

# Guidelines on Penile Cancer

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# 1. INTRODUCTION

The European Association of Urology (EAU) Guidelines Group on Penile Cancer has prepared this guidelines document to assist medical professionals in the management of penile cancer. The guidelines aim to provide detailed, up-to-date information, based on recent developments in our understanding and management of penile squamous cell carcinoma (SCC). However, it must be emphasised that these guidelines provide an updated, but not yet standardised general approach to treatment and that they provide guidance and recommendations without legal implications.

## 1.1 Publication history

The Penile Cancer Guidelines were first published in 2000, with a number of subsequent full text updates in 2001, 2004 and 2009. A limited updated was achieved in 2010. This text presents a complete update of the 2009 guidelines document. Several scientific summaries have been published in the EAU scientific journal, *European Urology* (1-3). The literature search for the 2013 update covered the period from August 2008 to November 2013. The reason to present an update after four years can be attributed to the recent increase in research in penile cancer and changes in management since 2009.

This document was peer-reviewed prior to publication.

## 1.2 Potential conflict of interest statement

The panel members have submitted potential conflict of interest statements which can be viewed on the EAU website: <http://www.uroweb.org/guidelines/online-guidelines/>.

# 2. METHODOLOGY

A systematic literature search on penile cancer was performed by all members of the EAU Penile Cancer Working Group covering the period between August 2008 and November 2013. At the onset of the project, the relevant literature databases were searched. All titles relating to penile cancer (n = 1,602) were reviewed by two panel members (OWH and CP). After exclusion of case reports, many reviews and irrelevant papers as well as non-English language literature, the remaining papers were reviewed by abstract (n = 582). After further exclusion of irrelevant literature, the remaining papers (n = 352) were retrieved and reviewed. This literature was discussed at a panel meeting and necessary changes to the guideline were agreed. Other national and international guideline documents on penile cancer were reviewed as well (National Comprehensive Cancer Network (4), French Association of Urology (5) and the European Society of Medical Oncology (6). A draft for discussion was circulated among all panel members several times December 2013, reviewed and finally agreed.

References used in the text have been assessed according to their level of scientific evidence (table 1), and guideline recommendations have been graded (table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (7). The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given. Due to the relative rarity of penile cancer, there is a uniform lack of large series and randomized controlled trials. As a result of this, the levels of evidence (LE) and grades of recommendation (GR) provided in the document are by necessity relatively low compared to those in guidelines concerning more common diseases. All texts can be viewed and downloaded for personal use at the society website: <http://www.uroweb.org/guidelines/online-guidelines/>.

**Table 1: Level of evidence\***

Type of evidence	LE
Evidence obtained from meta-analysis of randomised trials	1a
Evidence obtained from at least one randomised trial	1b
Evidence obtained from one well-designed controlled study without randomisation	2a
Evidence obtained from at least one other type of well-designed quasi-experimental study	2b
Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.	3
Evidence obtained from expert committee reports or opinions or clinical experience of respected Authorities	4

\*Modified from (7).

**Table 2: Grade of recommendation\***

Nature of recommendations	GR
Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial	A
Based on well-conducted clinical studies, but without randomised clinical trials	B
Made despite the absence of directly applicable clinical studies of good quality	C

\*Modified from (7).

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## 3. DEFINITION OF PENILE CANCER

Penile carcinoma is mostly a squamous cell carcinoma (SCC) but other types of carcinoma exist as well (see Chapter 6, table 6). It usually originates from the epithelium of the inner prepuce or the glans. Also, penile SCC occurs in several histological subtypes. Penile SCC shares similar pathology with SCC of the oropharynx, the female genitalia (cervix, vagina and vulva) and the anus and it is therefore assumed that it also shares to some extent the natural history.

