

# **Konsultationsfassung: Evidenztabelle der S3- Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit Vulvakarzinom und seiner Vorstufen**

Version 1.01 – Mai 2026

AWMF-Registernummer: 032 - 0590L

## **Evidenztabelle**

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# 1 Informationen zu dieser Leitlinie

## 1.1 Herausgeber

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

## 1.2 Federführende Fachgesellschaft(en)

**AGO Studiengruppe**  
Arbeitsgemeinschaft Gynäkologische Onkologie  
Arbeitsgruppe



**DGGG**  
Deutsche Gesellschaft für Gynäkologie und  
Geburtshilfe (DGGG)



## 1.3 Finanzierung der Leitlinie

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

## 1.4 Kontakt

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## 1.5 Zitierweise

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Konsultationsfassung: Evidenztabellen der S3-Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit Vulvakarzinom und seiner Vorstufen, Version 1.01, 2023, AWMF-Registernummer: 032 - 0590L <https://www.leitlinienprogramm-onkologie.de/leitlinien/vulvakarzinom>; Zugriff am [tt.mm.jjjj]

## 1.6 Abkürzungsverzeichnis

**Tabelle 1: Abkürzungsverzeichnis**

Abkürzung	Erläuterung
18-FDG	18-Fluordesoxyglucose
18F-FDG PET-CT	Fluorine-18-Fluordesoxyglucose Positron-Emissionstomographie
95%-KI	95% Konfidenzintervall
ABO	Arbeitsgemeinschaft Bildgebung in der Onkologie (DKG)
ADT	Arbeitsgemeinschaft Deutscher Tumorzentren
AG	Arbeitsgruppe
AG CPC	Arbeitsgemeinschaft Zervixpathologie und Kolposkopie (DGGG)
AGO	Arbeitsgemeinschaft für Gynäkologie in der DKG
AGSMO	Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie
AIO	Arbeitsgemeinschaft Internistische Onkologie der DKG
AOP	Arbeitsgemeinschaft Onkologische Pathologie (DKG)
ARO	Arbeitsgemeinschaft für Radiologie in der DKG
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.
AZÄD	Arbeitsgemeinschaft zytologisch tätiger Ärzte in Deutschland
BDP	Bundesverband Deutscher Pathologen
BLFG	Bundesarbeitsgemeinschaft Leitender Ärztinnen und Ärzte in der Frauenheilkunde und Geburtshilfe e. V.
BMG	Bundesministerium für Gesundheit
BMI	Body-Mass-Index
BNGO	Berufsverband Niedergelassener Gynäkologischer Onkologen in Deutschland
BVDST	Berufsverband Deutscher Strahlentherapeuten e.V.
BVF	Berufsverband der Frauenärzte

<b>Abkürzung</b>	<b>Erläuterung</b>
CAM	complementary and alternative medicine, Komplementär- und Alternativmedizin
CEBM	Centre for Evidence-Based Medicine (Oxford, UK)
CHT	Chemotherapie
CIN	Cervicale Intraepitheliale Neoplasie
Col	Conflict of Interest
CT	Computertomographie
DDG	Deutsche Dermatologische Gesellschaft (DDG)
DEGRO	Deutsche Gesellschaft für Radioonkologie
DEGUM	Deutsche Gesellschaft für Ultraschall in der Medizin
DELBI	Deutsches Leitlinienbewertungsinstrument
DGAV	Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie
DGGG	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe
DGHO	Deutsche Gesellschaft für Hämatologie und Onkologie
DGN	Deutsche Gesellschaft für Nuklearmedizin
DGP	Deutsche Gesellschaft für Palliativmedizin e.V.
DGP	Deutsche Gesellschaft für Pathologie
DGU	Deutsche Gesellschaft für Urologie e.V.
DKG	Deutsche Krebsgesellschaft e.V.
DKH	Stiftung Deutsche Krebshilfe
DRG	Deutsche Röntgengesellschaft
DVSG	Deutsche Vereinigung für Soziale Arbeit im Gesundheitswesen
EBM	Evidenzbasierte Medizin
EK	Expertenkonsens (siehe zur Erläuterung Kapitel "Expertenkonsens" unter "Grundlagen der Methodik")

<b>Abkürzung</b>	<b>Erläuterung</b>
EQ-5D	European Quality of Life 5 Dimensions
ESGO	European Society of Gynaecological Oncology
FDG	Fluorodesoxyglucose
FDG-PET	Fluorodeoxyglucose positron emission tomography
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
G-BA	Gemeinsamer Bundesausschuss
G-I-N	Guidelines International Network
GEKID	Gesellschaft der epidemiologischen Krebsregister in Deutschland
ggf.	gegebenenfalls
GKFP	Gesetzliches Krebsfrüherkennungsprogramm
GKV	Gesetzliche Krankenversicherung
GoR	Grade of recommendation
Gy	Gray
HDR	High dose rate
HE-Färbung	Hämatoxylin-Eosin-Färbung
HPV	Humanes Papillomavirus
HR	Hazard Ratio
HR-HPV	Hochrisiko-Genotypen des Humanen Papilloma-Virus
HSIL	High Grade Squamous Intraepithelial Lesion
i.v.	intravenös
ICCR	International Collaboration on Cancer Reporting
ICD-10	Internationale Klassifikation der Krankheiten, 10. Revision
ICF	International Classification of Functioning, Disability and Health

<b>Abkürzung</b>	<b>Erläuterung</b>
ICG	Indocyaningrün
IK	Interessenkonflikt
IMRT	intensitätsmodulierte Radiotherapie
IORT	Intraoperative Radiotherapie
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITC	Isolierte Tumorzellen
k.a.	keine Angaben
KOF	Körperoberfläche
KOK	Konferenz onkologischer Kranken- und Kinderkrankenpflege, AG in der DKG
KPE	komplexe Physikalische Erstauungstherapie
LEEP	Loop Electrical Excision Procedure
LK	Lymphknoten
LL	Leitlinie
LNE	Lymphonodektomie/ Lymphadenektomie
LoE	Level of Evidence
LSIL	Low Grade Squamous Intraepithelial Lesion
MD	Medizinischer Dienst
MFS	metastasis-free survival
MRT	Magnetresonanztomographie
n.s.	not significant
NACT	neoadjuvante Chemotherapie
NAKOS	Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen
NCCN	National Comprehensive Cancer Network

Abkürzung	Erläuterung
NCP	National Cancer Plan
NGC	National Guideline Clearinghouse (USA)
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NII	Nodi lymphatici
NOS	Not otherwise specified
OEGGG	Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe
OL	Leitlinienprogramm Onkologie
OMD	Oligometastasierte Erkrankung
OP	Operation
OS	Overall survival
Pap	zytologischer Abstrich nach Papanicolaou
PET	Positronen-Emissions-Tomographie
PET/CT	Positronen-Emissions-Tomographie/Computertomographie
PICO	Population, Intervention, Comparison, Outcome
PrIO	Arbeitsgemeinschaft Prävention und integrative Onkologie
PTV	Planning target volume
QI	Qualitätsindikator
RCHT	Simultane Radiochemotherapie
RCT	Randomized Controlled Trial
RF	Risikofaktor
RKI	Robert Koch-Institut
Rö-Thorax	Röntgenthorax

Abkürzung	Erläuterung
RTX	Radiotherapie
SCC	squamous cell carcinoma
SGB	Sozialgesetzbuch
SIGN	Scottish Intercollegiate Guidelines Network
Sono	Sonographie
SOP	Standard operating procedure
SPECT	Single-Photon-Emissionscomputertomographie
SR	Systematic review
STD	Sexually transmitted disease
STIKO	ständige Impfkommision des Robert-Koch-Institut
TILs	tumorinfiltrierende Lymphozyten
TNM	TNM-Klassifikation
TNM-Klassifikation	Klassifikation nach T=Tumor, N=Nodes, Lymphknoten und M=Metastasen (Tumor-Nodes-Metastases)
TVS	Transvaginalsonographie
UICC	Union international contre le cancer
VIN	Vulväre intraepitheliale Neoplasie
WHO	World Health Organization
AIDS	Acquired Immune Deficiency Syndrome
CIS	Carcinoma in situ
HIV	Humanes Immunschwäche-Virus / Human Immunodeficiency Virus
RR	Relatives Risiko
AUC	Fläche unter der Kurve (engl.: Area Under the Curve)
LR	likelihood ratio (dt.: Wahrscheinlichkeitsverhältnis)

Abkürzung	Erläuterung
NPV	negativ prädiktiver Wert / negative predictive value
PPV	Positiv prädiktiver Wert (engl.: positive predictive value)
CNB	Core Needle Biopsy
FNA	Feinnadelaspiration
FNAB	Feinnadelaspirationsbiopsie
FNAC	Feinnadelaspirationszytologie
SLNB	Sentinel-Lymphknotenbiopsie (sentinel lymph node biopsy)
CE-MRT	kontrastmittelgestützte Magnetresonanztomographie
VaIN	Vaginal intraepithelial neoplasia
JÜR	Jahresüberlebensrate
CSS	krebsspezifisches Überleben (cause specific survival)
DFS	Krankheitsfreies Überleben (engl. disease-free survival)
DSS	krankheitsspezifisches Überleben (disease-specific survival)
OS	Gesamtüberleben / overall survival
PFS	progressionsfreies Überleben (engl.: progression-free survival)
RFS (eng)	relapse-free survival, recurrence free survival
FNA	Fine-needle aspiration
FNAC	Feinnadelaspirationszytologie / fine-needle aspiration cytology
OR	Chancenverhältnis (engl. Odds-Ratio)
SLN	Sentinel-Lymphknoten
bzw.	beziehungsweise
u.a.	unter anderem
i.d.R.	In der Regel

Abkürzung	Erläuterung
SIR	Standardisierte Inzidenzrate
bzgl.	bezüglich
CAP	College of American Pathologists
VEGF	Vascular endothelial growth factor
DWI	Diffusion-weighted imaging
PDT	Photodynamische Therapie
5YSR	5-Jahres Überlebensrate, 5 Year Survival Rate
Abb.	Abbildung
ABO	Working Group on Imaging in Oncology (DKG)
ASMR	altersstandardisierten Mortalitätsrate
ASR	altersstandardisierten Inzidenzrate
DEVIL	Differentiated Exophytic Vulvar Intraepithelial Lesion
dVIN	differenzierte Vulväre Intraepitheliale Neoplasie
ECSVD	European College for the Study of Vulval Disease
EFC	European Federation for Colposcopy
ISSVD	International Society for the Study of Vulvovaginal Disease
Kap.	Kapitel
LS	Lichen sclerosus
MBA	morphometrische binäre Bewertung
MUP	morphometrisches Ultraschallmuster
Node-RADS	Node Reporting and Data System
ROC-Kurve	Receiver-Operating-Characteristic Kurve
sog.	sogenannt

<b>Abkürzung</b>	<b>Erläuterung</b>
SR	Überlebensrate, Survival Rate
SROC	summarische ROC-Kurve
Tab.	Tabelle
uVIN	usual type vulvar intraepithelial neoplasia
VAAD	Vulvar Acanthosis with Altered Differentiation
VAM	Vulvar Aberrant Maturation
vaVIN	verruciform acanthotic Vulvar Intraepithelial Neoplasia

## 2 Evidenztabelle

### Kapitel 3: Epidemiologie und Risikofaktoren

#### Kapitel 3.1: Modifizierbare und nicht-modifizierbare Risikofaktoren für VIN und Vulvakarzinom

Verknüpfte Empfehlungen:

**Empfehlung 3.8:**

Patientinnen mit behandelter HSIL/dVIN zeigen gegenüber Patientinnen mit unbehandelter HSIL/dVIN eine geringere Rezidivrate und ein niedrigeres Risiko für die Entwicklung eines Vulvakarzinoms.

**Literaturreferenzen:** [\[1\]](#)

[\[1\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low → cohort studies and case reports	1 review (data from 71 cohort studies/ case reports)	Progression to invasive vulvar carcinoma	/	/	-1 (data on wrong population: women with VIN III, not representing directly the PICO population)	-2 (only few participants, narrative summary with no confidence intervals)	Low confidence in results of the review (assessed with AMSTAR-2 tool).	⊕⊖⊖⊖ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
					of women with HSIL/dVIN)			

**Verknüpfte Empfehlungen:****Empfehlung 3.8:**

Patientinnen mit behandelter HSIL/dVIN zeigen gegenüber Patientinnen mit unbehandelter HSIL/dVIN eine geringere Rezidivrate und ein niedrigeres Risiko für die Entwicklung eines Vulvakarzinoms.

**Literaturreferenzen:** [\[1\]](#)

[\[2\]](#), [\[1\]](#)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Bucci, 2022 Systematic literaturreview	Types of studies: original study or a systematic review or a meta-analysis  Searched from inception (since January 1980) until April 2021  Databases:  PubMed  <i>Additionally: Cancer Incidence in Five Continents, a publication of the International</i>	Question/ Aim:  To provide an updated and complete overview of descriptive and analytical epidemiology of <b>Vulvar Cancer (VC)</b> . Specifically, we aimed at: (1) summarizing worldwide VC incidence rates and trends using comparable indicators; and (2) performing a	69studies included in the review, no further information of number of participants (none of the included studies are relevant for this guideline PICO)  <b>Descriptive statistics:</b>  No details reported in the review	<b>No relevant outcomes reported</b>	Overall confidence in results of SR (AMSTAR-2): “low”  PICO elements: no  A priori design: yes  Justification for design: no  Literature search >= 2 databases, search strategy + other sources: no  Selection in duplicate: yes	69 included studies

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Association of Cancer Registries edited by the International Agency for Research on Cancer</p> <p>Search terms: (((vulvar OR vulva) AND (cancer OR neoplasm OR carcinoma) AND (incidence))) AND English [Language] AND ("2000" [Date—Publication]: "2021" [Date—Publication])  (((vulvar OR vulva) AND (cancer OR neoplasm OR carcinoma OR Neoplasms [MeSH Terms]) AND (risk))) AND English [Language] AND ("1980" [Date—</p>	<p>systematic literature review of all known and putative risk factors for the disease.</p> <p><b>“This study was not aimed at reviewing the risk factors for preinvasive vulvar disease.”</b></p>			<p>Data extraction in duplicate: yes (checking by 2<sup>nd</sup>)</p> <p>List of excluded studies: no</p> <p>sufficient detail on studies: no</p> <p>RoB assessed: no</p> <p>Funding of incl. studies: no</p> <p>MA appropriate: NA</p> <p>RoB considered in MA: NA</p> <p>RoB in interpretation: no</p> <p>Heterogeneity explained: no</p> <p>Publication bias investigated: no</p> <p>Sources of Col: “The authors declare no conflict of interest.”</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Publication]: “2021” [Date—Publication]).</p> <p>Inclusion criteria</p> <p>(1) article reporting an original study or a systematic review or a meta-analysis addressing the association between epidemiologic risk factors and primary VC (topography code C51 according to the IC-D-O, third ed.</p> <p>(2) article providing a quantitative estimate of the association as obtained using a cohort or a case-control control approach; and</p> <p>(3) article in English.</p> <p>Exclusion criteria:</p> <p>Not reported</p>					

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	Only exclusion reasons at full text level from the PRISMA flowchart.					
Van Seters, 2005 Systematic review of patient data	<p>Types of studies: Non-RCTs, case reports</p> <p>Searched from inception until November 2004</p> <p>Databases: computer searches of MEDLINE (from 1964), CANCELIT (from 1980), EMBASE (from 1974), BIOSIS PREVIEWS AB (from 1970) and SCIENCE CITATION INDEX (from 1970)</p> <p>key words were used: vulvar neoplasms in combination with intraepithelial</p>	<p>Question/Aim: The aim of this study was, by means of a systematic review, to assess both the risk of progression of VIN III in untreated patients and the effect of surgical treatment in relation to recurrences and progression of VIN III.</p> <p>(Surgical treatment was defined as cold knife surgery, laser excision, laser evaporation, LEEP excision or cryosurgery)</p>	<p>97studies on 3322 pts with VIN III</p> <p>29 studies on treatment results, progression and regression of VIN III</p> <p>12 case reports only gave data on progression of VIN III</p> <p>6 case reports only dealt with regression of VIN III.</p> <p><b>Descriptive statistics:</b></p> <p>Only for total population and from studies reporting descriptive data</p>	<p><b>Recurrence rate</b></p> <p>A: Recurrences could be found after vulvectomy (N = 613) in 19%, after partial vulvectomy (N = 62) in 18%, after local excision (N = 808) in 22%, after laserevaporization (N = 253) in 23% and after cryocoagulation (N = 16) in 56%.</p> <p>B: not reported</p> <p><b>Progression to invasive vulvar carcinoma</b></p> <p>A: 3.3 %</p>	<p>Overall confidence in results of SR (AMSTAR-2): "low"</p> <p>PICO elements: no</p> <p>A priori design: yes</p> <p>Justification for design: no</p> <p>Literature search &gt;= 2 databases, search strategy + other sources: yes</p> <p>Selection in duplicate: NR</p> <p>Data extraction in duplicate: NR</p> <p>List of excluded studies: no</p>	<p><u>Non-RCTs</u></p> <p>29 studies on treatment results, progression and regression of VIN III</p> <p>12 case reports only gave data on progression of VIN III</p> <p>6 case reports only dealt with regression of VIN III</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>neoplasia, Bowen, bowenoid, Queyrat, carcinoma simplex, early vulvar cancer, hyperplastic dystrophy, condylomatous dysplasia, intraepithelial carcinoma, carcinoma in situ, vulvar atypia and precancerous conditions</p> <p><b>Inclusion criteria:</b></p> <p>(1) articles written in English, German or French and</p> <p>(2) data, clearly retrievable, on the surgical treatment and/or progression and/or regression of VIN III.</p> <p>Exclusion criteria:</p>	<p>A: treated women (68 studies reported on N=1921)</p> <p>B: untreated women (no treatment at all (N= 61), or in whom gross macroscopic VIN III was left behind (N = 27) (10 studies reported on N=88)</p>	<p>Age (mean)</p> <p>mean age = 46 (48 studies, 2152 patients)</p> <p>mean minimum age was 21 (59 studies, 2585 patients) and the mean maximum age was 80 (56 studies, 2467 patients)</p> <p>Vulvar Lesion characteristics</p> <p>multifocal VIN III: 49% (1878 patients, 45 studies).</p> <p>multicentric genital tract neoplasia: 32% (2067 patients, 46 studies)</p> <p>Location of the tumour</p> <p>Tumour size (% , cm)</p>	<p>mean time to progression = 55 months (range 4-216)</p> <p>B: 8/88 (9%)</p> <p>9 % progressed in 12 to 96 months --&gt; "untreated patients do have a 9% risk of progression to invasive vulvar carcinoma. Previous radiotherapy and immunosuppression may have played a role in the progression of those untreated patients."</p> <p><b>Narrative summary of the review:</b></p> <p>"Invasion may occur many years after VIN III was diagnosed. Most of these invasive carcinomas are superficial and</p>	<p>sufficient detail on studies: yes</p> <p>RoB assessed: no</p> <p>Funding of incl. studies: no</p> <p>MA appropriate: NA</p> <p>RoB considered in MA: NA</p> <p>RoB in interpretation: no</p> <p>Heterogeneity explained: no</p> <p>Publication bias investigated: no</p> <p>Sources of Col: NR</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Articles in which data of VIN III were not distinguishable from data of VIN I-II, (micro)invasive vulvar carcinoma or other vulvar diseases, were excluded.</p> <p>Case histories were excluded, except those concerning regression or progression of VIN III.</p>		<p>xx</p> <p>Tumour depth (% mm)</p> <p>xx</p>	<p>overdiagnosing early invasion is well known. Spontaneous regression may occur (1.2%). At this moment, there is not enough evidence from the available data to support the removal of all involved vulvar skin which would give many psychosexual sequelae. Only a prospective registration with standardized pathology examination will give information about the real natural history of VIN III.“</p>		

**Verknüpfte Empfehlungen:****Empfehlung 3.9:**

Lichen sclerosus ist ein Risikofaktor für das Entstehen einer dVIN/eines Vulvakarzinoms. Patientinnen mit behandeltem Lichen sclerosus zeigen gegenüber Patientinnen mit unbehandeltem Lichen sclerosus eine geringere Rezidivrate und ein niedrigeres Risiko für die Entwicklung einer VIN/eines Vulvakarzinoms.

**Empfehlung 4.3:**

Ein Lichen sclerosus der Vulva sollte auch unter dem Gesichtspunkt der Prävention eines Vulvakarzinoms gemäß den aktuellen Empfehlungen konsequent therapiert werden.

**Empfehlung 4.2:**

Die konsequente Therapie eines Lichen sclerosus der Vulva kann das Risiko für die Entstehung vulvärer Neoplasien senken.

**Literaturreferenzen:** [\[3\]](#), [\[4\]](#), [\[5\]](#), [\[6\]](#)

[\[6\]](#), [\[4\]](#), [\[5\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Chin, 2020 Retrospective study	11 pts with vLS and previous vSCC and/or dVIN  Inclusion criteria (for analysis): patients with vLS who received long-term topical corticosteroid therapy  All patients were treated with topical corticosteroids after	Interventions  All patients were treated with topical corticosteroids after primary excision of vSCC or dVIN. Agents used included betamethasone dipropionate, 0.05%, methylprednisolone aceponate, 0.1%, hydrocortisone, 1%, clobetasol	<b>Recurrence rate / recurrence-free</b> NR  <b>Progression to squamous cell carcinoma of the vulva</b> NR  Progression to vulval intraepithelial neoplasia (VIN)	<b>General information</b> Median follow-up: 12 months  <b>Funding:</b> NR  <b>Col:</b> Non reported  Risk of bias considerations (adapted from SIGN cohort study checklist)  Study type: retrospective study

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>primary excision of vSCC or dVIN</p> <p>Exclusion criteria (for analysis): NR</p> <p>Enrolment period From January 1, 2008, to April 30, 2019,</p> <p><b>Descriptive statistics</b></p> <p>Age (mean, range) mean age at diagnosis of primary lesion = 62.9 years (26-88)</p>	<p>propionate, 0.02% and 0.05%, and desonide, 0.05%</p> <p>Analysis Type of analysis: NR</p> <p>Matching: NR</p> <p>Confounders: NR</p>	<p>NR</p> <p><b>Additional outcomes: recurrence of vSCC or VIN (all women treated with vLS)</b></p> <p>8/11 (73%) no recurrence</p> <p>2/11 (18%) recurrence of vSCC (1 of whom developed multiple recurrences of vSCC, and 1 patient (9%) had recurrence of their dVIN)</p>	<p>Populations comparable: NA</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: NA</p> <p>Assessed more than once: NA</p> <p>Possibly affected by knowledge of outcome status?: NA</p> <p>Drop-out rate &amp; reasons reported: no</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): NA</p> <p>Main cofounders taken into account: NR</p> <p>Confidence intervals reported: NR</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Steinkasserer, 2023 Retrospective study	<p>56 cases with various vulvar diseases (N=499 cases with various vulvar diseases were derived from the database, N=436 cases excluded due to another diagnosis than LS à final study population N=56 cases)</p> <p>Inclusion criteria (for analysis):</p> <p>Cases with possible LS were included in this study:</p> <p>Possible LS included cases with interface dermatitis that could fit with an early phase of LS.</p> <p>Cases were also classified as LS when no histology was done, but the clinical appearance indicated LS.</p> <p>Further cases were included where LS was diagnosed within the scope of VSCC treatment.</p> <p>(The patient population was searched for the following</p>	<p>For this study, histological findings and clinical data of patients with various vulvar pathologies, who were registered at the Department of Obstetrics and Gynecology of Hannover Medical School (MHH) from 2008 to 2020 were identified retrospectively.</p> <p>Interventions</p> <p>No intervention or treatment comparison</p> <p>“The therapy for patients with lichen sclerosus usually includes local therapy with cortisone ointment according to the following schedule: 6 weeks daily, 4 weeks 2–3 times a week and then permanently 1–2 times a week. The follow-up of the patients includes an annual follow-up in our dysplasia consultation with anamnesis of the symptoms,</p>	<p><b>Recurrence rate / recurrence-free</b></p> <p>NR</p> <p>Progression to squamous cell carcinoma of the vulva</p> <p>NR</p> <p>Progression to vulval intraepithelial neoplasia (VIN)</p> <p>NR</p> <p><b>Additional outcomes: VSCC development in LS patients</b></p> <p>27/56 LS pts. developed VSCC</p> <p>18/27 (66.6%) confirmed LS</p> <p>“In 18 patients who developed vulvar carcinoma in course, both LS and VIN were confirmed (66.6%).”</p> <p>“Five cases of LS were diagnosed only at or after diagnosis of VSCC”</p>	<p>Selective reporting (comparison with protocol): NA</p> <p><b>General information</b></p> <p>Median follow-up: NA</p> <p><b>Funding:</b> Open Access funding enabled and organized by Projekt DEAL. Funding provided by the Department of Obstetrics and Gynecology of Hannover Medical School (MHH).</p> <p><b>Col:</b> The authors declare that they have no competing interests.</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective study</p> <p>Populations comparable: yes</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>International Statistical Classification of Diseases codes (ICD-10): N90.4, N90.5, N90.6, N90.8, N90.9 and C51. Every report contains patient identification, all diagnoses of the patients, the exact date of diagnosis, codes of surgery and routines ("Operationen- und Prozeduren-Schlüssel"; OPS), physician's letters, and pathological findings and histology. HPV status was performed by PCR method in our pathology department.)</p> <p>Exclusion criteria (for analysis):</p> <p>NR</p> <p>Enrolment period</p> <p>2008-2020</p> <p>Descriptive statistics (for all women with LS)</p> <p>Age (median, range)</p> <p>All women with LS: 60.25 (16-85)</p>	<p>vulvoscopy and, if necessary, biopsy."</p> <p>Analysis</p> <p>Type of analysis: Distribution was examined with the Shapiro-Wilk normality test, and groups were compared with an unpaired t test or Mann-Whitney-U test as appropriate after checking for outliers.</p> <p>Matching: NR</p> <p>Confounders: NR</p>	<p>29/57 LS pts. without VSCC</p> <p><b>Narrative summary:</b></p> <p>"Theoretically, the detection of LS can represent a significant advantage for the affected patients to prevent progression to VSCC, as they are more amenable to follow-up examinations. Even if progression cannot be prevented, the earlier possible detection of a malignant change would enable a faster appropriate therapy.</p>	<p>Assessment reliable: yes</p> <p>Assessed more than once: NR</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: NR</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: NA</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): NA</p> <p>Main cofounders taken into account: NA</p> <p>Confidence intervals reported: NA</p> <p>Selective reporting (comparison with protocol): NA</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Menopausal status at time of diagnosis (all women with LS)</p> <p>Postmenopausal: 78.57%</p> <p>Prämenopausal: 21.43%</p> <p>HPV status positive</p> <p>10.72%</p> <p>Nicotine abuse</p> <p>Yes: 14.29%</p> <p>No: 76.79%</p> <p>Ex-smokers: 3.57</p> <p>Pre-existing diseases</p> <p>Arterial hypertension: 42.86</p> <p>Hypothyroidism: 26.79</p> <p>Diabetes mellitus: 23.21</p> <p>Presence of VIN</p> <p>VIN I-III 44.04%</p> <p>VIN I: 20%</p> <p>VIN II: 28%</p> <p>VIN II-III: 4%</p> <p>VIN III: 48%</p>			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Lee 2015 prospective longitudinal cohort study	<p>507 women with biopsy-proved VLS</p> <p>Inclusion criteria (for analysis): age older than 18 years, biopsy-proved VLS, and having been followed up for a minimum of 2 years</p> <p>Exclusion criteria (for analysis): NR</p> <p>Enrolment period January 2, 2008 - September 26, 2014</p> <p>Descriptive statistics (for all women with LS)</p> <p>Age (mean, range) 55.4 (18-86)</p> <p>Duration of symptoms at presentation: 5.0 years (range, 0.1-40.0 years)</p> <p>Menopausal status: 158 (31.2%): premenopausal</p>	<p>Intervention <u>à just one intervention group</u></p> <p>Preventive treatment using topical corticosteroid (TCSs) of various potencies, adjusted to meet a target outcome of normal skin color and texture, with regular long-term follow-up by a dermatologist or gynecologist.</p> <p>à Comparison between:</p> <p>Compliant patients (N=357, 70.4%)</p> <p>Partially Compliant patients (N=150, 26.6% of total)</p> <p>(Patients were considered compliant if they self-reported that they followed treatment instructions “most of the time” or “all of the time” and partially compliant if they self-reported that they followed treatment instructions “some of the time,” “little of the time,” or “none of the time,” either in terms of</p>	<p><b>Recurrence rate / recurrence-free</b> NR</p> <p>Progression to squamous cell carcinoma of the vulva (SCC) or vulval intraepithelial neoplasia (VIN)</p> <p>Compliant: 0/357 Partially compliant: 7/150</p> <p><b>Additional outcomes:</b> <b>Suppression of symptoms occurred</b> Compliant: 333 (93.3%)/357 Partially compliant: 87 (58.0%)/150</p> <p><b>Adhesions and scarring occurred:</b> Compliant: 12 (3.4%)/357 Partially compliant: 60 (40.0%)/150</p> <p><b>Reversible TCS-induced cutaneous atrophy:</b></p>	<p><b>General information</b> Median follow-up: 4.7 years (range, 2.0-6.8 years)</p> <p><b>Funding:</b> This study was supported in part by the Dermatology Department of Royal North Shore Hospital for the submission of the project for ethics review.</p> <p>Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.</p> <p><b>Col:</b> None reported.</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: cohort study Populations comparable: yes</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>307 (60.6%): postmenopausal and not using hormone therapy</p> <p>42 (8.3%) postmenopausal and using either topical or systemic hormone therapy</p>	<p>frequency of application and/or potency of TCS)</p> <p>Analysis</p> <p>Type of analysis: NR</p> <p>Matching: NR</p> <p>Confounders: NR</p>	<p>Compliant: 4 (1.1%)/357</p> <p>Partially compliant: 3 (2.0%)/150</p> <p><b>Initial symptom control with loss of itching</b></p> <p>Compliant: 326 (91.3%)/357</p> <p>Partially compliant: 109 (72.7%)/150</p> <p><b>Narrative summary:</b></p> <p>“This prospective, single-center, longitudinal cohort study of adult patients with VLS suggests that individualized preventive TCS regimens that achieve objective normality of skin color and texture and are used by compliant patients who attend regular long-term follow-up visits may modify the course of the disease. There was a significant difference in symptom control, scarring, and occurrence of vulvar carcinoma between compliant and partially compliant patients.</p>	<p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: NR</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: NR</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: NA</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): NA</p> <p>Main cofounders taken into account: NA</p> <p>Confidence intervals reported: NA</p> <p>Selective reporting (comparison with protocol): NA</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
			The adverse effects of TCSSs were minimal.”	

**Verknüpfte Empfehlungen:****Empfehlung 3.9:**

Lichen sclerosus ist ein Risikofaktor für das Entstehen einer dVIN/eines Vulvakarzinoms. Patientinnen mit behandeltem Lichen sclerosus zeigen gegenüber Patientinnen mit unbehandeltem Lichen sclerosus eine geringere Rezidivrate und ein niedrigeres Risiko für die Entwicklung einer VIN/eines Vulvakarzinoms.

**Empfehlung 4.3:**

Ein Lichen sclerosus der Vulva sollte auch unter dem Gesichtspunkt der Prävention eines Vulvakarzinoms gemäß den aktuellen Empfehlungen konsequent therapiert werden.

**Empfehlung 4.2:**

Die konsequente Therapie eines Lichen sclerosus der Vulva kann das Risiko für die Entstehung vulvärer Neoplasien senken.

