-month OS rate in the ITT population was 81% in the Trametinib group and 67% in the chemotherapy group. The HR for death in the	Jaded-Score: 3 Funding: GlaxoSmithKline	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Trametinib group was 0.54 (95% CI, 0.32-0.92; P=0.01), even though 51 of 108 patients (47%) in the chemotherapy group crossed over to receive Trametinib. Median overall survival had not been reached at the time of this report.		
				Overall response rate (ORR)	ORR 22% (95% CI, 17-28) in the Trametinib group and 8% (95% CI, 4-15) in the chemotherapy group		
				Duration of response	Median duration of response was 5.5 months (95% CI, 4.1 to 5.9) in the Trametinib group (in 47 pts.) and had not been		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Safety	reached in the chemotherapy group (in 9 pts). Rash, diarrhoea, and peripheral oedema were the most common toxic effects in the Trametinib group and were managed with dose interruption and dose reduction; asymptomatic and reversible reduction in the cardiac ejection fraction and ocular toxic effects occurred infrequently. Secondary skin neo-plasms were not observed.		
Hauschild et al. 2012	To assess whether Dabrafenib was better than standard Dacarbazine	Open-label, 2-armed Phase III RCT, randomly assigned 3:1	Patients aged 18 years or older with previously untreated, stage IV or unresectable	PFS (by investigator)	Median PFS was 5.1 months for Dabrafenib and 2.7 months for Dacarbazine, with	Jaded-Score: 3 Funding: GlaxoSmithKline	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	chemo-therapy, we did a phase 3, multi-centre, randomised trial in previously untreated melanoma patients whose tumours harboured a BRAFV600E mutation.	Group A: Dabrafenib 150mg bid p.o. (n=187) Group B: Dacarbazine 1000mg/m² iv q21 (n=63)	stage III BRAFV600E mutation-positive melanoma	PFS (by Independent Review) OS ORR	a HR of 0.30 (95% CI 0.18–0.51; p<0.0001). Median PFS for Dabrafenib was 6.7 months versus 2.9 months for Dacarbazine (HR 0.35; 95% CI 0.20–0.61). The overall survival HR was 0.61 (95% CI 0.25–1.48) in favour of Dabrafenib. Confirmed OR was reported by the IR in 93 (50%, 95% CI 42.4–57.1) of 187 patients randomly assigned to Dabrafenib (6 [3%] had a complete response and 87 [47%] had a partial response). In the Dacarbazine group, confirmed		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					responses were seen by the IR in four (6%, 95% CI 1.8–15.5) of 63 patients. Confirmed OR was reported by the investigator in 99 (53%, 95% CI 45.5-60.3) of the 187 patients (6 [3%] had a CR and 93 [50%] had a PR). Confirmed responses for the Dacarbazine group were reported by the investigator in 12 (19%, 10.2–30.9) patients (all 12 patients had a partial response).		
				PFS after cross-over	28 patients randomly assigned to Dacarbazine have crossed over to Dabrafenib at data cutoff; 13 (46%) patients have		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					had PR but, among these patients, no CR has been noted.		
				Duration of response	The estimated median duration of response for Dabrafenib was 5.5 months for IR and 5.6 months for investigator assessment. The estimated median duration of response for Dacarbazine was not reached at time point of data cut.		
				Quality of life	Quality of life analyses are ongoing and will be reported separately.		
				Safety & Tolerability	In patients receiving Dabrafenib, the most common AEs		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					were cutaneous (hyperkeratosis, papillomas, palmar-plantar erythrodysaesthesia), pyrexia, fatigue, headache, and arthralgia. Toxic effects of grade 3–4 were uncommon.		
Larkin et al. 2014	To confirm and build on these early data, we report on the primary end point of coBRIM, an inter-national, multicenter, randomized phase 3 study that evaluated the efficacy and safety of cobimetinib combined with vemurafenib in previously untreated patients with advanced BRAF-mutated melanoma.	Double-blinded, 2-armed Phase III RCT Group A: Vemurafenib 960 mg bid po Cobimetinib (at a dose of 60 mg once daily for 21 days, followed by 7 days off) (n=247) Group B: Vemurafenib 960 mg bid po Placebo (n=248)	Histologically confirmed unresectable, locally advanced stage IIIC or stage IV melanoma with a BRAF V600 mutation detected with the use of a real-time polymerase-chain-reaction assay (Cobas 4800 BRAF V600 Mutation Test, Roche Molecular Systems)	PFS as assessed by the investigator, Overall Survival	VEM+COBI: Median PFS of 9.9 months (95% CI, 9.0 to not reached), as compared with 6.2 months (95% CI, 5.6 to 7.4) in patients treated with VEM and placebo. HR for death or progression of disease: 0.51 (95% CI, 0.39 to 0.68; P<0.001) The interim analysis of OS in the ITT-population showed that the	Jaded-Score: 5 Funding: F Hoffmann-La Roche-Genentech	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				ORR	rate of overall survival at 9 months for the combination of VEM+COBI was 81% (95% CI, 75-87), as compared with 73% (95% CI, 65-80) with VEM+Placebo 68% of patients in the combination group had an objective response, as compared with 45% in the control group (P<0.001). The rate of complete response was also significantly higher in the combination group than in the control group (10% vs. 4%).		
				Duration of response	The median duration of response was 7.3 months in the		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				PFS as assessed by an independent review facility	control group, and the median was not reached in the combination group. 11.3 months for VEM+COBI (95% CI 5.6-7.5) vs 6.0 months for VEM+Placebo (95% CI 8.5-NE); HR 0.6 (95% CI 0.45-0.79, p=0.0003)		
				Safety	The combination of VEM and COBI was associated with a higher frequency of certain events than the single-agent therapy, including central serous retinopathy, gastrointestinal events (diarrhoea, nausea, or vomiting), photo-sensitivity, elevated		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					aminotransferase levels, and an increased creatine kinase level; the majority (>50%) of these individual events were grade 1 or 2. We observed equivalent rates of grade 3 events (49%) in the two study groups and substantially fewer grade 4 events (9% in the control group vs. 13% in the combination group).		
Long et al. 2014	To compare the combination of Dabrafenib and Trametinib with Dabrafenib alone as first-line therapy in patients who had metastatic melanoma with BRAF V600E or V600K mutations	Double-blinded, 2-armed Phase III RCT Group A: Dabrafenib 150mg bid po Trametinib 2mg/d (n=211) Group B:	Histologically confirmed, unresectable stage IIIC or stage IV metastatic melanoma with BRAF V600E or V600K mutations, as determined by means of an investigational-use-	PFS (investigator-assessed)	In the ITT population, median PFS was longer in the Dabrafenib–Tra-metinib group than in the Dabrafenib-only group (9.3 months vs. 8.8 months); the hazard ratio for	Jaded-Score: 5 Funding: GlaxoSmithKline	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Dabrafenib 150mg bid po Placebo (n=212)	only polymerase-chain-reaction assay (ThxID BRAF Assay, bioMérieux) performed at a central reference laboratory.	OS Response rate	disease progression or death was 0.75 (95% CI, 0.57 to 0.99; P = 0.03). At the time of the interim survival analysis, 40 patients (19%) in the Dabrafenib–Trametinib group and 55 patients (26%) in the Dabrafenib-only group had died (HR for death, 0.63; 95% CI, 0.42 to 0.94; P = 0.02). At 6 months, the OS rate was 93% in the Dabrafenib–Trametinib group and 85% in the Dab-rafenib-only group. At the time of this report, neither group had reached a median overall survival.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Response duration	The ORR as assessed by investi-gators was 67% (95% CI, 60-73) in the Dabrafenib–Trametinib group vs 51% (95% CI, 45-58) in the Dabrafenib-only group (P=0.002) In the Dabrafenib–Trametinib group, 22 patients (10%) had a complete response, and 118 (56%) had a partial response. In the Dabrafenib-only group, 18 (9%) had a complete response, and 90 (43%) had a partial response. The median duration of response was 9.2 months in the Dabrafenib–Trametinib group		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Safety	and 10.2 months in the Dabrafenib-only group on the basis of data that were highly censored because the majority of investigator-assessed responses (60%) were still ongoing. Rates of AEs were similar in the two groups, although more dose modifications occurred in the Dabrafenib–Trametinib group. The rate of cutaneous squamous-cell carcinoma was lower in the Dabrafenib–Trametinib group than in the Dabrafenib-only group (2% vs. 9%), whereas pyrexia		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					occurred in more patients (51% vs. 28%) and was more often severe (grade 3, 6% vs. 2%) in the Dabrafenib–Trametinib group.		
Long et al. 2015	To report the final overall survival analysis for the randomised, double-blind phase 3 study of Dabrafenib combined with Trametinib compared with Dabrafenib combined with placebo in previously untreated patients with BRAF Val600Glu/Lys mutation-positive metastatic melanoma, and provide the latest findings for progression-free	Double-blinded, 2-armed Phase III RCT Group A: Dabrafenib 150mg bid po Trametinib 2mg/d (n=211) Group B: Dabrafenib 150mg bid po Placebo (n=212)	Histologically confirmed, unresectable stage IIIC or stage IV metastatic melanoma with BRAF V600E or V600K mutations, as determined by means of an investigational-use-only polymerase-chain-reaction assay (ThxID BRAF Assay, bioMérieux) performed at a central reference laboratory.	PFS (investigator-assessed) OS Response rate	11.0 months for the combination (95% CI: 8.0-13.9) vs. 8.8 months for the Dabrafenib-only group (95% CI: 5.9-9.3), HR=0.67 (0.53-0.84),p=0.0004 Median OS for the Dabrafenib+Trametinib group was 25.1 months (95% CI,: 19.2–NR) vs. 18.7 months (95% CI 15.2–23.7); HR= 0.71 (95% CI: 0.55–0.92), p=0.0107 69% (95% CI: 62-75) for the	Jaded-Score: 5 Funding: GlaxoSmithKline Same as previous trial but with longer follow up and overall survival data	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	survival, response rate, duration of response, and safety.			Response duration Safety	Dabrafenib+Trametinib group vs. 53% (95% CI: 46-60), p=0.014 12.9 months (95% CI: 9.4-19.5) vs. 10.6 months (95% CI: 9.1-13.8) Treatment-related AEs occurred in 181 (87%) of 209 patients in the Dabrafenib and Trametinib group and 189 (90%) of 211 patients in the Dabrafenib only group; the most common was pyrexia (108 patients, 52%) in the Dabrafenib and Trametinib group, and hyperkeratosis (70 patients, 33%) in the Dabrafenib only group. Grade 3 or 4 adverse events occurred in		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					67 (32%) patients in the Dabrafenib and Trametinib group and 66 (31%) patients in the Dabrafenib only group.		
McArthur et al. 2014	To present an update of safety and efficacy for the BRIM-3 study with extended follow-up for the entire population, and also analyse the efficacy and safety of Vemurafenib versus Dacarbazine in patients with BRAFV600E and BRAFV600K mutation-positive disease	Open-label, Phase III RCT Group A: Vemurafenib (960 mg bid po) (n=337) Group B: Dacarbazine 1000mg/m² iv q21 (n=338)	Treatment-naive metastatic melanoma (unresectable stage IIIc or stage IV M1a, M1b, or M1c disease) with tumour tissue positive for the presence of BRAFV600 mutations by the cobas test.	OS	Median OS censored at crossover, was 13.6 months (95% CI 12.0–15.2) in the Vemurafenib group versus 9.7 months (7.9–12.8) in the Dacarbazine group; 12 month overall survival was 56% (95% CI 50–61) for Vemurafenib and 44% (38–51) for Dacarbazine censored at crossover. HR for death was 0.70 (95% CI 0.57–0.87; p=0.0008). An ITT analysis of OS using the observed	Jaded-Score: 3 Funding: F Hoffmann-La Roche-Genentech Updated data for the BRIM3 trial	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				PFS	survival times, without regard to crossover, resulted in an HR of 0.76 (95% CI 0.63–0.93; p=0.0068). Median PFS censored at crossover was also significantly longer in the Vemurafenib group than in the Dacarbazine group (6.9 months [95% CI 6.1–7.0] vs 1.6 months [1.6–2.1]), respectively; HR 0.38, 95% CI 0.32–0.46; log-rank p<0.0001		
				Proportion of patients with a confirmed response (CR or PR).	Objective responses, confirmed by an IR, were noted in 57% of patients receiving Vemurafenib and 9% of patients treated with		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Time to response Duration of response Time to treatment failure Pharmacokinetic profile Tolerability and safety	Dacarbazine Independently confirmed CR were attained by 6% of the patients in the Vemurafenib group and 1% of patients in the Dacarbazine group. Not reported Not reported Not reported Most common grade 3/4 AEs of interest in patients treated with Vemurafenib were cutaneous squamous-cell carcinomas, increased liver function tests,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					keratoacanthomas, rash, and arthralgia. Grade 4 or worse adverse events occurred in 29 (8%) patients in the Vemurafenib group (three [1%] increased liver function test, one [<1%] neutropenia), and 32 (11%) patients in the Dacarbazine group (nine [3%] were neutropenia). Seven (2%) patients in the Dacarbazine group and eight (2%) in the Vemurafenib group had grade 5 events. Additionally, eight (2%) patients in the Vemurafenib group reported new primary melanomas. 673 of the 675		
				Validation of the cobas test			

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients (336 patients in the Vemurafenib group and 337 in the Dacarbazine group) to differentiate BRAFV600E and BRAFV600K mutations. Of these 673 patients, Sanger/454 sequencing could not provide a valid result for 14 patients. Therefore, 657 (98%) of 671 patients had tumours that were cobas-positive at screening and for whom Sanger 454 sequencing results were available. Of these 657 tumours, 598 (91%) carried the BRAFV600E mutation, 57 (9%) had the		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					BRAFV600K mutation		
Robert et al. 2015	To evaluate the effect of combination therapy with Dabrafenib plus Trametinib versus Vemurafenib monotherapy on overall survival in previously untreated patients with unresectable stage IIIC or IV melanoma with BRAF V600E or V600K mutations.	Open-label, Phase III RCT Group A: Dabrafenib 150mg bid po Trametinib 2mg/d (n=211) Group B: Vemurafenib 960mg/d bid po	Patients with metastatic melanoma with a BRAF V600 mutation. The presence of BRAF V600E or V600K mutations was centrally determined with the investigational use of the THxID BRAF assay (bioMérieux).	OS PFS	100 patients (28%) in the combination-therapy group and 122 (35%) in the Vemurafenib group had died (HR for death in the combination-therapy group, 0.69; 95% CI, 0.53-0.89; P=0.005) Median OS was 17.2 months for patients in the Vemurafenib group and had not been reached for patients in the combination group Median PFS was longer in the combination group than in the Vemurafenib group (11.4 months vs. 7.3 months; of	Jaded-Score: 3 Funding: Glaxo-SmithKline	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				ORR	response was 13.8 months (95% CI, 11.0 to not reached) and 7.5 months (95% CI, 7.3-9.3), respectively. The response rate for the BRAF V600E subgroup was similar to that in the overall population in both study groups: 64% in the combination group and 52% in the Vemurafenib group; in the BRAF V600K subgroup, the response rates were 65% and 44%, respectively.		
				Duration of response	13.8 months (95% CI: 11.0–NR) vs 7.5 months (95% CI: 7.3–9.3)		
				Safety	Rates of severe adverse events and		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					study-drug discontinuations were similar in the two groups. Cutaneous squamous-cell carcinoma and keratoacanthoma occurred in 1% of patients in the combination-therapy group and 18% of those in the Vemurafenib group.		

7.2.4.2.4. Reviews

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Aubin et al. 2013	To review the available literature on liver resection for metastatic melanoma in a systematic manner, and to compare oncological outcomes for surgery with standard therapy using meta-analytical techniques.	Systemic review and meta-analysis Initial literature search revealed 423 potential reports Finally 22 selected for full review after checking eligibility criteria	579 patients who underwent liver resection	Overall survival (OS) Hazard ratios (HRs) Disease-free survival (DFS)	Median OS: 14-41 months (R0, 22–66months, R2, 10–16months; R0 versus R1/R2: HR 0.52, 95% CI 0.37 to 0.73). Comparison of OS with resection and non-operative management favoured resection (HR 0.32, 95% CI 0.22 to 0.46). Median DFS: 8 to 23months	5 studies describe a comparison between surgical excision of liver metastases and systemic treatment of patients suffering from hepatic metastases. Overall, there is a trend to a favourable prolongation in OS for patients receiving excision of liver lesions. Overall a valuable review/meta-analysis, however – as the authors admit – with studies of low quality involved.	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Buder at al. 2013	To review the present status of systemic treatment of metastatic uvea melanoma and evaluate therapy outcome measured by overall response rate (ORR)	Systematic review PubMed search was performed for “metastatic” [and] “uveal” [and] “melanoma” as well as for “melanoma” [and] “eye” [and] “treatment” for the time period between 1980 and May 2013. “Web of Knowledge” and congress abstract search via the ASCO homepage was per-formed. The ClinicalTrials.gov website was searched for terms “melanoma” and “eye”. Of 2017 references, 40 studies were selected for final analyses	841 patients out of 40 studies	Overall response rate (ORR)	39/841 patients with remission (overall response rate [ORR] 4.6%; 95% confidence intervals [CI] 3.3–6.3%) No responses were observed in 22/40 studies. Progression-free survival ranged from 1.8 to 7.2, median overall survival from 5.2 to 19.0 months as reported in 21/40 and 26/40 studies, respectively. Best responses were seen for chemoimmunotherapy (ORR 10.3%; 95% CI 4.8–18.7%) though mainly in first-line patients. Immunotherapy	Uvea melanoma only. Well described, however due to lack of appropriate studies, no phase III data included	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					with ipilimumab, antiangiogenetic approaches, and kinase inhibitors have not yet proven to be superior to chemotherapy.		
Dequen et al. 2012	To perform a systematic literature review and network meta-analysis to compare overall survival with 3 mg/kg ipilimumab with alternative therapies in the treatment of pre-treated patients with unresectable stage III or IV melanoma.	Systematic review of randomized controlled trials unresectable stage III or IV melanoma, Systematic literature search performed in MEDLINE, MEDLINE-In-Pro-cess, EMBASE, and the Cochrane Library. Key words and free text were combined to include the dis-ease-specific search terms “skin-neoplasms” and	2739 patients from 15 studies	Mean OS	Ipilimumab, at a dose of 3 mg/kg, was associated with a greater mean OS time (18.8 months; 95% credible interval [CrI], 15.5–23.0 months) than single-agent chemotherapy (12.3 months; 95% CrI, 6.3–28.0 months), chemotherapy combinations (12.2 months; 95% CrI, 7.1–23.3 months), biochemotherapies (11.9 months; 95% CrI, 7.0–22.0 months), single-	Statistically sophisticated review with a Bayesian network meta-analysis approach. Interestingly, a parametric survival distribution (Gompertz) was selected for analysis. Meta-analyses missed BRAF/MEK inhibitors.	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		"melanoma"; the disease-staging terms "metastatic," "advanced," and "stage III/3 or IV/4"; and non-proprietary drug names. 1,793 references detected, 38 studies finally included. During evaluation the number of studies had to be reduced to 15 studies			agent immunotherapy (11.1 months; 95% CrI, 8.5–16.2 months), and immunotherapy combinations (14.1 months; 95% CrI, 9.0–23.8 months).		
Jiang et al. 2014	To comprehensively analyse the data from clinical RCTs to evaluate the efficacy and safety of DTIC alone versus DTIC combined targeted therapy in treatment of metastatic melanoma.	Systematic review and meta-analyses The Cochrane Library, MEDLINE, EBSCO, EMBASE, Ovid databases and clinical trial websites from 2003 to 2013 were scanned. The search strategy included the	2,221 patients included in 8 randomized controlled trials	Overall response (CR+PR). 1-year survival	The overall response in the arm for DTIC combined targeted therapy was higher than that in the arm for DTIC alone (combined RR=1.60; 95% CI, 1.27–2.01, Z=3.98) The 1-year survival in the arm for DTIC	Meta-analyses also for adverse events	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		keyword ''DTIC'' combined with the Medical Subject Headings (MeSH) ''metastatic melanoma'' and ''randomized controlled trials''. Chinese databases such as CNKI and CBMDisc using the above search terms were used. 1,286 records identified. 8 studies included for final evaluation.		Adverse event: Nausea Adverse Event: Vomiting Adverse Event: Fatigue	combined targeted therapy was higher than that in the arm for DTIC alone (combined RR=1.34; 95% CI, 1.20–1.49, Z=5.25, P<0.00001) Significant difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.22, 95% CI: 1.10–1.37, Z=3.64, P=0.0003) significant difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.73, 95% CI: 1.41–2.12, Z=5.19, P<0.00001) Failed to show a significant		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.09, 95% CI: 0.96–1.24, Z=1.29, P=0.20)		
				Adverse Event: Constipation	Failed to show a significant difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.07, 95% CI: 0.87–1.32, Z=0.67, P=0.51)		
				Adverse Event: Anaemia	Significant difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.36, 95% CI: 1.06–1.74, Z=2.39, P=0.02)		
				Adverse Event: Neutropenia	Significant		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					difference between DTIC combined targeted therapy and DTIC alone (combined RR=1.63, 95% CI: 1.28–2.06, Z=4.03, P<0.0001)		
Jiang et al. 2013	To evaluate the efficacy and safety of temozolomide alone and temozolomide - based combination chemotherapy on melanoma by using meta-analysis research methodology	Systematic review and meta-analysis Search of the Cochrane library, MEDLINE, EBSCO, EMBASE, and Ovid databases as well as clinical trial websites with the search term “temozolomide” as a keyword combined with “melanoma” and “randomized controlled trials” as medical subject headings. Chinese databases such as CNKI and CBMDisc using the above	703 patients in 5 RCTs	Overall response (CR+PR). 1-year survival Adverse event: Nausea+Vomiting	ORR in the TMZ-based combination drug therapy was greater than that in TMZ alone (RR:1.44 [(95 % CI, 1.06–1.95), Z=2.30, P=0.02] 1-year survival rate in the two groups was not significantly different (RR=1.13; 95 % CI, 0.92–1.40; P=0.87. Incidence of nausea and vomiting between TMZ and combination	Meta-analyses also for adverse events	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		search terms were used. 1,064 records identified. 5 RCTs included for final evaluation.		Adverse Event: Headache, Fatigue Adverse Event: Constipation Adverse Event: Anaemia, neutropenia, thrombocytopenia	chemo-therapy not significantly different [RR=1.16, (95 %CI, 0.90–1.48), Z=1.15, P=0.25>0.05]. No significant difference for the incidence of head-ache and fatigue. RR=0.53 (95% CI 0.21–1.37) and RR=0.77 (95% CI 0.49–1.22). No difference for the incidence of constipation between the two groups (RR= 1.05 [95% CI, 0.71–1.56]) No a significant toxicity between single-agent TMZ and combination chemotherapy. RR: 1.24 (95% CI 0.72–2.14) for		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					anaemia, RR: 1.52 (95% CI 0.53–4.34) for neutropenia RR=0.98 (95% CI 0.46–2.09) for thrombocytopenia.		
Mai et al. 2015	To establish the optimum treatment for metastatic melanoma, we did a random-effects network meta-analysis to compare combined BRAF and MEK inhibition	Systemic review and meta-analysis Search of PubMed, the Cochrane Collaboration Central Register of Controlled Clinical Trials, Cochrane Systematic Reviews, and ClinicalTrials. gov for RCT without year and language restrictions, using the following algorithm: combined targeted therapy AND melanoma. After the combinations of dabrafenib–trametinib or	5,976 patients randomized to receive two of the six treatment strategies in 16 different trials	PFS OS	Combined BRAF-MEK inhibition improved significant prolonged PFS, as compared with BRAF inhibition (HR: 0.58, 95%CI: 0.51-0.67, P < 0.0001) or MEK inhibition alone (HR: 0.29, 95%CI: 0.22-0.37, P < 0.0001). Ranking probabilities of treatment from the network meta-analysis of OS indicated that, of the 6 therapeutic strategies,	Statistically sophisticated report using a comprehensive (Bayesian) network meta-analysis approach.	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		vemurafenib–cobimetinib have been identified, the keywords of individual inhibition of BRAF (dabrafenib, vemurafenib, sorafenib) and MEK (trametinib, cobimetinib, selumetinib), trial and melanoma were used to search relevant studies 451 relevant records identified, 16 eligible RCTs		ORR	combined BRAF-MEK inhibition had the highest. probability of being the best treatment arm for MM. Combined BRAF-MEK inhibition improved significant prolonged OS comparing with BRAF inhibition (HR: 0.67, 95%CI: 0.56-0.81, P < 0.0001) or MEK inhibition alone (HR: 0.48, 95%CI: 0.36-0.65, P < 0.0001). Single BRAF inhibition had a statistically significantly longer in OS than MEK inhibition alone (HR: 0.72, 95%CI: 0.56-0.91, P = 0.008), and combined BRAF		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					inhibition and chemotherapy (HR: 0.60, 95%CI: 0.47-0.73, P < 0.0001). Compared with chemotherapy, combined BRAF-MEK inhibition improved highest ORR (OR: 29.46, 95%CI: 20.04-43.57, P < 0.0001), followed by BRAF inhibition alone (OR: 14.65, 95%CI: 10.49-20.90, P < 0.0001), and combined MEK-chemotherapy (OR: 2.18, 95%CI: 1.10-4.23, P = 0.5982). ORR was superior in patients who received combined BRAF-MEK inhibition compared with those who received BRAF inhibition		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(OR: 2.00, 95%CI: 1.66-2.44, P < 0.0001) or MEK inhibition alone (OR: 20.66, 95%CI: 12.22-35.47, P < 0.0001). The single BRAF inhibition yielded better response rate than MEK inhibition alone (OR: 10.34, 95%CI: 6.23-17.60, P < 0.0001).		
Teimouria et al. 2013	To compare the efficacy and side effects of dacarbazine with those of temozolomide in the treatment of malignant melanoma	Systemic review and meta-analysis PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched. The search terms were 'dacarbazine' and 'temozolomide' and 'malignant melanoma'.	1,314 patients from 3 clinical trials	Response to treatment (CR/PR/SD)	CR RR=0.83 (95% CI= 0.26–2.64), which was nonsignificant (P=0.76). PR: RR=1.35 (95% CI=0.95–1.91), which was nonsignificant (P=0.1) SD:	Methodically correct meta-analysis, but nly 3 studies included. Also analyses for adverse events presented.	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		547 relevant records identified, 3 eligible head-to-head studies taken for meta-analysis			RR=1.05 (95% CI=0.85–1.3), which was nonsignificant (P=0.65) Disease control rate: RR=2.64 (95% CI=0.97–1.36), which was nonsignificant (P=0.11). Anaemia, neutron-penia, and thrombocytopenia: RR (for all grades) = 1.14 (95% CI=0.57–2.27), 1.09 (95% CI=0.74–1.60), and 0.97 (95% CI=0.65–1.46). All of which were nonsignificant. The summary of RR for anaemia, neutropenia, and thrombocytopenia		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(for grades 3 and 4) was 1.8 (95% CI=0.9–3.62), 0.97 (95% CI=0.48–1.97), and 1.44 (95% CI=0.9–2.3). All of which were nonsignificant. The summary of RR for lymphopenia (for grades 3 and 4) of temozolomide in comparison with DTIC was 3.79 (95% CI=1.38–10.39), which was significant (P=0.01).		

7.2.5. Literatur

Agarwala SS, Glaspy J, O'Day SJ, et al. Results from a randomized phase III study comparing combined treatment with histamine dihydrochloride plus interleukin-2 versus interleukin-2 alone in patients with metastatic melanoma. J Clin Oncol 2002;20:125-133
Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. J Clin Oncol. 2015;33(25):2780-2788.
Aubin JM, Rekman J, Vandenbroucke-Menu F, et al. Systematic review and meta-analysis of liver resection for metastatic melanoma. Br J Surg. 2013;100(9):1138-1147.
Avril MF, Aamdal S, Grob JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol 2004;22:1118-1125
Bafaloukos D, Tsoutsos D, Kalofonos H, et al. Temozolomide and cisplatin versus temozolomide in patients with advanced melanoma: a randomized phase II study of the Hellenic Cooperative Oncology Group. Ann Oncol 2005;16:950-957
Bedikian AY, DeConti RC, Conry R, et al. Phase 3 study of docosahexaenoic acid-paclitaxel versus dacarbazine in patients with metastatic malignant melanoma. Ann Oncol 2011;22:787-793

Bedikian AY, Millward M, Pehamberger H, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. J Clin Oncol 2006;24:4738-4745
Buder K, Gesierich A, Gelbrich G, Goebeler M. Systemic treatment of metastatic uveal melanoma: review of literature and future perspectives. Cancer Med. 2013;2(5):674-686.
Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-2516
Chauvergne J, Bui NB, Cappelaere P, et al. Chemotherapy in advanced malignant melanoma. Results of a controlled trial comparing a combination of dacarbazine (DTIC) and detorubicin with dacarbazine alone. Sem Hop 1982;58:2697-2701
Danson S, Lorigan P, Arance A, et al. Randomized phase II study of temozolomide given every 8 hours or daily with either interferon alfa-2b or thalidomide in metastatic malignant melanoma. J Clin Oncol 2003;21:2551-2557
Daponte A, Signoriello S, Maiorino L, et al. Phase III randomized study of fotemustine and dacarbazine versus dacarbazine with or without interferon-alpha in advanced malignant melanoma. J Transl Med. 2013;11:38.
Dequen P, Lorigan P, Jansen JP, van Baardewijk M, Ouwens MJ, Kotapati S. Systematic review and network meta-analysis of overall survival comparing 3 mg/kg ipilimumab with alternative therapies in the management of pretreated patients with unresectable stage III or IV melanoma. Oncologist. 2012;17(11):1376-1385.
Dummer R, Garbe C, Thompson JA, et al. Randomized dose-escalation study evaluating peginterferon alfa-2a in patients with metastatic malignant melanoma. J Clin Oncol 2006;24:1188-1194
Eisen T, Trefzer U, Hamilton A, et al. Results of a multicenter, randomized, double-blind phase 2/3 study of lenalidomide in the treatment of pretreated relapsed or refractory metastatic malignant melanoma. Cancer 2010;116:146-154
Falkson CI, Falkson G, Falkson HC. Improved results with the addition of interferon alfa-2b to dacarbazine in the treatment of patients with metastatic malignant melanoma. J Clin Oncol 1991;9:1403-1408
Falkson CI, Ibrahim J, Kirkwood JM, et al. Phase III trial of dacarbazine versus dacarbazine with interferon alpha-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon alpha-2b and tamoxifen in patients with metastatic malignant melanoma: an Eastern Cooperative Oncology Group study. J Clin Oncol 1998;16:1743-1751
Flaherty KT, Lee SJ, Zhao F, et al. Phase III trial of carboplatin and paclitaxel with or without sorafenib in metastatic melanoma. J Clin Oncol. 2013;31(3):373-379.
Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367(2):107-114.
Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. 2012; N Engl J Med 367: 107-114
Glaspy J, Atkins MB, Richards JM, et al. Results of a multicenter, randomized, double-blind, dose-evaluating phase 2/3 study of lenalidomide in the treatment of metastatic malignant melanoma. Cancer 2009;115:5228-5236
Hauschild A, Agarwala SS, Trefzer U, et al. Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. J Clin Oncol 2009;27:2823-2830
Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358-365.
Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012; 380: 358-365
Hersey P, McLeod GR, Thomson DB. Treatment of advanced malignant melanoma with recombinant interferon alfa-2a in combination with DTIC: long-term follow-up of two phase II studies. Br J Haematol 1991;79 Suppl 1:60-66
Hersey P, Sosman J, O'Day S, et al. A randomized phase 2 study of etaracizumab, a monoclonal antibody against integrin alpha(v)beta(3), + or - dacarbazine in patients with stage IV metastatic melanoma. Cancer 2010;116:1526-1534
Hersh EM, O'Day SJ, Powderly J, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naive patients with advanced melanoma. Invest New Drugs 2011;29:489-498
Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-723
Jiang G, Li RH, Sun C, Jia HY, Lei TC, Liu YQ. Efficacy and safety between temozolomide alone and temozolomide-based double therapy for malignant melanoma: a meta-analysis. Tumour Biol. 2014;35(1):315-322.
Jiang G, Li RH, Sun C, Liu YQ, Zheng JN. Dacarbazine combined targeted therapy versus dacarbazine alone in patients with malignant melanoma: a meta-analysis. PLoS One. 2014;9(12):e111920.
Jungnelius U, Ringborg U, Aamdal S, et al. Dacarbazine-vindesine versus dacarbazine-vindesine-cisplatin in disseminated malignant melanoma. A randomised phase III trial. Eur J Cancer 1998;34:1368-1374
Kaufmann R, Spieth K, Leiter U, et al. Temozolomide in combination with interferon-alfa versus temozolomide alone in patients with advanced metastatic melanoma: a randomized, phase III, multicenter study from the Dermatologic Cooperative Oncology Group. J Clin Oncol 2005;23:9001-9007
Kefford RF, Clingan PR, Brady B, et al. A randomized, double-blind, placebo-controlled study of high-dose bosentan in patients with stage IV metastatic melanoma receiving first-line dacarbazine chemotherapy. Mol Cancer 2010;9:69
Keilholz U, Goey SH, Punt CJ, et al. Interferon alfa-2a and interleukin-2 with or without cisplatin in metastatic melanoma: a randomized trial of the European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. J Clin Oncol 1997;15:2579-2588
Kim KB, Sosman JA, Fruehauf JP, et al. BEAM: A Randomized Phase II Study Evaluating the Activity of Bevacizumab in Combination With Carboplatin Plus Paclitaxel in Patients With Previously Untreated Advanced Melanoma. J Clin Oncol 2012;30:34-41
Kirkwood JM, Bastholt L, Robert C, et al. Phase II, Open-Label, Randomized Trial of the MEK1/2 Inhibitor Selumetinib as Monotherapy versus Temozolomide in Patients with Advanced Melanoma. Clin Cancer Res 2012;18:555-567

Kirkwood JM, Lee S, Moschos SJ, et al. Immunogenicity and antitumor effects of vaccination with peptide vaccine+/-granulocyte-monocyte colony-stimulating factor and/or IFN-alpha2b in advanced metastatic melanoma: Eastern Cooperative Oncology Group Phase II Trial E1696. Clin Cancer Res 2009;15:1443-1451
Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371(20):1867-1876.
Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(1):23-34.
Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877-1888.
Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444-451.
Mai R, Zhou S, Zhong W, et al. Therapeutic efficacy of combined BRAF and MEK inhibition in metastatic melanoma: a comprehensive network meta-analysis of randomized controlled trials. Oncotarget. 2015.
Maio M, Grob JJ, Aamdal S, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol. 2015;33(10):1191-1196.
Maio M, Mackiewicz A, Testori A, et al. Large randomized study of thymosin alpha 1, interferon alfa, or both in combination with dacarbazine in patients with metastatic melanoma. Journal of Clinical Oncology 2010;28:1780-1787
McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014;15(3):323-332.
McDermott D, Haanen J, Chen TT, Lorigan P, O'Day S. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). Ann Oncol. 2013;24(10):2694-2698.
McDermott DF, Sosman JA, Gonzalez R, et al. Double-blind randomized phase II study of the combination of sorafenib and dacarbazine in patients with advanced melanoma: a report from the 11715 Study Group. J Clin Oncol 2008;26:2178-2185
Middleton M, Hauschild A, Thomson D, et al. Results of a multicenter randomized study to evaluate the safety and efficacy of combined immunotherapy with interleukin-2, interferon-{alpha}2b and histamine dihydrochloride versus dacarbazine in patients with stage IV melanoma. Ann Oncol 2007;18:1691-1697
Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 2000;18:158-166
O'Day S, Gonzalez R, Lawson D, et al. Phase II, randomized, controlled, double-blinded trial of weekly elesclomol plus paclitaxel versus paclitaxel alone for stage IV metastatic melanoma. J Clin Oncol 2009;27:5452-5458
O'Day S, Pavlick A, Loquai C, et al. A randomised, phase II study of intetumumab, an anti-alpha(v)-integrin mAb, alone and with dacarbazine in stage IV melanoma. Br J Cancer 2011
O'Day SJ, Eggermont AM, Chiarion-Sileni V, et al. Final results of phase III SYMMETRY study: randomized, double-blind trial of elesclomol plus paclitaxel versus paclitaxel alone as treatment for chemotherapy-naive patients with advanced melanoma. J Clin Oncol. 2013;31(9):1211-1218.
Patel PM, Suciu S, Mortier L, et al. Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV melanoma: Final results of a randomised phase III study (EORTC 18032). Eur J Cancer 2011;47:1476-1483
Polyzos A, Legha SS, Burgess AM, et al. Phase II study of AMSA alone and in combination with DTIC in patients with metastatic melanoma. Invest New Drugs 1988;6:57-61
Presant CA, Bartolucci AA, Balch C, et al. A randomized comparison of cyclophosphamide, DTIC with or without piperazinedione in metastatic malignant melanoma. Cancer 1982;49:1355-1357
Ranson M, Hersey P, Thompson D, et al. Randomized trial of the combination of lomeguatrib and temozolomide compared with temozolomide alone in chemotherapy naive patients with metastatic cutaneous melanoma. J Clin Oncol 2007;25:2540-2545
Reichle A, Vogt T, Coras B, et al. Targeted combined anti-inflammatory and angiostatic therapy in advanced melanoma: a randomized phase II trial. Melanoma Res 2007;17:360-364
Ribas A, Kefford R, Marshall MA, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol. 2013;31(5):616-622.
Ringborg U, Rudenstam CM, Hansson J, et al. Dacarbazine versus dacarbazine-vindesine in disseminated malignant melanoma: a randomized phase II study. Med Oncol Tumor Pharmacother 1989;6:285-289
Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372(1):30-39.Bedikian AY, Garbe C, Conry R, Lebbe C, Grob JJ. Dacarbazine with or without oblimersen (a Bcl-2 antisense oligonucleotide) in chemotherapy-naive patients with advanced melanoma and low-normal serum lactate dehydrogenase: 'The AGENDA trial'. Melanoma Res. 2014;24(3):237-243.
Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-330.
Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521-2532.
Robert C, Schadendorf D, Messina M, Hodi FS, O'Day S. Efficacy and safety of retreatment with ipilimumab in patients with pretreated advanced melanoma who progressed after initially achieving disease control. Clin Cancer Res. 2013;19(8):2232-2239.
Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517-2526
Schadendorf D, Hodi FS, Robert C, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol. 2015;33(17):1889-1894.
Schadendorf D, Ugurel S, Schuler-Thurner B, et al. Dacarbazine (DTIC) versus vaccination with autologous peptide-pulsed dendritic cells (DC) in first-line treatment of patients with metastatic melanoma: a randomized phase III trial of the DC study group of the DeCOG. Ann Oncol 2006;17:563-570
Schwartzentruber DJ, Lawson DH, Richards JM, et al. Gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma. N Engl J Med 2011;364:2119-2127

Sparano JA, Fisher RI, Sunderland M, et al. Randomized phase III trial of treatment with high-dose interleukin-2 either alone or in combination with interferon alfa-2a in patients with advanced melanoma. J Clin Oncol 1993;11:1969-1977
Tarhini AA, Millward M, Mainwaring P, et al. A phase 2, randomized study of SB-485232, rhIL-18, in patients with previously untreated metastatic melanoma. Cancer 2009;115:859-868
Teimouri F, Nikfar S, Abdollahi M. Efficacy and side effects of dacarbazine in comparison with temozolomide in the treatment of malignant melanoma: a meta-analysis consisting of 1314 patients. Melanoma Res. 2013;23(5):381-389.Agarwala SS, Ferri W, Gooding W, et al. A phase III randomized trial of dacarbazine and carboplatin with and without tamoxifen in the treatment of patients with metastatic melanoma. Cancer 1999;85:1979-1984
Thomson DB, Adena M, McLeod GR, et al. Interferon-alpha 2a does not improve response or survival when combined with dacarbazine in metastatic malignant melanoma: results of a multi-institutional Australian randomized trial. Melanoma Res 1993;3:133-138
Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375-384.
Weber JS, Zarour H, Redman B, et al. Randomized phase 2/3 trial of CpG oligodeoxynucleotide PF-3512676 alone or with dacarbazine for patients with unresectable stage III and IV melanoma. Cancer 2009;115:3944-3954
Young AM, Marsden J, Goodman A, et al. Prospective randomized comparison of dacarbazine (DTIC) versus DTIC plus interferon-alpha (IFN-alpha) in metastatic melanoma. Clin Oncol (R Coll Radiol) 2001;13:458-465

7.2.6. Evidenztabellen 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ascierto, P., et al. 2016	To report the results of an updated progression-free survival analysis and the final overall survival analysis for the coBRIM trial. Additionally, we report the results of exploratory analyses correlating molecular markers of MAPK and PI3K pathway activation in pre-treatment tumour samples with overall survival.	Double-blinded, 2-armed Phase III RCT	Group A: Vemurafenib 960 mg bid po Cobimetinib (at a dose of 60 mg once daily for 21 days, followed by 7 days off) (n=247) Group B: Vemurafenib 960 mg bid po Placebo (n=248) Histologically confirmed unresectable, locally advanced stage IIIC or stage IV melanoma with a BRAF V600 mutation detected with the use of a	PFS as assessed by the investigator Overall Survival	Median progression-free survival was 12.3 months (95% CI 9·5–13·4) for cobimetinib and vemurafenib vs. 7.2 months (5.6–7.5) for placebo and vemurafenib (HR 0.58 [95% CI 0.46–0.72], p<0·0001) Median overall survival was 22.3 months (95% CI 20.3–not estimable) for cobimetinib and vemurafenib vs. 17.4 months (95% CI 15.0–19.8) for placebo and vemurafenib (HR 0·70, 95% CI 0.55–0.90; p=0.005).	Category: BRAF/MEK Update of a previously reported trial. Jaded-Score: 5 Funding: F Hoffmann-La Roche-Genentech	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			real-time polymerase-chain reaction assay (Cobas 4800 BRAF V600 Mutation Test, Roche Molecular Systems)				
Chen, R., et al., 2016	To evaluate the positive benefit and effective dose of anti-PD-1 therapy for the treatment of malignant tumors.	Systematic review and meta-analysis, number of studies included n=4	Databases electronically for all the anti-PD-1 therapy-related studies, published or unpublished, ongoing or pending, from January 1980 to December 2014	Overall response	The result of our analysis suggested that nivolumab may improve the overall response rate in treating melanoma relative to chemotherapy and has few associated adverse events. Similarly, in metastatic melanoma patients, nivolumab had a significant advantage over dacarbazine in terms of 1-year survival, progression-free survival, and objective response rate. Regarding dose	Category: Immunotherapy Only four studies fulfilled inclusion criteria for meta-analysis	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					levels of nivolumab for patients with metastatic renal cell carcinoma, the outcomes in response to 2 and 10 mg/kg were similar, but both had significant advantages over 0.3 mg/kg. In addition, pembrolizumab showed similar outcomes in response to 2- and 10-mg/kg treatment. Anti–PD-1 immunotherapy appears to be safe and effective for patients with melanoma or metastatic renal cell carcinoma.		
Guan, X., et al., 2016	To investigate the efficacy and safety of programmed cell death 1 (PD-1) and	Systematic literature search of studies published until July 2015 was performed in	Trials that involved treatment with an anti-PD-1 antibody or an anti-PD-L1	Objective response rate (ORR) Median progression-free	No significant difference was observed in the ORR upon comparisons among a low-dose cohort (1 mg/kg), a	Category : Immunotherapy Also, non-RCT included	IA

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	programmed cell death 1 ligand (PD-L1) inhibitors using a meta-analysis of present trials for advanced melanoma	EMBASE, Medline, Cochrane Controlled Trials Register Databases, and the Chinese Biomedical Literature Database for relevant articles published in any language, number of studies n=12	antibody for the treatment of melanoma	survival (PFS) Adverse events	median-dose cohort (2 or 3 mg/kg) and a high-dose cohort (10 mg/kg) A significantly prolonged PFS was observed in the PD-1 inhibition group According to the included clinical trials, the most common AEs of PD-1 and PD-L1 inhibitors included fatigue, decreased appetite, diarrhea, nausea, cough, dyspnea, constipation, vomiting, rash, pyrexia, and headache		
Hersh, E.M., et al., 2015	To evaluate the efficacy and safety of nab-paclitaxel versus dacarbazine in patients with	Open-label, multicenter phase III study, number of patients n=529	Chemotherapy-naïve patients with stage IV melanoma; April 2009 and June 2011	PFS OS	The median PFS (primary end point) was 4.8 months with nabpaclitaxel and 2.5 months with dacarbazine	Category : Chemotherapy Jaded Score:3 Funding : Celgene Corporation	IB

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastatic melanoma				The median OS was 12.6 months with nab-paclitaxel and 10.5 months with dacarbazine		
Mai, R., et al., 2015	To compare combined BRAF and MEK inhibition in term of PFS, OS and ORR, respectively	Network meta-analysis, number of studies n=16	The databases of PubMed and trial registries were researched for randomized clinical trials of targeted therapy. Data of outcome were extracted on progression-free survival (PFS), objective response rate (ORR), and overall survival (OS)	PFS OS	PFS were significantly prolonged in patients who received combined BRAF-MEK inhibition compared with those who received BRAF inhibition or MEK inhibition alone Combined BRAF-MEK inhibition also improved the OS over BRAF inhibition or MEK inhibition alone. The ORR was superior in combined BRAF and MEK inhibition comparing with BRAF inhibition or MEK inhibition alone	Category : Targeted Therapy	IA
Petrelli, F.,	To assess	Meta-analysis of	Systematic	Correlation PFS	The correlation of	Category : Systemic	IA

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
et al., 2016	whether median progression-free survival, and 1 and 2-year overall survival (OS) rates are reliable surrogate endpoints for median OS	published trials, number of studies n=14	literature search was conducted of PubMed, Web of Science, SCOPUS, and Embase up to July 3, 2015	with 1-year OS Correlation PFS with 2-year OS	progression-free survival with OS was not significant. Tthe correlation between 1-year OS and median OS was very strong (R=0.93, 95% confidence interval [CI] 0.84–0.96, P<.00001), as was the correlation between 2-year OS and OS (R=0.79, 95% CI 0.51–0.91, P=.0001). The correlation between the treatment effects on 1-year OS and OS was also significant (R= 0.86, 95% CI 0.3 to 0.97, P=.01). Similar results were obtained for 2-year OS. According to the available study data, 1-year OS rate could be regarded as a potential surrogate for median OS in novel immunotherapy	therapy	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					trials of metastatic MM		
Pike E., et al., 2015	To compare the relative effectiveness and cost-effectiveness of seven new drugs used for the treatment of advanced malignant melanoma patients in the Norwegian setting	Meta-analyses, number of trials n=17	Randomized controlled trials in February 2015 and September 2015	OS PFS Quality of life	Nivolumab and pembrolizumab in monotherapy, as well as nivolumab combined with ipilimumab, vemurafenib combined with cobimetinib, and dabrafenib combined with trametinib seemed to have a higher probability of good performance than the other available treatment strategies Dabrafenib combined with trametinib and vemurafenib combined with cobimetinib seem to have a higher probability of good performance than the other available treatment	Category : BRAF/MEK Immunotherapy Manually added	IA

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					strategies. Due to insufficient data we did not perform a network meta-analysis for health related quality of life		
Quinn, C., et al., 2016	To examine the relative treatment effect of talimogene laherparepvec compared with ipilimumab and vemurafenib	meta-analyses, number of trials n=4	Relevant trials were identified through a systematic review conducted in September 2015 of English-language studies, published since January 1990	OS	Median OS for ipilimumab and vemurafenib increased significantly when adjustment was applied, demonstrating that variation in disease and patient characteristics was biasing OS estimates; adjusting for this made the survival data more comparable. For both ipilimumab and vemurafenib, the adjustments improved Kaplan–Meier OS curves; the observed talimogene	Category : Immunotherapy Funding : AMGEN	IA

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					laherparepvec OS curve remained above the adjusted OS curves for ipilimumab and vemurafenib, showing that long-term survival could differ from the observed medians.		
Yun, S., et al., 2016	To determine the efficacy and safety of immune checkpoint inhibitors in comparison with conventional regimens	Meta-analyses, number of trials n=6	Eligible studies were (1) randomized controlled trials, (2) assessing patients with unresectable metastatic cutaneous melanoma, (3) treated with either immune check point inhibitors	PFS	Progression-free survival (PFS) rate at 6 months was 28.5% versus 17.7% , overall survival (OS) rate at 1 year was 51.2% versus 38.8% , and overall response rate (ORR) at 6 months was 29.6% versus 17.7% favoring immune check point inhibitors over chemotherapies or vaccination.	Category : Immunotherapy	IA

7.2.7. Literatur

Ascierto, P.A., et al., Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol, 2016. 17(9): p. 1248-60.

Chen, R., et al., Anti-Programmed Cell Death (PD)-1 Immunotherapy for Malignant Tumor: A Systematic Review and Meta-Analysis. Transl Oncol, 2016. 9(1): p. 32-40.
Guan, X., et al., The Efficacy and Safety of Programmed Cell Death 1 and Programmed Cell Death 1 Ligand Inhibitors for Advanced Melanoma: A Meta-Analysis of Clinical Trials Following the PRISMA Guidelines. Medicine (Baltimore), 2016. 95(11): p. e3134.
Hersh, E.M., et al., A randomized, controlled phase III trial of nab-Paclitaxel versus dacarbazine in chemotherapy-naive patients with metastatic melanoma. Ann Oncol, 2015. 26(11): p. 2267-74.
Petrelli, F., et al., Early analysis of surrogate endpoints for metastatic melanoma in immune checkpoint inhibitor trials. Medicine (Baltimore), 2016. 95(26): p. e3997.
Pike, E., et al., NIPH Systematic Reviews, in A Health Technology Assessment of the New Drugs for Inoperable or Metastatic Malignant Melanoma Patients. 2015, Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH)
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Quinn, C., et al., Indirect Treatment Comparison of Talimogene Laherparepvec Compared with Ipilimumab and Vemurafenib for the Treatment of Patients with Metastatic Melanoma. Adv Ther, 2016. 33(4): p. 643-57.
Yun, S., et al., Targeting immune checkpoints in unresectable metastatic cutaneous melanoma: a systematic review and meta-analysis of anti-CTLA-4 and anti-PD-1 agents trials. Cancer Med, 2016. 5(7): p. 1481-91.

7.3. Frage VI.4. Biochemotherapie - Adaptation

Frage VI.4. Führt die Gabe von Biochemotherapien im metastasierten Stadium zu mehr objektiven Remissionen / zu einer Verbesserung des Gesamtüberlebens ?

7.3.1. Synopse Quellleitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
Führt die Gabe von Biochemotherapien im metastasierten Stadium zu mehr objektiven Remissionen?	Ja Interferon-alpha und IL-2 verbessern Ansprechen von Monotherapien aber nicht das Gesamtüberleben allein oder in Kombination mit Chemotherapien.	Ja Dacarbazin plus Interferon alpha führt zu besserem Ansprechraten, nicht zu einer Verlängerung des Gesamtüberlebens.	*Leitlinie enthält keine Empfehlungen zu Therapien im fernmetastasierten Stadium*	Ja
Zugrunde liegende Evidenz	level of evidenz II (4 Studien)	Evidenz Review, S.315 (1 Metaanalyse)		9 Studien zu Biochemotherapien (Standardchemotherpie mit Il-2 oder IFN) 7 Studien geben Ansprechraten an, 2 Studien mit verbessertem Ansprechen, 5 Studien kein Unterschied, gepoolt: besseres Ansprechen
Führt die Gabe von Biochemotherapien im	Nein	Nein	-	Nein

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
metastasierten Stadium zu einer Verbesserung des Gesamtüberlebens?	Interferon-alpha und IL-2 verbessern Ansprechen von Monotherapien aber nicht das Gesamtüberleben allein oder in Kombination mit Chemotherapien.	Durch Verwendung einer Polychemotherapie wird das Gesamtüberleben nicht verlängert		
Zugrunde liegende Evidenz	level of evidenz II (4 Studien)	Evidenz Review, S.315 (1 Metaanalyse, 1 Review, 1 Leitlinie)		9 Studien zu Biochemotherapien (Standardchemotherapie mit Il-2 oder IFN). Keine Studie zeigt ein verbessertes Gesamtüberleben

7.3.2. Empfehlung, Hintergrundstext und Literatur Kanadische Quell Leitlinie

Quellleitlinie: Biochemotherapy for the Treatment of Metastatic Malignant Melanoma: A Clinical Practice Guideline (Cancer Care Ontario) 2007

Question: What is the role of biochemotherapy in the treatment of metastatic malignant melanoma?

For the purposes of this report, "biochemotherapy" is defined as a therapeutic regimen that includes, at a minimum, chemotherapy (either single agent or combination) and interleukin-2. Outcomes of interest include response rate, disease-free survival, overall survival, quality of life, and incidence of grade 3 and 4 toxicities.

Recommendation

Due to the inconsistent results of the available studies with regard to benefit (response, time-to-progression, and survival) and consistently high toxicity rates, biochemotherapy is not recommended for the treatment of metastatic melanoma.

Key Evidence

Nine randomized controlled trials of biochemotherapy for patients with metastatic malignant melanoma were eligible for inclusion in this systematic review of the evidence. Six randomized controlled trials compared chemotherapy alone to chemotherapy combined with interleukin-2 and interferon, two randomized trials compared a combination of chemotherapy and interferon with chemotherapy combined with interleukin-2 and interferon, and one trial compared interferon and interleukin-2 with versus without chemotherapy.

Seven of the nine trials reporting on response rate outcomes provided statistical comparisons. Only two trials reported statistically significant response rates favouring treatment with biochemotherapy, while five trials failed to detect any significant differences. None of the nine trials detected a statistically significant survival improvement with biochemotherapy.

When data were pooled, biochemotherapy was superior to chemotherapy in terms of better response (relative risk, 1.52; 95% confidence interval, 1.24 to 1.87; p<0.0001) and delayed progression at six months (relative risk, 0.85; 95% confidence interval, 0.75 to 0.96; p=0.008) but not decreased mortality at 12 months (relative risk, 0.98; 95% confidence interval, 0.84 to 1.16; p=0.85).

Biochemotherapy is a toxic therapy, and patients are likely to experience serious hematologic, gastrointestinal, cutaneous, and constitutional toxicities. In addition, there are risks of cardiovascular toxicities such as myocardial events and arrhythmias, hypotension, capillary leak syndrome, hepatotoxicity, and renal toxicity. When conducted in the correct setting, grade 3 and 4 toxicities appear to be manageable, and treatment-related death can be minimized.

Literatur:

Atkins MB, Lee S, Flaherty LE, Sosman JA, Sondak VK, Kirkwood JM. A prospective randomized phase III trial of concurrent biochemotherapy (BCT) with cisplatin, vinblastine, dacarbazine (CVD), IL-2 and interferon alpha-2b (IFN) versus CVD alone in patients with metastatic melanoma (E3695): An ECOG-coordinated intergroup trial [abstract]. Proc Am Soc Clin Oncol 2003;22:A2847.

Atzpodien J, Neuber K, Kamanabrou D, et al. Combination chemotherapy with or without s.c. IL-2 and IFN-alpha: results of a prospectively randomized trial of the Cooperative Advanced Malignant Melanoma Chemoimmunotherapy Group (ACIMM). Br J Cancer 2002;86:179-184

Bajetta E, Del Vecchio M, Nova P, et al. Multicenter phase III randomized trial of polychemotherapy (CVD regimen) versus the same chemotherapy (CT) plus subcutaneous interleukin-2 and interferon-alpha2b in metastatic melanoma. Ann Oncol 2006;17:571-577

Eton O, Legha SS, Bedikian AY, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. J Clin Oncol 2002;20:2045-2052

Hauschild A, Garbe C, Stolz W, et al. Dacarbazine and interferon alpha with or without interleukin 2 in metastatic melanoma: a randomized phase III multicentre trial of the Dermatologic Cooperative Oncology Group (DeCOG). Br J Cancer 2001;84:1036-1042

Keilholz U, Goey SH, Punt CJ, et al. Interferon alfa-2a and interleukin-2 with or without cisplatin in metastatic melanoma: a randomized trial of the European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. J Clin Oncol 1997;15:2579-2588

Keilholz U, Punt CJ, Gore M, et al. Dacarbazine, cisplatin, and interferon-alfa-2b with or without interleukin-2 in metastatic melanoma: a randomized phase III trial (18951) of the European Organisation for Research and Treatment of Cancer Melanoma Group. J Clin Oncol 2005;23:6747-6755

Ridolfi R, Chiarion-Sileni V, Guida M, et al. Cisplatin, dacarbazine with or without subcutaneous interleukin-2, and interferon alpha-2b in advanced melanoma outpatients: results from an Italian multicenter phase III randomized clinical trial. J Clin Oncol 2002;20:1600-1607

Rosenberg SA, Yang JC, Schwartzentruber DJ, et al. Prospective randomized trial of the treatment of patients with metastatic melanoma using chemotherapy with cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon alfa-2b. J Clin Oncol 1999;17:968-975

7.4. Frage VI.5. Polychemotherapie – De novo Recherche

Frage VI.5. Führt die Gabe von Polychemotherapien im metastasierten Stadium zu mehr objektiven Remissionen / zu einer Verbesserung des Gesamtüberlebens als die Gabe von Dacarbazin?

7.4.1. PICO, Suchwörter

PICO – Schema			
Population	Intervention	Comparison	Outcome
Advanced melanoma patients stage IV, unresectable stage III	Polychemotherapy	DTIC	Response, Overall Survival

Suchwörter				
Stichwort	melanoma	review	Chemotherapy	Stage IV Stage 4
Synonyme				palliative
Ober-/Unterbegriffe			Systemic therapy	Salvage metastatic
Mesh Term	melanoma	Review [Publication Type]	Drug Therapy	

7.4.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (review [ti] AND system*[ti]) AND (“systemic therapy”[tiab] OR chemotherapy[tiab] OR "drug therapy"[MeSH] OR metastatic[tiab] OR palliative[tiab] OR disseminated[tiab] OR advanced[tiab] OR "stage IV"[tiab] OR "stage 4"[tiab] OR salvage[tiab])	05.12.2011	27 (Auswahl 2 Reviews)
Update Suche			
Medline	s.o.	07.02.2012	28 (0 dazu)
Cochrane Library	(melanoma and (random* or phase 3) and (systemic therapy or chemotherapy or metastatic or palliative or advanced or salvage)).ti,ab. and (review).ti.	07.02.2012	14 (Auswahl 3 Reviews)

7.4.3. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer		69
Einschlusskriterien	Systematische Reviews zur medikamentösen Systemtherapie bei Melanompatienten im Stadium IV, nicht resektables St. III, die Studien zu Kombinationschemotherapien versus DTIC enthalten	
Ausschlusskriterien	Nicht systematische Reviews, RCTs, Kohortenstudien, Case Reports, Dosisfindungsstudie, Kollektive mit gemischten Tumorentitäten	
Anzahl nach Abstractscreening, vorgesehen für Bewertung		5
Anzahl ausgewählter Volltexte		4

7.4.4. Evidenztabelle

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Eigentler et al. 2003	To investigate rates of response to various treatment modalities and the outcome for the melanoma patients	Systematic Review	41 RCTs, patients with metastatic melanoma 7 RCTs Polychemotherapy vs. DTIC included Chiarion Sileni et al. 2001 Chapman et al. 1999 Ringborg et al. 1989 Luikart et al. 1984 Chauvergne et al. 1982 Carter et al. 1976 Moon et al. 1975	Response Rate Overall Survival	DTIC vs. Polychemotherapy (without IFN), 7 RCTs benefit No difference	Quality assessment of studies reported Search terms and databases not mentioned	1a
Huncharek et al. 2001	To report the results of a meta-analysis comparing the response rates of DTIC as single agent therapy for metastatic melanoma with combination chemotherapy	Systematic Review Treatment: DTIC versus Combination therapies	20 RCTs, 3273 patients with metastatic melanoma	Response Rate Overall Survival	DTIC versus Combination therapies (without IFN) 10 RCT´s OR 1.33 (95% CI 0.99-1.78) No difference	Literature search reported no quality assessment of studies	1a

Ausgeschlossene Studien

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Garbe et al. 2011	*To present the success of current treatments and the promise of those still in clinical development that may yield incremental improvements in the treatment of advanced, metastatic melanoma*	*Systematic Review* *Treatment: Adjuvant and palliative treatment*	*RCTs Adjuvant and palliative treatment* *No RCTs for Polychemotherapy vs. DTIC included*			*No RCTs for Polychemotherapy vs. DTIC included → study excluded*	
Sasse et al. 2009	*To compare the effects of chemotherapy alone versus combined therapy with chemotherapy and immunotherapy (chemoimmunotherapy) in people with metastatic malignant melanoma.*	*Systematic Review* *Treatment: Chemotherapy versus Chemoimmunotherapy*	*18 RCTs, 2625 patients with metastatic melanoma*	*1 year Survival* *Response Rates*	*n.s. RR 1.06 (95% CI 0.91 -1.24) p = 0.48* *sign. difference in favor of chemoimmunotherapy RR 1.40 (95% CI 1.20 -1.63), p < 0.0001*	*No RCTs for Polychemotherapy vs. DTIC included → study excluded*	
Crosby et al. 2009	*To review the benefits from the use of systemic*	*Systematic Review* *Treatment:*	*0 RCTs*	*Overall survival Median survival Progression free*	*No RCTs were retrieved, so no analysis of the*	*No RCTs for Polychemotherapy vs. DTIC included*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	therapies in metastatic cutaneous melanoma compared to best supportive care/placebo, and to establish whether a 'standard' therapy exists which is superior to other treatments	*Systemic therapies versus best supportive care/placebo*		*survival*	*effects of the interventions was carried out.*	*→ study excluded*	

7.4.5. Literatur

Carter RD, Krementz ET, Hill GJ,2nd, et al. DTIC (nsc-45388) and combination therapy for melanoma. I. Studies with DTIC, BCNU (NSC-409962), CCNU (NSC-79037), vincristine (NSC-67574), and hydroxyurea (NSC-32065). Cancer Treat Rep 1976;60:601-609
Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol 1999;17:2745-2751
Chauvergne J, Bui NB, Cappelaere P, et al. Chemotherapy in advanced malignant melanoma. Results of a controlled trial comparing a combination of dacarbazine (DTIC) and detorubicin with dacarbazine alone. Sem Hop 1982;58:2697-2701
Chiarion Sileni V, Nortilli R, Aversa SM, et al. Phase II randomized study of dacarbazine, carmustine, cisplatin and tamoxifen versus dacarbazine alone in advanced melanoma patients. Melanoma Res 2001;11:189-196
Crosby T, Fish R, Coles B, et al. Systemic treatments for metastatic cutaneous melanoma. Cochrane Database of Systematic Reviews 2009;1
Eigentler TK, Caroli UM, Radny P, et al. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. Lancet Oncol 2003;4:748-759
Garbe C, Eigentler TK, Keilholz U, et al. Systematic review of medical treatment in melanoma: current status and future prospects. Oncologist 2011;16:5-24
Huncharek M, Caubet JF, McGarry R. Single-agent DTIC versus combination chemotherapy with or without immunotherapy in metastatic melanoma: a meta-analysis of 3273 patients from 20 randomized trials. Melanoma Res 2001;11:75-81
Luikart SD, Kennealey GT, Kirkwood JM. Randomized phase III trial of vinblastine, bleomycin, and cis-dichlorodiammine-platinum versus dacarbazine in malignant melanoma. J Clin Oncol 1984;2:164-168
Moon JH, Gailani S, Cooper MR, et al. Comparison of the combination of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and vincristine with two dose schedules of 5-(3,3-dimethyl-1-triazino) imidazole 4-carboxamide (DTIC) in the treatment of disseminated malignant melanoma. Cancer 1975;35:368-371
Ringborg U, Rudenstam CM, Hansson J, et al. Dacarbazine versus dacarbazine-vindesine in disseminated malignant melanoma: a randomized phase II study. Med Oncol Tumor Pharmacother 1989;6:285-289
Sasse AD, Sasse EC, Clark GOL, et al. Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma. Cochrane Database of Systematic Reviews 2011;1

7.4.5.1. Aktualisierungsrecherche 2016

Auf eine eigenständige Literaturrecherche zur Polichemotherapie wurde verzichtet. Relevante Daten sind in den Evidenztabellen der Schlüsselfragen VI.2 und VI.3 inkludiert.

7.5. Frage VI.7. Lebermetastasen – De novo Recherche

Frage VI.7. Welche medikamentösen Therapien können bei Lebermetastasierung empfohlen werden?