## 4. EPIDEMIOLOGY

In Western countries, primary penile cancer is uncommon, with an incidence of less than 1.00 per 100,000 males in Europe and the United States (1,2). However, there are significant geographical variations within Europe (Figure 1) reporting an incidence greater than 1.00 per 100,000 men (3). Incidence is also affected by race and ethnicity in North America (1), with the highest incidence of penile cancer found in white Hispanics (1.01 per 100,000), followed by a lower incidence in Alaskan, Native American Indians (0.77 per 100,000), blacks (0.62 per 100,000) and white non-Hispanics (0.51 per 100,000), respectively. In contrast, in some other parts of the world such as South America, South East Asia and parts of Africa the incidence of penile cancer is much higher and can represent 1-2% (3) of malignant diseases in men. Penile cancer is common in regions with a high prevalence of human papilloma virus (HPV) (1). The annual age-adjusted incidence is 0.7-3.0 per

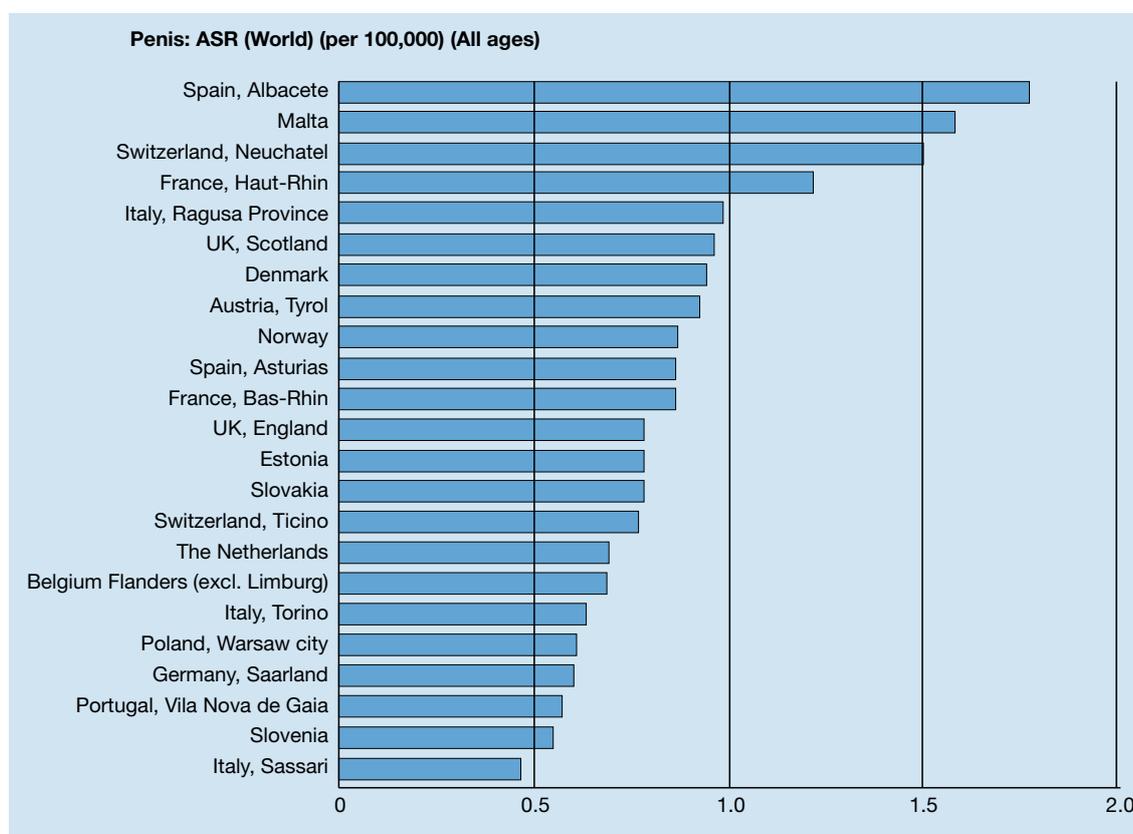
100,000 men in India, 8.3 per 100,000 men in Brazil and even higher in Uganda, where it is the most commonly diagnosed cancer in men (3,4). Much knowledge about penile cancer comes from research in countries with a high incidence of the disease.