**Literaturreferenzen:** [\[3\]](#), [\[4\]](#), [\[5\]](#), [\[6\]](#)

[\[3\]](#)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Spekreijse, 2020 Systematic Review	Types of studies: retrospective cohort study design  Searched from inception until July 2019	Question/ Aim:  To systematically review the absolute risk (AR) and incidence rate (IR) of developing SCC in patients with anogenital Lichen	23studies including either women or men in secondary or tertiary care with a diagnosis of LS (none of the studies are relevant for this guideline PICO)	<b>Recurrence rate / recurrence-free</b>  NR  Progression to squamous cell carcinoma of the vulva	Overall confidence in results of SR (AMSTAR-2): "xx"  PICO elements: no  A priori design: no  Justification for design: no	<a href="#">23</a> retrospective cohort study design

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Databases: PubMed and Embase</p> <p>keywords used were 'lichen sclerosis', 'anogenital' and 'carcinoma', including all synonyms</p> <p>Inclusion criteria</p> <p>studies including patients with LS in the anogenital region with a prognostic study design of the evaluation of LS into SCC.</p> <p>Articles in English, Dutch, French and German were included</p> <p>Exclusion criteria:</p> <p>Articles with no full text available were excluded</p>	<p>sclerosis (LS), as well as patient characteristics that influence the risk of developing LS associated squamous cell carcinoma (SCC).</p>	<p><b>Descriptive statistics:</b></p> <p>NR (beschrieben für jede einzelne eingeschlossene Studie)</p>	<p>NR</p> <p>Progression to vulval intraepithelial neoplasia (VIN)</p> <p>NR</p>	<p>Literature search &gt;= 2 databases, search strategy + other sources: no</p> <p>Selection in duplicate: yes</p> <p>Data extraction in duplicate: NR</p> <p>List of excluded studies: yes</p> <p>sufficient detail on studies: yes</p> <p>RoB assessed: yes</p> <p>Funding of incl. studies: no</p> <p>MA appropriate: NA</p> <p>RoB considered in MA: NA</p> <p>RoB in interpretation: yes</p> <p>Heterogeneity explained: NR</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
					Publication bias investigated: no  Sources of Col: "All authors declare to have no conflicts of interest."	

**Verknüpfte Empfehlungen:****Empfehlung 4.2:**

Die konsequente Therapie eines Lichen sclerosus der Vulva kann das Risiko für die Entstehung vulvärer Neoplasien senken.

**Empfehlung 4.3:**

Ein Lichen sclerosus der Vulva sollte auch unter dem Gesichtspunkt der Prävention eines Vulvakarzinoms gemäß den aktuellen Empfehlungen konsequent therapiert werden.

**Empfehlung 3.9:**

Lichen sclerosus ist ein Risikofaktor für das Entstehen einer dVIN/eines Vulvakarzinoms. Patientinnen mit behandeltem Lichen sclerosus zeigen gegenüber Patientinnen mit unbehandeltem Lichen sclerosus eine geringere Rezidivrate und ein niedrigeres Risiko für die Entwicklung einer VIN/eines Vulvakarzinoms.

**Literaturreferenzen:** [\[3\]](#), [\[4\]](#), [\[5\]](#), [\[6\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low	1 prospective cohort study		/	/	-2 (indirect evidence, data on wrong study population: women being “treatment compliant” compared to women being “partially compliant”)	-1 (narrative outcome, few study participants, RR: 0.03, 95%CI 0.00-0.49)	Note: indirect evidence	⊕⊖⊖⊖ Very low

## Kapitel 4: Prävention und Früherkennung

### Kapitel 4.1: Primärprävention

#### Verknüpfte Empfehlungen:

#### Empfehlung 4.1:

Eine Primärprävention der HPV-assoziierten VIN ist durch eine HPV-Impfung möglich. Durch die Primärprävention der Vorstufen ist auch eine Prävention des Vulvakarzinoms zu erwarten.

Literaturreferenzen: [\[7\]](#), [\[8\]](#)

[\[7\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High	3 post hoc analyses of RCTs	VIN/VaIN1+ recurrence	-2 (serious ROB)	-1 (some heterogeneity)	-1 (VIN and VaIN reported together)	-1 (wide CI: RR 1.30, 95% CI 0.23-7.43)	/	⊕⊕⊕⊕ Very low
High	3 post hoc analyses of RCTs	VIN/VaIN2+ recurrence	-2 (serious ROB)	/	-1 (VIN and VaIN reported together)	-2 (only few events and wide CI: (RR 1.01, 95% CI 0.24-4.15)	/	⊕⊕⊕⊕ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low → RCT and case-control study	1 RCT & 1 case-control study	VIN/VaIN2+ recurrence	/ (moderate)	/	-1 (VIN and VaIN reported together)	-2 (only few events: 3 and very wide CI: RR 0.56, 95% CI 0.01-35.16)	/	⊕⊖⊖⊖ Very low

**Verknüpfte Empfehlungen:****Empfehlung 4.1:**

Eine Primärprävention der HPV-assoziierten VIN ist durch eine HPV-Impfung möglich. Durch die Primärprävention der Vorstufen ist auch eine Prävention des Vulvakarzinoms zu erwarten.

**Literaturreferenzen:** [7], [8]

[7]

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Kechagias 2022 SR	Searched from inception until 31 March 2021  Databases:  PubMed (Medline), Scopus, Cochrane, Web of Science, and ClinicalTrials.gov  Inclusion criteria  Studies reporting on HPV infection rates and recurrence of diseases related to HPV infection after local surgical	Question/ Aim: To explore the efficacy of human papillomavirus (HPV) vaccination on the risk of HPV infection and recurrent diseases related to HPV infection in individuals undergoing local surgical treatment.  A: HPV vaccination  B: no NPV vaccination	5 studies (1 RCT, 1 prospective case control study, 3 post hoc analyses of RCTs) on 1968 pts with vulvar or vaginal intraepithelial neoplasia (grade 1 or 2)  <b>Descriptive statistics:</b>  Age (median, range): NR  Stage (nach FIGO, %): NR	Rezidivrate (VIN/VaIN2+ recurrence (RCT: Pieralli 2018, case-control study: Ghelardi 2021))  A: 8/131  B: 27/165  Pooled RR: 0.56 (95% CI 0.01-35.16; p=0.35, I <sup>2</sup> =0%) in favour of A (vaccine group)  Population: women who were vaccinated	<b>Overall confidence in results of SR (AMSTAR-2): „moderate-high“</b>  PICO elements: yes  A priori design: NR  Justification for design: yes  Literature search >= 2 databases, search strategy + other sources: yes  Selection in duplicate: yes	Pieralli 2018  Ghelardi 2021  Joura 2012  Garland 2016  Zhao 2020

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>treatment for genital diseases related to HPV in individuals who were vaccinated. For the meta-analysis, only studies that also reported results from a cohort who were not vaccinated.</p> <p>Exclusion criteria:</p> <p>Studies exploring the vaccine efficacy after treatment for invasive disease and extragenital HPV-related diseases, such as respiratory papillomatosis and cutaneous skin warts. Studies on immunodeficient or paediatric patients and experimental animal models. Studies were also</p>		<p>Location of the tumour: NR</p> <p>Tumour size (% , cm): NR</p> <p>Tumour depth (% , mm): NR</p>	<p>and treated locally for cervical, vulvar or vaginal intraepithelial neoplasia grade 2 or higher compared with women not vaccinated.</p> <p>Rezidivrate (VIN/VaIN1+ recurrence (post hoc analyses of RCTs: Joura 2023, Garland 2016 &amp; Zhao 2020))</p> <p>A: 20/744</p> <p>B: 23/926</p> <p>Pooled RR: 1.30 (95% CI 0.23-7.43; p=0.24, I<sup>2</sup>=29%) in favour of B (non-vaccine group)</p> <p>Rezidivrate (VIN/VaIN2+ recurrence (post hoc from Joura 2023,</p>	<p>Data extraction in duplicate: yes</p> <p>List of excluded studies: no</p> <p>sufficient detail on studies: no</p> <p>RoB assessed: yes</p> <p>Funding of incl. studies: no</p> <p>MA appropriate: yes</p> <p>RoB considered in MA: yes</p> <p>RoB in interpretation: yes</p> <p>Heterogeneity explained: yes</p> <p>Publication bias investigated: yes</p> <p>Sources of Col: yes</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	excluded if the intervention included experimental vaccines or immunotherapy and studies that used non-surgical treatment (i.e. salicylic acid or imiquimod cream).			Garland 2016 & Zhao 2020)) A: 5/738 B: 6/928 Pooled RR: 1.01 (95% CI 0.24-4.15; p=0.74, I <sup>2</sup> =0%) no effect Population: women treated for genital HPV related disease		

**Verknüpfte Empfehlungen:****Empfehlung 4.1:**

Eine Primärprävention der HPV-assoziierten VIN ist durch eine HPV-Impfung möglich. Durch die Primärprävention der Vorstufen ist auch eine Prävention des Vulvakarzinoms zu erwarten.

**Literaturreferenzen:** [7], [8]

[8]

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Zhao 2022 RCT (long-term follow-up study of: base study, NCT00834106)	368 (LTFU) Chinese women (median follow-up of 94 months), of these 49 were referred for colposcopy due to abnormal TCT results and of these, 27 underwent colposcopy and biopsy  Inclusion criteria (from base study):  women were 20–45years of age with 1–4 lifetime sexual partners (or planned to become sexually active within the first 3months of the study); had no history of genital warts or cervical disease, active cervical disease, or prior vaccination	Interventions  A: three doses of 4vHPV vaccine  N = 171  B: placebo during the base study  N = 197  Analysis  Type of analysis: frequencies	Rezidivrate (vulvar intraepithelial neoplasia (VIN), or vaginal intraepithelial neoplasia (VaIN))  A: 0/8 (among 27 participants who underwent colposcopy and biopsy due to cervical cytological abnormalities or HPV infection)  B: 0/19 (among 27 participants...)  Pooled RR/HR/OR: NR	<b>General information</b>  Follow-up: median follow-up of 94 months  <b>Funding:</b> Association for Maternal and Child Health Studies [2018AMCHS008, 2018AMCHS00803] and Project of Development center for medical science & technology, NHC  <b>Col:</b> Chao Zhao, Yun Zhao, Jingran Li, Mingzhu Li, Danhua Shen, and Lihui Wei have received grants/research support from MSD R&D (China).

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>with HPV vaccine; and were not pregnant</p> <p>Included for this analysis: Participants with any of the following abnormal findings referred for colposcopy</p> <p>Exclusion criteria (for analysis): NR</p> <p>Enrolment period 2009-2016</p> <p>Descriptive statistics Age (median, range) A: NR B: NR</p> <p>Stage (FIGO, %): NR for this population</p> <p>Location of the tumour: NR for this population</p> <p>Tumour size (% , cm): NR for this population</p> <p>Tumour depth (% , mm): NR for this population</p>			<p>Risk of bias considerations (RoB 1):</p> <p>Analysis ITT: NI</p> <p>Randomisation: low</p> <p>Allocation concealment: NI</p> <p>Blinding: low</p> <p>Attrition bias: NI</p> <p>Selective reporting: NI</p> <p><b>Other limitations or comments:</b> this is only a long term follow-up study, so a lot of information on the included participants and their characteristics are missing. It is hard to assess any risk of bias due to bad reporting of characteristics and data. à some concerns to high ROB</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Lymph node metastases (% yes): NR for this population			

## Kapitel 5: Therapie der VIN

### Kapitel 5.1: HSIL (uVIN 2/3) und dVIN (nach WHO 2014)

#### Kapitel 5.1.1: Imiquimod

Verknüpfte Empfehlungen:

**Empfehlung 8.3:**

Zur Therapie einer HSIL (VIN2/3) kann auch Imiquimod 5% topisch eingesetzt werden.

**Literaturreferenzen:** [\[9\]](#)

[\[10\]](#), [\[11\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High à RCT	1 RCT (Trutnovsky, 2022)	Recurrent disease or partial response (imiquimod vs. surgery)	-1 (high risk of bias due to per protocol analysis)	/	/	-2 (wide confidence intervals and only few events and participants: 20 in 98 pts; RR 0.92, 95% CI 0.42-2.03)	/	⊕⊕⊕⊕ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High à RCT	1 RCT (Trutnovsky, 2022)	Invasive carcinoma rate (imiquimod vs. surgery)	-1 (high risk of bias due to per protocol analysis)	/	/	-2 (wide confidence intervals and only few events and participants: 4 in 98 pts; RR 0.13, 95% CI 0.01-2.27)	/	⊕⊕⊕⊕ Very low

## Kapitel 6: Therapie des M. Paget der Vulva

### Kapitel 6.1: Operative Therapie

**Verknüpfte Empfehlungen:**

**Empfehlung 9.1:**

Der beste primäre Therapieansatz (medikamentös/chirurgisch) beim nicht-invasiven M. Paget ist unklar.

**Literaturreferenzen:** [\[12\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Case series à Low	9 retrospective case series from Edey 2019 SR (Crawford 1999; Curtin 1990; Fanning 1999; Lee 1977; Molinie 1993; Parker 2000; Pierie 2003; Roh 2010; Niikura 2006)	Survival	-2 (High risk of bias due to retrospective design)		-1 different treatment modalities	-2 (very new participants, narrative summary only:  8 studies provided data on survival, including information on 306 women and reported 23 deaths (14 deaths related to disease, 5 deaths from other	“Due to the retrospective nature of all the studies, there were no morbidity data available, or patient satisfaction analysis, and, therefore, no comment can be made on QoL following treatments. This is	⊕⊕⊕⊕ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
						<p>malignancies, 4 deaths related to other causes). Since nearly all treatment in the studies was surgical, we could not comment on mortality to treatment modality.</p> <p>Two studies used chemotherapy as first-line treatment (Niikura 2006; Parker 2000).</p> <p>1 woman in the Niikura 2006 study received</p>	<p>significant when considering radical surgery, and re-excision after previous surgery. Selection bias is challenging when dealing with retrospective studies, when radicality of treatment would be dependent on surgeon choice. Most of the women in the studies had treatment before the advent of the multidisciplinary team, and, therefore, alternative</p>	

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
						<p>chemotherapy using cisplatin plus fluorouracil for stage IV disease and she died of the disease.</p> <p>Survival was again shown to be worse after radiotherapy, but</p> <p>the same caveats applied as to their comments on chemotherapy.</p>	<p>treatments to surgery may not have been available, or not considered.“</p>	

**Verknüpfte Empfehlungen:****Empfehlung 9.3:**

Bei der operativen Therapie des extramammären M. Paget sollte eine Exzision im Gesunden angestrebt werden.

In Abhängigkeit von der Lokalisation und Größe des Defekts ist eine plastische Deckung unter Beachtung von Komorbiditäten in Erwägung zu ziehen.

**Literaturreferenzen:** [\[13\]](#)[\[13\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort study	1 retrospective observational cohort study	Local recurrence rate (5-year rates)	/	/	-1 (not matching the exact PICO question in terms of comparison)	-2 (no confidence intervals, no hazard risk ratios provided)	/	⊕⊕⊕⊕ Very low
Low à cohort study	1 retrospective observational cohort study	Distant recurrence rate	/	/	-1 (not matching the exact PICO question in terms of comparison)	-2 (no confidence intervals, no hazard risk ratios provided)	/	⊕⊕⊕⊕ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort study	1 retrospective observational cohort study	OS (5-year)	/	/	-1 (not matching the exact PICO question in terms of comparison)	-2 (no confidence intervals, no hazard risk ratios provided)	/	⊕⊖⊖⊖ Very low

**Verknüpfte Empfehlungen:****Empfehlung 9.3:**

Bei der operativen Therapie des extramammären M. Paget sollte eine Exzision im Gesunden angestrebt werden.

In Abhängigkeit von der Lokalisation und Größe des Defekts ist eine plastische Deckung unter Beachtung von Komorbiditäten in Erwägung zu ziehen.

**Literaturreferenzen:** [\[13\]](#)[\[14\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort study	1 cohort study (retrospective and prospective data)	3-years RFS	-1	/	-1 (data on population: female genital EMPD with primary or recurrent EMPD of vulva and/or perianal region of the body)	-1 (wide confidence intervals, only few participants)	Different source of population for the comparison group.	⊕⊖⊖⊖ Very low

**Verknüpfte Empfehlungen:****Empfehlung 9.3:**

Bei der operativen Therapie des extramammären M. Paget sollte eine Exzision im Gesunden angestrebt werden.

In Abhängigkeit von der Lokalisation und Größe des Defekts ist eine plastische Deckung unter Beachtung von Komorbiditäten in Erwägung zu ziehen.

**Literaturreferenzen:** [\[13\]](#)

[\[13\]](#), [\[15\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Matsuo, 2021 Nationwide multicenter retrospective observational study (secondary analysis of the study JGOG-1075S)	139 (108 pts with surgical margin status data) pts with stage I-IV invasive vulvar Paget's disease  Inclusion criteria (for analysis): Women with stage I-IV invasive vulvar Paget's disease who received surgical treatment from 2001-2010 were eligible for analysis.  Exclusion criteria (for analysis): Exclusion criteria included non-surgical cases and unknown type of surgery.  Enrolment period	Interventions (a sensitivity analysis in the study)  A: positive surgical margin (n=49)  B: margin <1 cm (n=41)  Analysis  Type of analysis: For overall survival the Kaplan-Meier method was used to construct the survival curves, and statistical difference between groups was assessed with log-rank test on univariable analysis. A Cox proportional	<b>Local recurrence rate (5-year rates)</b> A: 35.8% B: 10.5% p=0.003 (in favour of B, increased risk of local-recurrence for positive surgical margin)  <b>Distant recurrence rate</b> A: 18.3% B: 12.8% p=0.346  Recurrence free survival	<b>General information</b> Median follow-up: median follow-up of 5.8 years  <b>Funding:</b> Ensign Endowment for Gynecologic Cancer Research (K.M.)  <b>Col:</b> Honorarium, Chugai, Astra Zeneca (T.E.); research funding, Merck Sharp & Dorne (S.M.); honorarium, Chugai, textbook editorial expense, Springer, and investigator meeting attendance expense, VBL therapeutics (K.M.).

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	2001-2010 Descriptive statistics Age at diagnosis (median, range) Total: 71 (37-95) Positive margin: 71.5 (IQR 65-74.5) <1 cm margin: 71.5 (IQR 65-74.5) Stage Total: Stage I Paget disease: 85 (61.2%) Stage II Paget disease: 28 (20.1%) Stage III Paget disease: 15 (10.8%) Stage IV Paget disease: 11 (7.9%) Positive margin: stage I-II (n= 38, 77.6%) stage III-IV (n= 11, 22.4%)	hazard regression model was fitted to estimate the hazard ratio for all-cause mortality with 95% confidence interval on multivariable model  Matching: NR Confounders: NR	NR DFS NR <b>OS (5-year)</b> A: 72.6% B: 91.6% p=0.012 (in favour of B, lower overall survival rate for positive surgical margin) <b>CSS (cancer specific survival)</b> NR	Risk of bias considerations (adapted from SIGN cohort study checklist)  Study type: retrospective observational study Populations comparable: yes Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention Assessment reliable: yes Assessed more than once: no Possibly affected by knowledge of outcome status?: no Drop-out rate & reasons reported: no Outcome Outcome measure is well-defined, valid and reliable: yes Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no?

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>&lt;1 cm margin:</p> <p>stage I-II (n= 32, 78%)</p> <p>stage III-IV (n= 9, 22%)</p> <p>Tumor size</p> <p>Total:</p> <p>5.0 (IQR 3.0-6.9) cm</p> <p>&lt; 5 cm: 41 (29.5%)</p> <p>≥ 5 cm: 52 (37.4%)</p> <p>Positive margin:</p> <p>5.0 (IQR 3.3-7.3)</p> <p>&lt; 5 cm: 13 (26.5%)</p> <p>≥ 5 cm: 20 (40.8%)</p> <p>&lt;1 cm margin:</p> <p>5.0 (IQR 3.4-7.0)</p> <p>&lt; 5 cm: 15 (36.6%)</p> <p>≥ 5 cm: 19 (46.3%)</p> <p>Surgical margin</p> <p>Positive margin: 49 (35.3%)</p> <p>&lt; 1 cm: 41 (29.5%)</p> <p>≥ 1 cm: 18 (12.9%)</p>			<p>Main cofounders taken into account: no</p> <p>Confidence intervals reported: no</p> <p>Selective reporting (comparison with protocol): no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>NR: 31 (22.3%)</p> <p>Surgery type:</p> <p>Simple vulvectomy: <i>n</i>=64, 46.0%</p> <p>positive margin (<i>n</i>=25, 39.1%)</p> <p>&lt;1cm margin (<i>n</i>=20, 31.3%)</p> <p>radical vulvectomy: <i>n</i>=39, 28.1%</p> <p>positive margin (<i>n</i>=16, 41%)</p> <p>&lt;1cm margin (<i>n</i>=9, 23.1%)</p> <p>Partial vulvectomy: <i>n</i>=36, 25.9%</p> <p>positive margin (<i>n</i>=8, 22.2%)</p> <p>&lt;1cm margin (<i>n</i>=12, 33.3%)</p> <p>Chemotherapy</p> <p>positive margin Yes: <i>n</i>=4, 8.2%</p> <p>&lt;1cm margin Yes: <i>n</i>=3, 7.3%</p> <p>Radiotherapy</p> <p>positive margin Yes: <i>n</i>=6, 12.2%</p> <p>&lt;1cm margin Yes: <i>n</i>=1, 2.4%</p>			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
<p>Bruce, 2023</p> <p>Prospective observational cohort trial (NCT03564483)</p> <p>èComparison data from retrospective cohort study (Long 2017 (10.1016/j.ygyno.2017.09.008))</p>	<p>87 pts with Extramammary Paget's disease (female genital EMPD)</p> <p>24 pts from the prospective cohort (MMS-guided WLE) (Bruce, 2023)</p> <p>63 pts retrospective cohort (WLE) (Long 2017 (10.1016/j.ygyno.2017.09.008))</p> <p>Inclusion criteria (for analysis):</p> <p>Females</p> <p>Age 18 years or older</p> <p>Diagnosed (histologically confirmed female genital EMPD) with primary or recurrent EMPD of vulva and/or perianal region of the body</p> <p>Willing and able to provide signed informed consent</p> <p>Exclusion criteria (for analysis):</p> <p>Males</p>	<p>Interventions</p> <p>A: surgical excision guided by Mohs micrographic surgery (MMS-guided WLE) (n=24)</p> <p>B: Wide local excision (WLE) (n=63)</p> <p>Analysis</p> <p>Type of analysis: Kaplan-Meier method was used</p> <p>Matching: NR</p> <p>Confounders: NR</p>	<p><b>Local recurrence rate</b></p> <p>NR</p> <p>Recurrence free survival (3-years RFS)</p> <p>A: 93.3% (95% CI 81.5%-100.0%), 1/24 pts with noninvasive perianal disease experienced recurrence within 3 years after MMS</p> <p>B: 65.9% (95% CI 54.2%-80.0%), 18/63 pts experienced recurrence within 3 years of WLE (at a median of 1.6 years; IQR, 0.7-2.1)</p> <p>p=0.04</p> <p>DFS</p> <p>NR</p> <p><b>OS (3-year)</b></p> <p>A: 100%</p> <p>B: 100%</p> <p><b>CSS (cancer specific survival)</b></p> <p>NR</p>	<p><b>General information</b></p> <p>Median follow-up: NR</p> <p><b>Funding:</b> This research was funded by an anonymous donor interested in advancing the knowledge and treatment of Paget's disease. W.A.C. receives research funding as the Virgil S. Counseller, MD, Professor of Surgery. Career development and mentorship of K.H.B. was supported by grant number UL1 TR002377 from the National Center for Advancing Translational Sciences (NCATS).</p> <p><b>Col:</b> NR</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: Prospective observational cohort (compared with data from retrospective cohort)</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Diagnosis of Paget's Disease in body areas other than vulvar or perianal region</p> <p>Enrolment period</p> <p>January 1, 2018- July 30, 2022</p> <p>prospective cohort was compared with a retrospective cohort of patients who underwent traditional WLE between January 1, 1990, and December 31, 2015</p> <p>Descriptive statistics</p> <p>Age at Pagets surgery (y, mean, SD)</p> <p>MMS-guided WLE: 65.2 (9.5)</p> <p>WLE: 70.3 (10.5)</p> <p>Primary site</p> <p>MMS-guided WLE</p> <p>Genital (vulvar, periclitoral, and/or vaginal): 15 (62.5)</p> <p>Perianal: 3 (12.5)</p>		<p><b>Other outcomes:</b></p> <p><b>Surgical specimen size:</b></p> <p>A: median 11.3cm (IQR, 7.5-14.0)</p> <p>B: median 9.5cm (IQR, 6.9-13.0)</p> <p>P= 0.20</p> <p><b>Grade 3 or higher postoperative complications</b></p> <p>A: 0.0%</p> <p>B: 2.4%</p> <p>P= 0.99</p> <p><b>Complex reconstructive procedures</b></p> <p>A: 66.7%</p> <p>B: 30.2%</p> <p>P&lt;0.01</p>	<p>Populations comparable: no information</p> <p>Rate of participation/Exclusions reported (selection bias into the study): NR (note: not sure how they came up with N= 63 pts from the retrospective WLE cohort, "based on inclusion criteria")</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: nr</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: no</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Genital and perianal: 6 (25.0) WLE Genital (vulvar, periclitoral, and/or vaginal): 44 (69.8) Perianal: 10 (15.9) Genital and perianal: 9 (14.3) Depth of invasion MMS-guided WLE No invasion (in situ): 22 (91.7) Superficial or focal ( $\leq 1$ mm): 1 (4.2) Invasion ( $>1$ mm): 1 (4.2) WLE No invasion (in situ): 60 (95.2) Superficial or focal ( $\leq 1$ mm): 3 (4.8) Invasion ( $>1$ mm): / Race (white) MMS-guided WLE: 22 (91.7%) WLE: 60 (95.2%)			Main cofounders taken into account: no Confidence intervals reported: yes (for RFS) Selective reporting (comparison with protocol): no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Surgical specimen size (cm): media (IQR)  MMS-guided WLE: 11.3 (7.5– 14.0)  WLE: 9.6 (6.9–13.0)			

**Verknüpfte Empfehlungen:****Empfehlung 9.3:**

Bei der operativen Therapie des extramammären M. Paget sollte eine Exzision im Gesunden angestrebt werden.

In Abhängigkeit von der Lokalisation und Größe des Defekts ist eine plastische Deckung unter Beachtung von Komorbiditäten in Erwägung zu ziehen.

**Literaturreferenzen:** [\[13\]](#)[\[16\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
NRS à Low	1 retrospective study from Lawrie, 2016 SR (Van Esch 2013)	Recurrence-free survival (Surgical excision versus laser vaporization or other)	/ (NRS had a relatively low risk of bias and adjusted appropriately on multivariate analysis)		/	-1 (few participants: p-value 0.142, with 73 women)		⊕⊖⊖⊖ Very low

**Verknüpfte Empfehlungen:****Empfehlung 9.3:**

Bei der operativen Therapie des extramammären M. Paget sollte eine Exzision im Gesunden angestrebt werden.

In Abhängigkeit von der Lokalisation und Größe des Defekts ist eine plastische Deckung unter Beachtung von Komorbiditäten in Erwägung zu ziehen.

**Literaturreferenzen:** [\[13\]](#)

[\[17\]](#), [\[18\]](#)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Lawrie et al., 2016 èSR	Types of studies: 6 RCT, 5 NRS  Searched from inception until 2015  Databases: MEDLINE, EMBASE, Cochrane Gynaecological Cancer Group Trials Register, Cochrane Central Register of Controlled Trials  Inclusion criteria	Question/ Aim: To determine which interventions are the most effective, safe and tolerable for treating women with high-grade VIN (uVIN).  1.Summary of findings tabke 1: Imiquimod compared with placebo for usual-type vulval intraepithelial neoplasia à not	11 studies on 975 pts with usual-type vulval intraepithelial neoplasia (data from 5 studies are relevant for this guideline PICO)  <b>Descriptive statistics:</b>  Described for each study separated in the review,	Results from comparison 3 of the SR:  <u>3.1 Surgical excision versus laser vaporization or other</u>  Recurrence-free survival  <u>Van Esch 2013</u>  37/73 women (51%) experienced recurrence:	Overall confidence in results of SR (AMSTAR-2): “moderate”  PICO elements: yes  A priori design: yes  Justification for design: yes  Literature search >= 2 databases, search strategy + other sources: yes	<u>RCTs</u>  Mathiesen 2007 Naik 2006  Sterling 2005  Tristram 2014  van Seters 2008  <b>von Gruenigen 2007</b>  <u>Non-RCTs (NRS)</u>  Fehr 2001  <b>Fehr 2013</b>  <b>Leufflen 2013</b>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Women aged over 18 years with a confirmed histological diagnosis of uVIN, VIN 2 or 3, high-grade VIN or vulval HSIL, which was either unifocal or multifocal</p> <p>Exclusion criteria: women with a histological diagnosis of Paget's disease, vulval carcinoma and VIN 1</p>	<p>applicable for this guideline PICO 1</p> <p>2.Summary of findings table 2: Imiquimod compared with cidofovir for usual-type vulval intraepithelial neoplasia</p> <p>à not applicable for this guideline PICO 1</p> <p>3.Summary of findings table 3: Surgical interventions compared with photodynamic therapy or other interventions for usual-type vulval intraepithelial neoplasia</p> <p>3.1 Surgical excision versus laser vaporization or other</p>		<p>16/33 (48.5%) in excision group</p> <p>14/25 (56%) in laser vaporization group</p> <p>No difference, p-value = 0.142 (1 NRS with 73 women, low-certainty evidence)</p> <p><u>Leufflen 2013 ((laser vaporisation versus excision, one year follow-up)</u></p> <p>HR = 5.9, 95% CI 1.3 to 26.3; P value &lt; 0.01</p> <p>“favours excision over laser vaporisation as initial VIN treatment. It is not clear whether the recurrence-free survival data reported in Leufflen 2013 were adjusted for all important</p>	<p>Selection in duplicate: yes</p> <p>Data extraction in duplicate: yes</p> <p>List of excluded studies: yes</p> <p>sufficient detail on studies: yes</p> <p>RoB assessed: yes</p> <p>Funding of incl. studies: yes</p> <p>MA appropriate: yes</p> <p>RoB considered in MA: yes</p> <p>RoB in interpretation: yes</p> <p>Heterogeneity explained: yes</p> <p>Publication bias investigated: yes</p>	<p><b>van Esch 2013</b></p> <p><b>Vlastos 2002</b></p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
		<p>3.2 Laser vaporisation versus CUSA</p> <p>3.3 Photodynamic therapy versus laser vaporisation and surgical excision</p> <p>3.4 LEEP versus laser vaporisation and surgical excision</p>		<p>confounders (including differentiated-type VIN (dVIN) and multifocality); therefore this finding should be interpreted with caution.”</p> <p>recurrence rate one year after treatment = 22% (11 women)</p> <p><u>Fehr 2013 (excision versus laser vaporisation)</u></p> <p>OR = 1.79, 95% CI 1.11 to 2.91; P value = 0.017</p> <p>123/411 women (30%) experienced recurrent disease at least one year after initial diagnosis</p>	Sources of Col: none declared	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				<p>“favoured laser vaporisation over excision”</p> <p>àThe evidence from Fehr 2013 and Leufflen 2013 of treatment effect on recurrence is contradictory and of a very low quality, mainly due to design limitations of the NRSs. The evidence in van Esch 2013 of no difference between the types of treatment in recurrence-free survival is of a better quality than the other two studies and we graded this evidence as higher quality than that from the other two NRSs (low-quality evidence).</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				<p><b>Progression to vulval cancer</b></p> <p>Van Esch 2013: 15.1% women developed invasive disease</p> <p>Fehr 2013: 5.8% women developed invasive disease</p> <p>Leufflen 2013: 2% women developed invasive disease</p> <p><b>Severe adverse events</b></p> <p>NR</p> <p><u>3.2 Carbon dioxide (CO2) laser vaporisation versus ultrasonic surgical aspiration (CUSA)</u></p> <p>Recurrence rate</p> <p>RR = 1.53, 95% CI 0.65-4.15 (1 RCT)</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				<p>with 30 women, low-certainty evidence) (von Gruenigen 2007)</p> <p><b>Severe adverse events</b></p> <p>Pain: mean difference (MD) 1.70, 95% CI -26.80 to 23.40</p> <p>Scarring: 5/16 versus 0/14 in the laser and CUSA groups, respectively.</p> <p>Dysuria or burning on micturition: RR 0.66, 95% CI 0.18 to 2.44</p> <p>Adhesions: 1/16 versus 0/14 in the laser and CUSA groups, respectively</p> <p>Infection (yeast, urinary tract infection, other): RR</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio- nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				<p>0.88, 95% CI 0.14 to 5.42</p> <p>Abnormal discharge: RR 1.75, 95% CI 0.18 to 17.29)</p> <p>Eschar: RR 0.88, 95% CI 0.14 to 5.42</p> <p><u>3.3 Photodynamic therapy versus laser vaporisation and surgical excision</u></p> <p>Disease-free survival (DFS)</p> <p>No difference, p-value = 0.67 (1 NRS with 52 women, very low-certainty evidence) (Fehr 2001)</p> <p>èNot applicable for this guideline</p> <p><u>3.4 Loop electrosurgical excision procedure (LEEP) versus laser</u></p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Edey et al., 2019 èSR (ohne Resultate)	Types of studies: RCT & well-designed NRS	Question/ Aim To evaluate the benefits and harms	0 studies on 0 pts with Paget's disease of the vulva	<p><u>vaporisation and surgical excision</u></p> <p>Recurrence-free survival</p> <p>No difference, p-value = 0.194 (1 NRS with 62 women, very low-certainty evidence) (Vlastos 2002)</p> <p>Other outcomes:</p> <p>Rate of invasive carcinoma</p> <p>NR</p> <p>Side effects:</p> <p>NR</p> <p>Quality of life</p> <p>NR</p>	Overall confidence in results of SR	NR (keine Studien eingeschlossen)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Searched from inception until 2019</p> <p>Databases: Cochrane Central Register of Controlled Trials, MEDLINE, Embase</p> <p>Inclusion criteria RCT &amp; well-designed NRS</p> <p>women aged 18 years or older with Paget's disease of the vulva, n=10 - &gt;10</p> <p>Exclusion criteria: no participants exclusion criteria. excluded case-controlled studies, uncontrolled observational</p>	<p>of different treatment modalities for the management of Paget's disease of the vulva.</p> <p>A: Tumour-free margin: NR</p> <p>B: Tumour-free margin: NR</p>	<p><b>Descriptive statistics:</b></p> <p>NA</p>	<p>Rate of invasive carcinoma</p> <p>NR</p> <p>Side effects and adverse events</p> <p>NR</p> <p>Quality of life</p> <p>NR</p>	<p>(AMSTAR-2): "moderate"</p> <p>PICO elements: yes</p> <p>A priori design: yes</p> <p>Justification for design: yes</p> <p>Literature search &gt;= 2 databases, search strategy + other sources: yes</p> <p>Selection in duplicate: yes</p> <p>Data extraction in duplicate: yes</p> <p>List of excluded studies: yes</p> <p>sufficient detail on studies: yes</p> <p>RoB assessed: no</p> <p>Funding of incl. studies: no</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	studies and case series of fewer than 10 women.				MA appropriate: no RoB considered in MA: no RoB in interpretation: no Heterogeneity explained: no Publication bias investigated: no Sources of Col: none declared	

**Verknüpfte Empfehlungen:****Empfehlung 9.3:**

Bei der operativen Therapie des extramammären M. Paget sollte eine Exzision im Gesunden angestrebt werden.

