Leitlinienprogramm Onkologie

Evidenzbericht zur S3 Leitlinie Vulvakarzinom und seine Vorstufen

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Evidenzbericht

Schlüsselfragen bearbeitet durch das Institut für Öffentliches Gesundheitswesen, Universität zu Köln

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Inhaltsverzeichnis

1 Abkürzungsverzeichnis 7

2 Informationen zum Evidenzbericht 9

2.1 Autor*innen und Beteiligte 9

3 Methodisches Vorgehen 10

3.1 Formulierung der Schlüsselfragen 10

3.2 Systematische Recherche und Sichtung der Literatur 14

3.2.1 Systematische Reviews 14

3.2.2 Primärstudienrecherchen 14

3.3 Datenextraktion und Bewertung des Verzerrungsrisikos (Risk of Bias) 14

3.4 Meta-analytisches Vorgehen 15

3.5 Evidenzklassifikation nach GRADE 15

3.6 Formulierung der Empfehlungen und formale Konsensusfindung 16

3.6.1 Schema der Empfehlungsgraduierung 17

3.6.2 Festlegung des Empfehlungsgrades 17

3.6.3 Formale Konsensusverfahren und Konsensuskonferenzen 18

4 PICO-übergreifendes methodisches Vorgehen und Resultate 20

4.1 Definierte Schlüsselfragen im PICO-Format 20

4.2 Evidenzrecherche für die extern recherchierten Schlüsselfragen 23

4.2.1 Evidenzrecherche nach systematischen Reviews 23

4.2.2 RCT Suche 26

5 PICO-spezifisches methodische Vorgehen 30

5.1 Kapitel Diagnostik – PICO 3.1a 30

5.1.1 Fragestellung und geplantes Vorgehen 30

5.1.2 Studienselektion 30
5.1.3 Evidenzrecherche nach non-RCTs 31
5.2 Kapitel Diagnostik – PICO 3.1b 32
5.2.1 Fragestellung und geplantes Vorgehen 32
5.2.2 Studienselektion 32
5.2.3 Evidenzrecherche 33
5.3 Kapitel Therapie der VIN und M. Paget – PICO 5.1 34
5.3.1 Fragestellung und geplantes Vorgehen 34
5.3.2 Studienselektion 35
5.3.3 Evidenzrecherche 36
5.4 Kapitel Therapie der VIN und M. Paget – PICO 5.2 38
5.4.1 Fragestellung und geplantes Vorgehen 38
5.5 Kapitel Operatives Management des Primärtumors – PICO 6.1 39
5.5.1 Fragestellung und geplantes Vorgehen 39
5.5.2 Studienselektion 42
5.5.3 Evidenzrecherche 42
5.6 Kapitel Operatives Management des Primärtumors – PICO 6.3 44
5.6.1 Fragestellung und geplantes Vorgehen 44
5.7 Kapitel Operatives Management des Primärtumors – PICO 6.6 45
5.7.1 Fragestellung und geplantes Vorgehen 45
5.8 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.2 46
5.8.1 Fragestellung und geplantes Vorgehen 46
5.9 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.3 46
5.9.1 Fragestellung und geplantes Vorgehen 46
5.9.2 Studienselektion 48
5.9.3 Evidenzrecherche 48
5.10 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.5 50

5.10.1 Fragestellung und geplantes Vorgehen 50
5.10.2 Studienselektion 51
5.10.3 Evidenzrecherche 51
5.11 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.6 52
5.11.1 Fragestellung und geplantes Vorgehen 52
5.11.2 Studienselektion 53
5.11.3 54
5.11.4 Evidenzrecherche 54
5.12 Kapitel Strahlentherapie – PICO 8.1 54
5.12.1 Fragestellung und geplantes Vorgehen 54
5.13 Kapitel Strahlentherapie – PICO 8.3 und 8.4a–4d 55
5.13.1 Fragestellung und geplantes Vorgehen 55
6 Ergebnisse der extern recherchierten Schlüsselfragen 57
6.1 Kapitel Diagnostik – PICO 3.1a 57
6.1.1 PRISMA Flowdiagramm 58
6.2 Kapitel Diagnostik – PICO 3.1b 58
6.2.1 PRISMA Flowdiagramm 59
6.3 Kapitel Therapie der VIN und M. Paget – PICO 5.1 60
6.3.1 PRISMA Flowdiagramm 60
6.3.2 Evidenztabellen 61
6.3.3 Bewertung der Evidenz (nach GRADE) 67
6.4 Kapitel Therapie der VIN und M. Paget – PICO 5.2 68
6.4.1 Evidenztabellen 68
6.4.2 Forest plots 79
6.4.3 Bewertung der Evidenz (nach GRADE) 80
6.5 Kapitel Operatives Management des Primärtumors – PICO 6.1 85
6.5.1 PRISMA Flowdiagramm 86

6.5.2 Evidenztabellen 87
6.5.3 Forest plots 123
6.5.4 Bewertung der Evidenz (nach GRADE) 124
6.5.5 Kapitel Operatives Management des Primärtumors – PICO 6.3 124
6.6 Kapitel Operatives Management des Primärtumors – PICO 6.6 124
6.6.1 Evidenztabellen 124
6.6.2 Forest plots 130
6.6.3 Bewertung der Evidenz (nach GRADE) 133
6.7 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.2 135
6.7.1 Evidenztabellen 135
6.7.2 Forest plots 137
6.7.3 Bewertung der Evidenz (nach GRADE) 138
6.8 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.3 140
6.8.1 PRISMA Flowdiagramm 141
6.8.2 Evidenztabellen 142
6.8.3 Bewertung der Evidenz (nach GRADE) 151
6.9 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.5 154
6.9.1 PRISMA Flowdiagramm 155
6.9.2 Evidenztabellen 156
6.9.3 Forest plots 162
6.9.4 Bewertung der Evidenz (nach GRADE) 163
6.10 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.6 164
6.10.1 PRISMA Flowdiagramm 165
6.10.2 Evidenztabellen 166
6.10.3 Forest plots 175
6.10.4 Bewertung der Evidenz (nach GRADE) 176
6.11 Kapitel Strahlentherapie – PICO 8.1 177

6.12 Kapitel Strahlentherapie – PICO 8.3 und 8.4a–4d 177
6.12.1 Evidenztabellen 178
6.12.2 Forest plots 183
6.12.3 Bewertung der Evidenz (nach GRADE) 184

7 Ergebnisse der intern recherchierten Schlüsselfragen 185

7.1 Kapitel Epidemiologie und Risikofaktoren – PICO 1.2a 185
7.1.1 Evidenztabellen 185
7.1.2 Bewertung der Evidenz (nach GRADE) 190
7.2 Kapitel Epidemiologie und Risikofaktoren – PICO 1.2b 191
7.2.1 Evidenztabellen 191
7.2.2 Bewertung der Evidenz (nach GRADE) 200
7.3 Kapitel Prävention und Früherkennung – PICO 2.1 201
7.3.1 Evidenztabellen 201
7.3.2 Bewertung der Evidenz (nach GRADE) 205
7.4 Kapitel Operatives Management des Primärtumors – PICO 6.2 206
7.4.1 Evidenztabellen 206
7.5 Kapitel Operatives Management des Primärtumors– PICO 6.4 211
7.5.1 Evidenztabellen 211
7.5.2 Bewertung der Evidenz (nach GRADE) 216
7.6 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.1 216
7.6.1 Evidenztabellen 216
7.6.2 Bewertung der Evidenz (nach GRADE) 228
7.7 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.4a und 7.4b 228
7.7.1 Evidenztabellen 228
7.7.2 Bewertung der Evidenz (nach GRADE) 237
7.8 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.7 240
7.8.1 Evidenztabellen 240

7.8.2 Bewertung der Evidenz (nach GRADE) 248
7.9 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.8 248
7.9.1 Evidenztabellen 248
7.9.2 Bewertung der Evidenz (nach GRADE) 256
8 Literaturverzeichnis 257

1 Abkürzungsverzeichnis

Abkürzung	Erläuterung
95%-CI	95% confidence interval
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
LR	Local recurrence
N	Number
NR	Not reported
NRCS	Non-randomized controlled study
NRSI	Non-randomized study of intervention
OR	Odds Ratio
RCT	Randomized controlled trial
RoB	Risk of Bias
RR	Risk Ratio
RChT	Radiochemotherapie
RT	Radiotherapy
SR	Systematic review
LSIL	Low-grade Squamous Intraepithelial Lesion
HSIL	High-grade Squamous Intraepithelial Lesion
VIN	Vulväre intraepitheliale Neoplasie
LK	Lymphknote

Abkürzung	Erläuterung
LNE	Lymphonodektomie
LAW	Lymphabflusswege
IFL	Inguinofemoral lymphadenectomy
DFS	Disease-Free Survival
PFS	Progression-Free Survival
MFS	Metastasis-Free Survival
OS	Overall Survival

2 Informationen zum Evidenzbericht

2.1 Autor*innen und Beteiligte

Institut für Öffentliches Gesundheitswesen, Universität zu Köln: Univ-Prof. Dr. med. Nicole Skoetz, Dr. Nina Kreuzberger, Dr. Claire Iannizzi

3 Methodisches Vorgehen

3.1 Formulierung der Schlüsselfragen

Nach dem Kick-off-Meeting im Juli 2022 wurden innerhalb der multidisziplinären Arbeitsgruppe relevante Fragestellungen zum Thema der Diagnostik, Therapie und Nachsorge der Patientin mit Vulvakarzinom und seiner Vorstufen gesammelt. Nachfolgend wurden die Fragestellungen in der Gruppe diskutiert, modifiziert, thematisch sortiert und zusammengefasst. Im Nachgang lag eine kondensierte Liste mit Fragen im PICO-Format (P = Patient, I = Intervention, C = Comparison, O = Outcome) vor.

Folgende Schlüsselfragen wurden extern von Frau Dr. Kreuzberger und Frau Dr. Iannizzi vom Institut für Öffentliches Gesundheitswesen der Universität zu Köln recherchiert und bewertet:

Kapitel Diagnostik

PICO 3.1a. Verbessert/verändert bei Patientinnen mit ED Vulvakarzinom die Vulvoskopie + apparative Diagnostik (1. gyn. Sonographie, 2.MRT, 3. CT, 4. PET) verglichen mit dem pathologischen Befund (Histologie) die Diagnosestellung (Sensitivität, Spezifität, NPV, PPV, Staging, OS, DFS, Lebensqualität, Rezidivrate, Therapiestrategie)?

PICO 3.1b. Verbessert bei Patientinnen mit ED HSIL / M. Paget die apparative Diagnostik Vulvoskopie versus Vulvoskopie plus Mapping die Rezidivrate und Persistenz (R1)?

Kapitel Therapie der VIN und M. Paget

PICO 5.1. Verbessert bei Patientinnen mit ED HSIL / M. Paget und primärer Exzision ein bestimmter operativer Sicherheitsabstand das Risiko für ein Lokalrezidiv (local recurrence rate / (local) recurrence free survival), DFS, OS, CSS (cancer specific survival)?

PICO 5.2. Zeigen bei Patientinnen mit LSIL / HSIL / M. Paget die (topische) medikamentöse Therapie versus operative Exzision versus Laservaporisation ähnliche Ergebnisse bzgl. Rezidivrate / Rate invasives Karzinom / Nebenwirkungen / Komplikationen / Lebensqualität?

Kapitel Operatives Management des Primärtumors

PICO 6.1. Verbessert bei Patientinnen mit ED Vulvakarzinom ein bestimmter operativer Sicherheitsabstand das Risiko für ein Lokalrezidiv, Lymphknotenrezidiv, DFS, OS?

PICO 6.3. Zeigt die primär operative Therapie von Patientinnen mit Vulvakarzinom ab Stadium T2 gegenüber der primär operativen Therapie von Patientinnen im Stadium T1 eine erhöhte Rate für postoperative Harninkontinenz und anorektale Inkontinenz?

PICO 6.6. Verbessert bei Patientinnen mit ED Vulvakarzinom T2 und T3 die primäre RT (Radiotherapie) und RChT (Radiochemotherapie) gegenüber der primär operativen Therapie die Rezidivrate, Rate der Exenterationen, Nebenwirkungsspektrum, DFS (Disease-Free Survival), PFS (Progression-Free Survival), MFS (Metastasis-Free Survival), OS (Overall Survival)?

Kapitel Operative Therapie der Lymphabflusswege

PICO 7.2. Verbessert bei Patientinnen mit ED Vulvakarzinom, befallenen inguinalen LK (Lymphknoten) und Indikation zur inguinalen Strahlentherapie mit bildgebend unauffälligen pelvinen LK die systematische pelvine LNE (Lymphonodektomie) +/- Radiatio in Abhängigkeit nachgewiesener LK-Metastasen versus der pelvinen Radiatio ohne operatives Staging die Rate der LK-Rezidive (insbesondere pelvin) / Morbidität / DFS / OS?

PICO 7.3a. Verbessert eine bds. systematische inguinofemorale LNE plus adj. Radiatio der Lymphabflusswege (LAW) gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und 1 inguinalen LK-Makrometastase die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.3b. Verbessert eine bds. systematische inguinofemorale LNE plus adj. Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und mind. 2 inguinalen LK-Metastasen die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.3c. Verbessert eine bds. systematische inguinofemorale LNE (Lymphonodektomie) plus adj. Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und inguinaler LK-Metastase mit extrakapsulärem Wachstum die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.3d. Verbessert eine bds. systematische inguinofemorale LNE plus adj. Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und fixierten bzw. exulzerierten inguinalen LK-Metastasen die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.5. Verbessert bei Patientinnen mit ED Vulvakarzinom und bulky nodes inguinal und/oder pelvin eine bds. Systematische inguinofemorale bzw. pelvine LNE mit adjuvanter Radiatio gegenüber der alleinigen Entfernung der auffälligen LK mit adjuvanter Radiatio die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.6a. Verbessert bei Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unauffälligen LAW und bds. inguinofemoraler LNE mit histologisch mind. 1 befallenem LK die inguinofemorale LNE mit mind. 6 entfernten LK pro Leiste gegenüber der inguinofemoralen LNE mit < 6 entfernten LK die Rate der LK-Rezidive seitenbezogen / Morbidität / DFS / OS?

PICO 7.6b. Verbessert bei Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unauffälligen LAW und bds. inguinofemoraler LNE mit histologisch negativen LK die inguinofemorale LNE mit mind. 6 entfernten LK pro Leiste gegenüber der inguinofemoralen LNE mit < 6 entfernten LK die Rate der LK-Rezidive / Morbidität / DFS / OS?

Kapitel Strahlentherapie

PICO 8.1a. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R0 mit minimalen Resektionsrand von > 3 mm die Rezidivrate, DFS, PFS, MFS, OS?

PICO 8.1b. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R0 mit minimalem Resektionsrand </=3mm die Rezidivrate, DFS, PFS, MFS, OS?

PICO 8.1c. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R1 die Rezidivrate, DFS, PFS, MFS, OS?

PICO 8.1d. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit L1 die Rezidivrate, DFS, PFS, MFS, OS?

PICO 8.3. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit mind. 2 befallenen inguinalen LK eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

PICO 8.4a. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit einem befallenen inguinalen LK mit Makrometastase eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

PICO 8.4b. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit inguinal extrakapsulärem Metastasenwachstum eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

PICO 8.4c. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit fixierten bzw. exulzerierten inguinalen LK-Metastasen eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

PICO 8.4d. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler und pelviner LNE mit inguinal und pelvin befallenen LK eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

Folgende Schlüsselfragen wurden intern vom Universitätsklinikum Augsburg (Frau Strieder) recherchiert und extern von Frau Kreuzberger und Frau Dr. Iannizzi vom Institut für Öffentliches Gesundheitswesen der Universität zu Köln bewertet:

Kapitel Epidemiologie und Risikofaktoren

PICO 1.2a. Zeigen Patientinnen mit behandelter HSIL / dVIN gegenüber Patientinnen mit unbehandelter HSIL/ dVIN eine geringere Rezidivrate und ein niedrigeres Risiko für die Entwicklung eines Vulvakarzinoms?

PICO 1.2b. Zeigen Patientinnen mit behandeltem Lichen sclerosus gegenüber Patientinnen mit unbehandeltem Lichen sclerosus eine geringere Rezidivrate und ein niedrigeres Risiko für die Entwicklung einer VIN / eines Vulvakarzinoms?

Kapitel Prävention und Früherkennung

PICO 2.1. Beeinflusst die HPV-Impfung das Risiko für das Auftreten eines Vulvakarzinoms / VIN?

Kapitel Operatives Management des Primärtumors

PICO 6.2. Haben Patientinnen mit einer plastischen Vulvarekonstruktion nach Tumorresektion ein verbessertes psychosoziales / funktionelles Outcome / QoL im Vergleich zu Frauen mit primärem Wundverschluss oder offener Wundheilung?

PICO 6.4. Verbessert eine Exenteration bei Patientinnen im palliativen Stadium mit Fistelbildung / Kloakenbildung / starken Schmerzen die Lebensqualität, Nebenwirkungsrate, OS?

Kapitel Operative Therapie der Lymphabflusswege

PICO 7.1. Verbessert bei Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unilateral / bilateral unauffälligen inguinalen LK und einseitig positivem Sentinel-LK die kontralaterale systematische inguinofemorale LNE gegenüber keiner Behandlung der kontralateralen Leiste die Leistenrezidivrate / DFS / OS?

PICO 7.4a. Verbessert bei Patientinnen mit ED Vulvakarzinom mit klinisch und bildgebend unauffälligen LK und Z.n. SNB mit histologisch isolierten Tumorzellen oder Mikrometastase die ipsilaterale inguinofemorale LNE +/- Radiatio der inguinalen LAW gegenüber einer alleinigen ipsilateralen Radiatio der inguinalen LAW die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.4b. Verbessert bei Patientinnen mit ED Vulvakarzinom mit klinisch und bildgebend unauffälligen LK und Z.n. SNB mit histologisch Makrometastase einseitig die ipsilaterale inguinofemorale LNE +/- Radiatio der inguinalen LAW gegenüber einer alleinigen ipsilateralen Radiatio der inguinalen LAW die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.7. Verbessert bei Patientinnen mit ED Vulvakarzinom und Indikation zum Leisten-Lymphonodektomie die systematische inguinofemorale LNE gegenüber einer modifizierten (weniger radikalen) LNE die Leistenrezidivrate / DFS / OS?

PICO 7.8. Ist bei Patientinnen mit ED Vulvakarzinom und Primärtumor < 4 cm sowie klinisch / bildgebend negativen Leisten das Sentinel-Lymphknotenbiopsie-Verfahren zum operativen Staging der Leisten der systematischen LNE hinsichtlich Morbidität, Rate an Leistenrezidiven sowie DFS sowie OS ebenbürtig?

Klinisch-methodischer Austausch

Es wurden mehrere virtuelle Termine für den engen Austausch zwischen Methodiker*innen und Kliniker*innen festgelegt. In diesen Treffen wurden die Schlüsselfragen genauer definiert, Endpunktgruppen erläutert, relevante Studien und systematische Reviews auf Relevanz überprüft, weitere Suchstrategien für nicht-randomisierte Studien besprochen und klinische Fragen geklärt.

Zu den Schlüsselfragen des Kapitels Operative Therapie des Karzinoms fand am 11. Juli 2023 ein Termin mit Prof. Dr. Hampl, Prof. Dr. Wohlmuth, Dr. Nina Kreuzberger und Dr. Claire Iannizzi statt.

Zu den Schlüsselfragen des Kapitels Operative Therapie der LAW fand am 19. Juli 2023 ein Termin mit Prof. Dr. med. Linn Woelber, Prof. Hans-Georg Schnürch, Dr. Nina Kreuzberger und Dr. Claire Iannizzi statt.

Zu den Schlüsselfragen des Kapitels der Diagnostik fand am 28. August 2023 ein Termin mit Dr. Küppers, Dr. Soergel, Dr. Nina Kreuzberger und Dr. Claire Iannizzi statt.

3.2 Systematische Recherche und Sichtung der Literatur

3.2.1 Systematische Reviews

Für die Beantwortung der Schlüsselfragen wurde eine Gesamtsuche nach systematischen Reviews erstellt. Diese wurde von einer erfahrenen Informationsspezialistin (IM) entworfen und durchgeführt (siehe Kapitel 0).

Diese Recherche wurde von zwei wissenschaftlichen Mitarbeitenden unabhängig voneinander auf Relevanz gesichtet und den definierten PICO-Fragen zugeordnet. Im Anschluss wurden die zugeordneten Reviews dem Kliniker*innenteam vorgestellt und auf ihre Anwendbarkeit überprüft.

Das ausgewählte systematische Review für eine Fragestellung wurde jeweils mit AMSTAR-II (A MeaSurement Tool to Assess systematic Reviews) bewertet und das weitere Vorgehen im Team besprochen.

3.2.2 Primärstudienrecherchen

Für Fragen, die nicht durch systematische Reviews beantwortet werden konnten, entwarf die erfahrene Informationsspezialistin Recherchestrategien und führte die systematischen Recherchen per Schlüsselfrage in verschiedenen relevanten Datenbanken durch. Die resultierenden Treffer wurden jeweils im zweistufigen Verfahren von wissenschaftlich Tätigen in enger Kooperation mit erfahrenen Kliniker*innen gesichtet und ausgewählt. Die einzelnen Literaturrecherchen mit Suchdatum, Flow Charts, Evidenztabellen und Bewertungen sind per Schlüsselfrage zusammengefasst.

3.3 Datenextraktion und Bewertung des Verzerrungsrisikos (Risk of Bias)

Die identifizierten Studien wurden systematisch von einem Mitarbeitenden in Datenextraktionsformulare via Microsoft Excel extrahiert, und von einem zweiten Mitarbeitenden geprüft. Bei methodischen Unklarheiten wurde ein weiterer Wissenschaftler hinzugezogen, bei klinischen Fragen das Kliniker*innenteam kontaktiert.

RCTs wurden mit dem Cochrane Risk of Bias 1 (ROB1) Tool bewertet:

- Generierung der Randomisierungssequenz (selection bias)
- Verdeckte Gruppenzuteilung (selection bias)
- Verblindung von Studienpersonal/-teilnehmer (performance bias)
- Verblindung der Endpunkterhebung/-bewertung (detection bias)
- Fehlende Daten bei der Endpunkterhebung/bewertung (attrition bias)
- Selektives Berichten von Endpunkten (reporting bias)
- Andere Ursachen für Bias

Nicht-randomisierte Studien wurden mit einer angepassten Version der SIGN Checkliste für Kohortenstudien bewertet:

- Populations comparable regarding main confounders, and if not, confounding taken into account?
- Rate of participation/Exclusions reported (selection bias into the study):
- Intervention
    - Was the assessment reliable:
    - Was the intervention assessed more than once:
    - Was the assignment to intervention possibly affected by knowledge of outcome status?
- Drop-out rate & reasons reported?
    - Drop-out rate and reasons similar across groups:
    - If the rate was high: comparison of those lost with available:
- Outcome
    - Outcome measure is well-defined, valid and reliable:
    - Blind outcome assessment to exposure:
    - If not, Knowledge of exposure status likely to influence the outcome?
- Confidence intervals reported:
- Selective reporting (comparison with protocol):
- Other limitations or comments

Die Charakteristika und Endpunktdaten der identifizierten Studien wurden außerdem von den Methodiker*innen in Evidenztabellen nach abgewandelter Vorlage des Onkologischen Leitlinienprogramms extrahiert.

3.4 Meta-analytisches Vorgehen

Meta-analysen wurden mit der Software RevMan erstellt. Generell wurden Random-Effects Meta-analysen von Risk Ratios durchgeführt. Wenn in einer Studie ein adjustierter Effektschätzer berichtet wurde, so wurde dieser vorzugsweise für die Meta-analyse verwendet. In Fällen, in denen keine adjustierten Schätzer vorlagen, wurden die Risk Ratios aus den unadjustierten absoluten Werten (Events, Stichprobengröße pro Gruppe) berechnet.

3.5 Evidenzklassifikation nach GRADE

Die Bewertung der Evidenz erfolgte gemäß der GRADE-Methodik (Grading of Recommendations Assessment, Development and Evaluation). Die Einstufung des Vertrauens in die Evidenz erfolgte getrennt für jede klinische Fragestellung und für jeden patientenrelevanten Endpunkt.

Ausgehend vom Studiendesign (randomisierte kontrollierte Studien: initial hohe Evidenzqualität; Beobachtungsstudien: initial niedrige Evidenzqualität) wurde die Evidenzqualität anhand der folgenden fünf GRADE-Domänen geprüft:

- Verzerrungsrisiko (Risk of Bias): Methodische Limitationen der eingeschlossenen Studien.
- Inkonsistenz der Ergebnisse: Nicht erklärbare Heterogenität der Effektschätzer zwischen den Studien.

- Indirektheit der Evidenz: Abweichungen hinsichtlich Population, Intervention, Vergleich oder Endpunkten im Vergleich zur definierten PICO-Fragestellung.
- Impräzision der Effektschätzung: Breite Konfidenzintervalle oder geringe Ereigniszahlen.
- Publikationsbias: Wahrscheinlichkeit einer systematischen Verzerrung durch selektive Publikation.

Bei Beobachtungsstudien bestand die Möglichkeit einer Aufwertung der Evidenzqualität bei Vorliegen besonderer Kriterien, insbesondere:

- großer oder sehr großer Effekt
- Nachweis einer Dosis-Wirkungs-Beziehung,
- plausible Residualkonfoundierung, die den beobachteten Effekt eher unterschätzen würde.

Die Qualität der Evidenz (Vertrauen in die Evidenz) wird nach GRADE eingeteilt in hoch, moderat, niedrig, und sehr niedrig. Die endpunktbezogene Bewertung der Evidenz (nach GRADE) ist in den Tabellen der jeweiligen PICO-Fragen ersichtlich.

Evidenzqualität	Beschreibung	Symbol
Hohe Evidenzqualität	Wir sind sehr sicher, dass der wahre Effekt nahe bei dem Effektschätzer liegt.	⊕⊕⊕⊕
Moderate Evidenzqualität	Wir haben mäßig viel Vertrauen in den Effektschätzer: der wahre Effekt ist wahrscheinlich nahe bei dem Effektschätzer, aber es besteht die Möglichkeit, dass er relevant verschieden ist.	⊕⊕⊕⊖
Geringe Evidenzqualität	Unser Vertrauen in den Effektschätzer ist begrenzt: Der wahre Effekt kann durchaus relevant verschieden vom Effektschätzer sein.	⊕⊕⊖⊖
Sehr geringe Evidenzqualität	Wir haben nur sehr wenig Vertrauen in den Effektschätzer: Der wahre Effekt ist wahrscheinlich relevant verschieden vom Effektschätzer.	⊕⊖⊖⊖

3.6 Formulierung der Empfehlungen und formale Konsensusfindung

Die eingeschlossenen Studien (systematisches Review und neu identifizierte Primärstudien), die Evidenztabellen, Meta-Analysen sowie die GRADE-Bewertung der Studien wurde den Kliniker*innen als Grundlage für das Formulieren der Empfehlungen zur Verfügung gestellt.

3.6.1 Schema der Empfehlungsgraduierung

Die Methodik des Leitlinienprogramms Onkologie sieht eine Vergabe von Empfehlungsgraden durch die Leitlinienautoren im Rahmen eines formalen Konsensusverfahrens vor. Im Rahmen der Leitlinienentwicklung erfolgte nach Diskussion von Änderungsvorschlägen in den Arbeitsgruppen und innerhalb der Steuergruppe eine jeweils mehrere Online-Abstimmungen über das Leitlinienentwicklungsportal und anschließende Online-Konsensuskonferenzen.

In der Leitlinie werden zu allen evidenzbasierten Statements und Empfehlungen das Evidenzlevel der zugrunde liegenden Studien sowie bei Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung werden in dieser Leitlinie drei Empfehlungsgrade unterschieden, die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln (siehe Tabelle 3).

Tabelle 1: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll/soll nicht
B	Empfehlung	sollte/sollte nicht
0	Empfehlung offen	kann/kann verzichtet werden

3.6.2 Festlegung des Empfehlungsgrades

Grundsätzlich erfolgte eine Anlehnung der evidenzbasierten Empfehlungen hinsichtlich ihres Empfehlungsgrades an die Stärke der verfügbaren Evidenz, d. h. ein hoher Evidenzgrad (z. B. Metaanalysen/systematische Übersichten von RCTs oder mehrere methodisch hochwertige RCTs), d. h. eine hohe Sicherheit bzgl. der Ergebnisse soll in der Regel auch zu einer starken Empfehlung (Empfehlungsgrad A, „soll“) führen.

Zusätzlich werden weitere Kriterien bei der Wahl des Empfehlungsgrades berücksichtigt. Diese folgenden berücksichtigten Kriterien konnten zu einem Abweichen der Empfehlungsstärke nach oben oder unten führen:

1. Konsistenz der Studienergebnisse

Bsp.: Die Effektschätzer der Studienergebnisse gehen in unterschiedliche Richtungen und zeigen keine einheitliche Tendenz.

2. Klinische Relevanz der Endpunkte und Effektstärken

Bsp.: Es liegen zwar Studien mit Ergebnissen in eine Richtung vor, jedoch wird die Bedeutung der gewählten Endpunkte und/oder Effektstärken als nicht relevant eingeschätzt.

3. Nutzen-Risiko-Verhältnis

Bsp.: Dem nachgewiesenen Nutzen einer Intervention steht ein relevanter Schadensaspekt gegenüber, der gegen eine uneingeschränkte Empfehlung spricht.

4. Ethische Verpflichtungen

Bsp.: Downgrading: Aus ethischen Gründen kann eine Intervention mit nachgewiesenem Nutzen nicht uneingeschränkt angeboten werden. Upgrading: Starke Empfehlung auf Basis von z.B. Fall-Kontroll-Studien, da aus ethischen Gründen ein RCT nicht durchführbar ist.

5. Patientinnenpräferenzen

Bsp.: Eine Intervention mit nachgewiesenem Nutzen wird nicht stark empfohlen, da sie von den Patientinnen als belastend oder nicht praktikabel abgelehnt wird.

6. Anwendbarkeit, Umsetzbarkeit in der Versorgung

Bsp.: Eine Intervention mit nachgewiesenen positiven Effekten kann nicht empfohlen werden, weil sie im regionalen Versorgungssystem aus strukturellen Gründen nicht angeboten werden kann.

3.6.3 Formale Konsensusverfahren und Konsensuskonferenzen

Die Abstimmung der Statements und Empfehlungen erfolgte zunächst als elektronische Vorabstimmungen über die Rückmeldeplattform des Leitlinienprogramms Onkologie. Empfehlungen mit einer Zustimmung >95 % und ohne inhaltliche Anmerkungen galten als angenommen. Alle anderen Statements und Empfehlungen wurden anschließend in insgesamt 4 Online-Konsensuskonferenzen unter neutraler Moderation durch Dr. Nothacker (AWMF-iMWI) sowie Dr. Follmann und Herr Langer (OL) am 25.10.2024, 29.11.2024, 07.03.2025 und 11.04.2025 diskutiert und abgestimmt.

Der Konsensusprozess nach dem Typ des National Institute of Health, Webkonferenz mit neutraler Moderation fand wie folgt statt:

- Vorstellung der Empfehlungsvorschläge durch Arbeitsgruppen
- Inhaltliche Klärungen
- Aufnahme von Änderungsvorschlägen, ggf. Zusammenfassung/Priorisierung Abstimmung
- Falls kein Konsens erreicht wurde, erneute Diskussion und ggf. Änderungsvorschläge
- Erneute Abstimmung

Für alle Empfehlungen wurde ein Konsens oder ein starker Konsens erzielt (siehe **Tabelle 4**).

Tabelle 2: Festlegungen hinsichtlich der Konsensusstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	>95% der Stimmberechtigten
Konsens	>75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	>50 – 75% der Stimmberechtigten
Keine mehrheitliche Zustimmung	<50% der Stimmberechtigten

4 PICO-übergreifendes methodisches Vorgehen und Resultate

4.1 Definierte Schlüsselfragen im PICO-Format

Für folgende Schlüsselfragen wurde extern durch das Institut für Öffentliches Gesundheitswesen der Universität zu Köln systematisch gesucht:

Kapitel Diagnostik

PICO 3.1a. Verbessert/verändert bei Patientinnen mit ED Vulvakarzinom die Vulvoskopie + apparative Diagnostik (1. gyn. Sonographie, 2.MRT, 3. CT, 4. PET) verglichen mit dem pathologischen Befund (Histologie) die Diagnosestellung (Sensitivität, Spezifität, NPV, PPV, Staging, OS, DFS, Lebensqualität, Rezidivrate, Therapiestrategie)?

PICO 3.1b. Verbessert bei Patientinnen mit ED HSIL / M. Paget die apparative Diagnostik Vulvoskopie versus Vulvoskopie plus Mapping die Rezidivrate und Persistenz (R1)?

Kapitel Therapie der VIN und M. Paget

PICO 5.1. Verbessert bei Patientinnen mit ED HSIL / M. Paget und primärer Exzision ein bestimmter operativer Sicherheitsabstand das Risiko für ein Lokalrezidiv (local recurrence rate / (local) recurrence free survival), DFS, OS, CSS (cancer specific survival)?

PICO 5.2. Zeigen bei Patientinnen mit LSIL / HSIL / M. Paget die (topische) medikamentöse Therapie versus operative Exzision versus Laservaporisation ähnliche Ergebnisse bzgl. Rezidivrate / Rate invasives Karzinom / Nebenwirkungen / Komplikationen / Lebensqualität?

Kapitel Operatives Management des Primärtumors

PICO 6.1. Verbessert bei Patientinnen mit ED Vulvakarzinom ein bestimmter operativer Sicherheitsabstand das Risiko für ein Lokalrezidiv, Lymphknotenrezidiv, DFS, OS?

PICO 6.3. Zeigt die primär operative Therapie von Patientinnen mit Vulvakarzinom ab Stadium T2 gegenüber der primär operativen Therapie von Patientinnen im Stadium T1 eine erhöhte Rate für postoperative Harninkontinenz und anorektale Inkontinenz?

PICO 6.6. Verbessert bei Patientinnen mit ED Vulvakarzinom T2 und T3 die primäre RT (Radiotherapie) und RChT (Radiochemotherapie) gegenüber der primär operativen Therapie die Rezidivrate, Rate der Exenterationen, Nebenwirkungsspektrum, DFS (Disease-Free Survival), PFS (Progression-Free Survival), MFS (Metastasis-Free Survival), OS (Overall Survival)?

Kapitel Operative Therapie der Lymphabflusswege

PICO 7.2. Verbessert bei Patientinnen mit ED Vulvakarzinom, befallenen inguinalen LK (Lymphknoten) und Indikation zur inguinalen Strahlentherapie mit bildgebend unauffälligen pelvinen LK die systematische pelvine LNE (Lymphonodektomie) +/- Radiatio

in Abhängigkeit nachgewiesener LK-Metastasen versus der pelvinen Radiatio ohne operatives Staging die Rate der LK-Rezidive (insbesondere pelvin) / Morbidität / DFS / OS?

PICO 7.3a. Verbessert eine bds. systematische inguinofemorale LNE plus adj. Radiatio der Lymphabflusswege (LAW) gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und 1 inguinalen LK-Makrometastase die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.3b. Verbessert eine bds. systematische inguinofemorale LNE plus adj. Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und mind. 2 inguinalen LK-Metastasen die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.3c. Verbessert eine bds. systematische inguinofemorale LNE (Lymphonodektomie) plus adj. Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und inguinaler LK-Metastase mit extrakapsulärem Wachstum die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.3d. Verbessert eine bds. systematische inguinofemorale LNE plus adj. Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und fixierten bzw. exulzerierten inguinalen LK-Metastasen die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.5. Verbessert bei Patientinnen mit ED Vulvakarzinom und bulky nodes inguinal und/oder pelvin eine bds. Systematische inguinofemorale bzw. pelvine LNE mit adjuvanter Radiatio gegenüber der alleinigen Entfernung der auffälligen LK mit adjuvanter Radiatio die Rate der LK-Rezidive / Morbidität / DFS / OS?

PICO 7.6a. Verbessert bei Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unauffälligen LAW und bds. inguinofemoraler LNE mit histologisch mind. 1 befallenem LK die inguinofemorale LNE mit mind. 6 entfernten LK pro Leiste gegenüber der inguinofemoralen LNE mit < 6 entfernten LK die Rate der LK-Rezidive seitenbezogen / Morbidität / DFS / OS?

PICO 7.6b. Verbessert bei Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unauffälligen LAW und bds. inguinofemoraler LNE mit histologisch negativen LK die inguinofemorale LNE mit mind. 6 entfernten LK pro Leiste gegenüber der inguinofemoralen LNE mit < 6 entfernten LK die Rate der LK-Rezidive / Morbidität / DFS / OS?

Kapitel Strahlentherapie

PICO 8.1a. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R0 mit minimalen Resektionsrand von > 3 mm die Rezidivrate, DFS, PFS, MFS, OS?

PICO 8.1b. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R0 mit minimalem Resektionsrand </=3mm die Rezidivrate, DFS, PFS, MFS, OS?

PICO 8.1c. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R1 die Rezidivrate, DFS, PFS, MFS, OS?

PICO 8.1d. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit L1 die Rezidivrate, DFS, PFS, MFS, OS?

PICO 8.3. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit mind. 2 befallenen inguinalen LK eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

PICO 8.4a. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit einem befallenen inguinalen LK mit Makrometastase eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

PICO 8.4b. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit inguinal extrakapsulärem Metastasenwachstum eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

PICO 8.4c. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit fixierten bzw. exulzerierten inguinalen LK-Metastasen eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

PICO 8.4d. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler und pelviner LNE mit inguinal und pelvin befallenen LK eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

4.2 Evidenzrecherche für die extern recherchierten Schlüsselfragen

4.2.1 Evidenzrecherche nach systematischen Reviews

Suchdatum aller Datenbanken: 31.10.2022	
Datenbanken	Suche
MEDLINE ALL (via Ovid)	535
Epistemonikos	166
Total	701
Total (after deduplication)	**601**

4.2.1.1 Suchstrategie

MEDLINE (via OVID)

#	Searches
1	Vulvar Neoplasms/
2	(vulva* adj5 (cancer* or tumor* or tumour* or neoplas* or carcino* or malignan* or sarcom* or melano* or adenocarcinom* or adenosquamous* or precancer* or pre-cancer* or premalignan* or pre-malignan*)).tw,kf.
3	vulvamalignom*.tw,kf.
4	Paget Disease, Extramammary/
5	(paget* adj1 (disorder* or cancer* or carcinom* or morbus*)).tw,kf.
6	(paget* and (vulva* or extramammar* or extra-mammar*)).tw,kf.
7	(kraurosis* adj1 vulvae*).tw,kf.
8	Carcinoma in Situ/ and vulva*.tw,kf.
9	carcinoma in situ/ and vulva/
10	(vulva* adj5 (intraepithel* adj2 neoplas*)).tw,kf.
11	(vulva* adj5 (intra-epithel* adj2 neoplas*)).tw,kf.
12	(vulva* adj5 (intraepithel* adj2 carcinom*)).tw,kf.
13	(vulva* adj5 (intra-epithel* adj2 carcinom*)).tw,kf.
14	((VIN or VINS or VIN1* or VIN2* or VIN3* or dVIN*) and vulva*).tw,kf.
15	Squamous Intraepithelial Lesions/
16	(hsil* or ("high grade" adj2 "squamous intraepithelial lesion")).tw,kf.
17	or/1-16
18	cochrane database of systematic reviews.jn. or search*.tw. or meta analysis.pt. or medline.tw. or systematic review.tw. or systematic review.pt.