7.5.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients with liver metastases	Local therapies, specific therapies	Standard chemotherapy	Response, Overall Survival

Suchwörter				
Stichwort	melanoma	liver metastasis/metastases	treatment	chemoembolization, perfusion, TACE, immunoembolization, IHP, HAI, resection, surgery, „radiofrequency ablation“, RFA, radioembolization, brachytherapy
Synonyme		hepatic metastasis/metastases	therapy	
Ober-/Unterbegriffe				

Mesh Term	melanoma			

7.5.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("melanoma"[tiab] OR "melanoma"[MeSH]) AND ((liver[tiab] AND metastas*[tiab]) OR (hepatic[tiab] AND metastas*[tiab])) AND (treatment[tiab] OR therapy[tiab] OR "chemoembolization"[tiab] OR TACE[tiab] OR immunoembolization[tiab] OR IHP[tiab] OR HAI[tiab] OR perfusion[tiab] OR resection[tiab] OR surgery[tiab] OR "radiofrequency ablation"[tiab] OR RFA[tiab] OR radioembolization[tiab] OR brachytherapy[tiab])	18.01.11	722
Embase	(melanoma and (liver or hepatic) and (treatment or therapy or chemoembolization or TACE or immunoembolization or IHP or HAI or perfusion or resection or surgery or radiofrequency ablation or RFA or radioembolization or brachytherapy)). ti,ab.	11.05.11	**1579**
Cochrane Library	(melanoma and (liver or hepatic) and (treatment or therapy or chemoembolization or TACE or immunoembolization or IHP or HAI or perfusion or resection or surgery or radiofrequency ablation or RFA or radioembolization or brachytherapy)). ti,ab.	21.07.11	**35**
Update Suche			
Medline	s.o.	30.01.12	**792** (3 dazu: Heusner et al. 2011, Farolfi et al. 2011, Gonsalves et al. 2011)
Embase	s.o.	23.01.12	**1691** (0 dazu)

Cochrane Library	s.o.	30.01.12	**37** (0 dazu)

7.5.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	2520
Einschlusskriterien	Studien zur medikamentösen Therapie von Lebermetastasen bei Melanompatienten Mangels RCTs: Einschluss von Phase I/II Studien, Fallserien ab 10 Patienten Mangels ausreichender Daten zu Lebermetastasen kutaner Melanome, Einschluss von Studien mit Lebermetastasen uvealer Melanome Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Studien zu Lebermetastasen anderer Tumorentitäten
Anzahl Volltexte	36
Ausgeschlossene Studien	6
Ausgewählte Studien	30

Die ausgewählten Arbeiten wurden wie folgt zusammengefasst:

- Resektion
- Isolierte hepatische Perfusion (IHP)
- Hepatische arterielle Infusion (HAI)
- Hepatische arterielle Chemoembolisation (HACE) / Trans-arterielle Chemoembolisation (TACE)
- Radioembolisation (selektive interne Radio-Therapie – SIRT)

7.5.4. Evidenztabelle

Resektion

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Caralt et al. 2010	To analyze the outcome of patients undergoing hepatic resection for melanoma liver metastases.	Case Series Treamtent: Liver resection	14 patients Ocular melanoma n=6 Cutaneous melanoma n=8	Recurrence Survival	liver recurrence 46.2% systemic recurrence 76.9% 1- and 3-year survivals: 77 and 49%	Small series	4
Frenkel et al. 2009	To evaluate the posthepatectomy survival of uveal melanoma patients with liver metastases.	Retrospective cohort study Treamtent: - Liver resection - No liver resection	74 uveal melanoma patients with metastases operated patients n=35 non-operated patients n=39	Survival	median survival operated patients: 23 months (95% CI: 13.3 – 41.3) non-operated patients: 6.8 (95% CI: 3.6 – 12.5)	No cutaneous melanoma patients Risk of selection bias Although similar demographic and ocular characteristics between the groups are mentioned, no baseline data are presented.	4* Poor qualitiy cohort study
Mariani et al. 2009	To review the surgical management of liver metastases from uveal melanoma in a	Retrospective evaluation Treamtent: - Surgery	798 uveal melanoma patients with liver metastase surgical resection	Survival	median overall postoperative survival All patients n=255: 14 months R0 resection n=76:	No cutaneous melanoma patients Multivariate analysis included Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	single institution with regard to survival and the determination of predictive factors for the optimal surgical candidate		n= 255	Predictive factors	27 months R1 resection n=22: 17 month R2 resection n=157: 11 months 4 variables independently correlate with prolonged survival: interval from primary diagnosis to liver metastases >24 months comprehensiveness of surgical resection (R0) number of metastases resected (< or = 4) absence of ffect s disease		
Woon et al. 2008	To assess the survival of melanoma patients with hepatic metastases who underwent surgery	Retrospective evaluation Treatment: Lobectomy Cryotherapy	15 patients with hepatic melanoma metastases, 9 patients suitable for surgical ffect s tion	Survival	Median survival for all patients: 7 months. Curative surgical group: 22 months palliative group: 6	Small series	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					months.		
Herman et al. 2007	To evaluate the experience of liver resection for patients with metastatic melanoma	Case Series Treatment: Liver resection	18 patients with metastatic melanoma, 10 were operated Ocular melanoma n=5 Cutaneous melanoma n=5	Survival	Overall median survival: 22 months Cutaneous melanoma n=5 (Follow up 46 months): 3 dead, 1 alive, disease free, 1 alive, recurrent disease	Small series	4
Pawlik et al. 2006	To evaluate the efficacy of hepatic resection in patients with metastatic ocular versus cutaneous melanoma and to assess additional factors that may affect survival after resection of melanoma metastatic to the liver.	Retrospective evaluation Treatment: Liver resection	40 patients with hepatic melanoma metastasis underwent resection at 4 major hepatobiliary centers Ocular melanoma n=16 Cutaneous melanoma n=24	Recurrence Median time to recurrence Survival	Cutaneous melanoma N=24 Tumor recurrence n=18 (75.0%) Median time to recurrence: 4.7 months Median Survival: 23.6 months 2-year-survival rate: 20.5% 5-year-survival	17 of 24 patients with cutaneous melanoma received systemic therapy	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					rate: 0%		
Rose et al. 2001	To identify patients treated by surgical resection for metastatic melanoma to the liver and to determine if any factors would be useful for identifying patients who should be treated with surgery	Retrospective evaluation Treatment: Liver resection	1750 patients with hepatic metastases surgery n=34 extensive intraabdominal disease identified at exploratory celiotomy, no resection n=10 curative resection n=18 (75%) palliative debulking n=6 (25%)	median disease-free survival (DFS) Overall survival (OS)	Median DFS 12 months Median OS 28 months 5-year DFS and OS: 12% and 29%. Macroscopically, complete resection of disease (P =.001) and histologically negative resection margins (P =.03) significantly improved DFS by univariate analysis	Uveal or cutaneous origin not mentioned	4
Salmon et al. 1998	To present the preliminary results of the therapeutic approach of laparotomy with hepatic resection (whenever possible), implantation of an	Prospective study Treatment: surgical approach removing as much liver disease as possible and intraarterial chemotherapy for	75 uveal melanoma patients with liver metastases	Survival	Median overall survival all patients: 9 months. Surgery plus chemotherapy (n=61): 10 months curative resection (n=19): 22 months	No cutaneous melanoma patients Combined treatment Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	intraarterial catheter and intraarterial chemotherapy (IACH).	6 months					

Isolierte hepatische Perfusion (IHP)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Heusner et al. 2011	To assess the overall survival time of patients suffering from metastasized uveal melanoma undergoing conventional transarterial hepatic chemoperfusion using melphalan	Case series	61 uveal melanoma patients with liver metastases	Response Survival	Response after first session (N=61) PR n=5 (8%) SD n=29 (49%) PD n=26 (43%) Median OS 10 months	Lack of control group	4
Rizell et al. 2008	To analyze the outcome of three treatment strategies using isolated hyperthermic liver perfusion (IHP)	Case series Treatment: IHP with modifications during 3 different time periods (IHP I,	27 melanoma patients with liver metastases Ocular melanoma n=20 Cutaneous	Response Mortality	Response (N=27): CR n=2 PR n=17 SD n=2 Overall response rate 70% Postoperative	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with melphalan for liver metastases of malignant melanoma	IHP II and IHP III), in technique and temperature (amount of melphalan: 0.5, 1.0 and 2 mg/kg body weight in the perfusate; 41, 40 and 40˚C)	melanoma n=5 Anal melanoma n=2	Survival	mortality n=6 Median Survival: 7.5 months (range 0 - 57), postoperative deaths excluded: 12.6 months (range 2.5-57 months)		
Alexander et al. 2003	To evaluate isolated hepatic perfusion (IHP) for patients with unresectable liver metastases from ocular melanoma	Case series Treatment: 60-min hyperthermic IHP using 1.5 mg/kg of melphalan	29 patients with unresectable liver metastases from ocular melanoma	Response Progression-free survival (PFS) Overall Survival (OS) Toxicity	Response (N=29) CR n=3 (10%) PR n=15 (52%) Median PFS: 8 months median OS: 12.1 months Grade 3 or greater hepatic toxicity (reversible) n=19 (65%)	No cutaneous melanoma patients	4

Hepatische arterielle Infusion (HAI)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Farolfi et al. 2011	To investigate	Case Series	23 melanoma	Response	PR n=3 (16.7%)	-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	direct hepatic intra-arterial chemotherapy of fotemustine or carboplatin in melanoma patients with liver metastases	Treatment: Hai, Fotemustine, Carboplatin	patients with unresectable liver metastases 78% uvea melanoma		SD n=4 (22.2%) PD n=11 (61.1%)		
Melichar et al. 2009	To evaluate hepatic arterial infusion of the combination of cisplatin, vinblastine and dacarbazine in patients with liver metastases of uveal melanoma.	Case Series Treatment: hepatic arterial infusion (HAI) of the combination of cisplatin, vinblastine and dacarbazine	10 patients with hepatic metastases of uveal melanoma	Response Survival	Response (n=10) PR n=2 SD n=4 PD n=4 Median survival 16 months (range 5 - 69)	Small series	4
Siegel et al. 2007	To compare the effectiveness of hepatic arterial Fotemustine infusion between liver metastases from ocular and cutaneous melanoma.	Retrospective evaluation	36 patients with hepatic metastases from ocular or cutaneous melanoma, 30 patients were treated Ocular melanoma n=18 Cutaneous	Response Survival Toxicity	cutaneous melanoma patients (N=12) PR n=4 (33%) SD n=4 (33%) PD n=4 (33%) Median survival: 12 months. Toxicity (all patients N=30) grade III-IV throm-		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			melanoma n=12		bocytopenia: 30% grade III-IV neutropenia: 7% nausea/vomiting: 17% (max. gr. I-II) abdominal pain 7% (max. gr. I-II)		
Peters et al. 2006	To investigate the use of fotemustine via direct intra-arterial hepatic (i.a.h.) administration in patients with uveal melanoma metastases	Retrospective evaluation Treatment: fotemustine, administered intra-arterially weekly for a 4-week induction period, and then as a maintenance treatment every 3 weeks	101 uveal melanomapatients from 7 centers with liver metastases	Response Survival	CR n=15 (15%) PR n=21 (21%) SD n=48 (48%) PD n=17 (17%) Median overall survival: 15 months (95% CI: 12.1-17.6) 1-year survival rate 67%, 3- year survival rate 12%	No cutaneous melanoma patients	4
Agarwala et al. 2004	To evaluate the addition of embolization to chemotherapy and to determine the role of escalation of intrahepaticarterial cisplatin dose,	Phase I/II trial escalating doses ofintrahepatic chemotherapywith cisplatin with orwithout polyvinylsponge (PVS)	19 patients with ocular melanoma and liver metastases	Toxicity Response	Toxicity: Grade 3 n=7 Grade 4 n=9 PR n=3 (16%) SD n=13 (68%) PD n=1 (5%) Not evaluable n=2 (11%)	No cutaneous melanoma patients	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	either alone or as part of chemoembolizatio n.						
Becker et al. 2002	To evaluate the activity of sequential fotemustine, interferon alpha, and interleukin 2 for metastatic uvea melanoma patientsin a prospectivephase II trial.	Phase I/II study Treatment: Fotemustine 100mg/m² via hepatic artery or i.v. followed by s.c. IL-2 on day 31 and s.c. interferonalpha on day 36	48 patients with metastatic ocular melanoma	Response Survival	CR n=1 (2%) PR n=6 (12.5%) SD n=18 (37.5%) Intraarterial versus i.v. fotemustin Responses 21.7% vs 8% Overall survival 369 vs 349 days	No cutaneous melanoma patients Study stratified according to presence or absence of extrahepatic metastases,resultin g in different prognostic factors between the groups.	4
Leyvraz et al. 1997	To evaluate the effectiveness and toxicity of hepatic intraarterial fotemustine when administered through the hepatic arterial route in the treatment of liver metastases from ocular melanoma	Phase II study Treatment: intraarterial fotemustine 100 mg/m² (4 hour infusion)	31 patients with liver metastases from ocular melanoma	Response Suvival	Response liver metastases (30 patients assessable) CR n=4 (13%) PR n=8 (27%) Minor Response n=2 SD n=13 PD n=3 Median overall survival 14 months	No cutaneous melanoma patients No overall response data	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Khayat et al. 1991	To evaluate hepatic intra-arterial infusion (HIAI) of fotemustine	Phase II Study Treatment: intraarterial fotemustine 100 mg/m² (4 hour infusion)	17 patients with exclusive or predominant liver metastases from malignant melanoma. 13 patients evaluable	Response	Hepatic Response (N=13) CR n=2 PR n=6 MR n=1 SD n=3 PD n=1 Overall extrahepatic response rate 6/14 (42.8%)	Uveal or cutaneous origin not mentioned	4
Storm et al. 1982	To evaluate combined treatment with intraarterial DTIC infusion and localized hyperthermia of patients with advanced liver metastases	Case Series Treatment: IA-DTIC plus heat	10 melanoma patients with liver metastases Ocular melanoma n=3 Cutaneous melanoma n=4 Unknown primary n=2	Response Survival	Response CR n=1 PR n=2 SD n=5 PD n=2 Median survival 8.5 months (range 3.5-18)	Small series	4

Hepatische arterielle Chemoembolisation (HACE) / Trans-arterielle Chemoembolisation (TACE)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ahrar et al. 2011	To evaluate the response rates and survival durations of patients with metastatic cutaneous melanomas who underwent chemoembolization.	Retrospective evaluation Treatment: Intra-arterial embolic agent followed by cisplatin (100 - 150mg)	42 patients with cutaneous melanoma metastatic to the liver extrahepatic disease n=36 no extrahepatic disease n=6 Evaluable n=36	Response Overall Survival (OS) Time to progression (TTP)	Response (N=36) CR n=0 PR n=5 (13.9%) MR n=9 (25%) SD n=17 (47.2%) PD n=5(13.9%) Median overall survival: 7.69 months TTP of liver disease: 6.01 months	Mulitvariate analysis included Lack of control group	4
Huppert et al. 2010	To evaluate response and survival in patients with liver metastases from uveal melanoma treated by chemoembolization following an invariable treatment protocol over a period of more than 6 years.	Phase II Study Treatment: Hepatic transarterial chemoembolization (TACE) 100mg/m² of cisplatine was continuously infused by means of a power injector preceding embolization by manual injection of	14 patients with hepatic metastases from uveal melanoma 34 TACE´s were performed	Response Time to progression Survival	Response (N=14) CR n=0 PR n=8 (57%) SD n=4 (29%) PD n=2(14%) Median time to progression 8.5 months (5-35 months) Median survival: 14.5 months in responders versus 10 months in nonresponders	No cutaneous melanoma patients	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		polyvinyl alcohol particles			(p=0.18, not significant)		
Schuster et al. 2010	To report the experience with transarterial chemoembolization (TACE) in uveal melanoma patients with pretreated liver metastases	Case Series Treatment: fotemustine-based or cisplatin-based TACE after treatment failure of systemic therapy	25 uveal melanoma patients with liver metastases	Toxicity Response progression-free survival (PFS) Overall survival (OS)	Toxicity: No grade IV toxicity or catheterassociated complications Response (N=25) CR n=0 PR n=4 (16%) SD n=14 (56%) PD n=7 (28%) PFS: 3 months (95% CI: 2-4 months) OS: 6 months (95% CI: 5-7 months)	No cutaneous melanoma patients	4
Yamamoto et al. 2009	To retrospectively evaluate prognostic factors for survival in patients with uveal melanoma who received chemoembolization (CE) with 1,3-bis (2-chloroethyl)-1-	Retrospective evaluation (of patients treated within 2 different Phase II studies) Treatment: Chemoembolization with BCNU or with	53 patients with uveal melanoma CE n=19 IE n=34	Overall survival (OS) Progression-free survival (PFS)	Median OS CE: 9.8 months Low-dose IE: 13.0 months High-dose IE: 20.4 months Median Liver PFS CE: 6.4 months Low-dose IE: 4.2	No cutaneous melanoma patients	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	nitrosourea or immunoembolization (IE) with granulocyte-macrophage colony-stimulating factor (GM-CSF) for hepatic metastases	GM-CSF			months High-dose IE: 9.3 months		
Fiorentini et al. 2009	To assess the safety and efficacy of TACE with irinotecan as drug-eluting beads	Phase II study Treatment: TACE-containing beads preloaded with IRI (100 mg)	10 patients with liver metastases from uveal melanoma	Response	Partial response: 10 patients	No cutaneous melanoma patients	4
Sharma et al. 2008	To present the outcomes with hepatic arterial chemoembolization for metastasis of stage 4 melanoma	Retrospective evaluation Treatment: hepatic arterial chemoembolization	20 patients with liver-dominant metastasis of ocular or cutaneous melanoma Ocular melanoma n=17 Cutaneous melanoma n=3	Response Overall survival Progression-free survival	Response CR n=0 PR n=0 SD n=13 (65%) PD n=7 (35%) median overall survival: 271 days no deaths within 30 days of treatment median progression-free survival: 185 days	Presence or absence of extrahepatic metastases not mentioned	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Vogl et al. 2006	To evaluate results in the palliative treatment of patients with liver metastases of uveal malignant melanoma using transarterial chemoembolization (TACE)	Case Series Treatment: transarterial chemoembolization (TACE) embolization suspension: 10 mg/m² Mitomycin C, 10 ml Lipiodol, and an injection of 200-450 mg resorbable microspheres for vascular occlusion	12 patients with liver metastases of uveal malignant melanoma	Side effects Response Survival	no relevant side effects. Response PR n=3 SD n=5 PD n=4 Mean survival after first embolization 19.5 months. Lower survival rates for the progressive group (16.5 months).	No cutaneous melanoma patients	4
Patel et al. 2005	To evaluate chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma	phase II study Treatment: chemoembolization of the hepatic artery with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) dissolved in ethiodized oil. Gelatin sponge particles were used as a transiently occlusive agent.	30 patients with hepatic metastases from uveal melanoma, 24 patients evaluable	responses in hepatic metastases Overall survival	Response (n=24) CR n=1 PR n=4 SD n=13 PD n=6 Median Survival ITTP 5.2 months CR+PR 21.9 months SD 8.7 months PD 3.3 month	No cutaneous melanoma patients	4

Radioembolisation (selektive interne Radio-Therapie – SIRT)

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Gonsalves et al. 2011	to assess the safety and efficacy of radioembolization in the management of hepatic metastasis of uveal melanoma after failure of immunoembolization or chemoembolization	Retrospective evaluation	32 patients with hepatic metastases from uveal melanoma	responses in hepatic metastases Median overall survival	CR n=1 PR n=1 SD n=18 PD n=12 10 months CR+PR+SD 14.7 months PD 4.9 months	No cutaneous melanoma patients	4
Kennedy et al. 2009	To evaluate Yttrium-90 microspheres (radioembolization) delivered via the hepatic artery	Case Series Treatment: Yttrium-90 microspheres (radioembolization) delivered via the hepatic artery	11 patients with liver metastases from uveal melanoma	Toxicity Response Survival	Toxicity: Grade 3: n=1 Response CR n=1 PR n=6 SD n=1 PD n=1 1 year survival 80%	No cutaneous melanoma patients	4

7.5.5. Literatur

Agarwala SS, Panikkar R, Kirkwood JM. Phase I/II randomized trial of intrahepatic arterial infusion chemotherapy with cisplatin and chemoembolization with cisplatin and polyvinyl sponge in patients with ocular melanoma metastatic to the liver. Melanoma Res 2004;14:217-222
Ahrar J, Gupta S, Ensor J, et al. Response, survival, and prognostic factors after hepatic arterial chemoembolization in patients with liver metastases from cutaneous melanoma. Cancer Invest 2011;29:49-55
Alexander HR,Jr, Libutti SK, Pingpank JF, et al. Hyperthermic isolated hepatic perfusion using melphalan for patients with ocular melanoma metastatic to liver. Clin Cancer Res 2003;9:6343-6349
Becker JC, Terheyden P, Kampgen E, et al. Treatment of disseminated ocular melanoma with sequential fotemustine, interferon alpha, and interleukin 2. Br J Cancer 2002;87:840-845

Cantore M, Fiorentini G, Aitini E, et al. Intra-arterial hepatic carboplatin-based chemotherapy for ocular melanoma metastatic to the liver. Report of a phase II study. Tumori 1994;80:37-39
Caralt M, Marti J, Cortes J, et al. Outcome of patients following hepatic resection for metastatic cutaneous and ocular melanoma. J Hepatobiliary Pancreat Sci 2010
Egerer G, Lehnert T, Max R, et al. Pilot study of hepatic intraarterial fotemustine chemotherapy for liver metastases from uveal melanoma: a single-center experience with seven patients. Int J Clin Oncol 2001;6:25-28
Farolfi A, Ridolfi L, Guidoboni M, et al. Liver metastases from melanoma: hepatic intra-arterial chemotherapy. A retrospective study. J Chemother 2011;23:300-305
Fiorentini G, Aliberti C, Del Conte A, et al. Intra-arterial hepatic chemoembolization (TACE) of liver metastases from ocular melanoma with slow-release irinotecan-eluting beads. Early results of a phase II clinical study. In Vivo 2009;23:131-137
Frenkel S, Nir I, Hendler K, et al. Long-term survival of uveal melanoma patients after surgery for liver metastases. Br J Ophthalmol 2009;93:1042-1046
Gonsalves CF, Eschelman DJ, Sullivan KL, et al. Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: a single-institution experience. AJR Am J Roentgenol 2011;196:468-473
Herman P, Machado MA, Montagnini AL, et al. Selected patients with metastatic melanoma may benefit from liver resection. World J Surg 2007;31:171-174
Heusner T-, Antoch G, Wittkowski-Sterczewski A, et al. Transarterial hepatic chemoperfusion of uveal melanoma metastases: Survival and response to treatment. RoFo Fortschritte auf dem Gebiet der Rontgenstrahlen und der Bildgebenden Verfahren 2011;183:1151-1160
Huppert PE, Fierlbeck G, Pereira P, et al. Transarterial chemoembolization of liver metastases in patients with uveal melanoma. Eur J Radiol 2010;74:e38-44
Kennedy AS, Nutting C, Jakobs T, et al. A first report of radioembolization for hepatic metastases from ocular melanoma. Cancer Invest 2009;27:682-690
Khayat D, Cour V, Bizzari JP, et al. Fotemustine (S 10036) in the intra-arterial treatment of liver metastasis from malignant melanoma. A phase II Study. Am J Clin Oncol 1991;14:400-404
Leyvraz S, Spataro V, Bauer J, et al. Treatment of ocular melanoma metastatic to the liver by hepatic arterial chemotherapy. J Clin Oncol 1997;15:2589-2595
Leyvraz S, Zografos L, Bauer J, et al. Phase II study of hepatic intraarterial fotemustine in patients with hepatic metastases from uveal malignant melanoma: Preliminary results. Regional Cancer Treatment 1992;5:ate of Pubaton: 1992
Mariani P, Piperno-Neumann S, Servois V, et al. Surgical management of liver metastases from uveal melanoma: 16 years' experience at the Institut Curie. Eur J Surg Oncol 2009;35:1192-1197
Melichar B, Dvorak J, Jandik P, et al. Intraarterial chemotherapy of malignant melanoma metastatic to the liver. Hepatogastroenterology 2001;48:1711-1715
Melichar B, Voboril Z, Lojik M, et al. Liver metastases from uveal melanoma: clinical experience of hepatic arterial infusion of cisplatin, vinblastine and dacarbazine. Hepatogastroenterology 2009;56:1157-1162
Noter SL, Rothbarth J, Pijl ME, et al. Isolated hepatic perfusion with high-dose melphalan for the treatment of uveal melanoma metastases confined to the liver. Melanoma Res 2004;14:67-72
Patel K, Sullivan K, Berd D, et al. Chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma: results of a phase II study. Melanoma Res 2005;15:297-304
Pawlik TM, Zorzi D, Abdalla EK, et al. Hepatic resection for metastatic melanoma: distinct patterns of recurrence and prognosis for ocular versus cutaneous disease. Ann Surg Oncol 2006;13:712-720
Peters S, Voelter V, Zografos L, et al. Intra-arterial hepatic fotemustine for the treatment of liver metastases from uveal melanoma: experience in 101 patients. Ann Oncol 2006;17:578-583
Rizell M, Mattson J, Cahlin C, et al. Isolated hepatic perfusion for liver metastases of malignant melanoma. Melanoma Res 2008;18:120-126
Rose DM, Essner R, Hughes TM, et al. Surgical resection for metastatic melanoma to the liver: the John Wayne Cancer Institute and Sydney Melanoma Unit experience. Arch Surg 2001;136:950-955
Salmon RJ, Levy C, Plancher C, et al. Treatment of liver metastases from uveal melanoma by combined surgery-chemotherapy. Eur J Surg Oncol 1998;24:127-130
Schuster R, Lindner M, Wacker F, et al. Transarterial chemoembolization of liver metastases from uveal melanoma after failure of systemic therapy: toxicity and outcome. Melanoma Res 2010;20:191-196
Sharma KV, Gould JE, Harbour JW, et al. Hepatic arterial chemoembolization for management of metastatic melanoma. AJR Am J Roentgenol 2008;190:99-104
Siegel R, Hauschild A, Kettelhack C, et al. Hepatic arterial Fotemustine chemotherapy in patients with liver metastases from cutaneous melanoma is as effective as in ocular melanoma. Eur J Surg Oncol 2007;33:627-632
Storm FK, Kaiser LR, Goodnight JE, et al. Thermochemotherapy for melanoma metastases in liver. Cancer 1982;49:1243-1248
van Etten B, de Wilt JH, Brunstein F, et al. Isolated hypoxic hepatic perfusion with melphalan in patients with irresectable ocular melanoma metastases. Eur J Surg Oncol 2009;35:539-545
Vogl T, Eichler K, Zangos S, et al. Preliminary experience with transarterial chemoembolization (TACE) in liver metastases of uveal malignant melanoma: local tumor control and survival. J Cancer Res Clin Oncol 2007;133:177-184
Woon WW, Haghighi KS, Zuckerman RS, et al. Liver resection and cryotherapy for metastatic melanoma. Int Surg 2008;93:274-277
Yamamoto A, Chervoneva I, Sullivan KL, et al. High-dose immunoembolization: survival benefit in patients with hepatic metastases from uveal melanoma. Radiology 2009;252:290-298

7.5.6. Aktualisierungsrecherchen 2016

7.5.6.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients with liver metastases	Local therapies, specific therapies	Standard therapy	Response, Overall Survival

Suchwörter				
Stichwort	Melanoma	Liver metastases/metastases	treatment	Chemoembolization, perfusion, TACE, immunoembolization, IHP, HAI, resection, surgery, “radiofrequency ablation”, RFA, radioembolization, brachytherapy
Synonyme		Hepatic metastasis/metastases		
Ober-/Unterbegriffe				
Mesh Term	Melanoma			

7.5.6.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("melanoma"[tiab] OR "melanoma"[MeSH]) AND ((liver[tiab] AND metastas*[tiab]) OR (hepatic[tiab] AND metastas*[tiab])) AND (treatment[tiab] OR therapy[tiab] OR "chemoembolization"[tiab] OR TACE[tiab] OR immunoembolization[tiab] OR IHP[tiab] OR HAI[tiab] OR perfusion[tiab] OR resection[tiab] OR surgery[tiab] OR "radiofrequency ablation"[tiab] OR RFA[tiab] OR radioembolization[tiab] OR brachytherapy[tiab]) Datumsfilter 2012/09/16 to 2016/12/31	10.09.2016	477
Cochrane Library	(melanoma and (liver or hepatic) and (treatment or therapy or chemoembolization or TACE or immunoembolization OR IHP or HAI or perfusion or resection or surgery or radiofrequency ablation or RFA or radioembolization or brachytherapy)). ti,ab.	17.09.2016	1 (0 dazu)

7.5.6.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	**478**
Einschlusskriterien	Studien zur medikamentösen Therapie von Lebermetastasen bei Melanompatienten Mangels RCTs: Einschluss von Phase I/II Studien, Fallserien ab 3 Patienten Mangels ausreichender Daten zu Lebermetastasen kutaner Melanome, Einschuss von Studien mit Lebemetastasen uvealer Melanome Sprachen: e, dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Studien zu Lebermetastasen anderer Tumorentitäten

Anzahl nach Abstractscreening, vorgesehen für Bewertung	34
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	28
Anzahl ausgewählter Volltexte	6

7.5.6.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Devaux, S., et al., 2013	To report data from three women with liver metastases of non-uveal melanoma treated by HACE using cisplatin.	Case series, number of patients n=3	Biopsy-proven melanoma metastases were located in the liver only (patient 1) or associated with other distant lesions (patients 2 and 3).	Clinical Benefit	Our results are more similar to Ahrar's data with protracted survival of our responding patient in whom the metastatic disease was limited to the liver, a significant predictor of response already suggested by previous reports		5
Edelhauser, G., et al. 2012	To retro-spectively evaluate response and survival in	Retrospective Single-Center Analysis, number of patients n=21	Patients with hepatic metastases from uveal melanoma, Between	Response Survival	Partial regression after TACE in three patients (14%). Six patients (29%) presented with		4

	patients with hepatic metastasis from uveal melanoma treated by palliative trans-arterial chemo-embolization (TACE) with fote-mustine		September 2003 and December 2010		stable disease but no significant change in tumor size after TACE, and 12 patients (57%) presented with progressive disease after TACE treatment. The overall response rate was 43%. The mean survival after diagnosis of hepatic metastasis was 28.7 months.		
Farshid, P., et al., 2013	To evaluate tumor response in patients with hypovascular liver metastases from the most common primary sites treated	Retrospective study, number of patients n= 190	Patients with cytologically or histologically documented liver metastases from the colon, breast, uvea, pancreas and	Local tumor response Survival Progression	Multiple comparison between the groups showed no statistical significant difference in local tumor response (H: 9.23; p > 0.05). Survival indexes of the patients, including survival rate, progression-		3b

	with chemoembolization.		stomach, between 1st August 2007 and 1st October 2 011		free survival rate, median survival time and time-to-progression, demonstrated significant difference between the groups during the follow-up period (H: 9.7; p = 0.045). The progression rate of treated liver metastases from colon, breast, uvea, pancreas and stomach were 16.6, 17.5, 30.0, 25.0 and 32.0%, respectively (p = 0.002).		
Hughes, M, et al., 2016	To report the results of a multi-center, randomized controlled trial comparing PHP-Mel	Randomized Controlled Multicenter Phase III Trial, number of patients n= 93	Between February 2006 and July of 2009, a total of 93 patients with liver-predominan	Hepatic and Overall Progression-Free Survival Objective Response	The median hPFS in the PHP-Mel group was 7.0 months compared with 1.6 months in the BAC group. The median oPFS in the PHP-Mel		1a Jaded-Score: 3 Funding: Intramural Program of the National Cancer Institute, National

	with best alternative care (BAC) for patients with ocular or cutaneous melanoma metastatic to the liver		t ocular or cutaneous melanoma were accrued to this trial	Follow-Up and Survival	group was 5.4 months, and 1.6 months in the BAC group The hOR for PHP-Mel was 36.4 % (n=16, all partial response), with an additional stable disease rate of 52.3 % (n=23), and an overall hepatic disease control rate of 75.0 %. On the BAC arm, a single patient (2.0 %) achieved a PR and 20 additional patients (40.8 %) achieved SD, for an overall disease control rate of 42.9 %. When comparing the hOR between the two treatment groups, there was a significant improvement in response favoring PHP-Mel patients.		Institutes of Health. Additional funding was supplied via a Cooperative Research and Development Agreement (CRADA) between Delcath Systems, Inc., and the Surgery Branch of the National Cancer Institute.

					Median OS was 10.6 months in the PHP-Mel group compared with 10.0 months in the BAC group. While there was no significant difference in OS between the two randomized groups, a subgroup analysis revealed median OS to be 13.1 months in BAC patients (n = 28, 57.1 %) who crossed over and received treatment with PHP-Mel		
Klingenstein, A., et al., 2013	To retrospectively evaluate the overall survival, safety, and efficacy of metastatic uveal melanoma patients	Retrospective study, number of patients n=13	Patients with histologically proven metastatic uveal melanoma were treated with radioembolization between	Tumor response Survival	Treatment response after radioembolization was PR in eight patients (62 %), SD in two patients (15 %), and PD in three patients (23 %) Median Kaplan–		3b

	after radioembolization as salvage therapy.		December 2005 and January 2011		Meier survival time after radioembolization was 7 months. Patient median survival after diagnosis of metastases was 19 months.		
Venturini, M., et al., 2012	To report our pre-liminary experience with trans-arterial chemoembolization with DEBIRI as a first-line approach in the treatment of five chemotherapy-naive patients affected by UM metastases confined to the liver	Prospective study, number of patients n=5	Patients affected by UM metastases confined to the liver and confirmed by histologic diagnosis were enrolled, between 2010 and 2011	Response rate PFS	An overall response rate of 80% was obtained per Response Evaluation Criteria In Solid Tumors. All patients were alive after mean follow-up durations of 10.6 months and 16.3 months, respectively, after the first treatment and the diagnosis of liver metastasis	Sehr geringe Patientenzahl	3b

7.5.6.5. Literatur

Devaux, S., et al., Hepatic transarterial chemoembolization (HACE) with cisplatin in liver metastases from cutaneous melanoma: a prospective study of three patients. J Eur Acad Dermatol Venereol, 2013. 27(2): p. e261-2.
Edelhauser, G., et al., Fotemustine chemoembolization of hepatic metastases from uveal melanoma: a retrospective single-center analysis. AJR Am J Roentgenol, 2012. 199(6): p. 1387-92.
Farshid, P., et al., Repetitive chemoembolization of hypovascular liver metastases from the most common primary sites. Future Oncol, 2013. 9(3): p. 419-26.
Hughes, M.S., et al., Results of a Randomized Controlled Multicenter Phase III Trial of Percutaneous Hepatic Perfusion Compared with Best Available Care for Patients with Melanoma Liver Metastases. Ann Surg Oncol, 2016. 23(4): p. 1309-19.
Klingenstein, A., et al., Radioembolization as locoregional therapy of hepatic metastases in uveal melanoma patients. Cardiovasc Intervent Radiol, 2013. 36(1): p. 158-65.
Venturini, M., et al., Transarterial chemoembolization with drug-eluting beads preloaded with irinotecan as a first-line approach in uveal melanoma liver metastases: tumor response and predictive value of diffusion-weighted MR imaging in five patients. J Vasc Interv Radiol, 2012. 23(7): p. 937-41.

7.6. Frage VI.8. Lebensqualität – De novo Recherche

Frage VI.8. Welche medikamentösen Therapieverfahren haben im metastasierten Stadium einen (positiven) Effekt auf die Lebensqualität?

7.6.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients, clinical stage III and IV	Systemic treatment	Observation, other systemic treatments	Quality of life

Suchwörter				
Stichwort	melanoma	Quality of life		
Synonyme		Qol		
Mesh Term	melanoma	Quality of life		

7.6.2. Datenbanken, Suchstrategien, Trefferzahlen

7.6.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(“melanoma”[tiab] OR “melanoma”[MeSH]) AND (“Quality of life” OR “QoI” OR “Quality of life” [Mesh])	24.02.11	399
Update Suche			
Medline	s.o.	31.01.12	435 (3 dazu: Hofmann et al. 2011, Robinson et al. 2011, Ziefle et al. 2011, Brandberg et al. 2011)
Cochrane Library	(melanoma and (“quality of life” or “QoL”)).ti,ab.	31.01.12	42 (0 dazu)
Embase	(melanoma and (“quality of life” or “QoL”)).ti,ab.	24.01.12	497 (0 dazu)

7.6.2.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
Medline	((((“melanoma”[tiab] OR “melanoma”[MeSH]) AND (“Quality of life”OR “QoI” OR “Quality of life” [Mesh]))) AND ("2011.02.25"[Date - Publication] : "3000"[Date - Publication])	16.09.2015	243
Cochrane Library	(melanoma and (“quality of life” or “QoL”)).ti,ab.	16.09.2015	61 (0 dazu)

7.6.3. Auswahlkriterien

7.6.3.1. Primärrecherche 2012

Auswahl der Literatur		
Gesamttreffer		974
Einschlusskriterien	Studien / System. Reviews zu Lebensqualität bei Melanompatienten unter Therapie Klinische adjuvante und palliative Therapiestudien / system. Reviews zum Melanom, die Lebensqualität als primären oder sekundären Endpunkt messen Sprachen: e,dt	
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitiäten Lebensqualität bei Melanompatienten nach/während chirurgischer Therapie Lebensqualität bei Melanompatienten ohne Therapie	
Anzahl nach Abstractscreening, vorgesehen für Bewertung		28
Anzahl ausgewählter Studien nach Handsuche (Durchsicht der Literaturlisten)		3
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte		10
Anzahl ausgewählter Volltexte		21
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst: - Reviews zu QoL bei Melanompatienten unter Therapie - Adjuvante Therapienstudien die QoL als Endpunkt enthalten - Palliative Therapienstudien die QoL als Endpunkt enthalten		

7.6.3.2. Aktualisierungsrecherche 2015

Auswahl der Literatur		
Gesamttreffer		304
Einschlusskriterien	System. Reviews zu Lebensqualität bei Melanompatienten unter Therapie Klinische palliative Phase III Therapiestudien / system. Reviews zum Melanom, die Lebensqualität als primären oder sekundären Endpunkt messen Sprachen: e,dt	
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitiäten Lebensqualität bei Melanompatienten nach/während chirurgischer Therapie Lebensqualität bei Melanompatienten ohne Therapie	
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst: • Reviews zu QoL bei Melanompatienten unter Therapie • Palliative Therapienstudien die QoL als Endpunkt enthalten		
Anzahl ausgewählter Volltexte		5

7.6.4. Evidenztabelle

7.6.4.1. Primärrecherche 2012

Reviews zu QoL bei Melanompatienten unter Therapie

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Cashin et al. 2008	To examine all of the information published so far on the impact of interventions on QoL, including all available treatment strategies or screening programs for MM	Systematic review Inclusion criteria: reports of original research related to QoL in MM and/or economics of MM	13 QoL studies (5 economic studies)	QoL Instruments Main QoL Results (Interventions, Clinical Outcome, Adverse Events)	QoL Instruments used: EORTC, EORTC QLQ-36, QLQ C30, QWB-SA, Linear analog self-assessment scale including the GLQ-8, GLQ-8, SF-36, Rotterdam Checklist Symptom questionaire, QWB-SA QOL Results: no significant improvements in QoL for any alternative for treating MM	Detailed description of studies and results	1a
Cornish et al. 2009	To systematically review the available literature on health-related quality of life	Systematic review Inclusion criteria: (HR)QOL assessment in	13 selected studies	HRQOL in patients with cutaneous melanoma	- 20 different instruments were used within the 13 studies - 3 distinct periods	Results of QoL measurements within the studies are not presented in detail.	1a-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(HRQOL) and melanoma	cutaneous melanoma			of HRQOL impact: diagnosis, treatment and follow-up - systemic drugs decreased patients´ HRQOL during treatment.	Methodological quality of included studies was measured by 14 not validated criteria	

Adjuvante Therapiestudien die QoL als Endpunkt enthalten

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ziefle et al. 2011	To evaluate QoL in patients with melanoma using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) before and during the first 12 months of adjuvant treatment with IFN-a-2a	QoL evaluation within a phase III trial QoL instrument: EORTC QLQ-C30 Time points: baseline, month 3, 6 and 12 Treatment: Group 1: IFN-a-2a 18 months Group 2: IFN-a-2a 60 months	QoL Assessment no. of forms received (expected) Baseline n=725 (850) all timepoints n=282 (850)	HRQOL at baseline HRQOL during treatment	HRQoL compared with the healthy reference population significant decrease of 9 of 15 QLQ-C30 subscales peaked at 3 months	No assessment of long term QoL Data (Group 2)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Brandbert et al. 2011	To compare health-related quality of life (HRQoL) and side-effects in patients with high-risk melanoma participating in a randomised phase III trial of adjuvant interferon alfa-2b	QoL evaluation within a phase III trial QoL instrument: EORTC QLQ-C30 Time points: baseline, month 3, 6 and 12 Treatment: Arm A: Observation Arm B: 1 year intermediate Dose IFN-a-2b Arm C: 2 years intermediate Dose IFN-a-2b	QoL Assessment no. of forms received > 80% all timepoints n=282 (850)	HRQOL during treatment compared to baseline HRQOL differences between groups	significant interactions between randomisation arm and time after randomisation for almost all EORTC QLQ-30 variables Arm A improved or remained at baseline levels ARM B+C significant negative impact on HRQoL of IFN treatment. the impact were reversible when treatment was stopped.	-	1b
Bottomley et al. 2009	To examine the health-related quality of life effects of adjuvant pegylated IFN-alpha-2b (PEG-IFN-alpha-2b) versus observation in	QoL evaluation within a phase III trial QoL instrument: EORTC QLQ-C30 Time points: baseline, month 3,	QoL Assessment no. of forms received (expected) Baseline Gr. 1: n=521 (629) Gr. 2: n=520 (627)	HRQOL at month 3	PEG-IFN-alpha-2b treatment arm: -decreased global HRQOL at month 3 (-11.6 points; 99% CI, -8.2 to -15.0) and year 2 (-10.5 points; 99% CI, -	Analysis was restricted to the first 3 years, as limited data existed at years 4 and 5. Conflict of interest	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with stage III melanoma	12, 24, 36, 48, 60. Treatment: Group 1 observation (n = 629) Group 2 PEG-IFN-alpha-2b (n = 627)	36 months Gr. 1: n=158 (352) Gr. 2: n=134 (347) 60 months Gr. 1: n=10 (26) Gr. 2: n=9 (30) of 1,256 patients with stage III melanoma		6.6 to -14.4) -statistically significant impaired (P< 0.0001) at 3 months after baseline: Social functioning Role functioning (at other timepoints no clinically meaningful differences between both treatment groups) -statistically significant impaired (P<.0001) over time: Appetite loss Fatigue	5 of 18 authors received funding, honoria or had consultant/advisory role (Schering Plough)	
Garbe et al. 2008	To evaluate adjuvant Interferon alpha and DTIC in terms of overall survival, recurrence-free survival and occurrence of	QoL Evaluation within a RCT QoL Instrument: EORTC QLQ-C30 Time points: Baseline + 6	HRQOL assessment No. of patients= 238 (54%)	HRQOL at month 6	better outcome for the general dimensions of QoL for patients with adjuvant therapy physical functioning (Arm A vs. Arm C: p =	Baseline HRQOL data not presented	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	adverse events. Health-related quality of life (QoL) was measured by a questionnaire.	months Treatment: Arm A: Interferon alpha (n=146) Arm B: Interferon plus Dacarbazine (n=148) Arm C: Observation (n= 147)			0.007) role functioning (Arm A vs. Arm C: p = 0.008) emotional functioning (Arm A vs. Arm C: p = 0.048) more drug-related symptoms fatigue symptom scale (Arm A vs. Arm C: p = 0.036) nausea and vomiting scale (Arm B vs. Arm C: p = 0.037)		
Dixon et al. 2006	To evaluate data on health-related quality of life (HRQoL) and costs of low-dose extended duration adjuvant interferon-alpha therapy in the treatment of malignant melanoma	QoL Evaluation within a RCT QoL Instrument: EORTC QLQ-C30 Time points: Baseline, 3, 6, 12, 24, 36, 48, 60 months Treatment:	QoL assessment (%) Group 1 n= 211 (68%) Group 2 n= 187 (56%) of 674 melanoma patients (clinical stage not	HRQoL over time between groups (Costs)	OBS group: significantly better mean follow-up QoL on 5 of 6 dimensions of the functional scales: RF (role functioning), EF (emotional f.), CF (cognitive f.), SF (social f.) and QL significantly better	due to missing data, follow-up QoL responses for each individual subject were summarised by taking the average of their follow-up QoL responses over time.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Group 1: IFN low dose, 60 months Group 2: Observation (OBS)	indicated)		mean follow-up QoL symptom scores on 7 of 9 dimensions: FA, NV, DY, AP, CO, DI and FI (after adjustment for baseline QoL and overall survival status (dead or censored)		
Loquai et al. 2011	To evaluate the impact on quality of life (QOL) in patients treated with once weekly 2 µg/kg PEG-IFN-α2b and to examine whether there is a difference in patients' and physicians' perception of QOL	Retrospective evaluation QoL Instrument: EORTC QLQ-C30 Time points: Baseline, every 3 months Treatment: 2 µg/kg PEG-IFN-α2b	30 patients	QOL changes Patients questionnaires compared to physician assessment	impairment in most QOL single dimensions QOL documented by physicians was significantly higher than QOL from the patients' questionnaires in all QOL dimensions	Small sample size	4
Ratai et al. 2005	to evaluate the impact of interferon (IFN) treatment on patients' quality of	Comparative Study QoL Instrument: EORTC QLQ-C30	220 patients Group 1 n=110 Group 2 n=110	QoL	The IFN-alpha-2b treatment significantly affected patients' physical condition,	Allocation to groups not indicated Baseline data not presented Timepoints of	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	life (QoL) after radical surgery of cutaneous melanoma	Time points: Baseline und during treatment Treatment: Group 1: INF-alpha-2b Group 2: Observation			mental health, and social life. In spite of several adverse effects, the patients assessed their QoL as good	assessment not indicated	
Trask et al. 2004	To assess the the longitudinal course of depression, fatigue, and QoL before and during interferon therapy	Observational study QoL Instruments: -BSI -FACT-BRM -RPFS -BDI Time points: Baseline, 1, 2, 3, 6 months post treatment Treatment: high dose interferon-alpha	16 patients	Depression QoL Fatigue	6-month post high-dose assessment: significantly increased somatic complaints, depression, and fatigue, reductions in QoL in the areas of Physical Well-Being, Functional Well-Being, and Additional Symptoms. QoL did not improve over the course of therapy	Small sample size data presented in detail	4
Cohen et al. 2002	To prospectively assess QoL in patients with	QoL Evaluation within a Phase Ib study	QoL assessment Baseline n=29 Week 3 n=28	Changes of PCS, MCS and IES over time	QoL remained stable during treatment, no	Missing data at all 3 timepoints. 2 of 3 missing	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant melanoma participating in a phase Ib immunotherapy cancer clinical trial of an autologous tumour-derived vaccine	QoL Instruments: -SF-36 (RAND scoring method, 8 scales, range 0 (worst) to 100 (best). Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores, computed by using items from the 8 subscales -Impact of Event Scale (IES) Time points: baseline, week 3 and follow-up Treatment: vaccine	Follow up n=27 of 30 evaluable patients with stage III or IV malignant melanoma	Association between IES, PCS and MCS Scores	significant time effect for the PCS score, MCS scores or the IES scores significant negative association between IES scores at baseline and mental health scores at each time point (< 0.002 for all).	assessments at follow up due to progressive disease. Mixed model regression analyses, analyses using the last observation carried forward and analyses using a complete cases approach were performed.	
Bender et al. 2000	To describe short- and long-term changes in cognitive function and quality of life in patients with melanoma	Pilot Study QoL instrument: FACT-G scale Time points: baseline, 3, 6, 9, 12 and 15 months	18 melanoma patients (part of ECOG EST 1690 trial) baseline Group A: n=6	QoL (cognitive function)	significant difference on the physical wellbeing dimension of quality of life from T1 to T2 in Goup A Group A and B:	Limitations: small sample size Baseline characteristics (e.g. gender, age) are not presented	4 Poor quality case control study

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	receiving interferon (IFN) alpha-2b	Treatment: Group A: high dose IFN alpha-2b n=6, Group B: low dose IFN alpha-2b n=6, Group C: control group n=6	Group B: n=6 Group C: n=6 15 months Group A: n=2 Group B: n=3 Group C: n=2		trend to diminished overall quality of life		

Palliative Therapiestudien die QoL als Endpunkt enthalten

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Robinson et al. 2012	To determinepatient-reported signs, symptoms, and functioning, HRQoL questionnaire psychometrics, and treatment impact on HRQoL	QoL Evaluation within a randomized phase II study QoL instrument: Melanoma Subscale (MS) of the Functional Assessment of Cancer Therapy-Melanoma Brief Pain Inventory (BPI) Treatment: DTIC + Intetumumab versus DTIC +	QoL Assessment 127 patients	Baseline QoL QoL at week 3	Baseline HRQoL scores differed according to ECOG performance status trend for HRQoL response in the dacarbazine+ 10 mg/kg intetumumab arm versus dacarbazine + placebo: MS 22 versus 10%, BPI 23 versus 5%	no. of forms received not indicated	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Placebo					
Hofmann et al. 2011	To compare best supportive care (BSC) alone with cisplatin, vindesine and dacabazine-based (CVD) chemotherapy and BSC in terms of overall survival, disease control rate and quality of life	QoL Evaluation within a cohort study QoL instrument: EORTC QLQ-C30 Treatment: Arm A: BSC (n=34) Arm B: BSC+CVD (n=83)	QoL Assessment no. of forms received (expected) Baseline n=83 (117) Arm A: 58.8% Arm B: 75.9%	Baseline QoL QoL at week 8	Arm A versus Arm B no significant differences in the function and symptom scales increase in dyspnoea and fatigue Arm B, not significant reduction in the Global Health status in both arms, not significant	Initial protocol: random assignment. Due to lack of patients consent for randomization the protocol was changed to treatment assignment based on patients choice	2b
Avril et al. 2004	To compare fotemustine and dacarbazine (DTIC) in terms of overall response rate (ORR) as primary end-point and overall survival, duration of responses, time to progression, time	QoL Evaluation within a randomized phase III study QoL instrument: EORTC QLQ-C30 Time points: baseline and after induction period	QoL assessment N=156 Fotemustine group n=83 (of 112) DTIC group n=73 (of 117) of 229 Stage IV melanoma patients	Quality of life (overall response rate, overall survival, duration of responses, time to progression, time to occurrence of brain metastases)	QoL: no statistically significant difference between groups. general tendency: degradation for all (presented) functional and symptom scales over time in both	QoL analysis only available for induction phase due to high number of missing questionnaires Data are presented for 7 scales only. Missing scales: Emotional functioning,	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	to occurrence of brain metastases (BM), and to assess safety and quality of life	Treatment: Fotemustine versus DTIC			groups. disease progression and performance status were the main factors for QoL impairment.	Cognitive functioning, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties	
Chiarion-Sileni et al. 2003	To analyse the health related quality of life (HRQOL) of advanced melanoma patients, in a randomised trial comparing bio-chemotherapy (bio-CT) versus chemotherapy (CT)	QoL Evaluation within a randomized phase III study QoL Instrument: Rotterdam Symptom Checklist (RSCL) Time points: Baseline, Cycle 1, 2, 3, 4, 5 and 6 Treatment: CT: cisplatin and DTIC alone Bio-CT: cisplatin, DTIC, IL-2 and IFN a-2b	Available QoL scores Baseline n=140 (of 178) Cycle 6 n=16 (of 57)	HRQOL difference HRQOL at baseline as prognostic factor	between treatment arms over time: statistically significant difference in the overall quality of life score (P=0.03) , decrease of 6.28 points in the bio-CT arm no significant difference between treamtents: activity level (P=0.20) physical symptom distress (P=0.08) psychological distress (P=0.25) (values always slightly inferior in the bio-CT arm)		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					deterioration over time: bio-CT arm: significantly in all domains (most important reduction in the activity level) CT arm: significant only for the activity level and the physical symptom distress (P<0.001). Prognostic Factors: overall quality of life score, the physical symptom distress score, and the serum LDH level were confirmed as independent prognostic factors in in mulitvariate analysis.		
Kiebert et al. 2003	To report detailed HRQL results of a phase III clinical	QoL Evaluation within a Phase III study	Available HRQL scores Baseline TMZ	HRQL differences -Between groups -Over time	between groups: baseline: no significant	At week 24 not enough data for interpretations.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	trial comparing temozolomide (TMZ) to dacarbazine (DTIC) in patients with metastatic melanoma	QoL Instrument: EORTC QLQ-C-30 Time points: baseline, week 12, 24 Treatment: Group 1 DTIC Group 2 Temozolomide	n=110 Baseline DTIC n=110 Week 12 TMZ n=50 Week 12 DTIC n=31 Week 24 TMZ n=22 Week 24 DTIC n=8 (of 305 advanced melanoma patients)		differences 12 weeks: TMZ group significantly better physical functioning, less fatigue and sleep disturbances, cognitive functioning equivalent, worse on nausea and vomiting. 24 weeks: all subscales (exception diarrhea) better for TMZ patients Over time: TMZ patients: clinically meaningful improvements in emotional functioning, cognitive functioning, and sleep disturbances at week 12. DTIC patients: poorer physical	More missing data in the DTIC group. Limited external validity: Privilege of receiving the new, maybe “better” drug in the TMZ group may influence the functioning scales more than the drug itself. p-values are only indicated for baseline characteristics.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					functioning, improved emotional well-being, and less nausea and vomiting, pain, appetite loss, and diarrhea at week 12. (not statistically significant or considered clinically meaningful)		
Young et al. 2001	To report the results of DTIC +IFN-alpha in patients with metastatic melanom	QoL evaluation within a phase III study QoL instrument: EORTC QLQ C30 (+3) Time points: baseline, at each visit Treatment: Group 1 DTIC Group 2 DTIC + IFN-alpha	41 (of 57) advanced melanoma patients completed at least 1 questionnaire Baseline n=38 Timepoint of tumor assessment n=27	QoL -between groups -over time	-no significant differences between the groups, both at baseline (z =70.82, P=0.41) and for the change in scores over time (z = 71.29, P=0.20) -for both groups the level of symptoms worsened over time, but patients' functioning ability appeared to be	Limitations: missing data	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					stable		
Middleton et al. 2000	To compare temozolomide and dacarbazine (DTIC) in terms of overall survival, progression-free survival (PFS), objective response, and safety, and to assess health-related quality of life (QoL) and pharmacokinetics of both drugs.	Randomized phase III study QoL Instrument: EORTC QLQ-C30 Timepoints: baseline, week 12 Treatment: Group 1 Temozolomide (TMZ) Group 2 DTIC	QoL Scores available Baseline n=251 Week 12 TMZ group n=51 DTIC group n=31 of 305 patients with advanced metastatic melanoma	QoL (secondary objective) -Differences of Scores at week 12 between groups -Differences of maintenance or improvement of scores compared to baseline between groups (primary objective: overall survival, further secondary objectives: PFS, Response Rates, Safety)	TMZ group: significant better scores for physical functioning, fatigue, insomnia. Similar results for responder subgroup analysis between groups. TMZ group: significant more patients with maintenance or improvement of physical and cognitive functioning	QoL data are not shown in detail Sample size seems to be too small for responder subgroup analysis (exact numbers not indicated, DTIC group: QoL Scores available n=31 of 149, responders n=18 of 149)	1b
Sigurdardottier et al. 1996	to describe QoL of patients with advanced melanoma during chemotherapy and to compare the clinical outcome variables and patients' self-assessed QoL	Longitudinal QoL study QoL Instruments: - EORTC QLQ-C36 - study-specific melanoma module - Hospital Anxiety and Depression (HAD) scale	95 patients with advanced melanoma (73 patients of a randomized clinical trial, 22 non-randomized patients with chemotherapy)	QoL -score differences between baseline and week 9	- significant deterioration in all QoL measurements, with the exception of pain and emotional functioning at week 9	No randomized design	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		Treatment: DTIC plus vindesine with or without cisplatin					
Thomson et al. 1993	To describe the prognostic associations of QL scores obtained during a multicentre randomised clinical trial comparing DTIC plus recombinant interferon-alfa 2a versus DTIC alone for patients with metastatic malignant melanoma.	QoL assessment within a Phase III study QoL instrument: linear analog self assessment (LASA) scales, GLQ-8 by physician: QL Index questionnaire Time points: Baseline, week 12 Treatment: Group 1: DTIC Group 2 DTIC + IFN-alpha-2a	176 advanced melanoma patients Number of QoL data not indicated	QoL (Response rate, Response duration, Time to disease progression, Toxicity, Overall Survival)	Quality of life was not significantly different in either group, except that fatigue, as measured at week 12 by LASA scales, and activity, as measured by the functional living index, were both improved in the combination	QoL data not presented in detail. Not clear, if score changes between baseline and week 12 or if absolute scores at week 12 are compared between the groups. Number of received questionnaires not mentioned.	2b poor quality

7.6.4.2. Aktualisierungsrecherche 2015

Palliative Therapiestudien die QoL als Endpunkt enthalten

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Grob et al. 2014	To compare the	QoL evaluation	Dabrafenib, n=187	HRQOL at week 6	For DTIC, all	BREAK-3 was not	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	change in QoL relative to baseline in BRAF V600E mutation-positive advanced and metastatic melanoma patients using the EORTC-QLQ-C30	within a phase III trial QoL instrument: EORTC QLQ-C30 Time points: baseline, at week 6, week 12, and week 15 during treatment, upon progression, and 4 weeks after progression was first determined. (before any study drug was administered) Treatment: Group 1: Dabrafenib 150mg/bid po Group 2: DTIC 1000mg/m^2 iv q21	DTIC, n=63 All required assessments 57 vs. 7 pts No baseline assessment 16 vs. 6 pts. No postbaseline assessments 8 vs. 10 pts. One or two missing postbaseline assessments 96 vs. 33 pts Three or more missing postbaseline assessments 10 vs. 7 pts		functional dimensions except role dimension worsened from baseline at follow-up. For dabrafenib, all functionality dimensions remained stable relative to baseline or improved at week 6; In the DTIC arm, symptom dimensions were unchanged or worsened from baseline for all symptoms except pain (week 6), with the greatest exacerbations observed for fatigue and nausea and vomiting. Mixed-model-repeated measures analyses showed significant ($P < 0.05$) and/or	powered to find a pre-specified difference between the two treatment arms for any symptom or functional dimension of QoL. QoL data	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					clinically meaningful improvements from baseline in favour of dabrafenib for emotional and social functioning, nausea and vomiting, appetite loss, diarrhoea, fatigue, dyspnoea, and insomnia at weeks 6 and/or 12. After crossing over to dabrafenib upon progression		
Hatswell et al. 2014	To report and compare pre- and post-progression health state utilities in advanced melanoma, when generated using different methods - via the EORTC QLQ-C30 and the SF-36	QoL data extracted from the clinical database of the phase III trial MDX010-20 Patients were asked to complete both the EORTC QLQ-C30 and SF-36v2 questionnaires on receipt of the first	EORTC QLQ-C30 was completed by 616 patients (1,237 observations) SF-36 was completed by 599 patients (1,205 observations).	Analyses by progression status and time to death on the patient-level data using generalised estimating equations fitted, and to analyse the predictive abilities of the two approaches.	Mean utility showed a decrease on disease progression in both the EORTC-8D and the SF-6D. Whilst higher utilities were obtained using the EORTC-8D, the relative decrease in utility on progression was	Not comparing QoL between treatment groups but between questionnaires and methods.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	To explore the validity, in advanced melanoma, of progression-based health-state utility modelling compared to modelling based upon time to death health states.	dose of treatment, at the end of treatment and 12 weeks after treatment. Treatment: 676 patients randomized 3:1:1 to ipilimumab + gp100, ipilimumab only, or gp100 only.			similar between measures. When analysed by time to death, both EORTC-8D and SF-6D showed a large decrease in utility in the 180 days prior to death. Compared to progression status alone, the use of time to death gave similar or better estimates of the original data when used to predict patient utility. Including both progression status and time to death further improved model fit. Utilities seen in MDX010-20 were also broadly comparable with those seen in the literature.		
Revicki et al. 2014	To analyse the	QoL data from the	EORTC QLQ-C30	QoL changes at	In the ipilimumab		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	HRQL outcomes during the 12 week treatment induction period in comparison to baseline data of the ipilimumab Phase III clinical trial (MDX010-20).	phase III trial MDX010-20 Treatment: 676 patients randomized 3:1:1 to ipilimumab + gp100, ipilimumab only, or gp100 only.	data was available in 95% of the patients; Week 12 assessments were available for 236 (62%), 85 (65%), and 80 (61%) of the patients treated with ipilimumab plus gp100, ipilimumab alone, and gp100 alone, respectively.	week 12 compared to baseline.	plus gp100 and ipilimumab alone groups, mean changes from baseline to Week 12 generally indicated “no change” or “a little” impairment across EORTC QLQ-C30 global health status, function, and symptom subscales. Significant differences in constipation, favouring ipilimumab, were observed ($p<0.05$). For ipilimumab alone arm, subscales with no or a little impairment were physical, emotional, cognitive, social function, global health, nausea, pain, dyspnoea,		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					constipation, and diarrhoea subscales. For the gp100 alone group, the observed changes were moderate to large for global health, role function, fatigue, and for pain.		
Schadendorf et al. 2014	To evaluate the impact of the MEKi, trametinib, on patients' QOL versus chemotherapy.	QoL evaluation within a phase III trial QoL instrument: EORTC QLQ-C30 Treatment: Patients randomized 2:1 to trametinib 2mg/d po or DTIC 1000mg/m² iv q21	EORTC QLQ-C30 data was available in n=178 of the patients receiving trametinib and n=95 of the patients receiving chemotherapy	QoL changes at week 6 and 12 compared to baseline.	In the primary efficacy population from baseline to weeks 6 and 12, patients' global health status scores worsened by 4–5 points with chemotherapy but improved by 2–3 points with trametinib. Rapid and substantive reductions in QOL functionality (e.g. role functioning, 8–11 points at weeks 6 and 12) and symptom		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					exacer-bation (e.g. fatigue, 4–8 points; nausea and vomiting, 5 points, both at weeks 6 and 12) were observed in chemotherapy-treated patients. In contrast, trametinib-treated patients reported small improvements or slight worsening from baseline at week 12, depending on the functional dimension and symptom.		
Schadendorf et al. 2015	To compare the effect of dabrafenib plus trametinib versus dabrafenib alone on HRQoL and symptoms (improvement or delay in	QoL evaluation within a phase III trial QoL instrument: EORTC QLQ-C30 Treatment: Patients	EORTC QLQ-C30 data was available in n=204 of the patients receiving dabrafenib and trametinib and n=202 of the patients Dabrafenib and	QoL changes at week 8, 16, 24, 32, 40 and at time point of progressive disease compared to baseline.	Baseline scores across both arms were comparable for all dimensions. Global health dimension scores were significantly better at weeks 8, 16 and 24 for		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	worsening) in patients with BRAF V600E or V600K mutation-positive metastatic melanoma enrolled in the COMBI-d trial.	randomized 1:1 to receive either a combination of oral dabrafenib (150 mg twice daily) and oral trametinib (2 mg once daily) or a combination of oral dabrafenib (150 mg twice daily) and placebo.	placebo at baseline >85% at week 40 and >70% at disease progression. Measurement was performed every 8 weeks.		patients receiving the combination during treatment and at progression. The majority of functional dimension scores (physical, social, role, emotional and cognitive functioning) trended in favour of the combination. Pain scores were significantly improved and clinically meaningful (6–13 point difference) for patients receiving the combination for all follow-up assessments versus those receiving dabrafenib monotherapy. For other symptom		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					dimensions (nausea and vomiting, diarrhoea, dyspnoea, and constipation), scores trended in favour of dabrafenib monotherapy.		

Ausgeschlossene Studien

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*LoE*
Adamina et al. 2008	*To assess the safety and immunogenicity of heterologous prime-boost immunotherapy of melanoma patients with Influenza virosomes, and recombinant Vaccinia virus. Quality of life will be assessed with a dedicated FACT-BRM 4*	*multi-centre phase I/II open labeled study* *LQ instrument: FACT-BRM 4 questionnaire*	*20 resected AJCC stages IIb-IV melanoma patients*			*QoL data are not presented excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	questionnaire						
Beguerie et al. 2010	*Tamoxifen vs. non-tamoxifen treatment for advanced melanoma: a meta-analysis*	*metaanalysis*	*9 randomized controlled trials*	*Secondary outcome quality of life* *(Response, mortality, toxicity, treatment-related mortality)*	*None of the trials reported QoL*	*excluded*	
Noorda et al. 2007	*To assess the long-term health-related quality of life (HRQL) of melanoma survivors who had undergone isolated limb perfusion (ILP) of the extremities, and to identify the patient-, tumour- and ILP-related factors associated most strongly with the patients' self-reported HRQL.*	*Comparative Study* *QoL Instrument: mailed questionnaire SF-36* *Time point: after ILP, at least 6 months disease free* *Comparison: normative sample of the Dutch general population of SF-36 scores*	*QoL assessment n=51 (89%) of* *51 patients after isolated limb perfusion* *median follow up after ILP 14 years (range 3-25 years)*	*SF-36 scores*	*SF-36 scores of the patient group were equal to or better than that of the general population, significantly for bodily pain, general health perceptions, and the physical and mental health component scores*	*Assessment after therapy, no baseline data* *Study excluded*	
Petrella et al. 2007	*To determine the role of single-agent interleukin-2 in the*	*systematic review*	*1 systematic review, 5 RCTs, 12 Phase II trials, 1*			*excluded (only 1 QoL report)*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treatment of adults with metastatic melanoma. Outcomes: objective and complete response rates, duration of response, toxicity and quality of life		*QoL report*				
Quirt et al. 2007	*To examine the role of temozolomide in patients with metastatic melanoma Outcomes: response rate, progression-free survival, overall survival, quality of life, and adverse effects*	*systematic review*	*Two randomized phase III trials and three randomized phase II trials*		*only 2 studies with QoL data*	*excluded*	
Schallreuter et al. 1991	*A quite promising clinical trial was conducted using the new nitrosourea fotemustine*	*phase II study*	*19 patients*		*quality of life of the patients during and after chemotherapy was not severely affected*	*no QoL assessment study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Verma et al. 2006	To examine the role of systemic adjuvant therapy in patients with high-risk, resected, primary melanoma Outcomes: overall survival, disease-free survival, adverse effects, and quality of life	systematic review	37 randomized controlled trials, 2 meta-analyses, and 1 systematic review were identified that investigated interferon, levamisole, vaccine, or chemotherapy as adjuvant therapy			only Q-TWiST data, no QoL data presented study exluded	
Sigurdardottier et al. 1993	To assiss the QoL of patients with melanoma before the start of treatment	quality of life (QoL) study QoL instruments: - EORTC QLQ-C36 - study-specific melanoma (MM) module -Hospital Anxiety and Depression (HAD) scale	89 patients		Before treatment the patients reported a relatively low symptom burden, good physical and social functioning, moderate psychological distress and a high overall QoL rating during the past week	No assessment under therapy study excluded	
Coates 1993	To measure aspects of quality of life (QL) prospectively by	QoL evaluation within a phase III study	Baseline QoL data available of 152 patients	Prognostic value of Quality of Life Scores at Baseline	In univariate analyses, Spitzer QL Index assessed by the doctor and	Only baseline QoL data Study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients using linear analogue self assessment (LASA) scales including the GLQ-8 and by doctors using Spitzer's QL Index within a clinical trial comparing dacarbazine (DTIC) plus recombinant interferon-alfa2a (IFN) versus DTIC alone	*QoL instruments: patients: 5 linear analog self assessment (LASA) scales, GLQ-8 physician: Spitzer's QL Index* *Treatment: DTIC plus interferon-alfa2a versus DTIC alone*			*LASA scores for physical wellbeing (PWB), mood, pain, appetite, nausea and vomiting, GLQ-8 total and overall QL were significant (P < 0.01) predictors of subsequent survival*		
Kilbridge et al. 2002	*To analyse quality-of-life-adjusted survival of the high-dose adjuvant interferon alpha-2b regimen*	*A quality-of-life--adjusted survival (QAS) analysis analysis of two cooperative group phase III trials, E1684 and E1690, was performed*			*E1684: increase in QAS for all sets of patient utilities, significant for 16% E1690: increase in QAS 77%, decrease 23%, not significant*	*Utility weights were obtained in a separate study of 95 low-risk melanoma patients and were combined with survival and toxicity data of E1684 and E1690* *QoL data of the trials are not presented*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						Study excluded	

7.6.5. Literatur

Avril MF, Aamdal S, Grob JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol 2004;22:1118-1125
Beguerie JR, Xingzhong J, Valdez RP. Tamoxifen vs. non-tamoxifen treatment for advanced melanoma: a meta-analysis. Int J Dermatol 2010;49:1194-1202
Bender CM, Yasko JM, Kirkwood JM, et al. Cognitive function and quality of life in interferon therapy for melanoma. Clin Nurs Res 2000;9:352-363
Bottomley A, Coens C, Suciu S, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma: a phase III randomized controlled trial of health-related quality of life and symptoms by the European Organisation for Research and Treatment of Cancer Melanoma Group. J Clin Oncol 2009;27:2916-2923
Brandberg Y, Aamdal S, Bastholt L, et al. Health-related quality of life in patients with high-risk melanoma randomised in the Nordic phase 3 trial with adjuvant intermediate-dose interferon alfa-2b. Eur J Cancer 2011
Cashin RP, Lui P, Machado M, et al. Advanced cutaneous malignant melanoma: a systematic review of economic and quality-of-life studies. Value Health 2008;11:259-271
Chiarion-Sileni V, Del Bianco P, De Salvo GL, et al. Quality of life evaluation in a randomised trial of chemotherapy versus bio-chemotherapy in advanced melanoma patients. Eur J Cancer 2003;39:1577-1585
Coates A, Thomson D, McLeod GR, et al. Prognostic value of quality of life scores in a trial of chemotherapy with or without interferon in patients with metastatic malignant melanoma. Eur J Cancer 1993;29A:1731-1734
Cohen L, Parker PA, Sterner J, et al. Quality of life in patients with malignant melanoma participating in a phase I trial of an autologous tumour-derived vaccine. Melanoma Res 2002;12:505-511
Cornish D, Holterhues C, van de Poll-Franse LV, et al. A systematic review of health-related quality of life in cutaneous melanoma. Ann Oncol 2009;20 Suppl 6:vi51-8
Dixon S, Walters SJ, Turner L, et al. Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial. Br J Cancer 2006;94:492-498
Garbe C, Radny P, Linse R, et al. Adjuvant low-dose interferon {alpha}2a with or without dacarbazine compared with surgery alone: a prospective-randomized phase III DeCOG trial in melanoma patients with regional lymph node metastasis. Ann Oncol 2008;19:1195-1201
Grob JJ, Amonkar MM, Martin-Algarra S, et al. Patient perception of the benefit of a BRAF inhibitor in metastatic melanoma: quality-of-life analyses of the BREAK-3 study comparing dabrafenib with dacarbazine. Ann Oncol. 2014;25(7):1428-1436.
Hatswell AJ, Pennington B, Pericleous L, Rowen D, Lebmeier M, Lee D. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. Health Qual Life Outcomes. 2014;12:140.
Hofmann MA, Hauschild A, Mohr P, et al. Prospective evaluation of supportive care with or without CVD chemotherapy as a second-line treatment in advanced melanoma by patient's choice: a multicentre Dermatologic Cooperative Oncology Group trial. Melanoma Res 2011;21:516-523
Kiebert GM, Jonas DL, Middleton MR. Health-related quality of life in patients with advanced metastatic melanoma: results of a randomized phase III study comparing temozolomide with dacarbazine. Cancer Invest 2003;21:821-829
Kilbridge KL, Cole BF, Kirkwood JM, et al. Quality-of-life-adjusted survival analysis of high-dose adjuvant interferon alpha-2b for high-risk melanoma patients using intergroup clinical trial data. J Clin Oncol 2002;20:1311-1318
Loquai C, Schmidtmann I, Beutel M, et al. Quality of life in melanoma patients during adjuvant treatment with pegylated interferon-alpha2b: patients' and doctors' views. Eur J Dermatol 2011
Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 2000;18:158-166
Noorda EM, van Kreij RH, Vrouenraets BC, et al. The health-related quality of life of long-term survivors of melanoma treated with isolated limb perfusion. Eur J Surg Oncol 2007;33:776-782
Petrella T, Quirt I, Verma S, et al. Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. Cancer Treat Rev 2007;33:484-496
Quirt I, Verma S, Petrella T, et al. Temozolomide for the treatment of metastatic melanoma: a systematic review. Oncologist 2007;12:1114-1123
Rataj D, Jankowiak B, Krajewska-Kulak E, et al. Quality-of-life evaluation in an interferon therapy after radical surgery in cutaneous melanoma patients. Cancer Nurs 2005;28:172-178
Revicki DA, van den Eertwegh AJ, Lorigan P, et al. Health related quality of life outcomes for unresectable stage III or IV melanoma patients receiving ipilimumab treatment. Health Qual Life Outcomes. 2012;10:66.
Robinson DW,Jr, Cormier JN, Zhao N, et al. Health-related quality of life among patients with metastatic melanoma: results from an international phase 2 multicenter study. Melanoma Res 2012;22:54-62

Schadendorf D, Amonkar MM, Milhem M, et al. Functional and symptom impact of trametinib versus chemotherapy in BRAF V600E advanced or metastatic melanoma: quality-of-life analyses of the METRIC study. Ann Oncol. 2014;25(3):700-706.
Schadendorf D, Amonkar MM, Stroyakovskiy D, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. Eur J Cancer. 2015;51(7):833-840.Adamina M, Weber WP, Rosenthal R, et al. Heterologous prime-boost immunotherapy of melanoma patients with Influenza virosomes, and recombinant Vaccinia virus encoding 5 melanoma epitopes and 3 co-stimulatory molecules. A multi-centre phase I/II open labeled clinical trial. Contemp Clin Trials 2008;29:165-181
Schallreuter KU, Wenzel E, Brassow FW, et al. Positive phase II study in the treatment of advanced malignant melanoma with fotemustine. Cancer Chemother Pharmacol 1991;29:85-87
Sigurdardottir V, Bolund C, Brandberg Y, et al. The impact of generalized malignant melanoma on quality of life evaluated by the EORTC questionnaire technique. Qual Life Res 1993;2:193-203
Sigurdardottir V, Bolund C, Sullivan M. Quality of life evaluation by the EORTC questionnaire technique in patients with generalized malignant melanoma on chemotherapy. Acta Oncol 1996;35:149-158
Thomson DB, Adena M, McLeod GR, et al. Interferon-alpha 2a does not improve response or survival when combined with dacarbazine in metastatic malignant melanoma: results of a multi-institutional Australian randomized trial. Melanoma Res 1993;3:133-138
Trask PC, Paterson AG, Esper P, et al. Longitudinal course of depression, fatigue, and quality of life in patients with high risk melanoma receiving adjuvant interferon. Psychooncology 2004;13:526-536
Verma S, Quirt I, McCready D, et al. Systematic review of systemic adjuvant therapy for patients at high risk for recurrent melanoma. Cancer 2006;106:1431-1442
Young AM, Marsden J, Goodman A, et al. Prospective randomized comparison of dacarbazine (DTIC) versus DTIC plus interferon-alpha (IFN-alpha) in metastatic melanoma. Clin Oncol (R Coll Radiol) 2001;13:458-465
Ziefle S, Egberts F, Heinze S, et al. Health-related quality of life before and during adjuvant interferon-alpha treatment for patients with malignant melanoma (DeCOG-trial). J Immunother 2011;34:403-408

7.6.6. Übersicht Fragebögen zur Erhebung der Lebensqualität

EORTC QLQ-C30 (Version 3.0 is currently the standard version of the QLQ-C30)

The QLQ-C30 is a questionnaire for patient self-completion, composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting and pain) and a global health status/QOL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial difficulties).

(http://groups.eortc.be/qol/index.htm)

EORTC QLQ-C36

first generation core questionnaire. The 36-item questionnaire was designed 1987 to be (1) cancer specific, (2) multidimensional in structure, (3) appropriate for self-administration (i.e. brief and easy to complete), and (4) applicable across a range of cultural settings.

(http://groups.eortc.be/qol/index.htm)

HADE Scale

Dimensionen: Angst, Depressivität; je 7 Items.

SF-36 (Short Form (36) Health Survey)

Entwickelt in den USA, Kurzform eines ursprünglich aus 149 Items bestehenden Fragebogens, der in den 60er und 70er-Jahren entwickelt wurde.

Deutsche Übersetzung durch M. Bullinger, I. Kirchberger, Hogrefe Verlag, Göttingen

Krankheitsübergreifendes Meßinstrument zur Erfassung der gesundheitsbezogenen Lebensqualität von Patienten.

2 Bereiche: körperliche Gesundheit und psychische Gesundheit

8 Dimensionen: Körperliche Funktionsfähigkeit, Körperliche Rollenfunktion, Körperliche Schmerzen, Allgemeine Gesundheitswahrnehmung, Vitalität, Soziale Funktionsfähigkeit, Emotionale Rollenfunktion und Psychisches Wohlbefinden.

QWB-SA

The Quality of Well-Being Scale (QWB) has been used in numerous clinical trials and studies over the years to evaluate medical and surgical therapies in conditions such as chronic obstructive pulmonary disease, HIV, cystic fibrosis, diabetes mellitus, atrial fibrillation, lung transplantation, arthritis, end stage renal disease, cancer, depression, and several other conditions. Further, the instrument has been used for health resource allocation modeling and served as the basis for an innovative experiment in the allocation of health care by the State of Oregon. Studies have also demonstrated that the QWB is responsive to clinical change derived from surgery or medical conditions such as rheumatoid arthritis, AIDS, and cystic fibrosis.

The self-administered form of the QWB (QWB-SA) was developed more recently. It has been shown to be highly correlated with the interviewer-administered QWB and to retain its psychometric properties. The QWB-SA combines preference-weighted values for symptoms and functioning. Symptoms are assessed by questions that ask about the presence or absence of different symptoms or conditions. Functioning is assessed by a series of questions designed to record functional limitations over the previous three days, within three separate domains (mobility, physical activity, and social activity). The four domain scores are combined into a total score that provides a numerical point-in-time expression of well-being that ranges from zero (0) for death to one (1.0) for asymptomatic optimum functioning.

http://www.healthmeasurement.org/Measures.html

GLQ-8

To measure quality of life in cancer patients receiving chemotherapy

Number of items: 8 plus one optional write-in

Administration mode: Self-administered

Author: Coates Alan S

http://www.proqolid.org/instruments/glq_8_glq_8

LASA scale

5 linear analog self assessment (LASA) scales, measuring physical wellbeing, mood, pain, nausea and vomiting and appetite

IES (Impact of Event Scale)

a 15-item, self-report scale that assesses two categories of cognitive responses to stressful events: intrusion (intrusively experienced ideas, images, feelings or bad dreams) and avoidance (consciously recognized avoidance of certain ideas, feelings or situations). The scale was originally developed to assess current distress associated with a specific trauma. Patients in the present study were asked to rate the frequency of intrusive thoughts and avoidance behaviours in relation to their current health status using a 4-point scale (0, ‘not at all’; 1, ‘rarely’; 2, ‘sometimes’; 3, ‘often’), with higher scores representing

worse functioning. The IES total score is the sum of the two subscale scores.