In Abhängigkeit von der Lokalisation und Größe des Defekts ist eine plastische Deckung unter Beachtung von Komorbiditäten in Erwägung zu ziehen.

**Literaturreferenzen:** [\[13\]](#)[\[19\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Trutnovsky, 2022 RCT (NCT 01861535)	110 patients with vHSIL (106 allocated and 98 per-protocol for clinical response)  Inclusion criteria (for analysis): female patients aged 18-90 years with histologically confirmed vHSIL with visible unifocal or multifocal lesions  Exclusion criteria (for analysis): clinical suspicion of invasion, a history of vulvar cancer or severe inflammatory dermatosis of the vulva,  any active treatment for vHSIL within the previous 3 months,	Interventions  A: 5% imiquimod cream (Aldara; Meda Pharma, Bad Homburg, Germany) (N=56 in intention-to-treat analysis, 46 in per protocol analysis)  B: surgery (excision or ablation) (N=53 in intention-to-treat analysis, 52 in per protocol analysis)  Analysis  Type of analysis: nr	<b>Recurrent disease or partial response*</b>  A: 9/46 (20%) B: 11/52 (21%)  * Seven of nine women with partial response after imiquimod showed a strong partial response (76–99% reduction of initial lesion size).  RR = 0.92, 95% CI 0.42-2.03, In favour of A  Rate of invasive carcinoma  A: 0/46 B: 4/52 (8%)	<b>General information</b>  <b>Follow-up:</b> at baseline and after 6 and 12 months after local imiquimod treatment or one surgical intervention  <b>Funding:</b> Austrian Science Fund (KLI 293) and the Austrian Gynaecological Oncology group, study sponsor: Medical University of Graz  <b>Col:</b> no competing interests  Risk of bias considerations (Cochrane ROB1 tool)  Analysis ITT: high risk, as per-protocol analysis was applied

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>known immunodeficiency, pregnancy, lactating women</p> <p>Enrolment period 07.06.2013-08.01.2020</p> <p><b>Descriptive statistics</b></p> <p>Age (mean, SD) A: 53 (15.7) B: 50.2 (14.4)</p> <p>Menopausal status: Premenopausal, A: 22 (39%), B: 30 (57%) Postmenopausal, A: 34 (61%), B: 23 (43%)</p> <p>HPV vaccination None, A: 54 (96%), B: 48 (91%)</p> <p>Started or completed, A: 2 (4%), B: 5 (9%)</p> <p>Previous treatment for VIN A: 13 (23%), B: 8 (15%) 1 surgery, A: 9 (75%), B: 6 (86%)</p>		<p>RR= 0.13, 95% CI 0.01-2.27, In favour of A</p> <p>Adverse events</p> <p><u>Symptoms reported by the investigator: Erosion</u></p> <p>A: Grade 1 (mild): 26%, Grade 2 (moderate): 11%</p> <p>B: Grade 1 (mild): 19%, Grade 2 (moderate): 6%, Grade 3 (severe): 2%</p> <p><u>Symptoms reported by the investigator: Erythema</u></p> <p>A: Grade 1 (mild): 37%, Grade 2 (moderate): 20%, Grade 3 (severe): 9%</p> <p>B: Grade 1 (mild): 33%, Grade 2 (moderate): 14%</p> <p>Quality of life NR</p> <p><u>Other outcomes</u></p> <p><b>Complete Clinical Response CCR</b> (no clinical evidence of vulvar lesion, meaning 100% reduction of primary lesion size)</p>	<p>Randomisation: low risk</p> <p>Allocation concealment: low risk</p> <p>Blinding: some concerns</p> <p>Attention bias: low risk</p> <p>Selective reporting: low risk</p> <p><b>Other limitations or comments:</b> nr</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>2–5 surgeries, A: 3 (25%), B: 1 (14%)</p> <p>Imiquimod, A: 1 (8%), B: 2 (25%)</p> <p>Vulvar Lesion characteristics</p> <p>A: 46 (82%) unifocal, 10 (18%) multifocal;</p> <p>B: 39 (74%) unifocal, 14 (26%) multifocal</p> <p>Histology:</p> <p>vHSIL or VIN 2, A: 10 (18%), B: 12 (23%)</p> <p>vHSIL or VIN 3, A: 46 (82%), B: 40 (76%)</p> <p>Four patients with p16-positive vHSIL on biopsy had coexisting mild stages of lichen planus or lichen sclerosus.</p>		<p>after primary allocated study treatment):</p> <p>Follow-up at 6 months:</p> <p>A: 37/46 (80%)</p> <p>B: 41/52 (79%)</p> <p>P=0.0056</p> <p>Follow-up at 12 months:</p> <p>A: 37/46 (80%)</p> <p>B: 47/52 (90%)</p> <p><b>HPV positive (6 month follow-up)</b></p> <p>A: 15/45 (33%)</p> <p>B: 11/43 (26%)</p> <p>P=0.43</p> <p>èBy per-protocol analysis, primary treatment with imiquimod was not inferior to surgery at 6 months</p>	

## Kapitel 7: Operatives Management des Primärtumors

### Verknüpfte Empfehlungen:

#### Empfehlung 10.1:

Die lokal-radikale Exzision soll als operative Methode der Wahl durchgeführt werden, dabei soll die Exzision allseits im Gesunden erfolgen. Der Sicherheitsabstand zum Tumor kann basierend auf der derzeitigen Datenlage nicht festgesetzt werden.

**Literaturreferenzen:** [\[20\]](#), [\[21\]](#), [\[22\]](#), [\[23\]](#), [\[24\]](#), [\[25\]](#), [\[26\]](#), [\[27\]](#), [\[28\]](#), [\[29\]](#), [\[30\]](#), [\[13\]](#), [\[31\]](#), [\[32\]](#), [\[33\]](#), [\[34\]](#), [\[35\]](#), [\[36\]](#)

[\[20\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort studies	19 cohort studies	Local recurrence	/	-1 (large heterogeneity, I <sup>2</sup> = 70%)	/	-1 (large confidence interval)	/	⊕⊖⊖⊖ Very low

**Verknüpfte Empfehlungen:****Empfehlung 10.1:**

Die lokal-radikale Exzision soll als operative Methode der Wahl durchgeführt werden, dabei soll die Exzision allseits im Gesunden erfolgen. Der Sicherheitsabstand zum Tumor kann basierend auf der derzeitigen Datenlage nicht festgesetzt werden.

**Literaturreferenzen:** [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [13], [31], [32], [33], [34], [35], [36]

[20]

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Nooij, 2016 SR/MA	cohort studies Searched from inception until October 2015 Databases: PubMed, Embase, Web of Science, Cochrane database, and ScienceDirect Inclusion criteria Studies on local recurrence risk in relation to the	Question/ Aim A: Tumour-free margin <8 mm B: Tumour-free margin ≥8 mm	10 studies on 1278 pts with vulvar squamous cell carcinoma (VSCC) disease <b>Descriptive statistics:</b> Age (median, range) A: NR B: NR Sex (% female) A: NR B: NR	Rezidivrate (local Recurrence) A: 148/535 B: 107/743 Pooled RR: 1.99 (95% CI 1.13-3.51; p=0.02, I <sup>2</sup> =73%) in favour of B	Overall confidence in results of SR (AMSTAR-2): <i>“moderate”</i> PICO elements: yes A priori design: no protocol Justification for design: yes Literature search ≥ 2 databases, search strategy + other sources: yes	Baiocchi, 2015 Chan, 2007 De Hullu, 2002 Groenen, 2010 Heaps, 1990 Iacoponi, 2013 Rouzier, 2002 Tantipalakorn, 2009 Viswanathan, 2013 Woelber, 2011

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	tumour-free margin in VSCC  Exclusion criteria:  Exclusion criteria were languages other than English, Dutch, German, French, or Italian. Studies that compared local recurrence risk for patients with tumour- positive margins with tumour-free margins were also excluded because we focused on comparison of close versus wide margins		Stage (nach FIGO, %) Ia: A: NR %, B: NR %  Ib: NR  II: NR  IIIa NR  IIIb NR  IIIc NR  Iva NR  IVb NR  Location of the tumour  Clitoris: NR  Labia majora: NR  Labia minora: NR  Sub-clitoral: NR  Posterior commissure: NR  Tumour size (% , cm)  ≤ 2: NR		Selection in duplicate: not explicitly mentioned  Data extraction in duplicate: not explicitly mentioned  List of excluded studies: no  sufficient detail on studies: yes  RoB assessed: yes  Funding of incl. studies: no  MA appropriate: yes  RoB considered in MA: no  RoB in interpretation: yes  Heterogeneity explained: yes  Publication bias investigated: no	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
			2.1-4: NR >4: NR Tumour depth (% mm) ≤ 1.0: NR 1.01-2.5: NR 2.51-5.0: NR >5.0 NR		Sources of Col: None declared.	

**Verknüpfte Empfehlungen:****Empfehlung 10.1:**

Die lokal-radikale Exzision soll als operative Methode der Wahl durchgeführt werden, dabei soll die Exzision allseits im Gesunden erfolgen. Der Sicherheitsabstand zum Tumor kann basierend auf der derzeitigen Datenlage nicht festgesetzt werden.

**Literaturreferenzen:** [\[20\]](#), [\[21\]](#), [\[22\]](#), [\[23\]](#), [\[24\]](#), [\[25\]](#), [\[26\]](#), [\[27\]](#), [\[28\]](#), [\[29\]](#), [\[30\]](#), [\[13\]](#), [\[31\]](#), [\[32\]](#), [\[33\]](#), [\[34\]](#), [\[35\]](#), [\[36\]](#)  
[\[29\]](#), [\[30\]](#), [\[13\]](#), [\[31\]](#), [\[32\]](#), [\[34\]](#), [\[35\]](#), [\[36\]](#), [\[20\]](#), [\[24\]](#), [\[21\]](#), [\[22\]](#), [\[23\]](#), [\[28\]](#), [\[37\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Nooij 2015/2016 Cohort study	148 pts. with primary VSCC  Inclusion criteria (for analysis):  Histological slides were collected from the pathology archive, and patient characteristics were gathered from electronic patient charts after approval by the institutional review board.  Exclusion criteria (for analysis):  44 pts. excluded:  infiltration depth of <1 mm  no residual tumour in the surgical specimen after	A: <8mm (n=92 (62%))  B: >/=8mm (n=26 (18%))  Analysis  Type of analysis: Cox proportional hazard model and multivariable analysis  Matching: NR  Confounders: Multivariable analysis included all variables with a p-value <0.1 in the univariable analysis because these variables were considered important factors for the probability of developing a recurrence. 40% of the patients in the <8 mm group received	Rezidivrate  <b>A: 9</b> (5 with re-excision or RT)/ <b>92</b> (15 having re-excision and 22 with RT)  <b>B: 3</b> (all having no adjuvant therapy)/ <b>26</b> (1 with RT)  Univariable analysis:  HR 1.18 (95% CI 0.32-4.35) in favour of A/B  Multivariable analysis (adjusted for tumor size, additional therapy):  HR 1.10 (95% CI 0.28-4.19) in favour of A/B	<b>General information:</b>  Median follow-up: 42 months (mean, 53.8 [range, 0-174] months)  <b>Funding:</b> NR  <b>Col:</b> none declared  Risk of bias considerations (adapted from SIGN cohort study checklist)  Study type: cohort study  Populations comparable: no, but adjusted for  Rate of participation/Exclusions reported (selection bias into the study): yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>excision biopsy at another hospital</p> <p>Enrolment period</p> <p>2000 - 2012 in the Leiden University Medical Centre</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>A: mean age=68</p> <p>B: mean age=69</p> <p>Sex (% female)</p> <p>A: 100%</p> <p>B: 100%</p> <p>Stage (FIGO, %)</p> <p>I: A: 57 (62.0%), B: 18 (69.2%)</p> <p>II: A: 2 (2.2%), B: 0</p> <p>III: A: 32 (34.8%), B: 8 (30.8%)</p> <p>IV: A: 1 (1.1%), B: 0 (0%)</p> <p>Location of the tumour</p> <p>NR</p> <p>Tumour size (% , cm)</p>	<p>additional treatment. Adjusted for: tumor size (=40mm), additional therapie (vulvar radiotherapie)</p>	<p>There was no significant difference regarding local recurrence risk between the group of patients with a tumour-free margin of &lt;8mm versus ≥8 mm. In summary, currently, there is no firm evidence on the optimal length of the tumour-free margin in the treatment of VSCC. Due to the low incidence of vulvar cancer, there are no large prospective studies concerning this important clinical issue. This work provides important data to question the commonly used 8 mm margin as a prognosticator for local recurrence. More research is needed to address the question of whether additional treatment improves the prognosis in patients with a tumour-free margin smaller than 8 mm and what the best cutoff for the tumour-free margin would be.</p>	<p>Exposure/Intervention</p> <p>Assessment reliable: yes, defined</p> <p>Assessed more than once: no</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: NR</p> <p>Similar across groups: NA</p> <p>If high: comparison of those lost with available: NA</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): yes</p> <p>Main cofounders taken into account: Adjusted for tumor size (=40mm), additional therapie (vulvar radiotherapie)</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>≤ 40 mm: A: 73 (79.3%), B: 23 (88.5%)</p> <p>&gt;40 mm: A: 19 (20.7%), B: 3 (11.5%)</p> <p>Tumour depth (% , mm)</p> <p>≤ 4mm: A: 37 (40.2%), B: 12 (46.2%)</p> <p>&gt;4mm: A: 55 (59.8%), B: 14 (53.8%)</p> <p>Lymph node metastases (% yes)</p> <p>Tumour-positive lymph nodes in the groin(s): A: 33 (35.9%), B: 9 (34.6%)</p> <p>Extracapsular spread: A: 13 /14.1%), B: 3 (11.5%)</p> <p>Additional/adjutant treatment:</p> <p>Vulvar radiotherapy:</p> <p>A: 22 (23.9%)</p> <p>B: 1 (3.8%)</p> <p>Reexcision:</p> <p>A: 15 (16.3%)</p> <p>B: 0</p>			<p>Confidence intervals reported: yes</p> <p>Selective reporting (comparison with protocol): NI (no information, as no protocol available)</p> <p><b>Other limitations or comments:</b> None</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Additional treatment was generally started within 6 weeks after the primary surgery and consisted of reexcision or radiotherapy.</p> <p>Additional treatment was recommended for patients with tumour-positive margins and was considered for patients with a tumour-free margin &lt;8 mm (A) who had other risk factors (advanced tumour stage, positive lymph nodes, or lymphovascular space invasion).</p>			
<p>Woelber 2016</p> <p>Retrospective study</p> <p>AGO-CaRE-1 study (node-negative subgroup)</p>	<p>289 pts.: This subgroup analysis focuses on solely surgically treated node-negative pts. with surgical groin staging, complete tumor resection (R0), and known margin distance</p> <p>Inclusion criteria (for analysis):</p> <p>Patients with squamous-cell vulvar cancer FIGO stage IB and higher (UICC-TNM-classification)</p>	<p>Interventions</p> <p>A: &lt;8mm</p> <p>B: &gt;/= 8mm</p> <p>Analysis</p> <p>ANCOVA (analysis of covariance) model and Cox proportional hazards models</p> <p>Matching: NR</p>	<p>Rezidivrate</p> <p>A: 24/191</p> <p>B: 10/98</p> <p>HR (per mm increase): 0.930 (95% CI 0.849-1.020) in favour of A/B</p> <p>The need for a minimal margin of 8 mm could not be confirmed in the large and homogeneous node-negative</p>	<p><b>General information</b></p> <p>Median follow-up: 35.1 months</p> <p><b>Funding:</b> CaRE-1 study supported by medac oncology without restriction in protocol or analysis</p> <p><b>Col:</b> None declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>and stage-groupings version 6) treated at 29 gynecologic cancer centers in Germany 1998-2008 (Arbeitsgemeinschaft Gynäkologische Onkologie (AGO))</p> <p>Exclusion criteria (for analysis):</p> <p>nr</p> <p>Enrolment period</p> <p>February 2011 – December 2011</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>A: 65.5 (22-94)</p> <p>B: 66.9 (31.5-93)</p> <p>Sex (% female)</p> <p>A: 100%</p> <p>B: 100%</p> <p>Stage (TNM, %)</p> <p>T1b: A: 88 (46.1%), B: 53 (54.1%)</p>	<p>Confounders: Multivariable analysis, but not reported if adjusted for confounder and which</p>	<p>cohort of the AGO-CaRE database.</p>	<p>Study type: retrospective study</p> <p>Populations comparable: yes</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: no</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: NR</p> <p>Similar across groups: NA</p> <p>If high: comparison of those lost with available: NA</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ) no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>T2: A: 96 (50.3%), B: 44 (44.9%)</p> <p>T3: A: 7 (3.7%), B: 1 (1.0%)</p> <p>Histologic grade:</p> <p>G1: A: 22 (11.5%), B: 23 (23.5%)</p> <p>G2: A: 122 (63.9%), B: 54 (55.1%)</p> <p>G3: A: 45 (23.6%), B: 18 (18.4%)</p> <p>Unknown: A: 2 (1.0%), B: 3 (3.1%)</p> <p>Location of the tumour</p> <p>NR</p> <p>Tumour diameter (mm):</p> <p>A: median = 20 (2-101)</p> <p>B: median = 20 (3- 345)</p> <p>Tumour depth (mm)</p> <p>A: median = 4 (1-60)</p> <p>B: median = 5 (1-55)</p> <p>Lymph node metastases (number of dissected LNs (groin) per patient)</p> <p>A: median = 14 (2-48)</p>			<p>Main cofounders taken into account: NR</p> <p>Confidence intervals reported: yes</p> <p>Selective reporting (comparison with protocol): no</p> <p><b>Other limitations or comments:</b> None</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>B: median = 15 (1-40)</p> <p>Additional/ adjuvant treatment:</p> <p>All patients underwent surgical staging of the groins (in 86.5% cases with full lymphadenectomy) and excision of the primary tumor with the result of complete resection and pathological tumor-free margins</p> <p>None of the patients received adjuvant treatment</p>			
<p>Minar 2018</p> <p>Retrospective study</p>	<p>47 pts.</p> <p>Inclusion criteria (for analysis):</p> <p>Only patients who were expected to complete primary staging surgery, i.e. patients without fixed inguinofemoral lymphadenopathy and with no suspicion of distant metastases, were included in the evaluation</p> <p>Exclusion criteria (for analysis):</p> <p>NR</p>	<p>Interventions</p> <p>A: margin distance &lt;8 mm</p> <p>B: margin distance ≥ 8 mm</p> <p>Analysis</p> <p>Type of analysis: Associations between prognostic factors and recurrence à Spearman correlation coefficient &amp; the chi-squared test. The Cox proportional hazard ratio was assessed to estimate risk factors for recurrences.</p>	<p>Rezidivrate</p> <p>Median recurrence period: 16 months (range 6-82 months), univariate analysis, <math>p &lt; 0.05</math></p> <p>DFS</p> <p>Mean (SD) DFS of 66.7 + 6.5 months</p> <p>95% CI: 54.0-79.5</p> <p>Kaplan-Meier curve</p> <p>OS</p>	<p><b>General information:</b></p> <p>Follow-up: range 4-118 months</p> <p><b>Funding:</b> work supported by Ministry of Health, the Czech Republic – conceptual development of research organisation</p> <p><b>Col:</b> none declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: Retrospective study</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Enrolment period January 2007 – December 2014 Descriptive statistics Age (median, range) 70.0 (44.0-85.0) Sex (% female) A: 100% B: 100% Stage (FIGO, %) I: 51.1 II: 6.3 III: 42.6 Location of the tumour NR Tumour size (mm) Median (range): 35.0 (6.0-120.0) <40 mm: 57.4% ≥40 mm: 42.6% Tumour depth (% , mm)	Matching: NR Confounders: NR	Mean (SD) OS of 69.7 + 6.2 months 95% CI: 57.6-81.8 Kaplan-Meier curve Risk of recurrence risk HR=12.42 (95% CI: 3.44-44.84) Cox regression	Populations comparable: NR Rate of participation/Exclusions reported (selection bias into the study): NR Exposure/Intervention Assessment reliable: NR Assessed more than once: NR Possibly affected by knowledge of outcome status?: NR Drop-out rate & reasons reported: NR Similar across groups: NA If high: comparison of those lost with available: NA Outcome Outcome measure is well-defined, valid and reliable: yes Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no Main cofounders taken into account: NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Median (range): 5.0 (0.5-12.0) ≤5 mm: 53.2% >5.0 mm: (46.8%) Lymph node metastases: No metastases: 57.4% Ipsilateral: 29.8% Bilateral: 12.8%			Confidence intervals reported: yes Selective reporting (comparison with protocol): NI (no information, as no protocol available) <b>Other limitations or comments:</b> None
Pleunis 2018 Retrospective cohort study	194 pts. with vulvar squamous cell carcinoma (SCC)/ 167 (inclusion for surgical treatment/ 152 (radical final resection margin) Inclusion criteria (for analysis): Patients who underwent surgical treatment for primary vulvar SCC between January 2005 and October 2015. Exclusion criteria (for analysis): FIGO stage IA or IV, other histology Treatment consisting of primary neo-adjuvant (chemo-) radiation, and recurrent disease	Interventions A: margin distance <8 mm B: margin distance ≥ 8 mm Analysis Type of analysis: frequencies Matching: NR Confounders: NR	Rezidivrate A: 20/80 B: 16/72 p-value = 0.787	<b>General information</b> Median follow-up: 40 months (0-133) <b>Funding:</b> none <b>Col:</b> None declared Risk of bias considerations (adapted from SIGN cohort study checklist) Study type: retrospective study Populations comparable: NR Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>at initial presentation in one of both referral centers.</p> <p>In calculating both the primary and secondary outcome, patients with a final positive resection margin (undergoing adjuvant radiotherapy or no adjuvant therapy at all) were excluded from analysis.</p> <p>Enrolment period</p> <p>January 2005 and October 2015</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>Total median age: 71 years (26-98)</p> <p>Sex (% female)</p> <p>A: 100%</p> <p>B: 100%</p> <p>Stage (FIGO, %)</p> <p>Ib: 89 (53.3 %)</p> <p>II: 31 (18.5%)</p>			<p>Assessment reliable: yes, defined</p> <p>Assessed more than once: no</p> <p>Possibly affected by knowledge of outcome status? no</p> <p>Drop-out rate &amp; reasons reported: NR</p> <p>Similar across groups: NA</p> <p>If high: comparison of those lost with available: NA</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account: NR</p> <p>Confidence intervals reported: no</p> <p>Selective reporting (comparison with protocol): NI (no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	IIIa: 30 (18.0%) IIIb: 7 (4.2%) IIIc: 10 (6.0%) Location of the tumour Unifocal lateral: 73 (43.7%) Unifocal near midline: 74 (44.3%) Multifocal: 20 (12.0%) Tumour size (mm) Mean lesion size: 23.0 (SD 14.1) Tumour depth (mm) Median stromal invasion depth: 5.0 (0.3-35.0) Lymph node metastases (% yes) A: NR Additional/ adjuvant treatment A: N=17 B: N= 8			information, as no protocol available) <b>Other limitations or comments:</b> None
Raimond 2019	124 (12 pts. were excluded of the study because of	Interventionen	Rezidivrate	General information

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Retrospective multicenter study From francogyn study group	<p>neoadjuvant treatment (n=2), missing data (n=9) and palliative care (n=1))/ 112 pts. surgically treated for a vulvar squamous cell cancer</p> <p>Inclusion criteria (for analysis): A histologically proven vulvar cancer, primary surgically treated. Patients were more than 18 year-old, affiliated to social security, able to read and speak French.</p> <p>Exclusion criteria (for analysis): Neoadjuvant therapy, other histological types than squamous cell</p> <p>Enrolment period 2005 - 2016</p> <p>Descriptive statistics Age (median, range) A: 69.9 (38 -88) B: 70.2 (29-96) C: 70.9 (45-84)</p>	<p>A: margin distance &lt;3 mm B: margin distance ≥ 3mm and &lt; 8mm C: ≥8 mm</p> <p>Analysis Type of analysis: Survival and Cox proportional hazard model Matching: NR Confounders: NR</p>	<p>A: 11/47 B: 9/48 C: 6/17 P = 0.43</p>	<p>Mean follow-up: 25 months (1-137)</p> <p><b>Funding:</b> NR <b>Col:</b> None declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective multicenter study</p> <p>Populations comparable: some concerns (no differences regarding FIGO stage, tumor size, histologic grade, lymphovascular space invasion between groups, but differences regarding stromal invasion (&gt;5mm more frequent in group 3)</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes, defined</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Sex (% female) A: 100% B: 100% Stage (FIGO, %) I: A: 38.3%, B: 56.2%, C: 52.9% Ia: A: 27.8%, B: 3.7%, C: 11.1% Ib: A: 61.1%, B: 92.6%, C: 77.8% II: A: 6.4%, B: 16.7%, C: 5.9% III: A: 40.4%, B: 20.8%, C: 41.2% IIIa: A: 36.8%, B: 40%, C: 71.4% IIIb: A: 21.1%, B: 50%, C: 14.3% IIIc: A: 26.3%, B: 10%, C: 14.3% IV: A: 2.1%, B: 6.2%, C: 0% IVa: A: 100%, B: 0%, C: 0% IVb: A: 0%, B: 33%, C: 0% Location of the tumour NR Tumour size (mean, cm) A: 3.2 (0.3-11) B: 3.2 (0.2-8.4)			Assessed more than once: no Possibly affected by knowledge of outcome status?: no Drop-out rate & reasons reported: NR Similar across groups: NA If high: comparison of those lost with available: NA Outcome Outcome measure is well-defined, valid and reliable: yes Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no Main cofounders taken into account: NR Confidence intervals reported: no Selective reporting (comparison with protocol): NI (no information, as no protocol available)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	C: 3.8 (0.6-8.2) Tumour depth (mean, mm) Stromal invasion: A: 7 (0-40) B: 5 (0-7) C: 6.5 (2-15) Lymph node metastases (% yes) NR Additional/ adjuvant treatment: A: 10 (40.4%) B: 13 (27.1%) C: 7 (41.2%) 34.8% patients (n=39) underwent adjuvant radiotherapy and 16.1% (n=18) patients received both radiotherapy and chemotherapy.			<b>Other limitations or comments:</b> None
Te Grootenhuis 2019 Cohort study	287 consecutive patients with vulvar squamous cell carcinoma (148/435 patients were excluded)	Interventions A: margin distance <8mm B: margin distance ≥8mm	Rezidivrate A: 36/130 B: 52/153	<b>General information</b> Median follow-up: 80 months (0-204)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Inclusion criteria (for analysis):</p> <p>Primary diagnosis of vulvar squamous cell carcinoma and primarily surgically treated at one of the two participating centers.</p> <p>Exclusion criteria (for analysis):</p> <p>Patients who suffered from multifocal disease, or patients who received neoadjuvant chemotherapy and/ or radiotherapy, definite (chemo) radiation or palliative treatment were excluded.</p> <p>Enrolment period</p> <p>2000 - 2010</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>Total median age: 73 years (26-100)</p> <p>Sex (% female)</p> <p>A: 100%</p> <p>B: 100%</p>	<p>Analysis</p> <p>Type of analysis: Univariable and multivariable Cox-regression analyses</p> <p>Matching: NR</p> <p>Confounders: NR</p>	<p>HR 1.25 (whole cohort n=287) (95% CI 0.81-1.93) in favour of A/B</p>	<p><b>Funding:</b> None</p> <p><b>Col:</b> None declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: cohort study</p> <p>Populations comparable: NR</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes, defined</p> <p>Assessed more than once: no</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: yes</p> <p>Similar across groups: NR</p> <p>If high: comparison of those lost with available: NA</p> <p>Outcome</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Stage (FIGO/ TNM stage, %) Ia/ T1aN0M0: 9 (3) Ib/ T1bN0M0: 124 (43) II/ T2N0M0: 5 (2) IIIa/ T1, 2N1a, bM0: 70 (24) IIIb/ T1, 2N2a, bM0: 13 (5) IIIc/ T1, 2N2cM0: 58 (20) Iva/ T1, 2N3M0, T3NanyM0: 5(2) IVb/ TanyNanyM1: 0(0) Missing: 3 (1) Location of the tumour Central: 211 (74) Lateral: 72 (25) Unknown: 4 (1) Tumour size (mm) Tumor diameter: 29.5 (1.5- 130.0) Tumour depth (mm) 5.6 (0.5-25.0)			Outcome measure is well- defined, valid and reliable: yes  Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): No  Main cofounders taken into account: NR  Confidence intervals reported: yes  Selective reporting (comparison with protocol): NI (no information, as no protocol available)  <b>Other limitations or            comments:</b> None