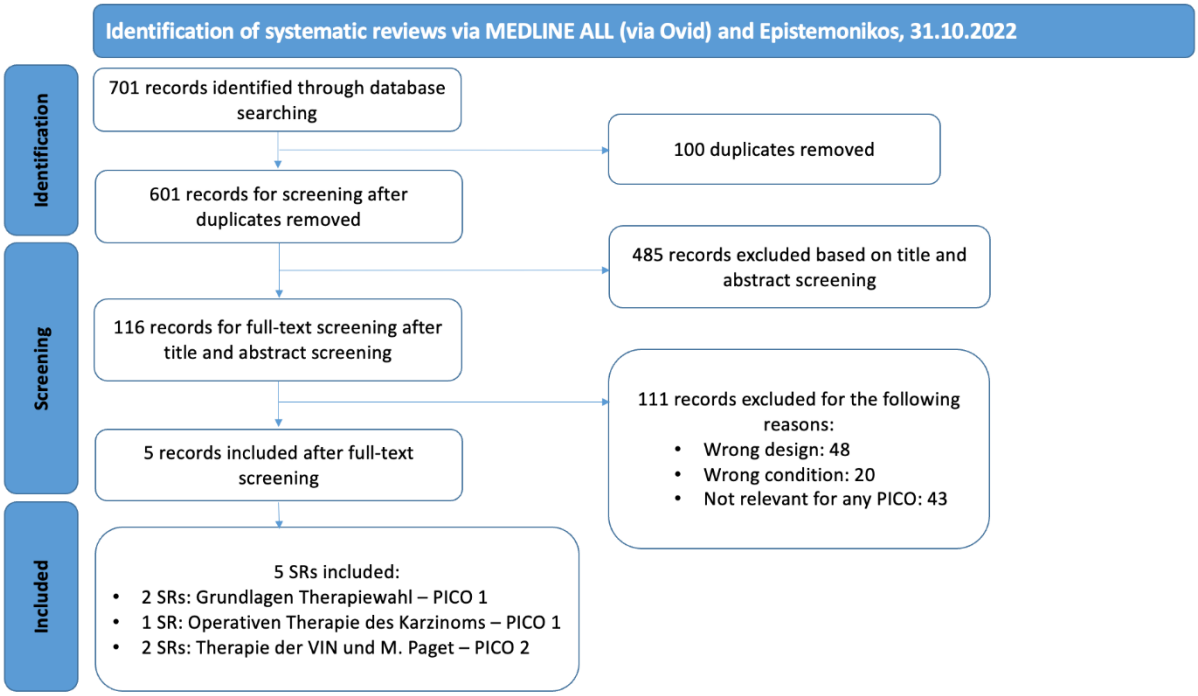
Epistemonikos

title:(vulva* AND (cancer* OR tumor* OR tumour* OR neoplas* OR carcino* OR malignan* OR sarcom* OR melano* OR adenocarcinom* OR adenosquamous* OR precancer* OR pre-cancer* OR premalignan* OR pre-malignan*)) OR (title:(paget* AND (disorder* OR cancer* OR carcinom* OR morbus* OR vulva* OR extramammar* OR extra-mammar*)) OR abstract:(paget* AND (disorder* OR cancer* OR carcinom* OR morbus* OR vulva* OR extramammar* OR extra-mammar*))) OR (title:(vulvamalignom* OR kraurosis* vulvae*) OR abstract:(vulvamalignom* OR kraurosis* vulvae*)) OR (title:(vulva* AND intraepithel* AND neoplas*) OR abstract:(vulva* AND intraepithel* AND neoplas*)) OR (title:(vulva* AND intra-epithel* AND neoplas*) OR abstract:(vulva* AND intra-epithel* AND neoplas*)) OR (title:(vulva* AND intraepithel* AND carcinom*) OR abstract:(vulva* AND intraepithel* AND carcinom*)) OR (title:(vulva* AND intra-epithel* AND carcinom*) OR abstract:(vulva* AND intra-epithel* AND carcinom*)) OR (title:(hsil* AND vulva*) OR abstract:(hsil* AND vulva*)) OR (title:("high grade" AND "squamous intraepithelial lesion" AND vulva*) OR abstract:("high grade" AND "squamous intraepithelial lesion" AND vulva*)) OR (title:((VIN OR VINS OR VIN1* OR VIN2* OR VIN3* OR dVIN*) AND vulva*) OR abstract:((VIN OR VINS OR VIN1* OR VIN2* OR VIN3* OR dVIN*) AND vulva*))

publication type: systematic review

4.2.1.2 PRISMA Flowdiagramm

Insgesamt wurden 701 Treffer erzielt und nach Deduplikation wurden 601 Treffer genauer begutachtet. Die 601 Treffer wurden im zwei-schrittigen Verfahren von zwei Wissenschaftlern unabhängig voneinander gescreent. Zwei systematische Reviews wurden eingeschlossen. Es konnten 5 Systematische Reviews eingeschlossen und den jeweiligen PICOs zugeordnet.



4.2.2 RCT Suche

Suchdatum aller Datenbanken: 31.10.2022	
Datenbanken	Suche
MEDLINE ALL (via Ovid)	2564
CENTRAL	625
CINAHL	573
Total	**3762**
Total (after deduplication)	**3363**

4.2.2.1 Suchstrategie

MEDLINE via OVID 1946 to October 27, 2022

#	Searches
1	Vulvar Neoplasms/
2	(vulva* adj5 (cancer* or tumor* or tumour* or neoplas* or carcino* or malignan* or sarcom* or melano* or adenocarcinom* or adenosquamous* or precancer* or pre-cancer* or premalignan* or pre-malignan*)).tw,kf.
3	vulvamalignom*.tw,kf.
4	Paget Disease, Extramammary/
5	(paget* adj1 (disorder* or cancer* or carcinom* or morbus*)).tw,kf.
6	(paget* and (vulva* or extramammar* or extra-mammar*)).tw,kf.
7	(kraurosis* adj1 vulvae*).tw,kf.
8	Carcinoma in Situ/ and vulva*.tw,kf.
9	carcinoma in situ/ and vulva/
10	(vulva* adj5 (intraepithel* adj2 neoplas*)).tw,kf.
11	(vulva* adj5 (intra-epithel* adj2 neoplas*)).tw,kf.
12	(vulva* adj5 (intraepithel* adj2 carcinom*)).tw,kf.
13	(vulva* adj5 (intra-epithel* adj2 carcinom*)).tw,kf.
14	((VIN or VINS or VIN1* or VIN2* or VIN3* or dVIN*) and vulva*).tw,kf.
15	Squamous Intraepithelial Lesions/
16	(hsil* or ("high grade" adj2 "squamous intraepithelial lesion")).tw,kf.
17	or/1-16
18	randomized controlled trial.pt.
19	controlled clinical trial.pt.
20	randomi?ed.ab.
21	placebo.ab.
22	drug therapy.fs.
23	randomly.ab.
24	trial.ab.
25	groups.ab.
26	or/18-25
27	exp animals/ not humans/
28	26 not 27

29 clinical trial, phase iii/
30 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.
31 (29 or 30) not 27
32 28 or 31
33 17 and 32

Cochrane Central Register of Controlled trials (Central, 2022, Issue 10)

ID Search
#1 MeSH descriptor: [Vulvar Neoplasms] explode all trees
#2 (vulva* NEAR/5 (cancer* or tumor* or tumour* or neoplas* or carcino* or malignan* or sarcom* or melano* or adenocarcinom* or adenosquamous* or precancer* or pre-cancer* or premalignan* or pre-malignan*)):TI,AB,KW
#3 vulvamalignom*:TI,AB,KW
#4 MeSH descriptor: [Paget Disease, Extramammary] this term only
#5 (paget* NEAR/1 (disorder* or cancer* or carcinom* or morbus*)):TI,AB,KW
#6 (paget* and (vulva* or extramammar* or extra-mammar*)):TI,AB,KW
#7 (kraurosis* adj1 vulvae*):TI,AB,KW
#8 MeSH descriptor: [Carcinoma in Situ] this term only
#9 MeSH descriptor: [Vulva] this term only
#10 vulva*:TI,AB,KW
#11 #8 and (#9 or #10)
#12 (vulva* NEAR/5 (intraepithel* NEAR/2 neoplas*)):TI,AB,KW
#13 (vulva* NEAR/5 (intra-epithel* NEAR/2 neoplas*)):TI,AB,KW
#14 (vulva* NEAR/5 (intraepithel* NEAR/2 carcinom*)):TI,AB,KW
#15 (vulva* NEAR/5 (intra-epithel* NEAR/2 carcinom*)):TI,AB,KW
#16 ((VIN or VINS or VIN1* or VIN2* or VIN3* or dVIN*) and vulva*):TI,AB,KW
#17 MeSH descriptor: [Squamous Intraepithelial Lesions] this term only
#18 (hsil* or ("high grade" NEAR/2 "squamous intraepithelial lesion")):TI,AB,KW
#19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18

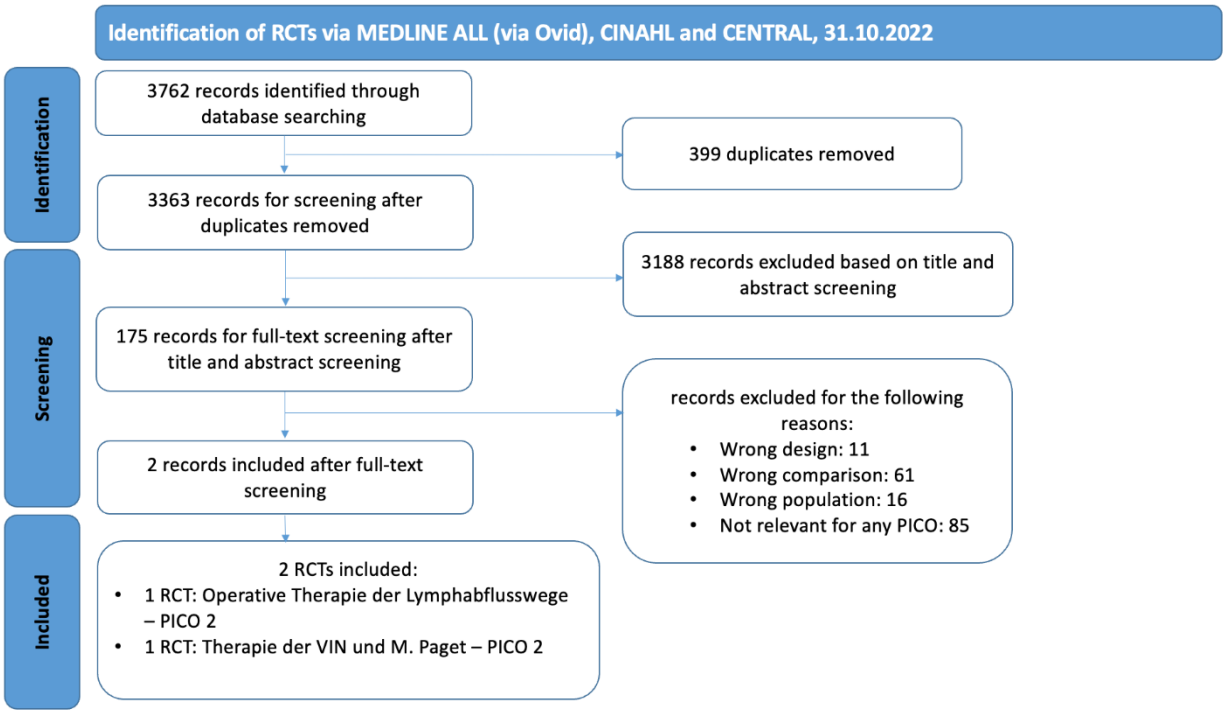
CINAHL via EBSCO

Query
S36 S17 AND S35
S35 S34 NOT S33
S34 S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
S33 S31 NOT S32
S32 MH human
S31 S29 OR S30
S30 TI animal model*
S29 MH animals+ OR MH animal studies
S28 AB cluster W3 RCT
S27 MH crossover design OR MH comparative studies
S26 AB control W5 group
S25 PT randomized controlled trial
S24 MH placebos
S23 MH sample size AND AB (assigned OR allocated OR control)
S22 TI trial
S21 AB random*
S20 TI randomised OR randomized

S19 MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pretest-posttest design OR MH cluster sample
S18 MH randomized controlled trials
S17 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
S16 TI ((hsil* or ("high grade" N2 "squamous intraepithelial lesion"))) OR AB ((hsil* or ("high grade" N2 "squamous intraepithelial lesion")))
S15 (MH "Squamous Intraepithelial Lesions")
S14 TI (((VIN or VINS or VIN1* or VIN2* or VIN3* or dVIN*) and vulva*)) OR AB (((VIN or VINS or VIN1* or VIN2* or VIN3* or dVIN*) and vulva*))
S13 TI (vulva* N5 (intraepithel* N2 carcinom*)) OR AB (vulva* N5 (intraepithel* N2 carcinom*)) OR TI (vulva* N5 (intraepithel* N2 carcinom*)) OR AB (vulva* N5 (intraepithel* N2 carcinom*))
S12 TI (vulva* N5 (intraepithel* N2 neoplas*)) OR AB (vulva* N5 (intraepithel* N2 neoplas*)) OR TI (vulva* N5 (intraepithel* N2 neoplas*)) OR AB (vulva* N5 (intraepithel* N2 neoplas*))
S11 S8 AND (S9 OR S10)
S10 TI vulva* OR AB vulva*
S9 (MH "Vulva")
S8 (MH "Carcinoma in Situ")
S7 TI (kraurosis* N1 vulvae*) OR AB (kraurosis* N1 vulvae*)
S6 TI ((paget* and (vulva* or extramammar* or extra-mammar*))) OR AB ((paget* and (vulva* or extramammar* or extra-mammar*)))
S5 TI ((paget* N1 (disorder* or cancer* or carcinom* or morbus*))) OR AB ((paget* N1 (disorder* or cancer* or carcinom* or morbus*)))
S4 (MH "Paget Disease, Extramammary")
S3 TI vulvamalignom* OR AB vulvamalignom*
S2 TI ((vulva* N5 (cancer* or tumor* or tumour* or neoplas* or carcino* or malignan* or sarcom* or melano* or adenocarcinom* or adenosquamous* or precancer* or pre-cancer* or premalignan* or pre-malignan*))) OR AB ((vulva* N5 (cancer* or tumor* or tumour* or neoplas* or carcino* or malignan* or sarcom* or melano* or adenocarcinom* or adenosquamous* or precancer* or pre-cancer* or premalignan* or pre-malignan*)))
S1 (MH "Vulvar Neoplasms")

4.2.2.2 PRISMA Flowdiagramm

Insgesamt wurden 3762 Treffer erzielt und nach Deduplikation wurden 3363 Treffer genauer begutachtet. Die 3363 Treffer wurden im zwei-schrittigen Verfahren von zwei Wissenschaftlern unabhängig voneinander gescreent. Zwei randomisiert kontrollierte Studien (RCTs) wurden eingeschlossen und den jeweiligen PICOs zugeordnet.



5 PICO-spezifisches methodische Vorgehen

5.1 Kapitel Diagnostik – PICO 3.1a

5.1.1 Fragestellung und geplantes Vorgehen

Verbessert/verändert bei Patientinnen mit ED Vulvakarzinom die Vulvoskopie + apparative Diagnostik (1. gyn. Sonographie, 2.MRT, 3. CT, 4. PET) verglichen mit dem pathologischen Befund (Histologie) die Diagnosestellung (Sensitivität, Spezifität, NPV, PPV, Staging, OS, DFS, Lebensqualität, Rezidivrate, Therapiestrategie)?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnte kein Systematischer Review (SR) oder RCT der PICO zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen.

Daraufhin wurde eine systematische Recherche nach nicht-randomisierten Studien entwickelt, welche mit dem klinischen Team geprüft wurde. Anschließend wurde die Recherche in relevanten Datenbanken laufen gelassen. Die resultierenden 275 Treffer wurden im zweischrittigen Verfahren von zwei Wissenschaftlern unabhängig voneinander gescreent. Es konnten allerdings keine relevante Studie identifiziert werden.

5.1.2 Studienselektion

5.1.2.1 Einschlusskriterien

Population: Patientinnen mit ED Vulvakarzinom

Intervention: Vulvoskopie + zusätzlich weitere Untersuchungen wie (1) MRT, (2) CT, (3) PET (4) Leisten Sonographie (in der gleichen Sitzung) (1, 2, und 4 als Staging Untersuchung)

Comparator: pathologische Befund (Histologie) / Diagnosestellung

Outcomes: Sensitivität, Spezifität, NPV, PPV, Staging, OS, DFS, Lebensqualität, Therapiestrategie

5.1.3 Evidenzrecherche nach non-RCTs

Suchdatum: 07.12.2023	
Datenbanken	Suche
MEDLINE ALL (via Ovid)	275
Total (after deduplication)	**275**

MEDLINE ALL (via OVID) 1946 to December 07, 2023

#	Searches
1	Carcinoma, Squamous Cell/su and vulva*.tw,kf.
2	Vulvar Neoplasms/
3	(vulva* adj7 (cancer* or tumor* or tumour* or neoplas* or carcino* or malignan* or sarcom* or melano* or adenocarcinom* or adenosquamous* or precancer* or pre-cancer* or premalignan* or pre-malignan* or preneoplast* or pre-neoplast*)).tw,kf.
4	Carcinoma in Situ/ and vulva*.tw,kf.
5	carcinoma in situ/ and vulva/
6	or/1-5
7	Colposcopy/
8	colposcop*.tw,kf.
9	vulv?scop*.tw.
10	or/7-9
11	6 and 10

5.2 Kapitel Diagnostik – PICO 3.1b

5.2.1 Fragestellung und geplantes Vorgehen

Verbessert bei Patientinnen mit ED HSIL / M. Paget die apparative Diagnostik Vulvoskopie versus Vulvoskopie plus Mapping die Rezidivrate und Persistenz (R1)?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnten keine relevanten Studiender Schlüsselfrage zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen.

Daraufhin wurde eine systematische Recherche nach nicht-randomisierten Studien entwickelt, welche mit dem klinischen Team geprüft wurde, und anschließend wurde die Suche in relevanten Datenbanken laufen gelassen. Es gab 90 Treffer in der Suche, diese wurden im zweischrittigen Verfahren von zwei Wissenschaftlern unabhängig voneinander gescreent. Es konnten allerdings keine relevante Studie identifiziert und der PICO zugeordnet werden.

5.2.2 Studienselektion

5.2.2.1 Einschlusskriterien

Population: Frauen mit Vorstufen High-grade squamous intraepithelial lesion (HSIL) / M.Paget)

Intervention: Vulvoskopie

Comparator: Vulvoskopie + Mapping

Outcomes: Rezidivrate, Persistenz (R1)

5.2.3 Evidenzrecherche

Suchdatum: 21.03.2024	
Datenbanken	Suche
MEDLINE ALL (via Ovid)	90
Total (after deduplication)	**90**

Ovid MEDLINE(R) ALL 1946 to March 20, 2024

#	Searches
1	Paget Disease, Extramammary/
2	(paget* adj1 (disorder* or cancer* or carcinom* or morbus*)).tw,kf.
3	(paget* and (vulva* or extramammar* or extra-mammar*)).tw,kf.
4	(kraurosis* adj1 vulvae*).tw,kf.
5	Carcinoma in Situ/ and vulva*.tw,kf.
6	carcinoma in situ/ and vulva/
7	(vulv* adj5 (intraepithel* adj2 neoplas*)).tw,kf.
8	(vulv* adj5 (intra-epithel* adj2 neoplas*)).tw,kf.
9	(vulv* adj5 (intraepithel* adj2 carcinom*)).tw,kf.
10	(vulv* adj5 (intra-epithel* adj2 carcinom*)).tw,kf.
11	((VIN or VINS or VIN1* or VIN2* or VIN3* or dVIN*) and vulva*).tw,kf.
12	Squamous Intraepithelial Lesions/
13	(hsil* or ("high grade" adj2 "squamous intraepithelial lesion")).tw,kf.
14	or/1-13
15	map*.ti,ab,kf.
16	14 and 15

5.3 Kapitel Therapie der VIN und M. Paget – PICO 5.1

5.3.1 Fragestellung und geplantes Vorgehen

Verbessert bei Patientinnen mit ED HSIL / M. Paget und primärer Exzision ein bestimmter operativer Sicherheitsabstand das Risiko für ein Lokalrezidiv (local recurrence rate / (local) recurrence free survival), DFS, OS, CSS (cancer specific survival)?

Subgroup Mohs surgery (MMS) vs. wide local excision (WLE)

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnte kein Systematischer Review (SR) oder RCT der PICO zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen. Daraufhin wurde eine systematische Recherche nach nicht-randomisierten Studien entwickelt, welche mit dem klinischen Team geprüft wurde. Anschließend wurde die Recherche in relevanten Datenbanken durchgeführt. Die 619 Treffer wurden im zwei-schrittigen Verfahren von zwei Wissenschaftlern unabhängig voneinander gescreent. Es konnten zwei relevante Kohortenstudie (Matsuo, 2021) (Bruce, 2023) identifiziert und den PICOs zugeordnet werden. Die Bruce 2023 Studie geht insbesondere auf die Subgruppe von Mohs surgery (MMS) und wide local excision (WLE) ein.

Literaturreferenz:

Matsuo K, Nishio S, Matsuzaki S, et al. Surgical margin status and recurrence pattern in invasive vulvar Paget's disease: A Japanese Gynecologic Oncology Group study. *Gynecol Oncol* 2021;160(3):748-54. https://doi.org/10.1016/j.ygyno.2020.12.023

Bruce KH, Kilts TP, Lohman ME, Vidal NY, Fought AJ, McGree ME, Keeney GL, Baum CL, Brewer JD, Bakkum-Gamez JN, Cliby WA. Mohs surgery for female genital Paget's disease: a prospective observational trial. Am J Obstet Gynecol. 2023 Dec;229(6):660.e1-660.e8. doi: 10.1016/j.ajog.2023.08.018.

Das weitere Vorgehen war wie folgt:

- Datenextraktion der Studien
- Methodische Bewertung der Kohortenstudien anhand der SIGN cohort study checklist
- GRADE (Bewertung der Vertrauenswürdigkeit in die gefundene Evidenz pro Endpunkt)

5.3.2 Studienselektion

5.3.2.1 Einschlusskriterien

Population: Patientinnen mit ED HSIL / M. Paget

Intervention: Primäre Exzision: Wide excision, MOH surgery

Komparator: andere primäre Exzision

Outcomes: Lokalrezidiv / RFS/ DFS / OS /CSS

5.3.3 Evidenzrecherche

Suchdatum: 13.02.2024	
Datenbanken	Suche
MEDLINE ALL (via Ovid)	619
Total (after deduplication)	**619**

Ovid MEDLINE(R) ALL 1946 to February 08, 2024

#	Searches
1	Carcinoma, Squamous Cell/su and vulva*.tw,kf.
2	Genital Neoplasms, Female/ or Vulvar Neoplasms/
3	Carcinoma in Situ/ and vulva*.tw,kf.
4	carcinoma in situ/ and vulva/
5	(vulva* adj7 (cancer* or tumor* or tumour* or neoplas* or carcino* or malignan* or sarcom* or melano* or adenocarcinom* or adenosquamous* or precancer* or pre-cancer* or premalignan* or pre-malignan* or preneoplast* or pre-neoplast*)).tw,kf.
6	vulvamalignom*.tw,kf.
7	Paget Disease, Extramammary/
8	(paget* adj1 (disorder* or cancer* or carcinom* or morbus*)).tw,kf.
9	(paget* and (vulva* or extramammar* or extra-mammar*)).tw,kf.
10	((kraurosis* adj1 vulvae*) or EMPD).tw,kf.
11	Carcinoma in Situ/ and vulva*.tw,kf.
12	carcinoma in situ/ and vulva/
13	(vulv* adj5 (intraepithel* adj2 neoplas*)).tw,kf.
14	(vulv* adj5 (intra-epithel* adj2 neoplas*)).tw,kf.
15	(vulv* adj5 (intraepithel* adj2 carcinom*)).tw,kf.
16	(vulv* adj5 (intra-epithel* adj2 carcinom*)).tw,kf.
17	((VIN or VINS or VIN1* or VIN2* or VIN3* or dVIN*) and vulva*).tw,kf.

18 Squamous Intraepithelial Lesions/
19 (hsil* or ("high grade" adj2 "squamous intraepithelial lesion")).tw,kf.
20 or/1-19
21 exp microsurgery/ or mohs surgery/
22 ((moh? adj3 (surger* or surgical* or biops*)) or (moh? adj2 (microsurg* or chemsurg*)) or (moh? adj3 (excision* or technique* or technic*))).tw,kf.
23 or/21-22
24 "margins of excision"/
25 (wide adj2 excision*).tw,kf.
26 ((primar* or first) adj2 excision*).tw,kf.
27 (margin? adj2 (patholog* or excision* or resection* or re-section* or surgical* or tumour* or tumor* or close? or large* or small* or positiv* or negativ* or status or free)).tw,kf.
28 or/24-27
29 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
30 ((control and study) or group* or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp.
31 or/29-30
32 (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
33 hi.fs. or case report.mp.
34 or/32-33
35 31 not 34
36 20 and (23 or 28) and 35
37 Remove duplicates from 36

5.4 Kapitel Therapie der VIN und M. Paget – PICO 5.2

5.4.1 Fragestellung und geplantes Vorgehen

Zeigen bei Patientinnen mit LSIL / HSIL / M. Paget die (topische) medikamentöse Therapie versus operative Exzision versus Laservaporisation ähnliche Ergebnisse bzgl. Rezidivrate / Rate invasives Karzinom / Nebenwirkungen / Komplikationen / Lebensqualität?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnten zwei Systematische Reviews (SR) und ein RCT der PICO zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen. Ein SR (Lawrie, 2016) beinhaltete relevante Ergebnisse und das zweite SR (Edey, 2019) wurde ohne Resultate publiziert. Das identifizierte RCT (Trutnovsky, 2022) wurde nach dem SR von Lawrie 2016) publiziert und berichtete Ergebnisse zur topischen medikamentösen Therapie versus operativen Exzision.

Literaturreferenz:

Lawrie TA, Nordin A, Chakrabarti M, Bryant A, Kaushik S, Pepas L. Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia. Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD011837.DOI: 10.1002/14651858.CD011837.pub2

Edey, KA, Allan, E, Murdoch, JB, Cooper, S, Bryant, A. Interventions for the treatment of Paget's disease of the vulva. Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD009245. DOI: 10.1002/14651858.CD009245.pub3

Trutnovsky G, Reich O, Joura EA, Holter M, Ciresa-König A, Widschwendter A, Schauer C, Bogner G, Jan Z, Boandl A, Kalteis MS, Regauer S, Tamussino K. Topical imiquimod versus surgery for vulvar intraepithelial neoplasia: a multicentre, randomised, phase 3, non-inferiority trial. Lancet. 2022 May 7;399(10337):1790-1798. doi: 10.1016/S0140-6736(22)00469-X. Epub 2022 Apr 25. Erratum in: Lancet. 2022 Oct 8;400(10359):1194. doi: 10.1016/S0140-6736(22)01888-8

Das weitere Vorgehen war wie folgt:

- Datenextraktion der Studien
- Methodische Bewertung der SRs anhand vom AMSTAR-2 Tool
- Methodische Bewertung des RCTs anhand des Cochrane Risk of Bias 1 Tool
- GRADE (Bewertung der Vertrauenswürdigkeit in die gefundene Evidenz pro Endpunkt)

5.5 Kapitel Operatives Management des Primärtumors – PICO 6.1

5.5.1 Fragestellung und geplantes Vorgehen

Verbessert bei Patientinnen mit ED Vulvakarzinom ein bestimmter operativer Sicherheitsabstand das Risiko für ein Lokalrezidiv, Lymphknotenrezidiv, DFS, OS?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews konnte ein systematisches Review der PICO zugeordnet werden. Im Folgenden wurden dieses SR mit dem klinischen Team besprochen und auf Relevanz geprüft. Da in dem identifizierten SR (Nooij, 2016) das Recherchedatum 2012 war, wurde zusammen mit dem klinischen Team beschlossen, eine aktualisierte Recherche durchzuführen, basierend auf der Suchstrategie von Nooij 2016. Es wurde nach allen Studiendesigns gesucht. Aus der Suche ergaben sich 957 Treffer, welche im zwei-schrittigen Verfahren von zwei Wissenschaftlern unabhängig voneinander gescreent.

In der PICO-übergreifenden Evidenzrecherche nach RCTs, konnte kein RCT der PICO zugeordnet werden.

Literaturreferenzen:

Nooij LS, van der Slot MA, Dekkers OM, Stijnen T, Gaarenstroom KN, Creutzberg CL, Smit VT, Bosse T, van Poelgeest MI. Tumour-free margins in vulvar squamous cell carcinoma: Does distance really matter? Eur J Cancer. 2016 Sep;65:139-49. doi: 10.1016/j.ejca.2016.07.006

Iacoponi, S., Zapardiel,I., Diestro, M. D., Alicia Hernandez, A. & De Santiago, J. Prognostic factors associated with local recurrence in squamous cell carcinoma of the vulva. J Gynecol Oncol. 2013 Jul;24(3):242-248. https://doi.org/10.3802/jgo.2013.24.3.242

Nooij LS, van der Slot MA, Dekkers OM, Stijnen T, Gaarenstroom KN, Creutzberg CL, Smit VT, Bosse T, van Poelgeest MI. Tumour-free margins in vulvar squamous cell carcinoma: Does distance really matter? Eur J Cancer. 2016 Sep;65:139-49. doi: 10.1016/j.ejca.2016.07.006

Liu, L., O'Donnell, P., Sullivan, R., Katalinic, A., Moser, E. C., de Boer, A. & Meunier, F. Cancer in Europe: Death sentence or life sentence?. European Journal of Cancer. 2016 Dez; 65:150-155. https://doi.org/10.1016/j.ejca.2016.07.007

Woelber, L., Griebel, L. F., Eulenburg, C., Sehouli, J., Jueckstock J., Hilpert, F. et al. Role of tumour-free margin distance for loco-regional control in vulvar cancer—a subset analysis of the Arbeitsgemeinschaft Gynäkologische Onkologie CaRE-1 multicenter study. European Journal of Cancer. 2016 Dez; 69, 180-188. https://doi.org/10.1016/j.ejca.2016.09.038

Gasimli, K., Straussner, M., Schmeil, I., Karn, T., Winkelmann, R., Becker, S. et al. Impact of re-excision of residual adjacent vulvar intraepithelial neoplasia (VIN III) and histological tumour-free margin (hTFM) on survival in primary squamous cell carcinoma of vulva. Gynecology and Obstetrics. 2018 Sep; 298: 945–950. https://dx.doi.org/10.1007/s00404-018-4887-1

Micheletti, L., Preti, M., Cintolesi, V., Corvetto, E., Privitera, S., Palmese, E. & Benedettol, C. Prognostic impact of reduced tumor-free margin distance on long-term survival in FIGO stage IB/II vulvar squamous cell carcinoma, J Gynecol Oncol. 2018 Sep;29(5): e61. https://doi.org/10.3802/jgo.2018.29.e61

Minar, L., Felsinger, M., Cihalova1, M., Zlamal, F. & Bienertova-Vasku, Vulvar cancer recurrence — an analysis of prognostic factors in tumour-free pathological margins patients groupJ. Ginekologia Polska. 2018 Aug; 89 (8): 425-432. https://dx.doi.org/10.5603/GP.a2018.0073

Pleunis, N., Leermakers, M. E.J., van der Wurff, A., Klinkhamer, P. J.J.M.,. Ezendam, N.P.M., Boll, D. et al. Surgical margins in squamous cell carcinoma, different for the vulva?. European Journal of Surgical Oncology. 2018 Okt; 44 (10): 1555-1561. https://doi.org/10.1016/j.ejso.2018.05.031

Raimond, E., Delorme, C., Ouldamer, L., Carcopino, X., Bendifallah, S., Touboul, C. et al. Surgical treatment of vulvar cancer: Impact of tumor-free margin distance on recurrence and survival. A multicentre cohort analysis from the francogyn study group. European Journal of Surgical Oncology. 2019 Nov; 45 (11) 2109-2114. https://doi.org/10.1016/j.ejso.2019.07.005

Te Grootenhuis, N. C., Pouwer, A.W., de Bock, G.H., Hollema, H., Bulten, J., van der Zee A.G.J. et al. Margin status revisited in vulvar squamous cell carcinoma. Gynecologic Oncology. 2019 Aug; 154 (2): 266-275. https://doi.org/10.1016/j.ygyno.2019.05.010

Barlow, E. L. Jackson, M. & Hacker, N.F. The Prognostic Role of the Surgical Margins in Squamous Vulvar Cancer: A Retrospective Australian Study. Cancers. 2020 Nov; 12(11): 3375 https://doi.org/10.3390/cancers12113375

Yang, J., Delara, R., Ghaith, S., Newman, H., Magrina, J., Butler, K. et al. Tumor-free margins and local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol. 2020 Sep;158(3):555-561. doi: 10.1016/j.ygyno.2020.06.503

Matsuo, K., Nishio, S., Matsuzaki, S., Iwase, H., Kagami, S., Soeda, S. et al. Surgical margin status and recurrence pattern in invasive vulvar Paget's disease: A Japanese Gynecologic Oncology Group study. Gynecologic Oncology. 2021; Mar: 160 (3): 748-754. https://doi.org/10.1016/j.ygyno.2020.12.023

Arvas, M., Kahramanoglu, I., Bese, T., Turan, H., Sozen, I., Ilvan, S. et al. The Role of Pathological Margin Distance and Prognostic Factors After Primary Surgery in Squamous Cell Carcinoma of the Vulva. International Journal of Gynecological cancer. 2018; 28 (3): 623-631. http://dx.doi.org/10.1097/IGC.0000000000001195

Di Donato, V., Page, Z., Bracchi, C., Tomao, F., Musella, A., Perniola, G. et al. The age-adjusted Charlson comorbidity index as a predictor of survival in surgically treated vulvar cancer patients. J Gynecol Oncol. 2019 Jan;30(1):e6. https://doi.org/10.3802/jgo.2019.30.e6

Ferrari, F., Forte, S., Ardighieri, L., Bonetti, E., Fernando, B., Sartori, E. et al. European Journal of Surgical Oncology. Multivariate analysis of prognostic factors in primary squamous cell vulvar cancer: The role of perineural invasion in recurrence and survival. 2019 Nov;45 (11): 2115-2119. https://doi.org/10.1016/j.ejso.2019.07.029

Gitas, G., Proppe, L., Baum, S., Kruggel, M., Rody, A., Tsolakidis, D. et al. A risk factor analysis of complications after surgery for vulvar cancer. Gynecologic Oncology. 2021 Jan.; 304: 511–519. https://dx.doi.org/10.1007/s00404-020-05949-w

Micheletti, L., Borella, F., Preti, M., Frau, V., Cosma, S., Privitera, S. et al. Perineural Invasion in Vulvar Squamous-Cell Carcinoma Is an Independent Risk Factor for Cancer-Specific Survival, but Not for Locoregional Recurrence: Results from a Single Tertiary Referral Center. Cancers, 2022 Jan;14(1):124. https://doi.org/10.3390/cancers14010124

Schleiss-Andreassen, J. L., Kristensen, E., Frøding, L. P., Stæhr, E., Høgdall, C. et al. Assessment of recurrence rate and risk factors of relapse in stage in IA vulvar carcinoma. Gynecologic Oncology. 2022 Mar; 164 (3): 543-549. https://doi.org/10.1016/j.ygyno.2021.12.020

Das weitere Vorgehen war wie folgt:

- Datenextraktion der Studien
- Methodische Bewertung der SRs anhand vom AMSTAR-2 Tool
- Methodische Bewertung der Kohortenstudien anhand der SIGN cohort study checklist
- GRADE (Bewertung der Vertrauenswürdigkeit in die gefundene Evidenz pro Endpunkt)

5.5.2 Studienselektion

5.5.2.1 Einschlusskriterien

Population: Frauen, Patientinnen mit ED Vulvakarzinom

Intervention: bestimmter operativer Sicherheitsabstand

Comparator: vergleichender operativer Sicherheitsabstand

Outcomes: Lokalrezidiv, Lymphknotenrezidiv, DFS, OS

5.5.3 Evidenzrecherche

Suchdatum: 25.07.2023	
Datenbanken	Suche
MEDLINE ALL (via Ovid)	960
Total (after deduplication)	**957**

Relevante PubMed ID's:

("23747330" or "21594705" or "17095080" or "2227541" or "12436 439" or "20606536" or "23875074" or "12468158" or "19305336" or "26507171" or "27837710").ui.

sind enthalten.

MEDLINE (via OVID) ALL 1946 to July 24, 2023

#	Searches
1	Carcinoma, Squamous Cell/su and vulva*.tw,kf.
2	Vulvar Neoplasms/
3	(vulva* adj7 (cancer* or tumor* or tumour* or neoplas* or carcino* or malignan* or sarcom* or melano* or adenocarcinom* or adenosquamous* or precancer* or pre-cancer* or premalignan* or pre-malignan*)).tw,kf.
4	Carcinoma in Situ/ and vulva*.tw,kf.
5	carcinoma in situ/ and vulva/
6	or/1-5
7	exp Gynecologic Surgical Procedures/
8	surgery.fs.
9	"margins of excision"/
10	Neoplasm Recurrence, Local/
11	(local* adj2 recurrenc*).tw.
12	(surg* or dissect* or resection* or margin*).tw.
13	(rate? adj3 (recurrenc* or recrudescenc*)).tw.
14	or/7-13
15	6 and 14
16	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/

17	((control and (study or group*)) or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp.
18	group?.tw.
19	or/16-18
20	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
21	hi.fs. or case report.mp.
22	or/20-21
23	19 not 21
24	15 and 23
25	limit 24 to yr="2012 -Current"
26	remove duplicates from 25

5.6 Kapitel Operatives Management des Primärtumors – PICO 6.3

5.6.1 Fragestellung und geplantes Vorgehen

Zeigt die primär operative Therapie von Patientinnen mit Vulvakarzinom ab Stadium T2 gegenüber der primär operativen Therapie von Patientinnen im Stadium T1 eine erhöhte Rate für postoperative Harninkontinenz und anorektale Inkontinenz?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnte kein Systematischer Review (SR) oder RCT der PICO zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen. Es wurde entschieden keine weitere Suche für diese PICO zu erstellen, aufgrund von vermuteter fehlender Evidenz zu der Fragestellung.

5.7 Kapitel Operatives Management des Primärtumors – PICO 6.6

5.7.1 Fragestellung und geplantes Vorgehen

Verbessert bei Patientinnen mit ED Vulvakarzinom T2 und T3 die primäre (Radiotherapie) RT und (Radiochemotherapie) RChT gegenüber der primär operativen Therapie die Rezidivrate, Rate der Exenterationen, Nebenwirkungsspektrum, DFS, PFS, MFS, OS?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews konnten zwei Systematische Reviews (SR) der PICO zugeordnet werden. Das erste SR untersucht die „Primäre RT und RChT versus primäre operative Therapie“ (Shylasree 2011) und das zweite SR untersucht die „Primäre RT der Leiste/Groin (primary radiotherapy of the inguinofemoral lymph nodes) versus Primäre operative Therapie der Leiset/Groin (inguinofemoral lymph node dissection)“ (van der Velden, 2011). Im Folgenden wurden diese systematischen Reviews mit dem klinischen Team besprochen und auf Relevanz geprüft.

In der PICO-übergreifenden Evidenzrecherche nach RCTs konnte keine RCTs identifiziert. Da zwei relevante systematische Reviews identifiziert werden konnten, wurde keine weitere Recherche nach nicht-randomisierten Studien durchgeführt.

Literaturreferenzen:

Shylasree TS, Bryant A, Howells REJ. Chemoradiation for advanced primary vulval cancer. Cochrane Database of Systematic Reviews 2011, Issue 4. Art. No.: CD003752. DOI: 10.1002/14651858.CD003752.pub3.

van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulvar cancer. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD002224. DOI: 10.1002/14651858.CD002224.pub2.

Das weitere Vorgehen war wie folgt:

- Datenextraktion der beiden SRs
- Methodische Bewertung der SRs anhand des AMSTAR-2 Tools
- GRADE (Bewertung der Vertrauenswürdigkeit in die gefundene Evidenz pro Endpunkt)

5.8 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.2

5.8.1 Fragestellung und geplantes Vorgehen

Verbessert bei Patientinnen mit ED Vulvakarzinom, befallenen inguinalen Lymphknoten (LK) und Indikation zur inguinalen Strahlentherapie mit bildgebend unauffälligen pelvinen LK die systematische pelvine Lymphonodektomie (LNE) +/- Radiatio in Abhängigkeit nachgewiesener Lymphknoten Metastasen versus der pelvinen Radiatio ohne operatives Staging die Rate der Lymphknotenrezidive (insbesondere pelvin) / Morbidität / DFS / OS?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnte kein systematisches Review (SR) der PICO zugeordnet werden, allerdings konnte ein RCT (Kunos, 2009) der PICO zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen.

Literaturreferenzen:

Kunos, Charles MD, PhD1; Simpkins, Fiona MD2,3,6; Gibbons, Heidi MS3; Tian, Chunqiao PhD4; Homesley, Howard MD5. Radiation Therapy Compared With Pelvic Node Resection for Node-Positive Vulvar Cancer: A Randomized Controlled Trial. Obstetrics & Gynecology 114(3):p 537-546, September 2009. DOI: 10.1097/AOG.0b013e3181b12f99

Das weitere Vorgehen war wie folgt:

- Datenextraktion des RCTs
- Methodische Bewertung des RCTs anhand des Cochrane Risk of Bias 1 Tool
- GRADE (Bewertung der Vertrauenswürdigkeit in die gefundene Evidenz pro Endpunkt)

5.9 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.3

5.9.1 Fragestellung und geplantes Vorgehen

7.3a. Verbessert eine beidseitige systematische inguinofemorale Lymphonodektomie (LNE) plus adjuvant Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und 1 inguinalen Lymphknoten Makrometastase die Rate der Lymphknoten Rezidive / Morbidität / DFS / OS?

7.3b. Verbessert eine beidseitige systematische inguinofemorale Lymphonodektomie (LNE) plus adjuvant Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und mind. 2 inguinalen Lymphknoten Metastasen die Rate der Lymphknotenrezidiv / Morbidität / DFS / OS?

7.3c. Verbessert eine beidseitige systematische inguinofemorale Lymphonodektomie (LNE) plus adjuvant Radiatio der LAW gegenüber der alleinigen beidseitige systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und inguinaler Lymphknoten Metastase mit extrakapsulärem Wachstum die Rate der Lymphknotenrezidiv / Morbidität / DFS / OS?

7.3d. Verbessert eine beidseitige systematische inguinofemorale Lymphonodektomie (LNE) plus adjuvant Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und fixierten bzw. exulzerierten inguinalen Lymphknoten Metastasen die Rate der Lymphknotenrezidiv / Morbidität / DFS / OS?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnte kein systematisches Review (SR) oder RCT der PICO zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen. Daraufhin wurde eine systematische Recherche nach nicht-randomisierten Studien für die vier Schlüsselfragen 3a, 3b, 3c, 3d gemeinsam entwickelt, welche mit dem klinischen Team geprüft wurde. Anschließend wurde die Recherche in relevanten Datenbanken durchgeführt. Die 1260 Treffer wurden im zwei-schrittigen Verfahren von zwei Wissenschaftlern unabhängig voneinander gescreent. Es konnten vier relevante Kohortenstudie (Rydzewski, 2018) (Fons, 2009) (Mahner, 2015) (Parthasarathy, 2006) identifiziert und den PICOs zugeordnet werden.