7.6.7. Aktualisierungsrecherche 2016

7.6.7.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients, clinical stage III and IV	Systemic treatment	Observation, other systemic treatments	Quality of life

Suchwörter				
Stichwort	melanoma	Quality of life		
Synonyme		QoI		
Mesh Term	melanoma	Quality of life		

7.6.7.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	((("melanoma"[tiab] OR "melanoma"[MeSH]) AND ("Quality of life"OR "QoI" OR "Quality of life" [Mesh]))) AND ("2016.09.17"[Date - Publication] : "3000"[Date - Publication])	17.09.2016	73
Cochrane Library	(melanoma and ("quality of life" or "QoL")).ti,ab.	17.09.2016	79 (0 dazu)

7.6.7.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	153
Einschlusskriterien	System. Reviews zur Lebensqualität bei Melanompatienten unter Therapie Klinische palliative Phase III Therapiestudien / system. Reviews zum Melanom, die Lebensqualität als primären oder sekundären Endpunkt messen Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitiäten Lebensqualität bei Melanompatienten nach/während chirurgischer Therapie Lebensqualität bei Melanompatienten ohne Therapie
Anzahl ausgewählter Volltexte	4
Die ausgewählten Arbeiten wurden wie folgt zusammengefasst: - Reviews zu QoL bei Melanompatienten unter Therapie - Palliative Therapienstudien die QoL als Endpunkt enthalten	

7.6.7.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bagge, A.S., et al., 2016	To describe HRQoL for patients with intransit extremity melanoma	Retrospective study, number of patients n=68	Patients with intransit metastases, between October	HRQoL for Patients with In-Transit Extremity Melanoma Metastases	The multivariate analysis showed that the negative effect of a more extensive tumor burden was		3a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases, to describe changes in HRQoL after ILP, and to correlate HRQoL with local toxicity and clinical response after ILP		2012 and May 2015, in Sweden	HRQoL After ILP HRQoL with Local Toxicity and Clinical Response After ILP	significant for FACT-M (p = 0.01), ACT-G (p = 0.01), and EWB (p = 0.01). The general HRQoL score 3, 6, and 12 months after ILP did not differ significantly from the baseline scores (paired analysis) The response was evaluable for 49 (94 %) of the 52 ILPs, and 30 procedures resulted in a CR (61 %), 8 resulted in a PR (16 %), 6 resulted in an SD (12 %) and 5 resulted in a PD (10 %). No significant differences in HRQoL depending on the response to treatment were		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					observed at 3 or 6 months.		
Grob, J.J., et al., 2015	To present the effects of treatments on health-related quality of life (HRQoL), an exploratory endpoint in the COMBI-v study	Randomised phase 3 study, number of patients n=704	Metastatic melanoma patients with a BRAF Val600 mutation were randomly assigned from June 4, 2012, to Oct 7, 2013	Overall survival by prospectively assessing HRQoL	From the patient's perspective, which integrates not only survival advantage but also disease-associated and adverse-event-associated symptoms, treatment with the combination of a BRAF inhibitor plus a MEK inhibitor (dabrafenib plus trametinib) adds a clear benefi t over monotherapy with the BRAF inhibitor vemurafenib and supports the combination therapy as standard of care in this population		1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Long, G.V., et al., 2016	To present prospectively collected analyses in CheckMate 066 that compared the impact of nivolumab and dacarbazine on HRQoL using reliable and validated patient-reported outcomes (PROs)	Randomized, double-blind study, number of patients n=418 Nivolumab (n = 210) or Dacarbazine (n = 208)	Metastatic melanoma patients in Europe, Israel, Australia, Canada, and South America between January 2013 and January 2014	HRQoL questionnaire completion rates Descriptive and cross-sectional HRQoL analyses	Questionnaires were completed over a maximum treatment period of 73 weeks in the nivolumab arm and 61 weeks in the dacarbazine arm. The adjusted questionnaire completion rates for the EORTC QLQ-30 and EQ-5D at baseline were 70% for the nivolumab arm and 65% for the dacarbazine arm The mean (SD) EORTC QLQ-30 global health status/QoL scores at baseline were similar for patients treated with nivolumab [68.9 (20.2)] and for those treated with dacarbazine [66.2 (25.1)]. The		1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					mean changes from baseline in global health status/ QoL scores that occurred, beginning at week 7		
Schadendorf, D., et al., 2016	To present health-related quality of life (HRQoL) outcomes from KEYNOTE-002	Randomised phase II KEYNOTE-002 study, number of patients n=540	Patients were randomly assigned 1:1:1 to pembrolizumab 2 or 10 mg/kg every 3 weeks (Q3W) or investigator-choice chemotherapy	Completion and compliance rate of the EORTC QLQ-C30, HRQoL analysis	Compliance rates at week 12 were 76.6% (n Z 108), 82.3% (n Z 121), and 86.4% (n Z 133) for the control, pembrolizumab 2 mg/kg Q3W, and pembrolizumab 10 mg/kg Q3W arms, respectively. From baseline to week 12, GHS/HRQoL scores were maintained to a higher degree in the pembrolizumab arms compared with the chemotherapy		1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					arm (decrease of 2.6 for each pembrolizumab arm versus 9.1 for chemotherapy		

7.6.7.5. Literatur

Bagge, A.S., et al., Health-Related Quality of Life for Patients Who have In-Transit Melanoma Metastases Treated with Isolated Limb Perfusion. Ann Surg Oncol, 2016. 23(6): p. 2062-9.
Grob, J.J., et al., Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol, 2015. 16(13): p. 1389-98.
Long, G.V., et al., Effect of nivolumab on health-related quality of life in patients with treatment-naive advanced melanoma: results from the phase III CheckMate 066 study. Ann Oncol, 2016. 27(10): p. 1940-6.
Schadendorf, D., et al., Health-related quality of life in the randomised KEYNOTE-002 study of pembrolizumab versus chemotherapy in patients with ipilimumab-refractory melanoma. Eur J Cancer, 2016. 67: p. 46-54.

7.7. Frage VI.9. Medikamentöse Therapie Hirnmetastasen – De novo Recherche

Frage VI.9. Welche medikamentösen Therapien können bei cerebraler Metastasierung empohlen werden?

7.7.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients with brain metastases	Systemic treatment	Observation, other systemic treatments	Survival, progression free survival, Quality of Life

Suchwörter

Stichwort	melanoma	Therapy	brain	Temo*, fotemustin
Synonyme		treatment	Cerebral, CNS	
Mesh Term				

7.7.2. Datenbanken, Suchstrategien, Trefferzahlen

7.7.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1.Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (treatment[tiab] OR therapy[tiab] OR therapy[MeSH] OR temo*[tiab] OR fotemustin[tiab]) AND (brain[tiab] OR cerebral[tiab] OR CNS[tiab] or Brain Neoplasms[MeSH])	30.05.11	1553 (Auswahl 19)
Embase	(melanoma and (treatment or therapy) and (brain or cerebral or CNS)).ti,ab.	11.05.11	1247 (Dedubliziert: 346, 0 dazu)
Cochrane Library	(melanoma and (treatment or therapy) and (brain or cerebral or CNS)).ti,ab.	20.05.11	28 (Auswahl 3 Dubletten, 0 dazu)
Update Suche			
Medline	s.o.	31.01.12	1625 (1 dazu , Weber et al. 2011)
Embase	s.o.	23.01.12	1349 (1 dazu, Heller et al. 2011-Abstrakt)

Datenbank	Suchstrategie	Datum	Treffer
Cochrane Library	s.o.	31.01.12	31 (0 dazu)

7.7.2.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (treatment[tiab] OR therapy[tiab] OR therapy[MeSH] OR temo*[tiab] OR fotemustin[tiab]) AND (brain[tiab] OR cerebral[tiab] OR CNS[tiab] or Brain Neoplasms[MeSH])	15.10.2015	587
Cochrane Library	(melanoma and (treatment or therapy) and (brain or cerebral or CNS)).ti,ab.	15.10.2015	45

7.7.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	3005
Einschlusskriterien	Systematische Reviews oder klinische Studien zur medikamentösen Therapie bei Melanompatienten mit Hirnmetastasen RCT´s die Patienten mit Hirnmetastasen eingeschlossen haben Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitiäten Kombination mit Radiotherapie
Anzahl nach Abstractscreening, vorgesehen für Bewertung	22

Anzahl ausgewählter Studien nach Handsuche (Durchsicht der Literaturlisten)	0
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	9
Anzahl ausgewählter Volltexte	13 (davon 1 Asco Abstract

Auswahl der Literatur	
Gesamttreffer	632
Einschlusskriterien	Systematische Reviews oder klinische Studien zur medikamentösen Therapie bei Melanompatienten mit Hirnmetastasen RCT´s die Patienten mit Hirnmetastasen eingeschlossen haben Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitiäten Kombination mit Radiotherapie RCT´s, in denen Patienten mit Hirnmetastasen lediglich ein Subkollektiv waren
Anzahl nach Abstractscreening, vorgesehen für Bewertung	133
Anzahl ausgewählter Volltexte	5

7.7.4. Evidenztabelle

7.7.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hodi et al. 2010	To compare ipilimumab (IPI), administered with or without a glycoprotein 100 (gp100) peptide vaccine with gp100 alone in patients with previously treated metastatic melanoma	RCT Treatment: Group A ipilimumab plus gp100 (n=403) Group B ipilimumab alone (n=137) Group C gp100 alone (n=136)	676 HLA-A*0201-positive patients with previously treated unresectable stage III or IV melanoma 82 patients with brain metastases	Median Overall survival Overall Response Rate	All patients (IPI +gp100 vs. IPI vs. gp100) 10.0 months vs. 10.1 months vs. 6.4 months, sign., (hazard ratio for death, 0.68; p<0.001). 5.7% (n=23) vs. 11% (n=15) vs. 1.5% (n=2), sign., p=0.04	Outcomes of patients with brain metastases not reported separately	4
Avril et al. 2004	To compare fotemustine and dacarbazine (DTIC) in in patients with disseminated cutaneous melanoma	RCT Treamtent: Arm A: Fotemustine Arm B: DTIC	229 patients with metastatic melanoma 43 patients with brain metastases (Arm A n=22, Arm B n=21)	Response	Patients with brain metastases n=43 Arm A Fotemustin vs. Arm B DTIC CR n=0 versus n=0 PR n=1 versus n=1 SD not reported PD not reported	Outcomes of patients with brain metastases not reported in detail. Author contacted, no reply	4
Weber et al. 2011	To further evaluate the efficacy and safety of ipilimumab at 10	Retrospective analysis of data from a phase II study	12 patients with stable brain metastases	Response Survival	PR n=2 of 12 SD n=3 of 12 Median OS: 14	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	mg/kg in melanoma patients with stable brain metastases.				months Both patients with a partial response and one with stable disease were alive at the last follow-up, with survival time of more than 4 years		
Amaravadi et al. 2009	To evaluate the combination of the oral alkylating agent temozolomide and the oral multikinase inhibitor sorafenib in advanced melanoma patients	Phase II study Treatment: Sorafenib 400mg twice daily + temozolomide	167 patients with metastatic melanoma 53 patients with brain metastases (Arm D)	Response rates 6-month PFS rate Median PFS Median OS	Evaluable patients (Arm D with brain metastases) n=52 CR rate: 0% PR rate: 15% SD rate: 48% PD rate: 37% 23% 3.5 months 8 months	Response assessed according RECIST criteria, CT every 8 weeks Lack of control group	4
Vestermark et al. 2008	To evaluate single agent antitumour activity and toxicity of Thalidomide in a phase II setting in patients with brain	Phase II study Treatment: thalidomide	36 patients with brain metastases	CNS Response CR+PR SD PD	Evaluable patients: n=35 n=0 n=5 n=30	Response assessed according RECIST criteria, CT or MRI every 3 months Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases associated with metastatic melanoma			Median PFS Median OS	1.7 months 3.1 months		
Larkin et al. 2007	To assess the maximum-tolerated dose (MTD), safety and efficacy of the combination of temozolomide and lomustine in melanoma metastatic to the brain	Phase I/II study Treatment: temozolomide + lomustine	26 patients with brain metastases	CNS Response CR+PR SD PD Median OS	Evaluable patients: n=20 n=0 n=10, 50% n=10, 50% 2 months	Response assessed according WHO criteria, CT or MRI after 3.+ 6. cycle (28days/cycle) only 10% of patients received more than 2 cycles of therapy Lack of control group	4
Schadendorf et al. 2006	To test a dose-intensified regimen of temozolomide in melanoma patients with brain metastases in a prospective, open-label, multicentre phase II trial	Phase II study Treatment: temozolomide	45 patients with asymptomatic brain metastases	CNS Response CR PR SD PD Median OS	Evaluable patients: n=40 (5 missing patients: no clinical response) n=0 n=2, 4.4% n=5 n=33 4.1 months	Response assessed according RECIST criteria, CT or MRI, week 8 and week 20, responses were confirmed 4 weeks later. Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hwu et al. 2005	To examine the efficacy and safety of temozolomide plus thalidomide in chemotherapy-naive patients with brain metastases	Phase II study Treatment: temozolomide + thalidomide	26 patients with brain metastases, 16 with symptomatic brain metastases	CNS Response CR PR SD PD Median OS	Evaluable patients: n=14 n=2 n=1 n=7 n=4 5 months	Response assessed according WHO criteria, CT or MRI every 8 weeks 11 patients did not complete first cycle Lack of control group	4
Bafaloukos et al. 2004	To evaluate the efficacy and toxicity of temozolomide-based chemotherapy in patients with cerebral metastases from melanoma.	Analyses of patients with brain metastases within 2 Phase II studies Treatment: temozolomide + docetaxel n=10, temozolomide + cisplatin n=9, temozolomide alone n=6	25 patients with brain metastases	CNS Response CR PR SD PD Median OS 1-year survival rate	Evaluable patients: n=24 n=0 n=6 n=5 n=13 4.7 months 20.9%	Response assessed according WHO criteria, CT or MRI every second cycle (28 days/cycle) Lack of control group	4
Agarwala et al. 2004	To assess the safety and efficacy of temozolomide in patients with brain metastases from metastatic	Phase II study Treatment: temozolomide	151 patients with brain metastases n=117 no prior chemotherapy n=34 prior	CNS Response CR PR SD	Evaluable patients: n=132 n=1 n=8 n=40	Large study Response assessed according WHO criteria, gadolinium-	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma		chemotherapy	PD Median OS	n=73 all patients (n=151) 3.2 months	enhanced MRI every second cycle (28 days/cycle), responses were confirmed 4 weeks later. Lack of control group	
Chang et al. 1994	To investigate the sequential administration of dacarbazine and fotemustine in the treatment of cerebral metastases from malignant melanoma	Phase II study Treatment: DTIC + fotemustine	34 patients with brain metastases	Response CR PR SD Median OS	Evaluable patients: n=34 n=2 n=2 n=9 duration of complete response: 12, 36+ months 4.5 months	Tumour response was defined according to World Health Organisation criteria Lack of control group	4
Jacquillat et al. 1990	To investigate the activity of fotemustine against cerebral metastases of disseminated malignant	Phase II study Treatment: fotemustine	42 patients with brain metastases 16 patients with only brain metastases, 23 patients with brain	Response CR PR SD PD	Evaluable patients: n=39 n=2 n=9 n=9 n=19	Tumor assessment according WHO criteria Lack of control groups	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	melanoma		+ extracerebral metastases	Median OS 1-year survival	26 weeks (6 months) 21%		
Heller et al. 2011	*To report safety and efficacy data of treatment with Ipilimumab in patients with brain metastases*	*open-label study* *Treatment: ipilimumab 3 or 10 mg/kg*	*165 with brain metastases at baseline (of 869 patients)*	*Toxicity* *1 year survival*	*drug-related serious adverse events of any grade: 26.1% (similar rate to pts without brain metastases)* *20%*	*only asco abstract available*	

7.7.4.2. Aktualisierungsrecherche 2015

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ajithkumar et al. 2015	To review the present understanding and evolving multimodal management of melanoma brain metastases, and the challenges of how best to integrate new systemic	Systematic review Categorized according to treatment modality	Patients suffering from brain metastases of melanoma	Not defined	"For patients with BRAF-mutant melanoma, BRAF-targeted agents could be used preferentially to radiotherapy while the potential benefi ts and risks of the combination of	Only descriptive information provided	3a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	therapies				radiotherapy and immunotherapy are still being studied“		
Dummer et al. 2013	To study the safety, tolerability and efficacy of Vemurafenib for patients with advanced melanoma and symptomatic brain metastases	Open-label, single-arm, two-centre, study designed Vemurafenib (960 mg bid) n=24	Patients with BRAFV600 mutation-positive metastatic melanoma with non-resectable, previously treated brain metastases.	Safety Best overall response rate (BORR) Progression-free	23 of 24 patients reported at least one adverse event (AE). Grade 3 AEs were reported in 4 (17%; 95% confidence interval [CI], 4.7–37.4%) patients and included cutaneous squamous cell carcinoma in 4 patients Overall partial response (PR) at both intracranial and extracranial sites was achieved in 10 of 24 (42%; 95% CI, 22.1–63.4) evaluable patients, with stable disease in nine	Funding: Roche	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				survival (PFS) Overall survival (OS)	Median PFS was 3.9 (95% CI, 3.0–5.5) months Median OS was 5.3 (95% CI, 3.9–6.6) months		
Goyal et al. 2015	To review the current evidence regarding the treatment of multiple brain metastases from melanoma.	Systematic review	2006 pts. treated with radiotherapy; 642 treated with chemotherapy; description of non-RCTs for Ipilimumab	Rate of Intracranial Failure, % Overall Intracranial Response Rate, % Median Overall Survival, mo Progression-Free Survival or Median Time to Progression	8-48% for SRS(+/-WBRT), 29-100% for WBRT 7-47% for CTX 6.5-7.5m for WBRT, 5.7-15.2m for SRS(+/-WBRT) 0-47monts for chemotherapy (+/-WBRT/SRS) 4.7-21.3m for ipilimumab (+/-Chemo/WBRT/SRS) 1.2-5m for chemotherapy (+/-WBRT/SRS) 2.7m-9.5m for	"At this time, the standard management for patients with MBM from melanoma includes SRS, WBRT, or a combination of both"	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Ipilimumab (+/- Chemo/WBRT/SRS)		
Long et al. 2012	To confirm the activity of dabrafenib in brain metastases, we assessed dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma and at least one brain metastasis who were either previously untreated for brain metastases or who had progressive metastases after previous local treatments.	Multicentre, open-label, phase 2 trial with 2 cohorts: Cohort A had not received previous local treatment for brain metastases (n=89) Cohort B had progressive brain metastases after previous local treatments (n=83) Patients in both cohorts received 150 mg oral Dabrafenib twice a day	Patients with BRAFV600 mutation-positive metastatic melanoma who had or had not received previous local treatment for brain metastases	Overall intracranial response (CR or PR) Safety	Cohort A (Val600Glu-Mutated) 29/74 pts. (39.2%, 95% CI 28.0–51.2) (Val600Lys-Mutated) 1/15 pts. (6.7%, 0.2–31.9) Cohort B (Val600Glu-Mutated) 20/65 pts. (30.8%, 19.9-43.4) (Val600Lys-Mutated) 4/18 pts. (22.2%, 6.4–47.6) Treatment-related AEs of grade 3 or worse occurred in 38 (22%) patients. Four grade 4 treatment-related AEs occurred in cohort A. Two	Funding: GSK	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					grade 4 events occurred in cohort B. 51 (30%) patients had a serious adverse event.		
Margolin et al. 2012	To assess efficacy and safety of ipi-limumab specifically in patients with melanoma and brain metastases in a prospective clinical trial	Open-label, phase 2 trial with two parallel cohorts Cohort A Neurologically asymptomatic; not receiving corticosteroid treatment at study entry (n=51) Cohort B symptomatic; stable dose of corticosteroids (n=21) Ipilimumab 10mg/kg iv q21 for four doses	Patients had to have at least one measurable index brain metastasis of 0.5–3 cm in diameter, or two measurable lesions larger than 0.3 cm visible on contrast MRI, or both.	Proportion of patients with disease control, defined as CR, PR, or stable disease after 12 weeks Proportion of patients with an objective response (CR/PR) Median PFS Overall survival	9/51 patients in cohort A exhibited disease control (18%, 95% CI 8–31) 1/21 patients in cohort B exhibited disease control (5%, 0.1–24). Cohort A: OR: 5/51 (10%, 3–21) Cohort B: OR: 1/21 (5%, 0.1–24) Cohort A: 1.4 (1.2–2.6) months Cohort B: 1.2 (1.2–1.3) months Cohort A: 7.0 (95%	Funding: BMS	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					CI 4.1–10.8) months Cohort B: 3.7 (95% CI 1.6–7.3) months		
				Safety & Tolerability	Most common AEs in both cohorts: Fatigue, diarrhoea, nausea, headache, rash, and pruritus. Most common grade 3 events overall: diarrhoea, fatigue, dehydration, hyperglycaemia, and increased concentrations of serum aspartate aminotransferase. One patient in each cohort experienced grade 4 confusion. 3 patients in cohort A had brain oedema (one grade 1 and two grade 2). A man in cohort A died for reasons		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					related to the study drug 24 days after his second dose of ipilimumab because of gangrenous colitis, despite treatment with corticosteroids. 15 pts. in cohort A completed induction. 28 pts. had discontinued treatment because of early progression of disease or death, five requested discontinuation without documented progression, three had adverse events. 5 patients in cohort B completed induction. 11 had		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					discontinued treatment because of disease progression or death, 3 requested discontinuation, and 2 had AEs.		

7.7.5. Literatur 2012

Ajithkumar T, Parkinson C, Fife K, Corrie P, Jefferies S. Evolving treatment options for melanoma brain metastases. Lancet Oncol. 2015;16(13):e486-497.
Amaravadi RK, Schuchter LM, McDermott DF, et al. Phase II Trial of Temozolomide and Sorafenib in Advanced Melanoma Patients with or without Brain Metastases. Clin Cancer Res 2009;15:7711-7718
Avril MF, Aamdal S, Grob JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol 2004;22:1118-1125
Bafaloukos D, Tsoutsos D, Kalofonos H, et al. Temozolomide and cisplatin versus temozolomide in patients with advanced melanoma: a randomized phase II study of the Hellenic Cooperative Oncology Group. Ann Oncol 2005;16:950-957
Chang J, Atkinson H, A'Hern R, et al. A phase II study of the sequential administration of dacarbazine and fotemustine in the treatment of cerebral metastases from malignant melanoma. Eur J Cancer 1994;30A:2093-2095
Dummer R, Goldinger SM, Turtschi CP, et al. Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. Eur J Cancer. 2014;50(3):611-621.
Goyal S, Silk AW, Tian S, et al. Clinical Management of Multiple Melanoma Brain Metastases: A Systematic Review. JAMA Oncol. 2015;1(5):668-676.
Heller KN, Pavlick A.C., Hodi F.S., et al. Safety and survival analysis of ipilimumab therapy in patients with stable asymptomatic brain metastases. Journal of Clinical Oncology, 2011 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2011;Vol 29:8581
Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-723
Hwu WJ, Lis E, Menell JH, et al. Temozolomide plus thalidomide in patients with brain metastases from melanoma: a phase II study. Cancer 2005;103:2590-2597
Jacquillat C, Khayat D, Banzet P, et al. Final report of the French multicenter phase II study of the nitrosourea fotemustine in 153 evaluable patients with disseminated malignant melanoma including patients with cerebral metastases. Cancer 1990;66:1873-1878
Larkin JM, Hughes SA, Beirne DA, et al. A phase I/II study of lomustine and temozolomide in patients with cerebral metastases from malignant melanoma. Br J Cancer 2007;96:44-48
Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(11):1087-1095.
Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012;13(5):459-465.Agarwala SS, Kirkwood JM, Gore M, et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. J Clin Oncol 2004;22:2101-2107
Schadendorf D, Hauschild A, Ugurel S, et al. Dose-intensified bi-weekly temozolomide in patients with asymptomatic brain metastases from malignant melanoma: a phase II DeCOG/ADO study. Ann Oncol 2006;17:1592-1597
Vestermark LW, Larsen S, Lindelov B, et al. A phase II study of thalidomide in patients with brain metastases from malignant melanoma. Acta Oncol 2008;47:1526-1530
Weber JS, Amin A, Minor D, et al. Safety and clinical activity of ipilimumab in melanoma patients with brain metastases: retrospective analysis of data from a phase 2 trial. Melanoma Res 2011;21:530-534

7.7.6. Aktualisierungsrecherche 2016

7.7.6.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients with brain metastases	Systemic treatment	Observation, other systemic treatments	Survival, progression free survival, Quality of Life

Suchwörter				
Stichwort	melanoma	Therapy	brain	Temo*, fotemustin
Synonyme		treatment	Cerebral, CNS	
Mesh Term				

7.7.6.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1.Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (treatment[tiab] OR therapy[tiab] OR therapy[MeSH] OR temo*[tiab] OR fotemustin[tiab]) AND (brain[tiab] OR cerebral[tiab] OR CNS[tiab] or Brain Neoplasms[MeSH]) AND ("2016.09.17"[Date - Publication] : "3000"[Date - Publication])	21.09.2016	159

Cochrane Library	(melanoma and (treatment or therapy) and (brain or cerebral or CNS)).ti,ab.	21.09.2016	79 (0 dazu)

7.7.6.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	238
Einschlusskriterien	Systematische Reviews oder klinische Studien zur medikamentösen Therapie bei Melanompatienten mit Hirnmetastasen RCT´s die Patienten mit Hirnmetastasen eingeschlossen haben Retrospektive Studien mit größerer Fallzahl (n>20) Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitiäten
Anzahl nach Abstractscreening, vorgesehen für Bewertung	60
Anzahl ausgewählter Volltexte	9

7.7.6.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ahmad, S.S., et al., 2015	To report outcome of a retrospective review of previously treated advanced	Retrospective study, number of patients n=193	Advanced melanoma patients who met the criteria to access ipilimumab	Treatment compliance and toxicity Outcome	In patients who failed to complete four cycles (n =90), the main reason for discontinuation was disease	Only a sub-group of patients (n=35) had brain metastases	3a

	melanoma patients in the UK who accessed ipilimumab in the European EAP and compared their outcomes with relevant clinical trial and EAP patient data reported in the literature to date.		through an EAP provided by Bristol Myers Squibb in Europe between 2010 and 2011	Survival	progression or death from melanoma for 67 (74%) patients. 70% were reported to have had at least one significant toxicity Among the 127 patients with RECIST response measurements available, one complete response (CR) and 23 partial responses (PR) were documented, giving a 19% overall objective response rate. At a median follow-up of 23 months, the median progression-free survival and OS were 2.8 and 6.1 months, respectively		

Ahmed, K.A., et al., 2016	To analyze outcomes of intact MBMs treated with single-session stereotactic radiosurgery (SRS) and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors(i), BRAFi, or conventional chemotherapy	Retrospective study, number of patients n=96	Patients were included if MBMs were treated with single-session SRS within 3 months of receiving systemic therapy, SRS treatment sessions at our institution between January 2007 and August 2015	Systemic progression-free survival Overall survival from SRS and cranial metastases diagnosis	The median sPFS from the date of SRS was 3.4 months (range: 0.47–45.9 months). Six- and 12-month sPFS rates following SRS were 41%/41% (anti-PD-1 therapy), 36%/27% (anti-CTLA-4 therapy), 58%/39% (BRAF/MEKi), 29%/12% (BRAFi), and 20%/5% chemotherapy) (P = 0.04). The median OS for all patients in the study was 8.9 months from the date of SRS and 10.5 months from the date of cranial metastases diagnosis. Six- and 12-month OS rates following SRS were 76%/48% (anti-PD-1 therapy),		3a

					68%/41% (anti-CTLA-4 therapy), 83%/65% (BRAF/MEKi), 52%/24% (BRAFi), and 60%/10% (chemotherapy) (P = 0.01).		
Ahmed, K.A., et al., 2016	To assess the toxicities and outcomes in patients treated with stereotactic radiation and anti-PD-1 therapy for melanoma BMs	Retrospective data from two nivolumab protocols enrolling 160 patients	Resected or unresectable metastatic melanoma at Moffitt Cancer Center. Patients underwent SRS or fractionated stereotactic radiotherapy (FSRT) between December 2010 and July 2014	Overall Survival	Median overall survival (OS) from the date of stereotactic radiation and nivolumab initiation was 11.8 and 12.0 months, respectively, in patients receiving nivolumab for unresected disease		3a
Geukes Foppen, M.H., et al., 2016	To determine the influence of new treatment modalities	Retrospective study, number of patients n=39	Patients diagnosed with LM from melanoma at The	Survival	Median overall survival of the entire cohort was 6.9 weeks (95% confidence interval 0.9–		3a

	and of prognostic factors on outcome in patients with leptomening eal metastases (LM).		Netherlands Cancer Institute between May 2010 and March 2015 was analyzed		12.8). Median overall survival of untreated patients after the diagnosis of LM was 2.9 versus 16.9 weeks for treated patients (P < 0.001). The median survival of 21 patients treated with systemic targeted therapy and/or immunotherapy, with or without RT was 21.7 weeks		
Kiess, A.P., et al., 2015	To investigate the safety and efficacy of stereo-tactic radiosurgery (SRS) for patients with melanoma brain metastases (BMs) who also received Ipi	Retrospective study, number of patients n=46	Patients with melanoma received Ipi and underwent single-fraction SRS for BMs, From 2005 to 2011	Treatment combinations OS	Fifteen patients received SRS during Ipi, 19 received SRS before Ipi, and 12 received SRS after Ipi Patients treated with SRS during or before Ipi had better OS and less regional recurrence than did those treated		3a

					with SRS after Ipi (1-year OS 65% vs 56% vs 40%, P=.008; 1-year regional recurrence 69% vs 64% vs 92%, P=.003).		
Mathew, M., et al., 2013	To evaluate the tumor activity of ipilimumab in patients with metastatic melanoma whose limited brain metastases were also treated with SRS	Retrospective study, number of patients n=58	Patients with limited brain metastases from melanoma, January 2008 and June 2011	Local control (LC) OS	6-month LC rates for patients who received ipilimumab and those who did not were 63 and 65%, respectively The overall median survival was 5.9 months after SRS with a median follow-up after SRS of 6 months. Specifically, 14 of 19 patients (74%) who received ipilimumab died with intracranial disease progression compared with 26 of 29 patients (90%) in the		IV

					nonipilimumab group		
Qian, J.M., et al., 2016	To determine the effect of the relative timing and type of immune checkpoint therapy on the response of melanoma brain metastases (BrMets) to treatment with stereotactic radiosurgery (SRS).	Retrospective study, number of patients n=75	All patients with melanoma BrMets treated with Gamma Knife SRS between 2007 and 2015	Lesion reduction OS	Concurrent use of immunotherapy and SRS resulted in a significantly greater median percent reduction in the lesion volume at 1.5 (263.1% vs 243.2%, P<.0001), 3 (283.0% vs 252.8%, P<.0001), and 6 months (294.9% vs 266.2%, P<.0001) in comparison with nonconcurrent therapy. The median overall survival for all patients from the first SRS treatment was 18.5 months. Of the patients who started on anti-CTLA-4 and had either only		3a

					nonconcurrent SRS treatment (n=19) or only concurrent SRS treatment (n519), the median overall survival was 8.0 months (range, 2.1-61.8 months) for nonconcurrent treatment and 19.1 months (range, 3.3-64.2) for concurrent treatment (P=.0858).		
Spagnolo, F., et al., 2016	To analyze outcomes of patients with melanoma BM treated with the new drugs, both in the setting of phase I–II–III clinical trials and in the ‘‘real world”.	Systematic review of phase I–II–III clinical trials; number of studies n=22	The search was performed on the 30th September 2015. Moreover, abstracts published by the ASCO, ESMO and SMR between 2010 and 2015	Median OS	Median OS was 7.9 months in phase I–II–III trials and 7.7 months in ‘‘real world” studies. In clinical trials, median OS was 7.0 months for patients treated with immunotherapy and 7.9 months for patients treated with BRAF inhibitors. In ‘‘real world” studies, median		2a

					OS was 4.3 months and 7.7 months for patients treated with immunotherapy and BRAF inhibitors, respectively		
Wolf, A., et al., 2016	To determine the impact of BRAF inhibitors on disease free progression and overall survival in patients with melanoma brain metastases having undergone SRS.	Single center, prospective study, number of patients n=80	All patients with metastatic melanoma to the brain who underwent SRS between 2012 and 2015 at NYU Langone Medical Center	Treatment characteristics Overall local control/ metastases/progression Median survival	Thirty-one of 35 (88.6 %) patients with a BRAF-M were treated with a BRAF inhibitor (dabrafenib = 15, vemurafenib = 9, or combination therapy = 7). Six patients were started on a BRAF inhibitor near the time of radiosurgery, 12 were on an inhibitor both before and after SRS, 12 after SRS ([1 months) and 1 was on BRAF inhibitor only prior to SRS There was no		3a

					significant difference in overall local control between BRAF-M on a BRAF inhibitor (94.6 % ± 20.8 %) and BRAF-WT (90.8 % ± 25.2 %) groups (p = 0.51). The time to progression/ new metastasis was significantly longer for the 20 patients with a BRAF-M treated with a BRAF inhibitor (median = 3.9 months, range 0.8–16.6 months) compared to the 26 BRAF-WT patients (median = 1.7 months, 0.4–9.3 months) (p = 0.02). The median survival for BRAF-M patients on a BRAF inhibitor was 13.2 months (95% CI 8.3–18.1		

					months) compared to 6.9 months (95% CI 4.4–9.3 months) for BRAF-WT patients.		
Xu, Z., et al., 2016	To examine the impact of BRAF mutation status and use of BRAFi in conjunction with stereotactic radiosurgery (SRS).	Single-center retrospective study, number of patients n=65	Patients who had developed cutaneous melanoma BM between June of 2010 and August of 2014.	Overall Survival Local Tumor Control	Medians for OS, BM survival, and SRS survival were 46, 9, and 6 months, respectively. Survival after the diagnosis of BM in patients with mutant BRAF and treated with SRS in conjunction with BRAFi was increased compared with survival in patientswith wild-type BRAF or those who had mutant BRAF but no BRAFi treatment given after the development of BM Six patients in		3a

					Group A (mutant BRAF but no BRAFi), 15 patients in Group B (mutant BRAF and BRAFi), and 28 patients in Group C (wild-type BRAF) had the available radiological follow-up.		

7.7.6.5. Literatur 2016

Ahmad, S.S., et al., Ipilimumab in the real world: the UK expanded access programme experience in previously treated advanced melanoma patients. Melanoma Res, 2015. 25(5): p. 432-42.
Ahmed, K.A., et al., Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. Ann Oncol, 2016. 27(12): p. 2288-2294.
Ahmed, K.A., et al., Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy. Ann Oncol, 2016. 27(3): p. 434-41.
Geukes Foppen, M.H., et al., Targeted treatment and immunotherapy in leptomeningeal metastases from melanoma. Ann Oncol, 2016. 27(6): p. 1138-42.
Kiess, A.P., et al., Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. Int J Radiat Oncol Biol Phys, 2015. 92(2): p. 368-75.
Mathew, M., et al., Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery. Melanoma Res, 2013. 23(3): p. 191-5.
Qian, J.M., et al., Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. Cancer, 2016. 122(19): p. 3051-8.
Spagnolo, F., et al., Survival of patients with metastatic melanoma and brain metastases in the era of MAP-kinase inhibitors and immunologic checkpoint blockade antibodies: A systematic review. Cancer Treat Rev, 2016. 45: p. 38-45.
Wolf, A., et al., Impact on overall survival of the combination of BRAF inhibitors and stereotactic radiosurgery in patients with melanoma brain metastases. J Neurooncol, 2016. 127(3): p. 607-15.
Xu, Z., et al., BRAF V600E mutation and BRAF kinase inhibitors in conjunction with stereotactic radiosurgery for intracranial melanoma metastases. J Neurosurg, 2017. 126(3): p. 726-734.

8. AG Nebenwirkungen

8.1. Frage VII.1. Kutane Nebenwirkungen – De novo Recherche

Frage VII.1. Für welche Substanzklassen, die zur medikamentösen Anwendung beim malignen Melanom kommen, sind kutane Nebenwirkungen beschrieben und welche Strategien zur Behandlung dieser Nebenwirkungen existieren?

8.1.1. Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients	Systemic treatment		Toxicity, Safety

Suchwörter				
Stichwort	melanoma	Systemic treatment	Side effect, adverse event	Cutaneous, skin
Mesh Term	melanoma	Systemic treatment	Side effect	Skin

8.1.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	((melanoma [tiab] OR melanoma[MeSH]) AND (side effect[tiab] OR	26.09.2016	755

	toxicity[tiab] OR adverse event[tiab]) AND (cutaneous[tiab] OR skin[tiab]))		
Cochrane Library	(melanoma and (systemic treatment) and ((side effect) or toxicity) and (cutaneous or skin)).mp.	26.09.2016	57

8.1.3. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer		812
Einschlusskriterien	Reviews, klinische Studien Intervention: BRAF-Inhibitoren, MEK-Inhibitoren, Ipilimumab, PD-1-Inhibitoren Sprachen: e,dt	
Ausschlusskriterien	Case Reports Chemotherapie Kollektive mit gemischten Tumorentitiäten	
Anzahl ausgewählter Studien		**25**

8.1.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Abdel-Wahab N, et al. 2016	To conduct a systematic review of case reports describing the	Systematic review; n=191 publications, 251 case reports.	Patients with cancer who develop irAEs following treatment	irAEs in patients treated with checkpoint blockade therapy and identify	Most patients had metastatic melanoma (95.6%), the majority were treated with ipilimumab		3a

	occurrence of irAEs in patients with cancer following checkpoint blockade therapy, primarily to identify potentially unrecognized or unusual clinical findings and toxicity.		with anti CTLA-4 (ipilimumab) or anti PD-1 (nivolumab or pembrolizumab) antibodies were included.	potentially unrecognized or unusual clinical findings and toxicity.	(93.2%). Autoimmune colitis, hepatitis, endocrinopathies, and cutaneous irAEs were the most frequently reported irAEs in ipilimumab treated patients. In the 234 patients who had received ipilimumab cutaneous irAEs were reported in 60 patients (25.6%). Rash was reported in 26 pts, pruritus in 15 pts, vitiligo 8 pts, dermatitis 7 pts, sweet syndrome 3 pts, drug eruptions 2 pts. The following irAEs were reported 1 pt each: poliosis, delayed hypersensitivity reaction, alopecia universalis, grover disease, pyoderma gangrenosum,		

					toxic epidermal necrolysis and chronic non-caseation granuloma. Pembrolizumab. Ten cases reported irAEs with pembrolizumab and 5 pts had cutaneous irAEs. Vitiligo was reported in 1 pt, dermatitis in 3 pts and bullous pemphigoid in 1 pt. Nivolumab. Seven cases reported irAEs with nivolumab. Cutaneous irAEs were reported in 2 patients - 1 pt with rash and 1 pt psoriasis.		
Anforth R, et al. 2015	To determine whether cutaneous toxicities	Prospective single center cohort study; n=163	All patients treated with the BRAF inhibitors	Cutaneous toxicities in patients treated with BRAF	Patients on single-agent BRAF inhibitor therapy suffered from	Extrem hoher Anteil an Morbus Grover, fraglich, ob hier die	3a

	persist in patients who have remained on BRAF inhibitor-based therapies for longer than 52 weeks, and therefore whether ongoing dermatology assessment is required.		vemurafenib or dabrafenib or combination BRAF inhibitor and mitogen-activated protein kinase kinase (MEK) inhibitor therapy at Westmead Hospital, Sydney, Australia between December 2009 and 1 November 2013.	inhibitor therapy for longer than 52 weeks.	Grover disease (45%), plantar hyperkeratosis (45%), verrucal keratosis (18%) and even cutaneous squamous cell carcinoma (16%). The most frequent adverse event seen in patients in the combination BRAF and MEK inhibitor group was an acneiform eruption (40%).	richtige Diagnose gestellt wurde.	
Anforth R, et al. 2014	To investigate the prevalence of acneiform eruptions in patients taking the	Retrospective review; n=43	Patients treated in with trametinib alone or in combination with dabrafenib	To investigate the prevalence of acneiform eruptions in patients taking the MEK inhibitor	In total, 77% of the trametinib group developed an acneiform eruption on the trial, while only 10% developed acneiform lesions		3a

	MEK inhibitor trametinib, alone and in combination with dabrafenib		in Westmead Hospital, Sydney Australia.	trametinib, both alone and in combination with dabrafenib.	in the combination trial.		
Arance AM, et al. 2016	To investigated safety, tolerability and efficacy of vemurafenib in Spanish patients participating in a clinical trial that evaluated Vemurafenib tolerability in patients with BRAFV600 mutated advanced melanoma.	Retrospective review; n=301	Spanish patients included in the following clinical trial "Vemurafenib in patients with BRAF(V600) mutated metastatic melanoma: an open-label, multicentre, safety study"	Safety, tolerability and efficacy	Rash was reported in 123 pts (113 pts grade 1/2 and 10 grade 3/4). Photosensitivity was reported in 103 pts (93 pts grade 1/2 and 10 grade 3/4). Skin neoplasms was reported in 63 pts (56 pts grade 1/2 and 7 grade 3/4). Alopecia was reported in 61 pts (61 pts grade 1/2 and 0 grade 3/4). Hyperkeratosis was reported in 60 pts (59 pts grade 1/2 and 1 grade 3/4). Cutaneous squamous cell carcinoma was reported in 50 pts (2 pts grade 1/2		3a

					and 48 grade 3/4). Pruritus was reported in 44 pts (44 pts grade 1/2 and 0 grade 3/4). Dry skin was reported in 38 pts (38 pts grade 1/2 and 0 grade 3/4). Skin papilloma was reported in 30 pts (30 pts grade 1/2 and 0 grade 3/4). Xerosis was reported in 21 pts (21 pts grade 1/2 and 0 grade 3/4). Keratosis pilaris was reported in 18 pts (18 pts grade 1/2 and 0 grade 3/4).		
Belum VR, et al. 2016	To report the incidence, relative risk (RR), and clinico-morphological pattern of dermatologic AE in pts treated with	Systematic review and meta-analysis; n=427 publications (nivolumab) and n=102 publications (pembrolizumab); n= 4244	Patients treated with nivolumab and pembrolizumab in clinical trials (and/or cohorts) that: 1)	Patterm of dermatologic IAEs The incidence and RR of dermatological adverse events Rash, pruritus	The calculated incidence of all-grade rash with pembrolizumab and nivolumab was 16.7% (RR=2.6) and 14.3% (RR=2.5), respectively. Other significant all-		2a

	nivolumab and pembrolizumab	pts included; n=1320 treated patients (assessed for AEs)	investigated the utility of pembrolizumab or nivolumab at the Food and Drug Administration-approved dose in the treatment of cancer; 2) clearly reported a dermatologic AE in their safety data, with or without the clinical severity grading; and 3) were published in the English language.	and vitiligo were found to be the most frequently reported dermatologic AEs.	grade AEs included pruritus (pembrolizumab: incidence, 20.2% [RR=49.9]; nivolumab: incidence, 13.2% [RR=34.5]) and vitiligo (pembrolizumab: incidence, 8.3% [RR=17.5]; nivolumab: 7.5% [RR=14.6]). Interestingly, all the vitiligo events were reported in trials investigating melanoma. The RR for developing dermatologic AEs in general, was 2.95 with pembrolizumab, and 2.3 with nivolumab.		
Boussemart L, et al. 2013	To report the incidence and classify the dermatological side effects	Retrospective review; n=42	Patients treated with vemurafenib between March 2010	To report the incidence and classify the dermatological side effects	All patients presented with at least one adverse skin reaction. The most common		3a

	associated with vemurafenib treatment		and March 2012 included in BRIM3 clinical trial and compassion ate use program;	associated with vemurafenib treatment	cutaneous side-effects consisted in verrucous papillomas (79%) and hand–foot skin reaction (60%). Other common cutaneous toxic effects were a diffuse hyperkeratotic perifollicular rash (55%), photosensitivity (52%) and alopecia (45%). Epidermoid cysts (33%) and eruptive nevi (10%) were also observed. Keratoacanthomas (KA) and squamous cell carcinoma (SCC) occurred in 14% and 26% of the patients, respectively.		
Di Giacomo AM, et al. 2010	To provide an overview of safety data on CTLA-4	Retrospective review; n=487	Patients treated with ipilimumab across	Frequency of dermatologic AEs	Study CA184-008: 49% pts had dermatological side effects - all		3a

	antagonists and of available strategies to optimize their clinical use in cancer patients.		phase II trials in melanoma (BMS trials CA184-008, 022 and 007)		grade, and 3% grade 3/4. Study CA184-022- dosage 0.3mg/kg: 13% pts had dermatological side effects - all grade, and 0% grade 3/4; dosage 3mg/kg: 45% pts had dermatological side effects - all grade, and 1% grade 3/4; dosage 10mg/kg: 47% pts had dermatological side effects - all grade, and 4% grade 3/4. Study CA184-007: 68% pts had dermatological side effects - all grade, and 0% grade 3/4		
Eigentler TK, et al. 2016	To review incidences and kinetics of onset and resolution of immune-mediated	Retrospective review; n=1826	Patients treated with nivolumab and pembrolizumab in the following	Incidences and kinetics of onset and resolution of immune-mediated AEOSI.	In trials CA209037/-066 skin and subcutaneous tissues disorders were reported in 39.5% patients (all		3a

	‘‘adverse events of specific interest” (AEOSI) of both approved PD-1 inhibitors nivolumab and pembrolizumab		clinical trials: CA209017/-063; CA209037/-066; P001/-002 and P001/-002 provided by databases of the FDA and EMA		grades) and 1.3% (grade ≥3). In trials P001/-002 (2 mg/kg q3w) skin and subcutaneous tissues disorders were reported in 43.2% patients (all grades) and grade ≥3 not reported. In trials P001/-002 (2 mg/kg q3w & 10 mg/kg q3w/q2w) skin and subcutaneous tissues disorders were reported in 46.3% patients (all grades) and grade ≥3 not reported.		
Fava P, et al. 2016	To provide practical advices to manage the drug related cutaneous reactions.	Retrospective review; n= 41	Patients treated with vemurafenib in the Dermatology Department of Turin University	Absolute frequency of vermurafenib induced cutaneous Aes Proportion of vemurafenib induced cutaneous AEs	29/39 patients (74.4%) developed cutaneous toxicities. Maculopapular rash (56%), warts (44%), plantar hyperkeratosis (18%), effluvium (15%), keratoacanthoma (15%),		3a

					photosensitivity (13%), hand edema (10%), follicular hyperkeratosis (5%), conjuntivitis (5%), hair changes (5%), milia (3%) and urticaria (3%).		
Hofmann L, et al. 2016	To report the incidence of cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy	Retrospective review; n=496	Patients with melanoma treated with nivolumab and pembrolizumab in fifteen study centers in Germany and Switzerland	Incidence and severity of cutaneous side-effects of anti-PD-1 therapy	43 patients (8.7%) presented with dermatological side-effects. These included common skin events like pruritus, rash and eczema in 19 patients (3.8%), vitiligo in 13 patients (2.6%), alopecia in 7 patients (1.4%), and lichenoid and cytotoxic skin reactions in 4 patients (0.8%). Psoriasis vulgaris and lichen planus mucosae were reported in two patient each. Sweet's syndrome, lichen planus, and		3a

					lichen sclerosus et atrophicus were documented in one patient each. Only three cutaneous AEs - lichenoid skin reaction, lichen ruber mucosae, and Sweet's syndromedwere graded as severe, i.e. grade 3. All other events were documented as grade 1-2.		
Kahler KC, et al. 2016	To describe the mechanisms of action of immune checkpoint blockade as well as its clinical effects in metastatic melanoma, with a detailed focus on the spectrum of	Retrospective review; n=1826	Patients inluded in CheckMate 067 and Keynote 002 trials	Safety profile	In pts treated with NIVO, cutaneous irAE were reported in 41.9% (all grades) and 1.6% (grades 3/4). Pruritus was reported in 18.8% (all grades) and 0% (grades 3/4). Rash was reported in 21.7% (all grades) and 0.3% (grades 3/4). Maculopapular rash was reported		3a

	adverse events and their therapeutic management				in 4.2% (all grades) and 0.3% (grades 3/4). In pts treated with IPI, cutaneous irAE were reported in 54% (all grades) and 2.9% (grades 3/4). Pruritus was reported in 35.4% (all grades) and 0.3% (grades 3/4). Rash was reported in 20.9% (all grades) and 1.6% (grades 3/4). Maculopapular rash was reported in 11.9% (all grades) and 0.3% (grades 3/4). In pts treated with NIVO + IPI, cutaneous irAE were reported in 59.1% (all grades) and 5.8% (grades 3/4). Pruritus was reported in 32.2% (all grades) and 1.9% (grades 3/4).		

					Rash was reported in 28.4% (all grades) and 2.9% (grades 3/4). Maculopapular In pts treated with PEM 2mg/kg, the following cutaneous irAE (all grades) were reported: pruritus 21%, rash 12% and maculopapular rash 2%. Maculopapular rash grade 3/4 was reported in 1%. In pts treated with PEM 10mg/kg the following cutaneous irAE (all grades) were reported: pruritus 23%, rash 10% and maculopapular rash 5%. Maculopapular rash grade 3/4 was reported in 1%.		

Khoja L, et al 2016	To evaluate the toxicity and the outcomes of all patients treated with Ipilimumab in a single institution	Retrospective review; n=129	Patients who received ipilimumab between 2008 and 2013, inclusively in Princess Margaret hospital	Safety	Cutaneous toxicity identified as rash was reported in 18 patients. Prednisone was required in 7 patients for rash grade ≥2.		3a
Lacouture ME, et al. 2014	To summarize ipilimumab efficacy results and safety profile, with particular attention to cutaneous events.	Retrospective review; n=1555	Patients treated with ipilimumab containing remines in clinical pahse II or III trials	Frequency of dermatologic Aes in different clincial trials	Weber et al, 2009 Cutaneous irAE were reported in 49%, pruritus in 25.2%, rash 25.2% and vitiligo 1.9%. Wolchock et al, 2010 - Cutaneous irAE were reported in 46.5%, pruritus in 32.4%, rash 22.5% and vitiligo % was NR. For CA184007 clinical trial in the 10mg/kg+placebo cutaneous irAE were reported in 68.4%, pruritus in 35.1%, rash 57.9%		3a

					and vitiligo 1.8%. For Hodi et al, 2010 clinical trial in the 3mg/kg +gp100 arm cutaneous irAE were reported in 40%, pruritus in 17.6%, rash 17.6% and vitiligo 3.7%. For Hodi et al, 2010 clinical trial in the 3mg/kg +placebo arm cutaneous irAE were reported in 43.5%, pruritus in 24.4%, rash 19.1% and vitiligo 2.3%. For Robert et al, 2011 clinical trial in the 10mg/kg +placebo arm pruritus was reported in 26.7% and rash 22.3%.		
Lemech C, et al. 2012	To describe the toxicities associated with new	Retrospective review; n=598	Patients treated with ipilimumab monotherap	Safety	For Robert et al, 2011 clinical trial in the 10mg/kg ipilimumab+placeb		3b

	melanoma therapies		y in different dosages and ipilimumab in combination with dacarbazine		o arm pruritus was reported in 26.7% (2% grade 3 and 0% grade 4) and rash 22.3% (1.2% grade 3 and 0% grade 4). For Hodi et al, 2010 clinical trial in the 3mg/kg ipilimumab+placeb o arm pruritus was reported in 24.4% (grade 3/4 - 0%), rash 19.1% (grade 3 - 0,8% and grade 4 -0%) and vitiligo 2.3% (grade 3/4 - 0%).		
Ma et al, 2013	To investigate the incidence rate of severe adverse events for ipilimumab, vemurafenib, IFN alpha-2b, dacarbazine and IL-2	Systematic review of 32 studies that fulfilled the inclusion criteria for the systematic review. The studies consisted of a total of 5802 subjects.	Patients entering clinical trials that evaluated safety and toxicity of ipilimumab, vemurafenib , IFN alfa-2b, dacarbazine or IL-2	Safety and Toxicity	Patients receiving vemurafenib developed keratoacanthomas and cutaneous squamous cell carcinoma at an incidence rate of 0.0025 cases per 100 person-years.		2a

Mandala M, et al. 2013	To summarize and critically review the state of the art of skin toxicity associated with BRAF inhibitors	Retrospective review	Patients treated with vemurafenib, dabrafenib, dabrafenib+trametinib and sorafenib+chemotherapy	Frequency and intensity of cutaneous side effects	In Flaherty et al, 2010 clinical trial, in patients treated with vemurafenib, the following grade ≤ 2 AE were reported: palmar-plantar dysesthesia 3%, rash 12%, photosensitivity reaction 7% and pruritus 5%. Palmar-plantar hyperkeratosis, alopecia and skin papilloma frequences were not reported. The following grade 3/4 AE were reported: palmar-plantar dysesthesia 2%, rash 3%, photosensitivity reaction 1%, pruritus 1%, cutaneous squamous cell carcinoma and keratoacanthoma 21%. Hyperkeratosis, palmar-plantar		IV

					hyperkeratosis, alopecia, skin papilloma, cutaneous basal cell carcinoma and other malignant skin tumors frequences were not reported. In Flaherty et al, 2012 clinical trial, in patients treated with dabrafenib+trametinib (150/1), the following grade ≤ 2 AE were reported: hyperkeratosis 6%, rash 20%, alopecia 9%, skin papilloma 7%. Palmar-plantar hyperkeratosis, palmar-plantar dysesthesia, photosensitivity reaction and prutitus frequences were not reported. The following grade 3/4 AE were		

					reported: photosensitivity reaction 2%, Cutaneous squamous cell carcinoma/keratoacanthoma 2%. Pruritus, cutaneous basal cell carcinoma and other malignant skin tumors frequence were not reported. For the dabrafenib+ trametinib (150/2) group, the following grade ≤ 2 AE were reported: hyperkeratosis 9%, rash 27%, alopecia 5%, skin papilloma 4% and keratoacanthoma 2%. Palmar-plantar hyperkeratosis, palmar-plantar dysesthesia, photosensitivity reaction and prutitus frequences were		

					not reported. The following grade 3/4 AE were reported: palmar-plantar dysesthesia 2% and cutaneous squamous cell 5%. Pruritus, cutaneous basal cell carcinoma and other malignant skin tumors frequence were not reported. In Flaherty et al, 2013 clinical trial, for patients treated with sorafenib and carboplatin + paclitaxel the following grade 3/4 AE were reported: palmar-plantar dysesthesia 12% and rash 14,8%. Hyperkeratosis, palmar-plantar hyperkeratosis, photosensitivity.		
Peuvrel L,	To determine	Retrospective	Patients	Safety	Among the 131		3a

et al. 2016	the rate of permanent vemurafenib discontinuation due to grade 3–4 skin toxicity, features of these toxicities, their recurrence rate after a switch to dabrafenib and their impact on overall survival.	review; n=131	treated with vemurafenib for melanoma between November 2010 and December 2014 in the Dermatology Department of Nantes University Hospital		vemurafenib-treated patients, 26% developed grade 3–4 skin toxicity. Forty-four percent of them permanently discontinued their treatment, mainly due to rash and classic skin adverse reactions (Steven–Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms). Conversely, photosensitivity and carcinomas rarely required treatment adjustment. Grade 3–4 rashes were associated with clinical or biological abnormalities in 94% of patients. Among the 10 patients who subsequently		

					switched to dabrafenib, skin toxicity recurred only in one patient.		
Rinderknecht JD, et al. 2013	To investigate the clinical and histological features of class-specific cutaneous adverse reactions in patients treated with vemurafenib	Retrospective review; n=28	Patients treated with vemurafenib in University Hospital of Zurich during June 2010 until June 2011 and included in one of the following trials: phase I NCT01164891 clinical trial; BRIM-3 trial, Roche MO25653 trial and Roche MO25515 trial.	Safety	In two patients the dose had to be reduced to 720 mg due to arthralgia. 26/28 patients (93%) experienced cutaneous side effects. Observed side effects included UVA dependent photosensitivity (n=16), maculopapular exanthema (n=14), pruritus (n=8), folliculitis (n=5), burning feet (n=3), hair thinning (mild alopecia) (n=8), curly hair (n=2) and nail changes (n=2). Keratosis pilaris and acanthopapilloma were common skin reactions		3b

					(n=12/n=13), as well as plantar hyperkeratosis (n=4), keratoacanthoma (n=5) and invasive squamous cell carcinoma (n=4). One patient developed a second primary melanoma after more than 4 months of therapy (BRAF and RAS wild type).		
Sanlorenzo M, et al. 2014	To investigate the cutaneous safety profile of BRAFi versus BRAFi and MEKi combination regimens.	Retrospective review; n=44	Patients with stage IV or unresectable stage III melanoma treated in and followed up at the University of California and San Francisco between November 2009 and	Comparison of safety profile	The development of cutaneous adverse events was significantly less frequent (p= 012) and occurred after longer treatment time (P=.025) in patients treated with BRAFi and MEKi combination regimen compared with patients treated with BRAFi monotherapy. Among patients		3a

			August 2013 and who received BRAFi monotherapy or BRAFi 1 MEKi combination therapy.		who received both BRAFi and the combination of BRAFi and MEKi at different time points during their treatment course, the development of squamous cell carcinoma or keratoacanthoma was significantly less frequent when they received the combination regimen (P=.008). Patients receiving vemurafenib developed more cutaneous adverse events (P=.001) and in particular more photosensitivity (P=.010) than patients who did not.		
Spain L, et al. 2016	To identify the rates of common and uncommon irAEs	Retrospective review	Patients treated with pembrolizumab, nivolumab,	Safety	In patients treated with pembrolizumab (2 mg/kg 2- and 3-weekly), the		3a

	associated with each immune checkpoint inhibitor (ICPI) and their timing of onset.		ipilimumab and ipilimumab + nivolumab in combination .		following cutaneous AE (all grade) were reported: pruritus 14%, rash 13-15%, vitiligo 9-11%, No grade 3/4 cutaneous AE were reported. In patients treated with nivolumab (3 mg/kg 2-weekly), the following cutaneous AE (all grade) were reported: pruritus 16-19%, rash 9-22%, vitiligo 5-11%. The following grade 3/4 AE were reported: pruritus <1%, rash <1%, vitiligo 0%. In patients treated with Ipilimumab (3 mg/kg 3-weekly) the following cutaneous AE (all grade) were reported: pruritus 25-35%, rash 15-		

					21%, vitiligo 2-4%. The following grade 3/4 AE were reported: pruritus <1%, rash In patients treated with Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks) the following cutaneous AE (all grade) were reported: pruritus 33%, rash 28%, vitiligo 7%. The following grade 3/4cutaneous AE were reported: pruritus 2%		
Vanneste L, et al. 2015	To study the timing, prevalence and response to treatment of skin lesions in patients receiving V-raf murine	Retrospective review; n=20	Patients with metastatic melanoma treated with a BRAF inhibitor between March 2012 and April 2013 at the	Safety	11 pts treated with vemurafenib (58%) developed cutaneous side-effects and 10 pts (42%) had more than one cutaneous AE. Verrucous papillomas were		3a

	sarcoma viral oncogene homolog B1 (BRAF) inhibitors.		University Hospitals Leuven.		observed in 8 pts (42%), after 1–12 weeks. 4 keratoacanthomas in 2 pts (11%) after 6–10 weeks and 2 squamous cell carcinomas in 2 pts (11%) after 10–16 weeks. 7 pts (37%) developed a hyperkeratotic, folliculocentric eruption. 4 pts (21%) presented a facial erythema, 2 pts (11%) a seborrhoeic dermatitis-like eczema on the scalp. 3 pts (16%) developed cystic lesions after 2–11 weeks. 3 pts (16%) presented a hand-foot skin reaction. Hyperkeratosis of the nipples was seen in 1 patient (5%). Phototoxic reactions after UV exposure were diagnosed in 5 pts		

					(26%) and alopecia in 2 pts (11%) after 8–10 weeks. 1 patient on dabrafenib developed curly hairs (24 weeks), keratotic papules, a keratoacanthoma and a hand–foot skin reaction.		
Villadolid J, et al 2015	To describe the optimal management of toxicities related to immune checkpoint inhibition from FDA approved agents targeting CTLA-4 and PD-1.	Retrospective review	Patients treated withagents targeting CTLA-4 and PD-1	Safety in patients treated with checkpoint inhibitors	In the Hodi FS et al. 2010 trial - IPI 3 mg/kg monotherapy every 3 weeks (n=131), the following cutaneous AE (all grades) were described: pruritus 24.4%, rash 19.1%, vitiligo 2.3%. Grade 3 rash was described in 0.8%. No grade 4 cutaneous AE were reported. In the IPI 3 mg/kg+gp100 every 3 weeks (n=380) arm, the following cutaneous AE (all		IV

					grades) were described: pruritus 17.6%, rash 17.6% and vitiligo 3.7%. Grade 3 pruritus was described in 0.3% patients and eash in 1.3%. Grade 4 cutaneous AE were described in 0.3%. In the Robert C et al. 2011 trial - IPI 10 mg/kg plus DTIC 850 mg/m2 every 3 weeks (n=247), the following cutaneous AE (all grades) were described: pruritus 26.7% and rash 22.3%. Grade 2 pruritus was described in 2.0% of patients and rash in 1.2%. No grade 4 cutaneous AE were described. In the Robert C et al. 2015 trial -		

					NIVO 3 mg/kg every 2 weeks (n=206), the following cutaneous AE (all grades) were described: pruritus 17%, rash 15% and vitiligo 10.7%. The following grade 3/4 cutaneous AE were described: pruritus 5.3%, rash 2.9% a In the Weber JS et al. 2015 trial - NIVO 3 mg/kg every 2 weeks (n=268) the the following cutaneous AE (all grades) were described: pruritus 16%, rash 9.3%, rash maculopapular 5.2%, vitiligo 5.2%, dermatitis 1.9% and rash erythematous 1.1%. Grade 3/4¾		

Weber JS, et al. 2016	To provide recomendations on how to manage irAEs associated with anti-PD1 agents	Retrospective review	Patients treated with anti-PD1 agents	Safety in patients treated with anti-PD1 agents	In the CheckMate 037 clinical trial, the following cutaneous AE (all grades) were described: pruritus 16% and rash 9.3%. Grade 3/4 rash was described in 0.4% of patients. In the CheckMate 066 clinical trial, the following cutaneous AE (all grades) were described: pruritus 17% and rash 15%. Grade 3/4 pruritus was described in 0.5% of patients and rash in 0.5%. In the CheckMate 067 clinical trial, in the NIVO treatment arm the following cutaneous AE (all grades) were described: pruritus 18.8% and rash 25.9%. Rash grade 3/4 was described		3a

					in 0.6% of the patients. In the NIVO + IPI treatment arm, the following cutaneous AE (all grades) were described: pruritus 33.2% and rash 40.3%. Grade 3/4 pruritus was described in 1.9% of patients and rash in 4.8%. In the IPI treatment arm, the following cutaneous AE (all grades) were described: pruritus 35.4% and rash 32.8%. Grade 3/4 pruritus was described in 0.3% of patients and rash in 1.9%. In the KEYNOTE-006 clinical trial, the following cutaneous AE (all grades) were associated with PEM treatment:		

					pruritus 14.1% and rash 13.4%. No grade 3/5 AE were described.		
Welsh SJ, et al. 2015	To review the most common and serious adverse events associated with BRAF targeted agents and suggest management algorithms	Retrospective review	Patients treated with BRAF and MEK inhibitors monotherapy or in combination.	Safety for BRAF, MEK and BRAF/MEK combinations	In the Chapman et al. 2011 and Larkin et al. 2014 trials combined the following cutaneous AE (all grades) were described in patiengts treated with vemurafenib: rash 41% and cutaneous SCC 9%. Grade 3/4 rash was described in 9% of the patients and cutaneous SCC in 19%. In the Hauschild et al. 2012 and 2013 trials combined the following cutaneous AE (all grades) were described in patients treated with dabrafenib: rash 30% and		3a

					cutaneous SCC 10%. Grade 3/4 cutaneous SCC was described in 4% of the patients. In the Flaherty et al. 2012 trial combined the following cutaneous AE (all grades) were described in patients treated with trametinib: rash 58%. Grade 3/4 rash was described in 8% of the patients. In the Flaherty et al. 2012 and Long et al. 2014 trials combined the following cutaneous AE (all grades) were described in patients treated with trametinib + dabrafenib: rash 27% and cutaneous SCC 7%. Grade 3/4		

					cutabeous SCC was described in 5% of the pat		

8.1.5. Literatur

Abdel-Wahab, N., M. Shah, and M.E. Suarez-Almazor, Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. PLoS One, 2016. 11(7): p. e0160221.
Anforth, R., et al., Cutaneous adverse events in patients treated with BRAF inhibitor-based therapies for metastatic melanoma for longer than 52 weeks. Br J Dermatol, 2015. 172(1): p. 239-43.
Anforth, R., et al., Acneiform eruptions: a common cutaneous toxicity of the MEK inhibitor trametinib. Australas J Dermatol, 2014. 55(4): p. 250-4.
Arance, A.M., et al., Safety of vemurafenib in patients with BRAF V600 mutated metastatic melanoma: the Spanish experience. Clin Transl Oncol, 2016. 18(11): p. 1147-1157.
Belum, V.R., et al., Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer, 2016. 60: p. 12-25.
Boussemart, L., et al., Prospective study of cutaneous side-effects associated with the BRAF inhibitor vemurafenib: a study of 42 patients. Ann Oncol, 2013. 24(6): p. 1691-7.
Di Giacomo, A.M., M. Biagioli, and M. Maio, The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. Semin Oncol, 2010. 37(5): p. 499-507.
Eigentler, T.K., et al., Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev, 2016. 45: p. 7-18.
Fava, P., et al., Dermatological approach to vemurafenib skin toxicity: a single centre experience. G Ital Dermatol Venereol, 2016. 151(1): p. 25-31.
Hofmann, L., et al., Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer, 2016. 60: p. 190-209.
Kahler, K.C., et al., Management of side effects of immune checkpoint blockade by anti-CTLA-4 and anti-PD-1 antibodies in metastatic melanoma. J Dtsch Dermatol Ges, 2016. 14(7): p. 662-81.
Khoja, L., et al., Real-world efficacy, toxicity and clinical management of ipilimumab treatment in metastatic melanoma. Oncol Lett, 2016. 11(2): p. 1581-1585.
Lacouture, M.E., et al., Ipilimumab in patients with cancer and the management of dermatologic adverse events. J Am Acad Dermatol, 2014. 71(1): p. 161-9.
Lemech, C. and H.T. Arkenau, Novel treatments for metastatic cutaneous melanoma and the management of emergent toxicities. Clin Med Insights Oncol, 2012. 6: p. 53-66.
Ma, C. and A.W. Armstrong, Severe adverse events from the treatment of advanced melanoma: a systematic review of severe side effects associated with ipilimumab, vemurafenib, interferon alfa-2b, dacarbazine and interleukin-2. J Dermatolog Treat, 2014. 25(5): p. 401-8.
Mandala, M., D. Massi, and V. De Giorgi, Cutaneous toxicities of BRAF inhibitors: clinical and pathological challenges and call to action. Crit Rev Oncol Hematol, 2013. 88(2): p. 318-37.
Peuvrel, L., et al., Profile of vemurafenib-induced severe skin toxicities. J Eur Acad Dermatol Venereol, 2016. 30(2): p. 250-7.
Rinderknecht, J.D., et al., RASopathic skin eruptions during vemurafenib therapy. PLoS One, 2013. 8(3): p. e58721.
Sanlorenzo, M., et al., Comparative profile of cutaneous adverse events: BRAF/MEK inhibitor combination therapy versus BRAF monotherapy in melanoma. J Am Acad Dermatol, 2014. 71(6): p. 1102-1109.e1.
Spain, L., S. Diem, and J. Larkin, Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev, 2016. 44: p. 51-60.
Vanneste, L., et al., Cutaneous adverse effects of BRAF inhibitors in metastatic malignant melanoma, a prospective study in 20 patients. J Eur Acad Dermatol Venereol, 2015. 29(1): p. 61-8.
Villadolid, J. and A. Amin, Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res, 2015. 4(5): p. 560-75.
Weber, J.S., et al., Management of Adverse Events Following Treatment With Anti-Programmed Death-1 Agents. Oncologist, 2016. 21(10): p. 1230-1240.
Welsh, S.J. and P.G. Corrie, Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. Ther Adv Med Oncol, 2015. 7(2): p. 122-36.

8.2. Frage VII.2. Reno-Kardiale Nebenwirkungen – De novo Recherche

Frage VII.2. Für welche Substanzklassen, die zur medikamentösen Anwendung beim malignen Melanom kommen, sind Nebenwirkungen im renokardio-vaskulären System beschrieben und welche Strategien zur Behandlung dieser Nebenwirkungen existieren?

8.2.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients	Systemic treatment		Toxicity, Safety

Suchwörter				
Stichwort	melanoma	Systemic treatment	Side effect, adverse event	Cardiac, renal
Mesh Term	melanoma	Systemic treatment	Side effect	

8.2.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	((melanoma [tiab] OR melanoma[MeSH]) AND (side effect[tiab] OR toxicity[tiab] OR adverse event[tiab]) AND (cardiac [tiab] OR "kidney failure"[tiab] OR renal[tiab]))	26.09.2016	555
Cochrane Library	(melanoma and (systemic treatment) and ((side effect) or toxicity) and	26.09.2016	48

	(kidney or renal or cardiac or heart)).mp.		