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Lymph node metastases (% yes)</p> <p>NR</p> <p>Additional/ adjuvant treatment:</p> <p>Radiotherapy to the vulva: 49 (17)</p> <p>Re-excision: 17 (6)</p> <p>Chemotherapy: 2 (1)</p> <p>None: 219 (76)</p>			
<p>Barlow 2020</p> <p>Retrospective study</p>	<p>345 pts.</p> <p>Inclusion criteria (for analysis):</p> <p>Patients with squamous cell carcinoma of the vulva treated primarily with surgery with curative intent</p> <p>Exclusion criteria (for analysis):</p> <p>No squamous pathology</p> <p>another synchronous cancer</p> <p>primary radiotherapy treatment</p> <p>palliative surgery</p> <p>lost to follow up</p>	<p>Interventions</p> <p>A: margin distance &lt;8 mm</p> <p>B: margin distance ≥ 8 mm</p> <p>Analysis</p> <p>Type of analysis: Cox proportional hazard models were used in univariable and multivariable analyses</p> <p>Matching: NR</p> <p>Confounders: NR</p>	<p>Rezidivrate</p> <p>A: 27/122</p> <p>B: 51/219</p> <p>P=0.65</p>	<p><b>General information</b></p> <p>Mean follow-up: 93 months (1-367)</p> <p><b>Funding:</b> None</p> <p><b>Col:</b> None declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective study</p> <p>Populations comparable: NR</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>To determine the relationship between peripheral margin distance and vulvar recurrence, patients with less than six months follow-up, none of whom had a vulvar recurrence, were excluded</p> <p>Enrolment period</p> <p>February 1987 – December 2016</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>70 (29-96)</p> <p>Sex (% female)</p> <p>A: 100%</p> <p>B: 100%</p> <p>Stage (FIGO)</p> <p>Ia: 37 (10%)</p> <p>Ib: 194 (56.2%)</p> <p>II: 12 (3.5%)</p> <p>IIIa: 35 (10.1%)</p> <p>IIIb: 14 (4.1%)</p>			<p>Exposure/Intervention</p> <p>Assessment reliable: yes, defined</p> <p>Assessed more than once: no</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: NR</p> <p>Similar across groups: NA</p> <p>If high: comparison of those lost with available: NA</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (älf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account: NR</p> <p>Confidence intervals reported: no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	IIIc: 32 (9.3%) IVa: 2 (0.6%) IVb: 3 (0.9%) Location of the tumour Clitoris: 39 (11.3%) Labium minus: 95 (27.5%) Labium majus: 118 (34.2%) Perineum: 15 (4.3%) Vulvar vestibulare: 35 (10.1%) Multifocal: 43 (12.5%) Tumour size (% , cm) ≤4: 82.9 >4: 17.1 Tumour depth (% , mm) ≤5mm: 64.3% >5.0mm: 35.7% Lymph node metastases (% yes) Groin node status: Unknown: 0.3 Negative: 70.1			Selective reporting (comparison with protocol): NI (no information, as no protocol available)  <b>Other limitations or comments:</b> None

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Positive: 29.6			
Yang 2020	<p>335 pts. with vulvar squamous cell carcinoma</p> <p>Inclusion criteria (for analysis): Patients with pathologically-confirmed invasive squamous cell carcinoma who were treated with primary surgery</p> <p>Exclusion criteria (for analysis): Patients with a history of vaginal cancer or pelvic radiation</p> <p>Enrolment period 2000 to 2018</p> <p>Descriptive statistics</p> <p>Age (mean, SD) A: 63.6 ± 14.9 B: 70.1 ± 14.1 C: 67.2 ± 15.6</p> <p>Sex (% female) 100%</p>	<p>Interventions</p> <p>A: margin distance &lt;3 mm N = 32</p> <p>B: margin distance ≥3 and &lt;8 mm N = 151</p> <p>C: margin distance ≥8 mm N = 152</p> <p>Analysis</p> <p>Type of analysis: Univariate and multivariate Cox proportional hazard ratio (HR)</p> <p>Matching: NR</p> <p>Confounders: adjusted for adjusted for tumor stage, grade, depth of stromal invasion, size, location and distribution by IPW</p>	<p>Rezidivrate</p> <p>A: 15/32 B: 38/151 C: 25/152</p> <p><u>Multivariate analysis: &lt;8 mm vs. ≥8 mm:</u></p> <p>HR 1.98, 95% CI 1.13–3.41, p=0.03, favour of C</p> <p>DFS (Local recurrence free survival)</p> <p><u>5 year DFS:</u></p> <p>A: 48.2% B: 81.5% C: 84.6%</p> <p>Log-rank test: p&lt;0.001</p> <p>Other outcomes</p> <p>DSS, Regional recurrence, distant recurrence</p>	<p><b>General information</b></p> <p>Follow-up: median 73 months</p> <p><b>Funding:</b> NR</p> <p><b>Col:</b> The authors have no conflict of interest or potential financial disclosures.</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: Retrospective study</p> <p>Populations comparable: yes</p> <p>Rate of participation/Exclusions reported (selection bias into the study): NR</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: no</p> <p>Possibly affected by knowledge of outcome status? no</p> <p>Drop-out rate &amp; reasons reported: NA</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Stage (FIGO, %) I: A: 75%, B: 80.8%, C: 84.9% II: A: 3.1%, B: 0%, C: 0.7% III: A: 21.9%, B: 19.2%, C: 14.5% IIIa A: 12.5%, B: 10.6%, C: 10.5% IIIb: A: 9.5%, B: 6%, C: 2% IIIc: A: 0%, B: 2.6%, C: 2% Location of the tumour Peri-clitoral: A: 6.3%, B: 17.2%, C: 30.3% Perianal: A: 12.5%, B: 23.8%, C: 13.2% Unilateral: A: 71.9%, B: 52.3%, C: 52.6% Bilateral: A: 9.4%, B: 6.6%, C: 3.9% Tumour size (median, cm) <2 cm: A: 13 (40.6), B: 68 (45), C: 74 (48.7) ≥2 cm <4 cm: A: 14 (43.8): B: 54 (35.8), C: 62 (40.8)			Similar across groups: NR If high: comparison of those lost with available: NR Outcome Outcome measure is well- defined, valid and reliable: yes Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?) no Main cofounders taken into account: adjusted for tumor stage, grade, depth of stromal invasion, size, location and distribution by IPW Confidence intervals reported: yes Selective reporting (comparison with protocol): NR, no protocol available <b>Other limitations or            comments:</b> None

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>≥4 cm: A: 5 (15.6), B: 29 (19.2), C: 16 (10.5)</p> <p>Tumour depth (n, %)</p> <p>≤1 mm: A: 5 (15.6), B: 32 (21.2), C: 18 (11.8)</p> <p>&gt;1 mm ≤5 mm: A: 12 (37.5), B: 62 (41.1), C: 83 (54.6)</p> <p>&gt;5mm: A: 15 (46.9), B: 57 (37.7), C: 51 (33.6)</p>			
Arvas 2018 Retrospective study	<p>107 pts. with squamous cell carcinoma of the vulvar</p> <p>Inclusion criteria (for analysis): squamous cell carcinoma of the vulva diagnosed and operated at Istanbul University Cerrahpasa Faculty of Medicine during January 1996 to December 2016</p> <p>Exclusion criteria (for analysis): Thirteen patients with positive surgical margin and 10 patients with missing data were excluded.</p>	<p>Interventions</p> <p>A: margin distance ≤2 mm</p> <p>B: margin distance &gt;2 mm to &lt;8mm</p> <p>C: margin distance ≥8mm</p> <p>Analysis</p> <p>Type of analysis: Chi-square test or Kruskal-Wallis H test, Kaplan-Meier, Cox-Regression, Hazard Model</p> <p>Matching: NR</p> <p>Confounders: NR</p>	<p>Rezidivrate</p> <p>A: 13/34</p> <p>B: 5/32</p> <p>C: 2/41</p> <p>P=0.008</p> <p>DFS</p> <p>A: 1.0</p> <p>B: 0.4 (0.1-1.1)</p> <p>C: 0.1 (0.02-0.4)</p> <p>Univariate analysis</p> <p>HR: P=0.006</p>	<p><b>General information:</b></p> <p>Median follow-up: 101 months</p> <p><b>Funding:</b> NR</p> <p><b>Col:</b> NR</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: Retrospective study</p> <p>Populations comparable: NR</p> <p>Rate of participation/Exclusions reported (selection bias into the study): NR</p> <p>Exposure/Intervention</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Enrolment period</p> <p>January 1996 - December 2016</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>66 years (31-90)</p> <p>Sex (% female)</p> <p>A: 100%</p> <p>B: 100%</p> <p>Stage (FIGO, %)</p> <p>Recurrence:</p> <p>I: 56.8</p> <p>II: 24.1</p> <p>III: 15.5</p> <p>IV: 3.4</p> <p>No recurrence:</p> <p>I: 20.4</p> <p>II: 14.2</p> <p>III: 51</p> <p>IV: 14.2</p> <p>Location of the tumour</p>		<p>Multivariate analysis:</p> <p>HR: p=0.01</p>	<p>Assessment reliable: yes, defined</p> <p>Assessed more than once: no</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: NR</p> <p>Similar across groups: NA</p> <p>If high: comparison of those lost with available: NA</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account: NR</p> <p>Confidence intervals reported: yes</p> <p>Selective reporting (comparison with protocol): NI (no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	NR Tumour size (% , cm) ≤3.5: recurrence: 36.7%, no recurrence: 60.3% >3.5: recurrence: 63.3%, no recurrence: 39.7% Tumour depth (% , mm) ≤9: recurrence: 40.8%, no recurrence: 81% >9: recurrence: 59.2%, no recurrence: 18.9% Lymph node metastases: No recurrence: negative 74.1%, positive: 10.3% Recurrence: negative: 30.6%, positive: 63.2%			information, as no protocol available) <b>Other limitations or comments:</b> None
Schleiss-Andreassen 2022	55 pts.	Interventions	Rezidivrate	<b>General information</b>
Retrospective study	Inclusion criteria (for analysis): Women diagnosed with vulvar cancer FIGO Stage IA SCC Exclusion criteria (for analysis):	A: margin distance <8mm B: margin distance ≥8mm Analysis	A: 6/26 B: 0/27 P=0.01	Follow-up: last day of follow up was 1 <sup>st</sup> June 2019 <b>Funding:</b> NR <b>Col:</b> None declared

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>FIGO Stage &gt;IA, other histology than SCC</p> <p>Enrolment period 2011-2017</p> <p>Descriptive statistics</p> <p>Age (median, range) 66 years (62-95)</p> <p>Sex (% female)</p> <p>A: 100%</p> <p>B: 100%</p> <p>Stage (FIGO/ TNM stage, %)</p> <p>IA: 100%</p> <p>Location of the tumour (p=0.63)</p> <p>Vulva without clitoral involvement: total: 63.6%, no recurrence: 63.3%, recurrence: 66.6%</p> <p>Perineum: total: 10.9%, no recurrence: 12.2%, recurrence: 0%</p>	<p>Type of analysis: Univariate Chi Square and Fischer's exact test were used</p> <p>Matching: NR</p> <p>Confounders: NR</p>		<p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective study</p> <p>Populations comparable: NR</p> <p>Rate of participation/Exclusions reported (selection bias into the study): NR</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: NR</p> <p>Possibly affected by knowledge of outcome status?: NR</p> <p>Drop-out rate &amp; reasons reported: NR</p> <p>Similar across groups: NR</p> <p>If high: comparison of those lost with available: NR</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Clitoral involvement: total: 25.5%, no recurrence: 24.5%, recurrence: 33.3%</p> <p>Tumour size (cm) (p=0.06)</p> <p>≤1: total: 92.6%, no recurrence: 98.0%, recurrence: 66.6%</p> <p>&gt;1-2: total: 7.4%, no recurrence: 2.0%, recurrence: 33.3%</p> <p>Tumour depth (mm)</p> <p>≤0.5: total: 41.3%, no recurrence: 37.5%, recurrence: 22.2%</p> <p>&gt;0.5-1: total: 39.7%, no recurrence: 39.6%, recurrence: 77.8%</p> <p>Lymph node metastases (% yes)</p> <p>Lymph vascular space invasion: yes: 0%, no: 100%</p> <p>Sentinel node:</p> <p>yes: total: 12.7%, no recurrence: 12.5%, recurrence: 0%</p>			<p>of exposure status likely to influence the outcome?: ) : no</p> <p>Main cofounders taken into account: NR</p> <p>Confidence intervals reported: no</p> <p>Selective reporting (comparison with protocol): no</p> <p><b>Other limitations or comments:</b> None</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>No: total: 87.3%, no recurrence: 87.5%, recurrence: 100%</p> <p>Additional/ adjuvant treatment:</p> <p>Radiotherapy to the vulva: 49 (17)</p> <p>Re-excision: 17 (6)</p> <p>Chemotherapy: 2 (1)</p> <p>None: 219 (76)</p>			
Iacoponi 2013 Retrospective study	<p>87 patients diagnosed of vulvar squamous cell carcinoma (84 squamous tumors (96.6%), 1 glandular tumor (1.1%), and 2 tumors of skin appendage origin (2.3%) according to WHO 2003 classification).</p> <p>Inclusion criteria (for analysis):</p> <p>single squamous cell carcinoma of the vulva with infiltration &gt;1 mm, tumoral size &lt;4 cm, negative inguinal exploration or suspicious inguinal nodes &lt;1.5 cm diameter in imaging techniques (CT-scan or MRI).</p> <p>Exclusion criteria (for analysis):</p>	<p>Interventions</p> <p>A: margin distance <math>\leq</math>8 mm (Prognostic factor)</p> <p>B: margin distance &gt;8 mm (Prognostic factor)</p> <p>C: margin distance <math>\leq</math>15 mm (Prognostic factor)</p> <p>D: margin distance &gt;15 (Prognostic factor)</p> <p>Analysis</p> <p>Type of analysis: Qualitative variables were presented with absolute values and percentages. Quantitative data between groups were</p>	<p>Rezidivrate</p> <p>A: 52.6%</p> <p>B: 43.5%</p> <p>P=0.50</p> <p>C: 55.6%</p> <p>D: 34.5%</p> <p>P=0.09</p> <p>The Kaplan-Meier curves on local relapse didn't show statistical significance with the Mantel-Cox test.</p>	<p><b>General information:</b></p> <p>Median follow-up: 120 months</p> <p><b>Funding:</b> NR</p> <p><b>Col:</b> None declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: Retrospective study</p> <p>Populations comparable: NR</p> <p>Rate of participation/Exclusions reported (selection bias into the study): NR</p> <p>Exposure/Intervention</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Patients were excluded, because we found 4 melanomas, 3 sarcomas, 1 granular tumor, and 1 gastrointestinal mesenchymal tumor, Patients with microinvasive carcinoma or intraepithelial neoplasia were excluded as well.</p> <p>Enrolment period January 2000 – December 2010</p> <p>Descriptive statistics</p> <p>Age (range)</p> <p>Median: 72.9 (60-85)</p> <p>Mean: 72.9 ±12.1</p> <p>Sex (% female)</p> <p>A: 100%</p> <p>B: 100%</p> <p>Stage (FIGO, %)</p> <p>NR</p> <p>Location of the tumour</p> <p>Among all squamous we found 67 keratinizing, 2 non-</p>	<p>compared using the Student t-test and ANOVA. Categorical variables were compared using chi-square test. Survival analysis was performed using Kaplan-Meier curves.</p> <p>Matching: NR</p> <p>Confounders: NR</p>		<p>Assessment reliable: NR</p> <p>Assessed more than once: NR</p> <p>Possibly affected by knowledge of outcome status?: NR</p> <p>Drop-out rate &amp; reasons reported:</p> <p>Similar across groups: NR</p> <p>If high: comparison of those lost with available: NR</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account: NR</p> <p>Confidence intervals reported: no</p> <p>Selective reporting (comparison with protocol): NI (no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>keratinizing, 5 basaloids, 4 verrucous, 1 bowenoid, 1 sarcomatoid, and 4 basal cell carcinomas. The glandular one corresponded to a Paget disease, and the last two were 1 sebaceous carcinoma and 1 malignant sweat gland tumor.</p> <p>Tumour size (% , cm)</p> <p>mean tumor size: 35.1±22.8 mm</p> <p>median (range) 35.4 (18.6-54)</p> <p>Tumour depth (% , mm)</p> <p>Stromal invasion: 7.7±6.6 mm</p> <p>median of 7.7 (1.1-14.3)</p> <p>Lymph node metastases:</p> <p>Nodal involvement: 33</p> <p>Ipsilateral nodes: 21</p> <p>Contralateral nodes: 2</p> <p>Bilateral nodes: 10</p>			<p>information, as no protocol available)</p> <p><b>Other limitations or comments:</b> None</p>
Di Donato 2019	<p>78 pts.</p> <p>Inclusion criteria (for analysis):</p>	<p>Interventions</p> <p>A: margin distance 5mm</p>	<p>NR</p> <p>Other outcomes</p>	<p><b>General information:</b></p> <p>Median follow-up:</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Inclusion criteria were histologically confirmed squamous carcinoma or adenocarcinoma of the vulva. Exclusion criteria were recurrent disease, pre-invasive lesions (VIN 1-3), or uncommon histology (melanoma, Paget's disease, basalioma).</p> <p>Exclusion criteria (for analysis): /</p> <p>Enrolment period 1998-2016</p> <p>Descriptive statistics Age (median, range) 67±10.3</p> <p>Sex (% female) A: 100% B: 100%</p> <p>Stage (FIGO, %) IA: 14.1% IB: 29.5%</p>	<p>B: margin distance &gt;5mm C: margin distance &gt;10mm</p> <p>Analysis Type of analysis: Kaplan-Meier, DFS, OS, CSS</p> <p>Matching: NR</p> <p>Confounders: age could represent a confounding factor.</p>	<p>Considering factors influencing local recurrence, there was a non-statistical association with close margins at logistic regression (OR=2.89; 95% CI = 0.87-9.54; p=0.08).</p> <p>In support of this, we found that the presence of close margins (&lt;5mm) are more frequently found among patients with intermediate (35%) or high risk (38%). ACCI was compared to low risk (14%), although it should be noted that this difference is not statistically significant.</p>	<p><b>Funding:</b> Sapienza Università di Roma (C26N15LL2Y/2015)</p> <p><b>Col:</b> None declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: Retrospective study</p> <p>Populations comparable: NA</p> <p>Rate of participation/Exclusions reported (selection bias into the study): NA</p> <p>Exposure/Intervention</p> <p>Assessment reliable: NA</p> <p>Assessed more than once: Possibly affected by knowledge of outcome status?: NA</p> <p>Drop-out rate &amp; reasons reported:</p> <p>Similar across groups: NA</p> <p>If high: comparison of those lost with available: NA</p> <p>Outcome</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	II: 16.7% III: 17.9% IV: 7.7% Missing: 14.1% Location of the tumour (p=0.63) NR Tumour size (cm) (p=0.06) 29.4±17.9 mm Tumour depth (mm) NR Lymph node metastases (% yes) Node positive patients: 24.4%			Outcome measure is well-defined, valid and reliable: NA Blind outcome assessment to exposure: (ãlf not, Knowledge of exposure status likely to influence the outcome?: ): NA Main cofounders taken into account: NA Confidence intervals reported: NA Selective reporting (comparison with protocol): NR
Gitas 2021	104 pts. Inclusion criteria (for analysis): women who had undergone surgery for squamous cell carcinoma of the vulva. Exclusion criteria (for analysis): Patients with inoperable vulva cancer or those who had	Interventions A: margin distance <3 mm B: margin distance 3-5 mm C: margin distance 5-8mm Analysis Type of analysis: Depending on the scaling and distribution of	NR Other outcomes Risk to develop postoperative complications	<b>General information:</b> Median follow-up: 2 years <b>Funding:</b> Open Access funding enabled and organized by Projekt DEAL. There is not any funding. <b>Col:</b> None declared

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>undergone pelvic exenteration were excluded.</p> <p>Enrolment period 2003-2018</p> <p>Descriptive statistics</p> <p>Age 69.4±15.3</p> <p>Sex (% female)</p> <p>A: 100%</p> <p>B: 100%</p> <p>Stage (FIGO, n)</p> <p>Ia: 16</p> <p>Ib: 73</p> <p>II: 6</p> <p>IIIa: 7</p> <p>IIIb: 8</p> <p>IIIc: 9</p> <p>Iva: 0</p> <p>Ivb:</p>	<p>the variables considered, either a Chi-square test, a Mann-Whitney U test, or a one-way-ANOVA was performed.</p> <p>Matching: NR</p> <p>Confounders: NR</p>		<p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: Retrospective study</p> <p>Populations comparable: NA</p> <p>Rate of participation/Exclusions reported (selection bias into the study): NA</p> <p>Exposure/Intervention</p> <p>Assessment reliable: NA</p> <p>Assessed more than once:</p> <p>Possibly affected by knowledge of outcome status?: NA</p> <p>Drop-out rate &amp; reasons reported:</p> <p>Similar across groups: NA</p> <p>If high: comparison of those lost with available: NA</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: NA</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>FIGO stage and tumor resection margin distance</p> <p>FIGO I: &lt;5mm: 37, ≥5mm: 38, total: 75</p> <p>FIGO II: &lt;5mm: 2, ≥5mm: 3, total: 5</p> <p>FIGO III: &lt;5mm: 12, ≥5mm: 10, total: 22</p> <p>FIGO IV: &lt;5mm: 1, ≥5mm: 1, total: 2</p> <p>Location of the tumour (n)</p> <p>Right side: 29</p> <p>Left side: 27</p> <p>Both sides: 60</p> <p>Undefined: 5</p> <p>Clitoris: 25</p> <p>Labia majora: 55</p> <p>Labia minora: 51</p> <p>Sub-clitoral: 30</p> <p>Posterior commissure: 14</p> <p>Tumour size (diameter in mm)</p>			<p>of exposure status likely to influence the outcome?: )): NA</p> <p>Main cofounders taken into account: NA</p> <p>Confidence intervals reported: NA</p> <p>Selective reporting (comparison with protocol): NR</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>29.2±22.3</p> <p>Tumour depth (mm)</p> <p>5.8±6.9</p> <p>Lymph node metastases:</p> <p>Patients with lymph-node metastasis (n): 27</p> <p>Lymph node metastasis by sentinel: 1±0</p> <p>Lymph node metastasis by IFLIND: 3.24±2.02</p>			
Matsuo 2021	<p>139 pts.</p> <p>Inclusion criteria (for analysis):</p> <p>Women with stage I-IV invasive vulvar Paget's disease who received surgical treatment from 2001-2010</p> <p>Exclusion criteria (for analysis):</p> <p>Exclusion criteria included non-surgical cases and unknown type of surgery.</p> <p>Enrolment period</p> <p>2001-2010</p>	<p>Interventions</p> <p>A: margin distance &lt;1 cm</p> <p>B: margin distance ≥1 cm</p> <p>Analysis</p> <p>Type of analysis:</p> <p>Chi-square test or Kruskal-Wallis H test. The Fine-Gray model was further fitted to estimate the effect size of positive surgical margin on local- or distant-recurrence risk in multivariable analysis, expressed by sub-distribution</p>	<p>On univariable analysis, a positive surgical margin was significantly associated with an increased rate of local recurrence compared to a negative surgical margin (5-year cumulative rates for positive versus negative margin: 35.8% versus 14.0%, P=0.010). After controlling for age and cancer stage, a positive surgical margin remained an independent factor associated with increases risk of local recurrence</p>	<p><b>General information</b></p> <p>Median follow-up: 5.8 years</p> <p><b>Funding:</b> Ensign Endowment for Gynecologic Cancer Research (K.M.)</p> <p><b>CoI:</b> NR</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: Retrospective study</p> <p>Populations comparable:</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Descriptive statistics Age (median, range) 70 (IQR 63-76) Sex (% female) A: 100% B: 100% Stage (FIGO, %) I: 61.2% II: 20.1% III: 10.8% IV: 7.9% Location of the tumour NR Tumour size (cm) 5.0 (IQR 3.0-6.9) <5 cm: 29.5% ≥5 cm (37.4%) Tumour depth (mm) NR Lymph node metastases (%)	hazard ratio and corresponding 95% confidence interval. Kaplan-Meier, Cox-Regression, Hazard Model Matching: NR Confounders: NR	(adjusted hazard ratio 2.8, 95% confidence interval: 1.18-6.63, P=0.020). In contrast, a positive surgical margin was not associated with an increased risk of distant-recurrence (18.3% versus 16.0%, P=0.567).	Rate of participation/Exclusions reported (selection bias into the study): NA Exposure/Intervention Assessment reliable: NA Assessed more than once: Possibly affected by knowledge of outcome status?: NA Drop-out rate & reasons reported: Similar across groups: NA If high: comparison of those lost with available: NA Outcome Outcome measure is well- defined, valid and reliable: NA Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): NA Main cofounders taken into account: NA

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>No metastasis: 48.9</p> <p>Single metastasis: 4.3</p> <p>Multiple metastases: 10.8</p> <p>Not examined: 36.0</p> <p>Additional/ adjuvant treatment:</p> <p>Radiotherapy: No: 94.2%, Yes: 5.8%</p>			<p>Confidence intervals reported: NA</p> <p>Selective reporting (comparison with protocol): NR</p>
Micheletti 2021	<p>223 pts.</p> <p>Inclusion criteria (for analysis): consecutive stage IB-IIIC VSCCs surgically treated at our institution We performed a retrospective study of all patients surgically treated for VSCC at the Department of Surgical Sciences, S. Anna Hospital, University of Turin, from 2000 to 2019.</p> <p>Exclusion criteria (for analysis): NR</p> <p>Enrolment period 2000-2019</p>	<p>Interventions</p> <p>A: margin distance &lt;3 mm</p> <p>B: margin distance &gt;5mm</p> <p>Analysis</p> <p>Type of analysis: Multivariate analysis (log rank)</p> <p>Univariate analysis</p> <p>Matching: NR</p> <p>Confounders: NR</p>	NR	<p><b>General information:</b></p> <p>Follow-up: 49 months (median 31, standard deviation ± 48, range 6–224)</p> <p><b>Funding:</b> None</p> <p><b>Col:</b> None declared</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Descriptive statistics</p> <p>Age at diagnosis (median, range)</p> <p>69.5 years (standard deviation <math>\pm 11</math>, range 27-89)</p> <p>Sex (% female)</p> <p>A: 100%</p> <p>B: 100%</p> <p>Stage (FIGO, %)</p> <p>I-II: No LRR: 61%, LRR: 39%</p> <p>III: No LRR: 58%, LRR: 42%</p> <p>Location of the tumour</p> <p>NR</p> <p>Tumour size (% , cm)</p> <p>Mean value: 29 mm</p> <p>&lt;20 mm: No LRR: Yes: 54%, No: 63%, LRR: Yes: 46%, No: 37%</p> <p>&lt;40 mm: No LRR: Yes: 56%, No: 68%, LRR: Yes: 44%, No: 32%</p> <p>Tumour depth (mm, standard deviation, range)</p>			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Mean: No LRR: <math>8.4 \pm 6.2</math> (2–40), LRR: <math>7.3 \pm 6.9</math> (2–55)</p> <p>&lt;8mm: No LRR: Yes: 56%, No: 65%, LRR: Yes: 44%, No: 35%</p> <p>Lymph node metastases:</p> <p>0-1: No LRR: 60%, LRR: 40%</p> <p>&gt;1: No LRR: 59%, LRR: 41%</p> <p>Additional therapy: Radiotherapy</p> <p>No LRR: Yes: 58%, No: 60%</p> <p>LRR: Yes: 42%, No 40%</p> <p>Perineural invasion:</p> <p>No LRR: Yes: 56%, No: 62%</p> <p>LRR: Yes: 44%, No: 36%</p>			

Forest plot of comparison: 1 Tumour-free margin <8 mm vs. Tumour-free margin  $\geq$ 8 mm, outcome: 1.1 local recurrence.

**Verknüpfte Empfehlungen:****Empfehlung 10.3:**

Bei lokal fortgeschrittenem Vulvakarzinom im Stadium T2 und T3 gibt es keine ausreichende Datenlage, welche die Überlegenheit eines bestimmten therapeutischen Vorgehens zeigt.

**Empfehlung 12.10:**

Die primäre Radiochemotherapie stellt beim lokal fortgeschrittenen Vulvakarzinom eine gleichwertige Alternative zur Operation dar.

**Literaturreferenzen:** [\[38\]](#), [\[39\]](#)

[\[40\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort study (aus SR)	1 non-RCT	OS	-1 (high risk of bias)	/	-1 (includes stage IV patients)	-1 (only few events: 17 in 63 pts and wide CI: Adjusted HR=1.09, 95% CI 0.37 - 3.17)	/	⊕⊖⊖⊖ Very low
Low à cohort study (aus SR)	2 non-RCTs	recurrence	-1 (high risk of bias)	/	-1 (includes stage IV patients)	-1 (only few events: 16 in 75 pts and wide CI: RR=0.56, 95% CI 0.22-1.40)	We pooled the results from the SR.	⊕⊖⊖⊖ Very low



**Verknüpfte Empfehlungen:****Empfehlung 10.3:**

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[\[41\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High	1 RCT	Groin recurrence	/	/	-1 (includes patients with T1-3 N0-1 M0)	-2 (only few events: 5/52 pts and very wide CI: HR=10.21 (95% CI 0.59 to 175.78)	The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis-benefit in the radiotherapy group.	⊕⊖⊖⊖ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High	1 RCT	Overall recurrence	/	/	-1 (includes patients with T1-3 N0-1 M0)	-2 (only few events: 10/52 pts and very wide CI: HR=3.70 (95% CI 0.87 to 15.80)	The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis-benefit in the radiotherapy group.	⊕⊕⊕⊕ Very low
High	1 RCT	Mortality - overall	/	/	-1 (includes patients with T1-3 N0-1 M0)	-2 (only few events: 13/52 pts and very wide CI: HR=3.09 (95% CI 0.96 to 9.94)	The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis-benefit in the radiotherapy group.	⊕⊕⊕⊕ Very low



**Verknüpfte Empfehlungen:****Empfehlung 10.3:**

Bei lokal fortgeschrittenem Vulvakarzinom im Stadium T2 und T3 gibt es keine ausreichende Datenlage, welche die Überlegenheit eines bestimmten therapeutischen Vorgehens zeigt.

**Empfehlung 12.10:**

Die primäre Radiochemotherapie stellt beim lokal fortgeschrittenen Vulvakarzinom eine gleichwertige Alternative zur Operation dar.

**Literaturreferenzen:** [\[38\]](#), [\[39\]](#)

[\[42\]](#), [\[43\]](#)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Shylasree 2011 Systematic Review (ohne Meta-analyse)	Types of studies: 1 RCT and 2 retrospective cohort studies  Searched from 1966 – July 2009  Databases:  Cochrane Central Register of	Question/ Aim: To evaluate the effectiveness and safety of neoadjuvant and primary chemoradiation for women with locally advanced primary squamous vulval cancer compared to	3 studies on 141 pts with advanced stage primary vulval cancer  <b>Descriptive statistics:</b>  Age (median, range)	Rezidivrate  <u>Landrum 2008:</u>  A (primary chemoradiation group): 5/33  B (primary surgery group): 7/30  <u>Mulayim 2004</u>	Overall confidence in results of SR (AMSTAR-2): “moderate”  PICO elements: yes  A priori design: yes  Justification for design: yes	2 non-RCTs:  <u>Landrum 2008 &amp; Mulayim 2004</u>  1 RC:  <u>Maneo 2003</u>  Landrum LM, Skaggs V, Gould N, Walker JL, McMeekin DS.