Literaturreferenz:

Fons, G., Groenen, S.M.A., Oonk, M.H.M., Ansink, A.C., van der Zee, A.G.J., Burger, M.P.M., Stalpers, L.J.A. & van der Velden, J. (2009). Adjuvant radiotherapy in patients with vulvar cancer and one intra capsular lymph node metastasis is not beneficial. Gynecologic Oncology 114; 343–345. https://dx.doi.org/10.1016/j.ygyno.2009.05.017

Rydzewski, N.R., Kanis, M.J., Donnelly, E. C., Lurain, J.R., Strauss, J.B. (2018). Role of adjuvant external beam radiotherapy and chemotherapy in one versus two or more node-positive vulvar cancer: A National Cancer Database study. Radiotherapy and Oncology,129 (3); 534-539.https://doi.org/10.1016/j.radonc.2018.03.023

Mahner, S., Jueckstock, J., Hilpert, F., Neuser, P., Harter, P., de Gregorio, N., Hasenburg, A., Sehouli, J et al. (2015) Adjuvant Therapy in Lymph Node–Positive Vulvar Cancer: The AGO-CaRE-1 Study. Journal of the National Cancer Institute, 107 (3); dju426. https://doi.org/10.1093/jnci/dju426

Parthasarathy, A., Cheung, M.K., Osann, K., Husain, A., Teng, N.N., Berek, J.S. Kapp, D.S. et al. (2006). The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. Gynecologic Oncology 103; 1095–1099. https://doi:10.1016/j.ygyno.2006.06.030

Das weitere Vorgehen war wie folgt:

- Datenextraktion der Studien
- Methodische Bewertung der Kohortenstudien anhand der SIGN cohort study checklist
- GRADE (Bewertung der Vertrauenswürdigkeit in die gefundene Evidenz pro Endpunkt)

5.9.2 Studienselektion

5.9.2.1 Einschlusskriterien

Population: Patientinnen mit ED Vulvakarzinom und 1 inguinalen Lymphknoten Makrometastase

Intervention: beidseitige systematische inguinofemorale Lymphonodektomie (LNE) plus adjuvant Radiatio der LAW

Komparator: der alleinigen beidseitige systematischen inguinofemoralen LNE

Outcomes: Lymphknotenrezidiv / Morbidität / DFS / OS

5.9.3 Evidenzrecherche

Suchdatum: 23.08.2023	
Datenbanken	Suche
MEDLINE ALL (via Ovid)	1260
Total (after deduplication)	**1260**

Relevante PubMed ID's: ("16889821" or "25618900" or "20537946" or "7773938" or "29631932" or "7923005" or " 19481242").ui. enthalten.

MEDLINE (via OVID) ALL, 2000 to August 22, 2023
Search Strategy:

#	Searches
1	Carcinoma, Squamous Cell/su and vulva*.tw,kf.
2	Vulvar Neoplasms/
3	(vulva* adj7 (cancer* or tumor* or tumour* or neoplas* or carcino* or malignan* or sarcom* or melano* or adenocarcinom* or adenosquamous* or precancer* or pre-cancer* or premalignan* or pre-malignan*)).tw,kf.
4	Carcinoma in Situ/ and vulva*.tw,kf.
5	carcinoma in situ/ and vulva/
6	or/1-5
7	groin/ or inguinal canal/
8	groin.tw.
9	or/7-8
10	lymph nodes/ or sentinel lymph node/
11	Lymphatic Metastasis/pa, rt, su [Pathology, Radiotherapy, Surgery]
12	Neoplasm Micrometastasis/pa, rt [Pathology, Radiotherapy]
13	Neoplasm Metastasis/pa, rt, su [Pathology, Radiotherapy, Surgery]
14	(node or nodes or nodal).tw,kf.
15	or/10-14
16	lymph node excision/ or sentinel lymph node biopsy/
17	(lymphadenectom* or dissection* or excision* or resection* or surger* or surgical).tw,kf.
18	(IFL or ILND or LAE).tw,kf.
19	or/16-18
20	inguin*.tw,kf.
21	pelvic*.tw.
22	20 or 21
23	6 and 22
24	6 and 9 and 15
25	6 and 19
26	23 or 24 or 25

27 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
28 ((control and (study or group*)) or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp. or group*.tw.
29 27 or 28
30 (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
31 hi.fs. or case report.mp.
32 30 or 31
33 29 not 32
34 26 and 33
35 ("16889821" or "25618900" or "20537946" or "7773938" or "29631932" or "7923005" or " 19481242").ui.
36 34 and 35
37 limit 34 to yr="2000 -Current"
38 limit 34 to yr="1980 - 2000"

5.10 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.5

5.10.1 Fragestellung und geplantes Vorgehen

Verbessert bei Patientinnen mit ED Vulvakarzinom und bulky nodes inguinal und/oder pelvin eine beidseitige systematische inguinofemorale bzw. pelvine LNE mit adjuvanter Radiatio gegenüber der alleinigen Entfernung der auffälligen Lymphknoten mit adjuvanter Radiatio die Rate der Lymphknotenrezidive / Morbidität / DFS / OS?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnte kein Systematischer Review (SR) oder RCT der PICO zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen. Daraufhin wurde eine systematische Recherche nach nicht-randomisierten Studien in relevanten Datenbanken laufen gelassen. Die 1260 Treffer wurden im zwei-schrittigen Verfahren von zwei Wissenschaftlern unabhängig voneinander gescreent. Es konnten drei relevante Kohortenstudie (Fons, 2023) (Hyde, 2007) (Nooij, 2015) identifiziert und der PICO zugeordnet werden.

Literaturreferenzen:

Fons G, Thuijs NB, Tjiong M, Stalpers LJA, van der Velden J. Selective Removal of Only Clinically Suspicious Positive Lymph Nodes Instead of a Complete Inguino-Femoral Lymph Node Dissection in Squamous Cell Carcinoma of the Vulva. Cancers (Basel). 2023 Jul 28;15(15):3844. doi: 10.3390/cancers15153844

Hyde SE, Valmadre S, Hacker NF, Schilthuis MS, Grant PT, van der Velden J. Squamous cell carcinoma of the vulva with bulky positive groin nodes-nodal debulking versus full groin dissection prior to radiation therapy. Int J Gynecol Cancer. 2007 Jan-Feb;17(1):154-8. doi: 10.1111/j.1525-1438.2006.00769.x

Nooij LS, Ongkiehong PJ, van Zwet EW, Bosse T, Creutzberg CL, Gaarenstroom KN, van Poelgeest MI. Groin surgery and risk of recurrence in lymph node positive patients with vulvar squamous cell carcinoma. Gynecol Oncol. 2015 Dec;139(3):458-64. doi: 10.1016/j.ygyno.2015.09.081

Das weitere Vorgehen war wie folgt:

- Datenextraktion der Studien
- Methodische Bewertung der Kohortenstudien anhand der SIGN cohort study checklist
- GRADE (Bewertung der Vertrauenswürdigkeit in die gefundene Evidenz pro Endpunkt)

5.10.2 Studienselektion

5.10.2.1 Einschlusskriterien

Population: Patientinnen mit ED Vulvakarzinom und bulky nodes inguinal und/oder pelvin

Intervention: bds. Systematische inguinofemorale bzw. pelvine Lymphonodektomie mit adjuvanter Radiatio

Komparator: alleinigen Entfernung der auffälligen LK mit adjuvanter Radiatio

Outcomes: LK-Rezidive / Morbidität / DFS / OS

5.10.3 Evidenzrecherche

Die Suche nach relevanten Referenzen (37568661 or 26432039 or 17291247) wurde gemeinsam mit der non-RCT PICO 3 Recherche durchgeführt und damit war keine separate Suche notwendig. Für die detaillierte Suchstrategie siehe 5.7.3.

5.11 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.6

5.11.1 Fragestellung und geplantes Vorgehen

7.6a. Verbessert bei Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unauffälligen LAW und bds. inguinofemoraler LNE mit histologisch mind. 1 befallenem LK die inguinofemorale Lymphonodektomie mit mind. 6 entfernten Lymphknoten pro Leiste gegenüber der inguinofemoralen Lymphonodektomie mit < 6 entfernten Lymphknoten die Rate der LK-Rezidive seitenbezogen / Morbidität / DFS / OS?

7.6b. Verbessert bei Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unauffälligen LAW und bds. inguinofemoraler Lymphonodektomie mit histologisch negativen LK die inguinofemorale Lymphonodektomie mit mind. 6 entfernten LK pro Leiste gegenüber der inguinofemoralen Lymphonodektomie mit < 6 entfernten LK die Rate der LK-Rezidive / Morbidität / DFS / OS?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnte kein systematisches Review oder RCT der PICO zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen. Daraufhin wurde eine systematische Recherche nach nicht-randomisierten Studien in relevanten Datenbanken durchgeführt. Die 1260 Treffer wurden im zwei-schrittigen Verfahren von zwei Wissenschaftlern unabhängig voneinander gescreent. Es konnten fünf relevante Kohortenstudie (Baiocchi, 2023) (Courtney-Brooks, 2010) (Diehl 2016) (Sopracordevole 2018) (Wu 2018) identifiziert und den PICOs zugeordnet werden.

Literaturreferenz:

Baiocchi G, Cestari FM, Rocha RM, Faloppa CC, Kumagai LY, Fukazawa EM, Badiglian-Filho L, Cestari LA, Rodrigues IS, Lavorato-Rocha A, Maia BM, Soares FA. Does the count after inguinofemoral lymphadenectomy in vulvar cancer correlate with outcome? Eur J Surg Oncol. 2013 Apr;39(4):339-43. doi: 10.1016/j.ejso.2013.02.012.

Courtney-Brooks M, Sukumvanich P, Beriwal S, Zorn KK, Richard SD, Krivak TC. Does the number of nodes removed impact survival in vulvar cancer patients with node-negative disease? Gynecol Oncol. 2010 May;117(2):308-11. doi: 10.1016/j.ygyno.2010.01.007.

Diehl A, Volland R, Kirn V, Thangarajah F, Eichler C, Einzmann T, Wirtz M, Ratiu D, Morgenstern B, Fridrich C, Mallmann P, Puppe J. The number of removed lymph nodes by inguinofemoral lymphadenectomy: impact on recurrence rates in patients with vulva carcinoma. Arch Gynecol Obstet. 2016 Jul;294(1):131-6. doi: 10.1007/s00404-015-3932-6.

Sopracordevole F, Clemente N, Giorda G, Canzonieri V, Alessandrini L, Del Fabro A, Serri M, Ciavattini A. Number of Nodes Removed With Inguinofemoral Lymphadenectomy and Risk of Isolated Groin Recurrence in Women With FIGO Stage IB-II Squamous Cell Vulvar Cancer. Int J Gynecol Cancer. 2018 Oct;28(8):1600-1605. doi: 10.1097/IGC.0000000000001326.

Wu SG, Zhang WW, Sun JY, Chen QH, He ZY, Zhou J. Prognostic Value of the Number of Removed Lymph Nodes in Vulvar Squamous Cell Carcinoma Patients With Node-Positive Disease: A Population-Based Study. Front Oncol. 2018 May 30;8:184. doi: 10.3389/fonc.2018.00184.

Das weitere Vorgehen war wie folgt:

- Datenextraktion der Studien
- Methodische Bewertung der Kohortenstudien anhand der SIGN cohort study checklist
- GRADE (Bewertung der Vertrauenswürdigkeit in die gefundene Evidenz pro Endpunkt)

5.11.2 Studienselektion

5.11.2.1 Einschlusskriterien

PICO 6a:

Population: Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unauffälligen LAW und bds. inguinofemoraler LNE mit histologisch mind. 1 befallenem LK

Intervention: inguinofemorale Lymphonodektomie mit mind. 6 entfernten LK pro Leiste

Komparator: inguinofemoralen Lymphonodektomie mit < 6 entfernten LK

Outcomes: LK-Rezidive seitenbezogen / Morbidität / DFS / OS

PICO 6a:

Population: Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unauffälligen LAW und bds. inguinofemoraler LNE mit histologisch negativen LK

Intervention: inguinofemorale Lymphonodektomie mit mind. 6 entfernten LK pro Leiste

Komparator: der inguinofemoralen Lymphonodektomie mit < 6 entfernten LK

Outcomes: LK-Rezidive / Morbidität / DFS / OS

5.11.3 Evidenzrecherche

Die Suche nach relevanten Referenzen ("23518307" or "23422324" or "26498758" or "30036227" or "26498758" or "24662136" or "29900126" or "30036227" or "23327062" or "20153883") wurde gemeinsam mit der non-RCT PICO 3 Recherche durchgeführt und damit war keine separate Suche notwendig. Für die detaillierte Suchstrategie siehe 5.7.3. Kapitel Strahlentherapie – PICO 8.1

5.11.4 Fragestellung und geplantes Vorgehen

8.1a. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R0 mit minimalen Resektionsrand von > 3 mm die Rezidivrate, DFS, PFS, MFS, OS?

8.1b. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R0 mit minimalem Resektionsrand </=3mm die Rezidivrate, DFS, PFS, MFS, OS?

8.1c. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R1 die Rezidivrate, DFS, PFS, MFS, OS?

8.1d. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit L1 die Rezidivrate, DFS, PFS, MFS, OS?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnte kein Systematischer Review (SR) oder RCT der PICO zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen. Es wurde beschlossen, diese PICOs (1a, 1b, 1c, 1d) also konsensbasierte Empfehlung einzuschließen und zu erwähnen, dass keine Studien (SR oder RCTs) gefunden wurden. Es wurde entschieden keine weitere Suche für diese PICO zu erstellen, aufgrund von fehlender Evidenz zu der Fragestellung.

5.12 Kapitel Strahlentherapie – PICO 8.3 und 8.4a-4d

5.12.1 Fragestellung und geplantes Vorgehen

8.3. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit mind. 2 befallenen inguinalen LK eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

8.4a. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit einem befallenen inguinalen LK mit Makrometastase eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

8.4b. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit inguinal extrakapsulärem Metastasenwachstum eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

8.4c. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit fixierten bzw. exulzerierten inguinalen LK-Metastasen eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

8.4d. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler und pelviner LNE mit inguinal und pelvin befallenen LK eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnten zwei Systematische Reviews (SR) und kein RCT der PICO zugeordnet werden. Im Folgenden wurden das weitere Vorgehen und die Ergebnisse mit dem klinischen Team besprochen. Die beiden identifizierten SRs (Kunos, 2009) (Stehman, 1992) wurden extrahier und bewertet, allerdings konnten die Studien aus den SRs nicht zusammengetragen (gepoolt) werden, da sie zu heterogen von der eingeschlossenen Population und Intervention waren. Die Ergebnisse wurden separat berichtet. Die Ergebnisse des rezentesten SR (Kunos 2009) wurde für die Bewertung der Evidenz nach GRADE berücksichtigt.

Literaturreferenzen:

Kunos, C., Simpkins, F., Gibbons, H. & Tian, C. (2009). Radiation Therapy Compared With Pelvic Node Resection for Node-Positive Vulvar Cancer and Howard Homesley. Obstetrics & Gynecology, 114(3): 537-546. https://dx.doi.org/10.1097/AOG.0b013e3181b12f99

Stehman, F., Bundy, B., Thomas, G., Varia, M., Okagaki, F., Roberts, J. et al. (1992). GROIN DISSECTION VERSUS GROIN RADIATION IN CARCINOMA OF THE VULVA: A GYNECOLOGIC ONCOLOGY GROUP STUDY. J Radiuriun Onmlog Biol Phvs. 24; 389-396. https://dx.doi.org/10.1097/AOG.0b013e3181b12f100

Das weitere Vorgehen war wie folgt:

- Datenextraktion der beiden SRs
- Methodische Bewertung der SRs anhand vom AMSTAR-2 Tool
- GRADE (Bewertung der Vertrauenswürdigkeit in die gefundene Evidenz pro Endpunkt)

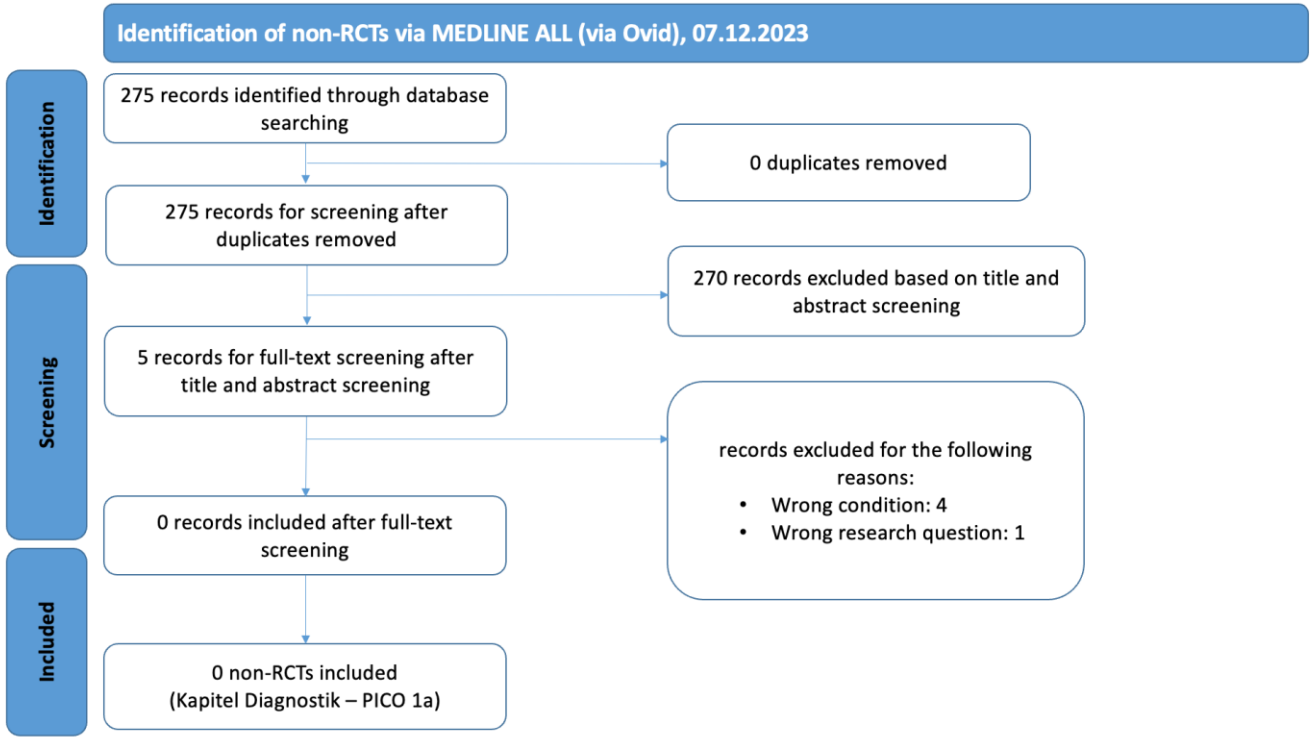
6 Ergebnisse der extern recherchierten Schlüsselfragen

6.1 Kapitel Diagnostik – PICO 3.1a

Verbessert/verändert bei Patientinnen mit ED Vulvakarzinom die Vulvoskopie + apparative Diagnostik (1. gyn. Sonographie, 2.MRT, 3. CT, 4. PET) verglichen mit dem pathologischen Befund (Histologie) die Diagnosestellung (Sensitivität, Spezifität, NPV, PPV, Staging, OS, DFS, Lebensqualität, Rezidivrate, Therapiestrategie)?

Es konnten keine relevante Studie identifiziert und der PICO zugeordnet werden.

6.1.1 PRISMA Flowdiagramm

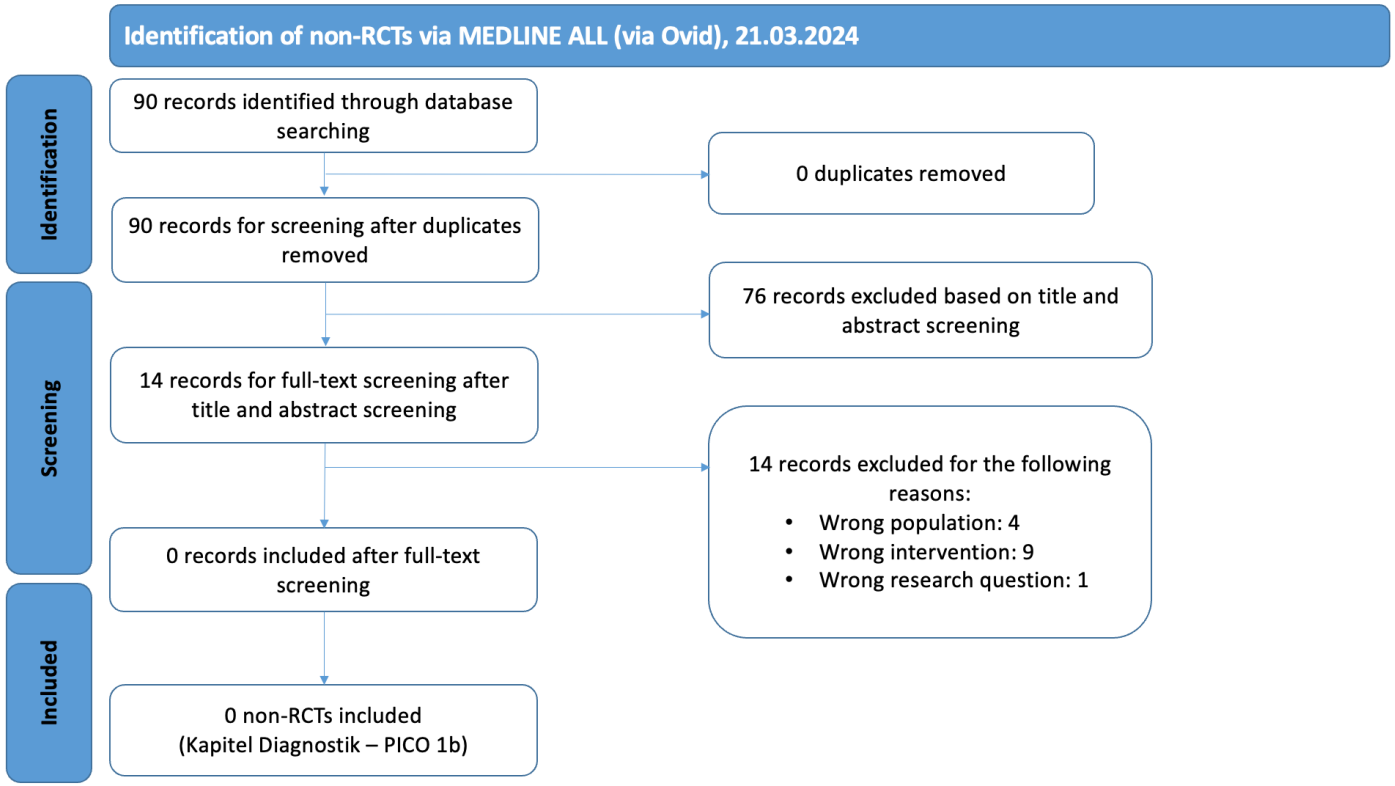


6.2 Kapitel Diagnostik – PICO 3.1b

Verbessert bei Patientinnen mit ED HSIL / M. Paget die apparative Diagnostik Vulvoskopie versus Vulvoskopie plus Mapping die Rezidivrate und Persistenz (R1)?

Es konnten keine relevante Studie identifiziert und der PICO zugeordnet werden.

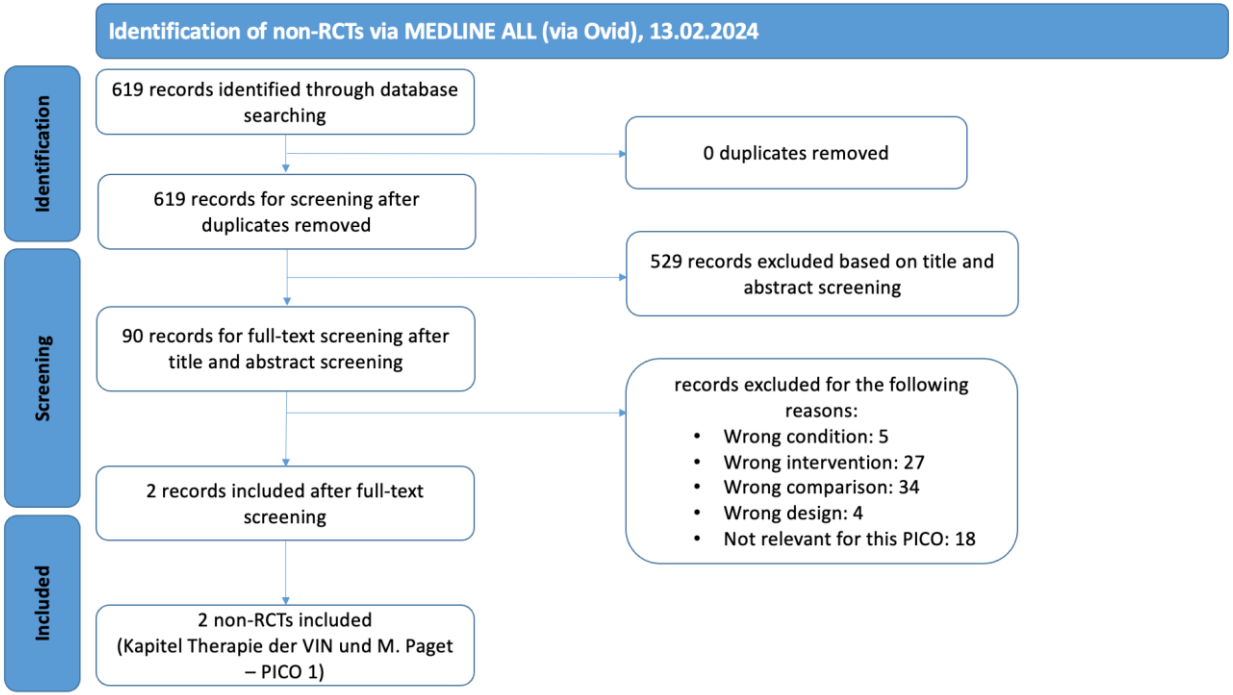
6.2.1 PRISMA Flowdiagramm



6.3 Kapitel Therapie der VIN und M. Paget – PICO 5.1

Verbessert bei Patientinnen mit ED HSIL / M. Paget und primärer Exzision ein bestimmter operativer Sicherheitsabstand das Risiko für ein Lokalrezidiv (local recurrence rate / (local) recurrence free survival), DFS, OS, CSS (cancer specific survival)?

6.3.1 PRISMA Flowdiagramm



6.3.2 Evidenztabellen

6.3.2.1 Primärstudien (non-RCTs)

Matsuo K, Nishio S, Matsuzaki S, et al. Surgical margin status and recurrence pattern in invasive vulvar Paget's disease: A Japanese Gynecologic Oncology Group study. *Gynecol Oncol* 2021;160(3):748-54. https://doi.org/10.1016/j.ygyno.2020.12.023

Bruce KH, Kilts TP, Lohman ME, Vidal NY, Fought AJ, McGree ME, Keeney GL, Baum CL, Brewer JD, Bakkum-Gamez JN, Cliby WA. Mohs surgery for female genital Paget's disease: a prospective observational trial. Am J Obstet Gynecol. 2023 Dec;229(6):660.e1-660.e8. doi: 10.1016/j.ajog.2023.08.018.

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** • 2001-2010 **Descriptive statistics** • Age at diagnosis (median, range)	**Interventions** **(a sensitivity analysis in the study)** A: positive surgical margin (n=49) B: margin <1cm (n=41) **Analysis** • Type of analysis: For overall survival the Kaplan-Meier method was used to construct the survival curves, and statistical	**Local recurrence rate (5-year rates)** • A: 35.8% • B: 10.5% p=0.003 (in favour of B, increased risk of local-recurrence for positive surgical margin) **Distant recurrence rate** • A: 18.3% • B: 12.8% p=0.346 **Recurrence free survival** • NR	**General information** • Median follow-up: median follow-up of 5.8 years • **Funding**: Ensign Endowment for Gynecologic Cancer Research (K.M.) • **CoI**: Honorarium, Chugai, Astra Zeneca (T.E.); research funding, Merck Sharp & Dorme (S.M.); honorarium, Chugai, textbook editorial expense, Springer, and investigator meeting attendance expense, VBL therapeutics (K.M.). **Risk of bias considerations (adapted from SIGN cohort study checklist)**

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· Total: 71 (37-95) · Positive margin: 71.5 (IQR 65-74.5) · <1cm 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%) · <1cm margin: stage I-II (n= 32, 78%) stage III-IV (n= 9, 22%) • Tumor size · Total: 5.0 (IQR 3.0-6.9) cm < 5 cm: 41 (29.5%) ≥ 5 cm: 52 (37.4%) · Positive margin: 5.0 (IQR 3.3-7.3) < 5 cm: 13 (26.5%) ≥ 5 cm: 20 (40.8%) · <1cm margin:	difference between groups was assessed with log-rank test on univariable analysis. A Cox proportional 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	**DFS** • NR **OS (5-year)** • A: 72.6% • B: 91.6% p=0.012 (in favour of B, lower overall survival rate for positive surgical margin) **CSS (cancer specific survival)** • NR	• 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: (→If not, Knowledge of exposure status likely to influence the outcome?:): no? • Main cofounders taken into account: no • Confidence intervals reported: no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	5.0 (IQR 3.4–7.0) < 5 cm: 15 (36.6%) ≥ 5 cm: 19 (46.3%) • Surgical margin · Positive margin: 49 (35.3%) · < 1cm: 41 (29.5%) · ≥ 1cm: 18 (12.9%) · NR: 31 (22.3%) • Surgery type: · Simple vulvectomy: *n*=64, 46.0% positive margin (n=25, 39.1%) <1cm margin (n=20, 31.3%) · radical vulvectomy: *n*=39, 28.1% positive margin (n=16, 41%) <1cm margin (n=9, 23.1%) · Partial vulvectomy: *n*=36, 25.9% positive margin (n=8, 22.2%) <1cm margin (n=12, 33.3%) • Chemotherapy · positive margin Yes: n=4, 8.2% · <1cm margin Yes: n=3, 7.3% • Radiotherapy · positive margin Yes: n=6, 12.2% · <1cm margin Yes: n=1, 2.4%			• Selective reporting (comparison with protocol): no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Bruce, 2023 Prospective observational cohort trial (NCT03564483) ➔ Comparison data from retrospective cohort study (Long 2017 (10.1016/j.ygyno.2017.09.008))	87 pts with Extramammary Paget's disease (female genital EMPD) · 24 pts from the prospective cohort (MMS-guided WLE) (Bruce, 2023) · 63 pts retrospective cohort (WLE) (Long 2017 (10.1016/j.ygyno.2017.09.008)) **Inclusion criteria (for analysis):** • Females • Age 18 years or older • Diagnosed (histologically confirmed female genital EMPD) with primary or recurrent EMPD of vulva and/or perianal region of the body • Willing and able to provide signed informed consent **Exclusion criteria (for analysis):** • Males • Diagnosis of Paget's Disease in body areas other than vulvar or perianal region **Enrolment period** • January 1, 2018– July 30, 2022 • prospective cohort was compared with a retrospective cohort of patients who	**Interventions** A: surgical excision guided by Mohs micrographic surgery (MMS-guided WLE) **(n=24)** B: Wide local excision (WLE) (n=63) **Analysis** • Type of analysis: Kaplan-Meier method was used • Matching: NR • Confounders: NR	**Local recurrence rate** • NR **Recurrence free survival (3-years RFS)** • A: 93.3% (95% CI 81.5%-100.0%), 1/24 pts with noninvasive perianal disease experienced recurrence within 3 years after MMS • 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=0.04 **DFS** • NR **OS (3-year)** • A: 100% • B: 100% **CSS (cancer specific survival)** • NR **Other outcomes:**	**General information** • Median follow-up: NR • **Funding**: 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). • **CoI**: NR **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: Prospective observational cohort (compared with data from retrospective cohort) • Populations comparable: no information • Rate of participation/Exclusions reported (selection bias into the

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	underwent traditional WLE between January 1, 1990, and December 31, 2015 **Descriptive statistics** • Age at Pagets surgery (y, mean, SD) · MMS-guided WLE: 65.2 (9.5) · WLE: 70.3 (10.5) • Primary site · MMS-guided WLE Genital (vulvar, periclitoral, and/or vaginal): 15 (62.5) Perianal: 3 (12.5) 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 (≤1 mm): 1 (4.2) Invasion (>1 mm): 1 (4.2) · WLE No invasion (in situ): 60 (95.2)		**Surgical specimen size:** • A: median 11.3cm (IQR, 7.5-14.0) • B: median 9.5cm (IQR, 6.9-13.0) • P= 0.20 Grade 3 or higher postoperative complications • A: 0.0% ◆ B: 2.4% P= 0.99 **Complex reconstructive procedures** • A: 66.7% • B: 30.2% P<0.01	study): NR (note: not sure how they cam up with N= 63 pts from the retrospective WLE cohort, "based on inclusion criteria") • Exposure/Intervention · Assessment reliable: yes · 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: yes · Blind outcome assessment to exposure: (→If not, Knowledge of exposure status likely to influence the outcome?:): no • 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
	Superficial or focal (≤1 mm): 3 (4.8) Invasion (>1 mm): / • Race (white) · MMS-guided WLE: 22 (91.7%) · WLE: 60 (95.2%) • Surgical specimen size (cm): media (IQR) · MMS-guided WLE: 11.3 (7.5-14.0) · WLE: 9.6 (6.9-13.0)			

6.3.3 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen:

Matsuo K, Nishio S, Matsuzaki S, et al. Surgical margin status and recurrence pattern in invasive vulvar Paget's disease: A Japanese Gynecologic Oncology Group study. *Gynecol Oncol* 2021;160(3):748-54. https://doi.org/10.1016/j.ygyno.2020.12.023

Positive margin versus margin distance <1cm								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → 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 → 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
Low → 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

Literaturreferenzen:

Bruce KH, Kilts TP, Lohman ME, Vidal NY, Fought AJ, McGree ME, Keeney GL, Baum CL, Brewer JD, Bakkum-Gamez JN, Cliby WA. Mohs surgery for female genital Paget's disease: a prospective observational trial. Am J Obstet Gynecol. 2023 Dec;229(6):660.e1-660.e8. doi: 10.1016/j.ajog.2023.08.018.

Subgroup: Mohs surgery (MMS) versus wide local excision (WLE)								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → 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

6.4 Kapitel Therapie der VIN und M. Paget – PICO 5.2

Zeigen bei Patientinnen mit LSIL / HSIL / M. Paget die (topische) medikamentöse Therapie versus operative Exzision versus Laservaporisation ähnliche Ergebnisse bzgl. Rezidivrate / Rate invasives Karzinom / Nebenwirkungen / Komplikationen / Lebensqualität?

6.4.1 Evidenztabellen

6.4.1.1 Systematische Reviews

Lawrie TA, Nordin A, Chakrabarti M, Bryant A, Kaushik S, Pepas L. Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia.Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD011837.DOI: 10.1002/14651858.CD011837.pub2.

Edey, KA, Allan, E, Murdoch, JB, Cooper, S, Bryant, A. Interventions for the treatment of Paget's disease of the vulva. Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD009245. DOI: 10.1002/14651858.CD009245.pub3.

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Lawrie et al., 2016 ➔ SR	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** • Women aged over 18 years with a confirmed histological diagnosis of uVIN, VIN 2 or 3, high-grade VIN or vulval HSIL, which was	**Question/ Aim:** To determine which interventions are the most effective, safe and tolerable for treating women with high-grade VIN (uVIN). **Summary of findings table 1:** Imiquimod compared with placebo for usual-type vulval intraepithelial neoplasia → not applicable for	11 studies on 975 pts with usual-type vulval intraepithelial neoplasia (data from 5 studies are relevant for this guideline PICO) **Descriptive statistics:** • Described for each study separated in the review,	**Results from comparison 3 of the SR:** Surgical excision versus laser vaporization or other **Recurrence-free survival** **Van Esch 2013** • 37/73 women (51%) experienced recurrence: · 16/33 (48.5%) in excision group · 14/25 (56%) in laser vaporization group • No difference, p-value = 0.142 (1 NRS with 73 women, low-certainty evidence) **Leufflen 2013 ((laser vaporisation versus excision, one year follow-up)**	• 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 • Data extraction in duplicate: yes • List of excluded studies: yes • sufficient detail on studies: yes • RoB assessed: yes	**RCTs** Mathiesen 2007 Naik 2006 Sterling 2005 Tristram 2014 van Seters 2008 von Gruenigen 2007 **Non-RCTs (NRS)** Fehr 2001 Fehr 2013 Leufflen 2013 van Esch 2013

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	either unifocal or multifocal **Exclusion criteria:** • women with a histological diagnosis of Paget's disease, vulval carcinoma and VIN 1	this guideline PICO 1 **Summary of findings table 2:** Imiquimod compared with cidofovir for usual-type vulval intraepithelial neoplasia → not applicable for this guideline PICO 1 **Summary of findings table 3:** Surgical interventions compared with photodynamic therapy or other interventions for usual-type vulval		• HR = 5.9, 95% CI 1.3 to 26.3; P value < 0.01 • "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 confounders (including differentiated-type VIN (dVIN) and multifocality); therefore this finding should be interpreted with caution." • recurrence rate one year after treatment = 22% (11 women) **Fehr 2013 (excision versus laser vaporisation)** • OR = 1.79, 95% CI 1.11 to 2.91; P value = 0.017 • 123/411 women (30%) experienced recurrent disease at least one year after initial diagnosis • "favoured laser vaporisation over excision"	• Funding of incl. studies: yes • MA appropriate: yes • RoB considered in MA: yes • RoB in interpretation: yes • Heterogeneity explained: yes • Publication bias investigated: yes • Sources of CoI: none declared	Vlastos 2002

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
		intraepithelial neoplasia **Surgical excision versus laser vaporization or other** **Laser vaporisation versus CUSA** **Photodynamic therapy versus laser vaporisation and surgical excision** **LEEP versus laser vaporisation and surgical excision**		→The 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). **Progression to vulval cancer** • Van Esch 2013: 15.1% women developed invasive disease		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				• Fehr 2013: 5.8% women developed invasive disease • Leufflen 2013: 2% women developed invasive disease **Severe adverse events** • NR **Carbon dioxide (CO2) laser vaporisation versus ultrasonic surgical aspiration (CUSA)** **Recurrence rate** • RR = 1.53, 95% CI 0.65–4.15 (1 RCT with 30 women, low-certainty evidence) (von Gruenigen 2007) **Severe adverse events** • Pain: mean difference (MD) 1.70, 95% CI -26.80 to 23.40 • Scarring: 5/16 versus 0/14 in the laser and CUSA groups, respectively.		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				• Dysuria or burning on micturition: RR 0.66, 95% CI 0.18 to 2.44 • Adhesions: 1/16 versus 0/14 in the laser and CUSA groups, respectively • Infection (yeast, urinary tract infection, other): RR 0.88, 95% CI 0.14 to 5.42 • Abnormal discharge: RR 1.75, 95% CI 0.18 to 17.29) • Eschar: RR 0.88, 95% CI 0.14 to 5.42 **Photodynamic therapy versus laser vaporisation and surgical excision** **Disease-free survival (DFS)** • No difference, p-value = 0.67 (1 NRS with 52 women, very low-certainty evidence) (Fehr 2001) ➔ Not applicable for this guideline		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
				Loop electrosurgical excision procedure (LEEP) versus laser vaporisation and surgical excision **Recurrence-free survival** • No difference, p-value = 0.194 (1 NRS with 62 women, very low-certainty evidence) (Vlastos 2002) **Other outcomes:** **Rate of invasive carcinoma** • NR **Side effects** • NR **Quality of life** • NR		
Edey et al., 2019	Types of studies: RCT & well-designed NRS	**Question/ Aim** To evaluate the benefits and	0 studies on 0 pts with Paget's disease of the vulva **Descriptive statistics:**	**Recurrence rate** • NR **Rate of invasive carcinoma**	**Overall confidence in results of SR (AMSTAR-2): "moderate"**	NR (keine Studien eingeschlossen)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
➔ SR (ohne Resultate)	Searched from inception until 2019 **Databases:** • Cochrane Central Register of Controlled Trials, MEDLINE, Embase **Inclusion criteria** • RCT &well-designed NRS • women aged 18 years or older with Paget's disease of the vulva, n=10 - >10 **Exclusion criteria:** • no participants exclusion criteria. • excluded case-controlled studies, uncontrolled observational	harms of different treatment modalities for the management of Paget's disease of the vulva. A: Tumour-free margin: NR B: Tumour-free margin: NR	• NA	• NR **Side effects and adverse events** • NR **Quality of life** • NR	• PICO elements: yes • A priori design: yes • Justification for design: yes • Literature search >= 2 databases, search strategy + other sources: yes • Selection in duplicate: yes • Data extraction in duplicate: yes • List of excluded studies: yes • sufficient detail on studies: yes • RoB assessed: no • Funding of incl. studies: no • MA appropriate: no • RoB considered in MA: no • RoB in interpretation: no • Heterogeneity explained: no	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	studies and case series of fewer than 10 women.				• Publication bias investigated: no **Sources of CoI:** none declared	

6.4.1.2 Primärstudien (RCT)

Trutnovsky G, Reich O, Joura EA, Holter M, Ciresa-König A, Widschwendter A, Schauer C, Bogner G, Jan Z, Boandl A, Kalteis MS, Regauer S, Tamussino K. Topical imiquimod versus surgery for vulvar intraepithelial neoplasia: a multicentre, randomised, phase 3, non-inferiority trial. Lancet. 2022 May 7;399(10337):1790-1798. doi: 10.1016/S0140-6736(22)00469-X. Epub 2022 Apr 25. Erratum in: Lancet. 2022 Oct 8;400(10359):1194. doi: 10.1016/S0140-6736(22)01888-8