The incidence of penile cancer is related to the prevalence of HPV in the population and this may account for the incidence variation as the worldwide HPV prevalence varies considerably. There is also an incidence variation in European regions although less pronounced (Figure 1). At least one third of cases can be attributed to HPV-related carcinogenesis. There are no data linking penile cancer to HIV or AIDS.

In the US, the overall age-adjusted incidence rate decreased between 1973 and 2002 from 0.84 per 100,000 in 1973-1982 to 0.69 per 100,000 in 1983-1992, and further to 0.58 per 100,000 in 1993-2002 (1). In European countries, the overall incidence has been stable from the 1980s until today (2). Recently, an increased incidence has been reported from Denmark (5) and the UK. A longitudinal study from the UK has confirmed a 21% increase in incidence over the period 1979-2009 (6).

The incidence of penile cancer increases with age (2), with an age peak during the sixth decade of life. However, the disease does occur in younger men (7).

**Figure 1: Annual incidence rate (world standardized) by European region/country\***



\*Adapted from (3).

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## 5. RISK FACTORS AND PREVENTION

Several risk factors for penile cancer have been identified by a review of the literature published from 1966 to 2000 (1). Strong risk factors (OR > 10) identified by case-control studies are given in table 3 (LE: 2a).

**Table 3: Recognized aetiological and epidemiological risk factors for the development of penile cancer**

Risk factors	Relevance
• Phimosis	OR 11-16 versus no phimosis (2,3)
• chronic penile inflammation (balanoposthitis related to phimosis) • balanitis xerotica obliterans (lichen sclerosus)	Risk (4)
• sporalene and UV-A phototherapy for various dermatologic conditions such as psoriasis	Incidence rate ratio 9.51 with > 250 treatments (5)
• smoking	5-fold increased risk (95% CI: 2.0-10.1) versus non-smokers (2,3,6)
• HPV infection condylomata acuminata	22.4% in verrucous SCC (7) 36-66.3% in basaloid-warty (8)
• Rural areas, low socio-economic status, unmarried	(9-12)
• multiple sexual partners early age of first intercourse	3-5-fold increased risk of penile cancer (2,3,13)

HPV = human papilloma virus; OR= odds ratio; SCC = squamous cell carcinoma; UV-A = ultraviolet-A.

Human papilloma virus infection is an important risk factor for developing penile cancer. DNA of HPV has been identified in 70-100% of intraepithelial neoplasia and in 30-40% of invasive penile cancer tissue samples (LE: 2a). The HPV virus plays an important role in oncogenesis through the interaction with oncogenes and tumour suppressor genes (P53, Rb genes) (14). The rate of HPV-positivity differs between different histological subtypes of penile cancer. This suggests that HPV is a cofactor in the carcinogenesis of some variants of penile SCC while other variants of penile cancer are not related to HPV (7). This corresponds to the finding of a higher incidence of penile cancer in regions with a high prevalence of HPV. HPV subtypes most commonly found in penile cancer are types 16 and 18 (15). The risk of penile cancer is increased in patients with condyloma acuminata (16) (LE: 2b).

It is not clear whether HPV-associated penile cancer differs in prognosis from non-HPV-associated penile cancer. A significantly better 5-year disease-specific survival has been reported for HPV-positive versus HPV-negative cases (93% vs 78%) in one study (17) while no difference in lymph node metastases and 10-year survival rate was reported in another (18).

There is no association between the incidence of penile cancer and cervical cancer except through the link with the prevalence of HPV infections (19,20). Female sexual partners of patients with penile cancer do not have an increased incidence of cervical cancer. There is at present no recommendation for the use of HPV vaccination in boys due to a different HPV-associated risk pattern in penile and anal cancer; furthermore, the epidemiological effects of HPV vaccination and its acceptance in girls will have to be assessed before any further recommendations can be made (21,22).