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Controlled Trials (CENTRAL) (<i>The Cochrane Library</i> 2009, Issue 3)</p> <p>Cochrane Gynaecological Cancer Collaborative Review Group Trial Register</p> <p>MEDLINE</p> <p>EMBASE</p> <p>Unpublished and grey literature: Metaregister, Physicians Data Query, <a href="http://www.controlled-trials.com/rct">www.controlled-trials.com/rct</a>, <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> and <a href="http://www.cancer.gov/clinicaltrials">www.cancer.gov/clinicaltrials</a> were</p>	<p>other primary modalities of treatment such as primary surgery or primary radiation. Locally advanced primary disease is defined as encompassing women who have FIGO stage III or IVa squamous vulval cancer.</p> <p>A: primary (2 non-RCTs) or neoadjuvant (1 RCT) chemoradiation</p> <p>B: primary surgery</p>	<p><u>In 2 Non-RCT studies (Landrum 2008 &amp; Mulayim 2004):</u> 64 (2-88) &amp; 73</p> <p><u>In RCT (Maneo 2003)</u> A and B: 74 (31-85)</p> <p>Sex (100% female)</p> <p>Stage (nach FIGO 1944, N/%)</p> <p><u>In 2 non-RCT studies (Landrum 2008 &amp; Mulayim 2004):</u> Stage III: N=57 Stage IV: N=19 (IVb: N=4)</p> <p><u>Maneo 2003 (RCT):</u> TNM status was as follows:</p>	<p>A (primary chemoradiation group): 1/6</p> <p>B (primary surgery group): 3/6</p> <p><u>In Maneo 2003</u> A (neoadjuvant chemoradiation arm): 13</p> <p>B (primary surgery group): 17</p> <p>No Pooled results</p> <p>DFS: NR</p> <p>PFS: NR</p> <p>MFS: NR</p> <p>OS</p> <p><u>Landrum 2008:</u></p>	<p>Literature search &gt;= 2 databases, search strategy + other sources: yes</p> <p>Selection in duplicate: yes</p> <p>Data extraction in duplicate: yes</p> <p>List of excluded studies: yes</p> <p>sufficient detail on studies: yes</p> <p>RoB assessed: yes</p> <p>Funding of incl. studies: no</p> <p>MA appropriate: no MA</p> <p>RoB considered in MA: no MA</p>	<p>Comparison of outcome measures in patients with advanced squamous cell carcinoma of the vulva treated with surgery or primary chemoradiation. <i>Gynecologic Oncology</i> 2008;108(3): 584-90.</p> <p>Mulayim N, Silver DF, Schwartz PE, Higgins S. Chemoradiation with 5-fluorouracil and mitomycin C in the treatment of vulvar squamous cell carcinoma. <i>Gynecologic Oncology</i> 2004;93: 659- 66.</p> <p>Maneo A, Landoni F, Colombo A, Colombo A, Villa A, Caspani G.</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>searched for ongoing trials.</p> <p>Inclusion criteria</p> <p>Randomised controlled trials (RCTs) or non-randomised studies that included multivariate analyses of chemoradiation in women with locally advanced, primary squamous cell carcinoma of the vulva.</p> <p>In our review we incorporated patients with biopsy proven, primary locally advanced squamous cell carcinoma of the vulva (stage III/IV).</p>		<p>T1 N + 1 (3%) versus 0 (0%)</p> <p>T2 N - 2 (7%) versus 10 (26%)</p> <p>T2 N + 15 (50%) versus 19 (50%)</p> <p>T3 N - 4 (13%) versus 4 (11%)</p> <p>T3 N + 8 (27%) versus 5 (13%)</p> <p>Adjuvant surgery or radiation:</p> <p>Landrum 2008: 8 (24%) patients underwent adjuvant surgery following primary chemoradiation and 19 patients (63%) underwent either adjuvant radiation or</p>	<p>A (primary chemoradiation group): 8/33</p> <p>B (primary surgery group): 9/30</p> <p>Adjusted HR=1.09, 95% CI 0.37 - 3.17</p> <p><u>Mulayim 2004</u></p> <p>A (primary chemoradiation group): 3/6</p> <p>B (primary surgery group): 6/6</p> <p><u>In Maneo 2003 (death at 5 years)</u></p> <p>A (neoadjuvant chemoradiation arm): 20/28</p> <p>B (primary surgery group): 19/37</p>	<p>RoB in interpretation: yes</p> <p>Heterogeneity explained: after the authors not relevant bc no MA</p> <p>Publication bias investigated: no, no adequate number of studies to assess</p> <p>Sources of Col: none</p>	<p>Randomised study between neoadjuvant chemoradiotherapy and primary surgery for the treatment of advanced vulval cancer. International Journal of Gynecological Cancer. 2003; Vol. 13 Suppl 1: 6, Abstract PL 19.</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Intervention: Chemoradiation (primary, neoadjuvant)</p> <p>Comparison Primary surgery</p> <p>Radiation (primary, neoadjuvant)</p> <p>Chemotherapy (neoadjuvant)</p> <p>Exclusion criteria: case-control studies, uncontrolled observational studies and case series of fewer than 10 patients</p>		<p>adjuvant chemoradiation following primary surgery.</p> <p>Mulayim 2004: 1 patient in the primary chemoradiation group underwent adjuvant surgery and all the patients who underwent primary surgery underwent adjuvant chemoradiation.</p> <p>Maneo 2003: in the primary surgery arm, 15 (15/37) patients underwent adjuvant radiation. Surgery was feasible in 24 out of 28 patients in the neoadjuvant arm.</p>	<p>RR=1.39, 95% CI 0.94 - 2.06</p> <p>No Pooled results</p> <p>Nebenwirkungsspektr um (primary chemoradiation vs. primary survery)</p> <p><u>Severe acute toxicity:</u> Hematologic toxicity</p> <p>There was no significant difference in the risk of severe acute hematologic toxicity between primary chemoradiation and surgery (RR 0.75, 95% CI 0.28 to 2.00).</p> <p>Gastrointestinal toxicity</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				<p>There was no significant difference in the risk of severe acute gastrointestinal toxicity between primary chemoradiation and surgery (RR 0.33, 95% CI 0.05 to 2.37).</p> <p>Skin toxicity</p> <p>There was no significant difference in the risk of severe acute skin toxicity between primary chemoradiation and surgery (RR 0.50, 95% CI 0.14 to 1.77).</p> <p><u>Severe Late toxicity:</u></p> <p>There was no significant difference in the risk of other</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				severe late toxicities between primary chemoradiation and surgery (RR 1.33, 95% CI 0.50 to 3.55).		
Van der Velden, 2011 Systematic Review (ohne Meta-analyse)	Types of studies: RCT Searched from 1966 – July 2010 (They searched again in January 2016 and no additional trails were identified) Databases: Cochrane Gynaecological Cancer Group Specialised Register, Cochrane Central Register of	Question/ Aim: To determine whether the effectiveness and safety of primary radiotherapy to the inguinofemoral lymph nodes in early vulvar cancer is comparable with surgery. A: primary radiotherapy of the inguinofemoral lymph nodes (Primary Groin Radiotherapy): N=27	1 study (RCT) on 52 pts with early squamous cell cancer of the vulva  <b>Descriptive statistics:</b> Age (median, range) 64 years Stage (nach FIGO, %) primary, previously untreated, squamous cell carcinoma of the vulva T1-3 N0-1 M0 (A radical vulvectomy	Rezidivrate <u>(recurrence overall)</u> A: 8/27 B: 2/25  Pooled RR: 3.70 (95% CI 0.87 to 15.80) in favour of B  <u>(groin recurrence)</u> A: 5/27 B: 0/25  Pooled RR: 10.21 (95% CI 0.59 to 175.78) in favour of B	Overall confidence in results of SR (AMSTAR-2): “moderate” PICO elements: yes A priori design: yes Justification for design: yes Literature search >= 2 databases, search strategy + other sources: yes Selection in duplicate: yes	Stehman 1992 Stehman FB, Bundy BN, Thomas G, Varia M, Okagaki T, Roberts J, et al. Groin dissection versus radiation in carcinoma of the vulva: a Gynecologic Oncology Group study. <i>International Journal of Radiation Oncology, Biology, Physics</i> 1992;24: 389-96.

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	Controlled Trials (CENTRAL), MEDLINE and EMBASE  Inclusion criteria  RCTs and NRS  Women diagnosed with early squamous cell carcinoma of the vulva i.e. clinical T1 to T2 N0 M0  Inguinal and femoral lymphadenectomy  Radiotherapy of the groin (radiotherapy to a volume including the inguinal and femoral lymph nodes)	B: inguinofemoral lymph node dissection (Primary Groin Surgery): N= 25	had to suffice to remove the lesion; patients with T1 tumours were eligible only if there was vascular space involvement or if invasion > 5 mm; no suspicious lymph nodes (N0-1); no distant metastases)  Location of the tumour A: Labia: 59,3% Clitoris: 18,5% Perineum: 6% B: Labia: 56% Clitoris: 24% Perineum: 12% Other: 8%	Mortality - overall A: 10/27 B: 3/25  Pooled RR: 3.09 (95% CI 0.96 to 9.94) in favour of B  Other outcomes <u>Disease-specific mortality:</u> A: 8/27 B: 2/25  RR 3.70, 95% CI 0.87 to 15.80 in favour of B  <u>lymphoedema</u> A: 0/27 B: 7/25	Data extraction in duplicate: yes  List of excluded studies: yes  sufficient detail on studies: yes  RoB assessed: yes  Funding of incl. studies: no  MA appropriate: NA  RoB considered in MA: NA  RoB in interpretation: yes  Heterogeneity explained: NA  Publication bias investigated: no  Sources of Col: none	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
			Tumour size (% , cm) A: <2.0 cm: 11,1% 2.1-4.0 cm: 70,4 % > 4.1 cm: 18,5 % B: <2.0 cm: 8% 2.1-4.0 cm: 72% > 4.1 cm: 20 % Tumour depth (% , mm) ≤ 1.0: 1.01-2.5: 2.51-5.0: >5.0	RR 0.06, 95% CI 0.00 to 1.03 in favour of A  <u>life-threatening            cardiovascular            complications</u>  A: 0/27 B: 5/25  RR 0.08, 95% CI 0.00 to 1.45 in favour of A  <u>Hospital Stay:</u> RR 0.28, 95% CI 0.13 to 0.58)	Andere Bemerkugne: The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis- benefit in the radiotherapy group. Radiotherapy was applied to a depth of 3cm only. The mean depth of deeper groin nodes is estimated at 4.5- 6.1 cm, therefore the radiotherapy dose used in this trial may have been insufficient for deep nodes.	



## Kapitel 8: Operative Therapie der Lymphabflusswege

### Kapitel 8.1: Umfang der Lymphknoten-Behandlung

#### Verknüpfte Empfehlungen:

#### Empfehlung 11.5:

Bei einer systematischen Lymphonodektomie der Leisten sollen sowohl die oberflächlichen (inguinalen) als auch die tiefen (femorale) Lymphknoten unter der Fascia cribrosa entfernt werden.

**Literaturreferenzen:** [\[44\]](#), [\[45\]](#), [\[46\]](#), [\[47\]](#)

[\[44\]](#), [\[45\]](#), [\[47\]](#), [\[48\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Gordinier 2003, Retrospective study (chart review)	9 pts with squamous cell carcinoma of the vulva (all were clinically negative groin nodes and underwent superficial lymphadenectomy)  Inclusion criteria (for analysis): patients with squamous histology, clinical and surgical stage I or II, depth of invasion greater than 1 mm, and primary treatment consisting of radical wide excision with negative margins and	Interventions All patients underwent superficial lymphadenectomy A: bilateral superficial inguinal lymphadenectomy (N=7) B: unilateral dissections(N=2)  Analysis Type of analysis: nr Matching: no Confounders: no	<b>Groin recurrence</b> Recurrence in right groin: N=4 Recurrence in left groin: N=4 Recurrence in both groins: N=1 DFS nr Overall survival nr <b>Additional outcomes: Death from disease</b>	<b>General information</b> Median follow-up: 63 months <b>Funding:</b> NR <b>Col:</b> NR Risk of bias considerations (adapted from SIGN cohort study checklist) Study type: retrospective chart review Populations comparable: yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>superficial inguinal lymphadenectomy</p> <p>Exclusion criteria (for analysis): nr</p> <p>Enrolment period</p> <p>patients treated at M. D. Anderson Cancer Center between 1986 and 1997 were reviewed</p> <p>Descriptive statistics</p> <p>Age (mean)</p> <p>59 years</p> <p>Stage</p> <p>Stage I: N=2/9</p> <p>Stage II: N=7/9</p> <p>Tumour size</p> <p>ranged in size from 0.2 to 4.0 cm</p> <p>Tumour depth (% , mm)</p> <p>median depth of invasion was 4.0 mm</p>		<p>Deaths: N=6</p> <p>median interval from recurrence to death was 6 months (range 4 to 54)</p>	<p>Rate of participation/Exclusions reported (selection bias into the study): no</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: nr</p> <p>Possibly affected by knowledge of outcome status?: nr</p> <p>Drop-out rate &amp; reasons reported: nr</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account: no</p> <p>Confidence intervals reported: no</p> <p>Selective reporting (comparison with protocol): nr</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>median tumor diameter 3 cm (range 1-3)</p> <p>median number of nodes resected per groin</p> <p>eight on the right and seven on the left (range 1 to 17).</p> <p>The nodes ranged in size from 0.2 to 4.0 cm</p>			
<p>Kirby 2005, Retrospective study (chart review)</p>	<p>65 pts with Stage I or II vulvar cancer who underwent a negative SupiL and vulvectomy</p> <p>Inclusion criteria (for analysis):</p> <p>Stage I and II patients</p> <p>All patients had separate incisions for the vulvectomy and SupiL</p> <p>Both partial and complete vulvectomy specimens were included, and surgeons typically</p> <p>attempted to obtain a 1-2 cm margin around the tumor.</p>	<p>Interventions</p> <p>èAll had superficial inguinal lymphadenectomy (SupiL) (N=65)</p> <p>A: bilateral SupiL (N=44)</p> <p>B: Ipsilateral SupiL (N=21)</p> <p>Analysis</p> <p>Type of analysis: Kaplan-Meier method with Fisher Exact and Chi-square tests</p> <p>Matching: no</p> <p>Confounders: no</p>	<p><b>Recurrence rate</b></p> <p>Recurrence on the vulva: N=11 (17%)</p> <p>recurred in the inguinal region: N=3 (4.6%)</p> <p>DFS (5-year)</p> <p>66% (SE 9.3%)</p> <p>Overall survival</p> <p>97% (SE 2.5%)</p> <p><b>Additional outcomes: Death</b></p> <p>Deaths: N=3</p>	<p><b>General information</b></p> <p>Mean follow-up: 36 months</p> <p><b>Funding:</b> nr</p> <p><b>Col:</b> nr</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective chart review</p> <p>Populations comparable: yes</p> <p>Rate of participation/Exclusions reported (selection bias into the study): no</p> <p>Exposure/Intervention</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Only patients with a pathologically negative SupIL</p> <p>Exclusion criteria (for analysis):</p> <p>NR</p> <p>Enrolment period</p> <p>1990–2001</p> <p>Descriptive statistics</p> <p>Age</p> <p>NR</p> <p>Stage (FIGO)</p> <p>Stage I: N=30/65</p> <p>Stage II: N=35/65</p> <p>Location of the tumour</p> <p>N=32 (49%) patients had midline lesions</p> <p>N=11 (17%) had <i>lesions involving the clitoris</i></p> <p>Tumour size</p> <p>Mean lesion size was 2.7 cm (range 0.4–6.5 cm).</p> <p>Tumour depth (% , mm)</p>			<p>Assessment reliable: yes</p> <p>Assessed more than once: nr</p> <p>Possibly affected by knowledge of outcome status?: nr</p> <p>Drop-out rate &amp; reasons reported: no</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account: nr</p> <p>Confidence intervals reported: nr</p> <p>Selective reporting (comparison with protocol): nr</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Mean depth of invasion was 4.4 mm (range 0.8–20 mm)</p> <p>Lymph node metastases (yes, %)</p> <p>NR</p>			
<p>Woolderink 2006</p> <p>Retrospective analysis</p>	<p>125 pts with squamous cell carcinoma of the vulva</p> <p>Inclusion criteria (for analysis):</p> <p>Patients with primary vulva cancer, without a previous history of vulvar cancer, and treated by the same surgeon (M.J.D)</p> <p>Exclusion criteria (for analysis):</p> <p>non-squamous cell carcinoma, chemoradiation because of very extensive vulvar cancer, no lymph node dissection because of extensive vulvar cancer or poor general condition</p> <p>Enrolment period</p> <p>January 1985 to</p> <p>December 1999</p>	<p>Interventions</p> <p>→ All had wide local excision and superficial inguinal lymphadenectomy (N=125)</p> <p>Analysis</p> <p>Type of analysis: Univariate Cox regression analyses</p> <p>Matching: no</p> <p>Confounders: no</p>	<p><b>Recurrence rate</b></p> <p>local recurrence: N= 29 (23%), groin recurrence: N= 11 (9%) distant recurrence: N=4 (3%)</p> <p>DFS (5-year)</p> <p>NR</p> <p>Overall survival</p> <p>NR</p> <p><b>Additional outcomes: overall relapse-free survival (5 years)</b></p> <p>58%</p>	<p><b>General information</b></p> <p>Median follow-up: 42 months (range 1–184 months)</p> <p><b>Funding:</b> nr</p> <p><b>Col:</b> nr</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective chart review</p> <p>Populations comparable: yes</p> <p>Rate of participation/Exclusions reported (selection bias into the study): no</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: nr</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Descriptive statistics Age Median: 72 years (range 23–91 years) Stage Stage 1A: N=15 (12%) Stage 1B: N=34 (27%) Stage II: N=42 (34%) Stage III: N= 22 (18%) Stage IVA: N= 12 (9%) Location of the tumour (N) 99 (79%) lateral, 22 (17%) Clitoris, 3 (2%) Perineum, 1 (0,8%) Vulvovaginal Tumour size (median, range) 25.0; (2–100) without recurrence 20.0; (2–75) with a local recurrence			Possibly affected by knowledge of outcome status?: nr Drop-out rate & reasons reported: no Outcome Outcome measure is well-defined, valid and reliable: yes Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no Main cofounders taken into account: nr Confidence intervals reported: nr Selective reporting (comparison with protocol): nr

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>25.0; (9–48) with a groin recurrence</p> <p>42.5; (8–70) with a distant recurrence</p> <p>Tumour depth (mm, median, range)</p> <p>4.0; (5.0) without recurrence,</p> <p>3.0; (5.0) with a local recurrence,</p> <p>6.0; (5.0) with a groin recurrence,</p> <p>6.0; (5.0) with a distant recurrence</p> <p>Lymph node metastases (yes, %)</p> <p>NR</p>			
Gonzalez Bosquet 2006 Cohort study	<p>330 pts with squamous cell carcinoma of the vulva</p> <p>Inclusion criteria (for analysis): lymphadenectomy as part of the initial treatment</p> <p>Exclusion criteria (for analysis):</p>	<p>Interventions</p> <p>→ All had underwent bilateral (314 patients) or ipsilateral (16 patients) inguinal lymphadenectomy</p> <p>A: patients without metastatic involvement of the</p>	<p><b>Recurrence rate of vulva</b></p> <p>Group A: N= 34 of 217, 15.7%</p> <p>Group B: N= 30 of 113, 26.5%</p> <p>DFS (5-year)</p> <p>NR</p>	<p><b>General information</b></p> <p>Mean follow-up: NR</p> <p><b>Funding:</b> nr</p> <p><b>Col:</b> nr</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	NR	inguinofemoral nodes at the first surgical procedure ( <i>n</i> = 217)	Disease-specific survival (local or vulva)	Risk of bias considerations (adapted from SIGN cohort study checklist)
	Enrolment period		83% after 2 years treatment	
	1955 - 1990			
	Descriptive statistics	B: patients with involvement of the inguinofemoral nodes at the first surgical procedure ( <i>n</i> = 113)	79% after 5 years	Study type: cohort study
	Age		66% after 10 years	Populations comparable: yes
	NR	Analysis	<b>Additional outcomes: death</b>	Rate of participation/Exclusions reported (selection bias into the study): no
	Stage (FIGO)	Type of analysis: Kaplan-Meier method	<i>N</i> =192	Exposure/Intervention
	NR		59 from <i>disease</i> (17.9% of the study population), 11 from <i>treatment complications</i> (3.3%), 120 from <i>other causes</i> (36.4%), and 2 <i>unknown</i> (0.6%).	Assessment reliable: yes
	Location of the tumour	Matching: no		Assessed more than once: nr
	metastases or recurrent cancer:	Confounders: no		Possibly affected by knowledge of outcome status?: nr
	31 groin, 64 vulva, 37 distant			Drop-out rate & reasons reported: no
	Tumour size		<b>Additional outcomes: treatment failure</b>	Outcome
	NR		88 (26.7%)	Outcome measure is well-defined, valid and reliable: yes
	Tumour depth (% , mm)			Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no
	NR			
	Lymph node metastases (yes, %)			
	113 lymph node positive, 217 negative			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
				Main cofounders taken into account: nr Confidence intervals reported: nr Selective reporting (comparison with protocol): nr

**Verknüpfte Empfehlungen:****Empfehlung 11.6:**

Es gibt zur Anzahl zu entfernender Lymphknoten aus der Leiste anlässlich einer systematischen inguinofemorale Lymphonodektomie keinen evidenzbasierten Cut-off-Wert.

**Literaturreferenzen:** [\[49\]](#), [\[50\]](#), [\[51\]](#), [\[52\]](#), [\[53\]](#)

[\[52\]](#), [\[53\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort study	1 cohort study (Sopracordevole ) 2018	Groin recurrence	/	/	Note: population of interest from the PICO may not be exactly represented in this study	-1 (only few events: 4 in 76 pts; wide CI: HR=0.09, 95% CI 0.00-1.54)	/	⊕⊕⊕⊕ Very low
Low à cohort study	1 cohort study (Wu 2018)	Overall survival	/	/	Note: population of interest from the PICO may not be exactly represented in this study & comparison groups deviate	-1 (only few participants: 352 pts; wide CI: HR=1.44, 95% CI 1.08-1.92)	/	⊕⊕⊕⊕ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
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slightly from PICO

**Verknüpfte Empfehlungen:****Empfehlung 11.6:**

Es gibt zur Anzahl zu entfernender Lymphknoten aus der Leiste anlässlich einer systematischen inguinofemorale Lymphonodektomie keinen evidenzbasierten Cut-off-Wert.

**Literaturreferenzen:** [\[49\]](#), [\[50\]](#), [\[51\]](#), [\[52\]](#), [\[53\]](#)

[\[49\]](#), [\[50\]](#), [\[51\]](#), [\[52\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Baiocchi 2013 Retrospective analysis	158 pts with vulvar SCC  Inclusion criteria (for analysis):  Surgical treatment at the Department of Gynecologic Oncology at AC Camargo Cancer Hospital  Exclusion criteria (for analysis): NR  Enrolment period 1980-2010  Descriptive statistics Age (mean, range)  All participants: 67 (15-90)	Interventions  A: <12 lymph nodes resected with lymphadenectomy  B: ≥12 lymph nodes resected with lymphadenectomy  Analysis  Type of analysis: Chi-square or Fischer's exact test  Matching: NA  Confounders: NR	Rezidivrate (groin recurrence)  A: 28.6%/13  B: 23%/145  P= 0.74  3-year OS  <u>Subgroup: patients with positive LNs (FIGOstage III)</u>  A: 20.8%/13  B: 48%/145  P=0.084  <i>“Resection of fewer than 12 LNs in vulvar cancer has a negative impact on outcome for patients with positive inguinal LNs.”</i>	<b>General information</b>  Median follow-up: 34 months (range: 1-301.5)  <b>Funding:</b> NR  <b>Col:</b> none declared  Risk of bias considerations (adapted from SIGN cohort study checklist)  Study type: retrospective analysis  Populations comparable: yes  Rate of participation/Exclusions reported (selection bias into the study): no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Stage (FIGO, %)</p> <p>NR</p> <p>Location of the tumour</p> <p>NR</p> <p>Tumour size (cm)</p> <p>median: 5 (range: 1-18)</p> <p>Tumour depth (% , mm)</p> <p>Median: 10 (range: 2-30) analyzed for N=54 pts.</p> <p>Lymph node metastases (yes, %)</p> <p>Yes, 50.6%</p> <p>Median of 2 positive LNs (range: 1-16). Of those with positive LNs, 19 (23.8%), 23 (28.8%), and 38 (47.5%) patients had 1, 2, and 3 or more positive LNs, respectively.</p>		<p><b>Additional outcomes:</b></p> <p>2-year PFS (progression free survival)</p> <p><u>Subgroup: patients with positive LNs (FIGOstage III)</u></p> <p>A: 20.8%/13</p> <p>B: 52.8%/145</p> <p>P=0.003</p> <p>3-year DSS (disease specific survival)</p> <p><u>Subgroup: patients with positive LNs (FIGOstage III)</u></p> <p>A: 20.8%/13</p> <p>B: 78.6%/145</p> <p>P=0.043</p>	<p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: yes</p> <p>Possibly affected by knowledge of outcome status?: yes</p> <p>Drop-out rate &amp; reasons reported: NA</p> <p>Similar across groups: /</p> <p>If high: comparison of those lost with available: /</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: no</p> <p>Main cofounders taken into account: NR</p> <p>Confidence intervals reported: no</p> <p>Selective reporting (comparison with protocol): NR</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Courtney-Brooks 2010 Retrospective analysis	<p>1135 pts with vulvar squamous cell carcinoma</p> <p>Inclusion criteria (for analysis):</p> <p>Clinical stages I, II, III</p> <p>ICD-9 histology codes included: 8070, 8071, 8072, 8075, 8076, 8077</p> <p>Pts. had undergone primary inguinal-femoral lymph node dissection between 1988 and 2003</p> <p>Exclusion criteria (for analysis):</p> <p>Pts. with lymph nodes positive for malignancy at the time of primary dissection were excluded</p> <p>Enrolment period</p> <p>2009</p> <p>Descriptive statistics</p> <p>Age</p> <p>Median age (all pts.): 68 (range: 12 – 85)</p>	<p>Interventions</p> <p>A: ≤10 lymph nodes removed with lymphadenectomy</p> <p>B: &gt;10 lymph nodes removed with lymphadenectomy</p> <p>Analysis</p> <p>Type of analysis: logrank test, Cox regression</p> <p>Matching: NR</p> <p>Confounders: Multivariate analysis taking into consideration stage, age, tumor size, number of lymph nodes removed, adjuvant radiation therapy, and race</p>	<p><b>Rezidivrate</b></p> <p>NR</p> <p>5-years OS</p> <p>A: 67±6.2%/ 401</p> <p>B: 77 ± 4.1%/ 629</p> <p>P=0.03</p> <p>Multivariate analysis (&lt; 10 nodes removed): HR= 1.5, 95% CI 1.16 – 1.94</p> <p>“An association with lower survival was seen in patients with fewer than 10 lymph nodes removed“</p> <p><u>Subgroup: women with stage II:</u></p> <p>A: 60 ± 10.4%/ 151</p> <p>B: 74 ± 6.5%/ 276</p> <p>P=0.04, in favour of B</p> <p><u>Subgroup: woman with stage III:</u></p> <p>A: 36 ± 23%/ 51</p> <p>B: 72 ± 10.6%/ 11</p>	<p><b>General information</b></p> <p>Follow-up: NR</p> <p><b>Funding:</b> NR</p> <p><b>Col:</b> none declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective analysis</p> <p>Populations comparable: yes</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: yes</p> <p>Possibly affected by knowledge of outcome status?: yes</p> <p>Drop-out rate &amp; reasons reported: no</p> <p>Outcome</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Stage (FIGO, %): all pts. I: 43% II: 41% III: 16% Location of the tumour NR Tumour size For pts. with stage I: median: 13 mm (range: 1-20) For pts. with stage II: median: 34 mm (21-130) For pts. with stage III: median: 40 mm (5 - 150) Tumour depth (% , mm) NR Lymph node metastases (yes, %) NR Median number of nodes removed Stage I: 11 (1-49)		P=0.03, in favour of B <u>Additional outcomes:</u> 5-year DSS A: 86.2 ± 4.7%/ 401 B: 92.2% ± 2.5 / 629 P = 0.06 Multivariate analysis (< 10 nodes removed): HR= 1.71, 95% CI: 1.08 - 2.71) “An association with lower survival was seen in patients with fewer than 10 lymph nodes removed“ <u>Subgroup: women with stage II:</u> A: 85 ± 8.2%/ 151 B: 92 ± 4.1%/ 276 P=0.25 <u>Subgroup: woman with stage            III:</u> A: 60 ± 24.3%/ 51 B: 85 ± 9%/ 114	Outcome measure is well- defined, valid and reliable: yes Blind outcome assessment to exposure: no Main cofounders taken into account: multivariable analysis Confidence intervals reported: yes for multivariate analysis Selective reporting (comparison with protocol): NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Stage II: 14 (1-53) Stage III: 15 (1-51)		P=0.02, in favour of B	
Diehl 2016 Retrospective single center study	45 pts with vulvar cancer Inclusion criteria (for analysis): Diagnosis of squamous cell carcinoma (SCC) of the vulva and receiving ipsilateral of bilateral IFL Exclusion criteria (for analysis): NR Enrolment period 1998 - 2011 Descriptive statistics Age Mean age: 58 (range: 31 -80) Stage (FIGO, %), all pts. I: 73.3% II: 2.2% III: 0 IV: 6.7%	Interventions A: < 6 lymph nodes removed with inguinofemoral lymphadenectomy B: ≥ 6 lymph nodes removed with inguinofemoral lymphadenectomy Analysis Type of analysis: survival curves according to Kaplan-Meier Matching: NA Confounders: NR	A: 27 groins (34.2%) had < 6 lymph nodes removed B: 48 groins (60.8%) had ≥ 6 lymph nodes removed Rezidivrate <u>Groin recurrence-free survival</u> No significant difference between A and B: p = 0.0619 <u>Local recurrence-free survival</u> No significant difference between A and B: p = 0.866 <u>Distant recurrence-free survival</u> No significant difference between A and B: p = 0.176	<b>General information</b> Follow-up: 61 months (0-153) <b>Funding:</b> none <b>Col:</b> none declared Risk of bias considerations (adapted from SIGN cohort study checklist) Study type: retrospective single center study Populations comparable: yes Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention Assessment reliable: yes Assessed more than once: yes Possibly affected by knowledge of outcome status?: yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Location of the tumour; all pts. Labia: 75.6% Between clitoris and urethra: 48.9% Several regions: 4.4% Tumour size; all pts. Median: 2 cm (range: 0.1 – 7.9) Tumour depth 4 mm (range: 1 - 35) for N = 26 pts. Lymph node metastases (yes, %) Yes, 13.9% of removed groins had LN metastases			Drop-out rate & reasons reported: NA Outcome Outcome measure is well-defined, valid and reliable: yes Blind outcome assessment to exposure: no Main cofounders taken into account: NR Confidence intervals reported: no Selective reporting (comparison with protocol): NR
Sopracordevole 2018 Retrospective cohort study	76 pts with squamous cell vulvar cancer Inclusion criteria (for analysis): Patients who underwent primary radical vulvar surgery and groin lymphadenectomy Tumor stages IB and II	Interventions A: < 6 lymph nodes removed with inguinofemoral lymphadenectomy B: ≥ 6 lymph nodes removed with inguinofemoral lymphadenectomy Analysis	Rezidivrate <u>Groin recurrence:</u> A: 4/33 B: 0/43 P= 0.03	<b>General information</b> Follow-up: at least two years to be considered for study <b>Funding:</b> NR <b>Col:</b> none declared

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Exclusion criteria (for analysis): Patients with positive inguinofemoral nodes were excluded</p> <p>Enrolment period 2005 - 2014</p> <p>Descriptive statistics Age A: mean: 69.1 ± 13.9 B: mean: 68.6 ± 11.8</p> <p>Stage (FIGO, %) Ib: 94.7% II: 5.3%</p> <p>Location of the tumour NR</p> <p>Tumour size (% , cm) A: 25.8 ± 16.5 B: 24.8 ± 19.6</p> <p>Tumour depth (% , mm) NR</p>	<p>Type of analysis: t test or Mann-Whitney U test</p> <p>Matching: NA</p> <p>Confounders: NR</p>		<p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective cohort study</p> <p>Populations comparable: yes</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: yes</p> <p>Possibly affected by knowledge of outcome status: yes</p> <p>Drop-out rate &amp; reasons reported: no</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: no</p> <p>Main cofounders taken into account: NR</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Lymph node metastases (yes, %) NR No distant metastasis			Confidence intervals reported: no Selective reporting (comparison with protocol): NR
Wu 2018 retrospective analysis	703 patients with node-positive vulvar squamous cell carcinoma (SCC) <b>Inclusion criteria (for analysis):</b> histologically confirmed node-positive vulvar SCC who received surgery including lymphadenectomy the exact number of RLNs and PLNs were recorded; patient characteristics including age, race/ethnicity, tumor grade, tumor size, and receipt of radiotherapy or chemotherapy were available <b>Exclusion criteria (for analysis):</b>	Interventions A: 1-6 removed lymph nodes (RLNs) n= 181 B: 7-10 removed lymph nodes, n= 171 C: 11-16 removed lymph nodes, n= 194 D: 17-45 removed lymph nodes, n=157 Analysis Type of analysis: $\chi^2$ test, Fisher's exact test, and one-way analysis of variance, Survival curves: Kaplan-Meier method, comparison by log-rank test, univariate analysis were entered into multivariate Cox regression models Matching: NR	<b>Rezidivrate</b> NR <b>3-year OS rates</b> A: 36,1%/181 B: 50,6%/171 C: 61,1%/194 D: 57,6%/157 Comparison 7-10 (B) vs. 1-6 (A): HR=1.44, 95% CI 1.08-1.91, p=0.013, in favour of B Comparison 7-10 (B) vs. 11-16 (C): HR=0.81, 95% CI 0.60-1.1, p=0.171, in favour of C Comparison 7-10 (B) vs. 17-45 (D): HR=0.87, 95% CI 0.64-1.18, p=0.38, in favour of D "In patients with node-positive vulvar SCC, our results	<b>General information</b> Mean follow-up: 21 months <b>Funding:</b> Natural Science Foundation of Fujian Province (No. 2015J01550, 2013D001), the Medical Innovation Foundation of Fujian Province (No. 2015-CXB-34), and the Foundation for Young Scholar of Fujian Provincial Health Department (No. 2014-ZQN-ZD-31) <b>Col:</b> none declared Risk of bias considerations (adapted from SIGN cohort study checklist) Study type: retrospective analysis Populations comparable: yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Patients who received preoperative radiotherapy or SLNB</p> <p><b>Enrolment period</b> 2004-2013</p> <p><b>Descriptive statistics</b> Age (median, range) mean age: 69; range 21-95 years (keine Angaben zu Gruppenunterschieden)</p> <p>Stage (FIGO 1988), from 252 dissected groins: &lt; T2: NR T2: A: NR &gt; T2: NR</p> <p>Location of the tumour (of 252 extracted groins): Central: NR Lateral: NR Missing: NR</p>	<p>Confounders: multivariate analysis</p>	<p>indicated that patients with =6 removed lymph nodes had a higher risk of death compared with patients with &gt;6 removed lymph nodes.”</p> <p><b>Additional outcomes:</b></p> <p><b>3-year cause-specific survival (CSS):</b></p> <ul style="list-style-type: none"> <li>· A: 48,9%/181</li> <li>· B: 65,9%/171</li> <li>· C: 73,1%/194</li> <li>· D: 67,3%/157</li> </ul> <p>Comparison 7-10 (B) vs. 1-6 (A): HR=1.73, 95% CI 1.20-2.49, p=0.003, in favour of B</p>	<p>Rate of participation/Exclusions reported (selection bias into the study): NR</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: yes</p> <p>Possibly affected by knowledge of outcome status?: yes</p> <p>Drop-out rate &amp; reasons reported: no</p> <p>Similar across groups: NR</p> <p>If high: comparison of those lost with available: NR</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account:</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Tumour size ≤ 20 mm: NR > 20 mm: NR mean: 35 mm (range 2–200 mm) Tumour depth (% , mm) A: NR B: NR Lymph node metastases (yes, %) NR			Confidence intervals reported: yes Selective reporting (comparison with protocol): NR <b>Other limitations or comments:</b> NR

## Kapitel 8.2: Lymphknoten Debulking

### Verknüpfte Empfehlungen:

#### Empfehlung 11.8:

Bei klinisch vergrößerten metastatisch befallenen Leistenlymphknoten kann eine isolierte operative Entfernung dieser Lymphknoten (Debulking) anstelle einer systematischen Lymphonodektomie vor der Radio(chemo)therapie die Morbidität der Gesamtbehandlung senken und die Zeit bis zum Beginn der Radio(chemo)therapie verkürzen.