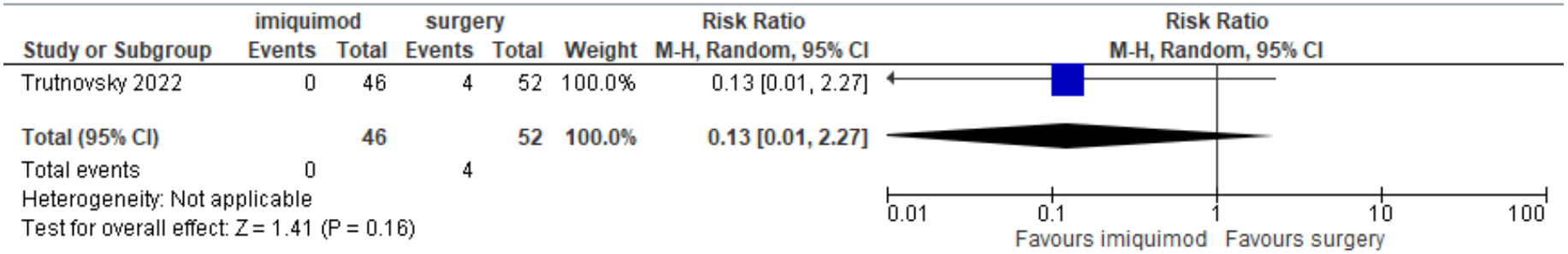
Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Trutnovsky, 2022 RCT (NCT 01861535)	110 patients with vHSIL (106 allocated and 98 per-protocol for clinical response) **Inclusion criteria (for analysis):** • female patients aged 18–90 years with histologically confirmed vHSIL with visible unifocal or multifocal lesions **Exclusion criteria (for analysis):** • clinical suspicion of invasion,	**Interventions** A: 5% imiquimod cream (Aldara; Meda Pharma, Bad Homburg, Germany) (N=56 in intention-to-treat analysis, 46	**Recurrent disease or partial response*** • 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**	**General information** • **Follow-up**: at baseline and after 6 and 12 months after local imiquimod treatment or one surgical intervention • **Funding**: Austrian Science Fund (KLI 293) and the Austrian Gynaecological Oncology group, study sponsor: Medical University of Graz • **CoI**: no competing interests

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• a history of vulvar cancer or severe inflammatory dermatosis of the vulva, • any active treatment for vHSIL within the previous 3 months, • known immunodeficiency, • pregnancy, lactating women **Enrolment period** • 07.06.2013–08.01.2020 **Descriptive statistics** • Age (mean, SD) · A: 53 (15.7) · B: 50.2 (14.4) • Menopausal status: · Premenopausal, A: 22 (39%), B: 30 (57%) · Postmenopausal, A: 34 (61%), B: 23 (43%) • HPV vaccination · None, A: 54 (96%), B: 48 (91%) · Started or completed, A: 2 (4%), B: 5 (9%) • Previous treatment for VIN · A: 13 (23%), B: 8 (15%) · 1 surgery, A: 9 (75%), B: 6 (86%) · 2–5 surgeries, A: 3 (25%), B: 1 (14%)	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	• A: 0/46 • B: 4/52 (8%) • RR= 0.13, 95% CI 0.01–2.27, In favour of A **Adverse events** **Symptoms reported by the investigator: Erosion** • A: Grade 1(mild): 26%, Grade 2 (moderate): 11% • B: Grade 1 (mild): 19%, Grade 2 (moderate): 6%, Grade 3 (severe): 2% **Symptoms reported by the investigator: Erythema** • A: Grade 1 (mild): 37%, Grade 2 (moderate): 20%, Grade 3 (severe): 9% • B: Grade 1 (mild): 33%, Grade 2 (moderate): 14% **Quality of life** • NR **Other outcomes** **Complete Clinical Response CCR** (no clinical evidence of vulvar lesion, meaning 100%	**Risk of bias considerations (Cochrane ROB1 tool)** • Analysis ITT: high risk, as per-protocol analysis was applied • Randomisation: low risk • Allocation concealment: low risk • Blinding: some concerns • Attition bias: low risk • Selective reporting: low risk • **Other limitations or comments**: nr

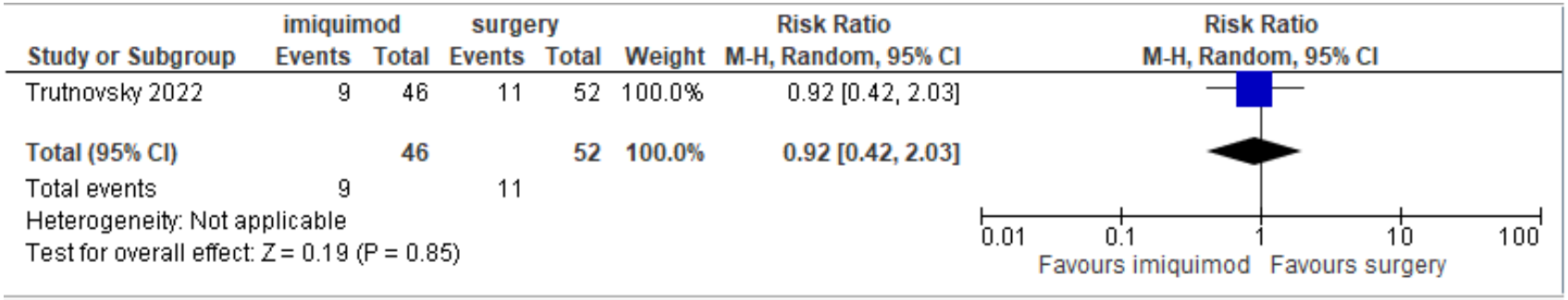
Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· Imiquimod, A: 1 (8%), B: 2 (25%) • Vulvar Lesion characteristics · A: 46 (82%) unifocal, 10 (18%) multifocal; · B: 39 (74%) unifocal, 14 (26%) multifocal • Histology: · vHSIL or VIN 2, A: 10 (18%), B: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

6.4.2 Forest plots

6.4.2.1 Forest plot of comparison: 5% imiquimod cream versus surgery, outcome: Invasive carcinoma rate



6.4.2.2 Forest plot of comparison: 5% imiquimod cream versus surgery, outcome: Recurrent disease or partial response



6.4.3 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen:

Trutnovsky G, Reich O, Joura EA, Holter M, Ciresa-König A, Widschwendter A, Schauer C, Bogner G, Jan Z, Boandl A, Kalteis MS, Regauer S, Tamussino K. Topical imiquimod versus surgery for vulvar intraepithelial neoplasia: a multicentre, randomised, phase 3, non-inferiority trial. Lancet. 2022 May 7;399(10337):1790-1798. doi: 10.1016/S0140-6736(22)00469-X. Epub 2022 Apr 25. Erratum in: Lancet. 2022 Oct 8;400(10359):1194. doi: 10.1016/S0140-6736(22)01888-8

5% Imiquimod versus Surgery								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
High → 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
High → 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

Literaturreferenzen:

Lawrie TA, Nordin A, Chakrabarti M, Bryant A, Kaushik S, Pepas L. Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia.Cochrane Database of Systematic Reviews 2016, Issue 1. Art. No.: CD011837.DOI: 10.1002/14651858.CD011837.pub2.

Laser vaporisation versus ultrasonic surgical aspiration (CUSA)								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
High → RCT	1 RCT from Lawrie, 2016 SR (von Gruenigen 2007)	Recurrence rate (laser vaporisation versus ultrasonic surgical aspiration (CUSA))	/ (some concerns)	/	/ (-1) fraglich ob "ultrasonic surgical aspiration (CUSA)" als operative Exzision / Surgery zählt?	-2 (very wide confidence intervals and only few participants: N=30 pts, RR 1.53, 95% CI 0.65-4.15)	/	⊕⊕⊖⊖ Low or ⊕⊖⊖⊖ Very low

Surgical excision versus laser vaporization or other								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
NRS → Low	1 retrospective study from Lawrie, 2016	Recurrence-free survival (Surgical excision versus laser vaporization or other)	/ (NRS had a relatively low risk of bias and adjusted appropriately		/	-1 (few participants: p-value 0.142, with 73 women)		⊕⊖⊖⊖ Very low

Surgical excision versus laser vaporization or other								
	SR (Van Esch 2013)		on multivariate analysis)					

Loop electrosurgical excision procedure (LEEP) versus laser vaporisation and surgical excision								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
NRS → Low	1 retrospective study from Lawrie, 2016 SR (Vlastos 2002)	Recurrence-free survival (Loop electrosurgical excision procedure (LEEP) versus laser vaporisation and surgical excision)	-1 (high risk of bias)	/	/ (-1) (fraglich ob der vergleich aus der Studie auch der PICO entspricht)	-1 (few participants: p-value 0.194, with 62 women)		⊕⊖⊖⊖ Very low

Literaturreferenzen:

Edey, KA, Allan, E, Murdoch, JB, Cooper, S, Bryant, A. Interventions for the treatment of Paget's disease of the vulva. Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD009245. DOI: 10.1002/14651858.CD009245.pub3.

Surgery and other treatment modalities								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Case series → 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 malignancies, 4 deaths related to other causes). Since nearly all treatment in the studies was surgical, we could not comment on mortality to	"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 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	⊕⊖⊖⊖ Very low

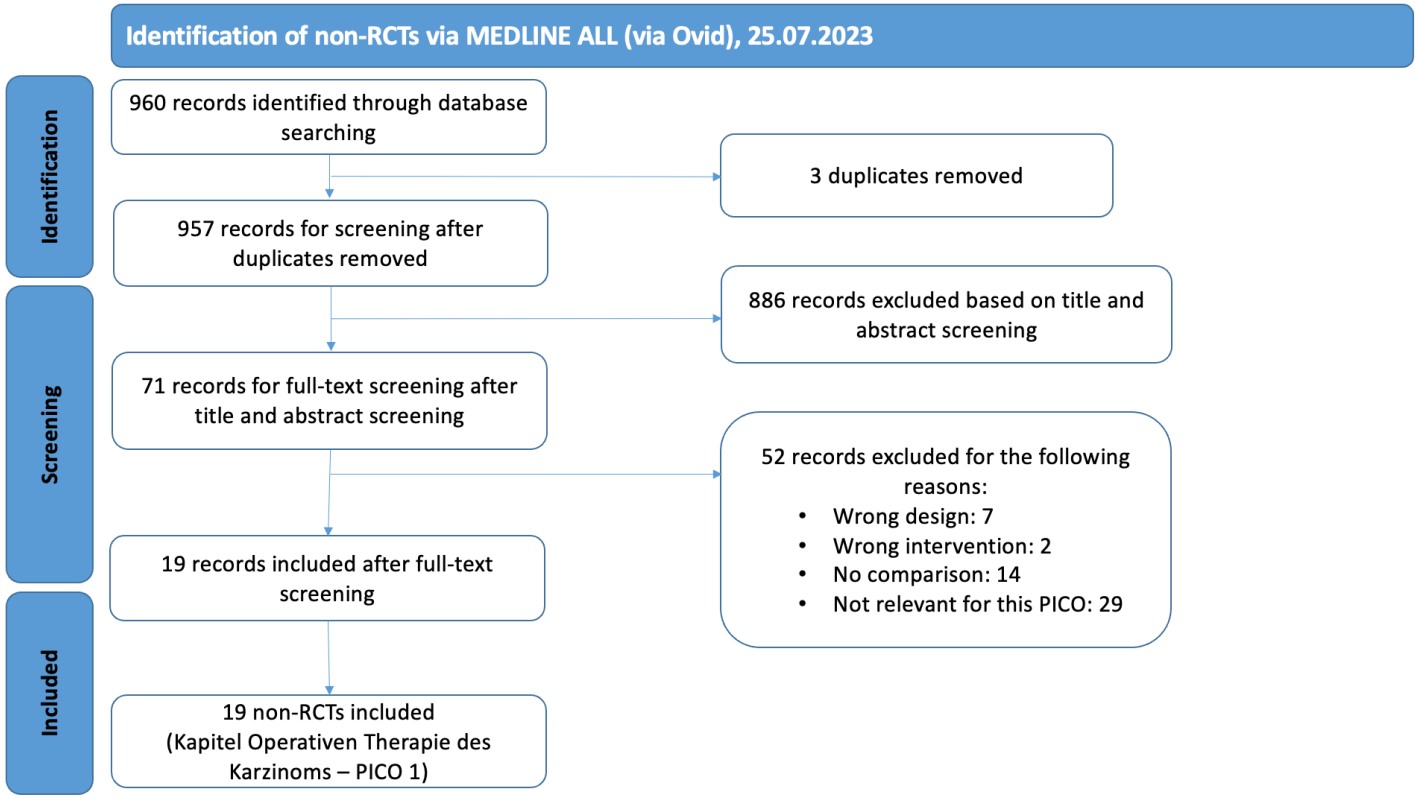
Surgery and other treatment modalities					
				treatment modality. Two studies used chemotherapy as first-line treatment (Niikura 2006; Parker 2000). 1 woman in the Niikura 2006 study received chemotherapy using cisplatin plus fluorouracil for stage IV disease and she died of the disease. Survival was again shown to be worse after radiotherapy, but the same caveats applied as to their comments on	dependent on surgeon choice. Most of the women in the studies had treatment before the advent of the multidisciplinary team, and, therefore, alternative treatments to surgery may not have been available, or not considered.“

chemotherapy.

6.5 Kapitel Operatives Management des Primärtumors – PICO 6.1

Verbessert bei Patientinnen mit ED Vulvakarzinom ein bestimmter operativer Sicherheitsabstand das Risiko für ein Lokalrezidiv, Lymphknotenrezidiv, DFS, OS?

6.5.1 PRISMA Flowdiagramm



6.5.2 Evidenztabellen

6.5.2.1 Systematisches Review

Nooij LS, van der Slot MA, Dekkers OM, Stijnen T, Gaarenstroom KN, Creutzberg CL, Smit VT, Bosse T, van Poelgeest MI. Tumour-free margins in vulvar squamous cell carcinoma: Does distance really matter? Eur J Cancer. 2016 Sep;65:139-49. doi: 10.1016/j.ejca.2016.07.006

Referenz/ Studientyp	**Untersuchte Studien**	**(verglichene) Interventionen**	**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 tumour-free margin in VSCC **Exclusion criteria:** • Exclusion criteria were languages other than English, Dutch,	**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 **Descriptive statistics:** • Age (median, range) · A: NR · B: NR • Sex (% female) · A: NR · B: NR • Stage (nach FIGO, %) · Ia: A: NR %, B: NR % · Ib: NR · II: NR	**Rezidivrate** (local Recurrence) • A: 148/535 • B: 107/743 Pooled RR: 1.99 (95% CI 1.13-3.51; p=0.02, I^2=73%) in favour of B	**Overall confidence in results of SR (AMSTAR-2):** ***"moderate"*** • PICO elements: yes • A priori design: no protocol • Justification for design: yes • Literature search >= 2 databases, search strategy + other sources: yes • Selection in duplicate: not explicitly mentioned • Data extraction in duplicate: not explicitly mentioned • List of excluded studies: no • sufficient detail on studies: 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
	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		· 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 · 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		• 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 • Sources of CoI: None declared.	

6.5.2.2 Primärstudien (non-RCTs)

Iacoponi, S., Zapardiel,I., Diestro, M. D., Alicia Hernandez, A. & De Santiago, J. Prognostic factors associated with local recurrence in squamous cell carcinoma of the vulva. J Gynecol Oncol. 2013 Jul;24(3):242-248. https://doi.org/10.3802/jgo.2013.24.3.242

Nooij LS, van der Slot MA, Dekkers OM, Stijnen T, Gaarenstroom KN, Creutzberg CL, Smit VT, Bosse T, van Poelgeest MI. Tumour-free margins in vulvar squamous cell carcinoma: Does distance really matter? Eur J Cancer. 2016 Sep;65:139-49. doi: 10.1016/j.ejca.2016.07.006

Liu, L., O'Donnell, P., Sullivan, R., Katalinic, A., Moser, E. C., de Boer, A. & Meunier, F. Cancer in Europe: Death sentence or life sentence?. European Journal of Cancer. 2016 Dez; 65:150-155. https://doi.org/10.1016/j.ejca.2016.07.007

Woelber, L., Griebel, L. F., Eulenburg, C., Sehouli, J., Jueckstock J., Hilpert, F. et al. Role of tumour-free margin distance for loco-regional control in vulvar cancer—a subset analysis of the Arbeitsgemeinschaft Gynäkologische Onkologie CaRE-1 multicenter study. European Journal of Cancer. 2016 Dez; 69, 180-188. https://doi.org/10.1016/j.ejca.2016.09.038

Gasimli, K., Straussner, M., Schmeil, I., Karn, T., Winkelmann, R., Becker, S. et al. Impact of re-excision of residual adjacent vulvar intraepithelial neoplasia (VIN III) and histological tumour-free margin (hTFM) on survival in primary squamous cell carcinoma of vulva. Gynecology and Obstetrics. 2018 Sep; 298: 945–950. https://dx.doi.org/10.1007/s00404-018-4887-1

Micheletti, L., Preti, M., Cintolesi, V., Corvetto, E., Privitera, S., Palmese, E. & Benedettol, C. Prognostic impact of reduced tumor-free margin distance on long-term survival in FIGO stage IB/II vulvar squamous cell carcinoma, J Gynecol Oncol. 2018 Sep;29(5): e61. https://doi.org/10.3802/jgo.2018.29.e61

Minar, L., Felsinger, M., Cihalova1, M., Zlamal, F. & Bienertova-Vasku, Vulvar cancer recurrence — an analysis of prognostic factors in tumour-free pathological margins patients groupJ. Ginekologia Polska. 2018 Aug; 89 (8): 425-432. https://dx.doi.org/10.5603/GP.a2018.0073

Pleunis, N., Leermakers, M. E.J., van der Wurff, A., Klinkhamer, P. J.J.M.,. Ezendam, N.P.M., Boll, D. et al. Surgical margins in squamous cell carcinoma, different for the vulva?. European Journal of Surgical Oncology. 2018 Okt; 44 (10): 1555-1561. https://doi.org/10.1016/j.ejso.2018.05.031

Raimond, E., Delorme, C., Ouldamer, L., Carcopino, X., Bendifallah, S., Touboul, C. et al. Surgical treatment of vulvar cancer: Impact of tumor-free margin distance on recurrence and survival. A multicentre cohort analysis from the francogyn study group. European Journal of Surgical Oncology. 2019 Nov; 45 (11) 2109-2114. https://doi.org/10.1016/j.ejso.2019.07.005

Te Grootenhuis, N. C., Pouwer, A.W., de Bock, G.H., Hollema, H., Bulten, J., van der Zee A.G.J. et al. Margin status revisited in vulvar squamous cell carcinoma. Gynecologic Oncology. 2019 Aug; 154 (2): 266-275. https://doi.org/10.1016/j.ygyno.2019.05.010

Barlow, E. L. Jackson, M. & Hacker, N.F. The Prognostic Role of the Surgical Margins in Squamous Vulvar Cancer: A Retrospective Australian Study. Cancers. 2020 Nov; 12(11): 3375 https://doi.org/10.3390/cancers12113375

Yang, J., Delara, R., Ghaith, S., Newman, H., Magrina, J., Butler, K. et al. Tumor-free margins and local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol. 2020 Sep;158(3):555-561. doi: 10.1016/j.ygyno.2020.06.503

Matsuo, K., Nishio, S., Matsuzaki, S., Iwase, H., Kagami, S., Soeda, S. et al. Surgical margin status and recurrence pattern in invasive vulvar Paget's disease: A Japanese Gynecologic Oncology Group study. Gynecologic Oncology. 2021; Mar: 160 (3): 748-754. https://doi.org/10.1016/j.ygyno.2020.12.023

Arvas, M., Kahramanoglu, I., Bese, T., Turan, H., Sozen, I., Ilvan, S. et al. The Role of Pathological Margin Distance and Prognostic Factors After Primary Surgery in Squamous Cell Carcinoma of the Vulva. International Journal of Gynecological cancer. 2018; 28 (3): 623-631. http://dx.doi.org/10.1097/IGC.0000000000001195

Di Donato, V., Page, Z., Bracchi, C., Tomao, F., Musella, A., Perniola, G. et al. The age-adjusted Charlson comorbidity index as a predictor of survival in surgically treated vulvar cancer patients. J Gynecol Oncol. 2019 Jan;30(1):e6. https://doi.org/10.3802/jgo.2019.30.e6

Ferrari, F., Forte, S., Ardighieri, L., Bonetti, E., Fernando, B., Sartori, E. et al. European Journal of Surgical Oncology. Multivariate analysis of prognostic factors in primary squamous cell vulvar cancer: The role of perineural invasion in recurrence and survival. 2019 Nov;45 (11): 2115-2119. https://doi.org/10.1016/j.ejso.2019.07.029

Gitas, G., Proppe, L., Baum, S., Kruggel, M., Rody, A., Tsolakidis, D. et al. A risk factor analysis of complications after surgery for vulvar cancer. Gynecologic Oncology. 2021 Jan.; 304: 511–519. https://dx.doi.org/10.1007/s00404-020-05949-w

Micheletti, L., Borella, F., Preti, M., Frau, V., Cosma, S., Privitera, S. et al. Perineural Invasion in Vulvar Squamous-Cell Carcinoma Is an Independent Risk Factor for Cancer-Specific Survival, but Not for Locoregional Recurrence: Results from a Single Tertiary Referral Center. Cancers, 2022 Jan;14(1):124. https://doi.org/10.3390/cancers14010124

Schleiss-Andreassen, J. L., Kristensen, E., Frøding, L. P., Stæhr, E., Høgdall, C. et al. Assessment of recurrence rate and risk factors of relapse in stage in IA vulvar carcinoma. Gynecologic Oncology. 2022 Mar; 164 (3): 543-549. https://doi.org/10.1016/j.ygyno.2021.12.020

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 excision biopsy at another hospital **Enrolment period** • 2000 – 2012 in the Leiden University Medical Centre **Descriptive statistics** • Age (median, range) • A: mean age=68 • B: mean age=69 • Sex (% female)	• 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	**Rezidivrate** • **A: 9** (5 with re-excision or RT)/**92** (15 having re-excision and 22 with RT) • **B: 3** (all having no adjuvant therapy)/**26** (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 therapie): HR 1.10 (95% CI 0.28–4.19) in favour of A/B There was no significant difference regarding local recurrence risk between the group of patients with a tumour-free margin of <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	**General information:** • Median follow-up: 42 months (mean, 53.8 [range, 0–174] months • Funding: NR • **CoI**: 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 • Exposure/Intervention · Assessment reliable: yes, defined · Assessed more than once: no · Possibly affected by knowledge of outcome status?: no • Drop-out rate & reasons reported: NR · Similar across groups: NA

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· A: 100% · B:100% • Stage (FIGO, %) · I: A: 57 (62.0%), B: 18 (69.2%) · II: A:2 (2.2%), B: 0 · III: A: 32 (34.8%), B: 8 (30.8%) · IV: A: 1 (1.1%), B: 0 (0%) • Location of the tumour · NR • Tumour size (%, cm) · ≤ 40 mm: A: 73 (79.3%), B: 23 (88.5%) · >40 mm: A: 19 (20.7%), B: 3 (11.5%) • Tumour depth (%, mm) · ≤ 4mm: A: 37 (40.2%), B: 12 (46.2%) · >4mm: A: 55 (59.8%), B: 14 (53.8%) • Lymph node metastases (% yes) · Tumour-positive lymph nodes in the groin(s): A: 33 (35.9%), B: 9 (34.6%) · Extracapsular spread: A: 13 /14.1%), B: 3 (11.5%)	received additional treatment. Adjusted for: tumor size (</=40mm), additional therapie (vulvar radiotherapie)	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.	· If high: comparison of those lost with available: NA • Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If not, Knowledge of exposure status likely to influence the outcome?:): yes • Main cofounders taken into account: Adjusted for tumor size (</=40mm), additional therapie (vulvar radiotherapie) • Confidence intervals reported: yes • Selective reporting (comparison with protocol): NI (no information, as no protocol available) Other limitations or comments: None

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Additional/adjuvant treatment: · Vulvar radiotherapy: · A: 22 (23.9%) · B: 1 (3.8%) · Reexcision: · A: 15 (16.3%) · B: 0 · Additional treatment was generally started within 6 weeks after the primary surgery and consisted of reexcision or radiotherapy. · Additional treatment was recommended for patients with tumour-positive margins and was considered for patients with a tumour-free margin <8 mm (A) who had other risk factors (advanced tumour stage, positive lymph nodes, or lymphovascular space invasion).			
Woelber 2016 Retrospective study AGO-CaRE-1 study (node-	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 **Inclusion criteria (for analysis):**	**Interventions** A: <8mm B: >/= 8mm **Analysis**	**Rezidivrate** • A: 24/191 • B: 10/98 HR (per mm increase): 0.930 (95% CI 0.849-1.020) in favour of A/B	**General information** • Median follow-up: 35.1 months • **Funding**: CaRE-1 study supported by medac oncology without restriction in protocol or analysis • **CoI**: None declared

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
negative subgroup)	• Patients with squamous-cell vulvar cancer FIGO stage IB and higher (UICC-TNM-classification and stage-groupings version 6) treated at 29 gynecologic cancer centers in Germany 1998-2008 (Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)) **Exclusion criteria (for analysis)**: • nr **Enrolment period** • February 2011 – December 2011 **Descriptive statistics** • Age (median, range) · A: 65.5 (22-94) · B: 66.9 (31.5-93) • Sex (% female) · A: 100% · B: 100% • Stage (TNM, %) · T1b: A: 88 (46.1%), B: 53 (54.1%) · T2: A: 96 (50.3%), B: 44 (44.9%) · T3: A: 7 (3.7%), B: 1 (1.0%) • Histologic grade: · G1: A: 22 (11.5%), B: 23 (23.5%)	• ANCOVA (analysis of covariance) model and Cox proportional hazards models ◆ Matching: NR • Confounders: Multivariable analysis, but not reported if adjusted for confounder and which	The need for a minimal margin of 8 mm could not be confirmed in the large and homogeneous node-negative cohort of the AGO-CaRE database.	**Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective 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: 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: (→If not, Knowledge of exposure status likely to influence the outcome?:) no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· G2: A: 122 (63.9%), B: 54 (55.1%) · G3: A: 45 (23.6%), B: 18 (18.4%) · Unknown: A: 2 (1.0%), B: 3 (3.1%) • Location of the tumour · NR • Tumour diameter (mm): · A: median = 20 (2–101) · B: median = 20 (3– 345) • Tumour depth (mm) · A: median = 4 (1–60) · B: median = 5 (1–55) • Lymph node metastases (number of dissected LNs (groin) per patient) · A: median = 14 (2–48) · B: median = 15 (1–40) • Additional/ adjuvant treatment: · 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			• Main cofounders taken into account: NR • Confidence intervals reported: yes • Selective reporting (comparison with protocol): no Other limitations or comments: None

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· None of the patients received adjuvant treatment			
Minar 2018 Retrospective study	47 pts. **Inclusion criteria (for analysis):** • 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 **Exclusion criteria (for analysis):** • NR **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	**Interventions** A: margin distance <8 mm B: margin distance ≥ 8 mm **Analysis** • Type of analysis: Associations between prognostic factors and recurrence → Spearman correlation coefficient & the chi-squared test. The Cox proportional hazard ratio was assessed to estimate risk factors for recurrences.	**Rezidivrate** • Median recurrence period: 16 months (range 6–82 months), univariate analysis, p<0.05 **DFS** • Mean (SD) DFS of 66.7 + 6.5 months • 95% CI: 54.0–79.5 • Kaplan–Meier curve **OS** • 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	**General information:** • Follow-up: range 4–118 months • **Funding**: work supported by Ministry of Health, the Czech Republic – conceptual development of research organisation • **CoI**: 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): NR • Exposure/Intervention · Assessment reliable: NR · Assessed more than once: NR · Possibly affected by knowledge of outcome status?: NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· 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) · 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%	• Matching: NR • Confounders: 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: (→If 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) Other limitations or comments: 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):**	**Interventions** A: margin distance <8 mm	**Rezidivrate** • A: 20/80 • B: 16/72	**General information** • Median follow-up: 40 months (0–133) • **Funding**: none • **CoI**: None declared

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• 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 at initial presentation in one of both referral centers. • 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. **Enrolment period** • January 2005 and October 2015 **Descriptive statistics** • Age (median, range) · Total median age: 71 years (26-98) • Sex (% female) · A: 100% · B: 100%	B: margin distance ≥ 8 mm **Analysis** • Type of analysis: frequencies • Matching: NR • Confounders: NR	p-value = 0.787	**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 · Assessment reliable: yes, defined · 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: (→If not, Knowledge of

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Stage (FIGO, %) · Ib: 89 (53.3 %) · II: 31 (18.5%) · 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			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) Other limitations or comments: None
Raimond 2019	124 (12 pts. were excluded of the study because of neoadjuvant treatment (n=2),	**Interventions**	**Rezidivrate**	**General information**

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Retrospective multicenter study From francogyn study group	missing data (n=9) and palliative care (n=1))/ 112 pts. surgically treated for a vulvar squamous cell cancer **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. **Exclusion criteria (for analysis):** • Neoadjuvant therapy, other histological types than squamous cell **Enrolment period** • 2005 - 2016 **Descriptive statistics** • Age (median, range) · A: 69.9 (38 -88) · B: 70.2 (29-96) · C: 70.9 (45-84) • Sex (% female) · A: 100% · B: 100% • Stage (FIGO, %)	A: margin distance <3 mm B: margin distance ≥ 3mm and < 8mm C: ≥8 mm **Analysis** • Type of analysis: Survival and Cox proportional hazard model • Matching: NR • Confounders: NR	• A: 11/47 • B: 9/48 • C:6/17 P = 0.43	• Mean follow-up: 25 months (1-137) • Funding: NR • CoI: None declared **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective multicenter study • Populations comparable: some concerns (no differences regarding FIGO stage, tumor size, histologic grade, lymphovascular space invasion between groups, but differences regarding stromal invasion (>5mm more frequent in group 3) • Rate of participation/Exclusions reported (selection bias into the study): yes • Exposure/Intervention · Assessment reliable: yes, defined · Assessed more than once: no · Possibly affected by knowledge of outcome status?: no • Drop-out rate & reasons reported: NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· 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) · 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)			· 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: (→If 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) Other limitations or comments: None

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· 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.			
Te Grootenhuis 2019 Cohort study	287 consecutive patients with vulvar squamous cell carcinoma (148/435 patients were excluded) **Inclusion criteria (for analysis):** • Primary diagnosis of vulvar squamous cell carcinoma and primarily surgically treated at one of the two participating centers. **Exclusion criteria (for analysis):** • Patients who suffered from multifocal disease, or patients who received neoadjuvant chemotherapy and/ or radiotherapy, definite (chemo) radiation or palliative treatment were excluded. **Enrolment period**	**Interventions** A: margin distance <8mm B: margin distance ≥8mm **Analysis** ◆ Type of analysis: Univariable and multivariable Cox-regression analyses ◆ Matching: NR	**R**ezidivrate • A: 36/130 • B: 52/153 HR 1.25 (whole cohort n=287) (95% CI 0.81-1.93) in favour of A/B	General information ◆ Median follow-up: 80 months (0-204) ◆ **Funding**: None ◆ **CoI**: None declared **Risk of bias considerations (adapted from SIGN cohort study checklist)** ◆ Study type: cohort 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
	• 2000 – 2010 **Descriptive statistics** • Age (median, range) · Total median age: 73 years (26-100) • Sex (% female) · A: 100% · B: 100% • 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)	◆ Confounders: NR		· Assessment reliable: yes, defined · Assessed more than once: no · Possibly affected by knowledge of outcome status?: no ◆ Drop-out rate & reasons reported: yes · Similar across groups: NR · If high: comparison of those lost with available: NA ◆ Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If 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) Other limitations or comments: None

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· Tumor diameter: 29.5 (1.5–130.0) • Tumour depth (mm) · 5.6 (0.5–25.0) • Lymph node metastases (% yes) · NR • Additional/ adjuvant treatment: · Radiotherapy to the vulva: 49 (17) · Re-excision: 17 (6) · Chemotherapy: 2 (1) · None: 219 (76)			
Barlow 2020 Retrospective study	345 pts. **Inclusion criteria (for analysis):** • Patients with squamous cell carcinoma of the vulva treated primarily with surgery with curative intent **Exclusion criteria (for analysis):** • No squamous pathology • another synchronous cancer • primary radiotherapy treatment • palliative surgery • lost to follow up	**Interventions** A: margin distance <8 mm B: margin distance ≥ 8 mm **Analysis** • Type of analysis: Cox proportional hazard models were used in univariable and	**Rezidivrate** • A: 27/122 • B: 51/219 P=0.65	**General information** • Mean follow-up: 93 months (1–367) • Funding: None • **CoI**: None declared **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective study • Populations comparable: NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• 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 **Enrolment period** • February 1987 – December 2016 **Descriptive statistics** • Age (median, range) · 70 (29-96) • Sex (% female) · A: 100% · B: 100% • Stage (FIGO) · Ia: 37 (10%) · Ib: 194 (56.2%) · II:12 (3.5%) · IIIa: 35 (10.1%) · IIIb: 14 (4.1%) · IIIc: 32 (9.3%) · Iva: 2 (0.6%) · IVb: 3 (0.9%) • Location of the tumour	multivariable analyses • Matching: NR • Confounders: NR		• Rate of participation/Exclusions reported (selection bias into the study): yes • Exposure/Intervention · Assessment reliable: yes, defined · 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: (→If not, Knowledge of exposure status likely to influence the outcome?:): no • Main cofounders taken into account: NR • Confidence intervals reported: no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· 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 · Positive: 29.6			• Selective reporting (comparison with protocol): NI (no information, as no protocol available) Other limitations or comments: None
Yang 2020	335 pts. with vulvar squamous cell carcinoma **Inclusion criteria (for analysis):**	**Interventions** A: margin distance <3 mm • N = 32	**Rezidivrate** • A: 15/32 • B: 38/151 • C: 25/152	**General information** • Follow-up: median 73 months • Funding: NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Patients with pathologically-confirmed invasive squamous cell carcinoma who were treated with primary surgery **Exclusion criteria (for analysis):** • Patients with a history of vaginal cancer or pelvic radiation **Enrolment period** ◆ 2000 to 2018 **Descriptive statistics** • Age (mean, SD) · A: 63.6 ± 14.9 · B: 70.1 ± 14.1 · C: 67.2 ± 15.6 • Sex (% female) · 100% • 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%	B: margin distance ≥3 and <8 mm • N = 151 C: margin distance ≥8 mm • N = 152 **Analysis** • Type of analysis : Univariate and multivariate Cox proportional hazard ratio (HR) • Matching: NR • Confounders: adjusted for adjusted for tumor stage, grade, depth of stromal invasion, size, location and distribution by IPW	Multivariate analysis: <8 mm vs. ≥8 mm: HR 1.98, 95% CI 1.13-3.41, p= 0.03, favour of C **DFS (Local recurrence free survival)** **5 year DFS:** • A: 48.2% • B: 81.5% • C: 84.6% Log-rank test: p<0.001 **Other outcomes** DSS, Regional recurrence, distant recurrence	• **CoI**: The authors have no conflict of interest or potential financial disclosures. **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: Retrospective study • Populations comparable: yes • Rate of participation/Exclusions reported (selection bias into the study): NR • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · Possibly affected by knowledge of outcome status? no • Drop-out rate & reasons reported: NA · Similar across groups: NR · If high: comparison of those lost with available: NR • Outcome · Outcome measure is well-defined, valid and reliable: yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• 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) · ≥4 cm: A: 5 (15.6) , B: 29 (19.2), C: 16 (10.5) • Tumour depth (n, %) · ≤1 mm: A: 5 (15.6), B: 32 (21.2), C: 18 (11.8) · >1 mm ≤5 mm: A: 12 (37.5), B: 62 (41.1), C: 83 (54.6) · >5mm: A: 15 (46.9), B: 57 (37.7), C: 51 (33.6)			· Blind outcome assessment to exposure: (→If 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 Other limitations or comments: None
Arvas 2018 Retrospective study	107 pts. with squamous cell carcinoma of the vulvar **Inclusion criteria (for analysis):**	**Interventions** A: margin distance ≤2 mm	Rezidivrate • A: 13/34 • B: 5/32	**General information:** • Median follow-up: 101 months • Funding: NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• squamous cell carcinoma of the vulva diagnosed and operated at Istanbul University Cerrahpasa Faculty of Medicine during January 1996 to December 2016 **Exclusion criteria (for analysis):** • Thirteen patients with positive surgical margin and 10 patients with missing data were excluded. **Enrolment period** • January 1996 – December 2016 **Descriptive statistics** • Age (median, range) · 66 years (31–90) • Sex (% female) · A: 100% · B:100% • Stage (FIGO, %) · Recurrence: · I: 56.8 · II: 24.1 · III: 15.5 · IV: 3.4 · No recurrence:	B: margin distance >2 mm to <8mm **C: margin distance ≥8mm** **Analysis** • Type of analysis: Chi-square test or Kruskal-Wallis H test, Kaplan-Meier, Cox-Regression, Hazard Model • Matching: NR • Confounders: NR	• C: 2/41 **P=0.008** **DFS** • A: 1.0 • B: 0.4 (0.1–1.1) • C: 0.1 (0.02–0.4) Univariate analysis HR: P=0.006 Multivariate analysis: HR: p=0.01	• **CoI**: NR **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): NR • Exposure/Intervention · Assessment reliable: yes, defined · 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: (→If not, Knowledge of

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· I: 20.4 · II: 14.2 · III: 51 · IV: 14.2 • Location of the tumour · 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%			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) Other limitations or comments: None
Schleiss-Andreassen 2022	55 pts. **Inclusion criteria (for analysis):**	**Interventions**	**Rezidivrate** • A: 6/26	**General information**

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Retrospective study	• Women diagnosed with vulvar cancer FIGO Stage IA SCC **Exclusion criteria (for analysis):** • FIGO Stage >IA, other histology than SCC **Enrolment period** • 2011–2017 **Descriptive statistics** • Age (median, range) · 66 years (62–95) • Sex (% female) · A: 100% · B: 100% • Stage (FIGO/ TNM stage, %) · IA: 100% • Location of the tumour (p=0.63) · Vulva without clitoral involvement: total: 63.6%, no recurrence: 63.3%, recurrence: 66.6% · Perineum: total: 10.9%, no recurrence: 12.2%, recurrence: 0% · Clitoral involvement: total: 25.5%, no recurrence: 24.5%, recurrence: 33.3%	A: margin distance <8mm B: margin distance ≥8mm **Analysis** • Type of analysis: Univariate Chi Square and Fischer's exact test were used • Matching: NR • Confounders: NR	• B: 0/27 P=0.01	• Follow-up: last day of follow up was 1st June 2019 • Funding: NR • **CoI**: 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): NR • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: NR · Possibly affected by knowledge of outcome status?: NR • Drop-out rate & reasons reported: NR · Similar across groups: NR · If high: comparison of those lost with available: NR • Outcome

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Tumour size (cm) (p=0.06) · ≤1: total: 92.6%, no recurrence: 98.0%, recurrence: 66.6% · >1-2: total: 7.4%, no recurrence: 2.0%, recurrence: 33.3% • Tumour depth (mm) · ≤0.5: total: 41.3%, no recurrence: 37.5%, recurrence: 22.2% · >0.5-1: total: 39.7%, no recurrence: 39.6%, recurrence: 77.8% • Lymph node metastases (% yes) · Lymph vascular space invasion: yes: 0%, no: 100% · Sentinel node: · yes: total: 12.7%, no recurrence: 12.5%, recurrence: 0% · No: total: 87.3%, no recurrence: 87.5%, recurrence: 100% • Additional/ adjuvant treatment: · Radiotherapy to the vulva: 49 (17) · Re-excision: 17 (6) · Chemotherapy: 2 (1) · None: 219 (76)			• Outcome measure is well-defined, valid and reliable: yes • Blind outcome assessment to exposure: (→If 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): no Other limitations or comments: None

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Iacoponi 2013 Retrospective study	• 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). **Inclusion criteria (for analysis):** • single squamous cell carcinoma of the vulva with infiltration >1 mm, tumoral size <4 cm, negative inguinal exploration or suspicious inguinal nodes <1.5 cm diameter in imaging techniques (CT-scan or MRI). **Exclusion criteria (for analysis):** • 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. **Enrolment period** • January 2000 – December 2010 **Descriptive statistics** • Age (range) · Median: 72.9 (60-85) · Mean: 72.9 ±12.1	**Interventions** A: margin distance ≤8 mm (Prognostic factor) B: margin distance >8 mm (Prognostic factor) C: margin distance ≤15 mm (Prognostic factor) D: margin distance >15 (Prognostic factor) **Analysis** • Type of analysis: Qualitative variables were presented with absolute values and percentages. Quantitative data between groups were compared using the Student	**Rezidivrate** • A: 52.6% • B: 43.5% **P=0.50** • C: 55.6% • D: 34.5% **P=0.09** **The Kaplan-Meier curves on local relapse didn't show statistical significance with the Mantel-Cox test.**	**General information:** • Median follow-up: 120 months • Funding: NR • **CoI**: 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): NR • Exposure/Intervention · Assessment reliable: NR · Assessed more than once: NR · Possibly affected by knowledge of outcome status?: NR • Drop-out rate & reasons reported: · Similar across groups: NR · If high: comparison of those lost with available: NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Sex (% female) · A: 100% · B:100% • Stage (FIGO, %) · NR • Location of the tumour · Among all squamous we found 67 keratinizing, 2 non-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. • Tumour size (%, cm) · mean tumor size: 35.1±22.8 mm · median (range) 35.4 (18.6-54) • Tumour depth (%, mm) · Stromal invasion: 7.7±6.6 mm · median of 7.7 (1.1-14.3) • Lymph node metastases:	t-test and ANOVA. Categorical variables were compared using chi-square test. Survival analysis was performed using Kaplan-Meier curves. • Matching: NR • Confounders: NR		◆ Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If 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) Other limitations or comments: None

