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Leitlinienprogramm Onkologie

Leitlinienreport S3-Leitlinie Diagnostik, Therapie und Nachsorge des Peniskarzinoms

Version 1.0 – August 2020
AWMF-Registernummer: 043-042OL

Leitlinienreport

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

Inhaltsverzeichnis

1. Informationen zum Leitlinienreport

1.1. Autoren des Leitlinienreports

Autorinnen des Leitlinienreports sind Dr. Julia Lackner und Dr. Stefanie Schmidt. Beide sind Mitarbeiterinnen von UroEvidence@Deutsche Gesellschaft für Urologie, Berlin.

1.2. Herausgeber

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

1.3. Federführende Fachgesellschaft der Leitlinie

Deutsche Gesellschaft für Urologie e. V. (DGU)

1.4. Finanzierung der Leitlinie

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

1.5. Kontakt

Office Leitlinienprogramm Onkologie
c/o Deutsche Krebsgesellschaft e. V.
Kuno-Fischer-Straße 8
14057 Berlin

leitlinienprogramm@krebsgesellschaft.de
www.leitlinienprogramm-onkologie.de

1.6. Zitierweise des Leitlinienreports

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Diagnostik, Therapie und Nachsorge des Peniskarzinoms, Leitlinienreport Version 1.0, 2020, AWMF-Registernummer: 043-042OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/peniskarzinom/ , (abgerufen am TT.MM.JJJJ)

1.7. Weitere Dokumente zur Leitlinie

Die Leitlinie liegt als Lang- und Kurzversion vor. Außerdem wird es eine Patientenleitlinie (Laienversion der Leitlinie) geben. Alle Dokumente zur Leitlinie sind über die folgenden Seiten zugänglich:

- Leitlinienprogramm Onkologie (https://www.leitlinienprogramm-onkologie.de/leitlinien/peniskarzinom/)
- AWMF (www.awmf.org)

Die Leitlinie ist außerdem in der App des Leitlinienprogramms Onkologie enthalten.

Weitere Informationen unter: https://www.leitlinienprogramm-onkologie.de/app/

1.8. Abkürzungsverzeichnis

Tabelle 1: Abkürzungsverzeichnis

Abkürzung	Erläuterung
18F-FDG	Fluorine-18 Fluorodeoxyglucose
5-FU	5-Fluorouracil
AAT	Acetic acid test
AF	Autofluorescence imaging
AG	Arbeitsgruppe
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.
BAD	British Association of Dermatologists
BASIC IDEA	Behavior, Affect, Sensation, Imagery, Cognition, Interpersonal, Drugs, Expectation, Attitude
CI	Confidence Interval
CIS	Carcinoma in situ
CMNI	Conformity to Masculine Norms Inventory
CO2	Carbon dioxide
CSS	Cancer Specific Survival
CT	Computed Tomography
d	days
DFS	Disease-Free Survival
DKG	Deutsche Krebsgesellschaft e. V.
DKH	Deutsche Krebshilfe
DS(L)NB	Dynamic Sentinel (Lymph) Node Biopsy

Abkürzung	Erläuterung
DSM III-R	Diagnostic and Statistical Manual of Mental Disorders of psychiatric illness
DSS	Disease Specific Survival
EAU	European Association of Urology
EBRT	External Beam Radiation Therapy
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDITS	Erectile Dysfunction Inventory of Treatment Satisfaction
EGFR	Epidermal Growth Factor Receptor
EK	Expertenkonsens
EORTC QLQ	EORTC Quality of Life Questionnaire
ES	Effect Size
EuroQol (EQ-5D-5L)	European Quality of life scale
FDG/PET-CT	Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography
FNAC	Fine-Needle Aspiration Cytology
FOXP3	Forkhead-Box-Protein P3
GHQ	General Health Questionnaire
GIN	Guidelines International Network
h	hours
HADS	Hospital Anxiety and Depression Scale
HDGF	Hepatoma-Derived Growth Factor
HPV	Human Papillomavirus
HR	Hazard Ratio

Abkürzung	Erläuterung
HRQOL	Health-Related Quality-Of-Life
HSI	Hornheider Screening Instrument
ICSmaleSF	International Continence Society male Short Form questionnaire
IES	Impact of Event Scale
IIEF	International Index of Erectile Function questionnaire
ILND	Inguinal Lymph Node Dissection
IMGI	Index of Male Genitalia Image
IOC	Impact of Cancer
IPSS	International Prostate Symptom Score
KSR	Kleijnen Systematic Review
KTP	Kaliumtitanylphosphat
LA	Leitlinienadaption
LAD	Lymphadenectomy
LiSat-11	Life Satisfaction-11
LN	Lymph Node
LUTS	Lower Urinary Tract Symptoms score
MCM2	Mini-Chromosome Maintenance 2 protein
MILND	Minimally Invasive Lymph Node Dissection
min	minutes
ml	millilitre
mm	microscopic margin

Abkürzung	Erläuterung
mo	month
MRI	Magnetic Resonance Imaging
mTor	mechanistic Target of Rapamycin
NCCN-DT	National Comprehensive Cancer Network Distress Thermometer
Nd:YAG laser	Neodymium Yttrium Aluminum Garnet
NR	Not Reached
OILND	Open Inguinal Lymph Node Dissection
OL	Leitlinienprogramm Onkologie
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
OSFQ	Overall Sexual Functioning Questionnaire
OSu	Orientierende Suche
PAIS	Psychosocial Adjustment to Illness Scale
PDD	Photodynamic Diagnosis
PD-L1	Programmed death-ligand 1
PET/CT	Positron Emission Tomography/Computed Tomography
PFS	Progression-Free Survival
PHQ-9	Patient Health Questionnaire
PLND	Pelvic Lymph Node Dissection
ppV	positive predictive Value

Abkürzung	Erläuterung
PROM	Patient-Reported Outcome Measure
PS	Performance Status
QEQ	Quality of Erection Questionnaire
QI	Qualitätsindikatoren
QoL	Quality of Life
RA-VEIL	Robot Assisted Video Endoscopic Inguinal Lymphadenectomy
RCT	Randomized Controlled Trial
RR	Relative Risk
SAS	Self-Rating Anxiety Scale
SD	Standard Deviation
SDS	Self-Rating Depression Scale
SEAR	Self-Esteem and Relationship questionnaire
SEER	Surveillance, Epidemiology and End Results
SEP	Sexual Encounter Profile
SES	Rosenberg Self-Esteem Scale
SF-36	Short Form Health 36
SFQ	Sexual Function Questionnaire
SLNB	Sentinel Lymph-Node Biopsy
SLNL	Sentinel Lymph Node Lymphoscintigraphy
SNB	Sentinel lymph Node excision Biopsy
SPECT	Single-Photon Emission Computed Tomography

Abkürzung	Erläuterung
SPQ	Social Problem Questionnaire
TPF	Taxane, Cisplatin, and 5-Fluorouracil
USA	United States of America
USS	Ultrasound Scan
VEGF-A	Vascular Endothelial Growth Factor-A
VEILND	Video-Endoscopic Inguinal Lymph Node Dissection
WHO PS	World Health Organization Performance Status
wk	weeks
WMD	Weighted Mean Difference
y	years

2. Geltungsbereich und Zweck der Leitlinie

2.1. Adressaten

Primäre Adressaten der Leitlinie sind Ärztinnen und Ärzte sowie andere medizinische Leistungserbringer, die an der Diagnostik, Therapie und Nachsorge der Patienten mit einem Peniskarzinom beteiligt sind (alle Stadien; ambulante und stationäre Versorgung sowie Rehabilitation). Auch Patienten und Angehörige gelten als primäre Adressaten dieser Leitlinie und werden im spezifischen Format einer laienverständlichen Patientenleitlinie berücksichtigt.

Die Leitliniengruppe setzt sich aus einem interdisziplinären Expertenkomitee zusammen. Damit wurden alle an der Versorgung beteiligten Leistungserbringer sowie Patientenvertreter bei der inhaltlichen Mitarbeit an dieser Leitlinie berücksichtigt.

2.2. Zielsetzung

Ziel dieser Leitlinie ist es, die aktuelle Evidenz für die Diagnose, Behandlung und Nachsorge von Patienten mit Peniskarzinom systematisch zusammenzufassen und zu bewerten. Weiterhin sollten auf dieser Basis Handlungsempfehlungen erstellt werden, die den an der Behandlung beteiligten Ärztinnen und Ärzten sowie den Patienten dienlich sind.

Spezifisches Ziel ist die Erstellung einer evidenzbasierten Diagnostik und Versorgung anhand wissenschaftlich gestützter Informationen (Behandlungsstandard), welche an den Strukturen des deutschen Gesundheitssystems angepasst sind. Das Peniskarzinom ist eine seltene Tumorentität mit schwerwiegenden psychosozialen Folgen. Aufgrund der wenigen Fälle und der daraus resultierenden geringen oder fehlenden persönlichen Erfahrung der Versorger kommt es zu unterschiedlichen Vorgehensweisen und Behandlungsergebnissen. Dies betrifft auch die pathologische Diagnostik. Daher soll diese Leitlinie sämtliche relevanten Versorgungsaspekte ansprechen, nämlich von der Diagnostik bis hin zur Nachsorge. Neben der Regulierung von Über- oder Fehlversorgung soll auch die interdisziplinäre Zusammenarbeit der Leistungserbringer verbessert werden.

Dabei muss betont werden, dass diese klinische Leitlinie mit ihren Inhalten als Handlungsempfehlung gesehen werden muss. Leitlinien können nie die klinische Expertise von Ärztinnen und Ärzten ersetzen. Die individuellen Behandlungsentscheidungen beinhalten im Sinne der evidenzbasierten Medizin auch die Integration und Berücksichtigung der persönlichen Werte und Präferenzen des Patienten sowie die Expertise der behandelnden Ärztin oder des behandelnden Arztes. Nur die Kombination dieser drei Ansätze führt zum optimalen Behandlungserfolg und hoher Patientenzufriedenheit.

2.3. Gültigkeitsdauer und Aktualisierungsverfahren

Die S3-Leitlinie ist bis zur nächsten Aktualisierung gültig, die Gültigkeitsdauer wird auf maximal fünf Jahre geschätzt. Vorgesehen sind regelmäßige Aktualisierungen, bei dringendem Änderungsbedarf werden diese in einer neuen Version der Leitlinie unter https://www.leitlinienprogramm-onkologie.de/leitlinien/peniskarzinom/ publiziert. Kommentare und Hinweise für den Aktualisierungsprozess sind ausdrücklich erwünscht und können an das Leitliniensekretariat adressiert werden:

Deutsche Gesellschaft für Urologie e. V.
Leitliniensekretariat UroEvidence
Martin-Buber-Str. 10
14163 Berlin
Email: peniskarzinom@leitlinienprogramm-onkologie.de

3. Zusammensetzung der Leitliniengruppe

3.1. Koordination und Redaktion

Tabelle 2: Koordination und Redaktion

Beteiligte Fachgesellschaften und Organisationen	Koordination und Redaktion
Koordinator (DGU)	Prof. Dr. Oliver Hakenberg
UroEvidence (DGU)	Dr. Stefanie Schmidt, MPH
UroEvidence (DGU)	Dr. Julia Lackner, MPH
Leitliniensekretariat (DGU)	Janine Weiberg
AG-Leiter Präkanzerosen, Therapie T1-T4	Prof. Dr. Oliver Hakenberg
AG-Leiter Therapie Lymphknoten, Therapie Metastasen	Prof. Dr. Chris Protzel
AG-Leiter Epidemiologie, Stadieneinteilung, Diagnostik	Prof. Dr. Andreas Erbersdobler
AG-Leiterin Patienteninformation, Nachsorge	Dr. Desiree Dräger

3.2. Beteiligte Fachgesellschaften und Autoren

Tabelle 3: Beteiligte Fachgesellschaften und Organisationen

Beteiligte Fachgesellschaften und Organisationen	Mandatsträger
Deutsche Gesellschaft für Radioonkologie e. V. (DEGRO)	Prof. Dr. Johannes Claßen (Stellvertr. Prof. Dr. Vratislav Strnad)*
Deutsche Gesellschaft für Hämatologie und Onkologie e. V. (DGHO)	Prof. Dr. Gunhild von Amsberg
Deutsche Gesellschaft für Pathologie e. V. (DGP)	Prof. Dr. Glen Kristiansen
Deutsche Gesellschaft für Palliativmedizin e. V. (DGP)	Dr. Sven Michels
Deutsche Gesellschaft für Nuklearmedizin e. V. (DGN)	Dr. Martin Heuschkel
Deutsche STI-Gesellschaft e. V. (DSTIG)	Prof. Dr. Peter Schneede (Stellvertr. Prof. Dr. Norbert Brockmeyer)*
Österreichische Gesellschaft für Urologie e. V. (ÖGU)	PD Dr. Stephan Seklehner
Schweizer Gesellschaft für Urologie e. V. (SGU)	PD Dr. Thomas Hermanns
Berufsverband der Deutschen Pathologen e. V. (BDP)	Prof. Dr. Andreas Erbersdobler
Berufsverband der Deutschen Urologen e. V. (BvDU)	Prof. Dr. Carsten Maik Naumann
Deutsche Röntgengesellschaft e. V. (DGR)	PD Dr. Dirk Beyersdorff

Beteiligte Fachgesellschaften und Organisationen	Mandatsträger
Arbeitsgemeinschaft Dermatologische Onkologie der DKG (ADO)	PD Dr. Stefan Esser (Stellvertr. Prof. Dr. Lars Schneider)
Arbeitskreis Psychosomatische Urologie und Sexualmedizin der DGU	Dr. Desiree Dräger
Arbeitskreis Schmerztherapie/ Supportivtherapie/ Lebensqualität/ Palliativmedizin der DGU	Dr. Matthias Beintker
Arbeitskreis Onkologie der DGU (AKO)	Prof. Dr. Chris Protzel
Arbeitsgemeinschaft für Onkologische Rehabilitation und Sozialmedizin (AGORS)	Prof. Dr. Dirk-Henrik Zermann
Arbeitsgemeinschaft Internistische Onkologie der DKG (AIO)	Prof. Dr. Maike de Wit
Arbeitsgemeinschaft Onkologische Pathologie der DKG (AOP)	PD Dr. Dr. Konrad Steinestel
Arbeitsgemeinschaft Palliativmedizin der DKG (APM)	Dr. Marianne Kloke
Arbeitsgemeinschaft Radiologische Onkologie der DKG (ARO)	Dr. Alexandros Papachristofilou (Stellvertr. PD Dr. Arndt-Christian Müller)*
Arbeitsgemeinschaft Psychoonkologie der DKG (PSO)	Dr. Andreas Werner
AG Uroradiologie und Urogenitaldiagnostik der DRG	Prof. Dr. Alexander Cavallaro
* Nicht aktiv an der Leitlinienentwicklung beteiligt.	

Tabelle 4: Arbeitsgruppen und deren Mitglieder

Arbeitsgruppe - Leiter/in	Mitglieder der Arbeitsgruppe
AG Epidemiologie, Stadieneinteilung, Diagnostik Prof. Dr. Andreas Erbersdobler	PD Dr. Dirk Beyersdorff Prof. Dr. Alexander Cavallaro Prof. Dr. Oliver Hakenberg Dr. Martin Heuschkel Prof. Dr. Glen Kristiansen Prof. Dr. Peter Schneede PD Dr. Dr. Konrad Steinestel
AG Präkanzerosen Prof. Dr. Oliver Hakenberg	PD Dr. Stefan Esser Prof. Dr. Peter Schneede
AG Therapie T1-T4 Prof. Dr. Oliver Hakenberg	Prof. Dr. Johannes Claßen Prof. Dr. Chris Protzel PD Dr. Stephan Seklehner
AG Therapie Lymphknoten, Therapie Metastasen Prof. Dr. Chris Protzel	Prof. Dr. Maike de Wit Dr. Desiree Dräger PD Dr. Thomas Hermanns

Arbeitsgruppe - Leiter/in	Mitglieder der Arbeitsgruppe
	Prof. Dr. Carsten Maik Naumann Dr. Alexandros Papachristofilou
AG Patienteninformation, Nachsorge Dr. Desiree Dräger	Dr. Matthias Beintker Udo Ehrmann Dr. Marianne Kloke Dr. Sven Michels Dr. Alexandros Papachristofilou Dr. Andreas Werner Prof. Dr. Dirk-Henrik Zermann
AG Qualitätsindikatoren PD Dr. Simone Wesselmann	Dr. Susanne Blödt, MScPH Clara Breidenbach Udo Ehrmann Dr. Markus Follmann, MPH MSc. Prof. Dr. Oliver Hakenberg Dr. Julia Lackner Dr. Maren Pflüger Dr. Stefanie Schmidt

3.3. Patientenbeteiligung

Die Leitlinie wurde unter direkter Beteiligung von einem Patientenvertreter erstellt. Herr Udo Ehrmann vom Bundesverband Prostatakrebs Selbsthilfe e. V. nahm mit Stimmrecht an der Konsensuskonferenz teil und unterstützte die Arbeitsgruppen bei der Texterstellung.

3.4. Methodische Begleitung

Die methodische Begleitung wurde durch das Leitlinienprogramm Onkologie (Dr. Markus Follmann und Dipl.-Soz. Wiss. Thomas Langer) übernommen. Die Einhaltung der AWMF-Leitlinienstandards wurde von den AWMF MitarbeiterInnen im vier-Augen Prinzip gesichert.

4. Fragestellungen und Gliederung

Entwicklung der Schlüsselfragen

Durch die Koordinatoren der Leitlinie in Zusammenarbeit mit den Arbeitsgruppen-Leitungen wurde ein Vorschlag für mögliche Schlüsselfragen sowie relevante Endpunkte auf Basis der gefundenen Literatur (Leitliniensynopse und systematische Übersichtsarbeiten) erarbeitet. Die finale Konsentierung der Schlüsselfragen wurde von der Leitliniengruppe beim Kick-Off-Treffen im April 2018 definiert. Insgesamt sind 24 Schlüsselfragen entstanden, zu denen die Leitlinie Stellung nehmen sollte. 20 Schlüsselfragen wurden durch eine DeNovo-Recherche (DeNovo) beantwortet. Von diesen wurden drei Schlüsselfragen ausschließlich durch die Suche nach aggregierter Evidenz beantwortet. Je eine Frage wurde durch eine orientierende Suche (OSu) und durch Expertenkonsens (EK) beantwortet. Zur Beantwortung zweier weiterer Fragen wurde einmal eine Leitlinienadaption in Kombination mit dem Expertenkonsens sowie eine DeNovo-Recherche nach aggregierter Evidenz mit Leitlinienadaption (LA) herangezogen.

Tabelle 5: Schlüsselfragen

AG	Fragestellung	DeNovo	LA	EK	OSu
AG Epidemiologie, Stadieneinteilung und Klassifikationssysteme, Diagnostik	Haben Patienten mit positivem HPV eine bessere Prognose?	X (aggregierte Evidenz)			
	Sollen Patienten mit Peniskarzinom und cN0 eine aktive Überwachung oder ein invasives Staging mit DSNB oder MILND erhalten?	X			
	Soll bei Patienten mit Peniskarzinom und cN0 die Diagnose durch eine DSNB oder durch eine MILND erfolgen?	X			
	Ist die inguinale Feinnadelbiopsie der Lymphknoten, die inguinale Feinnadelbiopsie und DSNB oder MILND geeigneter zur Diagnose von Patienten mit Peniskarzinom und cN0?	X			
	Soll die Diagnose bei Patienten mit Peniskarzinom mit oder ohne cN+ durch ein PET/CT vor invasiver Lymphknotendiagnostik (DSNB, MILND) erfolgen?	X			
	Inwiefern hat die Bestimmung von p53, p16, Ki-67 im Präparat eine prognostische Aussagekraft?	X			
AG Therapie Ta (Präkanzerosen), Tis	Ist die lokale Therapie mit 5-FU oder Imiquimod für Patienten mit pTis Peniskarzinom geeigneter als eine Lasertherapie?	X			
	Sollen Patienten mit pTis Peniskarzinom eine lokale Therapie mit Laser und photodynamischer Diagnostik oder ohne photodynamische Diagnostik erhalten?	X			
	Ist die lokale Strahlentherapie für Patienten mit pTa oder pT1 Peniskarzinom geeigneter als eine Lasertherapie oder chirurgische Exzision?	X			

AG	Fragestellung	DeNovo	LA	EK	OSu
AG Therapie T1-4	Sollen Patienten mit pT1-2 G2-3 Peniskarzinom organerhaltend mittels Glansektomie oder durch eine Penisteilamputation therapiert werden?	X			
	Sollen Patienten mit pT1, pT2, pT3 Peniskarzinom eine chirurgische Resektion mit knappem oder weitem Schnittrand erhalten?	X			
AG Therapie cN0-3, Systemtherapie	Soll bei Patienten mit cN2/3 eine neoadjuvante Chemotherapie vor inguinaler LAD durchgeführt werden?	X			
	Sollen Patienten mit pN+ eine adjuvante Chemotherapie nach inguinaler LAD erhalten?	X			
	Sollen Patienten mit pN+ eine adjuvante Strahlentherapie nach inguinaler LAD erhalten?	X			
	Sollen Patienten mit cN2/3 eine neoadjuvante Radio/Chemotherapie vor inguinaler LAD erhalten?	X			
	Wie soll die Systemtherapie durchgeführt werden?	X			
	Soll die Lymphadenektomie minimalinvasiv oder offen erfolgen?	X			
	Wie viele Lymphknoten sollen bei einer radikalen Lymphadenektomie entfernt werden?				X
AG Nachsorge, Quality of Life, Supportivtherapie, Palliativmedizin, Patientenkommunikation	Wie ist die Lebensqualität bei Patienten mit T1/T2 unter verschiedenen Therapieformen?	X			
	Wann tritt ein Lokalrezidiv auf?	X (aggregierte Evidenz)			
	Wann tritt ein Lymphknotenrezidiv auf?	X (aggregierte Evidenz)			

AG	Fragestellung	DeNovo	LA	EK	OSu
	Mit welchen Instrumenten soll die Lebensqualität/Sexualfunktion erfasst werden?			X	
	Ab welchem Stadium soll palliativ-medizinisch behandelt/ vorgestellt werden?		X	X	
	Wie soll die Therapie des Lymphödems der Beine und des Skrotums durchgeführt werden?	X (aggregierte Evidenz)	X		
Abkürzungen: EK = Expertenkonsens, LA = Leitlinienadaptation, OSu = Orientierende Suche					

5. Methodisches Vorgehen

5.1. Leitliniensynopse

Leitlinienrecherche

Die Suche nach publizierten Leitlinien zu Diagnostik und Therapie des Peniskarzinoms erfolgte im März 2018 über die Datenbank des Guidelines International Network (GIN) sowie die PubMed-Suchoberfläche der National Library of Medicine.

Um die Zahl der Treffer einzugrenzen, wurde der Recherchezeitraum für die PubMed-Suche auf Publikationen ab 2000 bis April 2018 eingegrenzt.

Die folgende Suchstrategie wurde angewandt:

"Penile Neoplasms"[Mesh] OR (("penis"[MeSH Terms] OR "penis"[All Fields] OR "penile"[All Fields]) AND (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields]))) AND ((Practice Guideline[ptyp] OR Guideline[ptyp] OR Consensus Development Conference, NIH[ptyp] OR Consensus Development Conference[ptyp]) AND "2008/04/12"[PDat] : "2018/04/09"[PDat] AND "humans"[MeSH Terms]

Zusätzlich zur Datenbanksuche wurden gezielt die Webseiten folgender Organisationen gesichtet:

- American Society of Clinical Oncology (ASCO)
- American Urological Association (AUA)
- Belgian Health Care Knowledge Center (KCE)
- Cancer Care Ontario (CCO)
- Cancer Control Alberta (CCA)
- Comprehensive Cancer Organisation, the Netherlands (IKNL)
- European Association of Urology (EAU)
- European Society of Medical Oncology (ESMO)
- London Cancer Alliance (LCA)
- National Comprehensive Cancer Network (NCCN)
- National Institute of Clinical Excellence (NICE)
- Oncoline (NL)
- Scottish Intercollegiate Guidelines Network (SIGN)

Die Suchbegriffe hierzu waren: *penis cancer* oder *penis carcinoma* oder *penis neoplasms* oder *penile cancer* oder *penile carcinoma* oder *penile neoplasms*.

Identifizierte Leitlinien wurden berücksichtigt, wenn sie alle folgenden Kriterien einer evidenzbasierten Leitlinie erfüllten:

1. Es erfolgte eine systematische Recherche nach Primär- bzw. Sekundärliteratur.
2. Für mehr als die Hälfte der Leitlinienthemen wurden systematische Recherchen durchgeführt.
3. Bei der Mehrheit der Empfehlungen ist eine Evidenz- und/oder Empfehlungseinstufung (Evidenzlevel und/oder Empfehlungsgrad) angegeben.

Als Einschlusskriterien wurden die Übereinstimmung bezüglich der Patientengruppe sowie die Verfügbarkeit in englischer und/oder deutscher Sprache festgelegt. Gab es innerhalb des Suchzeitraums mehrere Publikationen der gleichen Leitlinie, so wurde das aktuelle Dokument eingeschlossen.

Die methodische Bewertung der Leitlinien erfolgte mittels des DELBI-Instruments [1]. Leitlinien, die bei dieser Bewertung in der Domäne 3 („Methodische Exaktheit der Leitlinien-Entwicklung") einen standardisierten Domäne-Wert von < 0,5 erreichten, wurden nicht berücksichtigt.

Generelle Angaben sowie die Schlüsselempfehlungen der genannten Leitlinien wurden extrahiert.

Ergebnisse der Leitlinienrecherche

Die Recherche ergab 37 potenzielle Treffer: sechs aus der GIN-Suche, 25 aus der PubMed-Suche und sechs aus den Suchen auf den Webseiten. Nach genauer Durchsicht der Texte und nach Prüfung der Einschlusskriterien sowie der Qualität wurden drei potenziell relevante Leitlinien, die als Quellleitlinien herangezogen werden konnten, identifiziert.

Als Quellleitlinien herangezogen wurden:

- BAD 2014 [2]
- EAU 2018 [3]
- NCCN 2018 [4]

Über alle acht Domänen der DELBI-Bewertung hinweg können 136 Punkte erreicht werden [1]. Keine der drei Leitlinien erreichte den vollen Punktwert in der DELBI-Bewertung. Die drei in die Synopse aufgenommenen Leitlinien erreichten mindestens 75 Punkte. Generell wurden die Domäne „Klarheit und Gestaltung" (n=3 > 75 % der Punkte) sowie die Domäne „Methodische Gestaltung der Leitlinien-Entwicklung" (n=3 > 70 % der Punkte) am höchsten bewertet. Die niedrigsten Bewertungen wurden in der Domäne „Methodische Exaktheit der Leitlinien-Entwicklung bei Verwendung existierender Leitlinien" (n=3 < 13 % der Punkte) erreicht. Eine Synopse mit den inhaltlichen Kernaussagen der eingeschlossenen Leitlinien kann angefragt werden.

Andere relevante Leitlinien zu Schnittstellen

Andere für Deutschland relevante S3-Leitlinien der AWMF zu benachbarten Themenbereichen sind im Folgenden aufgeführt. Diese wurden nicht systematisch gesucht, sondern sind aus anderen Leitlinienprojekten sowie durch Benachrichtigung von Experten bekannt:

- Supportive Therapie bei onkologischen PatientInnen (AWMF Nr. 032/054OL, gültig bis 10.11.2021) [5]
- Psychoonkologische Diagnostik, Beratung und Behandlung von erwachsenen Krebspatienten (AWMF Nr. 032 - 051OL, gültig bis 30.01.2019) [6]
- Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung (AWMF Nr. 128 - 001OL, Konsultationsfassung März 2020) [7]

Aus zwei Leitlinien wurden insgesamt zwei Empfehlungen adaptiert (S3-Leitlinie Palliativmedizin aus 2019, S3-Leitlinie Psychoonkologie aus 2014).

5.2. Systematische Recherchen

Als Zeitraum für die Suche nach Primärliteratur wurde Januar 1980 bis Juni 2018 festgelegt. Englische und deutsche Literatur wurde berücksichtigt. Insgesamt wurden sechs Suchen in drei Datenbanken (MEDLINE, KSR Datenbank und Cochrane Library) durchgeführt. Zur Identifizierung möglichst hoher Evidenz wurden folgende Studiendesigns und Publikationsformen ausgeschlossen: Fallberichte, Editorials, Kommentare und Konferenzabstracts.

Für die Cochrane-Library wurde eine Hauptsuche am 02.07.2018, welche zu 129 Treffern führte, mit folgender Suchstrategie durchgeführt:

Suchstrategie für die Suche in der Cochrane Library

#	Suche
1	(penile* or penis*) near/4 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or "SCC" or lesion*)
2	[mh "Penile Neoplasms"] or "PSCC"
3	[mh "Carcinoma, Squamous Cell"] or [mh "Erythroplasia"] or [mh "Carcinoma in Situ"] or [mh "bowens disease"]
4	(cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas*) and "in situ"
5	Erythroplasi* or CIS or bowen's disease* or bowens disease*
6	#3 or #4 or #5
7	(penile* or penis* or glans*)
8	(#3 or #4 or #5) near/4 (penile* or penis* or glans*)
9	#1 or #2 or #3 or #8 Publication Year from 1980 to 2018

Die vier weiteren Suchen wurden in MEDLINE via Ovid durchgeführt. Für die Schlüsselfrage: „Haben Patienten mit positivem HPV eine bessere Prognose?“ wurde ausschließlich nach aggregierter Evidenz mit Hilfe der folgenden Suchstrategie am 02.07.2018 in MEDLINE gesucht:

Suchstrategie für die HPV-Suche in MEDLINE

#	Suche
1	exp penis cancer/ or exp Penile Neoplasms/

2	((penile* or penis*) adj4 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or "SCC" or lesion*)).tw,kw.
3	exp Carcinoma, Squamous Cell/ or exp Carcinoma in Situ/ or exp ERYTHROPLASIA/ or exp Bowen's Disease/
4	((cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas*) and "in situ").tw.
5	(Erythroplasi* or CIS or bowen's disease* or bowens disease*).tw.
6	3 or 4 or 5
7	(penile* or penis* or glans*).tw.
8	6 and 7
9	1 or 2 or 8
10	exp PAPILLOMAVIRIDAE/ or exp Papillomavirus Infections/
11	(HPV* or Papillomavir* or Papillomvir*).tw,kw.
12	10 or 11
13	9 and 12
14	exp Meta-Analysis/
15	exp "REVIEW LITERATURE AS TOPIC"/ or "REVIEW"/
16	(meta*analys* or systematic review or systematic*).tw.
17	14 or 15 or 16
18	13 and 17
19	bladder or prostate or lung or ovarian).ti,ab.
20	18 not 19
21	limit 20 to (yr="1980 -Current" and (english or german))

Die Suche ergab 226 Treffer. Eine Updatesuche erfolgte unter Verwendung der gleichen Suchstrategie im Oktober 2018. Dabei konnten fünf weitere Treffer identifiziert werden.

Für die Diagnostik, Prognose und Therapie wurden separate Suchstrategien in MEDLINE entwickelt. Die Suchen wurden am 03.07.2018 durchgeführt. Dabei konnten für die

Diagnostik 110 Treffer, für die Prognose 56 Treffer und für die Therapie 1649 Treffer identifiziert werden. Die entsprechenden Suchstrategien sind im Folgenden aufgeführt.

Suchstrategie für die Diagnostik-Suche in MEDLINE

#	Suche
1	exp penis cancer/ or exp Penile Neoplasms/
2	((penile* or penis*) adj4 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or "SCC" or lesion*)).tw,kw.
3	exp Carcinoma, Squamous Cell/ or exp Carcinoma in Situ/ or exp ERYTHROPLASIA/ or exp Bowen's Disease/
4	((cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas*) and "in situ").tw.
5	(Erythroplasi* or CIS or bowen's disease* or bowens disease*).tw.
6	3 or 4 or 5
7	(penile* or penis* or glans*).tw.
8	6 and 7
9	1 or 2 or 8
10	exp Sentinel Lymph Node Biopsy/ or exp Lymph Node Excision/ or exp NEOPLASM STAGING/ or exp Biopsy, Fine-Needle/
11	((lymph* or node*) adj3 (surg* or operation* or removal* or excis* or resect* or dissect* or biops* or diagnos* or ectom*)).tw.
12	exp Positron Emission Tomography Computed Tomography/
13	("Positron Emission Tomography Computed Tomography" or "PET CT" or PET*CT).tw.
14	10 or 11 or 12 or 13
15	exp "Sensitivity and Specificity"/
16	(specificity or sensitivity).tw.
17	predictive value*.tw.
18	likelihood ratio*.tw.
19	15 or 16 or 17 or 18

20	9 and 14 and 19
21	((exp animals/ or exp animal/ or exp animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not (humans/ or human/)) or ((rats or mice or mouse or cats or dogs or animal*) not (human* or men or women)).tw.
22	20 not 21
23	Conference Abstract.pt. or Congresses as Topic/ or note/ or editorial/ or letter/ or Comment/ or news/
24	22 not 23
25	limit 24 to (yr="1980 -Current" and (english or german))

Suchstrategie für die Prognose-Suche in MEDLINE

#	Suche
1	exp penis cancer/ or exp Penile Neoplasms/
2	((penile* or penis*) adj4 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or "SCC" or lesion*)).tw,kw.
3	exp Carcinoma, Squamous Cell/ or exp Carcinoma in Situ/ or exp ERYTHROPLASIA/ or exp Bowen's Disease/
4	((cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas*) and "in situ").tw.
5	(Erythroplasi* or CIS or bowen's disease* or bowens disease*).tw.
6	3 or 4 or 5
7	(penile* or penis* or glans*).tw.
8	6 and 7
9	1 or 2 or 8
10	exp PROGNOSIS/
11	(prognos* or predict*).tw.
12	10 or 11
13	exp Tumor Suppressor Protein p53/

14	exp Ki-67 Antigen/
15	exp Genes, p16/
16	(p53 or p 53 or p16 or p 16 or ki67 or ki 67).tw.
17	13 or 14 or 15 or 16
18	9 and 12 and 17
19	limit 18 to (yr="1980 -Current" and (english or german))

Suchstrategie für die Therapie-Suche in MEDLINE

#	Suche
1	exp penis cancer/ or exp Penile Neoplasms/
2	((penile* or penis*) adj4 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or "SCC" or lesion*)).tw,kw.
3	exp Carcinoma, Squamous Cell/ or exp Carcinoma in Situ/ or exp ERYTHROPLASIA/ or exp Bowen's Disease/
4	((cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas*) and "in situ").tw.
5	(Erythroplasi* or CIS or bowen's disease* or bowens disease*).tw.
6	3 or 4 or 5
7	(penile* or penis* or glans*).tw.
8	6 and 7
9	1 or 2 or 8
10	exp AMPUTATION/
11	exp General Surgery/
12	(organ adj (sparing or preserving or preservation)).tw.
13	(penectom* or glansectom*).tw.
14	(amputation* or surger* or surgical* or exicision* or resection*).tw.
15	exp FLUOROURACIL/

16	(5FU* or Fluorouracil or imiquimod* or Aldara* or Zyclara* or Beselna* or R837* or S26308*).mp.
17	exp PHOTOCHEMOTHERAPY/
18	(photodynamic diagnos* or PDD or photodynamic* or photochemo* or photo-dynamic* or photo-chemo*).tw.
19	exp Laser Therapy/
20	exp RADIOTHERAPY/
21	exp BRACHYTHERAPY/
22	exp Chemoradiotherapy/
23	exp Drug Therapy/
24	(brachytherap* or chemotherap* or chemoradiotherap* or chemoradiation therap* or radiotherap* or laser surger* or laser ablation* or laser treatment* or radio therap* or radio-therap* or lasertherap* or laser therap* or radiation therap* or radiation-therap*).tw.
25	exp NEOADJUVANT THERAPY/
26	(neo-adjuvant* or neoadjuvant* or adjuvant*).tw.
27	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	9 and 27
29	((exp animals/ or exp animal/ or exp animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not (humans/ or human/)) or ((rats or mice or mouse or cats or dogs or animal*) not (human* or men or women)).tw.
30	28 not 29
31	Conference Abstract.pt. or Congresses as Topic/ or note/ or editorial/ or letter/ or Comment/ or news/
32	30 not 31
33	(cervix or cervical or bladder or prostate or lung or ovarian).ti,ab.
34	32 not 33
35	limit 34 to (yr="1980 -Current" and (english or german))

Zusätzliche Suche

Für die Schlüsselfrage: „Wie soll die Therapie des Lymphödems der Beine und des Skrotums durchgeführt werden?“ wurde mit Hilfe der vorangegangenen Suchen nicht ausreichend Literatur gefunden. Am 11.12.2018 wurde daher eine zusätzliche Suche nach aggregierter Evidenz bei Medline sowie in der KSR-Datenbank durchgeführt. Dabei wurde für beide Datenbanken der Suchstring: „(Lymphedema and (scrotum or leg or limb)) and cancer” verwendet. Insgesamt wurden 32 Treffer identifiziert.

Auswahl Publikationen

Insgesamt wurden in MEDLINE, in der KSR-Datenbank und Cochrane 2285 Quellen identifiziert. Nach Duplikatentfernung wurden 2182 Treffer einer Titel- und Abstractprüfung unterzogen. Das Screening von Titel und Abstract erfolgte durch die Mitglieder der Arbeitsgruppen. Als Einschlusskriterien wurden Patienten mit allen Stadien des Peniskarzinoms (auch Präkanzerosen wie CIS, Bowen’s disease, Erythrosplasie Querat) festgelegt sowie alle Studiendesigns berücksichtigt. Ausgeschlossen wurden nur Treffer, bei denen es sich eindeutig nicht um die anvisierte Patientenpopulation handelte und Fallberichte mit n=1.

Das Volltextscreening erfolgte durch UroEvidence. Dabei wurden die identifizierten Studien auf die zuvor festgelegten formalen Ein- und Ausschlusskriterien bezüglich der zu berücksichtigenden Sprachen und Studiendesigns überprüft sowie eine Zuordnung zu den Schlüsselfragen vorgenommen. 239 Treffer erfüllten die Einschlusskriterien nach der Volltextsichtung (234 Treffer aus den Hauptsuchen und 5 Treffer aus der Zusatzsuche Lymphödem). Der Suchverlauf der Hauptsuchen sowie der Zusatzsuche zum Lymphödem ist im PRISMA Flowchart dargestellt (siehe Abbildung 1 und Abbildung 2).

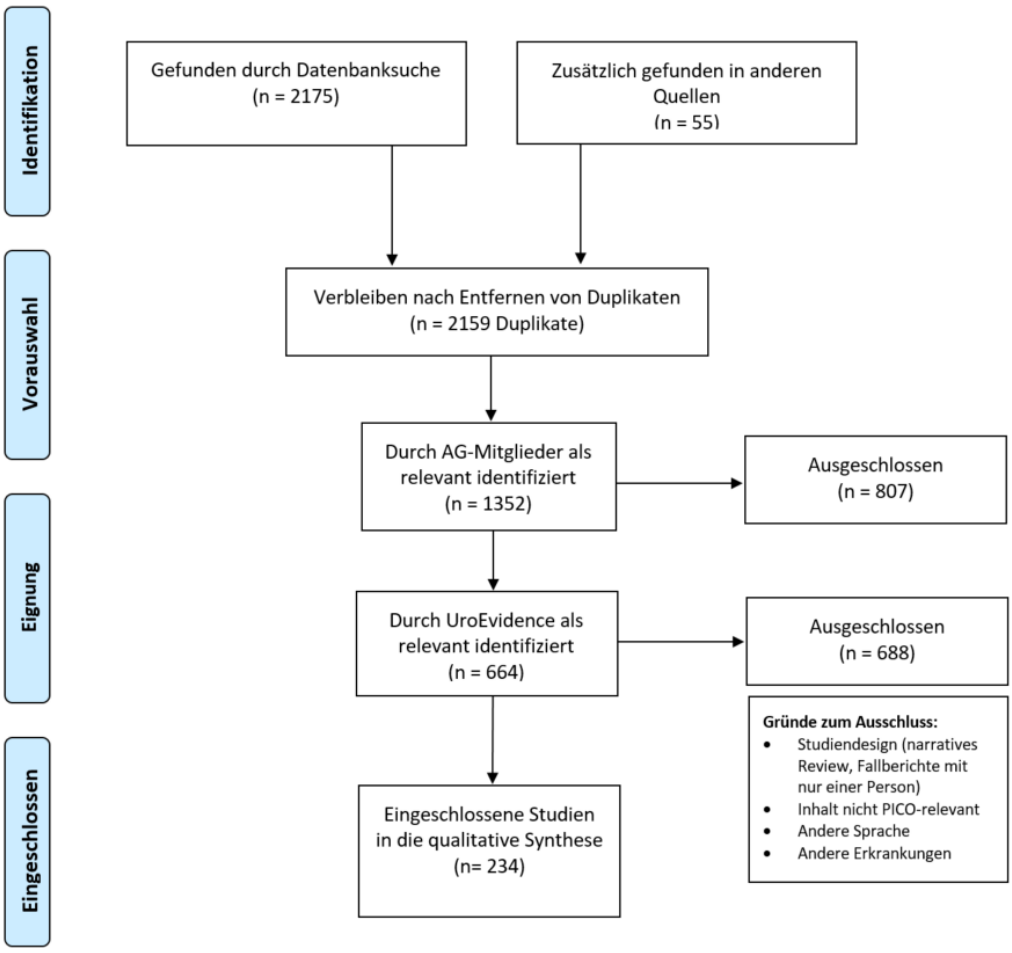


Abbildung 1: PRISMA Hauptsuchen

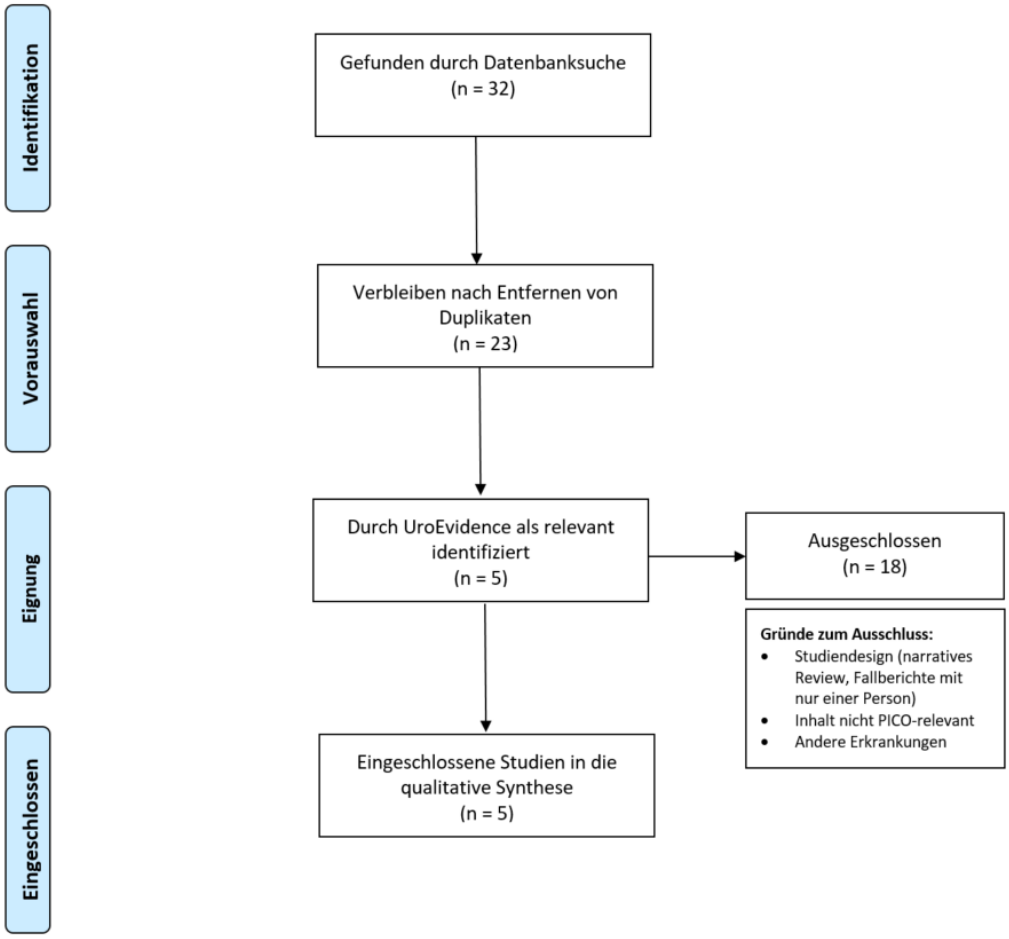


Abbildung 2: PRISMA Zusatzsuche Lymphödem

Zusammenfassung der Information

Die identifizierte Literatur wurde durch UroEvidence in Evidenztabellen zusammengefasst (siehe Anlage 10.1). Diese Tabellen wurden an die AGs zur Erstellung der Hintergrundtexte weitergeleitet. In den bereitgestellten Tabellen enthalten war eine Beschreibung der identifizierten Studien inklusive systematischer Bewertung als Arbeitsgrundlage für die AGs.

Bewertung des Risikos für Bias der Literatur

Für die Bewertung des Risikos für Bias wurde für randomisierte kontrollierte Studien (RCTs) das Cochrane Risk of Bias tool [8], für Diagnosestudien das QUADAS-2-Tool [9], für Prognosestudien das QUIPS-Tool [10], für Querschnittsstudien das EPHPP-Tool [11] sowie für Kohortenstudien und Fall-Kontroll-Studien die Newcastle Ottawa Quality Assessment Scale (NOS) [12] verwendet. Für systematische Übersichtsarbeiten und Metaanalysen wurde die Bewertung mit Hilfe des ROBIS-Tools [13] vorgenommen. Für Fallserien wurde von UroEvidence ein eigenes Instrument entwickelt, welches an die Publikation von Guo et al. (2016) angelehnt ist [14].

Das Instrument besteht aus den sieben Domänen „Studienziel“, „Studiendesign“, „Studienpopulation“, „Interventionen und Co-Interventionen“, „Endpunkte“, „Ergebnisse

und Schlussfolgerungen“ sowie „Interessenkonflikte und Finanzierung“ mit zehn Fragestellungen. Insgesamt beinhaltet es 30 Items. Für die Bewertung der Antwortmöglichkeiten wird folgendes Schema empfohlen: 2 Punkte für jede „ja“-Antwort, 1 Punkt für jede „teilweise“-Antwort und 0 Punkte für jede „nein“- oder „unklar“-Antwort.

Insgesamt können maximal 20 Punkte erzielt werden. Ein Schwellenwert, welcher eine Bewertung zwischen einem hohen und einem niedrigen Risiko vornimmt, wurde nicht ermittelt.

Tabelle 6: Bewertungsinstrumente

Studiendesign	Instrument	Quelle
Diagnostische Studien	QUADAS-2-Tool	Whiting et al. 2011
Fall-Kontroll-Studien	NOS	Wells et al.
Fallserien	UroEvidence Tool	basierend auf Guo et al. 2016
Kohortenstudien	NOS	Wells et al.
Prognosestudien	QUIPS	Hayden et al. 2013
Querschnittsstudien	EPHPP	Effective Public Heath Practice Project 1988
Randomisierte kontrollierte Studien	RoB Tool Cochrane	Higgins et al. 2011
Systematische Reviews und Metaanalysen	ROBIS-Tool	Whiting et al. 2016

5.3. Schema der Evidenzklassifikation

Tabelle 7: Schema der Evidenzgraduierung nach Oxford 2011 (deutsche Übersetzung durch UroEvidence) (OCEBM Levels of Evidence Working Group 2011)

Frage	Schritt 1 (Evidenzgrad 1*)	Schritt 2 (Evidenzgrad 2*)	Schritt 3 (Evidenzgrad 3*)	Schritt 4 (Evidenzgrad 4*)	Schritt 5 (Evidenzgrad 5*)
Wie häufig ist das Problem?	Lokale und aktuelle Stichproben-erhebung (oder Volkszählung)	Systematischer Review von Erhebungen, die eine Anpassung an die örtlichen Gegebenheiten ermöglichen**	Lokale nicht-zufällige Stichprobe**	Fallserien**	Nicht anwendbar
Ist der Diagnose- oder Überwachungs-test genau? (Diagnose)	Systematischer Review von Querschnitts-studien, welche durchweg den Referenz-standard anwendeten und verblindet durchgeführt wurden	Individuelle Querschnittsstu dien, welche durchweg den Referenz-standard anwendeten und verblindet durchgeführt wurden	Nicht-konsekutive Studien oder Studien ohne konsequent angewandten Referenz-standard**	Fallserien oder schlechte und nicht-unabhängige Referenz-standards	Beweisführung aufgrund von Mechanismen
Was passiert, wenn wir keine Therapie anbieten/ hinzufügen? (Prognose)	Systematischer Review von frühzeitig beginnenden Kohortenstudien	Frühzeitig beginnende Kohortenstudie	Kohortenstudie oder Kontrollarm eines RCTs	Fallserien oder Fall-Kontroll-Studien oder prognostische Kohorten-studien von schlechter Qualität**	Nicht anwendbar
Hilft diese Intervention? (Nutzen einer Behandlung)	Systematischer Review von RCTs oder “N-of-1”-Studien	RCT oder Beobachtungsst udie mit dramatischen Effekt	Nicht-randomisierte kontrollierte Kohorten- oder Nach-beobachtungs-studie	Fallserien oder Fall-Kontroll-Studien oder Studien mit historischer Kontroll-gruppe**	Beweisführung aufgrund von Mechanismen
Was sind häufige Nachteile der Behandlung?	Systematischer Review von RCTs oder genesteten Fall-Kontroll-Studien, “N-of-1”-Studie mit Patient aus Zielpopulation oder Beobachtungs-studie mit dramatischen Effekt		Nicht-randomisierte kontrollierte Kohorten- oder Nach-beobachtungs-Studie mit ausreichend großer Stichprobe und ausreichend langer Nach-beobachtung		

Frage	Schritt 1 (Evidenzgrad 1*)	Schritt 2 (Evidenzgrad 2*)	Schritt 3 (Evidenzgrad 3*)	Schritt 4 (Evidenzgrad 4*)	Schritt 5 (Evidenzgrad 5*)

* Evidenzgrad kann aufgrund der Studienqualität, Ungenauigkeit, einem indirekten Bezug auf die Schlüsselfrage, sehr kleiner absoluter Effektstärke oder bei inkonsistenten Studien herabgesetzt oder bei großer oder sehr großer Effektgröße heraufgesetzt werden

** Systematische Reviews sind im Allgemeinen einer Einzelstudie gegenüber zu bevorzugen.

Übersetzung angelehnt an [15]

Es erfolgte eine Einordnung bezüglich des Evidenzlevels aller eingeschlossenen Referenzen nach den Evidenzleveln des Oxford Centre for Evidence-Based Medicine 2011 [16]. In der Bezeichnung des Evidenzlevels der Empfehlungen und Statements wurde das jeweils höchste Evidenzlevel ausgewählt, auch wenn im Hintergrundtext mehrere Quellen mit unterschiedlichen Evidenzleveln zitiert wurden.

Empfehlungen und Statements werden nur als evidenzbasiert bezeichnet, wenn diese anhand einer Schlüsselfrage systematisch gesucht wurden. Alle anderen Empfehlungen und Statements sind als konsensbasiert einzustufen, auch wenn Literatur in den Hintergrundtexten aufgeführt ist, da diese selektiv ergänzt wurde.

5.4. Formulierung der Empfehlungen und formale Konsensusfindung

5.4.1. Schema der Empfehlungsgraduierung

In der Leitlinie wird zu allen Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung werden in der Leitlinie drei Empfehlungsgrade unterschieden (siehe Tabelle 8), die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln.

Tabelle 8: Verwendete Empfehlungsgrade

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll/soll nicht
B	Schwache Empfehlung	sollte/sollte nicht
0	Offene Empfehlung	kann

5.4.2. Festlegung des Empfehlungsgrades

Methodisches Vorgehen bei der Formulierung der Empfehlungen/Statements

Die Empfehlungen und Statements der Leitlinie wurden von den einzelnen AGs ausgearbeitet und anschließend der gesamten Leitliniengruppe vorgelegt und von dieser konsentiert. Um von der Evidenz zur Empfehlung zu gelangen, wurden folgende

Aspekte berücksichtigt: Das Evidenzlevel der Studien [16], Konsistenz der Studienergebnisse; klinische Relevanz der Endpunkte und Effektstärken; Nutzen-Risiko-Verhältnis; ethische, rechtliche, ökonomische Erwägungen; Patientenpräferenzen; Anwendbarkeit und Umsetzbarkeit.

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) führt in der Regel auch zu einer starken Empfehlung (Empfehlungsgrad A, „soll“).

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

- Konsistenz der Studienergebnisse
- Klinische Relevanz der Endpunkte und Effektstärken
- Nutzen-Risiko-Verhältnis
- Ethische Verpflichtungen
- Patientenpräferenzen
- Anwendbarkeit, Umsetzbarkeit in der Versorgung

5.4.3. Formale Konsensusverfahren und Konsensuskonferenz

Für die Verabschiedung von Empfehlungen galten die Konsensregeln gemäß AWMF-Regelwerk.

Die formulierten Empfehlungen und Statements aller Kapitel wurden in einem zweiphasigen Abstimmungsvorgang strukturiert konsentiert. Das heißt, es wurde über alle Empfehlungen und Statements vor der Konsensuskonferenz via Vorabstimmung votiert. Diese Vorabstimmung hatte zum Ziel, die Effizienz der zweitägigen Konsensuskonferenz zu erhöhen. Grundsätzlich wurden mit starkem Konsens (> 95 %) angenommene Empfehlungen/Statements ohne relevante inhaltliche Kommentare als verabschiedet gewertet.

Erreichten die Empfehlungen und Statements einen ≤ 95 %-igen Konsens, so wurden sie in der zweitägigen Konsensuskonferenz am 05. und 06. Juli 2019 erneut abgestimmt. Auch wurden Empfehlungen und Statements mit > 95 % Konsens besprochen, welche inhaltlich relevante Kommentare aus der Online-Abstimmung enthielten. Die Konsensuskonferenz wurde durch zwei AWMF-zertifizierte Leitlinienberater (Dr. Blödt, Dr. Follmann) moderiert. Alle Verfahren der Konsensusfindung folgten dem Regelwerk „Leitlinien der AWMF“ [17] gemäß dem Verfahren einer strukturierten Konsensuskonferenz nach dem National Institute of Health (NIH)-Typ:

- Vorstellung des Kapitels und der Empfehlungen durch die AG-Leiter
- gegebenenfalls inhaltliche Klärung und Aufnahme von Änderungsvorschlägen
- Abstimmung aller Vorschläge
- falls kein Konsens > 75 % erzielt wurde, erneute Diskussion und Abstimmung.

Alle Empfehlungen und Statements konnten im Konsens oder starken Konsens verabschiedet werden. Sonder- oder Minderheitsvoten als Lösung für Meinungsverschiedenheiten zu bilden, war nicht erforderlich.

Abstimmungsberechtigt waren die jeweiligen Mandatsträger (in ihrer Abwesenheit der jeweilige Stellvertreter) der Fachgesellschaften und Arbeitskreise, der Leitlinienkoordinator und der Patientenvertreter. Insgesamt waren 21 Stimmberechtigte anwesend. Von der Abstimmung ausgeschlossen waren Methodiker und externe Experten. Für die Abstimmung wurde ein TED-System genutzt.

Tabelle 9: Festlegungen hinsichtlich der Konsensstärke

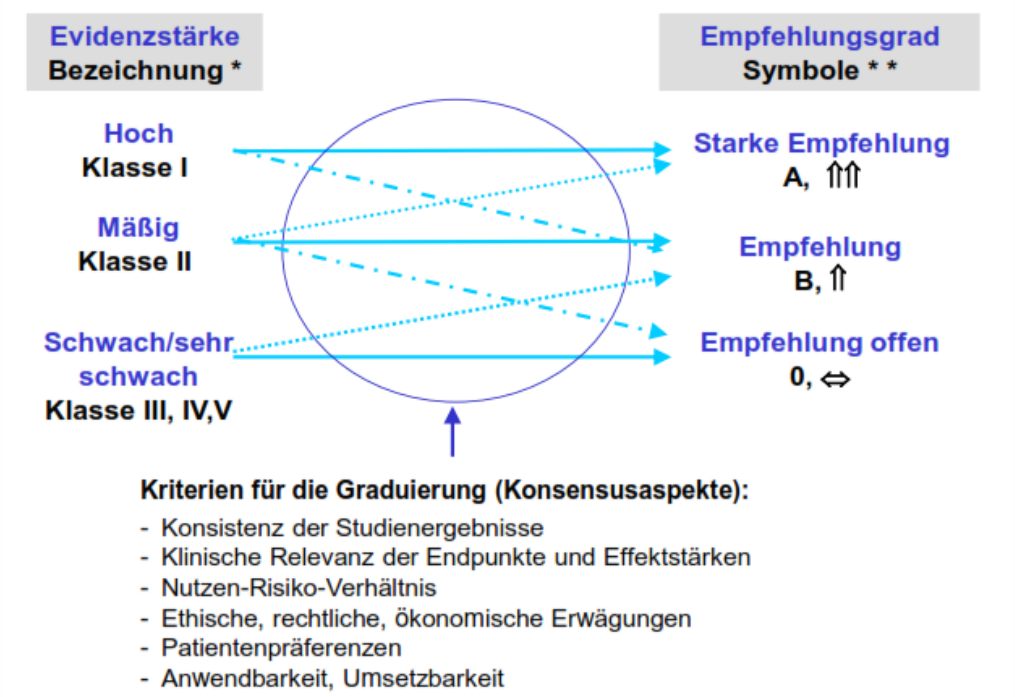
Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95 % der Stimmberechtigten
Konsens	> 75 – 95 % der Stimmberechtigten
Mehrheitliche Zustimmung	> 50 – 75 % der Stimmberechtigten
Dissens	< 50 % der Stimmberechtigten

5.4.4. Festlegung des Empfehlungsgrades

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

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

- Konsistenz der Studienergebnisse, Bsp.: Die Effektschätzer der Studienergebnisse gehen in unterschiedliche Richtungen und zeigen keine einheitliche Tendenz.
- 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.
- Nutzen-Risiko-Verhältnis, Bsp.: Dem nachgewiesenen Nutzen einer Intervention steht ein relevanter Schadensas-pekt gegenüber, der gegen eine uneingeschränkte Empfehlung spricht.
- 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.
- Patientenpräferenzen, Bsp.: Eine Intervention mit nachgewiesenem Nutzen wird nicht stark empfohlen, da sie von den Patienten als belastend oder nicht praktikabel abgelehnt wird.
- 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.