Phimosis is strongly associated with the development of invasive penile cancer (3,9,23,24), probably due to associated chronic infection since smegma is not a carcinogen (23). A further risk factor suggested by epidemiological studies is cigarette smoking, which is associated with a 4.5-fold increased risk (95% CI: 2.0-10.1) (24). The incidence of lichen sclerosus (balanitis xerotica obliterans) in patients with penile cancer

is relatively high but is not associated with increased rates of adverse histopathological features, including carcinoma in situ.

Other epidemiological factors associated with penile cancer are a low socio-economic status and a low level of education (9).

Neonatal circumcision reduces the incidence of penile cancer in countries and cultures where this is routinely practiced. The lowest incidence of penile cancer is reported from Israel amongst Jews (0.3/100,000/year). Medical circumcision in adult life does not influence the incidence of penile cancer. The controversial discussion about any preventive value of neonatal circumcision must take into consideration that circumcision removes about 50% of the tissue that can develop penile cancer. The protective effect of neonatal circumcision against invasive penile cancer (OR 0.41) - which does apparently not apply to CIS (OR 1.0) - is much weaker when the analysis is restricted to men without a history of phimosis (OR 0.79, 95% CI 0.29-2 (3)).

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## 6. TNM CLASSIFICATION AND PATHOLOGY

### 6.1 TNM classification

The 2009 TNM classification for penile cancer (1) stratifies the T1 category into two prognostically different risk groups depending on whether lymphovascular invasion is present or not or depending on grading (table 4). In addition, a subclassification of the T2 category regarding invasion of the corpus spongiosum only or the corpora cavernosa as well would be desirable as it has been shown that the prognosis for corpus spongiosum invasion only is much better than for corpora cavernosa invasion (2, 3). Importantly, the 2009 TNM classification includes any inguinal lymph node metastasis with extracapsular extension as pN3 recognising the significant adverse effect of extracapsular spread on prognosis (1).

Retroperitoneal lymph node metastases are classified as extraregional nodal and therefore distant metastases which corresponds to the clinical course of the disease.

**Table 4: 2009 TNM clinical and pathological classification of penile cancer (1)**

<b>Clinical classification</b>	
<b>T - Primary Tumour</b>	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i>
Ta	Non-invasive carcinoma
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)
T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)
T2	Tumour invades corpus spongiosum and/or corpora cavernosa
T3	Tumour invades urethra
T4	Tumour invades other adjacent structures
<b>N - Regional Lymph Nodes</b>	
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph node
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple unilateral or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral
<b>M - Distant Metastasis</b>	
M0	No distant metastasis
M1	Distant metastasis
<b>Pathological classification</b>	
The pT categories correspond to the clinical T categories. The pN categories are based upon biopsy or surgical excision.	
<b>pN - Regional Lymph Nodes</b>	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Intranodal metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of any regional lymph node metastasis
<b>pM - Distant Metastasis</b>	
pM0	No distant metastasis
pM1	Distant metastasis
<b>G - Histopathological Grading</b>	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated/undifferentiated

## 6.2 Pathology

Squamous cell carcinoma accounts for more than 95% of cases of malignant diseases of the penis. It is not known how often SCC is preceded by premalignant lesions (Table 5) (4-7). Although SCC is the most common penile neoplasia, distinct different histological types with varying growth patterns, clinical aggressiveness and HPV association have been identified (8-10) (tables 5 and 6).

Some variants of primary penile cancer that have been described have so far not been included in the WHO classification (pseudohyperplastic carcinoma, carcinoma cuniculatum, pseudoglandular carcinoma, warty-basaloid carcinoma).

Numerous mixed forms exist such as the warty-basaloid form, which is the most common variant of mixed penile SCC (50-60%), other combinations such as usual- verrucous (hybrid), usual-warty, usual-basaloid or usual-papillary do occur, other more rare combinations as well.

Other malignant lesions of the penis unrelated to penile SCC are melanocytic lesions, mesenchymal tumours, lymphomas and secondary tumours, i.e. metastases. These are all much less common than penile SCC. Aggressive sarcoma of different types occurring in the penis have been reported. Penile metastases from other neoplasias are frequently of prostatic or colorectal origin.