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· Nodal involvement: 33 · Ipsilateral nodes: 21 · Contralateral nodes: 2 · Bilateral nodes: 10			
Di Donato 2019	78 pts. **Inclusion criteria (for analysis):** • 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). **Exclusion criteria (for analysis):** • / **Enrolment period** • 1998-2016 **Descriptive statistics** • Age (median, range) · 67±10.3 • Sex (% female) · A: 100% · B: 100%	**Interventions** A: margin distance 5mm B: margin distance >5mm C: margin distance >10mm **Analysis** • Type of analysis: Kaplan-Meier, DFS, OS, CSS • Matching: NR • Confounders: age could represent a confounding factor.	NR **Other outcomes** 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). In support of this, we found that the presence of close margins (<5mm) are more frequently found among patients with intermediate (35%) or high risk (38%). ACCI was compared to low risk (14%), although it should e noted that this difference is not statistically significant.	**General information:** • Median follow-up: • **Funding**: Sapienza Universita di Roma (C26N15LL2Y/2015) • **CoI**: None declared **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 • Exposure/Intervention · Assessment reliable: NA · Assessed more than once: · Possibly affected by knowledge of outcome status?: NA

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Stage (FIGO, %) · IA: 14.1% · IB: 29.5% · 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%			• 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: (→If 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):**	**Interventions** A: margin distance <3 mm B: margin distance 3-5 mm	NR **Other outcomes** • Risk to develop postoperative complications	**General information:** • Median follow-up: 2 years • **Funding**: Open Access funding enabled and organized by Projekt DEAL. There is not any funding. • **CoI**: None declared

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Patients with inoperable vulva cancer or those who had undergone pelvic exenteration were excluded. **Enrolment period** • 2003–2018 **Descriptive statistics** • Age · 69.4 ± 15.3 • Sex (% female) · A: 100% · B:100% • Stage (FIGO, n) · Ia: 16 · Ib: 73 · II: 6 · IIIa: 7 · IIIb: 8 · IIIc: 9 · Iva: 0 · Ivb: • FIGO stage and tumor resection margin distance · FIGO I: <5mm: 37, ≥5mm: 38, total: 75	C: margin distance 5–8mm **Analysis** • Type of analysis: Depending on the scaling and distribution of the variables considered, either a Chi-square test, a Mann-Whitney U test, or a one-way-ANOVA was performed. • Matching: NR • Confounders: 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 • 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: (→If not, Knowledge of exposure status likely to influence the outcome?:): NA

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· FIGO II: <5mm: 2, ≥5mm: 3, total: 5 · FIGO III: <5mm: 12, ≥5mm: 10, total: 22 · FIGO IV: <5mm: 1, ≥5mm: 1, total: 2 • Location of the tumour (n) · Right side: 29 · Left side: 27 · Both sides: 60 · Undefined: 5 · Clitoris: 25 · Labia majora: 55 · Labia minora: 51 · Sub-clitoral: 30 · Posterior commissure: 14 • Tumour size (diameter in mm) · 29.2 ± 22.3 • Tumour depth (mm) · 5.8 ± 6.9 • Lymph node metastases: · Patients with lymph-node metastasis (n): 27 · Lymph node metastasis by sentinel: 1 ± 0 · Lymph node metastasis by IFLIND: 3.24 ± 2.02			• Main cofounders taken into account: NA • Confidence intervals reported: NA • Selective reporting (comparison with protocol): NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Matsuo 2021	139 pts. **Inclusion criteria (for analysis):** • Women with stage I-IV invasive vulvar Paget's disease who received surgical treatment from 2001-2010 **Exclusion criteria (for analysis):** • Exclusion criteria included non-surgical cases and unknown type of surgery. **Enrolment period** • 2001-2010 **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%	**Interventions** A: margin distance <1cm B: margin distance ≥1cm **Analysis** • Type of analysis: 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 hazard ratio and corresponding 95% confidence interval.	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 (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).	**General information** • Median follow-up: 5.8 years • **Funding**: Ensign Endowment for Gynecologic Cancer Research (K.M.) • **CoI**: NR **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: Retrospective study • Populations comparable: • 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

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• 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 (%) · No metastasis: 48.9 · Single metastasis: 4.3 · Multiple metastases: 10.8 · Not examined: 36.0 • Additional/ adjuvant treatment: · Radiotherapy: No: 94.2%, Yes: 5.8%	• Kaplan-Meier, Cox-Regression, Hazard Model • Matching: NR • Confounders: NR		• Outcome · Outcome measure is well-defined, valid and reliable: NA · Blind outcome assessment to exposure: (→If 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
Micheletti 2021	223 pts. **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	**Interventions** A: margin distance <3 mm B: margin distance >5mm **Analysis**	NR	**General information:** • Follow-up: 49 months (median 31, standard deviation ± 48, range 6–224) • Funding: None • **CoI**: None declared

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Surgical Sciences, S. Anna Hospital, University of Turin, from 2000 to 2019. **Exclusion criteria (for analysis):** • NR **Enrolment period** • 2000–2019 **Descriptive statistics** • Age at diagnosis (median, range) 69.5 years (standard deviation ±11, range 27–89) • Sex (% female) · A: 100% · B:100% • Stage (FIGO, %) · I–II: No LRR: 61%, LRR: 39% · III: No LRR: 58%, LRR: 42% • Location of the tumour · NR • Tumour size (%, cm) · Mean value: 29 mm · <20 mm: No LRR: Yes: 54%, No: 63%, LRR: Yes: 46%, No: 37%	• Type of analysis: Multivariate analysis (log rank) • Univariate analysis • Matching: NR • Confounders: NR		

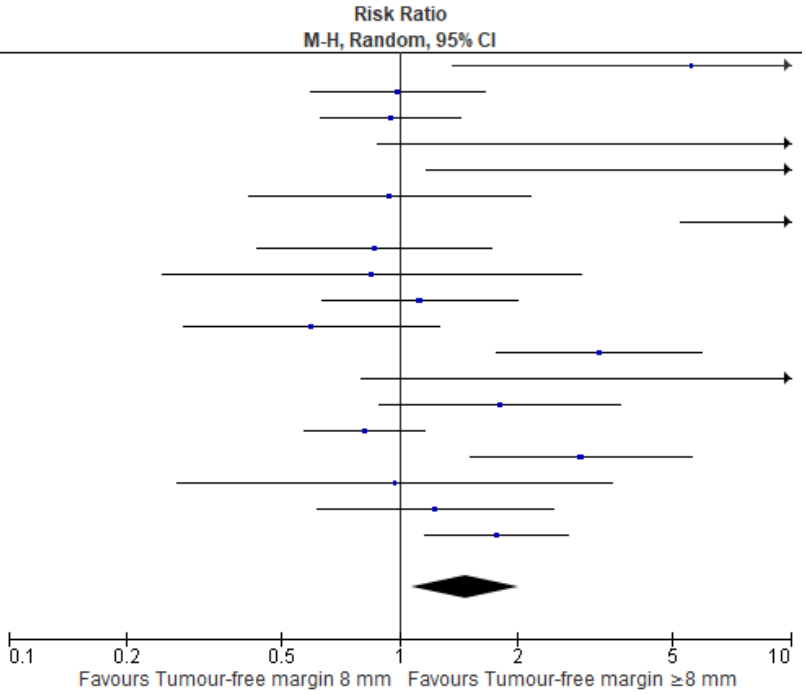
Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· <40 mm: No LRR: Yes: 56%, No: 68%, LRR: Yes: 44%, No: 32% • Tumour depth (mm, standard deviation, range) · Mean: No LRR: 8.4 ± 6.2 (2–40), LRR: 7.3 ± 6.9 (2–55) · <8mm: No LRR: Yes: 56%, No: 65%, LRR: Yes: 44%, No: 35% • Lymph node metastases: · 0–1: No LRR: 60%, LRR: 40% · >1: No LRR: 59%, LRR: 41% • Additional therapy: Radiotherapy · No LRR: Yes:58%, No: 60% · LRR: Yes: 42%, No 40% • Perineural invasion: · No LRR: Yes: 56%, No: 62% · LRR: Yes: 44%, No: 36%			

6.5.3 Forest plots

6.5.3.1 Forest plot of comparison: Tumour-free margin <8 mm vs. Tumour-free margin ≥8 mm, outcome: local recurrence

Study or Subgroup	Tumour-free margin <8 mm Events	Total	Tumour-free margin ≥ 8 mm Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arvas 2018	18	66	2	41	3.3%	5.59 [1.37, 22.85]
Baiocchi, 2015	18	79	29	126	7.5%	0.99 [0.59, 1.66]
Barlow 2020	27	122	51	219	8.1%	0.95 [0.63, 1.43]
Chan 2007	12	53	0	30	1.2%	14.35 [0.88, 234.13]
De Hullu 2002	9	38	0	39	1.1%	19.49 [1.17, 323.49]
Groenen 2010	11	50	7	30	5.7%	0.94 [0.41, 2.17]
Heaps 1990	17	37	0	91	1.2%	84.74 [5.23, 1373.55]
Iacoponi 2013	7	22	24	65	6.5%	0.86 [0.43, 1.72]
Nooij 2015 (cohort)	9	92	3	26	3.9%	0.85 [0.25, 2.91]
Pleunis 2018	20	80	16	72	7.2%	1.13 [0.63, 2.00]
Raimond 2019	20	95	6	17	6.2%	0.60 [0.28, 1.27]
Rouzier 2002	15	44	18	171	7.1%	3.24 [1.78, 5.90]
Schleiss-Andreassen 2022	6	26	0	27	1.1%	13.48 [0.80, 227.87]
Tantipalakorn 2009	8	24	17	92	6.4%	1.80 [0.89, 3.67]
Te Grootenhuis 2019	36	130	52	153	8.4%	0.81 [0.57, 1.16]
Viswanathan 2013	44	116	9	69	6.7%	2.91 [1.51, 5.58]
Woelber 2011	7	72	3	30	3.7%	0.97 [0.27, 3.51]
Woelber 2016	24	191	10	98	6.5%	1.23 [0.61, 2.47]
Yang 2020	53	183	25	153	8.0%	1.77 [1.16, 2.71]
Total (95% CI)		**1520**		**1549**	**100.0%**	**1.48 [1.07, 2.03]**
Total events	361		272			

Heterogeneity: Tau² = 0.28; Chi² = 60.29, df = 18 (P < 0.00001); I² = 70%
Test for overall effect: Z = 2.38 (P = 0.02)



6.5.4 Bewertung der Evidenz (nach GRADE)

Tumour-free margin <8 mm versus Tumour-free margin ≥8 mm								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → cohort studies	19 cohort studies	Local recurrence	/	-1 (large heterogeneity, I^2= 70%)		/	-1 (large confidence interval) /	⊕⊖⊖⊖ Very low

6.5.5 Kapitel Operatives Management des Primärtumors – PICO 6.3

Zeigt die primär operative Therapie von Patientinnen mit Vulvakarzinom ab Stadium T2 gegenüber der primär operativen Therapie von Patientinnen im Stadium T1 eine erhöhte Rate für postoperative Harninkontinenz und anorektale Inkontinenz?

In der PICO-übergreifenden Evidenzrecherche nach systematischen Reviews und nach RCTs konnte kein Systematischer Review (SR) oder RCT der PICO zugeordnet werden.

6.6 Kapitel Operatives Management des Primärtumors – PICO 6.6

Verbessert bei Patientinnen mit ED Vulvakarzinom T2 und T3 die primäre RT und RChT gegenüber der primär operativen Therapie die Rezidivrate, Rate der Exenterationen, Nebenwirkungsspektrum, DFS, PFS, MFS, OS?

6.6.1 Evidenztabellen

6.6.1.1 Systematische Reviews

Shylasree TS, Bryant A, Howells REJ. Chemoradiation for advanced primary vulval cancer. Cochrane Database of Systematic Reviews 2011, Issue 4. Art. No.: CD003752. DOI: 10.1002/14651858.CD003752.pub3.

van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulvar cancer. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD002224. DOI: 10.1002/14651858.CD002224.pub2.

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 Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 3) • Cochrane Gynaecological Cancer Collaborative Review Group Trial Register • MEDLINE • EMBASE • Unpublished and grey literature: Metaregister, Physicians Data Query, www.controlled-trials.com/ rct, www.clinicaltrials.gov	**Question/ Aim** To evaluate the effectiveness and safety of neoadjuvant and primary chemoradiation for women with locally advanced primary squamous vulval cancer compared to other primary modalities of treatment such as primary surgery or primary radiation. Locally	3 studies on 141 pts with advanced stage primary vulval cancer **Descriptive statistics:** • Age (median, range) <u>In 2 Non-RCT studies (Landrum 2008 & Mulayim 2004):</u> • 64 (2-88) & 73 <u>In RCT (Maneo 2003)</u> • A and B: 74 (31-85) • Sex (100% female) • Stage (nach FIGO 1944, N/%) <u>In 2 non-RCT studies (Landrum 2008 & Mulayim 2004):</u> • Stage III: N=57 • Stage IV: N=19 (IVb: N=4) <u>Maneo 2003 (RCT):</u> TNM status was as follows:	**Rezidivrate** <u>Landrum 2008:</u> • A (primary chemoradiation group): 5/33 • B (primary surgery group): 7/30 <u>Mulayim 2004</u> • A (primary chemoradiation group): 1/6 • B (primary surgery group): 3/6 <u>In Maneo 2003</u> • A (neoadjuvant chemoradiation arm): 13 • B (primary surgery group): 17 No Pooled results **DFS**: NR	**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 • 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: no MA • RoB considered in MA: no MA • RoB in interpretation: yes	2 non-RCTs: <u>Landrum 2008 & Mulayim 2004</u> 1 RC: <u>Maneo 2003</u> • Landrum LM, Skaggs V, Gould N, Walker JL, McMeekin DS. Comparison of outcome measures in patients with advanced squamous cell carcinoma of the vulva treated with surgery or primary chemoradiation. *Gynecologic Oncology* 2008;**108**(3):584-90.

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
	and www.cancer.gov/clinicaltrials were searched for ongoing trials. **Inclusion criteria** • 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. • In our review we incorporated patients with biopsy proven, primary locally advanced squamous cell carcinoma of the vulva (stage III/IV). Intervention:	advanced primary disease is defined as encompassing women who have FIGO stage III or IVa squamous vulval cancer. A: primary (2 non-RCTs) or neoadjuvant (1 RCT) chemoradiation B: primary surgery	• T1 N + 1 (3%) versus 0 (0%) • T2 N - 2 (7%) versus 10 (26%) • T2 N + 15 (50%) versus 19 (50%) • T3 N - 4 (13%) versus 4 (11%) • T3 N + 8 (27%) versus 5 (13%) Adjuvant surgery or radiation: • Landrum 2008: 8 (24%) patients underwent adjuvant surgery following primary chemoradiation and 19 patients (63%) underwent either adjuvant radiation or adjuvant chemoradiation following primary surgery. • Mulayim 2004: 1 patient in the primary chemoradiation group underwent adjuvant surgery and all the patients who underwent primary surgery underwent adjuvant chemoradiation. • Maneo 2003: in the primary surgery arm, 15 (15/37)	**PFS:** NR **MFS**: NR **OS** <u>Landrum 2008:</u> • A (primary chemoradiation group): 8/33 • B (primary surgery group): 9/30 • Adjusted HR=1.09, 95% CI 0.37 – 3.17 <u>Mulayim 2004</u> • A (primary chemoradiation group): 3/6 • B (primary surgery group): 6/6 <u>In Maneo 2003 (death at 5 years)</u>	• Heterogeneity explained: after the authors not relevant bc no MA • Publication bias investigated: no, no adequate number of studies to assess • Sources of CoI: none	• Mulayim N, Silver DF, Schwartz PE, Higgins S. Chemoradiation with 5-fluorouracil and mitomycin C in the treatment of vulvar squamous cell carcinoma. *Gynecologic Oncology* 2004;**93**:659- 66. • Maneo A, Landoni F, Colombo A, Colombo A, Villa A, Caspani G. Randomised study between neoadjuvant chemoradiotherapy and primary surgery for the treatment of advanced vulval cancer. International

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
	• Chemoradiation (primary, neoadjuvant) Comparison: • Primary surgery • Radiation (primary, neoadjuvant • Chemotherapy (neoadjuvant) **Exclusion criteria:** • case-control studies, uncontrolled observational studies and case series of fewer than 10 patients		patients underwent adjuvant radiation. Surgery was feasible in 24 out of 28 patients in the neoadjuvant arm.	• A (neoadjuvant chemoradiation arm): 20/28 • B (primary surgery group): 19/37 RR=1.39, 95% CI 0.94 - 2.06 No Pooled results **Nebenwirkungsspektrum (primary chemoradiation vs. primary survery)** Severe acute toxicity: • Hematologic toxicity · 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). • Gastrointestinal toxicity · There was no significant difference in the risk of		Journal of Gynecological Cancer. 2003; Vol. 13 Suppl 1:6, Abstract PL 19.

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 acute gastrointestinal toxicity between primary chemoradiation and surgery (RR 0.33, 95% CI 0.05 to 2.37). • Skin toxicity · 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). Severe Late toxicity: • There was no significant difference in the risk of other severe late toxicities between primary chemoradiation and surgery (RR 1.33, 95% CI 0.50 to 3.55).		

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 January 2016 and no additional trails were identified) **Databases:** • Cochrane Gynaecological Cancer Group Specialised Register, • Cochrane Central Register of Controlled Trials (CENTRAL), • MEDLINE and • EMBASE **Inclusion criteria** • RCTs and NRS • Women diagnosed with early squamous cell carcinoma of the	**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 **Descriptive statistics:** • 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 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%	**Rezidivrate** (recurrence overall) • A: 8/27 • B: 2/25 Pooled RR: 3.70 (95% CI 0.87 to 15.80) in favour of B (groin recurrence) • A: 5/27 • B: 0/25 Pooled RR: 10.21 (95% CI 0.59 to 175.78) in favour of B **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** **Disease-specific mortality:** • A: 8/27	**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 • 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	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. *International Journal of Radiation Oncology, Biology, Physics* 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
	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	Clitoris: 18,5% Perineum: 6% · B: Labia: 56% Clitoris: 24% Perineum: 12% Other: 8% • 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:	• B: 2/25 **RR 3.70, 95% CI 0.87 to 15.80 in favour of B** **lymphoedema** • A: 0/27 • B: 7/25 **RR 0.06, 95% CI 0.00 to 1.03 in favour of A** **life-threatening cardiovascular complications** • A: 0/27 • B: 5/25 **RR 0.08, 95% CI 0.00 to 1.45 in favour of A** **Hospital Stay:** **RR 0.28, 95% CI 0.13 to 0.58)**	• Heterogeneity explained: NA • Publication bias investigated: no **Sources of CoI: none** **Andere Bemerkungen:** **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 4.5-6.1cm, therefore the radiotherapy dose used in this trial may have been insufficient for deep nodes.**	

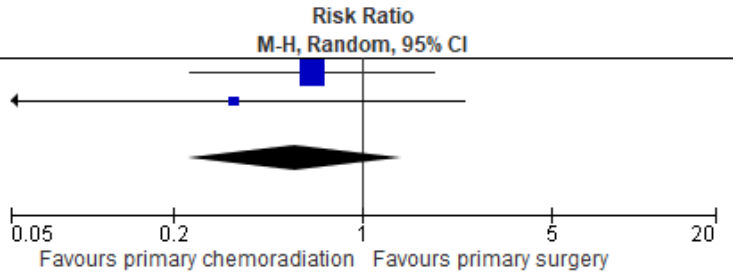
6.6.2 Forest plots

6.6.2.1 Forest plot of comparison: primary RChT vs. primary surgery, outcome: Recurrence

(forest plot erstellt mit RevMan 5.4.1)

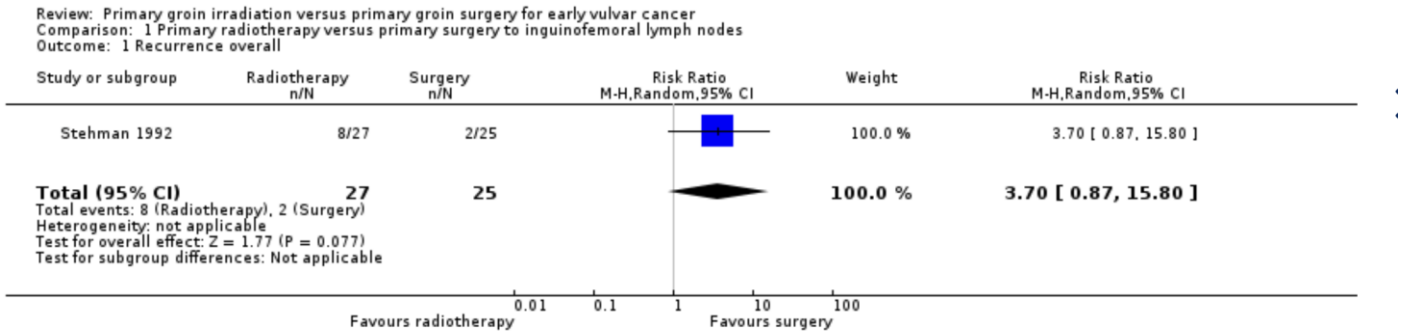
Study or Subgroup	primary RChT Events	Total	primary surgery Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Landrum 2008	5	33	7	30	78.2%	0.65 [0.23, 1.83]
Mulayim 2004	1	6	3	6	21.8%	0.33 [0.05, 2.37]
Total (95% CI)		**39**		**36**	**100.0%**	**0.56 [0.22, 1.40]**
Total events	6		10			

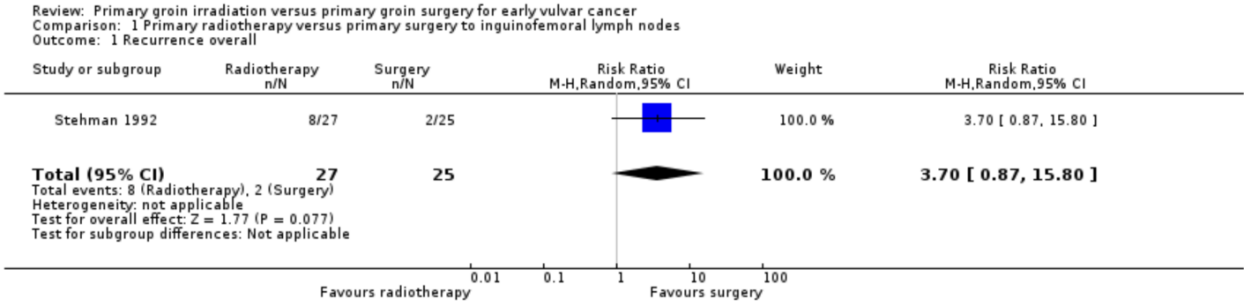
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.22)

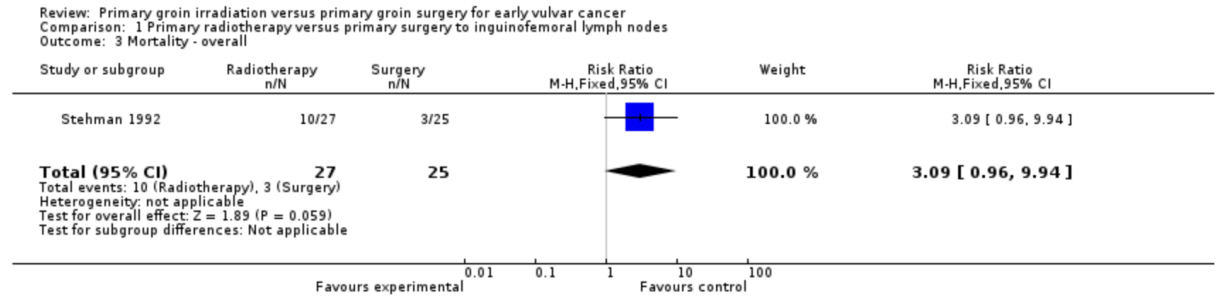


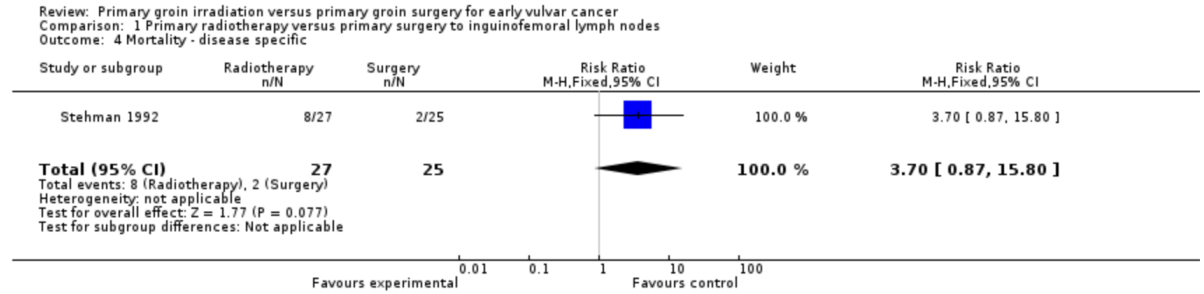
6.6.2.2 Forest plots of comparison: primary radiotherapy of the inguinofemoral lymph nodes versus inguinofemoral lymph node dissection

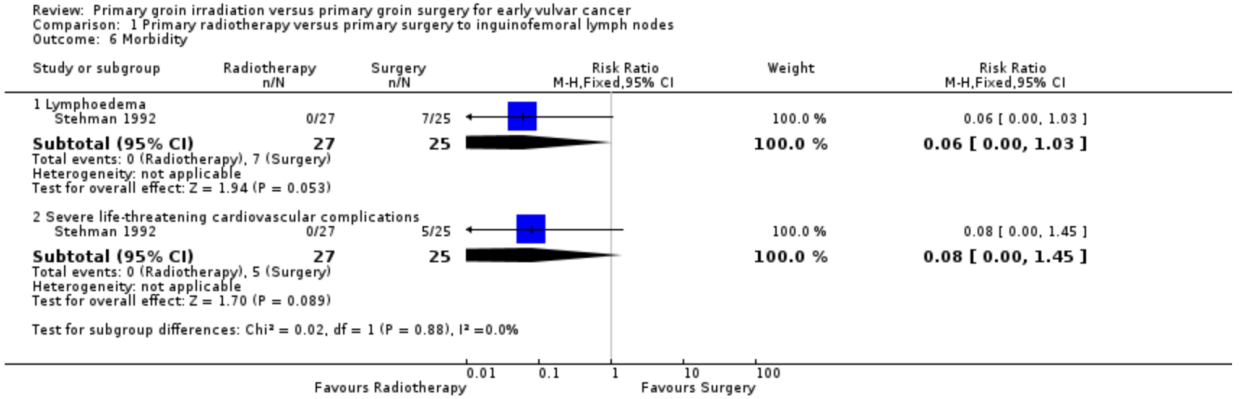
(forest plots aus dem SR)




Review: Primary groin irradiation versus primary groin surgery for early vulvar cancer
Comparison: 1 Primary radiotherapy versus primary surgery to inguinofemoral lymph nodes
Outcome: 1 Recurrence overall
Study or subgroup
Radiotherapy n/N
Surgery n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
Stehman 1992 8/27 2/25 100.0 % 3.70 [0.87, 15.80]
Total (95% CI) 27 25 100.0 % 3.70 [0.87, 15.80]
Total events: 8 (Radiotherapy), 2 (Surgery)
Heterogeneity: not applicable
Test for overall effect: Z = 1.77 (P = 0.077)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours radiotherapy
Favours surgery


Review: Primary groin irradiation versus primary groin surgery for early vulvar cancer
Comparison: 1 Primary radiotherapy versus primary surgery to inguinofemoral lymph nodes
Outcome: 3 Mortality - overall
Study or subgroup
Radiotherapy n/N
Surgery n/N
Risk Ratio M-H,Fixed,95% CI
Weight
Risk Ratio M-H,Fixed,95% CI
Stehman 1992 10/27 3/25 100.0 % 3.09 [0.96, 9.94]
Total (95% CI) 27 25 100.0 % 3.09 [0.96, 9.94]
Total events: 10 (Radiotherapy), 3 (Surgery)
Heterogeneity: not applicable
Test for overall effect: Z = 1.89 (P = 0.059)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours experimental
Favours control


Review: Primary groin irradiation versus primary groin surgery for early vulvar cancer
Comparison: 1 Primary radiotherapy versus primary surgery to inguinofemoral lymph nodes
Outcome: 4 Mortality - disease specific
Study or subgroup
Radiotherapy n/N
Surgery n/N
Risk Ratio M-H,Fixed,95% CI
Weight
Risk Ratio M-H,Fixed,95% CI
Stehman 1992 8/27 2/25 100.0 % 3.70 [0.87, 15.80]
Total (95% CI) 27 25 100.0 % 3.70 [0.87, 15.80]
Total events: 8 (Radiotherapy), 2 (Surgery)
Heterogeneity: not applicable
Test for overall effect: Z = 1.77 (P = 0.077)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours experimental
Favours control



6.6.3 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen:

Shylasree TS, Bryant A, Howells REJ. Chemoradiation for advanced primary vulval cancer. Cochrane Database of Systematic Reviews 2011, Issue 4. Art. No.: CD003752. DOI: 10.1002/14651858.CD003752.pub3.

Primäre RT und RChT versus primäre operative Therapie								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → 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

Primäre RT und RChT versus primäre operative Therapie								
Low → 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

Literaturreferenzen:

van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulvar cancer. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD002224. DOI: 10.1002/14651858.CD002224.pub2.

Primäre RT der Leiste/Groin (primary radiotherapy of the inguinofemoral lymph nodes) versus Primäre operative Therapie der Leiset/Groin (inguinofemoral lymph node dissection)								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
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
High	1 RCT	Overall recurrence	/	/	-1 (includes patients with T1-3 N0-1 M0)	-2 (only few events: 10/52 pts and very	The original sample size was 300 patients but the trial was stopped early, after 58 enrolments, due to	⊕⊖⊖⊖ Very low

Primäre RT der Leiste/Groin (primary radiotherapy of the inguinofemoral lymph nodes) versus Primäre operative Therapie der Leiset/Groin (inguinofemoral lymph node dissection)								
						wide CI: HR=3.70 (95% CI 0.87 to 15.80)	perceived dis-benefit in the radiotherapy group.	
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

6.7 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.2

Verbessert bei Patientinnen mit ED Vulvakarzinom, befallenen inguinalen LK (Lymphknoten) und Indikation zur inguinalen Strahlentherapie mit bildgebend unauffälligen pelvinen LK die systematische pelvine LNE (Lymphonodektomie) +/- Radiatio in Abhängigkeit nachgewiesener LK-Metastasen versus der pelvinen Radiatio ohne operatives Staging die Rate der LK-Rezidive (insbesondere pelvin) / Morbidität / DFS / OS?

6.7.1 Evidenztabellen

6.7.1.1 Primärstudien (RCT)

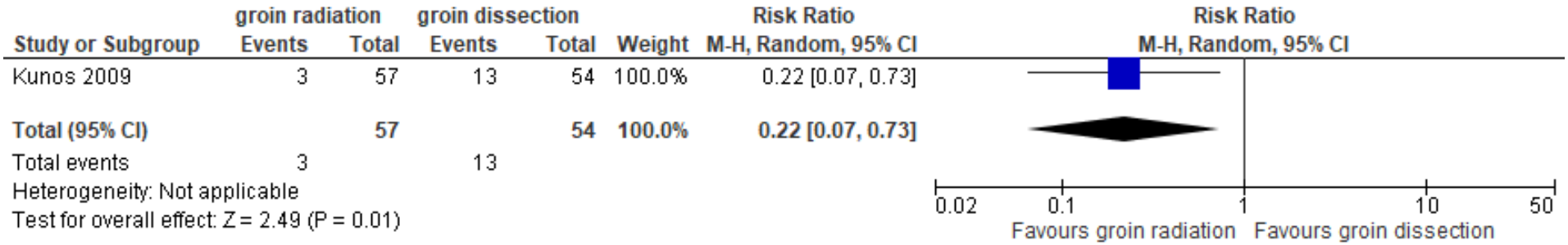
Kunos, Charles MD, PhD1; Simpkins, Fiona MD2,3,6; Gibbons, Heidi MS3; Tian, Chunqiao PhD4; Homesley, Howard MD5. Radiation Therapy Compared With Pelvic Node Resection for Node-Positive Vulvar Cancer: A Randomized Controlled Trial. Obstetrics & Gynecology 114(3):p 537-546, September 2009. DOI: 10.1097/AOG.0b013e3181b12f99

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):** • primary invasive squamous cell carcinoma of the vulva • unilateral or bilateral groin metastasis • primary lesions and groin nodes were amenable to radical vulvectomy and bilateral inguinal lymphadenectomy **Exclusion criteria (for analysis):** • vulvar cancer recurrence • prior malignancies • positive groin nodes not resected at surgery **Enrolment period** • 1977 to 1984 **Descriptive statistics** • Age (median, range) · median age A & B: 70 years • Stage (FIGO, %) · A: NO/N1: 47% N2: 37%	**Interventions** A: Pelvic and groin radiation B: Ipsilateral pelvic node resection **Analysis** • Type of analysis: Cox proportional hazards models • adjusted for age and adverse tumor characteristics	**Recurrence free survival** HR=0.39 (95% CI 0,17–0,88; p=0,02) in favour of A **→Recurrence at any site** • A: 21/57 • B: 27/54 **→ Groin Recurrence** • A: 3/57 • B: 13/54 RR=0.22 (95% CI 0.07 to 0.73) **6-year overall survival (all-cause death)** HR=0.61, (95% CI 0.30–1.3, P=0.02), in favour of A "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<.001) persisted" →After adjusting for age, treatment, and tumor characteristics, the hazard ratio of overall death in patients with 20% positive	Kunos 2009, RCT

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	N3: 15% · B: N0/N1: 35% N2: 45% N3: 18% • Location of the tumour · NR • Tumour size (%, cm) · NR • 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%		groin nodes was 3.9 (95% CI 2.1–7.4, P<.001), favoring radiation. **6-years cancer-related death rate** A: 18/57 B: 28/54 HR= 0.49, (95% CI 0.28–0.87, P=015) in favour of A	

6.7.2 Forest plots

6.7.2.1 Forest plot of comparison: groin radiation vs. groin dissection/resection, outcome: groin recurrence



6.7.3 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen

Kunos, Charles MD, PhD1; Simpkins, Fiona MD2,3,6; Gibbons, Heidi MS3; Tian, Chunqiao PhD4; Homesley, Howard MD5. Radiation Therapy Compared With Pelvic Node Resection for Node-Positive Vulvar Cancer: A Randomized Controlled Trial. Obstetrics & Gynecology 114(3):p 537-546, September 2009. DOI: 10.1097/AOG.0b013e3181b12f99

Groin radiation vs. groin dissection/resection								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
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

6.8 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.3

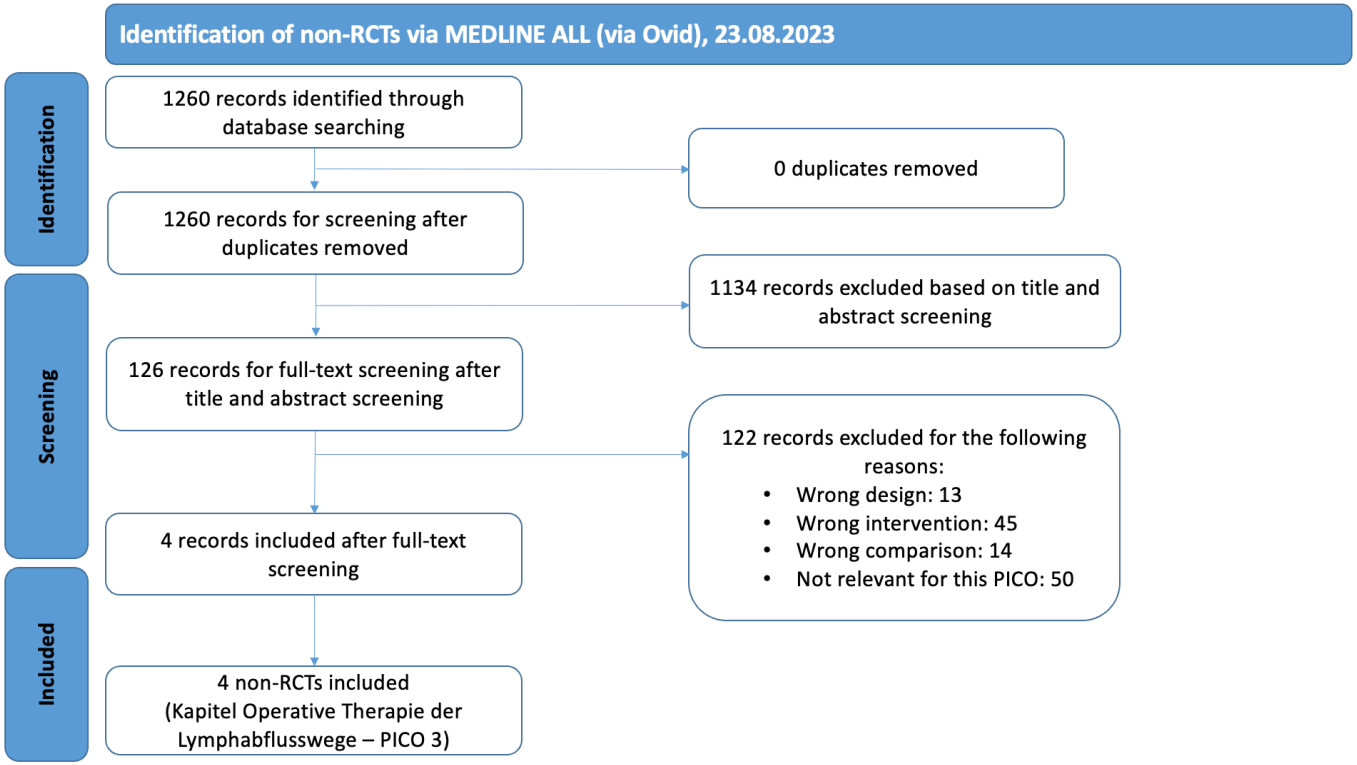
7.3a. Verbessert eine bds. systematische inguinofemorale LNE plus adj. Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und 1 inguinalen LK-Makrometastase die Rate der LK-Rezidive / Morbidität / DFS / OS?

7.3b. Verbessert eine bds. systematische inguinofemorale LNE plus adj. Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und mind. 2 inguinalen LK-Metastasen die Rate der LK-Rezidive / Morbidität / DFS / OS?

7.3c. Verbessert eine bds. systematische inguinofemorale LNE (Lymphonodektomie) plus adj. Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und inguinaler LK-Metastase mit extrakapsulärem Wachstum die Rate der LK-Rezidive / Morbidität / DFS / OS?

7.3d. Verbessert eine bds. systematische inguinofemorale LNE plus adj. Radiatio der LAW gegenüber der alleinigen bds. systematischen inguinofemoralen LNE bei Patientinnen mit ED Vulvakarzinom und fixierten bzw. exulzerierten inguinalen LK-Metastasen die Rate der LK-Rezidive / Morbidität / DFS / OS?