Literaturreferenzen: [\[54\]](#), [\[55\]](#), [\[56\]](#)

[\[54\]](#), [\[55\]](#), [\[56\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort study	1 cohort study (Nooij 2015)	Groin recurrence	/	/	Note: population of interest from the PICO may not be exactly represented in this study (not all participants received adjuvant groin radiotherapy)	-1 (only few events and few participants, N=68) (IFL vs. debulking, RR= 0.84, 95% CI 0.26-2.72)	/	⊕⊖⊖⊖ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort study	1 cohort study (Hyde 2007)	DFS	/	/	Note: population of interest from the PICO may not be exactly represented in this study	-1 (only few events and few participants, N=40) (debulking vs. IFL, HR= 0.407, 95% CI 0.137-1.207)	/	⊕⊕⊕⊕ Very low
Low à cohort study	1 cohort study (Fons 2023)	Overall survival	/	/	Note: population of interest from the PICO may not be exactly represented in this study	-1 (only few events and few participants, N=77) (debulking vs. IFL, P=0.286)	/	⊕⊕⊕⊕ Very low

**Verknüpfte Empfehlungen:****Empfehlung 11.8:**

Bei klinisch vergrößerten metastatisch befallenen Leistenlymphknoten kann eine isolierte operative Entfernung dieser Lymphknoten (Debulking) anstelle einer systematischen Lymphonodektomie vor der Radio(chemo)therapie die Morbidität der Gesamtbehandlung senken und die Zeit bis zum Beginn der Radio(chemo)therapie verkürzen.

**Literaturreferenzen:** [\[54\]](#), [\[55\]](#), [\[56\]](#)

[\[54\]](#), [\[55\]](#), [\[56\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Fons 2023 Retrospective single center cohort study	241 pts with squamous cell cancer of the vulva Inclusion criteria (for analysis): Patients with SCC and positive inguino-femoral lymph nodes Treatment between 1985 and 2020 in a curative setting Exclusion criteria (for analysis): NR Enrolment period 1985 - 2020 Descriptive statistics Age (median, range)	Interventions A: nodal debulking + radiotherapy B: IFL + radiotherapy Analysis Type of analysis: Cox model, Cox proportional hazard model Matching: yes (matching with historical controls) Confounders: NR	<b>5-year groin recurrence-free</b> A: 80.6%/ 40 B: 79.4%/ 37 p=0.421 Overall survival A: 29.4%/40 B: 23.8%/37 P=0.286 5- years DSS (disease-specific survival) A: 43.1%/ 40 B: 41.1%/ 37	<b>General information</b> Median follow-up: 31.5 months (range: 3 - 395) <b>Funding:</b> none <b>Col:</b> none declared Risk of bias considerations (adapted from SIGN cohort study checklist) Study type: retrospective single center cohort study Populations comparable: yes Rate of participation/Exclusions reported (selection bias into the study): yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>A: 74 (36-90)</p> <p>B: 77 (34-92)</p> <p>Stage (FIGO, %)</p> <p>IIIa: A: 15%, B: 11%</p> <p>IIIb: A: 20%, B: 18%</p> <p>IIIc: A: 50%, B: 57%</p> <p>IVa: A: 5%, B: 0%</p> <p>IVb: A: 10%, B: 14%</p> <p>Location of the tumour</p> <p>NR</p> <p>Tumour size</p> <p>Median: A: 46 mm (range: 10-150), B: 48 mm (range: 20-90)</p> <p>Tumour depth (% , mm)</p> <p>NR</p> <p>Lymph node metastases (yes, %)</p> <p>Yes, diameter of nodal metastasis &gt; 15 mm: A: 32/40 (80%), B: 29/ 37 (78%)</p>		<p>Debulking vs. IFL: HR= 0.45 (95% CI 0.15 – 1.29; p=0.14)</p>	<p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: yes</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: no</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no?</p> <p>Main cofounders taken into account: NR</p> <p>Confidence intervals reported: yes for DSS</p> <p>Selective reporting (comparison with protocol): NR</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Hyde 2007 Retrospective multi-institutional study	40 pts with squamous cell carcinoma of the vulva Inclusion criteria (for analysis): Patients with squamous cell carcinoma of the vulva who had clinically suspicious and histologically confirmed groin nodes Exclusion criteria (for analysis): NR Enrolment period 1982-2003 Descriptive statistics Age (median, range) A: 71.1 (33-93) B: 68.8 (34-90) Stage (FIGO, %) NR Location of the tumour NR Tumour size (cm)	Interventions A: lymph node debulking + adjuvant radiotherapy (n=17) B: formal groin dissection (full inguino-femoral lymphadenectomy) + adjuvant radiotherapy(n=23) Analysis Type of analysis: Cox proportional hazard model Matching: NR Confounders: NR	<b>Groin recurrence rate</b> (expressed as groin recurrence-free survival) P=0.247 no difference between A and B DFS Univariate analysis: p=0.03, in favour of A Multivariate analysis: HR: 0.407 (95% CI 0.137-1.207; p=0.105) “In a univariate analysis, both overall and disease-free survival were better in the group of patients treated by nodal debulking. However, in a multivariate analysis, other variables such as extracapsular growth were independent predictors for survival while the method of surgical dissection for the groin had no independent significant impact on survival.”	<b>General information</b> Follow-up: 140-500 months <b>Funding:</b> NR <b>Col:</b> NR Risk of bias considerations (adapted from SIGN cohort study checklist) Study type: retrospective multi-institutional study Populations comparable: yes Rate of participation/Exclusions reported (selection bias into the study): NR Exposure/Intervention Assessment reliable: yes Assessed more than once: yes Possibly affected by knowledge of outcome status?: no Drop-out rate & reasons reported: NR Outcome

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>≤ 4: A: 11, B: 9</p> <p>&gt;4: A: 6, B: 14</p> <p>Tumour depth (% , mm)</p> <p>NR</p> <p>Lymph node metastases (yes, %)</p> <p>Yes, number of positive nodes:</p> <p>A: 17, B: 23</p>			<p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: ) : no</p> <p>Main cofounders taken into account: NR</p> <p>Confidence intervals reported: yes for DFS</p> <p>Selective reporting (comparison with protocol): NR</p>
<p>Nooij 2015</p> <p>Retrospective cohort study</p>	<p>72 pts with newly diagnosed VSCC</p> <p>Inclusion criteria (for analysis):</p> <p>Newly diagnosed VSCC and metastases to the groin nodes</p> <p>Patients who were referred to Leiden University Medical Center</p> <p>Only patients with cytologically and histologically proven lymph node metastases</p> <p>Exclusion criteria (for analysis):</p>	<p>Interventions</p> <p>A: standard full inguinofemoral lymphadenectomy (IFL) + 66.7% of n received groin radiotherapy</p> <p>B: debulking of clinically involved lymph nodes + 89.5% of n received groin radiotherapy</p> <p>(C: Sentinel node removal procedure + 68.8% of n received groin radiotherapy)</p> <p>Analysis</p>	<p>Groin recurrence</p> <p>A: 13.3% (4/30)</p> <p>B: 15.8% (6/38)</p> <p>C: 25% (4/16)</p> <p>P=0.495</p> <p>IFL vs. debulking: RR= 0.84 (95% CI 0.26-2.72)</p> <p><b>Groin recurrence-free time</b> (Multivariate analysis)</p> <p>IFL vs. debulking: HR= 1.782 (95% CI 0.447-7.102)</p>	<p><b>General information</b></p> <p>Mean follow-up: 33.4 months (range: 0-146 months)</p> <p><b>Funding:</b> NR</p> <p><b>Col:</b> none declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective cohort study</p> <p>Populations comparable: NR</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Patients who received primary radiotherapy to the groins</p> <p>Enrolment period 2000-2012</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>Mean: all pts.: 70.8 (range: 35-94)</p> <p>Stage (FIGO, %), for all patients:</p> <p>III: 79.4%</p> <p>IV: 20.6%</p> <p>Location of the tumour; for all pts.:</p> <p>Midline: 22%</p> <p>Unilateral: 63.3%</p> <p>Bilateral: 8.8%</p> <p>Multifocal: 4.4%</p> <p>Not specified: 1.5%</p> <p>Tumour size (% , cm), for all pts.:</p> <p>≤ 2: 22.1%</p>	<p>Type of analysis: Cox regression</p> <p>Matching: NR</p> <p>Confounders: Adjusted for age</p>	<p>“The risk of groin recurrence was similar in all treatment groups.”</p>	<p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: yes</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: no</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: no</p> <p>Main cofounders taken into account: only age was adjusted for</p> <p>Confidence intervals reported: yes</p> <p>Selective reporting (comparison with protocol): NR</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	2.1-4: 39.7% >4: 38.2% Tumour depth (% mm), for all pts.: 1.0-4.0: 30.9% >4: 69.1% Lymph node metastases yes			

## Kapitel 8.3: Sentinel-Lymphonodektomie

### Kapitel 8.3.1: Indikation

#### Verknüpfte Empfehlungen:

#### Empfehlung 11.10:

Bei unifokalem Primärtumor mit < 4 cm Durchmesser und klinisch und bildgebend negativen Leistenlymphknoten soll die Sentinel-Lymphonodektomie für das operative Staging der Leistenlymphknoten eingesetzt werden, unter Beachtung der unter genannten Voraussetzungen.

Kann keine Sentinel-Lymphonodektomie durchgeführt werden oder gelingt keine Darstellung, soll eine systematische inguinofemorale Lymphonodektomie erfolgen.

**Literaturreferenzen:** [\[57\]](#), [\[58\]](#), [\[59\]](#), [\[60\]](#), [\[61\]](#)

[\[59\]](#)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Covens 2015 Systematic Review	Types of studies: SRs and individual studies (non-RCTs)  Searched from October 2011 to March 2013 and update search on September 2014	Question/ Aim:  This study aims to assess whether SLNB can safely be used as an alternative to inguinofemoral lymph node dissection (IFLD) to identify women with	3 SRs and 11 individual studies included (altogether 29 studies reporting detection rate, 35 studies reporting false negative rate, 23 studies reporting recurrence rate. (data	<b>Mortality</b> NR  <b>Recurrence rate in negative groin</b>  SLNB: rate of 0.03, 95% CI 0.02-0.04), 3.4% (1.8-5.4	Overall confidence in results of SR (AMSTAR-2): <i>“poor”</i>  PICO elements: no  A priori design: no  Justification for design: no	<u>Non-RCTs (NRS)</u>  C.F. Levenback, S. Ali, R.L. Coleman, <i>et al.</i> Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Databases: MEDLINE, Embase, Cochrane Database of Systematic Reviews,</p> <p>Exclusion criteria</p> <p>Case reports with fewer than 5 patients.</p> <p>Reports of only en- block ('butterfly incision') radical vulvectomy with concurrent bilateral lymphadenectomy.</p> <p>Studies where patients underwent vulvar/groin reconstructive procedures.</p> <p>Studies using coverings/foreign materials in the groin in all patients.</p>	<p>node-negative, early stage (FIGO stage T1 or T2, less than 4 cm) squamous cell cancer of the vulva.</p> <p>A: Sentinel lymph node biopsy (negative SLNB) (N=..)</p> <p>B: inguinofemoral lymph node dissection (negative IFLD divided into superficial and complete group) (N=..)</p>	<p>from 23 studies are relevant for this guideline PICO)</p> <p><b>Descriptive statistics:</b></p> <p>NR</p> <p>Age (median, range)</p> <p>NR</p> <p>Sex (% female)</p> <p>NR</p> <p>Location of the tumour</p> <p>NR</p> <p>Tumour size (% , cm)</p> <p>NR</p> <p>Tumour depth (% , mm)</p> <p>NR</p>	<p>Superficial IFLD: rate of 0.07, 95% CI 0.04- 0.09, 6.6% (4.4-9.0)</p> <p>Complete IFLD: rate of 0.01, 95% CI 0.00- 0.03, 1.4% (0.4-2.9)</p> <p>DFS</p> <p>NR</p> <p>Overall survival</p> <p>NR</p> <p><b>Additional outcome:</b> complication rates</p> <p>wound breakdown rate: A: 11.7%, B: 34%</p> <p>cellulitis: A: 4.5%, B: 21.3%</p> <p>lymphedema: A: 1.9%, B: 25.2%</p>	<p>Literature search &gt;= 2 databases, search strategy + other sources: yes</p> <p>Selection in duplicate: no</p> <p>Data extraction in duplicate: no</p> <p>List of excluded studies: no</p> <p>sufficient detail on studies: no</p> <p>RoB assessed: no</p> <p>Funding of incl. studies: no</p> <p>MA appropriate: na</p> <p>RoB considered in MA: na</p> <p>RoB in interpretation: na</p> <p>Heterogeneity explained: yes</p>	<p>vulva: a gynecologic oncology group study. J. Clin. Oncol., 30 (31) (2012)</p> <p>A. Garcia-Iglesias, M.O. Rodriguez- Martin, R. Ruano, <i>et al.</i> Sentinel node dissection in the treatment of early stages of vulvar cancer. Eur. J. Gynaecol. Oncol., 33 (2) (2012)</p> <p>M. Novackova, M.J. Halaska, H. Robova, <i>et al.</i> A prospective study in detection of lower-limb lymphedema and evaluation of quality of life after vulvar cancer surgery. Int. J. Gynecol. Cancer, 22 (6) (2012),</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>Studies of only stage 1A or clinically advanced/recurrent disease (clinical stage 3 or 4, or clinically involved lymph nodes).</p> <p>Studies with pregnant patients only, or with a specific focus on treatment of vulvar cancer in pregnancy.</p> <p>Studies on vulvar melanoma only.</p> <p>Studies including previously published patient data.</p> <p>Inclusion criteria:</p> <p>Studies were included if they contained the outcomes of interest, including:</p> <p>Detection rates for SLNB, defined as the</p>				<p>Publication bias investigated: no</p> <p>Sources of Col: yes</p>	<p>A.A. Soliman, M. Heubner, R. Kimmig, <i>et al.</i> Morbidity of inguinofemoral lymphadenectomy in vulval cancer. <i>ScientificWorldJournal</i>, 2012 (2012),</p> <p>J. Zekan, A. Mutvar, D. Huic, <i>et al.</i> Reliability of sentinel node assay in vulvar cancer: the first Croatian validation trial. <i>Gynecol. Oncol.</i>, 126 (1) (2012)</p> <p>R. Farrell, V. GebSKI, N.F. Hacker. Quality of life after complete lymphadenectomy for vulvar cancer: do women prefer sentinel lymph node biopsy? <i>Int. J. Gynecol. Cancer</i>, 24 (4) (2014)</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>number of groins where a SLN was identified divided by the number of groins evaluated</p> <p>False negative rates for SLNB, defined as the number of false negatives (FN) (negative SLN but metastatic lymph nodes present in the same groin on IFLD) divided by the number of true positives (TP) plus false negatives (FN / TP + FN)</p> <p>Complications of interest related to surgical evaluation of inguino-femoral lymph nodes by SLNB or IFLD, including wound infection or breakdown,</p>					<p>K. Robison, D. Roque, C. McCourt, <i>et al.</i> Long-term follow-up of vulvar cancer patients evaluated with sentinel lymph node biopsy alone. <i>Gynecol. Oncol.</i>, 133 (3) (2014)</p> <p>M. Underwood, J.K. Yap, A. Elattar, <i>et al.</i> The use of sentinel node sampling in vulval cancer. <i>J. Obstet. Gynaecol.</i>, 33 (8) (2013)</p> <p>A.G. Van der Zee, M.H. Oonk, J.A. De Hullu, <i>et al.</i> Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. <i>J. Clin. Oncol.</i>, 26 (6) (2008)</p> <p><u>3 systematic reviews</u></p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>lymphocysts, and/or lymphedema</p> <p>Reports of groin recurrence after negative IFLD or SLNB.</p>					<p>M. Hassanzade, M. Attaran, G. Treglia, <i>et al.</i> Lymphatic mapping and sentinel node biopsy in squamous cell carcinoma of the vulva: systematic review and meta-analysis of the literature. <i>Gynecol. Oncol.</i>, 130 (1) (2013)</p> <p>C. Meads, A.J. Sutton, A.N. Rosenthal, <i>et al.</i> Sentinel lymph node biopsy in vulval cancer: systematic review and meta-analysis. <i>Br. J. Cancer</i>, 110 (12) (2014)</p> <p>A. Wills, A. Obermair. A review of complications associated with the</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
						surgical treatment of vulvar cancer. Gynecol. Oncol., 131 (2) (2013)

## Kapitel 8.3.2: Weiterbehandlung bei SN-positiven Befunden

### Verknüpfte Empfehlungen:

#### Empfehlung 11.15:

Bei Nachweis minimaler Metastasierung in den Sentinel-Lymphknoten ( $\leq 2$  mm / isolierte Tumorzellen) sollte auf eine systematische inguinofemorale Lymphonodektomie zugunsten einer alleinigen Radiotherapie der betroffenen Leiste verzichtet werden.

#### Empfehlung 12.5:

Die postoperative Strahlentherapie der befallenen Leiste(n) soll bei Nachweis einer extrakapsulären Extension (ECE) und/oder fixierter bzw. exulzierter inguinaler Lymphknoten-Metastasen unabhängig von der Anzahl der Lymphknoten durchgeführt werden.

Literaturreferenzen: [\[62\]](#), [\[63\]](#), [\[64\]](#)

[\[65\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High à RCT	1 RCT (from SR van der Velden)	OS	/	/	-1 (population differs)	-3 (only few events and few participants: 13/52 pts and extreme wide Confidence intervals: RR 4.31, 95% CI 1.03-18.15)	The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis-benefit in the	⊕⊕⊕⊕ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High à RCT	1 RCT (from SR van der Velden)	Morbidity (lymphedema)	/	/	-1 (population differs)	-2 (only few events and few participants: 7/52 pts and wide Confidence intervals: RR 0.06, 95% CI 0.00-1.03)	radiotherapy group.  The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis-benefit in the radiotherapy group.	⊕⊕⊕⊕ Very low
High à RCT	1 RCT (from SR van der Velden)	Morbidity (life-threatening cardiovascular complications)	/	/	-1 (population differs)	-2 (only few events and few participants: 5/52 pts and wide Confidence intervals: RR 0.08, 95% CI 0.00-1.45)	The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis-benefit in the	⊕⊕⊕⊕ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High à RCT	1 RCT (from SR van der Velden)	Morbidity (length of hospitalization)	/	/	-1 (population differs)	-1 (only few participants: 52 pts)	radiotherapy group.  The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis-benefit in the radiotherapy group.	⊕⊕⊕⊖ Low
High à RCT	1 RCT (from SR van der Velden)	Groin Recurrence (unklar ob damit LK-Rezidive gemeint ist)	/	/	-1 (population differs)	-2 (only few events and few participants: 5/52 pts and very wide Confidence intervals: RR 3.70, 95% CI 0.87-15.80)	The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis-benefit in the	⊕⊕⊕⊖ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
							radiotherapy group.	

**Verknüpfte Empfehlungen:****Empfehlung 11.15:**

Bei Nachweis minimaler Metastasierung in den Sentinel-Lymphknoten ( $\leq 2$  mm / isolierte Tumorzellen) sollte auf eine systematische inguinofemorale Lymphonodektomie zugunsten einer alleinigen Radiotherapie der betroffenen Leiste verzichtet werden.

**Empfehlung 11.16:**

Wird im Sentinel-Lymphknoten eine Makrometastase nachgewiesen ( $> 2$  mm), soll auf der betroffenen Seite eine systematische inguinofemorale Lymphonodektomie erfolgen.

**Empfehlung 12.5:**

Die postoperative Strahlentherapie der befallenen Leiste(n) soll bei Nachweis einer extrakapsulären Extension (ECE) und/oder fixierter bzw. exulzierter inguinaler Lymphknoten-Metastasen unabhängig von der Anzahl der Lymphknoten durchgeführt werden.

**Literaturreferenzen:** [\[62\]](#), [\[63\]](#), [\[64\]](#)

[\[66\]](#)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Van der Velden, 2011 Systematic Review (ohne Meta-analyse)	Types of studies: RCT Searched from 1966 – July 2010 (They searched again in	Question/ Aim: To determine whether the effectiveness and safety of primary	1 study (RCT) on 52 pts with early squamous cell cancer of the vulva	Lymph nodes recurrence  NR	Overall confidence in results of SR (AMSTAR-2): “moderate”	Stehman FB, Bundy BN, Thomas G, Varia M, Okagaki T, Roberts J, et al. Groin

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>January 2016 and no additional trails were identified)</p> <p>Databases:</p> <p>Cochrane Gynaecological Cancer Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE</p> <p>Inclusion criteria</p> <p>RCTs and NRS</p> <p>Women diagnosed with early squamous cell carcinoma of the</p>	<p>radiotherapy to the inguinofemoral lymph nodes in early vulvar cancer is comparable with surgery.</p> <p>A: primary radiotherapy of the inguinofemoral lymph nodes (Primary Groin Radiotherapy): N=27</p> <p>B: inguinofemoral lymph node dissection (Primary Groin Surgery): N= 25</p>	<p><b>Descriptive statistics:</b></p> <p>Age (median, range)</p> <p>64 years</p> <p>Stage (nach FIGO, %)</p> <p>primary, previously untreated, squamous cell carcinoma of the vulva</p> <p>T1-3 N0-1 M0 (A radical vulvectomy had to suffice to remove the lesion; patients with T1 tumours were eligible only if there was vascular space involvement or if invasion &gt; 5 mm; no suspicious lymph</p>	<p>Groin Recurrence (unklar ob damit LK-Rezidive gemeint ist)</p> <p>A: 5/27</p> <p>B: 0/25</p> <p>RR: 10.21 (95% CI 0.59 to 175.78) in favour of B</p> <p>Morbidity</p> <p>à Lymphedema:</p> <p>A: 0/27</p> <p>B: 7/25</p> <p>RR 0.06, 95% CI 0.00 to 1.03 in favour of A</p> <p>à life-threatening cardiovascular complications:</p> <p>A: 0/27</p>	<p>PICO elements: yes</p> <p>A priori design: yes</p> <p>Justification for design: yes</p> <p>Literature search &gt;= 2 databases, search strategy + other sources: yes</p> <p>Selection in duplicate: yes</p> <p>Data extraction in duplicate: yes</p> <p>List of excluded studies: yes</p> <p>sufficient detail on studies: yes</p> <p>RoB assessed: yes</p> <p>Funding of incl. studies: no</p>	<p>dissection versus radiation in carcinoma of the vulva: a Gynecologic Oncology Group study. <i>International Journal of Radiation Oncology, Biology, Physics</i> 1992;24: 389-96.</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>vulva i.e. clinical T1 to T2 N0 M0</p> <p>Inguinal and femoral lymphadenectomy</p> <p>Radiotherapy of the groin (radiotherapy to a volume including the inguinal and femoral lymph nodes)</p>		<p>nodes (N0-1); no distant metastases)</p> <p>Location of the tumour</p> <p>A: Labia: 59,3%</p> <p>Clitoris: 18,5%</p> <p>Perineum: 6%</p> <p>B: Labia: 56%</p> <p>Clitoris: 24%</p> <p>Perineum: 12%</p> <p>Other: 8%</p> <p>Tumour size (% cm)</p> <p>A: &lt;2.0 cm: 11,1%</p> <p>2.1-4.0 cm: 70,4 %</p> <p>&gt; 4.1 cm: 18,5 %</p> <p>B: &lt;2.0 cm: 8%</p> <p>2.1-4.0 cm: 72%</p>	<p>B: 5/25</p> <p>RR 0.08, 95% CI 0.00 to 1.45 in favour of A</p> <p><i>à Hospital Stay:</i></p> <p>RR 0.28, 95% CI 0.13 to 0.58)</p> <p>DFS</p> <p>NR</p> <p>OS</p> <p>A: 10/27</p> <p>B: 3/25</p> <p>RR: 4.31 (95% CI 1.03 to 18.15) in favour of B</p> <p><b><u>Other outcomes:</u></b></p> <p>Disease-specific survival:</p> <p>A: 8/27</p>	<p>MA appropriate: NA</p> <p>RoB considered in MA: NA</p> <p>RoB in interpretation: yes</p> <p>Heterogeneity explained: NA</p> <p>Publication bias investigated: no</p> <p>Sources of Col: none</p> <p>Andere Bemerkugne:</p> <p>The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to perceived dis-benefit in the radiotherapy group. Radiotherapy was applied to a depth of</p>	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte (narrative oder gepoolte Meta- analyse)	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
			> 4.1 cm: 20 % Tumour depth (%, mm) ≤ 1.0: 1.01-2.5: 2.51-5.0: >5.0	B: 2/25 RR 3.70, 95% CI 0.87 to 15.80 in favour of B	3cm only. The mean depth of deeper groin nodes is estimated at 4.5- 6.1cm, therefore the radiotherapy dose used in this trial may have been insufficient for deep nodes.	

**Verknüpfte Empfehlungen:****Empfehlung 11.15:**

Bei Nachweis minimaler Metastasierung in den Sentinel-Lymphknoten ( $\leq 2$  mm / isolierte Tumorzellen) sollte auf eine systematische inguinofemorale Lymphonodektomie zugunsten einer alleinigen Radiotherapie der betroffenen Leiste verzichtet werden.

**Empfehlung 11.16:**

Wird im Sentinel-Lymphknoten eine Makrometastase nachgewiesen ( $> 2$  mm), soll auf der betroffenen Seite eine systematische inguinofemorale Lymphonodektomie erfolgen.

**Empfehlung 12.5:**

Die postoperative Strahlentherapie der befallenen Leiste(n) soll bei Nachweis einer extrakapsulären Extension (ECE) und/oder fixierter bzw. exulzierter inguinaler Lymphknoten-Metastasen unabhängig von der Anzahl der Lymphknoten durchgeführt werden.