*: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence', schwarz = Evidenzklassifikation bzgl. Einzelstudien, z. B. nach Oxford

**: Empfehlungsgraduierung im Programm für Nationale Versorgungsleitlinien

Abbildung 3: Zusammenhang Evidenzstärke und Empfehlungsgrad (modifiziert AWMF-Regelwerk [17]).

Die Empfehlungen werden nach Möglichkeit analog formuliert:

- Starke Empfehlung: „soll"
- (abgeschwächte) Empfehlung: „sollte"
- Negativ-Empfehlungen: werden entweder rein sprachlich ausgedrückt („nicht"/„kann verzichtet werden") bei gleichen Symbolen oder sprachlich mit zusätzlich nach unten gerichteten Pfeilen
- Offene Empfehlungen: drücken eine Handlungsoption in Unsicherheit aus („kann erwogen werden"/„kann verzichtet werden")

6. Ableitung der Qualitätsindikatoren

Im Rahmen des Leitlinienprogramms Onkologie werden Qualitätsindikatoren in einem standardisierten Prozess aus den Empfehlungen der Leitlinien abgeleitet und aktualisiert. Die detaillierte Beschreibung der Methodik findet sich auf der Homepage des Leitlinienprogramms Onkologie [18].

Die Generierung der Qualitätsindikatoren wurde in folgenden Schritten durchgeführt.

6.1. Bestandsaufnahme

Bei der Suche nach bereits definierten internationalen und nationalen Qualitätsindikatoren außerhalb des OL-Verfahrens erfolgte eine Einschränkung des Suchzeitraums (2009 bis 10.09.2019). Es erfolgte keine Einschränkung der Sprache.

Die Suche wurde in folgenden Quellen durchgeführt:

- Literaturdatenbanken: Medline über https://www.ncbi.nlm.nih.gov/ & Cochrane über http://www.cochranelibrary.com/
- Webseiten von nationalen Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Webseiten von internationalen Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Internetrecherche via www.google.de

Recherchestrategie und -vokabular richten sich nach den Möglichkeiten der jeweiligen Recherchequelle, wurden entsprechend modifiziert und sind im Anhang 10.2 dargelegt.

Die Recherche führte zu keinem nationalen oder internationalen Qualitätsindikator (Kapitel 10.2.3).

6.2. Vorbereitung Anwesenheitstreffen (Erstellung einer Primärliste potenzieller Qualitätsindikatoren)

Soweit möglich wurden im Vorfeld des Anwesenheitstreffens (siehe Kapitel 6.3) aus den starken Empfehlungen der Leitlinie (n=54) potenzielle Indikatoren mit Definition von Zähler und Nenner abgeleitet. Diese Liste und das Dokument mit den Ergebnissen der Recherche zu den internationalen Qualitätsindikatoren wurden den Mitgliedern der Arbeitsgruppe im Vorfeld des Anwesenheitstreffens zugesandt.

6.3. Anwesenheitstreffen (Diskussion und primäre Sichtung)

Das Treffen der Arbeitsgruppe Qualitätsindikatoren (AG QI), die aus Mitgliedern der Leitliniengruppe inklusive Patientenvertreter und je einem Vertreter der klinischen Krebsregister, des Zertifizierungssystems und des OL bestand, fand am 17.10.2019 statt. In dem Treffen wurde den Teilnehmern der Prozessablauf der QI-Erstellung sowie das Bewertungsinstrument des OL erläutert.

Darüber hinaus wurde die unter Kapitel 6.2. Vorbereitung Anwesenheitstreffen generierte Zusammenstellung aus den starken Empfehlungen der Leitlinie diskutiert

und entschieden, ob aus der jeweiligen Empfehlung ein potenzieller Qualitätsindikator generiert werden könne. Folgende Ausschlusskriterien kamen bei diesem ersten Screening zur Anwendung:

Tabelle 10: Gründe für einen Ausschluss der Empfehlung aus der Liste der potenziellen Qualitätsindikatoren

Nr.	1	2	3	4
Begründung	Empfehlung ist nicht operationalisierbar (Messbarkeit nicht gegeben)	Fehlender Hinweis auf Verbesserungspotential	Fehlende Verständlichkeit und/oder großer Erhebungsaufwand in Verhältnis zu Nutzen	Sonstiges (mit Freitexteingabe in Liste der Empfehlungen)

Die Diskussion und primäre Sichtung ergab ein Set von acht potenziellen Qualitätsindikatoren.

6.4. Bewertung

Die acht potenziellen Qualitätsindikatoren wurden mit dem Bewertungsinstrument des Leitlinienprogramms Onkologie durch die stimmberechtigten Mitglieder der AG QI bewertet. Jeweils mit dem unten abgebildeten Bogen erhielten die Bewertenden seitens der Krebsregister und des Zertifizierungssystems der DKG pro Indikatorvorschlag die Informationen zur Datenverfügbarkeit. Angenommen wurden die Qualitätsindikatoren, bei denen mindestens 75 % der Teilnehmer die Kriterien 1, 2, 3 und 5 mit „Ja“ und das Kriterium 4 mit „Nein“ bewertet haben. Die Auswertung dieser Abstimmungen erfolgte durch einen Methodiker, der nicht am Qualitätsindikatoren-Entwicklungsprozess teilgenommen hat.

Tabelle 11: Bewertungsinstrument des Leitlinienprogramms Onkologie

QI-Nr.	Möglicher Qualitätsindikator		Empfehlung	Angaben der S3-Leitlinie im Hinblick auf a) Qualitätsziel und b) Evidenzgrundlage
1.	Z			
	N			

Information zur Datenverfügbarkeit (Stand 10/2019**):**

[dies wird von den Registern und den Zentren ausgefüllt]

Die Erfassung ist seitens der Klinischen Krebsregister über den einheitlichen Onkologischen Basisdatensatz und seiner Module gewährleistet: ja / nein

Die Erfassung ist Teil des Zertifizierungssystems der DKG: ja / nein

Ggf. welche Ergänzungen wären erforderlich?

		Nein	Ja
1.	**Kriterium:** Der Qualitätsindikator erfasst für den Patienten relevante Verbesserungspotentiale.		
2.	**Kriterium:** Der Indikator ist klar und eindeutig definiert.		
3.	**Kriterium:** Der Qualitätsindikator bezieht sich auf einen Versorgungsaspekt, der von den Leistungserbringern beeinflusst werden kann.		
4.	**Kriterium:** Gibt es Risiken zur Fehlsteuerung durch den Indikator, die nicht korrigierbar sind?		
5.	**Kriterium:** Die Daten werden beim Leistungsbringer routinemäßig dokumentiert oder eine zusätzliche Erhebung erfordert einen vertretbaren Aufwand.		

Zusätzlich bestand die Möglichkeit, zu den im Folgenden genannten Kriterien Kommentare abzugeben:

Tabelle 12: Bewertungsinstrument des Leitlinienprogramms Onkologie

	Kommentar
Risikoadjustierung Können spezifische Merkmale von Patienten z. B. Alter, Komorbidität oder Schweregrad der Erkrankung die Ausprägung des QI beeinflussen?	
Implementierungsbarrieren Gibt es Implementierungsbarrieren, die es zu beachten gilt?	

6.5. Telefonkonferenz

Nach der schriftlichen Bewertung erfolgte am 28.10.2018 eine moderierte Telefonkonferenz, in der die Ergebnisse der Bewertung diskutiert wurden. Auf Basis der Bewertungen und der Diskussion wurde ein finales Set von acht Qualitätsindikatoren konsentiert.

Die Primärliste der potenziellen Qualitätsindikatoren inklusive der Ausschlussgründe, die oben genannte Zusammenstellung der internationalen Qualitätsindikatoren und die Ergebnisse der schriftlichen Bewertung sind auf Anfrage im Leitliniensekretariat oder Office des Leitlinienprogramms Onkologie erhältlich.

7. Reviewverfahren und Verabschiedung

Diese Leitlinie sowie der Leitlinienreport wurden nach Fertigstellung vom AWMF-IMWi im 4-Augenprinzip sowie dem Leitlinienprogramm Onkologie (Dr. Follmann, Gregor Wenzel) begutachtet. Im Anschluss wurde die Leitlinie als Konsultationsfassung auf der Internetseite des Leitlinienprogramms Onkologie und der AWMF publiziert und konnte sechs Wochen lang von der Fachöffentlichkeit kommentiert werden. Des Weiteren wurde die Leitlinie den beteiligten Fachgesellschaften zur Kommentierung und formalen Zustimmung vorgelegt.

Die eingegangenen Kommentare wurden gesammelt und durch das Steuerungsteam (Leitlinien-Koordinator, Arbeitsgruppenleitungen, UroEvidence) geprüft und Vorschläge zum Umgang formuliert. Diese wurden anschließend der Leitliniengruppe mit der Möglichkeit zur Stellungnahme vorgelegt.

Alle redaktionellen Änderungsvorschläge wurden umgesetzt. Inhaltliche Änderungen, welche die Empfehlungen betrafen, wurden lediglich bei Empfehlung 4.7 vorgenommen (siehe Kapitel 10.4). Nicht direkt umsetzbare Hinweise können bei der Leitlinieaktualisierung berücksichtigt werden. Die meisten Änderungsvorschläge bezogen sich auf die begriffliche Schärfung im Bereich palliative Behandlung. Ebenso wurde ein Unterkapitel gestrichen, da hier eine inhaltiche Dopplung vorlag (Thema Palliativversorgung).

Die Kommentare zur Konsultationsfassung sowie der Umgang mit den Kommentaren ist im Kapitel 10.4 dargestellt.

8. Unabhängigkeit und Umgang mit Interessenkonflikten

Beim Kick-Off-Treffen im April 2018 wurde beschlossen, dass eine Arbeitsgruppe geschaffen wird, welche die Interessenkonflikte sichten und ein Management zum Umgang von Interessenkonflikte innerhalb der Leitlinie festlegen soll (Mitglieder: Dr. Blödt, Dr. Follmann, Prof. Dr. Hakenberg, Dipl.-Soz. Wiss. T. Langer, Dr. Schmidt). Die Interessenkonflikte der Leitliniengruppenmitglieder wurden mit dem AWMF-Formblatt aus 2018 erhoben. Diese wurden von der Arbeitsgruppe gesichtet und in einer Telefonkonferenz wurden Definitionen vorgeschlagen, auf deren Grundlage das Management erfolgen sollte. Die Interessenerklärungen und der Umgang mit Interessenkonflikten wurden zu Beginn der Konsenskonferenz diskutiert.

Folgende Kriterien zum Management der thematisch relvanten Interessenkonflikte wurden festgehalten: Als GERING wurden industrielle Drittmittelforschung und bezahlte Vorträge bis < 10.000 € pro Jahr und Firma eingeordnet. Als MODERAT wurden die Advisory Board Tätigkeit und bezahlte Gutachtertätigkeit eingeordnet. Als HOCH wurde eingestuft, wenn das Haupteinkommen aus Medizinprodukten-/Pharmaindustrie stammt oder Patent- oder Aktienbesitz vorliegt.

Die Bewertung der Interessenserklärungen vorab und im Rahmen der Konsenskonferenz zeigte, dass keine oder keine relevanten Interessenkonflikte vorlagen, die eine Konsequenz wie Stimmenthaltung erforderlich gemacht hätten. Die Ergebnisse der Interessenkonflikterklärung sind in Kapitel 10.3 dargestellt.

9. Verbreitung und Implementierung

Die Publikation erfolgt primär über die Websites des Leitlinienprogramms Onkologie und der AWMF. Darüber hinaus soll die Leitlinie über Kongresse und Fachzeitschriften bekannt gemacht werden. Eine Vorstellung auf dem Deutschen Krebskongress 2020 und dem Jahreskongress der Deutschen Gesellschaft für Urologie 2020 wird erfolgen. Weitere Kongresspräsentationen werden geplant. Zur Leitlinie wird nach der finalen Publikation eine Laienversion (Patientenleitlinie) erstellt und ebenfalls frei verfügbar sein. Ebenfalls wird nach Publikation der Leitlinien voraussichtlich die Implementierung der Qualitätsindikatoren in das Zertifizierungssystem der DKG und die Krebsregister erfolgen. Es wird zeitgleich zur Langversion, eine Kurzversion der Leitlinie publiziert. Eine englische Publikation zur Disseminierung auf internationaler Ebene ist geplant. Die Leitlinieninhalte sind außerdem über die OL-App abrufbar.

10. Anhang

10.1. Evidenztabellen

10.1.1. Schlüsselfragen der AG Epidemiologie, Stadieneinteilung, Diagnostik

Tabelle 13: „Haben Patienten mit HPV eine bessere Prognose?“

Referenz	Studien-design	Studien-charakteri sitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE
Sand, 2018, Cancer Epi-demiology, Biomarkers & Prevention	Systemati c review with meta-analysis	n= 20 studies 1992-2017 Europe, USA, Brazil, Canada	To examine the association between HPV DNA and p16 status with survival in men diagnosed with penile cancer.	n= 1107 men tested for HPV G1-4 Stages I-IV Tis or Ta Median age ranging from 52-70.9 y	HPV+ n= 437	HPV- n= 670	DSS HR 0.61 (95% CI 0.38-0.98) OS HR 1.04 (95% CI 0.69-1.57) DFS (n= 3 studies, pooled analysis not available) First study: p= 0.552 Second study: HR 0.8 (95% CI 0.1-4.2, p= 0.825) Third study: p= 0.779	This systematic review and meta-analysis suggests that men with HPV DNA or p16-positive penile cancer have a significantly more favorable DSS compared with HPV/ p16-negative. Neither HPV nor p16 status were predictive markers for OS.	Detailed results of quality assessment and detailed search strategy are not reported.	LoE 3 ROBIS: Low

Tabelle 14: „Sollen Patienten mit Peniskarzinom und cN0 eine aktive Überwachung oder ein invasives Staging mit DSNB oder MILND erhalten?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/RoB
Beech, 2015, Canadian Urological Association Journal	Retrospective cohort study	n= 42 Canada 2005-2015 Median follow-up 25 mo (11-48 mo)	To report the first penile cancer experience at a teriary care centre in Canada.	G1-3 T1-3 N0-N3 Mean age 66 y (56-78 y)	**N0** Surveillance n= 16 low risk patholgy patients all other patients reveiced other treatments (n= 25)	**N0** Sentinel node biopsy n= 1 high risk pathology patient	Surveillance group 1/16 progression Sentinel node biopsy Biopsy negative, recurred in nodes 3 y later and died	These findings confirm the poor survival of patients with penile squamous cell carcinoma. Patients with pN0 after ILND had a durable CSS.	Ergebnisse nur für N0 dargestellt	LoE 3 NOS 7/9
Brkovic, 1997, Eur Urol	Retrospective cohort study	n= 51 Switzerland 1968-1994 Median follow-up 8.5 y (22 mo-21 y)	To establish oncological guidelines for the surgical treatment of invasive penile cancer.	T1-T4 N0-N+ Clinical groin status n= 25 cN0-patients Mean age 60.5 y (36-85 y)	**Patients with T1/2 N0** (n= 25) • Surveillance (n= 11)	**Patients with T1/2 N0** (n= 25) • Primary inguinal or ilioinguinal lymphadenectomy(n= 7) • External radiation (n= 7)	Local recurrence rates Lymphadenectomy: 29% Radiation: 42% Surveillance: 36% (no statistical significance)	There was no significant difference related to regional recurrence between surveillance, inguinal radiation and lymphadenectomy for stage N0 tumors.	Ergebnisse nur für N0 dargestellt	LoE 3 NOS 7/9
Hegarty, 2006, BJU Int	Retrospective case serie	n= 100 United Kingdom 2002-2005 Mean follow-up 29 mo (up to 50 mo)	To prospectively assess the outcome of patients treated according to the European Association of Urology guidelines on the management of penile cancer.	pTis pT1-3 N0-2 Median age 62 y (30-86 y)	Surveillance n= 43	Lymphadenectomy n= 58	No man under surveillance developed inguinal lymph node involvement or distant metastasis. 18/25 men with palpable lymph nodes had positive lymph nodes on subsequent histology 6/33 men with	The overall survival of men with penile cancer is high, with a clear benefit for early lymphadenectomy in men with positive nodal disease.		LoE 4 RoB 11/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/RoB
							impalpable nodes and a prophylactic dissection had positive nodal disease 2/12 men with pelvic lymphadenectomy had involved pelvic lymph nodes			
Horenblas, 1993, Journal of Urology	Retrospective cohort study	n= 110 Netherlands 1956-1989 Follow-up at least 2 ½ y	To establish a rational and uniform treatment protocol.	Grade 1-3 N0-N+ Clinical groin status n= 66 cN0-patients Median age 65 y (31-94 y)	**cN0-patients** • Surveillance (n= 57)	**cN0-patients** • Lymph node dissection (n= 4) • Lymph node dissection+ external beam radiation therapy (n= 1) • External beam radiation therapy (n= 4)	**N0** Regional recurrence Surveillance: 5/57 Lymph node dissection: 0/4 Lymph node dissection+ external beam radiation therapy: 1/1 External beam radiation therapy: 1/4 Death from tumor Surveillance: 2/57 Lymph node dissection: 0/4 Lymph node dissection+ external beam radiation therapy: 1/1 External beam radiation therapy: 1/4	We found a clear relationship among T category, grade and the probability of lymph node invasion. Patients with stage T1 tumors and stage T2, grades 1 and 2 tumors presented significantly less often with lymphatic invasion than those with other categories of disease and were less likely to have a regional recurrence after treatment of the primary tumor only. In these categories we recommend surveillance of the regional lymph nodes in patients	Ergebnisse nur für N0 dargestellt.	LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/RoB
								who present with unsuspected nodes.		
Hughes, 2010, European Urology	Retrospective cohort study	n= 117 Netherlands & United Kingdom 1956–2005 Median follow-up 44 mo (6–358 mo)	To establish the risk of lymph node metastasis in G2T1 disease.	G2T1 cN0= 105 cN1= 12 Median age 63 y (32–92 y)	Watchful waiting n= 31 cN0–patients	Surgical staged n= 74 cN0–patients • iLND (n= 10) • DSLNB (n= 64)	LN metastases 0/10 iLND 5/64 DSLNB 4/31 Watchful waiting The overall risk of lymph node metastasis at initial staging or during surveillance was 9% (9:105) in cN0–patients. Deaths 2= Watchful waiting 1= cN1pN+ cohort (surgically staged)	We consider that in cN0 patients with G2T1 penile cancer, the risk of developing metastases during surveillance warrants surgical and potentially curative staging. The morbidity of prophylactic bilateral ILND is too great to justify a detection rate of 9%. Less morbid alternatives such as DSLNB are advisable in G2T1 disease.		LoE 3 NOS 7/9
Kulkarni, 1994, Eur Urol	Prospective three arm cohort study	n= 64 India 1979–1982 Follow-up 60–180 mo	To find the optimum treatment in the latter group (N0, N1–2a), we conducted a propective three–arm study: prophylactic bilateral groin node dissection, prophylactic radiotherapy and surveillance.	N0–2 T1–3 G1–3 Median age 35 y (30–70 y)	Surveillance n= 19	Bilateral groin node dissection n= 27 Radiotherapy n= 18 (N0= 12 patients, N+= 6 patients)	5 y–survival Radiotherapy: 66% Prophylactic bilateral groin node dissection: 74% Surveillance: 63% Relapses Overall: 15% Surveillance: 7/19 Radiotherapy: 2/18 Bilateral groin node dissection: 1/27	Prophylactic radiotherapy and surveillance appear to be of less therapeutic value in our set up because of the large number of patient presenting in a late stage of disease who are likely to be lost to follow–up.		LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/RoB
							Morbidity Bilateral groin node dissection • Flap necrosis (25%) • Prolonged lymphedema (14%) • Mild swelling oft he legs (35%) • Severe lymphoedema (44%) Radiotherapy • Mild/moderate lymphedema (16%) • Skin changes and fibrosis leading to mild stiffness (60%)			
Lont, 2003, Journal of Urology	Retrospectiv e cohort study	n= 162 Netherlands 1956 – 1994 initial surveillance 1994–2001 DSNB Median follow-up Surveillance: 179 mo (60–541 mo) DSNB: 56 mo (16–99 mo)	Evaluation of the clinical outcome of clinically node negative penile carcinoma managed by surveillance or further diagnosed by DSNB with subsequent resection of LN metastases.	T2–3 G1–3 N0 M0 Mean age Surveillance: 64.5 y DSNB: 63.8 y	Initial surveillance n= 85	DSNB n= 68	3 y-DSS Surveillance: 79% (95% CI 70–88%) DSNB: 91% (95% CI 84–98%) p= 0.04 3 y-OS Surveillance: 66% DSNB: 82% **Metastases** Surveillance 24% Median-recurrence-free interval: 6 mo (1–24 mo) DSNB	Early detection of LN metastases by DSNB and subsequent resection in clinically node negative T2–3 penile carcinoma improves survival compared with a policy of surveillance.		LoE 3 NOS 8/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/RoB
							21% DSNB sensitivity for occult metastases: 80%			
Naumann, 2005, Onkologie	Retrospective cohort study	n= 16 Germany 1992–2003 Median follow-up 53.5 mo (9–146 mo)	To evaluate the risk of metastatic disease in patients with pT1 G2 squamous cell carcinoma of the penis.	pT1 G1–3 cN0–cN+ Mean age 61.5 y (36–87 y)	Early ILND n= 10	Surveillance n= 6	Early ILND 1 patient showed inguinal micrometastastes 1 patient with G3-tumor died of metastatic disease Surveillance 3 patients recurrence 2/3 died of metastatic disease	The natural behaviour of pT1 G2 squamous penile carcinoma and its metastatic potential has been underestimated in recent literature. Since morbidity after early ILND has markedly decreased and its superiority over delayed ILND has been shown, we advocate the early modified inguinal lymph node dissection until strong prognostic factors for positive inguinal lymph nodes have been validated.	Ggf. Überschnei-dungen zwischen dem Patienten-kollektiv von Naumann 2006 oder Naumann 2008	LoE 3 NOS 7/9
Naumann, 2006, Urologe	Retrospective cohort study	n= 37 1995–2005 Follow-up 62 mo (22–162 mo)	The aim of this study was to evaluate the metastatic risk of T1 carcinoma and to compare	T1–2 G1–3 N0–N+ 30 Patienten mit unauffälligem inguinalen	Prophylaktische ILND n= 14	Surveillance n= 16	**Prophylaktische ILND** 3/14 metastasierter Befall **Surveillance** 8/16 unauffälliger Verlauf	The metastatic potential of T1 penile carcinoma has been underestimated in the recent literature. Tumor grading has	Ggf. Überschnei-dungen zwischen dem Patienten-kollektiv von	LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/RoB
			it with that of T2 carcinoma.	Lymphknoten-status Mean age 61 y (34-84 y)			7/16 inguinale Metastasen **Surveillance** Falsch-negative Rate cN0: 33% Falsch-positive Rate bei suspektem Lymphknotenstatus: 43% Keiner der G1-Tumore, aber alle der G3-Tumore haben unabhängig vom Tumorstadium inguinale Lymphknotenmetastasen entwickelt. 38% der G2-Tumore zeigten einen syn- oder metachronen Befall der Leistenlymphknoten Nichtmetastasierte Karzinome: 8 T1- und 8 T2-Tumore	substantially stronger impact on the metastatic risk in T1 and T2 penile carcinoma than tumor stage, indicating a surgical lymph node staging starting at the pT1G2 stage.	Naumann 2005 oder Naumann 2008	
Naumann, 2008, BJUI	Retrospective cohort study	n= 20 1996-2005 Mean follow-up 31.4 mo (11-83 mo)	To evaluate the metastatic risk of pT1 G2 squamous cell carcinoma of the penis.	pT1 G2 cN0-cN+ Clinical groin status n= 16 cN0-patients n= 4 cN+-patients	**cN0** Surveillance n= 11	**cN0** ILND n= 4 DSNB n= 1	Nodal status of clinical cN0-patients Surveillance: 6 pN+ (1 N1, 3 N2, 2 N3) 5 cN0 Clinical groin status had no significant effect on	As the metastatic risk of pT1 G2 penile SCC was 50% in this series of patients, and 44% in those with an initially negative groin,	Ggf. Überschnei-dungen zwischen dem Patienten-kollektiv von Naumann 2005 oder	LoE 3 NOS 4/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/RoB
				Mean age 65 y (39–84 y)			pathological nodal status (p= 0.582) Metastatic risk Overall: 50% Clinical cN0 group: 44% Recurrence and death Surgical staging group: No recurrence or death Surveillance group: died because of • Toxicity of neoadjuvant chemotherapy (n= 1) • Progressive metastatic disease despite extensive surgical treatment and subsequent adjuvant chemotherapy (n= 2) Side effects Surgical staging group: • Mild wound dehiscence (n= 2) • Lymphocele (n= 1) • Complexe wound healing failure (n= 2) • Lymphorrhoea and recurrent lymphoceles (n= 2)	surgical staging of inguinal lymph nodes is recommended in patients with pT1 G2 penile squamous cell carcinoma.	Naumann 2006 Ergebnisse nur für cN0 dargestellt	
Neto, 2011, Annals of	Systematic review with	n= 10 2003–2009	To evaluate the accuracy of	n= 519 patients	Wait-and-see program	DSNB n= 4 studies	**Wait-and-see program** Sensitivity	The use of dynamic sentinel lymph node	Überschnei-dung: 2	LoE 3

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/RoB
Surgical Oncology	meta-analysis	Follow-up wait-and-see varied from 18 to 37 mo	DSNB in penile cancer.	n= 993 analyzed groins T1-4 G1-3	n= 4 studies		87.9% (80.6-93.2%) Specificity 100% (99.4-100%) Positive likelihood ratio 277.35 (68.36-1125.2) Negative likelihood ratio 0.13 (0.08-0.21) False-negative rate 3.5%	biopsy to detect lymph node metastasis appears to be justified.	Studien sind ebenfalls im Zou-Review enthalten	ROBIS low
Protzel, 2009, Eur Urol	Collaborative review	n= 22 1966-2008	To analyse the existing published data on the surgical management of inguinal nodes in penile cancer regarding morbidity and survival.	Penile carcinoma patients	Surveillance	Surgical lymph node staging • Modified inguinal lymphadenectomy • Sentinel node biopsy • Video endoscopic lymphadenectomy • Radical inguinal lymphadenectomy	**Surveillance** (n= 4) • EAU strongly recommend this approach in patients with superficial and well-differentiated tumours: pTis, pTa, pT1G1, and pT1G2 with superficial growth and without vascular invasion • 3-y-DSS (pT/pT3 N0): 91% DSNB vs. 79% surveillance • higher risk of recurrence in patients undergoing surveillance management **Modified inguinal lymphadenectomy** (n= 11)	Surveillance strategies are no longer generally recommended except in well-informed, low-risk patients. In all other patients with clinically unaffected nodes, lymphadenectomy is a diagnostic staging procedure. DSNB seems adequate for staging but should be routinely performed only in specialised centres. A modified bilateral lymphadenectomy should be performed for all cases with		LoE 4 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/RoB
							• Morbidity of this procedure is reduced compared with radical lymphadenectomy • Reducing the field of dissection increases the possibility of false-negative cases • Major complications: 14% (n= 5) • Minor complications: 6.8-36.8%) **DSNB** (n= 10) • initially reported a high false-negative rate of 17-22% • modifications of the technique: false-negative rate of 4.8% • Major complications: 1.3% (n= 5) • Minor complications: 6.6-39% (n= 5)	pT1G2 or more invasive stages with clinically unaffected nodes.		
Ravi, 1993, Jpn J Clin Oncol	Three arms retrospectiv e cohort study	n= 423 India 1962-1984 Follow-up minimum of five years or until their death	Clarify the role of prophylactic lymphadenecto my, expectant management and selective node biopsies in these patients.	T2-4 Mean age 44 y (23-82 y)	Observation n= 258	Prophylactic lymphadenect omy n= 113 Inguinal biopsy n= 52	5 y-DSS Lymphadenectomy: 94% Observations: 93% Inguinal biopsy: 85% 5 y-DSS with node positive patients Lymphadenectomy: 100% Observation: 76%	Neither prophylactic lymphadenectomy nor inguinal biopsy are justified in these patients. Close observation of the groin nodal status would be appropriate.		LoE 3 NOS 6/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/RoB
							Morbidity Lymphadenectomy Wound breakdown: 61% Wound infections: 18% Lymphedema: 25%			
Zou, 2016, International Urology & Nephrology	Systematic review with meta-analysis	n= 27 studies up to 2016	To assess the accuracy of the procedure in penile cancer with cN0 disease and explore its relative factors on the basis of current evidences.	3545= DSNB prodecures cN0	Follow-up n= 21 studies	DSNB	**Pooled sensitivity for follow-up studies** Minimum follow-up time less than 2 y 0.88 (0.83-0.92) p= 0.0021 Minimum follow-up time 2 y or more 0.86 (0.80-0.91) p= 0.0277	Radiocolloid-based DSNB is a promising staging modality to detect regional inguinal micrometastasis and should be strictly limited to penile cancer without clinically obviously positive inguinal lymph node.	Überschneidung: 2 Studien sind ebenfalls im Neto-Review enthalten	LoE 3 ROBIS low

Tabelle 15: „Soll bei Patienten mit Peniskarzinom und cN0 die Diagnose durch eine dynamische Sentinel Lymphknotenbiopsie oder durch eine modifizierte inguinale Lymphadenektomie erfolgen?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/ RoB
Ferreira, 2008, Int Braz J Urol	Prospective two arms comparative diagnostic study	n= 18 2000-2005 Mean follow-up 28.3 mo (8-58 mo)	To evaluate the effectiveness of the sentinel lymph node biopsy using lymphoscintigraphy in patients with penile cancer and at least one negative inguinal region.	Patients had penile cancer and at least one clinically negative in-guinal region Mean age 57.7 y (44-81 y)	Dynamic sentinel lymph node biopsy	Modified radical lymphadenectomy	**DSNB** Sensitivity 66% Specificity 79.3% False-negative rate 0%	Sentinel lymph node biopsy is a feasible method of assessing the presence of regional metastasis in patients with penile cancer and clinically negative inguinal regions.		LoE 3 QUADAS-2: low
Hughes, 2010, European Urology	Retrospective cohort study	n= 117 Netherlands & United Kingdom 1956-2005 Median follow-up 44 mo (6-358 mo)	To establish the risk of lymph node metastasis in G2T1 disease.	G2T1 cN0= 105 cN1= 12 Median age 63 y (32–92 y)	Watchful waiting n= 31 cN0-patients	Surgical staged n= 74 cN0-patients • iLND (n= 10) • DSLNB (n= 64)	LN metastases 0/10 ILND 5/64 DSLNB 4/31 Watchful waiting The overall risk of lymph node metastasis at initial staging or during surveillance was 9% (9:105) in cN0-patients. Deaths 2= Watchful waiting 1= cN1pN+ cohort (surgically staged)	We consider that in cN0 patients with G2T1 penile cancer, the risk of developing metastases during surveillance warrants surgical and potentially curative staging. The morbidity of prophylactic bilateral ILND is too great to justify a detection rate of 9%. Less morbid alternatives such as DSLNB are advisable in G2T1 disease.		LoE 3 NOS 7/9
Jakobsen, 2016, BJUI	Prospective two arms comparative diagnostic study	n= 222 patients Denmark 200-2010 Median follow-up 6.6 y (5-10 y)	To estimate the diagnostic accuracy of sentinel lymph node biopsy in patients with penile cancer and assess sentinel lymph node biopsy complications in a national	G1-3 T1-4 Median age 64.3 y (58.1-70.7 y)	Sentinel lymph node biopsy n= 409 cN0 groins	ILND (of affected groins)	**Sentinel node biopsy** False-negative groins 8/409 False-negative rate/patient 13.3% (7.0–25.4%) False-negative rate/groin 10.8% (5.6–20.8%) Sensitivity per groin	Penile cancer sentinel lymph node biopdy with a close follow-up stages lymph node involvement reliably and has few complications in a national multicentre setting. Inguinal lymph node dissection was avoided in 76% of patients.	ILND only of affected groins (66 groins positive at sentinel lymph node biopsy + 8 false negative groins during follow-up)	LoE 3 QUADAS-2: high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/ RoB
			multicentre setting.				89.2% (95 CI 79.8-95.2%) Sensitivity per patient 86.7% (95 CI 75.4-94.1%) Negative predictive value/patient 95.3% (90.9–97.9%) Negative predictive value/groin 97.7% (95.5–99.0%) Complications (Clavien-Dindo grade I–IIIa) 28/222 patients (13%)			
Kathiresan, 2016, Indian Journal of Urology	Prospective two arms comparative diagnostic study	n= 20 (40 groins) India 2010-2012 Median follow-up 26 mo (7-42 mo)	Evaluate the role of DSLNB in patients diagnosed with carcinoma penis and clinically N0 disease using superficial inguinal dissection as the standard staging modality.	T1-3 G1-3 N0 Median age 52.5 y (23-75 y)	DSNB	Modified superficial inguinal dissection	**DSNB** Sensitivity 90% Specificity 100% Accuracy 97.5% False-negative rate 10%	DSLNB is a relatively accurate and safe technique to identify the involved nodes in patients with cN0 groins in carcinoma penis and helps to reduce the morbidity involved in staging inguinal dissection without compromising oncological outcomes.		LoE 3 Quadas 2: low
Neto, 2011, Annals of Surgical Oncology	Systematic review with meta-analysis	n= 10 2003-2009 Follow-up varied from 18 to 37 mo	To evaluate the accuracy of DSNB in penile cancer.	n= 519 patients n= 993 analyzed groins T1-4 G1-3	DSNB n= 10	Inguinal lymph node dissection n= 5 studies radical ILND n= 2 studies modified ILND	**DSNB** Sensitivity 77.1% (62.7-88%) Specificity 97.3% (93.7-99.1) Positive likelihood ratio 32.4 (11.7-89.6) Negative likelihood ratio 0.25 (0.16-0.39)	The use of dynamic sentinel lymph node biopsy to detect lymph node metastasis appears to be justified.	Überschnei-dung: 5 Studien (n= 75 Patienten) sind ebenfalls im Zou-Review enthalten	LoE 3 ROBIS: low

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/ RoB
							False-negative rate ILND: 3.1%			
Perdona, 2005, Urology	Retrospective two arms comparative diagnostic study	n= 70 1994-2000 radical inguinal lymphadenectomy 2001-2004 DSNB Median follow-up Radical inguinal lymphadenectomy: 98 mo (52-115 mo) DSNB: 27 mo (6-46 mo)	To evaluate the reliability and morbidity of dynamic sentinel node biopsy compared with radical inguinal lymphadenectomy in the treatment of selected patients with squamous cell penile carcinoma.	Patients with clinically node-negative Stage pT2-pT3 penile cancer G1-3 Mean age Radical inguinal lymphadenectomy: 63 y DSNB: 67 y	DSNB n= 22	Radical inguinal lymphadenectomy n= 48	**DSNB** Negative predictive value 89% Sensitivity 90% False-negative rate 11% Metastasen noted in 36.4% (8/22). All classified at high risk. 13/22 DSNB findings negative (6 at high risk, 7 at intermediate risk) **Lympadenectomy** 39.6% nodal disease (19/48) **Complications** Total early complications DSNB: 13.6% Lympadenectomy: 47.5% p< 0.001 Total late complications DSNB: 0 Lympadenectomy: 37.5% DSNB Seroma formation: 2 Wound infection: 1 Lympadenectomy Skin necrosis: 4	Dynamic sentinel node biopsy is a minimally invasive technique that is easy to perform, with similar results to those of radical inguinal lymphadenectomy, but lower morbidity. This procedure offers the possibility of less-extensive surgery for clinically node-negative penile carcinoma.	Als LoE 3 klassifiziert, da unklar ist, ob die Patienten konsekutiv einge-schlossen worden.	LoE 3 QUADAS-2: low

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/ RoB
							Seroma formation: 6 Lymphorrea: 7 Wound infection: 4 Skin necrosis requiring skin graft: 2 Lymphocele: 2 Deep venous thrombosis: 4 Leg edema: 10			
Perdona, 2006, Journal of Surgical Oncology	Prospective two arms comparative diagnostic study	n= 17 2001-2003	We report our initial experience with a relatively new technique, the so-called ''dynamic sentinel node biopsy'', in patients with penile cancer.	T2-3 Grade I-III bilateral, clinically node negative penile cancer Mean age 67 y (49-77 y)	DSNB	Inguinal node dissection	**DSNB** Negative predictive value 100% Sensitivity 88% Complications DSNB: • Wound infection (n= 1) • Lymphocele/ seroma (n= 1) Inguinal lymph node dissection: • Major complications (skin edge necrosis, lymphedema, deep venous thrombosis) (n= 4) • Minor complications (lymphocele/ seroma, wound dihescence) (n= 1)	We believe that dynamic sentinel node biopsy is a minimally invasive procedure that can be easily performed. The goal is to offer the possibility of less extensive surgery for selected low risk patients.		LoE 3 QUADAS-2: low
Protzel, 2009, Eur Urol	Collaborative review	n= 22 1966-2008	To analyse the existing published data on the surgical management of inguinal nodes in penile cancer regarding morbidity and survival.	Penile carcinoma patients	Surveillance	Surgical lymph node staging • Modified inguinal lymphadenectomy • Sentinel node biopsy • Video endoscopic lymphadenectomy	**Modified inguinal lymphadenectomy** (n= 11) • Morbidity of this procedure is reduced compared with radical lymphadenectomy • Reducing the field of dissection increases the possibility of false-negative cases	DSNB seems adequate for staging but should be routinely performed only in specialised centres. A modified bilateral lymphadenectomy should be performed for all cases with pT1G2 or more invasive stages with		LoE 4 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/ RoB
						• Radical inguinal lymphadenectomy	• Major complications: 14% (n= 5) • Minor complications: 6.8-36.8%) **DSNB** (n= 10) • initially reported a high false-negative rate of 17–22% • modifications of the technique: false-negative rate of 4.8% • Major complications: 1.3% (n= 5) • Minor complications: 6.6-39% (n= 5)	clinically unaffected nodes.		
Ravi, 1993, Jpn J Clin Oncol	Three arms retrospective cohort study	n= 423 India 1962-1984 Follow-up minimum of five years or until their death	Clarify the role of prophylactic lymphadenectomy, expectant management and selective node biopsies in these patients.	T2-4 Mean age 44 y (23-82 y)	Inguinal biopsy (including sentinel node area) n= 52	Prophylactic lymphadenectomy n= 113 Observation n= 258	5 y-DSS Lymphadenectomy: 94% Observations: 93% Inguinal biopsy: 85% 5 y-DSS with node positive patients Lymphadenectomy: 100 % Observation: 76% **Morbidity** Lymphadenectomy Wound breakdown: 61% Wound infections: 18% Lymphedema: 25%	Neither prophylactic lymphadenectomy nor inguinal biopsy are justified in these patients. Close observation of the groin nodal status would be appropriate.	Studienkollektiv von 1962-1984 unklar, ob Intervention passend.	LoE 3 NOS 6/9
Spiess, 2007, Journal of Urology	Prospective two arms comparative diagnostic study	n= 31 Median follow-up 3 y (4.7 mo-12.3 y)	To assess the sensitivity of preoperative lymphoscintigraphy and dynamic sentinel node biopsy for staging the inguinal region of patients with penile cancer and no palpable	T1-3 clinical N0 stage Median age 55 y (33-87 y)	DSNB	Superficial lymph node dissection	Sensitivity of preoperative lymphoscintigraphy drainage 86% Sensitivity of dynamic sentinel node biopsy per groin 71%	In our experience preoperative lymphoscintigraphy and dynamic sentinel node biopsy as currently performed remain insufficient for detecting occult inguinal disease. Superficial lymph node dissection remains the gold standard for	Als LoE 3 klassifiziert, da unklar ist, ob die Patienten konsekutiv ein-geschlossen worden.	LoE 3 QUADAS-2: high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/ RoB
			inguinal adenopathy.				2 false-negative results obtained by using dynamic sentinel node biopsy with blue dye plus radiotracer	detecting inguinal microscopic metastasis in select patients.		
Zou, 2016, International Urology & Nephrology	Systematic review with meta-analysis	n= 27 studies (18 full-texts, 7 conference abstracts, 2 English abstracts of non-English articles) up to 2016	To assess the accuracy of the procedure in penile cancer with cN0 disease and explore its relative factors on the basis of current evidences.	3545= DSNB prodecures cN0	DSNB	ILND n= 6 studies	**ILND** Pooled sensitivity 0.95 (95% CI 0.82-0.99) p= 0.4574	Radiocolloid-based DSNB is a promising staging modality to detect regional inguinal micrometastasis and should be strictly limited to penile cancer without clinically obviously positive inguinal lymph node.	Überschnei-dung: 5 Studien (n= 75 patients) sind ebenfalls im Neto-Review enthalten	LoE 3 ROBIS: low
Indirekte Evidenz										
Horenblas, 1993, Journal of Urology	Retrospectiv e cohort study	n= 110 Netherlands 1956-1989 Follow-up at least 2 ½ y	To establish a rational and uniform treatment protocol.	Grade 1-3 N0-N+ Clinical groin status n= 66 cN0-patients Median age 65 y (31-94 y)	**cN0-patients** • Surveillance (n= 57)	**cN0-patients** • Lymph node dissection (n= 4) • Lymph node dissection+ external beam radiation therapy (n= 1) • External beam radiation therapy (n= 4)	**N0** Regional recurrence Surveillance: 5/57 Lymph node dissection: 0/4 Lymph node dissection+ external beam radiation therapy: 1/1 External beam radiation therapy: 1/4 Death from tumor Surveillance: 2/57 Lymph node dissection: 0/4 Lymph node dissection+ external beam radiation therapy: 1/1 External beam radiation therapy: 1/4	We found a clear relationship among T category, grade and the probability of lymph node invasion. Patients with stage T1 tumors and stage T2, grades 1 and 2 tumors presented significantly less often with lymphatic invasion than those with other categories of disease and were less likely to have a regional recurrence after treatment of the primary tumor only. In these categories we recommend surveillance of the regional lymph nodes in patients who present with unsuspected nodes.	Ergebnisse nur für N0 dargestellt	LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/ RoB
Hungerhuber, 2006, World J Urol	Case serie	n= 15 patients 2001-2004 Follow-up 18 mo (2-42 mo)	To determine if the remaining lymphatic tissue in the groin is indeed negative for tumor in case of a negative sentinel node, in particular in patients with clinically suspicious nodes.	n= 30 inguinal areas T1-3 G1-3 9/15 clinically suspicious nodes 11/15 MRT/CT positive Mean age 56.5 y (43-80 y) In all patients lymph nodes with high radioactivity uptake were detected bilaterally	DSNB n= 15	Afterwards: Standard radical groin dissection n= 15	10/30 inguinal areas histopathologically positive lymph nodes **DSNB** 4/10 positive lymph nodes were positive for tumor 6/10 lymph node metastases were found despite a negative sentinel node (patients had clinically palpable lymph nodes) If no palpable nodes were present dynamic sentinel biopsy detected the positive nodes.	The current study showed that dynamic sentinel node biopsy in patients with clinically suspicious lymph nodes is of low value for detection of lymphatic spread in penile cancer. Therefore the gold standard in these patients remains the radical groin dissection.	Indirekte Evidenz, da "clinically suspicious nodes"	LoE 3 QUADAS-2: high
Lont, 2003, Journal of Urology	Retrospective cohort study	n= 162 Netherlands 1956 – 1994 initial surveillance 1994-2001 DSNB Median follow-up Surveillance: 179 mo (60-541 mo) DSNB: 56 mo (16-99 mo)	Evaluation of the clinical outcome of clinically node negative penile carcinoma managed by surveillance or further diagnosed by DSNB with subsequent resection of LN metastases.	T2–3 G1-3 N0 M0 Mean age Surveillance: 64.5 y DSNB: 63.8 y	Initial surveillance n= 85	DSNB n= 68	3 y-DSS Surveillance: 79% (95% CI 70-88%) DSNB: 91% (95% CI 84-98%) p= 0.04 3 y-OS Surveillance: 66% DSNB: 82% **Metastases** Surveillance 24% Median-recurrence-free interval: 6 mo (1-24 mo) DSNB 21% DSNB sensitivity for occult metastases: 80%	Early detection of LN metastases by DSNB and subsequent resection in clinically node negative T2–3 penile carcinoma improves survival compared with a policy of surveillance.		LoE 3 NOS 8/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/ RoB
Naumann, 2005, Onkologie	Retrospective cohort study	n= 16 Germany 1992-2003 Median follow-up 53.5 mo (9-146 mo)	To evaluate the risk of metastatic disease in patients with pT1 G2 squamous cell carcinoma of the penis.	pT1 G1-3 cN0-cN+ Mean age 61.5 y (36-87)	Early ILND n= 10	Surveillance n= 6	Early ILND 1 patient showed inguinal micrometastastes 1 patient with G3-tumor died of metastatic disease Surveillance 3 patients recurrence 2/3 died of metastatic disease	The natural behaviour of pT1 G2 squamous penile carcinoma and its metastatic potential has been underestimated in recent literature. Since morbidity after early ILND has markedly decreased and its superiority over delayed ILND has been shown, we advocate the early modified inguinal lymph node dissection until strong prognostic factors for positive inguinal lymph nodes have been validated.	Ggf. Überschnei-dungen zwischen dem Patienten-kollektiv von Naumann 2006 oder Naumann 2008	LoE 3 NOS 7/9
Naumann, 2006, Urologe	Retrospective cohort study	n= 37 1995-2005 Follow-up 62 mo (22-162 mo)	The aim of this study was to evaluate the metastatic risk of T1 carcinoma and to compare it with that of T2 carcinoma.	T1-2 G1-3 N0-N+ 30 Patienten mit unauffälligem inguinalen Lymphknoten-status Mean age 61 y (34-84 y)	Prophylaktische ILND n= 14	Surveillance n= 16	**Prophylaktische ILND** 3/14 metastasierter Befall **Surveillance** 8/16 unauffälliger Verlauf 7/16 inguinale Metastasen **Surveillance** Falsch-negative Rate cN0: 33% Falsch-positive Rate bei suspektem Lymphknotenstatus: 43% Keiner der G1-Tumore, aber alle der G3-Tumore haben unabhängig vom Tumorstadium inguinale	The metastatic potential of T1 penile carcinoma has been underestimated in the recent literature. Tumor grading has a substantially stronger impact on the metastatic risk in T1 and T2 penile carcinoma than tumor stage, indicating a surgical lymph node staging starting at the pT1G2 stage.	Ggf. Überschnei-dungen zwischen dem Patienten-kollektiv von Naumann 2005 oder Naumann 2008	LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/ RoB
							Lymphknotenmetastasen entwickelt. 38% der G2-Tumore zeigten einen syn- oder metachronen Befall der Leistenlymphknoten Nichtmetastasierte Karzinome: 8 T1- und 8 T2-Tumore			
Naumann, 2008, BJU International	Retrospective cohort study	n= 20 1996-2005 Mean follow-up 31.4 mo (11-83 mo)	To evaluate the metastatic risk of pT1 G2 squamous cell carcinoma of the penis.	pT1 G2 cN0-cN+ Clinical groin status n= 16 cN0-patients n= 4 cN+-patients Mean age 65 y (39-84 y)	**cN0** Surveillance n= 11	**cN0** ILND n= 4 DSNB n= 1	Nodal status of clinical cN0-patients Surveillance: 6 pN+ (1 N1, 3 N2, 2 N3) 5 cN0 Clinical groin status had no significant effect on pathological nodal status (p= 0.582) Metastatic risk Overall: 50% Clinical cN0 group: 44% Recurrence and death Surgical staging group: No recurrence or death Surveillance group: died because of • Toxicity of neoadjuvant chemotherapy (n= 1) • Progressive metastatic disease despite extensive surgical treatment and subsequent adjuvant chemotherapy (n= 2)	As the metastatic risk of pT1 G2 penile SCC was 50% in this series of patients, and 44% in those with an initially negative groin, surgical staging of inguinal lymph nodes is recommended in patients with pT1 G2 penile squamous cell carcinoma.	Ggf. Überschneidungen zwischen dem Patientenkollektiv von Naumann 2005 oder Naumann 2006 Ergebnisse nur für cN0 dargestellt.	LoE 3 NOS 4/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerungen	Bemer-kungen	LoE/ RoB
							Side effects Surgical staging group: • Mild wound dehiscence (n= 2) • Lymphocele (n= 1) • Complexe wound healing failure (n= 2) • Lymphorrhoea and recurrent lymphoceles (n= 2)			

Tabelle 16: „Ist die inguinale Feinnadelbiopsie der Lymphknoten oder die inguinale Feinnadelbiopsie und DSNB oder modifizierte inguinale Lymphadenektomie geeigneter zur Diagnose von Patienten mit Peniskarzinom und cN0?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerungen	Bemerk-ungen	LoE/ RoB
Crawshaw, 2009, The British Journal of Radiology	Prospective diagnostic study	n= 64 patients 2004-2006 Median follow-up 11 mo (6-28 mo)	To assess the utility of sentinel lymph node lymphoscintigraphy and ultrasound-guided fine needle aspiration cytology in patients with penile carcinoma.	stage T1 Grade 2 or greater clinically N0 Mean age 59 y (26-88 y) Group A (n= 31): primary tumour in situ at the time of SNB Group B (n= 33): primary tumour excised or partly excised	SLNL with ultrasound-guided FNAC n= 38 inguinal basins (If the ultrasound showed any abnormal nodes, FNAC was performed)	SLNL without ultrasound-guided FNAC n= 82 inguinal basins	**Ultrasound sound alone vs. sentinel lymph node excision biopsy** Sensitivity 74% Specificity 77% Positive predictive values 37% Negative predictive values 94% **FNAC** • 8/8 positive for malignancy confirmed at surgery (4 group A, 4 group B) • 24/24 negative for malignancy confirmed at SNB (12 group A, 12 group B) 2 patients were initially node-negative by SNB and positive by FNAC. Subsequent histological reexamination shows micro-metastases.	The combination of sentinel lymph node excision biopsy and groin ultrasonography, with or without FNAC, identifies accurately those with occult nodal metastases. Ultrasonography alone is not adequate as a staging technique, and SNB alone might miss between 5% and 10% of metastases.		LoE 3 QUADAS-2: high
Djajadiningrat, 2014, Journal of Urology	Retrospective diagnostic study	n= 247 patients Mean follow-up 45 mo (24-74 mo)	To asess the role of ultrasound guided FNAC for detecting lymph node metastases of the groin during followup.	1360 groins pTis pT1-3 Median age 69 y (37-91 y)	Ultrasound and FNAC n= 217 suspicious (In nodes suspicious on US immediate FNAC is	Ultrasound alone n= 1143 not suspicious	**Ultrasound guided FNAC** Sensitivity 87.3% (95% CI 78.9-95.6%) Specificity 99.9% (95 CI % 99.8-100%) Positive predictive value 98% (95% CI 93.9-100%)	Although inguinal recurrence manifests clinically in most patients, ultrasound guided fine needle aspiration cytology detected 80% of metastatic disease in patients with nonpalpable disease.		LoE 3 QUADAS-2: high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerungen	Bemerk-ungen	LoE/ RoB
					performed.)		Negative predictive value 99.5% (95% CI 99.1-99.9%)	Therefore, it has great value for detecting lymph node metastases during followup.		
Kroon, 2005, BJU International	Diagnostic study	n= 43 patients 2001-2004 Median follow-up 18 mo (2-36 mo)	To assess the accuracy of ultrasonography -guided FNAC for detecting occult lymph node metastases in patients with squamous cell carcinoma of the penis.	83 clinically node negative inguinal regions Mean age 63 y (34-82 y)	FNAC n= 34 suspicious groins (Groins considered to be suspicious by US were aspirated.)	DSNB n= 74 groins Inguinal lymph node dissection n= 23 groins	Sensitivity FNAC 39% Specificity FNAC 100% There were no more false-negative DSNBs after introducing ultrasonography-guided-guided FNAC for screening before DSNB.	Ultrasonography-guided FNAC can be used as the initial investigation in clinically node-negative groins. If tumour is confirmed then therapeutic inguinal lymph node dissection can be earlier and fewer DSNBs are required.		LoE 3 QUADAS-2: high
Lam, 2013, Eur Urol	Prospective three arm diagnostic study	n= 264 patients United Kingdom 2004-2010 Median follow-up 57 mo (21-94 mo)	To determine the long-term outcome of patients undergoing DSNB and ultrasound scan FNAC in our cohort of newly diagnosed cN0 squamous cell carcinoma of the penis patients, as well as to analyse any variation in sensitivity of the procedure.	cN0 ≥T1G2 Mean age 66.5 y	USS with/without FNAC n= 39 patients DSNB with USS+ FNAC n= 63 patients (FNAC is performed if abnormal nodes are detected.)	DSNB n= 63 patients	Technical sensitivity (per inguinal basin) USS with/without FNAC: 65% DSNB: 92% DSNB with USS+ FNAC: 95% Clinical sensitivity (per patient) USS with/without FNAC: 64% DSNB: 91% DSNB with USS+ FNAC: 94%	DSNB in combination with ultrasound scan has excellent performance characteristics to stage patients with cN0 squamous cell carcinoma of the penis patients, with a 5% false-negative rate per node basin and a 6% false-negative rate per patient.		LoE 3 QUADAS-2: high
Scappini, 1986, Cancer	Two arms comparative diagnostic study	n= 29 Germany Follow-up 19-65 mo	Delineates the role of aspiration biopsy cytology in the staging of patients with penile carcinoma.	T1-T4 N0-N+ Age: 39-81 y	Aspiration biopsy cytology	Lymphadenect omy and histologic examination	Identifying true stage of the disease 100% 1 node were not detected	Aspiration biopsy cytology should be considered the procedure of choice and an alternative to surgery in the preliminary detection of metastatic nodal involvement, thereby sparing some patients	Als LoE 3 klassifizier t, da unklar ist, ob die Patienten konsekuti v eingeschlo	LoE 3 Quadas 2: unclear

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerungen	Bemerk-ungen	LoE/ RoB
								the risk of unnecessary removal of disease-free ileo-inguinal nodes.	ssen worden.	
Zou, 2016, International Urology & Nephrology	Systematic review with meta-analysis	n= 27 studies up to 2016	To assess the accuracy of the procedure in penile cancer with cN0 disease and explore its relative factors on the basis of current evidences.	3545= DSNB prodecures cN0	DSNB n= 27	ILND n= 6 studies Surveillance n= 21 studies	**cN0** Sensitivity DSNB without ultrasonic scan ± FNAC 84% (95% CI 75–91%) Sensitivity cN0 determined by negative USS∓ FNAC 87% (95% CI 82–91%) Sensitivity impalpable groin and palpable groin with negative USS∓ FNAC 92% (95% CI 85–96%)	Radiocolloid-based DSNB is a promising staging modality to detect inguinal micrometastasis in penile cancer without clinically positive inguinal lymph node. Preoperative ultrasonic scan ± FNAC and surgical exploration are effective supplements to exclude potentially clinical involvement, and immunohistochemistry makes the diagnosis of occult metastasis in sentinel lymph node more likely.		LoE 3 ROBIS: low

Tabelle 17: „Soll die Diagnose bei Patienten mit Peniskarzinom mit oder ohne cN+ durch ein PET/CT vor invasiver Lymphknotendiagnostik (DSNB/MILND) erfolgen?“

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerung	Bemer-kungen	LoE/ RoB
Graafland, 2009, European Urology	Retrospective two arms comparative diagnostic study	n= 18 2005-2008 Median follow-up 7 mo (1-31 mo)	To evaluate the diagnostic accuracy of 18F-FDG-PET/CT scanning in determining further metastatic spread in patients with tumour-positive inguinal nodes.	n= 12 unilateral tumour-positive inguinal nodes n= 6 bilateral disease Median age 62 y (46-73 y)	18F-FDG-PET/CT before Inguinal node dissection and DSNB	Inguinal node dissection and DSNB	**18F-FDG-PET/CT** Sensitivity 91% (95% CI 58–100%) Specificity 100% (95% CI 80–100%) Diagnostic accuracy 96% (95% 82-100%) Positive predictive value 100% (95% CI 69–100%) Negative predictive value 94% (95% CI 73–100%)	PET/CT scanning appears promising for detecting pelvic lymph node metastases with great accuracy, and it identifies distant metastases in penile carcinoma patients with inguinal lymph node involvement.		LoE 3 QUADAS 2: High
Jakobsen, 2016, BJU International	Prospective two arms comparative diagnostic study	n= 129 patients (254 groins) Denmark Centre 1 from 2010 Centre 2 from 2013 Median follow-up 23.3 mo (14-35 mo)	To estimate the diagnostic accuracy of SNB combined with preoperative 18F-FDG PET/CT for inguinal lymph node evaluation in patients with invasive penile squamous cell carcinoma with no clinical evidence of inguinal metastases at two tertiary centres with complete clinical follow-up.	cN0 T1-T3 G1-G3 Median age 68.1 y (61-73 y)	18F-FDG PET/CT before SNB	SNB	**Combined FDG PET/CT-SNB** Sensitivity 94.4% (95% CI 81–99%) per groin False negative rate 5.6% (95% CI 1–19%) per groin Complications grade I-III 11.6%	The combination of FDG PET/CT and SNB seems to be a promising diagnostic approach.		LoE 3 QUADAS 2: Low
Leitje, 2009, BJU International	Prospective two arms comparative diagnostic study	n= 24 patients (42 groins) 2006-2007 Median follow-up	To evaluate the role of hybrid PET/CT for assessing the inguinal node status in cN0-	cN0 T1-2 Median age 61 y (46-82 y)	18F-FDG PET/CT before DSNB	DSNB	**18F-FDG-PET/CT** Specificity 92% Positive predictive value	The role of PET/CT in evaluating the groins of patients with cN0 penile cancer appears to be limited, due to its low sensitivity.		LoE 3 QUADAS 2: Low

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerung	Bemer-kungen	LoE/ RoB
		15.4 mo (11-28 mo)	groins in patients with penile carcinoma.				25% Negative predictive value 89%	Only one of the five tumour positive groins was identified. Surgical staging is therefore still the method of choice in the managing patients with cN0 penile cancer.		
O'Brien, 2017, Journal of Urology	Systematic review	n= 65 studies 1980-2016	Provide an objective update of the recent trends in the management of penile squamous cell carcinoma, and inguinal and pelvic lymph node metastases.		PET/CT before DSNB or radical inguinal lymphadenectomy	DSNB or radical inguinal lymphadenectomy	**PET/CT** Sensitivity • 90%-100% (study with small number of patients, Schlenker 2012) Pooled sensitivity cN+ patients: 96%, cN0 patients: 57% (Meta-analysis, Sadeghi 2012) 68 node negative patients: 94% sensitivity and % false-negative rate (Jakobsen, 2016) Limitations Poor diagnostic accuracy in patients presenting with an impalpable groin	Current data suggest that dynamic sentinel lymph node biopsy provides excellent sensitivity and specificity for detecting lymph node metastases.		LoE 3 ROBIS: high
Rosevear, 2012, Urologic Oncology	Retrospective case report	n= 3 patients Follow-up of at least 6 mo	Review a single institutional experience of 18F-FDG PET/CT imaging of penile squamous cell carcinoma to assess for accuracy and potential impact on clinical management.	No patient received chemotherapy or radiation before the 18F-FDG PET/CT or surgery	18F-FDG PET/CT subsequent inguinal lymph node dissection	Subsequent inguinal lymphadenectomy	**Frist patient** BMI> 30, clinically node negative, 18F-FDG PET/CT showed inflammation.Histologic examination showed a positive 2 cm right inguinal metastatic node. **Second patient** 18F-FDG PET/CT showed a suspicious 1 cm left inguinal node.	18F-FDG PET/CT has shown initial promise in the staging of penile squamous cell carcinoma. Our review shows that false negative studies occur at alarmingly high rates, and 18F-FDG PET/CT is poor in detection of micro-metastasis.		LoE 4 RoB 6/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerung	Bemer-kungen	LoE/ RoB
							Histologically, the suspicious lymph node was positive for penile squamous cell carcinoma as second positive 2 cm lymph node not identified on preoperative 18F-FDG PET/CT. Clinical exam of this patient was negative. **Third patient** 18F-FDG PET/CT and clinically negative but subsequently developed a palpable lymph node approximately 1 month later, which was suspicious on repeat 18F-FDG PET/CT and positive for penile squamous cell carcinoma on histological examination.			
Sadeghi, 2012, Clinical Nuclear Medicine	Systematic review with meta-analysis	n= 7 studies 2009-2011	To evaluate the accuracy of 18F-FDG PET/CT for inguinal lymph node staging in penile squamous cell carcinoma and possible influential factors.	cN0-cN+ Age range 43-81 y	18F-FDG PET/CT before inguinal lymph node dissection or sentinel node biopsy	Inguinal lymph node dissection (or sentinel node biopsy)	**PET/CT** **Overall** Pooled sensitivity 0.809 (95% CI 0.695-0.894) Pooled specificity 0.924 (95% CI 0.868-0.962) Negative likelihood ratio 0.29 (95% CI 0.094-0.878) Positive likelihood ratio	18F-FDG PET/CT imaging has relatively low sensitivity (especially in cN0 patients) for detection of inguinal lymph node involvement in penile cancer patients, which does not justify its routine use. Patients with clinically palpable lymph nodes may benefit from 18F-FDG PET/CT because the sensitivity in this subgroup of patients is high.		LoE 3 ROBIS: low

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerung	Bemer-kungen	LoE/ RoB
							6.461 (95% CI 2.088-19.993) Diagnostic odds ratio 27.619 (95% CI 5.295-144.07) **cN0** Pooled sensitivity 0.565 (95% CI 0.345-0.768) Pooled specificity 0.859 (95% CI 0.756-0.930) Negative likelihood ratio 0.615 (95% CI 0.279-1.356) Positive likelihood ratio 3.029 (95% CI 1.510-6.078) Diagnostic odds ratio 7.532 (95% CI 2.040-27.808) **cN+** Pooled sensitivity 0.964 (95% CI 0.817-0.999) Pooled specificity 1 (95% CI 0.839-1) Negative likelihood ratio 0.101 (95% CI 0.027-0.378) Positive likelihood ratio			

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerung	Bemer-kungen	LoE/ RoB
							16.96 (95% CI 2.54-113.242) Diagnostic odds ratio 229.2 (95% CI 17.743-2960.9)			
Scher, 2005, Journal of Nuclear Medicine	Prospective two arms comparative diagnostic study	n= 13 patients Follow-up of at least 6 mo	To investigate the pattern of 18F-FDG uptake in the primary malignancy and its metastases and to determine the diagnostic value of 18F-FDG PET/CT in the staging and restaging of penile cancer.	Mean age 64 y (25–81 y) n= 3 follow-up after resection or partial amputation of the penis secondary to penile cancer n= 1 suspected lymph node metastases	18F-FDG PET/CT before biopsy or surgery	Histopathologi c findings obtained at biopsy or during surgery	**18F-FDG PET/CT** Sensitivity detection primary lesions 75% Specificity detection primary lesions 75% Sensitivity per-patient 80% Specificity per-patient 100% Sensitivity per node 100% Specificity per node 89%	18F-FDG PET/CT showed high sensitivity and specificity in the staging and restaging of penile cancer.		LoE 3 Quadas 2: Low
Schlenker, 2012, Urologic Oncology	Prospective two arms comparative diagnostic study	n= 35 patients 2003-2008 Mean follow-up 48.4 mo (31-68 mo)	To prospectively analyze the diagnostic accuracy of 18F-FDG-PET/CT-scan in the assessment of inguinal lymph node involvement in patients with invasive penile carcinoma.	pT1-pT3 N0-N3 G1-3 Mean age 60.6 y (36-80 y)	18F-FDG-PET/CT-scan n= 35	Radical inguinal lymph node dissection n= 22 Physical examination & 1 additional second imaging procedure n= 13	**18F-FDG-PET/CT-scan** Sensitivity 88.2% Specificity 98.1% Positive predictive value 93.8% Negative predictive value 96.3%	18F-FDG-PET/CT is a promising staging tool in assessing the inguinal lymph node involvement of patients with penile carcinoma.		LoE 3 QUADAS-2: High
Souillac, 2012, J Urol	Prospective two arms comparative diagnostic study	n= 30 France 2005-2010	We prospectively evaluated 18F-FDG PET-CT to assess inguinal lymph node status, the	n= 22 cN0 n= 8 cN+ Mean age	18F-FDG PET-CT before inguinal	Inguinal Lymphadenect omy	**Overall PET-CT** Sensitivity 91% Specificity	18F-FDG PET-CT is a useful staging examination for invasive penile cancer. It confirms inguinal		LoE 3 QUADAS-2: Unclear

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerung	Bemer-kungen	LoE/ RoB
			main prognostic factor in invasive squamous cell carcinoma of the penis.	69 y (41-94 y)	lymphadene ctomy		89.8% Positive predictive value 66.7% Negative predictive value 97.8% **cN0 PET-CT** Sensitivity 75% Specificity 87.5% Positive predictive value 37.5% Negative predictive value 97.2% **cN+ PET-CT** Sensitivity 100% Specificity 100% Positive predictive value 100% Negative predictive value 100%	lymph node invasion and can detect subclinical inguinal lymph node invasion.		
Zhang, 2016, Oncotarget	Prospective two arms comparative diagnostic study	n= 48 China 2009-2012	This study investigated the value of 18F-FDG-PET/CT imaging in the management of patients with	ECOG performance status: 0-2 Median age	Before biopsy or serial CT/MRI • FDG-PET/CT (n= 39)	Biopsy n= 19 Follow-up scan n= 23	**Overall FDG-PET/CT** Sensitivity 82% Specificity 93%	FDG-PET/CT has good sensitivity and specificity in the detection of metastatic penile cancer. It provides more		LoE 3 QUADAS-2: High

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerung	Bemer-kungen	LoE/ RoB
			advanced penile cancer.	56.6 y (29-77 y)	MRI (n= 9)		**FDG-PET/CT vs. follow-up scan** Sensitivity 75% Specificity 91% **FDG-PET/CT vs. biopsy** Sensitivity 83% Specificity 100% FDG-PET/CT detected more malignant diseases than CT/MRI (33%) **Organ-specific lesion-based analysis of suspicious FDG-PET/CT uptake** Lymph node Sensitivity: 93% (95% CI 72-99%) Specificity: 85% (95% CI 60-94%) Lung Sensitivity: 86% (95% CI 62-95%) Specificity: 84% (95% CI 62-98%) Bone Sensitivity: 90% (95% CI 65-100%) Specificity: 100% (95% CI 66-100%) Liver	diagnostic information to enhance clinical management than CT/MRI.		