6.8.1 PRISMA Flowdiagramm



6.8.2 Evidenztabellen

6.8.2.1 Primärstudien (non-RCTs)

Fons, G., Groenen, S.M.A., Oonk, M.H.M., Ansink, A.C., van der Zee, A.G.J., Burger, M.P.M., Stalpers, L.J.A. & van der Velden, J. (2009). Adjuvant radiotherapy in patients with vulvar cancer and one intra capsular lymph node metastasis is not beneficial. Gynecologic Oncology 114; 343–345. https://dx.doi.org/10.1016/j.ygyno.2009.05.017

Mahner, S., Jueckstock, J., Hilpert, F., Neuser, P., Harter, P., de Gregorio, N., Hasenburg, A., Sehouli, J et al. (2015) Adjuvant Therapy in Lymph Node–Positive Vulvar Cancer: The AGO-CaRE-1 Study. Journal of the National Cancer Institute, 107 (3); dju426. https://doi.org/10.1093/jnci/dju426

Parthasarathy, A., Cheung, M.K., Osann, K., Husain, A., Teng, N.N., Berek, J.S. Kapp, D.S. et al. (2006). The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. Gynecologic Oncology 103; 1095–1099. https://doi:10.1016/j.ygyno.2006.06.030

Rydzewski, N.R., Kanis, M.J., Donnelly, E. C., Lurain, J.R., Strauss, J.B. (2018). Role of adjuvant external beam radiotherapy and chemotherapy in one versus two or more node-positive vulvar cancer: A National Cancer Database study. Radiotherapy and Oncology,129 (3); 534-539.https://doi.org/10.1016/j.radonc.2018.03.023

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 metastasis (single intra capsular lymph node metastasis, without extra capsular spread) • radical vulvectomy or wide local excision of the tumor and an inguino-femoral lymphadenectomy **Exclusion criteria (for analysis):** • NR **Enrolment period** • 1984-2005 **Descriptive statistics** • Age (median, range) · A: mean age 75 years · B: mean age 72 years • Stage (FIGO, %) · NR • Location of the tumour · NR	**Interventions** A: adjuvant radiotherapy to the groins and pelvis (N=31) B: No intervention (just surgery LNE) (N=44) **Analysis** • Type of analysis: Cox's proportional hazards model • Matching: NR • Confounders: NR	**Rezidivrate** • A: 12/31 • B: 14/44 RR: 1.22 (95% CI 0.66-2.26) **5-year DFS (disease-free survival)** • A: 20/31 • B: 27/44 HR: 0.98 (95% CI 0.45-2.14; p= 0.97) **DSS (disease-specific survival)** A: 21/31 B: 30/44 HR: 1.02 (95% CI 0.42-2.14; p= 0.96) **PFS:** NR **OS:** NR	**General information** • **Follow-up:** 75 months • Funding: NR • **CoI**: 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?: no • Drop-out rate & reasons reported: no drop-out · Similar across groups: yes · If high: comparison of those lost with available: na • Outcome

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Tumour depth (%, cm) · 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			· Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If 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
Mahner et al., 2015	n=1249 primary or recurrent squamous cell vulvar cancer stage IB-IV (with surgical groin staging and known lymph node status positive or negative)	**Interventions** A: adjuvant radiotherapy (directed at the groins+/-	**Rezidivrate (of the vulva only)** • A: 28.1% **3-year PFS**	**General information** • **Follow-up:** 39 months • **Funding**: Medac oncology

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
retrospective cohort study	**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 • Stage (FIGO, %) • TNM- Classification A: · pT1b: 16,4% · pT2: 63,1% · pT3: 18,9% · pT4: 0,8% B:	pelvis+/-vulva) & node positive (N=183) B: no adjuvant radiotherapy & node positive (N=165) **Analysis** • Type of analysis: Cox's proportional hazards model Kaplan-Meier method, log-rank test, • Matching: NR • Confounders: NR	• 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-year OS** ◆ A: 57.7%/ 183 ◆ B: 51.4%/ 165 HR = 0.79, 95% CI 0.56 - 1.11, *P* = .17 **DFS** • NR	• **CoI**: 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 · If high: comparison of those lost with available: no • Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If not, Knowledge of

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· 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) · B: 7 (1 - 70) • Lymph node metastases (yes, %) · Yes n=447 · 1: 38,5% · 2: 22,8% · 3: 13,9% · >3: 19,5% · Unknow: 5,4% • Additional/ adjuvant treatment: · NR			exposure status likely to influence the outcome?:): no • Main cofounders taken into account: yes • Confidence intervals reported: yes • Selective reporting (comparison with protocol): yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Parthasarathy et al., 2006 retrospective cohort study	n=208 singel node-positive vulvar cancers, stage III **Inclusion criteria (for analysis):** • vulvar cancers single positive inguinal node **Exclusion criteria (for analysis):** • NR **Enrolment period** • 01.01.1988-31.12.2001 **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	**Interventions** A: adjuvant radiotherapy (N=102) B: no adjuvant radiotherapy (N=106) **Analysis** • Type of analysis: Cox's proportional hazards model Kaplan-Meier method, • Matching: NR • Confounders: yes	**Rezidivrate:** NR **DSS:** • A: 77%/102 • B: 61,2%/106 HR: 0.57 CI: 0.32-1.03 **PFS:** NR **MFS:** NR **OS: NR**	General information • **Follow-up:** 60 months • Funding: NR • **CoI**: NR **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: yes · If high: comparison of those lost with available: no • Outcome

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· unknow: n=11 • Location of the tumour · NR • Tumour size (%, cm) · NR • Tumour depth (%, mm) · NR • Lymph node metastases (yes, %) · NR			· Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If 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
Rydzewski et al., 2018 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	**Interventions** A: adjuvant external beam radiation therapy (EBRT) (N=974, 502 with 1pos Node & 472 with >/=2 pos Nodes) B: no adjuvant treatment (N=1061, 620 with 1pos Node & 441 with >/=2 pos Nodes) C: adjuvant external beam radiation	**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	**General information** • **Follow-up**: NR • **Funding**: NR • **CoI**: 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

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	of income, education or insurance status, unknown stage or who had distant metastases at diagnosis **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, %) TNM- Classification	therapy with chemotherapy (N=744, 314 with 1pos Node & 430 with >/=2 pos Nodes) **Analysis** • Type of analysis: Cox's proportional hazards model Kaplan-Meier method, log-rank test • Matching: NR • Confounders: yes	**DFS: NR** **PFS: NR** **MFS: NR**	• Exposure/Intervention · Assessment reliable: yes · Assessed more than once: no · 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: (→If 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
	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 • Tumour depth (%, mm) · NR • Lymph node metastases (yes, %) · Positive Nodes			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	A: · 1 Positive Node: n=502 · 2 or More Positive Nodes: n=472 B: · 1 Positive Node: n=620 · 2 or More Positive Nodes: n=441 C: · 1 Positive Node: n=314 · 2 or More Positive Nodes: n=430			

6.8.3 Bewertung der Evidenz (nach GRADE)

PICO 3a:

Fons, G., Groenen, S.M.A., Oonk, M.H.M., Ansink, A.C., van der Zee, A.G.J., Burger, M.P.M., Stalpers, L.J.A. & van der Velden, J. (2009). Adjuvant radiotherapy in patients with vulvar cancer and one intra capsular lymph node metastasis is not beneficial. Gynecologic Oncology 114; 343–345. https://dx.doi.org/10.1016/j.ygyno.2009.05.017

Adjuvant radiotherapy to the groins and pelvis versus no intervention (surgery LNE)								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität

Adjuvant radiotherapy to the groins and pelvis versus no intervention (surgery LNE)								
Low → cohort study	1 cohort study (Fons 2009)	Recurrence	/	/	Note: population of interest from the PICO may differ from the population in this study (P: squamous cell cancer of the vulva and single intra capsular lymph node metastasis)	-2 (only few events, few participants and wide CI: RR= 1.22, 95% CI 0.66-2.26)	/	⊕⊖⊖⊖ Very low
Low → cohort study	1 cohort study (Fons 2009)	DFS	/	/	Note: population of interest from the PICO may differ from the population in this study (P: squamous cell cancer of the vulva and single intra capsular lymph node metastasis)	-2 (only few events, few participants and wide CI: HR= 0.98, 95% CI 0.45-2.14)	/	⊕⊖⊖⊖ Very low

PICO 3b:

Rydzewski, N.R., Kanis, M.J., Donnelly, E. C., Lurain, J.R., Strauss, J.B. (2018). Role of adjuvant external beam radiotherapy and chemotherapy in one versus two or more node-positive vulvar cancer: A National Cancer Database study. Radiotherapy and Oncology,129 (3); 534-539.https://doi.org/10.1016/j.radonc.2018.03.023

Adjuvant external beam radiation therapy (EBRT) versus no adjuvant treatment								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität

Adjuvant external beam radiation therapy (EBRT) versus no adjuvant treatment								
Low → cohort study	1 cohort study (Rydzewski 2018)	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

PICO 3a-3d:

Mahner, S., Jueckstock, J., Hilpert, F., Neuser, P., Harter, P., de Gregorio, N., Hasenburg, A., Sehouli, J et al. (2015) Adjuvant Therapy in Lymph Node-Positive Vulvar Cancer: The AGO-CaRE-1 Study. Journal of the National Cancer Institute, 107 (3); dju426. https://doi.org/10.1093/jnci/dju426

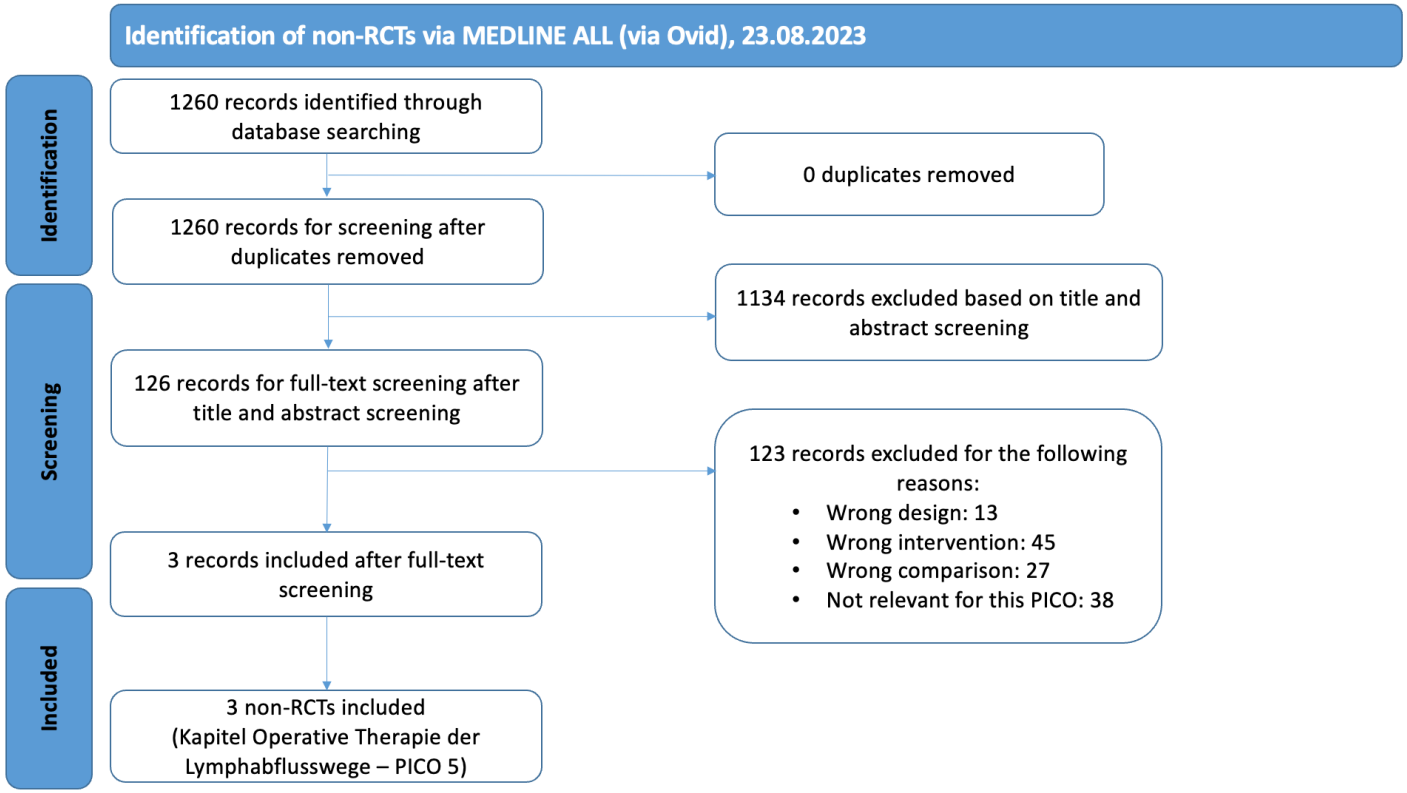
Adjuvant radiotherapy (directed at the groins+/-pelvis+/-vulva) & node positive versus no adjuvant radiotherapy & node positive								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → cohort study	1 cohort study (Mahner 2015)	PFS	/	/	Note: population of interest from the PICO may differ from the population in this study (P: primary or recurrent squamous cell vulvar cancer stage IB-IV with surgical groin staging & lymph node status positive)	-1 (only few events, few participants, HR=0.67, 95% CI 0.51 to 0.88)	/	⊕⊖⊖⊖ Very low

Adjuvant radiotherapy (directed at the groins+/−pelvis+/−vulva) & node positive versus no adjuvant radiotherapy & node positive								
Low → cohort study	1 cohort study (Mahner 2015)	OS	/	/	Note: population of interest from the PICO may differ from the population in this study (P: primary or 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

6.9 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.5

Verbessert bei Patientinnen mit ED Vulvakarzinom und bulky nodes inguinal und/oder pelvin eine bds. Systematische inguinofemorale bzw. pelvine LNE mit adjuvanter Radiatio gegenüber der alleinigen Entfernung der auffälligen LK mit adjuvanter Radiatio die Rate der LK-Rezidive / Morbidität / DFS / OS?

6.9.1 PRISMA Flowdiagramm



6.9.2 Evidenztabellen

6.9.2.1 Primärstudien (non-RCTs)

Fons G, Thuijs NB, Tjiong M, Stalpers LJA, van der Velden J. Selective Removal of Only Clinically Suspicious Positive Lymph Nodes Instead of a Complete Inguino-Femoral Lymph Node Dissection in Squamous Cell Carcinoma of the Vulva. Cancers (Basel). 2023 Jul 28;15(15):3844. doi: 10.3390/cancers15153844

Hyde SE, Valmadre S, Hacker NF, Schilthuis MS, Grant PT, van der Velden J. Squamous cell carcinoma of the vulva with bulky positive groin nodes-nodal debulking versus full groin dissection prior to radiation therapy. Int J Gynecol Cancer. 2007 Jan-Feb;17(1):154-8. doi: 10.1111/j.1525-1438.2006.00769.x

Nooij LS, Ongkiehong PJ, van Zwet EW, Bosse T, Creutzberg CL, Gaarenstroom KN, van Poelgeest MI. Groin surgery and risk of recurrence in lymph node positive patients with vulvar squamous cell carcinoma. Gynecol Oncol. 2015 Dec;139(3):458-64. doi: 10.1016/j.ygyno.2015.09.081

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**	**Interventions** A: nodal debulking + radiotherapy B: IFL + radiotherapy **Analysis** • Type of analysis: Cox model, Cox	**5-year groin recurrence-free** • 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)**	**General information** • Median follow-up: 31.5 months (range: 3 - 395) • **Funding**: none • **CoI**: none declared **Risk of bias considerations (adapted from SIGN cohort study checklist)**

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• 1985 – 2020 **Descriptive statistics** • Age (median, range) · A: 74 (36–90) · B: 77 (34–92) • Stage (FIGO, %) · IIIa: A: 15%, B: 11% · IIIb: A: 20%, B: 18% · IIIc: A: 50%, B: 57% · IVa: A: 5%, B: 0% · IVb: A: 10%, B: 14% • Location of the tumour · NR • Tumour size · Median: A: 46 mm (range: 10–150), B: 48 mm (range: 20–90) • Tumour depth (%, mm) · NR • Lymph node metastases (yes, %) · Yes, diameter of nodal metastasis > 15 mm: A: 32/40 (80%), B: 29/ 37 (78%)	proportional hazard model • Matching: yes (matching with historical controls) • Confounders: NR	• A: 43.1%/ 40 • B: 41.1%/ 37 Debulking vs. IFL: HR= 0.45 (95% CI 0.15 – 1.29; p=0.14)	• Study type: retrospective single center 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: yes · 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: (→If not, Knowledge of exposure status likely to influence the outcome?:): no? • Main cofounders taken into account: NR • Confidence intervals reported: yes for DSS • Selective reporting (comparison with protocol): NR

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) · ≤ 4: A: 11, B: 9	**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	**Groin recurrence rate** (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."	**General information** • Follow-up: 140–500 months • **Funding**: NR • **CoI**: 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 · Outcome measure is well-defined, valid and reliable: yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· >4: A: 6, B: 14 • Tumour depth (%, mm) · NR • Lymph node metastases (yes, %) · Yes, number of positive nodes: · A: 17, B: 23			· Blind outcome assessment to exposure:): no • Main cofounders taken into account: NR • Confidence intervals reported: yes for DFS Selective reporting (comparison with protocol): NR
Nooij 2015 Retrospective cohort study	72 pts with newly diagnosed VSCC • Inclusion criteria (for analysis): • Newly diagnosed VSCC and metastases to the groin nodes • Patients who were referred to Leiden University Medical Center • Only patients with cytologically and histologically proven lymph node metastases **Exclusion criteria (for analysis):** • Patients who received primary radiotherapy to the groins **Enrolment period** • 2000–2012 **Descriptive statistics**	**Interventions** A: standard full inguinofemoral lymphadenectomy (IFL) + 66.7% of n received groin radiotherapy B: debulking of clinically involved lymph nodes + 89.5% of n received groin radiotherapy (C: Sentinel node removal procedure +	**Groin recurrence** • A: 13.3% (4/30) • B: 15.8% (6/38) • C: 25% (4/16) • P=0.495 IFL vs. debulking: RR= 0.84 (95% CI 0.26-2.72) **Groin recurrence-free time** (Multivariate analysis) • IFL vs. debulking: HR= 1.782 (95% CI 0.447–7.102) "The risk of groin recurrence was similar in all treatment groups."	**General information** • Mean follow-up: 33.4 months (range: 0–146 months) • **Funding**: NR • **CoI**: none declared **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective cohort study • Populations comparable: NR • Rate of participation/Exclusions reported (selection bias into the study): yes • Exposure/Intervention · Assessment reliable: yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Age (median, range) · Mean: all pts.: 70.8 (range: 35–94) • Stage (FIGO, %), for all patients: · III: 79.4% · IV: 20.6% • Location of the tumour; for all pts.: · Midline: 22% · Unilateral: 63.3% · Bilateral: 8.8% · Multifocal: 4.4% · Not specified: 1.5% • Tumour size (%, cm), for all pts.: · ≤ 2: 22.1% · 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	68.8% of n received groin radiotherapy) **Analysis** • Type of analysis: Cox regression • Matching: NR • Confounders: Adjusted for age		· Assessed more than once: yes · 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: no • Main cofounders taken into account: only age was adjusted for • Confidence intervals reported: yes Selective reporting (comparison with protocol): NR

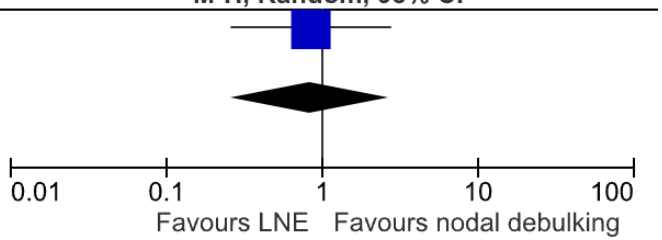
Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung

6.9.3 Forest plots

6.9.3.1 Forest plot of comparison: standard full inguinofemoral lymphadenectomy (IFL) vs. debulking of clinically involved lymph nodes, outcome: groin recurrence

	Experimental		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Nooij 2015	4	30	6	38	100.0%	0.84 [0.26, 2.72]	
Total (95% CI)		**30**		**38**	**100.0%**	**0.84 [0.26, 2.72]**	
Total events	4		6				

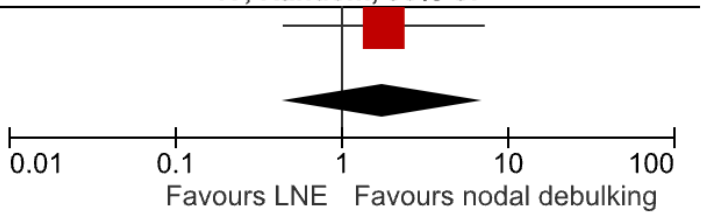
Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)



6.9.3.2 Forest plot of comparison: standard full inguinofemoral lymphadenectomy (IFL) vs. debulking of clinically involved lymph nodes, outcome: Groin recurrence-free time

				Hazard Ratio	Hazard Ratio
Study or Subgroup	**log[Hazard Ratio]**	**SE**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Nooij 2015	0.5777	0.7056	100.0%	1.78 [0.45, 7.10]	
Total (95% CI)			**100.0%**	**1.78 [0.45, 7.10]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



6.9.4 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen

Nooij LS, Ongkiehong PJ, van Zwet EW, Bosse T, Creutzberg CL, Gaarenstroom KN, van Poelgeest MI. Groin surgery and risk of recurrence in lymph node positive patients with vulvar squamous cell carcinoma. Gynecol Oncol. 2015 Dec;139(3):458-64. doi: 10.1016/j.ygyno.2015.09.081

Inguinofemoral lymphadenectomy (IFL) versus debulking of clinically involved lymph nodes								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → 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 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

Literaturreferenzen

Fons G, Thuijs NB, Tjiong M, Stalpers LJA, van der Velden J. Selective Removal of Only Clinically Suspicious Positive Lymph Nodes Instead of a Complete Inguino-Femoral Lymph Node Dissection in Squamous Cell Carcinoma of the Vulva. Cancers (Basel). 2023 Jul 28;15(15):3844. doi: 10.3390/cancers15153844

Hyde SE, Valmadre S, Hacker NF, Schilthuis MS, Grant PT, van der Velden J. Squamous cell carcinoma of the vulva with bulky positive groin nodes-nodal debulking versus full groin dissection prior to radiation therapy. Int J Gynecol Cancer. 2007 Jan-Feb;17(1):154-8. doi: 10.1111/j.1525-1438.2006.00769.x

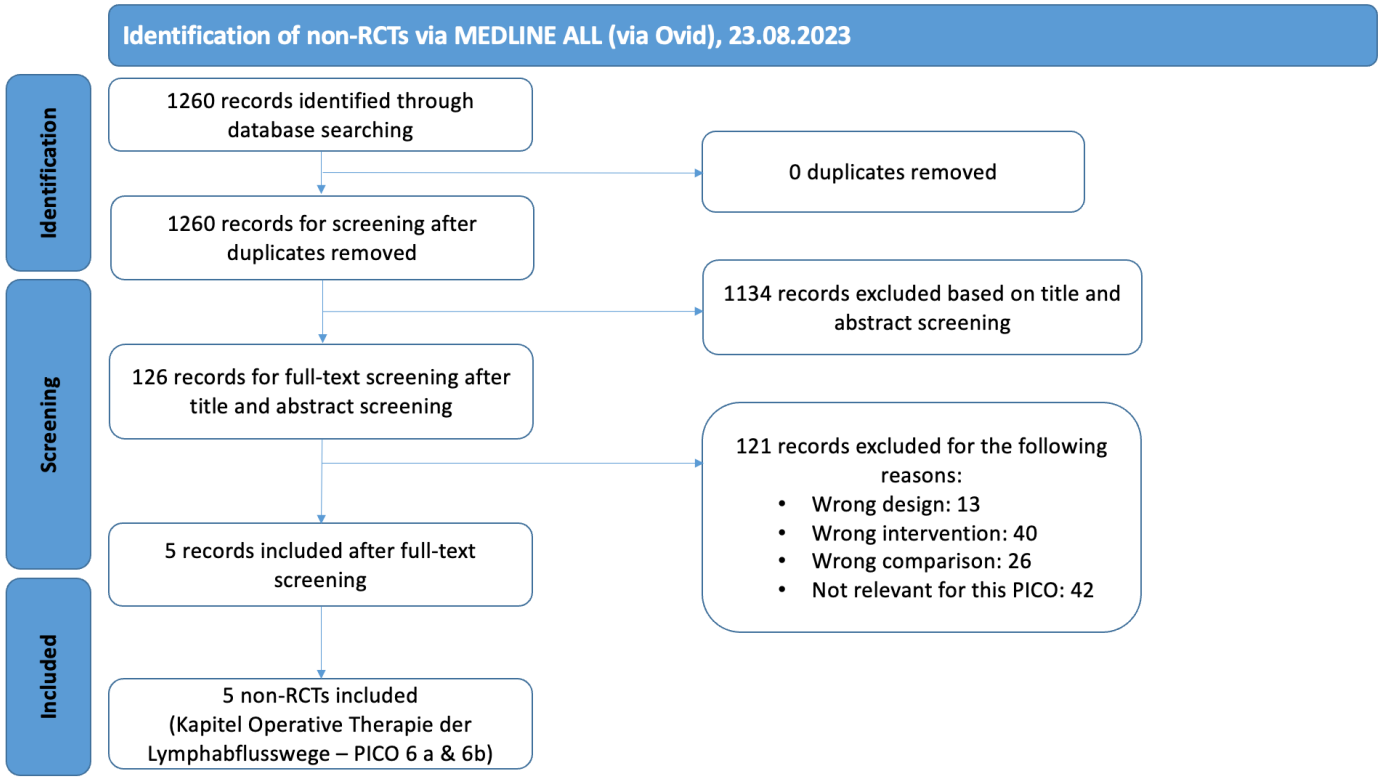
Debulking versus IFL								
Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → cohort study	1 cohort study (Hyde 2007)	DFS	/	/	Note: population of interest from the PICO may not be exactly represented in this study	-1 (only few events and few participants, N=40) (debulking vs. IFL, HR= 0.407, 95% CI 0.137-1.207)	/	⊕⊖⊖⊖ Very low
Low → 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

6.10 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.6

7.6a. Verbessert bei Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unauffälligen LAW und bds. inguinofemoraler LNE mit histologisch mind. 1 befallenem LK die inguinofemorale LNE mit mind. 6 entfernten LK pro Leiste gegenüber der inguinofemoralen LNE mit < 6 entfernten LK die Rate der LK-Rezidive seitenbezogen / Morbidität / DFS / OS?

7.6b. Verbessert bei Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unauffälligen LAW und bds. inguinofemoraler LNE mit histologisch negativen LK die inguinofemorale LNE mit mind. 6 entfernten LK pro Leiste gegenüber der inguinofemoralen LNE mit < 6 entfernten LK die Rate der LK-Rezidive / Morbidität / DFS / OS?

6.10.1 PRISMA Flowdiagramm



6.10.2 Evidenztabellen

6.10.2.1 Primärstudien (non-RCTs)

Baiocchi G, Cestari FM, Rocha RM, Faloppa CC, Kumagai LY, Fukazawa EM, Badiglian-Filho L, Cestari LA, Rodrigues IS, Lavorato-Rocha A, Maia BM, Soares FA. Does the count after inguinofemoral lymphadenectomy in vulvar cancer correlate with outcome? Eur J Surg Oncol. 2013 Apr;39(4):339-43. doi: 10.1016/j.ejso.2013.02.012.

Courtney-Brooks M, Sukumvanich P, Beriwal S, Zorn KK, Richard SD, Krivak TC. Does the number of nodes removed impact survival in vulvar cancer patients with node-negative disease? Gynecol Oncol. 2010 May;117(2):308-11. doi: 10.1016/j.ygyno.2010.01.007.

Diehl A, Volland R, Kirn V, Thangarajah F, Eichler C, Einzmann T, Wirtz M, Ratiu D, Morgenstern B, Fridrich C, Mallmann P, Puppe J. The number of removed lymph nodes by inguinofemoral lymphadenectomy: impact on recurrence rates in patients with vulva carcinoma. Arch Gynecol Obstet. 2016 Jul;294(1):131-6. doi: 10.1007/s00404-015-3932-6.

Sopracordevole F, Clemente N, Giorda G, Canzonieri V, Alessandrini L, Del Fabro A, Serri M, Ciavattini A. Number of Nodes Removed With Inguinofemoral Lymphadenectomy and Risk of Isolated Groin Recurrence in Women With FIGO Stage IB-II Squamous Cell Vulvar Cancer. Int J Gynecol Cancer. 2018 Oct;28(8):1600-1605. doi: 10.1097/IGC.0000000000001326.

Wu SG, Zhang WW, Sun JY, Chen QH, He ZY, Zhou J. Prognostic Value of the Number of Removed Lymph Nodes in Vulvar Squamous Cell Carcinoma Patients With Node-Positive Disease: A Population-Based Study. Front Oncol. 2018 May 30;8:184. doi: 10.3389/fonc.2018.00184.

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	**Interventions** A: <12 lymph nodes resected with lymphadenectomy	**Rezidivrate (groin recurrence)** • A: 28.6%/13 • B: 23%/145 **P= 0.74**	**General information** • Median follow-up: 34 months (range: 1-301.5) • **Funding**: NR • **CoI**: none declared

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	Exclusion criteria (for analysis): • NR **Enrolment period** • 1980–2010 **Descriptive statistics** • Age (mean, range) · All participants: 67 (15–90) • Stage (FIGO, %) · NR • Location of the tumour · NR • Tumour size (cm) · median: 5 (range: 1–18) • Tumour depth (%, mm) · Median: 10 (range: 2–30) analyzed for N=54 pts. • Lymph node metastases (yes, %) · Yes, 50.6% · 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,	B: ≥12 lymph nodes resected with lymphadenectomy **Analysis** • Type of analysis: Chi-square or Fischer's exact test • Matching: NA • Confounders: NR	**3-year OS** **Subgroup: patients with positive LNs (FIGOstage III)** • A: 20.8%/13 • B: 48%/145 P=0.084 "Resection of fewer than 12 LNs in vulvar cancer has a negative impact on outcome for patients with positive inguinal LNs." Additional outcomes: **2-year PFS (progression free survival)** **Subgroup: patients with positive LNs (FIGOstage III)** ◆ A: 20.8%/13 ◆ B: 52.8%/145 P=0.003 **3-year DSS (disease specific survival)** **Subgroup: patients with positive LNs (FIGOstage III)** ◆ A: 20.8%/13 ◆ B: 78.6%/145	**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 • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: yes · Possibly affected by knowledge of outcome status?: yes • Drop-out rate & reasons reported: NA · 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: no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	2, and 3 or more positive LNs, respectively.		P=0.043	• Main cofounders taken into account: NR • Confidence intervals reported: no • Selective reporting (comparison with protocol): NR
Courtney-Brooks 2010 Retrospective analysis	1135 pts with vulvar squamous cell carcinoma **Inclusion criteria (for analysis):** • Clinical stages I, II, III • ICD-9 histology codes included: 8070, 8071, 8072, 8075, 8076, 8077 • Pts. had undergone primary inguinal-femoral lymph node dissection between 1988 and 2003 **Exclusion criteria (for analysis):** • Pts. with lymph nodes positive for malignancy at the time of primary dissection were excluded **Enrolment period** • 2009 **Descriptive statistics** • Age	**Interventions** A: ≤10 lymph nodes removed with lymphadenectomy B: >10 lymph nodes removed with lymphadenectomy **Analysis** • Type of analysis: logrank test, Cox regression • Matching: NR • Confounders: Multivariate analysis taking into consideration stage, age, tumor size,	**Rezidivrate** NR **5-years OS** • A: 67±6.2%/ 401 • B: 77 ± 4.1%/ 629 • P=0.03 • Multivariate analysis (< 10 nodes removed): HR= 1.5, 95% CI 1.16 – 1.94 "An association with lower survival was seen in patients with fewer than 10 lymph nodes removed" Subgroup: women with stage II: • A: 60 ± 10.4%/ 151 • B: 74 ± 6.5%/ 276 P=0.04, in favour of B	**General information** • Follow-up: NR • **Funding**: NR ◆ **CoI**: 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): 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
	· Median age (all pts.): 68 (range: 12 – 85) • 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) · Stage II: 14 (1–53) · Stage III: 15 (1–51)	number of lymph nodes removed, adjuvant radiation therapy, and race	Subgroup: woman with stage III: • A: 36 ± 23%/ 51 • B: 72 ± 10.6%/ 11 P=0.03, in favour of B Additional outcomes: **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" Subgroup: women with stage II: • A: 85 ± 8.2%/ 151 • B: 92 ± 4.1%/ 276 P=0.25 Subgroup: woman with stage III:	• Drop-out rate & reasons reported: no • Outcome · 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
			• A: 60 ± 24.3%/ 51 • B: 85 ± 9%/ 114 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 Local recurrence-free survival • No significant difference between A and B: p = 0.866 Distant recurrence-free survival • No significant difference between A and B: p = 0.176	**General information** • Follow-up: 61 months (0-153) • **Funding**: none • **CoI**: 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

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 8range: 1 – 35) for N = 26 pts. • Lymph node metastases (yes, %) · Yes, 13.9% of removed groins had LN metastases			· Possibly affected by knowledge of outcome status?: yes • 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 **Exclusion criteria (for analysis):** • Patients with positive inguinofemoral nodes were excluded **Enrolment period**	**Interventions** A: < 6 lymph nodes removed with inguinofemoral lymphadenectomy B: ≥ 6 lymph nodes removed with inguinofemoral lymphadenectomy	**Rezidivrate** Groin recurrence: • A: 4/33 • B: 0/43 P= 0.03	**General information** • Follow-up: at least two years to be considered for study • **Funding**: NR • **CoI**: none declared **Risk of bias considerations (adapted from SIGN cohort study checklist)**

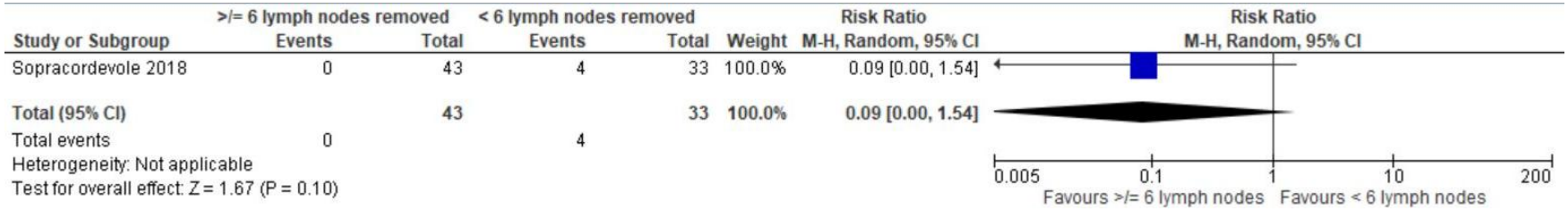
Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• 2005 – 2014 **Descriptive statistics** • Age · A: mean: 69.1 ± 13.9 · B: mean: 68.6 ± 11.8 • Stage (FIGO, %) · Ib: 94.7% · II: 5.3% • Location of the tumour · NR • Tumour size (%, cm) · A: 25.8 ± 16.5 · B: 24.8 ± 19.6 • Tumour depth (%, mm) · NR • Lymph node metastases (yes, %) · NR · No distant metastasis	**Analysis** • Type of analysis: t test or Mann-Whitney U test • Matching: NA • Confounders: NR		• 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: yes · Possibly affected by knowledge of outcome status: yes • Drop-out rate & reasons reported: no • 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

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Wu 2018 retrospective analysis	703 patients with node-positive vulvar squamous cell carcinoma (SCC) **Inclusion criteria (for analysis):** • 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 **Exclusion criteria (for analysis):** • Patients who received preoperative radiotherapy or SLNB **Enrolment period** • 2004–2013 **Descriptive statistics** • Age (median, range) mean age: 69; range 21–95 years (keine Angaben zu Gruppenunterschieden)	**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: χ2 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	**Rezidivrate** NR **3-year OS rates** ◆ 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 indicated that patients with </=6 removed lymph nodes had a higher risk of death compared with patients with >6 removed lymph nodes." **Additional outcomes:** **3-year cause-specific survival (CSS):** • A: 48,9%/181	**General information** • Mean follow-up: 21 months • **Funding**: 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) • **CoI**: 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): NR • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: yes

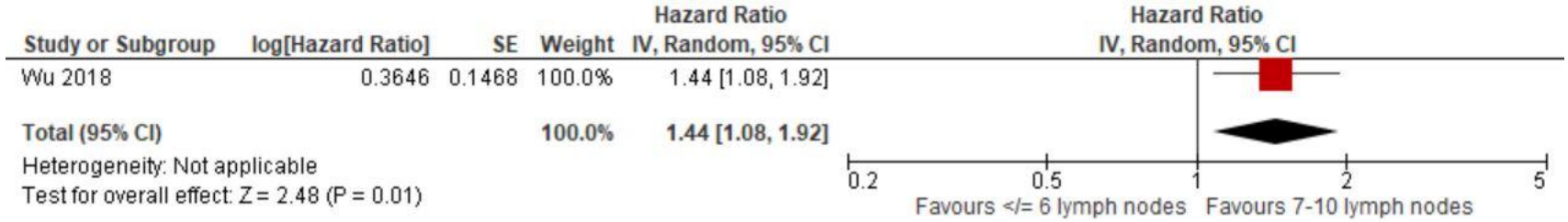
Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Stage (FIGO 1988), from 252 dissected groins: · < T2: NR · T2: A: NR · > T2: NR • Location of the tumour (of 252 extracted groins): · Central: NR · Lateral: NR · Missing: NR • Tumour size · ≤ 20 mm: NR · > 20 mm: NR · mean: 35 mm (range 2–200 mm) • Tumour depth (%, mm) · A: NR · B: NR • Lymph node metastases (yes, %) · NR	multivariate Cox regression models • Matching: NR • Confounders: multivariate analysis	• B: 65,9%/171 • C: 73,1%/194 • D: 67,3%/157 Comparison 7–10 (B) vs. 1–6 (A): HR=1.73, 95% CI 1.20–2.49, p=0.003, in favour of B	· Possibly affected by knowledge of outcome status?: yes • Drop-out rate & reasons reported: no · 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: (→If not, Knowledge of exposure status likely to influence the outcome?:): no • Main cofounders taken into account: • Confidence intervals reported: yes • Selective reporting (comparison with protocol): NR Other limitations or comments: NR

6.10.3 Forest plots

6.10.3.1 Forest plot comparison: >/=6 lymph nodes removed vs. <6 lymph nodes removed, outcome: groin recurrence



6.10.3.2 Forest plot comparison: 7-10 lymph nodes removed vs. </=6 lymph nodes removed, outcome: overall survival



6.10.4 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen:

Sopracordevole F, Clemente N, Giorda G, Canzonieri V, Alessandrini L, Del Fabro A, Serri M, Ciavattini A. Number of Nodes Removed With Inguinofemoral Lymphadenectomy and Risk of Isolated Groin Recurrence in Women With FIGO Stage IB-II Squamous Cell Vulvar Cancer. Int J Gynecol Cancer. 2018 Oct;28(8):1600-1605. doi: 10.1097/IGC.0000000000001326.

>/=6 lymph nodes removed versus <6 lymph nodes removed

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → 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

Literaturreferenzen:

Wu SG, Zhang WW, Sun JY, Chen QH, He ZY, Zhou J. Prognostic Value of the Number of Removed Lymph Nodes in Vulvar Squamous Cell Carcinoma Patients With Node-Positive Disease: A Population-Based Study. Front Oncol. 2018 May 30;8:184. doi: 10.3389/fonc.2018.00184.

7-10 lymph nodes removed vs. </=6 lymph nodes removed

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität

7-10 lymph nodes removed vs. </=6 lymph nodes removed							
Low → 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 slightly from PICO	-1 (only few participants: 352 pts; wide CI: HR=1.44, 95% CI 1.08-1.92)	/	⊕⊖⊖⊖ Very low

6.11 Kapitel Strahlentherapie – PICO 8.1

8.1a. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R0 mit minimalen Resektionsrand von > 3 mm die Rezidivrate, DFS, PFS, MFS, OS?

8.1b. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R0 mit minimalem Resektionsrand </=3mm die Rezidivrate, DFS, PFS, MFS, OS?

8.1c. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit R1 die Rezidivrate, DFS, PFS, MFS, OS?

8.1d. Verbessert eine postoperative Radiatio des Tumorbettes gegenüber keiner postoperativen Radiatio des Tumorbettes bei Patientinnen mit ED Vulvakarzinom und primär operativer Therapie mit L1 die Rezidivrate, DFS, PFS, MFS, OS?

Es wurde beschlossen, diese PICOs (1a, 1b, 1c, 1d) also **konsensbasierte Empfehlung** einzuschließen und zu erwähnen, dass keine Studien (SR oder RCTs) gefunden wurden.

6.12 Kapitel Strahlentherapie – PICO 8.3 und 8.4a-4d

8.3. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit mind. 2 befallenen inguinalen LK eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

8.4a. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit einem befallenen inguinalen LK mit Makrometastase eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

8.4b. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit inguinal extrakapsulärem Metastasenwachstum eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

8.4c. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler LNE mit fixierten bzw. exulzerierten inguinalen LK-Metastasen eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

8.4d. Verbessert bei Patientinnen mit ED Vulvakarzinom, bildgebend unauffälligen pelvinen LK und Z.n. bds. systematischer inguinofemoraler und pelviner LNE mit inguinal und pelvin befallenen LK eine adjuvante kombinierte inguinale und pelvine Radiatio gegenüber einer alleinigen adjuvanten inguinalen Radiatio die Lymphknotenrezidivrate, DFS, MFS, OS?