**Table 5: Premalignant penile lesions (precursor lesions)**

Lesions sporadically associated with SCC of the penis
<ul style="list-style-type: none"> <li>• Cutaneous horn of the penis</li> <li>• Bowenoid papulosis of the penis</li> <li>• Lichen sclerosus (balanitis xerotica obliterans)</li> </ul>
Premalignant lesions (up to one-third transform to invasive SCC)
<ul style="list-style-type: none"> <li>• Intraepithelial neoplasia grade III</li> <li>• Giant condylomata (Buschke-Löwenstein)</li> <li>• Erythroplasia of Queyrat</li> <li>• Bowen's disease</li> <li>• Paget's disease (intradermal ADK)</li> </ul>

**Table 6: Histological subtypes of penile carcinomas, their frequency and outcome**

Subtype	frequency (% of cases)	prognosis
common SCC	48-65	depends on location, stage and grade
basaloid carcinoma	4-10	poor prognosis, frequently early inguinal nodal metastasis (11)
warty carcinoma	7-10	good prognosis, metastasis rare
verrucous carcinoma	3-8	good prognosis, no metastasis
papillary carcinoma	5-15	good prognosis, metastasis rare
sarcomatoid carcinoma	1-3	very poor prognosis, early vascular metastasis
mixed carcinoma	9-10	heterogeneous group
*pseudohyperplastic carcinoma	< 1	foreskin, related to lichen sclerosus, good prognosis, metastasis not reported
carcinoma cuniculatum	< 1	variant of verrucous carcinoma, good prognosis, metastasis not reported
pseudoglandular carcinoma	< 1	high grade carcinoma, early metastasis, poor prognosis
warty-basaloid carcinoma	9-14	poor prognosis, high metastatic potential (12) (higher than in warty, lower than in basaloid SCC)
adenosquamous carcinoma	< 1	central and peri-meatal glans, high grade carcinoma, high metastatic potential but low mortality
mucoepidermoid carcinoma	< 1	highly aggressive, poor prognosis
clear cell variant of penile carcinoma	1-2	exceedingly rare, associated with HPV, aggressive, early metastasis, poor prognosis, outcome lesion dependent, frequent lymphatic metastasis (13)

### **Gross handling**

Tissue sections determine the accuracy of histological diagnosis. Small lesions should be totally included, bigger lesions should have at least 3-4 blocks. Lymph nodes have to be totally included in order to be sure to detect micro-metastases. Surgical margins have to be completely included.

### **Pathology report**

This has to include the anatomical site of the primary tumour, the histological type/subtypes, grade, perineural invasion, depth of invasion, vascular invasion (venous/lymphatic), irregular growth and front of invasion, urethral invasion, invasion of corpus spongiosum/cavernosum and surgical margins.

### **Grading**

Tumour grade has been included into the penile cancer TNM classification because of its prognostic relevance. However, tumour grading in penile cancer has been shown to be highly observer-dependent for the Broder's classification which is no longer used as well as for the WHO grading system (14). For the recommended grading of the pTNM see table 4.

### **Pathologic prognostic factors**

Carcinomas limited to the foreskin have a better prognosis and a lower risk of regional metastasis (15). Perineural invasion and histological grade are very strong predictors of a poor prognosis and cancer-specific mortality (16).

Tumour grade is a predictor of metastatic spread but in heterogeneous tumours, grading can be problematic. Lymphatic invasion is also an independent predictor of metastasis. Venous embolism is frequently seen in advanced stages.

The following types of penile SCC have an excellent prognosis: verrucous, papillary, warty, pseudohyperplastic and carcinoma cuniculatum. These SCC variants are locally destructive, rarely metastasize and have a very low risk of cancer-related mortality. High-risk SCC variants are the basaloid, sarcomatoid, adenosquamous and poorly differentiated types. In addition to locally destructive growth, they metastasize early and mortality is high. There is an intermediate-risk group which comprises the usual SCC, mixed forms and the pleomorphic form of warty carcinomas.