8.2.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	603
Einschlusskriterien	Reviews, klinische Studien Intervention: BRAF-Inhibitoren, MEK-Inhibitoren, Ipilimumab, PD-1-Inhibitoren Sprachen: e,dt
Ausschlusskriterien	Case Reports Chemotherapie Kollektive mit gemischten Tumorentitiäten
Anzahl ausgewählter Studien	**9**

8.2.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Eigentler TK, et al. 2016	To review incidences and kinetics of onset and resolution of immune-mediated ‘‘adverse	Retrospective review; n=1826	Patients treated with nivolumab and pembrolizumab in the following clinical	Frequency Kinetics	In trials CA209037/-066 with nivolumab 3 mg/kg q2w (n=474) renal and urinary disorders were reported in 2.1% patients (all		3a

	events of specific interest" (AEOSI) of both approved PD-1 inhibitors nivolumab and pembrolizumab		trials: CA209017/-063; CA209037/-066; P001/-002 and P001/-002		grades) and 0.6% (grade ≥3). In trials P001/-002 with pembrolizumab 2 mg/kg q3w (n=340) were reported in patients 0.9% (all grades) and grade ≥3 were not reported. In trials P001/-002 with pembrolizumab 2 mg/kg q3w & 10 mg/kg q3w/q2w (n= 1012) renal and urinary disorders were reported in 1.6% patients (all grades) and grade ≥3 were not reported. Median time to onset of renal-select events is highly variable, ranging from 6 weeks to 10.5 weeks, and up to 30 weeks for the different		

					pembrolizumab regimen.		
Hofmann L, et al. 2016	To report the incidence of cutaneous, gastrointestina, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy	Retrospective review; n=496	Patients with melanoma treated with nivolumab and pembrolizumab in fifteen study centers in Germany and Switzerland	Frequency and intensity	3 patients (0.4%) developed renal irAE: 1 case with nephritis with renal failure (grade 3) and 2 cases with nephritis (one grade 1 and one grade 2)		3a
Hurabielle C, et al. 2016	To evaluate the frequency and the mechanisms of increases in plasma creatinine level in patients receiving vemurafenib for advanced melanoma.	Retrospective review; n=70	Patients treated with vemurafenib between March 2013 and December 2014 in one center	Frequency and the mechanisms of increases in plasma creatinine level	97% of the patients displayed an immediate, and thereafter stable, increase in creatinine (+22.8%) after vemurafenib initiation. In 44/52 patients in whom vemurafenib was discontinued, creatinine levels returned to baseline. Serum cystatin C increased, although		3a

					proportionally less than serum creatinine, showing that creatinine increase under vemurafenib was indeed partly due to a renal function impairment. In addition, renal explorations demonstrated that vemurafenib induced an inhibition of creatinine tubular secretion.		
Kahler KC, et al. 2016	To describe the mechanisms of action of immune checkpoint blockade as well as its clinical effects in metastatic melanoma, with a detailed	Retrospective review; n=1826	Patients included in CheckMate 067 and Keynote 002 trials; selected case reports	Frequency and intensity	Treatment-related renal side effects have only rarely been observed during therapy with ipilimumab, nivolumab, and pembrolizumab (< 1 % of treated patients). In seven published case reports on ipilimumab-associated renal		3a

	focus on the spectrum of adverse events and their therapeutic management				disease six patients had acute renal failure and one had nephrotic syndrome, which had occurred six to twelve weeks after initiation of ipilimumab therapy. On pathology, three cases showed granulomatous interstitial nephritis with or without acute tubular necrosis; the patient with nephrotic syndrome had membranous lupus nephritis.		
Spain L, et al. 2016	To identify the rates of common and uncommon irAEs associated with each immune checkpoint inhibitor	Retrospective review	Patients treated with pembrolizumab, nivolumab, ipilimumab and ipilimumab + nivolumab in	Frequency and intensity	In patients treated with pembrolizumab (2 mg/kg 2- and 3-weekly - Robert et al. 2015), the following reno-cardio-vascular AE (all grade) were reported: renal		3a

	(ICPI) and their timing of onset.		combination .		injury 1% and cardiac % not reported. The following reno-cardio-vascular grade 3/4 AE were reported: renal injury 0% and cardiac 1-2% . In patients treated with nivolumab (3 mg/kg 2-weekly - Robert et al. 2015, Weber et al. 2015, Larkin et al. 2015), the following reno-cardio-vascular AE (all grade) were reported: renal injury 1% and cardiac 1 G5 event. The following reno-cardio-vascular grade 3/4 AE were reported: renal injury <1%. Cardiac AE % was not reported. In patients treated with Ipilimumab (3		

					mg/kg 3-weekly - Robert et al. 2015, Larkin et al 2015) the following reno-cardio-vascular AE (all grade) were reported: renal injury <1%. Cardiac AE % was not reported. The following grade 3/4 reno-cardio-vacular AE were reported: renal injury <1%. Cardiac AE % was not reported. In patients treated with Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks - Larkin et al 2015) % of reno-cardio-vascular AE was not reported.		
Teuma C, et al. 2016	To report acute kidney injury (AKI) in patients treated with	Retrospective review; n=74	Patients with metastatic BRAF mutated melanoma	Incidence and severity of AKI	Of the 74 patients, 30 (40.5 %) were AKI−, and of the 44 AKI+ patients (59.5 %), 29 (66 %) were		3a

	vemurafenib		treated with vemurafenib in Lyon Sud Hospital University, France, between June 2011 and August 2014.		diagnosed within the first three months of treatment. There were significantly more men in the AKI+ group: n = 33 (75 %) versus n = 12 (40 %) women, p = 0.004 with an odds ratio for developing AKI of 4.6 (95 % CI 1.48–14.23). Most AKI + cases were considered as stage 1 (n = 40; 91 %) and the remaining four (9 %) as stage 2 AKI. Kidney biopsies revealed interstitial fibrosis and acute focal tubular damage. Renal failure was reversible in 80 % of patients within 3 months of VMF discontinuation.		
Villadolid	To describe	Retrospective	Patients	Frequency and	In the Robert C et		3a

J, et al 2015	the optimal management of toxicities related to immune checkpoint inhibition from FDA approved agents targeting CTLA-4 and PD-1.	review	treated with agents targeting CTLA-4 and PD-1	intensity	al. 2015 trial - nivolumab 3 mg/kg every 2 weeks (n=206), the following reno-cardio-vascular AE (all grades) were described: renal 1.9%. Grade 3/4 renal AE was described in 0.5% of the patients. In the Weber JS et al. 2015 trial - nivolumab 3 mg/kg every 2 weeks (n=268) the following reno-cardio-vascular AE (all grades) were described: renal 1.5%. Grade 3/4 renal AE was described in 0.4% of the patients.		
Welsh SJ, et al. 2015	To review the most common and serious adverse events	Retrospective review	Patients treated with BRAF and MEK inhibitors monotherap	Frequency and intensity	In the Chapman et al. 2011 and Larkin et al. 2014 trials combined reno-cardio-vascular AE % were		3a

	associated with BRAF targeted agents and suggest management algorithms		y or in combination		not reported. In the Hauschild et al. 2012 and 2013 trials combined hypertension was reported in 4% (all grades) and 0% (grade3/4) In the Flaherty et al. 2012 trial combined cardiac AE were reported in 7% (all grades) and 1% (grade3/4). Hypertension was reported in 15% (all grades) and 12% (grade3/4). In the Flaherty et al. 2012 and Long et al. 2014 trials combined cardiac AE were reported in 9% (all grades) and 0% (grade3/4). Hypertension was reported in 9% (all grades) and 2% (grade3/4).		

Zimmer L, et al. 2016	To report neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy	Retrospective review; n=496	Patients with metastatic melanoma from 15 skin diferent cancer centres that were treated with pembrolizumab or nivolumab.	Frequency and intensity	A total of 242 irAEs in 138 patients were reported. In 77 of the 138 patients, side-effects affected respiratory tract (24 patients), musculoskeletal system (21 patients), nervous system (16 patients), eyes (8 patients), heart (5 patients), and blood (3 patients). In addition, in 15 patients rare constitutional and/or infectious side-effects were reported. Under treatment with ipilimumab isolated cases of cardiac AEs have been reported. In <1% myocarditis, pericardial effusion and cardiomyopathy		IV

					and uncommon cardiac AEs like arrhythmia and atrial fibrillation occurred. Voskens CJ, et al (2013) reported one patient under ipilimumab showed myocardial fibrosis in conjunction with hepatitis. Larkin J, et al (2015) reported a fatal cardiac arrest due to toxic effects of ipilimumab. Laubli H, et al (2015) reported the only case of a cardiac AE under anti-PD-1 that is an acute heart failure due to autoimmune myocarditis under pembrolizumab.		

8.2.5. Literatur

Eigentler, T.K., et al., Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev, 2016. 45: p. 7-18.
Hofmann, L., et al., Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer, 2016. 60: p. 190-209.
Hurabielle, C., et al., Mechanisms Underpinning Increased Plasma Creatinine Levels in Patients Receiving Vemurafenib for Advanced Melanoma. PLoS One, 2016. 11(3): p. e0149873.
Kahler, K.C., et al., Management of side effects of immune checkpoint blockade by anti-CTLA-4 and anti-PD-1 antibodies in metastatic melanoma. J Dtsch Dermatol Ges, 2016. 14(7): p. 662-81.

Spain, L., S. Diem, and J. Larkin, Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev, 2016. 44: p. 51-60.
Teuma, C., et al., New insights into renal toxicity of the B-RAF inhibitor, vemurafenib, in patients with metastatic melanoma. Cancer Chemother Pharmacol, 2016. 78(2): p. 419-26.
Villadolid, J. and A. Amin, Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res, 2015. 4(5): p. 560-75.
Welsh, S.J. and P.G. Corrie, Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. Ther Adv Med Oncol, 2015. 7(2): p. 122-36.
Zimmer, L., et al., Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer, 2016. 60: p. 210-25.

8.3. Frage VII.3. Ophtalmologische Nebenwirkungen – De novo Recherche

Frage VII.3. Für welche Substanzklassen, die zur medikamentösen Anwendung beim malignen Melanom kommen, sind ophtalmologische Nebenwirkungen beschrieben und welche Strategien zur Behandlung dieser Nebenwirkungen existieren?

8.3.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients	Systemic treatment		Toxicity, Safety

Suchwörter				
Stichwort	melanoma	Systemic treatment	Side effect, adverse event	Ocular, Ophtalmic
Mesh Term	melanoma	Systemic treatment	Side effect	Ocular

8.3.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	((melanoma [tiab] OR melanoma[MeSH]) AND (side effect[tiab] OR toxicity[tiab] OR adverse event[tiab]) AND (ocular[tiab] OR ophtalmic[tiab]))	26.09.2016	98
Cochrane Library	(melanoma and (systemic treatment) and ((side effect) or toxicity) and	26.09.2016	5

	ocular).mp.		

8.3.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	103
Einschlusskriterien	Reviews, klinische Studien Intervention: BRAF-Inhibitoren, MEK-Inhibitoren, Ipilimumab, PD-1-Inhibitoren Sprachen: e,dt
Ausschlusskriterien	Case Reports Chemotherapie Kollektive mit gemischten Tumorentitiäten
Anzahl ausgewählter Studien	**6**

8.3.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Abdel-Wahab N, et al. 2016	To conduct a systematic review of case reports describing the occurrence of irAEs in	Systematic review; n=191 publications, 251 case reports.	Patients treated with checkpoint-inhibitors	irAEs in patients treated with checkpoint blockade therapy and identify potentially unrecognized or unusual clinical	Ophtalmological irAE were reported in 24 patients (10.3%) treated with ipilimumab, namely: uveitis 4.3% (one patient developed keratitis		3a

	patients with cancer following checkpoint blockade therapy, primarily to identify potentially unrecognized or unusual clinical findings and toxicity.			findings and toxicity.	with uveitis, one patient developed choroidal neovascularization with uveitis, and two patients developed optic neuropathy with uveitis), conjunctivitis 2.1%, orbital inflammation 2.1%, grave's ophthalmology 0.9%, choroidal neovascularization 0.9%, optic neuropathy 0.9%, keratitis 0.4%, retinopathy 0.4%.		
Choe CH, et al. 2014	To determine the frequency of ocular adverse effects associated with vemurafenib (PLX4032) treatment for metastatic cutaneous	Retrospective review of the clinical study reports from the clinical pharmacology , phase 1, phase 2, and phase 3 trials of vemurafenib	Patients treated with vemurafenib		Among the 568 patients treated with vemurafenib, ocular adverse effects developed in 22% (95% confidence interval [CI], 18.5–25.6). he most common ocular diagnosis was uveitis (4.0%; 95% CI, 2.6–6.0),		3a

	melanoma.				followed by conjunctivitis (2.8%; 95% CI, 1.6–4.5) and dry eyes (2.0%; 95% CI, 1.1–3.7). All were successfully managed while vemurafenib therapy was continued.		
Niro A, et al. 2015	To report the clinical features and management of ocular side effects in 4 patients treated with MEK inhibitor.	Interventional case series; n=4	Patients treated with MEK-Inhibitors	Ophtalmological toxicity	Ocular adverse events appeared early in the treatment. In 3 patients optical coherence tomography revealed subfoveal neuroretinal elevation, often asymptomatic, also after discontinuation and re-starting of MEK inhibitor. Vascular injury appeared in 2 patients, in 1 case associated with a visual field defect reduced after		4

					discontinuation of the drug and use of systemic therapy. In 1 case an inflammatory reaction was observed in the anterior chamber. Visual symptoms were usually mild and short-lived.		
Spain L, et al. 2016	To identify the rates of common and uncommon irAEs associated with each immune checkpoint inhibitor (ICPI) and their timing of onset.	Retrospective review	Patients treated with checkpoint-Inhibitors	Safety profile	In patients treated with pembrolizumab (2 mg/kg 2- and 3-weekly - Robert et al. 2015) uveitis was reported in <1% (all grade) and 0.1% (grade 3/4) of the patients. In patients treated with nivolumab (3 mg/kg 2-weekly - Robert et al. 2015, Weber et al. 2015, Larkin et al. 2015), uveitis% not reported. In patients treated		3a

					with Ipilimumab (3 mg/kg 3-weekly - Robert et al. 2015, Larkin et al 2015) uveitis was reported as 0%. In patients treated with Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks - Larkin et al 2015) uveitis% not reported.		
van Dijk EH, et al. 2015	To analyze the clinical characteristics of a serous retinopathy associated with mitogen-activated protein kinase kinase (MEK) inhibition with binimetinib treatment for metastatic cutaneous	Prospective observational, cohort-based, cross-sectional study; n=35	Patients teated with MEK-Inhibitors (Binimetinib)	Safety profile	Six CM patients (20%) and 2 UM patients (40%) reported visual symptoms during the study. The median time to the onset of symptoms, which were all mild and transient, was 3.5 days (range, <1 hour to 3 weeks). On optical coherence tomography, subretinal fluid		2a

	melanoma (CM) and uveal melanoma (UM), and to determine possible pathogenetic mechanisms that may lead to this retinopathy.				(SRF) was detected in 77% of CM patients and 60% of UM patients. In the 26 patients with SRF, the fovea was affected in 85%. After the start of the medication, an EOG was performed in 19 eyes of 11 patients; 16 of these eyes (84%) developed SRF on OCT. Fifteen of these eyes (94%) showed an abnormal Arden ratio (<1.65). A broad pattern of anti-retinal antibodies was found in 3 CM patients and 2 UM patients tested, whereas anti-RPE antibodies were detected in all 6 tested patients.		
Zimmer L, et al.	To report neurological,	Retrospective review; n=496	Patients with oculae AEs	Safety profile	The ocular effects in eight patients		3a

2016	respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy				(1.6%) were iritis, uveitis, conjunctivitis, dry eyes and blurred vision. In all cases topical non steroidal or steroidal therapy was sufficient.		

8.3.5. Literatur

Abdel-Wahab, N., M. Shah, and M.E. Suarez-Almazor, Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. PLoS One, 2016. 11(7): p. e0160221.
Choe, C.H., et al., Ocular toxicity in BRAF mutant cutaneous melanoma patients treated with vemurafenib. Am J Ophthalmol, 2014. 158(4): p. 831-837.e2.
Niro, A., et al., Ocular Toxicity in Metastatic Melanoma Patients Treated With Mitogen-Activated Protein Kinase Kinase Inhibitors: A Case Series. Am J Ophthalmol, 2015. 160(5): p. 959-967.e1.
Spain, L., S. Diem, and J. Larkin, Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev, 2016. 44: p. 51-60.
van Dijk, E.H., et al., Serous Retinopathy Associated with Mitogen-Activated Protein Kinase Kinase Inhibition (Binimetinib) for Metastatic Cutaneous and Uveal Melanoma. Ophthalmology, 2015. 122(9): p. 1907-16.
Zimmer, L., et al., Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer, 2016. 60: p. 210-25.

8.4. Frage VII.4. Endokrinologische Nebenwirkungen – De novo Recherche

Frage VII.4. Für welche Substanzklassen, die zur medikamentösen Anwendung beim malignen Melanom kommen, sind endokrinologische Nebenwirkungen beschrieben und welche Strategien zur Behandlung dieser Nebenwirkungen existieren?

8.4.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients	Systemic treatment		Toxicity, Safety

Suchwörter				
Stichwort	melanoma	Systemic treatment	Side effect, adverse event	Endocrine
Mesh Term	melanoma	Systemic treatment	Side effect	

8.4.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	((melanoma[tiab] OR melanoma[MeSH]) AND (([side effect[tiab] OR toxicity[tiab] OR adverse event[tiab]]) AND ([diabetes[tiab] OR adrenal[tiab] OR pancreas*[tiab] OR pancreat*[tiab] OR thyroid*[tiab] OR hypophy*[tiab] OR hypothyroi*[tiab]]))))	2(.09.2016	196

Cochrane Library	(melanoma and (systemic treatment) and ((side effect) or toxicity) and endocrine) .mp.	26.09.2016	17

8.4.3. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer		213
Einschlusskriterien	Reviews, klinische Studien Intervention: BRAF-Inhibitoren, MEK-Inhibitoren, Ipilimumab, PD-1-Inhibitoren Sprachen: e,dt	
Ausschlusskriterien	Case Reports Chemotherapie Kollektive mit gemischten Tumorentitiäten	
Anzahl ausgewählter Studien		**12**

8.4.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Abdel-Wahab N, et al. 2016	To conduct a systematic review of case reports describing the occurrence of irAEs in	Systematic review; n= 191 publications; 251 patients	Patients treated with anti CTLA-4 (ipilimumab) or anti PD-1 (nivolumab or pembrolizu	Safety profile	Tthe majority were treated with ipilimumab (93.2%). Autoimmune colitis, hepatitis, endocrinopathies, and cutaneous		3a

	patients with cancer following checkpoint blockade therapy, primarily to identify potentially unrecognized or unusual clinical findings and toxicity.		mab) with reported irAE's until August 2015.		irAEs were the most frequently reported irAEs in ipilimumab treated patients. The following endocrine irAE were described in 79 patients (33.7%) treated with ipilimumab: hypophysitis (manifested as panhypopitutaris) 29.1%, thyrotoxicosis 1.7%, hypothyroid 1.7%, syndrome of inappropriate secretion of antidiuretic hormone 0.4%, central adrenal insufficiency 0.4%, primary adrenal insufficiency 0.4%. The following endocrine irAE were described in 2 patients (20%) treated with		

					pembrolizumab: hypothyroid 10% and diabetes mellitus 10%. The following endocrine irAE were described in 3 patients (42.9%) treated with nivolumab: thyrotoxicosis 14.3% and hypothyroid 28.6%.		
Boutros C, et al. 2016	To describe the adverse event profile of checkpoint inhibitors targeting CTLA-4 and PD-1, used both as monotherapies and in combination and aim to provide some general guidelines, based upon the	Systematic review	Patients included in the following clinical trials: CA-184-002, KEYNOTE-001, KEYNOTE-001 (randomized cohorts), KEYNOTE-002, KEYNOTE-006, CheckMate	Safety profile	In patients treated with ipilimumab 3 mg/Kg + nivolumab 1 mg/kg, the following number of adverse events were described: adrenal insufficiency 6 AE (all grade) and 1 AE (grade 3/5); blood TSH decreased 5AE (all grades); hyperthyroidism 35AE (all grade) and 3AE		2a

	mechanisms of action of these therapies and on the management of these immune related adverse events.		037, CheckMate-066, CheckMate-067, and CheckMate-069		(grade3/5); hypophysitis 24AE (all grade) and 5AE grade 3/5; hypothyroidism 62AE (all grade) and 1AE (grade 3/5). In patients treated with ipilimumab 3 mg/kg Q3W, the following number of adverse events were described: adrenal insufficiency 4AE (all grade) and 1 AE (grade 3/5); blood TSH decreased 2AE (all grade) and 1 AE (grade 3/5); blood TSH increased 2AE; decrease in serum corticotropin 2AE; hyperthyroidism 9AE (all grade) and 1AE (grade 3/5); hypophysitis 21AE (all grade) and 12AE (grade3/5); hypopituitarism 3AE (all grade) and		

					1AE (grade3/5); hypothyroidism 24AE (all grade); In patients treated with Nivolumab 3mg/kg Q2W the following number of adverse events were described: blood TSH decreased 3AE (all grade); diabetes mellitus 1AE, hyperthyroidism 25AE (all grade) and 1AE (garde 3/5); hypophysitis 3AE (all grades) and 2AE (grade3/5); hypothyroidism 51AE (all grade); In patients treated with Pembrolizumab 10 mg/kg Q2W, the following number of adverse events were described: blood TSH decreased 3AE (all		

					grade); blood TSH increased 2AE; hyperglycemia 1AE; hyperthyroidism 17AE (all grade); hypocalcemia 6AE; hypothyroidism 34AE (all grade) and 2AE (grade3/5); In patients treated with Pembrolizumab 10 mg/kg Q3W, the following number of AE were described: blood TSH decreased 2AE (all grade), blood TSH increase 3AE (all grade); hyperthyroidism 2AE (all grade); hypothyroidism 10AE (all grade) and 3AE (grade 3/5); In patients treated with pembrolizumab 2		

					mg/kg Q3W the following number of AE were described: blood TSH increased 1AE; hyperglycemia 1AE; hyperthyroidism 1AE (all grade); hypophysitis 2AE (all grade) and 1AE (grade 3/5); hypothyroidism 15AE (all grade);		
Eigentler TK, et al. 2016	To review incidences and kinetics of onset and resolution of immune-mediated ‘‘adverse events of specific interest” (AEOSI) of both approved PD-1 inhibitors nivolumab and pembrolizum	Retrospective review; n=1826	Patients treated with nivolumab and pembrolizumab in the following clinical trials: CA209017/-063; CA209037/-066; P001/-002 and P001/-002	Incidences and kinetics of onset and resolution of immune-mediated AEOSI	In trials CA209037/-066 with nivolumab 3 mg/kg q2w (n=474) endocrine disorders were reported in 8% of the patients (all grades) and 0.4% (grade ≥3). In trials P001/-002 with pembrolizumab 2 mg/kg q3w (n=340) endocrine disorders were reported in 10 % of the patients (all grades) and grade		3a

	ab				≥3 were not reported. In trials P001/-002 with pembrolizumab 2 mg/kg q3w & 10 mg/kg q3w/q2w (n= 1012) endocrine disorders were reported in 9.3% patients (all grades) and grade ≥3 were not reported. In patients treated with nivolumab 3 mg/kg q2w, the following endocrine AEOSI were reported: hypothyroidism 5.7% (all grade); hyperthyroidism 2.5% (all grade) and 0.2% (grade ≥3); hypophysitis 0.2% (all grade) and 0.2% (grade ≥3); adrenal insufficiency 0.2% (all grade); diabetes mellitus		

					0.2% (all grade) and diabetic ketoacidosis 0.2% (all grade) and 0.2% (grade ≥3).		
Gonzalez-Rodriguez E, et al. 2016	To describe the incidence, timing patterns and clinical presentation of endocrine AE associated with immune check-poin inhibitors.	Retrospective review; n=unclear	Patients treated with immune check-point inhibitors and included in clinical trials prublished in PubMed and MEDLINE before June 30, 2015 and with endocrine AE.	Safety profile	CTLA4 inhibitors: Frequence and severity of irAE with ipilimumab are dose-dependent and have been reported in 0-29% of the patients. Hypophysitis is most frequent grade 3/4. Hypothyroidism and hyperthyroidism are the second most frequent. Fewer data is available for tremelimumab, which is associated with fewer reported endocrinopathies overall (0-8.3%). Hypophisitis incidence:	Sample size undefined	4

					ipilimumab 0-17.4% and tremelimumab 2.6%. Thyroid disorders incidence: Ipilimumab 0-7.4%; hypothiroidism 0-9% and hyperthyroidism 0-2.8%. Thyroiditis has not been reported. Tramelimumab 0-5.2%. Rare endocrinopathies incidence: Graves ophtalmopathy - incidence not reported; autoimmune adrenalitis 0-1.6%. PD-1 and PD-L1 inhibitors: Hypophysitis incidence: pembrolizumab 1.2% and nivolumab 0.9%. Thyroid disorders incidence:pembrolizumab 0-19.2%.		

					Nivolumab: In one phase I trial, thyroidopathies were reported in 40% of the patients; in further studies incidence was between 0-18.5% Rare endocrinopathies incidence: autoimmune adrenalitis - 0-4.3% with pembrolizumab and 0-3.3% with nivolumab. Type 1 diabetes mellitus has beeen rarely reported, with only 4 cases known to the date. PD-L1 - avelumab: 10% maximum reported incidence of endocrine AE; atezolizumab 6% and durvalumab 11%. Endocrinopathies due to PD-L1 antibodies are almost exclusively		

					thyroid related. CTLA-4 and PD1/PD-L1 combined blockade: For ipilimumab plus nivolumab combination - endocrinopathies occur in 14-50% patients, with Thyroid AE's being the most frequent 7-28%, followed by hypophysitis 0-12.8%, with grade 3/4 events occurring in 1-20%. For pembrolizumab and ipilimumab combination - endocrinopathies have been described in 28% of the treated patients (all diseases) and the thyroid gland is the most affected organ (18.1%-24%), mostly in the form		

					of hypothyroidism (6-13.6%).		
Corsello SM, et al. 2013	To analyze in parallel the available findings that characterize “classic” and anti CTLA4-induced hypophysitis, highlighting common features and some differences. In addition, clinical and pathogenic aspects of the other endocrine IRAEs (E-IRAEs) are scrutinized.	Retrospective review; n=unclear	Patients treated with the following therapies: immune check-point inhibitors, ipilimumab, tremelimumab, PD-1, and PD-1-L and had one or more of endocrine side effects, including the following: hypophysitis, hypopituitarism, thyroid and adrenal insufficiency.	Safety profile	The spectrum of endocrine disease experienced by patients treated with ipilimumab includes most commonly hypophysitis, more rarely thyroid disease or abnormalities in thyroid function tests, and occasionally primary adrenal insufficiency. Hypophysitis has emerged as a distinctive side effect of CTLA4-blocking antibodies, establishing a new form of autoimmune pituitary disease. This condition, if not promptly recognized, may be life-threatening	Sample size undefined	4

					(due to secondary hypoadrenalism). Hypopituitarism caused by these agents is rarely reversible, and prolonged or lifelong substitutive hormonal treatment is often required. The precise mechanism of injury to the endocrine system triggered by these drugs is yet to be fully elucidated. In initial trials, the incidence of hypophysitis induced by anti-CTLA4-mAbs (anti-CTLA4-H) varied considerably (0–17%). In more recent larger trials, the incidence seemed not to exceed 5%. Although most data are from		

					patients affected by cutaneous melanoma, anti-CTLA4-H has been reported in patients with different tumor types. Only 1 case has been associated with diabetes insipidus The incidence of thyreopathy induced by anti-CTLA4- mAbs(anti-CTLA4-T) varies between 0 and 4%. In 2 studies, tremelimumab was associated with 4% thyreopathy. With ipilimumab, the incidence seems lower (0–2%), with subclinical or mild (G1–2) hypothyroidism being the most frequent event. In the large phase III trial leading to approval of		

					ipilimumab, the drug was associated with thyroid disorders or abnormal thyroid function tests in approximately 2% of patients. Similar incidence of G1–2 thyroiditis is reported in trials evaluating ipilimumab as a single agent or in combination with chemotherapy in cutaneous melanoma or other malignancies. In a small report on 27 patients with refractory melanoma receiving a high dose of ipilimumab (10 mg/kg for 4 doses, followed by further doses in case of clinical benefit), G2 hypothyroidism occurred in 7% of		

					cases.		
Hofmann L, et al. 2016	To report the incidence of cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy	Retrospective review; n=496	Patients with melanoma treated with nivolumab and pembrolizumab in fifteen study centers in Germany and Switzerland	Incidence of endocrine side-effects	496 patients with metastatic melanoma were treated with pembrolizumab or nivolumab; 242 side-effects were described in 138 patients. In 116 of the 138 patients, side-effects affected the skin, gastrointestinal tract, liver, endocrine, and renal system. Rare side-effects included diabetes mellitus, lichen planus, and pancreas insufficiency due to pancreatitis. IrAEs of the endocrine system are well known from ipilimumab. Common endocrinopathies under anti-CTLA-4		3a

					include hyperthyroidism, hypothyroidism (1.5%), hypophysitis (1.8%), and adrenal insufficiency (1.5%). Under treatment with anti-PD-1 antibodies, incidence of hypothyroidismof any grade is approximately 8% and of hyperthyroidism approximately 1-5%. In the reported analysis, 30 patients (6.0%) developed endocrine disorders. Approximately 25% of the events were grade 3-4. Hypothyroidism was reported in 9 patients (1.8%) and hyperthyroidism including thyroiditis in 11		

					patients (2.2%). Four patients (0.8%) developed hypophysitis and two patients adrenal insufficiency. Furthermore, Hashimoto's disease was documented in two cases. Four patients (0.8%) developed diabetes mellitus under treatment with nivolumab or pembrolizumab.		
Kahler KC, et al. 2016	To describe the mechanisms of action of immune checkpoint blockade as well as its clinical effects in metastatic melanoma, with a detailed	Retrospective review; n=1826	Patients inluded in CheckMate 067 and Keynote 002 trials	Safety; to compare side effects of ipilimumab and nivolumab monotherapy vs. combination therapy	In the CheckMate 067 trial, in the NIVO + IPI (n = 313) arm, endocrine AE were reported in 30% (all grades) and 4.8% (grade 3/4). Hypofisitis was reported in 15% (all grades) and 0.3% (grade 3/4). In the NIVO (n = 313) arm,		3a

	focus on the spectrum of adverse events and their therapeutic management				endocrine AE were reported in 14.4% (all grades) and 0.6% (grade 3/4). Hypofisitis was reported in 8.6% (all grades) and 0% (grade 3/4). In the IPI (n = 311) arm, endocrine AE were reported in 10.9% (all grades) and 2.3% (grade 3/4). Hypofisitis was reported in 4.2% (all grades) and 0% (grade 3/4). In the Keynote 002 trial, in the PEMBRO 2 mg/kg (n = 178) arm, endocrine AE were reported in 1% (all grades) and 1% (grade 3/4). In the PEMBRO 10 mg/kg (n = 179) arm, endocrine AE were reported in 1% (all grades) and 0% (grade 3/4).		

Lam T, et al. 2015	To reviewed the clinical and biochemical characteristics of 10 patients with ipilimumab-induced hypophysitis (IH), and develope guidelines for the early detection and management of IH based on our experiences at three major teaching hospitals in Sydney.	Retrospective review; n=10	Patients with advanced and/or metastatic melanoma treated with ipilimumab in four diferent centers in Australia between 2010 and 2014.	Clinical and biochemical characteristics of 10 patients with ipilimumab-induced hypophysitis (IH)	All 10 patients had advanced melanoma, and nine patients received standard therapy with ipilimumab 3 mg/kg every 3 weeks. One patient received four doses of induction ipilimumab at 10 mg/kg followed by maintenance therapy every 3 months. Three patients received dacarbazine before ipilimumab, and one patient received pembrolizumab, 8 months before treatment with ipilimumab. One patient received the NY-ESO-1 vaccine prior to commencement of ipilimumab. Five patients underwent plasma		4

					cortisol monitoring during ipilimumab treatment, with a variable decrease prior to presentation. Nine patients had low early morning cortisol levels at presentation, associated with inappropriately low levels of ACTH consistent with secondary adrenal insufficiency. Five patients had low fT4 and inappropriately low TSH levels at diagnosis which was consistent with secondary hypothyroidism. Total testosterone levels were low in five of nine men. Luteinising hormone was low in one patient and inappropriately low in three of seven patients for the		

					level of testosterone, consistent with secondary hypogonadism. Age-corrected insulinlike growth factor 1 (IGF-1), an integrated measure of growth hormone secretion and action, was low in two of six patients. Prolactin levels were normal (low to midrange) in the six patients in whom they were measured. Common presenting symptoms were profound fatigue and nausea, with mean onset of symptoms 9 weeks, headache was present in six patients and significant hyponatraemia in one patient.		

					Imaging abnormalities were present in the five of the six patients who presented with headache. Four patients had and MRI evidence of pituitary enlargement, while two patients had abnormal pituitary uptake on positron emission tomography scan.Omne patient had normal pituitary imaging on CT scan, 4 days after commencement of hydrocortisone.		
Marlier J, et al. 2014	To describe four cases of involvement of the pituitary gland during treatment with ipilimumab	Retrospective review; n=4 (n=215 melanoma patients, 39 received ipilimumab)	Melanoma patients treated with ipilimumab between 2010 and 2013 in the Ghent University	Description of four cases of involvement of the pituitary gland during treatment with ipilimumab	Of all patients treated with ipilimumab at this institution, 10 % presented with a hypophysitis with involvement of one or more pituitary axes. The clinical		3a

			Hospital		presentation was as follows: 1 patient with hypophysitis with failure of the thyroid gland, the adrenal and gonadal axis; 1 patient with hypophysitis with failure of the ACTH axis; 1 patient with hypophysitis with hypothyroidism and secondary adrenal insufficiency; 1 patient with hypophysitis with secondary adrenal deficiency and thyroid dysfunction.		
Spain L, et al. 2016	To identify the rates of common and uncommon irAEs associated with each immune	Retrospective review	Patients treated with pembrolizumab, nivolumab, ipilimumab and ipilimumab	Safety profile	In patients treated with pembrolizumab (2 mg/kg 2- and 3-weekly - Robert et al. 2015) hypothyroidism 9-10%,		3a

	checkpoint inhibitor (ICPI) and their timing of onset.		+ nivolumab in combination .		hyperthyroidism 3-7%, hypophysitis <1% (all grade) and hypothyroidism <1%, hyperthyroidism 0%, hypophysitis <1% (grade 3/4) were reported. In patients treated with nivolumab (3 mg/kg 2-weekly - Robert et al. 2015, Weber et al. 2015, Larkin et al. 2015), hypothyroidism 4-9%, hyperthyroidism 2-4%, hypophysitis <1% (all grade) and hypothyroidism 0%, hyperthyroidism <1%, hypophysitis <1% (grade3/4) were reported. In patients treated with Ipilimumab (3 mg/kg 3-weekly - Robert et al. 2015, Larkin et al 2015)		

					hypothyroidism 2-4%, hyperthyroidism 1-2%, hypophysitis 2-4% (all grade) and hypothyroidism 0%, hyperthyroidism <1%, hypophysitis 2% (grade 3/4) were reported. In patients treated with Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks - Larkin et al 2015) hypothyroidism 15%, hyperthyroidism 10%, hypophysitis 8% (all grade) and hypothyroidism <1%, hyperthyroidism 1%, hypophysitis 2% (grade 3/4) were reported).		
Tanaka R, et al. 2016	To describe nivolumab-induced	Retrospective review; n= 14	Patients treated with nivolumab	To describe nivolumab-induced thyroid	One patient achieved complete remission;		4

	thyroid dysfunction in 4 patients		in University of Tsukuba Hospital Japan	dysfunction	suggesting that in some patients, the occurrence of immune-related adverse events, including thyroid dysfunction, might reflect the drug's antitumour efficacy. No patient died or discontinued nivolumab treatment owing to thyroid dysfunction. Although thyroid dysfunction first appeared to be asymptomatic, two of the three patients developed symptoms related to hypothyroidism soon after, requiring hormone replacement therapy. Another patient developed hyperthyroidism that was initially asymptomatic; the patient		

					subsequently developed myalgia with fever >39.5°C after two additional courses of nivolumab. Treatment with nivolumab was therefore discontinued, and treatment with prednisolone was initiated. Symptoms resolved within a few days, and thyroid function normalized.		
Torino F, et al. 2016	To update the literature on the incidence and pathophysiology of endocrine toxicities induced by these agents, and discuss management guidance.	Retrospective review; n= not clear	Patients treated with immune checkpoint inhibitors in diferent clinical trials	To describe endocrinological side-effects of immune checkpoint inhibitors	The relative risk of all-grade hypophysitis, hypothyroidism, hyperthyroidism, and adrenal insufficiency was 22.03, 8.26 and 3.87, respectively. Hypophysitis: incidence of ipilimumab-induced hypophysitis are	Sample size not defined	4

					reported among different trials between 0-25%. For patients treated with tremelimumab the incidence is 0.5–4%. In a small phase I trial ipilimumab in combination with an antiprostate-specific antigen T-cell vaccine was associated with 25% pituitary dysfunction. For patients treated with nivolumab, all grade hypophysitis occurred in 0.5–0.9% of patients, rarely leading to drug (according to results of the published studies). When nivolumab plus a multipeptide vaccine was investigated as adjuvant therapy in stage IIIC-IV,		

					melanoma, G2 hypophysitis was reported in 6% of cases. For pembrolizumab, as single agent, all grade hypophysitis occurred in 13/1567 (0.8%) of melanoma patients. In patients treated with ipilimumab + nivolumab, all grade hypophysitis was 8–12% (grade 3/4: 2%) in combination arm, 4–7% (grade G3/4: 2–4%) in ipilimumab arm, and 1% (grade G3/4: 0%) in nivolumab arm, respectively. Tremelimumab caused primary thyroid dysfunction in 4% of patients. The incidence of ipilimumab-		

					induced primary thyroid dysfunction is lower (0–2%) when 3 mg/kg (standard dose) is administered as a single agent or combined with cytotoxic drugs. Higher rates of thyroiditis have been reported in small trials with higher dose (10mg/kg) alone or when combined with bevacizumab, an anti- VEGF agent (7 and 19%of cases, respectively). Hypothyroidism was diagnosed in 13.3% of patients who received ipilimumab (5–10mg/kg) in combination with an antiprostate specific antigen T-cell vaccine. Anti-PD1-mAbs are		

					associated with higher incidence of thyroid disease, compared with ipilimumab: 1.8–9% of patients in larger trials. In melanoma patients treated with nivolumab, hyperthyroidism and hypothyroidism, or autoimmune thyroiditis occurred in 4.4 and 9% of cases, respectively. Hyperthyroidism occurred in 1.8% of melanoma patients receiving pembrolizumab. In patients treated with ipilimumab + nivolumab thyroiditis/ hypothyroidism was described in 22% and hyperthyroidism in 8% of the patients.		

					In a phase II trial on 142 melanoma patients treated with ipilimumab with/without nivolumab, primary adrenal crisis (PAI) was registered in 6% patients. In a large phase III trial of patients with advanced melanoma who received the same drugs as single agent or in combination, no case of PAI was reported Type 1 diabetes mellitus and/or diabetic ketoacidosis can occur with each immune checkpoint inhibitor at the rate of less than 1%, independently of the drug, the dose and the		

					clinical indication. Interestingly, the incidence of type 1 diabetes mellitus and/or diabetic ketoacidosis doubled (1.5%) with the use of ipilimumab + nivolumab combination.		
Villadolid J, et al 2015	To describe the optimal management of toxicities related to immune checkpoint inhibition from FDA approved agents targeting CTLA-4 and PD-1.	Retrospective review	Patients treated withagents targeting CTLA-4 and PD-1	Safety in patients treated with checkpoint inhibitors	In the Hodi FS et al. 2010 trial - ipilimumab 3 mg/kg monotherapy every 3 weeks (n=131), endocrine AE (all grades) were described in 7.6% of the patients. Grade 3 endocrine AE were described in 2.3% of the patients and grade 4 in 1.5%. In the ipilimumab 3 mg/kg plus gp 100 every 3 weeks (n=380) arm, endocrine AE (all grades) were		3a

					described in 3.9% of the patients. Grade 3 endocrine AE were described in 1.1% of the patients and grade 4 endocrine AE were not described. In the Robert C et al. 2014 trial - pembrolizumab 2 mg/kg every 3 weeks (n=89), grade 3/4 increased amilase was described in 1.1% of the patients. In the pembrolizumab 10 mg/kg every 3 weeks (n=84) arm, grade 3/4 pancreatitis was described in 1.2% of the patients. In the Robert C et al. 2015 trial - nivolumab 3 mg/kg every 2 weeks (n=206),		

					endocrine AE (all grades) were described in 7.3% of the patients. Grade 3/4 endocrine AE were described in 0.5% of the patients. In the Weber JS et al. 2015 trial - nivolumab 3 mg/kg every 2 weeks (n=268) endocrine AE (all grades) were described in 7.8% of the patients. No grade 3/4 endocrine AE were described.		

8.4.5. Literatur

Abdel-Wahab, N., M. Shah, and M.E. Suarez-Almazor, Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. PLoS One, 2016. 11(7): p. e0160221.
Boutros, C., et al., Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol, 2016. 13(8): p. 473-86.
Eigentler, T.K., et al., Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev, 2016. 45: p. 7-18.
Gonzalez-Rodriguez, E. and D. Rodriguez-Abreu, Immune Checkpoint Inhibitors: Review and Management of Endocrine Adverse Events. Oncologist, 2016. 21(7): p. 804-16.
Corsello, S.M., et al., Endocrine side effects induced by immune checkpoint inhibitors. J Clin Endocrinol Metab, 2013. 98(4): p. 1361-75.
Hofmann, L., et al., Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer, 2016. 60: p. 190-209.
Kahler, K.C., et al., Management of side effects of immune checkpoint blockade by anti-CTLA-4 and anti-PD-1 antibodies in metastatic melanoma. J Dtsch Dermatol Ges, 2016. 14(7): p. 662-81.
Lam, T., et al., Ipilimumab-induced hypophysitis in melanoma patients: an Australian case series. Intern Med J, 2015. 45(10): p. 1066-73.
Marlier, J., et al., Ipilimumab, not just another anti-cancer therapy: hypophysitis as side effect illustrated by four case-reports. Endocrine, 2014. 47(3): p. 878-83.
Spain, L., S. Diem, and J. Larkin, Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev, 2016. 44: p. 51-60.
Tanaka, R., et al., Nivolumab-induced thyroid dysfunction. Jpn J Clin Oncol, 2016. 46(6): p. 575-9.
Torino, F., S.M. Corsello, and R. Salvatori, Endocrinological side-effects of immune checkpoint inhibitors. Curr Opin Oncol, 2016. 28(4): p. 278-87.
Villadolid, J. and A. Amin, Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res, 2015. 4(5): p. 560-75.

8.5. Frage VII.5. Gastrointestinale Nebenwirkungen – De novo Recherche

Frage VII.5. Für welche Substanzklassen, die zur medikamentösen Anwendung beim malignen Melanom kommen, sind gastrointestinale Nebenwirkungen beschrieben und welche Strategien zur Behandlung dieser Nebenwirkungen existieren?

8.5.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients	Systemic treatment		Toxicity, Safety

Suchwörter				
Stichwort	melanoma	Systemic treatment	Side effect, adverse event	Gastrointestinal
Mesh Term	melanoma	Systemic treatment	Side effect	

8.5.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	((melanoma[tiab] OR melanoma[MeSH]) AND ((side effect[tiab] OR toxicity[tiab] OR adverse event[tiab]) AND (gastrointestinal[tiab] OR colon[tiab] OR colitis[tiab] OR ileitis[tiab] OR stomach[tiab])))	26.09.2016	404

Cochrane Library	(melanoma and (systemic treatment) and ((side effect) or toxicity) and gastrointestinal) .mp.	26.09.2016	30

8.5.3. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer		434
Einschlusskriterien	Reviews, klinische Studien Intervention: BRAF-Inhibitoren, MEK-Inhibitoren, Ipilimumab, PD-1-Inhibitoren Sprachen: e,dt	
Ausschlusskriterien	Case Reports Chemotherapie	
Anzahl ausgewählter Studien		**11**

8.5.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Abdel-Wahab N, et al. 2016	To conduct a systematic review of case reports describing the occurrence of irAEs in patients with	Systematic review; n=191 publications; 251 patients	Patients treated with anti CTLA-4 (ipilimumab) or anti PD-1 (nivolumab or pembrolizumab) with	Safety profile	Autoimmune colitis, hepatitis, endocrinopathies, and cutaneous irAEs were the most frequently reported irAEs in ipilimumab treated patients.		3a

	cancer following checkpoint blockade therapy, primarily to identify potentially unrecognized or unusual clinical findings and toxicity.		reported irAE's until August 2015.		The following gastrointestinal irAE were described in 93 patients (39.7%) treated with ipilimumab: colitis/enterocolitis 68 patients (29.1%), colitis complicated by intestinal perforation 12 patients (5.1%), hepatitis 17 patients (7.3%), pancreatitis 2 patients (0.9%). No gastrointestinal irAE were described in patients treated with pembrolizumab and nivolumab.		
Berman D, et al. 2010	To promote an understanding of the underlying mechanism of action and to identify potential biomarkers	Randomized trial; n=115, same as Weber-J, 2009	Treatment-naïve or previously treated patients with unresectable stage III/IV melanoma who	To determine wether prophylactic budesonide prevent ipilimumab-induced bowel inflammation To report	Ipilimumab resulted in dysregulation of gastrointestinal mucosal immunity as evidenced by altered antibody levels to enteric flora, inflammatory cell infiltration into gastrointestinal		1B Same cohort as in Weber-J 2009

	that could help in the prediction and management of ipilimumab-induced gastrointestinal irAE		received open-label ipilimumab (10 mg/kg every 3 weeks for four doses) were randomized to receive concomitant blinded prophylactic oral budesonide (9 mg/d with gradual taper through week 16) or placebo.	histologic assessment of bowel biopsies and assessment of serologic markers of inflammatory bowel disease (IBD), fecal calprotectin levels, and polymorphisms in immune-related genes.	mucosa, and increased fecal calprotectin associated with diarrhea and clinical evidence of colitis. The pattern of ipilimumab-induced antibody titers to microbial flora and the histologic features and location of the inflammation were distinct from classic IBD. Despite an observed association between colonic inflammation and grade 2 or higher diarrhea, no baseline biomarkers could reliably predict development of gastrointestinal toxicity. Although classic IBD and ipilimumab-related gastrointestinal toxicity are both immune mediated, the observed		

					pattern of biomarkers suggests ipilimumab-related gastrointestinal toxicity may be a distinct clinicopathologic entity.		
Di Giacomo AM, et al. 2010	To provide an overview of safety data on CTLA-4 antagonists and of available strategies to optimize their clinical use in cancer patients.	Retrospective review; n=487	Patients treated with ipilimumab across phase II trials in melanoma (BMS trials CA184-008, 022 and 007)	Safety profile	Study CA184-008: - 31% patients had GI AE all grade, and 8% grade 3/4. Study CA184-022- dosage 0.3mg/kg: 17% pts had gastrointestinal side effects - all grade, and 0% grade 3/4; dosage 3mg/kg: 32% pts had gastrointestinal side effects - all grade, and 3% grade 3/4; dosage 10mg/kg: 39% pts had gastrointestinal side effects - all grade, and 3% grade 3/4. Study CA184-007: 46% pts had gastrointestinal side effects - all grade,		3a

					and 23% grade 3/4.		
Eigentler TK, et al. 2016	To reviews incidences and kinetics of onset and resolution of immune-mediated ‘‘adverse events of specific interest” (AEOSI) of both approved PD-1 inhibitors nivolumab and pembrolizumab	Retrospective review; n=1826	Patients treated with nivolumab and pembrolizumab in the following clinical trials: CA209017/-063; CA209037/-066; P001/-002 and P001/-002	Incidences and kinetics of onset and resolution of immune-mediated AEOSI	In trials CA209037/-066 with nivolumab 3 mg/kg q2w (n=474) gastrointestinal AE were reported in 34.8% of the patients (all grades) and 1.9% (grade ≥3). In trials P001/-002 with pembrolizumab 2 mg/kg q3w (n=340) gastrointestinal AE were reported in 25.9 % of the patients (all grades) and grade ≥3 were not reported. In trials P001/-002 with pembrolizumab 2 mg/kg q3w & 10 mg/kg q3w/q2w (n= 1012) gastrointestinal AE were reported in 31.2% patients (all grades) and grade ≥3 were not reported.		3a

					In patients treated with nivolumab 3 mg/kg q2w, the following gastrointetinal AEOSI were reported: diarrhea 15.8%(all grade) and 0.3% (grade ≥3); colitis 1.1% (all grade) and 0.6% (grade ≥3).		
Hofmann L, et al. 2016	To report the incidence of cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy	Retrospective review; n=496	Patients with melanoma treated with nivolumab and pembrolizumab in fifteen study centers in Germany and Switzerland	Incidence of gastrointestinal side-effects of anti-PD-1 therapy	Gastrointestinal irAEs are common under a treatment with checkpoint inhibitors. Ipilimumab-induced diarrhoea and colitis have been described in 32.8% and abdominal pain in 15.3% with grade 3-4 AEs in approximately 5%. Patients under treatment with anti-PD-1 antibodies showed gastro-intestinal AEs like diarrhoea in 6.0-		3a

					16.0% with grade 3-4 AEs in up to 2.2%. Compared to ipilimumab, the incidence and severity of anti-PD-1 antibody-induced gastro-intestinal AEs are much lower. Nevertheless, intestinal perforations under anti-PD-1 treatment have been reported. An elevated calprotectin concentration in the feces before initiation of anti-CTLA-4 antibody therapy or a rapid increasing concentration under treatment seems to correlate with more severe autoimmune-related colitis. As reported for ipilimumab to avoid mucosal biopsies, a non-invasive method for diagnosing		

					checkpoint inhibitor-induced colitis in vivo is confocal laser endomicroscopy. In this study, 21 patients (4.2%) were reported with gastrointestinal AEs including diarrhoea (10 patients), colitis (2 patients), abdominal pain (4 patients), coprostasis (3 patients), xerostomia (3 patients), and oesophagitis (1 patient). The majority of gastrointestinal events were mild and only four grade 3 AEs (diarrhoea) were reported. In persisting grade 2 and grade 3 AEs, checkpoint inhibitor treatment was interrupted and prednisolone (1.0-2.0 mg/kg body		

					weight po. or iv) administered. Two of the patients suffering from grade 3 diarrhoea received treatment with infliximab (5 mg/kg body weight i.v.). All gastrointestinal events resolved or were ongoing but improving.		
Kahler KC, et al. 2016	To describe the mechanisms of action of immune checkpoint blockade as well as its clinical effects in metastatic melanoma, with a detailed focus on the spectrum of adverse events and their	Retrospective review; n=1826	Patients inluded in CheckMate 067 and Keynote 002 trials	Safety profile Comparison side effects of ipilimumab and nivolumab monotherapy vs. combination therapy	In the CheckMate 067 trial, in the NIVO + IPI (n=313) arm, gastrointestinal AE were reported in 46.3% (all grades) and 14.7% (grade 3/4). Diarrhea was reported in 44.1% (all grades) and 9.3% (grade 3/4); colitis was reported in 11.8% (all grades) and 7.7% (grade 3/4). In the NIVO (n = 313) arm, gastrointestinal AE were reported in		3a

	therapeutic management				19.5% (all grades) and 2.2% (grade 3/4). Diarrhea was reported in 19.2% (all grades) and 2.2% (grade 3/4); colitis was reported in 1.3% (all grades) and 0.2% (grade 3/4). In the IPI (n = 311) arm, gastrointestinal AE were reported in 36.7% (all grades) and 11.6% (grade 3/4). Diarrhea was reported in 33.1% (all grades) and 6.1% (grade 3/4); colitis was reported in 11.6% (all grades) and 8.7% (grade 3/4). In the Keynote 002 trial, in the PEMBRO 2 mg/kg (n = 178) arm, diarrhea and colitis were reported in 8% and 1% (all grades), respectively. In the PEMBRO 10 mg/kg		

					(n = 179) arm, diarrhea was reported in 9% (all gardes) and 1% (garde 3/4) and colitis was reported in 2% (all grades) and 1% (grade 3/4).		
Spain L, et al. 2016	To identify the rates of common and uncommon irAEs associated with each immune checkpoint inhibitor (ICPI) and their timing of onset.	Retrospective review	Patients treated with pembrolizumab, nivolumab, ipilimumab and ipilimumab + nivolumab in combination.	Safety	In patients treated with pembrolizumab (2 mg/kg 2- and 3-weekly - Robert et al. 2015) diarrhea 14-17%, colitis 2-4% (all grade) and diarrhea 1-3%, colitis 1-3% (grade 3/4) were reported. In patients treated with nivolumab (3 mg/kg 2-weekly - Robert et al. 2015, Weber et al. 2015, Larkin et al. 2015), diarrhea 11-19%, colitis 1%, (all grade) and diarrhea 0-2%, colitis <1% (grade3/4) were reported.		3a

					In patients treated with Ipilimumab (3 mg/kg 3-weekly - Robert et al. 2015, Larkin et al 2015) diarrhea 23-33%, colitis 8-12% (all grade) and diarrhea 3-6%, colitis 7-9% (grade 3/4) were reported. In patients treated with Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks - Larkin et al 2015) diarrhea 44%, colitis 12% (all grade) and diarrhea 9%, colitis 8% (grade 3/4) were reported.		
Verschuren EC, et al. 2016	To characterize the clinical, endoscopic and histologic feactures of ipilimumab-	Retrospective review; n=27	Patients with castration-resistant prostate cancer or metastatic melanoma, treated with	Safety	All pts had diarrhea (range, 3-20 stools per day); 26 % had concurrent rectal blood loss and 30% had abodminal pain. These symptoms usually started after		3a

	induced colitis and evaluate the efficacy of therapy for this reaction.		ipilimumab from April 2007 through September 2012 in one center in The Netherlands.		2 infusions of ipilimumab (range, 1-4) and all pts except for 1 (who received no treatment for colitis) were given corticosteroids. Twelve pts had steroid-refractory colitis, for which they received infliximab (5mg/kg). Diarrhea resolved in all pts. Colon erythema was detected by endoscopy in 84% of pts, with an absent vascular pattern in all pts. In hystologic analyses, colon biopsy specimens ranged form having normal architecture to severe active inflamation. Intraepithelial neutrophilic leucocytes were detected in 72% of samples, cryptitis in 92% , and crypt		

					abscesses in 60%. Crypt irregularities were found in 40% of colon biopsy specimens, indicating chronic disease.		
Villadolid J, et al 2015	To describe the optimal management of toxicities related to immune checkpoint inhibition from FDA approved agents targeting CTLA-4 and PD-1.	Retrospective review	Patients treated with agents targeting CTLA-4 and PD-1	Safety profile	In the Hodi FS et al. 2010 trial - ipilimumab 3 mg/kg monotherapy every 3 weeks (n=131), gastrointestinal AE (all grades) were described in 29 % of the patients. Grade 3 gastrointestinal AE were described in 7.6% of the patients and grade 4 in 0%. In the ipilimumab 3 mg/kg plus gp 100 every 3 weeks (n=380) arm, gastrointestinal AE (all grades) were described in 32.1% of the patients. Grade 3 gastrointestinal AE were described in 5.3% of the patients		3a

					and grade 4 in 0.5%. In the Robert C et al. 2011 trial - ipilimumab 10mg/kg plus dacarbazine 850 mg/m2 every 3 weeks (n=247) diarrhea was described in 38.2% of the patients (all grades) and 10% grade 3. Colitis was described in 4.5% of the patients (all grade), 1.6 % (grade 3) and 0.4% (grade 4). In the Robert C et al. 2014 trial - pembrolizumab 10 mg/kg every 3 weeks (n=84) arm, grade 3/4 diarrhea was described in 1.2% of the patients. In the Robert C et al. 2015 trial - nivolumab 3 mg/kg every 2 weeks (n=206), gastrointestinal AE		

					(all grades) were described in 17% of the patients. Grade 3/4gastrointestinal AE were described in 1.5% of the patients. In the Weber JS et al. 2015 trial - nivolumab 3 mg/kg every 2 weeks (n=268) gastrointestinal AE (all grades) were described in 11.6% and grade 3/4 in 1.1% of the patients.		
Weber J, et al. 2009	To determine whether prophylactic budesonide (Entocort EC), a nonabsorbed oralsteroid, reduced the rate of grade ≥2 diarrhea in ipilimumab-treated	Randomized, double-blind, placebo-controlled, multicenter, multinational phase II trial Group A (Ipi+Budesonide) n=58 Group B (ipi+Placebo) n=57	Previously treated and treatment-naïve patients (N=115) with unresectable stage III or IV melanoma received open-label ipilimumab	Safety, tolerability and efficacy	Budesonide did not affect the rate of grade ≥2 diarrhea, which occurred in 32.7% and 35.0% of patients in groups A and B, respectively. There were no bowel perforations or treatment-related deaths.		1b Jaded-Score: 3 Grant by BMS

	patients with advanced melanoma.		(10 mg/kg every 3 weeks for 4 doses) with daily blinded budesonide or placebo through week 16.				
Weber JS, et al. 2016	To review the management of irAEs after treatment with anti-programmed death-1 (anti-PD-1) antibodies (nivolumab or pembrolizumab) as monotherapy or in combination with anti-cytotoxic T lymphocyte antigen-4 inhibition (ipilimumab) in patients with advance	Retrospective review	Patients included in the CheckMate 037, 066 and 067 and Keynote 006 clinical trials	Safety	In CheckMate 067 clinical trial, in the NIVO arm, the following gastrointestinal AE were described: diarrhea 19.2% (all grade) and 2.2% (grade 3/4); colitis 1.3% (all grades) and 0.6% (grade 3/4). In the NIVO+IPI arm, the following gastro-intestinal AE were described: diarrhea 44.1% (all grade) and 9.3% (grade 3/4); colitis 11.8% (all grades) and 7.7% (grade 3/4). In the IPI arm, the following		3a

					gastrointestinal AE were described: diarrhea 33.1% (all grade) and 6.1% (grade 3/4); colitis 11.6% (all grades) and 8.7% (grade 3/4). In the KEYNOTE-006, the following gastrointestinal AE were described: diarrhea 14.4% (all grade) and 1.1% (grade 3/4); colitis 2.9% (all grades) and 1.8% (grade 3/4). In the CheckMate 037, the following gastrointestinal AE were described: diarrhea 11.2% (all grade) and 0.4% (grade 3/4); colitis 1.1% (all grades) and 0.7% (grade 3/4). In the CheckMate 066, the following		

					gastrointestinal AE were described: diarrhea 16% (all grade) and 1% (grade 3/4); colitis 1% (all grades) and 0.5% (grade 3/4).		

8.5.5. Literatur

Abdel-Wahab, N., M. Shah, and M.E. Suarez-Almazor, Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. PLoS One, 2016. 11(7): p. e0160221.
Berman, D., et al., Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab results in dysregulation of gastrointestinal immunity in patients with advanced melanoma. Cancer Immun, 2010. 10: p. 11.
Di Giacomo, A.M., M. Biagioli, and M. Maio, The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. Semin Oncol, 2010. 37(5): p. 499-507.
Eigentler, T.K., et al., Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev, 2016. 45: p. 7-18.
Hofmann, L., et al., Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer, 2016. 60: p. 190-209.
Kahler, K.C., et al., Management of side effects of immune checkpoint blockade by anti-CTLA-4 and anti-PD-1 antibodies in metastatic melanoma. J Dtsch Dermatol Ges, 2016. 14(7): p. 662-81.
Spain, L., S. Diem, and J. Larkin, Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev, 2016. 44: p. 51-60.
Verschuren, E.C., et al., Clinical, Endoscopic, and Histologic Characteristics of Ipilimumab-Associated Colitis. Clin Gastroenterol Hepatol, 2016. 14(6): p. 836-842.
Villadolid, J. and A. Amin, Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res, 2015. 4(5): p. 560-75.
Weber, J., et al., A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res, 2009. 15(17): p. 5591-8.
Weber, J.S., et al., Management of Adverse Events Following Treatment With Anti-Programmed Death-1 Agents. Oncologist, 2016. 21(10): p. 1230-1240.

8.6. Frage VII.6. Pulmonale Nebenwirkungen – De novo Recherche

Frage VII.6. Für welche Substanzklassen, die zur medikamentösen Anwendung beim malignen Melanom kommen, sind pulmonale Nebenwirkungen beschrieben und welche Strategien zur Behandlung dieser Nebenwirkungen existieren?

8.6.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients	Systemic treatment		Toxicity, Safety

Suchwörter				
Stichwort	melanoma	Systemic treatment	Side effect, adverse event	Pulmonary
Mesh Term	melanoma	Systemic treatment	Side effect	

8.6.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	((melanoma[tiab] OR melanoma[MeSH]) AND (([side effect[tiab] OR toxicity[tiab] OR adverse event[tiab]]) AND ([lung[tiab] OR pulmonary[tiab] OR breath[tiab]]))))	26.09.2016	713
Cochrane Library	(melanoma and (systemic treatment) and ((side effect) or toxicity) and	26.09.2016	1

	pulmonal) .mp.		

8.6.3. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer		714
Einschlusskriterien	Reviews, klinische Studien Intervention: BRAF-Inhibitoren, MEK-Inhibitoren, Ipilimumab, PD-1-Inhibitoren Sprachen: e,dt	
Ausschlusskriterien	Case Reports Chemotherapie	
Anzahl ausgewählter Studien		6

8.6.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Abdel-Wahab N, et al. 2016	To conduct a systematic review of case reports describing the occurrence of irAEs in patients with cancer	Systematic review; n=191 publications; 251 patients	Patients treated with anti CTLA-4 (ipilimumab) or anti PD-1 (nivolumab or pembrolizumab) with reported	Safety profile	The following respiratory irAE were described in 6 patients (2.5%) treated with ipilimumab: pneumonitis (2.1%) and acute respiratory distress 0.4%.		3a

	following checkpoint blockade therapy, primarily to identify potentially unrecognized or unusual clinical findings and toxicity.		irAE's until August 2015.		Pneumonitis was described in 1 patient treated with pembrolizumab and in 3 patients treated with nivolumab. Acute respiratory distress was also described in 2 patients of the patients treated with nivolumab.		
Eigentler TK, et al. 2016	To reviews incidences and kinetics of onset and resolution of immune-mediated ‘‘adverse events of specific interest” (AEOSI) of both approved PD-1 inhibitors nivolumab and pembrolizumab	Retrospective review; n=1826	Patients treated with nivolumab and pembrolizumab in the following clinical trials: CA209017/-063; CA209037/-066; P001/-002 and P001/-002	Incidences and kinetics of onset and resolution of immune-mediated AEOSI	In patients treated with nivolumab 3 mg/kg q2w, Pneumonitis incl. ILD as AEOSI was reported in 2.3% patients.		3a

Kourie HR, et al. 2016	To report on the different side-effects of the checkpoint inhibitor-based combination therapies and to discuss the future perspectives of these new modalities.	Retrospective review	Patients treated immune checkpoint inhibitors in different phase I, II and III clinical trials.	Safety	In the phase II trial (Postow et al. NEJM 2015), in patients treated with ipilimumab and nivolumab, pneumonitis was described in 11% patients (all grade) and 2% (grade 3/4). In patients treated with ipilimumab, pneumonitis was described in 4% (all grades) and 2% (grade 3/4).		3a
Spain L, et al. 2016	To identify the rates of common and uncommon irAEs associated with each immune checkpoint inhibitor (ICPI) and their timing of onset.	Retrospective review	Patients treated with pembrolizumab, nivolumab, ipilimumab and ipilimumab + nivolumab in combination.	Safety	In patients treated with nivolumab (3 mg/kg 2-weekly - Robert et al. 2015, Weber et al. 2015, Larkin et al. 2015) pneumonitis 1-2% (all grade) and pneumonitis <1% (grade3/4) was reported. In patients treated with Ipilimumab (3 mg/kg 3-weekly -		3a

					Robert et al. 2015, Larkin et al 2015) pneumonitis 0-2% (all grade) and pneumonitis <1% (grade 3/4) was reported. In patients treated with Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks - Larkin et al 2015) pneumonitis 6% (all grade) pneumonitis 1% (grade 3/4) was reported.		
Villadolid J, et al 2015	To describe the optimal management of toxicities related to immune checkpoint inhibition from FDA approved agents targeting CTLA-4 and PD-1.	Retrospective review	Patients treated with agents targeting CTLA-4 and PD-1	Safety profile	In the Robert C et al. 2014 trial - pembrolizumab 2 mg/kg every 3 weeks, n=89, pneumonitis was described in 1.1% of the patients (grade 3/4). In the pembrolizumab 10 mg/kg every 3 weeks arm, n=84, dyspnea was described in 1.2% of		3a

					the patients (grade 3/4). In the Robert C et al. 2015 trial - nivolumab 3 mg/kg every 2 weeks (n=206), pneumonitis was described in 1.5% (all grade) of the patients. In the Weber JS et al. 2015 trial, nivolumab 3 mg/kg every 2 weeks, n=268, respiratory AE were described in 2.2% (all grade) and pneumonitis in 1.9% (all grade) of the patients.		
Zimmer L al, 2016	To report neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy	Retrospective review; n=496	Patients with metastatic melanoma from 15 skin different cancer centres that were treated with	Safety in patients treated with anti-PD-1 therapy	Eight patients (1.6%) showed autoimmune-related pneumonitis including organizing inflammatory pneumonia,		3a

			pembrolizumab or nivolumab.		pneumonitis with sarcoid-like lesions and one patient with pneumonitis and subsequent lung fibrosis. In general, grade 1e2 pneumonitis was treated with prednisolone (0.5-2.0 mg/kg body weight p.o. or i.v.), grade 3 additionally required an interruption of treatment. One patient with grade 3 pneumonitis also required infliximab. Furthermore, seven patients (1.4%) developed cough and four patients (0.8%) dyspnoea under treatment with nivolumab or pembrolizumab. One patient presented with haemoptysis and a		

					larynx oedema with resulting voice changes. An increased phlegm in upper airways occurred in three patients and sinusitis and bronchitis in one case.		

8.6.5. Literatur

Abdel-Wahab, N., M. Shah, and M.E. Suarez-Almazor, Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. PLoS One, 2016. 11(7): p. e0160221.
Eigentler, T.K., et al., Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev, 2016. 45: p. 7-18.
Kourie, H.R. and J.A. Klastersky, Side-effects of checkpoint inhibitor-based combination therapy. Curr Opin Oncol, 2016. 28(4): p. 306-13.
Spain, L., S. Diem, and J. Larkin, Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev, 2016. 44: p. 51-60.
Villadolid, J. and A. Amin, Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res, 2015. 4(5): p. 560-75.
Zimmer, L., et al., Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer, 2016. 60: p. 210-25.

8.7. Frage VII.7. Hepatische Nebenwirkungen – De novo Recherche

Frage VII.7. Für welche Substanzklassen, die zur medikamentösen Anwendung beim malignen Melanom kommen, sind hepatische Nebenwirkungen beschrieben und welche Strategien zur Behandlung dieser Nebenwirkungen existieren?

8.7.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients	Systemic treatment		Toxicity, Safety

Suchwörter				
Stichwort	melanoma	Systemic treatment	Side effect, adverse event	Hepatic
Mesh Term	melanoma	Systemic treatment	Side effect	

8.7.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	((melanoma[tiab] OR melanoma[MeSH]) AND (([side effect[tiab] OR toxicity[tiab] OR adverse event[tiab]]) AND ([liver[tiab] OR hepatic[tiab] OR transaminitis[tiab]]))))	26.09.2016	477

Cochrane Library	(melanoma and (systemic treatment) and ((side effect) or toxicity) and (hepatic or liver)) .mp.	26.09.2016	49

8.7.3. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer		714
Einschlusskriterien	Reviews, klinische Studien Intervention: BRAF-Inhibitoren, MEK-Inhibitoren, Ipilimumab, PD-1-Inhibitoren Sprachen: e,dt	
Ausschlusskriterien	Case Reports Chemotherapie	
Anzahl ausgewählter Studien		6

8.7.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Abdel-Wahab N, et al. 2016	To conduct a systematic review of case reports describing the occurrence of irAEs in patients with	Systematic review; n=191 publications; 251 patients	Patients treated with anti CTLA-4 (ipilimumab) or anti PD-1 (nivolumab or pembrolizumab) with	Safety profile	Hepatitis was described in 17 (7.3%) patients treated with ipilimumab. No hepatitis or other hepatic irAE were described in		3a

	cancer following checkpoint blockade therapy, primarily to identify potentially unrecognized or unusual clinical findings and toxicity.		reported irAE's until August 2015.		patients treated with nivolumab and pembrolizumab.		
Eigentler TK, et al. 2016	To reviews incidences and kinetics of onset and resolution of immune-mediated ‘‘adverse events of specific interest” (AEOSI) of both approved PD-1 inhibitors nivolumab and pembrolizumab	Retrospective review; n=1826	Patients treated with nivolumab and pembrolizumab in the following clinical trials: CA209017/-063; CA209037/-066; P001/-002 and P001/-002	Incidences and kinetics of onset and resolution of immune-mediated AEOSI	In patients treated with nivolumab 3 mg/kg q2w, hepatic events considered AOESI were reported in 6.1% of the patients (all grade) and 1.9% (grade ≥3).		3a

Hofmann L, et al, 2016	To report the incidence of cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy	Retrospective review; n=496	Patients with melanoma treated with nivolumab and pembrolizumab in fifteen study centers in Germany and Switzerland	Safety	Elevated transaminases are reported in <10% in ipilimumab-treated patients and in 3.7-10.0% anti-PD-1 antibody-treated patients. Also, a cyto-megalovirus (CMV)-induced hepatitis after treatment with ipilimumab has been reported. However, 20% of patients treated for advanced hepatocellular carcinoma showed an increase in transaminases due to treatment with nivolumab.		3a
Johncilla M, et al. 2015	To characterize the histologic features and clinical course of ipilimumab-associated	Retrospective review; n=11	Patients with clinical suspicion of ipilimumab-induced hepatitis, due to the developmen	histologic features and clinical course of ipilimumab-associated hepatitis.	Nine biopsies showed active hepatitis with 2 distinct histologic patterns: panlobular hepatitis in 6 cases and zone 3		4

	hepatitis.		t of abnormal liver function tests (LFTs) while receiving treatment, and who underwent liver biopsy in the Brigham and Women's Hospital and Massachusetts General Hospital, Boston, between 2008 and 2014.		hepatitis in 3. The inflammatory infiltrate was similar in composition in both patterns, composed predominantly of CD8+ T lymphocytes, admixed histiocytes, scattered plasma cells, and eosinophils. Prominent histiocytic sinusoidal infiltrates were present in 7 cases and frequently formed loose histiocytic aggregates. Central vein endothelialitis was present in 8 cases. Patients in this group tended to have markedly elevated ALT, AST, and total bilirubin. Two cases did not		

					fit into the above 2 histologic groups: 1 showed portal inflammation with cholangitis, and the other showed morphologic features indistinguishable from non-alcoholic steatohepatitis.		
Postow MA. 2015	To describe the side-effect profile of the checkpoint blocking antibodies that target CTLA-4 and PD-1/PD-L1 and to provide suggestions on how to manage specific irAEs	Retrospective review	Patients treated with anti CTLA-4 or anti PD-1/PD-L1.	Safety	Hepatitis, as determined by elevations in AST, ALT and less commonly, total bilirubin, occasionally is seen in patients treated with checkpoint blockade. Although most episodes present only as asymptomatic laboratory abnormalities, some patients have an associated fever. Rates of AST and ALT elevations		3a

					with CTLA-4 blockade vary among clinical trials, but they typically have been reported in less than 10% of patients. In large trials of PD 1–blocking antibodies, the rates of hepatitis were similarly low (below 5%) and grade 3/4 toxicity was even rarer. Among patients who develop hepatitis, the most common onset is 8 to 12 weeks after initiation of treatment, although early or delayed events also may be seen. Radiographic findings are not typical. In severe cases, however, findings on CT scans may include mild		

					hepatomegaly, periportal edema, or periportal lymphadenopathy. Liver biopsies have described pathologic changes that include severe panlobular hepatitis with prominent perivenular infiltrate with endothelialitis or a primary biliary pattern with mild portal mononuclear infiltrate around bile ductules. Hepatic function (transaminases and bilirubin) should be monitored before each dose of ipilimumab. If AST and ALT increase, viral and other drug-induced causes of hepatitis should be		

					excluded. As with treating other irAEs, if no other cause is obvious, prompt treatment with corticosteroids is necessary. In rare cases, elevations in AST and ALT are steroid-refractory and 500 mg every 12 hours of mycophenolate mofetil may be helpful. The use of antithymocyte globulin therapy also was described in a case report. Unlike for patients with diarrhea/colitis, infliximab should not be given to patients with hepatitis because infliximab carries a risk of hepatotoxicity. Hepatitis may persist for quite some time and		

					require prolonged or repeated corticosteroid tapers (minimum of 3 weeks suggested) and/or additional immunosuppression.		
Spain L, et al. 2016	To identify the rates of common and uncommon irAEs associated with each immune checkpoint inhibitor (ICPI) and their timing of onset.	Retrospective review	Patients treated with pembrolizumab, nivolumab, ipilimumab and ipilimumab + nivolumab in combination	Safety	In patients treated with pembrolizumab (2 mg/kg 2- and 3-weekly - Robert et al. 2015) hepatitis 1-2% (all grade) hepatitis 1-2% (grade 3/4) was reported. In patients treated with nivolumab (3 mg/kg 2-weekly - Robert et al. 2015, Weber et al. 2015, Larkin et al. 2015) hepatitis 3-6% (all grade) and hepatitis 2-3% (grade3/4) was reported. In patients treated		3a

					with Ipilimumab (3 mg/kg 3-weekly - Robert et al. 2015, Larkin et al 2015) hepatitis 1-7% (all grade) and hepatitis 0-2% (grade 3/4) was reported. "In patients treated with Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks - Larkin et al 2015) hepatitis 30% (all grade) and hepatitis 19% (grade 3/4) was reported."		
Wen X, et al. 2016	To determine the tolerability of Chinese melanoma patients, particularly those with hepatitis B virus (HBV) infection, to immune checkpoint	Retrospective cohort study; n=23	Patients with metastatic melanoma who received ipilimumab or pembrolizumab in one chinese center between August	Tolerability	Liver function abnormalities were noted in 22% of patients. Eleven patients had a history of HBV infection. Three of these patients received antiviral therapy with entecavir before antibody infusion because of active		3a

	inhibitor therapy		2012 and July 2015		infection. Three patients received ipilimumab therapy, one of whom experienced grade 1 elevated transaminase levels that returned to normal within 1 week. Five patients, one of whom had active HBV infection, received pembrolizumab infusion; none experienced liver damage. Three patients received concurrent therapy, of whom, two had active infection, including one who experienced grade 3 elevated transaminase levels without jaundice. Normal liver function was restored after 4 weeks of high-dose corticosteroid treatment. The HBV-DNA load did not		

					increase during the course of treatment. Patients with pre-existing HBV infection did not show an increase in grade 3/4 hepatic toxicity (9% for HBV-positive patients vs. 17% for HBV negative patients).		