6.12.1 Evidenztabellen

6.12.1.1 Primärstudien (RCTs)

Kunos, C., Simpkins, F., Gibbons, H. & Tian, C. (2009). Radiation Therapy Compared With Pelvic Node Resection for Node-Positive Vulvar Cancer and Howard Homesley. Obstetrics & Gynecology, 114(3): 537-546. https://dx.doi.org/10.1097/AOG.0b013e3181b12f99

Stehman, F., Bundy, B., Thomas, G., Varia, M., Okagaki, F., Roberts, J. et al. (1992). GROIN DISSECTION VERSUS GROIN RADIATION IN CARCINOMA OF THE VULVA: A GYNECOLOGIC ONCOLOGY GROUP STUDY. J Radiuriun Onmlog Biol Phvs. 24; 389-396. https://dx.doi.org/10.1097/AOG.0b013e3181b12f100

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):** • primary invasive squamous cell carcinoma of the vulva • unilateral or bilateral groin metastasis • primary lesions and groin nodes were amenable to radical vulvectomy and bilateral inguinal lymphadenectomy **Exclusion criteria (for analysis):** • vulvar cancer recurrence • prior malignancies • positive groin nodes not resected at surgery **Enrolment period** • 1977 to 1984 **Descriptive statistics** • Age (median, range) · median age A & B: 70 years • Stage (FIGO, %) · A: NO/N1: 47% N2: 37%	**Interventions** A: Pelvic and groin radiation B: Ipsilateral pelvic node resection **Analysis** • Type of analysis: Cox proportional hazards models • adjusted for age and adverse tumor characteristics	**Recurrence free survival** HR=0.39 (95% CI 0,17-0,88; p=0,02) in favour of A **→Recurrence at any site** • A: 21/57 • B: 27/54 **→ Groin Recurrence** • A: 3/57 • B: 13/54 RR=0.22 (95% CI 0.07 to 0.73) **6-year overall survival (all-cause death)** **HR=0.61, (95% CI 0.30-1.3, P=0.02), in favour of A** "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<.001) persisted" →After adjusting for age, treatment, and tumor characteristics, the hazard ratio of overall death in patients with 20% positive	**General information** • Follow-up: 74 months • **Funding**: NR • **CoI**: Authors did not report any potential conflicts of interest **Risk of bias considerations (ROB1)** • Analyse ITT: low ROB • Random sequence generation (selection bias): unclear ROB, not described • Allocation concealment (selection bias): unclear ROB, not described • Blinding (performance bias and detection bias): unclear ROB, not described. • Incomplete outcome data (attrition bias): low ROB • Selective reporting (reporting bias): unclear ROB Other limitations or comments: no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	N3: 15% · B: N0/N1: 35% N2: 45% N3: 18% • Location of the tumour · NR • Tumour size (%, cm) · NR • 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%		groin nodes was 3.9 (95% CI 2.1–7.4, P<.001), favoring radiation. **6-years cancer-related death rate** A: 18/57 B: 28/54 HR= 0.49, (95% CI 0.28–0.87, P=015) in favour of A	

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Stehman, 1992 RCT	n= 52 patients with squamous cell carcinoma of the vulva **Inclusion criteria (for analysis):** • primary previously untreated squamous cell carcinoma of the vulva • radical vulvectomy had to suffice to remove the primary lesion **Exclusion criteria (for analysis):** • medically unsuited for operation patients • received any prior radiation therapy or chemotherapy • any prior malignancy other than nonmelanoma skin cancer of a site other than the vulva. **Enrolment period** • 1986 to 1990 **Descriptive statistics** • Age (median, range) median age A & B: 64 years • Stage (FIGO, %) · NR • Location of the tumour	**Interventions** A: bilateral groin radiation B: groin dissection: bilateral inguinal-femoral lymphadenectomy **Analysis** • Type of analysis: Pearson's chi-squared test, log-rank test	**Groin recurrence** • A: 5/27 • B: 0/25 RR= 10.21 (95% CI 0.59-175.78) → progression-free interval: p= 0.03, in favour of B "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." **Survival** A: 10/27 deaths B: 3/25 deaths → survival: p= 0.04, in favour of B **Toxicity** • A: 10/27 • B: 14/25 HR, CI:NR	**General information** • Follow-up: 36 month • **Funding**: NR • **CoI**: NR **Risk of bias considerations (ROB1)** • Analyse ITT: NR • Random sequence generation (selection bias): low ROB • Allocation concealment (selection bias): unclear ROB, not described • Blinding (performance bias and detection bias): unclear ROB, not described. • Incomplete outcome data (attrition bias): low ROB • Selective reporting (reporting bias): low ROB Other limitations or comments: Abbruch der Studie nach 6 Monaten

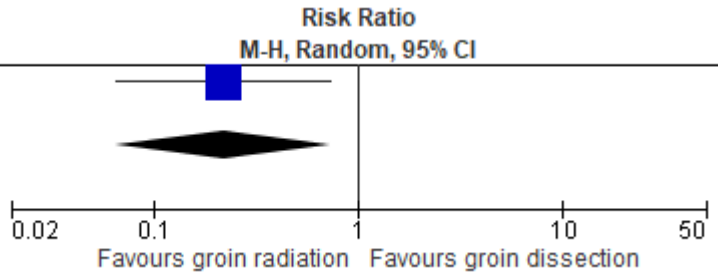
Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	A: · Labia: 59,3% · Clitoris: 18,5% · Perineum: 6% B: · Labia: 56% · Clitoris: 24% · Perineum: 12% · Other: 8% • Tumour size (%, cm) A: · <2.0 cm: 11,1% · 2.1–4.0 cm: 70,4 % · > 4.1 cm: 18,5 % B: · <2.0 cm: 8% · 2.1–4.0 cm: 72% · > 4.1 cm: 20 % • Tumour depth (%, mm) · NR • Lymph node metastases (yes, %) NR			

6.12.2 Forest plots

6.12.2.1 Forest plot of comparison: groin radiation vs. groin dissection/resection, outcome: groin recurrence (Kunos 2009)

Study or Subgroup	groin radiation Events	Total	groin dissection Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kunos 2009	3	57	13	54	100.0%	0.22 [0.07, 0.73]
Total (95% CI)		**57**		**54**	**100.0%**	**0.22 [0.07, 0.73]**
Total events	3		13			

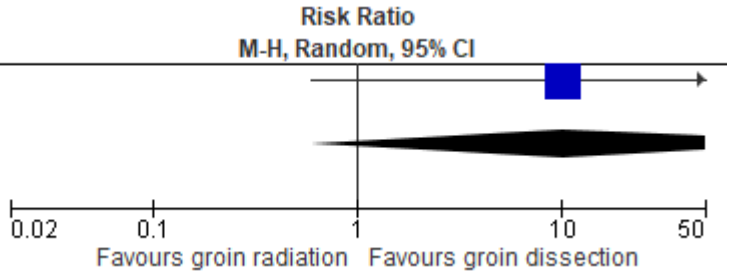
Heterogeneity: Not applicable
Test for overall effect: Z = 2.49 (P = 0.01)



6.12.2.2 Forest plot of comparison: groin radiation vs. groin dissection/resection, outcome: groin recurrence 2 (Stehman 1992)

Study or Subgroup	groin radiation Events	Total	groin dissection Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Stehman 1992	5	27	0	25	100.0%	10.21 [0.59, 175.78]
Total (95% CI)		**27**		**25**	**100.0%**	**10.21 [0.59, 175.78]**
Total events	5		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)



6.12.3 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen:

Kunos, C., Simpkins, F., Gibbons, H. & Tian, C. (2009). Radiation Therapy Compared With Pelvic Node Resection for Node-Positive Vulvar Cancer and Howard Homesley. Obstetrics & Gynecology, 114(3): 537-546. https://dx.doi.org/10.1097/AOG.0b013e3181b12f99

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
High	1 RCT (most recent)	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 (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)	-1 (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.

7 Ergebnisse der intern recherchierten Schlüsselfragen

7.1 Kapitel Epidemiologie und Risikofaktoren – PICO 1.2a

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

7.1.1 Evidenztabellen

7.1.1.1 Systematisches Review

Bucchi L, Pizzato M, Rosso S, Ferretti S. New Insights into the Epidemiology of Vulvar Cancer: Systematic Literature Review for an Update of Incidence and Risk Factors. Cancers (Basel). 2022 Jan 13;14(2):389. doi: 10.3390/cancers14020389.

M. van Seters, M. van Beurden and A. J. de Craen. 2005. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. Gynecol Oncol 2005 Vol. 97 Issue 2 Pages 645-51. DOI: 10.1016/j.ygyno.2005.02.012

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Bucci, 2022 Systematic literatur review	**Types of studies:** original study or a systematic review or a meta-analysis Searched from inception (since January 1980) until April 2021 **Databases:**	**Question/ Aim:** To provide an updated and complete overview of descriptive and analytical epidemiology of	69 studies included in the review, no further information of number of participants (none of the included studies are relevant for this guideline PICO) **Descriptive statistics:**	No relevant outcomes reported	Anmerkung: In diesem Review wird nichts zu HSIL oder dVIN berichtet: „This study was not aimed at reviewing the risk factors for preinvasive vulvar disease"	69 included studies

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	• PubMed • *Additionally: Cancer Incidence in Five Continents*, a publication of the International Association of Cancer Registries edited by the International Agency for Research on Cancer **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	**Vulvar Cancer (VC).** Specifically, we aimed at: (1) summarizing worldwide VC incidence rates and trends using comparable indicators; and (2) performing a systematic literature review of all known and putative risk factors for the disease. "This study was not aimed at reviewing the risk factors for preinvasive vulvar disease."	· No details reported in the review		**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 • Data extraction in duplicate: yes (checking by 2nd) • List of excluded studies: no • sufficient detail on studies: no • RoB assessed: no • Funding of incl. studies: no • MA appropriate: NA • RoB considered in MA: NA • RoB in interpretation: no	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	Terms]) AND (risk))) AND English [Language]) AND ("1980" [Date—Publication]: "2021" [Date—Publication]). **Inclusion criteria** • (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. • (2) article providing a quantitative estimate of the association as obtained using a cohort or a case-control control approach; and • (3) article in English.				• Heterogeneity explained: no • Publication bias investigated: no • Sources of CoI: "The authors declare no conflict of interest."	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	Exclusion criteria: • Not reported • Only exclusion reasons at full text level from the PRISMA flowchart.					
Van Seters, 2005 Systematic review of patient data	Types of studies: Non-RCTs, case reports Searched from inception until November 2004 **Databases**: • computer searches of MEDLINE (from 1964), CANCERLIT (from 1980), EMBASE (from 1974), BIOSIS PREVIEWS AB (from 1970) and SCIENCE CITATION INDEX (from 1970) • key words were used: vulvar neoplasms in combination with intraepithelial neoplasia, Bowen,	**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.	97 studies on 3322 pts with VIN III · 29 studies on treatment results, progression and regression of VIN III · 12 case reports only gave data on progression of VIN III · 6 case reports only dealt with regression of VIN III. **Descriptive statistics:** · Only for total population and from studies reporting descriptive data	**Recurrence rate** • 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%. • B: not reported **Progression to invasive vulvar carcinoma** • A: 3.3 %	**Anmerkung: In diesem Review sind Frauen mit VIN III eingeschlossen.** **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: yes • Selection in duplicate: NR • Data extraction in duplicate: NR	Non-RCTs 29 studies on treatment results, progression and regression of VIN III 12 case reports only gave data on progression of VIN III 6 case reports only dealt with regression of VIN III

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	bowenoid, Queyrat, carcinoma simplex, early vulvar cancer, hyperplastic dystrophy, condylomatous dysplasia, intraepithelial carcinoma, carcinoma in situ, vulvar atypia and precancerous conditions **Inclusion criteria:** • (1) articles written in English, German or French and • (2) data, clearly retrievable, on the surgical treatment and/or progression and/or regression of VIN III. **Exclusion criteria:** • Articles in which data of VIN III were not distinguishable from data of VIN I–II,	(Surgical treatment was defined as cold knife surgery, laser excision, laser evaporization, LEEP excision or cryosurgery) A: treated women (68 studies reported on N=1921) B: untreated women (no treatment at all (*N*= 61), or in whom gross macroscopic VIN III was left behind (*N* = 27) (10 studies	• Age (mean) · mean age = 46 (48 studies, 2152 patients) · mean minimum age was 21 (59 studies, 2585 patients) and the mean maximum age was 80 (56 studies, 2467 patients) • Vulvar Lesion characteristics · multifocal VIN III: 49% (1878 patients, 45 studies). · multicentric genital tract neoplasia: 32% (2067 patients, 46 studies)	· mean time to progression = 55 months (range 4–216) • B: 8/88 (9%) · 9 % progressed in 12 to 96 months –-> "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." **Narrative summary of the review:** "Invasion may occur many years after VIN III was diagnosed. Most of these invasive carcinomas are superficial and overdiagnosing early invasion is well known.	• List of excluded studies: no • sufficient detail on studies: yes • RoB assessed: no • Funding of incl. studies: no • MA appropriate: NA • RoB considered in MA: NA • RoB in interpretation: no • Heterogeneity explained: no • Publication bias investigated: no **Sources of CoI: NR**	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	(micro)invasive vulvar carcinoma or other vulvar diseases, were excluded. • Case histories were excluded, except those concerning regression or progression of VIN III.	reported on N=88)		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.“		

7.1.2 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen

M. van Seters, M. van Beurden and A. J. de Craen. 2005. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. Gynecol Oncol 2005 Vol. 97 Issue 2 Pages 645-51. DOI: 10.1016/j.ygyno.2005.02.012

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
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 of women with HSIL/dVIN)	-2 (only few participants, narrative summary with no confidence intervals)	Low confidence in results of the review (assessed with AMSTAR-2 tool).	⊕⊖⊖⊖ Very low

7.2 Kapitel Epidemiologie und Risikofaktoren – PICO 1.2b

Zeigen Patientinnen mit behandeltem Lichen sclerosus gegenüber Patientinnen mit unbehandeltem Lichen sclerosus eine geringere Rezidivrate und ein niedrigeres Risiko für die Entwicklung einer VIN / eines Vulvakarzinoms?

7.2.1 Evidenztabellen

7.2.1.1 Systematisches Review

Spekreijse JJ, Streng BMM, Vermeulen RFM, Voss FO, Vermaat H, van Beurden M. The risk of developing squamous cell carcinoma in patients with anogenital lichen sclerosis: A systematic review. Gynecologic oncology 2020;157(3):671-77. doi: 10.1016/j.ygyno.2020.02.020

Anmerkung: Dieses Systematic Review beantwortet nicht die Schlüsselfrage 2b, sondern untersucht das absolute Risiko und Rate der Neufälle von Squamous Cell Carcinoma bei Frauen und Männer mit Lichen sclerosus („the absolute risk (AR) and incidence rate (IR) of developing SCC in patients with anogenital Lichen sclerosis (LS), as well as patient characteristics that influence the risk of developing LS associated squamous cell carcinoma (SCC)").

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	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 Databases: PubMed and Embase ◆ keywords used were 'lichen sclerosis', 'anogenital' and 'carcinoma', including all synonyms **Inclusion criteria** • studies including patients with LS in the anogenital region with a prognostic study design of the evaluation of LS into SCC.	**Question/ Aim:** To systematically review the absolute risk (AR) and incidence rate (IR) of developing SCC in patients with anogenital Lichen sclerosis (LS), as well as patient characteristics th at influence the risk of developing LS associated squamous cell carcinoma (SCC).	23 studies 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) **Descriptive statistics:** • NR (beschrieben für jede einzelne eingeschlossene Studie)	**Recurrence rate / recurrence-free** • NR **Progression to squamous cell carcinoma of the vulva** • NR **Progression to vulval intraepithelial neoplasia (VIN)** • NR	**Overall confidence in results of SR (AMSTAR-2):** ***"low"*** • PICO elements: no • A priori design: no • Justification for design: no • Literature search >= 2 databases, search strategy + other sources: no • Selection in duplicate: yes • Data extraction in duplicate: NR • 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	23 retrospective cohort study design

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	• Articles in English, Dutch, French and German were included **Exclusion criteria:** • Articles with no full text available were excluded				• Heterogeneity explained: NR • Publication bias investigated: no • Sources of CoI: "All authors declare to have no conflicts of interest."	

7.2.1.2 Primärstudien (non-RCTs)

Lee A, Bradford J, Fischer G. Long-term Management of Adult Vulvar Lichen Sclerosus: A Prospective Cohort Study of 507 Women. JAMA Dermatol. 2015 Oct;151(10):1061-7. doi: 10.1001/jamadermatol.2015.0643.

> **Anmerkung**: Diese retrospektive Studie schließt nur behandelte Frauen mit LS ein und untersucht die Entwicklung einer VIN / eines Vulvakarzinoms. Die Studie vergleicht „treatment compliant patients" mit „partially compliant patients", allerdings wurde keine der beiden Gruppen komplett unbehandelt. Es gibt dementsprechend keinen Vergleich zwischen behandelten und unbehandelten Frauen mit LS.

Chin S, Scurry J, Bradford J, Lee G, Fischer G. Association of Topical Corticosteroids With Reduced Vulvar Squamous Cell Carcinoma Recurrence in Patients With Vulvar Lichen Sclerosus. JAMA Dermatol. 2020 Jul 1;156(7):813-814. doi: 10.1001/jamadermatol.2020.1074.

> **Anmerkung**: Diese retrospektive Studie schließt nur behandelte Frauen mit LS ein (mit history of vSCC oder dVIN) und untersucht die Rezidivrate. Es gibt also keinen Vergleich zwischen behandelten und unbehandelten Frauen mit LS. Keine Beantwortung der Schlüsselfrage 2b.

Steinkasserer L, Hachenberg J, Hillemanns P, Jentschke M. Characterization of patients with vulvar lichen sclerosus and association to vulvar carcinoma: a retrospective single center analysis. Arch Gynecol Obstet 2023;307(6):1921-28. doi: 10.1007/s00404-022-06848-y

Anmerkung: Diese retrospektive Studie untersucht und berichtet einige Risikofaktoren für die Entwicklung eines Vulvakarzinoms, einschließlich lichen sclerosus (LS) Diagnose, Alter bei LS Patientinnen, VIN, HPV Status, rauchen, Komorbiditäten und Symptome. Allerdings sind keine Daten berichtet zum Risikofaktor LS Behandlung, daher kann diese Studie nicht zur Beantwortung der Schlüsselfrage 2b beitragen und es gibt keine Daten zum Vergleich behandeltes LS vs. unbehandeltes LS.

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 primary excision of vSCC or dVIN **Exclusion criteria (for analysis):** • NR **Enrolment period** • From January 1, 2008, to April 30, 2019, **Descriptive statistics** • Age (mean, range) · mean age at diagnosis of primary lesion = 62.9 years (26-88)	**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 propionate, 0.02% and 0.05%, and desonide, 0.05% **Analysis**	**Recurrence rate / recurrence-free** • NR **Progression to squamous cell carcinoma of the vulva** • NR **Progression to vulval intraepithelial neoplasia (VIN)** • NR **Additional outcomes: recurrence of vSCC or VIN (all women treated with vLS)** • 8/11 (73%) no recurrence • 2/11 (18%) recurrence of vSCC (1 of whom developed multiple recurrences of vSCC, and 1 patient (9%) had recurrence of their dVIN)	**General information** • Median follow-up: 12 months • **Funding**: NR • **CoI**: Non reported **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): yes • Exposure/Intervention · Assessment reliable: NA · Assessed more than once: NA · Possibly affected by knowledge of outcome status?: NA • Drop-out rate & reasons reported: no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
		• Type of analysis: NR • Matching: NR • Confounders: NR		• Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If not, Knowledge of exposure status likely to influence the outcome?:): NA • Main cofounders taken into account: NR • Confidence intervals reported: NR • Selective reporting (comparison with protocol): NA
Steinkasserer, 2023 Retrospective study	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 → final study population N=56 cases) **Inclusion criteria (for analysis):** • Cases with possible LS were included in this study: · Possible LS included cases with interface dermatitis that could fit with an early phase of LS.	**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.**	**Recurrence rate / recurrence-free** • NR **Progression to squamous cell carcinoma of the vulva** • NR **Progression to vulval intraepithelial neoplasia (VIN)** • NR **Additional outcomes: VSCC development in LS patients** • 27/56 LS pts. developed VSCC · 18/27 (66.6%) confirmed LS	**General information** • Median follow-up: NA • **Funding**: Open Access funding enabled and organized by Projekt DEAL. Funding provided by the Department of Obstetrics and Gynecology of Hannover Medical School (MHH). • **CoI**: The authors declare that they have no competing interests. **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective study

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· Cases were also classified as LS when no histology was done, but the clinical appearance indicated LS. · Further cases were included where LS was diagnosed within the scope of VSCC treatment. • (The patient population was searched for the following 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.) **Exclusion criteria (for analysis):** • NR **Enrolment period** • 2008-2020 **Descriptive statistics (for all women with LS)**	**Interventions** • No intervention or treatment comparison • "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, vulvoscopy and, if necessary, biopsy." **Analysis**	"In 18 patients who developed vulvar carcinoma in course, both LS and VIN were confirmed (66.6%)." "Five cases of LS were diagnosed only at or after diagnosis of VSCC" • 29/57 LS pts. without VSCC **Narrative summary:** "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.	• Populations comparable: yes • Rate of participation/Exclusions reported (selection bias into the study): yes • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: NR · Possibly affected by knowledge of outcome status?: no • Drop-out rate & reasons reported: NR • Outcome · Outcome measure is well-defined, valid and reliable: NA · Blind outcome assessment to exposure: (→If 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): NA

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Age (median, range) · All women with LS: 60.25 (16-85) • Menopausal status at time of diagnosis (all women with LS) · Postmenopausal: 78.57% · Prämenopausal: 21.43% • HPV status positive · 10.72% • Nicotine abuse · Yes: 14.29% · No: 76.79% · Ex-smokers: 3.57 • Pre-existing diseases · Arterial hypertension: 42.86 · Hypothyroidism: 26.79 · Diabetes mellitus: 23.21 • Presence of VIN · VIN I-III 44.04% · VIN I: 20% · VIN II: 28% · VIN II-III: 4% · VIN III: 48%	• Type of analysis: Distribution was examined with ther Shapiro-Wilk normality test, and groups were compared with an unpaired t test or Mann-Whitney-U test as appropriate after checking for outliers. • Matching: NR • Confounders: NR		

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Lee 2015 prospective longitudinal cohort study	**507 women with biopsy-proved VLS** **Inclusion criteria (for analysis):** • age older than 18 years, biopsy-proved VLS, and having been followed up for a minimum of 2 years **Exclusion criteria (for analysis):** • NR **Enrolment period** • January 2, 2008 – September 26, 2014 **Descriptive statistics (for all women with LS)** • Age (mean, range) · 55.4 (18–86) • Duration of symptoms at presentation: · 5.0 years (range, 0.1–40.0 years) • Menopausal staus: · 158 (31.2%): premenopausal · 307 (60.6%): postmenopausal and not using hormone therapy · 42 (8.3%) postmenopausal and using either topical or systemic hormone therapy	**Intervention** **→just one intervention group** • 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. →Comparison between: · Compliant patients (N=357, 70.4%) · Partially Compliant patients (N=150, 26.6% of total)	**Recurrence rate / recurrence-free** • NR **Progression to squamous cell carcinoma of the vulva (SCC) or vulval intraepithelial neoplasia (VIN)** • Compliant: 0/357 • Partially compliant: 7/150 **Additional outcomes: Suppression of symptoms occurred** • Compliant: 333 (93.3%)/357 • Partially compliant: 87 (58.0%)/150 **Adhesions and scarring occurred:** • Compliant: 12 (3.4%)/357 • Partially compliant: 60 (40.0%)/150 **Reversible TCS-induced cutaneous atrophy:** • Compliant: 4 (1.1%)/357 • Partially compliant: 3 (2.0%)/150	**General information** • Median follow-up: 4.7 years (range, 2.0–6.8 years) • **Funding**: This study was supported in part by the Dermatology Department of Royal North Shore Hospital for the submission of the project for ethics review. • 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. • **CoI**: None reported. **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: cohort study • Populations comparable: yes • Rate of participation/Exclusions reported (selection bias into the study): yes • Exposure/Intervention · Assessment reliable: yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
		(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 frequency of application and/or potency of TCS) **Analysis** • Type of analysis: NR	**Initial symptom control with loss of itching** • Compliant: 326 (91.3%)/357 • Partially compliant: 109 (72.7%)/150 **Narrative summary:** "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. The adverse effects of TCSs were minimal."	· Assessed more than once: NR · Possibly affected by knowledge of outcome status?: no • Drop-out rate & reasons reported: NR • Outcome · Outcome measure is well-defined, valid and reliable: NA · Blind outcome assessment to exposure: (→If 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): NA

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
		• Matching: NR • Confounders: NR		

7.2.2 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen

Lee A, Bradford J, Fischer G. Long-term Management of Adult Vulvar Lichen Sclerosus: A Prospective Cohort Study of 507 Women. JAMA Dermatol. 2015 Oct;151(10):1061-7. doi: 10.1001/jamadermatol.2015.0643.

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → cohort study	1 prospective cohort study		/	/	-1 (data on wrong population: women with VIN III, not representing directly the PICO population of women with HSIL/dVIN)	-2 (only few participants, narrative summary with no confidence intervals)	Low confidence in results of the review (assessed with AMSTAR-2 tool).	⊕⊖⊖⊖ Very low

7.3 Kapitel Prävention und Früherkennung – PICO 2.1

Beeinflusst die HPV-Impfung das Risiko für das Auftreten eines Vulvakarzinoms / VIN?

7.3.1 Evidenztabellen

7.3.1.1 Systematisches Review

Literaturreferenzen:

Kechagias KS, Kalliala I, Bowden SJ, Athanasiou A, Paraskevaidi M, Paraskevaidis E, Dillner J, Nieminen P, Strander B, Sasieni P, Veroniki AA, Kyrgiou M. Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: systematic review and meta-analysis. BMJ. 2022 Aug 3;378:e070135. doi: 10.1136/bmj-2022-070135

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Kechadias 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	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) **Descriptive statistics:** • Age (median, range): NR • Stage (nach FIGO, %): NR • Location of the tumour: NR • Tumour size (%, cm): NR • Tumour depth (%, mm): 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^2=0%) in favour of A (vaccine group) **Population:** women who were vaccinated and treated locally for cervical, vulvar or vaginal	Overall confidence in results of SR (AMSTAR-2): *„moderate-high“* • PICO elements: yes • A priori design: NR • Justification for design: yes • Literature search >= 2 databases, search strategy + other sources: yes • Selection in duplicate: yes • Data extraction 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
	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. **Exclusion criteria:** • 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 excluded if the intervention included experimental vaccines or immunotherapy and	HPV infection in individuals undergoing local surgical treatment. A: HPV vaccination B: no NPV vaccination		intraepithelial neoplasia grade 2 or higher compared with women not vaccinated. **Rezidivrate (VIN/VaIN1+ recurrence (post hoc ananlyses of RCTs: Joura 2023, Garland 2016 & Zhao 2020))** • A: 20/744 • B: 23/926 Pooled RR: 1.30 (95% CI 0.23-7.43; p=0.24, I^2=29%) in favour of B (non-vaccine group) **Rezidivrate (VIN/VaIN2+ recurrence (post hoc from Joura 2023, Garland 2016 & Zhao 2020))** • A: 5/738 • B: 6/928	• List of excluded studies: no • sufficient detail on studies: no • RoB assessed: yes • Funding of incl. studies: no • MA appropriate: yes • RoB considered in MA: yes • RoB in interpretation: yes • Heterogeneity explained: yes • Publication bias investigated: yes • Sources of CoI: yes	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventio-nen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	studies that used non-surgical treatment (i.e. salicylic acid or imiquimod cream).			Pooled RR: 1.01 (95% CI 0.24–4.15; p=0.74, I^2=0%) no effect **Population**: women treated for genital HPV related disease		

7.3.1.2 Primärstudien (RCT)

Literaturreferenzen:

C. Zhao, Y. Zhao, J. Li, M. Li, Y. Su, X. Mi, et al. The eight-year long-term follow-up on the effectiveness of the quadrivalent human papillomavirus vaccine in Chinese women 20-45 years of age. Human vaccines & immunotherapeutics. 2022;18(5):2052700. Doi: 10.1080/21645515.2022.205270

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):**	**Interventions** • A: three doses of 4vHPV vaccine · N = 171	**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)	**General information** • Follow-up: median follow-up of 94 months • **Funding**: Association for Maternal and Child Health Studies [2018AMCHS008, 2018AMCHS00803] and Project of

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• women were 20–45 years of age with 1–4 lifetime sexual partners (or planned to become sexually active within the first 3 months of the study); had no history of genital warts or cervical disease, active cervical disease, or prior vaccination with HPV vaccine; and were not pregnant • Included for this analysis: Participants with any of the following abnormal findings referred for colposcopy **Exclusion criteria (for analysis):** • NR **Enrolment period** • 2009–2016 **Descriptive statistics** • Age (median, range) · A: NR · B: NR • Stage (FIGO, %): NR for this population • Location of the tumour: NR for this population • Tumour size (%, cm): NR for this population	• B: placebo during the base study · N = 197 **Analysis** • Type of analysis: frequencies	• B: 0/19 (among 27 participants…) Pooled RR/HR/OR: NR	Development center for medical science & technology, NHC • **CoI**: Chao Zhao, Yun Zhao, Jingran Li, Mingzhu Li, Danhua Shen, and Lihui Wei have received grants/research support from MSD R&D (China). **Risk of bias considerations (RoB 1):** • Analysis ITT: NI • Randomisation: low • Allocation concealment: NI • Blinding: low • Attrition bias: NI • Selective reporting: NI **Other limitations or comments**: 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. → some concerns to high ROB

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

7.3.2 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen

Kechagias KS, Kalliala I, Bowden SJ, Athanasiou A, Paraskevaidi M, Paraskevaidis E, Dillner J, Nieminen P, Strander B, Sasieni P, Veroniki AA, Kyrgiou M. Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: systematic review and meta-analysis. BMJ. 2022 Aug 3;378:e070135. doi: 10.1136/bmj-2022-070135

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
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

7.4 Kapitel Operatives Management des Primärtumors – PICO 6.2

Haben Patientinnen mit einer plastischen Vulvarekonstruktion nach Tumorresektion ein verbessertes psychosoziales / funktionelles Outcome / QoL im Vergleich zu Frauen mit primärem Wundverschluss oder offener Wundheilung?

7.4.1 Evidenztabellen

7.4.1.1 Primärstudien (non-RCTs)

Aviki EM, Esselen KM, Barcia SM, et al. Does plastic surgical consultation improve the outcome of patients undergoing radical vulvectomy for squamous cell carcinoma of the vulva? Gynecologic oncology 2015;137(1):60-5. doi: 10.1016/j.ygyno.2015.02.001

Weikel W, Hofmann M, Steiner E, Knapstein PG, Koelbl H. Reconstructive surgery following resection of primary vulvar cancers. Gynecologic oncology 2005;99(1):92-100. doi: 10.1016/j.ygyno.2005.05.031

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Aviki, 2015 Retrospective review of patient data	88 pts with invasive squamous cell cancer (iSCC) of the vulva who underwent vulvectomy **Inclusion criteria (for analysis):** • invasive squamous cell cancer (iSCC) of the vulva who underwent vulvectomy **Exclusion criteria (for analysis):** • "Exclusions included 80 cases of vulvar intraepithelial neoplasia, 19 cases of malignant melanoma, 14 cases of Paget's disease, 11 cases of basal cell carcinoma, 7 cases of other rare tumors, 30 cases with no residual	**Interventions** A: radical vulvectomy with plastic-assisted vulvar closure (plastics, n = 15) (14 underwent a local V-Y fasciocutaneous advancement flap and 1 underwent a regional rectus abdominis myocutaneous flap)	**Psychosocial outcome** • NR **Functionality** • NR **Quality of life (QoL)** • NR **Additional outcomes:** **Experienced complications** • A: 10/15 (67%) • B: 26/73 (36%)	**General information** • Median follow-up:.5 months (range, 0-107) • **Funding**: NR • **CoI**: The authors report no conflicts of interests. **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: Retrospective review of patient data • Populations comparable: yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	tumor, and 28 cases with benign pathology." **Enrolment period** • 2004–2013 **Descriptive statistics** • Age (mean, range) · A: 71 (32–86) · B: 66 (39–92) • Primary disease · A: 47% · B: 90% • Recurrent disease · A: 53% · B:10% • FIGO stage · A: I 80%, II 13%, III 7% · B: I 70%, Ii 10%, III 21% • History of prior vulvectomy: yes · A: 27% · B: 11% • History of radiation therapy: yes · A: 40%	B: radical vulvectomy without plastic-assisted vulvar closure (no plastics, n = 73) **Analysis** • Type of analysis: Logistic regression analysis was performed using backwards step-wise selection (p > 0.15) to identify factors independently associated with the occurrence of any complication. • Matching: no • Confounders: yes	P=0.04, in favor of B **Wound dehiscence:** · A: 47% · B: 23% (p=0.06) **Cellulitis:** · A: 20% · B: 21% (p=0.96) **Abscess:** · A: 7% · B: 7% (p=0.98) **Hematoma:** · A: 7% · B: 0% **Deep venous thrombosis:** · A: 7% · B: 1% (p=0.31)	• Rate of participation/Exclusions reported (selection bias into the study): NR • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: NR · Possibly affected by knowledge of outcome status?: no • Drop-out rate & reasons reported: NR • Outcome · Outcome measure is well-defined, valid and reliable: NR · Blind outcome assessment to exposure: (→If not, Knowledge of exposure status likely to influence the outcome?:): no • Main cofounders taken into account: yes • Confidence intervals reported: no • Selective reporting (comparison with protocol): NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· B: 5% • Vulvectomy location · A: Lateral hemivulvectomy 53%, Anterior vulvectomy 0%, posterior 20%, complete 27% · B: Lateral hemivulvectomy 45%, Anterior vulvectomy 33%, posterior 10%, complete 12% • Tumor size (Mean tumor size in cm (range)) · A: 3.73 (0.2–7.8) · B: 2.03 (0.1–7.0) • Margin status · A: Average cancer free margin (cm) 0.75 Positive margins: 7% Adequate margins (≥ 0.8 cm): 53% Close margins (< 0.8 cm): 43% · B: Average cancer free margin (cm) 0.59 Positive margins: 8% Adequate margins (≥ 0.8 cm):29% Close margins (< 0.8 cm): 69%			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Weikel, 2005 Retrospective study	213 patients with vulvar cancer treated between 1973 and 2002 at the Department of Obstetrics and Gynecology of the University of Mainz. **Inclusion criteria (for analysis):** • Treatment was adapted in accordance with the size of the tumor in question, the intention being to ensure that the excised tissue exhibited adequately large tumor-free margins while, at the same time, achieving an optimal functional and cosmetic outcome. The surgical treatment employed comprised straightforward excision, radical resection, partial or total exenteration and reconstruction using myocutaneous skin-flaps; it thus embodied the basic principles of the 'reconstructive ladder or elevator.' **Exclusion criteria (for analysis):** • Tissue expansion and/or microvascular transplantation was not included in the operative procedures employed. **Enrolment period**	**Interventions** There were no interventions compared to each other: "The aim of our study was to pinpoint reliable indicators of reconstructive plastic surgery, as well as to assess the prospects of patient recovery and wound healing in relation to the size of the tumor in question, along with the correspondence between the surgical procedure employed and subsequent patient survival."	**Psychosocial outcome** • NR **Functionality** • NR **Quality of life (QoL)** • NR **Additional outcomes:** **Primary wound healing** (direct wound closure vs. the insertion of various types of flaps): • Direct wound closure: 81/129 (63%) • local flap ((so-called transposition skin-flaps): 41/65 (62.9%) • Regional myocutaneous skin-flaps: 16/19 (84.2%) **Narrative summary:** From such a comparison, it can be seen that, with primary wound healing being achieved in 63% of the cases, the results obtained using local flaps were just as good as those obtained when direct wound closure was performed.	**General information** • Median follow-up: NR • **Funding**: NR • **CoI**: 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): no • Exposure/Intervention · Assessment reliable: NA · Assessed more than once: NA · Possibly affected by knowledge of outcome status?: NA • Drop-out rate & reasons reported: no • Outcome · Outcome measure is well-defined, valid and reliable: NR

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• between 1973 and 2002 **Descriptive statistics** • NR	Some comparison: • Direct wound closure versus the insertion of various types of flaps (local flap and regional flap) • Plastic reconstruction versus no reconstruction **Analysis** • Type of analysis: NR • Matching: NR • Confounders: NR	However, the employment of regional flaps produced markedly better results, with primary healing occurring in 84% of cases. As such flaps were most frequently used in cases who had undergone exenteration, the good healing results observed for this type of operation can be traced back to this operative factor. **Recurrence for radical vulvectomy (plastic vs. no reconstruction):** • Plastic reconstruction: 47 (38.3%) • No Reconstruction: 65 (47.7%) • "No statistically significant correlation between the relapse rate and reconstructive surgery could be detected, although the relapse rate was 10% lower in those patients whose surgical intervention included reconstruction"	· Blind outcome assessment to exposure: (→If not, Knowledge of exposure status likely to influence the outcome?:): NA • Main cofounders taken into account: no • Confidence intervals reported: no Selective reporting (comparison with protocol): NR

7.5 Kapitel Operatives Management des Primärtumors- PICO 6.4

Verbessert eine Exenteration bei Patientinnen im palliativen Stadium mit Fistelbildung / Kloakenbildung / starken Schmerzen die Lebensqualität, Nebenwirkungsrate, OS?

7.5.1 Evidenztabellen

7.5.1.1 Systematisches Review

Literaturreferenzen:

Ang C, Bryant A, Barton DPJ, Pomel C, Naik R. Exenterative surgery for recurrent gynaecological malignancies. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD010449. DOI: 10.1002/14651858.CD010449.pub2

➔ In diesem Systematic Review konnten keine Studien identifiziert und eingeschlossen werden.

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
Ang 2014 SR	Searched from inception until February 2013. **Databases:** • Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE • Additional searches: · registers of clinical trials	Question/ Aim: To evaluate the effectiveness and safety of exenterative surgery versus other treatment modalities for women with recurrent gynaecological	No studies were identified that compared exenterative surgery versus medical management for women with recurrent gynaecological malignancies (other than ovarian cancer, which has been examined in a separate review). Therefore, the question of whether exenterative surgery is	**Qualitiy of life** • NR **Adverse events** • NR **Overall survival** • NR **Authors' conclusions** We found no evidence to inform decisions about exenterative surgery for	**Overall confidence in results of SR (AMSTAR-2):** ***„moderate-high“*** • PICO elements: yes • A priori design: NR • Justification for design: yes • Literature search >= 2 databases, search strategy + other sources: yes • Selection in duplicate: yes	No studies met the inclusion criteria for this review, resulting in no evidence for assessment.

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	· conference proceedings and abstracts through ZETOC · contacted experts in the field, including Nick Spirtos, Denis Chi, Charlie Chan, Achim Schneider, Christardt Kohler, Michael Hockel, John Shepherd, William Cliby and Neville Hacker. · handsearched the citation lists of studies that were retrieved in full text, key textbooks and previous systematic reviews. · handsearched reports of conferences	cancer, excluding recurrent ovarian cancer. A: exenterative surgery B: medical management for women with recurrent gynaecological malignancies	associated with a survival benefit in terms of overall and recurrence-free survival as well as other important outcomes cannot be answered by this review. **Descriptive statistics:** • NR	women with recurrent cervical, endometrial, vaginal or vulvar malignancies. Ideally, a large RCT or, at the very least, well-designed non-randomised studies that use multivariate analysis to adjust for baseline imbalances are needed to compare exenterative surgery versus medical management, including palliative care.	• Data extraction in duplicate: yes • List of excluded studies: yes • sufficient detail on studies: yes • RoB assessed: NA • Funding of incl. studies: no • MA appropriate: NA • RoB considered in MA: NA • RoB in interpretation: NA • Heterogeneity explained: NA • Publication bias investigated: NA • Sources of CoI: NA	

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	Inclusion criteria • Randomised controlled trials (RCTs) or non-randomised studies with concurrent comparison groups that included multivariate analyses of exenterative surgery versus medical management in women with recurrent gynaecological malignancies. • Non-randomised trials, prospective and retrospective cohort studies and case series of 30 or more participants were sought for inclusion. • Adult women (aged 18 years or older) diagnosed with a					

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	recurrent gynaecological cancer. • Exenterative surgery (anterior (removal of the bladder with or without urethra and formation of urinary diversion; an ileal conduit or a continent urinary diversion with or without hysterectomy, with or without resection of the vagina and perineum), posterior (removal of the rectosigmoid colon and, in some patients, the anal canal with a primary anastomosis or formation of an end colostomy with or without hysterectomy) or total pelvic exenteration. Some more extensive recurrences also require resection of the					

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	vulva. Exenterative procedures for recurrent (or progressive) vulvar cancers as well. ◆ Comparison: Chemotherapy, radiotherapy, chemoradiotherapy or expectant management. **Exclusion criteria:** • Case-control studies and case series of fewer than 30 participants were excluded. • Women with recurrent ovarian cancer were excluded					

7.5.2 Bewertung der Evidenz (nach GRADE)

Ang, C, Bryant, A, Barton, DP, Pomel, C, Naik, R, Exenterative surgery for recurrent gynaecological malignancies. Cochrane Database Syst Rev, 2014. 2014 (2)(2): p. CD010449., https://pubmed.ncbi.nlm.nih.gov/24497188/

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
	1 Systematic Review (Ang, 2014) with 0 included studies	No studies met the inclusion criteria for this review, resulting in no evidence for assessment.						Not applicable

Die eingeschlossenen Studien haben nicht die Endpunkte aus der Schlüsselfrage 2 berichtet (verbessertes psychosoziales / funktionelles Outcome / QoL), darum gibt es keine zusammenfassende Bewertung nach GRADE auf Endpunkt Ebene.

7.6 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.1

Verbessert bei Patientinnen mit ED Vulvakarzinom, klinisch und bildgebend unilateral / bilateral unauffälligen inguinalen LK und einseitig positivem Sentinel-LK die kontralaterale systematische inguinofemorale LNE gegenüber keiner Behandlung der kontralateralen Leiste die Leistenrezidivrate / DFS / OS?

7.6.1 Evidenztabellen

7.6.1.1 Primärstudien (non-RCTs)

Literaturreferenzen:

Gonzalez Bosquet J, Magrina JF, Magtibay PM, et al. Patterns of inguinal groin metastases in squamous cell carcinoma of the vulva. Gynecologic oncology 2007;105(3):742-6. doi: S0090-8258(07)00142-4 [pii] 10.1016/j.ygyno.2007.02.014

Anmerkung: Diese Studie untersucht nicht den Vergleich aus der Schlüsselfrage: “more than 95% percent of the patients included in this study underwent bilateral inguinofemoral lymphadenectomy” und staging war ein Einschlusskriterium für die Teilnahme an der Studie.