**Literaturreferenzen:** [\[62\]](#), [\[63\]](#), [\[64\]](#)

[\[63\]](#), [\[Oonk, MHM et al. 2021\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
OonK 2021, prospective multicenter phase-II single-arm treatment trial Netherlands Trial Register (NTR608/ NL552)	1535 pts with early-stage squamous cell cancer of the vulva N=1213 had negative SN N=160 had micrometastases N=162 had macrometastases Inclusion criteria (for analysis):	Interventions àonly for SN positive patients (Group 1: micro and Group 2: macrometastases) A: SN biopsy with subsequent inguinofemoral radiotherapy (N=177) (126 in	èPatients With SN <u>Micrometastases <math>\leq 2</math> mm</u> (N=160) <b>Lymph node recurrence</b> NR <b>Ipsilateral groin recurrence</b> A: 3/126	<b>General information</b> Median follow-up: nr <b>Funding:</b> Roche, Genmab, Amgen, Oncinvent; AstraZeneca, AbbVie, Leo Pharma AB, Genentech/Roche, Clovis Oncology, Seattle Genetics, KCI, Tesaro, Genentech, FATE Therapeutics,

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>unifocal macroinvasive squamous cell carcinoma of the vulva &lt; 4 cm;</p> <p>preoperative imaging of groins (CT), magnetic resonance imaging, or ultrasound) showing no suspicious nodes (where inguinal nodes appeared suspicious in size [<math>&gt; 15</math> mm] or morphology, metastatic disease was ruled out by fine needle aspiration cytology);</p> <p>written informed consent</p> <p>Exclusion criteria (for analysis):</p> <p>Inoperable tumors and tumors with diameter &gt; 4cm</p> <p>Patients with inguino-femoral lymph nodes, at palpation clinically suspect for metastases, at radiology enlarged (<math>&gt;1.5</math> cm) / suspicious groin nodes and with cytologically proven inguino-femoral lymph node metastases</p>	<p>micrometastases, 51 in macrometastases)</p> <p>B: inguino-femoral lymphadenectomy (with or without radiotherapy) (N=121) (16 in micrometastases, 105 in macrometastases)</p> <p>C: SN biopsy and no further treatment(N=24) (18 in micrometastases, 6 in macrometastases)</p> <p>Analysis</p> <p>Type of analysis: competing-risk methods</p> <p>Matching: nr</p> <p>Confounders: NR</p>	<p>B: 1/16</p> <p>C: 2/18</p> <p>Radiotherapy versus no further treatment (A vs. C): HR, 0.11; 95% CI, 0.02 to 0.76)</p> <p>DFS</p> <p>NR</p> <p>Overall survival</p> <p>NR</p> <p><u>Patients With SN Macrometastases &gt; 2 mm (N=162)</u></p> <p><b>Lymph node recurrence</b></p> <p>NR</p> <p><b>Ipsilateral groin recurrence</b></p> <p>A: 11/51</p> <p>B: 7/105</p> <p>C: 1/6</p> <p>Per protocol analysis, radiotherapy versus IFL (A vs. B): HR, 3.2; 95% CI, 1.2 to 8.3</p>	<p>Morphotek, Bayer, Merck, Regeneron, GOG Partners Trial, Elekta, Varian Medical Systems</p> <p><b>Col:</b> further conflicts listed in the study</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: prospective multicenter phase-II single-arm treatment trial</p> <p>Populations comparable: no</p> <p>Rate of participation/Exclusions reported (selection bias into the study): no</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: nr</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: yes</p> <p>Outcome</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Patients with multifocal tumors</p> <p>Enrolment period</p> <p>December 2005 - October 2016</p> <p>Descriptive statistics</p> <p>Age (median, IQR)</p> <p>SN-negative: 66 (55-76)</p> <p>Micrometastases: 67 (55-77)</p> <p>Macrometastases: 65 (55-75)</p> <p>Stage (FIGO, %)</p> <p>nr</p> <p>Location of the tumour</p> <p>SN-negative:</p> <p>617 (50.9%) midline</p> <p>529 (43.6%) lateralized</p> <p>Mikrometastasen:</p> <p>85 (53.1%) midline</p> <p>68 (42.5%) lateralized</p> <p>Makrometastasen:</p> <p>103 (63.6%) midline</p> <p>68 (42.5%) lateralized</p>		<p>DFS</p> <p>NR</p> <p>Death of vulvar cancer</p> <p>A: 13/51 (25.5%)</p> <p>B: 24/105 (22.9%)</p> <p>Overall survival</p> <p>NR</p> <p>Narrative summary:</p> <p>“Inguinofemoral radiotherapy is a safe alternative for IFL in patients with SN micrometastases, with minimal morbidity. For patients with SN macrometastasis, radiotherapy with a total dose of 50 Gy resulted in more isolated groin recurrences compared with IFL.”</p>	<p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: nr (âlf not, Knowledge of exposure status likely to influence the outcome?): yes</p> <p>Main cofounders taken into account: no</p> <p>Confidence intervals reported: yes</p> <p>Selective reporting (comparison with protocol): no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Tumour size (median, IQR)  SN-negative: 18 mm (10-25)</p> <p>Mikrometastasen: 23.2 mm (15-30)</p> <p>Makrometastasen: 25 mm (15-30)</p> <p>Tumour depth of invasion (median, IQR)  SN-negative: 2.1 mm (1.5-4)</p> <p>Mikrometastasen: 3.5 mm (1.7-4)</p> <p>Makrometastasen: 2.9 mm (15-30)</p> <p>Treatments of 3 groups:  à SN-negative:  à Patients With SN  Micrometastases ≤ 2 mm (N=160)</p> <p>126 (78.8%): inguinofemoral radiotherapy (81 bilateral, 38 unilateral, 7 unknown)</p> <p>16 (10%): IFL</p>			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>18 (11.3%) no further treatment)</p> <p>à Patients With SN Macrometastases &gt; 2 mm (N=162)</p> <p>51: radiotherapy to the groins (39 bilateral, 8 unilateral, 4 unknown)</p> <p>105 (64.8%): IFL</p> <p>6: no further treatment after SN removal</p>			
Oonk 2010, prospective multicentre observational study (GROINSS-V)	<p>403 pts with early stage squamous cell cancer of the vulva. N=135 (33%) original pathological assessment showed metastatic disease in one or more sentinel nodes. (positive SN)</p> <p>Inclusion criteria (for analysis): diameter &lt;4 cm, T1-T2</p> <p>Exclusion criteria (for analysis): nr</p>	<p>Interventions</p> <p>Note: Treatment consisted of excision of the primary tumour and the sentinel-node procedure (using radioactive tracer and blue dye). In case of a positive sentinel node, the protocol specified inguinofemoral lymphadenectomy by separate incisions</p> <p>A: inguinofemoral lymphadenectomy (N=115)</p>	<p><b>Lymph node recurrence</b></p> <p>NR</p> <p><b>Groin recurrence rate</b></p> <p>NR</p> <p>DFS</p> <p>NR</p> <p>Overall survival</p> <p>NR</p>	<p><b>General information</b></p> <p>Median follow-up: median follow-up: 31 months (range 0–109), updated until January 2009</p> <p><b>Funding:</b> no funding source</p> <p><b>Col:</b> none declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: prospective multicentre observational study</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Enrolment period 2000 - 2006</p> <p>Descriptive statistics (for N=135)</p> <p>Age</p> <p>≤70 years: 59 (43%), &gt;70 years: 76 (56%)</p> <p>Location of the tumour</p> <p>42 (31%) Lateralised, 93 (69%) midline</p> <p>Diameter of primary tumour.</p> <p>≤2 · 0 cm (T1): 46 (34%), &gt;2 · 0 cm (T2): 87 (64%), Unknown: 2 (1%)</p> <p>Tumour depth (% , mm)</p> <p>62 (46%) ≤5 · 0 mm, 63 (47%) &gt;5 · 0 mm</p> <p>Unilaterally or bilaterally positive SN</p> <p>106 (79%) Unilateral,</p>	<p>(85%) of 135 patients with positive sentinel nodes)</p> <p>B: radiotherapy to the groins instead of lymphadenectomy (N=14)</p> <p>C: no treatment (N=6)</p> <p>èNo comparison made between different treatment groups</p> <p>Analysis</p> <p>Type of analysis: Kaplan-Meier method</p> <p>Matching: nr</p> <p>Confounders: nr</p>		<p>Populations comparable: na</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: yes</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: nr</p> <p>Outcome</p> <p>Outcome measure is well- defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: nr (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account: no</p> <p>Confidence intervals reported: no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	29 (21%) Bilateral Additional treatments			Selective reporting (comparison with protocol): nr
	115 (85%) Inguinofemoral lymphadenectomy			
	29% Unilateral			
	71% Bilateral			
	14 (10%) Radiotherapy			
	6 (4%) No additional treatment			

**Verknüpfte Empfehlungen:****Empfehlung 11.16:**

Wird im Sentinel-Lymphknoten eine Makrometastase nachgewiesen (> 2 mm), soll auf der betroffenen Seite eine systematische inguinofemorale Lymphonodektomie erfolgen.

**Empfehlung 12.5:**

Die postoperative Strahlentherapie der befallenen Leiste(n) soll bei Nachweis einer extrakapsulären Extension (ECE) und/oder fixierter bzw. exulzierter inguinaler Lymphknoten-Metastasen unabhängig von der Anzahl der Lymphknoten durchgeführt werden.

**Literaturreferenzen:** [\[62\]](#), [\[63\]](#), [\[58\]](#), [\[64\]](#), [\[46\]](#)

[Oonk, MHM et al. 2021]

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort	1 prospective multicenter phase-II single-arm treatment trial	Ipsilateral groin recurrence	/	/	/	-2 (only few events and few participants: 17/156 pts and very wide Confidence intervals: HR, 3.2; 95% CI, 1.2 to 8.3)		⊕⊕⊕⊕ Very low

## Kapitel 8.3.3: Kontralaterales Vorgehen bei einseitig positivem Sentinellymphknoten

### Verknüpfte Empfehlungen:

#### Empfehlung 11.17:

Bei nur einseitig positivem Sentinellymphknoten nach bilateraler Sentinel-Lymphonodektomie kann auf die systematische inguinofemorale Lymphonodektomie der kontralateralen Seite in Abwägung mit der individuellen Risikosituation der Patientin unter Berücksichtigung evtl. Komorbiditäten und des leicht erhöhten kontralateralen Leistenrezidivrisikos verzichtet werden.

**Literaturreferenzen:** [\[62\]](#), [\[67\]](#), [\[68\]](#), [\[69\]](#), [\[70\]](#), [\[71\]](#), [\[72\]](#)

[\[72\]](#), [\[67\]](#), [\[68\]](#), [\[71\]](#), [\[69\]](#), [\[70\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Gonzales Bosquet, 2007 retrospective study	320 pts with primary squamous cell carcinoma (SCC) of the vulva (More than 95% percent of the patients included in this study underwent bilateral inguinofemoral lymphadenectomy)  Inclusion criteria (for analysis): complete surgical staging for SCC of the vulva (defined as vulvar radical treatment of the primary lesion with either bilateral groin lymphadenectomy or only ipsilateral inguinofemoral	Interventions  There was no comparison in this study: “more than 95% percent of the patients included in this study underwent bilateral inguinofemoral lymphadenectomy” and staging was an inclusion criteria for the study population.  Analysis  Type of analysis: univariate and multivariate logistic regression models	<b>Groin recurrence rate / groin recurrence-free</b>  A: NR B: NA  DFS A: NR B: NR  Overall survival A: NR B: NR	<b>General information</b>  Median follow-up: NA  <b>Funding:</b> NR  <b>Col:</b> NR  Risk of bias considerations (adapted from SIGN cohort study checklist)  Study type: retrospective study  Populations comparable: NA  Rate of participation/Exclusions reported (selection bias into the study): NA

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	lymphadenectomy when these nodes were negatives) information of the exact location of the primary vulvar lesion Exclusion criteria (for analysis): nr Enrolment period 1955-1990 Descriptive statistics Age NR Stage (FIGO, %) nr Location of the tumour <b>Unilateral lesion: N=163 patients</b> bilateral lesions: N=75 pts. midline lesions: N=40 pts. mediolateral lesions: N=42 pts. LN involvement: +LN	Matching: NR Confounders: NR		Exposure/Intervention Assessment reliable: yes Assessed more than once: nr Possibly affected by knowledge of outcome status?: yes Drop-out rate & reasons reported: yes Outcome Outcome measure is well-defined, valid and reliable: no Blind outcome assessment to exposure: no (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>à among 163 pts. with unilateral</p> <p>37/163 (22.7%): ipsilateral groin involvement</p> <p>3/163 (1.8%): contralateral positive LN</p> <p>8/163 (4.9%) bilateral LN invasion</p> <p>à among 75 pts. with bilateral</p> <p>14/75 (18.7%): ipsilateral groin involvement</p> <p>0 contralateral positive LN</p> <p>13/75 (17.3%) bilateral LN invasion</p> <p>LN involvement: -LN</p> <p>à among 163 pts. with unilateral</p> <p>115/163 (70.6%)</p> <p>à among 75 pts. with bilateral</p> <p>48/75 (64%)</p> <p>Inguinofemoral LN involvement</p> <p>à among 163 pts. with unilateral</p>			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>48/163 in unilateral</p> <p>Tumour size (among Inguinofemoral LN involvement)</p> <p>N=80/150 (53%) ≤ 2 cm, N=70/150 (47%) &gt; 2 cm</p> <p>Tumour depth (among Inguinofemoral LN involvement)</p> <p>N=89/144 (62%) ≤ 5 mm, N=55/144 (38%) &gt; 5 mm</p>			
<p>Van der Kolk, 2022, Kohortenstudie (prospective multicenter study)</p>	<p>1898pts (data from GROINSS-V I and II cohort studies) with squamous cell cancer of the vulva (N=366 women with unilateral metastatic SN)</p> <p>Inclusion criteria (for analysis):</p> <p>unifocal VSCC &lt;4 cm</p> <p><b>Exclusion criteria (for analysis):</b></p> <p>suspicious groin nodes at palpation or at imaging</p> <p>Enrolment period</p>	<p>Interventions</p> <p>Only among Women with unilateral metastatic SN (n = 366)</p> <p>A: unilateral IFL (N=70)</p> <p>B: no additional groin treatment (N=24)</p> <p>C: bilateral IFL (N=105)</p> <p>(D: unilateral radiotherapy (N=45))</p> <p>(E: bilateral radiotherapy (N=122))</p>	<p><b>Contralateral groin recurrence</b></p> <p>A: 2/70 (2.9%), 95% CI 1.4%-5.8%</p> <p>B: 0/24 (0%)</p> <p>(D: 0/45 (0%))</p> <p>(E: 1/122 (0.8%))</p> <p>Contralateral (non-SN) groin metastases</p> <p>C: 5/105 (4.8%)</p> <p>DFS</p>	<p><b>General information</b></p> <p>Median follow-up: nr (until at least 2 years after primary treatment)</p> <p><b>Funding:</b> Dutch Cancer Society</p> <p><b>Col:</b> nr</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: cohort study (prospective multicenter studies)</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>enrolment: 2000-2006 and study conducted: 2005 to 2016</p> <p>Descriptive statistics</p> <p>Age (mean, SD)</p> <p>65.2 years (+/- 14.3)</p> <p>Location of the tumour</p> <p>723 (38.1%) Lateralized tumor</p> <p>530 (27.9%) Near midline tumor</p> <p>645 (34.0%) True midline tumor</p> <p>Tumour size</p> <p>1.991 cm (SD=1.046)</p> <p>Tumour depth</p> <p>3.81 mm (SD= 4.20)</p> <p>Lymph node metastases (yes, %)</p> <p>441 (23.2%),</p> <p>Among whom 366 (83.0%) had unilateral metastatic SN and 75 (17.0%) had bilateral</p>	<p>Analysis</p> <p>Type of analysis: frequencies, One Way ANOVA</p> <p>Matching: nr</p> <p>Confounders: nr</p>	<p>Nr</p> <p>Overall survival</p> <p>Nr</p> <p>Narrative summary:</p> <p>“The rate of contralateral non-SN metastases/groin recurrences in patients with unilateral SN-involvement who underwent a successful SN biopsy is low (2.9%), with a relatively narrow confidence interval [95% CI: 1.4%-5.8%]. Accordingly, we consider unilateral groin treatment by either IFL or inguinofemoral radiotherapy safe.”</p>	<p>Populations comparable: na</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: unclear</p> <p>Assessed more than once: NR</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: nr</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account: no</p> <p>Confidence intervals reported: yes</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
				Selective reporting (comparison with protocol): nr
Ignatov, 2021, multicenter retrospective registry-based study	<p>202 pts (among 476 pts assessed) with squamous cell cancer of the vulva included in the analysis (N=62 received contralateral lymphadenectomy)</p> <p>Inclusion criteria (for analysis): squamous and adenosquamous vulvar cancer</p> <p>Exclusion criteria (for analysis): no SLN biopsy missing information regarding lymphadenectomy basaloid carcinoma negative SLN bilateral SLN metastases no contralateral lymphadenectomy despite of unilateral SLN metastases</p> <p>Enrolment period</p>	<p>Interventions</p> <p>Only among 66 patients with unilateral metastatic SLN</p> <p>A: contralateral IFL (N=62) (18 after unilateral and 44 after bilateral SLN biopsy)</p> <p>Analysis</p> <p>Type of analysis: frequencies</p> <p>Matching: nr</p> <p>Confounders: nr</p>	<p><b>Groin recurrence rate</b></p> <p>nr</p> <p>DFS</p> <p>nr</p> <p>Overall survival</p> <p>nr</p> <p><b>Narrative summary:</b></p> <p>“The risk of contralateral LN metastases in patients with unilateral SLN metastases is low. However, the limitations do not allow us to draw general conclusions, whether contralateral lymphadenectomy should be performed or not. Further studies are needed.”</p>	<p><b>General information</b></p> <p>Median follow-up: 35 months (range 1–114 months)</p> <p><b>Funding:</b> nr</p> <p><b>Col:</b> none</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: multicenter retrospective registry-based study</p> <p>Populations comparable: na</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: nr</p> <p>Possibly affected by knowledge of outcome status?: no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	January 2000 - September 2017 Descriptive statistics Age, mean (range) Lymph nodes positive: 75 (33-95) LN negative: 72 (34-91) Location of the tumour nr Tumour size nr Tumour depth (% , mm) nr			Drop-out rate & reasons reported: yes Outcome Outcome measure is well-defined, valid and reliable: yes Blind outcome assessment to exposure: no (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): nr
Wölber, 2016	140 pts with squamous cell cancer of the vulva Inclusion criteria (for analysis): a successful SLN dissection with radioactive tracer ± blue dye Informed consent	Interventions A*: unilateral lymphadenectomy LAE despite negative SLNs (n = 7) A**: bilateral lymphadenectomy LAE despite negative SLNs (n = 5)	<b>Groin recurrence</b> B*: 0/4 Other: nr DFS nr Overall survival	<b>General information</b> Median follow-up: 29 months <b>Funding:</b> internal departmental sources (University Medical Center Hamburg-Eppendorf) <b>Col:</b> none

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Exclusion criteria (for analysis): nr	B*: positive unilateral/bilateral SLN and consecutive unilateral (n = 4)	nr	Risk of bias considerations (adapted from SIGN cohort study checklist)
	Enrolment period 2001 – 2013	B**: positive unilateral/bilateral SLN and consecutive bilateral lymphadenectomy LAE (n = 37)	<b>Narrative summary:</b> “In case of bilateral SLN biopsy for clinically node-negative disease and only unilaterally positive SLN, the risk for contralateral non-SLN metastases appears to be low. These data support the omission of contralateral LAE to reduce surgical morbidity.”	Study type: retrospective Kohortenstudie
	Descriptive statistics Age, median (range) 57 years (range 20–87)	C: negative unilateral/bilateral SLN <b>without further LAE</b> (N= 84)		Populations comparable: unclear
	Median tumour diameter (mm, range) 17.5 (1–75)	Analysis Type of analysis: Multivariate logistic regression		Rate of participation/Exclusions reported (selection bias into the study): yes
	Median tumour depth (mm, range) 3 (0.4–27)	Matching: nr Confounders: nr		Exposure/Intervention Assessment reliable: yes
	Recurrence localisation 18 Vulva, (12 N-, 6 N+), 4 groin (1 N-, 3 N+)			Assessed more than once: nr Possibly affected by knowledge of outcome status?: no Drop-out rate & reasons reported: no Outcome Outcome measure is well-defined, valid and reliable: no Blind outcome assessment to exposure: nr (àlf not, Knowledge of exposure status

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
				likely to influence the outcome?: ) : no Main cofounders taken into account: no Confidence intervals reported: no Selective reporting (comparison with protocol): nr
Winarno, 2021, retrospective single-center analysis	51 with positive SLNB (from 420 pts with bilateral SLNB of the GROINSS-V study) and squamous cell cancer of the vulva  Inclusion criteria (for analysis): Stage IB, II VC; tumor size less than 6 cm without suspicious groin LN clinically  Exclusion criteria (for analysis): negative metastasis of SLNB; multifocality; tumor size above 4 cm with highly suspicious groin LN and	Interventions  1. With ipsi-unilateral IF-L (SLNB metastasis) (N=12)  2a/b. Undergo Bilateral IFL (neg/neg IFL) (N=14)  2c. Undergo Bilateral IFL (pos contralateral IFL) (N=4)  Analysis  Type of analysis: frequencies  Matching: nr  Cofounders: nr	<b>Groin recurrence rate</b>  1: 1/12 (8.3%) 2a/b: 0/14 2c: 0/4  <b>Groin recurrence rate</b>  1: 1/12 (8.3%) 2a/b: 1/14 (7.1%) 2c: 1/4 (25%)  DFS nr  Overall survival  1: 90.9%	<b>General information</b>  Median follow-up: nr  <b>Funding:</b> Open Access funding enabled and organized by Projekt DEAL  <b>Col:</b> none  Risk of bias considerations (adapted from SIGN cohort study checklist)  Study type: retrospective single-center analysis  Populations comparable: NA  Rate of participation/Exclusions reported (selection bias into the study): na

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>distant metastasis at initial diagnosis;</p> <p>consent refusal of the patients due to the potential increased risks of groin recurrence</p> <p>Enrolment period</p> <p>2002-2018</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>1. With ipsi-unilateral IF-L (SLNB metastasis) (N=12): 50 (28-79)</p> <p>2a/b. Undergo Bilateral IFL (neg/neg IFL) (N=14): 52.5 (27-82)</p> <p>2c. Undergo Bilateral IFL (pos contralateral IFL) (N=4): 55 (51-67)</p> <p>Location of the tumour</p> <p>1: 9 (75%) midline, 3 (25%) lateralized,</p> <p>2a/b: 11 (78.6%) midline, 3 (21.4%) lateralized</p> <p>2c: 4 (100%), 0 lateralized</p>		<p>2a/b: 80%</p> <p>2c: 75%</p> <p><b>Narrative Summary:</b></p> <p>“Current guideline for bilateral IFL should remain as the standard management. Therefore, this depth may be taken into account as an indication for bilateral IFL. The management of VC and SLNB should be performed in a high volume center with an experienced team in marking SLN and performing the adequate surgical procedure. Well conducted counseling of the patients outlining advantages but also potential oncological risks of this technique especially concerning rate of groin recurrence is critical.”</p>	<p>Exposure/Intervention</p> <p>Assessment reliable: unclear</p> <p>Assessed more than once: nr</p> <p>Possibly affected by knowledge of outcome status?: yes</p> <p>Drop-out rate &amp; reasons reported: no</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account: no</p> <p>Confidence intervals reported: no</p> <p>Selective reporting (comparison with protocol): nr</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Tumour size (Diameter)</p> <p>1: 7 (58.3%) &lt;20 mm, 3 (25%) ≥20 mm but&lt;40 mm, 2 (16.7%) ≥40 mm,</p> <p>2a/b: 7 (50%) &lt;20 mm, 5 (35.7%) ≥20 mm but&lt;40 mm, 2 (14.3%) ≥40 mm</p> <p>2c: 1 (25%) &lt;20 mm, 3 (75%) ≥20 mm but&lt;40 mm</p> <p>Tumour depth (median, range)</p> <p>1: 3.0 (1.8–6.0),</p> <p>2a/b: 6.0 (2.0–15.0)</p> <p>2c: 8.5 (5.0–23.0)</p>			
Nica, 2019, retrospective observational cohort study	<p>159 pts with squamous cell cancer of the vulva (N=39 with positive SLN)</p> <p>Inclusion criteria (for analysis):</p> <p>Patients with any primary tumor size, including multifocal disease</p> <p>Exclusion criteria (for analysis):</p> <p>NR</p>	<p>Interventions</p> <p>A: unilateral IFL (groin dissection) (N=9)</p> <p>B: bilateral IFL (groin dissection) (N=19)</p> <p>Analysis</p> <p>Type of analysis:</p> <p>Matching: nr</p>	<p><b>Contralateral groin recurrence</b></p> <p>A: 0/9</p> <p>B: 2/19 (5%)</p> <p>DFS</p> <p>nr</p> <p>Overall survival</p> <p>nr</p>	<p><b>General information</b></p> <p>Median follow-up: 31 months</p> <p><b>Funding:</b> nr</p> <p><b>Col:</b> none declared</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective observational cohort study</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Enrolment period 2008–2015</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>Positive SLN: 69.0 years (48.0–94.0)</p> <p>Location of the tumour</p> <p>Positive SLN: 22 (57.9%) midline, 16 (42.1%) lateralized</p> <p>Tumour size (diameter)</p> <p>Positive SLN: 16 (44.4%) &lt;20mm;</p> <p>Positive SLN: 13 (36.1%) ≥20 but &lt;40mm;</p> <p>Positive SLN: 7 (19.5%) ≥40mm</p> <p>Tumour depth (median, range)</p> <p>Positive SLN: 5.5 mm (0.5–20.0)</p>	<p>Confounders: nr</p>	<p><b>Narrative Summary:</b></p> <p>“These data suggest it is reasonable to omit a full groin dissection for micrometastatic disease in the SLN, and to perform a unilateral groin dissection in patients with unilateral SLN metastasis. SLN alone in larger tumors may have a higher groin recurrence rate.”</p>	<p>Populations comparable: unclear</p> <p>Rate of participation/Exclusions reported (selection bias into the study): na</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: nr</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: yes</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p> <p>Blind outcome assessment to exposure: nr (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no</p> <p>Main cofounders taken into account: no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
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Confidence intervals reported:  
no

Selective reporting (comparison  
with protocol): nr

## Kapitel 8.4: Pelvine Lymphknoten

### Kapitel 8.4.1: Indikation zur Behandlung

#### Verknüpfte Empfehlungen:

##### **Empfehlung 11.18:**

Finden sich in der Leiste  $\geq 3$  Lymphknotenmetastasen oder  $\geq 2$  Lymphknotenmetastasen  $\geq 5$  mm, dann sollen die pelvinen Lymphknoten dieser Seite einem operativen Staging unterzogen oder in die adjuvante Radio(chemo)therapie einbezogen werden.

Bei Patientinnen, bei denen in der Leiste eine große Einzelmetastase (in der Regel  $\geq 10$  mm) und/oder ein extrakapsuläres Tumorwachstum der Lymphknotenmetastasen vorliegt, sollten die pelvinen Lymphknoten dieser Seite einem operativen Staging unterzogen oder in die adjuvante Radio(chemo)therapie einbezogen werden.

##### **Empfehlung 12.7:**

Bei Nachweis minimaler Metastasierung in den Sentinel-Lymphknoten ( $\leq 2$  mm / isolierte Tumorzellen) sollte auf eine Lymphonodektomie zugunsten einer alleinigen Bestrahlung der betroffenen Leiste verzichtet werden.

##### **Empfehlung 12.9:**

Finden sich in der Leiste  $\geq 3$  Lymphknotenmetastasen  $< 5$  mm oder  $\geq 2$  Lymphknotenmetastasen  $\geq 5$  mm, dann soll die pelvine Strahlentherapie durchgeführt werden, auch wenn kein operatives pelvines Staging erfolgt.

**Literaturreferenzen:** [\[67\]](#), [\[73\]](#), [\[74\]](#), [\[75\]](#), [\[76\]](#), [\[77\]](#), [\[78\]](#), [\[79\]](#), [\[80\]](#), [\[81\]](#)

[\[80\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High	1 RCT	Groin recurrence	/	/	-2 (population of the study might not exactly represent population of the PICO) (intervention does not exactly represent the intervention of the PICO)	-1 (only few events and participants: 16/111 pts)		⊕⊕⊕⊕ Very low
High	1 RCT	Overall survival	/	/	-2 (population of the study might not exactly represent population of the PICO) (intervention does not exactly represent the intervention of the PICO)	-1 (only few participants: 111)	.	⊕⊕⊕⊕ Very low



**Verknüpfte Empfehlungen:****Empfehlung 11.18:**

Finden sich in der Leiste  $\geq 3$  Lymphknotenmetastasen oder  $\geq 2$  Lymphknotenmetastasen  $\geq 5$  mm, dann sollen die pelvinen Lymphknoten dieser Seite einem operativen Staging unterzogen oder in die adjuvante Radio(chemo)therapie einbezogen werden.

Bei Patientinnen, bei denen in der Leiste eine große Einzelmetastase (in der Regel  $\geq 10$  mm) und/oder ein extrakapsuläres Tumorwachstum der Lymphknotenmetastasen vorliegt, sollten die pelvinen Lymphknoten dieser Seite einem operativen Staging unterzogen oder in die adjuvante Radio(chemo)therapie einbezogen werden.

**Empfehlung 12.7:**

Bei Nachweis minimaler Metastasierung in den Sentinel-Lymphknoten ( $\leq 2$  mm / isolierte Tumorzellen) sollte auf eine Lymphonodektomie zugunsten einer alleinigen Bestrahlung der betroffenen Leiste verzichtet werden.

**Empfehlung 12.9:**

Finden sich in der Leiste  $\geq 3$  Lymphknotenmetastasen  $< 5$  mm oder  $\geq 2$  Lymphknotenmetastasen  $\geq 5$  mm, dann soll die pelvine Strahlentherapie durchgeführt werden, auch wenn kein operatives pelvines Staging erfolgt.

**Literaturreferenzen:** [\[67\]](#), [\[73\]](#), [\[74\]](#), [\[75\]](#), [\[76\]](#), [\[77\]](#), [\[78\]](#), [\[79\]](#), [\[80\]](#), [\[81\]](#)

[\[80\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Kunos 2009, RCT	n=114 patients with primary invasive squamous cell carcinoma of the vulva Inclusion criteria (for analysis):	Interventions A: Pelvic and groin radiation B: Ipsilateral pelvic node resection	Recurrence free survival HR=0.39 (95% CI 0,17-0,88; p=0,02) in favour of A àRecurrence at any site	Kunos 2009, RCT

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>primary invasive squamous cell carcinoma of the vulva</p> <p>unilateral or bilateral groin metastasis</p> <p>primary lesions and groin nodes were amenable to radical vulvectomy and bilateral inguinal lymphadenectomy</p> <p>Exclusion criteria (for analysis):</p> <p>vulvar cancer recurrence</p> <p>prior malignancies</p> <p>positive groin nodes not resected at surgery</p> <p>Enrolment period</p> <p>1977 to 1984</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>median age A &amp; B: 70 years</p> <p>Stage (FIGO, %)</p> <p>A:</p> <p>NO/N1: 47%</p>	<p>Analysis</p> <p>Type of analysis: Cox proportional hazards models adjusted for age and adverse tumor characteristics</p>	<p>A: 21/57</p> <p>B: 27/54</p> <p>à Groin Recurrence</p> <p>A: 3/57</p> <p>B: 13/54</p> <p>RR=0.22 (95% CI 0.07 to 0.73)</p> <p>6-year overall survival (all-cause death)</p> <p>HR=0.61, (95% CI 0.30-1.3, P=0.02), in favour of A</p> <p>“Six-year overall survival benefit for radiation in patients with clinically suspected or fixed ulcerated groin nodes (P=.004) and two or more positive groin nodes (P&lt;.001) persisted”</p> <p>àAfter adjusting for age, treatment, and tumor characteristics, the hazard ratio of overall death in patients with 20% positive groin nodes was 3.9 (95% CI 2.1-7.4, P&lt;.001), favoring radiation.</p>	

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>N2: 37%</p> <p>N3: 15%</p> <p>B:</p> <p>N0/N1: 35%</p> <p>N2: 45%</p> <p>N3: 18%</p> <p>Location of the tumour</p> <p>NR</p> <p>Tumour size (% , cm)</p> <p>NR</p> <p>Tumour depth (% , mm)</p> <p>NR</p> <p>Lymph node metastases (yes, %)</p> <p>A:</p> <p>Single groin lymph node metastasis: 32%</p> <p>Two groin lymph node metastases: 27%</p> <p>Three or more groin lymph node metastases: 41%</p>		<p>6-years cancer-related death rate</p> <p>A: 18/57</p> <p>B: 28/54</p> <p>HR= 0.49, (95% CI 0.28–0.87, P=015)in favour of A</p>	

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	B: Single groin lymph node metastasis: 38% Two groin lymph node metastases: 16% Three or more groin lymph node metastases: 45%			

## Kapitel 9: Strahlentherapie

### Kapitel 9.1: Postoperative adjuvante Strahlentherapie

#### Kapitel 9.1.1: Postoperative adjuvante Strahlentherapie der inguinalen Lymphabflusswege

##### Verknüpfte Empfehlungen:

##### Empfehlung 12.4:

Die postoperative Strahlentherapie der befallenen Leiste(n) nach systematischer inguinofemorale Lymphonodektomie soll bei  $\geq 2$  befallenen inguinofemorale Lymphknoten unabhängig von der Größe der Metastasen durchgeführt werden.

Literaturreferenzen: [\[73\]](#), [\[82\]](#), [\[78\]](#), [\[80\]](#)

[\[80\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High	1 RCT (most recent)	Groin recurrence	/	/	-2 (population of the study might not exactly represent population of the PICO) (intervention does not exactly)	-1 (only few events and participants: 16/111 pts)		⊕⊕⊕⊕ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
					represent the intervention of the PICO)			
High	1 RCT (most recent)	Overall survival	/	/	-2 (population of the study might not exactly represent population of the PICO) (intervention does not exactly represent the intervention of the PICO)	-2 (only few participants: 111)	.	⊕⊕⊕⊕ Very low

Note: The two identified RCTs were not pooled, as they included very heterogeneous results and populations and the intervention was not exactly the same. Therefore, only Kunos 2009 was included in the GRADE overview tables, as this was the most recent study.

**Verknüpfte Empfehlungen:****Empfehlung 12.4:**

Die postoperative Strahlentherapie der befallenen Leiste(n) nach systematischer inguinofemoraler Lymphonodektomie soll bei  $\geq 2$  befallenen inguinofemorale Lymphknoten unabhängig von der Größe der Metastasen durchgeführt werden.