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Interventio n	Kontrolle	Ergebnisse	Schlussfolgerung	Bemer-kungen	LoE/ RoB
							Sensitivity: 56% (95% CI 28-90%) Specificity: 100% (95% CI 51-100%) Soft tissue Sensitivity: 100% (95% CI 45-100%) Specificity: 80% (95% CI 44-100%) Adrenal Sensitivity: 100% (95% CI 34-100%) Specificity: 100% (95% CI 45-100%) Kidney Sensitivity: 100% (95% CI 21-100%) Specificity: 100% (95% CI 28-100%)			

Tabelle 18: „Inwiefern hat die Bestimmung von p53, p16, Ki-67 im Präparat eine prognostische Aussagekraft?“

Referenz	Studien -design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
p16									
Bethune, 2012, Oncology	Retrospe ctive cohort study	n= 43 patients Canada 1997-2009 Mean follow-up 3.9 y ± 3.3 y	To analyze, in a clinicopathologic correlation study, a small population of primarily white men with invasive squamous cell carcinoma of the penis for potential	G1-3 T1-3 N0-2 Mean age 63y ± 12.5 y	Immunohistochemistry • positive, strong cytoplasmic and nuclear staining in >30% of tumor cells • equivocal, strong staining in <30% of tumor cells or weak to moderate staining in >30% of tumor cells	**Lack of p16INK4a** OS HR 0.54 (95% CI 0.31-0.93) p= 0.026 CSS HR 0.53 (95% CI 0.26-1.06) p= 0.073	Our results have shown that 53% of the invasive penile squamous cell carcinoma cases in this population were associated with human papillomavirus, using p16INK4a as a surrogate marker of human papillomavirus infection.		LoE 3 QUIPS: moderate

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			prognostic predictors.		• negative, weak to moderate staining in <5% of tumor cells or no staining 2 investigators		These patients had a statistically significant survival advantage, independent of other prognostic factors.		
Bezerra, 2015, Human Pathology	Retrospective cohort study	n= 53 patients USA 1985-2013	To evaluate the correlation of p16INK4a expression and high-risk human papillomavirus with clinicopathological features and outcome in a cohort of patients with penile squamous cell carcinomas.	pTa-4 pN0-3 Stage 0-IV Median age 65 y (38-93 y)	Immunohistochemistry • Negative p16INK4a expression: Complete absence of p16INK4a staining or only focal positivity • Positive p16INK4a expression: Strong and diffuse nuclear and cytoplasmic p16INK4a positivity in most tumor cells 2 uropathologists	**p16INK4a overexpression** Tumor recurrence OR 1.43 (95% CI 0.15-13.02) p= 0.99 Tumor progression OR 1.54 (95% CI 0.46-5.20) p= 0.47 Overall mortality OR 0.80 (95% CI 0.25-2.48) p= 0.85 Cancer-specific mortality OR 0.61 (95% CI 0.11-2.66) p= 0.57 Overexpression of p16INK4a was found in 23 cases (44%) showing a significant association with histologic subtype (p= 0.01) and lymphovascular invasion (p= 0.015).	p16INK4a overexpression was significantly associated with histologic subtype and presence of lymphovascular invasion.		LoE 3 QUIPS: moderate
Cubilla, 2012, American Journal of Surgical Pathology	Case serie	n= 12 Spain, Paraguay, Mexico, USA Median follow-up (n= 11) 48 mo	To characterizing their clinical, morphologic, differential, and outcome features in detail, as well as their association with specific HPV genotypes.	n= 5 noninvasive tumors 11/12 HPV 9/12 HPV-16 12/12 overexpression of p16ink4a Median age	Immunochemistry	7/12 alive with no evidence of metastatic disease 3/12 died from other causes 1/12 died postoperatively 1/12 recurrence	The overall prognosis was excellent. Deeply invasive tumors were associated with regional nodal metastasis indicating a potential for tumor-related death.		LoE 4 QUIPS: high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
				79 y (35-90 y)					
Ferrandiz-Pulido, 2013, JAAD	Retrospective cohort study	n= 82 patients Spain 1987-2010	We sought to provide novel data about the prevalence of HPV in a large series of penile intraepithelial neoplasia and invasive penile squamous cell carcinoma, correlating the results with the histologic subtype, p16INK4a immunostaining, and prognosis.	n= 69 invasive penile squamous cell carcinoma n= 13 penile intraepithelial neoplasia Median age 69 y (35-96 y)	Immunohistochemical expression Cut-off point H-Score for positive cases: 50 2 independent observers	**Tumor stage** (p> 0.05) Tumor stage I p16 positive: 29% p16 negative: 71% Tumor stage >1 p16 positive: 36% p16 negative: 64% **Lymph node metastases** (p> 0.05) Lymph node metastases p16 positive: 26% p16 negative: 74% No lymph node metastases p16 positive: 37.5% p16 negative: 62.5% **Died of disease** (p> 0.05) Died p16 positive: 18% p16 negative: 82% Alive p16 positive: 37.5% p16 negative: 62.5%	p16INK4a overexpression had a trend toward higher tumoral stages, development of lymph node metastases, disease-related death, or a combination of these, without reaching statistical significance.		LoE 3 QUIPS: moderate
Gunia, 2012, Journal of Urology	Retrospective cohort study	n= 92 patients Germany 1993-2010 Median follow-up 32 mo (6-66 mo)	To assess the prognostic role of p16INK4a expression in penile cancer with respect to cancer specific survival.	pT1a-pT3 pN0-N+ G1-G3 n= 38 P16INKa negative n= 54 P16INKa positive Mean age 67.2 ± 12.1 y	Immunohistochemistry Negative: • 0: absent p16INK4a expression in all epithelial cells, pattern Positive: • 1: spotty, patchy and discontinuous immunostaining in	2 y-CSS Negative P16INKa: 73% Positive P16INKa: 95% 5 y-CSS Negative P16INKa: 57% Positive P16INKa: 85% p= 0.011 Prognostic parameter (multivariate analysis)	Results show that p16INK4a seems to be a prognostic parameter for primary invasive penile cancer with excellent interobserver reproducibility.		LoE 3 QUIPS: moderate

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
					suprabasal epithelial cells, pattern • 2: comparatively more extensive but discontinuous suprabasal expression and pattern • 3: full-thickness, continuous immunostaining in all epithelial cells except in the parakeratotic layer two pathologist	Model 2 incorporating dichotomized p16INK4a: HR 0.25 (95% CI 0.08-0.079) p= 0.018 Model 3 incorporating nondichotomized p16INK4a: HR 0.44 (95% CI 0.23–0.84) p= 0.013			
McDaniel, 2015, Cancer Res	Retrospe ctive cohort study	n= 43 patients USA 2005-2013	We performed comprehensive, targeted next-generation sequencing to identify relevant somatic genomic alterations.	n= 60 fixed tumor samples	Immunohistochemistry two pathologist	**p16 expression** Event-free survival log-rank test p= 0.03	Positive p16 expression was significantly associated with longer event-free survival.	Only result of p16 are extracted here.	LoE 3 QUIPS: high
Sand, 2018, Cancer Epi-demioloy, Biomarkers & Prevention	Systemat ic review with meta-analysis	n= 20 studies Europe, United States, Brazil, Canada 1992-2017	To examine the association between HPV DNA and p16 status with survival in men diagnosed with penile cancer.	n= 646 men tested for p16 expression G1-4 Stages I-IV Tis or Ta Median age ranging from 52-70.9 y	s. Bemerkungen	DSS p16-positive vs. p16-negative HR 0.45 (95% CI 0.30-0.69) OS p16-positive vs. p16-negative HR 0.88 (95% CI 0.49-1.59)	This systematic review and meta-analysis suggests that men with HPV DNA or p16-positive penile cancer have a significantly more favorable DSS compared with HPV/ p16-negative. Neither HPV nor p16 status were predictive markers for OS.	Many different definitions of p16 over-expressio n were applied in the studies included, which we were unable to take into account in the analysis.	LoE 3 ROBIS: Low
Steinestel, 2015, BMC Cancer	Retrospe ctive cohort study	n= 58 patient tissues Germany 1995-2012 Follow-up	We analysed penile squamous cell carcinoma tissue samples for expression of p16INK4a and	pTis-pT4 N0-N+ M0-M+ HPV+ 29.3%	Immunohistochemistry one pathologist	p16INK4a positivity and histologic differentiation grade (G1-2 vs. G3-4) were not significantly	Our results confirm intense nuclear positivity for p16INK4a, rather than histologic subtype, as a good predictor for presence of HR-HPV DNA in penile squamous		LoE 3 QUIPS: high

Referenz	Studien -design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		up to 204 mo	presence of HPV DNA and correlated the results with tumour- and patient-specific characteristics as well as CSS.	Positive immunostaining for p16INK4a: 58.6% (wide variety in p16INK4a expression patterns) Mean age 64.5 y (31-93 y)		associated with CSS (p= 0.49 and p= 0.15). Histopathologic tumour grade was not significantly associated with presence of HPV DNA. Expression of p16INK4a and presence of HR-HPV DNA, but not histologic grade, were inversely associated with penile squamous cell carcinoma tumour invasion (p= 0.01, p= 0.03, and p= 0.71). For verified nodal involvement or distant metastasis, there was no significant association with HPV status, p16INK4a positivity or grade of differentiation of the primary tumour (p = 0.22, p = 0.25, and p = 0.41). **Test statistics for basaloid histologic subtype and p16INK4a immunostaining to predict HR-HPV positivity** Basaloid histologic subtype ppV: 40% Sensitivity: 11% Specificity: 95%	cell carcinoma. HR-HPV / p16INK4a positivity, independent of histological tumour grade, indicates a less aggressive local behaviour; however, its value as an independent prognostic indicator remains to be determined. Since local invasion can be judged without p16INK4a/HPV-detection on microscopic evaluation, our study argues against routine testing in the setting of penile squamous cell carcinoma.		

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
						Any positivity for p16INK4a ppV: 53% Sensitivity: 100% Specificity: 60% Intense nuclear p16INK4a staining ppV: 75% Sensitivity: 100% Specificity: 85%			
Tang, 2015, Journal of Urology	Retrospective cohort study	n= 119 patients USA 1998-2013 Median follow-up 30 mo	We evaluated high risk human papillomavirus status with respect to various clinical features, including recurrence and OS, among others.	Tis-T2+ N1-3 P16ink4a over expression: 49.5% Median age 64 y (33-88 y)	Immunohistochemistry Over expression: Diffuse, continuous and strong nuclear and cytoplasmic staining of the neoplastic cells on both tissue cores Negative for P16ink4a over expression: Discontinuous, focal and weak staining as well as the absence of staining one genitourinary pathologist	Recurrence after primary resection and positive lymph node dissection (multivariate analysis) P16 negative: OR 1.0 (reference) P16 positive: OR 0.066 (95% CI 0.007-0.556) p= 0.012 P16ink4a expression vs. • Overall recurrence (p= 0.0383) • Recurrence after positive lymph nodes at diagnosis (p= 0.0018) • Tumor stage (p= 0.518) • Histological grade (p= 0.225) • Lymphovascular invasion (p= 0.388) • OS (p= 0.156) • Lymph node metastasis (p= 0.748) • DSS (p= 0.605)	These data suggest that P16ink4a/high risk human papillomavirus status is associated with recurrence, especially in patients with positive lymph nodes at diagnosis. Patients with P16ink4a negative penile cancer, particularly those with lymph node metastases, may warrant closer observation after surgery.		LoE 3 QUIPS: low
Zargar-Shoshtari,	Retrospective	n= 57 patient tissues	To assess clinical utility of p16ink4a	T1-4 N0-N3	Immunohistochemistry	**p16 positive vs. negative**	p53 and p16 status showed clinical utility in predicting		LoE 3

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
2016, Clinical Geni-tourinary Cancer	cohort study	USA 1999-2013 Median follow-up 22 mo	and p53 staining in a contemporary cohort of patients treated for penile cancer.	Median age 60 y (53-73 y)	Overexpression of p16ink4a: continuous strong nuclear and cytoplasmic staining of the entire carcinoma one specialized genitourinary pathologist	OS HR 0.33 (95% CI 0.13-0.85) p= 0.02 CSS HR 0.36 (95% CI 0.13-0.99) p= 0.05	nodal disease as well as survival.		QUIPS: moderate
Zhang, 2018, BioMed Research Inter-national	Systemat ic review with meta-analysis	n= 5 studies Canada, Germany, Spain, USA Mean or median follow-up 1.8-3.9 y	We performed this meta-analysis to clarify the prognostic value of P16INK4a for penile squamous cell carcinoma.	n= 323 cases Mean or median age 60-69 y	Immunohistochemistry different cut-off values for P16INK4a expression	Pooled outcome of five eligible studies on the association between P16INK4a positive expression and penile cancer prognosis HR: 0.45 (95% CI 0.3-0.67) p< 0.001	P16INK4a positive expression is independently associated with improved CSS for patients with penile squamous cell carcinoma.		LoE 3 ROBIS: low
p53									
Bethune, 2012, Oncology	Retrospe ctive cohort study	n= 43 patients Canada 1997-2009 Mean follow-up 3.9 y ± 3.3 y	To analyze, in a clinicopathologic correlation study, a small population of primarily white men with invasive squamous cell carcinoma of the penis for potential prognostic predictors.	G1-3 T1-3 N0-2 Mean age 63y ± 12.5 y	Immunohistochemistry Positive: >5% of the tumor cells showed nuclear staining Negative: Nuclear staining of <5% 2 investigators	p53-positive staining 9/17 have distant metastasis 5/17 died of disease Without p53-positive staining 5/26 have distant metastasis 4/26 died of disease p53 status did not show significant differences in survival in our analysis.	p53 and Ki-67, were not independent predictors of outcome in our analysis		LoE 3 QUIPS: moderate
Ferrandiz-Pulido, 2013, Journal of Urology	Retrospe ctive cohort study	n= 67 patients Spanish Mediterranean population 1987-2010 Median follow-up	To assess a possible role for mTOR signaling pathway activation as a potential predictive biomarker of	pT1-3 G1-4 Median age 70 y (40-96 y)	Immunohistochemical staining Over expression was considered when the H-score of each marker was greater than the median H-score of that marker for all invasive penile squamous cell cancer.	p53 over expression was associated with disease related death on Kaplan-Meier plots (p <0.001). Over expression of p53 was significantly	Over expression of p53 is a prognostic factor of poor survival in penile squamous cell carcinoma cases.		LoE 3 QUIPS: moderate

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		27 mo (1-247 mo)	outcome and a therapeutic target for penile cancer.		2 investigators	associated with lymph node disease. p53 correlated with a poor outcome, including recurrence, metastasis or disease specific death.			
Gunia, 2012, Journal of Clinical Pathology	Retrospe ctive cohort study	n= 110 patients 1993-2010 Median follow-up 32 mo (6-66 mo)	To evaluate the role of p53, p21 and cyclin D1 expression in patients with penile cancer.	pT1a-pT3 pN0-N+ G1-G3 n= 62 p53 negative n= 30 p53 positive Mean age 67.2 ± 12.1 y	Immunostaining Negative absent or weak nuclear expression restricted to basal cells Positive at least moderately strong nuclear expression in basal and suprabasal cells two independent pathologists	5 y-CSS Negative p53: 84% Positive p53: 51% p= 0.003 p53 expression vs. no p53 expression (univariate analysis) HR 4.22 (1.50-11.91) p= 0.007	In patients with penile cancer, the expression of p53 in the primary tumour specimen can be reproducibly assessed and is negatively associated with cancer specific survival.		LoE 3 QUIPS: low
Liu, 2013, World Journal of Urology	Retrospe ctive cohort study	n= 146 patients China 1998-2011 Follow-up 42 mo (13-108 mo)	To evaluate factors in penile squamous cell carcinoma predictive of pelvic lymph node metastasis and survival.	Grade I-III T1-4 Mean age 51 y (24-82 y)	The immunoreactivity of p53 staining was graded as positive when at least 20% of cells were stained in the nucleus. reviewed by pathologists	**Prognostic factors for pelvic lymph node metastasis** Immunoreactivity of p53 (weak vs. strong) OR/HR: 22.431 (95% CI 3.928–128.111) p<0.001 **Multivariate Cox regression analysis of prognostic factors for overall survival** Immunoreactivity of p53 (weak vs. strong) OR: 5.997 (95% CI 1.615–22.275) p= 0.007	Strong p53 expression, vascular or lymphatic invasion of the primary tumor, involvement of more than two inguinal lymph nodes and 30 % or greater lymph node density were independent prognostic factors for pelvic lymph node metastasis.		LoE 3 QUIPS: low
Lopes, 2002, Journal of Urology	Retrospe ctive cohort study	n= 82 tisusses Brazil 1953-1992	To evaluate the prognostic value of immunohistochem	T2-4 N0-3 Grade I-II	Immunohistochemical testing p53 staining was graded as positive when at least 20% of	**OS** 5 y- OS Positive p53: 30.2% Negative p53: 65.2%	Immunoreactivity of p53 is an independent factor for lymph node metastasis. The		LoE 3 QUIPS: moderate

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		Mean follow-up 88.7 mo (0.1-453 mo)	ical p53 staining in the primary tumor.	n= 57 HPV positive n= 34 p53 positive Mean age 52 y (27-77 y)	cells were stained in the nucleus. 1 pathologist	10 y- OS Positive p53: 26.4% Negative p53: 54.6% (p= 0.009) HPV and p53 neg 5 y-survival: 65.3% 10 y-surival: 54.5% p= 0.017 HPV and p53 pos 5 y-survival: 12.5% 10 y-survival: 12.5% (p= 0.017)	association of positive p53 with positive HPV DNA was related to a worse prognosis.		
Martins, 2002, Journal of Urology	Retrospective cohort study	n= 50 tissues Brazil 1978-1995 Median follow-up 9 y (5-22 y)	To examine p53 protein and proliferating cell nuclear antigen immunoexpression as prognostic factors to the outcome of squamous cell carcinoma of the penis in 50 patients.	pT1-4 G1-2 N0-N+ Median age 59 y (35-88 y)	Immunohistochemistry two investigators	**Cause-specific death** Overall p53 labeling index <10% vs. p53 labeling index >10% p< 0.0001 (95% CI 3.7778-2.220) N0 p53 labeling index <10% vs. p53 labeling index >10% p= 0.003 (95% CI 2.174-51.01) **Multivariate analysis of p53 in relation to nodal metastasis** Overall p= 0.002 (95% CI 3.820-493.9) N0 p= 0.02 (95% CI 1.600-2.66.436)	Over expression of p53 was associated with regional lymphatic spread, recurrence and cause specific death.		LoE 3 QUIPS: moderate
McDaniel, 2015, Cancer Res	Retrospective cohort study	n= 43 patients USA 2005-2013	We performed comprehensive, targeted next-	n= 60 fixed tumor samples	Immunohistochemistry two pathologist	Event-free survival TP53 expression p= 0.01	TP53 expression (p= 0.01) was significantly associated with shorter event-free survival.		LoE 3 QUIPS: high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			generation sequencing to identify relevant somatic genomic alterations.						
Necci, 2016, Clinical Geni-tourinary Cancer	Retrospe ctive cohort study	n= 21 patients 2004-2012 Follow-up 52 mo (47.6-100.4 mo)	To identify whether some prognostic factors might be found to guide further research in the field of adjuvant therapy for penile squamous cell carcinoma.	N1-3 pN0, N2, N3 n= 11 p53 positive n= 8 p53 negative Median age 63 y (55-69 y) all patients received TPF chemotherapy	Immunohistochemistry Positive percentage of positive nuclei ≥90% Negative percentage of positive nuclei <90% two pathologist	p53 positive vs. negative (multivariate analysis) DFS: 3.76 (95% CI 0.79-17.96 p= 0.096) OS: HR 4.29 (95% CI 0.89-20.57) p=0.068 Median DFS for p53-expressing patients 8.9 mo (5.9-22.7 mo) Median OS for p53-expressing patients 17.2 mo (12.8-22.7 mo) Kaplan-Meier curves for DFS and OS according to the immunohistochemistry expression of was statistically significant for OS (DFS: p= 051, OS: p= 0.037)	In patients who had received adjuvant TPF for node-positive penile squamous cell carcinoma, p53 immunohistochemistry expression seemed to be associated with a poorer outcome, and further study is warranted in larger data sets to confirm these findings.		LoE 3 QUIPS: moderate
Rocha, 2012, Human Pathology	Cohort study	n= 297 patients Brazil 1980-2009	To examine the immunohistochem ical expression of p53 and murine double minute 2 in 297 cases of penile carcinoma, to determine whether protein alterations were associated to gene and chromosomal	G1-3 Average age 55 y	Immunohistochemistry two evaluator	Survival analysis positive p53 (multivariate analysis) HR 1.83 (95% CI 1.11-3.04) p= 0.024 OS p53 negative vs. p53 positive p= 0.0013 Patients who died of disease expressed higher levels of p53	We demonstrated the prognostic value of evaluating p53 in penile cancer because survival declined in patients with p53-positive tumors.		LoE 3 QUIPS: moderate

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			numeric alterations or to gene mutations.			compared with patients with no evidence of disease (p= 0.0030).			
Zargar-Shoshtari, 2016, Clinical Geni-tourinary Cancer	Retrospe ctive cohort study	n= 57 patients USA 1999-2013 Median follow-up 22 mo	To assess clinical utility of p16ink4a and p53 staining in a contemporary cohort of patients treated for penile cancer.	T1-4 N0-N3 n= 31 p53 negative Median age 60 y (53-73 y)	Immunohistochemistry Negative p53 expression no staining or weak staining of ≤5% (ie, H score ≤5) Significant p53 expression expression of moderate intensity at 50% or greater or any strong p53 expression (H score of ≥150) one specialized genitourinary pathologist	p16 status had a more pronounced protective influence on CSS in p53-negative (H < 5) patients (p16 positive vs. p16 negative; median, not reached; p= 0.07), than in p53-positive patients. (median, not reached; p= 0.89).	p53 and p16 status showed clinical utility in predicting nodal disease as well as survival.		LoE 3 QUIPS: moderate
Zhu, 2007, BJUI	Cohort study	n= 73 patients China 1990-2005	To evaluate the prognostic significance of p53, Ki-67, epithelial cadherin and matrix metalloproteinase-9 in primary penile cancer.	T1 - ≥T2 G1- ≥ 2 33% high expression of p53 45% high expression of KI-67 Median age 55 y (27-75 y)	Immunohistochemical staining p53 expression was categorized as high when >20% of the tumour nuclei were stained two observers	Multivariate analysis showed that the expression of p53 (RR 5.31, 95% CI 1.477–19.086) was the only independent predictor of CSS. CSS (multivariate analysis) p53 low vs. high: p= 0.016 3 y-CSS (multivariate analysis) p53 low vs. high: p= 0.011	The expression of p53 is an independent predictor of CSS in Chinese patients with penile cancer. In stage T1 tumours, p53 staining is an important variable determining the prognosis and treatment outcome.		LoE 3 QUIPS: moderate
Zhu, 2010, Journal of Urology	Retrospe ctive cohort study	n= 110 patients China 1990-2008	To develop and evaluate a nomogram to stratify patients who are suitable candidates for further treatment.	T1-3 G1-3 N0-3 n= 78 weak p53 expression	Immunohistochemical staining Cutoff: strong p53 expression was 20%	Multivariate analysis of clinicopathological factors to predict inguinal lymph node metastasis p53 expression strong (reference p53 weak): OR 3.22 (95% CI 0.96-10.86) p= 0.058	Lymphovascular invasion was the only independent lymph node metastasis prognostic factor in clinically lymph node negative cases of penile cancer. p53 expression failed to achieve statistical significance.		LoE 3 QUIPS: moderate

Referenz	Studien -design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
				n= 32 strong p53 expression					
Ki-67									
Berdjis, 2005, BJU Int	Retrospe ctive case serie	n= 44 patients Germany 1992-2003 Mean follow-up 25.6 mo	To investigated the relationship of Ki-67 labelling in primary penile carcinoma with relevant clinicopathological variables and survival of the patients.	G1-3 T1-2 N0-1 Mean age 61.4 y (35-89 y)	Immunohistochemistry The mean Ki-67 labelling index was defined as the percentage of total tumour cell nuclei that were Ki-67-positive. two observer	Mean Ki-67 labelling index: 40.5 (6.4-93%) High mean Ki-67 LI was significantly inversely correlated with tumour differentiation ($p<$ 0.005). There was a tendency for high Ki-67 expression with advanced local tumour stage (p= 0.07), nodal metastasis (p= 0.07) and disease progression (p= 0.06).	The Ki-67 labelling index is correlated with tumour grade in penile cancer, and may indicate a greater risk of nodal metastasis.		LoE 4 QUIPS: high
Bethune, 2012, Oncology	Retrospe ctive cohort study	n= 43 patients Canada 1997-2009 Mean follow-up 3.9 y ± 3.3 y	To analyze, in a clinicopathologic correlation study, a small population of primarily white men with invasive squamous cell carcinoma of the penis for potential prognostic predictors.	G1-3 T1-3 N0-2 Mean age 63y ± 12.5 y	Immunohistochemistry Positive: >10% of the tumor cells showed nuclear staining Negative: Nuclear staining of <10% 2 investigators	No significant differences or trends were identified with respect to outcome and Ki-67 status, most likely because of the overwhelming percentage of Ki-67 positive cases (36 [86%] of 43).	p53 and Ki-67, were not independent predictors of outcome in our analysis.		LoE 3 QUIPS: moderate
Kayes, 2009, Clinical Cancer Research	Retrospe ctive cohort study	n= 141 patients United Kingdom 1988-2007 Survival follow-up	We have analyzed replication licensing factors, together with DNA ploidy status, to investigate their role in progression of penile squamous cell	G1-3 T1-4 N0-3 M0-1 Mean age 62.7 y (27-86)	Immunohistochemistry one uro-oncology pathologist	Univariate analysis showed that Mcm2 (p= 0.02) and Ki67 (p= 0.04) expression and Ki67-geminin score (p= 0.03) were all significantly associated with overall survival.	Mcm2 and Ki67 LIs, Ki67-geminin score, age, tumor stage, depth of invasion, tumor extent, vascular invasion, and nodal and ploidy status were all identified as predictors of overall survival, with lymph node status, tumor extent,		LoE 3 QUIPS: moderate

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		20.1 mo (1-160 mo)	carcinoma and to assess their utility as novel prognostic tools.				and ploidy status identified as independent predictors of overall survival.		
Li, 2013, Medical Oncology	Retrospective cohort study	n= 54 patients China 2004-2011	The expressions of HDGF, VEGFA, and Ki-67 proteins were detected by immunohistochemistry to investigate their correlations with both clinicopathologic factors and clinical prognosis.	Median age 61 y (22-86 y)	Immunohistochemistry	Overall survival Ki-67 Positive: 57.7% Negative: 53.6% Risk: 1.182 (95% CI 0.403-3.465), p= 0.761	Age, tumor size, grade, lymphatic involvement, cell subtype, smoking status, and VEGF-A and Ki-67 expressions, were insignificantly related with survival rate of penile squamous cell carcinoma patients.		LoE 3 QUIPS: moderate
May, 2013, BJUI	Retrospective cohort study	n= 158 tissues Germany 1992-2010 Median follow-up 33 mo (3-63 mo)	To assess the role of cell proliferation-associated biomarkers to predict CSS in patients with surgically treated squamous cell carcinoma of the penis.	pTa/CIS-pT3 pN0-N+ G1-3 M0 Median age 67y (57-74.3 y)	Immunohistochemistry Score 1+ marker expression predominantly in basal cell nuclei with no more than occasional extension to suprabasal cell nuclei Score 2+ nuclear expression in basal and many suprabasal cell nuclei, but no full-thickness marker expression Score 3+ nuclear marker expression throughout the entire neoplastic epithelium corresponding to full-thickness marker expression two independent study pathologists	**KI-67 expression** CSS (univariate analysis) HR 1.47 (95% CI 1.01–1.82) p= 0.047 Multivariate analysis: not statistically significant	Ki-67, MCM2 and geminin do not represent independent prognostic parameters but reflect a more aggressive behaviour in surgically treated squamous cell carcinoma of the penis.		LoE 3 QUIPS: moderate

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Protzel, 2007, Histology & Histo-pathology	Case serie	n= 28 patients 1993-2003 <u>Median follow-up</u> 46.1 mo (2-105 mo)	To gain insight into the role of Ki67 and HPV infection in PSCC, Ki67 expression was assessed immunohistochemically in the present study in penile squamous cell carcinoma primary tumors.	pT1-4 N1-3 M0-1 10,5% HPV+	Immunohistochemistry <u>Weak</u> less than 15% of the nuclei positive <u>Intermediate</u> 15-60% of nuclei positive <u>Strong</u> more than 60% of the nuclei positive two independent observers	**Ki67 expression and presence of HPV DNA in relation to nodal metastasis** <u>N0</u> <15% 4/4 patients 15-60% 8/17 patients >60% 0/7 patients <u>N+</u> <15% 0/4 patients 15-60% 9/17 patients >60% 7/7 patients p= 0.005 **Ki67 expression and presence of HPV DNA in relation to nodal metastasis** <u>M0</u> <15% 4/4 patients 15-60% 8/17 patients >60% 3/7 patients <u>M+</u> <15% 0/4 patients 15-60% 2/17 patients >60% 4/7 patients p= 0.026 Chi-Square test showed a significant association between HPV status and Ki67 expression (p=0.009).	Our study demonstrated a strong Ki67 labeling index significantly associated to positive lymph nodes, we suggest Ki67 expression as a prognostic marker for lymph node metastasis in penile squamous carcinoma.		LoE 4 QUIPS: moderate
Stankiewicz 2012, Journal of Clinical Pathology	Retrospective cohort study	n= 148 samples United Kingdom 2001-2007	To determine whether Ki-67 immunoexpression in penile squamous cell carcinoma has a prognostic value and correlates with lymph node	G1-3 N0-3	Immunohistochemistry Cut-off point for antibody positivity: >40% one genitourinary pathologist	**Positive vs. negative Ki-67 expression** CSS: HR= 1.00 (95% CI 0.99-1.02) p= 0.54 OS: HR= 1.00 (95% CI 0.99-1.02) p= 0.45 There was no significant difference	Ki-67 is only a moderate surrogate marker for HPV infection in penile squamous cell carcinoma. It does not show prognostic value for cancer-specific survival and overall survival in penile squamous cell carcinoma.		LoE 3 QUIPS: moderate

Referenz	Studien -design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Testverfahren/ Schwellenwert/ Anzahl der Testevaluatoren	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			metastasis, HPV infection and patient survival.			in OS (p= 0.5538) and CSS (p= 0.6221) for patients with positive and negative Ki-67 expression.			
Zhu, 2007, BJUI	Cohort study	n= 73 China 1990-2005	To evaluate the prognostic significance of p53, Ki-67, epithelial cadherin and matrix metalloproteinase-9 in primary penile cancer.	T1 - ≥T2 G1- ≥ 2 33% high expression of p53 45% high expression of KI-67 Median age 55 y (27-75 y)	Immunohistochemical staining Overall mean expression score (20%) was used as the threshold. two observers	CSS (multivariate analysis) Ki-67 low vs. high: p= 0.861 3 y-CSS (multivariate analysis) Ki-67 low vs. high: p= 0.323	The expression of p53 is an independent predictor of CSS in Chinese patients with penile cancer.	Ergebnisse zur Ki-67 wurden nicht in die Schluss-folgerungen aufge-nommen, da diese nicht signifikant waren.	LoE 3 QUIPS: moderate

10.1.2. Schlüsselfragen der AG Präkanzerosen

Tabelle 19: „Ist die lokale Therapie mit 5-FU oder Imiquimod für Patienten mit pTis Peniskarzinom geeigneter als eine Lasertherapie?“

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Direkte Evidenz										
Cardamakis, 1997, Eur J Gynaecol Oncol	Retrospect ive cohort study	n= 1372 1986-1991 Mean follow-up 18.65 mo (7-50 mo)	To assess the effectiveness of CO2 laser, 5-FU topical application and Interferon parenterally in the therapy of penile intraepithelial neoplasia.	n= 208 treated for penile intraepithelial neoplasia 81.81% were between 26-35 y	5-FU (n= 19) CO2 laser (n= 33) CO2 laser+ 5-FU (n= 62) 5-FU+ Interferon α2a (n= 32) CO2 laser+ Interferon α2a (n= 10) CO2 laser+ 5-FU+ Interferon α2a (n= 52)		Treatment failures 5-FU: 12/19 CO2 laser: 15/33 5-FU+ CO2 laser: 8/62 5-FU+ Interferon α2a low dose: 10/32 5-FU+ Interferon α2a high dose: 2/10 CO2 laser+ 5-FU+ Interferon α2a high dose: 2/52 Best treatment modalities CO2 laser+ 5-FU+ Interferon α2a high dose (96.15%) CO2 laser+ 5-FU (87.09%) CO2 laser+ Interferon α2a high dose (80%) p< 0.001 Complications 5-FU: 14% (acute, erosive chemoinflamation)	The addition of 5-FU and CO2 laser vaporization to Interferon therapy give better cure rates in a shorter time periode (20 days). Interferon α2a (low dose) can be usead as first line treatment combination with 5-FU in patients with penile intraepithelial neoplasia II, and as adjuvant treatment (high dose) in patients with recurrent penile intraepithelial neoplasia I and III.		LoE 3 RoB 8/9
Indirekte Evidenz (keine Vergleichsgruppe)										
Alnajjar, 2012, European Urology	Retrospect ive case serie	n= 86 2001-2011 Mean follow-up 34 mo (12-180 mo)	To establish the response rate of 5-FU and imiquimod in the treatment of penile CIS in a large contemporary	Cis Mean age 62.6 y (47.5-77.7 y)	First-line: 5-FU n= 44 Second-line: Imiquimod n= 9		Complete response (overall following treatment with topical chemotherapy agents): 57% 5-FU	Topical chemotherapy agents are moderately effective first-line therapy in the treatment of penile CIS. Toxicity and adverse events were few with our treatment protocol.		LoE 4 RoB 16/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			series in a supraregional network.				Complete response: 50% Partial response: 31% Nonresponse: 31% Local toxicity: 10% Adverse events: 5% <u>Imiquimod</u> Complete response: 44% Partial response: 0% Nonresponse: 56% Local toxicity: 0% Adverse events: 11%			
Alessi, 2009, Clinics	Retrospective case serie	n= 123 lesions Brazil 2003-2008	To analyze the use of imiquimod on cutaneous tumors at the Dermatology Department of Hospital das Clinicas.	Women to men-ratio: 1.28:1 <u>Mean age</u> 63.1 y (11-92 y) <u>Tumor locations:</u> Face (n= 54) Back (n= 18) Trunk (n= 18) Legs (n= 13) Arms (n= 10) Neck (n= 6) Penis (n= 2) Lower lip (n= 1) Axillae (n= 1)	topical 5% imiquimod cream		Overall lesions 45% no response 17.5% partial response 38% complete response Tumors located on the penis presented no recurrence.	Our experience confirms imiquimod as an effective treatment option for several types of cutaneous tumors, especially in patients without the cutaneous comorbidities cited above and with low-risk tumors. Imiquimod has a relatively low cost compared to other therapeutic options and can be delivered via ambulatory care to patients with surgery contraindications, and its side effects are tolerable.	Only two penile lesions.	LoE 4 RoB 11/20
Bandieramonte, 1987, Journal of Urology	Case serie	n= 47 Italy 1982-1985	To report our experience in the management of 47 consecutive patients with superficial penile lesions treated with carbon dioxide laser microsurgery.	n= 4 Ca in situ-patients <u>Mean age</u> 42 y (22-73 y)	CO2 laser		<u>Recurrence</u> - 1 patient with microsopically invasive carcinoma (4 mo after laser treatment) - patients new disease in an untreated area <u>Mean healing time</u> 6 wks (3-8 wks)	The short-term results of this surgical technique for penile lesions are satisfactory.	ggf. Überschneid-ungen mit dem Patientenkollektiv von Bandieramonte 2008 und 1988	LoE 4 RoB 13/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Mean postoperative hospitalization 3 days Complications Arterial hemorrhage (n= 1) Delayed generalized oozing of thw wound bed (n= 1)			
Bandieramonte, 1988, Acta Oncologica	Case serie	n= 15 1983-1987 Median follow-up 7 mo (2-48 mo)	To report the expierence with total resection of glans penis surface by CO2 laser microsurgery.	n= 3 carcinoma in situ patients Mean age 54 y (32-72 y)	CO2 laser		Complications Operative bleeding: minimal Delayed hemorrgage (n= 1) Postoperative pain: minimal to absent Edema: minimal Infection: none Mean healing time: 7 wks (5-8 wks) Scars: Absent Statisfactory sexual activity: 14/15 Disease persistence or early recurrence: 1/15 (invasive tumor)	Satisfactory cosmetic and functional results were observed in all cases. The procedure can be considered for conservative treatment of wide or multiple superficial lesions of the glans penis.	ggf. Überschneid-ungen mit dem Patientenkollektiv von Bandieramonte 2008 und 1987	LoE 4 RoB 8/20
Bandieramonte, 2008, European Urology	Retrospective case serie	n= 224 Italy 1982-2006 Median follow-up 66 mo (35-132 mo)	To evaluate the outcome of peniscopically controlled laser excision of early-stage penile carcinoma.	n= 106 Cis n= 78 initially invasive (≤1 mm) squamous cell carcinoma n= 40 superficially invasive (>1 mm) squamous cell carcinoma Median age 57 y (20-83 y)	CO2 laser excision		Recurrent cases Cis: 12/106 Initially invasive squamous cell carcinoma: 11/78 Superficially invasive squamous cell carcinoma: 9/40 10 y cumulative incidence curves of recurrence Cis: 15.7% Initially invasive squamous cell carcinoma: 15.8%	Early-stage penile carcinomas can be effectively treated with the organ-sparing strategy described here. Because local recurrences occur in a minority of patients and can be safely treated, organ preservation is compatible with local disease control.	ggf. Überschneid-ungen mit dem Patienten-kollektiv von Bandieramonte 1988 und 1987	LoE 4 RoB 16/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Superficially invasive squamous cell carcinoma: 23.1% p= 0.61 Complications No intraoperative complications Postoperative bleeding Local edema Postoperative pain Slight color changes Urethral stenosis			
Boon, 1988, Eur J Surg Oncol	Case serie	n= 16 1983-1987 Mean follow-up 17 mo (4-36 mo)	To report the experience with sapphire probe laser excision.	Tis, T1-2 N0M0 Mean age 67 y (41-84 y)	Nd:YAG laser		Recurrence 13/16 no recurrence 3/16 local recurrence	Sapphire probe laser excision is a safe procedure leading to a good cosmetic aspect with maintenance of the functional integrity of the penis.		LoE 4 RoB 9/11
Deen, 2017, Australasian Journal of Dermatology	Systematic Review	n= 29 articels (22 case reports, 7 case series) 1997-2015 Follow-up 6 wk-48 mo	To summarise the available evidence for the potential role of imiquimod in the non-surgical management of penile intraepithelial neoplasia specifically.	n= 48 patients Erythro-plasia of Queyrat (n= 32) Bowen's disease (n=16)	Imiquimod		Response Complete: 30/48 Partial: 4/48 No response: 14/48 Recurrence: 4%	Patients with penile intraepithelial neoplasia have variable responses to imiquimod which seem less effective than previously reported. If imiquimod treatment is instituted in penile intraepithelial neoplasia, clinicians should counsel their patients about the effects associated with treatment, the potential for a partial or no response to treatment, and the risk of recurrence.		LoE 4 ROBIS high
Frimberger, 2002, Journal of Urology	Case serie	n= 29 Germany 1987-2000 Mean follow-up 46.7 mo	To compare outcome data from the last 13 years on patients with penile carcinoma treated with Nd:YAG laser coagulation with outcome data on conventional	Cis T1-2 Mean age 55.1 y (30-93 y)	Nd:YAG laser n= 12 (patients with T1-2 tumour)	Nd:YAG laser n= 17 (patients with Cis)	Recurrence 1/10 T1 tumour patient 1/17 Cis patient All patients are alive. No side effects or complications in both groups.	Recurrence rates after Nd:YAG laser treatment for T1 tumors are comparable to those after partial amputation. Excellent cosmetic and functional results can be achieved without compromising oncological principles. For patients with metastasis prognosis is limited by the		LoE 4 RoB 8/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			organ sparing techniques.					distant disease and, therefore, amputation is only necessary to achieve local control.		
Lenk, 1991, Dermatologische Monatsschrift	Case reports	n= 6 Germany Follow-up 6-24 mo	To report our initial experience with the application of laser surgery in penile tumours.	n= 2 penile cancer patients n= 2 giant condyloma Buschke-Löwenstein n= 2 candylo-mata acuminata	CO2 or neodymium-YAG laser		Recurrence 5/6 no recurrence 1/6 recurrence after 5 wk (giant condyloma patient)	In our experience laser surgery is the treatment of choice in superficial penile tumours preserving normal erectile function.		LoE 4 RoB 7/20
Lucky, 2015, BJU International	Retrospective case serie	n= 57 United Kingdom 2003-2010 Mean follow-up 3.5 y (2-8 y)	To review outcomes of the treatment of CIS of the penis at a large supra-regional penile cancer network, where centralisation has permitted greater experience with treatment outcomes, and suggest treatment strategies.	Cis Mean age 61 y (34-91 y)	Circumcision n= 18 Circumcision+ 5-FU n= 19	Circumcision+ local excision n= 20	Recurrence Circumcision+ local excision: 20% Circumcision+ 5-FU: 0% Complete response Circumcision+ 5-FU: 73.7% Complications 5-FU Severe inflammatory response (n= 2) Moderate inflammation (n= 4) Neo-phimosis (n= 1) Burning and ulceration (n= 1)	Treatment with topical 5-FU is safe and effective in the treatment of widespread CIS of the glans penis.		LoE 4 RoB 14/20
Mahto, 2010, International Journal of STD & AIDS	Systematic Review	n= 46 articles 1997-2009 Mean follow-up for penile neoplasia studies 7.5 mo (1-22 mo)	To assess the effectiveness of 5% imiquimod cream in the treatment of vulvar, penile and anal intraepithelial neoplasias.	**Penile neoplasia** n= 17 articles (15 case reports, 2 cohort studies) n= 27 patients Mean age 55 y (23-78 y)	Imiquimod		**Penile neoplasia** Response (overall studies) Complete: 78% Partial: 19% (all HIV+) Nonresponse: 4% Pooled summary (2 cohort studies on penile cancer) Mean complete response: 70%	Although the results for penile neoplasia look the best. The body of evidence is weak for penile neoplasia and being supported only by uncontrolled cohort studies and case reports, hence its effectiveness particularly difficult to verify.	LoE bezieht sich auf die eingeschlossenen Peniskarzinomstudien.	LoE 4 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
				15% HIV+			Mean partial response: 10% Recurrence rate: 10% Follow-up: 10-12 mo			
Malloy, 1988, Urology	Case serie	n= 16 1983-1986 Mean follow-up 26.2 mo (18-29 mo)	To report results of Nd:YAG laser treatment.	Tis T1-T2 N0 M0	Nd:YAG laser		Recurrence-free 0/5 Tis patients 6/9 T1 patients 2 T2-patients had tumor mass reduction, but were not cured.	In our present series of patients it is obvious that the Nd:YAG laser is extremely effective in patients with TIS (100 % cure rate). In patients with Tl, N-O, M-O cancer of the penis, 67 percent were tumor-free at an average of twentysix-month follow-up. Obviously in the 2 patients with T2 lesions (2-5 cm primary lesion) the results were not successful.		LoE 4 RoB 9/11
Maranda, 2016, Lasers in Medical Science	Systematic review	n= 18 studies 1980-2014 Mean follow-up 13.4 mo	To comprehensively review the available reports and discuss which modalities may be the most promising for Erythroplasia of Queyrat treatment.	n= 101 patients with Erythroplasia of Queyrat n= 34 patients treated with laser (27 CO2, 7 Nd:YAG) n= 67 patients treated with photodynamic therapy	Laser therapy n= 8 studies	Photodynamic therapy n= 10 studies	**Laser therapy** - 97.1% complete remission (follow-up: 6 wks-40 mo) - 81.4% complete remission after CO2 laser treatment **Adverse effects** - Some pain or slight burning sensation during treatment (n= 2 studies) **Photodynamic therapy** - 62.5% complete remission after treatment with methyl aminolevulinate photodynamic therapy - 58.3% complete remission after aminolevulinic acid treatment **Adverse effects**	Of the two laser modalities presented in this review, the CO2 laser therapy is the most promising method. Based on the data presented, a low recurrence rate is to be expected, and the most common side effects would be slight pain and/or discomfort during the administration of the therapy.		LoE 4 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							- Temporary tingling, burning, pain, or other discomfort during and after the therapy (n= 59 patients) - Discontinuation of treatment because of intolerance of the therapy-associated pain (n= 2 patients) - Temporary dysuria (n= 2 studies) - Mild swelling and redness with a small number of patients developing a hematoma, erosion/ulceration blistering, and dyschromia/hyperpigmentation			
Meijer, 2007, Urology	Retrospective case serie	n= 44 Netherlands 1986-2003 Mean follow-up (SD) 52.1 mo (±43.3 mo)	To assess the disease-free period after laser therapy, evaluate the recurrence rate related to the primary stage, and, finally, evaluate the prognosis of thoroughly applied organ-sparing therapy.	Tis (n= 6) T1-2 Mean age (SD) 60.4 y (±12.8 y)	Nd:YAG laser		**Overall** Recurrence Total: 66% Local: 48% Not Local: 20% **Tis** (n= 6) Total: 67% 1 recurrence: 1 patient 2 recurrences: 1 patient ≥3 recurrences: 2 patients Median time to recurrence: 9.3 mo (3.9-13.5 mo) **T1G1** (n= 13) Total: 54% 1 recurrence: 1 patient 2 recurrences: 3 patients ≥3 recurrences: 3 patients	From the high recurrence rate in our series, we decided to perform a wider initial laser excision and to diminish the number of retreatments to less than three. We also now believe that laser therapy is best for Stage Tis and T1 tumors exclusively. Only selected patients with T2 tumors should be treated in combination with early lymph node resection.		LoE 4 RoB 14/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Median time to recurrence: 19.2 mo (5.1-118.6 mo) **T1G2** (n= 8) Total: 63% 1 recurrence: 3 patients 2 recurrences: 2 patients ≥3 recurrences: 0 patients Median time to recurrence: 7.9 mo (2.3-11.8 mo) **T2G1** (n= 9) Total: 56% 1 recurrence: 1 patient 2 recurrences: 0 patients ≥3 recurrences: 4 patients Median time to recurrence: 7.0 mo (2.7-10.8 mo) **T2G2-3** (n= 8) Total: 100% 1 recurrence: 2 patients 2 recurrences: 3 patients ≥3 recurrences: 3 patients Median time to recurrence: 8.9 mo (2.1-65.9 mo)			
Musi, 2018, World Journal of Urology	Case serie	n= 26 2013-2016 Median follow-up 24 mo (15-30 mo)	To evaluate the oncological and functional outcomes of patients diagnosed with penile cancer undergoing conservative	Tis-T3 Median age 61 y (54-72 y) Patients treated with thulium-	Nd:YAG		17.4% recurrence (3 invasive recurrences pTis-pT1 G3, 1 in situ failure pTis G1) Post-treatment sexual	Early stage penile carcinomas can be effectively treated with an organ preservation strategy. Tm:YAG conservative laser treatment is easy, safe and offers good functional outcome, with a		LoE 4 RoB 12/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			treatment through thulium–yttrium aluminium–garnet laser ablation.	yttrium aluminium–garnet laser ablation			activity was achieved within the first month in 82.6% patients.	minor impact on patient's quality of life.		
Schlenker, 2010, BJU international	Retrospective case serie	n= 54 Germany 1979-2008 Mean follow-up 87 mo (9-366 mo)	To provide a long-term follow-up of patients treated with organ-preserving laser therapy for penile cancer.	Tis (n= 11) T1-2	3.Nd:YAG		Overall Local recurrence: 42% Mean time to local recurrence: 53 mo (9-132 mo) There was no statistically significant difference in recurrence rates for patients with Tis or invasive penile carcinoma (p= 0.574).	Organ-preserving laser therapy showed a relatively high recurrence rate in patients with a long-term follow up, but the oncological outcome and survival were not compromised by local recurrence. Therefore, laser therapy appears to be appropriate for treating premalignant lesions and early stages of penile carcinoma. Patients should be informed about the potential for late recurrence.		LoE 4 RoB 14/20
Tang, 2018, Urologic Oncology	Retrospective case serie	n= 161 1985-2015 Median follow-up 57.7 mo (28-90 mo)	To assess the clinical outcomes of penile cancer patients treated with only laser ablation.	pTa/Tis pT1a-b pT2 G1-3/4 Median age 62 y (52-71 y)	CO2 or Nd:YAG laser		Recurrence-free survival Overall: 43% 5-year: 46% 5-y local recurrence-free survival pTa/Tis: 50% pT1a: 41% pT1b: 38% pT2: 52% 5-y inguinal/pelvic nodal recurrence-free survival pTa/Tis: 2% pT1a: 5% pT1b: 18% pT2: 22% No differences among stages with respect to recurrence-free survival (p= 0.98) or OS (p= 0.20).	Laser ablation therapy may be used as primary penile sparing treatment in patients with pT1a disease or lower.		LoE 4 RoB 12/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Torelli, 2017, Clin Genitourin Cancer	Case serie	n= 10 2010-2015 Mean follow-up 26 mo (12-58 mo)	To evaluate the pathologic response (primary endpoint) and the local toxicity and adverse effects of topical imiquimod (secondary endpoints).	Cis of the glans pT0-1, Cis HPV: 7/10 Age 41-66 y	topical imiquimod followed by carbon dioxide laser ablation		**Clinical response** Complete: 6/10 Progressive: 2/10 (2 patients with progressive disease underwent total penectomy) **Relapses** Complete Response No relapse Patients with no response - 1 became disease free only after laser ablation (disease-free survival, 22 months) - 1 had developed relapsed CIS in the same excisional area after 10 mo **Side effects** - One patient stopped treatment because of scrotal ulceration. - Local burning and erythema (n= 10) - Inguinal adenopathy (n= 3)	Local treatment with IQ for glans CIS is effective mainly for human papillomavirus-related lesions. Topical IQ is an effective first-line therapy for penile CIS.		LoE 4 RoB 10/20
Windhal, 2003, Journal of Urology	Prospective case serie	n= 67 Sweden 1986-2002 Median follow-up 42 mo (12-186 mo)	To evaluate local disease control, side effects and cause specific survival of penile carcinoma treated with laser therapy.	pTis pTa pT1-3 Grade I-III Mean age 60 y	Combined treatment with the carbon dioxide/ neodymium:YAG laser		13 patients with local recurrence: 3 patients with Cis 4 patients with pT1G1 2 patients with pT1G2 3 patients with pT2G2 (one died of metastatic disease) 1 patient with pT3G2 Survival 59 alive 8 died (2 of penile cancer, 6 of concurrent disease)	The results of this study show that treating penile carcinoma with the combination of carbon dioxide and neodymium:YAG lasers can safely be done with highly satisfactory cosmetic results as well as good local tumor control.		LoE 4 RoB 14/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Side effects Minor postoperative bleeding (n= 5) Pain			
Zreik, 2017, Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland	Retrospective case serie	n= 47 United Kingdom 2008-2015 Average length of follow-up 29 mo (1-76 mo)	To evaluate the outcome of carbon dioxide (CO2) laser treatment of penile intraepithelial neoplasia.	Penile intraepithelial neoplasia Average age 59 y (21-88 y)	CO2 laser		Recurrence: 17% Average time to recurrence: 19.4 mo (6-48 mo) Disease-specific survival: 100% OS: 98%	Carbon dioxide laser treatment for penile intra-epithelial neoplasia is effective due to its 100% response rate, low progression rate and lower recurrence rate compared with topical agents. The laser has minimal morbidity with cosmetically acceptable outcomes compared to more invasive resurfacing surgeries.		LoE 4 13/20