8.7.5. Literatur

Abdel-Wahab, N., M. Shah, and M.E. Suarez-Almazor, Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. PLoS One, 2016. 11(7): p. e0160221.
Eigentler, T.K., et al., Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev, 2016. 45: p. 7-18.
Hofmann, L., et al., Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer, 2016. 60: p. 190-209.
Johncilla, M., et al., Ipilimumab-associated Hepatitis: Clinicopathologic Characterization in a Series of 11 Cases. Am J Surg Pathol, 2015. 39(8): p. 1075-84.
Postow, M.A., Managing immune checkpoint-blocking antibody side effects. Am Soc Clin Oncol Educ Book, 2015: p. 76-83.
Spain, L., S. Diem, and J. Larkin, Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev, 2016. 44: p. 51-60.
Wen, X., et al., Safety of immune checkpoint inhibitors in Chinese patients with melanoma. Melanoma Res, 2016. 26(3): p. 284-9.

8.8. Frage VII.8. Andere Organsysteme Nebenwirkungen – De novo Recherche

Frage VII.8. Für welche Substanzklassen, die zur medikamentösen Anwendung beim malignen Melanom kommen, sind Nebenwirkungen in anderen Organsystemen beschrieben und welche Strategien zur Behandlung dieser Nebenwirkungen existieren?

8.8.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients	Systemic treatment		Toxicity, Safety

Suchwörter				
Stichwort	melanoma	Systemic treatment	Side effect, adverse event	Organ systems
Mesh Term	melanoma	Systemic treatment	Side effect	

8.8.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	(melanoma[tiab] OR "melanoma"[MeSH Terms]) AND (side effect[tiab] OR toxicity[tiab] OR adverse event[tiab])	26.09.2016	3822
Cochrane Library	(melanoma and (systemic treatment) and ((side effect) or toxicity) NOT	26.09.2016	47

	(liver OR lung OR skin OR eye OR Colitis))		

8.8.3. Auswahlkriterien

Auswahl der Literatur		
Gesamttreffer		3869
Einschlusskriterien	Reviews, klinische Studien Intervention: BRAF-Inhibitoren, MEK-Inhibitoren, Ipilimumab, PD-1-Inhibitoren Sprachen: e,dt	
Ausschlusskriterien	Case Reports Chemotherapie	
Anzahl ausgewählter Studien		6

8.8.4. Evidenztabellen

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Abdel-Rahman O, et al. 2016	To evaluate the efficacy and toxicity of such combinations compared to BRAF-inhibitor monotherapy	Systematic review and meta-analysis of the efficacy and toxicity of doublet BRAF/MEK inhibition vs single-agent BRAF inhibitor	Melanoma patients receiving BRAF oder BRAF+MEK Inhibitors	Relatives Risiko für eine Toxizität zwischen BRAF+MEK vs. BRAF alleine	RR of all grade hypertension was 1.22 [95 % CI (0.99, 1.52); P = 0.07]; while for high grade hypertension was 0.78 [95 % CI (0.33, 1.82); P = 0.56]	Siehe auch Schlüsselfrage VIII.2	2a

Abdel-Wahab N, et al. 2016	To conduct a systematic review of case reports describing the occurrence of irAEs in patients with cancer following checkpoint blockade therapy, primarily to identify potentially unrecognized or unusual clinical findings and toxicity.	Systematic review; n=191 publications; 251 patients	Patients treated with anti CTLA-4 (ipilimumab) or anti PD-1 (nivolumab or pembrolizumab) with reported irAE's until August 2015.	Safety profile	Well-defined diseases such as sarcoidosis, polyarthritis, polymyalgia rheumatica/arteritis, lupus, celiac disease, dermatomyositis, and Vogt-Koyanagi-like syndrome were reported.		3a
Eigentler TK, et al. 2016	To reviews incidences and kinetics of onset and resolution of immune-mediated ‘‘adverse events of specific	Retrospective review; n=1826	Patients treated with nivolumab and pembrolizumab in the following clinical trials: CA209017/-	Incidences and kinetics of onset and resolution of immune-mediated AEOSI.	Hypersensitivity/infusion reaction events are between 0.2 and 5.3%.		3a

	interest" (AEOSI) of both approved PD-1 inhibitors nivolumab and pembrolizumab		063; CA209037/-066; P001/-002 and P001/-002				
Lee et al. 2014	To investigate the clinicopathological correlates of pyrexia, clinical features of pyrexic events and strategies to manage and prevent pyrexia in patients treated with combination of dabrafenib and trametinib (CombiDT).	Retrospetive analyses of a Phase I/II study programme	All patients enrolled in the phase 1/2 trial (BRF113220) of CombiDT between November 2010 and May 2012 at Westmead Hospital were included for retrospective analysis.	Clinico-pathological features of pyrexic events	44% of the patients developed pyrexia (temperature≥38.5 ˚C). Pyrexia was recurrent in 11/14 (79%). The median time to pyrexia was 38 days. Pyrexia was not associated with age, sex nor disease burden, and did not correlate with RECIST response, progression-free nor overall survival.		4

Spain L, et al. 2016	To identify the rates of common and uncommon irAEs associated with each immune checkpoint inhibitor (ICPI) and their timing of onset.	Retrospective review	Patients treated with pembrolizumab, nivolumab, ipilimumab and ipilimumab + nivolumab in combination.	Safety	Although rare and occurring in no more than 3% of patients (3% with a 10 mg/kg dose of ipilimumab, <1% in other studies), neurological irAEs require prompt recognition and treatment to avoid substantial morbidity. Median onset in one adjuvant ipilimumab trial was at 13 weeks. Myasthenia gravis and Guillain Barre syndrome (including one fatal case) have been reported with ipilimumab, nivolumab and pembrolizumab. Posterior reversible leukoencephalopath, radiculoneuropathy, Bell's palsy and aseptic meningitis have been		3a

					reported with ipilimumab. Pembrolizumab has also been associated with central nervous system toxicity. A range of neurological events have been described with nivolumab, including polyneuropathy, facial and abducens nerve paresis and demyelination. Myalgias and arthralgias are commonly reported AEs with ICPIs (2–12%), especially with anti-PD-1 agents. Higher grade toxicity occurs infrequently (1%). A pattern associated with inflammatory rheumatological		

					conditions (ie. morning stiffness, synovitis, proximal weakness) may be elicited. Two cases of polyarticular inflammatory arthritis have been reported, characterised by synovitis and tenosynovitis and managed with bisphosphonates and salazopyrin. Vasculitis, polymyositis, myositis and temporal arteritis have also been described.		
Voskens C et al., 2013	To summarize rare and difficult-to-treat ipilimumab-induced side effects among 19 skin cancer	Retrospective review, n=752	MM-patients receiving Ipilimumab	Safety in patients treated with IPI	120 AEs were reported. These included fatigue, flu-like symptoms, rigor/chills, eosinophilia and rashes (38 pts), which were not further evaluated. A total of 88 rare	Siehe auch Schlüsselfragen VIII.1-VIII-7	3a

	centers				AEs in 82 pts affecting skin (23 pts), endocrine system (14 pts), nervous system (11 patients), liver (11 pts), respiratory tract (8 patients), gastrointestinal tract (6 pts), pancreas (3 pts), sinuses (3 pts), renal system (2 pts), musculosceletal system (2 pts), heart (1 pt), eyes (1 pt), and upper extremities (1 pt) were observed. In addition, a systemic grade IV anaphylactoid reaction and a fatal case of tumor mass liquefication were reported.		
Zimmer L al, 2016	To report neurological, respiratory, musculoskele	Retrospective review; n=496	Patients with metastatic melanoma from 15 skin	Safety in patients treated with anti-PD-1 therapy	Checkpoint inhibitor-associated neuro-logical AEs are very		3a

	tal, cardiac and ocular side-effects of anti-PD-1 therapy		different cancer centres that were treated with pembrolizumab or nivolumab.		rare, difficult to diagnose and potentially life-threatening. Symptoms like tremor, vision disorders, dysarthria, ataxia, paresis, paraesthesia, and seizure are indicative, but symptoms can also be unspecific like headache, dizziness, asthenia, and lethargy. Under treatment with ipilimumab rare neurologic syndromes like aseptic meningitis, Tolosa-Hunt syndrome, granulomatous inflammation of the central nervous system, Guillain-Barre´ syndrome (GBS), transverse myelitis and enteric neuropathy		

					have been reported. For anti-PD-1 antibodies only very few cases of neurological AEs are documented with dys- and hypogeusia, in- and hypersomnia, restless legs syndrome, tremor, lethargy, disturbance of memory, vertigo, neuropathy, dysarthria, cerebral oedema, and paresis. Peripheral neuropathy grade 1/2 and bilateral neuritis of the optical nerve have been reported under treatment with nivolumab. Also focal seizure and epilepsy accompanied by inflamed lesions of the cerebral parenchyma occurred in one		

					patient. Under anti-PD-L1 antibody a case of myasthenia gravis has been reported. GBS occurred under treatment with pembrolizumab and under treatment with nivolumab in combination with ipilimumab. Furthermore, a multifocal central nervous system demyelination has been reported. In this study, paraesthesia, paresis/paralysis, and polyneuropathy developed in three (0.6%) patients, respectively. In two patients (0.4%), seizures were documented. GBS, (meningo)-radiculitis, aphasia, and		

					parkinsonoid syndrome combined with bradykinesia occurred in one patient (0.2%) each. Furthermore, one patient (0.2%) suffered from polyradiculitis with symptoms of GBS. In general, neurological AEs should be diagnosed in cooperation with neurologists and promptly treated with systemic corticosteroids.		

8.8.5. Literatur

Abdel-Rahman, O., H. ElHalawani, and H. Ahmed, Doublet BRAF/MEK inhibition versus single-agent BRAF inhibition in the management of BRAF-mutant advanced melanoma, biological rationale and meta-analysis of published data. Clin Transl Oncol, 2016. 18(8): p. 848-58.
Abdel-Wahab, N., M. Shah, and M.E. Suarez-Almazor, Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports. PLoS One, 2016. 11(7): p. e0160221.
Eigentler, T.K., et al., Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev, 2016. 45: p. 7-18.
Lee, C.I., et al., Features and management of pyrexia with combined dabrafenib and trametinib in metastatic melanoma. Melanoma Res, 2014. 24(5): p. 468-74.
Spain, L., S. Diem, and J. Larkin, Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev, 2016. 44: p. 51-60.
Voskens, C.J., et al., The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. PLoS One, 2013. 8(1): p. e53745.
Zimmer, L., et al., Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer, 2016. 60: p. 210-25.

9. AG Radiotherapie

9.1. Frage VIII.1. Radiotherapie Primärtumor

Frage VIII.1. Hat eine Radiotherapie von inoperablen Primärtumoren oder eine postoperative Radiotherapie nach R1 oder R2-Resektion von Primärtumoren bzw. bei Vorhandensein anderer Risikofaktoren (nicht einhaltbare Sicherheitsabstände) einen Einfluss auf das progressionsfreie Überleben oder Gesamtüberleben?

9.1.1. PICO, Suchwörter

PICO - Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients with primary tumor, prior or after (partial) resection	radiotherapy	no radiotherapy	PFS, OS

Suchwörter				
Stichwort	melanoma	radiotherapy	primary	margin
Synonyme		Radiation, irradiation		
Ober-/Unterbegriffe	Lentigo maligna, cutaneous, skin			Resection, R1, R2, inoperable, unresectable, adjuvant, postoperative
Mesh Term	melanoma	radiotherapy, radiation		

9.1.2. Datenbanken, Suchstrategien, Trefferzahlen

9.1.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH]) AND (primary OR "lentigo maligna" OR margin* OR resection OR R1 OR R2 OR inoperab* OR unresectab*) NOT (uvea*[ti] OR anorectal[ti] OR mucosal[ti])	20.04.11	1836 (Auswahl 22 Studien)
Medline -Erweiterte Suchstrategie	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH] OR irradiation) AND (skin OR cutaneous OR primary OR "lentigo maligna" OR margin* OR resection OR R1 OR R2 OR postoperative OR inoperab* OR unresectab*) NOT (uvea*[ti] OR anorectal[ti] OR mucosal[ti])	16.05.11	5435 (Auswahl 8 Studien)
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation) and (skin or cutaneous or primary or "lentigo maligna" or margin* or resection or R1 or R2 or adjuvant or postoperative or inoperab* or unresectab*) not (uvea* or anorectal or mucosal)).ti,ab.	20.04.11	42 (0)
Embase	(melanoma and (radiotherapy or radiation or irradiation) and (skin or cutaneous or primary or "lentigo maligna" or margin* or resection or R1 or R2 or adjuvant or postoperative or inoperab* or unresectab*) not (uvea* or anorectal or mucosal)).ti,ab.	11.05.11	3272 (Auswahl 3 Studien)
Update Suche			
Medline	s.o.	31.01.12	5613 (1Studie dazu, Hedblad et al. 2011)
Cochrane Library	s.o.	31.01.12	42 (0 dazu)

Embase	s.o.	23.01.12	3475 (0 dazu)

9.1.2.2. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH]) AND (primary OR "lentigo maligna" OR margin* OR resection OR R1 OR R2 OR inoperab* OR unresectab*) NOT (uvea*[ti] OR anorectal[ti] OR mucosal[ti])	16.09.2016	1836 (Auswahl 22 Studien)
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation) and (skin or cutaneous or primary or "lentigo maligna" or margin* or resection or R1 or R2 or adjuvant or postoperative or inoperab* or unresectab*) not (uvea* or anorectal or mucosal)).ti,ab.	16.09.2016	42 (0)

9.1.3. Auswahlkriterien

9.1.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	8721
Einschlusskriterien	Mangels RCT´s Einschluss von Kohortenstudien und Fallserien ab 20 Patienten Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kombinationstherapien

	Arbeiten zu RT von nicht invasiven Melanomen (Melanoma in situ/Lentigo maligna) Kollektive mit gemischten Tumorentitäten Arbeiten älter als 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	34
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	19
Anzahl ausgewählter Volltexte	**15**

9.1.3.2. Aktualisierungsrecherche 2016

Auswahl der Literatur	
Gesamttreffer	647
Einschlusskriterien	Mangels RCT´s Einschluss von Kohortenstudien und Fallserien ab 20 Patienten Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kombinationstherapien Arbeiten zu RT von nicht invasiven Melanomen (Melanoma in situ/Lentigo maligna) Kollektive mit gemischten Tumorentitäten Arbeiten älter als 2012
Anzahl nach Abstractscreening, vorgesehen für Bewertung	59
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	12
Anzahl ausgewählter Volltexte	**4**

9.1.4. Evidenztabelle

9.1.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Wasif et al. 2011	To study the surgical management of desmoplastic melanoma (DM), identify prognostic factors, and impact of treatment options	Retrospective cohort study	1735 patients with desmoplastic melanoma 143 (8%) of patients in the cohort received adjuvant radiotherapy	survival	adjuvant radiation therapy: negative impact on survival [HR 1.65 (95% CI 1.17-2.31)]	Adverse impact of RT probably reflects selection bias	3b Cohort study with imbalance of groups
Chen et al. 2008	To describe the clinicopathologic features of desmoplastic neurotropic melanoma (DNM), to update outcomes, and to explore the role of adjuvant radiation treatment in the management of this entity	Retrospective cohort study Treatment: Surgery + different RT modalities and schedules	128 patients with DNM 27 patients received radiotherapy after local excision	Local recurrence Prognostic factors	RT group, N=27: n=2 (7.4%) Surgery only, N=101: n=6 (5.9%) significant predictors of local recurrence: -a positive margin (P < .001) -head and neck location (P = .03)	Imbalance of groups: RT group included more patients with worse prognostic factors (closer exicision margin, higher tumor thicknes, more head and neck tumors)	3b Cohort study with imbalance of groups
Hedblad et al. 2011	To evaluate Grenz ray treatment in a structured way for	Retrospective cohort study	593 patients with Lentigo maligna or early lentigo	Complete clearance	88%	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	treatment of Lentigo maligna melanoma as an alternative to surgery	Treatment: Grenz ray treatment	maligna melanoma				
Vongtama et al. 2003	To address the role of radiation therapy in local control of desmoplastic malignant melanoma (DMM)	Retrospective cohort study (1976 – 1999) Treatment: Surgery alone Surgery + RT, median dose 50 Gy	44 patients with DMM 14 patients with postoperative RT after local recurrence 1 patient with preoperative RT	Local recurrence Local control in re current DMM Distant metastasis	Overall: n=21 (48%) Surgery +RT (15 pts) n=15 Surgery alone (7pts) n=3 nonirradiated patients 35% irradiated patients 40%	Possible selection bias, Imbalance of groups, small sample size	4 Cohort study with imbalance of groups and small sample size
Foote et al. 2008	To address the role of radiotherapy in the local control of desmoplastic melanoma	Retrospective evaluation Treatment: Surgery + wide field radiotherapy with a 3- to 4-cm margin	24 patients with DM received surgical excision as initial treatment followed by postoperative radiotherapy	3-year in-field relapse-free survival 3-year relapse-free survival 3-year overall survival	91% (95% confidence interval 68.1–97.6%) 86% (95% confidence interval 63.2–95.4%) 83% (95% confidence interval 54.9–94.3%).	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Arora et al. 2005	To determine local recurrence rates for patients with desmoplastic melanoma who underwent wide excision alone	Retrospective evaluation Treatment: surgery alone	65 Patients with DM received surgical excision alone	Local recurrence rate	n=2 (4%) of 49 patients with minimum of 2 years of follow-up	Lack of control group	4
Farshad et al. 2002	To perform a retrospective study of 150 patients with lentigo maligna (LM) and lentigo maligna melanoma (LMM) treated with radiotherapy using Grenz or soft X-rays.	Retrospective evaluation Treatment: Grenzrays (12 kV) X-rays (20 or 30 kV) LM: 10-12 Gy x 10 fractions LMM 7-9 Gy x 6 fractions	150 patients with LM or LMM treated at the skin cancer unit of the Department of Dermatology, University of Zurich (Switzerland) between 1950 and 2000	Local recurrence rate	n=7 (7%) of 101 patients followed up for at least 2 years	Lack of control group	4
Schmid-Wendtner et al. 2000	To present the results of a fractionated radiation therapy (modified Miescher's technique) in 64 patients with LM or LMM treated between 1987 and	Retrospective evaluation Treatment: superficial x-ray unit (Dermopan, Siemens, Erlangen, Germany) 100 Gy applied in 10 fractions, safety	64 patients with LM (n =42) and LMM (n= 22)	Local recurrence rate	LM n=0 (0%) of 42 patients LMM n=2 (9%) of 22 patients median follow up 15 months	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	1998.	margin: 0.5 - 2.0 cm					
Stevens et al. 2000	To assess local recurrence and survival of patients treated with surgery and postoperative hypofractionated radiation therapy	Retrospective evaluation Treatment: TD 30–36 grays (Gy), 5–7 fractions, twice weekly	174 Stage I–III melanoma patients received postoperative radiation therapy Group A n=32: primary tumor site (Group B n=142: lymph node involvement)	Local recurrence rate 3-years metastasis free survival	n=20 (11%) (Group A and B) 60% (Group A)	Lack of control group No baseline characteristics presented	4
Panizzon et al. 1999	To report radiation treatment results of 129 patients with the precursor lesion lentigo maligna and 27 patients with lentigo maligna melanoma	Retrospective evaluation Treatment: RT alone	27 patients with lentigo maligna melanoma	Complete response	n=25 (92.8%)	Lack of control group	4
Ang et al. 1994	To assess the efficacy and toxicity of elective-adjunctive radiotherapy given in five 6-Gy	Retrospective evaluation Treatment: (most patients) electrons, mostly	174 melanoma patients Group 1 (n=79) RT after wide excision Group 2 (n=32)	5-year local-regional control Survival	88% (all patients) 87% (Group 1) 47% (all patients) 62% (Group 1)	Lack of control group	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	fractions to patients with cutaneous melanoma of the head and neck at high risk for local-regional relapse	9-12 MeV, 6-Gy dose per fraction, twice a week, total dose 30Gy	RT+limited neck dissection Group 3 (n=63) RT after neck ecur ttion for nodal relapse	Pattern of failure (after median follow-up of 35 months)	Group 1 NED n=51 Dermal r ecur. N=2 Nodal relapse n=2 D+N n=1 Distant met. N=21		
Storper et al. 1993	To elucidate the efficacy of external beam irradiation in the treatment of head and neck malignant melanoma, in comparison with the efficacy of surgical excision and the efficacy of surgical excision combined with external beam irradiation	Retrospective evaluation Treatment: -surgery (SE), n=26 -primary external beam irradiation (XRT), n=10 -adjuvant external beam irradiation (SE+XRT), n=8	44 melanoma patients with recurrent disease	Survival	SE 19% XRT 20% SE+XRT 37%	Imbalance of prognostic factors between groups Site of RT not mentioned	4
Phipps et al. 1992	To examine the effect of immediately preoperative adjuvant radiotherapy in the surgical treatment	Retrospective evaluation (1958-1970) Treatment: All patients: 400 cGy external beam	77 melanoma patients, clinical Stage I	5-years survival 10-year survival Local recurrence	68% 57% 14% Follow-up minimum 10 years	Lack of control group Tumor thickness not mentioned	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of primary cutaneous malignant melanoma	radiotherapy, 52 patients additional single-fraction 2000 cGy Surgery within 24h					
Elsmann et al. 1991	To facilitate clinical decisions the authors report on their results using soft X-ray therapy of primary melanomas	Retrospective evaluation (1974-1989) Treatment: Soft X-ray 30 - 100kV TD 48 – 105 Gy, fraction size 3.5 – 7 Gy after total excision n=23 after partial excision n=41 without prior excision n=19	83 melanoma patients LMM n=64 SSM n=8 NMM n=6 Not classified n=5 pT1 n=17 pT2 n=13 pT3 n=19 pT4 n=13 pT classification not available n=2 not biopsied n=19	Local recurrence Survival	n=1 (skin metastasis) RT after total excision n=1 (recurrent tumor nodule) RT without total excision 60%, (melanoma deaths 9.6%, other diseases 30.1%) Follow-up median 42 months	Lack of control group	4
Harwood et al. 1983	To review the results of radiation treatment of 51 patients with LM and LMM.	Retrospective evaluation (1958-1982) Treatment: LMM 125, 140 or 175 KEV	28 patients with Lentigo maligna melanoma	Local recurrence or residual tumor No local recurrence Not assessable	n=2 (7%) n=23 (82%) n=3 (11%)	Lack of control group	4

Ausgeschlossene Studien

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Zygogianni et al. 2011	*To assess the potential impact of radiotherapy (RT) on local control, quality of life and overall survival*	*Review*	*Pubmed 1978 - 2010*			*Non systematic Review, excluded*	
Newlin et al. 2005	*To report our experience with neurotropic melanoma*	*Case Series* *Treatment: Surgery + x-rays (6 MV)*	*3 patients with neurotropic melanoma received RT after incomplete excision (n=2) and adjuvant RT after complete excision (n=1)*	*Local control*	*1 patient: recurrence in a regional lymph node after 30 months* *2 patients disease-free (after 34 and 14 months)*	*<20 patients, study excluded*	
Cooper et al. 2001	*To report our initial results with elective radiation therapy after definitive surgery for selected patients who have high-risk malignant melanomas.*	*Retrospective evaluation* *Treatment: Surgery + 6Gy per fraction, 5 or 6 fractions*	*40 patients with high-risk malignant melanomas* *29 patients with recurrent primary or regional disease* *9 patients: close or microscopically involved surgical margins*	*5-year local-regional control rate*	*84%*	*majority of patients received RT for recurrent disease. Analyses were performed together for the very heterogenous group,* *study excluded*	
Seegenschmiedt et al. 1999	*To analyze relevant endpoints*	*Retrospective evaluation*	*2 917 melanoma patients*	*Response at 3 months*	*CR n=7 (64%)* *PR n=4 (36%)*	*<20 patients RT primary tumor,*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	(tumor response, local tumor control, survival) and to identify prognostic factors for achievement of these endpoints in long-term follow-up (FU)	*Treatment: linac 6–10 MV photons or 4–18 MeV electrons*	*121 received RT, thereof 11 patients with relapsed/residual MM (UICC IIB)*	*Recurrence rate* *In-field local relapse* *Regional in-transit metastases*	*n=3 (27%)* *n=2 (18%)* *n=1 (9%)* *of 11 patients*	*study excluded*	
Tsang et al.	*To report the experience with radiotherapy for lentigo maligna*	*Retrospective evaluation*	*54 patients with lentigo maligna*			*No patients with lentigo maligna melanoma study excluded*	*4*
Umebayashi et al 1995	*To answer whether or not the proton beam can provide useful treatment for cutaneous melanoma*	*Case series* *Treatment: proton beam, total dose of around 100 Gy, fractionated into single doses of approximately 10 Gy*	*7 patients* *with 5 primary melanomas and 3 metastatic lymph nodes*	*Regression primary melanoma*	*100% n=1* *90% n=2* *80% n=1* *85% n=1*	*<20 patients, study excluded*	
Rounsaville et al. 1988	*Radiotherapy in the management of cutaneous melanoma: effect of time, dose, and fractionation*	*Review*				*Non systematic Review, excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Von Rottkay et al. 1987	*Radiation therapy in malignant melanoma using accelerated fractionation. Remission and preliminary results of local tumor control*	*Retrospective evaluation (1982-1985)*	*14 patients at different clinical stages*			*<20 patients, different stages, study excluded*	
Blake et al. 1985	*To report the results of treatment of malignant melanoma by fast neutrons*	*Retrospective evaluation* *Treatment: 156OcGy in 12 fractions (4 weeks) or 1395cGy in 6 fractions (2 weeks)*	*7 patients with primary melanomas* *(of 48 melanoma patients with 87 tumors)*	*Response*	*CR n=6 (86%) of 7 primary melanomas*	*<20 patients, study excluded*	
Overgaard et al. 1980	*Radiation Treatment of malignant melanoma*	*Retrospective evaluation (1970-1980)* *Treatment: Different fractions and dose schedules*	*36 patients with 24 skin lesions and 25 lymph node metastases*	*Response* *CR* *PR* *No response* *Progression* *CR* *PR* *No response* *Progression*	*skin lesions n=24* *n=7* *n=10* *n=6* *n=1* *lymph node metastases n=25* *n=5* *n=10* *n=8* *n=2*	*Baseline characteristics missing primary melanomas and skin metastases are not distinguished* *study excluded*	
Tonak et al. 1976	*To present the treatment results*					*published before 1980, study*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of 195 melanoma patients (clinical stages I and II)					*excluded*	
Von Lieven et al. 1976	*To investigate the correlation between the total dose needed for a local healing and the period of treatment*					*published before 1980, study excluded*	
König et al. 1970	*Problems in the radiological treatment of malignant melanomas of the skin. Report on 136 patients followed-up over long period of time*					*published before 1980, study excluded*	
Stein et al. 1965	*The avoiding of a combination-effect in combined surgical-radiological treatment of malignant skin tumors*					*published before 1980, study excluded*	
Hellriegel et al. 1963	*To present radiotherapentic*					*published before 1980, study*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	improvements and results in malignant melanomas					*excluded*	
Wernsdoerfer et al. 1960	*On the treatment and prophylaxis of malignant melanoma skin tumors*					*published before 1980, study excluded*	
Spoljar et al. 1959	*The treatment of malignant melanoma*					*published before 1980, study excluded*	
Nitter et al. 1956	*The treatment of malignant melanoma with special reference to the possible effect of radiotherapy*					*published before 1980, study excluded*	
Greve et al. 1952	*Roentgen irradiation of skin tumors*					*published before 1980, study excluded*	

9.1.4.2. Literatur

Ang KK, Peters LJ, Weber RS, et al. Postoperative radiotherapy for cutaneous melanoma of the head and neck region. Int J Radiat Oncol Biol Phys 1994;30:795-798
Arora A, Lowe L, Su L, et al. Wide excision without radiation for desmoplastic melanoma. Cancer 2005;104:1462-1467
Blake PR, Catterall M, Errington RD. Treatment of malignant melanoma by fast neutrons. Br J Surg 1985;72:517-519
Chen JY, Hruby G, Scolyer RA, et al. Desmoplastic neurotropic melanoma: a clinicopathologic analysis of 128 cases. Cancer 2008;113:2770-2778
Cooper JS, Chang WS, Oratz R, et al. Elective radiation therapy for high-risk malignant melanomas. Cancer J 2001;7:498-502
Elsmann HJ, Ernst K, Suter L. Radiotherapy of primary human melanomas--experiences and suggestions. Strahlenther Onkol 1991;167:387-391

Farshad A, Burg G, Panizzon R, et al. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. Br J Dermatol 2002;146:1042-1046
Foote MC, Burmeister B, Burmeister E, et al. Desmoplastic melanoma: the role of radiotherapy in improving local control. ANZ J Surg 2008;78:273-276
GREVE W. Roentgen irradiation of skin tumors. Strahlentherapie 1952;89:401-408
Harwood AR. Conventional fractionated radiotherapy for 51 patients with lentigo maligna and lentigo maligna melanoma. Int J Radiat Oncol Biol Phys 1983;9:1019-1021
Hedblad MA, Mallbris L. Grenz ray treatment of lentigo maligna and early lentigo maligna melanoma. J Am Acad Dermatol 2011
HELLRIEGEL W. Radiation therapy of primary and metastatic melanoma. Ann N Y Acad Sci 1963;100:131-141
Koenig H. Problems in the radiological treatment of malignant melanomas of the skin. Report on 136 patients followed-up over long period of time. Z Arztl Fortbild (Jena) 1970;64:770-779
Newlin HE, Morris CG, Amdur RJ, et al. Neurotropic melanoma of the head and neck with clinical perineural invasion. Am J Clin Oncol 2005;28:399-402
Nitter L. The treatment of malignant melanoma with special reference to the possible effect of radiotherapy. 1956.
Overgaard J. Radiation treatment of malignant melanoma. Int J Radiat Oncol Biol Phys 1980;6:41-44
Panizzon R.G. Radiotherapy of lentigo maligna and lentigo maligna melanoma. 1999.
Phipps AR, Godfrey AM, Durrant KR, et al. The effect of immediately preoperative adjuvant radiotherapy in the surgical treatment of primary cutaneous malignant melanoma. Br J Plast Surg 1992;45:30-33
Rounsaville MC, Cantril ST, Fontanesi J, et al. Radiotherapy in the management of cutaneous melanoma: effect of time, dose, and fractionation. Front Radiat Ther Oncol 1988;22:62-78
Schmid-Wendtner MH, Brunner B, Konz B, et al. Fractionated radiotherapy of lentigo maligna and lentigo maligna melanoma in 64 patients. J Am Acad Dermatol 2000;43:477-482
Seegenschmiedt MH, Keilholz L, Altendorf-Hofmann A, et al. Palliative radiotherapy for recurrent and metastatic malignant melanoma: prognostic factors for tumor response and long-term outcome: a 20-year experience. Int J Radiat Oncol Biol Phys 1999;44:607-618
Spoljar M., Franicevic N., Kubovic M. The treatment of malignant melanoma. 1959.
Stein G. The avoiding of a combination-effect in combined surgical-radiological treatment of malignant skin tumors. Strahlentherapie 1965;128:347-350
Stevens G, Thompson JF, Firth I, et al. Locally advanced melanoma: results of postoperative hypofractionated radiation therapy. Cancer 2000;88:88-94
Storper IS, Lee SP, Abemayor E, et al. The role of radiation therapy in the treatment of head and neck cutaneous melanoma. Am J Otolaryngol 1993;14:426-431
Tonak J, Hermanek P, Hornstein OP, et al. Treatment of malignant melanoma (clinical stages I and II) (author's transl)]. Dtsch Med Wochenschr 1976;101:435-450
Tsang RW, Liu FF, Wells W, et al. Lentigo maligna of the head and neck. Results of treatment by radiotherapy. Arch Dermatol 1994;130:1008-1012
Umebayashi Y, Uyeno K, Tsujii H, et al. Proton radiotherapy for malignant melanoma of the skin. Dermatology 1995;190:210-213
von Lieven H, Skopal D. Radiosensitivity of malignant melanoma]. Strahlentherapie 1976;152:1-4
von Rottkay P. Radiation therapy in malignant melanoma using accelerated fractionation. Remission and preliminary results of local tumor control. Strahlenther Onkol 1987;163:139-143
Vongtama R, Safa A, Gallardo D, et al. Efficacy of radiation therapy in the local control of desmoplastic malignant melanoma. Head Neck 2003;25:423-428
Wasif N, Gray RJ, Pockaj BA. Desmoplastic melanoma - the step-child in the melanoma family? J Surg Oncol 2011;103:158-162
Wernsdoerfer R. On the treatment and prophylaxis of malignant melanoma skin tumors. Strahlentherapie 1960;Suppl 46:43-48
Zygogianni A, Kyrgias G, Kouvaris J, et al. Melanoma: The Radiotherapeutic Point of View; Review of the Current Literature. Rev Recent Clin Trials 2011

9.1.4.3. Aktualisierungsrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Baker et al. 2016	To more fully evaluate the impact of radiotherapy on the survival of patients with locoregionally	A retrospective study of the Surveillance, Epidemiology, and End Results (SEER) database	Patients with locoregionally confined cutaneous melanoma treated surgically between 2004 and 2009	Cancer-specific mortality All-cause mortality	Cancer specific mortality (HR 1.57, p < 0.0002) for radiated patients All-cause (HR 1.44, p < 0.0003) for	Schlechteres Überleben für radiotherapierte Patienten, möglicherweise durch Selektion bedingt	3b

	confined cutaneous melanoma	Matched 319 radiotherapy patients with 319 non-radiotherapy controls			radiated patients		
Guadagnolo et al 2014	To evaluate outcomes, specifically with respect to adjuvant radiotherapy, for patients with desmoplastic melanoma	Retrospective evaluation on 130 patients record	Patients who presented between 1985 and 2009 with non-metastatic desmoplastic melanoma and were treated curatively with either surgery alone (59 patients; 45%) or surgery and postoperative radiotherapy (71 patients; 55%)	Local recurrences	Of the patients who underwent surgery without receiving postoperative radiotherapy, 14 (24%) experienced local recurrence. Of the 71 patients treated with surgery and postoperative radiotherapy, 5 (7%) experienced local recurrence.		3b
Rule et al. 2016	To examine the utilization and efficacy of adjuvant radiation therapy (RT) in patients with resected desmoplastic melanoma	Prospective, Phase II trial, 20 patients	Adult patients with resected, margin-negative, and nonmetastatic desmoplastic melanoma	2-year local recurrence rate Incidence of regional and distant metastatic disease Progression-free survival	10% No regional or distant failures occurred Overall survival at	Prospektive Studie, jedoch geringe Fallzahl	2b

				Overall survival Treatment-related toxicity	2 and 5 years was 95 and 77%, respectively No grade 3 or higher acute or late adverse events that were related to the protocol therapy		
Wushou et al. 2015	To clarify the benefits of postoperative adjuvant radiotherapy	Systematic review A total of 423 patients were available from eight studies and the median sample size was 53 cases.	Patients with head and neck melanoma receiving surgery alone and surgery plus postoperative adjuvant radiotherapy.	loco-regional recurrence 3-Y-OS 5-Y-OS	Odds ratio = 0.36, 95% confidence interval [CI] = 0.22-0.60, P = 0.000 Postoperative adjuvant radiotherapy had no impact on 3-year and 5-year OS (hazard ratio [HR] = 1.14, 95% CI = 0.80-1.61, P = 0.472 and HR = 1.34, 95% CI = 0.97-1.85, P = 0.227, respectively)		2a

9.1.4.3.1. Literatur

Baker, A., et al., A retrospective analysis of the role of adjuvant radiotherapy in the treatment of cutaneous melanoma. Cancer Biol Ther, 2016: p. 1-5.
Guadagnolo, B.A., et al., The role of adjuvant radiotherapy in the local management of desmoplastic melanoma. Cancer, 2014. 120(9): p. 1361-8.

Rule, W.G., et al., Results of NCCTG N0275 (Alliance) - a phase II trial evaluating resection followed by adjuvant radiation therapy for patients with desmoplastic melanoma. Cancer Med, 2016. 5(8): p. 1890-6.
Wushou, A., et al., Postoperative adjuvant radiotherapy improves loco-regional recurrence of head and neck mucosal melanoma. J Craniomaxillofac Surg, 2015. 43(4): p. 553-8.

9.2. Frage VIII.2. und VIII.3. Radiotherapie Intransit- und Fernmetastasen

Frage VI.3. Welche Radiotherapie-Indikationen bestehen im Stadium der Fernmetastasierung?

Frage VI.2. Hat eine Radiotherapie von Satelliten- und In-transit-Metastasen einen Einfluss auf das Progressionsfreie Überleben oder Gesamtüberleben?

9.2.1. PICO, Suchwörter

PICO – Schema (Intransitmetastasen)			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients with satellite or intransit metastases	radiotherapy	no radiotherapy	PFS, OS

Suchwörter (Instransitmetastasen)				
Stichwort	Melanoma	radiotherapy	Satellite metastases	salvage
Synonyme		Radiation, irradiation	Satellite metastasis, In-transit metastases, In-transit metastasis, Intransit metastases, Intransit metastasis	
Ober-/Unterbegriffe	cutaneous, skin, subcutaneous		Local recurrence, Locoregional recurrence,	relapse

			Locoregional spread, Locoregional metastases, Locoregional metastasis, relapse	
Mesh Term	melanoma	radiotherapy, radiation	Neoplasm Recurrence, Local	

PICO – Schema (Fernmetastasen)			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients with distant metastases, Stage IV	radiotherapy	no radiotherapy	Lesion response, overall response, survival, toxicity, quality of life

Suchwörter (Fernmetastasen)				
Stichwort	melanoma	radiotherapy	Postoperative palliative	metastases
Synonyme		Radiation, irradiation		Stage IV
Ober-/Unterbegriffe		radiosurgery		lung, pulmonal bone spinal cord spine liver, hepatic visceral skin, dermal

Mesh Term	melanoma			

9.2.2. Datenbanken, Suchstrategien, Trefferzahlen

9.2.2.1. Primärrecherche 2012

Datenbank	Suchstrategie (Instransitmetastasen)	Datum	Treffer
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH]) AND ("Satellite metastases" OR "Satellite metastasis" OR "In-transit metastases" OR "In-transit metastasis" OR "Intransit metastases" OR "Intransit metastasis" OR "Local recurrence" OR "Locoregional recurrence" OR "Locoregional spread" OR "Locoregional metastases" OR "Locoregional metastasis" OR “Neoplasm Recurrence, Local”[MeSH]) NOT (uvea*[ti] OR anorectal[ti] OR mucosal[ti])	14.04.11	477
Medline – erweiterte Suchstrategie	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH] OR irradiation) AND (skin OR cutaneous OR subcutaneous OR "Satellite metastases" OR "Satellite metastasis" OR "In-transit metastases" OR "In-transit metastasis" OR "Intransit metastases" OR "Intransit metastasis" OR "Local recurrence" OR "Locoregional recurrence" OR "Locoregional spread" OR "Locoregional metastases" OR "Locoregional metastasis" OR “Neoplasm Recurrence, Local”[MeSH] OR salvage OR relapse) NOT (uvea*[ti] OR anorectal[ti] OR mucosal[ti])	04.07.11	4872
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation) and (skin or cutaneous or subcutaneous or Satellite metastases or Intransit metastases or Locoregional metastases or salvage or relapse or recurrence or locoregional spread)).ti,ab.	10.06.11	33
Embase	(melanoma and (radiotherapy or radiation or irradiation) and (skin or cutaneous or subcutaneous or Satellite metastases or Intransit metastases or Locoregional metastases or salvage or relapse or recurrence or locoregional spread)).ti,ab.	11.05.11	2710

Datenbank	Suchstrategie (Instransitmetastasen)	Datum	Treffer
Update Suche			
Medline	s.o.	31.01.12	4980 (0 dazu)
Cochrane Library	s.o.	31.01.12	33 (0 dazu)
Embase	s.o.	23.01.12	2889 (0 dazu)
Gesamttreffer			7902

Datenbank	Suchstrategie (Fernmetastasen)	Datum	Treffer
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiation[MeSH] OR radiosurgery[tiab] OR irradiation[tiab]) AND (postoperative[tiab] OR palliative[tiab] OR metastas*[tiab] OR "stage IV"[tiab] OR lung[tiab] OR pulmonal[tiab] OR bone[tiab] OR "spinal cord"[tiab] OR "spine"[tiab] OR liver[tiab] OR hepatic[tiab] OR visceral[tiab] OR skin[tiab] OR dermal[tiab])	16.05.11	3273
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation or radiosurgery) and (postoperative or palliative or metastasases or "stage IV" or lung or pulmonal or bone or "spinal cord" or "spine" or liver or hepatic or visceral or skin or dermal)).ti,ab.	19.05.11	28
Embase	(melanoma and (radiotherapy or radiation or irradiation or radiosurgery) and (postoperative or palliative or metastasases or "stage IV" or lung or pulmonal or bone or "spinal cord" or "spine" or liver or hepatic or visceral or skin or dermal)).ti,ab.	11.05.11	2915

Update Suche			
Medline	s.o.	31.01.12	3359 (0 dazu)
Cochrane Library	s.o.	31.01.12	28 (0 dazu)
Embase	s.o.	23.01.12	3032 (0 dazu)
Gesamttreffer			6419

9.2.2.2. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	(((advanced OR disseminated) AND melanoma[tiab] AND radiation)) AND ("2015/01/01"[Date - Entrez] : "2016/09/16"[Date - Entrez])	16.09.2016	108
Cochrane Library	(advanced or disseminated) and melanoma and Radiation	16.09.2016	93 (0)

9.2.3. Auswahlkriterien

9.2.3.1. Primärrecherche 2012

Auswahl der Literatur (Intransit- und Fernmetastasen)	
Gesamttreffer (Intransit- und Fernmetastasen)	14321

Einschlusskriterien	Arbeiten die die Radiotherapie von Fern- und Intransitmetastasen bei Patienten mit metastasiertem Melanom beschreiben Mangels RCT´s Einschluss von Kohortenstudien und Fallserien ab 20 Patienten, bzw. ab 20 Läsionen (bei Angabe von läsionsbezogenen Responsedaten) Sprachen: e,dt
Ausschlusskriterien	ausschliesslich ZNS Metastasen (siehe Frage VI.4.) Kollektive mit gemischten Tumorentitiäten Nicht systematischer Review Publikation vor 1980
Anzahl ausgewählter Volltexte	23
Bermerkungen: Da zum Thema keine ranomisierten Studien existieren, wurden Fallberichte aufgenommen (Level 4). Kollektive mit ausschliesslicher ZNS Metastasierung wurden ausgeschlossen. Arbeiten mit historischen Verfahren (Bremer et al. 1999) wurden ausgeschlossen. Aufgrund der Überlappung der gefundenen Arbeiten aus beiden Suchen wurden diese in einer gemeinsamen Evidenztabelle zusammengefasst	

9.2.3.2. Aktualisierungsrecherche 2016

Auswahl der Literatur	
Gesamttreffer	647
Einschlusskriterien	Mangels RCT´s Einschluss von Kohortenstudien und Fallserien ab 20 Patienten Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kombinationstherapien Arbeiten zu RT von nicht invasiven Melanomen (Melanoma in situ/Lentigo maligna) Kollektive mit gemischten Tumorentitäten Arbeiten älter als 2014

Anzahl nach Abstractscreening, vorgesehen für Bewertung	43
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	7
Anzahl ausgewählter Volltexte	**4**

9.2.4. Evidenztabelle

9.2.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Overgaard et al. 2009 (original publication 1996)	To investigate the value of hyperthermia as an adjuvant to radiotherapy in treatment of malignant melanoma	RCT Treatment RT vs RT+Hyperthermia (HT) RT; high voltage photons or electrons	70 patients, 134 lesions, skin lesions: n=93	Response Overall 5-year Survival Rate	128 evaluable tumors, RT vs RT + HT CR: 35% vs 62% , sign., p=0.003 PR: 37% vs 27% n.s. NR: 28% vs 11% n.s. 68 evaluable patients: 19%	Randomisation based on lesions, not on patients Response assessment was not blinded response was not analyzed separately for node and cutaneous lesions	4 1b (question RT vs RT + HT)
Richtig et al. 2005	To evaluate the organ-specific response rate, local response rate of each therapeutic measure and	Retrospective evaluation Treatment: RT: TD 30 – 50 Gy, fraction size 2 - 4	68 patients with unresectable stage IV disease 46 treatment periods	Response	CR+PR (in regard to treatment periods): Total 12/46 (26%) Lymph Node 3/9 Bone 0/10	No patient related response data available	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	survival of 68 patients with stage IV disease	Gy Gama knife Surgery Local hyperthermia Chemotherapy	radiotherapy (total: 410 treatment periods)		Cutaneous / subcutaneous 2/3 Other 2/3 Brain 5/21		
Kirova et al. 1999	To assess the response rate and efficacy of palliative radiation therapy in patients with metastatic melanoma	Retrospective evaluation Treatment (most patients): TD 30 or 20 Gy, fraction size 3 or 4 Gy	28 patients, 35 sites, bone and soft tissue metastases n=20, brain metastases n=8	Response	Clinical response bone metastases 67%	Response was defined as relief of symptoms Lack of response and survival data	4
Seegenschmiedt et al. 1999	To analyze different endpoints and prognostic factors in patients with locally advanced, recurrent or metastatic melanoma	Retrospective evaluation Treatment: median TD 48 (range 20 - 66) Gy, fraction size 2–6 Gy	121 patients of a melanoma registry with 2,917 patients Stage IV n=53 (distant LN, SK, ST mets n=7, visceral organ mets n=46)	Response Suvival Rate (mean follow up 7.8 years)	Stage IV (n=53), at 3 months CR n=9 (17%) PR n=17 (32%) NC n=12 (23%) PD n=15(28%) Stage III (n= 57) CR n=25 (44%) PR n=19 (33%) NC n=5 (9%) PD n=8 (14%) Stage IV 6% Stage III 30%)	Detailed analyses, large cohort, Results are reported separately for different stages, stage III includes lymph node and intransit-metastases response was not analyzed separately for node and cutaneous lesions	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Engin et al. 1993	To present the experience with hyperthermia combined with radiation in advanced melanoma patients between 1980-1988	Retrospective evaluation Treatment: RT mean TD 37 (range 13 - 66) Gy, mean fraction size 3.6 Gy (range 2 - 5.5) combined with hyperthermia	40 melanoma patients with 48 lesions, Stage IV lesions n=26	Response	Evaluable lesions (n=33) CR n=12 (36%) PR n=17 (52%)	WHO/UICC criteria were used to assess tumor response	4
Pyrhönen et al. 1992	To present 15 patients with histologically proven recurrent or metastatic cutaneous melanomas treated with large fractions between April 1987 and May 1991	Case Series Treatment: Electron beams at appropriate energies (6-15 MeV). A total dose of 40 Gy was given in 8 fractions (fraction size 5 Gy) over 23 days.	15 melanoma patients, 89 treated lesions skin n=68 (76%) transplanted skin n=3 (3 %) subcutaneous n=11 (12%) lymph nodes n=7 (8%)	Response	Evaluable lesions (n=89) CR n=61 (69%) PR n=25 (28%) No response n=3 (3%)		4
Herbert et al. 1991	To evaluate the efficacy of palliative radiation therapy in the treatment of spinal cord and cauda equina compression due	Retrospective evaluation Treatment: RT (all patients), decompressive laminectomy (n=11), steroids	35 patients with spinal cord and cauda equina compression, 38 sites treated	Response Median Overall	28 sites (in 26 patients) evaluable CR 11 sites (39%) PR 13 sites (46%) ORR 24 sites (86%) OS all patients: 11	multivariate analysis performed but not presented in detail, small sample size	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	to metastatic malignant melanoma	(n=32) RT: cobalt-60, 6 or 15 MV, median TD 2850 cGy (range, 500 to 4000 cGy), fraction size 200-800 cGy		Survival (OS)	weeks (range 4 – 35 weeks)		
Chadha et al. 1990	To evaluate the role of brachytherapy in the management of locally advanced malignant melanoma.	Retrospective evaluation (1979-1986) Treatment: brachytherapy, temporary and permament implants, different doses	33 melanoma patients with locally advanced disease with/without nodal disease or distant metastases	Local control/Implant site:	33 patients 80% at 6 months 42% at 1 year Extremity vs. Intrathoracic and chest wall vs. Gynecologic & intra-abdominal vs. Head and neck n=13 of 14 vs. n=4 of 9 vs. n=3 of 7 vs. n=0 of 2	Baseline characteristics are not presented in detail, clinical stages not indicated	4
Konefal et al. 1988	To see if the use of larger dose fractions increased the rate of palliation of visceral melanoma	Retrospective evaluation Treatment: TD range <2000 - 5000 cGy, fraction	63 patients, 89 visceral metastases treated, 65 evaluable	Response	40 of 65 lesions (62%) 19 of 28 bone metastases (68%)	response was defined as the significant relief from symptoms for at least 2 months	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases	size < 200 to > 600					
Rate et al. 1988	To present the experience with palliative radiotherapy for malignant melanoma metastatic to brain, to bone, or with spinal cord compression.	Retrospective evaluation Treatment: TD 1100 - 4000 cGy, fraction size 115 cGy - 1100 cGy	26 patients with 39 bone metastases, 17 patients with spinal cord compression	Response	Bone: 33 of 39 lesions (85%) Spinal cord compression: (8/17) 47% Partial palliation 24% (4/17).	response was defined as pain relief	4
Rounsaville et al. 1988	To review the experience of three San Francisco radiation oncology departments	Retrospective evaluation Treatment: TD range 600 – 7700 cGy, fraction size 180 - 1000	81 patients 29 patients (51 sites) with measurable tumor (Lymph node, skin, liver, mucosa, spleen) 15 patients (28 sites) with bone metastes	Response	Measurable tumor: CR 4 of 51 sites (8%) PR 22 of 51 sites (43%) Bone metastases: 24 of 28 sites (86%)	Definition response in bone metastases: marked regression or elimination of pain	4
Mameghan et al. 1988	To assess the acute skin reaction after treatment and to measure the response of the melanoma	Case Series Treatment: Radiotherapy alone (15 lesions) Heat therapy alone	12 melanoma patients with 32 lesions subcutaneous tissue n=26 Lymph node n=5	Response	All lesions (n=32) CR n=14(44%) PR n=10(31%) No response n=2(6%)		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		(6 lesions) Combined radiation and heat therapy (11 lesions)	Cheek n=1		Not evaluable n=6 (19%) Lesions treated with radiotherapy alone (n=15) CR n=8 PR n=2 No response n=1 Not evaluable n=4		
Konefal et al. 1987	To retrospectively analyze the results of 67 cutaneous or lymph node metastatic lesions, focusing on dosetime fractionation and tumor response	Retrospective evaluation (1970-1985) Treatment: TD 18-66 Gy, fraction size 1.5 - 8 Gy, intervals daily to weekly	35 melanoma patients with 67 cutaneous or lymph node metastatic lesions, 30 cutaneous lesions	Response	All lesions (n=67) Overall Tumor Control n=14 CR n=16 PR n=23 No response n=28	Overall tumor control indicates that lesions were controlled at the time of patient´s death or at last follow-up PR was defined as >50% reduction of tumor size	4
Overgaard et al. 1987	To present the experience with hyperthermia and radiotherapy in metastatic melanoma patients	Retrospective evaluation Treatment: - Radiation alone (TD 15-30 Gy) n=62 sites - Simultaneous heat plus radiation	36 patients, many patients with disseminated disease, 118 lymph node and cutaneous metastases	Response	102 lesions evaluable CR n=57 (56%) PR n=32 (31%) NR n=13 (13%)	Patient baseline characteristics are missing, no response data available for tumors treated with radiation alone. PR was defined as	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		n=26 - Sequential radiation plus heat n=27 - heat alone n=3				>50% reduction of tumor size	
Overgaard et al. 1986	Some factors of importance in the radiation treatment of malignant melanoma	Retrospective evaluation Treatment: TD median 40 Gy, range 8-77, fraction size median 5 Gy, range 2 – 11, number of fractions median 10, range 1-27.	204 cutaneous or lymph node lesions in 114 patients with recurrent or metastatic melanoma, 45 patients with only local or regional disease	Local tumor control 3 year survival	45 patients with regional disease n=26 of 45 (58%) 56%	Baseline characteristics are not presented in detail, clinical stages not indicated, response for node and cutaneous lesions was not analyzed separately	4
Blake et al. 1985	Treatment of malignant melanoma by fast neutrons	Retrospective evaluation Treatment: 75 MeV neutron beam, TD 156O or 1395 cGy in 12 or 6 fractions	48 patients, 87 primary, recurrent or metastatic tumors	Response Recurrence Complications	All sites n= 87 CR n=62 (71%) n=8 (9%) n=19 (22%)	Baseline characteristics are not presented in detail, clinical stages not indicated, response for primary, recurrent or metastatic lesions was not analyzed	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						separately	
Khan et al. 1984	To evaluate the results of different modes of treatment the records of 182 melanom patients, referred to the Regional Radiotherapy Centre, Newcastle upon Tyne between January 1975 and December 1980 have been reviewed	Retrospective evaluation Treatment: external beam radiotherapy (collimated beam from cobalt-60 and caesium-137 teletherapy units, or 100-250 keV or 4-8 MeV X-rays) different fractionation regimes and tumor doses	63 melanoma patients (42 Stage 2, 21 Stage 3) with 74 sites of disease (skin and lymph nodes, 58; bone, 8; brain, 8)	Response Duration of remission	Overall response rate 73% CR 47% PR 26% Sites with skin and lymph node metastases (58): CR 35 (60%) PR 8 (14%) Bone metastases (8): CR 0 PR 6 (75%) Median duration of remission 7 months (range 1-72)		4
Johanson et al. 1983	To report the the experience of the Princess Margaret Hospital with large dose per fraction (800 rad) radiotherapy in the curative and	Retrospective evaluation (1975-1980) Treatment: TD 2400 rad, fraction size 800 rad, given on day 0, day 7,	23 patients with recurrent melanoma	Response	n= 23 patients CR, no local recurrence n=7 CR, local recurrence n=2 PR n=5 SD n=3	clinical stages not indicated, response was not analyzed separately	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	palliative treatment of nodular melanoma	and day 21			no response n=6		
Doss et al. 1982	To review the institutional experience	Retrospective evaluation Treatment: TD range 500 to <4500 cGy, fraction size 100 - 1250	27 patients, 41 lesions	Response	CR 15/41 (37%)	Definition complete response: disappearance of measurable lesions, symptoms ceased within 2 months after RT	4
Adam et al. 1982	Response rate of malignant melanoma to large fraction irradiation		22 patients, 24 sites, visceral sites n=2				
Katz et al. 1981	To determine if results in the irradiation of soft tissue, visceral, and bone metastases were comparable to those previously reported in the literature	Retrospective evaluation Treatment: TD range 1000 to 6000 rad, fraction size 200 – 1000 rad	86 patients 16 patients with visceral metastases (20 lesions) 32 patients with bone metastases (48 lesions) 8 patients with skin metastases (14 lesions)	Response	Visceral lesions 13 of 20 lesions (65%) Bone lesions 37 of 48 lesions (77%)	Definition response: subjective decrease in bone pain, reduction in size to a degree which significantly relieved the local tumor-associated symptoms	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Lobo et al. 1981	To evaluate the experience in the radiotherapeutic management of patients with malignant melanoma	Retrospective evaluation Treatment: (bone lesions) TD range 2700-3000 rad, fraction size 300 rad	45 patients, 69 lesions Bone n=22, lung n=3, liver n=3	Response	bone: 15 of 22 (68%) lung: 1 of 3 liver 0 of 3	Response was defined as improvement of symptoms	4
Strauss et al. 1981	To evaluate clinical responses of metastatic melanoma to four radiation dose fractionation schemes.	Retrospective evaluation Treatment: fraction size 180 rad to 800 rad	48 patients, 83 sites	Response	Soft tissue:29 of 46 sites (63%) Bone: 7 of 9 sites	Response was defined as improvement of symptoms	4

9.2.4.1.1. Literatur

Adam JS, Habeshaw T, Kirk J. Response rate of malignant melanoma to large fraction irradiation. Br J Radiol 1982;55:605-607
Blake PR, Catterall M, Errington RD. Treatment of malignant melanoma by fast neutrons. Br J Surg 1985;72:517-519
Chadha M, Hilaris B, Nori D, et al. Role of brachytherapy in malignant melanoma: a preliminary report. J Surg Oncol 1990;43:223-227
Doss LL, Memula N. The radioresponsiveness of melanoma. Int J Radiat Oncol Biol Phys 1982;8:1131-1134
Engin K, Tupchong L, Waterman FM, et al. Hyperthermia and radiation in advanced malignant melanoma. Int J Radiat Oncol Biol Phys 1993;25:87-94
Herbert SH, Solin LJ, Rate WR, et al. The effect of palliative radiation therapy on epidural compression due to metastatic malignant melanoma. Cancer 1991;67:2472-2476
Johanson CR, Harwood AR, Cummings BJ, et al. 0-7-21 Radiotherapy in Nodular Melanoma. Cancer 1983;51:226-232
Katz HR. The results of different fractionation schemes in the palliative irradiation of metastatic melanoma. Int J Radiat Oncol Biol Phys 1981;7:907-911
Khan MS, Ross WM. Management of malignant melanoma: a retrospective analysis of 182 patients. Clin Radiol 1984;35:151-154
Kirova YM, Chen J, Rabarijaona LI, et al. Radiotherapy as palliative treatment for metastatic melanoma. Melanoma Res 1999;9:611-613
Konefal JB, Emami B, Pilepich MV. Analysis of dose fractionation in the palliation of metastases from malignant melanoma. Cancer 1988;61:243-246
Konefal JB, Emami B, Pilepich MV. Malignant melanoma: analysis of dose fractionation in radiation therapy. Radiology 1987;164:607-610
Lobo PA, Liebner EJ, Chao JJ, et al. Radiotherapy in the management of malignant melanoma. Int J Radiat Oncol Biol Phys 1981;7:21-26
Mameghan H, Knittel T. Response of melanoma to heat and radiation therapy--a review of the literature and experience from The Prince of Wales Hospital, Sydney. Med J Aust 1988;149:474-6, 478-81
Overgaard J, Gonzalez Gonzalez D, Hulshof MC, et al. Hyperthermia as an adjuvant to radiation therapy of recurrent or metastatic malignant melanoma. A multicentre randomized trial by the European Society for Hyperthermic Oncology. 1996. Int J Hyperthermia 2009;25:323-334
Overgaard J, Overgaard M. Hyperthermia as an adjuvant to radiotherapy in the treatment of malignant melanoma. Int J Hyperthermia 1987;3:483-501

Overgaard J, Overgaard M, Hansen PV, et al. Some factors of importance in the radiation treatment of malignant melanoma. Radiother Oncol 1986;5:183-192
Pyrhonen SO, Kajanti MJ. The use of large fractions in radiotherapy for malignant melanoma. Radiother Oncol 1992;24:195-197
Rate WR, Solin LJ, Turrisi AT. Palliative radiotherapy for metastatic malignant melanoma: brain metastases, bone metastases, and spinal cord compression. Int J Radiat Oncol Biol Phys 1988;15:859-864
Richtig E, Ludwig R, Kerl H, et al. Organ- and treatment-specific local response rates to systemic and local treatment modalities in stage IV melanoma. Br J Dermatol 2005;153:925-931
Rounsaville MC, Cantril ST, Fontanesi J, et al. Radiotherapy in the management of cutaneous melanoma: effect of time, dose, and fractionation. Front Radiat Ther Oncol 1988;22:62-78
Seegenschmiedt MH, Keilholz L, Altendorf-Hofmann A, et al. Palliative radiotherapy for recurrent and metastatic malignant melanoma: prognostic factors for tumor response and long-term outcome: a 20-year experience. Int J Radiat Oncol Biol Phys 1999;44:607-618
Strauss A, Dritschilo A, Nathanson L, et al. Radiation therapy of malignant melanomas: an evaluation of clinically used fractionation schemes. Cancer 1981;47:1262-1266

9.2.4.2. Aktualisierungsrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bostel, T., et al., 2016	To evaluate the stability of spinal metastases in malignant melanoma patients following RT	Retrospective study, number of patients n= 41	Patients with spinal metastases, irradiated at University Clinics of Heidelberg and Mainz between July 2003 and October 2013	Overall Survival	5-year OS was 23.3% and median bone survival was 4 month. Only 36.6% of the patients were still alive 6 months after RT.		3a
Chandra, R.A., et al., 2015	To systematically evaluate abscopal responses to radiotherapy in a large cohort of patients at our institution who had metastatic melanoma treated with ipilimumab	Retrospective study, number of patients n= 47	Metastatic melanoma patients treated with ipilimumab and receiving RTX	OS Treatment response	Median survival was 28 months, with an estimated 20% 5-y survival. Index lesions shrank in 7 instances prior to radiation therapy (11%), compared with 16 instances (25%) after radiation therapy; in 11 of the latter		3a

					instances (69%), the index lesion had been increasing in size prior to radiotherapy		
Grimaldi, A.M., et al., 2014	To analyse the outcome of patients with advanced melanoma treated with ipilimumab followed by radiotherapy (RT)	Retrospective study, number of patients n= 21	Metastatic patients receiving ipilimumab followed by RT	CR (%) PR (%) SD (%) OS	Abscopal response was observed in 11 patients (52%), 9 of whom had partial responses (43%) and 2 had stable disease (10%). The median time from RT to an abscopal response was 1 month. Median OS for all 21 patients was 13 months. Median OS for patients with abscopal responses was extended to 22.4 months vs. 8.3 months without.		3a
Hecht, M., et al., 2015	To provide a reliable data on the frequency and	Retrospective study, number of patients n=161	Melanoma patients treated with whole-brain radiation	Safety / Frequency of adverse events	With radiotherapy and concomitant BRAF inhibitor	Multicentric analysis	3a

	severity of radiosensitizing effects of vemurafenib and dabrafenib in enough patients		with/without BRAF inhibitors between 1998 and 2014		therapy the rate of acute radiodermatitis ≥2° was 36% and follicular cystic proliferation was seen in 13% of all radiotherapies. Non-skin toxicities included hearing disorders (4%) and dysphagia (2%). Following whole-brain radiotherapy, rates of radio-dermatitis ≥2° were 44% and 8% (P < 0.001) for patients with and without BRAF inhibitor therapy, respectively. Concomitant treatment with vemurafenib induced acute radiodermatitis ≥2° more frequently than treatment with dabrafenib		

					(40% versus 26%, P=0.07)		
Qin, R., et al., 2016	To describe outcomes of metastatic melanoma patients receiving radiotherapy and ipilimumab	Retrospective study, number of patients n= 88	Stage 3 (unresectable) or 4 melanoma patients treated with ipilimumab (with or without extracranial RT) from January 2011 to September 2014	OS PFS Survival compared between ablative vs. conventionally fractioned radiotherapy	Overall survival and progression-free survival were not statistically different. Patients receiving ablative RT had none statistically significantly improved median overall survival (19.6 vs 10.2 months), as well as 6-month (95.1% vs 72.7%) and 12-month (79.7% vs 48.5%) survival rates, compared with those treated with conventionally fractionated RT.		3a
Theurich, S., et al., 2016	To test whether the combination of local radiotherapy with ipilimumab seems feasible	Retrospective, multicenter analysis, number of patients n=127	Ipilimumab-treated patients with malignant melanoma	OS	The addition of LPT to ipilimumab significantly prolonged overall survival (OS; median OS 93 vs. 42 weeks,		3a

				Adverse events	unadjusted HR, 0.46; P= 0.0028). Adverse immune-related events were not increased by the combination treatment, and local radiotherapy-induced local toxicities were in most cases mild		

9.2.4.2.1. Literatur

Bostel, T., et al., Stability, prognostic factors and survival of spinal bone metastases in malignant melanoma patients after palliative radiotherapy. Tumori, 2016. 102(2): p. 156-61.
Chandra, R.A., et al., A systematic evaluation of abscopal responses following radiotherapy in patients with metastatic melanoma treated with ipilimumab. Oncoimmunology, 2015. 4(11): p. e1046028.
Grimaldi, A.M., et al., Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. Oncoimmunology, 2014. 3: p. e28780.
Hecht, M., et al., Radiosensitization by BRAF inhibitor therapy-mechanism and frequency of toxicity in melanoma patients. Ann Oncol, 2015. 26(6): p. 1238-44.
Qin, R., et al., Safety and Efficacy of Radiation Therapy in Advanced Melanoma Patients Treated With Ipilimumab. Int J Radiat Oncol Biol Phys, 2016. 96(1): p. 72-7.
Theurich, S., et al., Local Tumor Treatment in Combination with Systemic Ipilimumab Immunotherapy Prolongs Overall Survival in Patients with Advanced Malignant Melanoma. Cancer Immunol Res, 2016. 4(9): p. 744-54.

9.3. Frage VIII.4. Radiotherapie und Chirurgie Hirnmetastasen

Frage VI.4. Wie ist der Einfluss unterschiedlicher Behandlungsmodalitäten und deren Kombinationen (Operation, Ganzhirnbestrahlung, Einzeitbestrahlung) auf das Gesamtüberleben, die lokale Kontrolle, die intrakranielle Kontrolle, Verlängerung der symptomfreien Zeit und Lebensqualität bei Patienten mit cerebralen Metastasen?