Van der Kolk WL, Van der Zee AGJ, Slomovitz BM, et al. Unilateral inguinofemoral lymphadenectomy in patients with early-stage vulvar squamous cell carcinoma and a unilateral metastatic sentinel lymph node is safe. Gynecologic oncology 2022;167(1):3-10. doi: 10.1016/j.ygyno.2022.07.017

Ignatov T, Gaßner J, Bozukova M, et al. Contralateral lymph node metastases in patients with vulvar cancer and unilateral sentinel lymph node metastases. Acta Obstet Gynecol Scand 2021;100(8):1520-25. doi: 10.1111/aogs.14157

Woelber L, Eulenburg C, Grimm D, et al. The Risk of Contralateral Non-sentinel Metastasis in Patients with Primary Vulvar Cancer and Unilaterally Positive Sentinel Node. Ann Surg Oncol 2016;23(8):2508-14. doi: 10.1245/s10434-016-5114-6

Winarno AS, Mondal A, Martignoni FC, Fehm TN, Hampl M. The potential risk of contralateral non-sentinel groin node metastasis in women with early primary vulvar cancer following unilateral sentinel node metastasis: a single center evaluation in University Hospital of Dusseldorf. BMC women's health 2021;21(1):23. doi: 10.1186/s12905-020-01165-5

Nica A, Covens A, Vicus D, et al. Sentinel lymph nodes in vulvar cancer: Management dilemmas in patients with positive nodes and larger tumors. Gynecologic oncology 2019;152(1):94-100. doi: S0090-8258(18)31362-3 [pii] 10.1016/j.ygyno.2018.10.047

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	**Groin recurrence rate / groin recurrence-free** • A: NR • B: NA **DFS** • A: NR • B: NR **Overall survival** • A: NR	**General information** • Median follow-up: NA • **Funding**: NR • **CoI**: NR **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective study • Populations comparable: 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 · Unilateral lesion: N=163 patients · bilateral lesions: N=75 pts. · midline lesions: N=40 pts. · mediolateral lesions: N=42 pts. • LN involvement: +LN → among 163 pts. with unilateral · 37/163 (22.7%): ipsilateral groin involvement	inclusion criteria for the study population. **Analysis** • Type of analysis: univariate and multivariate logistic regression models • Matching: NR • Confounders: NR	• B: NR	• Rate of participation/Exclusions reported (selection bias into the study): NA • 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 (→If 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
	· 3/163 (1.8%): contralateral positive LN · 8/163 (4.9%) bilateral LN invasion → among 75 pts. with bilateral · 14/75 (18.7%): ipsilateral groin involvement · 0 contralateral positive LN · 13/75 (17.3%) bilateral LN invasion • LN involvement: -LN → among 163 pts. with unilateral · 115/163 (70.6%) → among 75 pts. with bilateral · 48/75 (64%) • Inguinofemoral LN involvement →among 163 pts. with unilateral · 48/163 in unilateral • Tumour size (among Inguinofemoral LN involvement) · N=80/150 (53%) ≤ 2 cm, N=70/150 (47%) > 2 cm • Tumour depth (among Inguinofemoral LN involvement) · N=89/144 (62%) ≤ 5 mm, N=55/144 (38%) > 5 mm			

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Van der Kolk, 2022, Kohortenstudie (prospective multicenter study)	1912 pts with squamous cell cancer of the vulva **Inclusion criteria (for analysis):** • Unifocal SCC <4 cm **Exclusion criteria (for analysis):** • suspicious groin nodes at palpation or at imaging **Enrolment period** • 2000–2006 bzw. 2005–2016 **Descriptive statistics** • Age (mean or median hier angeben) · 65.2 years (14.3) • Stage (FIGO, %) · nr • Location of the tumour · 723 Lateralized tumor (138 Fälle), · 530 Near midline tumor (112 Fälle), · 645 True midline tumor (116 Fälle) • Tumour size · 1.991 cm (SD=1.046)	**Interventions** A: unilateral IFL (N=70) B: bilateral IFL (N=105) (C: unilateral radiotherapy (N=45)) (D: bilateral radiotherapy (N=122)) E: no additional groin treatment (N=24) **Analysis** • Type of analysis: frequencies • Matching: nr • Confounders: Stratifizierung nach	**Groin recurrence rate / groin recurrence-free** • A: 2/70 (2,9%) • B: 1/105 (2,6%) • (C: 0/45 (0%)) • (D: 1/122 (0,8%)) • E: 0/24 (0%) **DFS** • Nr **Overall survival** • Nr	**General information** • Median follow-up: nr (until at least 2 years after primary treatment) • **Funding**: Dutch Cancer Society • **CoI**: nr **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: Kohortenstudie (prospective multicenter studies) • Populations comparable: unclear • Rate of participation/Exclusions reported (selection bias into the study): yes • Exposure/Intervention · Assessment reliable: unclear · Assessed more than once: NR · Possibly affected by knowledge of outcome status?: no • Drop-out rate & reasons reported: nr • Outcome

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Tumour depth (%, mm) · 3.81 mm (4.20) • Lymph node metastases (yes, %) · insgesamt 441 (23.2%), · davon unilateral 366 (83.0%) · bilateral 75 (17.0%)	Tumor location subgroups		· Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If 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): unclear
Ignatov, 2021, multicenter retrospective registry-based study	476 pts with squamous cell cancer of the vulva **Inclusion criteria (for analysis):** • squamous and adenosquamous vulvar cancer **Exclusion criteria (for analysis):** • no SLN biopsy • missing information regarding lymphadenectomy • basaloid carcinoma • negative SLN • bilateral SLN metastases	**Interventions** A: contralateral IFL (N=62) **Analysis** • Type of analysis: frequencies • Matching: nr • Confounders: nr	**Groin recurrence rate / groin recurrence-free** • A: 8/62 **DFS** • nr **Overall survival** • nr	**General information** • Median follow-up: 35 months (range 1-114 months) • **Funding**: nr • **CoI**: none **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: multicenter retrospective registry-based study • Populations comparable: na

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• no contralateral lymphadenectomy despite of unilateral SLN metastases **Enrolment period** • January 2000 – September 2017 **Descriptive statistics** • Age (mean or median hier angeben) · 75 (33-95) • Stage (FIGO, %) · mr • Location of the tumour · nr • Tumour size · nr • Tumour depth (%, mm) · nr • Lymph node metastases (yes, %) · 5 bilateral, 66 unilateral			• Rate of participation/Exclusions reported (selection bias into the study): yes • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: nr · Possibly affected by knowledge of outcome status?: no • Drop-out rate & reasons reported: yes • Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: no (→If 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): unclear
Wölber, 2016	140 pts with squamous cell cancer of the vulva **Inclusion criteria (for analysis):**	**Interventions** A: unilateral IFL (N=4)	**Groin recurrence rate / groin recurrence-free** • A: 0/4 • B: nr	**General information** • Median follow-up: 29 months

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• a successful SLN dissection with radioactive tracer ± blue dye • Informed consent **Exclusion criteria (for analysis):** • nr **Enrolment period** • 2001 – 2013 **Descriptive statistics** • Age (mean or median hier angeben): · 57 years (range 20–87) • Stage (FIGO, %) · NR • Location of the tumour · 18 Vulva, (12 N–,6 N+), · 4 groin (1 N–, 3 N+) • Tumour size · 17.5 (1–75) • Tumour depth (%, mm) · 3 (0.4–27) • Lymph node metastases (yes, %)	B: bilateral IFL (N=37) **Analysis** • Type of analysis: Multivariate logistic regression analysis • Matching: nr • Confounders: nr	**DFS** • nr **Overall survival** • nr	• **Funding**: internal departmental sources (University Medical Center Hamburg-Eppendorf) • **CoI**: none **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective Kohortenstudie • Populations comparable: unclear • Rate of participation/Exclusions reported (selection bias into the study): yes • Exposure/Intervention · Assessment reliable:yes · 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

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	nr			· Blind outcome assessment to exposure: nr (→If 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): unclear
Winarno, 2021, retrospective single-center analysis	420 pts with 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 distant metastasis at initial diagnosis;	**Interventions** A: ipsilateral IFL B: bilateral IFL **Analysis** • Type of analysis: frequencies • Matching: nr • Confounders: nr	**Groin recurrence rate / groin recurrence-free** • A: 2/12 • B: 2/18 xx vs. xx: HR/RR/OR= xx, 95% CI xx-xx; p=xx **DFS** • nr xx vs. xx: HR/RR/OR= xx, 95% CI xx-xx; p=xx **Overall survival** • A: 90,9% (N=12)	**General information** • Median follow-up: nr • **Funding**: Open Access funding enabled and organized by Projekt DEAL • **CoI**: none **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective single-center analysis • Populations comparable: yes • Rate of participation/Exclusions reported (selection bias into the study): na

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• consent refusal of the patients due to the potential increased risks of groin recurrence **Enrolment period** • 2002–2018 **Descriptive statistics** • Age (mean or median hier angeben) · A: 50 (28–79), · B: 52.5 (27–82) bzw. 55 (51–67) für IFL+ contralateral • Stage (FIGO, %) · nr • Location of the tumour · A: 9 (75%) midline, 3 (25%) lateralized, · B: 11 (78.6%) bzw. 4 (100%) midline für IFL+ contralateral, 3 (21.4%) bzw. 0 lateralized für IFL+ contralateral • Tumour size · A: 7 (58.3%) <20 mm, 3 (25%) ≥20 mm but<40 mm, 2 (16.7%) ≥40 mm,		• B: 80% bei negative oder positive ipsilateral IFL, 75 % bei positive contralateral IFL (N=18) xx vs. xx: HR/RR/OR= xx, 95% CI xx-xx; p=xx	• Exposure/Intervention · Assessment reliable: unclear · Assessed more than once: nr · Possibly affected by knowledge of outcome status?: yes • Drop-out rate & reasons reported: no • Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If not, Knowledge of exposure status likely to influence the outcome?:): no • Main cofounders taken into account: yes • Confidence intervals reported: no • Selective reporting (comparison with protocol): nr

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· B: 7 (50%) <20 mm, 5 (35.7%) ≥20 mm but<40 mm, 2 (14.3%) ≥40 mm bzw. 1 (25%) <20 mm, 3 (75%) ≥20 mm but<40 mm • Tumour depth (%, mm) · A: 3.0 (1.8–6.0), · B: 6.0 (2.0–15.0) bzw. 8.5 (5.0–23.0) • Lymph node metastases (yes, %) · 30 unilateral			
Nica, 2019, retrospective study	159 pts with squamous cell cancer of the vulva **Inclusion criteria (for analysis):** • identification of at least 1 SLN **Exclusion criteria (for analysis):** • **Enrolment period** • 2008–2015 **Descriptive statistics** • Age (mean or median hier angeben) · 69.0 years (48.0–94.0)	**Interventions** A: unilateral IFL (groin dissection) B: bilateral IFL (groin dissection) **Analysis** • Type of analysis: • Matching: nr • Confounders: nr	**Groin recurrence rate / groin recurrence-free** • A: 0/9 • B: 2/19 **DFS** • nr **Overall survival** • nr	**General information** • Median follow-up: nr • **Funding**: nr • **CoI**: none declared **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: etrospective observational cohort study • Populations comparable: unclear

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Stage (FIGO, %) · nr • Location of the tumour · 22 (57.9%) midline, 16 (42.1%) lateralized • Tumour size · 16 (44.4%) <20 mm; · 13 (36.1%) ≥20 but <40 mm; · 7 (19.5%) ≥40 mm • Tumour depth (%, mm) · 5.5 mm (0.5–20.0) • Lymph node metastases (yes, %) · 28 unilateral			• Rate of participation/Exclusions reported (selection bias into the study): na • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: nr · Possibly affected by knowledge of outcome status?: no • Drop-out rate & reasons reported: yes • Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: nr (→If 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): unclear

7.6.2 Bewertung der Evidenz (nach GRADE)

Die eingeschlossenen Studien haben nicht die Endpunkte aus der Schlüsselfrage berichtet, darum gibt es keine zusammenfassende Bewertung nach GRADE auf Endpunkt Ebene.

7.7 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.4a und 7.4b

7.4a. Verbessert bei Patientinnen mit ED Vulvakarzinom mit klinisch und bildgebend unauffälligen LK und Z.n. SNB mit histologisch isolierten Tumorzellen oder Mikrometastase die ipsilaterale inguinofemorale LNE +/- Radiatio der inguinalen LAW gegenüber einer alleinigen ipsilateralen Radiatio der inguinalen LAW die Rate der LK-Rezidive / Morbidität / DFS / OS?

7.4b. Verbessert bei Patientinnen mit ED Vulvakarzinom mit klinisch und bildgebend unauffälligen LK und Z.n. SNB mit histologisch Makrometastase einseitig die ipsilaterale inguinofemorale LNE +/- Radiatio der inguinalen LAW gegenüber einer alleinigen ipsilateralen Radiatio der inguinalen LAW die Rate der LK-Rezidive / Morbidität / DFS / OS?

7.7.1 Evidenztabellen

7.7.1.1 Systematisches Review

Literaturreferenzen:

van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulvar cancer. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD002224. DOI: 10.1002/14651858.CD002224.pub2.

Anmerkungen: In diesem Systematischen Review wird der Vergleich „primary radiotherapy of the inguinofemoral lymph nodes“ mit „inguinofemoral lymph node dissection“ untersucht, allerdings repräsentiert die untersuchte Population eher nicht die Personengruppe aus der Schlüsselfrage 4a und 4b (es gibt keine Angaben zu Mikrometastase oder Makrometastase).

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 January 2016 and no additional trails were identified) **Databases:** • Cochrane Gynaecological Cancer Group Specialised Register, • Cochrane Central Register of Controlled Trials (CENTRAL), • MEDLINE and • EMBASE **Inclusion criteria** • RCTs and NRS • Women diagnosed with early squamous cell carcinoma of the	**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, Stehman 1992) on 52 pts with early squamous cell cancer of the vulva **Descriptive statistics:** • 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 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%	**Lymph nodes recurrence** • NR **Groin Recurrence (unklar ob damit LK-Rezidive gemeint ist)** • A: 5/27 • B: 0/25 RR: 10.21 (95% CI 0.59 to 175.78) in favour of B **Morbidity** **→ Lymphedema:** • A: 0/27 • B: 7/25 RR 0.06, 95% CI 0.00 to 1.03 in favour of A **→ life-threatening cardiovascular complications:** • A: 0/27 • B: 5/25	**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 • 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	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. *International Journal of Radiation Oncology, Biology, Physics* 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
	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	Clitoris: 18,5% Perineum: 6% · B: Labia: 56% Clitoris: 24% Perineum: 12% Other: 8% • 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 0.08, 95% CI 0.00 to 1.45 in favour of A** **→ Hospital Stay:** RR 0.28, 95% CI 0.13 to 0.58) **DFS** • NR **OS** • A: 10/27 • B: 3/25 RR: 4.31 (95% CI 1.03 to 18.15) in favour of B ***Other outcomes:*** **Disease-specific survival:** • A: 8/27 • B: 2/25 RR 3.70, 95% CI 0.87 to 15.80 in favour of B	• Heterogeneity explained: NA • Publication bias investigated: no Sources of CoI: none Andere Bemerkungen: 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 4.5-6.1cm, therefore the radiotherapy dose used in this trial may have been insufficient for deep nodes.	

7.7.1.2 Primärstudien (non-RCTs)

Literaturreferenzen:

Oonk MHM, Slomovitz B, Baldwin PJW, et al. Radiotherapy Versus Inguinofemoral Lymphadenectomy as Treatment for Vulvar Cancer Patients With Micrometastases in the Sentinel Node: Results of GROINSS-V II. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2021;39(32):3623-32. doi: 10.1200/jco.21.00006

Anmerkung: In dieser Studie gibt es Ergebnisse für Schlüsselfrage 4a

Oonk MH, van Hemel BM, Hollema H, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. Lancet Oncol 2010;11(7):646-52. doi: 10.1016/S1470-2045(10)70104-2

Anmerkung: In dieser Studie wird kein Vergleich der Behandlungen untersucht (keine Ergebnisse für die Schlüsselfragen)

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):** • unifocal macroinvasive squamous cell carcinoma of the vulva < 4 cm; • preoperative imaging of groins (CT), magnetic resonance imaging, or ultrasound) showing no suspicious nodes (where inguinal nodes appeared	**Interventions** **→only for SN positive patients (Group 1: micro and Group 2: macrometastases)** A: SN biopsy with subsequent inguinofemoral radiotherapy (N=177) (126 in	Patients With SN Micrometastases ≤ 2 mm (N=160) **Lymph node recurrence** ◆ NR **Groin recurrence** ◆ A: 3/126 (2 with isolated ipsilateral groin recurrences and 1 with contralateral SN-negative groin) ◆ B: 1/16 (contralateral) ◆ C: 2/18	**General information** • Median follow-up: nr • **Funding**: Roche, Genmab, Amgen, Oncoinvent; AstraZeneca, AbbVie, Leo Pharma AB, Genentech/Roche, Clovis Oncology, Seattle Genetics, KCI, Tesaro, Genentech, FATE Therapeutics, Morphotek, Bayer, Merck, Regeneron, GOG Partners Trial, Elekta, Varian Medical Systems • **CoI**: further conflicts listed in the study

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	suspicious in size [> 15 mm] or morphology, metastatic disease was ruled out by fine needle aspiration cytology); • written informed consent **Exclusion criteria (for analysis):** • Inoperable tumors and tumors with diameter > 4cm • Patients with inguinofemoral lymph nodes, at palpation clinically suspect for metastases, at radiology enlarged (>1.5 cm) / suspicious groin nodes and with cytologically proven inguinofemoral lymph node metastases • Patients with multifocal tumors **Enrolment period** • December 2005 - October 2016 **Descriptive statistics** • Age (median, IQR) · SN-nagative: 66 (55-76) · Micrometastases: 67 (55-77) · Macrometastases: 65 (55-75) • Stage (FIGO, %)	micrometastases, 51 in macrometastases) B: inguinofemoral lymphadenectomy (with or without radiotherapy) (N=121) (16 in micrometastases, 105 in macrometastases) C: SN biopsy and no further treatment (N=24) (18 in micrometastases, 6 in macrometastases) **Analysis** • Type of analysis: competing-risk methods • Matching: nr • Confounders: NR	Radiotherapy versus no further treatment (A vs. C): HR 0.11; 95% CI 0.02 to 0.76) (Patients who underwent IFL instead of radiotherapy were excluded) --> not answering PICO4a **DFS** • NR **Overall survival** • NR **Morbidity outcomes:** • NR **Patients With SN Macrometastases > 2 mm (N=162)** **Lymph node recurrence** • NR **Ipsilateral groin recurrence** • A: 11/51 • B: 7/105 • C: 1/6	**Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: prospective multicenter phase-II single-arm treatment trial • Populations comparable: no • Rate of participation/Exclusions reported (selection bias into the study): no • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: nr · Possibly affected by knowledge of outcome status?: no • Drop-out rate & reasons reported: yes • Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: nr (→If not, Knowledge of exposure status likely to influence the outcome?:): yes • Main cofounders taken into account: no • Confidence intervals reported: yes • Selective reporting (comparison with protocol): no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· nr • Location of the tumour · SN-nagative: 617 (50.9%) midline 529 (43.6%) lateralized · Mikrometastasen: 85 (53.1%) midline 68 (42.5%) lateralized · Makrometastasen: 103 (63.6%) midline 68 (42.5%) lateralized • Tumour size (median, IQR) · SN-nagative: 18 mm (10-25) · Mikrometastasen: 23.2 mm (15-30) · Makrometastasen: 25 mm (15-30) • Tumour depth of invasion (median, IQR) · SN-nagative: 2.1 mm (1.5-4) · Mikrometastasen: 3.5 mm (1.7-4) · Makrometastasen: 2.9 mm (15-30) • Treatments of 3 groups: → SN-nagative: → Patients With SN Micrometastases ≤ 2 mm (N=160)		Per protocol analysis, radiotherapy versus IFL (A vs. B): HR, 3.2; 95% CI, 1.2 to 8.3 **DFS** • NR **Death of vulvar cancer** • A: 13/51 (25.5%) • B: 24/105 (22.9%) **Overall survival** • NR **Disease-specific death at 2 years** • A: 24.4% [95% CI, 12.4 to 36.4] • B: 24.2% [95% CI, 15.7 to 32.6] **Patients with SN macrometastasis: IFL (± radiotherapy) compared with radiotherapy only: P = .88** **Unspecified population:** **Overall survival** • patients with SN micrometastases: 88.3% (95% CI, 83.2 to 93.4)	

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· 126 (78.8%): inguinofemoral radiotherapy (81 bilateral, 38 unilateral, 7 unknown) · 16 (10%): IFL · 18 (11.3%) no further treatment) → Patients With SN Macrometastases > 2 mm (N=162) · 51: radiotherapy to the groins (39 bilateral, 8 unilateral, 4 unknown) · 105 (64.8%): IFL · 6: no further treatment after SN removal		• patients with SN macrometastases: 69.3% (95% CI, 62.0 to 76.6) • SN-negative patients: 95.2% (95% CI, 94.0 to 96.5) **Morbidity outcomes:** **Lymphedema at 6 and 12 months** • A: 16.4% and 10.7% • B: 32.0% and 22.9% • C: 5.1% and 4.1% **Lymphedema at 6 and 12 months** • A: 16.4% and 10.7% • B: 32.0% and 22.9% • C: 5.1% and 4.1% **Narrative summary:** "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	

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
			isolated groin recurrences compared with IFL."	
Oonk 2010, prospective multicentre observational study (GROINSS-V)	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) **Inclusion criteria (for analysis):** • diameter <4 cm, • T1-T2 **Exclusion criteria (for analysis):** • nr **Enrolment period** • 2000 - 2006 **Descriptive statistics (for N=135)** • Age · ≤70 years: 59 (43%), · >70 years: 76 (56%) • Location of the tumour · 42 (31%) Lateralised, · 93 (69%) midline	**Interventions** 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 A: inguinofemoral lymphadenectomy (N=115 (85%) of 135 patients with positive sentinel nodes) B: radiotherapy to the groins instead of	**Lymph node recurrence** • NR **Groin recurrence rate** • NR **DFS** • NR **Overall survival** • NR	**General information** • Median follow-up: median follow-up: 31 months (range 0-109), updated until January 2009 • **Funding**: no funding source • **CoI**: none declared **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: prospective multicentre observational study • Populations comparable: na • 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?: no • Drop-out rate & reasons reported: nr

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Diameter of primary tumour. · ≤2·0 cm (T1): 46 (34%), · >2·0 cm (T2): 87 (64%), · Unknown: 2 (1%) • Tumour depth (%, mm) · 62 (46%) ≤5·0 mm, · 63 (47%) >5·0 mm • Unilaterally or bilaterally positive SN · 106 (79%) Unilateral, · 29 (21%) Bilateral • Additional treatments · 115 (85%) Inguinofemoral lymphadenectomy 29%) Unilateral 71% Bilateral · 14 (10%) Radiotherapy · 6 (4%) No additional treatment	lymphadenectomy (N=14) C: no treatment (N=6) ➔ No comparison made between different treatment groups **Analysis** • Type of analysis: Kaplan-Meier method • Matching: nr • Confounders: nr		• Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: nr (→If 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

7.7.2 Bewertung der Evidenz (nach GRADE)

Literaturreferenzen:

van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vulvar cancer. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD002224. DOI: 10.1002/14651858.CD002224.pub2.

Anmerkung: In diesem Systematic Review wird der Vergleich „primary radiotherapy of the inguinofemoral lymph nodes“ mit „inguinofemoral lymph node dissection“ untersucht, allerdings repräsentiert die untersuchte Population eher nicht die Personengruppe aus der Schlüsselfrage 4a,b (es gibt keine Angaben zu Mikrometastase oder Makrometastase). Es handelt sich hier um indirekte Evidenz.

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
High → RCT	1 RCT (from SR van der Velden)	OS	/	/	-2 (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 radiotherapy group.	⊕⊖⊖⊖ Very low
High → RCT	1 RCT (from SR van der Velden)	Morbidity (lymphedema)	/	/	-2 (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)	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	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
High → RCT	1 RCT (from SR van der Velden)	Morbidity (life-threatening cardiovascular complications)	/	/	-2 (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 radiotherapy group.	⊕⊖⊖⊖ Very low
High → RCT	1 RCT (from SR van der Velden)	Morbidity (length of hospitalization)	/	/	-2 (population differs)	-1 (only few participants: 52 pts)	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 → RCT	1 RCT (from SR van der Velden)	Groin Recurrence (unklar ob damit LK-Rezidive gemeint ist)	/	/	-2 (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 radiotherapy group.	⊕⊖⊖⊖ Very low

Schlüsselfrage 4a – Mikrometastase

Oonk MHM, Slomovitz B, Baldwin PJW, et al. Radiotherapy Versus Inguinofemoral Lymphadenectomy as Treatment for Vulvar Cancer Patients With Micrometastases in the Sentinel Node: Results of GROINSS-V II. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2021;39(32):3623-32. doi: 10.1200/jco.21.00006

Anmerkung: Es gibt Daten zum Vergleich "radiotherapy versus no further treatment" aber die Gruppe die LNE +/- Radiatio bekommen haben sind ausgeschlossen für diesen Endpunkt.

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → cohort	1 prospective multicenter phase-II single-arm treatment trial (Oonk 2021)	Ipsilateral groin recurrence		/	-1 (Comparison: radiotherapy versus no further treatment. Patients who underwent IFL instead of radiotherapy were excluded)	-2 (only few events and few participants: 4/144 pts and wide Confidence intervals: HR 0.11; 95% CI 0.02 to 0.76) (Patients who underwent IFL instead of radiotherapy were excluded)		⊕⊖⊖⊖ Very low

Schlüsselfrage 4b – Subgruppe Makrometastase

Oonk MHM, Slomovitz B, Baldwin PJW, et al. Radiotherapy Versus Inguinofemoral Lymphadenectomy as Treatment for Vulvar Cancer Patients With Micrometastases in the Sentinel Node: Results of GROINSS-V II. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2021;39(32):3623-32. doi: 10.1200/jco.21.00006

Anmerkung: Es handelt sich hier um indirekte Evidenz

Startpunkt der Bewertung	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamt-qualität
Low → cohort	1 prospective multicenter phase-II single-arm treatment trial (Oonk 2021)	Ipsilateral groin recurrence		/	-2 (indirect evidence, as the study was stopped for this population)	-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

7.8 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.7

Verbessert bei Patientinnen mit ED Vulvakarzinom und Indikation zum Leisten-Lymphonodektomie die systematische inguinofemorale LNE gegenüber einer modifizierten (weniger radikalen) LNE die Leistenrezidivrate / DFS / OS?

7.8.1 Evidenztabellen

7.8.1.1 Primärstudien (non-RCT)

Literaturreferenzen:

Gordinier ME, Malpica A, Burke TW, et al. Groin recurrence in patients with vulvar cancer with negative nodes on superficial inguinal lymphadenectomy. Gynecologic oncology 2003;90(3):625-8. doi: S0090825803003743

Anmerkung: Diese Studie schließt nur Patientinnen ein die eine „superficial lymphadenectomy“ bekommen haben, es ist also kein Vergleich (wie beschrieben in Schlüsselfrage 7) möglich.

Kirby TO, Rocconi RP, Numnum TM, et al. Outcomes of Stage I/II vulvar cancer patients after negative superficial inguinal lymphadenectomy. Gynecologic oncology 2005;98(2):309-12. doi: S0090-8258(05)00373-2

Anmerkung: Diese Studie schließt nur Patientinnen ein die eine „superficial inguinal lymphadenectomy“ bekommen haben, es ist also kein Vergleich (wie beschrieben in Schlüsselfrage 7) möglich.

Woolderink JM, de Bock GH, de Hullu JA, Davy MJ, van der Zee AG, Mourits MJ. Patterns and frequency of recurrences of squamous cell carcinoma of the vulva. Gynecologic oncology 2006;103(1):293-9. doi: S0090-8258(06)00230-7 [pii]

Anmerkung: Diese Studie schließt nur Patientinnen ein die eine „wide local excision und superficial inguinal lymphadenectomy" bekommen haben, es ist also kein Vergleich (wie beschrieben in Schlüsselfrage 7) möglich.

Gonzalez Bosquet J, Magrina JF, Gaffey TA, et al. Long-term survival and disease recurrence in patients with primary squamous cell carcinoma of the vulva. Gynecologic oncology 2005;97(3):828-33. doi: S0090-8258(05)00179-4 [pii]

→ Diese Studie schließt nur Patientinnen ein die eine „inguinal lymphadenectomy" bekommen haben, es ist also kein Vergleich (wie beschrieben in Schlüsselfrage 7) möglich.

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 superficial inguinal lymphadenectomy **Exclusion criteria (for analysis):**	**Interventions** all patients underwent superficial lymphadenectomy A: bilateral superficial inguinal lymphadenectomy (N=7) B: unilateral dissections (N=2) **Analysis**	**Groin recurrence** • Recurrence in right groin: N=4 • Recurrence in left groin: N=4 • Recurrence in both groins: N=1 **DFS** • nr **Overall survival** • nr **Additional outcomes: Death from disease** • Deaths: N=6	**General information** • Median follow-up: 63 months • **Funding**: NR • **CoI**: NR **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective chart review • Populations comparable: yes • Rate of participation/Exclusions reported (selection bias into the study): no

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• nr **Enrolment period** • patients treated at M. D. Anderson Cancer Center between 1986 and 1997 were reviewed **Descriptive statistics** • Age (mean) · 59 years • Stage · Stage I: N=2/9 · Stage II: N=7/9 • Tumour size · ranged in size from 0.2 to 4.0 cm • Tumour depth (%, mm) · median depth of invasion was 4.0 mm · median tumor diameter 3 cm (range 1-3) • median number of nodes resected per groin · eight on the right and seven on the left (range 1 to 17).	• Type of analysis: nr • Matching: no • Confounders: no	• median interval from recurrence to death was 6 months (range 4 to 54)	• Exposure/Intervention · Assessment reliable: yes · Assessed more than once: nr · Possibly affected by knowledge of outcome status?: nr • Drop-out rate & reasons reported: nr • Outcome · Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If 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
	· The nodes ranged in size from 0.2 to 4.0 cm			
Kirby 2005, Retrospective study (chart review)	65 pts with Stage I or II vulvar cancer who underwent a negative SupIL and vulvectomy **Inclusion criteria (for analysis):** • Stage I and II patients • All patients had separate incisions for the vulvectomy and SupIL • Both partial and complete vulvectomy specimens were included, and surgeons typically • attempted to obtain a 1–2 cm margin around the tumor. • Only patients with a pathologically negative SupIL **Exclusion criteria (for analysis):** • NR **Enrolment period** • 1990–2001 **Descriptive statistics** • Age	**Interventions** All had superficial inguinal lymphadenectomy (SupIL) (N=65) A: bilateral SupiL (N=44) B: Ipsilateral SupiL (N=21) **Analysis** • Type of analysis: Kaplan–Meier method with Fisher Exact and Chi–square tests • Matching: no • Confounders: no	**Recurrence rate** • Recurrence on the vulva: N=11 (17%) • recurred in the inguinal region: N=3 (4.6%) **DFS (5–year)** • 66% (SE 9.3%) **Overall survival** • 97% (SE 2.5%) Additional outcomes: Death ◆ Deaths: N=3	**General information** • Mean follow–up: 36 months • **Funding**: nr • **CoI**: nr **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective chart review • Populations comparable: yes • Rate of participation/Exclusions reported (selection bias into the study): no • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: nr · Possibly affected by knowledge of outcome status?: nr • Drop–out rate & reasons reported: no • Outcome

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	· NR • Stage (FIGO) · Stage I: N=30/65 · Stage II: N=35/65 • Location of the tumour · N=32 (49%) patients had midline lesions · N=11 (17%) had lesions involving the clitoris • Tumour size · Mean lesion size was 2.7 cm (range 0.4–6.5 cm). • Tumour depth (%, mm) · Mean depth of invasion was 4.4 mm (range 0.8–20 mm) • Lymph node metastases (yes, %) · NR			· Outcome measure is well-defined, valid and reliable: yes · Blind outcome assessment to exposure: (→If 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
Woolderink 2006	125 pts with squamous cell carcinoma of the vulva **Inclusion criteria (for analysis):**	**Interventions** All had wide local excision and superficial inguinal	**Recurrence rate** • local recurrene: N= 29 (23%), • groin recurrence: N= 11 (9%)	**General information** • Median follow-up: 42 months (range 1-184 months)

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Retrospective analysis	• Patients with primary vulva cancer, without a previous history of vulvar cancer, and treated by the same surgeon (M.J.D) **Exclusion criteria (for analysis):** • non-squamous cell carcinoma, chemoradiation because of very extensive vulvar cancer, no lymph node dissection because of extensive vulvar cancer or poor general condition **Enrolment period** • January 1985 **to** December 1999 **Descriptive statistics** • Age · Median: 72 years (range 23-91 years) • Stage · Stage 1A: N=15 (12%) · Stage IB: N=34 (27%) · Stage II: N=42 (34%) · Stage III: N= 22 (18%) · Stage IVA: N= 12 (9%) • Location of the tumour (N)	lymphadenectomy (N=125) **Analysis** • Type of analysis: Univariate Cox regression analyses • Matching: no • Confounders: no	• distant recurrence: N=4 (3%) **DFS (5-year)** NR **Overall survival** NR Additional outcomes: overall relapse-free survival (5 years) · 58%	• **Funding**: nr • **CoI**: nr **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: retrospective chart review • Populations comparable: yes • Rate of participation/Exclusions reported (selection bias into the study): no • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: nr · 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: (→If 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
	· 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 · 25.0; (9-48) with a groin recurrence · 42.5; (8-70) with a distant recurrence • Tumour depth (mm, median, range) · 4.0; (<1.0->5.0) without recurrence, · 3.0; (<1.0->5.0) with a local recurrence, · 6.0; (<1.0->5.0) with a groin recurrence, · 6.0; (<1.0->5.0) with a distant recurrence • Lymph node metastases (yes, %) · NR			• Confidence intervals reported: nr • Selective reporting (comparison with protocol): nr

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
Gonzalez Bosquet 2006 Cohort study	330 pts with squamous cell carcinoma of the vulva **Inclusion criteria (for analysis):** • lymphadenectomy as part of the initial treatment **Exclusion criteria (for analysis):** • NR **Enrolment period** • 1955 – 1990 **Descriptive statistics** • Age · NR • Stage (FIGO) · NR • Location of the tumour · metastases or recurrent cancer: 31 groin, 64 vulva, 37 distant • Tumour size · NR • Tumour depth (%, mm) · NR	**Interventions** All had underwent bilateral (314 patients) or ipsilateral (16 patients) inguinal lymphadenectomy A: patients without metastatic involvement of the inguinofemoral nodes at the first surgical procedure *(n = 217)* B: patients with involvement of the inguinofemoral nodes at the first surgical procedure *(n = 113)* **Analysis** • Type of analysis: Kaplan-Meier method • Matching: no	**Recurrence rate of vulva** • Group A: N= 34 of 217, 15.7% • Group B: N= 30 of 113, 26.5% **DFS (5-year)** • NR **Disease-specific survival (local or vulva)** • 83% after 2 years treatment • 79% after 5 years • 66% after 10 years **Additional outcomes: death** • N=192 · 59 from disease (17.9% of the study population), 11 from treatment complications (3.3%), 120 from other causes (36.4%), and 2 unknown (0.6%). **Additional outcomes: treatment failure** • 88 (26.7%)	**General information** • Mean follow-up: NR • **Funding**: nr • **CoI**: nr **Risk of bias considerations (adapted from SIGN cohort study checklist)** • Study type: cohort study • Populations comparable: yes • Rate of participation/Exclusions reported (selection bias into the study): no • Exposure/Intervention · Assessment reliable: yes · Assessed more than once: nr · Possibly affected by knowledge of outcome status?: nr • Drop-out rate & reasons reported: no • Outcome · Outcome measure is well-defined, valid and reliable: yes

Referenz/ Studientyp	Untersuchte Population	Interventionen	Hauptergebnisse	Methodische Bewertung
	• Lymph node metastases (yes, %) · 113 lymph node positive, 217 negative	• Confounders: no		· Blind outcome assessment to exposure: (→If 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

7.8.2 Bewertung der Evidenz (nach GRADE)

Es ist keine Bewertung nach dem GRADE Ansatz möglich, da keine Ergebnisse in den Studien für die Endpunkte der Schlüsselfrage berichtet werden.

7.9 Kapitel Operative Therapie der Lymphabflusswege – PICO 7.8

Ist bei Patientinnen mit ED Vulvakarzinom und Primärtumor < 4 cm sowie klinisch / bildgebend negativen Leisten das Sentinel-Lymphknotenbiopsie-Verfahren zum operativen Staging der Leisten der systematischen LNE hinsichtlich Morbidität, Rate an Leistenrezidiven sowie DFS sowie OS ebenbürtig?

7.9.1 Evidenztabellen

7.9.1.1 Systematisches Review

Literaturreferenzen:

Covens A, Vella ET, Kennedy EB, Reade CJ, Jimenez W, Le T. Sentinel lymph node biopsy in vulvar cancer: Systematic review, meta-analysis and guideline recommendations. Gynecologic oncology 2015;137(2):351-61. doi: 10.1016/j.ygyno.2015.02.014

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	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 **Databases:** • MEDLINE, Embase, Cochrane Database of Systematic Reviews, **Exclusion criteria** • Case reports with fewer than 5 patients. • Reports of only en-block ('butterfly incision') radical vulvectomy with concurrent bilateral lymphadenectomy. • Studies where patients underwent vulvar/groin	**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 node-negative, early stage (FIGO stage T1 or T2, less than 4 cm) squamous cell cancer of the vulva. A: Sentinel lymph node biopsy (negative SLNB) (N=..)	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 from 23 studies are relevant for this guideline PICO) **Descriptive statistics:** · NR • Age (median, range) · NR • Sex (% female) · NR • Location of the tumour · NR • Tumour size (%, cm) · NR • Tumour depth (%, mm)	**Mortality** • NR **Recurrence rate in negative groin** • SLNB: rate of 0.03, 95% CI 0.02-0.04), 3.4% (1.8-5.4 • Superficial IFLD: rate of 0.07, 95% CI 0.04-0.09, 6.6% (4.4-9.0) • Complete IFLD: rate of 0.01, 95% CI 0.00-0.03, 1.4% (0.4-2.9) **DFS** • NR **Overall survival** • NR **Additional outcome: complication rates** • wound breakdown rate: A: 11.7%, B: 34%	**Overall confidence in results of SR (AMSTAR-2): *"poor"*** • PICO elements: no • A priori design: no • Justification for design: no • Literature search >= 2 databases, search strategy + other sources: yes • Selection in duplicate: no • Data extraction in duplicate: no • List of excluded studies: no • sufficient detail on studies: no • RoB assessed: no • Funding of incl. studies: no • MA appropriate: na • RoB considered in MA: na • RoB in interpretation: na	Non-RCTs (NRS) C.F. Levenback, S. Ali, R.L. Coleman, *et al.* Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. J. Clin. Oncol., 30 (31) (2012) A. Garcia-Iglesias, M.O. Rodriguez-Martin, R. Ruano, *et al.* Sentinel node dissection in the treatment

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	reconstructive procedures. • Studies using coverings/foreign materials in the groin in all patients. • Studies of only stage 1A or clinically advanced/recurrent disease (clinical stage 3 or 4, or clinically involved lymph nodes). • Studies with pregnant patients only, or with a specific focus on treatment of vulvar cancer in pregnancy. • Studies on vulvar melanoma only. • Studies including previously published patient data. **Inclusion criteria:** • Studies were included if they contained the	B: inguinofemoral lymph node dissection (negative IFLD devided into superficial and complete group) (N=..)	· NR	• cellulitis: A: 4.5%, B: 21.3% • lymphedema: A: 1.9%, B: 25.2%	• Heterogeneity explained: yes • Publication bias investigated: no • Sources of CoI: yes	of early stages of vulvar cancer. Eur. J. Gynaecol. Oncol., 33 (2) (2012) M. Novackova, M. J. Halaska, H. Robova, *et al.* 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), A.A. Soliman, M. Heubner, R. Kimmig, *et al.* Morbidity of

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	outcomes of interest, including: • Detection rates for SLNB, defined as the number of groins where a SLN was identified divided by the number of groins evaluated • 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) • Complications of interest related to surgical evaluation of inguino-femoral lymph nodes by SLNB or IFLD, including wound					inguinofemoral lymphadenectomy in vulval cancer. ScientificWorldJournal, 2012 (2012), J. Zekan, A. Mutvar, D. Huic, *et al.* Reliability of sentinel node assay in vulvar cancer: the first Croatian validation trial. Gynecol. Oncol., 126 (1) (2012) R. Farrell, V. Gebski, N.F. Hacker. Quality of life after complete lymphadenectomy for vulvar

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
	infection or breakdown, lymphocysts, and/or lymphedema • Reports of groin recurrence after negative IFLD or SLNB.					cancer: do women prefer sentinel lymph node biopsy? Int. J. Gynecol. Cancer, 24 (4) (2014) K. Robison, D. Roque, C. McCourt, *et al.* Long-term follow-up of vulvar cancer patients evaluated with sentinel lymph node biopsy alone. Gynecol. Oncol., 133 (3) (2014) M. Underwood, J. K. Yap, A. Elattar, *et al.* The use of sentinel node

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
						sampling in vulval cancer. J. Obstet. Gynaecol., 33 (8) (2013) A.G. Van der Zee, M.H. Oonk, J .A. De Hullu, *et al.* Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. J. Clin. Oncol., 26 (6) (20 08) 3 systematic reviews M. Hassanzade, M. Attaran, G. Tre glia, *et al.*

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
						Lymphatic mapping and sentinel node biopsy in squamous cell carcinoma of the vulva: systematic review and meta-analysis of the literature. Gynecol. Oncol., 130 (1) (2013) C. Meads, A.J. Sutton, A.N. Rosenthal, *et al.* Sentinel lymph node biopsy in vulval cancer: systematic review and meta-analysis. Br. J.

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen	Ergebnisse Beschreibung Studien / Population	Ergebnisse der untersuchten Endpunkte	methodische Bemerkungen	Literaturbelege/ eingeschlossene Publikationen
						Cancer, 110 (12) (2014) A. Wills, A. Ober mair. A review of complications associated with the surgical treatment of vulvar cancer. Gynecol. Oncol., 131 (2) (2 013)

7.9.2 Bewertung der Evidenz (nach GRADE)

Das Systematic Review berichtet keine Daten die einen direkten Vergleich ermöglichen, daher konnte keine GRADE Bewertung erfolgen.

8 Literaturverzeichnis

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