Tabelle 20: „Sollen Patienten mit pTis Peniskarzinom eine lokale Therapie mit Laser und photodynamischer Diagnostik oder ohne photodynamische Diagnostik erhalten?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerkungen	LoE/ RoB
Frimberger, 2002, Urological Research	Case serie	n= 12	The value of photodynamic diagnosis and autofluorescence imaging in detecting malignant lesions on the penis was evaluated.	Cis T1 G1-2 Mean age 62 y (47-68 y) 8/12= HPV+	Nd:YAG laser therapy and: • White light • Autofluorescence imaging • Photodynamic diagnosis • Acetic acid test		Nonmalignant biopsies taken from the non-suspicious areas under autofluorescence imaging, photodynamic diagnosis and acetic acid test 12/12 Results of the autofluorescence imaging correlated with the photodynamic diagnosis results No side effects from the autofluorescence imaging, the photodynamic diagnosis or the acetic acid test were observed.	The combination of fluorescence detection and laser treatment of penile carcinoma is a promising technique for the performance of penile sparing surgery.		LoE 4 RoB 10/20
Schlenker, 2011, Urol Oncol	Retrospective case serie	n= 26 Germany 1999-2005 Mean follow-up 71.1 mo (41-104 mo)	The aim of our study was to investigate the long-term recurrence rate of patients treated by fluorescence-guided laser therapy for penile carcinoma and its impact on oncologic outcome.	n= 11 Tis n= 15 invasive penile carcinoma (T1, Tx) Mean age 55.5 y (22-83 y)	Fluorescence-guided laser therapy		Tis no local recurrence, no invasive penile carcinoma, no lymph node positive, no partial amputation or lymph node dissection Invasive penile carcinoma 4/15 local recurrence (16 mo, 41 mo, 53 mo, 60 mo) 1/15 lymph node metastasis No intra- or perioperative adverse effects caused by PDD imaging technique were observed.	Local recurrence rate of laser therapy can be reduced by fluorescence guidance without impairing cosmetic or functional results. The necessary equipment is available in many centers that perform PDD for urothelial bladder cancer. PDD, therefore, can be considered to be cost-effective and easy to perform.		LoE 4 RoB 12/20

Tabelle 21: „Ist die lokale Strahlentherapie für Patienten mit pTa oder pT1 Peniskarzinom geeigneter als eine Lasertherapie oder chirurgische Exzision?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerung	Bemerk-ungen	LoE
Systematic Reviews										
Hasan, 2015, Brachytherapy	Systematic review with meta-analysis	n= 20 studies 1984-2012 Median follow-up Penectomy: 59 mo Brachytherapy: 67 mo	To compare the OS and local control rates between penectomy and brachytherapy for penile cancer.	n= 2178 Tis-T4 Grade 1-3 Median age 61 y (21-98 y)	Penectomy n= 659 patients with Tis, T1 or T2 without nodal involvement	Brachytherapy n= 209 patients with Tis, T1 or T2 without nodal involvement	**Subset analysis** (Tis, T1 or T2 without nodal involvement) 5 y-OS OR 0.95 (0.65-1.38) p= 0.771 5 y-local control OR 1.13 (0.73-1.74) p= 0.594	The collective data represented in this meta-analysis suggest that with early stage disease, brachytherapy has been as effective as penectomy for both local control rates and OS.	LoE 4, da sowohl vergleichende als auch nicht-vergleichende Studien eingeschlossen wurden und das RoB als high bewertet wurde.	LoE 4 ROBIS: High
Hu, 2017, Oncotarget	Systematic review with meta-analysis	n= 22 studies 1992-2016 Follow-up at least one year	To compare the efficacy of brachytherapy and penectomy in patients with penile cancer.	n= 2560 patients I-III stage	Brachytherapy n= 746	Penectomy n= 1814	5-year OS Brachytherapy: 76% (71-81%) Penectomy: 74% (69-79%) OR 1.11 (95% CI 0.91–1.36) p= 0.284 5-year local control rate Brachytherapy: 80% (77-83%) Penectomy: 85% (82-88%) OR 0.72 (95% CI 0.58–0.90) p= 0.003 DFS Brachytherapy: 72% (64-80%) Penectomy: 77% (70-83%) OR 0.77 (95% CI 0.63–0.93) p= 0.008	Both of penectomy and brachytherapy can improve the survival status. Penectomy provided better control efficacy, and not improved the survival status compared with brachytherapy solely.	LoE 4, da sowohl vergleichende als auch nicht-vergleichende Studien eingeschlossen wurden.	LoE 4 ROBIS: Low

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerung	Bemerk-ungen	LoE
Primary Studies										
Burt, 2014, International Journal of Radiation Oncology, Biology, Physics	Retrospective cohort study	n= 2458 USA 1988-2006 Median follow-up for survivors 45 mo	We evaluated the stage distributions and outcomes for surgery and radiation therapy in a U.S. population database.	T1-4 N0-3 M0-1 G1-3 Median age 66.8 y (17-102 y)	Surgery alone n= 2185 (n= 1458 T1 patients) External beam radiation therapy alone n= 54 (n= 23 T1 patients)	External beam radiation therapy+ surgery n= 180 (n= 87 T1 patients)	Number of dead Surgery only: 296 External beam radiation therapy + surgery: 60 External beam radiation therapy alone: 16	Although outcomes for radiation monotherapy versus surgery could not adequately be compared in this National Cancer Institute SEER database evaluation, small retrospective studies have found similar cause-specific survival rates for external beam radiation therapy, with salvage surgery if necessary, compared to surgery.		LoE 3 NOS 7/9
el-Demiry, 1984, British Journal of Urology	Case serie	n= 80 United Kingdom 1963-1983	This study reviews our long-term results in the light of the critics of radiation therapy.	Stage I-IV Mean age 68 y (35-95 y)	Iridium mould n= 27 (n= 23 T1 patients) External beam n= 20 (n= 10 T1 patients)	(Partial) Amputation n= 16 (n= 7 T1 patients with partial amputation) Surgical+ external radiation+ bleomycin n= 13	**T1 patients** Iridium mould Local and regional recurrence rate: 21.7% Deaths from metastases: 8.6% 5-y survival rate: 89% External beam Local and regional recurrence rate: 70% Deaths from metastases: 20% 5-y survival rate: 76% Partial amputation Local and regional recurrence rate: 29% Deaths from metastases: 14.2% 5-y survival rate: 71% All methods (n= 40) Local and regional recurrence rate: 35% Deaths from metastases: 13% 5-y survival rate: 80%	The iridium mould technique was used as the method of choice whenever possible in a series of 80 cases of cancer of the penis. When the growth was confined to the glans penis the survival rate was 89% but local recurrence called for subsequent amputation in 22%. When tumour had invaded the corpus cavernosum, irradiation improved the survival rate but amputation was required in 75 to 80%.	Ergebnisse sind nur für T1-Patienten berichtet.	LoE 4 RoB 8/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerung	Bemerk-ungen	LoE
Krieg, 1981, Urology	Retrospective cohort study	n= 29 USA 1960-1977 Follow-up at least three years	To review cases treated by surgery and radiation therapy.	Tis-T4 N0-2	Surgical treatment Circumcision Local excision n= 17	External beam radiation n= 12	Over-all local surgical control rate Surgical treatment: 88% Radiation therapy: 75% Radiation therapy with surgical salvage: 92% Death Surgical treatment: 4 Radiation therapy: 1 **Radiation therapy** Complications 1= penile necrosis and one year later death of radiation enteritis 2= developed urethral strictures 1= developed a cutaneous-urethral fistula Sexual function 7/12 able to maintain potency and normal sexual functioning	Radiation therapy appears to be the treatment of choice for early stage lesions, reserving surgery for salvage. Prophylactic ilioinguinal lymph node dissection for N0 lesions is not warranted.		LoE 3 NOS 7/9
Modig, 1993, Acta Oncologica	Retrospective cohort study	n=44 Sweden All patients included since 1966 Follow-up more than 8 years or until death	To compare surgically treatment and a combination of irradiation and bleomycin in patients with squamous cell carcinoma of the penis stage TI-T2, N0.	T1-T2 G1-3 N0 Median age 60 y (31-83 y)	Surgical treatment n= 19 (n = 11 T1 patients)	Irradiation & bleomycin n= 25 (n= 16 T1 patients)	Overall 3 y-OS: 80% 5 y-OS: 77% 10 y-OS: 60% Death Surgical treatment: 2/19 Irradiation group: 0/25 Local recurrence Irradiation group: 5/25	Radiation therapy combined with bleomycin in patients with squamous cell carcinoma of the penis in stage TI-T2, NO, MO seems to give survival results comparable to those of primary surgery. The sexual ability is preserved in the originally sexually active man.		LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerung	Bemerk-ungen	LoE
Ozasahin, 2006, International Journal of Radiation Oncology, Biology, Physics	Retrospective cohort study	n= 60 1962-1994 Median follow-up 62 mo (6-454 mo)	To assess the prognostic factors and the outcomes in patients with squamous-cell carcinoma of the penis.	T1-3 N0-3 Grade 1-3 Median age 61 y (35-85 y)	Surgery n= 27	Radiotherapy n= 51	Local failure Partial penectomy with or without radiotherapy: 13% Organ-sparing treatment: 56% p= 0.0008 10-y CSS Definitive radiotherapy: 56% (95% CI 31-81%) Primary surgery: 53% (95% CI 32-74%) p= 0.16 Surviving with intact penis after definitive radiotherapy 5 y-probability: 43% (95% CI 25–61%) 10 y-probability: 26% (95% CI 5– 47%) Complications after primary radiation therapy 10% reversible urethral stenosis	Based on our study findings, in patients with penile cancer, local control is superior with surgery. There is no difference in survival between patients treated with surgery and those treated with definitive radiotherapy, with 52% organ preservation.		LoE 3 NOS 3/9
Zouhair, 2001, European Journal of Cancer	Retrospective cohort study	n= 41 USA 1962-1994 Median follow-up 70 mo (20-331)	To assess the prognostic factors and the outcome in patients with squamous-cell carcinoma of the penis treated in our department.	T1-3 N0-3 29% T1 patients Median age 59 y (35-76 y)	Surgery (n= 16 partial penectomy ± postoperative radiotherapy)	Radiotherapy (n= 23 radiotherapy alone)	Relapse (overall patients) Overall: 63% Local: 18 Locoregional: 2 Regional: 3 (2 surgery group, 1 radiotherapy group) Distant: 3 Local failure 25% partial penectomy± postoperative radiotherapy	In patients with squamous-cell carcinoma of the penis, local control is better in patients treated with surgery. There seems to be no difference in terms of survival between patients treated by surgery and those treated by primary radiotherapy ± salvage surgery, with 39% having organ preservation.		LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerung	Bemerk-ungen	LoE
							61% primary radiotherapy p= 0.06 <u>Local control</u> Surgery± radiotherapy: 81% (95% CI 44-100%) Primary radiotherapy: 41% (95% CI 25-57%) p= 0.009 <u>Locoregional control</u> Surgery± radiotherapy: 75% (95% CI 54-96%) Primary radiotherapy: 31% (95% CI 11-51%) p= 0.008 <u>Surviving with penis preservation after primary radiotherapy</u> 5 y-probability: 36% (95% CI 22–50%) 10 y-probability: 18% (95% CI 2– 34%) <u>Complications after primary radiation therapy</u> 9% reversible urethral stenosis			

10.1.3. Schlüsselfragen der AG Therapie T1-4

Tabelle 22: „Sollen Patienten mit pT1-2 G2-3 Peniskarzinom organerhaltend mittels Glansektomie oder durch eine Penisteilamputation therapiert werden?“

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
Systematic Reviews										
Kamel, 2017, Journal of Urology	Systematic review	n= 50 articles 1985-2016 Follow-up 24 mo or longer	To increase awareness of organ sparing surgery for penile cancer and their applicability, to evaluate the techniques objectively and to provide guidance to the practicing urologist.		Organ-sparing surgery		Glansectomy is indicated in T1 and T2 tumors confined to the glans. Partial penectomy requires more aggressive resection compared to other organ sparing surgery techniques, it offers a significantly lower local recurrence rate. The reported local recurrence rate is 0% in T1 tumors and 18% to 20% in T2 tumors, and most patients are able to void upright postoperatively.	In properly selected patients with penile cancer organ sparing surgery provides comparable oncologic outcomes to conventional techniques, including total and subtotal amputations. Many patients are able to urinate while standing and a significant number are able to have intercourse.		LoE 3 ROBIS high
Pompeo, 2015, Current Opinion in Urology	Systematic review	1990-2014	To update the contemporary knowledge related to penile-sparing surgeries.		• Partial amputation • Glansectomy • Mohs procedure • Laser surgery		Partial amputation If risk factors for local or distant recurrence are absent (pT1 and Grades I–II), reduction of surgical margins (≤1.0 cm) is proposed. Recent review suggests that 1.0–1.5 cm margin is safe. For Grade III or ≥T2 tumors, 1.5–2.0 cm margin is still the rule. Glansectomy Partial or total glans resections have been strongly proposed for selected cases of distal glans lesions (stage Ta-1 or T2). For small	Penile-sparing surgery are simple and reproducible procedures, conferring satisfactory disease control with superior cosmetic results. PSSs are indicated for selected Ta-T1, Tis and small T2 lesions or for salvage after irradiation failures.		LoE 3 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							lesions, Tis, Ta-1 and selected T2 (and far from the urethra), a partial glansectomy with resection until exposition of tunica albuginea of the corpora is performed.			
Primärstudien										
Brkovic, 1997, Eur Urol	Retrospective cohort study	n= 51 Switzerland 1968-1994 Median follow-up 8.5 y (22 mo-21 y)	To establish oncological guidelines for the surgical treatment of invasive penile cancer.	T1-T4 N0-N+ Mean age 60.5 y (36-85 y)	Penis-conserving procedures (circumcision, tumor excision, laser coagulation or external beam) n= 14 (n= 13 T1-2 patients)	(Partial) Amputation n= 35 (n= 32 T1-2 patients)	**Local recurrence** Penis-conserving treatments T1: 56% T2: 100% T3: 100% Amputative procedures T1: 0% T2: 18% T3: 0%	Organ-preserving procedures include a high risk of local and regional recurrence.		LoE 3 NOS 7/9
Chipollini, 2018, Clinical Genitourinary Cancer	Retrospective cohort study	n= 4231 USA 1998-2012 Median follow-up 39.6 mo (19.9-69.6 mo)	To analyse contemporary trends and predictors in the use of organsparing treatment for low-stage invasive penile tumors as well as to ascertain its impact on overall mortality in those with high-risk (pT2) disease.	pT2= 929 cN0M0	Organ-sparing therapies • Laser therapy using neodymium-doped yttrium aluminium garnet or carbon dioxide mediums • Mohs surgery • Circumcision • Glansectomy and/or glans resurfacing	Partial penectomy n= 670 pT2 patients	OS organsparing vs. partial penectomy (overall patients) HR 0.83 (95% CI, 0.52-1.31) p= 0.419	No impact on overall mortality was observed for those with high-risk cases treated with organ-sparing at intermediate follow-up.		LoE 3 NOS 8/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
					n= 71 pT2 patients					
Djajadiningrat, 2014, Journal of Urology	Retrospective cohort study	n= 859 1956-2012 Median follow-up 65 mo (41-101 mo)	To assess whether penile sparing therapies were increasingly applied in our penile squamous cell carcinoma cohort with time and whether penile sparing affected 5-year cancer specific survival.	Grade 1-3 pT1-4 pN0-3 Median age 65 y (56-73 y)	Penile preservation n= 451	(Partial) Amputation n= 408	no significant difference in survival between treatments **Recurrence** Local Penile preservation: 27% Partial amputation: 4% Local+ regional Penile preservation: 5% Partial amputation: 4% Local+ distant Penile preservation: 27% Partial amputation: 4% Regional +/- distant Penile preservation: 9% Partial amputation: 20% 5 y cumulative incidence of local recurrence Penile preservation: 27% (95% CI 23-32%) Partial amputation: 3.8% (95% CI 2.3-6.2%) p < 0.0001	Patients treated with penile preservation experienced more local recurrences, 5-year cancer specific survival was not jeopardized		LoE 3 NOS 8/9
Ficcara, 1999, Urologia Internationalis	Retrospective cohort study	n= 47 Italy 1976-1997 Mean follow-up 69.43 mo (1-268 mo)	To evaluate our experience with the surgical treatment of penile squamous carcinoma, analyzing the therapeutic results in terms of local recurrence rates,	pTis-pT3 G1-3 N0-N+ Mean age 62.9 y (35-83 y)	Partial penectomy n= 30 (n= 27 pT1/2) Total penectomy n= 5	Penis-conserving surgery n= 8 Emasculation n= 4	Local recurrence 43% T1 tumors treated with local excision or circumcision Penis-conserving surgery 50% alive and disease-free 37.5% died of the tumor	Partial penectomy gives better results than conservative treatment in the local management of the T1 stage tumor.	Darstellung der Ergebnisse nur für pT1/2-Patienten mit Penisteil-amputation und konservati	LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
			survival and mortality rates.				12.5% died of other causes <u>Partial penectomy</u> 36.7% alive and disease-free 33.3% died of the tumor 30% died of other causes		ver Therapie.	
Guimaraes, 2009, Journal of Urology	Retrospect ive case serie	n= 333 Brazil <u>Mean follow-up</u> 100 mo (8-453 mo)	To evaluate clinicopathologic al features and outcomes in patients with penile squamous cell carcinoma	G1-3 T1-3 N0-N+	Circumcision n= 4 Local excision n= 2	Partial penectomy n= 194 Total penectomy n= 133	<u>Circumcision</u> Dead of disease: 0% Disease: 0% Dead of other cause: 75% No disease evidence: 25% <u>Local excision</u> Dead of disease: 0% Disease: 0% Dead of other cause: 50% No disease evidence: 50% <u>Partial penectomy</u> Dead of disease: 8% Disease: 7% Dead of other cause: 32% No disease evidence: 42% <u>Total penectomy</u> Dead of disease: 27% Disease: 5% Dead of other cause: 33% No disease evidence: 29% Patients with partial or total penectomy had a higher cancer specific mortality rate than	The metastatic rate was higher in patients with partial or total penectomy compared with the rate in those with local resection or circumcision.		LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							those with circumcision or local excision (p= 0.038)			
Leijte, 2008, European Urology	Retrospective case series	n= 747 (overall) n= 547 Netherlands 1956-2006 n= 202 Sweden 1984-2007 <u>Median follow-up:</u> 60.6 mo (3-358 mo)	To give insight into the recurrence patterns of penile carcinoma in different treatment settings and provide recommendations for follow up.	Tis-T4 <u>Age at diagnosis</u> Netherlands: 65 y Sweden: 64 y	Penile-preserving therapy (laser or local excision) n= 415 patients with Tis, Ta, T1, T2 tumours < 2 cm or < 3 cm	Partial or total amputation n= 285 patients with higher staged tumours	**Recurrences** <u>Overall</u> 205/700 patients 92.2% occured within the first 5 years <u>Local</u> Overall: 18.6% Penile-preserving therapy: 27.7% Amputation: 5.3% T1G2: 25.8% T1G3: 20% T2G2: 25% T2G3: 31.6% <u>Regional</u> 9.3% All regional recurrences occurred within 50 mo. <u>Distant</u> 1.4% All distant recurrences occurred within 16 mo. **5y-DSS** Overall: 60.6% (95% CI 53.8-68.2%) Local recurrence: 92% Regional recurrence: 32.7% Distant recurrence: all died within 22 mo	Patients undergoing penile-preserving therapy, patients surgically staged as pN+, and those undergoing a wait-and-see policy for the nodal status are at high risk of developing a recurrence.		LoE 4 RoB 16/20
Lont, 2006, Journal of Urology	Retrospective cohort study	n= 257 Netherlands 1956-2001 <u>Median follow-up</u> 106 mo (16-541 mo)	To evaluate our experience with primary tumor treatment for T1 and T2 penile squamous cell carcinoma and	T1, T2 G1-3 N0-N+ <u>Mean age</u> 63 y (29-94 y)	Penis preservation n= 157	(Partial) Amputation n= 100	**Local recurrence** <u>Penis conservation (overall)</u> T1: 31% T2: 37% Total: 34%	T1 and small T2 (less than half of the glans, usually less than 3 cm) tumors can both be treated safely by penis conserving methods.		LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
			discussed the clinical implications of a local recurrence				Penis amputation (overall) T1: 29% T2: 23% Total: 25% Local surgery T1: 23% T2: 36% Total: 29% Radiotherapy T1: 29% T2: 40% Total: 35% Local surgery+ radiotherapy T1: 20% T2: 14% Total: 17% Excision/Nd:YAG laser T1: 29% T2: 40% Total: 35% Excision/CO2 laser T1: 37% T2: 40% Total: 34% Penis amputation (partial) T1: 0% T2: 11% Total: 10% Penis amputation (total) T1: - T2: 0% Total: 0% **5 y- local recurrence-free**			

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							similar for T1 and T2 tumors p= 0.1 Overall Penis amputation: 88% (95% CI 81-95%) Penis preservation: 63% (95% CI 54-72%) p= 0.0001 **Complications (overall)** • Urethral stenosis (after (partial) amputation and radiotherapy) • Skin changes (after radiotherapy) • Edema (after radiotherapy) • Phimosis (after radiotherapy) • Complete deformation of the glans with sexual dysfunction (after radiotherapy) • Local infection (after local excision) • Postoperative haemorrhage (after laser treatment) • Delayed epithelialization (after laser treatment) • Persistent irritating papules on the glans disturbing sexual function (after laser treatment) • Pulmonary embolism			

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Mistry, 2007, BJU International	Retrospective cohort study	n= 65 United Kingdom 1993-2003	To audit the penile cancer workload, management and outcome within a regional cancer network serving a population of ≈1 million in the West Midlands, comparing these data to that published by the British Association of Urological Surgeons National Cancer Registry, the United Kingdom National Institute of Clinical Excellence and the European Associations of Urology guidelines.	G1-3 Tis-T4 N0-N2 M0-M1 Mean age 63 y (27-94 y)	Conservative Treatment (local excision, topical chemotherapy, radiotherapy, glansectomy) n= 36 Glansectomy (n= 3) • T1 (n= 2) • T2 (n= 1)	(Partial) Penectomy n= 25 Partial penectomy (n= 18) • T1 (n= 9) • T2 (n= 4)	**Recurrence** Partial penectomy 1/18 developed local recurrence 4 y-survival after salvage penectomy 75%	Rates of conservative therapy were good in this group and associated with good survival. Survival could be improved by identifying and aggressively treating those patients at high risk of lymph node disease.	Ergebnisse wurden nur für die Zielpopulation extrahiert	LoE 3 NOS 5/9
Rempelakos, 2004, Journal of B.U.On.	Retrospective cohort study	n= 360 Greece 1974-1993	To report the therapeutic results of 360 cases of squamous cell carcinoma of the penis treated by surgery.	T1-T4 N1-3 Mean age	• Circumcision (n= 32) • Local excision (n= 12) • Partial amputation (n= 227) • Total amputation (n= 80) • Cystostomy (n= 5)		Local recurrence • No after partial or total amputation • 7/32 with circumcision • 4/12 with local excision Complications • Urethral meatus stenosis (n= 24) Satisfactory Partial amputation: • 26% retained satisfactory sexual function	Partial amputation with at least 1.5cm margin proximal to the tumor gives excellent local control and rare recurrences.		LoE 3 NOS 6/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							• All patients had satisfactory voiding and continence. **Overall** 5 y-survival T1-3N0: 91% T1-3N1-2: 59% T1-3N3: 29% 10 y-survival T1-3N0: 80% T1-3N1-2: 49% T1-3N3: 0%			
Veeratterapillay, 2015, Urology	Retrospective cohort study	n= 203 United Kingdom 2000-2011 Median follow-up 61 mo	To report contemporary treatment outcomes of penile squamous cell carcinoma at a United Kingdom supraregional center, including patterns of therapy, oncologic results, and long-term survival.	pTis-4 N0-N3 M0-M1 Median age 62.6 y (32-89 y) pT1: 59 patients pT2: 73 patients	Penile preserving surgery n= 99 • Wide local excision (n= 42) • Glansectomy and glanuloplasty (n= 49) • Glans reling (n= 2) • Distal coporectomy and glans restruction (n= 6)	Partial penectomy n= 49 Radical penectomy n= 48 Chemo- or radiotherapy n= 7	Local recurrence 18/99 penile preserving patients after a median of 9 mo (6-42 mo) 4/97 after radical/partial penectomy Local recurrence rate Organpreserving surgery: 18% Amputative surgery: 4%	Nearly half of all tumors are managed by organ-preserving techniques, but local recurrence rates are higher although most of the recurrences could be managed without amputative surgery.		LoE 3 NOS 6/9
Yang, 2014, Journal of Urology	Retrospective cohort study	n= 171 2004-2012	To evaluate whether glans preservation would be more helpful for patients to regain satisfactory sexual competency postoperatively than partial amputation.	pTis-pT2 N0 M0 n= 135 glans preserving surgery n= 36 partial amputation Mean age 55.1 y (38-73 y)	Glans preservation n= 135	Partial amputation n= 36	**Complication rate** Total 31.8% glans preserving 91.7% partial amputation No severe complication in both groups Erectile dysfunction Glans preserving: 1.5% Partial amputation: 41.7% p< 0.001	Glans preserving surgery effectively preserves the functional anatomy and cosmetic appearance of the glans penis. Glans preservation contributes to minimizing postoperative erectile dysfunction and negative psychological impediments, and promotes return to satisfactory sexual performance. Patients	Nur signifikante Ergebnisse dargestellt. Vollständige Ergebnisse sind in Table 1 und 2 dargestellt.	LOE 3 NOS 8/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							Erectile pain Glans preserving: 1.5% Partial amputation: 11.1% p= 0.018 Urethral stricture Glans preserving: 2.2% Partial amputation: 11.1% p= 0.036 **Erectile function** Preoperativ Glans preserving: 20.6 ± 4.0 Partial amputation: 20.2 ± 3.9 p= 0.591 Postoperativ Glans preserving: 22.4 ± 3.9 Partial amputation: 14.9 ± 4.2 p< 0.001 **Orgasmic function** Preoperativ Glans preserving: 6.4 ± 2.5 Partial amputation: 6.2 ± 2.7 p= 0.743 Postoperativ Glans preserving: 7.7 ± 1.6 Partial amputation: 5.7 ± 1.4 p< 0.001 **Sexual desire** Preoperativ Glans preserving: 6.2 ± 1.8	treated with glans preservation have more advantages in obtaining sexual acceptance from their partners than those who undergo amputation.		

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							Partial amputation: 6.1 ± 1.5 p= 0.692 <u>Postoperativ</u> Glans preserving: 6.9 ± 1.4 Partial amputation: 6.8 ± 1.3 p= 0.784 **Intercourse statisfaction** <u>Preoperativ</u> Glans preserving: 7.7 ± 3.6 Partial amputation: 6.8 ± 2.9 p= 0.161 <u>Postoperativ</u> Glans preserving: 9.7 ± 2.3 Partial amputation: 5.9 ± 2.2 p< 0.001 **Overall statisfaction** <u>Preoperativ</u> Glans preserving: 5.3 ± 1.7 Partial amputation: 5.1 ± 1.9 p= 0.435 <u>Postoperativ</u> Glans preserving: 6.4 ± 2.1 Partial amputation: 4.3 ± 1.1 p< 0.001			
Zhu, 2015, Oncology Letters	Retrospect ive case serie	n= 1292 USA 1998-2009	To examine the penile cancer-specific survival following	T1-4 G1-4 <u>Median age</u> 67 y (57-77 y)	Local tumor excision n= 313	Partial penectomy n= 801	<u>Multivariate analyses of predictors of penile cancer-specific</u> mortality in patients treated with local	The current population-based study provides evidence supporting the oncological safety of		LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
		Median follow-up 55 mo (45-65 mo)	conservative surgery in a population-based setting, and to compare oncological outcomes between penile sparing surgery and partial/total penectomy in stage T1 disease	T1: 54% T2: 29.5% G1: 28.3% G2: 49.5%		Total penectomy n= 178	tumor excision (n= 313) Tumor stage T2-T4: HR 0.49 (95% CI 0.15-1.55) p= 0.22 Tumor grade II: HR 0.76 (95% CI 0.29-2) p= 0.58 Tumor grade III-IV: HR 0.94 (95% CI 0.27-3.23) p= 0.92 4-year penile cancer-specific mortality (matched T1 patients) Local tumor excision: 8.9% (95% CI 5-12.8%) Partial/total penectomy: 10% (95% CI 6-14%) p= 0.93	penile sparing surgery compared with partial/total penectomy in early-stage disease.		
indirekte Evidenz										
Albersen, 2018, Urol Oncol	Retrospective case serie	n= 117 United Kingdom 2005-2016 Median follow-up 33.7 mo (26.8-40.3 mo)	To investigate predictive pathological factors for local recurrence after glansectomy for penile squamous cell carcinoma and to develop a risk score for prediction of local recurrence after glansectomy.	pT1-3 G1-3 Cis N0-3	Glansectomy and glans reconstruction		Local recurrences: 12.8% Univariate Cox proportional hazards regression revealed that the risk factors for recurrence were the presence of perineural invasion, carcinoma in situ, positive margin on definitive pathology, and high-grade disease.	Perineural invasion, carcinoma in situ, positive definitive margins, and the presence of high-grade squamous cell carcinoma predict local recurrence Following glansectomy. These factors can be used to stratify patients into low-, intermediate-, and high-risk groups for recurrence which may be used to tailor follow-up.		LoE 4 RoB 13/20
Gunia, 2014, Journal of Clinical Pathology	Retrospetive cohort study (multi-centre)	n= 87 Germany 1993-2010 Median follow-up 34 mo (6-70 mo)	To evaluate the prognostic impact of the width of negative surgical margins and associated and preinvasive lesions at the	pT1-3 pN0-N+ G1-3 cM0 Median age 68 y (57-77 y) n= 44 pT1	Partial penectomy n= 61	Total penectomy n= 26	Median width of negative surgical margins: 18mm **Overall patients** No recurrence Cancer-specific survival rates	Since the width of the negative surgical margin does not seem to represent an independent prognostic parameter in patients with negative surgical margins, unnecessary radical surgery should		LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
			negative surgical margins in patients with penile squamous cell cancer.	n= 26 pT2			1-year: 92% 3-years: 73% 5-years: 68% **Multivariable analysis for predicting cancer-specific mortality** Width of negative surgical margins (continuous per mm) HR 0.95 (0.89-1.02) p= 0.166 Partial penectomy (Reference: total penectomy) HR 0.10 (0.01-2.10) p= 0.14	be replaced by more conservative surgical techniques in the treatment of penile cancer.		
Hoffmann, 1999, Cancer	Retrospect ive case serie	n= 14 Mean follow-up Partial penectomy: 33.1 mo (3-75 mo) Total penectomy: 40 mo	To evaluate the relation between paraffin section microscopic pathologic margins and local recurrence.	pTis- >T1	Partial penectomy Range mean mm: 3.5-14.4 mm n= 7	Total penectomy Range mean mm: 10.8-25 mm n= 7	Partial penectomy 1/7 died 1/7 metastatic squamous cell carcinoma 0/7 local or regional recurrences Total penectomy 0/7 local recurrences 2/7 clinically positive inguinal lymph nodes 2/7 died **Overall** 7/9 T1 patients or greater had microscopic pathologic margins ≤ 10 mm 0/7 local recurrences 1/7 inguinal lymph node metastases	Adequate treatment of invasive squamous cell carcinoma of the penis does not appear to mandate a 15–25-mm macroscopic margin. The presence of a microscopic pathologic margin of 10 mm appears sufficient to control local disease.		LoE 3 NOS 6/9
Korets, 2007, Annals of	Retrospect ive case serie	n= 32 USA 1989-2005	To present our institutions experience with squamous cell	pTis pT1-3 G1-3	Partial penectomy		3y-OS Overall: 56% (95% CI 38-75%)	Partial penectomy for squamous cell carcinoma of the penis provides		LoE 4 RoB 13/20

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Surgical Oncology		Mean follow-up 37 mo (2-151 mo)	carcinoma of the penis, with analysis of oncologic efficacy and survival.	Median age 61 y (29-97 y)			pTis+pT1: 70% (95% CI 41-98%) pT2/3: 51% (95% CI 28-74%) well-differentiated tumors: 86% (95% CI 60–100%) moderate- and poor-differentiated tumors: 48% (95% CI 26–70%) 12 patients died • 9/12 related to penile cancer • 3/12 unknown causes Complications • Decreased erectile function (n= 6) • Lower extremity swelling (n= 5) • Decreased libido (n= 1) • Decreased force of urinary stream (n= 1)	excellent local control, with low recurrence rate, and acceptable maintenance of urinary and sexual function.		
Li, 2011, Urology	Retrospective case serie	n= 32 China 2006-2010 Median follow-up 26. 5 mo (2-61 mo)	To evaluate the complications and outcomes of organ-sparing surgery in penile cancer.	Tis-T2 G1-3 Mean age 45.5 y (24-70 y)	Organsparing surgery • Radical circumcision (n= 8) • Wide local excision (n= 18) • wide local excision+ circumcision (n= 6) n= 32		**Organ-sparing surgery** Postoperative morbidity 9.4% had minor complications (grade 1 dehiscence, grade II abcess) Local control 90.6% all recurrences occured within 6 mo **Partial/Total penectomy** Postoperative morbidity	Organ-sparing surgery, such as radical circumcision and wide local excision is an appropriate treatment option for selected penile cancer patients. It preserves sexual and urination function without significantly increasing the risk of recurrence.	Vergleichs-gruppe „Partial/ total penectomy (n= 84)“ war nicht Teil der Studie, wurde aber im Ergebnisteil als Vergleich herangezogen.	LoE 4 RoB 11/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							13.1% hematoma, abscess, wound infection, and urethra orifice necrosis Recurrence 7.1% There was no statistically significant difference in rates of recurrence and morbidity between extirpative surgery and conservative treatment (p= 0.71 and 0.75, respectively)			
Lümmen, 1999, Urologe	Retrospektive case serie	n= 22 Germany 1986-1994	Darstellung der Krankheitsverläufe und Behandlungsergebnisse der Patienten mit Peniskarzinom.	T1-4 N0-2 M0 G1-3 Mean age 56 y (37-90 y)	Partial amputation n= 19	Penectomy n= 3	Dreijahresüberlebensrate T1-2N1M0: 67% T3-4N1M0: 25% Lokalrezidiv Teilamputation: 3/19 Amputation: keine Angabe	Nach unseren Ergebnissen bietet nur die radikale Operation in niedrigen Tumorstadien unter Resektion der inguinalen Lymphknoten die Chance auf eine Heilung.		LoE 4 RoB 13/20
McDougal, 2005, Journal of Urology	Case serie	n= 7 Follow-up 1-5 y	To report our experience with techniques that we have developed to preserve the penis, while eradicating local disease.	T1-2 N0-3 Age 46-78 y	Partial glans excision n= 5	Full-thickness graft n= 2	**Recurrence** Partial glans excision 3/5 no recurrence after 5 y 1/5 recurrence after 6 mo 1/5 2mm area of dysplasia at the margin Shaft skin excision 2/2 no recurrence after 2 y	In select cases wide local excision with grafting or skin advancement results in a normal phallic appearance without jeopardizing cancer control.		LoE 4 RoB 10/20
Morelli, 2009, International Journal of Impotence Research	Retrospective case serie	n= 15 Italy 2003-2008 Mean follow-up	To present the outcome data of patients who underwent total glansectomy with split-	Ta-T3 G1-3 Mean age 51 y (42-59 y)	Glansectomy with split-thickness skin graft		Local recurrence none Complications • Partial graft loss (n= 2)	Our results with the described technique of neoglansplasty produce good oncological, cosmetic and functional results with minimal		LoE 4 RoB 13/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
		36 mo (10-67 mo)	thickness skin graft as treatment of glans carcinoma.				• Meatal stenosis (n= 1) • Phimosis (n= 1) Death 1 patient with pT1G2 for systemic recurrence (29 mo after surgery)	morbidity. The cosmetic and functional results with regard to the penis using this technique are superior to amputation alone, without sacrificing cancer control.		
Nam, 2017, The World Journal of Mens Health	Retrospective case serie	n= 52 South Korea 2005-2015 Mean follow-up 61.4 mo (7-120 mo)	The aim of this study was to assess the clinicopathologic characteristics of penile cancer, including patterns of therapy, oncologic results, and survival	T≤1-4 N0-N3 M0-M1 Mean age 64.3 y (16-67 y)	Partial penectomy n= 34	Total penectomy n= 12 Chemo- or radiotherapy n= 6	**Overall** 5-y CSS 84% **Associations with survival** (univariate analysis) Operative method (total vs. partial penectomy) HR 0.315 (95% CI 0.053-1.88) p= 0.205	Partial penectomy was the most common treatment of penile lesions. The oncologic outcomes were good, with a 5-year CSS of 84.0%.		LoE 3 NOS 5/9
O'Kane, 2011, Advances in Urology	Retrospective case serie	n= 25 1998-2008 Mean follow-up 28 mo (6-66 mo)	To report outcome data for patients with penile cancer treated surgically with glansectomy and skin grafting.	Cis T1-3 G1-3 Mean age 60 y (39-83 y)	Glansectomy and skin grafting 7= T1G2 2= T1G3 1= T2G2 2= T2G3		DSS: 92% Recurrence • 2 patients who had positive nodes at lymph node dissection developing groin recurrence • 1 patient (G2T1) developed a local recurrence Sexuality 9/11 able to achieve erections 6/11 sexual active 1/11 having fathered a child Complications 2/25 meatal stenosis requiring dilatation	Penile preserving surgery with glansectomy and skin grafting is a successful technique with minimal complications for local control of penile carcinoma arising on the glans. Careful followup to exclude local recurrence is required.		LoE 4 RoB 11/20
Parnham, 2018,	Retrospective case serie	n= 177 United Kingdom	To show the efficacy and safety of	Age 61.3 ± 13.5 y	Glansectomy and split-		Local recurrence 9.3%	Glansectomy and split-thickness skin graft comprise a safe		LoE 4

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
European Journal		2005-2016 Median follow-up 41.4 mo (1.9-155 mo)	glansectomy and split-thickness skin graft reconstruction.		thickness skin graft		Median time to local recurrence: 8.7 mo (95% CI 3.2-19.9 mo) 10.7% died of penile cancer 2.8% developed meatal stenosis managed with urethral dilatation	procedure in terms of oncologic control and complications for patients with penile cancer confined to the glans penis.		RoB 11/20
Philippou, 2012, Journal of Urology	Retrospective cohort study	n= 179 2002-2010 Mean follow-up 42.8 mo (4-107 mo)	To assess the oncological outcome of penile conserving surgery and identified parameters predicting local recurrence, including resection margins.	T1-3 G1-3 Mean age 60.9 y (28-89 y)	Circumcision (n= 13) Wide local excision + primary closure or split skin graft reconstruction (n= 29) Glansectomy + split skin graft reconstruction (n= 87) Glansectomy, distal corporectomy + split skin graft reconstruction (n= 50)		Recurrences Circumcision Local: 15.4% Regional: - Distant: - Wide local excision + primary closure or split skin graft reconstruction Local: 10.3% Regional: 3.4% Distant: - Glansectomy + split skin graft reconstruction Local: 6.9% Regional: 12.6% Distant: 2.3% Glansectomy, distal corporectomy + split skin graft reconstruction Local: 10% Regional: 14% Distant: 14% Patients with local recurrence after penile preserving surgery • T1: 6.8% • T1G2: 5.3% • T1G3: 8.3% • T2: 10.3%	Penile conserving surgery is oncologically safe and a surgical excision margin of less than 5 mm is adequate.		LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							• T2G2: 5.4% • T2G3: 18.5% • T3: 13% <u>Mean time to recurrence (overall)</u> Local: 26.1 mo (5-66 mo) Regional: 26.8 mo (6-71 mo) Metastatic: 11.7 mo (3-17 mo) Tumor grade (G3) (p= 0.003), stage (T2 or greater) (p= 0.021) and lymphovascular invasion (p= 0.014) were identified as independent predictors for local recurrence. <u>Overall 5 y-local recurrence-free rate</u> 86.3% (95% CI 82.6-90.4%)			
Pietrzak, 2004, BJU International	Prospectiv e cohort study	n= 78 <u>Mean follow-up</u> 16 mo	To present early outcome data from patients treated for invasive penile cancers with organ-sparing surgery, as the treatment of such malignancies has traditionally either been amputative surgery or radical radiotherapy, both associated with significant physical and	Ta-T3 G1-G3 <u>Mean age</u> 61 y (35-83 y)	Penile preserving surgery (n= 39) Partial glansectomy with primary repair (n= 5) Partial glansectomy with graft reconstruction (n= 5) Glansectomy with reconstruction (n= 21)		<u>Recurrence</u> Of those who had partial glansectomy, one had a tumour recurrence on the residual glans; none of those who had the glans removed had tumour recurrence <u>Complications</u> Required revisional surgery for positive margins (n= 2) Partial graft loss requiring re-grafting (n= 1) Radionecrosis (n= 1)	With careful patient selection and meticulous follow-up, most patients with invasive penile carcinoma can be offered penile-preserving surgery.		LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
			psychosexual morbidity.		Glansectomy, distal corporectomy + reconstruction (n= 8)		Graft overgrowth of the external urethral meatus (n= 2)			
Schlenker, 2011, Urol Oncol	Retrospective case serie	n= 38 Germany 1982-2008 Mean follow-up 78.1 mo (9-285 mo)	To analyze the oncologic outcome of patients with penile carcinoma with long-term follow-up in a single-center study	T1G2 pN0-N+ Mean age 61 y (25-93 y)	• Nd:YAG laser-therapy (n= 22) • Excision or circumcision (n= 5) • Partial amputation (n= 11)		Local recurrence Overall: 12 recurrences (31.6%) Lasertherapy: 9 recurrences Circumcision: 1 recurrence (Partial) Amputation: 2 recurrences Cancer-related deaths Without recurrence: 5/26 With recurrence: 2/12 p= 0.7944	For patients with T1 G2 penile cancer, organ preserving therapy appears to be a suitable treatment option.		LoE 4 RoB 14/20
Smith, 2007, European Urology	Prospective case serie	n= 178 United Kingdom Mean follow-up 27 mo (4-68 mo)	To present medium-term outcome data for patients with invasive penile cancer treated with glansectomy and reconstruction with a split-thickness skin graft.	T1-2 G1-3 N0-N+ Mean age 60 y (27-87 y)	• Glans resurfacing (n= 18) • Circumcision (n= 36) • Wide local excision with primary closure (n= 39) • Partial glansectomy and reconstruction (n= 8) • Glansectomy and reconstruction (n= 8) • Glansectomy and reconstruction (n= 72)		Recurrence 3/72 late recurrence (two patients with G1T1, one patient with G3T2)	Glansectomy appears to be an oncologically safe and effective procedure for patients with glans-confined squamous cell tumours. It preserves maximum phallic length and results in a very satisfactory cosmetic penile appearance after reconstruction.		LoE 4 RoB 12/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
					• Glansectomy, distal corporectomy and reconstruction (n= 26) • Partial penectomy (n= 11) • Radical penectomy (n= 19)					
Tang, 2017, Urology	Retrospective case serie	n= 410 1999-2016 Median follow-up 42 mo (29-56 mo)	To analyze the recurrence and survival outcomes of glansectomy in patients with penile squamous cell carcinoma.	pTa/Tis pT2-4 G1-3 Median age 64 y (53-72 y) pT1: 26.3% pT2: 58.5%	Glansectomy		Recurrence Local: 7.6% Regional: 3.4% Distant: 2.2% Overall recurrence-free survival 1-y: 98% 2-y: 94% 5-y: 78% ≤pT1 recurrence-free survival 1-y: 100% 2-y: 96% 5-y: 81% pT2 recurrence-free survival 1-y: 96% 2-y: 95% 5-y: 81% pT3 or pT4 recurrence-free survival 1-y: 96% 2-y: 95% 5-y: 88% There were no differences in recurrence location among pathologic stages (p= 0.15)	Penile sparing surgery with glansectomy remains a safe treatment option for penile squamous carcinoma. Appropriately selected tumors classified as pT2 can also be safely treated with glansectomy as there was no difference in recurrence or survival among pathologic stages.		LoE 4 RoB 14/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							5 y-OS: 82% There were no differences in OS when stratified by pathologic stage (p= 0.67)			
Veeratterapillay, 2012, BJU International	Cohort study	n= 65 United Kingdom 2001-2008 <u>Median follow-up</u> 40 mo (12-72 mo)	To describe the outcomes of organpreserving surgery for penile cancer at a United Kingdom tertiary referral centre.	Cis G1-3 Tis-T2 <u>Mean age</u> 62 y (32-89 y) G2-3: 72%	Penile-preserving surgery • Glansectomy and glanuloplasty (n= 46) • Partial glansectomy and reconstruction with splitthickness skin graft (n= 1) • Glans relining (n= 3) • Glansectomy, distal corporectomy and reconstruction (n= 15)		<u>Local recurrence</u> Glansectomy and glanuloplasty: 6% Glansectomy, distal corporectomy and reconstruction: 13% Median time to recurrence: 15 mo <u>Complications</u> • Partial graft loss (1.5%) • Graft contractures (4.5%) • Meatal stenosis (7.5%) • Deemed to had a poor cosmetic outcome (5%) 85% reported good erections	Penile-preserving surgery can achieve good penile cancer control with minimal morbidity and reduced psychosexual side-effects.	Im Ergebnisteil und Abstract werden nur 6% lokale Rezidive berichtet. Tabelle 2 zeigt aber noch 13% lokale Rezidive.	LoE 3 NOS 4/9

Tabelle 23: „Sollen Patienten mit pT1, pT2, pT3 Peniskarzinom eine chirurgische Resektion mit knappem oder weitem Schnittrand erhalten?“

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Agrawal, 2000, BJU International	Prospective case serie	n= 64 India 1996-1998	To explore the possibility of reducing the margin of clearance at surgery for carcinoma of the penis without causing an increase in the incidence of local tumour recurrence, so that the functional and cosmetic compromise associated with penectomy might be minimized.	T1= 63 patients T4= 1 patient G1-3 Mean age 52.9 y	Partial or total penectomy		**Histological extent beyond the gross tumour margin** Grade 1 (n= 20) 5 mm: 2 patients 10 mm: 0 patients 15 mm: 0 patients Grade 2 (n= 32) 5 mm: 5 patients 10 mm: 0 patients 15 mm: 0 patients Grade 3 (n= 12) 5 mm: 2 patients 10 mm: 3 patients 15 mm: 0 patients	We conclude that all carcinomas of the penis should be graded histologically to determine the margin of clearance required at surgery. For grade 3 lesions, which are more aggressive, a 15-mm margin of normal proximal shaft needs to be lost, whereas for grade 1 and 2 tumours, a margin of 10 mm is sufficient, thereby leaving a more acceptable penile stump length.		LoE 4 RoB 15/20
Chuanyu, 2011, Annals Dermatology	Retrospective case serie	n= 11 China 2002-2009 Mean follow-up 36 mo	To report the surgical treatment for 11 cases of penile verrucous carcinoma.	Tumor size: 2-10 cm Mean age 62 y (49-85 y)	Partial penectomy n= 8 Surgical margin: 2cm	Local excision n= 3 Surgical margin: 0.5~1 cm were adopted according to the size of tumor.	All the patients were disease-free with no case of recurrence and metastasis.	We suggest that lymphadenectomy is not necessary in case of the patients with the final diagnosis of penile verrucous carcinoma by histologic examination.		LoE 4 RoB 8/20
Gunia, 2014, Journal of Clinical Pathology	Retrospetive cohort study	n= 87 Germany 1992-1993 Median follow-up 34 mo (6-70 mo)	To evaluate the prognostic impact of the width of negative surgical margins and associated and preinvasive lesions at the negative surgical margins in patients with penile squamous cell cancer.	pTa1-pT3 pN0-N+ G1-3 cM0 Median age 68 y (55-77 y)	Partial penectomy n= 61	Total penectomy n= 26	Median width of negative surgical margins: 18 mm No recurrence **Multivariable analysis for predicting cancer-specific mortality** Width of negative surgical margins (continuous per mm)	Since the width of the negative surgical margin does not seem to represent an independent prognostic parameter in patients with negative surgical margins, unnecessary radical surgery should be replaced by more conservative surgical techniques in the		LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							HR 0.95 (0.89-1.02) p= 0.166 The width of the negative surgical margin failed to represent independent predictive parameters in terms of cancer-specific mortality.	treatment of penile cancer.		
Hegarty, 2014, BJU International	Systematic review	n= 48 articles Follow-up ≥24 months follow-up	To gather current evidence-based recommendations for the management of primary penile tumours.		Different organ-sparing techniques		• The evidence base for using a 2-cm clearance margin is unknown • Only 12 of 64 tumours had microscopic extension beyond the gross tumour margin. Three of 12 tumours had extension of 10–15 mm from the edge of the visible tumour (all grade 3). Nine tumours had microscopic extension limited to 5–10 mm from the macroscopic edge. • 48% of patients had clear surgical margins of ≤10 mm, while 90% had margins of <20 mm. • At a mean follow-up of 26 mo only 4% of cases had local recurrence, managed successfully with further local excision.	The authors concluded that adequate oncological control is achieved with excision margins of only a few millimetres.		LoE 3 ROBIS high
Hoffmann, 1999, Cancer	Retrospect ive cohort study	n= 14	To evaluate the relation between paraffin section	pTis- >T1	Partial penectomy	Total penectom y	Partial penectomy 1/7 died	Adequate treatment of invasive squamous cell carcinoma of the penis		LoE 3 NOS 6/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		Mean follow-up Partial penectomy: 33.1 mo (3-75 mo) Total penectomy: 40 mo	microscopic pathologic margins and local recurrence.		Range mean mm: 3.5-14.4 mm n= 7	Range mean mm: 10.8-25 mm n= 7	1/7 metastatic squamous cell carcinoma 0/7 local or regional recurrences Total penectomy 0/7 local recurrences 2/7 clinically positive inguinal lymph nodes 2/7 died **Overall** 7/9 T1 patients or greater had microscopic pathologic margins ≤ 10 mm 0/7 local recurrences 1/7 inguinal lymph node metastases	does not appear to mandate a 15–25-mm macroscopic margin. The presence of a microscopic pathologic margin of 10 mm appears sufficient to control local disease.		
Kamel, 2017, Journal of Urology	Systematic review	n= 50 articles 1985-2016 Follow-up 24 mo or longer	To increase awareness of organ sparing surgery for penile cancer and their applicability, to evaluate the techniques objectively and to provide guidance to the practicing urologist.		Organ-sparing surgery		These studies reveal that a 2 cm safety margin is unnecessary as long as intraoperative frozen sections are negative. Currently a 5 mm margin is accepted. Patients with positive margins in the permanent specimens should undergo repeat excision until negative margins are achieved.	In properly selected patients with penile cancer organ sparing surgery provides comparable oncologic outcomes to conventional techniques, including total and subtotal amputations. Many patients are able to urinate while standing and a significant number are able to have intercourse.		LoE 3 ROBIS high
Minhas, 2005, BJU International	Three arms cohort study	n= 51 2000-2004 Median follow-up 26 mo (2–55 mo)	Review our experience of conservative surgery for penile cancer and to determine the excision margin required to achieve oncological control.	Grade Cis-3 Stage Tis-T3 Mean age 61 y (35-82 y)	Glansectomy n= 26	Partial penectomy n= 16 Wide localized excision n= 9	**Overall distribution of surgical resection distances from the tumour edge** Involved: 6% >20 mm: 4% 11-20 mm: 42% 6-10 mm: 16% 0-5 mm: 32%	A traditional 2-cm excision margin is unnecessary for treating squamous cell carcinoma of the penis. Conservative techniques, involving excision margins of only a few millimetres, appear to offer excellent oncological control.		LoE 3 NOS 6/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							4% developed local tumour recurrence **Wide localized excision** Involved: 2 (skin), 1 (deep) >20 mm: 0 11-20 mm: 5 (skin), 3 (deep) 6-10 mm: 0 (skin), 2 (deep) 0-5 mm: 3 (skin), 5 (deep) **Glansectomy** Involved: 0 (skin), 3 (deep) >20 mm: 0 (skin), 1 (deep) 11-20 mm: 12 (skin), 11 (deep) 6-10 mm: 12 (skin), 2 (deep) 0-5 mm: 4 (skin), 14 (deep) **Partial penectomy** Involved: 0 >20 mm: 2 (skin), 1 (deep) 11-20 mm: 5 (skin), 7 (deep) 6-10 mm: 0 0-5 mm: 3 (skin), 4 (deep)			
Philippou, 2012, Journal of Urology	Retrospect ive cohort study	n= 179 2002-2010 Mean follow-up 42.8 mo (4-107 mo)	To assess the oncological outcome of penile conserving surgery and identified parameters predicting local recurrence, including resection margins.	T1-3 G1-3 Mean age 60.9 y (28-89 y)	Circumcision (n= 13) Wide local excision + primary closure or split skin graft		Recurrences Circumcision Local: 15.4% Regional: - Distant: - Wide local excision + primary closure or split skin graft reconstruction	Penile conserving surgery is oncologically safe and a surgical excision margin of less than 5 mm is adequate.		LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
					reconstruction (n= 29) Glansectomy + split skin graft reconstruction (n= 87) Glansectomy, distal corporectomy + split skin graft reconstruction (n= 50)		Local: 10.3% Regional: 3.4% Distant: - <u>Glansectomy + split skin graft reconstruction</u> Local: 6.9% Regional: 12.6% Distant: 2.3% <u>Glansectomy, distal corporectomy + split skin graft reconstruction</u> Local: 10% Regional: 14% Distant: 14% <u>Patients with local recurrence after penile preserving surgery</u> • T1: 6.8% • T1G2: 5.3% • T1G3: 8.3% • T2: 10.3% • T2G2: 5.4% • T2G3: 18.5% • T3: 13% <u>Mean time to recurrence (overall)</u> Local: 26.1 mo (5-66 mo) Regional: 26.8 mo (6-71 mo) Metastatic: 11.7 mo (3-17 mo) Tumor grade (G3) (p= 0.003), stage (T2 or greater) (p= 0.021) and lymphovascular invasion (p= 0.014) were identified as			

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							independent predictors for local recurrence. Overall 5 y-local recurrence-free rate 86.3% (95% CI 82.6-90.4%)			
Pompeo, 2015, Current Opinion in Urology	Systematic review	1990-2014	To update the contemporary knowledge related to penile-sparing surgeries.		• Partial amputation • Glansectomy • Mohs procedure • Laser surgery		Partial amputation If risk factors for local or distant recurrence are absent (pT1 and Grades I–II), reduction of surgical margins (≤1.0cm) is proposed. Recent review (Hegarty 2014 see above in this table) suggests that 1.0–1.5cm margin is safe. For Grade III or ≥T2 tumors, 1.5–2.0cm margin is still the rule.	Penile-sparing surgery are simple and reproducible procedures, conferring satisfactory disease control with superior cosmetic results. Penile-sparing surgeries are indicated for selected Ta-T1, Tis and small T2 lesions or for salvage after irradiation failures.		LoE 3 ROBIS high
Rempelakos, 2004, Journal of B.U.On.	Retrospective cohort study	n= 360 Greece 1974-1993	To report the therapeutic results of 360 cases of squamous cell carcinoma of the penis treated by surgery.	T1-T4 N1-3 Mean age 65 y (29-91 y)	• Circumcision (n= 32) • Local excision (n= 12) • Partial amputation (n= 227) • Total amputation (n= 80) • Cystostomy (n= 5)		Local recurrence • No after partial or total amputation • 7/32 with circumcision • 4/12 with local excision Complications • Urethral meatus stenosis (n= 24) Satisfactory Partial amputation: • 26% retained satisfactory sexual function • All patients had satisfactory voiding and continence. **Overall** 5 y-survival T1-3N0: 91%	Partial amputation with at least 1.5cm margin proximal to the tumor gives excellent local control and rare recurrences.		LoE 3 NOS 6/9

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							T1-3N1-2: 59% T1-3N3: 29% <u>10 y-survival</u> T1-3N0: 80% T1-3N1-2: 49% T1-3N3: 0%			
Smith, 2007, European Urology	Prospectiv e case serie	n= 178 United Kingdom <u>Mean follow-up</u> 27 mo (4-68 mo)	To present medium-term outcome data for patients with invasive penile cancer treated with glansectomy and reconstruction with a split-thickness skin graft.	T1-2 G1-3 N0-N+ <u>Mean age</u> 60 y (27-87 y)	• Glans resurfacing (n= 18) • Circumcisio n (n= 36) • Wide local excision with primary closure (n= 39) • Partial glansectomy and reconstructi on (n= 8) • Glansectom y and reconstructi on (n= 8) • Glansectom y and reconstructi on (n= 72) • Glansectom y, distal corporecto my and reconstructi on (n= 26) • Partial penectomy (n= 11) • Radical penectomy (n= 19)		<u>Distance to nearest excision margin (n= 61)</u> Margin involved: 6 specimens Nearest margin <1 mm: 6 specimens Nearest margin 1-5 mm: 25 specimens Nearest margin 6-10: 14 specimens Nearest margin >11 mm: 10 specimens Of the 6 patients with a nearest resection involved margin 4 patients were observed (for 12, 13, 19, and 23 mo) with no evidence of recurrence. 2 patients were observed briefly but showed evidence of recurrence within a few weeks and underwent local excision with no further problems. <u>Recurrence</u> 3 late recurrence (two patients with G1T1, one patient with G3T2) <u>Complications</u> • Partial graft loss (n= 2)	As our understanding of penile cancer increases, it is becoming increasingly apparent that the traditionally advocated resection margin has resulted in over treatment of many patients. With close postoperative observation, glansectomy is an ideal treatment for patients with T1 and T2 penile carcinoma confined to the corpus spongiosus.		LoE 4 RoB 12/20