**Literaturreferenzen:** [73], [82], [78], [80]

[80], [83]

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Kunos 2009, RCT	<p>n=114 patients with primary invasive squamous cell carcinoma of the vulva</p> <p>Inclusion criteria (for analysis):</p> <p>primary invasive squamous cell carcinoma of the vulva</p> <p>unilateral or bilateral groin metastasis</p> <p>primary lesions and groin nodes were amenable to radical vulvectomy and bilateral inguinal lymphadenectomy</p> <p>Exclusion criteria (for analysis):</p> <p>vulvar cancer recurrence</p> <p>prior malignancies</p>	<p>Interventions</p> <p>A: Pelvic and groin radiation</p> <p>B: Ipsilateral pelvic node resection</p> <p>Analysis</p> <p>Type of analysis: Cox proportional hazards models adjusted for age and adverse tumor characteristics</p>	<p>Recurrence free survival</p> <p>HR=0.39 (95% CI 0,17-0,88; p=0,02) in favour of A</p> <p>à Recurrence at any site</p> <p>A: 21/57</p> <p>B: 27/54</p> <p>à Groin Recurrence</p> <p>A: 3/57</p> <p>B: 13/54</p> <p>RR=0.22 (95% CI 0.07 to 0.73)</p> <p>6-year overall survival (all-cause death)</p>	<p><b>General information</b></p> <p>Follow-up: 74 months</p> <p><b>Funding:</b> NR</p> <p><b>Col:</b> Authors did not report any potential conflicts of interest</p> <p>Risk of bias considerations (ROB1)</p> <p>Analyse ITT: low ROB</p> <p>Random sequence generation (selection bias): unclear ROB, not described</p> <p>Allocation concealment (selection bias): unclear ROB, not described</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>positive groin nodes not resected at surgery</p> <p>Enrolment period 1977 to 1984</p> <p>Descriptive statistics</p> <p>Age (median, range) median age A &amp; B: 70 years</p> <p>Stage (FIGO, %)</p> <p>A:</p> <p>N0/N1: 47%</p> <p>N2: 37%</p> <p>N3: 15%</p> <p>B:</p> <p>N0/N1: 35%</p> <p>N2: 45%</p> <p>N3: 18%</p> <p>Location of the tumour</p> <p>NR</p> <p>Tumour size (% , cm)</p> <p>NR</p>		<p>HR=0.61, (95% CI 0.30-1.3, P=0.02), in favour of A</p> <p>“Six-year overall survival benefit for radiation in patients with clinically suspected or fixed ulcerated groin nodes (P=.004) and two or more positive groin nodes (P&lt;.001) persisted”</p> <p>àAfter adjusting for age, treatment, and tumor characteristics, the hazard ratio of overall death in patients with 20% positive groin nodes was 3.9 (95% CI 2.1-7.4, P&lt;.001), favoring radiation.</p> <p>6-years cancer-related death rate</p> <p>A: 18/57</p> <p>B: 28/54</p> <p>HR= 0.49, (95% CI 0.28-0.87, P=0.015)in favour of A</p>	<p>Blinding (performance bias and detection bias): unclear ROB, not described.</p> <p>Incomplete outcome data (attrition bias): low ROB</p> <p>Selective reporting (reporting bias): unclear ROB</p> <p><b>Other limitations or comments:</b> no</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Tumour depth (% , mm) NR Lymph node metastases (yes, %) A: Single groin lymph node metastasis: 32% Two groin lymph node metastases: 27% Three or more groin lymph node metastases: 41% B: Single groin lymph node metastasis: 38% Two groin lymph node metastases: 16% Three or more groin lymph node metastases: 45%			
Stehman, 1992 RCT	n=52 patients with squamous cell carcinoma of the vulva Inclusion criteria (for analysis):	Interventions A: bilateral groin radiation	Groin recurrence A: 5/27 B: 0/25	<b>General information</b> Follow-up: 36 month <b>Funding:</b> NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>primary previously untreated squamous cell carcinoma of the vulva</p> <p>radical vulvectomy had to suffice to remove the primary lesion</p> <p>Exclusion criteria (for analysis):</p> <p>medically unsuited for operation patients</p> <p>received any prior radiation therapy or chemotherapy</p> <p>any prior malignancy other than nonmelanoma skin cancer of a site other than the vulva.</p> <p>Enrolment period</p> <p>1986 to 1990</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>median age A &amp; B: 64 years</p> <p>Stage (FIGO, %)</p> <p>NR</p> <p>Location of the tumour</p>	<p>B: groin dissection: bilateral inguinal-femoral lymphadenectomy</p> <p>Analysis</p> <p>Type of analysis: Pearson's chi-squared test, log-rank test</p>	<p>RR= 10.21 (95% CI 0.59-175.78)</p> <p>à progression-free interval: p= 0.03, in favour of B</p> <p>"Radiation of the intact groins as given in this study is significantly inferior to groin dissection in patients with squamous carcinoma of the vulva and N o-1, nodes."</p> <p>Survival</p> <p>A: 10/27 deaths</p> <p>B: 3/25 deaths</p> <p>à survival: p= 0.04, in favour of B</p> <p>Toxicity</p> <p>A: 10/27</p> <p>B: 14/25</p> <p>HR, CI: NR</p>	<p><b>Col:</b> NR</p> <p>Risk of bias considerations (ROB1)</p> <p>Analyse ITT: NR</p> <p>Random sequence generation (selection bias): low ROB</p> <p>Allocation concealment (selection bias): unclear ROB, not described</p> <p>Blinding (performance bias and detection bias): unclear ROB, not described.</p> <p>Incomplete outcome data (attrition bias): low ROB</p> <p>Selective reporting (reporting bias): low ROB</p> <p><b>Other limitations or comments:</b></p> <p>Abbruch der Studie nach 6 Monaten</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>A:</p> <p>Labia: 59,3%</p> <p>Clitoris: 18,5%</p> <p>Perineum: 6%</p> <p>B:</p> <p>Labia: 56%</p> <p>Clitoris: 24%</p> <p>Perineum: 12%</p> <p>Other: 8%</p> <p>Tumour size (% , cm)</p> <p>A:</p> <p>&lt;2.0 cm: 11,1%</p> <p>2.1-4.0 cm: 70,4 %</p> <p>&gt; 4.1 cm: 18,5 %</p> <p>B:</p> <p>&lt;2.0 cm: 8%</p> <p>2.1-4.0 cm: 72%</p> <p>&gt; 4.1 cm: 20 %</p> <p>Tumour depth (% , mm)</p> <p>NR</p>			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
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Lymph node metastases (yes,  
%)

NR

**Verknüpfte Empfehlungen:****Empfehlung 12.4:**

Die postoperative Strahlentherapie der befallenen Leiste(n) nach systematischer inguinofemorale Lymphonodektomie soll bei  $\geq 2$  befallenen inguinofemorale Lymphknoten unabhängig von der Größe der Metastasen durchgeführt werden.

**Literaturreferenzen:** [\[73\]](#), [\[82\]](#), [\[78\]](#), [\[80\]](#)

[\[84\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort study	1 cohort study (Rydzewski2018)	OS	/	/	Note: population of interest from the PICO may differ from the population in this study (P: inguinal 2 or more node positive vulvar cancer)	-1 (only few events, HR=0.59, 95% CI 0.49-0.70)	/	⊕⊕⊕⊕ Very low

**Verknüpfte Empfehlungen:****Empfehlung 12.4:**

Die postoperative Strahlentherapie der befallenen Leiste(n) nach systematischer inguinofemoraler Lymphonodektomie soll bei  $\geq 2$  befallenen inguinofemorale Lymphknoten unabhängig von der Größe der Metastasen durchgeführt werden.

**Empfehlung 12.5:**

Die postoperative Strahlentherapie der befallenen Leiste(n) soll bei Nachweis einer extrakapsulären Extension (ECE) und/oder fixierter bzw. exulzierter inguinaler Lymphknoten-Metastasen unabhängig von der Anzahl der Lymphknoten durchgeführt werden.

**Empfehlung 12.6:**

Die postoperative Strahlentherapie der befallenen Leiste(n) kann bereits ab 1 befallenen Lymphknoten  $\geq 10$  mm nach inguinofemoraler Lymphonodektomie erwogen werden.

**Literaturreferenzen:** [\[73\]](#), [\[82\]](#), [\[78\]](#), [\[80\]](#)

[\[85\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort study	1 cohort study (Mahner 2015)	PFS	/	/	Note: population of interest from the PICO may differ from the population in this study (P: primary or	-1 (only few events, few participants, HR=0.67, 95% CI 0.51 to 0.88)	/	⊕⊖⊖⊖ Very low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
Low à cohort study	1 cohort study (Mahner 2015)	OS	/	/	recurrent squamous cell vulvar cancer stage IB-IV with surgical groin staging & lymph node status positive)	-1 (only few events, few participants, HR = 0.79, 95% CI 0.56 - 1.11)	/	⊕⊕⊕⊕ Very low



**Verknüpfte Empfehlungen:****Empfehlung 12.4:**

Die postoperative Strahlentherapie der befallenen Leiste(n) nach systematischer inguinofemoraler Lymphonodektomie soll bei  $\geq 2$  befallenen inguinofemorale Lymphknoten unabhängig von der Größe der Metastasen durchgeführt werden.

**Empfehlung 12.5:**

Die postoperative Strahlentherapie der befallenen Leiste(n) soll bei Nachweis einer extrakapsulären Extension (ECE) und/oder fixierter bzw. exulzierter inguinaler Lymphknoten-Metastasen unabhängig von der Anzahl der Lymphknoten durchgeführt werden.

**Empfehlung 12.6:**

Die postoperative Strahlentherapie der befallenen Leiste(n) kann bereits ab 1 befallenen Lymphknoten  $\geq 10$  mm nach inguinofemoraler Lymphonodektomie erwogen werden.

**Literaturreferenzen:** [\[73\]](#), [\[82\]](#), [\[78\]](#), [\[80\]](#)

[\[86\]](#)

[\[87\]](#), [\[88\]](#), [\[89\]](#)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Fons et al., 2009, retrospective cohort study	n=75 with squamous cell cancer of the vulva  Inclusion criteria (for analysis): squamous cell cancer of the vulva and one lymph node	Interventions A: adjuvant radiotherapy to the groins and pelvis (N=31) B: No intervention (just surgery LNE) (N=44)  Analysis	Rezidivrate A: 12/31 B: 14/44 RR: 1.22 (95% CI 0.66-2.26)	<b>General information</b> <b>Follow-up:</b> 75 months <b>Funding:</b> NR <b>Col:</b> no conflicts of interest

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>metastasis (single intra capsular lymph node metastasis, without extra capsular spread)</p> <p>radical vulvectomy or wide local excision of the tumor and an inguino-femoral lymphadenectomy</p> <p>Exclusion criteria (for analysis):</p> <p>NR</p> <p>Enrolment period</p> <p>1984-2005</p> <p>Descriptive statistics</p> <p>Age (median, range)</p> <p>A: mean age 75 years</p> <p>B: mean age 72 years</p> <p>Stage (FIGO, %)</p> <p>NR</p> <p>Location of the tumour</p> <p>NR</p> <p>Tumour depth (% , cm)</p>	<p>Type of analysis: Cox's proportional hazards model</p> <p>Matching: NR</p> <p>Confounders: NR</p>	<p>5-year DFS (disease-free survival)</p> <p>A: 20/31</p> <p>B: 27/44</p> <p>HR: 0.98 (95% CI 0.45-2.14; p= 0.97)</p> <p><b>DSS (disease-specific survival)</b></p> <p>A: 21/31</p> <p>B: 30/44</p> <p>HR: 1.02 (95% CI 0.42-2.14; p= 0.96)</p> <p>PFS: NR</p> <p>OS: NR</p>	<p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective cohort study</p> <p>Populations comparable: yes</p> <p>Rate of participation/Exclusions reported (selection bias into the study): yes</p> <p>Exposure/Intervention</p> <p>Assessment reliable: yes</p> <p>Assessed more than once: no</p> <p>Possibly affected by knowledge of outcome status?: no</p> <p>Drop-out rate &amp; reasons reported: no drop-out</p> <p>Similar across groups: yes</p> <p>If high: comparison of those lost with available: na</p> <p>Outcome</p> <p>Outcome measure is well-defined, valid and reliable: yes</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	NR Tumour size (% , mm) A: <4 cm= 58% >/=4cm= 42% B: <4 cm= 64% >/=4cm= 36% Lymph node metastases (yes, %) lymph vascular space involvement. A: neg.=n22 pos.=n4 B: neg.=32 pos.=11 Additional/ adjuvant treatment: NR			Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?): no Main cofounders taken into account: no Confidence intervals reported: yes Selective reporting (comparison with protocol): no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
<b>Mahner et al., 2015</b> retrospective cohort study	n=1249 primary or recurrent squamous cell vulvar cancer stage IB-IV (with surgical groin staging and known lymph node status positive or negative)  Inclusion criteria (for analysis): invasive vulvar cancer greater than stage pT1a 18 years old  Exclusion criteria (for analysis): benign or precursor lesions, nonsquamous neoplasia of the vulva, verrucous vulvar cancer, or those with secondary cancers interfering with the treatment of vulvar cancer  Enrolment period 02.-12.2011  Descriptive statistics Age (median, range) A: median age 67 years B: mean age 72 years	Interventions  A: adjuvant radiotherapy (directed at the groins+/-pelvis+/-vulva) & node positive (N=183)  B: no adjuvant radiotherapy & node positive (N=165)  Analysis  Type of analysis: Cox's proportional hazards modelKaplan-Meier method, log-rank test,  Matching: NR  Confounders: NR	Rezidivrate (of the vulva only)  A: 28.1%  3-year PFS A: 39.6%/183  B: 25.9%/ 165  HR=0.67, 95% CI 0.51 to 0.88, P = .004  <u>Subgroups:</u>  1 pos LN: HR=0.87, 95% CI = 0.53 to 1.42, P = .004  2 pos LN: HR=0.44, 95% CI = 0.25 to 0.78, P = .004  3 pos LN: HR=0.37, 95% CI = 0.18 to 0.74, P = .004  >3 pos LN: NR=45, 95% CI = 0.25 to 0.82, P = .007  3-yeas OS A: 57.7%/ 183 B: 51.4%/ 165  HR = 0.79, 95% CI 0.56 - 1.11, P = .17	<b>General information</b>  <b>Follow-up:</b> 39 months  <b>Funding:</b> Medac oncology  <b>Col:</b> no conflicts of interest  Risk of bias considerations (adapted from SIGN cohort study checklist)  Study type: retrospective cohort study  Populations comparable: yes  Rate of participation/Exclusions reported (selection bias into the study): yes  Exposure/Intervention  Assessment reliable: yes  Assessed more than once: no  Possibly affected by knowledge of outcome status?: yes  Drop-out rate & reasons reported:  Similar across groups: no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Stage (FIGO, %)		DFS	If high: comparison of those lost with available: no
	TNM-Classification		NR	Outcome
	A:			Outcome measure is well-defined, valid and reliable: yes
	pT1b: 16,4%			Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no
	pT2: 63,1%			Main cofounders taken into account: yes
	pT3: 18,9%			Confidence intervals reported: yes
	pT4: 0,8%			Selective reporting (comparison with protocol): yes
	B:			
	pT1b: 17,8%			
	pT2: 65,7%			
	pT3: 14,2%			
	pT4: 2,4%			
	Location of the tumour			
	NR			
	Tumour size (median mm)			
	A: 35mm (2.8-200)			
	B: 35mm (2-240)			
	Median depth of invasion (median mm)			
	A: 8 (0.25-110)			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>B: 7 (1 – 70)</p> <p>Lymph node metastases (yes, %)</p> <p>Yes n=447</p> <p>1: 38,5%</p> <p>2: 22,8%</p> <p>3: 13,9%</p> <p>&gt;3: 19,5%</p> <p>Unknow: 5,4%</p> <p>Additional/ adjuvant treatment:</p> <p>NR</p>			
<p><b>Parthasarathy et al., 2006</b></p> <p>retrospective cohort study</p>	<p>n=208 singel node-positive vulvar cancers, stage III</p> <p>Inclusion criteria (for analysis):</p> <p>vulvar cancers single positive inguinal node</p> <p>Exclusion criteria (for analysis):</p> <p>NR</p> <p>Enrolment period</p> <p>01.01.1988-31.12.2001</p>	<p>Interventions</p> <p>A: adjuvant radiotherapy (N=102)</p> <p>B: no adjuvant radiotherapy (N=106)</p> <p>Analysis</p> <p>Type of analysis: Cox's proportional hazards modelKaplan-Meier method,</p> <p>Matching: NR</p>	<p>Rezidivrate: NR</p> <p>DSS:</p> <p>A: 77%/102</p> <p>B: 61,2%/106</p> <p>HR: 0.57 CI: 0.32-1.03</p> <p>PFS: NR</p> <p>MFS: NR</p> <p>OS: NR</p>	<p><b>General information</b></p> <p><b>Follow-up:</b> 60 months</p> <p><b>Funding:</b> NR</p> <p><b>Col:</b> NR</p> <p>Risk of bias considerations (adapted from SIGN cohort study checklist)</p> <p>Study type: retrospective cohort study</p>

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Descriptive statistics Age (mean, range) A: 65.1 ± 1.4 B: 71.2 ± 1.5 Stage (FIGO, %) A: Grade 1: n=13 Grade 2: n=51 Grade 3: n=32 unknow: n=6 B: Grade 1: n= 15 Grade 2: n=51 Grade 3: n=29 unknow: n=11 Location of the tumour NR Tumour size (% , cm) NR Tumour depth (% , mm)	Confounders: yes		Populations comparable: yes Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention Assessment reliable: yes Assessed more than once: no Possibly affected by knowledge of outcome status?: yes Drop-out rate & reasons reported: Similar across groups: yes If high: comparison of those lost with available: no Outcome Outcome measure is well-defined, valid and reliable: yes Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no Main cofounders taken into account: yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	NR Lymph node metastases (yes, %) NR			Confidence intervals reported: yes Selective reporting (comparison with protocol): no
<b>Rydzewski et al., 2018</b> retrospective cohort study	n=2770 squamous cell carcinoma Inclusion criteria (for analysis): squamous cell carcinoma, including keratinizing and non-keratinizing who had surgical removal of the primary tumor along with inguinal lymphadenectomy (LND) with pathologically confirmed positive lymph nodes and positive inguinal nodes Exclusion criteria (for analysis): no record of number of nodes positive, no record of number of nodes examined, no record of income, education or insurance status, unknown stage or who had distant metastases at diagnosis	Interventions A: adjuvant external beam radiation therapy (EBRT) (N=974, 502 with 1 pos Node & 472 with >/=2 pos Nodes) B: no adjuvant treatment (N=1061, 620 with 1 pos Node & 441 with >/=2 pos Nodes) C: adjuvant external beam radiation therapy with chemotherapy (N=744, 314 with 1 pos Node & 430 with >/=2 pos Nodes) Analysis Type of analysis: Cox's proportional hazards modelKaplan-Meier method, log-rank test Matching: NR	Rezidivrate: NR OS 1 pos node: A: 55.9%/502 B: 46.1%/472 HR=0.8,1 95% CI 0.67-0.98, p=0.027 >/2 pos nodes: A: 29.4%/620 B: 21.2%/441 HR=0.59, 95% CI 0.49-0.70, p<0.001 DFS: NR PFS: NR MFS: NR	<b>General information</b> <b>Follow-up:</b> NR <b>Funding:</b> NR <b>Col:</b> no conflicts of interest Risk of bias considerations (adapted from SIGN cohort study checklist) Study type: retrospective cohort study Populations comparable: yes Rate of participation/Exclusions reported (selection bias into the study): yes Exposure/Intervention Assessment reliable: yes Assessed more than once: no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Enrolment period 2004-2014 Descriptive statistics Age (median, range) A: <49-49: n=86 50-59: n=168 60-69: n=200 70- >70: n=520 B: <49-49: n=104 50-59: n=135 60-69: n=175 70- >70: n=647 C: <49-49: n=156 50-59: n=196 60-69: n=188 70- >70: n=204 Stage (FIGO, %)	Confounders: yes		Possibly affected by knowledge of outcome status?: yes Drop-out rate & reasons reported: no Similar across groups: If high: comparison of those lost with available: Outcome Outcome measure is well-defined, valid and reliable: yes Blind outcome assessment to exposure: (àlf not, Knowledge of exposure status likely to influence the outcome?: ): no Main cofounders taken into account: yes Confidence intervals reported: yes Selective reporting (comparison with protocol): no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	TNM-Classification A: Early stage: n=52 T1b: n= 443 T2: n=399 T3/T4: n=80 B: Early stage: n=55 T1b: n= 470 T2: n=443 T3/T4: n=93 C: Early stage: n=45 T1b: n= 376 T2: n=219 T3/T4: n=41 " Location of the tumour NR Tumour size (% , cm) NR			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	<p>Tumour depth (% , mm)</p> <p>NR</p> <p>Lymph node metastases (yes, %)</p> <p>Positive Nodes</p> <p>A:</p> <p>1 Positive Node: n=502</p> <p>2 or More Positive Nodes: n=472</p> <p>B:</p> <p>1 Positive Node: n=620</p> <p>2 or More Positive Nodes: n=441</p> <p>C:</p> <p>1 Positive Node: n=314</p> <p>2 or More Positive Nodes: n=430</p>			

## Kapitel 9.1.2: Postoperative adjuvante Strahlentherapie der pelvinen Lymphabflusswege

### Kapitel 9.2: Simultane Radiochemotherapie

#### Kapitel 9.2.1: Primäre Radiochemotherapie

#### Kapitel 9.2.2: Adjuvante Radiochemotherapie

##### Verknüpfte Empfehlungen:

##### **Empfehlung 12.13:**

Bei Indikation zur adjuvanten Strahlentherapie kann diese in Kombination mit einer simultanen Chemotherapie erfolgen, insbesondere bei nodal-positiven Patientinnen.

Als Ausnahme gilt die Indikation zur Bestrahlung der inguinalen Lymphabflusswege aufgrund einer Metastase im Sentinel-Lymphknoten von  $\leq 2$  mm und nicht erfolgter inguinofemoraler Lymphadenektomie. Hier soll keine simultane Chemotherapie sondern eine alleinige Radiatio analog der GROINSS-V II Studie erfolgen.

##### **Empfehlung 12.13:**

Bei Indikation zur adjuvanten Strahlentherapie kann diese in Kombination mit einer simultanen Chemotherapie erfolgen, insbesondere bei nodal-positiven Patientinnen.

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Literaturreferenzen: [\[90\]](#), [\[91\]](#), [\[80\]](#)

[\[92\]](#)

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
High à RCT	1 RCT (Kunos 2009)	OS (6 years)	/	/	-1 (population of interest might not exactly match the guideline PICO)	-1 (only few participants (n=114) and wide CI (HR=0.6; 95% CI 0.30-1.30))	/	⊕⊕⊕⊖ Low
Low à cohort study	1 non-RCT (Rao 2017)	OS (5 years)	/	/	-1 (population of interest might not exactly match the guideline PICO)	/ 1352 participants (HR =0.73; 95% CI 0.59-0.91)	/	⊕⊕⊕⊖ Very low
High à RCT	1 RCT (Kunos 2009)	Recurrence	/	/	-1 (population of interest might not exactly match	-1 (only few participants (n=114) and wide CI	/	⊕⊕⊕⊖ Low

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungsrisiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
					the guideline PICO)	(RR=0.74; 95% CI 0.48-1.14)		

**Verknüpfte Empfehlungen:****Empfehlung 12.13:**

Bei Indikation zur adjuvanten Strahlentherapie kann diese in Kombination mit einer simultanen Chemotherapie erfolgen, insbesondere bei nodal-positiven Patientinnen.

Als Ausnahme gilt die Indikation zur Bestrahlung der inguinalen Lymphabflusswege aufgrund einer Metastase im Sentinel-Lymphknoten von  $\leq 2$  mm und nicht erfolgter inguinofemoraler Lymphadenektomie. Hier soll keine simultane Chemotherapie sondern eine alleinige Radiatio analog der GROINSS-V II Studie erfolgen.

**Empfehlung 12.13:**

Bei Indikation zur adjuvanten Strahlentherapie kann diese in Kombination mit einer simultanen Chemotherapie erfolgen, insbesondere bei nodal-positiven Patientinnen.

Als Ausnahme gilt die Indikation zur Bestrahlung der inguinalen Lymphabflusswege aufgrund einer Metastase im Sentinel-Lymphknoten von  $\leq 2$  mm und nicht erfolgter inguinofemoraler Lymphadenektomie. Hier soll keine simultane Chemotherapie sondern eine alleinige Radiatio analog der GROINSS-V II Studie erfolgen.

**Empfehlung 12.13:**

Bei Indikation zur adjuvanten Strahlentherapie kann diese in Kombination mit einer simultanen Chemotherapie erfolgen, insbesondere bei nodal-positiven Patientinnen.

Als Ausnahme gilt die Indikation zur Bestrahlung der inguinalen Lymphabflusswege aufgrund einer Metastase im Sentinel-Lymphknoten von  $\leq 2$  mm und nicht erfolgter inguinofemoraler Lymphadenektomie. Hier soll keine simultane Chemotherapie sondern eine alleinige Radiatio analog der GROINSS-V II Studie erfolgen.

**Literaturreferenzen:** [\[90\]](#), [\[91\]](#), [\[80\]](#)

[\[93\]](#)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Tagliaferri L. et al, 2021, Systematic Review	<p><b>Types of studies:</b> 1 RCT, 18 non-RCTs (Cohort studies)</p> <p><b>1 RCT (Kunos 2009) and 2 non-RCT (Rao 2017, Rydzewski 2018) most relevant and recent</b></p> <p><b>Search from:</b> 15.06.2021</p> <p><b>Databases:</b> PubMed, Scopus, Cochrane library</p> <p><b>Inclusion criteria</b></p> <p>clinical prospective or retrospective studies on patients with histological confirmation of primary VC</p> <p>sample size <math>\geq 10</math> patients</p>	<p><b>Question/ Aim:</b></p> <p>„The aim of this review is to summarise the main evidence published in the last 30 years on the role of RT in the multidisciplinary management of locally advanced VC.“</p> <p>A: Neoadjuvant Radio-Chemotherapy (neoadjuvant setting)</p> <p><b>B: Exclusive Radio-Chemotherapy (Exclusive setting)</b></p> <p><b>C: Adjuvant Radiotherapy Plus/ Minus Chemotherapy (adjuvant setting)</b></p> <p>D: Interventional Radiotherapy (Brachytherapy)</p>	<p>19 studies with 7536 pts with vulvar squamous cell carcinoma (VSCC) disease</p> <p><b>Descriptive statistics:</b></p> <p>Age median, range)</p> <p><u>Systematic review insgesamt</u></p> <p>A: median: 68 years; range 88–73.5 years</p> <p><b>B: median 70 years; range 56.5–80 years</b></p> <p><b>C: median 69 years; range 65–74.4 years</b></p> <p>D: median: 67 years; range 27–93 years</p> <p><u>Kunos 2009:</u></p> <p>70 (23–89)</p> <p><u>Rao 2017:</u></p>	<p><u>Insgesamte Effektschätzer, von allen eingeschlossenen Studien des SRs:</u></p> <p>DFS</p> <p>A: 55% (nach 2 Jahren) bzw. 65.9% (nach 3 Jahren, sic)</p> <p><b>B: 45.6% (nach 5 Jahren)</b></p> <p><b>C: 61.2% (nach 5 Jahren)</b></p> <p>D: 44.5% (nach 5 Jahren)</p> <p>OS:</p> <p>A: 69% (nach 2 Jahren) bzw. 57-61% (nach 3 Jahren) bzw. 57% nach 5 Jahren</p> <p><b>B: 49.9% (nach 5 Jahren)</b></p>	<p>Overall confidence in results of SR (AMSTAR-2): “<i>moderate to low</i>”</p> <p>PICO elements: No</p> <p>A priori design: partial yes</p> <p>Justification for design: No</p> <p>Literature search <math>\geq 2</math> databases, search strategy + other sources: partial yes</p> <p>Selection in duplicate: yes</p> <p>Data extraction in duplicate: yes</p> <p>List of excluded studies: No</p> <p>sufficient detail on studies: partial yes</p> <p>RoB assessed: No</p>	<p><b>Relevante Studien:</b></p> <p>Kunos et al. Radiationtherapy compared with pelvic noderection for node positive vulv cancer: A randomized controlled trial. Obstet. Gynecol. 2009, 114, 537–546</p> <p>Rao et al. Improved survival with definitive chemoradiation compared to definitive radiation alone in squamous cell carcinoma of the vulva: A review of the National Cancer Database. Gynecol. Oncol. 2017, 146, 572–579</p> <p>Rydzewski NR, Kanis MJ, Donnelly ED,</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	<p>RT delivered with or without concurrent chemotherapy in adjuvant, neoadjuvant, or definitive setting studies published in English between 1997 and 2021 studies reporting oncological outcomes and/or toxicity</p> <p>Exclusion criteria: Planning studies, case reports, surveys, letters, editorials, book chapters, review articles, and conference abstracts</p>	<p><u>Rao 2017 (non-RCT), exclusive setting:</u></p> <p>A: CRT, n= 999 (chemoradiation)</p> <p>B: RT alone, n =353</p> <p>adjusting for age, race, insurance status, income, high school education, urban and rural region, Charlson-Deyo comorbidity score, year of diagnosis, and FIGO stage.</p> <p><u>Kunos 2009 (RCT), adjuvant setting:</u></p> <p>A: Adjuvant RT, n=59 (pelvic and groin radiation),</p> <p>B: No Adjuvant RT, n =55 (pelvic node resection)</p>	<p>A (CRT): median: 63 years (23-90)</p> <p>B (RT): median: 80 years (30-90)</p> <p>Sex (% female)</p> <p>A: NR</p> <p>B: NR</p> <p>C: NR</p> <p>D: NR</p> <p>Stage (nach FIGO, %)</p> <p><u>Rao 2017</u></p> <p>Ia: A: 0, B: 0</p> <p>Ib: A: 0, B: 0</p> <p>II: A: 202, B: 99</p> <p>III: A: 453, B: 113</p> <p>Iva: A: 279, B: 76</p> <p><u>Kunos 2009</u></p> <p>III-IV: A: 59, B: 55</p> <p><u>Rydzewski 2018</u></p>	<p><b>C: 63% (nach 5 Jahren)</b></p> <p>D: 50.5% (nach 5 Jahren)</p> <p><u>Kunos 2009:</u></p> <p>Rezidivrate (any site)</p> <p>A: 21/57</p> <p>B: 27/54</p> <p>RR: 0.74 (95%CI 0.48-1.14) in favour of A</p> <p><b>Relapse/recurrence-free</b></p> <p>HR: 0.39 (95% CI 0.17-0.88; p=0.02) in favour of A</p> <p>Mortality</p> <p>A: 32/57 deaths, 18/57 cancer-related deaths</p>	<p>Funding of incl. studies: No</p> <p>MA appropriate: No</p> <p>RoB considered in MA: No</p> <p>RoB in interpretation: No</p> <p>Heterogeneity explained: No</p> <p>Publication bias investigated: No</p> <p>Sources of Col: yes</p>	<p>Lurain JR, Strauss JB. Role of adjuvant external beam radiotherapy and chemotherapy in one versus two or more node-positive vulvar cancer: A National Cancer Database study. <i>Radiother Oncol.</i> 2018 Dec;129(3): 534-539. doi: 10.1016/j.radonc.2018.03.023</p> <p><b>Sonstige eingeschlossene Publikationen:</b></p> <p>Beriwal 2013; Gaudineau 2012; Natesan 2017; Richman 2020; Moore 1998;</p> <p>Han 2000; Sakanaka 2017; Rishi 2020;</p>

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
		adjusting for age and adverse tumor characteristics  <u>Rydzewski 2018 (non-RCT), adjuvant setting:</u>  A: No adjuvant RT, n=1061  B: Adjuvant RT (external beam radiation therapy EBRT), n=974  C: Adjuvant CRT (EBRT with chemotherapy), n=744  Covariates for multivariate analysis include number of nodes examined, T stage, grade, age, race/ethnicity, income, education, insurance status, comorbidity score, type	III-IV: 974, B: 774, C: 1061  Location of the tumour  Clitoris NR: Labia majora: NR Labia minora: NR Sub-clitoral: NR Posterior commissure: NR Tumour size (% , cm) nur bei Rao ≤ 2: A: 37, B: 69 2.1-4: 86, B: 197 >4: 110, B: 398 Tumour depth (% , mm) ≤ 1.0: NR 1.01-2.5: NR 2.51-5.0: NR	B: 30/54 deaths, 28/54 cancer-related deaths  OS (6-year)  HR: 0.61(95% CI 0.30-1.30; p=0.18) in favour of A  <u>Rydzewski 2018</u>  OS (5-year), patients with 1 positive node: A: 46.1% B: 55.9% C: 68.1%  HR (group C vs. B): 0.93 (95% CI 0.0.70-1.23; p=0.605), n=707 people, in favour of C  OS (5-year), patients with 2/more positive nodes: A: 21.2%		Tans 2011; Alanyali 2016; Logar 2017; Tagliaferri 2020;  Gill 2015;  Mahner 2015; Laliscia 2017; Rydzewski 2018; Parthasarathy 2006

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
		of hospital, distance from hospital and year of diagnosis.	>5.0 NR	<p>B: 29.4 % C: 49.1%</p> <p>HR (group C vs. B): 0.79 (95% CI 0.65- 0.97; p=0.022), n=802 people, in favour of C</p> <p>OS (5-year)</p> <p>HR (group B vs. A): 0.68 (95% CI 0.60- 0.77) in favour of B</p> <p>HR (group C vs. A): 0.56 (95% CI 0.47- 0.66) in favour of C</p> <p><u>Rao 2017:</u></p> <p>OS (5-year)</p> <p>A: 49.9% B: 27.4%</p> <p>HR (propensity matched analysis): 0.73 (95% CI 0.59-</p>		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				0.91; p=0.005) in favour of A		

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