9.3.1. PICO, Suchwörter

PICO - Schema			
Population	**Intervention**	**Comparison**	**Outcome**

Melanoma patients with cerebral metastases	Radiotherapy, surgery, stereotactic radiosurgery, combinations	no therapy	OS, local control, time without symptoms, QoL

Suchwörter				
Stichwort	Melanoma	radiotherapy	surgery	brain
Synonyme		Radiation, irradiation	resection, excision	Cerebral CNS Central Nervous System
Ober-/Unterbegriffe		Stereotactic radiosurgery		
Mesh Term	melanoma	radiotherapy, radiation		

9.3.2. Datenbanken, Suchstrategien, Trefferzahlen

9.3.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] OR radiation[tiab] OR radiation[MeSH] OR “Irradiation”[tiab] OR Stereotatic[tiab] OR radiosurgery[tiab] OR surgery[tiab] OR resection[tiab] OR excision[tiab]) AND (brain[tiab] OR cerebral[tiab] OR CNS[tiab] OR "Central Nervous System"[tiab])	19.09.11	874 (Auswahl 64)

Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation or stereotatic or radiosurgery or surgery or resection or excision) and (brain or cerebral or CNS)).ti,ab.	19.09.11	10 (Auswahl: Mornex, Dublette, zusätzliche Auswahl 0)
Embase	(melanoma and (radiotherapy or radiation or irradiation or stereotatic or radiosurgery or surgery or resection or excision) and (brain or cerebral or CNS)).ti,ab.	10.05.11	823 (zusätzliche Auswahl 0)
Update Suche			
Medline	s.o.	31.01.12	889 (0 dazu)
Cochrane Library	s.o.	31.01.12	10 (0 dazu)
Embase	s.o.	23.01.12	903 (0 dazu)

9.3.2.2. Aktualisierungsrecherche 2015

Datenbank	Suchstrategie	Datum	Treffer
Medline	(((melanoma[tiab] OR melanoma[MeSH]) AND (radiotherapy[tiab] OR radiotherapy[MeSH] ORradiation[tiab] OR radiation[MeSH] OR “Irradiation”[tiab] OR Stereotatic[tiab] OR radiosurgery[tiab] OR surgery[tiab] OR resection[tiab] OR excision[tiab]) AND (brain[tiab] OR cerebral[tiab] OR CNS[tiab] OR "Central Nervous System"[tiab]))) AND ("2011.09.20"[Date - Publication] : "2015.09.16"[Date - Publication])	16.09.2015	246
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation or stereotatic or radiosurgery or surgery or resection or excision) and (brain or cerebral or CNS)).ti,ab.	16.09.2015	39

9.3.2.3. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer (Auswahl)
1. Suche			
Medline	(((advanced OR disseminated) AND melanoma[tiab] AND radiation)) AND ("2015/01/01"[Date - Entrez] : "2016/09/16"[Date - Entrez])	16.09.2016	108
Cochrane Library	(advanced or disseminated) and melanoma and Radiation	16.09.2016	93 (0)

9.3.3. Auswahlkriterien

9.3.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	1802
Einschlusskriterien	Studien, die mind. einen der Parameter Gesamtüberleben, lokale Kontrolle, symptomfreie Zeit oder Lebensqualität bei Melanompatienten nach Radiotherapie oder Operation von Hirnmetastasen beschreiben Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitiäten
Erweitertes Ausschlusskriterium	Studien ohne Vergleichsgruppe Retrospektive Kohortenstudie ohne Multivariatanalyse Publikation vor 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	64

Auswahl der Literatur	
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	57
Anzahl ausgewählter Volltexte	7

9.3.3.2. Aktualisierungsrecherche 2015

Auswahl der Literatur	
Gesamttreffer	285
Einschlusskriterien	Studien, die mind. einen der Parameter Gesamtüberleben, lokale Kontrolle, symptomfreie Zeit oder Lebensqualität bei Melanompatienten nach Radiotherapie oder Operation von Hirnmetastasen beschreiben RCTs Systemische Reviews Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitiäten Non-RCTs
Erweitertes Ausschlusskriterium	Studien ohne Vergleichsgruppe Retrospektive Kohortenstudie ohne Multivariatanalyse Publikation vor 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	64
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	57
Anzahl ausgewählter Volltexte	3

9.3.3.3. Aktualisierungsrecherche 2016

Auswahl der Literatur	
Gesamttreffer	647
Einschlusskriterien	Mangels RCT´s Einschluss von Kohortenstudien und Fallserien ab 20 Patienten Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kombinationstherapien Arbeiten zu RT von nicht invasiven Melanomen (Melanoma in situ/Lentigo maligna) Kollektive mit gemischten Tumorentitäten Arbeiten älter als 2014
Anzahl nach Abstractscreening, vorgesehen für Bewertung	43
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	21
Anzahl ausgewählter Volltexte	4

9.3.4. Evidenztabelle

9.3.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Eigentler et al. 2011	To identify prognostic factors in patients with brain metastases (BM) from	Retrospective survival analysis Treatment: SRS + Surgery	692 patients	Median Survival (from date of diagnosis of brain metastases)	Entire cohort (n=672) 5 months SRS + Surgery vs.	Retrospective study large cohort SRS vs. Surgery was not compared	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	malignant melanoma	(n=122) WBRT + Chemotherapy (n=92)			WBRT + Chemotherapy Single BM: 9 vs. 6 months, p=0.036 <3 BM: 6 vs. 7 months, p=0.448 <u>multivariate analysis</u> independent prognostic factors - entire cohort: single vs. multiple BM, HR 1.6, 95% CI 1.3-2.7, p=0.002 LDH not elevated vs. elevated, HR 1.6, 95% CI 1.1-2.4, p=0.01 - Single BM: SRS or surgery vs. WBRT and/or chemotherapy, HR 1.5, 95% CI 1.1-1.9, p=0.0061	Funding: in part by an educational grant from Essex/Schering-Plough.	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Staudt et al. 2010	To identify prognostic factors in patients with brain metastases from cutaneous melanoma	Retrospective survival analysis Treatment: Surgery (n=63) SRS (n=31) WBRT (n=122) chemotherapy (n=28) no therapy (n=12)	265 patients 36.7% had local treatment (neurosurgery or stereotactic radiosurgery (SRS)	Median Survival (from date of diagnosis of brain metastases)	Entire cohort (n=265) 5 months, 95% CI 4.3–5.7 months surgery vs. SRS vs. WBRT vs. chemotherapy vs. no therapy 9 vs. 9 vs. 4 vs. 3 vs. 1 month(s) <u>multivariate analysis</u> independent favourable prognostic factors: LDH level, type of therapy, number of brain metastases, presence of bone metastasis surgery (n=63) vs. SRS (n=31): HR 1.0, 95% CI 0.6 – 1.8	Retrospective study detailed data, few missing cases follow up time not mentioned (but at time of analysis already 253 deaths) Funding: not mentioned	3b
Raizer et al. 2008	To gain a better understanding of patient and disease	Retrospective survival analysis Treatment:	355 patients	Median Survival (from date of diagnosis of brain metastases)	Entire cohort (n=335) 5.2 months (range 0.1 – 155 months)	Retrospective study Median follow up	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	characteristics that have the greatest impact on overall survival in melanoma patients with brain metastases	Surgery (n=126) SRS (n=78) Temozolomide (n=113) WBRT (n=190)			surgery vs. SRS vs. Temozolomide vs. WBRT 9.3 vs. 10.0 vs. 7.9 vs. 6.1 months multivariate analysis surgery: RR 0.56, 95% CI 0.43 – 0.75 SRS: RR 0.69, 95% CI 0.50 – 0.94	among surviving patients 18.4 months Funding: Schering-Plough International	
Fife et al. 2004	To analyze prognostic factors, effects of treatment, and survival for patients with cerebral metastases from melanoma.	Retrospective survival analysis Treatment: surgery+RT (n=158) surgery (n=47) radiotherapy (n=236) supportive care alone (n=210)	1137 patients with cerebral metastases; 686 with therapy	Median survival (from date of diagnosis of brain metastases)	Entire cohort (n=1137) 4.1 months (range, 0 to 17.2 years) Surgery+RT vs. surgery vs. RT vs. supp.care 8.9 vs. 8.7 vs. 3.4 vs. 2.1 months multivariate analysis Prognostic factors: surgical treatment	Retrospective study Large cohort results of univariate analyses not shown, only 578 of 686 patients included missing data not adressed Funding: Supported by the Melanoma Foundation of the University of Sydney and the	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(p<0.0001), no concurrent extracerebral metastases (p<0.0001), younger age (p=0.0007), longer disease-free interval (p=0.036)	Melanoma and Skin Cancer Research Institute	
Mornex et al. 2003	To compare a combined regimen of fotemustine plus whole brain irradiation with fotemustine alone	RCT Treatment: Group A: Fotemustine (n = 39) Group B: fotemustine + WBRT (n = 37)	76 patients	Median survival cerebral response after 7 weeks control rates (objective responses + stable disease) after 7 weeks time to cerebral progression	Group A vs. B (ITT population) 86 days (2.8 months) vs. 105 days (3.4 months) n.s. 5.1% (95% CI 1–17%) vs. 8.1% (95% CI 2–22%), p=0.60 23.1% (95% CI 10–36%) vs. 37.8% (95% CI 22–54%), p=0.16 49 days (1.6 months) vs. 80 days (2.6 months),	Early termination of study, small sample size Independent tumor assessment Funding: not mentioned	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					p=0.030		
Wronski et al. 2000	To review the surgical experience in a series of patients with brain metastases from primary melanoma	Retrospective survival analysis Treatment: Surgery alone (n=29) Surgery + WBRT (n=49)	91 patients	Median survival following craniotomy survival rates 1 year 2 years 3 years 5 years	Entire cohort (n=91) 6.7 months 36.3% 18.7% 13.2% 6.6% Surgery alone (n=29) vs. Surgery+WBRT (n=49) 8.3 vs. 9.5 months, p = 0.67 <u>multivariate analysis</u> negative impact on survival: lack of resection of recurrent brain tumor (p =0.0003) and infratentorial location of brain metastases (p = 0.0013)	Retrospective study, small sample size, results of multivariate analyses not presented in detail Funding: not mentioned	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Stevens et al. 1992	To analyze factors affecting survival in 129 patients with cerebral metastases from malignant melanoma	Retrospective survival analysis Treatment: Radiotherapy (n=74) Surgery + Radiotherapy (n=45)	129 patients	Median survival after detection of cerebral metastases	Entire cohort (n=127) 5 months Radiotherapy vs. Surgery + Radiotherapy 4 vs. 9 months (p<0.001) multivariate analysis Independently associated with a prolonged survival: Surgery, p=0.004	Retrospective study, multivariate analysis not presented in detail Funding: not mentioned	3b

Ausgeschlossene Studien

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*LoE*
Lonser et al. 2011	*to determine the effectiveness of resection and the effects of immunotherapy on brain metastasis management*	*Retrospective analyses* *Treatment: Surgery, Immunotherapy, whole brain radiation*	*41 patients*		*Duration of survival from brain metastasis diagnosis was not significantly different between patients who received WBRT (mean 24.9 months) and those*	*Combination with Immunotherapy → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					who did not (mean 23.3 months) (p > 0.05)		
Salvati et al. 2011	*To report on 84 patients with single melanoma brain metastasis surgically treated from 1997 to 2007*	*Retrospective analysis* *Treatment: Surgery*	*84 patients with single melanoma brain metastasis*	*1-year survival rate* *2 years survival rate*	*52% (32 patients)* *14% (12 patients)*	*Lack of comparison group → study excluded*	
Skeie et al. 2011	*To review a series of patients who underwent Gamma Knife surgery (GKS)*	*Retrospective analysis* *Treatment: Gamma Knife*	*77 patients with a total of 143 metastases*	*Growth control* *median survival after GKS*	*59 of 70 (84.3%) patients* *7 months (range 0-73 months)*	*Lack of comparison group → study excluded*	
Rades et al. 2010	*To investigate a potential benefit from escalation of the whole-brain radiotherapy (WBRT) dose beyond the "standard" regimen 30 Gy in 10 fractions*	*Retrospective analysis, Cohort study* *Treatment: WBRT* *10x3 Gy (n = 33)* *40 Gy/20 fractions (n = 11)* *45 Gy/15 fractions (n = 7)*	*51 patients*	*6 months survival (OS)* *12 months OS* *6 months local (intracerebral) control (LC)* *12 months LC*	*Standard vs. high dose* *27% vs. 50% (p = 0.009)* *4% vs. 20%* *23% vs. 50%* *0% vs.13%.*	*Lack of comparison group → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Redmond et al. 2008	*To investigate which patient- or treatment-specific factors influence survival of patients with melanoma brain metastases*	*Retrospective analysis, Prognosis study* *Treatment:* *GKS*	*59 patients*		*Survival was significantly better in patients with solitary metastasis (p = 0.04), lesions without evidence of pre-GKS hemorrhage (p = 0.004), and in patients with total tumor volume treated < 4 cm(3) (p = 0.02)*	*Lack of comparison group → study excluded*	
Mathieu et al. 2007	*to assess clinical outcomes and identify prognostic factors for survival and cerebral disease control after Gamma knife radiosurgery*	*Retrospective analysis, Prognosis study* *Treatment:* *GKS*	*244 patients*	*median survival* *Sustained local control*	*5.3 months* *86.2% of tumors*	*Lack of comparison group → study excluded*	
Hofmann et al. 2007	*To examine prognostic factors and the evaluation of different treatment options*	*Retrospective survival analysis* *Treatment:* *Surgery (n=34)* *SRS (n=43)* *WBRT (n=33)* *corticosteroids*	*133 patients*	*Median Survival (from date of diagnosis of brain metastases)*	*Entire cohort (n=133)* *24 weeks (5.1 months) (range 1–196 weeks)* *surgery vs. SRS vs. WBRT vs.*	*univariate analysis is missing, small sample size → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		(n=63)			*corticosteroids: 57 vs. 40 vs. 24 vs. 17 weeks*		
Samlowski et al. 2007	*To report a retrospective analysis of our institutional experience of multimodality treatment utilizing linear accelerator (Linac)-based stereotactic radiosurgery (SRS)*	*Retrospective analysis* *Treatment: stereotactic radiosurgery (SRS)*	*44 patients*	*median survival with brain metastases* *1-year survival* *2-year survival*	*11.1 months (95% confidence interval [CI]: 8.2-14.9 months) from diagnosis* *47.7%* *17.7%* *Addition of WBRT to maintain control of brain metastases in a subset of patients did not improve survival*	*Lack of comparison group → study excluded*	
Christopoulou et al. 2006	*To investigate the effect of gamma knife surgery on the local control of cerebral metastases from melanoma and to assess survival*	*Retrospective analysis* *Treatment: GKS*	*29 patients*	*local control* *median survival*	*61.5% of 96 metastases regressed by more than 50% of the pretreatment volume, 25% regressing by more than 90% and 13.5% completely* *5.7 months*	*Lack of comparison group → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				from gamma knife surgery			
Gaudy-Marqueste eta l. 2006	*To assess retrospectively a strategy that uses Gamma-Knife radiosurgery in the management of patients with brain metastases of malignant melanoma*	*Retrospective analysis* *Treatment: GKS*	*106 patients, 221 brain metastases*	*Median survival from the time of GKR* *Control rate* *complete response* *partial response* *stabilization*	*5.09 months* *83.7%* *14% (14 BMs)* *42% (41 BMs)* *43% (43 BMs)*	*Lack of comparison group → study excluded*	
Koc et al. 2005	*To evaluate retrospectively the effectiveness of Gamma Knife radiosurgery for intracranial metastatic melanoma and to identify prognostic factors related to survival*	*Retrospective analysis* *Treatment: GKS*	*26 patients, 72 brain metastases*	*Overall median survival after GKS* *1-year survival*	*6 months* *25%*	*Lack of comparison group → study excluded*	
Meier et al. 2004	*to determine the factors influencing survival in a retrospective review of patients*	*Retrospective survival analysis* *Treatment: WBRT (n=54)*	*100 patients*	*median overall survival* *6-month survival*	*Entire cohort (n=100)* *4.8 months* *36%*	*< 20 patients in one of the treatment groups → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with melanoma brain metastases to permit more specific recommendations regarding therapy	*surgery (n=37) SRS (n=17) chemotherapy (n=38)*		*1-year survival 2-year survival*	*14% 5% WBRT vs. surgery vs. radiosurgery vs. chemotherapy vs. temozolomide 5.5 vs. 10.6 vs. 10.3 vs. 6.6 vs. 10.1 months*	*Only 63 patients included in multivariate analysis due to missing data*	
Morris et al. 2004	*To determine the outcome of patients with metastatic malignant melanoma (MMM) treated with palliative whole brain radiotherapy (WBRT)*	*Retrospective analysis Treatment: WBRT*	*112 patients*	*median survival after WBRT*	*51 days (range 3-1386)*	*Lack of comparison group → study excluded*	
Radbill et al. 2004	*To identify associated prognostic indicators for patients receiving gamma knife (GK) radiosurgery in the initial treatment of*	*Retrospective analysis Treatment: GKS*	*51 patients, 188 brain metastases*	*median overall survival from time of GKS*	*26 weeks Subgroup analysis: 77 weeks for patients presenting with a single lesion, compared with 20 weeks for*	*Lack of comparison group → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	intracranial melanoma metastases				*patients presenting with multiple lesions (P = 0.003)*		
Stone et al. 2004	*To evaluate overall survival in patients with brain metastases from malignant melanoma*	*Retrospective survival analysis* *Treatment:* *SRS+WBRT (n=8)* *Surgery + WBRT (n=16)* *WBRT (n=59)*	*91 patients*	*Overall Survival*	*A survival benefit of 7.3 months (p = 0.05) was found to be associated with gamma knife radiosurgery or surgical excision plus radiation therapy over radiation therapy alone after controlling for differences in age, number of brain lesions, and presence of symptoms.*	*< 20 patients in one of the treatment groups → study excluded*	
Selek et al. 2004	*To report on the outcome of patients with melanoma brain metastases treated with stereotactic radiosurgery (SRS)*	*Retrospective analysis* *Treatment:* *SRS alone (61 patients), SRS + whole-brain radiotherapy (WBRT) (12*	*103 patients, 153 intracranial melanoma metastases*	*1-year local control (LC) for all patients treated with SRS*	*49%*	*< 20 patients in one of the treatment groups → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		patients), and salvage SRS after WBRT (30 patients)					
Herfarth et al. 2003	*Stereotactic radiosurgery is an alternative option to neurosurgical excision in the management of patients with brain metastases.*	*Retrospective analysis* *Treatment: Stereotactic radiosurgery*	*64 patients, 122 brain metastases*	*Median survival* *1 year local control*	*10.6 months* *81%*	*Lack of comparison group → study excluded*	
Buchsbaum et al. 2002	*To determine whether various therapies provided any benefit at all in a population of patients with brain metastases from melanoma*	*Retrospective analysis* *Treatment: surgical resection, WBRT, stereotactic radiosurgery, or WBRT combined with local therapy*	*74 patients with brain metastases*	*median survival was for all patients*	*5.5 months* *combined treatment offered significantly better survival (P < 0.0001; combined vs. other)* *median survival was 8.8 months (range, 1.8-99.2 months) for the combined therapy group, 4.8 months (range, 1.2-27.8 months) for the local therapy alone*	*< 20 patients in one of the treatment groups → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					group, 2.3 months (range, 0.2-9.6 months) for the WBRT alone group, and 1.1 months (0.1-3.0 months) for the group that received no therapy		
Gonzales-Martinez et al. 2002	to evaluate retrospectively the effectiveness of stereotactic radiosurgery for intracranial metastatic melanoma and to identify prognostic factors	Retrospective analysis Treatment: stereotactic radio surgery	24 patients, 115 lesions	mean survival after radiosurgery	5.5 months no difference in terms of survival between patients who underwent WBRT or chemotherapy and those who did not significant difference ($p < 0.05$) in mean survival was observed between patients receiving immunotherapy or those with a Karnofsky Performance Scale (KPS) score of	Lack of comparison group → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					greater than 90		
Mingione et al. 2002	To evaluate the usefulness and limitations of gamma surgery in the treatment of brain metastases from melanoma.	Retrospective analysis Treatment: GKS	45 patients, 92 brain metastases	Follow-up imaging studies available: 35 patients, 66 lesions	24% percent of the lesions disappeared, 35% shrank, 23% remained unchanged, and 18% increased in size.	Lack of comparison group → study excluded	
Noel et al. 2002	To evaluate the efficacy and toxicity of stereotactic radiotherapy in the treatment of brain metastases of melanoma.	Retrospective analysis Treatment: stereotactic radiotherapy	25 patients, 61 metastases	Median survival overall survival rates 3- month 6- month 12-month Progression local control rates 3- month 6- month 12-month	8 months 75 +/- 9% 53 +/- 10% 29 +/- 10% n=5 (9.8%) 95 +/- 3% 90 +/- 5% 84 +/- 7%	Lack of comparison group → study excluded	
Yu et al. 2002	To identify important prognostic factors predictive of survival and tumor	Retrospective analysis Treatment: GKS	122 patients, 332 intracranial melanoma metastases	median overall survival from time of radiosurgery	7.0 months	Lack of comparison group → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	control in patients with metastatic melanoma to the brain who underwent gamma knife radiosurgery						
Zacest et al. 2002	*to review the outcome of patients who underwent surgery for treatment of cerebral metastatic melanoma*	*Retrospective analysis* *Treatment: surgery*	*147 patients*	*median survival from the time of surgery*	*8.5 months*	*Lack of comparison group → study excluded*	
Ellerhorst et al. 2001	*To obtain a description of the population offered WBRT*	*Retrospective analysis* *Treatment: WBRT*	*87 patients*	*median survival*	*19 weeks*	*Lack of comparison group → study excluded*	
Konstadoulakis et al. 2000	*To evaluate the prognostic parameters and treatment modalities of malignant melanoma patients with brain metastases*	*Retrospective analysis* *Treatment: Surgery surgery + radiotherapy (n=2) surgery + chemotherapy*	*136 patients*	*1-year survival rate*	*surgery 28.3% radiotherapy and/or chemotherapy 6.67% no treatment 3.45% (p=0.006)*	*Subgroups < 20 patients→ study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		(n=17)					
Lavine et al. 1999	To analyze the effectiveness of Leksell gamma unit therapy for metastatic melanoma to the brain	Retrospective analysis Treatment: GKS	45 patients, 59 Leksell gamma unit treatment sessions	Median overall survival from the time of gamma knife treatment improved or stable neurological symptomatology local tumor control rate	8 months (range, 1-20 months) 78% 97%	Lack of comparison group → study excluded	
Friehs et al. 1998	To determine the effectiveness of gamma knife radiosurgery in patients with malignant melanoma metastases	prospective multicenter study Treatment: GKS	45 patients, 96 lesions	median overall survival tumor control	4.2 months 86% of lesions	Lack of comparison group → study excluded	
Sampson et al. 1998	To identify demographic factors associated with the development of clinically significant brain metastases in 702	Retrospective survival analysis Treatment: Surgery (n=52) Surgery+WBRT (n=87) WBRT (n=180)	702 patients	median overall survival	Entire cohort (n=702) 3.7 months surgery vs. surgery+WBRT vs. WBRT vs. chemotherapy:	no multivariate analysis included → study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	of these patients and to determine the factors influencing the prognosis of this population to permit more informed recommendations regarding surgical therapy	*Chemotherapy (n=205) Symptomatic treatment (n=178)*			*8.8 vs. 6.4 vs. 3.9 vs. 1.3 months*		
Fletcher et al. 1998	*To reviewe the results of surgical resection*	*Retrospective analysis* *Treatment: surgery*	*77 patients, different sites, brain n = 12*			*<20 patients with brain metastases → study excluded*	
Grob et al. 1998	*To evaluate the effectiveness of radiosurgery without whole brain radiotherapy in the palliative treatment of melanoma brain metastases*	*Retrospective analysis* *Treatment: radiosurgery*	*35 patients*	*Median overall survival* *local control rate at 3 months*	*22 months (solitary brain metastasis) 7.5 months (single brain metastasis + metastases elsewhere) 4 months (multiple brain metastases) 98.2% (55/56 metastases)*	*Lack of comparison group → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Mori et al. 1998	*To evaluate results after stereotactic radiosurgery (SR) for patients with metastastic melanoma to identify patient outcomes and factors for survival*	*Retrospective analysis* *Treatment:* *SR alone n=9* *SR+WBRT n=51*	*60, 118 melanoma brain metastases*	*Median survival after SR* *local control rate of evaluable tumors (n = 72)* *disappearance* *shrinkage* *stable*	*7 months* *90%* *11%* *44%* *35%*	*< 20 patients in one of the treatment groups → study excluded*	
Seung et al. 1998	*To evaluate the efficacy and toxicity of gamma knife radiosurgery in the treatment of melanoma metastases to the brain*	*Retrospective analysis* *Treatment:* *GKS*	*55 patients, 140 lesions*	*median overall survival*	*35 weeks* *35 weeks for patients with solitary metastases versus 33 weeks for those with multiple metastases*	*Lack of comparison group → study excluded*	
Gupta et al. 1997	*To report the experience of 31 patients who presented with cerebral metastasis of cutaneous melanoma*	*Retrospective analysis* *Treatment:* *Surgery (n=17)* *Surgery + radiotherapy (n=6)*	*31 patients*	*median overall survival*	*4 months*	*< 20 patients in one of the treatment groups → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Gieger et al. 1997	*to determine the radiographic response of intracranial metastatic melanomas to SRS*	*Retrospective analysis* *Treatment: stereotactic radiosurgery*	*12 patients with 21 intracranial melanoma metastases*			*Lack of comparison group → study excluded*	
Isokangas et al. 1996	*To report the long-term results of the irradiation of intracranial malignant melanoma*	*Retrospective analysis* *Treatment: Radiotherapy TD 40 Gy vs. normalized TD at 3 Gy (NTD3Gy) with 30 Gy as cutpoints*	*60 patients*	*median survival*	*4.1 months* *Those with higher total doses to the tumour area had significantly better (P = 0.0006) survival*	*Lack of comparison group → study excluded*	
Skibber et al. 1996	*To evaluate postoperative adjunctive cranial irradiation in 34 patients with solitary brain metastases*	*Retrospective analysis* *Treatment: Surgery alone n=12 Surgery + WBRT n=22*	*34 patients, 34 brain metastases*		*Overall survival was significantly improved in the 22 patients who received adjunctive cranial irradiation versus that in the 12 patients who had surgery alone*	*< 20 patients in one of the treatment groups → study excluded*	
Willner et al. 1995	*To show treatment results and to define prognostic subgroups in*	*Retrospective analysis* *Treatment:*	*30 patients*	*Overall survival rate 6 months 1 year*	*39% 23%*	*Lack of comparison group → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients undergoing radiotherapy for brain metastases from malignant melanoma	*Radiotherapy*					
Somaza et al. 1993	*To determine local tumor control rates and survival of patients with melanoma metastases to the brain*	*Retrospective analysis* *Treatment: stereotactic radiosurgery + WBRT*	*23 patients, 32 tumors*	*median survival period after diagnosis* *local tumor control rate*	*9 months (range 3 to 38 months)* *97%*	*Lack of comparison group → study excluded*	
Davey et al. 1991	*To determine how many patients might be candidates for radiosurgery, a retrospective analysis of computed tomographic brain scans performed on 41 patients with cerebral metastases from malignant melanoma was undertaken*		*41 patients*			*No survival + efficacy data → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Hagen et al. 1990	*To report treatment results of patients with brain metastasis from melanoma*	*Retrospective analysis* *Treatment: Surgery + postoperative radiation n=19* *Surgery alone n=16*	*35 patients*		*Group A had a longer interval to CNS relapse compared with group B, but survival was similar.*	*< 20 patients in one of the treatment groups → study excluded*	
Oredsson et al. 1990		*Retrospective analysis* *Treatment: Surgery*	*40 patients*	*median survival* *3-year survival* *5-year survival* *Neurological improvement* *surgical mortality rate*	*8 months* *25%* *15%* *25 patients* *less than 5%* *Quality of life as judged by Karnofsky index was improved after surgery and maintained on an acceptable level for the remaining time of survival*	*Lack of comparison group → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Guazzo et al. 1989		*Retrospective analysis* *Treatment: Surgery*	*31 patients*	*Significant and life-threatening complications* *relief of symptoms:*	*5 patients (17%)* *64% had complete remission of symptoms while a further 20% were substantially improved*	*Lack of comparison group → study excluded*	
Mendez et al. 1988		*Retrospective analysis* *Treatment: Surgery, Radiotherapy*	*55 patients with neurological signs and symptoms secondary to metastases to the brain*	*6 month survival*	*58% if surgical excision was possible*	*< 20 patients in one of the treatment groups → study excluded*	
Rate et al. 1988	*To review the records of all patients receiving palliative radiotherapy for malignant melanoma metastatic to brain, to bone, or with spinal cord compression*	*Retrospective analysis* *Treatment: Radiotherapy*	*77 patients with brain metastases*	*median survival from the initiation of radiotherapy*	*14 week*	*Lack of comparison group → study excluded*	
Retsas et al. 1988		*Retrospective*	*100 patients*	*Median survival*	*2.5 months*	*Lack of*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		analysis *Treatment: Different treatments*				*comparison group → study excluded*	
Wornom et al. 1986		*Retrospective analysis* *Treatment: surgery*	*65 patients, 94 metastatic lesions (brain, lung, abdomen, distant subcutaneous sites, and distant lymph nodes)*	*Median survival after excision of brain metastases* *Relief of symptoms*	*8 months* *77% of brain metastases*	*Lack of comparison group → study excluded*	
Ziegler et al. 1986	*To examine the records of 72 patients who received various regimens of radiotherapy for cerebral metastases from malignant melanoma*	*Retrospective analysis* *Treatment: WBRT 300 cGy (conventional fractionation, CF) vs. 500-600 cGy (high-dose-per-fraction, HDF) to a total of 3000 cGy*	*72 patients*		*No difference in response could be attributed to dose schedules, either overall or in the subgroups of patients who had solitary or multiple brain metastases*	*Lack of comparison between different treatments → study excluded*	
Choi et al. 1985		*Retrospective analysis* *Treatment:*	*194 patients with intracranial metastatic melanoma*			*Lack of comparison group → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
		WBRT					
Stridsklev et al. 1984	To analyze patients who completed whole-brain irradiation treatment for brain metastases from malignant melanoma	Retrospective analysis Treatment: WBRT	39 patients	Median survival clinical improvement objective regression of the brain metastases	2 months n=21 (53.8%) 6 of 15 evaluable patients (40%)	Lack of comparison group → study excluded	
Madajewicz et al. 1984	To review 8 years of Roswell Park Memorial Institute's (RPMI) experience with the management of malignant melanoma CNS metastases (1972-1980)	Retrospective analysis Treatment: None (n=15) Steroids (n=17) radiotherapy (n=23) surgery (n=20) chemotherapy	125 patients with brain metastases (73% multiple metastases)	median survival	The median survival of the untreated group of patients was 3 weeks as compared with that of 6 weeks for the patients maintained on steroids only, 9 weeks for those who received radiotherapy, 11 weeks for the patients treated with intraarterial chemotherapy, and 26 weeks for the	< 20 patients in one of the treatment groups, no multivariate analysis→ study excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					patients who underwent successful surgical excision of a solitary lesion.		
Byrne et al. 1983		*Retrospective analysis* *Treatment: Group 1, multiple brain metastases treated with radiation therapy (RT) (n = 49)* *Group 2, single brain metastasis treated with RT (n = 17)* *Group 3, single brain metastasis treated with surgery with or without RT (n = 9).*	*81 patients with brain metastasis*	*Median survival*	*Groups 1 vs 2 vs 3* *11, 9 and 41 weeks*	*No multivariate analysis included → study excluded*	
Vlock et al. 1982	*To examine the results in 46 patients treated*	*Retrospective analysis*	*46 patients*		*high-dose fraction group vs. low-dose fraction group*	*Lack of comparison between different*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	with high- or low-dose fractions for intracranial metastases	*Treatment: 26 patients received high-dose fraction therapy, generally 600 rad/fraction/week to 2400--3600 rad; 20 patients received low-dose fraction radiotherapy with 125--400 rad/fraction daily*		*Median survival* *Improvement* *Stability* *deterioration*	*3 months vs. 2 1/2 months* *38 vs. 35%,* *23 vs. 25%* *38 vs. 40%*	*treatments → study excluded*	
Katz et al. 1981	*To records of all patients who received radiotherapy for melanoma metastatic to brain (63 patients*	*Retrospective analysis* *Treatment: corticosteroids, radiotherapy, surgery (n=8)*	*63 patients*	*Response*	*73% to corticosteroids 42% to radiotherapy*	*< 20 patients in one of the treatment groups → study excluded*	
Carella et al. 1980	*To determine the response to whole brain irradiation*	*Retrospective analysis* *Treatment: WBRT*	*60 patients*	*Median survival*	*Study 1 patients 10 weeks (range 1-200) vs. Study II patients 14 weeks (range 1-76)* *significant benefit from radiation therapy in terms of*	*Lack of comparison group → study excluded*	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					symptomatic and neurologic function improvement. Symptomatic improvement was observed in 76%, with 31% completely improved		
Cooper et al. 1980		*Retrospective analysis* *Treatment: WBRT*	*30 patients, 35 courses*		*Marked improvement in neurologic status occurred in approximately 35%. Slight to moderate improvement was evident in an additional 35%.*	*Lack of comparison group → study excluded*	
Hafstrom et al. 1980		*Retrospective analysis* *Treatment: Surgery*	*25 patients*	*median survival*	*5 months*	*Lack of comparison group → study excluded*	
Pennington et al. 1975		*Retrospective analysis* *Treatment:*	*57 patients*			*Publication <1980 → study excluded*	

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*LoE*
		Radiotherapy, chemotherapy, surgery and immunotherapy					

9.3.4.2. Aktualisierungsrecherche 2015

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Fogarty et al. 2015	To analyze the distant intracranial failure on magnetic resonance imaging (MRI) within twelve months of randomization for pts. receiving WBRT vs. observation after local treatment of brain mets.	Randomized controlled trial Treatment: WBRT with at least 30Gy in 10 fractions Vs. Observation	200 pts randomized to WBRT or observation	Proportion of patients with distant intracranial failure as determined by magnetic resonance imaging (MRI) assessment within twelve months of randomization Time to intracranial failure (local, distant and overall) as determined by MRI Quality of life as measured by	Only data quality of the first 100 pts reported so far.	Only data quality of the first 100 pts reported so far.	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				EORTC QLQ-C30 and BN-20 Neurocognitive function as measured by Hopkins Verbal Learning Test, Controlled Oral Word Association Test, Trail Making Test Part A & B, Stroop - Colour and Word Test and Digit Span (Forwards and Backwards). Overall survival ECOG Performance status			
Goyal et al. 2015	To review the current evidence regarding the treatment of multiple brain metastases from melanoma.	Systematic review	2006 pts. treated with radiotherapy; 642 treated with chemotherapy; description of non-RCTs for Ipilimumab	Rate of Intracranial Failure, % Overall Intracranial Response Rate, % Median Overall	8-48% for SRS(+/-WBRT), 29-100% for WBRT 7-47% for CTX 6.5-7.5m for	"At this time, the standard management for patients with MBM from melanoma includes SRS, WBRT, or a combination of	1a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				Survival, mo Progression-Free Survival or Median Time to Progression	WBRT, 5.7-15.2m for SRS(+/-WBRT) 0-47monts for chemotherapy (+/-WBRT/SRS) 4.7-21.3m for ipilimumab (+/-Chemo/WBRT/SRS) 1.2-5m for chemotherapy (+/-WBRT/SRS) 2.7m-9.5m for Ipilimumab (+/-Chemo/WBRT/SRS)	both“	
Hauswald et al. 2013	To exploratory investigate the treatment response to conventional whole brain radiotherapy applying 30 Gy in 10 fractions versus whole brain helical tomotherapy applying 30 Gy in 10 fractions with an integrated boost of 50 Gy to	Randomized controlled trial Treatment: WBRT 30 Gy in 10 fractions Vs. WBHT applying 30 Gy in 10 fractions with an integrated boost of 50 Gy to the brain	50 pts randomized 1:1 to WBRT or WBHT+ integrated boost	Toxicity (frequency and intensity according to CTCAE Ver. 4) every 2 months for one year		No results published so far	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	the brain metastases as well as hippocampal-sparing in patients with brain metastases from malignant melanoma	metastases as well as hippocampal-sparing					

9.3.4.2.1. Literatur

Buchsbaum JC, Suh JH, Lee SY, et al. Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. Cancer 2002;94:2265-2272
Byrne TN, Cascino TL, Posner JB. Brain metastasis from melanoma. J Neurooncol 1983;1:313-317
Carella RJ, Gelber R, Hendrickson F, et al. Value of radiation therapy in the management of patients with cerebral metastases from malignant melanoma: Radiation Therapy Oncology Group Brain Metastases Study I and II. Cancer 1980;45:679-683
Choi KN, Withers HR, Rotman M. Intracranial metastases from melanoma. Clinical features and treatment by accelerated fractionation. Cancer 1985;56:1-9
Christopoulou A, Retsas S, Kingsley D, et al. Integration of gamma knife surgery in the management of cerebral metastases from melanoma. Melanoma Res 2006;16:51-57
Cooper JS, Carella R. Radiotherapy of intracerebral metastatic malignant melanoma. Radiology 1980;134:735-738
Davey P, O'Brien P. Disposition of cerebral metastases from malignant melanoma: implications for radiosurgery. Neurosurgery 1991;28:8-14; discussion 14-5
Eigentler TK, Figl A, Krex D, et al. Number of metastases, serum lactate dehydrogenase level, and type of treatment are prognostic factors in patients with brain metastases of malignant melanoma. Cancer 2011;117:1697-1703
Ellerhorst J, Strom E, Nardone E, et al. Whole brain irradiation for patients with metastatic melanoma: a review of 87 cases. Int J Radiat Oncol Biol Phys 2001;49:93-97
Fife KM, Colman MH, Stevens GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. J Clin Oncol 2004;22:1293-1300
Fletcher WS, Pommier RF, Lum S, et al. Surgical treatment of metastatic melanoma. Am J Surg 1998;175:413-417
Fogarty GB, Hong A, Dolven-Jacobsen K, et al. First interim analysis of a randomised trial of whole brain radiotherapy in melanoma brain metastases confirms high data quality. BMC Res Notes. 2015;8:192.
Friehs GM, Legat J, Zheng Z, et al. Outcomes in patients treated with gamma knife radiosurgery for brain metastases from malignant melanoma. Neurosurg Focus 1998;4:e1
Gaudy-Marqueste C, Regis JM, Muracciole X, et al. Gamma-Knife radiosurgery in the management of melanoma patients with brain metastases: a series of 106 patients without whole-brain radiotherapy. Int J Radiat Oncol Biol Phys 2006;65:809-816
Gieger M, Wu JK, Ling MN, et al. Response of intracranial melanoma metastases to stereotactic radiosurgery. Radiat Oncol Investig 1997;5:72-80
Gonzalez-Martinez J, Hernandez L, Zamorano L, et al. Gamma knife radiosurgery for intracranial metastatic melanoma: a 6-year experience. J Neurosurg 2002;97:494-498
Goyal S, Silk AW, Tian S, et al. Clinical Management of Multiple Melanoma Brain Metastases: A Systematic Review. JAMA Oncol. 2015;1(5):668-676.
Grob JJ, Regis J, Laurans R, et al. Radiosurgery without whole brain radiotherapy in melanoma brain metastases. Club de Cancerologie Cutanee. Eur J Cancer 1998;34:1187-1192
Guazzo EP, Atkinson RL, Weidmann M, et al. Management of solitary melanoma metastasis of the brain. Aust N Z J Surg 1989;59:321-324
Gupta G, Robertson AG, MacKie RM. Cerebral metastases of cutaneous melanoma. Br J Cancer 1997;76:256-259
Hafstrom L, Jonsson PE, Stromblad LG. Intracranial metastases of malignant melanoma treated by surgery. Cancer 1980;46:2088-2090
Hagen NA, Cirrincione C, Thaler HT, et al. The role of radiation therapy following resection of single brain metastasis from melanoma. Neurology 1990;40:158-160
Hauswald H, Habl G, Krug D, et al. Whole brain helical Tomotherapy with integrated boost for brain metastases in patients with malignant melanoma-a randomized trial. Radiat Oncol. 2013;8:234.
Herfarth KK, Izwekowa O, Thilmann C, et al. Linac-based radiosurgery of cerebral melanoma metastases. Analysis of 122 metastases treated in 64 patients. Strahlenther Onkol 2003;179:366-371

Hofmann MA, Coll SH, Kuchler I, et al. Prognostic factors and impact of treatment in melanoma brain metastases: better prognosis for women? Dermatology 2007;215:10-16
Isokangas OP, Muhonen T, Kajanti M, et al. Radiation therapy of intracranial malignant melanoma. Radiother Oncol 1996;38:139-144
Katz H.R. The relative effectiveness of radiation therapy, corticosteroids, and surgery in the management of melanoma metastatic to the central nervous system. 1981.
Koc M, McGregor J, Grecula J, et al. Gamma Knife radiosurgery for intracranial metastatic melanoma: an analysis of survival and prognostic factors. J Neurooncol 2005;71:307-313
Konstadoulakis MM, Messaris E, Zografos G, et al. Prognostic factors in malignant melanoma patients with solitary or multiple brain metastases. Is there a role for surgery? J Neurosurg Sci 2000;44:211-8; discussion 219
Lavine SD, Petrovich Z, Cohen-Gadol AA, et al. Gamma knife radiosurgery for metastatic melanoma: an analysis of survival, outcome, and complications. Neurosurgery 1999;44:59-64; discussion 64-6
Lonser RR, Song DK, Klapper J, et al. Surgical management of melanoma brain metastases in patients treated with immunotherapy. J Neurosurg 2011;115:30-36
Madajewicz S, Karakousis C, West CR, et al. Malignant melanoma brain metastases. Review of Roswell Park Memorial Institute experience. Cancer 1984;53:2550-2552
Mathieu D, Kondziolka D, Cooper PB, et al. Gamma knife radiosurgery in the management of malignant melanoma brain metastases. Neurosurgery 2007;60:471-81; discussion 481-2
Meier S, Baumert BG, Maier T, et al. Survival and prognostic factors in patients with brain metastases from malignant melanoma. Onkologie 2004;27:145-149
Mendez IM, Del Maestro RF. Cerebral metastases from malignant melanoma. Can J Neurol Sci 1988;15:119-123
Mingione V, Oliveira M, Prasad D, et al. Gamma surgery for melanoma metastases in the brain. J Neurosurg 2002;96:544-551
Mori Y, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. Int J Radiat Oncol Biol Phys 1998;42:581-589
Mornex F, Thomas L, Mohr P, et al. A prospective randomized multicentre phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma. Melanoma Res 2003;13:97-103
Morris SL, Low SH, A'Hern RP, et al. A prognostic index that predicts outcome following palliative whole brain radiotherapy for patients with metastatic malignant melanoma. Br J Cancer 2004;91:829-833
Noel G, Simon JM, Valery CA, et al. Linac radiosurgery for brain metastasis of melanoma. Stereotact Funct Neurosurg 2002;79:245-255
Oredsson S, Ingvar C, Stromblad LG, et al. Palliative surgery for brain metastases of malignant melanoma. Eur J Surg Oncol 1990;16:451-456
Pennington DG, Milton GW. Cerebral metastasis from melanoma. Aust N Z J Surg 1975;45:405-409
Radbill AE, Fiveash JF, Falkenberg ET, et al. Initial treatment of melanoma brain metastases using gamma knife radiosurgery: an evaluation of efficacy and toxicity. Cancer 2004;101:825-833
Rades D, Heisterkamp C, Huttenlocher S, et al. Dose escalation of whole-brain radiotherapy for brain metastases from melanoma. Int J Radiat Oncol Biol Phys 2010;77:537-541
Raizer JJ, Hwu WJ, Panageas KS, et al. Brain and leptomeningeal metastases from cutaneous melanoma: survival outcomes based on clinical features. Neuro Oncol 2008;10:199-207
Rate WR, Solin LJ, Turrisi AT. Palliative radiotherapy for metastatic malignant melanoma: brain metastases, bone metastases, and spinal cord compression. Int J Radiat Oncol Biol Phys 1988;15:859-864
Redmond AJ, Diluna ML, Hebert R, et al. Gamma Knife surgery for the treatment of melanoma metastases: the effect of intratumoral hemorrhage on survival. J Neurosurg 2008;109 Suppl:99-105
Retsas S, Gershuny AR. Central nervous system involvement in malignant melanoma. Cancer 1988;61:1926-1934
Salvati M, Frati A, D'Elia A, et al. Single brain metastases from melanoma: remarks on a series of 84 patients. Neurosurg Rev 2011
Samlowski WE, Watson GA, Wang M, et al. Multimodality treatment of melanoma brain metastases incorporating stereotactic radiosurgery (SRS). Cancer 2007;109:1855-1862
Sampson JH, Carter JH,Jr, Friedman AH, et al. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. J Neurosurg 1998;88:11-20
Selek U, Chang EL, Hassenbusch SJ,3rd, et al. Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. Int J Radiat Oncol Biol Phys 2004;59:1097-1106
Seung SK, Sneed PK, McDermott MW, et al. Gamma knife radiosurgery for malignant melanoma brain metastases. Cancer J Sci Am 1998;4:103-109
Skeie BS, Skeie GO, Enger PO, et al. Gamma knife surgery in brain melanomas: absence of extracranial metastases and tumor volume strongest indicators of prolonged survival. World Neurosurg 2011;75:684-91; discussion 598-603
Skibber JM, Soong SJ, Austin L, et al. Cranial irradiation after surgical excision of brain metastases in melanoma patients. Ann Surg Oncol 1996;3:118-123
Somaza S, Kondziolka D, Lunsford LD, et al. Stereotactic radiosurgery for cerebral metastatic melanoma. J Neurosurg 1993;79:661-666
Staudt M, Lasithiotakis K, Leiter U, et al. Determinants of survival in patients with brain metastases from cutaneous melanoma. Br J Cancer 2010;102:1213-1218
Stevens G, Firth I, Coates A. Cerebral metastases from malignant melanoma. Radiother Oncol 1992;23:185-191
Stone A, Cooper J, Koenig KL, et al. A comparison of survival rates for treatment of melanoma metastatic to the brain. Cancer Invest 2004;22:492-497
Stridsklev IC, Hagen S, Klepp O. Radiation therapy for brain metastases from malignant melanoma. Acta Radiol Oncol 1984;23:231-235
Vlock DR, Kirkwood JM, Leutzinger C, et al. High-dose fraction radiation therapy for intracranial metastases of malignant melanoma: a comparison with low-dose fraction therapy. Cancer 1982;49:2289-2294
Willner J, Bohndorf W. CNS metastases in malignant melanomas. Strahlenther Onkol 1995;171:165-173
Wornom IL,3rd, Smith JW, Soong SJ, et al. Surgery as palliative treatment for distant metastases of melanoma. Ann Surg 1986;204:181-185
Wronski M, Arbit E. Surgical treatment of brain metastases from melanoma: a retrospective study of 91 patients. J Neurosurg 2000;93:9-18
Yu C, Chen JC, Apuzzo ML, et al. Metastatic melanoma to the brain: prognostic factors after gamma knife radiosurgery. Int J Radiat Oncol Biol Phys 2002;52:1277-1287

Zacest AC, Besser M, Stevens G, et al. Surgical management of cerebral metastases from melanoma: outcome in 147 patients treated at a single institution over two decades. J Neurosurg 2002;96:552-558
Ziegler JC, Cooper JS. Brain metastases from malignant melanoma: conventional vs. high-dose-per-fraction radiotherapy. Int J Radiat Oncol Biol Phys 1986;12:1839-1842

9.3.4.3. Aktualisierungsrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Ahmed, K.A., et al., 2016	To analyse the outcomes of patients managed with vemurafenib and ipilimumab with stereotactic radiation in melanoma brain metastases (MBM)	Retrospective study, number of patients n= 96	Patients with melanoma suffering from brain metastases treated at the University of South Florida Institutional January 2007 and August 2015.	Distant and local control Progression-free	12-month Kaplan–Meier distant MBM control rates distant melanoma brain metastases control rates at 6 and 12 months across all treatment sessions were 36% and 18%. Six- and 12-month distant melanoma brain metastases control rates were 61%/38% (anti-PD-1 therapy), 26%/21% (anti-CTLA-4 therapy), 53%/20% (BRAF/MEKi), 30%/8% (BRAFi), and 15%/5% (conventional chemotherapy) following radiosurgery sessions.		3a

				and overall survival	Treatment with anti-PD-1, anti-CTLA-4, or BRAF/MEKi significantly improved OS on both uni- and multivariate analyses when compared with chemo-therapy, HR 2.7 (95% CI 1.4–5.7; P = 0.005), 2.5 (95% CI 1.3–5.0; P = 0.007), and 2.5 (95% CI 1.2–5.5; P = 0.02), respectively. The median OS for all patients in the study was 8.9 months (range: 0.47–48 months) from the date of stereotactic session and 10.5 months (0.5–48.2 months) from the date of cranial metastases diagnosis		

Gupta, A., et al., 2016	To compare whole brain radiation (WBRT) alone with WBRT plus vandetanib in the treatment of patients with melanoma brain metastases	Randomised phase 2 trial, number of patients n= 24	Patients with advanced melanoma, study conducted at seven hospitals across the UK	Brain-specific PFS OS	Median PFS brain was 3.3 months (90% confidence interval (CI): 1.6–5.6) in the vandetanib group and 2.5 months (90% CI: 0.2–4.8) in the placebo group (P=0.34). Median overall survival (OS) was 4.6 months (90% CI: 1.6–6.3) and 2.5 months (90% CI: 0.2–7.2), respectively (P=0.54).	Low sample size, Study closed early due to poor recruitment.	2a
Kiess, A.P., et al., 2015	To investigate the safety and efficacy of this combination for treatment of melanoma BMs	Retrospective study, number of patients n= 46	Patients with melanoma received Ipilimumab and underwent single-fraction SRS for BMs, from 2005 to 2011	OS, local recurrence	OS was significantly associated with the timing of SRS/Ipi (P=.035) and melanoma-specific graded prognostic assessment (P=.013). Patients treated with SRS during or before Ipi had better OS and less		3a

					regional recurrence than did those treated with SRS after Ipi (1-year OS 65% vs 56% vs 40%, P=.008; 1-year regional recurrence 69% vs 64% vs 92%, P=.003).		
Knisely, J.P., et al., 2012	To address our questions, we reviewed our experience with the use of SRS in patients with melanoma brain metastases who did or did not receive ipilimumab.	Prospective study, number of patients n= 77	Patients who underwent definitive radiosurgery, the Yale Cancer Center, initiated in 2004	OS	Median survival for the entire cohort was 8.8 months. For patients who received ipilimumab, median survival was 21.3 months compared with 4.9 months for those who did not. Further, 2-year survival was 47.2% in the ipilimumab group compared with 19.7% in the non-ipilimumab group.	Titled as prospective but likely to be retrospective	3b

					The median survival for patients who received ipilimumab before SRS was 19.8 months, and for those who received ipilimumab after SRS the median survival was 21.3 months.		
Ly, D., et al., 2015	To hypothesize that the addition of BRAF inhibitor therapy will improve local control in patients with melanoma who undergo SRS for brain metastases.	Retrospective study, number of patients n= 52	Patients who received their first course of radiation for brain metastases with SRS at the University of Utah and completed testing for BRAF mutation between 2009 and 2012	Local control OS	1-year local control rate for all the brain lesions was 69.2%. At 1 year, the local control rate for brain lesions in patients with wild-type BRAF was 67.1%, whereas the 1-year local control rate for brain lesions in patients with BRAF mutation was 70.0% (p =0.12) At 1 year, the		3a

					overall survival rate was 48.0% (median survival 12 months). Survival was not associated with BRAF mutation status. At 1 year, the overall survival rates were 50.2% and 42.9% for patients who had BRAF inhibitor treatment and those who had no treatment, respectively (p= 0.82)		
Patel, K.R., et al., 2016	To report our own institutional experience with SRS and BRAFi for MBM patients	Retrospective study, number of patients n= 87	Patients with 157 MBM treated with SRS alone from 2005 to 2013	OS	One-year outcomes – OS (64.3 vs. 40.4%, P=0.205), local failure (3.3 vs. 9.6%, P=0.423), and distant intracranial failure (63.9 vs. 65.1%, P=0.450) were not statistically different between the SRS+BRAFi and SRS alone groups, respectively.		3a

Qian, J.M., et al., 2016	To explore the possible interaction between immunotherapy and radiation	Retrospective study, number of patients n=75	Patients with 566 BrMets were treated with both SRS and immune checkpoint therapy between 2007 and 2015 at a single institution	Early Lesional Response with Respect to the Timing of Treatment Early Lesional Response by Treatment Type Overall Survival	The median percent reduction in the lesion volume was significantly greater for the concurrent group than the nonconcurrent group at 1.5 (263.1% vs 243.2%, P<.0001), 3 (283.0% vs 252.8%, P<0.0001), and 6 months (294.9% vs 266.2%, P<.0001). The median percent reduction in the lesion volume was significantly greater for anti–PD-1 than anti–CTLA-4 at 1.5 (271.1% vs 248.2%, P<.0001), 3 (289.3% vs266.2%, P<.0001), and 6 months (295.1% vs 275.9%, P5.0004) The median overall		3a

					survival for all patients from the first SRS treatment was 18.5 months. Of the patients who started on anti-CTLA-4 and had either only on concurrent SRS treatment (n=19) or only concurrent SRS treatment (n=19), the median overall survival was 8.0 months for nonconcurrent treatment and 19.1 months for concurrent treatment (P=.0858).		
Wolf, A., et al., 2016	To evaluate the impact of BRAF inhibitors on survival outcomes in patients receiving stereotactic radiosurgery (SRS) for melanoma brain metastases	Prospective study, number of patients n= 80	Patients with melanoma brain metastases who underwent SRS, between 2012 and 2015 at NYU Langone Medical Center	DFS Local Control Rate	Median time to intracranial progression was 3.9 months on a BRAF inhibitor and 1.7 months without. The local control rate for all treated tumors was 92.5		2a

					%, with no difference based on BRAF status		
				OS	Median overall survival from first SRS procedure was 6.7, 11.2 months if treated with a BRAF inhibitor and 4.5 months for BRAF-WT. Actuarial survival rates for BRAF-M patients on an inhibitor were 54 % at 6 months and 41 % at 12 months from the time of SRS. In contrast, BRAF-WT had overall survival rates of 28 % at 6 months and 19 % at 12 months.		

9.3.4.3.1. Literatur

Ahmed, K.A., et al., Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. Ann Oncol, 2016. 27(12): p. 2288-2294.
Gupta, A., et al., RADVAN: a randomised phase 2 trial of WBRT plus vandetanib for melanoma brain metastases - results and lessons learnt. Br J Cancer, 2016. 115(10): p. 1193-1200.
Kiess, A.P., et al., Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. Int J Radiat Oncol Biol Phys, 2015. 92(2): p. 368-75.
Knisely, J.P., et al., Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. J Neurosurg, 2012. 117(2): p. 227-33.
Ly, D., et al., Local control after stereotactic radiosurgery for brain metastases in patients with melanoma with and without BRAF mutation and treatment. J Neurosurg, 2015. 123(2): p. 395-401.
Patel, K.R., et al., BRAF inhibitor and stereotactic radiosurgery is associated with an increased risk of radiation necrosis. Melanoma Res, 2016. 26(4): p. 387-94.

Qian, J.M., et al., Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. Cancer, 2016. 122(19): p. 3051-8.
Wolf, A., et al., Impact on overall survival of the combination of BRAF inhibitors and stereotactic radiosurgery in patients with melanoma brain metastases. J Neurooncol, 2016. 127(3): p. 607-15.

9.4. Frage VIII.5. Adjuvante Radiotherapie Regionale Lymphknotenstation

Frage VIII.5. Beeinflusst eine adjuvante Radiotherapie der Lymphknotenstation das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?

9.4.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
melanoma patients after nodal surgery	radiotherapy	no radiotherapy	Overall survival, progression free survival

Suchwörter				
Stichwort	melanoma	adjuvant radiotherapy	postoperative	lymph node lymph nodes
Synonyme		radiation		nodal
Ober-/Unterbegriffe				
Mesh Term	melanoma	adjuvant radiotherapy		lymphoid tissue

9.4.2. Datenbanken, Suchstrategien, Trefferzahlen

9.4.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	("melanoma"[tiab] OR "melanoma"[MeSH]) AND ("adjuvant radiotherapy"[tiab] OR "Radiation"[tiab] OR "postoperative"[tiab] OR adjuvant radiotherapy[MeSH Terms]) AND ("lymph node"[tiab] OR "lymph nodes"[tiab] OR "nodal "[tiab] OR "lymphoid tissue"[MeSH])	04.11.11	455
Cochrane Library	(melanoma and ("adjuvant radiotherapy" or radiation) and lymph*).ti,ab	07.11.11	7
Embase	(melanoma and ("adjuvant radiotherapy" or radiation) and lymph*).ti,ab	12.10.10	475
Update Suche			
Medline	s.o.	31.01.12	459 (0 dazu)
Cochrane Library	s.o	31.01.12	7 (0 dazu)
Embase	s.o.	23.01.12	590 (0 dazu)

9.4.2.2. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	((("melanoma"[tiab] OR "melanoma"[MeSH]) AND ("adjuvant radiotherapy"[tiab] OR "Radiation"[tiab] OR "postoperative"[tiab] OR adjuvant radiotherapy[MeSH Terms]) AND ("lymph node"[tiab] OR "lymph nodes"[tiab] OR "nodal "[tiab] OR "lymphoid tissue"[MeSH]))) AND	16.09.2016	72

	("2015.09.16"[Date - Publication] : "3000.09.16"[Date - Publication])		
Cochrane Library	(melanoma and ("adjuvant radiotherapy" or radiation) and lymph*).ti,ab	16.09.2016	42

9.4.3. Auswahlkriterien

9.4.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	1056
Einschlusskriterien	Studien, die das Outcome (regionale Kontrollrate, Gesamtüberleben) einer adjuvanten Radiotherapie nach erfolgter Lymphknotendissektion beschreiben Mangels RCT´s Einschluss von Kohortenstudien ab 20 Patienten Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kollektive mit gemischten Tumorentitäten Publikationen vor 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	32
Anzahl ausgewählte Volltexte	11

9.4.3.2. Aktualisierungsrecherche 2016

Auswahl der Literatur	
Gesamttreffer	1056

Einschlusskriterien	Systematische Reviews RCTs, die das Outcome (regionale Kontrollrate, Gesamtüberleben) einer adjuvanten Radiotherapie nach erfolgter Lymphknotendissektion beschreiben Sprachen: e,dt
Ausschlusskriterien	Case Reports Kohortenstudien Nicht Kollektive mit gemischten Tumorentitäten
Anzahl nach Abstractscreening, vorgesehen für Bewertung	32
Anzahl ausgewählte Volltexte	1

9.4.4. Evidenztabelle

9.4.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Burmeister et al. 2012	To compare adjuvant radiotherapy with observation alone in patients at high risk of lymph-node field relapse who had undergone therapeutic	Multicenter randomized study Treatment: Group A: surgery alone n=127 Group B: surgery + RT (TD 48Gy, 20	250 patients after lymphadenectomy	**Lymph node field relapse** Relapse-free survival	Surgery alone vs. Surgery + RT 34 patients vs. 20 patients relapsed (HR 0.56, 95% CI 0.32 – 0.98, **p=0.041**)	Jadad Score 3 Limitations: high number of ineligible patients Funding: National Health and Medical Research	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	lymphadenectomy for metastatic melanoma in regional lymph nodes	fractions) after lymphadenectomy, n=123		Overall survival	73 vs. 70 events, n.s. (HR 0.91, 95% CI 0.65 – 1.26, p=0.56) 47 vs. 59 deaths, n.s. (HR 1.37, 95% CI 0.94 – 2.01, p=0.12)	Council of Australia, Cancer Australia, Melanoma Insitute Australia and the Cancer Council of South Australia	
Gojkovic-Horvat et al. 2011	To determine the efficacy of and criteria for postoperative radiotherapy (PORT) in patients with palpable melanoma metastases to the groin	Retrospective cohort study Treatment: Group A: surgery alone, n=64 Group B: surgery + RT (TD range 50 - 72 Gy, fraction size 2 - 3 Gy), n=37	101 patients, 103 nodal dissections	Recurrence 2-year regional control rates	Surgery alone vs. Surgery + RT 14 of 66 dissections (21.2%; 95% CI, 12.1-33.0%) vs. 5 of 37 (13.5%; 95% CI, 4.5-28.8%) (p=0.431) 86% (95% CI, 76-95%) and 91% (95% CI, 81-100%), respectively (p=0.395)	retrospective study, Imbalance of prognostic factors between the groups: worse prognostic factors in the surgery + RT group	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				2 years overall survival	56% (95% CI, 44-68%) vs. 56% (95% CI, 39-72%), (p=0.813)		
Bibault et al. 2011	To analyze the outcome after adjuvant radiation therapy with standard fractionation regimen in metastatic lymph nodes (LN) from cutaneous melanoma	Retrospective cohort study Treatment: Group A: surgery alone, n=26 Group B: surgery + RT (median TD 50Gy, range 30-70 Gy, fraction size 2 - Gy), n=60	86 patients with lymphadenectomy Indications for radiation therapy: >/= 4 involved LNs, extracapsular extension, LN size > 3 cm	Regional control Overall survival	Surgery alone vs. Surgery + RT No improvement of regional control (p=0.17) or overall survival (p=0.18) Subgroup RT > 50 Gy (n=30) vs. no RT (n=26): better regional control p=0.004, better survival p=0.005 control rates / regions: Axillary 90 vs. 70% inguinal 80 vs. 72% cervical 85 vs. 50% Subgroup extracapsular	retrospective study, Imbalance of groups: worse prognostic factors in the surgery + RT group (Ulceration, number of positive LN, extracapsular extension)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					extension: RT <50Gy vs. RT <50Gy 5 year regional control 80 vs. 35%, p=0.03		
Strojan et al. 2010	To review experiences in the treatment of regionally advanced melanoma to the neck and/or parotid with adjuvant radiotherapy.	Retrospective cohort study Treatment: Group A: surgery alone, n=40 Group B: surgery + RT (median eqTD2 60 Gy, range 47.8–78.8, fraction size 5 Gy, range 2–6 Gy), n=43	83 patients after surgery on metastases to the neck and/or parotid gland lymph nodes, no distant metastases	2-year regional control rates 2-year distant metastasis-free survival rates 2-year survival rates (all deaths considered as events)	Surgery alone vs. Surgery + RT 56% (CI 40–72%) vs. 78% (CI 63–92%) (p =0.015) 55% (CI 40–70%) vs. 40% (CI 25–56%), n.s. 51% (CI 36–66%) vs. 58% (CI 42–73%), n.s.	retrospective study. Due to Imbalance of groups (irradiated patients had more extensive surgery, a significantly higher median number of involved nodes, more frequently extracapsular tumor extension, nonradical surgery, less systemic immunotherapy with interferon) a risk factor score was used for retrospective grouping of patients.	3b
Agrawal et al.	To evaluate the	Retrospective	615 patients after		Surgery alone vs.	retrospective	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
2009	impact of adjuvant radiation therapy (RT) on regional recurrence and survival after therapeutic lymphadenectomy	cohort study Treatment: Group A: surgery alone, n=106 Group B: surgery + RT (most patients: TD 30 Gy, fraction size 6 Gy, 2.5 weeks), n=509	lymphadenectomy (cervical, axillary, inguinal)	Recurrence (at a median follow-up 60 months) 5-year regional control rate	Surgery + RT Regional recurrence: 43 of 106 pts (40.6%) vs. 52 of 509 pts (10.2%) distant recurrence: 73.6% (78 of 106 pts) vs. 55.4% (282 of 509 pts) all sites 52 vs. 87%, p<0.0001 cervical 43 vs. 93%, p<0.0001 axillary 48 vs. 91%, p<0.0001 inguinal 69 vs. 69%, n.s. multivariate analysis: DMFS and DSS both were influenced by the number of positive lymph nodes and the number of lymph nodes removed. In	study, large series. P-values for recurrence missing. data for overall survival not compared between groups	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					addition, DSS was influenced by primary tumor thickness and the receipt of adjuvant RT. The most common complication was symptomatic lymphedema		
Hamming et al. 2009	To examine the effect of adjuvant radiotherapy on regional control of melanoma neck node metastasis.	Retrospective cohort study Treatment: Group A: surgery alone, n=24 Group B: surgery + RT (TD 24 - 36 Gy, fraction size 6 Gy) n=40	64 patients with nelanoma neck node metastasis	2-year ipsilateral regional recurrence rate 2-year disease-free survival (DFS) 2-year overall	Surgery alone vs. Surgery + RT 46% vs. 18%, n.s. (p=0.16) <u>multivariate analysis:</u> significant reduction of the RR rate after correction for the number of involved nodes (p=0.04) 29% vs. 18%, n.s. (p=0.30)	retrospective study, short median follow-up (2.5 years), small sample size,- Imbalance of prognostic factors between the groups	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
				survival (OS).	58% vs. 26%, n.s. (p=0.07)		
Moncrieff et al. 2008	To examine the effectiveness of adjuvant radiotherapy in controlling regional disease in high-risk patients	Retrospective cohort study Treatment: Group A: surgery alone, n=587 Group B: surgery + RT (median TD 33 (range 30 - 60 Gy, most patients: fraction size 5.5 Gy, 2x/week) n=129	716 patients after cervical lymph node surgery	6 years regional recurrence rate Overall survival	Surgery alone vs. Surgery + RT 6.1% vs. 10.1%, n.s. no benefit to patients with adjuvant radiotherapy multivariate analysis: ulceration in the primary tumor: only significant independent predictor of regional recurrence (p = 0.005; hazard ratio, 5.60; 95% confidence interval, 1.7–18.4)	retrospective study, large series, imbalance of groups: the surgery plus RT group includes significantly less patients with microscopic than macroscopic disease and significantly more patients with extensive surgery	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					nodal status, extracapsular spread and ulceration of the primary tumor: significant independent predictors of survival (p = 0.001, p = 0.014, and p = 0.003)		
Fuhrmann et al. 2001	To evaluate the usefulness of adjuvant radiotherapy following resection of lymph node metastases	Retrospective cohort study Treatment: Group A: surgery alone, n=58 Group B: surgery + RT (most patients TD 50-65 Gy, fraction size 2 – 3.8 Gy) n=58	116 patients, Stage III after resection of lymph node metastases	Local recurrence rate Overall survival (after a follow up of 12-14 years)	Surgery alone vs. Surgery + RT 79% vs. 84%, n.s. 26% vs. 17% , n.s.	retrospective study, Imbalance of groups: pairs were only matched for gender and number of tumour-bearing lymph nodes. Group B includes more head and neck melanomas and thicker tumours. Groups were treated in 2 different german centres using the same follow up	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						schedule. missing data, e.g. median follow up, p-values	
Shen et al. 2000	To examine the incidence of cervical recurrence among patients who did not receive postoperative radiotherapy after surgical management of nodepositive head and neck melanoma	Retrospective cohort study Treatment: Group A: surgery alone, n=196 Group B: surgery + RT (treatment Schedule not indicated) n=21	217 patients with head and neck melanoma after regional lymph node dissection	Cervical recurrence rate 5 years overall survival 5 years disease free survival	Surgery alone vs. Surgery + RT 14% (25/183) vs. 15% (2/13), n.s. 32% 21% mulitvariate analysis: extranodal disease: only independent predictor for cervical recurrence	Baseline characteristics for the surgery+RT group were not indicated, no statistical analyses for this group due to small sample size, retrospective study	3b
O'Brien et al. 1997	To analyze the influence of the number of positive nodes, extracapsular spread, and the	retrospective cohort study Treatment: Group A: surgery alone, n=107	143 patients after neck or parotid dissection, 152 lymphadenectomy sites	Local recurrence	Surgery alone vs. Surgery + RT 18.7% (20 of 107) vs. 6.5% (3 of 45), p=0.055	retrospective study, imbalance of groups, difficult to compare data for recurrence with other studies as	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	use of adjuvant radiotherapy on regional control and survival	(sites) Group B: surgery + RT (TD 33 Gy, fraction size 5.5 Gy, 3 weeks) n=45 (sites)		5 years survival	35% vs. 40%, n.s.	they do not refer to patients but to irradiated sites.	
Creagan et al. 1978	To assess the role of postoperative radiation therapy directed to the regional node area in patients undergoing lymphadenectomy for metastatic melanoma	RCT Treatment: Group A: surgery alone, n=29 Group B: surgery + RT (TD 5000 rad, fraction size 2500 rad) n=27	56 patients after lymphadenectomy	Time to recurrence Survival	Surgery alone vs. Surgery + RT 9 months vs. 20 months, n.s. (p=0.07) 22 months vs. 33 months, n.s. (p=0.09)	Limitations: randomization scheme not appropriate (group assignment predictable), small sample size, Imbalance of groups (more younger patients and more patients with only one positive node in the RT group	2b poor quality RCT

9.4.4.1.1. Literatur

Agrawal S, Kane JM,3rd, Guadagnolo BA, et al. The benefits of adjuvant radiation therapy after therapeutic lymphadenectomy for clinically advanced, high-risk, lymph node-metastatic melanoma. Cancer 2009;115:5836-5844
Bibault JE, Dewas S, Mirabel X, et al. Adjuvant radiation therapy in metastatic lymph nodes from melanoma. Radiat Oncol 2011;6:12
Creagan ET, Cupps RE, Ivins JC, et al. Adjuvant radiation therapy for regional nodal metastases from malignant melanoma: a randomized, prospective study. Cancer 1978;42:2206-2210
Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. Lancet Oncol 2012; 13: 589-597

Fuhrmann D, Lippold A, Borrosch F, et al. Should adjuvant radiotherapy be recommended following resection of regional lymph node metastases of malignant melanomas? Br J Dermatol 2001;144:66-70
Gojkovic-Horvat A, Jancar B, Blas M, et al. Adjuvant Radiotherapy for Palpable Melanoma Metastases to the Groin: When to Irradiate? Int J Radiat Oncol Biol Phys 2011
Hamming-Vrieze O, Balm AJ, Heemsbergen WD, et al. Regional control of melanoma neck node metastasis after selective neck dissection with or without adjuvant radiotherapy. Arch Otolaryngol Head Neck Surg 2009;135:795-800
Henderson MA, Burmeister B, Thompson JF, et al. Adjuvant radiotherapy and regional lymph node field control in melanoma patients after lymphadenectomy: Results of an intergroup randomized trial (ANZMTG 01.02/TROG 02.01). J Clin Oncol (Meeting Abstracts) 2009;27:LBA9084
Moncrieff MD, Martin R, O'Brien CJ, et al. Adjuvant postoperative radiotherapy to the cervical lymph nodes in cutaneous melanoma: is there any benefit for high-risk patients? Ann Surg Oncol 2008;15:3022-3027
O'Brien CJ, Petersen-Schaefer K, Stevens GN, et al. Adjuvant radiotherapy following neck dissection and parotidectomy for metastatic malignant melanoma. Head Neck 1997;19:589-594
Shen P, Wanek LA, Morton DL. Is adjuvant radiotherapy necessary after positive lymph node dissection in head and neck melanomas? Ann Surg Oncol 2000;7:554-9; discussion 560-1
Strojan P, Jancar B, Cemazar M, et al. Melanoma metastases to the neck nodes: role of adjuvant irradiation. Int J Radiat Oncol Biol Phys 2010;77:1039-1045

9.4.4.2. Aktualisierungsrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Danish, H.H., et al., 2016	To investigate the impact of adjuvant radiation on OS for stage III cutaneous melanoma patients with pathologically positive nodes.	Retrospective study, number of patients n= 912	Melanoma patients diagnosed between 2003–2011 Pathologic stage III; surgery to regional lymph nodes; pathologically confirmed involved regional lymph nodes	Overall survival	5-year OS: 69.0, 51.1, and 30.6% for stage IIIA, IIIB, and IIIC, respectively. In this NCDB analysis, we found that the adjuvant radiotherapy for node-positive, stage III melanoma patients did not improve OS.		3b

9.4.4.2.1. Literatur

Danish, H.H., et al., The influence of postoperative lymph node radiation therapy on overall survival of patients with stage III melanoma, a National Cancer Database analysis. Melanoma Res, 2016. 26(6): p. 595-603.

9.5. Frage VIII.6. Fraktionierung

Frage VIII.6. Hat das Fraktionierungsschema einen Einfluss auf die Effektivität der Radiotherapie bei Melanompatienten?

9.5.1. PICO, Suchwörter

PICO – Schema			
Population	**Intervention**	**Comparison**	**Outcome**
melanoma patients	Radiotherapy high dose per fraction	Radiotherapy low dose per fraction	effectiveness

Suchwörter				
Stichwort	Melanoma	radiotherapy	fraction	
Synonyme		Radiation, irradiation	dose	
Ober-/Unterbegriffe				
Mesh Term	melanoma	radiotherapy, radiation		

9.5.2. Datenbanken, Suchstrategien, Trefferzahlen

9.5.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	((melanoma[ti] OR melanoma[MeSH]) AND (radiotherapy[ti] OR radiotherapy[MeSH] OR	14.07.11	216 (Auswahl 9)

	radiation[MeSH] OR radiation[ti] or irradiation[ti]) AND (fraction*[ti] OR dose[ti]))		
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation) and fraction*).ti.	14.07.11	3 (Overgaard, Chang, Sause – alles Dubletten, 0 dazu)
Embase	(melanoma and (radiotherapy or radiation or irradiation) and fraction*).ti.	11.05.11	49 (Katz - Dublette)
Update Suche			
Medline	s.o.	31.01.12	221 (0 dazu)
Cochrane Library	s.o.	31.01.12	3 (0 dazu)
Embase	s.o.	23.01.12	52 (0 dazu)

9.5.2.2. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	((melanoma[ti] OR melanoma[MeSH]) AND (radiotherapy[ti] OR radiotherapy[MeSH] OR radiation[MeSH] OR radiation[ti] or irradiation[ti]) AND (fraction*[ti] OR dose[ti])) AND ("2012/01/24"[Date - Entrez] : "2016/09/16"[Date - Entrez])	20.09.16	43
Cochrane Library	(melanoma and (radiotherapy or radiation or irradiation) and fraction*).ti.	20.09.16	3 (0 dazu)

9.5.3. Auswahlkriterien

9.5.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	276
Einschlusskriterien	RCT´s Sprachen: e,dt
Ausschlusskriterien	Case Reports Nicht systematische Reviews Kombinationstherapien Kollektive mit gemischten Tumorentitiäten Arbeiten älter als 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	9
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	7
Anzahl ausgewählter Volltexte	2

9.5.3.2. Aktualisierungsrecherche 2016

Auswahl der Literatur	
Gesamttreffer	41
Einschlusskriterien	RCT´s Sprachen: e,dt
Ausschlusskriterien	Case Reports

	Nicht systematische Reviews Kombinationstherapien Kollektive mit gemischten Tumorentitiäten Arbeiten älter als 1980
Anzahl nach Abstractscreening, vorgesehen für Bewertung	4
Anzahl der ausgeschlossenen Studien nach Sichtung der Volltexte	2
Anzahl ausgewählter Volltexte	2

9.5.4. Evidenztabelle

9.5.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Sause et al. 1991	To evaluate the effectiveness of high dose per fraction irradiation in the treatment of melanoma	RCT Treatment: Group A: 4 fractions, 8.0 Gy, days 0, 7, 12 and 21 Group B: 20 fractions, 2.5 Gy, 5 days a week	137 patients with skin, soft tissue and nodal lesions Group A n=67 patients Group B n=70 patients	Response	Group A vs. Group B: no significant differences CR 24.2% vs. 23.4% PR 35.5% vs. 34.4% NC 33.9% vs. 39.1% PD 6.5% vs. 3.1%	Randomization scheme not described assessment not blinded	1b
Overgaard et al. 1985	To compare two high-dose per	RCT	14 patients, 35 skin and lymph	Response	Group A vs. Group B: no significant	Randomization scheme not	2b low quality

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	fraction radiation schedules in recurrent or metastatic malignant melanoma	Treatment: Group A: 9 Gy X 3, 2 fractions per week Group B: 5 Gy X 8, 2 fractions per week	node metastases		differences CR n=11 (65%) vs. n=13 (72%) PR n=5 (29%) vs. n=5 (28%) NC n=1 (6%) vs. n=0 (0%)	described, assessment not blinded, lesions not patients were randomized, very heterogeneous population, small sample size	RCT

9.5.4.1.1. Literatur

Overgaard J, von der Maase H, Overgaard M. A randomized study comparing two high-dose per fraction radiation schedules in recurrent or metastatic malignant melanoma. Int J Radiat Oncol Biol Phys 1985;11:1837-1839
Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. Int J Radiat Oncol Biol Phys 1991;20:429-432

9.5.4.2. Aktualisierungsrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Rades et al, 2014	To compare two different dose groups (20 Gy *versus* 21-22.5 Gy) in respect to local control of the treated metastases, freedom from new brain metastases and overall survival	Retrospective review of patient files	54 melanoma patient with 1-3 newl diagnosed brain metastases; 20 Gy (N=36) and 21-22.5 Gy (N=18)	1-Y Local control rate Freedom from new cerebral metastases OS	12-month local control was 72% after 20 Gy and 100% after 21-22.5 Gy (p=0.020). Freedom from new cerebral metastases (p=0.13) and survival (p=0.13) showed no		3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					association with SRS dose.		
Rades et al, 2014	To compare three different doses of stereotactic radiosurgery alone with respect to treatment outcomes in order to contribute to the definition of the most appropriate dose.	Retrospective review of patient files	134 patients were assigned to three groups according to the SRS dose given to the margins of the lesions: 13–16 Gy (*n*=33), 18 Gy (*n*=18), and 20 Gy (*n*=83)	1-Y Local control rate Freedom from new cerebral metastases OS	For 13–16 Gy, 18 Gy, and 20 Gy, the 1-year local control rates were 31, 65, and 79%, respectively (p<0.001). The SRS dose maintained significance on multivariate analysis (risk ratio: 2.25; 95% CI: 1.56–3.29; p<0.001). On intergroup comparisons of local control, 20 Gy was superior to 13–16 Gy (p<0.001) but not to 18 Gy (p=0.12); 18 Gy showed a strong trend toward better local control when compared with 13–16 Gy (p=0.059). Freedom from new brain metastases	Overlapping patients with the previous publication	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(*p*=0.57) and survival (*p*=0.15) were not associated with SRS dose in the univariate analysis.		