Referenz	Studien-design	Studien-charak-terisitika	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							• Graft overgrowth of the external urethral meatus (n= 1)			
Sri, 2018, BJU International	Case serie	n= 332 2001-2013 Follow-up at least 24 mo	To evaluate the significance of close surgical margins in organsparing surgery in the treatment of penile squamous cell carcinoma and clinicopathological factors that may influence local recurrence.	G1-3 T1-3 Mean age 63.5 y (SD 13.6 y)	Organ-sparing surgery		Overall local recurrence: 4% Recurrence clear margin ≤1 mm: 15% 1 to ≤5 mm: 1% 5 to ≤10 mm: 4% >10 mm: 5% Clear margin of <5 mm vs. clear margin of >5 mm No statistical difference (p=1.0) Close clear margin of <1 mm vs. clear margin of >1 mm RR 5.9 (p< 0.001) <1 mm clear margin cohort had a significantly increased risk of recurrence over time compared to the other cohorts (p= 0.01)	We conclude that a deep clear margin of >1 mm has a very low risk of local recurrence in penile organ-sparing surgery.		LoE 4 RoB 11/20

10.1.4. Schlüsselfragen der AG Therapie cN0-3

Tabelle 24: „Soll bei Patienten mit cN2/3 eine neoadjuvante Chemotherapie vor ing. LAD durchgeführt werden?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
Bermejo, 2007, Journal of Urology	Retrospectiv e case serie	n= 10 1985-2000 Median follow-up 62 mo (48-84 mo)	To report the experience with surgical consolidation for a select group of patients with clinically evident or pathologically proven lymph node involvement who initially demonstrated stable disease or an objective response to chemotherapy.	Tx-3 N1-3 M0-1 Median age 56 y (41-86 y)	Induction chemotherapy Paclitaxel, ifosfamide+ cisplatin Methotrexate, bleomycin+ cisplatin Paclitaxel+ carboplatin		Response 4/10 complete 1/10 partial 5/10 stable disease 5 y-OS 50% Median survival (3 or fewer positive lymph nodes, n= 3) 23 mo (3-30 mo) Toxicity 3/10 grade III nonhematological toxicity, including 1 episode each of bleomycin toxicity, acute renal failure and deep venous thrombosis	Selected patients with metastatic penile cancer that show disease stabilization or a response to chemotherapy should be considered for surgical consolidation to extend survival.		LoE 4 RoB 13/20
Chen, 2009, Japanese Journal of Clinical Oncology	Retrospectiv e case serie	n= 5 2005-2009 Mean follow-up 24.2 mo (17-34 mo)	To evaluate the efficacy and adverse effects of intra-arterial chemotherapy in the treatment of penile cancer	N0-N+ M0 Median age 61 y (48-79 y)	Inguinale LAD+ intra-arterial chemotherapy Methotrexate (110 mg/ m2/day), mitomycin C (4.5 mg/m2/day), bleomycin (15 mg/ m2/day), cisplatin (35 mg/m2/day) and 5-fluorouracil (1200 mg/m2/day)		Response 2/2 partial Time to relapse 4 mo and 8 mo Adverse effects • Anemia (grade 3) • Anorexia (grade 1-2)	Our preliminary data indicated that a combination of intra-arterial chemotherapy, neoadjuvant chemotherapy and surgery may have the potential to achieve the goal in the treatment of penile cancer with negative lymph node.		LoE 4 RoB 12/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
					n= 2					
Chiang, 2014, British Journal of Cancer	Retrospectiv e case serie	n= 12 2005-2013 Follow-up 8-88 mo	To evaluate the role of intraarterial chemotherapy as first-line therapy for penile squamous cell carcinoma.	T1-3 N0-2 M0 N2= 3 patients Age 48-89 y 5 patients with palpable inguinal node received surgery (partial/ total penectemy with LAD)	Neoadjuvant intraarterial chemotherapy (methotrexate, mitomycin C, bleomycin, cisplatin and 5-fluorouracil)		Tumor response Overall: 83% Node-negativ patients: 100% Nodal invasion: 60% Dead of disease (N2) n= 2/3 **Side effects** Grade 1 or 2 Anorexia: 7/12 (58%) Grade 3 Haematological toxicity: 3/12	The preliminary results showed that intraarterial chemotherapy could be used as first-line therapy in any stage of penile squamous cell carcinoma before surgery.		LoE 4 RoB 11/20
Dickstein, 2016, BJU International	Retrospectiv e case serie	n= 61 USA 1993-2011 Follow-up 5 y	Describe the clinical and pathological response rates, survival, and predictors of survival when using contemporary perioperative chemotherapy and surgical resection for patients with regionally advanced squamous cell carcinoma of the penis.	N0-3 N2= 20 patients N3= 37 patients Median age 60.6 y (24.5-81.4 y)	**Induction regime** TIP (Paclitaxel/ ifosfamide/ cisplatin chemotherapy) Carboplatin/ paclitaxel 5-fluorouracil/ cisplatin methotrexate/ bleomycin/ cisplatin		Objective response 39 (65%) Median OS N2: 35.8 mo (HR 0.87, 95% CI 0.24-3.13) p= 0.83 N3: 17.3 mo (HR 1.22, 95% CI 0.37-4.10) p= 0.743 Recurrence-Free-Survival N2: 35.8 mo (HR 0.82, 95% CI 0.23-2.95) p= 0.763 N3: 10 mo (HR 1.47, 95% CI 0.44-4.85) p= 0.531	Contemporary chemotherapy resulted in clinically significant responses among patients with regionally advanced penile cancer.	Patients with resectable inguinal and pelvic lymph nodes underwent consolidative LAD after completing chemotherapy	LoE 4 RoB 12/20
Djajadiningrat, 2015, Clinical	Clinical trial	n= 26 2008-2012 Netherlands	To evaluate response, toxicity, PFS and disease-	rTx, T2, T4 N0, N2, N3	4 courses of TPF (docetaxel,		Overall response 60% (CI 95% 39-79%)	Despite a fairly good response percentage, survival was	Different procedures after	LoE 3

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
Genitourinary Cancer		Median follow-up 30 mo (6-17 mo)	specific survival in patients with advanced squamous cell carcinoma of the penis treated with neoadjuvant taxane-based combination chemotherapy.	N2= 3 patients N3= 15 patients Median age 61 y (35-73 y)	cisplatin and 5-fluorouracil)		Median PFS 7 mo (95% CI 1.9-17.1 mo) Median OS 10.1 mo (95% CI 6.7-28.1 mo) Median disease-specific survival 10.3 mo (95% CI 8-∞ mo) Toxicity 26/26 Grade 4: 2 Grade 3: 14	disappointing at the expense of considerable toxicity.	chemotherapy (partial/ total penectomy, inguinal/pelvic dissection and radiation therapy)	RoB 19/20
Joshi, 2018, JAMA Oncology	Retrospective cohort study	n= 1123 2004-2014 United States of America, Puerto Rico	To determine temporal trends in use of chemotherapy for patients with lymph node positive penile cancer without metastasis and to evaluate outcomes between those who did or did not receive LND, chemotherapy, and radiotherapy.	G1-4 N1-3 Age range 50-75 y 66.8% underwent LAD	LAD with or without chemotherapy or/and radiotherapy		Multivariable model predicting use of chemotherapy N2: OR 1.54 (1.08-2.19) p= 0.02 N3: OR 2.15 (1.52-3.04) p< 0.001 Multivariable OS analysis N2: HR 1.44 (1.17-1.78) p= 0.001 N3: HR 1.93 (1.52-2.45) p< 0.001 LAD: HR 0.64 (0.52-0.78) p< 0.001 Chemotherapy: HR 1.01 (0.8-1.26) p= 0.95 **Median OS** LAD 28.8 mo (95% CI 24-40.3 mo) LAD+ Chemotherapy 44.6 mo (95% CI 23.5-114.6 mo)	Receipt of LAD, but not chemotherapy or radiotherapy, is associated with overall survival.	Unklar, ob LAD sich nur auf inguinale LAD bezieht	LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							LAD+ Chemotherapy+ Radiotherapy 37.2 (95% CI 20.7-68.1 mo) **N2/N3 subgroups** Survival Chemotherapy: HR 0.91 (95% CI 0.71-1.18) p= 0.49 Radiotherapy: HR 0.88 (95% CI 0.71-1.10) p= 0.26 Chemoradiotherapy: HR 0.97 (95% CI 0.88-1.07 p= 0.53) LND+ Chemotherapy: p= 0.77 LND+ Radiotherapy: p= 0.99			
Leitje, 2007, European Urology	Retrospectiv e case serie	n= 20 Netherlands 1972-2005 Median follow-up 23 mo (1-134 mo)	To assess the value of neoadjuvant chemotherapy in 20 patients with irresectable penile carcinoma treated at our institute.	T1-T4 N0-N3 Mean age 62 y (35-79 y)	**Neoadjuvant therapies** until 1985 Single-agent therapy with bleomycin 1986-1999 Combination chemotherapy with bleomycin, vincristin and methotrexate 1999-2001 Combination therapy of 5-fluorouracil and cisplatin Since 2001		5 y-OS 32% (95% CI 17-62%) No correlation beetween survival and: T category (p= 0.75) N category (p= 0.85) Tumor differention (p= 0.65) Age (p= 26) Responder 9/20 (2 complete, 7 partial) **Toxicity** Death: 3 Severe toxicity: 4 Side effects	These results suggest that neoadjuvant chemotherapy is a valuable treatment option for patients with irresectable penile carcinoma, which is otherwise considered incurable. Surgery should be performed only in patients showing clinical response to chemotherapy because prognosis for nonresponding patients who underwent surgery was dismal and local control was not improved.	Fünf verschiede ne Therapiefo rmen von 1972-2005, wobei die Ergebnisse für alle durch-geführten neoadjuva nten Therapien berichtet werden. Surgery after chemother	LoE 4 RoB 15/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
					Cisplatin, bleomycin and methotrexate		Grade 1 and 2: Nausea, fatigue, Grade 1 or 2: Alopecia		apy were inguinal/ pelvic LAD and partial and total penectom y	
Mitropoulos, 1994, Journal of Urology	Prospective case serie	n= 13 Greece 1990-1992 Follow-up: 11-38+ mo	Invastigate the antitumor activity and toxicity of cisplatin and interferon-alpha 2B as the primary treatment of penile carcinoma.	T2-3 M0 N0-3 Median age 62 y (27-74 y) Surgery planned 9/13 Penectomy + node dissection	20 mg/m² cisplatin intravenously and 5 x 10(6) µ/m² interferon-alpha 2B subcutaneousl y daily for 5 consecutive days		N2 (n= 1) Partial penectomy & node dissection Partial response Disease-free after 22 mo N3 (n= 1) Partial penectomy & node dissection Non-responder Died of metastatic disease (11 mo) Toxicity Flu-like symptoms (13/13) Haematological toxic effects (5/12) Renal complication rate (3/13)	Primary treatment with cisplatin and interferon-alpha 2B induced responses in 75% of 12 patients with penile carcinoma and allowed for a less radical operation than originally scheduled.	Unklar, ob „node dissection “ sich nur auf inguinale LAD bezieht	LoE 4 RoB 16/20
Necchi, 2017, Clinical Genitourinary Cancer	Retrospectiv e three arms cohort study	n= 201 12 centers Europe, USA & Canada 1990 onwards	Evaluate the impact of neoadjuvant chemotherapy alone or in conjunction with radiotherapy in patients with lymph node positive disease.	T1-4 N0-3 Median age 67 y (35-87 y) HPV-: 38 HPV+: 8	Neoadjuvant chemotherapy n= 94 N2= 20 (21.3%) N3= 45 (47.9%)	Adjuvant chemother apy n= 78 N2= 29 (37.2%) N3= 19 (24.4%) Neoadjuva nt & adjuvant chemother apy n= 21	**Median relapse-free survival** Neoadjuvant 7.7% (95% CI 6.4-9.8%) Adjuvant 32.8% (95% CI 9.7-132.7%) Both 11.1% (95% CI 9.5-24.3%) **Median OS** Neoadjuvant 17.1% (95% CI 12.5-21.5%)	Substantial uncertainties still exist regarding the indications for perioperative chemotherapy and the net benefit of administering multimodal treatment compared to surgery alone in patients with advanced penile squamous cell carcinoma and high-risk features, namely those with pelvic or	Unklar, ob LAD sich nur auf inguinale LAD bezieht	LoE 3 NOS 6/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
						N2= 8 (38.1%)	Adjuvant 105.3% (95% CI 19.8%-NE) Both 18.5% (95% CI 11.8-30.2%<) Relapse-Free Survival (N2) HR 0.78 (95% CI 0.48-1.29) OS (N2) HR 0.87 (95% CI 0.50-1.52)	bilateral lymph node involvement.		
Nicolai, 2016, Clinical Genitourinary Cancer	Retrospective cohort study	n= 47 2004-2012 Follow-up 22 mo (17-42 mo)	Evaluation of the efficacy of a combination of taxane, cisplatin and 5-fluorouracil in neoadjuvant and adjuvant settings.	N2-3 ECOG 0-1	**Neoadjuvant** Taxane, cisplatin,and 5-fluorouracil n= 28	**Adjuvant** Taxane, cisplatin,and 5-fluorouracil n= 19	**Alive and maintained progression free** Neoadjuvant 28.6% (95% CI 15.2-47.3) Median time: 17 mo (15-25 mo) Adjuvant 52.6% (95% CI 31.8-72.6) Median time: 42 mo (9-68 mo) **Relapses** Neoadjuvant 42.8% (95% CI 23.2-63.7) Median time: 8 mo (5-10) Adjuvant 42.1% (95% CI 23.2-63.7) Median time: 8 mo (9-10 mo) **Dead of Disease:** Adjuvant 42.1%	The taxane, cisplatin and 5-fluorouracil regimen is well tolerated and compares with other regimens in terms of activity and efficacy in the neoadjuvant setting. The role of perioperative treatment in these patients remains controversial.		LoE 3 NOS 8/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							Median time: 15 mo (12-23 mo) Neoadjuvant 32.1% Median time: 10 mo (4-16 mo)			
Otto, 2003, Urologe	Case serie	n= 15 Mean follow-up 15 mo	Beschreibung der Therapie des fortgeschrittenen Peniskarzinoms.	T3-4 Mean age 74 y	Neoadjuvante Chemotherapie 2–4 Kurse Polychemotherapie mit Cisplatin, Methotrexat und Bleomycin, 3 Wochen später Tumorresektion		Partielle Remission: 3 Tod: 4 (tumorbedingt) Fernmetastasen: 5 Nebenwirkungen: 11/15 Grad 2 gastrointestinal 9/15 Grad 3 hämatologisch 3/15 Grad 4 hämatologisch	Die Ergebnisse belegen, dass die Kombination von Chemotherapie und ausgedehntem operativen Vorgehen einerseits das Überleben des alten Patienten nicht nachhaltig beeinflusst, andererseits die Lebensqualität des symptomatischen Patienten entscheidend verbessert, was vorrangig auf die operative Behandlung zurückzuführen ist.	Keine Aussagen zum Node-Status	LoE 4 RoB 7/20
Pagliaro, 2010, Journal of Clinical Oncology	Clinical trial (phase 2 study)	n= 30 2000-2008 Median follow-up 34 mo (14-59 mo)	Determining the response rate, time to progression and OS of neoadjuvant chemotherapy among patients with bulky adenopathy.	N2-N3 M0 Median age 57.5 y (24-78 y) n= 22 complete chemotherapy and then LAD	Neoadjuvant treatment 175 mg/m² paclitaxel intravenously over 3 hours day 1; ifosfamide 1,200 mg/m² on days 1 to 3; and cisplatin 25 mg/m² on days 1 to 3		Median time to progression: 8.1 mo (95% CI 5.4-50+) (20/30 patients died) OS 17.1 mo (95% CI 10.3-60+)	The neoadjuvant regimen of paclitaxel, ifosfamide, and cisplatin induced clinically meaningful responses in patients with bulky regional lymph node metastases from penile cancer.		LoE 3 RoB 17/20
Pizzocaro, 2009, European Urology	Prospective case serie	n= 6 2004-2006 Italien	To evaluate the therapeutic activity of taxanes in combination with cisplatin-fluorouracil for salvage of	G1-3 T1-3 N0-3 Age 44-74 y	Neoadjuvant treatment Paclitaxel, cisplatin, and 5-fluorouracil		No evidence of disease 3/6 Follow-up: 25, 27 and 46 mo Dead of disease	Paclitaxel, cisplatin, and 5-fluorouracil chemotherapy for unresectable or recurrent nodal metastases from squamous cell		LoE 4 RoB 17/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
			primarily unresectable or relapsed nodal metastases from squamous cell carcinoma of the penis.				3/6 Follow-up: 4, 6 and 11 mo Toxicity 1/6 patients: severe nausea and vomiting, hematologic toxicity	carcinoma of the penis is promising, and the standard four courses of therapy are to be completed in responding patients.		
Pizzocaro, 1988, Acta Oncologica	Retrospective case series	n= 17 1979-1985 Italien Median follow-up 42 mo (18-102 mo)	To describe the results of adjuvant and neoadjuvant treatment with vincristine, bleomycin, and methotrexate for inguinal metastases from squamous cell carcinoma of the penis.	Age Adjuvant: 21-74 y (median: 55y) Neoadjuvant: 40-62 y	Neoadjuvant with 12 weekly courses of vincristine, bleomycin and methotrexate n= 5	Adjuvant vincristine, bleomycin and methotrexate n= 12	Neoadjuvant group Partial remission: 3 Minor remission: 2 Free of disease: 3 (20, 27 and 72 mo) Death: 2 (1 and 4 mo) Adjuvant group 11/12 free of disease 1/12 relapsed (16 mo) Survival 3= free of disease (20, 27 and 72 mo) 2= died (1 and 4 mo) Toxicity 1= Myelosuppression 2= Lung fibrosis 4= Hyperpyrexia >38°C 8= Hyperpigmentation 1= Stomatitis	Our results suggest that this low-dose combination chemotherapy is also efficient in squamous cell carcinoma of the penis.	N-Status unklar	LoE 4 RoB 9/20
Protzel, 2009, Urologia Internationalis	Systematic review	1966-2008	To review the available literature concerning chemotherapy regimens for penile cancer with response rates and	n= 7 studies with neoadjuvant setting	**Neoadjuvant treatment** • Vinblastine, Methrotrexate, Bleomycin (n= 2)	Monochemo-therapies, polychemo-therpies and adjuvant	Cisplatin (20-30 mg/m2) Methotrexate (200 mg/m2) Bleomycin (15 mg/m2) Response: 6/10	Neoadjuvant treatment should be given in all cases of fixed lymph node metastasis and possibly for all patients with suspected		LoE 3 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
			survival when reported.		• Cisplatin, Methotrexate, Bleomycin (n= 2) • Paclitaxel+ Carboplatin (n= 1) • Paclitaxel, Cisplatin, Ifosfamide (n= 1) • Paclitaxel, Cisplatin, 5-Fluoruracil (n= 1) • Cisplatin, Irinotecan (n= 1)	chemo-therapies	Treatment-related death: 2/10 Cisplatin (20 mg/m2) Methotrexate (200 mg/m2) Bleomycin (10 mg/m2) Response: 3/3 stable disease Treatment-related death: 0/3 Median survival: 7 mo Vinblastine, Methotrexate, Bleomycin Response: 6/10 Treatment-related death: 1/10 Paclitaxel+ Carboplatin Response: 3/3 Paclitaxel, Cisplatin, Ifosfamide Response: 4/5 Complete response: 3/5 Median survival: 30 mo Paclitaxel, Cisplatin, 5-Fluoruracil Response: 3/3 Complete response: 2/3 Median survival: 11 mo Cisplatin, Irinotecan Response: 6/7	lymph nodes metastasis. Adjuvant treatment should be proven with new regimens, which might also be able to improve the poor prognosis of patients with distant metastasis.		

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							Complete response: 1/7			
Tang, 2018, Urologic Oncology	Case report	n= 3 Follow-up 9-12 mo	Describe an aggressive approach for isolated retroperito- neal recurrences using a multimodal approach with systemic chemotherapy followed by consolidative lymph node dis-section in a small cohort of patients	PT3N1M0 PT2N3M0 PT3N3M0 Age 61-71 y	Postchemotherapy 3 cycles of paclitaxel, ifosfamide, and cisplatin		Response Complete: 1/3 Partial: 2/3 No Evidence of Disease 3/3	It must be appreciated that such an aggressive multimodal strategy may only prove beneficial to a subset of penile cancer patients, which should be encompassed within our important therapeutic education and discussions.	Bezieht sich auf die Behandlung von Patienten, die bereits einen Rückfall haben	LoE 4 RoB 10/20
Theodore, 2008, Annals of Oncology	Prospective phase II study	n= 28 2004-2006	To determine efficacy and feasibility of the combination regimen irinotecan and cisplatin in patients with cisplatin advanced penile cancer.	T3-4 N1-3 M1 Median age 55 y (36-77 y) WHO PS: 0-2	Neoadjuvant therapy Combination of irinotecan (60 mg/m²) on days 1, 8 and 15 and cisplatin (80mg/m²) every 28 days n= 7 (3/7 underwent a lymphadenectomy after chemotherapy)		**Neoadjuvant setting** Overall response rate 2/7 (28.6%, 95% CI 3.7% to 71%) • 1/7 complete • 1/7 partial **Overall** Clincal adverse events Grade 4: • Hypotension (n= 1) • Cardiac (thrombosis) (n= 1) • Fatigue (n= 1) • Neutropenic infection (n= 2) • Pulmonary (embolus) (n= 1) • Haemorrhage (n= 1) Grade 3: • Hypotension (n= 1)	The study fails to demonstrate a response rate significantly >30%.	Unklar, welcher N-Status bei den Patienten, die neoadjuvant therapiert wurden und in welchem Bereich die LAD durchgeführt wurde.	LoE 3 RoB 14/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							• Cardiac (thrombosis) (n= 2) • Fatigue (n= 2) • Neutropenic infection (n= 1) • Pulmonary (embolus) (n= 1) • Diarrhoe (n= 3)			
Zou, 2014, Journal of Cancer Research & Clinical Oncology	Retrospective case serie	n= 24 China 2001-2010 Mean follow-up 50.1 mo (7-122 mo)	To evaluate the efficacy of preoperative neoadjuvant chemotherapy combined with a BMP regimen including bleomycin, methopterin and cisplatin for treating advanced penile cancer patients.	T1-3 pN3 Mean age 53.4 y (38-71 y)	Neoadjuvant chemotherapy followed by surgery (lymphadenectomy and/or (partial) penectomy) + chemotherapy n= 15		**Neoadjuvant + surgery group** Response Complete: 0% Partial: 62.5% Progressive disease: 8.33% Recurrence 3/14 inguinal lymph node 0/14 local **Overall** Adverse events Bone marrow depression (83.3%) Oral mucous damage (45.8%) Surgery related: Lower extremity lymphedema (86.7%) Delayed wound healting (66.7%) Perineal edema (6.67%) Dysuria (6.67%)	Neoadjuvant chemotherapy combined with a bleomycin, methopterin and cisplatin regimen followed by surgery is beneficial to patients with advanced penile cancer.	Ergebnisse sind nur die PICO-Frage betreffend dargestellt.	LoE 4 RoB 15/20

Tabelle 25: „Sollen Patienten mit pN+ eine adjuvante Chemotherapie nach ing. LAD erhalten?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
Giannatempo, 2014, J Clin Oncol	Cohort study	n= 47 2004-2012 Median follow-up 22 mo (17-42 mo)	Survival analyses of adjuvant or neoadjuvant combination of a taxane plus cisplatin and 5-fluorouracil in patients with bulky nodal metastases from squamous cell carcinoma of the penis .	N2-3 M0 ECOG 0-1 Median age 63 y (41-78 y)	Neoadjuvant Paclitaxel (120 mg/m2, d1) or docetaxel (75 mg/m2 d1) plus cisplatin (75-100 mg/m2 d1) and 5-fluorouracil (5FU, 750-1000 mg/m2 96h d1) n= 28	Adjuvant Paclitaxel (120 mg/m2, d1) or docetaxel (75 mg/m2 d1) plus cisplatin (75-100 mg/m2 d1) and 5-fluorouracil (5FU, 750-1000 mg/m2 96h d1) n= 19	Durable remissions Adjuvant: 52.6% Neoadjuvant: 28.6% Median time to event Adjuvant: 42 mo (16-68 mo) Neoadjuvant: 17 mo (15-25 mo) Relapses Adjuvant: 42.1% Neoadjuvant: 42.8% Median time to relapse Adjuvant: 8 mo (9-10 mo) Neoadjuvant: 8 mo (5-10 mo) Dead of disease Adjuvant: 42.1% Neoadjuvant: 32.1% Median time to dead Adjuvant: 15 mo (12-23 mo) Neoadjuvant: 10 mo (4-16 mo) **Adverse events** Anemia Adjuvant: 5.2% Neoadjuvant: 7.1% Neutropenia Adjuvant: 21% Neoadjuvant: 28.5% Trombocytopenia Adjuvant: 3.5% Neoadjuvant: 5.2% Febrile neuropenia	Adjuvant chemotherapy was the most important favourable predictor of OS and PFS. Adjuvant T-PF results are among the best available ones. Neoadjuvant T-PF compares with other recent schedules in terms of activity and efficacy. Surgery remains the mainstay treatment for resectable nodal metastases from squamous cell carcinoma of the penis.	Conference poster Zusätzlich aufgenommen	LoE 3

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							Adjuvant: - Neoadjuvant: 3.5% <u>Stomatitis (Mucositis)</u> Adjuvant: 5.2% Neoadjuvant: 3.5% <u>Diarrhea</u> Adjuvant: 5.2% Neoadjuvant: 7.1% <u>Neurotoxicity</u> Adjuvant: - Neoadjuvant: 3.5% <u>Nephrotoxicity</u> Adjuvant: - Neoadjuvant: 3.5% Cardiac toxicity Adjuvant: - Neoadjuvant: 7.1% <u>Toxic death</u> Adjuvant: - Neoadjuvant: 3.5%			
Hakenberg, 2006, BJU International	Retrospecti ve case serie	n= 13 1996-2003 <u>Mean follow-up</u> 54 mo (41-76 mo)	To evaluate the efficacy and toxicity of chemotherapy with cisplatinum, methotrexate and bleomycin in the adjuvant and palliative setting, and its effect on survival in patients with locally advanced or metastatic penile carcinoma.	pT1-4 pN0-3 M0-1 <u>Mean age</u> 54 y (31-73 y)	Cisplatinum, methotrexate and bleomycin		**Response** <u>Adjuvant treatment (radically resected N+)</u> 4/8 progression 1/8 death from therapy Mean remission time: 26 mo **<u>Toxicity</u>** <u>Grade 4</u> Haematological toxicity (24/45 series)	Adjuvant chemotherapy with cisplatinum, methotrexate and bleomycin can achieve cure in a proportion of patients with pN+ penile cancer after radical surgical treatment, but in metastatic penile cancer the responses to chemotherapy alone are transient and the toxicity of treatment is high.		LoE 4 RoB 12/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							Deep-venous thrombosis (4/45 series) Stomatitis (7/45 series) Epistaxis (1/45 series) Lymphatic oedema (5/45 series) Paravasation (2/45 series) Pulmonary emboli (1/45 series) Interstitial pneumonia (2/45 series) One toxicity-related death			
Maiche, 1983, British Journal of Urology	Case serie	n= 19	To describe adjuvant treatment using bleomycin in squamous cell carcinoma of penis.	T1-3 N0-2 M0-1 Mean age 57 y (34-71 y)	Bleomycin (between 9 mg/m² and 212 mg/m²) or combination with vincristine and methotrexate		Response 4/8 without M1 Survival 2/11 with M1 5/8 without M1 2 y-Survival 5/19	Bleomycin could be effective in the treatment of well differentiated squamous cell penile carcinoma, but it seems that very high doses are required and this is dangerous	Chemotherapy regimes may have changed over timde and therefore results should be interpreted with caution.	LoE 4 RoB 6/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
							3 y-Survival 3/13 5 y-Survival 1/13 Toxicity 3/19 pneumonitis 6/19 fibrotic changes in both lungs	because of the side effects.		
Pizzocaro, 1988, Acta Oncologica	Retrospecti ve case series	n= 17 1979-1985 Italien Median follow-up 42 mo (18-102 mo)	To describe the results of adjuvant and neoadjuvant treatment with vincristine, bleomycin, and methotrexate for inguinal metastases from squamous cell carcinoma of the penis.	Age Adjuvant: 21-74 y (median age: 55 y) Neoadjuvant: 40-62 y	Neoadjuvant with 12 weekly courses of vincristine, bleomycin and methotrexate n= 5	Adjuvant vincristine, bleomycin and methotrexate n= 12	Adjuvant group 11/12 free of disease 1/12 relapsed (16 mo) Toxicity (overall) • Myelosuppression (n=1) • Lung fibrosis (n= 2) • Hyperpyrexia >38°C (n= 4) • Hyperpigmentation (n= 8) • Stomatitis (n= 1)	The results of adjuvant vincristine, bleomycin and methotrexate seemed quite statisfactory. Our results suggest that this low-dose combination chemotherapy is also efficient in squamous cell carcinoma of the penis.		LoE 4 RoB 9/20
Protzel, 2009, Urologia Internationalis	Systemati c review	1966-2008	To review the available literature concerning chemotherapy regimens for penile cancer with response rates and survival when reported.	n= 4 studies with adjuvant setting	**Adjuvant treatment** • Vinblastine, Methrotrexate, Bleomycin • Cisplatin, Methotrexate, Bleomycin	Monochemoth erapies and polychemother pies	Vinblastine, Methotrexate, Bleomycin Progression: 1/12 Treatment-related death: 0/12 Mean duration of remission: 42 mo Cisplatin Methotrexate Bleomycin Progression: 4/8 Treatment-related death: 1/8 Mean duration of remission: 26 mo 5 y-survival Adjuvant group: 82% Without adjuvant treatment: 37%	Adjuvant treatment should be proven with new regimens, which might also be able to improve the poor prognosis of patients with distant metastasis.		LoE 3 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerk-ungen	LoE/ RoB
Sharma, 2015, Urologic Oncology	Retrospecti ve cohort study	n= 84 1978-2013 Median follow-up 12.1 mo (6.5-40.9 mo)	Is adjuvant chemotherapy associated with improved survival after lymph node dissection for patients with penile cancer who have positive pelvic lymph nodes?	pT1-4 pN3 Median Age 65 y (55-71 y)	No adjuvant chemotherapy n= 48	Adjuvant chemotherapy n= 36	Median OS Adjuvant chemotherapy: 21.7 mo (11.8-104 mo) Without: 10.1 mo (5.6-48.1 mo) P = 0.048 OS (multivariate analysis) HR: 0.40 95% CI (0.19-87) p= 0.021	Adjuvant chemotherapy is associated with improved OS.	Signifikante Unterschiede zwischen den beiden Gruppen in Bezug auf den zusätzlichen Einsatz von adjuvanter Strahlen-therapie.	LoE 3 NOS 7/9

Tabelle 26: „Sollen Patienten mit pN+ eine adjuvante Strahlentherapie nach ing. LAD erhalten?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Chen, 2004, World Journal of Urology	Retrospective cohort study	n= 45 Taiwan 1989-2000 Mean follow-up 37 mo (6-179 mo)	To discuss the extent of therapeutic lymphadenoec tomy and the effect of adjuvant radiotherapy in patients with positive inguinal lymph nodes.	Stage I-IV Ta-T4 N0-N+ n= 17 pathologic lymph node positve Median Age 64 y (29-87 y)	Operation+ radiotherapy (pathologic lymph node positive) n= 9	Operation alone (pathologic lymph node positive) n= 5	Recurrence: Operation+ radiotherapy: 3/9 (1 regional, 2 distant) Operation alone: 4/5 (3 regional, 1 distant)	Adjuvant radiotherapy with an adequate effective dose by innovative technology such as 3D conformal radiotherapy or intensity modulation radiotherapy might increase local control for positive groin metastasis with acceptable complications.		LoE 3 NOS 6/9
Demkow, 1999, International Urology & Nephrology	Retrospective case series	n= 64 1988-1998 Median follow-up 33 mo (3 mo-10 y)	To show the treatment experience in 64 cases.	Tis-T4 N0-N+ Median age 64 y (21-86 y) n= 35 bilateral inguinal LAD	Radiotherapy n= 12		10/12 died of recurrent cancer • n= 5 pT2N+ • n= 4 pT3N+ • n= 1 pT4N+ Mean survival N+: 8 mo (30 days -16 mo)	Our results indicated that adjuvant radiotherapy in high-risk patients did not prevent regional recurrences.		LoE 4 RoB 5/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							5 y-DFS N+: 40% N0: 82%			
Franks, 2011, Journal of Urology	Retrospective two-arm cohort studie	n= 23 United Kingdom 2002-2008 Median follow-up 27 mo (8-84 mo)	We studied the outcomes in patients with node positive penile cancer who received radiotherapy to inguinal and pelvic nodes.	N+ Median age 58 y (40-81 y)	Radiotherapy to the inguinal/pelvic nodes as adjuvant treatment after lymphadenectomy n= 14	High grade palliation for extensive/fixed nodes (n= 8) or extensive local tumor (n= 1) n= 9	3 y-OS 66% vs. 11% (p< 0.001) Locoregional relapse-free survival 56% vs. 22% (p < 0.03) Locoregionally relapses Adjuvant group: 6/14 Palliation group: 7/9 Toxicity 19/23 skin toxicity 6/23 scrotal/ penile or lower limb lymphedema 5/23 groin telangiectasia/fibrosis 1/23 late bowel symptoms	Adjuvant radiotherapy appears to have a role after inguinal lymphadenectomy, particularly in patients with extracapsular nodal spread, in whom historically survival rates have been poor.		LoE 3 NOS 6/9
Gerbaulet, 1992, Urologic Clinics of North America	Case serie	n= 109	To review the different irradiation approaches, particulaely intestinal brachytherapy using afterloading techniques with iridium-192 wires, one of the technic of references.	Tis T1-4 N0-N3 n= 20 N+ patients	Brachytherapy (Iridium-192) after surgery		5 y-survival rate 36% Side effects • 40% minor side effects	Irradiation of the regional lymph nodes is indicated postoperatively if there is extensive node involvement or in patients with recurrent or inoperable metastatic lymphatic disease.		LoE 4 RoB 6/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Graafland, 2011, Journal of Urology	Case serie	n= 161 Netherlands 1956-2012	To investigate the treatment results and outcomes of patients with pathological node positive penile carcinoma who experienced an inguinal recurrence after therapeutic lymphadenectomy, and determined the clinicopathological features predictive of such recurrences.	pT1-4 pN1-3 Median age 64 y (33-91 y)	Adjuvant radiotherapy n= 67		Overall recurrences 26/161 Recurrences after postoperative radiotherapy 11/26	Despite less surgery being performed on regional nodes, 5-year cancer specific survival has improved in patients with cN0 disease. The number of tumor positive nodes, extranodal extension and pelvic involvement were highly associated with worse cancer specific survival in patients with pN+ disease.		LoE 4 RoB 15/20
Hasan, 2015, Brachy-therapy	Systematic review with meta-analysis	n= 20 studies 1984-2012 Median follow-up Penectomy: 59 mo Brachytherapy: 67 mo	To compare the OS and local control rates between penectomy and brachytherapy for penile cancer.	n= 2178 Tis-T4 Grade 1-3 Median age 61 y (21-98 y)	Penectomy n= 1505	Brachytherapy n= 673	DFS Penectomy: 77% ± 3% Brachytherapy: 71% ± 2% OR: 1.37 (1.11-1.68) p= 0.003 5 y-OS Penectomy: 76% ± 17% Brachytherapy: 73% ± 6% OR: 1.17 (0.95-1.44) p= 0.128 5 y-local control Penectomy: 84% ± 13%	The collective data represented in this meta-analysis suggest that with early stage disease, brachytherapy has been as effective as penectomy for both local control rates and OS. When evaluating all patients regardless of the extent of tumor burden, penectomy offered better control but no OS benefit, implying that recurrent cases following brachytherapy are typically salvageable with surgery.	Indirekte Evidenz: We also allowed adjuvant radiation or lymph node dissection in any of the main treatment groups. It is likely that node-positive patients with delayed lymph	LoE 4 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Brachytherapy: 79% ± 5% OR: 1.45 (1.09-1.92) p= 0.009		node dissection had poorer survival than those with immediate dissection and this was not controlled for. LoE 4, da sowohl vergleichende als auch nicht-vergleichende Studien einge-schlossen wurden und das RoB als high bewertet wurde.	
Horenblas, 1993, Journal of Urology	Case serie	n= 123 Netherlands 1956-1989 Follow-up at least 2 ½ y	To establish a rational and uniform treatment protocol.	Grade 1-3 N0-N+ Median age 65 y (31-94 y)	Lymph node dissection+ adjuvant radiation therapy n= 12		7/12 died of reccurent cancer • n= 1 pN1 • n= 4 pN2 • n= 1 pN3 • n= 1 pNx	Based on experiences from head and neck region adjuvant postoperative external radiation therapy is recommended in all cases with extracapsular growth and/or with 2 or more invaded nodes.		LoE 4 RoB 9/20
Hu, 2017, Oncotarget	Systematic review with meta-analysis	n= 22 studies 1992-2016 Follow-up at least one year	To compare the efficacy of brachytherapy and penectomy in	n= 2560 patients I-III stage	Brachytherapy n= 746	Penectomy n= 1814	5-year OS Brachytherapy: 76% (71-81%) Penectomy: 74% (69-79%)	Both of penectomy and brachytherapy can improve the survival status. Penectomy provided better control efficacy, and not improved the survival status	Indirekte Evidenz: The brachyther apy group consisted	LoE 4 ROBIS Low

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			patients with penile cancer.				OR 1.11 (95% CI 0.91–1.36) p= 0.284 <u>5-year local control rate</u> Brachytherapy: 80% (77-83%) Penectomy: 85% (82-88%) OR 0.72 (95% CI 0.58–0.90) p= 0.003 <u>DFS</u> Brachytherapy: 72% (64-80%) Penectomy: 77% (70-83%) OR 0.77 (95% CI 0.63–0.93) p= 0.008	compared with brachytherapy solely.	of some patients with adjuvant radiation or lymph node dissection. No information on the lymph node involvement of the groups. LoE 4, da sowohl vergleichende als auch nicht-vergleichende Studien einge-schlossen wurden.	
Kulkarni, 1994, Eur Urol	Prospective three arm cohort-study	n= 64 India 1979-1982 <u>Follow-up</u> 60-180 mo	To find the optimum treatment in the latter group (N0, N1-2a), we conducted a propective three-arm study: prophylactic bilateral groin node dissection, prophylactic radiotherapy	N0-2 T1-3 G1-3 <u>Median age</u> 35 y (30-70 y)	Radiotherapy n= 18 (N0= 12 patients, N+= 6 patients)	Surveillance n= 19 Bilateral groin node dissection n= 27	<u>5 y-survival</u> Radiotherapy: 66% Prophylactic bilateral groin node dissection: 74% Surveillance: 63% <u>Relapses</u> 3/18	Prophylactic radiotherapy and surveillance appear to be of less therapeutic value in our set up because of the large number of patients presenting in a late stage of disease who are likely to be lost to follow-up.	Indirekte Evidenz, da eine prophylak-tische Radiothera pie der Lymphkno ten durchgefü hrt wurde.	LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			and surveillance.							
Langsen-lehner, 2008, Strahlenther Onkol	Retrospective case series	n= 24 Austria 1987-2006 Median follow-up 58.4 mo	To retrospectively assess the outcome in patients treated with adjuvant radiotherapy for penile cancer.	T1-T3 N0, N+ Median age 62.7 y (35.5-90.4 y)	Inguinal lymph node dissection+ radiotherapy n= 8		Regional relapse 0/8	Radiotherapy of the regional lymph nodes might also be effective in preventing regional recurrence and can be considered in case of high-risk features and following excision of extensive lymph node involvement.		LoE 3 RoB 11/20
Ravi, 1994, British Journal of Urology	Retrospective case serie	n= 156 India 1959-1988	To study the effectiveness of radiation therapy for the primary tumour and for groin node and distant metastases in patients with squamous cell carcinoma of the penis.	T1-4 N0-N+ M0-M1	Post-operative inguinale radiation-therapy n= 14 groins (12 patients)		5 y- DFS 8%	Radiation therapy is ideal for patients with T1 and T2 primary cancers of the penis. Pre-operative RT is useful for patients with mobile lymph nodes > or = 4 cm in size in the groin. RT provides effective palliation in patients with advanced regional disease and/or distant metastases.		LoE 4 RoB 11/20
Robinson, 2018, European Urology	Systematic review	n= 6 retrospective case series + 1 conference abstract 1994-2016 Median follow-up varies 9.4 – 83 mo	Undertake a systematic review of the evidence on adjuvant inguinal radiotherapy in node-positive men with penile squamous cell carcinoma.	n= 1605 extracapsular nodal extension, ≥ 2 involved inguinal lymph nodes or pN2/3 Median age varies 58-65y	Adjuvant inguinal radiotherapy		Regional recurrence rate 10-91.7% OS 16.7-66% Adjuvant vs. no adjuvant treatment (n=2 studies) Recurrence and survival: no significant Toxicity (n=1 study) grade 2–3 lymphoedema, urethral stenosis,	The evidence indicates that men treated with adjuvant inguinal radiotherapy do not gain benefit with respect to relapse or survival.		LoE 4 ROBIS Low

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							severe inguinal radionecrosis			
Tang, 2017, Urologic Oncology	Retrospective cohort study	n= 92 1980-2013 Median follow-up 9.3 mo (5.2-19.8 mo)	To evaluate the association of adjuvant pelvic radiation with survival and recurrence for patients with penile cancer and positive pelvic lymph nodes after lymph node dissection.	pT1-4 Grade 1-3/4 pN3 Median age 65.3 y (53.6-70.6 y)	No radiation n= 52	Radiation therapy n= 40	Median DSS No radiation: 8 mo Radiation: 14.4 mo p= 0.023 HR 1.9 (95% CI: 1.09-.3.36 p=0.02) Median OS No radiation: 8 mo Radiation: 14.2 mo HR 1.7 (95%CI 1.01–2.92), p= 0.04 Median time to recurrence No radiation: 7.7 mo Radiation: 5.3 mo p= 0.042	The results of this study suggest that pelvic adjuvant radiation for pN3 disease is associated with improved survival and decreased recurrence in penile carcinoma.	Indirekte Evidenz: Bezieht sich auf pelvic radiation	LoE 3 NOS 6/9
Winters, 2018, Urologic Oncology	Retrospective cohort study	n= 589 1998-2012	To evaluate factors associated with receiving adjuvant radiation and the influence of adjuvant radiation on OS.	pT1-3 N1-2 Stage III Mean age 61.8 y ± 13.7y	Adjuvant radiation n= 136	No adjuvant radiation n= 453	**Overall** OS HR 0.58 (95% CI 0.39-0.86) 3 y-OS Adjuvant radiation: 84% No adjuvant radiation: 74% 5 y-OS Adjuvant radiation: 64% No adjuvant radiation: 53% **N1** OS HR 1.36 (95% CI 0.60–3.09) **N2**	We find evidence of a survival benefit with the use of adjuvant radiation in those with higher nodal stage (N2 vs. N1).		LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							OS HR 0.53 (95% CI 0.32–0.88)			
Zouhair, 2001, European Journal of Cancer	Retrospective cohort study	n= 41 Switzerland 1962-1994 Median follow-up 70 mo (20-331 mo)	Tx-T3 N0-3 Median age 59 y (35-76 y)	To assess the prognostic factors and the outcome in patients with squamous-cell carcinoma of the penis.	Surgery + postoperative radiotherapy n= 14 Indications for postoperative radiotherapy were positive surgical margins and/or lymph node involvement.	Primary radiotherapy+ surgery n= 23	Local failure Surgery + postoperative radiotherapy: 25% Primary radiotherapy+ surgery: 61% p= 0.06 **Multivariate analyses** Local control Surgery+ radiotherapy vs. primary radiotherapy: RR 6.25 (p= 0.02) Locoregional control Surgery+ radiotherapy vs. primary radiotherapy: 5.65 (p= 0.01)	In patients with squamous-cell carcinoma of the penis, local control is better in patients treated with surgery. There seems to be no difference in terms of survival between patients treated by surgery and those treated by primary radiotherapy± salvage surgery, with 39% having organ preservation.		LoE 3 NOS 5/9

Tabelle 27: „Sollen Patienten mit cN2/3 eine neoadjuvante Radio/Chemotherapie vor ing. LAD erhalten?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Bermejo, 2007, Journal of Urology	Retrospective case serie	n= 10 1985-2000 Median follow-up 62 mo (48-84 mo)	To report the experience with surgical consolidation for a select group of patients with clinically evident or pathologically proven lymph node involvement who initially demonstrated stable disease or an objective response to chemotherapy.	Tx-3 N1-3 M0-1 Median age 56 y (41-86 y)	Induction chemotherapy Paclitaxel, ifosfamide+ cisplatin Methotrexate, bleomycin+ cisplatin Paclitaxel+ carboplatin		Response 4/10 complete 1/10 partial 5/10 stable disease 5 y-OS 50% Median survival (3 or fewer positive lymph nodes, n= 3) 23 mo (3-30 mo) Toxicity 3/10 grade III nonhematological toxicity, including 1 episode each of bleomycin toxicity, acute renal failure and deep venous thrombosis	Selected patients with metastatic penile cancer that show disease stabilization or a response to chemotherapy should be considered for surgical consolidation to extend survival.		LoE 4 RoB 13/20
Chen, 2009, Japanese Journal of Clinical Oncology	Retrospective case serie	n= 5 2005-2009 Mean follow-up 24.2 mo (17-34 mo)	To evaluate the efficacy and adverse effects of intra-arterial chemotherapy in the treatment of penile cancer	N0-N+ M0 Median age 61 y (48-79 y)	Inguinale LAD+ intra-arterial chemotherapy Methotrexate (110 mg/ m2/day), mitomycin C (4.5 mg/m2/day), bleomycin (15 mg/ m2/day), cisplatin (35 mg/m2/day) and 5-fluorouracil (1200 mg/m2/day) n= 2		Response 2/2 partial Time to relapse 4 mo and 8 mo Adverse effects • Anemia (grade 3) • Anorexia (grade 1-2)	Our preliminary data indicated that a combination of intra-arterial chemotherapy, neoadjuvant chemotherapy and surgery may have the potential to achieve the goal in the treatment of penile cancer with negative lymph node.		LoE 4 RoB 12/20
Chiang, 2014, British Journal of Cancer	Retrospective case serie	n= 12 2005-2013 Follow-up 8-88 mo	To evaluate the role of intraarterial chemotherapy as first-line therapy for penile	T1-3 N0-2 M0 N2= 3 patients Age	Neoadjuvant intraarterial chemotherapy (methotrexate, mitomycin C, bleomycin,		Tumor response Overall: 83% Node-negativ patients: 100% Nodal invasion: 60% Dead of disease (N2)	The preliminary results showed that intraarterial chemotherapy could be used as first-line therapy in any stage of penile squamous cell carcinoma before surgery.		LoE 4 RoB 11/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			squamous cell carcinoma.	48-89 y 5 patients with palpable inguinal node received surgery (partial/ total penectemy with LAD)	cisplatin and 5-fluorouracil)		n= 2/3 **Side effects** Grade 1 or 2 Anorexia: 7/12 (58%) Grade 3 Haematological toxicity: 3/12			
Dickstein, 2016, BJU International	Retrospective case serie	n= 61 USA 1993-2011 Follow-up 5 y	Describe the clinical and pathological response rates, survival, and predictors of survival when using contemporary perioperative chemotherapy and surgical resection for patients with regionally advanced squamous cell carcinoma of the penis.	N0-3 N2= 20 patients N3= 37 patients Median age 60.6 y (24.5-81.4 y)	**Induction regime** TIP (Paclitaxel/ ifosfamide/ cisplatin chemotherapy) Carboplatin/ paclitaxel 5-fluorouracil/ cisplatin methotrexate/ bleomycin/ cisplatin		Objective response 39 (65%) Median OS N2: 35.8 mo (HR 0.87, 95% CI 0.24-3.13) p= 0.83 N3: 17.3 mo (HR 1.22, 95% CI 0.37-4.10) p= 0.743 Recurrence-Free-Survival N2: 35.8 mo (HR 0.82, 95% CI 0.23-2.95) p= 0.763 N3: 10 mo (HR 1.47, 95% CI 0.44-4.85) p= 0.531	Contemporary chemotherapy resulted in clinically significant responses among patients with regionally advanced penile cancer.	Patients with resectable inguinal and pelvic lymph nodes underwent consolidative LAD after completing chemotherapy	LoE 4 RoB 12/20
Djajadiningrat, 2015, Clinical Genitourinary Cancer	Clinical trial	n= 26 2008-2012 Netherlands Median follow-up 30 mo (6-17 mo)	To evaluate response, toxicity, PFS and disease-specific survival in patients with advanced squamous cell carcinoma of the penis treated with neoadjuvant taxane-based combination chemotherapy.	rTx, T2, T4 N0, N2, N3 N2= 3 patients N3= 15 patients Median age 61 y (35-73 y)	4 courses of TPF (docetaxel, cisplatin and 5-fluorouracil)		Overall response 60% (CI 95% 39-79%) Median PFS 7 mo (95% CI 1.9-17.1 mo) Median OS 10.1 mo (95% CI 6.7-28.1 mo) Median disease-specific survival 10.3 mo (95% CI 8- ∞ mo)	Despite a fairly good response percentage, survival was disappointing at the expense of considerable toxicity.	Different procedures after chemotherapy (partial/ total penectomy, inguinal/pelvic dissection and radiation therapy)	LoE 3 RoB 19/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Toxicity 26/26 Grade 4: 2 Grade 3: 14			
Gotsadze, 2000, European Urology	Case serie	n= 223 patients 1959-1996 Median follow-up 6.5 y (3 mo-14 y)	T1-3 N0-2 M0 Median age 53.8 y (25-82 y)	The results of different conservative organ-sparing methods (radiotherapy, chemotherapy and radio-chemotherapy) in the treatment of penile carcinoma were studied.	**Neoadjuvant chemotherapy** n= 33 (5 patients with N2-N3) **Radiochemotherapy** n= 35 (5 patients with N2-N3) Chemotherapy regimes Bleomycin Vinblastine+ bleomycin Cisplatin+ bleomycin Cisplatin+ vinblastine	**Radiotherapy** n= 155 (13 patients with N2-N3)	**Results for neoadjuvant chemotherapy** Objective response: 84.8% **Local recurrence** Bleomycin No reccurence Vinblastine+ bleomycin No recurrence Cisplatin+ bleomycin T1: 2/6 T2: 1/4 T3: 0/1 Cisplatin+ vinblastine no recurrence **Complete response** Bleomycin T1: 2/3 T2: 5/8 Vinblastine+ bleomycin T1: 1/1 T2: 0/3 T3: 0/1 Cisplatin+ bleomycin T1: 4/6 T2: 2/4 T3: 0/1 Cisplatin+ vinblastine T1: 2/2 T2: 0/2 T3: 0/2	Neoadjuvant conservative treatment of inguinal groins is not justified and lymph node metastases should be managed surgically as soon as it possible.	Indirekte Evidenz: Die Ergebnisse für die Patienten mit N2-N3 sind nicht separate aufgeführt. Bei den Ergebnissen zur Radio- und Radio-chemotherapie handelt es sich nicht explizit um ein neoadjuvantes Setting.	LoE 4 RoB 9/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Partial response Bleomycin T1: 1/3 T2: 3/8 Vinblastine+ bleomycin T1: 0/1 T2: 2/3 T3: 0/1 Cisplatin+ bleomycin T1: 2/6 T2: 1/4 T3: 1/1 Cisplatin+ vinblastine T1: 0/2 T2: 1/2 T3: ½ **Radiochemotherapy** Objective response: 80% Complete local control: 60% **Radiotherapy** Objective response: 76.2% Complete local control: 63.2%			
Joshi, 2018, JAMA Oncology	Retrospective cohort study	n= 1123 2004-2014 United States of America, Puerto Rico	To determine temporal trends in use of chemotherapy for patients with lymph node positive penile cancer without metastasis and to evaluate outcomes between those who did or did not receive LND,	G1-4 N1-3 Age range 50-75 y 66.8% underwent LAD	LAD with or without chemotherapy or/and radiotherapy		Multivariable model predicting use of chemotherapy N2: OR 1.54 (1.08-2.19) p= 0.02 N3: OR 2.15 (1.52-3.04) p< 0.001 Multivariable OS analysis N2: HR 1.44 (1.17-1.78) p= 0.001 N3: HR 1.93 (1.52-2.45) p< 0.001	Receipt of LAD, but not chemotherapy or radiotherapy, is associated with overall survival.	Unklar, ob LAD sich nur auf inguinale LAD bezieht	LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			chemotherapy, and radiotherapy.				LAD: HR 0.64 (0.52-0.78) p< 0.001 Chemotherapy: HR 1.01 (0.8-1.26) p= 0.95 Radiotherapy: HR 0.85 (0.70-1.04) p= 0.11 **Median OS** LAD 28.8 mo (95% CI 24-40.3 mo) LAD+ Chemotherapy 44.6 mo (95% CI 23.5-114.6 mo) LAD+ Chemotherapy+ Radiotherapy 37.2 (95% CI 20.7-68.1 mo) **N2/N3 subgroups** Survival Chemotherapy: HR 0.91 (95% CI 0.71-1.18) p= 0.49 Radiotherapy: HR 0.88 (95% CI 0.71-1.10) p= 0.26 Chemoradiotherapy: HR 0.97 (95% CI 0.88-1.07 p= 0.53) LND+ Chemotherapy: p= 0.77 LND+ Radiotherapy: p= 0.99			
Kulkarni, 1994, Eur Urol	Prospectiv e three arm cohort-study	n= 64 India 1979-1982 Follow-up 60-180 mo	To find the optimum treatment in the latter group (N0, N1-2a), we conducted a propective three-arm study:	N0-2 T1-3 G1-3 Median age 35 y (30-70 y)	Radiotherapy n= 18 (N0= 12 patients, N+= 6 patients)	Surveillanc e n= 19 Bilateral groin node dissection	5 y-survival Radiotherapy: 66% Prophylactic bilateral groin node dissection: 74% Surveillance: 63%	Prophylactic radiotherapy and surveillance appear to be of less therapeutic value in our set up because of the large number of patients presenting in a late stage of disease who	Indirekte Evidenz, da eine prophylakt ische Radiothera pie der Lymphkno	LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			prophylactic bilateral groin node dissection, prophylactic radiotherapy and surveillance.			n= 27	Relapses 3/18	are likely to be lost to follow-up.	ten durchgefü hrt wurde.	
Leitje, 2007, European Urology	Retrospec tive case serie	n= 20 Netherlands 1972-2005 Median follow-up 23 mo (1-134 mo)	To assess the value of neoadjuvant chemotherapy in 20 patients with irresectable penile carcinoma treated at our institute.	T1-T4 N0-N3 Mean age 62 y (35-79 y)	**Neoadjuvant therapies** until 1985 Single-agent therapy with bleomycin 1986-1999 Combination chemotherapy with bleomycin, vincristin and methotrexate 1999-2001 Combination therapy of 5-fluorouracil and cisplatin Since 2001 Cisplatin, bleomycin and methotrexate		5 y-OS 32% (95% CI 17-62%) No correlation beetween survival and: T category (p= 0.75) N category (p= 0.85) Tumor differention (p= 0.65) Age (p= 26) Responder 9/20 (2 complete, 7 partial) **Toxicity** Death: 3 Severe toxicity: 4 Side effects Grade 1 and 2: Nausea, fatigue, Grade 1 or 2: Alopecia	These results suggest that neoadjuvant chemotherapy is a valuable treatment option for patients with irresectable penile carcinoma, which is otherwise considered incurable. Surgery should be performed only in patients showing clinical response to chemotherapy because prognosis for nonresponding patients who underwent surgery was dismal and local control was not improved.	Fünf verschiede ne Therapiefo rmen von 1972-2005, wobei die Ergebnisse für alle durchge-führten neoadjuva nten Therapien berichtet werden. Surgery after chemother apy were inguinal/ pelvic LAD and partial and total penectom y	LoE 4 RoB 15/20
Mitropoulos, 1994, Journal of Urology	Prospectiv e case serie	n= 13 Greece 1990-1992 Follow-up: 11-38+ mo	Invastigate the antitumor activity and toxicity of cisplatin and interferon-alpha 2B as the primary treatment of	T2-3 M0 N0-3 Median age 62 y (27-74 y) Surgery planned	20 mg/m² cisplatin intravenously and 5 x 10(6) µ/m² interferon-alpha 2B subcutaneously daily for 5 consecutive days		N2 (n= 1) Partial penectomy & node dissection Partial response Disease-free after 22 mo N3 (n= 1)	Primary treatment with cisplatin and interferon-alpha 2B induced responses in 75% of 12 patients with penile carcinoma and allowed for a less radical operation than originally scheduled.	Unklar, ob „node dissection “ sich nur auf inguinale LAD bezieht	LoE 4 RoB 16/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			penile carcinoma.	9/13 Penectomy + node dissection			Partial penectomy & node dissection Non-responder Died of metastatic disease (11 mo) <u>Toxicity</u> Flu-like symptoms (13/13) Haematological toxic effects (5/12) Renal complication rate (3/13)			
Necchi, 2017, Clinical Genitourinary Cancer	Retrospective three arms cohort study	n= 201 12 centers Europe, USA & Canada 1990 onwards	Evaluate the impact of neoadjuvant chemotherapy alone or in conjunction with radiotherapy in patients with lymph node positive disease.	T1-4 N0-3 <u>Median age</u> 67 y (35-87 y) HPV-: 38 HPV+: 8	Neoadjuvant chemotherapy n= 94 N2= 20 (21.3%) N3= 45 (47.9%)	Adjuvant chemotherapy n= 78 N2= 29 (37.2%) N3= 19 (24.4%) Neoadjuvant & adjuvant chemotherapy n= 21 N2= 8 (38.1%)	**Median relapse-free survival** <u>Neoadjuvant</u> 7.7% (95% CI 6.4-9.8%) <u>Adjuvant</u> 32.8% (95% CI 9.7-132.7%) Both 11.1% (95% CI 9.5-24.3%) **Median OS** <u>Neoadjuvant</u> 17.1% (95% CI 12.5-21.5%) <u>Adjuvant</u> 105.3% (95% CI 19.8%-NE) Both 18.5% (95% CI 11.8-30.2%<) <u>Relapse-Free Survival (N2)</u> HR 0.78 (95% CI 0.48-1.29) <u>OS (N2)</u> HR 0.87 (95% CI 0.50-1.52)	Substantial uncertainties still exist regarding the indications for perioperative chemotherapy and the net benefit of administering multimodal treatment compared to surgery alone in patients with advanced penile squamous cell carcinoma and high-risk features, namely those with pelvic or bilateral lymph node involvement.	Unklar, ob LAD sich nur auf inguinale LAD bezieht	LoE 3 NOS 6/9
Nicolai, 2016,	Retrospective	n= 47 2004-2012	Evaluation of	N2-3	**Neoadjuvant**	**Adjuvant**	**Alive and maintained progression free**	The taxane, cisplatin and 5-fluorouracil regimen is		LoE 3

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Clinical Genitourinary Cancer	cohort study	Follow-up 22 mo (17-42 mo)	the efficacy of a combination of taxane, cisplatin and 5-fluorouracil in neoadjuvant and adjuvant settings.	ECOG 0-1	Taxane, cisplatin,and 5-fluorouracil n= 28	Taxane, cisplatin,and 5-fluorouracil n= 19	Neoadjuvant 28.6% (95% CI 15.2-47.3) Median time: 17 mo (15-25 mo) Adjuvant 52.6% (95% CI 31.8-72.6) Median time: 42 mo (9-68 mo) **Relapses** Neoadjuvant 42.8% (95% CI 23.2-63.7) Median time: 8 mo (5-10) Adjuvant 42.1% (95% CI 23.2-63.7) Median time: 8 mo (9-10 mo) **Dead of Disease:** Adjuvant 42.1% Median time: 15 mo (12-23 mo) Neoadjuvant 32.1% Median time: 10 mo (4-16 mo)	well tolerated and compares with other regimens in terms of activity and efficacy in the neoadjuvant setting. The role of perioperative treatment in these patients remains controversial.		NOS 8/9
Otto, 2003, Urologe	Case serie	n= 15 Mean follow-up 15 mo	Beschreibung der Therapie des fortgeschrittenen Peniskarzinoms.	T3-4 Mean age 74 y	Neoadjuvante Chemotherapie 2–4 Kurse Polychemotherapie mit Cisplatin, Methotrexat und Bleomycin, 3 Wochen später Tumorresektion		Partielle Remission: 3 Tod: 4 (tumorbedingt) Fernmetastasen: 5 Nebenwirkungen: 11/15 Grad 2 gastrointestinal 9/15 Grad 3 hämatologisch 3/15 Grad 4 hämatologisch	Die Ergebnisse belegen, dass die Kombination von Chemotherapie und ausgedehntem operativen Vorgehen einerseits das Überleben des alten Patienten nicht nachhaltig beeinflusst, andererseits die Lebensqualität des symptomatischen Patienten entscheidend verbessert, was	Keine Aussagen zum Node-Status	LoE 4 RoB 7/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
								vorrangig auf die operative Behandlung zurückzuführen ist.		
Pagliaro, 2010, Journal of Clinical Oncology	Clinical trial (phase 2 study)	n= 30 2000-2008 Median follow-up 34 mo (14-59 mo)	Determining the response rate, time to progression and OS of neoadjuvant chemotherapy among patients with bulky adenopathy.	N2-N3 M0 Median age 57.5 y (24-78 y) n= 22 complete chemotherapy and then LAD	Neoadjuvant treatment 175 mg/m² paclitaxel intravenously over 3 hours day 1; ifosfamide 1,200 mg/m² on days 1 to 3; and cisplatin 25 mg/m² on days 1 to 3		Median time to progression: 8.1 mo (95% CI 5.4-50+) (20/30 patients died) OS 17.1 mo (95% CI 10.3-60+)	The neoadjuvant regimen of paclitaxel, ifosfamide, and cisplatin induced clinically meaningful responses in patients with bulky regional lymph node metastases from penile cancer.		LoE 3 RoB 17/20
Pizzocaro, 2009, European Urology	Prospectiv e case serie	n= 6 2004-2006 Italien	To evaluate the therapeutic activity of taxanes in combination with cisplatin-fluorouracil for salvage of primarily unresectable or relapsed nodal metastases from squamous cell carcinoma of the penis.	G1-3 T1-3 N0-3 Age 44-74 y	Neoadjuvant treatment Paclitaxel, cisplatin, and 5-fluorouracil		No evidence of disease 3/6 Follow-up: 25, 27 and 46 mo Dead of disease 3/6 Follow-up: 4, 6 and 11 mo Toxicity 1/6 patients: severe nausea and vomiting, hematologic toxicity	Paclitaxel, cisplatin, and 5-fluorouracil chemotherapy for unresectable or recurrent nodal metastases from squamous cell carcinoma of the penis is promising, and the standard four courses of therapy are to be completed in responding patients.		LoE 4 RoB 17/20
Pizzocaro, 1988, Acta Oncologica	Retrospec tive case serie	n= 17 1979-1985 Italien Median follow-up 42 mo (18-102 mo)	To describe the results of adjuvant and neoadjuvant treatment with vincristine, bleomycin, and methotrexate for inguinal metastases from squamous cell carcinoma of the penis.	Age Adjuvant: 21-74 y (median: 5 5y) Neoadjuvant: 40-62 y	Neoadjuvant with 12 weekly courses of vincristine, bleomycin and methotrexate n= 5	Adjuvant vincristine , bleomycin and methotrex ate n= 12	Neoadjuvant group Partial remission: 3 Minor remission: 2 Free of disease: 3 (20, 27 and 72 mo) Death: 2 (1 and 4 mo) Adjuvant group 11/12 free of disease 1/12 relapsed (16 mo) Survival	Our results suggest that this low-dose combination chemotherapy is also efficient in squamous cell carcinoma of the penis.	N-Status unklar	LoE 4 RoB 9/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							3= free of disease (20, 27 and 72 mo) 2= died (1 and 4 mo) Toxicity 1= Myelosuppression 2= Lung fibrosis 4= Hyperpyrexia >38°C 8= Hyperpigmentation 1= Stomatitis			
Pond, 2014, Clinical Geni-tourinary Cancer	Retrospec tive case serie	n= 26 Canada, Italy, USA 2000-2012	To examine clinical outcomes and potential prognostic factors of patients with penile squamous cell carcinoma receiving concurrent chemoradiothera py for unresectable locoregionally advanced or advanced disease.	Stage 2-4 Grade 0-3 N0-N+ M0-1 ECOG performance status: 0-3 Mean age 60.3 y	Chemoradio-therapy • 92.3% cisplatin-based regimeS • Median dose of external beam: 4900 cGy (1800-7000 cGy)		Median OS 6.9 % (95% CI 5-14%) 1-year OS 32.6% (95% CI 14.2-52.6%) Median PFS 5.1 % (95% CI 2.5-7%) 1-year PFS 18.7% (95% CI 18.7-36.9%)	Concurrent chemoradiotherapy demonstrated poor outcomes for locally advanced penile squamous cell carcinoma.	Indirekte Evidenz: “After chemoradi otherapy, none of the patients underwent surgical excision”. Ergebnisse nicht separate für N-Gruppen dargestellt.	LoE 4 RoB 17/20
Protzel, 2009, Urologia Intern-ationalis	Systemati c review	1966-2008	To review the available literature concerning chemotherapy regimens for penile cancer with response rates and survival when reported.	n= 7 studies with neoadjuvant setting	**Neoadjuvant treatment** • Vinblastine, Methrotrexate, Bleomycin (n= 2) • Cisplatin, Methotrexate, Bleomycin (n= 2) • Paclitaxel+ Carboplatin (n= 1) • Paclitaxel, Cisplatin, Ifosfamide (n= 1)	Monoche motherapi es, polychem otherpies and adjuvant chemother apies	Cisplatin (20-30 mg/m2) Methotrexate (200 mg/m2) Bleomycin (15 mg/m2) Response: 6/10 Treatment-related death: 2/10 Cisplatin (20 mg/m2) Methotrexate (200 mg/m2) Bleomycin (10 mg/m2) Response: 3/3 stable disease	Neoadjuvant treatment should be given in all cases of fixed lymph node metastasis and possibly for all patients with suspected lymph nodes metastasis. Adjuvant treatment should be proven with new regimens, which might also be able to improve the poor prognosis of patients with distant metastasis.		LoE 3 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
					• Paclitaxel, Cisplatin, 5-Fluoruracil (n= 1) • Cisplatin, Irinotecan (n= 1)		Treatment-related death: 0/3 Median survival: 7 mo Vinblastine, Methotrexate, Bleomycin Response: 6/10 Treatment-related death: 1/10 Paclitaxel+ Carboplatin Response: 3/3 Paclitaxel, Cisplatin, Ifosfamide Response: 4/5 Complete response: 3/5 Median survival: 30 mo Paclitaxel, Cisplatin, 5-Fluoruracil Response: 3/3 Complete response: 2/3 Median survival: 11 mo Cisplatin, Irinotecan Response: 6/7 Complete response: 1/7			
Tang, 2018, Urologic Oncology	Case report	n= 3 Follow-up 9-12 mo	Describe an aggressive approach for isolated retroperito- neal recurrences using a multimodal approach with systemic chemotherapy followed by consolidative	PT3N1M0 PT2N3M0 PT3N3M0 Age 61-71 y	Postchemotherapy 3 cycles of paclitaxel, ifosfamide, and cisplatin		Response Complete: 1/3 Partial: 2/3 No Evidence of Disease 3/3	It must be appreciated that such an aggressive multimodal strategy may only prove beneficial to a subset of penile cancer patients, which should be encompassed within our important therapeutic education and discussions.	Bezieht sich auf die Behandlung von Patienten, die bereits einen Rückfall haben	LoE 4 RoB 10/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			lymph node dis-section in a small cohort of patients							
Theodore, 2008, Annals of Oncology	Prospectiv e phase II study	n= 28 2004-2006	To determine efficacy and feasibility of the combination regimen irinotecan and cisplatin in patients with cisplatin advanced penile cancer.	T3-4 N1-3 M1 Median age 55 y (36-77 y) WHO PS: 0-2	Neoadjuvant therapy Combination of irinotecan (60 mg/m²) on days 1, 8 and 15 and cisplatin (80mg/m²) every 28 days n= 7 (3/7 underwent a lymphadenectomy after chemotherapy)		**Neoadjuvant setting** Overall response rate 2/7 (28.6%, 95% CI 3.7% to 71%) • 1/7 complete • 1/7 partial **Overall** Clincal adverse events Grade 4: • Hypotension (n= 1) • Cardiac (thrombosis) (n= 1) • Fatigue (n= 1) • Neutropenic infection (n= 2) • Pulmonary (embolus) (n= 1) • Haemorrhage (n= 1) Grade 3: • Hypotension (n= 1) • Cardiac (thrombosis) (n= 2) • Fatigue (n= 2) • Neutropenic infection (n= 1) • Pulmonary (embolus) (n= 1) • Diarrhoe (n= 3)	The study fails to demonstrate a response rate significantly >30%.	Unklar welcher N-Status bei den Patienten, die neoadjuva nt therapiert wurden und in welchem Bereich die LAD durchgefü hrt wurde.	LoE 3 RoB 14/20
Wang, 2015, Urology	Retrospec tive case serie	n= 19 USA 2000-2008	To estimate the efficacy of various treatments used in men with metastatic penile cancer that progress after first-line chemotherapy.	TxN2-3M0 with treatment failure Zubrod PS: 0-2 Median age 57 y (24-72 y)	Second-line treatment: Chemotherapy with cisplatin (n= 10) Chemo-radiotherapy with cisplatin (n= 2) Chemotherapy without cisplatin (n= 2)		Median OS Bleomycin, methotrexate, cisplatin: 4 mo Gemcitabine combination: 8.8 mo Erlotinib: 3.5 mo Biologic+ chemotherapeutic: 30.3 mo	The currently available treatments have minimal efficacy in the setting of recurrent metastatic penile cancer after first-line paclitaxel, ifosfamide, and cisplatin chemotherapy.		LoE 4 RoB 14/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
					Surgery alone (n= 2) Biologic therapy alone (n= 1)		Chemoradiaton: 12.2 mo Surgery: 10.2 mo Combined modality: 15.5 mo Best supportive care: 2.4 mo Cisplatin-containing chemotherapy: 5.6 mo Non-cisplatin-treated: 4.3 mo			
Zou, 2014, Journal of Cancer Research & Clinical Oncology	Retrospective case serie	n= 24 China 2001-2010 Mean follow-up 50.1 mo (7-122 mo)	To evaluate the efficacy of preoperative neoadjuvant chemotherapy combined with a BMP regimen including bleomycin, methopterin and cisplatin for treating advanced penile cancer patients.	T1-3 pN3 Mean age 53.4 y (38-71 y)	Neoadjuvant chemotherapy followed by surgery (lymphadenectomy and/or (partial) penectomy) + chemotherapy n= 15		**Neoadjuvant + surgery group** Response Complete: 0% Partial: 62.5% Progressive disease: 8.33% Recurrence 3/14 inguinal lymph node 0/14 local **Overall** Adverse events Bone marrow depression (83.3%) Oral mucous damage (45.8%) Surgery related: Lower extremity lymphedema (86.7%) Delayed wound healting (66.7%) Perineal edema (6.67%) Dysuria (6.67%)	Neoadjuvant chemotherapy combined with a bleomycin, methopterin and cisplatin regimen followed by surgery is beneficial to patients with advanced penile cancer.	Ergebnisse sind nur die PICO-Frage betreffend dargestellt.	LoE 4 RoB 15/20
Zouhair, 2001, European Journal of Cancer	Retrospective cohort study	n= 41 Switzerland 1962-1994 Median follow-up	Tx-T3 N0-3 Median age 59 y (35-76 y)	To assess the prognostic factors and the outcome in patients with squamous-cell	Primary radiotherapy + surgery n= 23	Surgery+ postoperative radiotherapy n= 14	Local failure Surgery + postoperative radiotherapy: 25% Primary radiotherapy+ surgery: 61% p= 0.06	In patients with squamous-cell carcinoma of the penis, local control is better in patients treated with surgery. There seems to be no difference in terms	Indirekte Evidenz, da unklar ist, welche cN-Gruppen neoadjuva	LoE 3 NOS 5/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		70 mo (20-331 mo)		carcinoma of the penis.		Indications for postoperative radiotherapy were positive surgical margins and/or lymph node involvement	**Multivariate analyses** Local control Surgery+ radiotherapy vs. primary radiotherapy: RR 6.25 (p= 0.02) Locoregional control Surgery+ radiotherapy vs. primary radiotherapy: 5.65 (p= 0.01)	of survival between patients treated by surgery and those treated by primary radiotherapy± salvage surgery, with 39% having organ preservation.	nt therapiert wurden.	

Tabelle 28: „Wie soll die Systemtherapie durchgeführt werden?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Carthon, 2014, BJU International	Retrospective case serie	n= 24 USA 2002-2009 Median follow-up 207 days (14-1441 days)	To evaluate the safety and efficacy of EGFR-targeted therapy in patients with advanced penile or scrotal cancer.	Tx,2,3,4 Nx,0,2,3 M0-1 Median age 59 y (36-71 y)	EGFR-targeted drug alone (cetuximab, erlotinib or gefitinib): 8 patients Cetuximab plus cisplatin: 12 patients Cetuximab plus carboplatin: 1 patient Paclitaxel, ifosfamide and cisplatin: 3 patients		Median time-to-disease-progression: 79 days (11-281 days) Response rate: 32.5% Median OS 29.6 weeks (2-205 weeks) Partial response 1/5 (20%) cetuximab alone 3/12 (25%) cetuximab plus cisplatin 2/3 paclitaxel, ifosfamide and cisplatin plus cetuximab Overall adverse effects 71% skin rash Grade 3 or 4 adverse events after cetuximab treatment Cellulitis (n= 1) Thrombocytopenia (n= 1) Bronchospasm (n= 1) Haemorrhage (n= 1)	Our results suggest that cetuximab has antitumour activity in metastatic penile cancer, and may enhance the effect of cisplatin-based chemotherapy.		LoE 4 RoB 18/20
Dexeaus, 1991, Journal of Urology	Case serie	n= 14 carcinoma patients USA 1987-1989	To review the results of the combination of methotrexate, bleomycin and cisplatin advanced squamous cell carcinoma of the male genital tract.	Tumor localisation Penis (n= 12) Scrotum (n= 1) Prostate (n= 1) T1-3 N+ Median age 49 y (42-76 y)	Combination of methotrexate, bleomycin and cisplatin		Response rate 72% (95% CI 57-92%) Complete: 2/14 (14%) Partial: 8/14 (57%) Median response duration 5.9 mo (4-24+ mo) Toxicity	The combination of methotrexate, bleomycin and cisplatin has significant activity in patients with advanced squamous cell carcinoma of the male genital tract.		LoE 4 RoB 12/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							13/69 courses are associated with mucositis 5/14 patients show bleomycin toxicity			
Di Lorenzo, 2009, Anti-Cancer Drugs	Single-arm phase II multicentre study	n= 12 2004-2008	To evaluate the use of paclitaxel in patients with advanced squamous cell penile cancer previously treated with neoadjuvant cisplatin-based chemotherapy.	Patients are pretreated with a platinum-based regimen in a neoadjuvant setting Median age 63 y (43-75 y) WHO PS: 0-2	175 mg/m2 paclitaxel at a 3-week interval		Partial responses 3/12 (25%, CI 95% 12-40%) Median PFS 4 mo (2-6 mo) Median OS 6 mo (3-10 mo) Side effects Grade 3: Neutropenia (25%) Oral mucositis (25%) Anemia (17%) Thrombocytopenia (17%) Peripheral neuropathy (17%) Alopecia (8%) Nausea/vomiting (8%) Constipation (8%) Diarrhea (8%) Grade 4: Neutropenia (8%)	Paclitaxel is well tolerated and associated with promising efficacy.		LoE 3 RoB 12/20
Di Lorenzo, 2011, European Urology	Single-arm phase II multicentre study	n= 25 2004-2011	To evaluate the activity and safety of paclitaxel in pretreated metastatic penile cancer.	Patients are pretreated with a platinum-based regimen in a neoadjuvant, adjuvant or advanced setting WHO PS: 0-2	175 mg/m2 paclitaxel at 3-wk intervals		Complete response 0% Partial objective response 20% (95% CI 8-32%) Median PFS 11 wk (95% CI 7–30 wk) Median OS	Final results of this study demonstrate that paclitaxel is moderately active and well tolerated.		LoE 3 RoB 16/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
				Median age 64 y (43-75 y)			23 wk (95% CI 13–48 wk) Side effects Grade 3: Neutropenia (20%) Anemia (16%) Thrombocytopenia (8%) Alopecia (4%) Oral mucositis (20%) Nausea/vomiting (8%) Constipation (8%) Diarrhea (4%) Peripheral neuropathy (8%) Grade 4: Neutropenia (8%) Thrombocytopenia (4%)			
Di Lorenzo, 2012, BJU International	Retrospective case serie	n= 25 2000-2011	To investigate the activity and toxicity of 5-FU as a first-line treatment in metastatic squamous cell carcinoma of the penis.	T1-T3 N0-N2/3 ECOG PS: 0-2 Median age 63 y (57-65 y)	intravenous cisplatin on day 1 followed by 5-FU as a continuous 24-h infusion for 4 days every 3 wks		Partial response 32% (95% CI 13.7-50.3%) Median PFS 20 wks (11-20 wks) Median OS 8 mo (7-12 mo) Side effects Grade 3: Neutropenia (16%) Anemia (8%) Thrombocytopenia (4%) Alopecia (4%) Oral mucositis (4%) Nausea/vomiting (4%) Constipation (4%) Diarrhea (4%) Peripheral neuropathy (8%)	5-FU is associated with a moderate response rate and is well tolerated in patients with metastatic squamous cell carcinoma of the penis.		LoE 4 RoB 14/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Grade 4: Neutropenia (8%) Thrombocytopenia (4%) Anaemia (4%)			
Gagliano, 1989, Journal of Urology	Case serie	n= 26	To report the treatment results of advanced epidermoid carcinoma of the penis.	Jackson Stage III-IV Karnofsky PS: 0-2 Median age 56 y (35-85 y)	50 mg. per M.² cis-diamminedichloro platinum intravenously on days 1 and 8 of 28-day cycles		Response 4/26 partial remission 0/26 complete remission Response rate 15.4% (95% CI 4.4-34.9%) Median survival: 4.7 mo **Toxicity** Leukopenia (3000-3999 cells/mm.³): 8% Thrombocytopenia (75000-99000cells/mm³): 4% Nausea/vomiting/anorexia Mild: 35% Moderate: 38% Neprotoxicity (creatine clearance, ml./min) 40-50: 23% 30-39: 4% 20-29: 8%	This agent cannot be recommended as treatment for advanced epidermoid carcinoma of the penis using this particular dose and schedule.		LoE 4 RoB 6/20
Gotsadze, 2000, European Urology	Case serie	n= 223 patients 1959-1996 Median follow-up 6.5 y (3 mo-14 y)	T1-3 T1-3 N0-2 M0 Median age 53.8 y (25-82 y)	The results of different conservative organ-sparing methods (radiotherapy, chemotherapy and radio-chemotherapy) in the	**Neoadjuvant chemotherapy** n= 33 Bleomycin (n= 11) Vinblastine+ bleomycin (n= 5) Cisplatin+ bleomycin (n= 11)		**Results for chemotherapy** **Local recurrence** Bleomycin No reccurence Vinblastine+ bleomycin No recurrence Cisplatin+ bleomycin	Conservative organ-sparing treatment of early-stage penile carcinomas is justified. Failure should be corrected by surgery without compromising survival.	Here, only the results for chemotherapy were reported.	LoE 4 RoB 9/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
				treatment of penile carcinoma were studied.	Cisplatin+ vinblastine (n= 6)		T1: 2/6 T2: 1/4 T3: 0/1 <u>Cisplatin+ vinblastine</u> no recurrence **Complete response** <u>Bleomycin</u> T1: 2/3 T2: 5/8 <u>Vinblastine+ bleomycin</u> T1: 1/1 T2: 0/3 T3: 0/1 <u>Cisplatin+ bleomycin</u> T1: 4/6 T2: 2/4 T3: 0/1 <u>Cisplatin+ vinblastine</u> T1: 2/2 T2: 0/2 T3: 0/2 **Partial response** <u>Bleomycin</u> T1: 1/3 T2: 3/8 <u>Vinblastine+ bleomycin</u> T1: 0/1 T2: 2/3 T3: 0/1 <u>Cisplatin+ bleomycin</u> T1: 2/6 T2: 1/4 T3: 1/1 <u>Cisplatin+ vinblastine</u> T1: 0/2 T2: 1/2			

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							T3: 1/2			
Haas, 1999, J Urol	Clinical trial (phase II)	n= 40 1986-1994, 31 institutions Median duration of treatment 10 weeks (max 60)	To evaluate efficacy and safety of combined cisplatin, methotrexate and bleomycin in locally advanced or metastatic penis cancer patients.	Median age 57 y (23-81 y)	75 mg/m2 cisplatin intravenously at a rate of 1 mg per minute and a concentration of 1 mg/cc in normal saline on day 1, intravenous bolus of 25 mg/m2 methotrexate on days 1 and 8, and intravenous bolus of 10 units per m2 bleomycin on days 1 and 8. Chemotherapy was repeated every 21 days. 2 cycles of chemotherapy constituted an adequate trial.		Complete response: 5 Partial response: 8 Unconfirmed response: 4 Stable: 17 Inadequate assessment: 6 Death, treatment-related: 5 Toxicities, treatment-related: 40 Grade 4: 14 Gastrointestinal: 33 Haematological: 27 Mucosal: 14	Study results were achieved at the price of considerable toxicity. Combination regimen warrants further investigation. A promising direction appears to be a simpler regimen that includes methotrexate but perhaps eliminates bleomycin.	6 patients completed treatment, Withdrawal 34 patients: due to toxicities n=9, due to progression n=17, due to death n=2, due to other n=6	LoE 3 RoB 12/20
Hakenberg, 2006, BJU International	Retrospektive case serie	n= 13 1996-2003, Mean follow-up 54 mo (41-76 mo)	To evaluate the efficacy and toxicity of chemotherapy with cisplatinum, methotrexate and bleomycin in the adjuvant and palliative setting, and its effect on survival in patients with locally advanced or metastatic penile carcinoma.	pT1-4 pN0-3 M0-1 Mean age 54 y (31-73 y)	Cisplatinum, methotrexate and bleomycin		**Response** Locally unresectable or with metastases 5/5 stable disease 1/5 death from therapy Adjuvant treatment (radically resected N+) 4/8 progression 1/8 death from therapy Mean remission time: 26 mo Toxicity Grade 4 Haematological toxicity (24/45 series)	Adjuvant chemotherapy with Cisplatinum, methotrexate and bleomycin can achieve cure in a proportion of patients with pN+ penile cancer after radical surgical treatment, but in metastatic penile cancer the responses to chemotherapy alone are transient and the toxicity of treatment is high.		LoE 4 RoB 12/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Deep-venous thrombosis (4/45 series) Stomatitis (7/45 series) Epistaxis (1/45 series) Lymphatic oedema (5/45 series) Paravasation (2/45 series) Pulmonary emboli (1/45 series) Interstitial pneumonia (2/45 series) One toxicity-related death			
Houédé, 2016, BJU International	Clinical trial (phase II trial)	n= 25 France 2004-2010 Median follow-up 26.97 mo (95% CI 2.4-11.73 mo)	To perform a phase II study evaluating a combination of gemcitabine and cisplatin in a population of patients with squamous cell carcinoma of the penis and unresected locoregional lymph nodes and/or distant metastases, who had a poor prognosis with no standard of chemotherapy.	T1-4 N0-3 M0-1 ECOG PS: 0-1 Median age 56.0 y (35-79 y)	Combination of gemcitabine (1250 mg/m2 on day 1 over 30 min) with cisplatin (50 mg/m2 on day 1 over 1 h, preceded and followed by hyperhydration) on days 1 and 15 of a 28-day cycle		ORR 8% (95% CI 0.98–26.0) Median time to progression 5.48 mo (95% CI 2.4-11.73 mo) Median OS 14.98 mo (95% CI 9.76–32.9 mo) 2-year OS rate 39.32% (95% CI 19.15–59.03) Toxicity Serious adverse events: 44% Grade 3/4: Neutropenia (16%) Anaemia (12%) Thrombocytopaenia (8%) Nausea/vomiting (8%) Renal failure (4%) Dysaesthesia (4%) Asthenia (4%)	Every 2 weeks' administration of the combination of gemcitabine and cisplatin showed non-significant responses in patients with unresected locoregional or metastatic penile squamous cell carcinoma. Despite manageable side-effects, this combination cannot be recommended as a standard of care, due to disappointing response rates seen in this negative study.		LoE 3 RoB 17/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Huang, 1999, Urologia International is	Case report	n= 3 Japan 1994-1999	We present the experience with multimodality treatment including intra-arterial infusion chemotherapy for penile carcinoma with deep inguinal lymph node metastasis.	T2N3M0 Age: 46 y, 58 y, 71 y	Intraarterial Infusion chemotherapy with monthly courses of cisplatin, methotrexate and bleomycin		<u>Partial response</u> 2/3 <u>Complete response</u> 1/3 <u>Survival</u> Patient 1: died at the 5-month treatment periode Patient 2: 8 mo after chemotherapy relapse, died 14 mo after relapse <u>Toxicity</u> 2/3 Mucositis 1/3 Deep skin ulceration 1/3 Peripheral neuropathy	The number of patients is too small to clarify the merit of the intra-arterial route, our excellent response suggests that intra-arterial chemotherapy has a role to play in the management of penile cancer with fixed inguinal lymph nodes.		LoE 4 RoB 10/20
Hussein, 1990, Cancer	Case serie	n= 6 carcinoma patients	Report our experience with six patients with advanced squamous cell carcinoma of the penis and urethra who were treated with the sequential combination of cisplatin and 5-FU.	<u>Tumor localisation</u> Penis (n= 5) Urethra (n= 1) Performance Status (Zubrod): 0-2 <u>Mean age</u> 56 y (50-60 y)	Cisplatin intravenously at a dose of 100 mg/m² followed 24 hours later by a continuous intravenous infusion of 5-FU at a dose of 960 mg/m2/d for five days every 3 to 4 wks		<u>Clinical Remission</u> 1 Complete response (urethral carcinoma) 5 Partial response (penile carcinoma) <u>Relapse after chemotherapy</u> 12 mo (urethral carcinoma) 18 mo <u>Toxicity</u> Alopecia (6/6 patients) Nausea & vomiting (12/21 courses) Mucositis (6/21 courses) Reversible increases in serum creatinine and blood urea nitrogen levels (1/21 courses)	After chemotherapy, surgery may be useful in selected patients to accurately assess response and excise localized residual tumors. Patients rendered tumor-free may achieve long-term survival.		LoE 4 RoB 8/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Kattan, 1993, Urology	Retrospective case serie	n= 14 France 1980-1992 Median follow-up 54 mo (7-133 mo)	To review twelve years' experience with penile cancer chemotherapy.	Stage: II-IV N0, N+ Performance Status: 0-1 Median age 50 y (31-66 y)	Cisplatin in combination with Methotrexate Adriamycin 5-FU Bleomycin+ Vinblastine Bleomycin+ Epibrubicin Bleomycin+ Methotrexate		Objective response 2/14 patients Death 12/14 patients Median survival 7.6 mo (1-26 mo)	Our experience with penile cancer chemotherapy suggests that combination chemotherapy has a moderate role in the management of these patients.		LoE 4 RoB 8/20
Liu, 2013, Chinese Journal of Cancer	Retrospective case serie	n= 12 China 1999-2011 Median follow-up 23.6 mo (5-50 mo)	To report the encouraging results of combination intraarterial chemotherapy with gemcitabine and cisplatin for 12 patients with locally advanced or recurrent penile squamous cell carcinoma.	T1-TX N2-N3 M0 Median age 53 y (29-78 y)	Intraarterial chemotherapy 900 mg/m² gemcitabine plus 30 mg/m² cisplatin over 15 to 20 min every 7 days		Median OS 24 mo (10-50 mo) Median time to progression 20 mo Side effects Leukoytopenia (25%) Nausea/vomiting (16.7%) Anorexia (16.7%) Anemia (16.7%) Thrombocytopenia (8.3%) Abnormal renal function (8.3%)	Our results suggest that intraarterial chemotherapy with gemcitabine and cisplatin may be effective and potentially curative in locoregionally advanced or recurrent penile squamous cell carcinoma.		LoE 4 RoB 11/20
Necchi, 2018, BJU International	Clinical trial (phase 2 study)	n= 28 2013-2016 Median follow-up 19.8 mo (6.3–25.7 mo)	To harness the frontline therapy in advanced penile squamous cell carcinoma, for which chemotherapy exerts moderate activity but poor efficacy.	n= 20 locally advanced disease n= 8 visceral metastatic disease ECOG PS: 0-1 Mean age 63.5 y (53.5-67.5 y)	Dacomitinib daily 45mg		ORR 32.1% (80% CI 21-43) **Median PFS** Overall 4.1 mo (95% CI 3.1 mo-NR) Locally advanced patients 4.3 mo (95% CI 3.3 mo-NR) Visceral metastatic patients 3.2 mo (95% CI 2.1 mo-NR)	Dacomitinib was active and well tolerated in patients with advanced penile squamous cell carcinoma and may represent an option when combined chemotherapy cannot be administered.		LoE 3 RoB 15/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Median OS Overall 13.7 mo (95% CI 9.9 mo-NR) Locally advanced patients 20 mo (95% CI 11.1 mo -NR) Visceral metastatic patients 9.9 mo (95% CI 7.0 mo-NR) Treatment realted adverse events Grade 1-2: 67.8% Grade 3 (skin rash): 10.7%			
Nicholson, 2013, British Journal of Cancer	Clinical trial (phase 2 study)	n= 29 UK 2009-2010 Median follow-up 14.5 mo	To study the effectivity of the combination of docetaxel, cisplatin and 5-FU.	TX-3 N0-X M0-M1 Median age 60.7 y (49.7-65.5 y)	Up to three cycles of chemotherapy docetaxel, cisplatin and 5-FU		ORR 38.5% (95% CI 20.2-59.4%) Median PFS 7.1 mo (95% CI: 2.7—upper limit not reached) Median OS 13.9 mo (6.1—upper limit not reached) **Toxicity** Any grade 3 or 4 toxicity 67.9 % (95% CI 47.6-84.1%) Most common grade 3 or 4 toxicity Neutropenia: 46.4% Febrile neutropenia or	Docetaxel, cisplatin and 5-FU did not reach the pre-determined threshold for further research and caused significant toxicity. Our results do not support the routine use of the combination of docetaxel, cisplatin and 5-FU.		LoE 3 RoB 15/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							neutropenic sepsis: 9.5%			
Noronha, 2012, Urology annals	Retrospective case serie	n= 19 tertiary cancer institute in a developing country 2008-2009 Median follow-up 15.33 mo (2-34 mo)	To study the efficacy and safety of paclitaxel and platinum doublet chemotherapy in penile cancer patients with high-risk features of local failure.	pT1-3 pN1-3 Stage: II-IV ECOG PS: 1-2 Median age 48 y (25-75 y)	Adjuvant chemotherapy Paclitaxel with cisplatin (n= 15) Paclitaxel with carboplatin (n= 4)		Median DFS 16.2 mo Median OS: not reached Relapses: 6 (loco-regional) Toxicity: Death (n= 1) Grade 3-4 gastrointestinal toxicity (n= 1) Grade 3 neurological toxicity (n= 1) Grade 5 neutropenia (n= 1)	The platinum and taxane doublet chemotherapy was found to be safe and effective.		LoE 4 RoB 13/20
Otto, 2003, Urologe	Case serie	n= 15 Mean follow-up 15 mo	Therapie des fortgeschrittenen Peniskarzinoms	T3-4 Mean age 74 y	Neoadjuvante Chemotherapie: 2-4 Kurse Polychemotherapie mit Cisplatin, Methotrexat und Bleomycin, 3 Wochen später Tumorresektion		Partielle Remission: 3 Tod: 4 (tumorbedingt) Fernmetastasen: 5 Nebenwirkungen: 11/15 gastrointestinale (Grad 2) 9/15 hämatologische (Grad 3) 3/15 hämatologisch (Grad 4)	Die Kombination von Chemotherapie und ausgedehntem operativen Vorgehen beeinflusst einerseits das Überleben des alten Patienten nicht nachhaltig, andererseits wird die Lebensqualität des symptomatischen Patienten entscheidend verbessert, was vorrangig auf die operative Behandlung zurückzuführen ist.	Neoadjuvante Systemtherapie	LoE 4 RoB 7/20
Pagliaro, 2010, Journal of Clinical Oncology	Clinical trial (phase 2 study)	n= 30 2000-2008 Median follow-up	Determining the response rate, time to progression and OS of neoadjuvant chemotherapy	N2-N3 M0 Median age 57.5 y (24-78 y)	Neoadjuvant treatment 175 mg/m² paclitaxel intravenously over 3 hours day 1; ifosfamide		Median time to progression: 8.1 mo (95% CI 5.4-50+) (20/30 patients died) OS	The neoadjuvant regimen of paclitaxel, ifosfamide, and cisplatin induced clinically meaningful responses in	Indirekte Evidenz: Bezieht sich nur auf neoadjuvante System-therapie	LoE 3 RoB 17/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		34 mo (14-59 mo)	among patients with bulky adenopathy.	n= 22 complete chemotherapy and then LAD	1,200 mg/m² on days 1 to 3; and cisplatin 25 mg/m² on days 1 to 3		17.1 mo (95% CI 10.3-60+)	patients with bulky regional lymph node metastases from penile cancer.		
Power, 2009, Urologic Oncology	Case study	n= 2 Follow-up 11-12 mo	Describe two cases of advanced penile cancer showing a sustained palliative response to cisplatin and gemcitabine with minimal toxicity.	ECOG PS: 1 HPV- Age 49 y, 64 y	Cisplatin (80mg/m2 on day 1) and gemcitabine (1,250mg/m2 on days 1 and 8) every 21 days		2/2 partial response 1/2 relapsed after 12 mo Toxicity Tinnitus (n= 1)	Our novel combination of cisplatin and gemcitabine in advanced penile cancer resulted in a sustained palliative response of 12 mo in one patient and an ongoing 11 mo in another. Our experience demonstrates that this is a well tolerated regimen active in this setting		LoE 4 RoB 10/20
Protzel, 2008, Urologe	Case serie	n= 7	Erfahrungen berichten über die Therapie des fortgeschrittenen Peniskarzinoms.	N+ M+ Alter 31-73 y	Chemotherapy Klassischen Dexeus-Schema (Cisplatin, Methotrexat, Bleomycin) (n= 5) Kombinierte Taxol-Carboplatin-Therapie (n= 2)		**Dexeus-Schema** Response 5/5 stable disease (davon 3 mit minor response) Progression 5/5 mit letalem Ausgang **Taxol-Carboplatin-Therapie** Komplette Remission 1/2 Taxol-Carboplatin-Therapie-Patienten Nebenwirkungen Dexeus-Schema: hämato- poetische Toxizitäten	Die ersten Fallberichte zum Einsatz von Taxanen in der Therapie des Peniskarzinoms erscheinen Erfolg versprechend. Allerdings sind Aussagen zu den effektiven Ansprechraten oder zum Überleben der Patienten noch nicht möglich.		LoE 4 RoB 9/20
Protzel, 2009, Urologia	Systemati c review	1966-2008	To review the available literature	n= 4 studies adjuvant setting	**Treatment regimes**		**Adjuvant setting**	Current chemotherapy in penile carcinomas is		LoE 3

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
International is			concerning chemotherapy regimens for penile cancer with response rates and survival when reported.	n= 7 neoadjuvant setting n= 11 studies advanced disease	• Vinblastine, Methrotrexate, Bleomycin • Cisplatin, Methotrexate, Bleomycin • Paclitaxel+ Carboplatin • Paclitaxel, Cisplatin, Ifosfamide • Paclitaxel, Cisplatin, 5-Fluoruracil • Cisplatin, Irinotecan • Cisplatin, 5-Fluoruracil		Vinblastine, Methotrexate, Bleomycin (n= 1 study) Progression: 1/12 Treatment-related death: 0/12 Mean duration of remission: 42 mo Cisplatin, Methotrexate, Bleomycin (n= 1 study) Progression: 4/8 Treatment-related death: 1/8 Mean duration of remission: 26 mo 5 y-survival Adjuvant group: 82% Without adjuvant treatment: 37% **Neoadjuvant setting** Cisplatin (20-30 mg/m2), Methotrexate (200 mg/m2), Bleomycin (15 mg/m2) (n= 1 study) Response: 6/10 Treatment-related death: 2/10 Cisplatin (20 mg/m2), Methotrexate (200 mg/m2), Bleomycin (10 mg/m2) (n= 1 study) Response: 3/3 stable disease Treatment-related death: 0/3 Median survival: 7 mo Vinblastine, Methotrexate,	characterized by high toxicities and poor prognosis of metastasized patients. Recent studies show promising results for new combinations of irinotecan and cisplatin and high efficacy of taxane-based combinations. Neoadjuvant treatment should be given in all cases of fixed lymph node metastasis and possibly for all patients with suspected lymph nodes metastasis. Adjuvant treatment should be proven with new regimens, which might also be able to improve the poor prognosis of patients with distant metastasis.		ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Bleomycin (n= 2 studies) Response: 6/10 Treatment-related death: 1/10 Paclitaxel+ Carboplatin (n= 2 studies) Response: 3/3 Paclitaxel, Cisplatin, Ifosfamide (n= 1 study) Response: 4/5 Complete response: 3/5 Median survival: 30 mo Paclitaxel, Cisplatin, 5-Fluoruracil (n= 1 study) Response: 3/3 Complete response: 2/3 Median survival: 11 mo Cisplatin, Irinotecan (n= 1 study) Response: 6/7 Complete response: 1/7 **Advanced carcinoma** Cisplatin (20 mg/m2), Methotrexate (200 mg/m2), Bleomycin (10 mg/m2) (n= 4 studies) Response: 28/43 Complete response: 6/43 Treatment related death: 2/43 Median survival: ranged from 6 to 32.7 mo			

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Cisplatin (75 mg/m2), Methotrexate (25 mg/m2), Bleomycin (10 mg/m2) (n= 1 study) Response: 13/40 Complete response: 5/40 Treatment related death: 5/40 Median survival: 28 mo Cisplatin (100 mg/m2), 5-Fluoruracil (960 mg/m2) (n= 1 study) Response: 5/5 Median survival: 6 mo Cisplatin (100 mg/m2), 5-Fluoruracil (1000 mg/m2) (n= 2 studies) Response: 3/12 Median survival: 5 mo Paclitaxel, Cisplatin, 5-Fluoruracil (n= 1 study) Response: 2/3 Complete response: 1/3 Cisplatin, Irinotecan (n= 1 study) Response: 10/21 Complete response: 1/21			
Roth, 2000, British Journal of Cancer	Retrospec tive case serie	n= 16 1983-1998	Describe an intra-arterial chemotherapy in locally advanced or Recurrent carcinomas of the penis and anal canal.	Tumor localisation Penis (n= 8) Anus (n= 8) Recurrent malignancies Penis (n= 6)	Eight push injections, given over a 48-h period, of the following drug combination: cisplatin 8.5 mg m–2, 5-FU 275 mg		**Penile carcinoma** Response Complete (3/8) Partial (3/8) Stable disease (1/8) Time to relapse 3 mo - >15y	These results show that intra-arterial chemotherapy is an useful therapeutic modality in advanced stage and relapsing penile carcinoma and anal canal		LoE 4 RoB 7/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
				Anus (n= 5) Advanced malignancies Penis (n= 2) Anus (n= 3) Age range (penile carcinoma): 48-83 y	m−2, methotrexate 27.5 mg m−2, mitomycin C 1.2 mg m−2, and bleomycin 4 mg m−2. Leucovorin was given po, 4 ´ 15 mg day−1, during the chemotherapy and for 3 days thereafter		**Overall** Toxicity Grade III-IV leukopenia (4/16) Grade III mucositis of the glans (1/16) Peripheral thromboembolism (1/16) Grade III asthenia (1/16) Cutaneous toxicity (9/16) Grade III-IV cutaneous lesions (5/16)	carcinoma, and that it is curative in some selected cases. It has manageable toxicity and can even be safely administered in geriatric patients.		
Shammas, 1992, Journal of Urology	Case serie	n= 8 Norway 1985-1990	To present the hospital experience with cisplatin and 5-fluorouracil in metastatic penile cancer.	Jackson stage III-IV N0-N+ Median age 55 y (35-78 y)	Chemotherapy with 100 mg./m2 cisplatin intravenously on day 1 and a 24-hour infusion of 1,000 mg./m.2 5 fluorouracil on days 1 to 5		Response Partial remission (2/8) Progressive disease (3/8) No Change (3/8) Survial without a response 2+ to 28 mo Tolerability Good (4/8) Poor (3/8) Moderate (1/8) Side effects Nausea and vomiting (8/8) Tinnitus (1/8) Impairment of renal function (3/8) Severe infection (2/8)	Poor tolerability especially in the elderly was the main reason for discontinuing chemotherapy. The combination of cisplatin and 5-fluorouracil may have a role in the management of advanced penile cancer together with surgery and radiotherapy.		LoE 4 RoB 8/20
Sklaroff, 1980, Cancer	Prospektive case serie	n= 8 USA	Summarizes the results at Memorial Sloan-Kettering Cancer Center of a prospective trial of methotrexate in	Karnofsky performance status: 50 (40-80) Mean age 57 y (34-68 y)	High-dose methotrexate, 250- 1500 mg/m2 with citrovorum rescue Q 2-4 weeks (5/8)		Partial remission 2/5 high-dose 1/3 low-dose	Methotrexate should be added to the list of chemotherapeutic agents that have demonstrated antitumor		LoE 4 RoB 6/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			eight patients with penile cancer.		Low-dose methotrexate (3/8)			activity in advanced metastatic penile cancer.		
Theodore, 2008, Annals of Oncology	Prospective phase II study	n= 28 2004-2006	To determine efficacy and feasibility of the combination regimen irinotecan and cisplatin in patients with cisplatin advanced penile cancer.	T3-4 N1-3 M0-1 WHO PS: 0-2 Median age 55 y (36-77 y) Settings Neo-adjuvant (n= 7) Advanced disease (n= 21)	Combination of irinotecan (60 mg/m²) on days 1, 8 and 15 and cisplatin (80mg/m²) every 28 days		Overall response rate 8/26 (30.8%, 95% CI 14.3-51.8%) • 2/26 complete • 6/26 partial Grade 4 clinical adverse events Neutropenic infection (2/28) Hypotension (1/28) Thrombosis (1/28) Fatigue (1/28) Pulmonary embolus (1/28) Hamorrhage (1/28)	The study fails to demonstrate a response rate significantly >30%.	The 28 treated patients were assessable for treatment administration and toxicity and 26 eligible patients were assessable for response.	LoE 3 RoB 14/20
Wang, 2015, Urology	Retrospective case serie	n= 19 USA 2000-2008	To estimate the efficacy of various treatments used in men with metastatic penile cancer that progress after first-line chemotherapy.	TxN2-3M0 with treatment failure Zubrod PS: 0-2 Median age 57 (24-72 y)	Second-line treatment Chemotherapy with cisplatin (n= 10) Chemo-radiotherapy with cisplatin (n= 2) Chemotherapy without cisplatin (n= 2) Surgery alone (n= 2) Biologic therapy alone (n= 1)		Median OS Bleomycin, methotrexate, cisplatin: 4 mo Gemcitabine combination: 8.8 mo Erlotinib: 3.5 mo Biologic+ chemotherapeutic: 30.3 mo Chemoradiaton: 12.2 mo Surgery: 10.2 mo Combined modality: 15.5 mo Best supportive care: 2.4 mo Cisplatin-containing chemotherapy: 5.6 mo Non-cisplatin-treated: 4.3 mo	The currently available treatments have minimal efficacy in the setting of recurrent metastatic penile cancer after first-line paclitaxel, ifosfamide, and cisplatin chemotherapy.		LoE 4 RoB 14/20
Zhu, 2010, Urologia International is	Case serie	n= 6 China 2008-2009	To describe the experience with sorafenib and sunitinib in the	G1-G3 ECOG PS: 2-3	Sorafenib n= 3	Sunitinib n= 3	PFS Sorafenib: 6-11 wk Sunitinib: 2-11 wk	The feasibility and activity of sorafenib and sunitinib in our series suggest that		LoE 4 RoB 14/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			treatment of chemotherapy-refractory advanced penile squamous cell carcinoma.	Recurrent and/or metastatic penile squamous cell carcinoma Age 28-60 y			OS Sorafenib: 6-15 wk Sunitinib: 9-16 wk Response 1/6 partial 4/6 stable disease 1/6 progressive disease	this approach may be a promising alternative in chemotherapy refractory advanced penile squamous cell carcinoma.		

Tabelle 29: „Soll die Lymphadenektomie minimalinvasiv oder offen erfolgen?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Direkte Evidenz										
Kumar, 2017, BJU Int	Prospectiv e cohort study	n= 68 ILND United Kingdom 2008-2015 (Before 2013 all procedures were OILNDs) Mean follow-up OLIND: 71 mo (30-99 mo) VEILND: 16 mo (4-35 mo)	To compare the complications and oncological outcomes between VEILND and OILND in men with carcinoma of the penis.	pT1-4 Grade 1-3 Mean age OLIND: 69.5 y VEILND: 65.8 y	OILND n= 35 procedures	VEILND n= 33 procedures	Mean operative time OILND: 94 min VEILND: 97 min not significant Mean number of lymph node yield OILND: 7.11 VEILND: 9.36 p= 0.0013 Mean positive lymph nodes OILND: 0.57 VEILND: 1.24 p= 0.03 Mean lymph node density OILND: 0.08 VEILND: 0.013 p= 0.13 Total wound complications OILND: 68% VEILND: 6% p= <0.001	We have shown that VEILND provides both adequate oncological control and carries a significantly lower morbidity than OILND.		LoE 3 NOS 6/9
Singh, 2018, Journal of Urology	Retro-spective cohort study	n= 151 2012-2016 Median follow-up 40 mo	To compare outcomes between RA-VEIL and OILND in patients without bulky nodal metastasis in a tandem contemporary cohort.	pT1-3 G1-3 N0-N2 Median age RA-VEIL: 58 y (50.3-68 y) OILND: 54 y (45-64 y) p= 0.047	RA-VEIL n= 51	OILND n= 100	No recurrence in both groups Lymph node yield RA-VEIL: 13 OILND: 12.5 Operative time RA-VEIL: 75 min OILND: 60 min p< 0.0001	RA-VEIL is a feasible technique which allows for a similar nodal yield while being associated with lower morbidity than open inguinal lymph node dissection in patients without bulky groin adenopathy.		LoE 3 NOS 8/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Median hospital stay RA-VEIL: 3 days OILND: 4 days p= 0.0008 Median days requiring drains to be kept in situ RA-VEIL: 12 days OILND: 15 days p< 0.0001 Major complications RA-VEIL: 2% OILND: 17% p= 0.0067 Edge necrosis RA-VEIL: 9.8% OILND: 23% p= 0.048 Flap necrosis RA-VEIL: 2% OILND: 13% p= 0.035 Severe limb edema RA-VEIL: 0% OILND: 9% p= 0.029 Independent risk factor for major complications Nodal stage: DAPLE OR 2.8 (95% CI 1.1-6.8) p-value 0.027 OILND: DAPLE OR 7.5 (95% CI 1.3-43) p= 0.024			
Tobias-Machado, 2008, J Endourol	Experimental study	n= 15 patients 2003-2006	To report the updated results of VEIL, an original	N0-1 patients underwent	VEIL n= 20 limbs	Standard open lymph node dissection n= 10 limbs	Operative time (min per limb) VEIL: 120 (90-160) Open: 92 (80-110)	This preliminary series suggests that VEIL can reduce morbidity, including		LoE 3 NOS 9/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		Mean follow-up 31.9 mo	minimally invasive procedure recently reported for extended inguinal node dissection in clinical settings.	penectomy 1 month before the inguinal procedure			p= 0.0002 Number of lymph nodes VEIL: 10.8 (7-16) Open: 9.7 (6-14) p= 0.4 Time for drainage <50ml (days) VEIL: 4.9 (3-12) Open: 6.4 (4-10) p= 0.008 **Complications** Skin-related events VEIL: 1 (5%) Open: 5 (50%) p= 0.009 Lymphatic complications VEIL: 2 (10%) Open: 2 (20%) p= 0.58 Hematoma VEIL: 1 (5%) Open: 0 p= 1 Total VEIL: 4 (20%) Open: 7 (70%) p= 0.011 Time to discharge VEIL+ open procedure: 6.4 d (5-10 d) Bilateral VEIL: 24h (12-36 h) p< 0.001 Time to return to usual activities	hospitalization times, compared with standard open surgery. Oncologic results are premature but seem similar to the results from the conventional open operation. VEIL is a promising minimally invasive approach for radical inguinal dissection in penile cancer patients with nonpalpable or low-volume palpable inguinal disease.		