9.5.4.2.1. Literatur

Rades D, Sehmisch L, Huttenlocher S et al. Radiosurgery Alone for 1-3 Newly-diagnosed Brain Metastases from Melanoma: Impact of Dose on Treatment Outcomes. Anticancer Res. 2014 Sep;34(9):5079-82.
Rades D, Hornung D, Blanck O et al. Stereotactic radiosurgery for newly diagnosed brain metastases: comparison of three dose levels. Strahlenther Onkol. 2014 Sep;190(9):786-91.

10. AG Nachsorge

10.1. Frage IX.3. Selbstuntersuchung im Rahmen der Nachsorge - Adaptation

Frage IX.3. Sollte die Selbstuntersuchung ein Bestandteil der Nachsorge sein?

10.1.1. Synopse (kurz)

Thema/Fragestellung	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005	LL Kanada Cancer Care Ontario 2007
3. Sollte die Selbstuntersuchung ein Bestandteil der Nachsorge sein?	Notwendiger Bestandteil der Nachsorge (C)	Bestandteil der Nachsorge für jeden Patienten, lebenslang; Durchführung von Schulungen zur Selbstuntersuchung durch Ärzte oder Pflegekräfte	LL Frankreich French National Authority for Health 2005	nur relevant für medikamentöse Therapien

10.1.2. Empfehlung, Hintergrundstext und Literatur australischen und französischen Quell-Leitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
Schlüsselempfehlungen	S. 122 1. Self-examination by patients is essential and they should be taught the	Empfehlungen zur Selbstuntersuchung in der NICE Guideline beziehen sich nur auf SCC und BCC, daher werden hier die Angaben aus dem Guideline Evidence	S. 51 Suivi Stade I AJCC

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	process. Routine follow-up by the patient's preferred health professional may be appropriate to emphasise sun smart behaviour and perform skin checks Grade of Recommendation: C	Review wiedergegeben:	Standards […] ■ éducation du patient à 'autodépistage d'un nouveau mélanome et à l'autodétection d'une récidive. *Nachsorge* *Stadium I nach AJCC* *Standards* *[…]* ■ *Anleitung des Patienten zur Selbstuntersuchung auf ein neues Melanom und zur selbständigen Erkennung eines Rezidivs.* Stades IIA et IIB AJCC Standards […] ■ éducation du patient à l'autodépistage d'un nouveau mélanome et à l'autodétection d'une récidive. *Stadien IIA und IIB* *Standards* *[…]* ■ *Anleitung des Patienten zur Selbstuntersuchung auf ein neues Melanom und zur selbständigen Erkennung eines Rezidivs.*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
			Stades IIC et III AJCC Standards […] ■ éducation du patient à l'autodépistage d'un nouveau mélanome et à l'autodétection d'une récidive. *Stades IIC et III AJCC* *Standards* *[…]* ■ *Anleitung des Patienten zur Selbstuntersuchung auf ein neues Melanom und zur selbständigen Erkennung eines Rezidivs.*
Hintergrundtexte	S. 121 – 122 19.2 Undertaking follow-up Current guidelines world-wide do not specify where routine follow-up should take place or who should do it. [6,7] However, it is becoming accepted by most [8–10] but not all [11–13] that patients themselves rather than doctors are likely to detect their own recurrence. Those studies reporting a high patient-detection rate attribute this to patients receiving thorough explanations of the signs and symptoms of recurrences and new primary melanomas. Despite such	S. 370 (Guideline Evidence Review) Patient self examination The questions *In the follow-up of patients with skin cancer, what is the usefulness of education for self examination?* The nature of the evidence Twelve papers were identified representing eleven studies (with one RCT reported at two stages of follow-up) as follows: · One RCT of good quality	S. 51 JUGEMENT ARGUMENTÉ DES EXPERTS […] Face à l'ensemble de ces considérations, il semble raisonnable d'envisager une surveillance minimale, à savoir basée essentiellement sur l'examen clinique et l'éducation du patient à l'autodépistage. Pour les mélanomes de stade I AJCC qui présentent globalement un faible risque de récidive, l'examen clinique annuel ou biannuel aura pour objectif la détection d'un éventuel second mélanome. Pour les patients de stades II et III AJCC, une

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	explanations, it is obvious that the ability of individual patients to detect recurrence varies. Some can identify recurrences that are not discernible to doctors, while others can be unaware of a large tumour mass. The existence of these latter patients perhaps explains the reticence of some centres to forego routine follow-up. In Australia, with its heightened awareness of the disease, up to 75% of patients detect their own recurrences. [14] World-wide the mean percentage is 62%. [1] The UK Medical Research Council has designed a 'framework for the design of an integrated follow-up program'. [15] One technique employed was to interview patients to determine their preferred follow-up requirements. Most supported follow-up by general practitioners, and felt that the main purpose of follow-up was reassurance. However, there was concern over travelling times, costs, brevity of consultations, and poor continuity. Nearly all queried the experience and skill of the general practitioners and said training would be vital, with rapid access	· One systematic review of good quality · One case control study of good quality · Eight observational studies, four of good quality, one of fair quality and three of poor quality Only one study originates from the UK. Seven studies are from the US, one study is from Australia and two studies are from Italy. Generalisability to the UK is therefore limited. Seven studies are of patients at risk of melanoma based upon family history or presence of naevi. Three studies are of screened populations and two studies are of patients with proven melanoma. Summary of the supporting evidence for the recommendations Self examination (SE) versus physician examination There is consistent evidence that expert physician examination has greater reliability than SE in detecting melanoma. Systematic review evidence suggests that melanoma lesions detected by physicians are thinner than those detected by patients. Observational study evidence suggests that detection by dermatologist	échographie ganglionnaire de la zone de drainage peut être envisagée en option (accord d'experts). Les autres examens d'imagerie (à la recherche de métastases à distance) n'ont pas apporté la preuve qu'ils pouvaient influer sur la survie en partie du fait de l'absence de thérapeutique efficace à ce stade. En l'absence d'études portant spécifiquement sur l'intérêt de la surveillance et de son rythme, il n'est pas apparu possible de formuler des conclusions *evidence-based* à partir de la littérature. De ce fait, les recommandations qui seront établies ne pourront reposer que sur des accords d'experts et seront le reflet d'un consensus pour un protocole de surveillance minimum basé sur l'examen clinique complet et l'éducation du patient à 'autodépistage. CONFRONTATION Les nouvelles données identifiées convergent globalement avec les données présentées dans les documents initiaux de 1995 et 1998 et apportent de nouveaux éléments, notamment

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	to specialist advice if necessary. Total skin examination, instruction in self-examination and the provision of more information were seen as desirable at visits to general practitioners. Other studies assessing patients' opinions of the value of follow-up [6,16] found that most considered routine follow-up worthwhile, with only a few considering that it was not. While favouring follow-up, more than half the patients in these studies reported anxiety before each visit. Evidence summary There is a consensus that the majority of patients detect their own recurrence if they have received a thorough explanation of the signs and symptoms of recurrences and new primary melanomas LoE: IV References: 14–16 Self-examination may be combined, if appropriate, with routine follow-up by the patient's preferred health professional LoE: IV	is associated with earlier melanoma diagnosis and that input by physicians is the strongest single determinant of SE, although there is little evidence for improved survival arising from recurrences of melanoma diagnosed by patients compared to recurrences diagnosed by hospital doctors. The same level of evidence suggests that SE based on naevi count has poor concordance with dermatological assessment for risk of melanoma and is not reliable. Factors affecting SE Studies have identified a number of patient characteristics and also events which are associated with SE. Systematic review evidence suggests that elderly men have lower rates of SE. There is observational study evidence that factors associated with greater likelihood of patients performing self skin examination are: · skin awareness · habitual sun protection · previous benign skin biopsy · family cancer history · personal history of skin cancer	concernant l'échographie ganglionnaire qui peut être proposée pour le suivi des patients opérés de stades II et III AJCC (option, accord d'experts). L'examen clinique complet et l'éducation à l'autodépistage du patient restent le standard. La fréquence est à adapter au stade du patient : une à deux fois par an pour les patients atteints d'un mélanome de stade I et tous les 3 mois pour les autres stades. S. 51 *BEGRÜNDETES URTEIL DER EXPERTEN* *[…]* *Im Angesicht dieser Überlegungen scheint es vernünftig, eine minimale Überwachung in Erwägung zu ziehen, das heißt im Prinzip basierend auf der klinischen Untersuchung und der Anleitung des Patienten zur Selbstuntersuchung.* *Bei Melanomen im Stadium I nach AJCC, die insgesamt ein geringes Rezidivrisiko haben, wird die jährliche oder zweijährliche klinische Untersuchung die Erkennung eines eventuellen zweiten*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
	References: 14–16	· physician or nurse examination or recommendation · help from a spouse (especially wives assisting husbands) · presence of a wall mirror · age <50 years The same level of evidence suggests that older patients may be less likely to perform SE. Rates of SE Estimates of rates of SE vary widely within the studies identified, according to factors such as populations studied and different definitions of SE or questions used by researchers to ascertain rates of SE. Subsequently, estimates of rates of SE from observational studies have range 9% to 87%. A rate of 71.6% for SE performed within the preceding year, was reported amongst first degree relatives of melanoma patients by Manne et al., (2004). Systematic review evidence suggests that the effect of promoting SE cannot be distinguished from that of routine screening in patients seeing the physician for unrelated reasons. RCT and case control study evidence suggests that rates of SE can be significantly improved	*Melanoms zum Ziel haben.* *Für Patienten in den Stadien II und III nach AJCC kann eine Lymphknoten-Sonographie des Abflussgebietes als Option ins Auge gefasst werden (Expertenmeinung).* *Andere bildgebende Verfahren (zur Suche nach Fernmetastasen) haben noch nicht den Beweis erbracht, dass sie das Überleben beeinflussen, zum Teil aufgrund einer fehlenden effektiven Therapie in diesem Stadium.* *Durch das Fehlen von Studien zum Thema Nachsorge und Nachsorge-Intervalle scheint es nicht möglich, aus der Literatur evidenzbasierte Schlussfolgerungen zu ziehen.* *Daher beruhen die gegebenen Empfehlungen nur auf Expertenmeinung und spiegeln einen Konsensus für eine minimale Nachsorge basierend auf vollständiger klinischer Untersuchung und Anleitung des Patienten zur Selbstuntersuchung wider.* *GEGENÜBERSTELLUNG* *Die neuen Daten deuten in die gleiche Richtung wie die Daten aus den ersten Dokumenten von 1995 bis 1998 und*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		through educational interventions. Role of photography in SE Evidence from one RCT suggests that the use of photography as an adjunct to health education produces no short term (i.e. same day as intervention) difference in compliance above standard education for SE but the same level of evidence is suggestive of a four month follow-up advantage in terms of rate of SE through the use of photographs. Benefit of SE Case control study evidence suggests that SE is associated with a marginally significant reduced risk of melanoma incidence: OR 0.66 [95% CI 0.44-0.99] which is reportedly an inexpensive screening method. Observational study evidence suggests that female sex, high educational level and performance of SE are associated with thinner melanoma tumours. · The prevalence study by Aitken et al. (2004) found that 25.9% of randomly selected adults reported whole body SE within the last 12 months and 1055	*bringen neue Elemente ein, vor allem bezüglich der Lymphknoten-Sonographie, die für die Nachsorge von operierten Patienten der Stadien II und III empfohlen werden kann (Option, Expertenkonsens).* *Die vollständige klinische Untersuchung und die Anleitung zur Selbstuntersuchung des Patienten bleiben Standard.* *Die Nachsorgefrequenz ist an das Stadium des Patienten anzupassen: ein- bis zweimal für Patienten mit Melanom Stadium I und alle 3 Monate für Patienten der anderen Stadien.*

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		(33.9%) within the last 3 years and concluded that input by physicians is the strongest single determinant of SE. · The case control study by Berwick et al. (1996) found that SE was performed by 15% of all subjects (patients with melanoma and population matched controls) and was associated with a marginally significant reduced risk of melanoma in all subjects: OR 0.66 [95% CI 0.44-0.99]. · The qualitative study by Berwick et al. (2000) found that amongst a sample of patients with a history of melanoma and also lower risk patients without a history of melanoma, the rate of reported SE was 32% at baseline, rising to 64% after an educational intervention (p = 0.03). · The survey of patients referred by their GPs to a pigmented lesion clinic undertaken by Carli et al. (2002) found poor concordance between SE and dermatological assessment for both common and atypical naevi and concluded that SE of melanoma risk is not reliable. · The case series study by Carli et al. (2003) found that 40.6% of patients with	

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		melanoma sampled self detected their melanoma tumour. Female sex (OR 0.70 [95% CI 0.50-0.97]), high educational level (0.44 [95% CI 0.24-0.79]) and performance of SE (0.65 [95% CI 0.45-0.93]) were factors associated with thinner tumours. 48% of patients performed SE, but only 20.4% regularly. · The systematic review by Helfan et al. (2001) found melanoma lesions detected by physicians to be thinner than those detected by patients. Elderly men had lower rates of SE and the authors recommended that physicians perform skin examination in these patients. The authors reported that the effect of promoting SE cannot be distinguished from that of routine screening in patients seeing the physician for unrelated reasons. · The qualitative survey of first degree relatives of patients with melanoma by Manne et al. (2004) found the rate of SE in the last year to be 71.6%. SE correlated closely with having received a clinical skin examination by a physician. · The case series study of patients with	

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		metastatic melanoma by Odili and Evans (2001) found that 56% of cases of recurrent melanoma were patient detected and no significant difference in survival between recurrences diagnosed by SE and those diagnosed by hospital doctor were found. · The qualitative study by Oliveria et al. (1999) found that amongst a sample of Caucasian people without melanoma, skin awareness was a strong factor associated with SE whereas older age and higher education was associated with a decreased likelihood of performing SE. · The RCT by Phelan et al. (2003) compared nurse education for SE and provision of skin photographs with nurse education and provision of standard brochure in patients with 5 or more dysplastic naevi, with or without a history of melanoma. The mean group scores for knowledge, awareness and confidence increased in both groups at immediate follow-up ($p < 0.0001$) but there were no significant differences in scores between the photography group and the brochure group.	

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005
		· The RCT of patients at high risk for melanoma based upon dysplastic naevi by Oliveria et al. (2004) provided further follow-up to the study by Phelan et al. (2003) and found that a teaching intervention with photo book demonstrated a 51% increase in 3 or more reported examinations at 4 month follow-up, compared to a 17.6% increase in the group which received teaching only [p = 0.001]. · The observational pilot study (as part of a subsequent trial) by Weinstock et al. (2004) found the rate of SE amongst patients attending for routine follow-up visits to be between 12% and 38%. Help from a partner and presence of a wall mirror were associated with higher rates of SE whereas visual impairment was found to be associated with lower rates of SE.	
Bemerkungen		Diese Leitlinie bezieht sich auf MM und auf NMSC.	Keine Literaturangaben zu Fragen der Selbstuntersuchung; Angaben sind daher nur konsensbasiert.

Literatur:

LL Australien New Zealand Guidelines Group 2008
7. Bain NS, Campbell NC, Ritchie LD, et al. Striking the right balance in colorectal cancer care--a qualitative study of rural and urban patients. Fam Pract 2002;19:369-374

11. Basseres N, Grob JJ, Richard MA, et al. Cost-effectiveness of surveillance of stage I melanoma. A retrospective appraisal based on a 10-year experience in a dermatology department in France. Dermatology 1995;191:199-203
6. Baughan CA, Hall VL, Leppard BJ, et al. Follow-up in stage I cutaneous malignant melanoma: an audit. Clin Oncol (R Coll Radiol) 1993;5:174-180
16. Dancey A, Rayatt S, Courthold J, et al. Views of UK melanoma patients on routine follow-up care. Br J Plast Surg 2005;58:245-250
1. Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localised primary cutaneous melanoma. Lancet Oncol 2005;6:608-621
14. Francken AB, Shaw HM, Accortt NA, et al. Detection of first relapse in cutaneous melanoma patients: implications for the formulation of evidence-based follow-up guidelines. Ann Surg Oncol 2007;14:1924-1933
27. Garbe C, Paul A, Kohler-Spath H, et al. Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy. J Clin Oncol 2003;21:520-529
13. Hofmann U, Szedlak M, Rittgen W, et al. Primary staging and follow-up in melanoma patients--monocenter evaluation of methods, costs and patient survival. Br J Cancer 2002;87:151-157
10. Jillela A, Mani S, Nair B, et al. The role for close follow-up of melanoma patients with AJCC stage I-III: a preliminary analysis. Proc Am Soc Clin Oncol 1995; 14:413
8. Kersey PA, Iscoe NA, Gapski JA, et al. The value of staging and serial follow-up investigations in patients with completely resected, primary, cutaneous malignant melanoma. Br J Surg 1985;72:614-617
15. Murchie P, Hannaford PC, Wyke S, et al. Designing an integrated follow-up programme for people treated for cutaneous malignant melanoma: a practical application of the MRC framework for the design and evaluation of complex interventions to improve health. Fam Pract 2007;24:283-292
12. Poo-Hwu WJ, Ariyan S, Lamb L, et al. Follow-up recommendations for patients with American Joint Committee on Cancer Stages I-III malignant melanoma. Cancer 1999;86:2252-2258
9. Ruark D, Shaw H, Ingvar C, et al. Who detects the primary recurrence in stage I cutaneous melanoma: patient or doctor? Melanoma Res 1993; 3(Supplement 1):44.

LL GB NICE 2006

Siehe Evidence Table 5.3, S. 375 – 379 des Guideline Evidence Review

10.2. Frage IX.4., IX.5. und IX.6. Nachsorge-Dauer und -Intervalle – De-novo-Recherche

Frage IX.4. Wie lange sollte die Nachsorge von Melanompatienten erfolgen?
Frage IX.5. In welchen Intervallen sollte die Nachsorge erfolgen?
Frage IX.6. Welche Untersuchungen sind im Rahmen der Nachsorge bei asymptomatischen Patienten indiziert?

10.2.1. PICO, Suchwörter

Suchwörter			
Stichwort	melanoma	Surveillance	Relapse
Synonyme		Follow-up, After-care, aftercare, post-operative care	recurrence
Ober-/Unterbegriffe, Mesh Term	S. Suchstrategie (Kapitel 7.4.2. und Kapitel I.6.)		

10.2.2. Datenbanken, Suchstrategien, Trefferzahlen

10.2.2.1. Primärrecherche 2012

Datenbank	**Suchstrategie**	**Datum**	**Treffer**
1. Suche			
Medline	"melanoma"[tiab] AND ("relapse"[tiab] OR "recurrence"[tiab] OR "surveillance"[tiab] OR “follow-up”[tiab] OR aftercare[tiab] OR “after-care”[tiab] OR “post-operative care”)	23.01.2012	7047
Cochrane Library	(melanoma and (surveillance or "follow up")).ti.	23.01.2012	278
Embase	(melanoma and (surveillance or "follow up")).ti.	23.01.2012	443

Datenbank	Suchstrategie	Datum	Treffer
2. Suche	s. “Evidenztabelle I.6, I.7, I.8, VII.6”, Kapitel I.6		
3. Suche/Ergänzungen	("second primary"[title] AND melanoma) OR "second melanoma"[title] OR ("multiple primary"[title] AND melanoma)	23.01.2012	186
Bemerkungen: Datum der Erst-Recherche (1. Suche) für Medline und Cochrane war der 21.12.2010 bzw. für die Ergänzungs-Recherche (3. Suche) der 08.06.2011. Die erste EMBASE-Recherche erfolgte am 11.05.2011. Eine letzte Update-Recherche (initiale Suche, Ergänzungsrecherche) erfolgte am 23.01.2012 für EMBASE, am 26.01.2012 für Medline bzw. am 19.01.2012 für Cochrane. In den Tabellen angegeben sind die Zahlen der letzten Update-Recherche. Die Daten für die zweite Suche für die Frage VII.6 entnehmen Sie bitte der Tabelle „I.6, I.7, I.8, VII.6“ unter Kapitel I.6.			

10.2.2.2. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	"melanoma"[tiab] AND ("relapse"[tiab] OR "recurrence"[tiab] OR "surveillance"[tiab] OR “follow-up”[tiab] OR aftercare[tiab] OR “after-care”[tiab] OR “post-operative care”) AND ("2012.01.24"[Date - Publication] : "3000"[Date - Publication])	02.10.2016	3004
Cochrane Library	(melanoma and (surveillance or "follow up")).ti.	04.10.2016	135

10.2.3. Auswahlkriterien

10.2.3.1. Primärrecherche 2012

Auswahl der Literatur	
Gesamttreffer	7954

Auswahl der Literatur		
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt	
Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research	
Anzahl nach Abstractscreening		163 (inkl. Dupletten)
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung		59
Bemerkungen Zum Thema “multiple melanomas” liegt ein Review von Francken et al. (2005) vor, das Studien bis Februar 2004 umfasst, das in diese Tabelle ebenfalls mit aufgenommen wurde. Die Tabelle enthält alle relevanten Rechercheergebnisse für die Fragen VII.4., VII.5., VII.6. Die Literatur wurde entsprechend der Fragestellungen zugeteilt, s. hierfür auch die Übersicht am Ende der Tabelle. Im Rahmen der AG-Treffen wurde durch die Experten eine konsensbasierte Beantwortung der Frage VII.5 entschieden. Da diese Entscheidung nach erfolgter Literatursuche getroffen wurde, sind die Ergebnisse der Frage VII.5 in dieser Tabelle aufgeführt. Auch die Nachsorgetabelle zu den verschiedenen Untersuchungen und Intervallen zu den jeweiligen Tumorstadien wurde konsensbasiert erstellt auf Basis der vorliegenden Literatur. Aufgrund der Studiendesigns und von thematischen Überschneidungen ist eine strikte Auftrennung der Literatur nach Fragestellung nicht möglich. Aus diesem Grund wurde die Literatur, bei gleicher Suchstrategie, in dieser Tabelle zusammengefaßt. Studien zu der Frage VII.6 zu der hier aufgeführten Suchstrategie befinden sich in dieser Tabelle. Weitere Studien zu der Frage VII.6, die im Rahmen der 2. Literaturrecherche/Ergänzungen (s.o.) identifiert wurden, sind in der Tabelle „I.6, I.7, I.8, VII.6_kurz“enthalten.		

10.2.3.2. Aktualisierungsrecherche 2016

Auswahl der Literatur		
Gesamttreffer		3139
Einschlusskriterien	Thematische Übereinstimmung Sprachen: e,dt	

Ausschlusskriterien	Case Reports, narrative Reviews, Bench Research
Anzahl nach Abstractscreening	84 (inkl. Dupletten)
Anzahl ausgewählter Volltexte, vorgesehen für Bewertung	40
Bemerkungen Die Tabelle enthält alle relevanten Rechercheergebnisse für die Fragen IX.4., IX.6.	

10.2.4. Evidenztabelle

10.2.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Leiter et al. (2011)	To analyze stage- and time-dependent hazard rates (HR) and to discuss current surveillance recommendations.	Prognostic study	33,384 patients with CM stage I-III	Overall survival Relapse-free survival Hazard ratios (HRs) for recurrences and secondary melanoma	melanoma-specific 5- and 10-year survival: 91.9% and 87.2%, respectively Recurrences recorded in 4999 patients (15.3%; stage I, 7.1%; stage II, 32.5%; and stage III, 51.0%) median RFS time: 44 months 10-year recurrence-free survival was 78.9% (95%	Very large and multi-center patient cohort	1b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					confidence interval 73.1-90.5); in stage I, 89.0%; stage II, 56.9%; and stage III, 36.0%. HR for recurrent CM: - Stage IA: constantly low level HR </= 1:125 per year - stage IB: higher HRs >/= 1:40 for the first 3 years and generally in stages II to III From 3 years of follow-up onward, stage II and III CIs overlapped/ no significant differences for the development of recurrences. After 10 years of follow-up HR of all 3 stages did not differ significantly.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Of all patients 2.3% developed secondary melanomas, with a consistently low HR < 1:220 per year		
Voit et al. (2001)	to evaluate whether early detection of metastases improves relapse-free and overall survival	Diagnostic study	829 consecutive macroscopically disease-free melanoma patients	Sensitivity Specificity Positive predictive value (PPV) negative predictive value (NPV) Survival relapse-free survival overall survival 2- and 4-year survival rates	Physical examination (PE): sensitivity 25.2%, (95% confidence interval [CI]: 19.9 – 31.2%), PPV 57.5%, (95% CI: 47.5–66.9%). specificity: 98,4%, NPV 93.8%. ultrasound B-scans (UBS): sensitivity 99.2%, 95% CI: 97.3–99.6%, specificity: 98.3% (95% CI: 97.7–98.7%), PPV: 83.3% (95% CI: 78.5–87.4%), NPV: 99.9% (95% CI: 99.6–100.0%. B-scan was highly	No information about the examiner (blinded for the results of the other examination?)	1b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					superior to physical examination (P = 0.001). Out of 242 proven melanoma metastases, 24.8% were detected by both methods simultaneously. Survival curbes: see full-text		
Francken et al. (2005)	To discuss frequency and duration of follow-up, type of health professional involved, optimum intensity of routine investigation, and patients' satisfaction with follow-up.	Systematic review (without meta-analysis)	72 articles included Given separately for every included study (see original article)	Various	first recurrence: - 20–28% local or in-transit recurrences - 26–60% regional recurrences - 15–50% distant metastases Ultimately - 3–5% local or in-transit recurrence - 5–13% regional nodes - 3–10% distant metastates	Systematic literature search, but no meta-analysis (no summary of effect measures)	2a

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					62% of patients detected their first recurrence themselves frequency of late recurrences (DFS>10 years) between 1% to 25% Incidence of subsequent PM: 2% to 7% Optimum frequency and length of follow-up services: no true evidence for follow-up surveillance in localised melanoma according to the articles In no study any benefit in DFS or OS associated with follow-up surveillance		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Peric et al (2011)	determine whether regular measurements of serum S100B are a useful tool for discovering patients with CM metastases and to evaluate the diagnostic value of PET-CT during the follow-up	Diagnostic study	115 CM patients included in regular follow up (82 patients with clinical signs of disease progression, 33 (28.7%) asymptomatic patients with two subsequent elevated values of S100B)	Sensitivity Specificity PPV NPV	S100B: Sensitivity, specificity, PPV and NPV 33.8%, 90.9%, 96.0% and 17.5% respectively in patients with clinical signs of disease progression. Sensitivity and PPV of S100 in asymptomatic patients were 100.0% and 69.7%. PET-CT: sensitivity, specificity, PPV and NPV of PET-CT for symptomatic patients: 98.5%, 90.9%, 98.5% and 90.9% sensitivity, specificity, PPV and NPV of PET-CT for asymptomatic patients: 100%, 90.0%, 95.8% and		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					100%		
Kruger et al. (2011)	to demonstrate the high efficacy of ultrasonography as a noninvasive technique for early detection of lymph node involvement during clinical follow-up, especially in patients with subclinical metastases.	Diagnostic study	433 melanoma patients with stage-dependent follow-up intervals of 3 to 12 months	Sensitivity Specificity	Sensitivity and specificity of combined clinical and sonographic investigations: 0.9394 (95% confidence interval: 0.7977–0.9926)] and 0.9808 (95% confidence interval: 0.9717–0.9875)] respectively. combinatorial approach was significantly superior with regard to detection of metastases compared with clinical investigations alone (P<0.0001) Significant differences between clinical	Prospective design	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					follow-up and sonographically assisted follow-up for stages I (P = 0.0389), III(P = 0.0101), and IV (P =0.0016).		
Turner et al. (2011)	to relate the estimated delay in diagnosis of recurrence or SPM in patients with stage I or II melanoma to the number of visits needed by two different monitoring schedules. Secondarily, to estimate the effect of prognostic factors on development of recurrence or SPM	Prognostic study	2,998 consecutive patients first diagnosed with stage I or II melanoma	Delay in diagnosis of recurrence predictors of developing new primary	small difference in modeled delay in diagnosis (extra 44.9 and 9.6 patients per 1,000 for recurrence and new primary, respectively, with delay >2 months) using a schedule that requires far fewer visits (3,000 fewer visits per 1,000 patients) than recommended by current guidelines. AJCC substage= predictor of recurrence age and date of	Big patient cohort	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					primary diagnosis=predictors of developing new primary		
Aukema TS et al. (2010)	to assess the clinical relevance of increased S-100B during follow up of high-risk melanoma patients and to determine the value of subsequent whole-body PET/CT and brain MRI.	Diagnostic study	46 melanoma patients who were found to have an elevated serum S-100B level during follow-up	survival Accuracy Sensitivity Specificity negative predictive value (NPV) positive predictive value (PPV) False-positives (FP) False negatives (FN)	Median of the elevated S-100B serum levels during follow-up: 0.14 µg/L, range 0.10–1.33 µg/L. PET/CT: hypermetabolic lesions in 27 of 46 patients (59%). FN: n=0 FP: n=4 by median follow-up of 1 year sensitivity: 100% specificity: 83% accuracy: 91% PPV: 85% NPV: 100%. MRI: Brain metastases in 1 patient (2%). NPV: 100%	sensitivity of MRI not determined because of the low incidence of brain metastases. Small population	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					specificity: 100% PPV of an elevated serum S-100B: 50% (S-100B level>0.10 µg/L). Of the 23 patients with a true positive PET/CT scan, 6 (26%) received surgical treatment with curative intent; 17 (74%) received palliative treatment or supportive care. 2-year-survival: 51.9% in patients with a positive PET/CT compared with 100% in the patients with normal PET/CT findings (P=0.002).		
Brown RE et al. (2010)	to determine the clinical efficacy of routine CXR for recurrence	Diagnostic study	1,235 patients with invasive cutaneous melanoma ≥1.0	Sensitivity Specificity	210 patients (17.0%) had a recurrence: local or in-transit in 36,2%,	post hoc analysis on data from a prospective, randomized,	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	surveillance in melanoma.		mm in Breslow thickness and without clinical evidence of regional or distant metastases	PPV NPV	distant (nonlung) metastases in 35,2%, lung-only metastases in 13,3%. 99% (n = 4,180) of CXR were read as either ''normal'' or falsely positive (FP). 0.9%(n = 38) of all CXR obtained were true positives (TP). Sensitivity and specificity: 7.7% and 96.5%, respectively.	multiinstitutional study on melanoma (Sunbelt Melanoma Trial) no information about reference standard	
Hohnheiser et al. (2010)	to identify factors that influence time to recurrence and survival after the first recurrence with a special interest in late recurrences.	Prognostic study	2487 patients with the first manifestation of a cutaneous malignant melanoma	Overall survival Time to first recurrence Prognostic factors	Significant independent prognostic factcors for survival (Cox regression analysis): - patient's age - sex - tumor localization, - pT	Retrospective review (prospective database) Large patient cohort	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- pN. median time to first recurrence: 24 months. 5-recurrence-rate: 81.6% late recurrences-rate (>10-years): 6.5% independent factors for time to recurrence. (Cox regression analysis) - age at primary - treatment - pT - pN - type of recurrence were found to be independent factor influencing survival after a first recurrence: - type of		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					recurrence (advanced age at diagnosis of recurrence male sex marginally significant)		
Leiter et al. (2010)	To investigate whether detection in an early phase is associated with prolonged survival and whether the observed longer survival times are a mere consequence of detection at an earlier time point (lead time bias).	Prognostic study	1969 patients with melanoma stage I – III, recurrences in 112 patients	disease-specific mortality Overall survival (OS) Survival after recurrence (SAR) Adjusted survival time by using sjourn time	disease-specific mortality: 69.6% (n=78). Overall 10-year survival rate: 36.1% 10-year SAR survival rate: 25.4% 10-year OS probability for detection in early phase: 42.6% for early phase vs. 25.6% for advanced phase (P = 0.012) Adjustment for lead time: 10-year OS probability: 40.5%	Adjustment for important confounding factor Estimated sojourn time (no evidence base available) Missing data in 10 of 112 patients for Cox proportional hazard model	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					(95 CI: 27.4, 53.6) for early phase recurrences vs.25.6% (95% CI: 12.5, 38.7) for advanced phase metastases (P=0.021) independent prognostic factors (multivariate analysis): - detection of early phase metastases (P = 0.022) - stage at primary diagnosis (P <0.0001)		
Rueth et al. (2010)	To examine whether conditional survival (CS) is more accurate in predicting longterm melanoma survival.	Prognostic study	8647 T2-T4 patients patients who underwent surgical treatment for melanoma	cancer-specific survival 10-year-survival rate	At diagnosis: 10-year survival rates: low-risk: 79.6% high-risk: 41.2% P<0.001 initial predictors of survival: age, gender, location, ulceration	Very large patient cohort Only available study which gives data for this outcome (conditional survival) CS is a function of	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					On CS analysis: - survival differences until 8 years after treatment - 10-year survival rates: low-risk :95.4% high-risk: 91.7% P = 0.51 On Multivariate analysis: age, gender, location, ulceration: no longer predictive after 8 years	the traditional survival estimates, adjusted to reflect the probability of survival conditioned on living to a certain point in follow-up the low-risk category: T2–T3, N0 high-risk category T4N0 or T2-4N1-3	
Murchie et al. (2010)	to evaluate the effects of GP-led melanoma follow-up on patient satisfaction, in comparison to hospital-led follow-up, follow-up guideline compliance, anxiety and depression, as well	RCT	142 melanoma patients free of recurrent disease	Patient satisfaction measured by questionnaire Adherence to guidelines Health status measured by SF-36 Anxiety and depression	cluster-adjusted mean summary satisfaction score: - at baseline no significant difference between groups - at follow-up significantly lower in the intervention group 26.4 (95% CI: 24.9–	Reliable randomization design; blinding not possible Study took place in Scotland; transferability to German health care system?	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	as health status.			measured by the Hospital Anxiety and Depression Scale HADS	27.9) vs 33.5 (95% CI: 32.5–34.4), Adherence o guidelines: - in the year before the study: 84,9% in the intervention group and 85.4% of the control group - At follow-up: 98.1% in the intervention group and 80.9% of the control group SF-36 scores and HADS score: no statistically significant differences between groups at either baseline or follow-up.		
Morton RL et al. (2009)	to evaluate the accuracy of detecting asymptomatic pulmonary	Diagnostic study	108 patients AJCC stage IIIA/B (N1a, N2a) disease	sensitivity specificity time to diagnosis	CXR: sensitivity, 48%; 95% confidence interval [95% CI], .27–.68) specificity, 78%;	Not all patients receive verification using a reference standard (only patients with	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	metastases by surveillance chest X-rays (CXRs) in melanoma patients with a positive SNB			survival	95% CI, .77–.79 Additional metastatic disease was apparent in 18% of CXR-detected versus 76% of non-CXR-detected patients (p<0.05) median time to diagnosis of pulmonary metastases: 24 months (95% CI, 12–41) vs. 16 months (95% CI, 10–30, p = 0.30 log rank). median survival of 42 months (95% CI, 24–84)vs. 36 months (95% CI, 18–46, p = 0.53 log rank)	positive CXR)	
Tarhini AA et al. (2009)	To asses the effect of elevated serum S100B level at baseline and	Progostic study	Sera from 670 patients with high risk melanoma (≥stage IIB disease)	Overall survival (OS) RFS	median OS time: 7.2 years (95% CI, 6.0 years to not reached). RFS time:	Patients were included in an intergroup trial E1694 was a	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	during therapy.		banked at baseline and 3 additional time points were tested for S100B		3.1 years (95% CI, 2.4 to 3.7 years). Multivariate analysis was performed adjusting for significant prognostic factors (ulceration and lymph node status) and treatment. Baseline S100B was a significant prognostic factor for survival (HR = 1.39; 95% CI, 1.01 to 1.92; P = 0.043) S100B values measured at later time points over 1 year were also demonstrated to be significant prognostic factors for RFS and OS. Lower S100B values at baseline and during follow-up were associated	randomized comparison of heGM2ganglioside vaccine (GMK) versus HDI that accrued 880 patients. No information about staging	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					with longer survival.		
Leiter et al. (2009)	To develop an efficient and cost-effective surveillance strategies, dependent on tumor stage	Economic study	Same cohort as Leiter et al. (2010) and Garbe et al. (2003) 1969 patients	Total costs Costs per recurrence detection	Total costs for routine melanoma follow-up during this 2-year period: 236.30€patient. Costs for follow-up examinations in: - stage I: 307914€/887261 - stage II: 62673€/252292$ - stage III: 89651€/352214$) costs for the detection of one recurrence for physical examination and LN sonography: - stage 14289€/4391$ and 18035€/131423$ - stage II: 500€/512$ and 1333€/9712$	Retrospective analysis of prospective study data For detailed tables of costs, see original publication The calculation of costs was based on the 2004 GOÄ (Germany) and on the 2004 Medicare fee reimbursement schedule (USA) .	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- stage III: 168€/171$ and 1250€ /9112$, respectively. Cost for CR to detectof one 1 recurrence: - stage I: 22886€/20 512$) (stage II and III: see full-text) Total costs amounted to 990.8€/2208$ per patient (stage I) and up to 1841€/ 4009$ per patient (stage III)		
Egberts et al. (2009)	to investigate whether a serial analysis of protein S-100B in serum with a luminescence immunoassay compared with routine LDH assessment could	Diagnostic study	97 patients with stage II/III disease treated within prospective randomized trials	Sensitivity Specificity PPV	sensitivity to detect metastasis: S-100B: 36.5% vs. LDH: 17,3%, (P=0.006). sensitivity in patients progressing to stage	Treatment bias: Patients were treated with different adjuvant therapies	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	be of value as an indicator of melanoma progression				IV: S-100B: 53.8% vs. LDH: 23.1% (P=0.008) Specificity 98% for both S-100B and LDH PPV: S-100B% 73% vs. LDH: 64%		
Moore Dalal et al. (2008)	to determine the effect of the method of detection of initial recurrences and timing of visit on post-recurrence survival in patients undergoing SLN biopsy	Prognostic study	198 Clinical stage I/II patients who developed recurrence after SLNB and who were evaluable for longterm follow-up	Method of recurrence detection Prognistic factors of survival	Median follow-up after first recurrence: 17 months. Self-detection of recurrences in 55% of patients, 78% were seen earlier than their scheduled visit. Self-detected physical diseases: -24% in-transit -23% nodal Physician detection in 45%, in 46% by a		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					scheduled radiographic test (CXR 16%; CT 29%; PET 1%). method of detection significantly predicted post-recurrence survival ($p<0.05$) Multivariate analysis adjusted for worst site of recurrence, method of detection remained significantly associated with post-recurrence survival ($P = 0.02$) Timing of visit did not affect survival		
Hengge et al. (2007)	to analyze the follow-up of melanoma patients under clinical and economic aspects	Economic analysis	526 melanoma patients stage I-III	Recurrence Method of examination	Detection of 57 recurrences in stages I-III (5-year follow-up period), 61% detected by	Retrospective data Patients kept only about 75% of follow-up	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	on an as-treated basis based on current recommendations of the AJCC/UICC 2002 and the German Dermatologic Society.			Direct medical costs per metastasis QALYs	physician and 39 % by patients. Detection of 25 SPM. The total costs for melanoma follow-up in stages I–III for the 5-year term at the tertiary care university center accounted for 725,095 € ($870,114) - Clinical examinations represented 21,437 € ($145,724) - technical examinations accounted for 286,656 € ($343,987) laboratory costs totaled 317,002 € ($380,402) respectively	appointments (real costs possibly even higher) Costs were calculated according to standardized average fees (GOÄ 2004)	
Ferrone et al. (2005)	To determine the incidence of	Prognostic study	4484 patients diagnosed with a	Incidence of MPM	For 74% of patients, the initial	Retrospective design (prospective	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	multiple primary melanomas (MPM) from a prospective, single-institution, multidisciplinary database, and to describe the clinical and pathological characteristics and risk factors specific to these patients.		first PM, 385 had >=PM	Risk factors for MPM	melanoma was the thickest tumor. estimated cumulative 5-year risk of: - a SPM for the whole cohort: 11.4%, with 5,5% occurring within the 1st year - a MPM for patients with a positive family history or dysplastic nevi: 19.1% and 23.7%, respectively. - a third PM from the date of the SPM: 30.9%, with 15.6% occurring within the 1st year	database)	
Machet et al. (2005)	to study the value of adding ultrasound lymph node examination (7.5 MHz) to the routine clinical	Diagnostic study	373 patients enrolled in a follow-up protocol	Sensitivity specificity	Sensitivity of clinical examination and ultrasound Examination: 71,4% [95%	No information about design (prospective/retrospective)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	examination recommended by French guidelines in melanoma follow-up.				confidence interval (CI) 55.4–84.3] and 92.9 (95% CI 80.5–98.5), respectively. P=0.02). Specificity of clinical examination and ultrasound examination: 99.6% (95% CI 99.2–99.8) and 97.8% (95% CI 97.0–98.4), respectively.		
Goggins et Tsao (2003)	To examine how the risk of a SPM tumor varied with time from diagnosis of CM and examined the patient-specific factors that modify a CM patient's risk of developing a second primary tumor.	Prognostic study	61,245 melanoma patients, of whom 2.32% developed >=1 additional primary CM	Incidence of additional primary CM Risk factors	>/= 1 additional CM in 2.32% of the 61,245 patients during follow-up, ca. 22% of these patients had 2 synchronous primary CMs. HRs correspond to mean rates of 271.3, 227.8, 229.3 and 224.4 cases per 100,000 per year from 1–4	Retrospective design Large patient cohort For cumulative risk and monthly hazard diagrams see original article	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					years, for 5–10 years, 10–15 years, and 15–20 years after diagnosis, respectively. presence of 1st CM on the face, neck, and trunk → increased risk for 2nd CM (in both univariate and multivariate models): stage IV disease → lower risk of 2nd CM		
Garbe et al. (2003)	To prospectively examine and evaluate the results of follow-up procedures in a large cohort of cutaneous melanoma patients.	Prospective cohort study	2,008 patients with stage I-IV	Recurrence detection Time to detection of recurrence Modes of detection	Detection of recurrences: - in 71% on scheduled follow-up examinations - in 17% by patients themselves, in 13% of these recurrences diagnosis was established during	Descriptive study Standardized follow-up procedures Detailed description of procedures and of follow-up of study drop-outs	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					subsequent regular follow-up examinations - in 12% by physicians not participating in the melanoma follow-up schedule In 2,3% of patients, SPM were identified. Modes of detection: see full-text	Data about yield of different imaging methods vs. physical examination not listed here (see original article)	
Manola et al. (2000)	To identify factors that are prognostic for survival in patients with metastatic melanoma treated in eight Eastern Cooperative Oncology Group (ECOG) trials conducted over the past 25 years.	Prognostic study	See fulltext	Survival Relative risks	Median survival: 6.4 months (95% confidence interval, 6.1 to 6.9 months.) F factors conferring the greatest increased risk of death: - number of metastatic sites (RR = 1.12) - ECOG		2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					performance status >= 1 (RR = 1.49) - metastatic disease in the GIT (RR = 1.49), liver (RR = 1.44), pleura (RR = 1.35), or lung (RR = 1.19). Prior immunotherapy (RR = 0.84) and female sex (RR = 0.87)were associated with prolonged survival. response to protocol treatment (RR = 0.57) was a significant prognostic factor: Prognostic for poorer survival: - increased number of sites of metastasis (RR = 1.30) - abnormal LDH (RR = 1.89)		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- abnormal alkaline phosphatase (RR = 1.76) - abnormal platelets (RR = 1.63) - GI metastases (RR 5 1.66)		
Schlagenhauff et al. (2000)	To evaluate the significance of serum protein S100 in screening for metastases during regular follow-up examinations of patients with malignant melanoma.	Diagnostic study	411 melanoma patients with PM with a tumour thickness >= 1.5 mm (237 patients stage II, 148 patients stage III, 26 stage IV)	Sensitivity Specificity False-negatives (FN) True-negative (TN) True-positives (TP) False-positives (FP) Positive predictive value (PPV) Negative predictive value (NPV) efficiency of protein S100 as a diagnostic test	Serum protein S100 cut-off value at 0.13 µg/l: FN: n=28 TN: n=355 TP: n=13 FP: n=15 PPV: 46 NPV: 93 Test efficiency (< 2): 1.39. The protein S100 values of the metastasis group were significantly higher (P =0.0.001). S100: sensitivity: 0.32, specificity: 0.96	Interval between relapse and serum analysis of S100: up to 2 months (clinical situation may change during this interval)	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					cut-off value of 0.08 µg/l (outcomes for this cut-off: see full-text):lower specificity, PPV and test efficiency sensitivity: 41%		
Brobeil et al. (1997)	To determine the impact of an intensive follow-up protocol on the stage of disease at diagnosis of subsequent primary melanomas.	Prevalence study	101 patients with SPM (67 with synchronous and 44 with metachronous SPM)	Incidence of MPM Tumor thickness in primary and secondary lesions	Of 2,600 patients: 4.3% of patients with SPM mean tumor thickness: 1,72 mm for PM vs. 0.58 mm for SPM mean thickness of metachronous melanoma: 2.27 (range 0.18-10.2) mm for PM vs. 0,90 (range 0.11-2.58) mm for SPM initial primary melanomas tended to be thicker (by an average of 3.8 mm, p = 0.008).	Retrospective design Predominantly male patients	2b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Basseres et al. (1995)	To assess the cost-effectiveness of surveillance in stage I melanoma.	Prevalence study	528 patients with melanoma stage I and Clark's level II or higher (214 males, 314 females)	Time to relapse	115/528 patients had relapses. The rate of relapse and the mean time between initial resection and relapse: 9.6% and 37 months for melanoma < 1.5 mm, 34% and 24 months for melanoma of 1.5 to 3 mm, 47.7% and 17 months for melanoma > 3 mm. Time between relapse and last follow-up examination: ≤ 2 months in 9% of cases, ≤ 3 months in 23% and ≤ 4 months in 34%.	Retrospective design For cost analysis see full text of paper	2b
De Giorgi et al. (2010)	To identify main risk factors associated with MPM and to investigate the	Prognostic study	40 patients with MPM	Thickness of SPM Odds ratio of having MPM	Overall mean thickness of melanoma: 0.517 mm for first melanoma and	Retrospective design Small patient sample with	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	association between regular follow up and tumour thickness of a SPM				0.64 mm for SPM (P = 0.12). Significant difference in mean tumour thickness in patients not attending follow up vs. patients adhered to follow up (1.22 mm vs. 0,36 mm) OR of having a diagnosis of MPM in comparison with SPM: - female 1.94 (vs. male) - >/= 1 atypical nevi 4.18 - positive family history 2.18	secondary melanoma	
Bower et al. (2010)	To determine the outcome and incidence of multiple primary melanoma (MPM) and other cancer types among	Prognostic factors	41 melanoma patients with multiple melanoma and no evidence of distant metastasis and no palpable nodal metastasis.	Disease-free-survival overall survival	Thickness of subsequent vs. primary melanomas: median 0,32 mm versus 1,50mm, p<0,0001)	Posthoc analysis from a multi-institutional prospective randomized trial Loss-to-follow-ups	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	patients with melanoma. The risk for secondary nonmelnoma malignancies was also assessed.		(Patients with synchronous lesions not included)		Multivariant analysis: age (p=0,028), lymphovascular invasion (p=0,010) and SSM subtype of the original melanoma (p=0,024) were associated with MPM. Patients with MPM vs. patients with single primary melanoma: - 5-year-DFS: 88,7 vs. 81.3%, p=0,380 - 5-years-OS 95,3 vs. 80%, p= 0,005 detection of secondary melanomas within the first year in 29,3% of patients, detection of subsequent	not commented Patients with melanoma <1mm excluded	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					melanoma within 60 days in 9,8 % after primary melanoma. Median time to development of second primary: 29 months. Nonmelanoma malignancies in 6,1% of patients		
Fusi et al. (1993)	To determine whether there are significant trends in the prognostic factors or in the timing and sites of recurrence.	Prognostic study	250 patients with recurrent malignant melanoma	Time to recurrence Sites of recurrence Survival	Sites of first recurrence: 52% regional nodes, 17% local recurrences, 8% in-transit metastases, 23% to a distant organ. Diagnosis of recurrences: 67% within 24 months, 81% within 36 months Survival after the diagnosis of recurrence was	Retrospective design Population not described in detail	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					independent of: - thickness of the primary tumor - duration of DFI (local, in-transit or regional nodal) diagnosis of distant organ metastasis: shorter survival local recurrence, in-transit metastasis, and regional nodal metassis: comparable survivals		
Romano et al. (2010)	implications for follow-up guidelines	Prognostic study	340 patients AJCC stage III who recurred	Relapse-free survival Overall survival Mode of relapse detection 5-year survivals	5-year RFS for stage IIIA, IIIB, and IIIIC patients was 63%, 32%, and 11%, respectively Site of first relapse: - local/in-transit 28% - regional nodal 21%	Retrospective design estimated site-specific risk of first relapse for each substage	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- systemic 51% 1st relapses detected by patient or family, physician, or by screening radiologic tests in 47%, 21%, and 32% of patients, respectively. Factors associated for better OS (multivariate analysis): - younger age - 1st relapse being local/in-transit or nodal, asymptomatic, or resectable. estimated 5-year survivals for stages IIIA, IIIB, and IIIC from time of 1st relapse: 20%, 20%, and, 11%, respectively.		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Survival curves showed a plateau at around 50 months in all substages.		
Stucky et al. (2010)	Understanding the risk factors for local and in-transit recurrences (LR/ITR) may help facilitate methods of prevention, early detection, and treatment.	Prognostic study	255 patients treated with surgical resection of a single melanoma and with at least 18 months of follow-up (26 patients with LR/ITR)	Time to recurrence Site of recurrence	average time to LR/ITR: 16.2 months (range, 4.2– 82.4 mo). Within 12 months of follow-up:LR/ITR in 53% of the patients within 18 months of follow up: 78% of recurrences patients with LR/ITR (n=26): - 3% local recurrences - 5% in transit recurrence - 2% both LR/ITR - 56% concurrent regional LN metastases.	Retrospective design	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					LR/ITR was associated with: - older age - thicker original tumor - presence of angiolymphatic invasion in the original melanoma		
Meyers et al. (2009)	To determine the impact of routine imaging on the method of detection of first recurrence in patients with stage II and sentinel lymph node–positive stage III melanoma.	Prognostic study	118 patients with stage II or III	Mode of recurrence detection Time to recurrence Overall survival Costs	Median time to recurrence: 14 months (range, 2–88 months) Types of recurrence: 9% local, 40% in transit, 16% regional lymph node basin, 35% distant Mode of detection: - self-detection in 37% asymptomatic patients - 30% of patients with symptoms that led to	Retrospective analysis of prospective database Small patient cohort	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					detection of recurrence - in 23% by physician during routine follow-up examination - in 7% by routine follow-up imaging - in 3% by high LDH values Median survival after recurrence: 22 months (locoregional disease) vs. 7 months (distant disease) no difference in survival among symptomatic vs. asymptomatic patients no significant difference in survival between a self-detected recurrence and recurrence		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					detected by either a physician or by routine diagnostic scans.		
Francken et al. (2008)	To calculate recurrence rates and establish prognostic factors for recurrence to help redesign a follow-up schedule.	Prognostic study .	4726 patients with a single invasive primary cutaneous melanoma and stage I or II disease	Recurrence rate Disease-free survival Disease-specific survival	Recurrence occurred in 18.9% (895 of 4748) of patients overall, 5.2% (95 of 1822) of those with stage IA disease, 18.4% (264 of 1436) with IB, 28.7% (215 of 750) with IIA, 40.6% (213 of 524) with IIB and 44.3% (86 of 194) with IIC disease. Overall, the median disease-free survival time was 2.6 years, but there were marked differences between AJCC subgroups. Primary tumour thickness, ulceration and tumour mitotic	Retrospective design Part of the cohort very old (starting 1959) For Kaplan-Meier curves for time to first recurrence see original article Time between relapse and last follow-up not measured	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					rate were important predictors of recurrence.		
Khan et al. (2006)	To help develop parameters for future trials, treatment history and	Prognostic study	212 patients with pathologically proven stage IV melanoma	survival	median survival of stage M1c: 6.0 months. Survival was longer for stage M1a and M1b and shorter in older patients. No significant differences were found in survival based on gender. Patients with a normal LDH level survived almost twice as long (median survival, 12.0 months, [95% CI 8.85–15.15]) compared to those with an elevated LDH level (median survival 6.0 months, [95% CI 3.51–8.49]); these were significantly		2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					different by the log-rank test ($\chi 2$ = 5.88, P = .0154).		
Martenson ED et al. (2001)	To evaluate whether S-100B protein in serum is an independent prognostic marker in malignant melanoma.	Prognostic study	1,007 consecutive patients for scheduled follow-up visits. (876 stage I, 35 stage II, 96 stage III)	Disease-specific survival	The mean serum concentration of S-100B protein was significantly related to clinical stage significant differences in disease-specific survival for patients with S-100B values > and < 0.10 mg/L, both when analyzed in the whole group of patients and in the subset of patients with metastatic disease (clinical stages II to III) Significantly lower levels in patients in whom the metastases had been resected	Follow-up diagnostic procedures not stated in article Study included in Mocellin et al. 2008 The three-stage system for classification of malignant melanoma	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					compared with patients with subcutaneous and/or LN metastases (P=0,004) or disseminated metastases (P < 0,001). multivariant analysis: In clinical stages II and III, the S-100B protein level in serum was the strongest independent prognostic factor for melanoma survival (P<0,001)		
Mruck et al. (1999)	To investigate the predictive value of the protein S100 as a tumor marker in the post-surgical follow-up staging of patients with high risk melanomas (Clark levels IV/V,	Diagnostic study	50 patients	Sensitivity Specificity Predictive values	FDG-PET: Sensitivity=100%, specificity=95% Conventional imaging: Sensitivity=92%, specificity=82% S100 :	Selection criteria not described No information about time interval between blood sample and imaging procedures	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	thickness>0,75 mm)				Cut-off-levels were 0,1µg/l and 0,2µg/l: Sensitivity=85%, specificity=55% when measured by RIA, Sensitivity=77%, specificity=61% when measured by LIA NPV=91% (RIA) and 88% (LIA) PPV=39% (RIA), 40% (LIA) At a cut-off level of 4,0µg/l, TK showed a sensitivity of 70% and a specificity of 41%.	Small patients cohort	
Poo-Hwu et al. (1999)	To evaluate the follow-up protocol instituted in 1987 at the Yale Melanoma Unit to improve upon the detection of	Retrospective prognostic study	373 patients followed according to the protocol schedule. AJCC Stage I-III	Recurrence-free interval Overall survival Modes of detection	median time interval to recurrence: - stage I:22.0 (range, 2.0–60.5) months - stage II 13.2	Detailed follow-up procedure given Retrospective design	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	disease recurrence in patients with American Joint Committee on Cancer Stage I-III cutaneous melanoma.				(range, 2.4 –71.0) months - stage III: 10.6 (range, 2.3–53.8) months 51% locoregional recurrences detected by patients, 64% distant metastases detected by physicians physician-detected recurrences: - 57% by history or physical examination - 18% by abnormal chest X-ray - 23% by CT scan or MRI - 2% by elevated LDH median survivals: 34 months for locoregional vs. 13 months for distant		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					recurrences All 19 patients with MPM were identified by physician-performed physical examination.		
von Schoultz et al. (1996)	To asses the potential prognostic value of serum concentrations of S-100ß	Serum levels of S-100ß protein were measured in a consecutive series of 643 patients with cutaneous malignant melanoma during 08/1990-10/1992	643 patients in total 553 patients: stage I (with/without satelilites within 5 cm), 24 patients: stage II (in-transit metastases and/or regional lymph node metastases), 66 patients: stage III (distant metastases)	Overall survival	Significant correlateion of serum concentrations of S-100ß to clinical stages. They were significant higher in men than in women (p<0,001). Association between OS rate with serum levels of S-100. observed/expected death ratio was markely increased with increasing levels of S-100ß (P<0,001). A fivefold increase in	No information about number of blood samples taken Poor information about population No information about study design (prospective/ retrospective?) Disease classification different from AJCC was used study included in Mocellin et al. 2008	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					relative hazard was indicated by a value of S-100ß >0,6µg/l (P<0,001) and when its cut-off level was used S100ß had additional prognostic value independent of clinical stage (P<0,001).		
Kaufmann, Crone-Münzbrock (1992)	To evaluate the value of CT and US in detecting abdominal metastases.	Diagnostic study	849 patients with malignant melanoma	Sensitivity specificity	Interval between therapy of primary melanoma and diagnostis of reccurence: 2,5 years US: sensitivity; 53%, specificity; 98% CT sensitivity 85%, specificity 94%	Selection criteria not described No information about time interval between ultrasound and CT	2b-
Kelly et al. (1985)	To develop guidelines for the follow-up of patients with	Prognostic study	295 patients with metastatic malignant melanoma(clinical	disease-free interval predictors of	independent significant predictor of DFI: tumor thickness (p	Incomplete patient records (of 295 patients, only 177 were included in	2b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	primary cutaneous melanoma		Stage I).	disease-free interval recurrence rate	= 0.0015) (not significant: sex, age, elective regional LN-dissection, tumor location) diminution of DFIfrom 3.97 years (< 1.0 mm) to 1.10 years (> 5.0 mm) is evident with increasing thickness. Association between increased risk of recurrence and increases in tumor thickness >1.5 mm in the first 4 years (greatest increase in risk is in the 1st year)	multivariate analysis) For details of survival and recurrence statistics, see original article	
Alvarado et al. (2011)	to assess the frequency of the pelvic metastases in patients with primary melanoma	Prevalence study	146 patients with primary melanoma who had adequate follow-up evaluation for at	incidence rate of metastases Survival	Recurrences in 75% of patients median time to the first recurrence: 13	Limitation of study and bias not described Patients with	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	in the head and neck to identify evidence supporting the use of pelvic CT scans in this group of patients.		least 5 years. (109: stage I or II disease, 33: patients stage III, 4: stage IV)	Time to recurrence	months. Median duration of the OS: 3.8 years. Median duration of the OS for the 110 patients with recurrences: 2.3 years. 48% of patients had remained alive >4 years from the time of the first diagnosis of melanoma, developement of metastases in 56% of patients, developement of pelvic metastases in 7% of patients most common sites of first recurrence: lymph nodes (n=41, 37%), satellite soft tissue (n=41, 37%), chest (n=33, 30%),	mucosal melanoma included	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					abdomen (n=13, 15%), and the brain (n=7, 6%).		
DeRose et al. (2011)	to determine the utility and cost effectiveness of radiological restaging of patients with stage IIB–IIIC melanoma at the 3-year follow-up time point	Economic and prevalence study	210 patients with stage IIB–IIIC melanoma	Recurrence rate Time to recurrence TP FP costs per diagnosis	Recurrences in 55% of patients, in 69% with disease symptoms 88% recurrences before 3 years (median time to recurrence 12 months, 95% confidence interval: 10–16 months) 25 head CTs, 27 head MRIs, 52 torso CTs were performed. In total: 3 FP and 2 TP Total cost per diagnosis:$312 990.	Reference standard not described	3b
Hansel et al. (2009)	To analyse the frequency of late recurrent MM in	Prevalence study	1881 patients in stage I or II (AJCC) with a follow-up of	Overall survival Relapse-free	20 patients with late recurrence of melanoma . largest	Conclusion about infrequence of late recurrence can be	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	south-eastern Germany		> or = 10 years (1 uveal melanoma, excluded)	survival	period from diagnosis of PM to recurrence: 25.1 years, median 13.9 Loco-regional metastases in 63.2%, distant metastases in 42%, deaths in 75% All but one of the survivors had in-transit metastases only (n=3). OS: between 10.9 and 35.7 years (median 14.7). Statistical variate analysis failed to identify possible factors significantly associated with late recurrence	drawn, but statistical conclusions inside this small cohort are not valid because of small patient sample	
Einwachter-Thompson, MacKie (2008)	To review patients with invasive melanoma thinner	cohort study	430 patients with invasive melanoma < 0.5 mm	Deaths Interval between	19% deaths from melanoma in the whole group.	Data on thin melanomas only	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	than 0.5 mm followed for at least 5 years to provide an evidence base for considering modification of guidelines.			two primaries	11 patients developed simultaneous or subsequent primary melanoma (3 simultaneously, 5 within 36 months, 1 between 3-5 years, 2 between 69 and 73 months after the first diagnosis.)	Retrospective design In some cases pathological review showed melanoma > 0.5 mm at diagnosis or some patients developed thicker SPM	
Francken AB et al. (2008)	To asses the frequency of patient detection of both first primary melanomas (FPMs) and second primary melanoms (SPMs)	Prevalance study	112 patients with recently diagnosed SPM	FPM and SPM-detection rate	Patients deteced 59% of the FPMs vs. 46% of the SPMs themselves significant predictors for a patient-de-tected FPM: - females gende - greater Breslow tumour thickness - younger age (OR 4,9; 3,2 and 0,9 respectively). predicting factors	Only patients with SPMs were interviewed (both in situ and invasive melanomas were included.) Excluded were patients who had multiple primary melanomas or who developed a recurrence earlier than the SPM (amongst others)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					for the patient detection of a SPM: - greater tumour thickness - ready visibility of the lesion to the patient (OR 1,9 and 3,6 respectively)		
Francken et al. (2007)	In this prospective study the frequency of detection of first melanoma recurrence (FMR) by patient or doctor was analyzed	Prevalence study	211 patients with a first melanoma recurrence (FMR) were interviewed	Median time to detection of an FMR Sites of recurrence Modes of detection Mean survival	median time to detection of FMR: 28 months (range, 2–322) Symptoms present in 74%, in 39% FMR detected as a consequence of symptoms. in 56 patients FMRs detection was at a follow-up visit: - 63% by physical examination - 14 % by chest x-ray - 11% by LN ultrasound	risk of bias (in group B, only patients with unambiguous information in patients records were included)	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					Detection of FMR: - in 154 patients by patient, partner, or relative - in 57 patients by a doctor mean survival time: 23.8 months.		
Zogakis et al. (2007)	To estimate survival and time to first recurrence in patients with negative sentinel nodes.	Prevalence study	773 melanoma patients with tumor-negative SLNs	Overall survival Disease-free survival Time to first recurrence	Recurrence in 8,9 % of patients with tumor-negative SLNs 1-year, 3-year, and 5-year DFS rates: 98%, 91%, and 88%, respectively. 1-year, 3-year, and 5-year OS rates: 99.7%, 96%, and 92.7%, respectively. Significant differences in survival between patients with	Subgroup of sentinel-node-negative patients Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					local/in-transit and nodal vs. distant first recurrence No significant difference in time to the development of local/in-transit vs. nodal vs.distant recurrence		
Beyeler M et al. (2006)	To compare the efficacy of imaging techniques and serum S100 in the early detection of melanoma progression	Diagnostic study	127 patients	Sensitivity Mode of detection	In 5.5% of patients, S100 was the first indicator of disease progression. 40.2% of relapses noted by the patients themselves, 27.6% diagnosed by a doctor. Imaging procedures lead to detection of melanoma recurrence in 26.8%. (US in 6 patients, PET scan in 12 patients,	Population not described. Small patient number in every stage specificity not given No information about time interval between imaging procedures and blood samples.	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					CT scan in 13 patients, PET-CT in 3 patients, chest x-ray in 0 patients) S100 sensitivity: 37%.		
DiFronzo et al. (2001)	To investigate whether routine reassessment and careful education of postoperative patients would facilitate earlier diagnosis of a subsequent second primary melanoma, as reflected by reduced thickness of that lesion.	cohort study	3310 patients with primary melanoma AJCC stage I/II	Rate of patients who developed SPM	114 patients with AJCC Stage I or II melanoma developed a SPM AJCC stages of SPM: - lower in 48% - same-stage in 50% mean tumor thickness for PM: 1.32 +- 1.02 mm, for SPM: 0.63 +- 0.52 mm level of invasion of SPM vs. PM - decreased in 60% - remained the same in 27% - increased in 13%	Standard follow-up procedure is defined	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					of patients. significant differences in stage, tumor thickness, and level of invasion between PM and SPM (paired t test)		
Dicker et al. (1999)	To address the following questions: (i) what is the overall risk of recurrence? (ii) When do recurrences occur? (iii) How are they detected? (iv) What is the risk of recurrence from melanomas which appeared to be confined to the epidermis when they were excised? (v) How are second primary melanomas detected? (vi) Do patients alter their	Prevalence study	1568 patients with stage I melanoma	Risk of recurrence First site and detection of recurrences Changes in behaviour (see full text)	Overall 19% developed recurrences 79% of recurrences occurred during the first 3 years. <8% after the 10-year interval. patients detected their recurrences more often than doctors at follow-up clinics The first site of recurrence was: - local 17% - in transit 6% - local nodes 56%	Large patient cohort No standardized follow-up protocol	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	behaviour after attending a melanoma follow-up clinic?				- distal 22%		
Johnson et al. (1998)	To characterize the subgroup of patients with multiple melanomas.	cohort study	60 with with multiple primary melanomas, and	Time to diagnosis of second melanoma Tumor thickness of second melanoma	In 30% MPM were diagnosed concurrently within 1 month, in 63% > 1 month apart, and in 7% concurrently and subsequently (>2 primaries). median time interval between subsequent diagnoses of 2nd PM: 63 months (range 2-456) in patients with > 2 PM: median time interval between subsequent lesions: 42 months (range 2-456). Appearance of subsequent primary	Retrospective design Small patient cohort	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- 42% within 3 years - 17% between 3-7 years - 42%> 7 years - 19% > 10 years - 6% > 15 years After initial diagnosis mean tumor thickness from the 1st primary lesion to the subsequent lesion(s) decreased from 0.98 to 0.90 mm.		
Sylaidis et al. (1997)	To investigate the incidence of recurrence in thick (> 4 mm) localized melanoma to draw conclusions about duration and frequency of follow-up.	cohort study	244 patients (176 patients had their first recurrence between years 1 and 10 postoperatively)	Overall survival (= disease specific survival in this study) Survival after first recurrence	5-year survival: 45% (95% CI 39%, 51%) 10-year survival: 37% (95% CI: 31%, 43%). - 42 patients with local recurrences: 5-year survival rate of 26% (95% CI: 13%, 39%).	Retrospective design Patient cohorts only includes patients with melanoma > 4 mm thickness No attempts to recover patients lost to follow up	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- 93 with regional recurrences: 5-year survival rate of 18% (95% CI: 10%, 26%). - 41 with distant metastases: 5-year survival rate of 5% (95% CI: 0%, 11%).	Patients who died of other diseases were excluded	
Martini et al. (1994)	To establish a follow-up guide for cutaneous melanoma.	Prevalence study	840 stage I cutaneous melanoma patients (recurrence in 202 patients)	Time to first recurrence Pathway of first recurrence	Mean time to first recurrence: 22.27 months (median 13.5 months). 45.54% of relapses occurred during the 1st year, 79.21% during the first 3 years, 89.6% in the first 4 years and 94.55% in the first 5 years. Recurrences significantly earlier (mean 18.18 months, median 10.5 months) in males than in females (mean 26.78 months,	Retrospective design with incomplete patients records (only 675 of 840 patients "histologically evaluable"). Patient cohort contains melanoma in situ (105 lesions not invasive).	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					median 17.5 months). Pathway of first recurrence: 81.19%: lymphatic 17.33%:hematic 1,48%: unknown		
Baughan et al. (1993)	To assess the objective value of follow-up in diagnosing and treating tumour relapse and its subjective value as perceived by patients.	cohort study	339 melanoma patients (65 patients developed recurrences)	Time to relapse 5-year-survival Questionnaire results (subjective value of follow-up to patients)	82% of first relapses occurred within 3 years and none has yet been seen after 7 years. Actuarial 5-year-survival (doctor-diagnosed vs. patient-diagnosed recurrences): 18 vs. 20 % (P>0,8) For time to first relapses over year of follow-up, see fig. 1 in original article.	Retrospective design No standard follow-up protocol	3b
Kang et al. (1992)	To examine the natural history and impact of regular	cohort study	41 patients with multiple cutaneous melanoma	Interval between melanoma diagnoses	In 39% the MPM were diagnosed concurrently (vs.	Retrospective design	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	follow-up evaluation of multiple primary cutaneous melanoma			Tumor thickness	61% subsequently). Significant decrease in Breslow's thickness from the 1st PM (1.21 ± 0.28 mm) to the second (0.51 ± 0.08 mm) (P<0.05) median time interval between sequential melanomas: 36 months (range 2-372)	Small patient cohort	
Brandt et al. (1990)	To investigate the prognostic value of several factors on cancer-specific survival and cancerspecific disease-free survival, from time of excision on, by performing life-table analysis on 206 evaluable patients.	Prevalance study	231 patients who underwent local excision as the single treatment of melanoma with a thickness of <= 1.5 mm.	Cancer-specific survival (CSS) cancer-specific disease-free survival	During follow-up: - 14/206 patients died. – (6 patients as a result of the disease, 8 from other causes) Recurrence in11 patients: - 4 local recurrences - 4 LN metastases - 3 distant disease.	Retrospective design No standard therapy and follow-up protocol Different excision margins have been used	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					- Actuarial 5-year CSS: 96.1% - 10-year CSS:92.3% - 15-year CSS: 92.3%. cancer-specific DFS after 5 years: 95.2%, after 10 years: 86.9%, after 15 years: 86.9%.		
McCarthy et al. (1988)	To re-examine follow-up regimens and provide follow-up guidelines tailored to the risk of the individual patient.	Prevalence study	886 melanoma patients with evidence of recurrent disease	Recurrence rate Site of first recurrence Time to first recurrence	Time to first recurrence depended upon: - thickness of the tumor - whether ELND was performed or not Times to recurrence for 50% respectively 95% of the recurrent patients in months: - 32 months and 134 months for 0.1 – 0.7 mm	Retrospective design Different follow-up schedules over time Large patient cohort	3b

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					tumor thickness - 25 months and 116 months for 0.8 – 1.5 mm tumor thickness without ELND - 36 months and 145 months for 0.8 – 1.5 mm tumor thickness with ELND - 16 months and 108 months for 1.6 – 3.0 mm tumor thickness without ELND, - 20 months and 112 months for 1.6 – 3.0 mm tumor thickness with ELND - 12 months and 60 months for > 3.0 mm tumor thickness without ELND - 19 months and 60 months for > 3.0 mm tumor thickness with ELND		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Buljan M et al. (2010)	To analyse the clinical, histopathological and epidemiological characteristics of 36 patients, with multiple primary melanomas (MPM)	cohort study	36 patients (3,6%) were diagnosed with MPM. 28 patients: 2 primary melanoma 6 had 3 melanoma and 2 had 4 melanomas.	Time interval between first and subsequent melanoma	Diagnosis was established synchronously in 11 patients in the the other patients time interval between PM and SPM varied from 1 month to 16 years, average time interval : 41 months.	Retrospective design Small population No data concerning examination intervals of follow-up	3b-
McMeniman et al. (2010)	To define the risk factors for multiple primary melanoma (MPM).	Prognostic factors	58 patients with more than one primary were interviewed via telephone	Rate of patients who developed MPM Age at diagnosis Tumor thickness Risk factors	50% of patients had their first melanoma between 40–59 years of age. 68% had the same or a less invasive level of melanoma on their subsequent lesion/s. With subsequent melanomas a greater proportion were found by the	Data incomplete or inaccurate on many patients Risk of recall bias Small patient cohort	3b-

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					dermatologist. Risk factors: see full-text		
Zissimopoulos et al. (2009)	To evaluate 111In-O Scintiscan in malignant melanoma for the detection of recurrence and metastatic disease, after clinical and histological diagnosis and initial surgery treatment and during 3 years of follow-up.	Diagnostic study	35 patients with malignant melanoma 20 female, 15 male, mean age 46±7, range 32-51 years Treatments in some patients: Interferon alpha, IL-2	Positive- rate	During 3 years of the follow-up period, 26/35 of the patients had clinical recurrence. (17 patients: regional lymph node metastases, 9 distal metastases) In 111In-O Scintiscan 20/26 patients had positive scans with 56 lesions, 6 had negative scans. CT images showed only 31 lesions.	Selection criteria not given Small sample size No information about false positives and false negatives. Positive CT: only number of metastases is given but not number of patients No information about interval between CT and 111In-O Scintiscan No information about results of other staging modalities	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Solivetti FM et al. (2006)	to assess the potential of ultrasonography (US) in the detection of in-transit or satellite metastases.	Diagnostic study	600 patients who had thick melanoma (>1 mm) and who were clinically free of in-transit or satellite melanoma metastases during follow-up.	Number of detected metastases US features of in-transit metastases	US suspicion of in-transit or satellite metastases in 63 patients. A total of 95 lesions were identified. Lesion diameter ranged from 4 mm to 17mm (mean diameter 8 mm). Four of 95 lesions had a diameter >1 cm; most (82 cases) had diameters of 6–8 mm. No false positive or false negative US US features: see full-text		4
Dancey et al. (2004)	To assess patient opinions on follow-up. To ascertain whether GPS would be willing to follow melanoma patients	cohort study	231 melanoma patients and 50 GPs who filled out a questionnaire	Patients` opinion on follow-up GP satisfaction	98% found the clinics to be useful 22,5% felt it was difficult to attend the clinic 53% expressed		4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	up in a primary care setting				some degree of anxiety at attending the outpatient department 12%: recurrence, 52% of them detected it themselves 60% of patients would be happy to consider routine follow-up with their GP 70% of local GPs would be unhappy to monitor their patients.		
Johnson et al. (1999)	To determine the value of follow-up in two subgroups of patients with a thin melanoma less than 0.76 mm and 0.76– 1.5 mm thick.	Prevalence study	306 patients: 178 with a melanoma < 0.76 mm (group 1) and 128 with a melanoma of 0.76 – 1.5 mm (group 2)	Recurrence rate	Recurrences in 4 patients (2.2%) in group 1 and 16 (12.5%) in group 2 group 1: all patients presented with untreatable,	Standardized follow-up procedure	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					widespread metastatic disease, detected by a clinician in the follow-up clinic. group 2: 1: local recurrence, 1 in-transit recurrence, 3 subcutaneous recurrence, 7 nodal metastases and 4 patients distant metastases. In 13/16 patients, recurrence was detected by clinician in the follow-up clinic.		
Mooney et al. (1998)	To asses the impact on survival by components of a surveillance program (physical examination, blood tests, and chest radiograph) used to detect recurrences in patients with	Prognostic study	1004 patients AJCC Stage I or II	Method of detection Survival 5-, 10- and 15-year survival	Physical examination detected 72% constitutional symptoms indicated 17% and chest radiograph revealed 11% of recurrences. Blood tests did not predict any	Retrospective design No information about verification/reference test	4

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
	cutaneous melanoma				recurrence. 9/17 patients with recurrences detected by chest radiograph alone underwent curative surgical resection. These patients had a statistically significant prolonged survival compared to those surgical candidates who did not undergo resection. No statistically significant difference in OS between patients with asymptomatic pulmonary recurrences and those with symptomatic pulmonary metastases The 5-year, 10-year, and 15-year OSrates, with their		

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					associated 95% CI, for patients who remained disease free: 92%±2%, 85% ±3%, and 77% ±4%, respectively. The rates for patients with recurrences are 46% ± 8%, 17% ± 6%, and 14% ± 6%, respectively.		
Mooney et al. (1997)	To assess costs and potential benefits of an intensive chest X-ray (CXR) screening program to detect asymptomatic pulmonary metastases in patients with intermediate-thickness, local, cutaneous melanoma.	Economical study	A hypothetical cohort of patients diagnosed in 1996 with intermediate-thickness, local, cutaneous melanoma. Intermediate thickness melanoma was defined as ≥ (AJCC) Stage I - classification pT2	Potential savings in years of life from surgical resection of lung metastases in quality-adjusted and non-quality adjusted life years (QALY AND NQALY), undiscounted and discounted Cost-effectiveness ratio (C/E) of CXR screening	For the base case, cost of screening per NQALY was $150,000 and was $165,000 for QALY in 1996 dollars using undiscounted health benefits. Screening accounted for approximately 80% of program costs and treatment accounted for 20%. Annual cost-effectiveness ratios were lowest in Years 3–10 of	No level of evidence was assigned because of unique study design and hypothetical cohort of patients	

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
					screening. The total cost of a 20-year screening program for patients diagnosed in 1996 was estimated to be between $27–$32 million.		