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							VEIL+ open procedure: 21 d (14-28 d) Bilateral VEIL: 14 d (7-18 d) p= 0.032 Recurrences no recurrences in both groups			
Wang, 2017, Anticancer Research	Cohort study	n= 34 patients China 2013-2015	To compare the efficiency and complications of VEIL and OILND.	N0-3 M0 Age 28-69 y	VEIL n= 19 lymph-adenectomies	OILND n= 21 lymph-adenectomies	Mean operative time VEIL: 139.5±45.52 min Open surgery: 169.8±55.19 min p= 0.08 Mean intraoperative blood loss VEIL: 22.50±14.24 ml Open surgery: 68.44±42.19 ml p= 0.00 Mean drainage tube removal time VEIL: 7.23±1.79 d Open surgery: 11.44±2.69 d p= 0.00 Mean suture removal time VEIL: 7.58±1.24 d Open surgery: 12.81±2.04 d p= 0.00 Mean length of hospital stay VEIL: 10.43±2.53 d Open surgery: 12.50±4.98 d p= 0.15 **Incidence of complications**			LoE 3 NOS 8/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Overall VEIL: 21.05% Open surgery: 61.9% p= 0.01 Grade 1 VEIL: 15.79% Open surgery: 38.1% p= 0.12 Grade 2 VEIL: 5.26% Open surgery: 23.81% p= 0.1 Grade 3 and 4 No complications in both groups			
Yadav, 2018, Urology	Ex-perimental study	n= 29 India 2013-2017 Mean follow-up 14 mo (7-28 mo)	To compare differences of morbidity profile, oncological yield, and efficacy between video endoscopic inguinal lymphadenectomy and open inguinal lymph-adenectomy cases.	Tis-T4 Mean age 52.4 y	VEIL	Open inguinal lymph-adenectomy	Mean operative time VEIL: 162.83 min Open group: 92.35 min p <0.001 Mean nodes removed VEIL: 7.6 Open group: 8.3 p= 0.681 Positive groins on histology VEIL: 7 Open group: 9 p= 0.89 Hospital stay VEIL: 4.65 d (4-8 d) Open group: 10.26 d (14-22 d) p< 0.01 Time to return to usual activities VEIL: 18 d (14-22 d)	A minimally invasive approach to performing inguinal lymphadenectomy holds promise for providing a procedure with reduced morbidity and comparable oncologic benefits to the traditional open approach for patients with penile cancer.		LoE 3 NOS 8/9

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Open group: 28 d (24-33 d) p< 0.01 **Postoperative complications** <u>Skin necrosis (grade 1)</u> VEIL: 2 Open group: 7 p< 0.01 <u>Skin necrosis (grade 3b)</u> VEIL: 0 Open group: 1 p> 0.01 <u>Lymphedema (grade 1)</u> VEIL: 3 Open group: 4 p> 0.01 <u>Lymph collection (grade 1)</u> VEIL: 3 Open group: 3 p> 0.01 <u>Lymph collection (grade 3a)</u> VEIL: 0 Open group: 1 p> 0.01 <u>Wound infection (grade 1)</u> VEIL: 0 Open group: 4 p< 0.01			
Indirekte Evidenz										
Gkegkes, 2017, Journal of	Systemati c review	n= 10 studies (4 case series, 6 case reports)	To review the up until recently	n= 51 carcinoma patients	Robotic-assisted inguinal		<u>Mean duration of hospitalization</u> 2 days	Until now there has not been sufficient evidence regarding the role of robotics in	Indirekte Evidenz: nur video-endoskopische	LoE 4 ROBIS low

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Robotic Surgery		Greece, India, Mexico, USA, Venezuela 2009-2017	available literature on the use of robotic technology on patients that require inguinal lymphadenect omy.	37= penile squamous cell carcinoma 12= vulvar carcinoma 1= while urethral squamous cell carcinoma 1= melanoma	lymphadenect omy		Duration of drainage ranged from 7 to 72 days <u>Postoperative complications</u> • Lymphocele (13.7%) • Lymphedema (7.8%) • Cellulitis (7.8%) • Seroma (3.9%) • Abscess (3.9%) • Wound breakdown/wound infection (3.9%) • Sepsis (1.9%) • Prolonged lymphorrhea (1.9%) • Skin necrosis (1.9%)	groin lymph node dissection, though this approach appears to be safe and oncologically effective, with morbidity rates relatively lower compared to open surgery.	Lymphknotene ntfernung und unter-schiedliche Krebsentitäten	
O'Brien, 2017, Journal of Urology	Systemati c review	n= 65 studies 1980-2016	Provide an objective update of the recent trends in the management of penile squamous cell carcinoma, and inguinal and pelvic lymph node metastases.				- high incidence of morbidity following open surgery (55% postoperative complications) - most of these complaints were minor and resolved without prolonged morbidity -most common issues: infection, lymphocele, skin flap necrosis, lymphedema and wound dehiscence	Minimally invasive ILND has demonstrated promise for further reducing the morbidity associated with open surgery while delivering comparable oncologic outcomes.	Ver-gleichendes Ergebnis zur offenen und minimal-invasiven Lymph-adenektomie stammt aus einem narrativen Review.	LoE 3 ROBIS high

Tabelle 30: „Wie viele Lymphknoten sollen bei einer radikalen Lymphadenektomie entfernt werden?“

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Minimally invasive procedures										
Canter, 2012, Canadian Journal of Urology	Prospective case serie	n= 10 patients USA 2008	To describe the technique for performing minimally invasive endoscopic groin dissection with inguinal lymphadenectomy and present the initial complication and short term oncologic data.	n= 19 groin dissections for squamous cell carcinoma of the penis Patients with high risk features (≥ T2, high grade histolgy, and/or lymphovascular invasion of the primary tumor)	Minimally invasive endoscopic groin dissection with inguinal lymphadenectomy		Median nodal yield 11 (3-26) nodes/side Median hospital length of stay 1 day (1-12 days) Drain duration 25 ays (8-101 days) Complications - No perioperative mortalities - Readmission for incision and drainage (n= 1) - Pneumomediastinum without significant sequelae (n= 1) - Readmission for superficial cellulitis requiring IV antibiotics (n= 1) - Seroma formation (n= 3) - Mild-moderate lymphedema (n= 1) - Superficial cellulitis requiring oral antibiotics (n= 1) Overall: 3 major and 4 minor complications (36.8%)	A minimally invasive approach to performing inguinal lymphadenectomy holds promise for providing a procedure with reduced morbidity and comparable oncologic benefits to he traditional open approach for patients with penile cancer.		LoE 4 RoB 10/20
Chaudhari, 2016, Urology annals	Prospective case serie	n= 14 India 2008-2015	To report our institutional experience with video	Mean age 57.8 y (45-70 y)	Video endoscopic inguinal lymphadenectomy		Mean lymph node yield 7.68 nodes (5-11 nodes) Complications	Video endoscopic inguinal lymphadenectomy is a safe and feasible technique in patients with penile carcinoma who require		LoE 4 RoB 13/20

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		Median follow-up 48 mo	endoscopic inguinal lymphadenectomy for radical management of inguinal nodes in patients with penile squamous cell carcinoma.				- No interoperative - No cutaneous - 27.2% localized lymphocele - 13.63% surgical emphysema Recurrence 0/10	radical inguinal lymphadenectomy. It allows the removal of inguinal lymph nodes within the same limits as in conventional surgical dissection and reduces surgical morbidity substantially.		
Cui, 2016, International urology and nephrology	Randomized controlled trial	n= 23 patients 2011-2013 China Median follow-up 38 mo	To evaluate the effect of saphenous vein sparing during bilateral inguinal lymphadenectomy for penile carcinoma patients.	T1-T4 Mean age 58 y	Laparoscopic prophylactic during bilateral inguinal lymph-adenectomy with saphenous vein sparing n= 23 lymph-adenectomies	Laparoscopic prophylactic during bilateral inguinal lymphadenectomy with saphenous vein ligated n= 23 lymph-adenectomies	Harvested number of node Spared: 8.78 ± 2.78 Ligated: 8.30 ± 1.39 p= 0.44 **Short-term postoperative complications** Acute cellulitis Spared: 8% Ligated: 26% p= 0.12 Seroma Spared: 0% Ligated: 8% p= 0.15 Acute lymphedema Spared: 26% Ligated: 56% p= 0.03 Wound breakdown Spared: 8% Ligated: 17% p= 0.38 **Long-term postoperative complications**	Laparoscopic prophylactic bilateral inguinal lymphadenectomy with saphenous vein sparing is beneficial in patients with penile carcinoma by reducing the incidence of short-term and long-term postoperative complications.	Vergleich zweier unter-schiedlicher laparaskopischer Verfahren	LoE 2 Cochrane RCT tool: high

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Lower limb lymphedema Spared: 8% Ligated: 34% p= 0.03 Cellulitis Spared: 8% Ligated: 0% p= 0.15			
Pahwa, 2013, World Journal of Surgical Oncology	Prospectiv e case serie	n= 10 Follow-up 3-14 mo	To present a critical perioperativ e assessment with points of technique.	T1-3 Mean age 51 y (39-62 y)	VEIL		Lymph node yield 7-12 nodes Drain removal 4-8 days Complications Lymphocele (20%)	VEIL was a safe and feasible technique in patients with penile carcinoma with non palpable inguinal lymph nodes. It allows the removal of inguinal lymph nodes within the same limits as in conventional surgical dissection and potentially reduces surgical morbidity.		LoE 4 RoB 13/20
Russel, 2017, Urology	Retrospecti ve case serie	n= 18 patients USA 2009-2015 Median follow-up 5.5 mo (IQR 3-10.8 mo)	To report and analyze the outcomes of endoscopic inguinal lymph node dissection, inclusive of VEIL and robotic-assisted ILND approaches.	n= 34 E-ILND procedures pT1 cN0-2 Median age 72.4 y (61.7-76.2 y)	n= 27 robotic-assisted ILND	n= 7 VEIL	**Overall** Median nodal yield 10 (IQR 6-12.5) Median length of stay 1 day (range 1-3 days) Regional or distant metastasis n= 3 at a median duration of 1.7 mo (IQR 0.9-3.9 mo) **Complications** Overall: 18% (of them 9% minor and 9% major) Robotic-assisted ILND: 11% VEIL: 43%	Endoscopic inguinal lymph node dissection is feasible from a technical standpoint, and our results demonstrate that lymph node counts are comparable with an open approach. Importantly, endoscopic inguinal lymph node dissection has the potential to reduce complication rates and time to convalescence when compared with open ILND.		LoE 4 RoB 16/20
Inguinal/pelvic lymphadenectomies										

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Ball, 2017, Investig Clin Urol	Retrospecti ve case serie	n= 28 patients USA 1988-2012 Mean follow-up 34 mo (1-174 mo)	To determine the impact of lymph node density on survival after inguinal lymph node dissection for penile cancer.	Cis T1-3 N0-3	Inguinal lymph node dissection		Median node yield 17.5 (12-22)	In this small, retrospective penile cancer cohort, the presence of nodal involvement >15% was associated with decreased recurrence-free survival and OS, and outperformed total number of positive LN as a prognostic indicator.		LoE 4 RoB 16/20
Coblentz, 2002, Journal of Urology	Retrospecti ve case serie	n= 11 patients USA 1995-2011 Mean follow-up 9 mo	To review the experience of the morbidity of the modified prophylactic inguinal lymph-adenectomies.	n= 22 lymph-adenectomies pT1 cN0 M0 Grades I-III Mean age 57 y (39-75 y)	Modified prophylactic inguinal lymphadenectomy		Bilateral inguinal lymphadenectomy Mean node yield: 27 (15-40) Pelvic lymphadenectomy (n= 5) Mean node yield: 12 (5-22)	Inguinal lymphadenectomy with saphenous vein sparing and thick skin flaps appears to offer excellent functional outcome in patients undergoing prophylactic bilateral inguinal lymphadenectomy for high risk disease. Early followup indicates that the local recurrence rate does not appear to increase compared to similar patients reported on in the literature treated with the classic dissection technique.		LoE 4 RoB 11/20
Djajadiningrat, 2015, Journal of Urology	Retrospecti ve case serie	n= 79 Netherlands since 2001 Median follow-up 59 mo (40-72 mo)	To analyze the characteristi cs of tumor positive inguinal regions predictive for pelvic lymph node involvement in patients prophylactic ally treated with pelvic lymph node dissection	chemotherapy naïve patients without preoperative evidence of pelvic disease Tis T1-4 G1-3 Median age 66 y (60-74 y)	Prophylactic pelvic lymphadenectomy		Median number of removed nodes 12 (8-17) Postoperative complication Overall: 18% • Wound complications (n= 9) • Nonwound complications: pneumonia, delirium, ileus (n= 5) Complication grade: • Grade I (n= 3) • Grade II (n= 8)	Inguinal extranodal extension, or 2 or more inguinal tumor positive lymph nodes are predictive of pelvic tumor positivity in patients without evidence of pelvic involvement. Disease specific survival remains poor in patients with pelvic node involvement who are treated with surgery only.		LoE 4 RoB 14/20

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							• Grade IIIb (n= 3) • Grade V: pneumonia and congestive heart failure (n= 1)			
Gopmann, 2015, BJU International	Retrospecti ve case serie	n= 327 Netherlands, USA, China, Germany 1995-2013	To assess the potential complication s associated with ILND and to determine the prognostic factors that best predict the developmen t of these complication s.	pT0-pT4 pN0-3 pM0-1 Median age 64 y (28-91 y)	Diagnostic/ therapeutic modified or extended ILND		Median lymph nodes harvest 18 (2-67) Median length of hospital stay 8 days (0-62 days) Median Jackson-Pratt drain days 9 days (0-61 days) Overall complications Minor: 65.7% Major: 34.3% Minor complications • Wound infection (34.8%) • Seroma (26.5%) • Lymphocele: no intervention (10.4%) • Wound dehiscence (7.2%) • Cellulitis (2.8%) • Scrotal oedema (1.7%) • Fever (1.1%) • Thigh numbness (0.6%) Major complications • Wound infection with i.v. antibiotics (22.1%) • Skin flap necrosis (12.7%) • Lymphocele: intervention (3.3%) • Non-healing wound (2.2%) • Haematoma (2.2%)	The majority of complications associated with ILND are minor and resolve without prolonged morbidity.		LoE 4 RoB 16/20

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							• Pulmonary embolism (0.6%) • Rectoscrotal fistula (0.6%)			
Johnson, 2010, Cancer	Retrospective case serie	n= 593 USA 1988-2005 Follow-up Until the end of 2005	We hypothesize that patients receiving lymph node dissection of 8 or more lymph nodes will have higher 5-year overall survival and that low percentage of patients with grade 3 or T2-4 disease receive lymph-adenectomy with a yield of at least 8 lymph nodes.	Grade 1-3 T1-4 Age < 65 y: 44.8% ≥ 65 y: 55.2%	Lymph node dissection ≥ 8 lymph nodes	Lymph node dissection < 8 lymph nodes	5y-OS (Grade 3 patients) ≥ 8 lymph nodes (n= 48): 49.2% (SD 9.0) < 8 lymph nodes (n= 244): 66.3% (SD 4.6) p= 0.10 5y-OS (pT2-4 patients) ≥ 8 lymph nodes (n= 320): 53.6% (SD 3.9) < 8 lymph nodes (n= 82): 70.2% (SD 6.3) p= 0.004 Multivariate Cox Survival Analyses of the association between 5-Year Overall mortality ≥ 8 lymph nodes: HR 1 < 8 lymph nodes: HR 1.86 (1.26-2.76) p= 0.002	Patients receiving lymph node dissections, those involving examination of ≥ 8 LNs experienced significantly higher overall 5-year survival.		LoE 4 RoB 12/20
Li, 2014, Urologic Oncology	Cohort study	n=146 patients China 2002-2012 Median follow-up 42 mo (12-162 mo)	To investigate the value of removed lymphnode count and lymph node density for predicting DSS rate following radical lymph-adenectomy in patients	≤ pT1 - ≥ pT3 G1-3 N0-N+ Median age 52 y (24-82 y)	Radical lymphadenectomy pN0= 75	Radical lymph-adenectomy pN+= 71	**DSS pN0** (multivariate analysis) <16 vs. ≥16 (total number of removed lymph nodes) HR 10.89 (1.80-65.93) p= 0.009 **DSS pN+** (multivariate analysis) <16 vs. ≥16 (total number of removed lymph nodes) HR 1.43 (0.52-3.90) p= 0.487	The removal of at least 16 lymph nodes was associated with a significantly longer DSS rate inpatients with pN0 penile cancer.		LoE 3 NOS 9/9

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
			with penile cancer.							
Matulewicz, 2016, Urology	Retrospective cohort study	n= 5046 USA 1998-2013	To assess the potential benefit of centralization of care in penile cancer.	Stage 0-4 Mean age Academic hospitals: 61.7 ± 14.7 Community hospitals: 67.1 ± 14.1	Pelvic/inguinal lymph node dissection in academic hospitals n= 2304	Pelvic/inguinal lymph node dissection in community hospitals n= 2745	Total lymph node yield Academic center: 18.5 Community center: 12.5 OR 2.29 (95% CI 1.95-2.68) p< 0.001 8+ nodes extracted Academic center: 79.2% Community center: 56.2% p< 0.001	At the time of diagnosis, equal number of patients is treated with penile-sparing surgery but there is greater use of lymph node dissection and higher lymph node yield at academic centers.		LoE 3 RoB 6/9
Naumann, 2005, Onkologie	Retrospective case serie	n= 16 Germany 1992-2003 Median follow-up 53.5 mo (9-146 mo)	To evaluate the risk of metastatic disease in patients with pT1 G2 squamous cell carcinoma of the penis.	pT1 G1-3 cN0-cN+ Mean age 61.5 y (36-87)	Early ILND n= 10	Surveillance n= 6	Average number of lymph nodes in ILND 9 per side (3-17)	The natural behavior of pT1 G2 squamous penile carcinoma and its metastatic potential has been underestimated in recent literature. Since morbidity after early ILND has markedly decreased and its superiority over delayed ILND has been shown, we advocate the early modified inguinal lymph node dissection until strong prognostic factors for positive inguinal lymph nodes have been validated.		LoE 4 RoB 11/20
Soodana-Prakash, 2018, Urologic Oncology	Retrospective cohort study	n= 364 USA 2004-2013 Median follow-up 32 mo (18.5-55.7 mo)	To determine whether a specific lymph node yield affects OS in patients with penile cancer.	T0-4 N0-2 M0 Charlson/ Deyo: 0-2 Median age 62 y (52-70.5 y)	Lymph node yield ≤ 15	Lymph node yield > 15	Median number of lymph node removed Total: 16 (9-23) Lymph node yield ≤ 15: 9 (4-12) Lymph node yield of >15 nodes: 23 (18.5-31.5) p <0.001 Multivariable Cox proportional hazards model predicting overall survival	In as ample of men undergoing ILND for penile squamous cell carcinoma, we found that a total lymph node yield of >15 nodes was independently associated with a decreased likelihood of death and was associated with improved 5-year OS compared to lymph node yield ≤15.		LoE 3 NOS 7/9

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							(adjusted) Lymph node yield ≤ 15: HR 1.75 (95% CI 1.14-2.70) Lymph node yield of >15 nodes: HR 1 p= 0.011			
Open vs. minimally invasive procedures										
Kumar, 2017, BJU Int	Cohort study	n= 68 ILND United Kingdom 2008-2015 (Before 2013 all procedures were OILNDs) Mean follow-up OLIND: 71 mo (30-99 mo) VEILND: 16 mo (4-35 mo)	To compare the complications and oncological outcomes between VEILND and OILND in men with carcinoma of the penis.	pT1-4 Grade 1-3 Mean age OLIND: 69.5 y VEILND: 65.8 y	OILND n= 35 procedures	VEILND n= 33 procedures	Mean number of lymph node yield OILND: 7.11 VEILND: 9.36 p= 0.0013 Total wound complications OILND: 68% VEILND: 6% p= <0.001	We have shown that VEILND provides both adequate oncological control and carries a significantly lower morbidity than OILND.		LoE 3 NOS 6/9
Singh, 2018, Journal of Urology	Retrospective cohort study	n= 151 2012-2016 Median follow-up 40 mo	To compare outcomes between RA-VEIL and OILND in patients without bulky nodal metastasis in a tandem contemporary cohort.	pT1-3 G1-3 N0-N2 Median age RA-VEIL: 58 y (50.3-68 y) OILND: 54 y (45-64 y) p= 0.047	RA-VEIL n= 51	OILND n= 100	Lymph node yield RA-VEIL: 13 OILND: 12.5	RA-VEIL is a feasible technique which allows for a similar nodal yield while being associated with lower morbidity than open inguinal lymph node dissection in patients without bulky groin adenopathy.		LoE 3 NOS 8/9
Tobias-Machado, 2008, J Endourol	Experimental study	n= 15 patients 2003-2006	To report the updated results of VEIL, an original	N0-1 patients underwent penectomy 1	VEIL n= 20 limbs	Standard open lymph node dissection	Number of lymph nodes VEIL: 10.8 (7-16) Open: 9.7 (6-14) p= 0.4	This preliminary series suggests that VEIL can reduce morbidity, including hospitalization times, compared with standard		LoE 3 NOS 9/9

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		Mean follow-up 31.9 mo	minimally invasive procedure recently reported for extended inguinal node dissection in clinical settings.	month before the inguinal procedure		n= 10 limbs	Time for drainage <50ml (days) VEIL: 4.9 (3-12) Open: 6.4 (4-10) p= 0.008 **Complications** Skin-related events VEIL: 1 (5%) Open: 5 (50%) p= 0.009 Lymphatic complications VEIL: 2 (10%) Open: 2 (20%) p= 0.58 Hematoma VEIL: 1 (5%) Open: 0 p= 1 Total VEIL: 4 (20%) Open: 7 (70%) p= 0.011 Time to discharge VEIL+ open procedure: 6.4 d (5-10 d) Bilateral VEIL: 24h (12-36 h) p< 0.001 Time to return to usual activities VEIL+ open procedure: 21 d (14-28 d) Bilateral VEIL: 14 d (7-18 d) p= 0.032 Recurrences	open surgery. Oncologic results are premature but seem similar to the results from the conventional open operation. VEIL is a promising minimally invasive approach for radical inguinal dissection in penile cancer patients with nonpalpable or low-volume palpable inguinal disease.		

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							no recurrences in both groups			
Wang, 2017, Anticancer Research	Cohort study	n= 34 patients China 2013-2015	To compare the efficiency and complications of video endoscopy, inguinal lymphadenectomy and open inguinal lymph node dissection.	N0-3 M0 Age 28-69 y	VEIL n= 19 lymphadenectomies	Open inguinal lymph node dissection n= 21 lymphadenectomies	Mean lymph node harvest VEIL: 10.78±5.22 Open surgery: 12.60±5.53 p= 0.24	Compared with open surgery, video endoscopy surgery achieved the same efficiency, and had the advantage of reduction of complications, suture removal time and in-surgery blood loss. VEIL is not recommended especially for those with large tumor size. Severe local infiltration makes it difficult to create sufficient space, that would prolong the surgical time. In these cases, open surgery would be the first choice.		LoE 3 NOS 9/9
Yadav, 2018, Urology	Experimental study	n= 29 India 2013-2017 Mean follow-up 14 mo (7-28 mo)	To compare differences of morbidity profile, oncological yield, and efficacy between video endoscopic inguinal lymph-adenectomy and open inguinal lymphadenectomy cases.	Tis-T4 Mean age 52.4 y	VEIL n= 29	Open inguinal lymphadenectomy n= 29	Mean nodes removed VEIL: 7.6 Open group: 8.3 p= 0.681 Hospital stay VEIL: 4.65 d (4-8 d) Open group: 10.26 d (14-22 d) p< 0.01 Time to return to usual activities VEIL: 18 d (14-22 d) Open group: 28 d (24-33 d) p< 0.01 **Postoperative complications** Skin necrosis (grade 1) VEIL: 2 Open group: 7 p< 0.01 Skin necrosis (grade 3b)	The present study clearly outlines the fact that VEIL can deliver an equivalent lymph node yield similar to open inguinal lymphadenectomy with significantly less morbidity and is not affected by either the palpability or the number of palpable nodes.		LoE 3 NOS 8/9

Referenz	Studien-design	Studien-charakter-isitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							VEIL: 0 Open group: 1 p> 0.01 <u>Lymphedema (grade 1)</u> VEIL: 3 Open group: 4 p> 0.01 <u>Lymph collection (grade 1)</u> VEIL: 3 Open group: 3 p> 0.01 <u>Lymph collection (grade 3a)</u> VEIL: 0 Open group: 1 p> 0.01 <u>Wound infection (grade 1)</u> VEIL: 0 Open group: 4 p< 0.01			

10.1.5. Schlüsselfragen der AG Patienteninformation, Nachsorge

Tabelle 31: „Wie ist die Lebensqualität bei Patienten mit T1/T2 unter verschiedenen Therapieformen?“

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
(Partial) Penectomy									
Bhat, 2018, Indian Journal of Surgery	Case serie	n=12 India Patient treated in the last 6 years	n= 2 total penectomy n= 10 partial penectomy Mean age Penile carcinoma patients: 51.08 (38-74 y) Partners: 37.92 y (26-55 y)	To evaluate post-surgery sexuality concerns in carcinoma penis patients and their partners.	SFQ	**Partial penectomy** Sexual interest Patients: 1.05 Partners: 0.83 Sexual desire Patients: 1.02 Partners: 1.05 Sexual arousal Patients: 1.2 Partners: 1.08 Sexual activity Patients: 0.78 Partners: 0.85 Sexual statisfaction Patients: 0.72 Partners: 0.90 Orgasm Patients: 1.60 Partners: 1.05 Masturbation Patients: 0.52 Partners: 0.23 Relationship Patients: 0.72 Partners: 0.74 **Total penectomy** Sexual interest Patients: 1.25 Partners: 1.25	Post-surgery, there is a marginal reduction in global sexual function in both patients and their partners, and this has effect on their interpersonal relationship as well. Patients suffer more from performance anxiety and loss of masculine image, but with the time, both the patients and their partners learn to satisfy each other with sexual activity, which need not always be the intercourse.		LoE 4 RoB 11/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						Sexual desire Patients: 1.33 Partners: 1.2 Sexual arousal Patients: 1.33 Partners: 1.2 Sexual activity Patients: 0.75 Partners: 0.88 Sexual statisfaction Patients: 0.5 Partners: 0.5 Orgasm Patients: 0.5 Partners: 0.5 Masturbation Patients: 0.49 Partners: 0.5 Relationship Patients: 0.53 Partners: 0.53			
D'Ancona, 1997, Urology	Case serie	n= 14 Brazil 1990-1995 Median follow-up 11.5 mo (6-72 mo)	T1-3 Median age 50.5 y (37-70 y) Partial penectomy	To investigate the impact of partial penectomy on the quality of life of patients with carcinoma of the penis.	Semistructured interview OSFQ SPQ GHQ-12 HADS	Psychological behavior and adjustment • No significant levels of anxiety and depression were found Sexuality • 64% overall sexual function was normal or slightly decreased • 14% had precarious or	Patients who undergo partial penectomy for penile cancer can maintain the quality of life (in social, psychological, and sexual terms) at levels similar to those that existed in the period before surgery.	Ergebnisse wurden nicht nach den Fragebögen, sondern nach den drei Bereichen „Psychological behavior and adjustment", "Sexuality" und "Social activity" dargestellt.	LoE 4 RoB 12/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						absent sexual function • No change: masculine self-image and the relationship with their partners • Sexual interest and statisfaction remained normal or slightly reduced in 9 and 12 patientsn= 3 no sexual intercourse after surgery <u>Social activity</u> • family life and other interaction remained as they were before surgery • n= 2 little unsatisfied with their jobs			
Ficcara, 2000, Urol Int	Cross-sectional study	n= 155 <u>Mean follow-up</u> Penile carcinoma patients: 69 mo	n= 16 squamous penile carcinoma <u>Mean age</u> Penile carcinoma patients: 63 y Patients treated with partial penectomy	To evaluate the general state of health and the psychological well-being in a group of 155 patients after surgery for urological malignant neoplasms.	HADS GHQ	<u>Impairment rates of the emotional and general state of health (GHQ)</u> Penis carcinoma patient: 37.5% Controls: 9% p= 0.008 <u>Levels of anxiety (HADS)</u> Penis carcinoma patient: 31% Controls: 2% p= 0.0001	Patients who underwent radical cystectomy for bladder carcinoma and those treated with partial penectomy for squamous penile carcinoma showed a significant impairment of the general state of health compared with controls. Higher levels of anxiety were observed in patients who underwent ileal conduit after radical cystectomy, in those treated with radical prostatectomy for prostate cancer and in those who underwent partial penectomy.	Zusätzlich aufgenommen	LoE 4 EPHPP weak
Romero, 2005, Urology	Before-after study	n= 18 Brazil 1998-2004	<u>Median age</u> 52 y	To compare sexual function and satisfaction	IIEF	<u>Erectile function</u> Before: 29.56 ± 1.42	The preoperative and postoperative scores were statistically different for all		LoE 4 RoB 13/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
		Median time from surgery 23.5 mo (6-62 mo)	Patients treated with partial penectomy	before and after partial penectomy and to evaluate possible dysfunctions that could modify postoperative sexual functioning.		After: 19.39 ± 12.44 p= 0.012 Orgasmic function Before: 9.94 ± 0.24 After: 7.67 ± 3.90 p= 0.027 Sexual desire Before: 8.89 ± 0.76 After: 7.61 ± 1.94 p= 0.018 Intercourse statisfaction Before: 12.67 ± 1.46 After: 6.89 ± 5.57 p= 0.002 Overall statisfaction Before: 8.61 ± 1.58 After: 6.11 ± 2.65 p= 0.001	domains of sexual function after partial penectomy.		
Sansalone, 2017, Asian Journal of Andrology	Before-after study	n= 25 Italy 2011-2013 Mean follow-up 19 mo (12-25 mo)	pT1-2 Mean age 61 y (25-75 y) Patients treated with partial penectomy	This study examined patients' sexual activity, self-esteem, and sexual relationships after penile cancer surgery as well as their partner's on with t.	IIEF-15 EDITS QEQ SEAR	**Postsurgery mean score** EDITS Patient: 74.97 Partner: 73.25 QEQ 77.46 SEAR SEAR 1-8: 68.06 SEAR 9-12: 73.25 SEAR 13-14: 74.5 **Postsurgery vs. presurgery score** IIEF-15	The final results showed that penile cancer leads to several sexual and psychosexual dysfunctions. Patients who undergo partial penectomy for penile cancer can maintain the sexual outcomes at levels slightly lower to those that existed in the period before surgery.		LoE 4 RoB 15/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						Significant differences in erectile function, orgasmic function, sexual desire, intercourse statisfaction, overall statisfaction			
Sosnowski, 2016, Central European Journal of Urology	Case serie	n= 10 Poland 2013 Median follow-up 16 mo (7-49 mo)	pT1-3 G1-3 N0-3 Median age 60.5 y (35-74 y) Patients treated with penectomy	To assess the quality of life in patients who had undergone total penectomy	EORTC QLQ C-30 SES CMNI IIEF-15 (modified) IPSS	Median SES 75% (67-87%) Median CMNI 88% (81-100%) Median IPSS 12.5 points (11-18 points) **EORTC** Median global health status: 50 Physical functioning: 70 Role functioning: 83.3 Emotional functioning: 70.8 Cognitive functioning: 83.3 Social functioning: 75 IIEF-15 (modified) A significant number of patients were sexually inactive.	The results obtained indicate that total amputation of the penis significantly affects one's sex life and overall quality of life. This does not have negative implications in terms of partner-ship relations, self-assessment or the evaluation of masculinity.		LoE 4 RoB 18/20
Yu, 2016, Scientific Reports	Before-after study	n= 51 China 2010-2013	Median age 56 y Patients treated with partial penetomy	To evaluate the sexual function after partial penectomy for penile carcinoma patients.	IIEF-15 SAS SDS	**IIEF-15** Erectile function Pre-operation: 26.70 ± 3.07 Postoperation: 17.81 ± 10.66 p< 0.01	Our preliminary findings suggest that the sexual function after partial penectomy was significantly reduced.		LoE 4 RoB 16/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						Orgasmic function Pre-operation: 8.44 ± 1.16 Postoperation: 5.81 ± 3.35 p< 0.01 Sexual desire Pre-operation: 8.33 ± 1.27 Postoperation: 6.28 ± 2.16 p< 0.01 Intercourse statisfaction Pre-operation: 12.30 ± 2.21 Postoperation: 7.07 ± 4.56 p< 0.01 Overall statisfaction Pre-operation: 7.88 ± 0.41 Postoperation: 8.21 ± 0.31 p= 0.01 **SAS** Pre-operation: 46.30 ± 8.73 Postoperation: 54.72 ± 11.74 p= 0.01 **SDS** Pre-operation: 43.60 ± 8.32 Postoperation: 51.26 ± 10.07 p= 0.04			

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
Brachytherapy									
Delaunay, 2014, Brachy-therapy	Case serie	n= 19 France 1992-2009	T1-2 N0 <u>Mean age</u> 64.7 y (38-84 y) Patients treated by penis brachytherapy	To assess the oncologic outcomes, sexual function, and the sexual behavior of men treated by penis brachytherapy for a cancer of the penis.	IIEF BASIC IDEA	• 58.8% sexually active after treatment • 94.4% had erections after treatment • 36.8% patients had no erectile dysfunction <u>IIEF</u> Patients who felt that brachytherapy had little or no changes in their sexuality had an IIEF-5 score (p= 0.016), IIEF-15 (p= 0.003), and a frequency of sexual intercourse (p= 0.026) significantly higher.	After treatment, most patients reported that penis brachytherapy has little or no effect on their sexuality. More than half of patients remained sexually active after treatment and almost all continued to have erections even if they were of lower quality. There was little damage to body image and sense of manliness.	Ergebnisse sind in der Studie nur geringfügig Fragebögen aufgeschlüsselt.	LoE 4 RoB 12/20
Gambachidze, 2018, Brachytherapy	Case serie	n= 23 France 1991-2015 <u>Median follow-up</u> 5.9 y (5.2-6.7 y)	T1, Tis N0-N+ <u>Median age</u> 63.4 y (49.7-67 y) Patients treated with brachytherapy	Long-term evaluation of urinary, sexual, and quality of life outcomes after brachytherapy for penile carcinoma.	IIEF-5 ICSmaleSF & LUTS IMGI EuroQol (EQ-5D-5L)	**Median IIEF-5 score** 20 (13-24) **ICSmaleSF & LUTS** Median LUTS score: 6 (2-10) Median pilling score: 2 (1-3) 26% painful ulceration of glans 30% selfcatheterization 13% urethral dilatation 70% sexual activity	Our results show the moderate impact of brachytherapy on functional outcomes, confirming that it is an adequate first-intent organ-sparing strategy in patients with localized penile carcinoma.		LoE 4 RoB 16/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						Median IMGI score 21 (16-22) **Median QoL assessment** 80 (65-90) <u>Pain</u> 57% none 39% moderate pain			
Seibold, 2016, Strahlen-therapie und Onkologie	Case serie	n= 13 2002-2014 <u>Median follow-up</u> 50 mo (13-155 mo)	T1-T3 G1-G2 <u>Mean age</u> 57.6 y (37-65 y) Patients treated with brachytherapy	To assess the efficacy and toxicity profile of protocolbased interstitial pulsed-dose-rate brachytherapy for penile carcinoma.	IIEF	72.2% never or only sometimes had erectile dysfunction 30.7% having severe erection problems and thus suffered from erectile dysfunction	Organ preservation and function saving is achievable for >80% of patients, whereas with radical surgery this is not possible. Compared with surgical methods, brachytherapy provides a maximum of organ preservation and functional integrity.		LoE 4 RoB 11/20
Soh, 2014, Basic & Clinical Andrology	Case control study	n= 38 France 2010	n= 19 patients treated by penile brachytherapy n= 19 controls T1 N0 <u>Mean age</u> Patients: 66 y (37-85 y) Controls: 65.4 y (37-85 y)	To assess sexual functions and behaviors of men treated by penile brachytherapy for a cancer of the penis.	IIEF BASIC IDEA (modified)	<u>Sexually active</u> Before treatment: 89.5% After treatment: 52.7% p= 0.006 <u>Sexual dysfunction</u> Before treatment: 21.1% After treatment: 57.8% p= 0.013 <u>Mastrubation (often)</u> Cases: 79% Controls: 16% p< 0.001 **Mean IIEF score** <u>Erectile function</u> Cases: 14.3 Controls: 9.5	Penile brachytherapy is a treatment of cancer of the penis that seems to have a moderated impact on sexual functions since most of sexual scores are not inferior in these patients than in age pair-matched controls.		LoE 4 NOS 5/9

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						p= 0.03 <u>Orgasmic function</u> Cases: 4.5 Controls: 4.4 p= 0.7 <u>Sexual desire</u> Cases: 5.9 Controls: 4.1 p= 0.027 <u>Intercourse statisfaction</u> Cases: 5.4 Controls: 4.0 p= 0.3 <u>Overall statisfaction</u> Cases: 8.2 Controls: 5.6 p= 0.004 <u>IIEF 15</u> Cases: 38.3 Controls: 27.5 p= 0.039 <u>IIEF 5</u> Cases: 12 Controls: 7.8 p= 0.018 No significant correlation among the sexuality items and the parameters of PB (dose, dose rate, number of needles, active length) and the tumor size.			

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Musi, 2018, World Journal of Urology	Case serie	n= 26 2013-2016 Median follow-up 24 mo (15-30 mo)	Tis-T3 Median age 61 y (54-72 y) Patients treated with thulium–yttrium aluminium–garnet laser ablation	To evaluate the oncological and functional outcomes of patients diagnosed with penile cancer undergoing conservative treatment through thulium–yttrium aluminium–garnet laser ablation.	Telephone interview and completed a non-validated six-item sexual function questionnaire	• 60% sexual activity with in less than a month from ablation • More than one-fourth reported a conserved penile sensitivity more than half better glans sensitivity • Over 80% no change penis length • 56.5% had an impact on their sexual life	Early stage penile carcinomas can be effectively treated with an organ preservation strategy. Thulium–yttrium aluminium–garnet conservative laser treatment is easy, safe and offers good functional outcome, with a minor impact on patient's quality of life.		LoE 4 RoB 12/20
Skeppner, 2015, Sexual Medicine	Before-after study	n= 29 Follow-up Baseline & 12 mo	n= 12 pT1 n= 14 G2 55% comorbidities Median age 60 y (37-73 y) Patients suitable for laser treatment and not previously treated with combined laser	To describe the dyadic aspects of sexual well-being and life satisfaction before and 1 year after organ-sparing laser treatment of penile carcinoma.	Structured interviews IIEF-5 LiSat-11 HADS	Patients statisfied with life as whole Baseline: 79% 12 mo: 76% Patients sexual activity Baseline: 21/29 12 mo: 17/29 Sexual statisfaction Baseline: 17/28 12 mo: 9/28 Life statisfaction Baseline: 23/29 12 mo: 22/29 IIEF-score "normal" (≥22) Baseline: 14 patients 12 mo: 11 patients	The couples' satisfaction with life as a whole is on a par with that of the general population. This is true also for several domains of life. They experienced lower satisfaction with health and with sexual life 1 year after treatment.	Keine separate Darstellung der Ergebnisse für LiSat-11 und HADS.	LoE 4 RoB 13/20

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Skeppner, 2008, European Urology	Case serie	n= 46 Sweden 1986-2000	Tis-T2 In situ – G3 N0 M0 Mean age 63 y (34-90 y) Patient treated with laser	To assess the initial symptoms of penile carcinoma and patients' time frame in treatment seeking, and to describe the effect of laser treatment on sexual activity and life satisfaction	Questionnaire with 53 items LiSat-11	Sexual activities during preceding 3 mo Patients: 63% Swedish men: 85% Life statisfaction Patients: 76% Swedish men: 72%	Men with lasertreated localised penile carcinoma resume their sexual activities to a large extent after the treatment. Except for satisfaction with somatic health, similar—or even higher—proportions of patients than comparators are satisfied with life as a whole and with other domains of life including satisfaction with sexual life.		LoE 4 RoB 15/20
Windahl, 2004, Journal of Urology	Before-after study	n= 67 Sweden 1986-2000	Treated with combined carbon dioxide and neodymium:YAG lasers Mean age 64 y	To evaluate sexual function, sexual satisfaction and cosmetic results after laser treatment of penile carcinoma.	Structured questionnaire of 53 items IIEF LiSat-11	**Sexual interest** Preoperativ Dysfunction: 8 Distress: 7 Postoperativ Dysfunction: 6 Distress: 4 No dysfunction: 24 (80%) **Erection** Preoperativ Dysfunction: 3 Distress: 2 Postoperativ Dysfunction: 6 Distress: 3 No dysfunction: 24 (80%) **Early ejaculation** Preoperativ Dysfunction: 2 Distress: 1 Postoperativ Dysfunction: 2 Distress: 0	Laser treatment of localized penile carcinoma preserves the penis and generally provides satisfactory sexual function and cosmetic results.	Ergebnisse nicht nach Fragebögen aufgelistet	LoE 4 RoB 8/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						No dysfunction: 28 (93%) **Delayed ejaculation** Preoperativ Dysfunction: 1 Distress: 0 Postoperativ Dysfunction: 3 Distress: 0 No dysfunction: 27 (90%) **Dyspareunia** Preoperativ Dysfunction: 7 Distress: 6 Postoperativ Dysfunction: 3 Distress: 3 No dysfunction: 27 (90%) **Cosmetic result** 78% statisfied or very statisfied			
Xu, 2013, Int Urol Nephrol	Before-after study	n= 11 China 2007-2012 Mean follow-up 3 y (1-5 y)	Patients with penile Paget's disease withsplit-thickness skin graft Mean age 52.4 y (42-68 y)	To investigate and improve our knowledge of the clinical features, diagnosis, therapeutic methods and outcome of penile Paget's disease.	IIEF	**Erectile function** Pre-operation: 23.73 ± 0.69 Postoperation: 24.09 ± 0.71 p= 0.317 **Orgasmic function** Pre-operation: 7.99 ± 0.34 Postoperation: 8.03 ± 0.18 p= 0.789 **Sexual desire**	Reconstruction of defects with split-thickness skin graft from autologous thigh is an ideal choice for treatment. Both the morphology of the penis and the function can be maintained using our approach.	Ggf. Ausschluss, da Paget's diseases nicht als Einschluss-kriterium definiert wurde	LoE 4 RoB 14/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						Pre-operation: 7.89 ± 0.20 Postoperation: 8.00 ± 0.11 p= 0.187 **Intercourse statisfaction** Pre-operation: 13.00 ± 0.30 Postoperation: 13.13 ± 0.21 p= 0.264 **Overall statisfaction** Pre-operation: 7.88 ± 0.41 Postoperation: 8.21 ± 0.31 p= 0.083			
Different treatments									
Dräger, 2017, Clinical Genitourinary Cancer	Case serie	n= 40 Germany 2014-2016	n= 29 surgery n= 11 systematic chemotherapy Median age 64 y (31-88 y)	To examine the effects of treatment on the psychological well-being of patients with localized or advanced penile cancer using screening questionnaires to determine the consecutive need for psychosocial care.	HSI NCCN-DT	NCCN-DT Average stress level: 4.5 47.5% had an increased stress level Main stressors: 44% sorrow 30% voiding problems 36% anxiety 32% exhaustion 32% limitations in mobility 24% sadness 24% pain 16% sexual dysfunction	Owing to the potentially mutilating surgery, patients with penile cancer experience increased psychological stress and, consequently, have an increased need for psychosocial care.	Keine Angabe zum Tumorstatus	LoE 4 RoB 17/20

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						<50 years emotional stressors dominate >65 years old, the somatic aspects dominate <u>HSI</u> • Regarding the need for psychosocial care and the desire for psychosocial support: no significant difference between age and treatment groups • All patient groups had an increased need for care • Patients with cancer recurrence had significantly increased psychosocial care needs compared with patients undergoing first treatment of the primary tumor (50% vs. 38% p< 0.001) • Patients undergoing chemotherapy, and patients with recurrence were also significantly			

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						more integrated into psychosocial care systems (p< 0.01) • Discrepancy in the self-reported need for support: 42.5% for all age groups vs. 5% by self-reported need in the HIS (p<0.001) Finally, 67% of all patients received inpatient psychosocial care.			
Dräger, 2018, Urologe	Systematic review	n= 10 Studien (2 prospektive, 8 retrospektive) Brasilien, Deutschland, Frankreich, Italien, Niederlande, Norwegen, Polen, Schweden 1994-2017	n= 309 <u>Mean age</u> 57.9 y (28-75 y) Patienten mit allen Behandlungs-formen	Darstellung der psychosozialen Auswirkungen bei Patienten mit Peniskarzinom.	OSFQ SPQ GHQ HADS HSI EORTC QLQ IIEF Bigelow & Young SF-36 IOC DSM III-R PAIS CMNI LiSAT-11	Erhöhter psychologischer Stress und Bedarf an psychosozialer Betreuung Sexuelle Funktion wird durch Therapie negative beeinflusst, bei Organerhalt und Rekonstruktion aber deutlich weniger Individuellen emotionalen und mentalen Belastung kann mithilfe von validierten Screeningtools erkannt und unterstützt warden.	Der Penis ist beim Mann Fokus der sexuellen Identität. Die Therapie des Peniskarzinoms verursacht den Patienten erheblichen Distress. Organerhaltende Therapien und rekonstruktive Operationen wirken sich positiv auf die Lebensqualität aus.		LoE 3 ROBIS low
Gulino, 2007, Journal of Urology	Before-after study	n= 14 2004-2006	n= 8 glans reconstruction	To evaluate anatomical, physiological	IIEF Bigelow-Young questionnaire	**IIEF** <u>Erection</u> (mean) Before: 21	Reconstructive glanuloplasty with distal urethra in penile tumor surgery is an innovative, easy		LoE 4

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
		Mean follow-up 13 mo	after simple glansectomy n= 6 amputation of the distal third of the shaft T1-2 N0 M0 G1-3 Mean age 54 y (41-63 y)	and esthetic features as well as short-term and long-term clinical outcomes.		6 mo postop: 20 12 mo postop: 22 Orgasm (mean) Before: 13 6 mo postop: 11 12 mo postop: 12 Libido (mean) Before: 8 6 mo postop: 9 12 mo postop: 9 **Bigelow-Young questionnaire** Unpleasant feelings Before: 14 During disease: 30 6 mo postop: 16 p < 0.01 Pleasant feelings Before: 35 During disease: 18 6 mo postop: 37 p < 0.01 Relationship family+ partner Before: 18 During disease: 4 6 mo postop: 16 p < 0.01 Relationship people+ social Before: 24 During disease: 20 6 mo postop: 22 Job quality Before: 25 During disease: 18 6 mo postop: 21	and rapid surgical technique with appreciable functional and esthetical results.		RoB 14/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
Gulino, 2013, Indian Journal of Urology	Before-after study	n= 42 Follow-up 6 mo	n= 6 diathermocoagulation n= 25 glandulectomy and glanduloplasty with urethral mucosa n= 11 glandulectomy and limited apical resection Ta, T1, T2 G1-3 Mean age 56 y	To assess the impact of organ potency-sparing surgery in locally confined carcinoma of the penis.	IIEF Bigelow-Young questionnaire	**IIEF** **Erections** Before disease Mean score: 21 6 mo after surgery Mean score: 20 Status of sexual function: 73% **Ejaculation** Before disease Mean score: 5 6 mo after surgery Mean score: 5 Status of sexual function: 76% **Orgasm** Before disease Mean score: 13 6 mo after surgery Mean score: 11 Status of sexual function: 76% **Libido** Before disease Mean score: 8 6 mo after surgery Mean score: 9 Status of sexual function: 71% **Bigelow-Young questionnaire** • Significant improvement at 6 mo after surgery from those of two weeks before	Potency sparing-sparing surgical treatments have a positive impact on a wide spectrum of the patient's life including family relationships, and social and working conditions		LoE 4 RoB 14/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						surgery (p< 0.01) • Unpleasant feelings descrease from 30 to 16 (p< 0.01) • Sexual pleasure increase from 18 to 37 (p< 0.01) and familiar and partner relations from 4 to 16 (p< 0.01) • No significant difference: relating to friend relationships and professional quality			
Hartung, 2017, European journal of cancer	Cross-sectional study	n= 4020 adult cancer patients n= 5018 general population Germany Mean time since diagnosis 14 mo	T1-4 ECOG 0-4 Mean age 58 y n= 4 penile carcinoma patients	To estimate the prevalence of depressive symptoms by cancer site, thereby identifying cancer patients with the highest prevalence of depression.	PHQ-9	OR for risk of depression Other cancer (3% penile carcinoma patients): 4.9 (95% CI 3.3-7.3) <0.001	The odds of being depressed among cancer patients were more than five times higher than in the general population. Patients with pancreatic, thyroid and brain tumours showed the highest prevalence, whereas patients with prostate cancer and malignant melanoma had the lowest levels of depressive symptoms.	Indirekte Evidenz. Peniskarzinom-Patienten wurden in der Gruppe „Other cancer“ ausgewertet und machten dort nur 3% aus.	LoE 4 EPHPP strong
Hegarty, 2014, BJU International	Systematic review	n= 48 articles Follow-up ≥24 months follow-up	Patients treated with organ-sparing techniques	To gather current evidence-based recommendations for the management of primary penile tumours.		- Penile cancer causes a negative impact on well-being in up to 40% of patients - Men who have undergone more mutilating surgery are more likely to have impaired well-being	Penile preservation is better for functional and cosmetic outcomes and should be offered as a primary treatment method in men with low-stage penile cancer.		LoE 3 ROBIS high

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						- Symptoms of psychiatric illness are seen in ≈50% - Sexual function may be impaired in up to two thirds of sufferers - Those who had received organ-preserving treatment appeared to have better sexual function - Unclear: negative psychological effects are result of the disease or the treatment - Relationships with family or partner were improved after treatment			
Kamel, 2017, Journal of Urology	Systematic review	n= 50 articles 1985-2016 Follow up 24 mo or longer	Patients treated with organ-sparing surgery	To increase awareness of organ sparing surgery for penile cancer and their applicability, to evaluate the techniques objectively and to provide guidance to the practicing urologist.	IIEF-15	- Partial penectomy patients fared worse in achieving orgasm and reduced frequency of sexual intercourse - Partial penectomy before and after: 68% achieved the same level of orgasm and ejaculation - Organ-sparing surgery: spraying of urine remains a problem, especially following partial penectomy	Overall, more radical surgery for PC has a worse impact on QoL. Patients undergoing alternative organ sparing surgery rather than partial penectomy do better on QoL measures.		LoE 3 ROBIS high

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						Patients treated with partial penectomy, glasectomy or laser therapy: - Mental illness incidence: 53% - Avoidance behaviour: 25% - Impaired overall well-being: 40%			
Kieffer, 2014, Journal of Urology	Retrospective cohort study	n= 147 2003-2008 Netherlands Mean follow-up 3.9 y (0.1-6.8 y)	n= 54 penile sparing surgery n= 36 (partial) penectomy Mean age 65.4 y (35.7-99.5 y)	To assess the impact of primary surgery, including penile sparing surgery vs (partial) penectomy and lymphadenectomy, on sexuality and health related quality of life.	IIEF-15 SF-36 IOC (version 2) Questions on urinary function	**Penile sparing surgery vs. partial penectomy** IIEF-15 Orgasmic function: ES 0.53 p= 0.03 SF-36 No statistically significant difference was observed between surgery types IOC Appearance concerns: ES 0.61 p= 0.008 Life interference: ES 0.49 p= 0.032 **Urinary problems** p< 0.001 **Lymphadenectomy vs. without lymphadenectomy** IOC Life interference: ES 0.50 p= 0.037 **Patients with penile cancer vs. dutch population**	(Partial) penectomy and lymphadenectomy were associated with more problems with orgasm, body image, life interference and urination.	Keine Beschreibung Tumorstage	LoE 3 NOS 7/9

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						SF-36 Physical component scale p= 0.044 Bodily pain subscale p< 0.001			
Li, 2012, Journal of Andrology	Before-after study	n= 12 2003-2008 Mean follow-up 62.5 mo (36-90 mo)	Ta, Tis, T1 G1-2 Median age 46 y (38-53 y) Patients treated with penis-preserving surgery	To investigate the safety and feasibility of glans-preserving surgery for superficial penile squamous cell carcinoma.	IIEF	• Same or better erectile function after surgery • 12/12 “moderately satisfied’’ or ‘‘very statisfied” with their overall sexual life/relationship • 83% satisfying/very satisfying with the cosmetic result	Sexual function and sexual satisfaction can be well maintained after this glans-preserving surgery, and the cosmetic results, judged by the patients themselves, are highly satisfactory. The present initial outcome data suggests that this glans-preserving surgical technique is technically safe and functionally and cosmetically satisfying.		LoE 4 RoB 12/20
Maddineni, 2009, BMC Urology	Systematic review	n= 6 studies 1994-2007 Mean follow-up ranged from 11.5-80 mo	n= 128 patients Patients with partial penectomy only, partial penectomy and glansectomy, laser therapy only and all treatments	To examine the current literature on the effects of curative penile treatment on sexual function, quality of life and psychological well-being.	ECOG GHQ HADS IIEF OSFQ SPQ LiSat-II DSM III-R PAIS Bigelow & Young questionnaire EORTC QLQ Self-made questionnares	Impaired well-being in up to 40% (n= 2 studies) Patients undergoing more mutilating treatments were more likely to have impaired well-being pathological anxiety up to 31% (n= 2 studies) 53% exhibiting mental illness, 25% avoidance behaviour and 40% impaired well-being 12/30 suffered from post-traumatic stress disorder	The treatment of penile cancer results in negative effects on well-being in up to 40% with psychiatric symptoms in approximately 50%. Up to two-thirds of patients report a reduction in sexual function.	Zusätzlich zur systematischen Suche aufgenommen LoE 4, da Mehrzahl der Studien keine Vergleichs-gruppe haben und das RoB high ist	LoE 4 ROBIS high

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						No sexual faunction varied: 36-67% Reduced sexual satisfaction to 78%			
Opjordsmoen, 1994a, British Journal of Urology	Case serie	n= 30 Norway 1971-1990 Median follow-up 80 mo (11-225 mo)	n= 5 local excision/ laser beam treatment n= 12 radiotherapy n= 9 partial penectomy n= 4 total penectomy Tis, T1 Median age 57 y (28-75 y)	To study the long-term psychosocial well-being of patients following successful physical treatment for cancer of the penis.	Semi-structured interview IES GHQ EORTC QLQ C-30	**GHQ** Overall values Sexual: 2.1 Employment: 2.6 Well-being: 3.1 Social: 3.2 (0= worst, 4= best) Comparison young vs. old Significant difference in the subscale: Sexual & Employment Comparison organ-sparing vs. (partial) amputation Significant difference in the subscale: Sexual **EORTC scale** • For the global well-being scale each of the six items was significantly correlated (0.84) • Scores correlated significantly with those of the EORTC scale for overall quality of life (p< 0.001) and the scale of psychological distress (p< 0.001) • No significant correlation with	Patients treated with partial or total penectomy had a worse outcome with regard to sexual function than patients treated conservatively, but there was no difference in the other domains of quality of life, indicating that even the more radically treated patients usually adapted adequately. Half of the individuals had mental symptoms at follow-up, and these patients were less satisfied and showed less social activity. Seven men reported that, if asked again, they would choose treatment with lower long-term survival to increase the chance of remaining sexually potent, but the majority gave priority to higher long-term survival.		LoE 4 RoB 10/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						the scale of psychological distress from EORTC **IES** (Cut-off point of 9) Intrusion: 23 Avoidance: 13			
Opjordsmoen, 1994b, British Journal of Urology	Case serie	n= 30 Norway 1971-1990 Median follow-up 80 mo (11-225 mo)	n= 5 local excision/ laser beam treatment n= 12 radiotherapy n= 9 partial penectomy n= 4 total penectomy Tis, T1 Median age 57 y (28-75 y)	To evaluate sexuality after successful treatment of penile cancer.	Semi-structured interview PAIS GHQ EORTC QLQ C-30	Global score of sexual function (mean) Laser beam/local excision: 2.2 (SD 1.0) Radiotherapy: 3.0 (SD 1.2) Partial penectomy: 1.3 (SD 1.1) Total penectomy: 1.0 (SD 0) (0= no sexual function, 4= normal)	Within the limitations due to the small number of patients studied, radiotherapy seems to be the treatment of choice in limited cancer of the penis if preservation of sexuality is a major therapeutic aim.	Gleiches Studienkollektiv wie Opjordsmoen, 1994a „Global score of sexual function“ wurde mit den unterschiedlichen Fragebögen ermittelt.	LoE 4 RoB 11/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
Scarberry, 2015, Sexual Medicine	Case serie	n= 6 USA 2003-2012 Mean follow-up 52 mo (25-84 mo)	Mean age 67 y (56-87 y) Patients treated with penile-sparing surgery (Glansectomy only, distal corporectomy)	To investigate patient satisfaction with their sexual and urinary outcomes following organ-preserving surgery, including glansectomy or distal corporectomy, for carcinoma of the penis.	IIEF-15 PROM	Sexual function 50% erections with normal rigidity 33% sexual activity with successful penetration, orgasm, and ejaculation 83% their sexual symptoms do not at all interfere with their daily lives Urinary function 67% normal strength of urinary stream 50% occasional wetness in their pants a few minutes after urinating 83% their urinary symptoms do not at all interfere with their daily lives Satisfaction 100% good or very good	Our study supports excellent overall QOL and urinary QOL after penile-sparing operations for penile cancer. Sexual function and desire are poorer, with 50% of respondents reporting no sexual function or desire. Curiously, sexual function outcomes did not seem to bear on perceived overall QOL for these men.	Keine Angaben T-Stage Ergebnisse beider Fragebögen wurden für die Auswertung beider Themenbereiche „Sexual function“ und „Urinary function“ genutzt.	LoE 4 RoB 11/20
Sedigh, 2015, Canadian Urological Association Journal	Before-after study	n= 41 2006-2013 Mean follow-up 34 mo (16-52 mo)	n= 12 wide local excision n= 23 glansectomy with urethral glanduloplasty n= 6 penile partial amputation without glans reconstruction pT1-2 N0	We compared the postoperative sexual function of patients who underwent wide local excision and glansectomy with urethral glanduloplasty for penile cancer.	IIEF SEP-2 SEP-3	**IIEF-15** Wide local excision Preoperative: 45.7 Postoperative: 40.9 p= 0.08 Glansectomy with urethral glanduloplasty Preoperative: 48.5 Postoperative: 37.1 p= 0.003 **SEP-2**	Among the conservative treatments for penile cancer, wide local excision leads to better sexual outcomes and less postoperative complications compared to glansectomy with urethral glanduloplasty. When feasible, wide local excision could represent the best conservative approach to treat localized primary penile cancer.		LoE 4 RoB 16/20

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
			Mean age 63 y (28-92 y)			• No significant changes were recorded postoperatively in the wide local excision-group SEP-2 & SEP-3 in the glansectomy-group • Decrease in the possibility of achieving penetrative intercourse (p= 0.006) • Perceived satisfaction during sexual activity (p= 0.004)			
Simpson, 2018, Clinical Genitourinary Cancer	Cross-sectional study	n= 6155 USA 1973-2013	G1-4	To investigate the risk of suicide in patients with penile cancer.		13/6155 suicides 50-59 y: 67/100000 person-years 60-69 y: 55/100000 person-years 70-79 y: 39/100000 Median time to OS for dead of suicide 37 mo Median time to OS for dead of causes other than suicide 25 mo	All 13 patients had undergone some form of surgical intervention of unknown approach. In contrast to previously reported data, our analysis demonstrates that penile cancer does increase the risk for suicide compared with age-adjusted controls.		LoE 4 EPHPP weak
Sosnowski, 2017, European Journal of	Three arms cohort study	n= 51 2007-2013	Treatment 21.6% total penectomy 52.9% partial penectomy	To compare various aspects of QoL in three groups of	EORTC QLQ-C30	**Spearman correlations between the level of aggressiveness**	The magnitude of disfigurement caused by surgical treatment of penile cancer had a significant impact on the selected QoL domains assessed by the EORTC		LoE 4 NOS 7/9

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
Oncology Nursing		Mean follow-up 36.3 mo (14-83 y)	25.5% Circumcision/ wide local excision Mean age 60 y (28-83 y)	patients surgically treated for penile cancer by local excision, partial penectomy, or total penectomy.		**of the surgery and EORTC QLQ results** (Spearman correlation) Global health status -0.3 (p= 0.04) Physical function -0.3 (p= 0.047) Role function -0.1 (p= 0.4) Emotional function -0.2 (p= 0.12) Cognitive function 0 (p= 0.91) Social function -0.3 (p= 0.06) 58.9% declared that their relations were not inferior to before the surgery (Type of surgery did not have an effect on patients' relations with their partners (p > 0.05).)	QLQ C-30 questionnaire. There was no correlation between the scope of surgical intervention and partner relations.		
Yang, 2014, Journal of Urology	Retrospective cohort study	n= 273 2004-2012	pTis-pT2 N0 M0 n= 135 glans preserving surgery n= 36 partial amputation Mean age 55.1 y (38-73 y)	To evaluated whether glans preserving surgery would be more helpful for patients to regain satisfactory sexual competency postoperativel	IIEF-15	**Complication rate** Total 31.8% glans preserving 91.7% partial amputation No severe complication in both groups Erectile dysfunction	Glans preserving surgery effectively preserves the functional anatomy and cosmetic appearance of the glans penis. Glans preservation contributes to minimizing postoperative erectile dysfunction and negative psychological impediments, and promotes return to satisfactory sexual performance. Patients treated with glans preservation have more advantages in obtaining sexual acceptance	Nur signifikante Ergebnisse dargestellt. Vollständige Ergebnisse sind in Table 1 und 2 dargestellt.	LOE 3 NOS 8/9

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
				y than conventional partial amputation.		Glans preserving: 1.5% Partial amputation: 41.7% p< 0.001 <u>Erectile pain</u> Glans preserving: 1.5% Partial amputation: 11.1% p= 0.018 <u>Urethral stricture</u> Glans preserving: 2.2% Partial amputation: 11.1% p= 0.036 **Erectile function** <u>Preoperativ</u> Glans preserving: 20.6 ± 4.0 Partial amputation: 20.2 ± 3.9 p= 0.591 <u>Postoperativ</u> Glans preserving: 22.4 ± 3.9 Partial amputation: 14.9 ± 4.2 p< 0.001 **Orgasmic function** <u>Preoperativ</u> Glans preserving: 6.4 ± 2.5 Partial amputation: 6.2 ± 2.7 p= 0.743 <u>Postoperativ</u>	from their partners than those who undergo amputation.		

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						Glans preserving: 7.7 ± 1.6 Partial amputation: 5.7 ± 1.4 p< 0.001 **Sexual desire** <u>Preoperativ</u> Glans preserving: 6.2 ± 1.8 Partial amputation: 6.1 ± 1.5 p= 0.692 <u>Postoperativ</u> Glans preserving: 6.9 ± 1.4 Partial amputation: 6.8 ± 1.3 p= 0.784 **Intercourse statisfaction** <u>Preoperativ</u> Glans preserving: 7.7 ± 3.6 Partial amputation: 6.8 ± 2.9 p= 0.161 <u>Postoperativ</u> Glans preserving: 9.7 ± 2.3 Partial amputation: 5.9 ± 2.2 p< 0.001 **Overall statisfaction** <u>Preoperativ</u> Glans preserving: 5.3 ± 1.7 Partial amputation: 5.1 ± 1.9 p= 0.435			

Referenz	Studien-typ	Studien-merkmale	Patienten-merkmale	Studienziel	Instrument	Ergebnisse	Schlussfolgerung	Bemerkungen	LoE/ RoB
						Postoperativ Glans preserving: 6.4 ± 2.1 Partial amputation: 4.3 ± 1.1 p< 0.001			

Tabelle 32: Ergänzungen zu den Fragebögen zur Lebensqualität

Abbreviation original reference	Full name	Number of items, dimensions	Range, Score interpretation
BASIC IDEA Lazarus AA. Multimodal behavior therapy: Treating the BASIC ID.J Nerv Ment Dis 1973;156:404e411	Behavior, Affect, Sensation, Imagery,, Cognition, Interpersonal, Drugs, Expectation, Attitude	**9 areas**: Behavior (B) Affect (A) Sensation (S) Imagery (I) Cognition (C) Interpersonal (I) Drugs (D) Expectation (E) Attitude (A)	*no score interpretation found*
CMNI Mahalik JR, Locke BD, Ludlow LH, Diemer M, Scott RPJ, Gottfried M. Development of the Conformity to Masculine Norms Inventory. Psychol Men Masc. 2003; 4: 3-25.	Conformity to Masculine Norms Inventory	94 items in 11 dimensions	Four-point Likert scale 1= strongly disagree 2= disagree 3= agree 4= strongly agree
EDITS Stanley E. Urology. 1999 Apr;53(4):793-9	Erectile Dysfunction Inventory of Treatment Satisfaction (Patient and Partner)	Items: for patient 11, for couple 5	scored from 0 to 4 0= disstatisfaction 4= high satisfaction

Abbreviation original reference	Full name	Number of items, dimensions	Range, Score interpretation
EORTC QLQ-C30 Sprangers MA. Qual Life Res 1993;2:287-295	EORTC Quality of Life Core Questionnaire	30 dimensions with five subscales (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning)	scored from 1 to 4 1= not at all 4= very much
EuroQol (EQ-5D-5L) van Hout B, Janssen MF, Feng Y-S, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15:708e715	European Quality of life scale	**5 dimension:** Mobility Self-care Usual activities Pain/ discomfort Anxiety/ depression	scored from 0 to 100 higher scores meaning better health state
GHQ Goldberg D, Psychol Med. 1979 Feb;9(1):139-45	General Health Questionnaire	**12, 28, 30 or 60 items with 4 subscales:** Somatic symptoms Anxiety/ insomnia Social dysfunction Severe depression	scored from 0 to 4 higher scores meaning better health/ function
HADS Zigmond AS. Acta Psychiatr Scand. 1983 Jun;67(6):361-70.,Br Med J (Clin Res Ed). 1986 Feb 1;292(6516):344.	Hospital Anxiety and Depression Scale	14 14 Items Anxiety (7 items) Depression (7 items)	scored from 0 to 3 higher scores meaning worse health
HIS Strittmatter G, Mawick R, Tilkorn M. Entwicklung und klinischer Einsatz von Screening—Instrumenten zur Identifikation betreuungsbedürftiger Tumorpatienten. In: Bullinger M, Siegrist J, Ravens-Sieberer U, eds. Lebensqualitätsforschung aus medizin-psychologischer und soziologischer Perspektive. Jahrbuch der Medizinischen Psychologie Hogrefe; Göttingen, Germany, 2000; 18:59-75.	Hornheider Screening Instrument	7 questions with 8 items	scored from 0 to 3 If the total value is greater than the predetermined threshold (≥ 4), the patient is considered in need of care.
ICSmaleSF Donovan, JL. J Urol. 2000 Dec;164(6):1948-55	International Continence Society male short-form score	**11 items** Voiding (5 items) Incontinence (6 items)	scored from 0 to 4 higher scores meaning worse health/ function
IES Horowitz MJ, Wilner N & Alvarez W (1979)	Impact of Event Scale	**15 Items** Intrusion (7 items) Avoidance (8 items)	scored from 0 to 75 higher scores meaning more powerful impact event

Abbreviation original reference	Full name	Number of items, dimensions	Range, Score interpretation
Impact of Event Scale: A measure of subjective stress. Psychosomatic Medicine, 41, 209-218.			
IIEF Rosen RC.Urology. 1997 Jun;49(6):822-30	International Index of Erectile Function	**15 or 5 with five dimensions:** Erectile function (items 1–5 and 15; maximum score 30) Orgasmic function (items 9 and 10; maximum score 10) Sexual desire (items 11 and 12; maximum score 10) Intercourse satisfaction (items 6–8; maximum score 15) Overall satisfaction (items 13 and 14; maximum score 10).	scored from 0 to 5 higher scores meaning better health/ function
IMGI Davis SN. J Urol. 2013 Oct;190(4):1335-9	Index of Male Genital Image	14 items, 6 domains, 1 overall	Seven-point Likert scale higher scores meaning higher satisfaction
IOC Crespi C, Ganz P, Petersen L et al: Refinement and psychometric evaluation of the impact of cancer scale. J Natl Cancer Inst 2008; 100: 1530.	Impact of Cancer	**2 higher order scales (positive and negative impact)** **Positive subscale:** Altruism and empathy Health awareness Meaning of cancer Positive self-evaluation **Negative subscale:** Appearance concerns Body change concerns Life interferences Worry	Five point Likert scale from 1 to 5 Higher scores on the positive subscale meaning a more positive response. Higher scores on the negative subscale meaning a more negative response.
IPSS Barry MJ. The American Urological Association Symptom Index for benign prostatic hyperplasia. Journal of Urol	International Prostate Symptom Score	**8 items:** Symptoms (7 items) Quality of life (1 item)	scored from 0 to 5 higher scores meaning worse health/ function
LiSat-11 Fugl-Meyer AR, Branholm IB, and Fugl-Meyer KS, Life Satisfaction in 18- to	Life-Satisfaction questionnaire	**11 items** Target important life domains: Vocational	scored from 1 to 6 higher scores meaning higher satisfaction

Abbreviation original reference	Full name	Number of items, dimensions	Range, Score interpretation
64-year old Swedes: In Relation to Gender, Age, Partner and Immigrant Status, J Rehabil Med, 34: 239-46, 2002		Financial and leisure situations Contacts with friends Sexual life Self-care management Family life Partner relationships Physical and psychological health	
LUTS Gambachidze, D., C. Lebacle, P. Maroun, A. Escande, A. Bossi, P. Blanchard, E. Deutsch, C. Haie-Meder, and C. Chargari. 2018. 'Long-term evaluation of urinary, sexual, and quality of life outcomes after brachytherapy for penile carcinoma', *Brachytherapy*, 17: 221-26.	Lower Urinary Tract Symptome score		0= asymptomatic 32= most symptomatic
OSFQ Opjordsmoen S, Waehre H, Aass N, and Fossa SD: Sexuality in patients treated for penile cancer: patients' experience and doctors' judgement. Br J Urol 73: 554-560, 1994.	Overall Sexual Functioning Questionnaire	**6 subscales:** Sexual interest Sexual ability Sexual statisfaction Relationship with partner Sexual identity Frequency of coitus	subscales scored from 0 to 4 Higher scores meaning better health/function
PAIS Derogatis LR. J Psychosom Res. 1986;30(1):77-91.	Psychosocial Adjustment to Illness Scale	**46 items, 7 domains:** Health care orientation (attitudes, perceptions, and expectations regarding one's health care Vocational environment Domestic environment Sexual relationships Extended family relationships Social environment Psychological distress	Four-point Likert scale from 0 to 3 higher *scores indicated* a lower level of *adjustment*
PHQ-9 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-13.	Patient Health Questionnaire	9 items	scored from 0 to 3 higher scores meaning worse health

Abbreviation original reference	Full name	Number of items, dimensions	Range, Score interpretation
PROM Jackson MJ, Sciberras J, Mangera A, Brett A, Watkin N, N'dow JM, Chapple CR, Andrich DE, Pickard RS, Mundy AR. Defining a patient-reported outcome measure for urethral stricture surgery. Eur Urol 2011;60:60–8.	Patient-Reported Outcome Measure	**22 items** Urinary symptoms Sexual function Perceptions of overall health and satisfaction with the operation	Comparison of pre- and postoperative statisfaction
QEQ Porst H. J Sex Med. 2007 Mar;4(2):372-81.	Quality of Erection Questionnaire	Unidimensional 6-item tool evaluating erection hardness, onset, and duration	scored from 0 to 100 higher scores meaning better health/function
NCCN-DT Psychosocial Distress Practice Guidelines Panel. NCCN Practice guidelines for the management of psychosocial distress. Oncology. 1999;13:113–47.	National Comprehensive Cancer Network Distress-Thermometer	1-item global screener of distress	11-point Likert scale from 0 to 10 higher scores meaning distress (cut-off score for distress: 3)
SAS Zung, W. W. A rating instrument for anxiety disorders. *Psychosomatics.* **12,** 371–379 (1971).	Self-rating Anxiety Scale	20 items	scored from 1 to 4 higher scores meaning worse anxiety levels
SDS William WK Zung. A Self-Rating Depression Scale. 12: Arch Gen Psychiatry 63-70. 1965.	Self-rating Depression Scale	20 items	scored from 25 to 100 higher scores meaning worse depression
SEAR Cappelleri JC, Int J Impot Res. 2004 Feb;16(1):30-8	Self-Esteem and Relationship Questionnaire	**14-items with two dimensions:** Sexual Relationship Confidence	scored from 0 to 5 0= least favorable 100= most favorable
SEP Ferguson D	Sexual Encounter Profile	5 item-questionnaire	measuring changes after sexual intercourse
(R)SES Rosenberg M. Rosenberg M. Society and the adolescent self-image. Princeton: Princeton University Press; 1965	Rosenberg Self-Esteem Scale	10 items	scored from 0 to 3 Higher scores meaning higher self esteem
SF-36 Ware JE. Med Care. 1992 Jun;30(6):473-83.	Short Form Health 36	**36 items, 8 dimensions:** Physical functioning (10 items) Role limitations because of physical health problems (4 items) Bodily pain (2 items)	0-100 Higher scores meaning better health/ function

Abbreviation original reference	Full name	Number of items, dimensions	Range, Score interpretation
		Social functioning (2 items) General mental health (5 items) Role limitations because of emotional problems (3 items) Vitality (4 items) General health perceptions (5 items)	
SFQ Syrjala KL, Schroeder TC, Abrams JR, Atkins TZ, Sanders JE, BrownW, et al. (2000) Sexual function measurement and outcomes in cancer survivors and matched controls. J Sex Res. 37:213–225	Sexual Function Questionnaire	**8 dimensions:** Sexual interest (4 items) Sexual desire (3 items) Sexual arousal (4 items) Sexual activity (4 items) Sexual satisfaction (2 items) Orgasm (3 items) Mastrubation (3 items) Relationship (6 items)	scored from 0 to 2 Higher scores meaning better sexual function
SPQ Corney RH: Development and use of a short self-rating instrument to screen for psychosocial disorders. J R Co11 Gen Pratt 38: 263-266, 1988.	Social Problem Questionnaire	20 items (male version) 21 items (female version) Two sections: Problems of living alone Legal problems	**Answer options:** Statisfied Slightly disstatisfied Markedly disstatisfied Severly disstatisfied

Tabelle 33: „Wann tritt ein Lokal- bzw. Lymphknotenrezidiv auf?“

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Nachsorgeschema Leitlinien										

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
EAU, 2018										

7.1.4 ***Guidelines for follow-up in penile cancer***

	Interval of follow-up		Examinations and investigations	Minimum duration of follow-up	Strength rating
	Years one to two	Years three to five			
Recommendations for follow-up of the primary tumour					
Penile-preserving treatment	Three months	Six months	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for penile intraepithelial neoplasia.	Five years	Strong
Amputation	Three months	One year	Regular physician or self-examination.	Five years	Strong
Recommendations for follow-up of the inguinal lymph nodes					
Surveillance	Three months	Six months	Regular physician or self-examination.	Five years	Strong
pN0 at initial treatment	Three months	One year	Regular physician or self-examination. Ultrasound with fine-needle aspiration biopsy optional.	Five years	Strong
pN+ at initial treatment	Three months	Six months	Regular physician or self-examination. Ultrasound with fine-needle aspiration cytology optional, computed tomography/ magnetic resonance imaging optional.	Five years	Strong

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
NCCN, 2018		**SURVEILLANCE SCHEDULE** **ANATOMIC SITE** / **INITIAL TREATMENT** / **SURVEILLANCE[x]** **Primary lesion** • Topical therapy • Laser therapy • Radiation/Chemoradiation therapy • Wide local excision • Glansectomy • Mohs surgery → Clinical exam:[y,z] years 1–2, every 3 mo then years 3–5, every 6 mo then years 5–10, every 12 mo • Partial penectomy • Total penectomy → Clinical exam:[y,z] years 1–2, every 6 mo then years 3–5, every 12 mo **Lymph nodes** Nx[w] → Clinical exam:[y,z] years 1–2, every 3 mo then years 3–5, every 6 mo N0, N1 → Clinical exam:[y,z] years 1–2, every 6 mo then years 3–5, every 12 mo N2, N3 → • Clinical exam:[y] ▸ years 1–2, every 3–6 mo then ▸ years 3–5, every 6–12 mo • Imaging: ▸ Chest (CT[f] or x-ray) ◊ years 1–2, every 6 mo ▸ Abdominal/pelvic (CT[f] or MRI[f]) ◊ year 1, every 3 mo then ◊ year 2, every 6 mo → For patients with recurrence at either local or distant sites, see Management of Recurrent Disease (PN-8) [f]With contrast unless contraindicated. [w]Patients on active surveillance of clinically negative nodes and at low risk for inguinal metastases. [x]See NCCN Guidelines for Survivorship. [y]Clinical exam includes examination of the penis and inguinal region. [z]If an abnormal clinical exam, obese patient, or prior inguinal surgery, then ultrasound, CT with contrast, or MRI with contrast of the inguinal region can be considered.					
Aggregierte Evidenz										
Hasan, 2015, Brachytherapy	Systematic review with meta-analysis	n= 20 studies 1984-2012 Median follow-up Penectomy: 59 mo	To compare the OS and local control rates between penectomy and brachytherapy for penile cancer.	n= 2178 Tis-T4 Grade 1-3 Median age 61 y (21-98 y)	Penectomy n= 1505	Brachytherapy n= 675	**Overall** DFS Penectomy: 77% ± 3% Brachytherapy: 71% ± 2%	The collective data represented in this meta-analysis suggest that with early	LoE 4, da sowohl vergleichende als auch nicht-vergleichende Studien eingeschlossen	LoE 4 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
		Brachytherapy: 67 mo					OR: 1.37 (1.11-1.68) p= 0.003 <u>5 y-OS</u> Penectomy: 76% ± 17% Brachytherapy: 73% ± 6% OR: 1.17 (0.95-1.44) p= 0.128 <u>5 y-local control</u> Penectomy: 84% ± 13% Brachytherapy: 79% ± 5% OR: 1.45 (1.09-1.92) p= 0.009 **Subset analysis** (Tis, T1 or T2 without nodal involvement) <u>5 y-OS</u> Penectomy: 78% ± 3% Brachytherapy: 79% ± 5% OR 0.95 (0.65-1.38) p= 0.771 <u>5 y-local control</u> Penectomy: 86% ± 4% Brachytherapy: 84% ± 6%	stage disease, brachytherapy has been as effective as penectomy for both local control rates and OS.	wurden und das RoB als high bewertet wurde.	

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							OR 1.13 (0.73-1.74) p= 0.594			
Hu, 2017, Oncotarget	Systematic review with meta-analysis	n= 22 studies 1992-2016 Follow-up at least one year	To compare the efficacy of brachytherapy and penectomy in patients with penile cancer.	n= 2560 patients I-III stage	Brachytherapy n= 746	Penectomy n= 1814	5-year OS Brachytherapy: 76% (71-81%) Penectomy: 74% (69-79%) OR 1.11 (95% CI 0.91–1.36) p= 0.284 5-year local control rate Brachytherapy: 80% (77-83%) Penectomy: 85% (82-88%) OR 0.72 (95% CI 0.58–0.90) p= 0.003 DFS Brachytherapy: 72% (64-80%) Penectomy: 77% (70-83%) OR 0.77 (95% CI 0.63–0.93) p= 0.008	Both of penectomy and brachytherapy can improve the survival status. Penectomy provided better control efficacy, and not improved the survival status compared with brachytherapy solely.	LoE 4, da sowohl vergleichende als auch nicht-vergleichende Studien eingeschlossen wurden.	LoE 4 ROBIS low
Maranda, 2016, Lasers in Medical Science	Systematic Review	n= 19 studies 1980-2014 Mean follow-up between 1.5-46.5 mo	This study seeks to comprehensively review the available reports and discuss which modalities may be the most promising for Erythroplasia of Queyrat treatment.	n= 101 patients Mean age between 38 - 87 y	**Laser therapy** n= 27 patients treated with CO2 laser n= 7 treated with Nd:YAG lasers	**Photodynamic therapy** n= 67 patients	**Relapses** CO2 laser Overall: 19% (n= 2 studies) Relapses in the 2 studies: • 4/12 patients (mean follow-up: 32 mo) • 1/8 patients (mean	Of the methods reviewed, the CO2 laser offered the most promising results with a cosmetically excellent prognosis.		LoE 4 ROBIS high

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							follow-up: 12 mo) Nd:YAG lasers (n= 1 study) 1/7 patients (mean follow-up: 32 mo) Photodynamic therapy 3 studies reported recurrence: • 3/4 patients (after 2 sessions) • 2/7 patients (mean follow-up: 46.5 mo) • 1/2 patients (mean follow-up: 65 mo)			
Robinson, 2018, European Urology	Systematic review	n= 6 retrospective case series + 1 conference abstract 1994-2016 Median follow-up varies 9.4 – 83 mo	Undertake a systematic review of the evidence on adjuvant inguinal radiotherapy in node-positive men with penile squamous cell carcinoma.	n= 1605 extracapsular nodal extension, ≥ 2 involved inguinal lymph nodes or pN2/3 Median age varies 58-65 y	Adjuvant inguinal radiotherapy		Regional recurrence rate 10-91.7% OS 16.7-66% Adjuvant vs. no adjuvant treatment (n=2 studies) Recurrence and survival: no significant difference	The evidence indicates that men treated with adjuvant inguinal radiotherapy do not gain benefit with respect to relapse or survival.		LoE 4 ROBIS low
Primärstudie										

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
Leijte, 2008, European Urology	Retrospective case series	n= 747 (overall) n= 547 Netherlands 1956-2006 n= 202 Sweden 1984-2007 <u>Median follow-up:</u> 60.6 mo (3-358 mo)	To give insight into the recurrence patterns of penile carcinoma in Different treatment settings and provide recommendations for follow up.	Tis-T4 <u>Age at diagnosis</u> Netherlands: 65 y Sweden: 64 y	Penile-preserving therapy (laser or local excision) n= 415 patients with Tis, Ta, T1, T2 tumours < 2 cm or < 3 cm	Partial or total amputation n= 285 patients with higher staged tumours	**Recurrences** <u>Overall</u> 205/700 patients 92.2% occured within the first 5 years <u>Local</u> Overall: 18.6% Penile-preserving therapy: 27.7% Amputation: 5.3% <u>Regional</u> 9.3% All regional recurrences occurred within 50 mo. <u>Distant</u> 1.4% All distant recurrences occured within 16 mo. **5y-DSS** Overall: 60.6% (95% CI 53.8-68.2%) Local recurrence: 92% Regional recurrence: 32.7% Distant recurrence: all died within 22 mo	Patients undergoing penile-preserving therapy, patients surgically staged as pN+, and those undergoing a wait-and-see policy for the nodal status are at high risk of developing a recurrence.		LoE 4 RoB 16/20

Referenz	Studien-design	Studien-charak-terisitika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemer-kungen	LoE/ RoB
							Recurrences after wait-and-see vs. surgical staging of the lymph nodes Wait-and-see: 9.1% (regional), 0.8% (distant) Surgical staged pN0: 2.3% (regional), 1.1% (distant) Surgical staged pN+: 19.1% (regional), 3.8% (distant)			

Tabelle 34: „Wie soll die Therapie des Lymphödems der Beine und des Skrotums durchgeführt werden?“

Referenz	Studien-design	Studien-merkmale	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerkungen	LoE/ RoB
Leitlinie										
S2k Leitlinie Diagnostik und Therapie der Lymphödeme AWMF Reg.-Nr. 058-001 Mai 2017										
Aggregierte Evidenz										
Cemal, 2013, Lymphat Res Biol	Systematic review	n= 6 studies (3 level II studies, 1 level II study, 2 level IV studies) 2005-2011	To identify valid treatment strategies for cancer-related lower limb lymphedema and analyze QoL outcomes.	n= 421 patients with cancer-related lower limb lymphedema	Evaluating the impact of different treatment strategies (n= 4 studies) • Complete decongestive physiotherapy (n= 2) • Exercise (n= 1) Compression bandaging (n= 1)		<u>Complete decongestive physiotherapy</u> • Significant improvement in HRQOL • More active lifestyle were found to have higher QoL in all domains specifying less pain, fatigue and anxiety and lower degrees of lymphedema • Patients with BMI’s more than 26.5 kg/m2 reported significantly decreased QoL • 1 mo after complete decongestive physiotherapy: QOL improved significantly in domains of physical and social functioning, mental and	Patients have voiced recurrent frustrations with respect to the lack of treatment resources and lymphedema research and are eager for research to be undertaken in order to find and try new treatments. Three studies reported an improvement in HRQOL after a treatment intervention (2 using complete decongestive physiotherapy and 1 using compression bandaging1) with most improvements in the domains of pain and physical functioning.	Indirekte Evidenz: Unterschiedliche Patienten-kollektive eingeschlossen und keine Angabe, inwiefern Peniskarzinom-Patienten involviert waren. LoE 3, da die Mehrzahl der inkludierten Studien eine Vergleichs-gruppe hatten.	LoE 3 ROBIS low

Referenz	Studien-design	Studien-merkmale	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerkungen	LoE/ RoB
							general health, and the role physical domain compared to baseline <u>Exercise</u> • Weight lifting did not improve HRQOL <u>Compression bandaging</u> • significantly improved HRQOL but this was greater in patients with lymphedema secondary to ulcers when compared to those whose lymphedema was secondary to cancer • Improvements were significant in the physical functioning, role physical, bodily pain social functioning, role emotional and mental health			
Leung, 2015, Palliative medicine	Systematic review	n= 7 studies (2 RCTs, 5 observational) 1993-2013 n= 2 studies with gynaecological malignancy	To evaluate the available evidence for the treatment of secondary lower limb lymphoedema in patients	n= 778 patients	2 RCTs evaluated graded compression stockings (n = 10) compared to conservative management without graded compression		<u>Graded compression stocking</u> • Reduce excess volume by 6.9% and mean lower limb volumes by 350mL	All included studies report lower limb volume reduction after treatment, which includes complex decongestion therapy, graded compression stockings and	Indirekte Evidenz: Unterschiedliche Patienten-kollektive involviert und keine Angabe, inwiefern Peniskarzinom-Patienten	LoE 3 ROBIS low

Referenz	Studien-design	Studien-merkmale	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerkungen	LoE/ RoB
		n= 1 study with classic Kaposi lymphoma patients n= 4 studies with different aetiologies	with malignancies.		stockings (n= 8) and Coumarin capsules (n= 10) compared to placebo (n = 11). 5 observational studies evaluated pneumatic compression devices (n= 196), lymphovenous microsurgical shunts (n= 260), manual lymphatic drainage with compression (n= 65) compression bandages alone (n= 50) and a herbal remedy combining Coumarin, Ginkgo and Melitoto (with or without manual lymphatic drainage) (n= 133).		<u>Pneumatic compression devices</u> • Mean lower limb volume reduction of 8% or 1150mL <u>Complex decongestion therapy</u> • Reduced the mean percentage excess volume by 20% <u>Herbal remedies including Coumarin</u> • Reduce limb circumference by 7.8%–17.6% and by 1.39% per month <u>Microsurgical lymphovenous shunts</u> • Reduce the mean circumferences ratio of oedematous versus normal limb by 20%–30% All evaluated treatments appeared to be safe. <u>Reported side effects:</u> • Muscle cramps and limb	lymphovenous microsurgical shunts.	eingeschlossen waren. LoE 3, da die Mehrzahl der inkludierten Studien Beobachtungs-studien mit Vergleichs-gruppe waren.	

Referenz	Studien-design	Studien-merkmale	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerkungen	LoE/ RoB
							erythema (physical compression treatments) Mild gastrointestinal upset (Herbal remedies containing Coumarin)			
Oremus, 2012, BMC Cancer	Systematic review	n= 44 studies (RCTs, observational studies) 1990-2010 n= 32 studies with breast-cancer patients Follow-up ranged from 24 h to 1 year	To examined the effectiveness of conservative treatments for secondary lymphedema, as well as harms related to these treatments.	Patients with secondary lymphedema	• Manual lymphatic drainage • Complex decongestive therapy • Mechanical treatments		• Intermittent pneumatic compression had benefits over complex decongestive therapy or selfmassage (n= 2 RCTs) • No benefits: Intermittent pneumatic compression compared to lymphatic massage, skin care or elastic sleeve (n= 3 RCTs) • Three-chamber intermittent pneumatic compression was better at redacting edema than a one-chamber sleeve (n= 1 RCT) • One of six RCTs report in the massage group no differences between massage and bandaging	The literature contains no evidence to suggest the most effective treatment for secondary lymphedema. Harms are few and unlikely to cause major clinical problems.	Indirekte Evidenz: Unterschiedliche Patienten-kollektive eingeschlossen und keine Angabe, inwiefern Peniskarzinom-Patienten involviert waren.	LoE 1 ROBIS low

Referenz	Studien-design	Studien-merkmale	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerkungen	LoE/ RoB
							alone, elastic sleeve or a less intensive form of massage • Laser treatment was superior to exercise, sham laser or no treatment (n= 3 studies) • Conflicting results concerning diets • Ultrasound was no different than intermittent pneumatic compression in reducing arm circumference (n= 1 observational study) • Modified manual lymphatic drainage reduced secondary lymphedema volume by 22% relative to standard manual lymphatic drainage (n= 1 observational study) • Group talks and exercise sessions added to manual lymphatic drainage and compression stockings improved			

Referenz	Studien-design	Studien-merkmale	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerkungen	LoE/ RoB
							'psychic well-being' ($p < 0.05$) yet made no difference in physical complaints (n= 1 observational study) • Manual lymphatic drainage in addition to compression bandaging experienced less pain than persons receiving bandaging alone ($p < 0.03$), no statistically significant reductions in absolute limb volume ($p = 0.07$) (n= 1 observational study) <u>Harms</u> • Rare (less than 1%) • None of these harms had major clinical impact			
Primärstudie										
Modolin, 2006, Clinics	Retro-spective case serie	Follow-up ranged from 6 mo to 6 y	To present the experience and results of the treatment of lymphedema	n= 17 patients <u>Mean age</u> 50.5 y <u>Etiology</u>	Modified Charles procedure (excision of the affected skin followed by scrotoplasty and midline suture		1/17 recurrence of scrotum lymphedema after lymphadenectomy with radiation therapy due to penile cancer	The modified Charles procedure for the treatment of penoscrotal lymphedema is easily reproducible and allows better	Indirekte Evidenz: Unterschiedliche Ätiologien involviert und nu rein Patient mit Peniskarzinom	LoE 4 RoB 8/20

Referenz	Studien-design	Studien-merkmale	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerkungen	LoE/ RoB
			of the penis and scrotum by removing affected tissues and correcting the penoscrotal region.	Lymphogranuloma venereum (n= 2) Blastomycosis (n= 1) Penile cancer (n= 1) Previous drainage of inguinal and perineal abscesses (n= 2) Filariasis (n= 7) Tuberculosis (n= 1) Obesity (n= 1) Syphelis (n= 1) Congenital (n= 1)	simulating the scrotal raphe)		No infections, dehiscence, or necrosis was observed. Clear improvement of the aspect of the external genitalia and subsequent improvement of ambulation, hygiene, and ability to void in the standing position were observed. Improvement of sexual performance could not be directly assessed, although some patients stated that sexual intercourse became more effective as regards penetration and satisfaction for patient and partner.	local hygiene, easier ambulation, voiding in the standing position, resuming sexual intercourse, and finally, better cosmetic results in the affected area with remarkable improvement in quality of life.		
Shim, 2018, Clinical and Experi-mental Dermatology	Retro-spective case serie	n= 41 2011-2016 Mean follow-up 3.1 ± 2.5 y	To describe and share our updated cumulative experience of a cohort of patients with penile lymphoedema.	Patients with penile lymphoedema excluded: pelvic- or urological cancer (and its treatment) related lymphoedema	Systemic antibiotics and specialized urological surgery circumcision and excision		All patients responded to systemic antibiotics. 13/41 were cured 23/41 stable with occasional fluctuation of disease activity	Treatment may comprise a multifaceted approach, including minimization of recurrent episodes of cellulitis with antibiotic prophylaxis,		LoE 4 RoB 8/20

Referenz	Studien-design	Studien-merkmale	Studien-ziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schluss-folgerung	Bemerkungen	LoE/ RoB
				Mean age 41.4 ± 14.7 y			3/41 awaiting further surgical management (2/41 loss to follow-up/ declined further treatment)	aggressive treatment of relapses with short courses of oral corticosteroids, surgical debulking and removal of the grossly dysfunctional prepuce, and long-term follow-up.		

10.2. Recherche nach nationalen und internationalen Qualitätsindikatoren zum Peniskarzinom

10.2.1. Rechercheauftrag

Die Recherche wurde vom Bereich Infoplattform (Steffi Derenz und Jessica Lobitz) zwischen dem 10.09.2019 und 24.09.2019 durchgeführt.

Als Recherchevokabular wurden folgende Begriffe verwendet:

Population:

Erwachsene Patienten mit Peniskarzinom in allen Versorgungssettings (ambulant/stationär).

Peniskarzinom OR Peniskrebs

neoplasms, penile

(penis OR penile)

(Erythroplasia OR bowens disease OR bowen's disease)

AND (tumor OR tumour OR cancer OR cancers OR carcinoma OR neoplasm OR neoplasms OR neoplasia)

Intervention:

Qualitätsindikator; Qualitätsindikatoren

Quality Indicators, Health Care

(quality OR performance) AND (indicator OR indicators OR measure OR measures)

Limits:

Bei der Suche erfolgte eine Einschränkung des Suchzeitraums (2009 bis 10.09.2019).

Weitere Einschränkungen bezüglich spezifischer Subgruppen innerhalb der Zielpopulation erfolgten nicht.

Die Suche wurde in folgenden Quellen durchgeführt:

- Literaturdatenbanken: Medline über https://www.ncbi.nlm.nih.gov/ & Cochrane über http://www.cochranelibrary.com/
- Webseiten von nationalen Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Webseiten von internationaler Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Internetrecherche via www.google.de

Recherchestrategie und -vokabular richten sich nach den Möglichkeiten der jeweiligen Recherchequelle, wurden entsprechend modifiziert und unter zwei Recherchestrategien dargelegt.

10.2.2. Recherchestrategien

10.2.2.1. Bibliographische Datenbanken

PubMed

Search	Query	Items found
#11	Search **#10 Filters: Publication date from 2009/01/01 to 2019/09/10; English; German**	36
#10	Search **#6 AND #9**	44
#9	Search **#7 OR #8**	266750
#8	Search **quality indicators, health care[MeSH Terms]**	19993
#7	Search **(quality[Title/Abstract] OR performance[Title/Abstract]) AND (indicator[Title/Abstract] OR indicators[Title/Abstract] OR measure[Title/Abstract] OR measures[Title/Abstract])**	254363
#6	Search **#4 OR #5**	7901
#5	Search **neoplasms, penile[MeSH Terms]**	5289
#4	Search **(#2 OR #3) AND #1**	6097
#3	Search **(tumor[Title/Abstract] OR tumour[Title/Abstract] OR cancer[Title/Abstract] OR cancers[Title/Abstract] OR carcinoma[Title/Abstract] OR neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR neoplasia[Title/Abstract])**	2807306
#2	Search **(Erythroplasia[Title/Abstract] OR bowens disease[Title/Abstract] OR bowen's disease[Title/Abstract])**	1992
#1	Search **(penis[Title/Abstract] OR penile[Title/Abstract])**	30109

Recherchedatum: (10.09.2019)

Cochrane

Search	Query	Items found
#1	Search **(penis OR penile):ti,ab,kw** (Word variations have been searched)	2318
#2	Search **(Erythroplasia OR bowens disease OR bowen's disease):ti,ab,kw** (Word variations have been searched)	121
#3	Search **(tumor OR tumour OR cancer OR cancers OR carcinoma OR neoplasm OR neoplasms OR neoplasia):ti,ab,kw** (Word variations have been searched)**:ti,ab,kw** (Word variations have been searched)	196127
#4	Search (#2 OR #3) AND #1	330
#5	Search **MeSH descriptor: [Penile Neoplasms]** explode all trees	23

Search	Query	Items found
#6	Search #4 OR #5	330
#7	Search **(quality OR performance) AND (indicator OR indicators OR measure OR measures):ti,ab,kw** (Word variations have been searched)	183800
#8	Search **MeSH descriptor: [Quality Indicators, Health Care]** explode all trees	447
#9	Search #7 OR #8	183971
#10	Search #6 AND #9; with Cochrane Library publication date from Jan 2009 to Sep 2019	57
	NOT Studienregister / NOT Editorial	42

Recherchedatum: (10.09.2019)

Anzahl der Treffer nach Duplikatecheck: 75

10.2.2.2. Nationale Qualitätsindikatorenprojekte/-programme

Institution	Quelle	Treffer
AQUA-Institut	Internetseite zur Sektorenübergreifenden Qualitätssicherung über https://sqg.de/front_content.php?idcat=15&lang=1	0
	QISA – Qualitätsindikatorensystem für die ambulante http://www.aok-gesundheitspartner.de/bund/qisa/themen/index.html	0
GKV-Spitzenverband	Qualitätsindikatoren-Thesaurus über http://quinth.gkv-spitzenverband.de/content/suche.php	0
IQTiG	Suchfunktion auf https://iqtig.org	0

10.2.2.3. Internationale Qualitätsindikatorenprojekte/-programme

Institution	Quelle	Treffer
AHRQ (Agency for Health Research and Quality) Quality Indicators	über http://www.qualityindicators.ahrq.gov/	0
AMA (American Medical Association)	Über https://www.thepcpi.org/	0
ASCO (American Society of Clinical Oncology) Quality Oncology Practice Initiative	http://qopi.asco.org/index.html QOPI® Measures & Reporting Pathways - Spring 2017	0
CIHI (Canadian Institute for Health Information) Health Indicators	http://www.cihiconferences.ca/indicators/2012/definitions12_e.html	0
CQCO (Cancer Quality Council of Ontario) Cancer System Quality Index – set of indicators	http://www.csqi.on.ca/all_indicators/#.UlJ9iW25OH4	0
ISD Scotland Health Indicators	http://www.isdscotland.org/Health-Topics/Cancer/ http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis/quality_performance_indicators.aspx	0
JCAHO (Joint Commission on Accrediation of Healthcare Organizations)	http://www.jointcommission.org/accountability_measures.aspx	0
NHS (National Health Services) Indicators for Quality Improvement	https://digital.nhs.uk/ https://digital.nhs.uk/data-and-information	0
NQF (National Quality Forum) Performance Measures	http://www.qualityforum.org/QPS/	0
OECD Health Care Quality Indicators	http://www.oecd.org/health/health-systems/hcqi-cancer-care.htm	0
RAND Corporation Quality of Care	http://www.rand.org/health/surveys_tools/qatools.html	0

Institution	Quelle	Treffer
Assessment Tools (QA Tools)		
Oncoline (Niederlande)	http://oncoline.nl/index.php	0
KCE (Belgien)	https://kce.fgov.be/	0

10.2.2.4. Suchmaschine

Suchmaschine: www.google.de

Suchbegriffe:

Suche deutsch:

Peniskarzinom Qualitätsindikator:	0 Treffer
Peniskrebs Qualitätsindikator:	0 Treffer

Suche englisch:

penis cancer quality indicator:	0 Treffer
penile cancer quality indicator:	0 Treffer
"penile cancer" "quality indicator":	0 Treffer
Recherchedatum:	12.09.2019
Anzahl der Treffer nach Screening:	0

10.2.3. Rechercheergebnisse

Ausschlussgründe:

A1: Doppelpublikation

A2: andere Entität

A3: kein Qualitätsindikator

A4: Publikationsart (z. B.: Letter, Editorial)

A5: Volltext nicht verfügbar

10.2.3.1. Bibliographische Datenbanken

Anzahl der Treffer nach Titel- und Abstractsichtung (Pubmed): 1

Treffer nach Volltextsichtung: 0

10.2.3.2. Nationale Qualitätsindikatoren

Recherchedatum: 20.09.2019

Treffer: 0

10.2.3.3. Internationale Qualitätsindikatoren

Recherchedatum: 20.09.2019

Treffer: 0

10.3. Ergebnisse der Interessenkonflikterklärungen

Tabelle 35: Zusammenfassung der Interessenerklärungen/Ergebnisse der Interessenkonfliktbewertung

Name	Berater- bzw. Gutachter-tätigkeit	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungstätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungs-vorhaben/ Durchführung klinischer Studien[1]	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fachgesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Koordination								
Prof. Dr. Oliver Hakenberg	Verschiedene Landgerichte	Nein	Janssen, SKB	Nein	Prefere, Astellas, Sofio, Bayer	Nein	DGU	Keine Relevanz
Dr. Stefanie Schmidt	Nein	Nein	Nein	Nein	Nein	Nein	DNEbM, Cochrane, DGU, UroEvidence	Keine
Dr. Julia Lackner	Nein	Nein	Nein	Nein	Nein	Nein	DGU, UroEvidence	Keine
Janine Weiberg	Nein	Nein	Nein	Nein	Nein	Nein	DGU	Keine
Mandatsträger der Arbeitsgemeinschaften								
Dr. Matthias Beintker	Nein	Nein	Nein	Nein	Nein	Nein	DGU, Thüringer Krebsgesellschaft, Mitteldeutsche Urologen	Keine
Prof. Dr. Alexander Cavallaro	Siemens Healthineers	Siemens Healthineers	Universität Erlangen, Technische Hochschule Nürnberg	Nein	BMWI-Projekte	Nein	Bayrische Landesärztekammer, DRG	Keine Relevanz

Name	Berater- bzw. Gutachter-tätigkeit	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungstätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungs-vorhaben/ Durchführung klinischer Studien[1]	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fachgesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Prof. Dr. Maike de Wit	DGU, ADHOK	Uroonkologisches Zentrum Mittelbrandenburg: Tumor-Board Patientenindividuelle Therapie des mCRPC AbbVie Deutschland: Rovalpituzumab-Teserine beim SCLC Boehringer-Ingelheim: Sequenzoptionen bei der Behandlung des EGFR-mutierten NSCLS, Neue Entwicklungen in der Erstlinientherapie des NSCLC Berliner Urologische Gesellschaft: Wissenschaftliche Abendveranstaltung Ipsen Pharma: Advisory Board HCC, Expertenrunde Onkologie Novartis: Dialogplattform Onkologische Versorgung 2020 Dres. Schlegel + Schmidt: Molekularpathol. Diagnostik in der Lungenkrebs-therapie	DGHO: Juniorakademie, Jahrestagung AstraZeneca: Krebskongress, DGP Onkologie - PACIFIC anlässlich des DGP Kongress 2018, Expertinnen im Dialog, ASCO MSD: Aktuelle und zukünftige Therapie des Lungenkarzinoms mit CPI, Krebskongress Janssen-Cilag: Aufbaumodul Hämatologie - Forum Berlin-Brandenburg | Hämatologisches Forum Berlin-Brandenburg | Hämatologie-Forum Ipsen Pharma: ASCO, Gastrointestinal Cancer Symposium BDI: Neue Entwicklungen mit Schwerpunkt Onkologie Daiichi Sankyo: Antikoagulation bei Krebspatienten Deutsche Gesellschaft für Radioonkologie: Jahrestagung	New England Journal of Medicine Dt. Stiftung für junge Erwachsene mit Krebs	Nein	Nein	DGHO, DKG, AIO, ASORS, ESMO, ASCO, DGIM	Keine Relevanz

Name	Berater- bzw. Gutachter-tätigkeit	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungstätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungs-vorhaben/ Durchführung klinischer Studien[1]	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fachgesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
		AstraZeneca: Advisory Board Lungenkrebs Pierre Fabre: Therapiefelder Vinorelbin Oral heute und morgen	Mediolanum Biosciences: ESMO AIO: Herbstkongress DIGM: Internistenupdate Berliner Gesellschaft für Innere Medizin: Kongressnachlese Sanofi-Aventis: RADIO Prostatakarzinom Roche: Der zweite Atem Astellas: Jahrestagung Pfizer Oncology: BIG Data – Einfluss auf pharmazeutische Innovationen BMS: ESMO Nationale Gesundheits-AKADEMIE: NGA Best of ASCO Sirtex Medical Europe: ASCO Promedicis: Excellence in Oncology – Nieren- und Urothelkarzinom Frauenheilkunde: Ausgewählte Themen der Frauenheilkunde MCI: AIO Herbstkongress					

Name	Berater- bzw. Gutachter-tätigkeit	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungstätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungs-vorhaben/ Durchführung klinischer Studien[1]	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fachgesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
			Strehlow GmbH: Die Immuntherapie – Personalisierte Medizin am Beispiel eines Lungenkrebspatienen Clinigen Healthcare Limited: Attendance of the German Extravasation Medical Educational Program Virtual Meeting Takeda: KOK Jahreskongress Betreuung von Patienten mit einem rezidivierten Hodgkin Lymphom – eine Gemeinschaftsaufgabe für Ärzte und Fachpflegekräfte | Meet the Expert: Behandlung von Hodgkin-Lymphomen					
PD Dr. Stefan Esser	Nein	Gilead, GSK, Janssen, MSD, ViiV	Gilead, GSK, Janssen, MSD, ViiV	Gilead, GSK	Gilead, GSK, Janssen, MSD, ViiV	Nein	DAIG, DAGNÄ, DDG, DGI, DSTIG	Keine Relevanz
Prof. Dr. Lars Alexander Schneider ADO (STv. Mandat)	Bis 2016 BÄK Südwürttemberg	Bis 2016: Roche, BMS, MSD, AMGEN	Christiane Weber Consulting	Nein	Nein	Nein	ADO, DKG, DDG, DGDC, ADF, VLK	Keine Relevanz
Dr. Marianne Kloke	Nein	Nein	Nein	Nein	Nein	Nein	DGP, DGHO, DKG	Keine

Name	Berater- bzw. Gutachter-tätigkeit	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungstätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungs-vorhaben/ Durchführung klinischer Studien[1]	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fachgesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Dr. Alexandros Papachristofilou	Nein	Nein	Nein	Nein	Rising Tide, Foundation Krebsliga	Nein	Deutsche Gesellschaft für Radioonkologie, Swiss Association of Scientific Radiation Oncology, Schweizerische Arbeitsgemeinschaft für klinische Krebsforschung, European Society for Therapeutic Radiology and Oncology	Keine
PD Dr. Konrad Steinestel	Nein	Novartis	Boehringer Ingelheim	Nein	Nein	Nein	DGP	Keine Relevanz
Dr. Andreas Werner	Nein	Nein	Nein	Nein	Nein	Nein	Verein Schmetterling e. V., Deutsche Arbeitsgemeinschaft psychosoziale Onkologie, PSO	Keine
Prof. Dr. Dirk-Henrik Zermann	Nein	Deutsche Akademie für Kurortwissenschaft und Rehabilitationsmedizin Bad Elster e. V.	Nein	siehe Pubmed	Technische Universität Chemnitz/ Angewandte Bewegungswissenschaften-Sportmedizin/ Sportbiologie	Nein	DGU, DGHO, DKG, Sächsische Gesellschaft für Urologie	Keine

Name	Berater- bzw. Gutachter-tätigkeit	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungstätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungs-vorhaben/ Durchführung klinischer Studien[1]	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fachgesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Mandatsträger der Fachgesellschaften								
PD Dr. Dirk Beyersdorff	Nein	Bayer	Ja	Nein	Nein	(Nichts im Zusammenhang mit Peniskarzinom)	DRG, ESR	Keine Relevanz
Prof. Dr. Johannes Claßen	Ärztekammer	Nein	Nein	„Taschenbuch Onkologie“	HD-Studien (Uni Köln), TopRoK-Studie (Uni HH), HICARE (Uni HD), RFEQUITE (EU), Lapatinib (Glaxe SK) HYPOSIB (Uni Lübeck)	Nein	DEGRO (AG Hodentumoren), ARO, ASTRO, Dt. Krebsgesellschaft, BVDST	Keine Relevanz
PD Dr. Thomas Hermanns	Nein	Bayer, MSD	Nein	Nein	Krebsliga Grant für Micro-RNA Forschungsprojekt bei Hodentumoren	Nein	Nein	Keine Relevanz
Dr. Martin Heuschkel	Nein	Nein	Sanofi, DGN, Strandklinik Boltenhagen, DRG, Novartis	Nein	TauRX Therapeutics, AMGEN, Piramal	Nein	Deutsche Gesellschaft für Nuklearmedizin, European Association of Nuclear Medicine, Deutsche Physikalischen Gesellschaft	Keine Relevanz

Name	Berater- bzw. Gutachter-tätigkeit	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungstätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungs-vorhaben/ Durchführung klinischer Studien[1]	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fachgesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Prof. Dr. Glen Kristiansen	Nein	Nein	Ja	Nein	Ja	Nein	ENUP-Vorsitzender, ISUP-Vorstandsmitglied	Keine Relevanz
Dr. Sven Michels	Nein	Nein	Nein	Nein	Nein	Nein	DGU, DGP	Keine
Prof. Dr. Carsten Maik Naumann	Nein	Nein	Ja	Ja	Ja	Nein	DGU, DGHO	Keine Relevanz
Prof. Dr. Peter Schneede	Nein	Mitglied des HPV-Management-Forums (PEG)	Mitglied des HPV-Management-Forums (PEG)	AWMF-Leitlinien Mitglied des HPV-Management-Forums (PEG)	Nein	Nein	DGU-Mitglied, Vorstand des AK-Infektiologie, DSTIG-Mitglied, Vorstandstätigkeiten, Leitlinien-Erstellung für AWMF, Wissenschaftlicher Mitarbeiter der LMU-München	Keine Relevanz
PD Dr. Stephan Seklehner	Nein	Nein	Nein	Nein	Nein	Nein	ÖGU, BvDU, EAU	Keine
Prof. Dr. Gunhild von Amsberg	Gerichtsgutachten	Roche, BMS, Astellas, Sanofi, MSD, Ipsen, EISAI	Roche, BMS, Sanofi, Astellas, Ipsen, EISAI, Pierre Fabre, Janssen, MSD, Astra Zeneca	Ipsen, Sanofi, BMS	Ipsen, MSD, BMS, Astra Zeneca, Sanofi, Incyte, Nektar	Nein	DGHO, AIO	Keine Relevanz
AG-Leiter								

Name	Berater- bzw. Gutachter-tätigkeit	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungstätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungs-vorhaben/ Durchführung klinischer Studien[1]	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fachgesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
Dr. Desiree Dräger	Nein	Nein	Nein	Nein	Nein	Nein	DGU, UroEvidence, PSO, DKG, SIOG, DPG	Keine
Prof. Dr. Erbersdobler	Nein	Nein	Solution Akademie GmbH: Vortrag zum Peniskarzinom beim Uroonkologischen Wintersymposion in Schwerin	Nein	Nein	Nein	DGP, BDP	Keine Relevanz
Prof. Dr. Chris Protzel	Nein	Nein	Ja Medac, Pfizer, Janssen	Nein	Nein	Nein	DGU, AUO, ASORS	Keine Relevanz
Patientenvertreter								
Udo Ehrmann	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied im Vorstand des Bundesverbands Prostatakrebs Selbsthilfe, themenbezogener Patientenvertreter im G-BA für Prostatakarzinom Patientenvertreter in der S3-Leitlinienkommission Prostatakarzinom	Keine

Name	Berater- bzw. Gutachter-tätigkeit	Mitarbeit in einem wissenschaftlichen Beirat (advisory board) [1]	Bezahlte Vortrags-/oder Schulungstätigkeit [1]	Bezahlte Autoren-/oder Coautoren-schaft[1]	Forschungs-vorhaben/ Durchführung klinischer Studien[1]	Eigentümer-interessen (Patent, Urheberrecht, Aktienbesitz) [1,2]	Indirekte, nicht-finanzielle Interessen (u.a. Mitglied in Fachgesellschaften, klinischer Schwerpunkt, pers. Beziehungen)[3]	Von CoI betroffene Themen der Leitlinie sowie Einstufung bzgl. der Relevanz
							Patientenvertreter (Beisitzer) im Vorstand des EBM-Netzwerks	
Externe Berater								
Dr. Klaus Kraywinkel	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine
Dr. Ekkehard Ost	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine

1 = Hier werden entsprechend §139b SGB V finanzielle Beziehungen zu Unternehmen, Institutionen oder Interessenverbänden im Gesundheitswesen erfasst. Folgende Frage wurde beantwortet: Haben Sie oder die Einrichtung, für die Sie tätig sind, innerhalb des laufenden Jahres oder der 3 Kalenderjahre davor Zuwendungen erhalten von Unternehmen der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), industriellen Interessenverbänden, kommerziell orientierten Auftragsinstituten, Versicherungen/Versicherungsträgern, oder von öffentlichen Geldgebern (z. B. Ministerien), Körperschaften/Einrichtungen der Selbstverwaltung, Stiftungen, oder anderen Geldgebern?

2 = Angaben zu Mischfonds waren nicht erforderlich

3 = Hierzu wurden folgende Aspekte abgefragt: Mitgliedschaft /Funktion in Interessenverbänden; Schwerpunkte wissenschaftlicher Tätigkeiten, Publikationen; Schwerpunkte klinischer Tätigkeiten; Federführende Beteiligung an Fortbildungen/Ausbildungsinstituten; Persönliche Beziehungen (als Partner oder Verwandter 1. Grades) zu einem Vertretungsberechtigten eines Unternehmens der Gesundheitswirtschaft; sonstige relevante Interessen

10.4. Kommentare zur Konsultationsfassung

Tabelle 36 Kommentare zur Konsultationsfassung (Stand 16.07.2020)

Anmerkung	Umgang mit den Kommentaren
Aus Sicht der Deutschen Gesellschaft für Palliativmedizin ist (…) eine begriffliche Schärfung an manchen Stellen vonnöten. Sinnvoll wäre bspw. eine Änderung der Begriffe „Palliativpflege“ (in Kap. 8) sowie „Palliativtherapie“ (in Kap. 8.3) hin zu „Palliativversorgung“. Im Kapitel 7.3.3 wird weiter „palliative Supportivtherapie“ als Begriff genutzt, welcher letztlich aber auch „Palliativversorgung“ meint. Die Vielzahl der synonym genutzten Begriffe führt zu Irritationen, so dass eine Begriffsschärfung unerlässlich erscheint.	Übernehmen, redaktionelle Änderung
Darüber hinaus kann überlegt werden, das Unterkapitel 7.3.3 „palliative Supportivtherapie“ zu streichen (es gibt hier keine SE), da auf Palliativversorgung im Kapitel 8.3. bereits dezidiert eingegangen wird.	Übernehmen, redaktionelle Änderung
Meine Anmerkungen zur LL Peniskarzinom: 4.1. Konsensbasiertes Statement 7.51. Punkt fehlt	übernehmen, redaktionelle Änderung
Das Kapitel Maligne Wunden ist in der erweiterten S3 Leitlinie Palliativmedizin hervorragend abgebildet. Deshalb denke ich, dass es sinnvoller ist, hier auf das Kapitel zu verweisen. Das maligne Lymphödem wurde nicht einbezogen, sollte von daher als Besonderheit beim Peniskarzinom so beibehalten werden.	Keine Änderung, da hier der Verweis zur S3 Leitlinie Palliativmedizin erfolgt und in dieser Leitlinie nur eine kurze Vertiefung erfolgt.
4.4. S. 28 Original: Der pathologische Befundbericht soll eine Klassifikation der histologischen Subtypen des Peniskarzinoms entsprechend der WHO-Klassifikation enthalten. Vorschlag: Der pathologische Befundbericht soll eine Klassifikation der histologischen Subtypen des Peniskarzinoms entsprechend der aktuellen WHO-Klassifikation enthalten.	bezieht sich auf Empfehlung 4.3 Übernehmen, redaktionelle Änderung

Anmerkung	Umgang mit den Kommentaren
Begründung: Es sollte tatsächlich die aktuelle WHO-Klassifikation verwandt werden und nicht irgendeine Auflage. „Aktuell“ steht zwar in den Hintergrundinformationen sollte aber m.E. in den Empfehlungen verankert werden.	
4.7. Seite 30 Original: Der pathologische Befundbericht der Lymphknoten soll die Zahl der präparierten Lymphknoten, die Zahl der befallenen Lymphknoten und die maximale Metastasengröße enthalten sowie Aussagen darüber, ob die Metastase auf den Lymphknoten beschränkt bleibt oder die Lymphknotenkapsel überschreitet. Vorschlag: Der pathologische Befundbericht der Lymphknoten soll die Zahl und Lokalisation der präparierten Lymphknoten, die Zahl der befallenen Lymphknoten und die maximale Metastasengröße enthalten sowie Aussagen darüber, ob die Metastase auf den Lymphknoten beschränkt bleibt oder die Lymphknotenkapsel überschreitet. Begründung: Durch die Angabe der Lokalisation der entfernten Lymphknoten sollte gesichert werden, dass nur regionäre Lymphknoten in der N/pN-Kategorie betrachtet und klassifiziert werden.	bezieht sich auf Empfehlung 4.7 Übernehmen, inhaltliche Änderung
Hintergrundempfehlung 4.6/Seite 30 Original … Lymphgefäßinvasion (L1) darüber hinaus Teil der T-Kategorie bei der TNM-Klassifikation, Vorschlag … lymphovaskuläre Invasion (L1) darüber hinaus Teil der T-Kategorie bei der TNM-Klassifikation,	Übernehmen, redaktionelle Änderung

Anmerkung	Umgang mit den Kommentaren
Begründung Durch die Angabe der Lokalisation der entfernten Lymphknoten sollte gesichert werden, dass nur regionäre Lymphknoten in der N/pN-Kategorie betrachtet und klassifiziert werden.	
Primärtumor 6.1/Seite 37 Original … lymphogen metastasierte Tumore, … Vorschlag … lymphogen metastasierte Tumoren, … Begründung Bitte einheitlich Tumoren im gesamten Text.	Übernehmen, redaktionelle Änderung
Empfehlung 6.5/Seite 40 Original Stadium pT1b Vorschlag Kategorie pT1b Begründung Das ist einzuhaltende Nomenklatur der UICC, unter Stadium versteht man etwas anderes. Sie auch Seiten: 44, 45, 54, 55, 61, 63, 66, 72, 95,	Keine Änderung, da von diesen Formulierungsanpassungen auch Empfehlungen betroffen wären und in der medizinischen Sprache diese Feinheiten eine kleinere Relevanz besitzten.
Q2 Befundbericht 4.6 Original	Übernehmen, redaktionelle Änderung

Anmerkung	Umgang mit den Kommentaren
Lymphgefäßinvasion Vorschlag Lymphovaskuläre Invasion Begründung Siehe oben, AJCC- und UICC-Nomenklatur	
Literatur 103, Seite 102 Original Wittekind, C., TNM Klassifikation Maligner Tumoren. Vol. 8. Auflage. 2017, Weinheim, Deutschland: Wiley-VCH Verlag Vorschlag Wittekind, C., TNM Klassifikation Maligner Tumoren. Vol. 8. Auflage. 2017, Weinheim, Deutschland: Wiley-VCH Verlag, Korrigierter Nachdruck 2020 Begründung Anpassung an neueste Literatur	Übernehmen, redaktionelle Änderung
Unter 1.9.2., Seite 9 muss es „Bundesverband Deutscher Pathologen e.V. (BDP)“ und nicht „Berufsverband der Deutschen Pathologen e.V. (BDP)“ heißen.	Übernehmen, redaktionelle Änderung
Desweiteren wollte ich Sie noch auf eine prospektiv randomisierte Studie unserer Arbeitsgruppe zur Wundversorgung nach inguinaler Lymphadenektomie beim Peniskarzinom aufmerksam machen, die in den kommenden Tagen veröffentlicht wird (siehe Anhang). Schmid SC, Seitz AK, Haller B, et al. Final results of the PräVAC trial: prevention of wound complications following inguinal lymph node dissection in patients with penile cancer using epidermal vacuum-assisted wound closure [published online ahead of print, 2020 May 5]. World J Urol.	Keine Änderung, kann bei der Leitlinien-Aktualisierung berücksichtigt werden.

Anmerkung	Umgang mit den Kommentaren
S. 81 Original „Palliative Supportivtherapie“ Vorschlag „Palliativmedizin“ Begründung Die für die Palliativmedizin (APM) und die Supportivtherapie (AGSMO) zuständigen Arbeitsgruppen bemühen sich seit Langem intensiv um eine stringente Benutzung der Begriffe „palliativ“ versus „supportiv“. Hier im Absatz 7.3.3 ist eindeutig die Palliativmedizin gemeint, und daher wird (dankenswerterweise!!) auch Bezug auf die S3-Querchschnittsleitlinie Palliativmedizin (und hier nicht auf die S3-Leitlinie Supportive Therapie) genommen. Das wäre wirklich wichtig zu ändern.	Übernehmen, redaktionelle Änderung
S. 87 Original „Palliativtherapie“ Vorschlag „Palliativpflege“ Begründung Der Begriff „Palliativtherapie“ führt immer wieder zu großen Mißverständnissen; häufig wurde in der Literatur versucht, diesen Begriff zu beziehen auf palliativ intendierte Tumortherapien. Hier im Kapitel 8.3 geht es ja vor allem um die pflegerisch durchgeführten Aspekte von Palliativmedizin (wie auch in der übergeordneten Überschrift bereits geschrieben, S. 83), daher sollte auch auf S. 87 konsequenterweise der Begriff „Palliativpflege“ benutzt werden.	redaktionelle Änderung Die nun verwendete Bezeichnung ist „Palliativversorgung“.

Anmerkung	Umgang mit den Kommentaren
möchte nun analog der Eingabe der DGP vorschlagen, den Abschnitt 7.3.3 zu streichen (da er lediglich auf die S3-Leitlinie Palliativmedizin verweist, was auch schon in 8.3 geschieht), und das Kapitel 8.3 mit „Palliativversorgung“ zu überschreiben, wie von der DGP schon zuvor erbeten.	Übernehmen, redaktionelle Änderung
E 7.36 Typo	Übernehmen, redaktionelle Änderung

11. Abbildungsverzeichnis

12. Tabellenverzeichnis

13. Literaturverzeichnis

1. Programm für Nationale Versorgungsleitlinien. *Deutsche Leilinien Bewertungsinstrument (DELBI).* Delbi 2.0. 04.11.2017]; Available from: http://www.leitlinien.de/leitlinien-grundlagen/leitlinienbewertung/delbi.
2. Morton, C.A., A.J. Birnie, D.J. Eedy, *British Association of Dermatologists' guidelines for the management of squamous cell carcinoma in situ (Bowen's disease) 2014.* Br J Dermatol, 2014. **170**(2): p. 245-60, https://onlinelibrary.wiley.com/doi/pdf/10.1111/bjd.12766
3. Hakenberg, O.W., et al., *EAU Guidelines on Penile Cancer 2018*, in *European Association of Urology Guidelines. 2018 Edition.* 2018, European Association of Urology Guidelines Office: Arnhem, The Netherlands.
4. National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology. Penile cancer.* 2018. **Version 1.2018**,
5. Leitlinienprogramm Onkologie, *S3-Leitlinie: Supportive Therapie bei onkologischen PatientInnen*. Langversion 1.1. AWMF Registernummer: 032/054OL. 2017.
6. Leitlinienprogramm Onkologie, *Psychoonkologische Diagnostik, Beratung und Behandlung von erwachsenen Krebspatienten.* Langversion 1.1. AWMF-Registernummer: 032/051OL, 2014, http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html
7. Leitlinienprogramm Onkologie, *Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung,.* Langversion 2.01 (Konsultationsfassung). AWMF-Registernummer: 128/001-OL, 2019, https://www.awmf.org/uploads/tx_szleitlinien/128-001OLl_KF_S3_Palliativmedizin_2018-12.pdf
8. Higgins, J., Green, S. (editors), *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration. 2011.
9. Whiting, P.F., A. W. Rutjes, M. E. Westwood, S. Mallett, J. J. Deeks, J. B. Reitsma, M. M. Leeflang, J. A. Sterne, and P. M. Bossuyt, *QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies.* Ann Intern Med, 2011. **155(8): 529-36**,
10. Hayden, J.A., et al., *Assessing bias in studies of prognostic factors.* Ann Intern Med, 2013. **158**(4): p. 280-6, https://annals.org/aim/article-abstract/1650776/assessing-bias-studies-prognostic-factors?doi=10.7326%2f0003-4819-158-4-201302190-00009
11. Effective Public Health Practice Project, *Quality Assessment Tool For Quantitative Studies.* 1988, Hamilton: Effective Public Health Practice Project.
12. Wells GA, S.B., O'Connell D, Peterson J, Welch V, Losos M, Tugwell P, *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
13. Whiting, P., et al., *ROBIS: A new tool to assess risk of bias in systematic reviews was developed.* J Clin Epidemiol, 2016. **69**: p. 225-34,
14. Guo, B., C. Moga, C. Harstall, D. Schopflocher, *A principal component analysis is conducted for a case series quality appraisal checklist.* J Clin Epidemiol, 2016. **69**: p. 199-207.e2,
15. Dolle, K. and G. Schulte-Körne, *Behandlung von depressiven Störungen bei Kindern und Jugendlichen.* Dtsch Arztebl International, 2013. **110**(50): p. 854-60, https://www.aerzteblatt.de/int/article.asp?id=151300
16. OCEBM Levels of Evidence Working Group, *The Oxford 2011 Levels of Evidence.* Oxford Centre for Evidence-Based Medicine, 2011, http://www.cebm.net/index.aspx?o=5653
17. AWMF, *AWMF-Regelwerk „Leitlinien".* Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)-Ständige Kommission Leitlinien, 2012. **1. Auflage 2012**, http://www.awmf.org/leitlinien/awmf-regelwerk.html
18. Leitlinienprogramm Onkologie, *Onkologische Qualitätsindikatoren: Leitlinienbasierte Qualitätsindikatoren im Leitlinienprogramm Onkologie (OL)*. Vol. 3.0. 2017.

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