10.2.4.2. Aktualisierungsrecherche 2016

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Bamboat, Z.M., et al., 2014	To characterize the populations undergoing nodal observation (no CLND) and CLND; To determine the pattern of initial recurrence between the no-CLND and CLND	Retrospective study, number of patients n=4310	Patients with a positive Sentinel-Lymph node (SLN) diagnosed from 1994 to 2012	Number of positive SLN and further procedure Time-to-Recurrence Survival	4,310 patients undergoing SLN biopsy (SLNB), 495 (11 %) had a positive SLN—167 (34 %) patients underwent nodal observation and 328 (66 %) had immediate CLND Median follow-up was 23 and 80 months for the no-CLND and CLND groups, respectively, and	Studie befasst sich zwar mit Nachsorge hat als Fokus jedoch den Vergleich von Patienen mit und ohne radikaler Lymphadenektomie	3a

	groups; To determine melanoma-specific survival of both patient groups; To characterize the outcome of no-CLND patients who experience a subsequent isolated nodal recurrence.				median time to recurrence was similar at 9 and 12 months, respectively (p = 0.48). While median recurrence-free survival was higher after CLND (34.5 vs. 20.9 months; p = 0.02), melanoma-specific survival was similar (not reached, no CLND vs. 110 months, CLND; p = 0.09)		
Cristofolini, M., et al., 2015	To evaluate the incidence of cutaneous melanoma in subjects who were found not affected in a previous screening programme and to compare this incidence	10-Year Follow-Up Study,number of patients n=3635	Subjects who contacted the Lega Italiana per la Lotta contro i Tumori (Italian League against Cancer) between January	Number of melanoms at screening Numer of melanoms during follow-up	A total number of 24,963 pigmented lesions were checked by the dermatologist. For the great majority of these lesions, the clinical diagnosis was common naevus (23,592, i.e. 94.5%). There were also 1,199	Studie untersucht Patienten mit einem hohen Risiko für die Entwicklung eines malignen Melanoms	4

	with that of the general population		2001 and December 2004 were followed up to December 2013 through linkage with the Trento Skin Cancer Registry		benign pigmented lesions (4.8%), 121 atypical naevi (0.48%), 34 malignant non-melanocytic lesions (0.14%) and 17 lesions (0.068%) for which a diagnosis of cutaneous melanoma was suspected. The median follow-up was 10 years for a total of 35,678 person-years. During the follow-up period, 14 new cases of cutaneous melanoma were diagnosed. During the follow-up, cutaneous melanoma was diagnosed on average after 5.7 years from the screening phase.		
Cromwell	To	Systematic	Scopus,	Variation in	The variation was	Deskriptiver	4

, K.D., et al., 2012	determine the variation in clinical practice patterns with respect to the stage-specific surveillance of melanoma patients by country and physician specialty	review, number of articles n=104	PubMed, and Cochrane Library databases were searched for articles published between January 1970 and October 2011 on the surveillance of patients with melanoma.	Surveillance practices Intercountry variations	greatest for patients with stage I disease, for whom the follow-up frequency ranged from one to six visits per year during years 1 and 2 after treatment. All four physician specialties agreed that for years 1–3, the follow-up frequency should be four times per year for all patients. For years 4 and 5, surgical oncologists recommended two follow-up visits per year, whereas general practitioners, dermatologists, and medical oncologists recommended four visits per year. Recommended	Charakter, keine wirklichen Zielvariablen	

					imaging and laboratory evaluations were most intense in the UK and most minimalist in the Netherlands. Although general practitioners did not recommend routine laboratory or imaging tests for surveillance, all other specialties utilized both in their surveillance practice. Self skin-examination was recommended for surveillance in all countries and by all practitioner specialties. There are significant intercountry and interspecialty variations in the surveillance of patients with melanoma. As the number of melanoma survivors increases, it will		

					be critical to examine the benefits and costs of various follow-up strategies to establish consensus guidelines for melanoma post-treatment surveillance.		
Damude, S., et al., 2016	To examine whether a reduced follow-up schedule affects: patient-reported outcome measures, detection of recurrences, and follow-up costs	Randomized, Clinical Trial, number of patients n=180 Conventional follow-up schedule group (CSG, 4 visits first year, n = 93) or experi-mental follow-up schedule group (ESG, 1–3 visits first year, n=87)	Patients treated for AJCC stage IB-II cutaneous melanoma treated with curative intent between February 2006 and November 2013	Patients' mental well-being Recurrence or second primary melanom Person detecting recurrence, Total hospital costs	After 1-year follow-up, the ESG reported significantly less cancer-related stress response symptoms than the CSG (p = 0.01), and comparable anxiety, mental HRQoL, and cancer-related worry. Mean cancer-related worry and stress response symptoms decreased over time (p<0.001), whereas mental HRQoL increased		1b Jadad Score: 3

					over time (p<0.001) in all melanoma patients. Recurrence rate was 9 % in both groups. Recurrences were mostly patient-detected and not physician-detected (CSG 63 %, ESG 43 %, p=0.45). Hospital costs of 1-year follow-up were reduced by 45 % in the ESG compared to the CSG.		
Idorn, L.W., et al., 2014	To measure changes in sun behavior from the first until the third summer after the diagnosis of CMM using matched	case-control study, number of patients n= 40	Patients suffering from cutaneous melanoma visiting an University hospital in Denmark	Exposure to UVR	Patients' daily UVR dose and UVR dose in connection with various behaviors increased during follow-up. No difference was found between groups in the number of days		3b

	controls as a reference				with body exposure or the number of days using sunscreen in the second and third years of follow-up		
Jones, E.L., et al., 2013	To analyze the predictors and patterns of recurrence of melanoma in patients with a negative sentinel lymph node biopsy result	Retrospective chart review, number of patients n=515	Patients with melanoma underwent a sentinel lymph node biopsy without evidence of metastatic disease between 1996 and 2008.	Time to recurrence OS	83 (16%) had a recurrence of melanoma at a median of 23 months during a median follow-up of 61 months. Of these 83 patients, 21 had melanoma that metastasized in the studied nodal basin for an in-basin false-negative rate of 4.0%. Patients with recurrence had deeper primary lesions Median survival following a recurrence was 21 months (range, 1-106 months). Favorable	Studie enthält nur wenig Information zum Follow-Up der Patienten	IV

					characteristics associated with lower risk of recurrence included younger age at diagnosis (mean, 49 vs 57 years) and female sex (9% vs 21% for males; P .001).		
Lott et al., 2015	To describe surgical delay among Medicare beneficiaries with melanoma. Specifically, to determine which tumor- and patient-level factors were associated with surgical delay and whetherthes pecialtyofthe physicians who deliver dermatologic care influenced	Retrospective cohort study of Medicare beneficiaries diagnosed as having melanoma from January 1, 2000, through December 31, 2009, using the Surveillance, Epidemiology , and End Results–Medicare database. (n=32 501)	Melanoma patients	Surgical delay, measured as the time from the biopsy to surgical excision.	The distribution of surgical delay ranged from 4 to 450 (median, 27.0; mean, 44.3) days and varied by specialty of the physician performing the biopsy and surgery. Physician specialty was also significantly associated with the risk for surgical delay (P<.001). For example, 21.9% of melanoma cases		IIb

	the delay				experienced a delay longer than 1.5 months when the biopsy was performed by a dermatologist compared with 25.0% when the biopsy was performed by a non-dermatologist.		
Livingstone, E., et al., 2015	To describe prospectively the current practice of melanoma follow-up and treatment in Germany in the first 2 years after melanoma diagnosis in a large and representative cohort of patients with melanoma from various centres around Germany; To	Prospective, longitudinal cohort study, number of patients n=1006	Patients diagnosed with melanoma and melanoma in situ between 1 April and 30 June 2008 in Germany	Follow-up adherence	The majority of stage I patients (70.0%) were seen at the correct follow-up intervals. In 20.8% the interval between visits was too short, and in 9.2% too long. Multivariate analysis showed that having shorter intervals than recommended between follow-up visits was significantly associated with younger age;		2a

	assess guideline adherence regarding followup frequency in stage I melanoma and adjuvant therapy in stage III disease.				female sex; location of the primary (head/neck vs. lower extremity; trunk vs. lower extremity); region (central Germany vs. southern Germany); implementation of diagnostic procedures and centre size (small vs. large)		
Livingstone, E., et al., 2015	To depict the current actual practice of melanoma follow-up care and treatment by prospectively following a large and representative cohort	Prospective longitudinal cohort study, number of patients n=668	Patients diagnosed with melanoma and melanoma in situ (MMis) between 1st April 2008 and 30th June 2008, in Germany	Follow-up adherence Patterns and detection of recurrence Costs of follow-up procedures	The majority of patients (N= 641, 96%) were in regular melanoma surveillance primarily by the recruiting centre. After 2+ years since initial diagnosis, only 25.3% of patients had been referred to a dermatologist in doctor's office for surveillance, few patients were		2a

					seen by general practitioners (GPs) (1.3%) or medical oncologists (0.9%). In year 3–4 of surveillance, only 55.6% of locoregionary metastases were detected during surveillance visits. Only 33.3% were self-detected by the patient even though 69.4% were documented as being clinically visible or palpable For patients under surveillance with stage MMis and I–IIC in 2012 (i.e. by definition no tumour progression detected during the follow-up period) (N= 550),		

					8672 individual staging procedures including clinical examination, lymph node ultrasound, abdominal		
Marciano, N.J., et al., 2014	To determine the extent of evidence-based support for clinical practice guideline recommendations concerning cutaneous melanoma follow up and to evaluate the methodological quality of these guidelines	Systematic Review, number of guidelines n= 9	A search of 11 electronic databases and websites was conducted to identify potentially relevant guidelines published in 2006 or later, in addition to use of a review article by Speijers et al.	Kind of recommondations	Most guideline recommendations concerning the frequency of routine skin examinations by a clinician and the use of imaging and diagnostic tests in the follow up of melanoma patients were based on low-level evidence or consensus expert opinion	Review hat Fokus auf der Qualität der Nachsorgeleitlinien, leitet wenige eigene Schlüsse ab	2a
Memari, N., et al., 2015	To determine how	Prospective study, number of	Data from the Melanoma	Follow-up frequency and patterns	During the first year of follow-up postsurgery, 34 %		4

	frequently a cohort of patients attended follow-up after surgical treatment at one Specialist Center	patients n=3813	Institute Australia (MIA) for patients with AJCC stage I/II melanoma diagnosed between January 2008 and December 2011		of stage I patients and 14 % of stage II patients had the number of follow-up visits recommended in the guidelines. A large proportion of melanoma patients did not appear to be routinely followed up at MIA, with 43.2 % of stage I patients and 28.7 % of stage II patients having either no visit or only one visit post-surgery		
Mitchell, J., et al., 2014	To collect the views of patients with a broad base of experience in melanoma follow-up care in Australia, investigating patient perceptions of both the	Retrospective study number of patients n=150 (64 used for analyses), online survey	Patients treated in Australia for primary melanoma since 1 January 2007	Patient Satisfaction Frequency of follow-up care Psychological Care	Participants reported that they did not receive adequate support during follow-up (51.6%), that they would have liked to receive more information from their health professionals (64.1%), and that they would like a	Mehr als die Hälfte der Patienten wurden als "Drop-Outs" nicht berücksichtigt.	4

	technical and interpersonal aspects of the quality of their follow-up care.				coordinator to organise their melanoma follow-up care (62.5%). Surgeons were the most frequently reported health professional seen (32 participants), followed by dermatologists (30 participants), although 8 patients saw both. Intervals between visits varied considerably across the patient group; patients with <1mm melanomas reported being seen 3 monthly. Although 31 patients reported that they regularly saw a general practitioner, it is possible that the reason for thesevisitsmay		

					nothavespecifically relatedtomelanoma follow-up. Aminority ofparticipants (22%) reported regular consults with three or more melanoma specialists. With respect to patients' fears and concerns, 29 (45.3%) participants reported that they received inadequate support. Concern was highest in relation to cancer recurrence and the impact on their children's health.		
Moloney, F.J., et al., 2014	To evaluate the impact of full-body examinations every 6 months	Observational study, number of patients n=311	Patients recruited from Sydney Melanoma Diagnostic	Median tumor thickness Cumulative risk	Median (IQR) Breslow thickness of postbaseline incident melanomas was in situ (in situ to	Studie befasst sich mit der frühzeitigen Erkennung von Melanomen in einer Hochrisiko-	3b

	supported by dermoscopy and total-body photography (TBP) on all patients and sequential digital dermoscopy imaging (SDDI), when indicated, on detecting primary melanoma in an extreme-risk population.		Centre and Melanoma Institute Australia who had a history of invasive melanoma and dysplastic nevus syndrome		0.60 mm). Thirty-eight percent were detected using TBP and 39% with SDDI. Five melanomas were greater than 1mm Breslow thickness, 3 of which were histologically desmoplastic; the other 2 had nodular components. Cumulative risk of developing a novel primary melanoma was 12.7% by year 2, with new primary melanoma incidence during the final 3 years of follow-up half of that observed during the first 2 years	Kohorte, die teilweise zuvor KEIN Melanom hatten.	
Morton, R.L., et al., 2013	To explore patients' perspectives of the value	Retrospective study, number of patients n=	Patients recruited from a single	Patient-perceived benefits and downsides of	The overwhelming benefit to patients was the	Sehr niedrige Patientenanzahl	4

	of follow-up care; including its benefits, limitations and potential downsides, To examine patients' thoughts and feelings about changes to the frequency of follow-up, and To elicit patient-centred recommendations for improving follow-up care	29	centre, Melanoma Institute Australia, between May and July 2010	follow-up Views about frequency of follow-up and risk perception	reassurance they gained from seeing a competent skin specialist whose findings they could trust. Patients varied in their engagement with skin self-examination, and their views on multiple skin excisions, but highly valued access to specialists for unscheduled visits. Most patients felt their follow-up intervals could be extended to 12 months if recommended by their clinician		
Podlipnik, S., et al., 2016	To analyze the performance of the follow-up components	Prospective study, number of patients n=290	Patients at the Melanoma Unit of the Hospital Clinic	Method of detection and patterns of metastatic disease	115 recurrences in 290 patients were recorded, of which computed tomography detected 48.3%;		2a

	and identify procedures that detect melanoma metastasis earlier		Barcelona, Spain, given a diagnosis of a primary melanoma in stage IIB, IIC, and III from January 2003 to July 2013, were included	Survival analysis and recurrence speed analysis	brain magnetic resonance imaging, 7.6%; laboratory test, 2.5%; physician, 23.7%; and patient, 17.8%. CT detected metastases constantly during all the years of follow-up, whereas MRI detected the majority within the first 2 years. Recurrence speed analysis showed that CT scan detects metastasis constantly for each year of follow-up (P = .267). When comparing the proportion of metastasis detected by MRI in the first 2 years (fast relapses) against patients who developed late		

					metastasis (slow relapses), most of the brain metastasis developed in the first 2 years (P = .045).		
Pomerantz, H., D. Huang, and M.A. Weinstock, 2015	To compare the risk of subsequent melanoma in the cohort whose first cancer was melanoma in situ to the risk in the cohort whose first cancer was invasive melanoma	Cohort study, number of patients n=168274	Patients data arvieved by searching the SEER 9 database from 1973 to 2011	Subsequent melanoma	Compared with the invasive melanoma cohort, the melanoma in situ cohort was more likely to develop subsequent melanoma of any stage after 2 years, subsequent invasive melanoma after 10 years, and subsequent melanoma in situ at all the time points (P<.001, P = .003, P<.001, respectively)		3a
Rowe, C.J., et	To determine	Retrospective study,	Patients with	Overall survival	Patients were followed for a		4

al., 2015	whether melanoma survival is worse for patients with MPM compared to those with a single invasive primary melanoma (SPM).	number of patients n= 1068	primary invasive melanomas diagnosed from 1982 to 2004 were sourced from a population-based Australian database, the Queensland Study of Melanoma		median of 24.4 (interquartile range: 22.2–26.8) years. Considering the entire cohort (n = 1068), 222 patients died during follow-up, including 39 deaths due to melanoma. Death from melanoma occurred more frequently in the MPM compared to the SPM group (n = 13 (6.8%) vs. n = 26 (3.0%), P = 0.010).		
Rychetnik, L., et al., 2013	To describe the views of melanoma clinicians on the functions of follow-up for patients with AJCC stage I/II melanoma, particularly the psychosocial aspects of	Semi-structured interviews with 16 clinicians	Qualitative interviews with 16 clinicians (surgical oncologists, dermatologists, melanoma unit physicians) who conduct follow-up at	Impressions	Follow-up is conducted for early detection of recurrences or new primary melanomas, to manage patient anxiety, support patient self-care, and as part of shared care. Recommended intervals are based on	Geringe Anzahl an Interviews	4

	care; To identify how melanoma clinicians currently determine the frequency of follow-up for stage I/II melanoma patients (i.e., factors that influence follow-up intervals); To identify important considerations for safely extending follow-up intervals for stage I/II melanoma patients		two of Australia's largest specialist centers.		guidelines but account for each patient's clinical risk profile, level of anxiety, patient education requirements, capacity to engage in skin self-examination, and how the clinician prefers to manage any suspicious lesions.		
Rychetnik, L., et al., 2012	To examine specialist melanoma clinicians' perspectives on the provision of post-	Semi-structured interviews with 16 clinicians	In-depth qualitative study based on semi-structured interviews, two melanoma	Follow-Up schedule	Melanoma unit clinicians utilised shared care in the follow-up of patients with early stage melanoma. Schedules were	Geringe Anzahl an Interviews	4

	treatment follow-up for patients with early stage melanoma in order to understand and inform future research on optimal models of care		units in NSW, Australia		determined by patients' clinical risk profiles. Final arrangements for delivery of those schedules (by whom and where) were influenced by additional psychosocial, professional and organizational considerations. Four models of shared care were described: (a) surgical oncologist alternating with dermatologist (in-house or local to patient); (b) melanoma unit dermatologist and other local doctor (e.g. family physician); (c) surgical oncologist and local doctor; or (d) melanoma physician and local doctor.		
Scally,	To help	Contemoprar	Studies	Intensity and	For stage IIb–IV,		4

C.P, 2014	practitioners examinations and improve their surveillance protocols based on the currently available data	y review	dealing with follow-up strategies in melanoma	Modalitiy of Surveillance Patterns of recurrence Summary and recommondations for follow-up	interval surveillance visits are recommended every 3–6 months for 2 years, then every 3–12 months for the following 3 years, followed by annual exams Local recurrences can usually be treated with re-excision. Overall reported rates of recurrence vary widely and are difficult to predict based on known clinicopathologic variables. In an extensive review of 72 studies, approximately one-half of recurrences are identified in regional lymph nodes; 20 % are local or regional recurrences, and the remaining 30 % are distant metastases		

					Low-intensive surveillance strategies do not appear to adversely affect patient outcomes and should be the preferred approach compared with high-intensity strategies		
Solivetti, F.M., et al., 2013	To verify the appropriateness of requests for the melanoma follow-up ultrasound (US) tests performed at our institute, a national public referral centre for dermatology and oncology	Prospective study, number of patients n=546 Patients were split into two groups on the basis of melanoma thickness: > 1 mm (Group A) and < 1 mm (Group B).	The requests for US tests of all patients referred to our institute for follow-up of malignant cutaneous melanoma, over a four-month period from July to October 2012	Appropriateness of requests	Out of 290 Group A patients, 104 patients (35%) did not meet the established congruity criteria. Group B was composed of 256 individuals, 92 patients (35.9%) of which were found to have at least one inappropriate request.		2a
Testori,	To	Survey of	Physicians	Specialist	Overall, follow-up		4

A., et al., 2013	determine how patients with melanoma are currently managed in Italian hospitals and present our findings regarding the follow-up programs after the diagnosis and therapy of the disease at different stages	Italian Hospitals. Italian hospitals with ≥ 200 beds (n=285) were subdivided into 145 hospitals with 200–399 beds and 140 hospitals with ≥ 400 beds and a proportionally stratified random sample (n = 120 centers), stratified by number of beds an	working in an Italian Hospital	Performing Follow-Up Duration of Follow-Up	for patients with stage II disease is managed by an oncologist in 76% of hospitals and by a dermatologist in 38%; however, oncologists are more likely to manage these cases in high-volume centers (87 vs. 64%, p = 0.001), while dermatologists are more likely to be in charge of follow-up in low-volume centers (52 vs. 26%, p = 0.002) For stage I and II a majority (43 and 45%, respectively) of high-volume centers monitor patients for 5 years; 19% monitor for 3 years. Among low-volume centers, 37%		

					follow stage II patients for 5 years and 34% forever. Most centers (58%) follow stage IV patients for their entire lives, 18% for 10 years and 20% for 5 years		
Watts, C.G., et al., 2015	To examine international clinical practice guidelines for identification, screening (prior to melanoma diagnosis) and follow-up (after melanoma diagnosis) of individuals at high risk of primary cutaneous melanoma, and the quality of the evidence supporting	Systematic review, number of guidelines n=34	Guidelines published between January 2000 and July 2014 were identified from a systematic search of Medline, Embase and four guideline databases	Guidelines dealing with recommendations for clinical management of individuals at high risk of melanoma Definition of high-risk groups Follow-up strategies for persons at a high-risk	High-risk characteristics that were consistently reported included many melanocytic naevi, dysplastic naevi, family history, large congenital naevi, and Fitzpatrick Type I and II skin types. Most guidelines identify risk factors and recommend that individuals at high risk of cutaneous melanoma be monitored, but only half of the guidelines	Befasst sich mit Personen, die ein hohes Risiko für die Entwicklung eines Melanoms haben.	2a

	their recommendations				provide recommendations for screening based on level of risk. High-level evidence supports long-term screening of individuals at high risk and monitoring using dermoscopy. Evidence is low for defining screening intervals and duration of follow-up, and for skin self-examination, although education about skin self-examination is widely encouraged.		
Wevers, K.P., et al., 2014	To gain insight into Dutch medical specialists'	Online-survey; 378 respondents (response=37%) started	All members of the Dutch Society of Surgical	Knowledge about guidelines Goals of	All but one of the medical specialists (99.7%) indicated they knew the		4

	opinions on melanoma FU and to assess their views on sentinel lymph node biopsy (SLNB).	the survey, including 173 surgeons (46%) and 205 dermatologists (54%).	Oncology and the Dutch Society of Dermatology and Venereology	Follow-up	content of the national melanoma skin cancer guideline. Of these, 36% responded they always followed the guideline's recommendations while 64% stated they incidentally deviated from it for an appropriate reason Ninety-seven percent of respondents (totally) agreed that detection of local recurrences was a goal of FU. Percentages of specialists (totally) agreeing on other purposes of FU were: 92% on detection of a second primary, 84% on detection of regional or distant metastases, 72%		

					on detection of late effects of treatment, and 65% on identifying psychological problems.		

10.2.5. Literatur

10.2.5.1. Primärrecherche 2012

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Alvarado et al. (2011)	x	x	x
Basseres et al. (1995)	x	x	x
Baughan et al. (1993)	x	x	
Beyeler et al. (2006)			x
Bower et al. (2010)	x	x	
Brandt et al. (1990)	x		
Brobeil et al. (1997)	x	x	
Brown et al. (2010)			x

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Buljan et al. (2010)	x	x	
Dancey et al. (2004)	x	x	
De Giorgi et al. (2010)	x	x	
DeRose et al. (2011)	x	x	x
Dicker et al. (1999)	x	x	
DiFronzo et al. (2001)	x	x	
Egberts et al. (2009)			x
Einwachter-Thompson, MacKie (2008)	x	x	
Ferrone et al. (2005)	x	x	
Francken et al. (2008)			
Francken et al. (2005)	x	x	
Francken et al. (2007)	x	x	x
Fusi et al. (1993)	x	x	
Garbe et al. (2003)	x	x	x

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Goggins et Tsao (2003)	x	x	
Hansel et al. (2009)	x	x	
Hengge et al. (2007)	x	x	x
Hohnheiser et al. (2010)	x	x	
Johnson et al. (1998)	x	x	
Johnson et al. (1999)	x	x	x
Kang et al. (1992)	x	x	
Krüger et al. (2011)			x
Kaufmann, Crone-Münzbrock (1992)		x	x
Leiter et al. (2009)			
Leiter et al. (2010)	x	x	
Leiter et al. (2011)	x	x	
Machet et al. (2005)			x
Manola et al (2000)	x		x

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Martenson et al. (2001)			
Martini et al. (1994)	x	x	
McCarthy et al. (1988)	x	x	
McMeniman et al. (2010)	x	x	
Meyers et al. (2009)	x	x	x
Mooney et al. (1997)			
Mooney et al. (1998)	x	x	x
Moore Dalal et al. (2008)	x	x	x
Morton RL et al. (2009)		x	x
Mruck S et al. (1999)			x
Murchie et al. (2010)	x	x	
Peric et al (2011)			x
Poo-Hwu et al. (1999)	x	x	
Rueth et al. (2010)		x	

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Schlagenhauff et al. (2000)			x
Solivetti et al. (2006)			x
Stucky et al. (2010)	x	x	
Sylaidis et al. (1997)	x	x	
Tarhini AA et al. (2009)	x		x
Turner et al. (2011)	x	x	
Voit et al. (2001)			x
von Schoultz et al. (1996)			x
Zissimopoulos et al. (2009)			x
Zogakis et al. (2007)	x	x	

Alvarado GC, Papadopoulos NE, Hwu W-, et al. Pelvic computed tomography scans for surveillance in patients with primary melanoma in the head and neck. Melanoma Res 2011;21:127-130
Aukema TS, Olmos RA, Korse CM, et al. Utility of FDG PET/CT and brain MRI in melanoma patients with increased serum S-100B level during follow-up. Ann Surg Oncol 2010;17:1657-1661
Basseres N, Grob JJ, Richard MA, et al. Cost-effectiveness of surveillance of stage I melanoma. A retrospective appraisal based on a 10-year experience in a dermatology department in France. Dermatology 1995;191:199-203
Baughan CA, Hall VL, Leppard BJ, et al. Follow-up in stage I cutaneous malignant melanoma: an audit. Clin Oncol (R Coll Radiol) 1993;5:174-180
Beyeler M, Waldispuhl S, Strobel K, et al. Detection of melanoma relapse: first comparative analysis on imaging techniques versus S100 protein. Dermatology 2006;213:187-191
Bower MR, Scoggins CR, Martin RC,2nd, et al. Second primary melanomas: incidence and outcome. Am Surg 2010;76:675-681
Brandt SE, Welvaart K, Hermans J. Is long-term follow-up justified after excision of a thin melanoma (less than or equal to 1.5 mm)? A retrospective analysis of 206 patients. J Surg Oncol 1990;43:157-160

Brobeil A, Rapaport D, Wells K, et al. Multiple primary melanomas: implications for screening and follow-up programs for melanoma. Ann Surg Oncol 1997;4:19-23
Brown RE, Stromberg AJ, Hagendoorn LJ, et al. Surveillance after surgical treatment of melanoma: futility of routine chest radiography. Surgery 2010;148:711-6; discussion 716-7
Buljan M, Situm M, Bolanca Z, et al. Multiple primary melanoma: epidemiological and prognostic implications; analysis of 36 cases. Coll Antropol 2010;34 Suppl 2:131-134
Dancey A, Rayatt S, Courthold J, et al. Views of UK melanoma patients on routine follow-up care. Br J Plast Surg 2005;58:245-250
de Giorgi V, Rossari S, Papi F, et al. Multiple primary melanoma: the impact of atypical naevi and follow up. Br J Dermatol 2010;163:1319-1322
DeRose ER, Pleet A, Wang W, et al. Utility of 3-year torso computed tomography and head imaging in asymptomatic patients with high-risk melanoma. Melanoma Res 2011;21:364-369
Dicker TJ, Kavanagh GM, Herd RM, et al. A rational approach to melanoma follow-up in patients with primary cutaneous melanoma. Scottish Melanoma Group. Br J Dermatol 1999;140:249-254
DiFronzo LA, Wanek LA, Morton DL. Earlier diagnosis of second primary melanoma confirms the benefits of patient education and routine postoperative follow-up. Cancer 2001;91:1520-1524
Egberts F, Hitschler WN, Weichenthal M, et al. Prospective monitoring of adjuvant treatment in high-risk melanoma patients: lactate dehydrogenase and protein S-100B as indicators of relapse. Melanoma Res 2009;19:31-35
Einwachter-Thompson J, MacKie RM. An evidence base for reconsidering current follow-up guidelines for patients with cutaneous melanoma less than 0.5 mm thick at diagnosis. Br J Dermatol 2008;159:337-341
Ferrone CR, Ben Porat L, Panageas KS, et al. Clinicopathological features of and risk factors for multiple primary melanomas. JAMA 2005;294:1647-1654
Francken AB, Accortt NA, Shaw HM, et al. Follow-up schedules after treatment for malignant melanoma. Br J Surg 2008;95:1401-1407
Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localised primary cutaneous melanoma. Lancet Oncol 2005;6:608-621
Francken AB, Shaw HM, Accortt NA, et al. Detection of first relapse in cutaneous melanoma patients: implications for the formulation of evidence-based follow-up guidelines. Ann Surg Oncol 2007;14:1924-1933
Francken AB, Shaw HM, Thompson JF. Detection of second primary cutaneous melanomas. Eur J Surg Oncol 2008;34:587-592
Fusi S, Ariyan S, Sternlicht A. Data on first recurrence after treatment for malignant melanoma in a large patient population. Plast Reconstr Surg 1993;91:94-98
Garbe C, Paul A, Kohler-Spath H, et al. Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy. J Clin Oncol 2003;21:520-529
Goggins WB, Tsao H. A population-based analysis of risk factors for a second primary cutaneous melanoma among melanoma survivors. Cancer 2003;97:639-643
Hansel G, Schonlebe J, Haroske G, et al. Late recurrence (10 years or more) of malignant melanoma in south-east Germany (Saxony). A single-centre analysis of 1881 patients with a follow-up of 10 years or more. J Eur Acad Dermatol Venereol 2010;24:833-836
Hengge UR, Wallerand A, Stutzki A, et al. Cost-effectiveness of reduced follow-up in malignant melanoma. J Dtsch Dermatol Ges 2007;5:898-907
Hohnheiser AM, Gefeller O, Gohl J, et al. Malignant Melanoma of the Skin: Long-term Follow-up and Time to First Recurrence. World J Surg 2010
Johnson RC, Fenn NJ, Horgan K, et al. Follow-up of patients with a thin melanoma. Br J Surg 1999;86:619-621
Johnson TM, Hamilton T, Lowe L. Multiple primary melanomas. J Am Acad Dermatol 1998;39:422-427
Kang S, Barnhill RL, Mihm MC,Jr, et al. Multiple primary cutaneous melanomas. Cancer 1992;70:1911-1916
Kaufmann PM, Crone-Munzebrock W. Tumor follow-up using sonography and computed tomography in the abdominal region of patients with malignant melanoma]. Aktuelle Radiol 1992;2:81-85
Kelly JW, Blois MS, Sagebiel RW. Frequency and duration of patient follow-up after treatment of a primary malignant melanoma. J Am Acad Dermatol 1985;13:756-760
Khan MA, Andrews S, Ismail-Khan R, et al. Overall and progression-free survival in metastatic melanoma: analysis of a single-institution database. Cancer Control 2006;13:211-217
Kruger U, Kretschmer L, Thoms KM, et al. Lymph node ultrasound during melanoma follow-up significantly improves metastasis detection compared with clinical examination alone: a study on 433 patients. Melanoma Res 2011;21:457-463
Leiter U, Buettner PG, Eigentler TK, et al. Is detection of melanoma metastasis during surveillance in an early phase of development associated with a survival benefit? Melanoma Res 2010;20:240-246
Leiter U, Marghoob AA, Lasithiotakis K, et al. Costs of the detection of metastases and follow-up examinations in cutaneous melanoma. Melanoma Res 2009;19:50-57
Leiter U, Buettner PG, Eigentler TK, et al. Hazard rates for recurrent and secondary cutaneous melanoma: An analysis of 33,384 patients in the German Central Malignant Melanoma Registry. J Am Acad Dermatol 2011
Machet L, Nemeth-Normand F, Giraudeau B, et al. Is ultrasound lymph node examination superior to clinical examination in melanoma follow-up? A monocentre cohort study of 373 patients. Br J Dermatol 2005;152:66-70
Manola J, Atkins M, Ibrahim J, et al. Prognostic factors in metastatic melanoma: a pooled analysis of Eastern Cooperative Oncology Group trials. J Clin Oncol 2000;18:3782-3793
Martenson ED, Hansson LO, Nilsson B, et al. Serum S-100b protein as a prognostic marker in malignant cutaneous melanoma. J Clin Oncol 2001;19:824-831
Martini L, Brandani P, Chiarugi C, et al. First recurrence analysis of 840 cutaneous melanomas: a proposal for a follow-up schedule. Tumori 1994;80:188-197
McCarthy WH, Shaw HM, Thompson JF, et al. Time and frequency of recurrence of cutaneous stage I malignant melanoma with guidelines for follow-up study. Surg Gynecol Obstet 1988;166:497-502
McMeniman E, De'Ambrosis K, De'Ambrosis B. Risk factors in a cohort of patients with multiple primary melanoma. Australas J Dermatol 2010;51:254-257
Meyers MO, Yeh JJ, Frank J, et al. Method of detection of initial recurrence of stage II/III cutaneous melanoma: analysis of the utility of follow-up staging. Ann Surg Oncol 2009;16:941-947
Mooney MM, Kulas M, McKinley B, et al. Impact on survival by method of recurrence detection in stage I and II cutaneous melanoma. Ann Surg Oncol 1998;5:54-63

Mooney MM, Mettlin C, Michalek AM, et al. Life-long screening of patients with intermediate-thickness cutaneous melanoma for asymptomatic pulmonary recurrences: a cost-effectiveness analysis. Cancer 1997;80:1052-1064
Moore Dalal K, Zhou Q, Panageas KS, et al. Methods of detection of first recurrence in patients with stage I/II primary cutaneous melanoma after sentinel lymph node biopsy. Ann Surg Oncol 2008;15:2206-2214
Morton RL, Craig JC, Thompson JF. The role of surveillance chest X-rays in the follow-up of high-risk melanoma patients. Ann Surg Oncol 2009;16:571-577
Mruck S, Baum RP, Rinne D, et al. Diagnostic accuracy and predictive value of the tumor-associated antigen S100 in malignant melanomas: validation by whole body FDG-PET and conventional diagnostics. Anticancer Res 1999;19:2685-2690
Murchie P, Nicolson MC, Hannaford PC, et al. Patient satisfaction with GP-led melanoma follow-up: a randomised controlled trial. Br J Cancer 2010;102:1447-1455
Peric B, Zagar I, Novakovic S, et al. Role of serum S100B and PET-CT in follow-up of patients with cutaneous melanoma. BMC Cancer 2011;11
Poo-Hwu WJ, Ariyan S, Lamb L, et al. Follow-up recommendations for patients with American Joint Committee on Cancer Stages I-III malignant melanoma. Cancer 1999;86:2252-2258
Romano E, Scordo M, Dusza SW, et al. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol 2010;28:3042-3047
Rueth NM, Groth SS, Tuttle TM, et al. Conditional survival after surgical treatment of melanoma: an analysis of the Surveillance, Epidemiology, and End Results database. Ann Surg Oncol 2010;17:1662-1668
Schlagenhauff B, Schittek B, Ellwanger U, et al. Significance of serum protein S100 levels in screening for melanoma metastasis: does protein S100 enable early detection of melanoma recurrence? Melanoma Res 2000;10:451-459
Solivetti FM, Di Luca Sidozzi A, Pirozzi G, et al. Sonographic evaluation of clinically occult in-transit and satellite metastases from cutaneous malignant melanoma. Radiol Med 2006;111:702-708
Stucky CC, Gray RJ, Dueck AC, et al. Risk factors associated with local and in-transit recurrence of cutaneous melanoma. Am J Surg 2010;200:770-775
Sylaidis P, Gordon D, Rigby H, et al. Follow-up requirements for thick cutaneous melanoma. Br J Plast Surg 1997;50:349-353
Tarhini AA, Stuckert J, Lee S, et al. Prognostic significance of serum S100B protein in high-risk surgically resected melanoma patients participating in Intergroup Trial ECOG 1694. J Clin Oncol 2009;27:38-44
Turner RM, Bell KJ, Morton RL, et al. Optimizing the frequency of follow-up visits for patients treated for localized primary cutaneous melanoma. J Clin Oncol 2011;29:4641-4646
Voit C, Mayer T, Kron M, et al. Efficacy of ultrasound B-scan compared with physical examination in follow-up of melanoma patients. Cancer 2001;91:2409-2416
von Schoultz E, Hansson LO, Djureen E, et al. Prognostic value of serum analyses of S-100 beta protein in malignant melanoma. Melanoma Res 1996;6:133-137
Zissimopoulos A, Karpouzis A, Kouskoukis C. Indium-111 pentetreotide scintigraphy and CT scans after 3 years in the follow-up of patients with malignant melanoma. Hellenic Journal of Nuclear Medicine 2009;12:142-145197
Zogakis TG, Essner R, Wang HJ, et al. Natural history of melanoma in 773 patients with tumor-negative sentinel lymph nodes. Ann Surg Oncol 2007;14:1604-1611

10.2.5.2. Aktualisierungsrecherche 2016

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Alvarado et al. (2011)	x	x	x
Basseres et al. (1995)	x	x	x
Baughan et al. (1993)	x	x	
Bamboat et al. (2014)	x	x	x

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Cristofolini et al. (2015)	x	x	x
Cromwell et al. (2012)	x	x	x
Damude et al (2016)	x	x	
Idorn et al (2014)			x
Jones et al (2013)	x	x	x
Lott et al (2015)	x		
Livingstone et al (2015)	x	x	x
Livingstone et al (2015)	x	x	x
Marciano et al (2014)	x	x	x
Memari et al (2015)		x	
Mitchell et al (2014)	x	x	x
Moloney et al (2014)	x	x	x
Morton et al (2013)	x	x	x
Podlipnik et al (2016)			x

Literatur:	Zuteilung zur Fragestellung:		
	VII.4	VII.5	VII.6
Pomerantz et al (2015)	x	x	xx
Rowe et al (2015)	x	x	x
Rychetnik et al (2013)	x	x	x
Rychetnik et al (2012)	x	x	x
Scally et al (2014)	x	x	x
Solivetti et al (2013)			x
Testori et al (2013)	x	x	x
Watts et al (2015)	x	x	x
Wevers et al (2014)	x	x	x

Bamboat, Z.M., et al., Observation after a positive sentinel lymph node biopsy in patients with melanoma. Ann Surg Oncol, 2014. 21(9): p. 3117-23.
Cristofolini, M., et al., A 10-Year Follow-Up Study of Subjects Recruited in a Health Campaign for the Early Diagnosis of Cutaneous Melanoma: Suggestions for the Screening Timetable. Dermatology, 2015. 231(4): p. 345-52.
Cromwell, K.D., et al., Variability in melanoma post-treatment surveillance practices by country and physician specialty: a systematic review. Melanoma Res, 2012. 22(5): p. 376-85.
Damude, S., et al., The MELFO-Study: Prospective, Randomized, Clinical Trial for the Evaluation of a Stage-adjusted Reduced Follow-up Schedule in Cutaneous Melanoma Patients-Results after 1 Year. Ann Surg Oncol, 2016. 23(9): p. 2762-71.
Idorn, L.W., et al., A 3-year follow-up of sun behavior in patients with cutaneous malignant melanoma. JAMA Dermatol, 2014. 150(2): p. 163-8.
Jones, E.L., et al., Long-term follow-up and survival of patients following a recurrence of melanoma after a negative sentinel lymph node biopsy result. JAMA Surg, 2013. 148(5): p. 456-61.
Lott, J.P., et al., Delay of Surgery for Melanoma Among Medicare Beneficiaries. JAMA Dermatol, 2015. 151(7): p. 731-41.
Livingstone, E., et al., Actual practice of melanoma follow-up and treatment in Germany: results of a prospective, longitudinal cohort study. Br J Dermatol, 2015. 172(6): p. 1646-50.
Livingstone, E., et al., Prospective evaluation of follow-up in melanoma patients in Germany - results of a multicentre and longitudinal study. Eur J Cancer, 2015. 51(5): p. 653-67.
Marciano, N.J., et al., To what extent are current guidelines for cutaneous melanoma follow up based on scientific evidence? Int J Clin Pract, 2014. 68(6): p. 761-70.
Memari, N., et al., How Often Do Patients with Localized Melanoma Attend Follow-Up at a Specialist Center? Ann Surg Oncol, 2015. 22 Suppl 3: p. S1164-71.

Mitchell, J., et al., The experience of melanoma follow-up care: an online survey of patients in australia. J Skin Cancer, 2014. 2014: p. 429149.
Moloney, F.J., et al., Detection of primary melanoma in individuals at extreme high risk: a prospective 5-year follow-up study. JAMA Dermatol, 2014. 150(8): p. 819-27.
Morton, R.L., et al., Patients' perspectives of long-term follow-up for localised cutaneous melanoma. Eur J Surg Oncol, 2013. 39(3): p. 297-303.
Podlipnik, S., et al., Performance of diagnostic tests in an intensive follow-up protocol for patients with American Joint Committee on Cancer (AJCC) stage IIB, IIC, and III localized primary melanoma: A prospective cohort study. J Am Acad Dermatol, 2016. 75(3): p. 516-524.
Pomerantz, H., D. Huang, and M.A. Weinstock, Risk of subsequent melanoma after melanoma in situ and invasive melanoma: a population-based study from 1973 to 2011. J Am Acad Dermatol, 2015. 72(5): p. 794-800.
Rowe, C.J., et al., Survival outcomes in patients with multiple primary melanomas. J Eur Acad Dermatol Venereol, 2015. 29(11): p. 2120-7.
Rychetnik, L., et al., Follow-up of early stage melanoma: specialist clinician perspectives on the functions of follow-up and implications for extending follow-up intervals. J Surg Oncol, 2013. 107(5): p. 463-8.
Rychetnik, L., et al., Shared care in the follow-up of early-stage melanoma: a qualitative study of Australian melanoma clinicians' perspectives and models of care. BMC Health Serv Res, 2012. 12: p. 468.
Scally, C.P. and S.L. Wong, Intensity of follow-up after melanoma surgery. Ann Surg Oncol, 2014. 21(3): p. 752-7.
Solivetti, F.M., et al., Cutaneous melanoma follow-up: appropriateness of requests for ultrasound tests--the S.Gallicano National Referral Centre Experience. J Exp Clin Cancer Res, 2013. 32: p. 73.
Testori, A., et al., Follow-up of melanoma: a survey of Italian hospitals. Dermatology, 2013. 226 Suppl 1: p. 32-8.
Watts, C.G., et al., Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systematic review. Br J Dermatol, 2015. 172(1): p. 33-47.
Wevers, K.P., et al., Cutaneous melanoma: medical specialists' opinions on follow-up and sentinel lymph node biopsy. Eur J Surg Oncol, 2014. 40(10): p. 1276-83.

11. AG Begleittherapie

11.1. Frage X.1. Misteltherapie

Frage X.1. Beeinflusst eine Misteltherapie das Gesamtüberleben und/oder die rezidivfreie Zeit von Melanompatienten?

11.1.1. PICO, Suchwörter

PICO - Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients	Mistletoe	Observation	Overall survival, progression free survival

Suchwörter				
Stichwort	melanoma	mistletoe	primary	
Synonyme				
Ober-/Unterbegriffe	Skin cancer	Viscum album		
Mesh Term	melanoma	mistletoe		

11.1.2. Datenbanken, Suchstrategien, Trefferzahlen

11.1.2.1. Primärrecherche 2012

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(“melanoma” OR “melanoma”[MeSH Terms] OR “skin cancer”) AND (“mistletoe” OR “viscum album” OR “mistletoe”[MeSH Terms])	28.09.10	41
Cochrane Library	(melanoma and (mistletoe or viscum album)).ti,ab.	28.09.10	2
Embase	(melanoma and (mistletoe or viscum album)).ti,ab.	12.10.10	47
Update Suche			
Medline	s.o.	26.01.12	42
Cochrane Library	s.o.	26.01.12	2
Embase	s.o.	23.01.12	53

11.1.2.2. Aktualisierungsrecherche 2016

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(“melanoma” OR “melanoma”[MeSH Terms] OR “skin cancer”) AND (“mistletoe” OR “viscum album” OR “mistletoe”[MeSH Terms] AND ("2011/04/13"[PDAT] : "2016/11/16"[PDAT]))	16.11.16	9

Cochrane Library	(melanoma and (mistletoe or viscum album))	16.11.16	2

11.1.3. Auswahlkriterien

11.1.3.1. Primärrecherche 2012

Auswahl der Literatur		
Gesamttreffer		97
Einschlusskriterien	Klinische Studien zur Misteltherapie bei Melanomapatienten, alle Stadien Vergleichsarm: Beobachtung oder Standardtherapie, Sprachen: e,dt	
Ausschlusskriterien	Studien oder Reviews mit Einschluss anderer/gemischter Tumorentitäten Case Reports, Experimentelle Arbeiten	
Anzahl nach Abstractscreening, vorgesehen für Bewertung		3
Anzahl ausgewählter Studien durch Handsuche (Durchsicht der Referenzlisten der ausgewählten Arbeiten)		3
Ausgeschlossene Studien (mangelhafte methodische Qualität)		3
Berücksichtigte Studien		3

11.1.3.2. Aktualisierungsrecherche 2016

Auswahl der Literatur		
Gesamttreffer		11
Einschlusskriterien	Klinische Studien zur Misteltherapie bei Melanomapatienten, alle Stadien	

	Vergleichsarm: Beobachtung oder Standardtherapie, Sprachen: e,dt
Ausschlusskriterien	Studien oder Reviews mit Einschluss anderer/gemischter Tumorentitäten Case Reports, Experimentelle Arbeiten

Anzahl nach Abstractscreening, vorgesehen für Bewertung	3
Anzahl ausgewählter Studien durch Handsuche (Durchsicht der Referenzlisten der ausgewählten Arbeiten)	3
Ausgeschlossene Studien (mangelhafte methodische Qualität)	3
Berücksichtigte Studien	0

11.1.4. Evidenztabelle

11.1.4.1. Primärrecherche 2012

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
Kleeberg et al. 2003 Final results of the EORTC 18871/DKG 80-1 randomised phase III trial:rIFN-a2b versus rIFN-g versus ISCADOR M1 versus observation after surgery in melanoma patients	To clarify whether claims of the efficacy of Iscador M were justified	Prospective, randomised phase III adjuvant trial	803 pts: 423 pts were randomized in the EORTC 18871 3-arm trial, 407 pts in the DKG-80-1 4-arm trial (102 pts in the control arm, 101 pts in the rIFN-alpha arm, 102 in the rIFN-gamma arm and 102 in Iscador-M arm).	Disease free Interval rate (DFI) Overall Survival (OS)	Iscador M1 versus control HR 1.32 (0.93, 1.87) HR 1.21 (0.84, 1.75) The data support, but do not provide	The trials were stopped after reaching the planned sample size for the IFN-question and after having the results of an interim evaluation showed an approximately 10% lower 2-year DFI rate in the Iscador arm	1b Individual RCT

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
with either high-risk primary (thickness >3 mm) or regional lymph node metastasis			Thus 204 pts were used to assess the value of Iscador: 102 controls vs. 102 pts in the Iscador group. Stage IIb: 48%/49% Stage III: 52%/51% Baseline characteristics were well balanced		significant proof of earlier warnings about a potential negative effect of mistletoe extracts in melanoma patients, since the observations did not reach significance.	compared with the control group. Funding: In part by grant DKG 80-1	
Augustin et al. 2005 Safety and Efficacy of the Long-term Adjuvant Treatment of Primary Intermediate- to High-Risk Malignant Melanoma (UICC/AJCC Stage II and III) with a Standardized Fermented European Misteltoe	To evaluate the therapeutic safety and efficacy of Fermented European Misteltoe Extract (FME)	Mulicenter, comparative, epidemiological cohort study	686 Patients, 329 treated with FME vs. 357 controls from 35 centers; UICC/AJCC tumor stage (II/III) % 91,5/8,5 vs 95.0/5.0 Treatment group: 83,3% patients received FME P 16,7% received FME M, Q or others median duration of	Prim. endpoint Tumor-related survival Sec. endpoint Overall Survival Disease-free-survival Brain metastasis-free survival	Significant reduction of tumor-related mortality hazard in the FME group Tumor-related mortality rate 8,9% FME group vs. 10,7% control group Adjusted hazard ratios (FME vs. control): HR Tumor-related survival = 0,41 HR Overall survival = 0,64	Limits: Not randomized design Thus, baseline characteristics were well balanced Potential biases were well addressed by using a standardized parallel goups study design, independent auditing of data quality, multivariate	2b Individual Cohort Study

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
(Viscum album L.) Extract			therapy: 30 months		HR Disease-free Survival = 0,73 HR Brain metastasis-free survival = 0,33	adjusted endpoint criteria for potential confounders and other measures. Funding: The study was supported by an educational grant of the Research Institute Hiscia, Arlesheim (Switzerland) (Iscador)	
Albarrán Weick, M. 1998 Retrospektive Fall-Kontroll-Studie zum Stellenwert der adjuvanten Therapie des malignen Melanoms mit Iscador P.c.Hg.	To evaluate the impact of adjuvant Iscador on progression free survival and Overall Survival	Matched pairs (1:3) retrospective cohort study	Of 1288 documented melanoma patients of the University HospitalFreiburg, 458 patients received Iscador. 273 of this patients were evaluated in the study Control group: 819 of more than 25 000 melanoma patients within the	Progression free survival Overall Survival	No significant differences between the groups regarding overall survival (p=0,9669) and progression free survival (p=0,5746) Iscador treatment had no detrimental effect on overall survival	Study is well reported Invasionlevel was not well balanced between the groups (more Level IV and III in control group) Limits: Retrospective design, Iscador preparation was not standardized Funding: not reported Inaugural	2b Individual Cohort Study

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
			German Central Malignant Melanoma Registry.			Dissertation	

Ausgeschlossene Studien

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*LoE*
Stumpf et al. 2003 *Retrospective Study of Melanoma Patients Treated with Mistletoe Extracts*	*to analyze survival time and survival rate of all patients with malignant melanoma who had been counseled at the Tumorambulanz Herdecke*	*Retrospective Study*	*284 melanoma patients of the Tumorambulanz Herdecke were included,* *94 patients with sufficent data were analysed, 66 of this patients received mistle toe treatment.* *This 66 patients were compared with patient data from the literature*	*Survival time* *Survival rate*	*Survival time and survival rate were comparable to controls of literature*	*Poor quality → study excluded* *Limits: retrospective design, heterogeneous patient collective: patients with and without metastases, clinical stage was not indicated, Comparison with literature data based on clark level* *Different treatment regimens (Iscador M, Iscador P and*	*4* *poor quality cohort study*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						others) *Funding:* *The study was partially initiated and financed by Helixor GmbH&Co*	
Grossarth-Maticek et al. 2007 *Efficacy and Safety of the Long-term Treatment of Melanoma with a Mistletoe Preparation (Iscador)*	*To investigate if the long-term application of the mistletoe preparation Iscador show any effect in prospective controlled studies on survival, tumor progression, and psychosomatic self-regulation of patients with melanoma*	*Study 1: Randomised matched-pair study (22 pairs)* *Study 2: Non-randomised matched-pair study (32 pairs)*	*Study population consisted of 1499 melanoma patients of different german centres* *Melanoma patients without metastases, receiving conventional therapies were matched to melanoma patients with same characteristics to receive additionally Iscador*	*Overall survival* *Progression free survival* *Self regulation*	*Overall survival:* *No difference between Iscador and control group* *Significant better progression free survival in Iscador group:* *HR, 95% CI* *Study 1:* *HR 0,49 (0,32, 0,75)* *Study 2:* *HR 0,72 (0,54, 0,97)* *Self regulation:* *Significant better self regulation after Iscador therapy p=0,0048*	*Poor quality → study excluded* *Recruitment period was between 1973 and 1988* *Two studies were analysed seperately but were reported together* *Limits* *Small sample size* *Questionable method of randomisation (two slips of paper with the names of two patients were drawn of a hat)* *kaplan meier curves available of overall survival (n.s.) but not of*	*4* *poor quality cohort study*

Study	Aims	Design	Population	Outcomes	Results	Comments	LoE
						progression free survival (significant) *Funding:* *No statement included* *Affiliation of Corresponding author: Institut Hiscia, CH-Arlesheim (Iscador)*	
Schuppli R. 1990 *Adjuvant treatment of malignant melanoma with Iscador P c Hg.]*	*To assess the therapeutic effect of Iscador plus Hg on overall survival*	*Controlled study*	*High risk melanoma patients* *114 patients treated with BCG alone* *84 patients treated with BCG and Iscador P c Hg*	*Overall survival*	*Risk factor Survival* *Iscador group: 3,4* *Contol group: 2,3*	*Poor quality → study excluded* *The study was conducted at the Department of Dermatology, Universitiy Basel, 1981-1988* *Limits:* *Study reporting of low quality* *No baseline charachteristics, (groups balanced?)* *Statistical methods were not reported* *Funding:* *No statement included*	*4* *poor quality cohort study*

11.1.4.1.1. Literatur

Albarranweick M. Retrospektive Fall-Kontroll-Studie zum Stellenwert der adjuvanten Therapie des malignen Melanoms mit Iscador P.c.Hg. 1998
Augustin M, Bock PR, Hanisch J, et al. Safety and efficacy of the long-term adjuvant treatment of primary intermediate- to high-risk malignant melanoma (UICC/AJCC stage II and III) with a standardized fermented European mistletoe (Viscum album L.) extract. Results from a multicenter, comparative, epidemiological cohort study in Germany and Switzerland. Arzneimittelforschung 2005;55:38-49
Grossarth-Maticek R, Ziegler R. Efficacy and safety of the long-term treatment of melanoma with a mistletoe preparation (Iscador). Schweizerische Zeitschrift fur GanzheitsMedizin 2007
Kleeberg UR, Suciu S, Brocker EB, et al. Final results of the EORTC 18871/DKG 80-1 randomised phase III trial. rIFN-alpha2b versus rIFN-gamma versus ISCADOR M versus observation after surgery in melanoma patients with either high-risk primary (thickness >3 mm) or regional lymph node metastasis. Eur J Cancer 2004;40:390-402
Schuppli R. Die adjuvante Behandlung des malignen Melanoms mit Iscador® c.Hg. Krebs und Alternativmedizin 1990
Stumpf C, Rosenberger A, Rieger S, et al. Retrospective study of malignant melanoma patients treated with mistletoe extracts. Forsch Komplementarmed Klass Naturheilkd 2003;10:248-255

11.1.4.2. Aktualisierungsrecherche 2016

Keine neuen Publikationen, die den Auswahlkriterien entsprechen

11.2. Frage X.2&3. Immunstimulationen und immunologische Therapie

Frage X.2. Welche Evidenz gibt es zur Anwendung von Immunstimulantien aus der sogenannten komplementären Medizin während einer Therapie mit modernene immunologischen Therapieverfahren?

Frage X.3. Wie sollten Patienten beraten werden, die überlegen, ob sie eine Therapie mit Immunstimulantien aus der sogenannten komplementären Medizin während einer Therapie mit modernen immunologischen Therapieverfahren anwenden möchten?

11.2.1. PICO, Suchwörter

PICO - Schema			
Population	**Intervention**	**Comparison**	**Outcome**
Melanoma patients	Complementary medicine	Observation	Overall survival, progression free survival

Suchwörter				
Stichwort	melanoma	Complementary medicine	primary	

Synonyme				
Ober-/Unterbegriffe	Skin cancer	Viscum album, Complementary medicine		
Mesh Term	melanoma	mistletoe		

11.2.2. Datenbanken, Suchstrategien, Trefferzahlen

Datenbank	Suchstrategie	Datum	Treffer
1. Suche			
Medline	(“melanoma” OR “melanoma”[MeSH Terms] OR “skin cancer”) AND (“mistletoe” OR “viscum album” OR “mistletoe”[MeSH Terms OR “complementary medicine”] AND (“immunotherapy”) AND ("2009/04/13"[PDAT] : "2016/11/16"[PDAT]))	16.11.16	0
Cochrane Library	(melanoma and (mistletoe or viscum album))	16.11.16	2

11.2.3. Auswahlkriterien

Auswahl der Literatur	
Gesamttreffer	11
Einschlusskriterien	Klinische Studien zur Misteltherapie bei Melanomapatienten, alle Stadien Vergleichsarm: Beobachtung oder Standardtherapie, Sprachen: e,dt
Ausschlusskriterien	Studien oder Reviews mit Einschluss anderer/gemischter Tumorentitäten Case Reports, Experimentelle Arbeiten

Anzahl nach Abstractscreening, vorgesehen für Bewertung	0
Anzahl ausgewählter Studien durch Handsuche (Durchsicht der Referenzlisten der ausgewählten Arbeiten)	0
Ausgeschlossene Studien (mangelhafte methodische Qualität)	0
Berücksichtigte Studien	0

11.2.4. Evidenztabelle

Keine Publikationen, die den Auswahlkriterien entsprechen

12. AG Versorgungsqualität und Qualitätsindikatoren

12.1. Frage XI.1. Klinische Studien - Adaptation

Frage XI.1. Welchen Patienten sollte eine Teilnehme an klinischen Studien empfohlen werden?

Die Frage wurde letztendlich Konsens-basiert beantwortet

12.1.1. Synopse Quellleitlinien (kurz)

Thema/Fragestellung	**LL Australien New Zealand Guidelines Group 2008**	**LL GB NICE 2006**	**LL Frankreich French National Authority for Health 2005**	**LL Kanada Cancer Care Ontario 2007**
1. Sollte Patienten die Teilnahme an klinischen Studien empfohlen werden?	Teilnahme an Studien sollte Patienten ab St. I nach Resektion des Primärtumors angeboten werden (B); Patienten sollten darüber informiert werden, dass sie von der Teilnahme an einer Studie wahrscheinlich keine Nachteile zu erwarten haben (A)	Teilnahme an Studien sollte allen Patienten ermöglicht werden, auch unter 19-jährigen; kein Beweis für Vor- oder Nachteile für den Patienten durch Studienteilnahme	Keine Erwähnung	*Nur relevant für medikamentöse Therapien*

12.1.2. Empfehlung, Hintergrundstext und Literatur australischen und französischen Quell-Leitlinien

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)	LL Kanada Cancer Care Ontario 2007
Schlüsselempfehlungen	S. 128 Patients can be informed that they are unlikely to be disadvantaged by participation in an RCT. Grade of Recommendation: A		Keine Erwähnung	Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Updated Guideline Recommendations 2009 S. 2 Recommendations Patients with high-risk melanoma should be encouraged to participate in appropriate clinical trials exploring novel therapeutics, given that at most a small OS benefit exists with currently available therapies.
Hintergrundtexte	S. 127 20. Clinical Trials The clinical trial is an instrument designed to assess the effectiveness of potentially new or altered interventions	Patient-centered care C. Evidence S. 41 Clinical trials	Keine Erwähnung	Keine Erwähnung

	LL Australien New Zealand Guidelines Group 2008	LL GB NICE 2006	LL Frankreich French National Authority for Health 2005)	LL Kanada Cancer Care Ontario 2007
	that involve a wide range of clinical activity. Trials frequently involve drug therapy, but may address new devices, surgical procedures, treatment by external instrumentation (e.g. radiotherapy), or psychosocial aspects of clinical management. [1] Commonly, the study question is whether a new treatment is better than the old one. It is customary to compare each new treatment group with a control group, the members of which must be offered treatment matching the best standard currently available for their consideration before joining the trial. [1] The randomised clinical trial (RCT), which involves random allocation of patients to their treatment or control group, is becoming the 'gold standard' for assessment of new management processes.	One high-quality systematic review investigated patient outcomes related to mortality and morbidity among participants and nonparticipants in clinical trials. RCTs of different specialities were included, but the largest proportion was of patients with cancer. The review found little evidence for better outcomes through participation in trials aside from those arising from the effects of the treatments compared, or differences between participants and non-participants. The same review found no evidence of greater risk arising from trial participation. A previous, poorer-quality systematic review than the one cited above examined evidence for better patient outcomes through RCT participation. The majority of RCTs were of patients with cancer. The review concluded that it is		

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	Clinical trials involve significant funding and require the informed consent from patients and frequently, the involvement of a number of centres and health professionals to obtain an appropriate number of subjects to ensure sound statistical power. The conduct of trials by cooperative groups of trialists is the most likely way to advance evidence-based medicine through well-designed protocols and rigorous evaluation. [2] However, in our community some people are concerned about RCTs, believing that patients involved in such trials may be at risk from factors that would not occur in treatment outside a trial. On the other hand, others see participation in an RCT as being of benefit to the trial subject and probably an optimal way of receiving the best contemporary care and	likely that clinical trials have a positive, rather than a negative, effect on survival and morbidity outcomes, with benefits arising from the use of trial protocols. One literature review found that children and adolescents with melanoma are not entered into clinical trials. Retrospective studies have found that adolescents with cancer are not as likely to be entered into clinical trials as children and adults. An audit of skin cancer MDT activity undertaken in the South West of England found that many trusts did not have sufficient infrastructure to ensure that patients are offered trial entry. An audit of implementation of recommendations made in the Calman–Hine Report (1995) undertaken by the Commission for Health Improvement (CHI) and the Audit Commission in 2001 found that only a small		

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	clinical oversight. A recent Cochrane Review assessed the effect of participation in RCTs ('trial effects') independent both of the effects of the clinical treatments being compared ('treatment effects') and any differences between patients who participated in RCTs and those who did not. [3] The outcome of this review led its authors to conclude that there is no greater risk from participating in RCTs than there is from being treated outside an RCT. The authors considered that the belief or assertion that results of RCTs cannot be applied to usual practice is challenged by the review. [2] This outcome would appear to provide a sound basis for clinicians to offer participation in RCTs to their patients. Any uncertainty about the effects of treatment can best be resolved through a randomised	proportion of patients with cancer are involved in clinical trials. Trial participation was less likely in settings outside of large cancer centres.		

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	trial as long as the eligibility criteria for the trial match the patient population seen in usual practice, or the trial treatment is applied only to patients who match the eligibility criteria. [4] Evidence summary Outcomes for patients who participate in RCTs on average do not differ from those of patients who receive similar treatments and do not participate in a trial. LoE: I Reference: [2]			

Literatur:

LL Australien New Zealand Guidelines Group 2008

4. Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. Cochrane Database Syst Rev 2007;(2):MR000012

3. Optimising Cancer Care in Australia. 1-122. 2002. Melbourne. Available from <http:/www.cosa.org.au/documents/optim_Cancer_Care_final.pdf>. Clinical Oncology Society of Australia, The Cancer Council Australia and The National Cancer Control Initiative.

1. The Cancer Council Victoria. About Clinical Trials. Available from <http:www.cancervic.org.au/browse.asp?ContainerID=about_clinical_trials> accessed 1 September 2007

2. Vist GE, Hagen KB, Devereaux PJ, et al. Outcomes of patients who participate in randomised controlled trials compared to similar patients receiving similar interventions who do not participate. Cochrane Database Syst Rev 2007;(2):MR000009

LL GB NICE 2006

1. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". J Clin Epidemiol 2001;54:217-224

2. Peppercorn JM, Weeks JC, Cook EF, et al. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. Lancet 2004;363:263-270

3. Poirier V, Wright S, Lucke T, Verne J, Sandhu J, De Berker D, et al. Auditing current Skin Cancer Multi-disciplinary Team (MDT) practices against the Manual of Cancer Services Standards in the South West Region.
4. Vist GE, Hagen KB, Devereaux PJ, et al. Systematic review to determine whether participation in a trial influences outcome. BMJ 2005;330:1175

13. Abkürzungsverzeichnis

AUC	area under curve
BCG	Bacille Calmette Guerin
BM	brain metastases
BT	Breslow Thickness
CD	conventional diagnostics
CI	confidence interval
CLND	Complete lymph node dissection
CM	cutaneous melanoma
CR	Complete Response
CR	conventional radiography
CS	conditional survival
CSP	conventional screening procedures
CT	chemotherapy
CWS, P3	cell wall skeleton and purified trehalose dimycolate
CXR	Chest X-ray CXR
DFI	disease-free interval
DFS	disease- free survival
DM	distant metastases
DMFD	distant metastasis-free survival
DMFI	distant metastasis-free interval
DMFS	distant metastasis-free survival
DMM	desmoplastic malignant melanoma
DNCB	Dinitrochlorobenzene
DNM	desmoplastic neurotropic melanoma
DPCP	Diphencyprone

DSS	disease-specific survival
DTIC	dacarbazine
ELND	´elective lymph node dissection`
FAS	full analyses set
FMR	first melanoma recurrence
FN	false negative
FP	false positives
GIT	gastrointestinal tract
GKS	Gamma Knife surgery
Gy	Gray
HACE	Hepatic artery chemoembolization
HAI	Hepatic artery infusion
HDI	high dose interferon
HR	Hazard ratio
HRQL	health related quality of life
IDI	intermediate dose interferon
IES	Impact of Event Scale
IFN	Interferon
IHP	Isolated hepatic perfusion
Il-2	Interleukin 2
IL-BCG	intralesionally - bacillus Calmette Guerin
ILP	isolated limb perfusion
incl.	including
ITT	Intent To Treat
LDI	low dose interferon
LM	lentigo maligna
LMM	lentigo maligna melanoma
LN	lymph node(s)
MCS	Mental Component Summary
MER	methanol extraction residue of bacillus Calmette-Guerin
Mets	metastases
MM	malignant melanoma
MPM	multiple primary melanomas
MPV-BCG	multiple puncture vaccination - bacillus Calmette Guerin

MUP	melanoma with unknown primary
MV	Megavolt
n.r.	not reported
n.s.	not significant
NC	no change
NED	no evidence of disease
NMM	nodular malignant melanoma
NR	not reached
OBS	observation
OR	Odds ratio
OS	Overall survival
PCS	Physical Component Summary
PD	Progressive Disease
PDS	power Doppler sonography
PE	physical eexamination
PM	primary melanoma
PP	Per protocol
PR	Partial Response
PV-10	10% w/v Rose Bengal in saline
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-free survival, Recurrence free survival
rIFN-beta	recombinant interferon beta
RR	Relapse Rate
RR	relative risk
RSCL	Rotterdam Symptom Checklist
RT	radiotherapy
s.c.	subcutaneous
SD	Stable Disease
SIRT	selektive interne Radio-Therapie
SLN	senitinel lymph node
SLNB	sentinel-lymph node biopsy
SM	second melanoma
SPM	second primary melanoma

SRS	stereotactic radiosurgery
SSM	superficial spreading melanoma
ST	soft tissue
TACE	Trans-arterial chemoembolization
TD	Total dose
TLND	therapeutic lymph –node-dissection
TMZ	temozolomide
TN	true negatives
TP	true positives
UICC	Union International Contre Cancer
US	ultrasound
WBRT	whole brain radiation therapy
WHO	World Health Organisation
Vs.	versus
Wb	whole body