Stage pT3 tumours invading the distal (glandular) urethra (seen in 25% of cases) are not associated with worse outcome (17). However, invasion of the more proximal urethra which also has to be classified as stage pT3 relates to a highly aggressive SCC with poor prognosis (for histological subtypes see table 6).

The classification of invasion of the corpus spongiosum and the corpora cavernosa into the same pT2 group is clinically problematic as these signify a very different prognosis. Rees et al. (2) reported 72 patients with pT2 tumours; local recurrence (35% vs. 17%) and mortality (30% vs. 21%) rates were higher in patients with tunica or cavernosal involvement versus glans-only invasion after a mean follow-up of 3 years (LE: 2b). The authors proposed defining T2a with spongiosum-only invasion and T2b with tunica or corpus cavernosum invasion. A retrospective analysis of the records of 513 patients treated between 1956 and 2006 also reported this prognostic difference (3).

Long-term survival in patients with T2 and T3 tumours and in patients with N1 and N2 disease (in the 1987-2002 TNM classification) does not seem to differ significantly (3) (LE: 2a).

Two nomograms which can be used to estimate prognosis in penile cancer have been developed but as usual in penile cancer are based on small numbers. Solsona et al. in a prospective validation of their nomogram suggested that pT1G1 tumours are low risk tumours regarding cancer-specific mortality, while pT2/3 G2/3 are high-risk tumours, with the others being intermediate risk. Lymph node metastases were observed in 0%, 33% and 83% of low-, intermediate- and high-risk cases, respectively (18). Similar findings were reported by Hungerhuber et al. who recommend prophylactic lymphadenectomy for high risk patients (19). Chaux et al. proposed a "prognostic index" based on findings in 193 patients which incorporates several pathological parameters such as grade, deepest anatomical level, perineural invasion and permits scoring in a ranking system which can be used to predict the likelihood of inguinal lymph node metastases and the likelihood of 5-year survival (20). Low scores confer a 95% chance of 5-year survival, intermediate scores a 65% and high scores a 45%.

### **Penile cancer and HPV**

An association between penile cancer and HPV has been demonstrated since the 1990s and this association is different for different histological subtypes of penile SCC. A high prevalence of HPV infection is found in basaloid (76%), mixed warty-basaloid (82%) and warty penile SCCs (39%). Verrucous and papillary penile SCCs are HPV-negative. The most frequently found HPV-types in penile SCC are HPV 16 (72%), HPV 6 (9%) and HPV 18 (6%).

Overall, only a third of penile SCCs display HPV infection at all and among those which are positive, multiple infections with different HPV types have been reported.

### **Molecular biology**

There are so far few data which link chromosomal abnormalities in penile SCC to biological behaviour and patient outcome (21). DNA copy number alterations found in penile carcinoma are comparable to those found in SCC of other origins. Lower copy numbers and alteration numbers in penile SCC have been linked to poorer survival. Alterations in the locus 8q24 seem to play a major role and have also been implicated in the carcinogenesis of other neoplasms such as prostate cancer (22,23). Telomerase activity has been

demonstrated in invasive penile carcinoma (24). Some authors have shown that aneuploidy changed according to tumour grade (25).

Epigenetic alterations evaluating the methylation pattern of CpG islands in *CDKN2A* have been described as well.

*CDKN2A* encodes for two tumour suppressor proteins (p16<sup>INK4A</sup> and p14<sup>ARF</sup>) which control cell growth through Rb and p53 pathways. Poetsch et al. showed that 62% of invasive SCC of the penis displayed allelic loss of p16 and 42% promoter hypermethylation. Tumours immunohistochemically negative for p16 showed hypermethylation of and/or LOH near the p16<sup>INK4A</sup> locus. In that study, p16 negativity was linked to lymph node metastasis, in another study to prognosis (26). Allelic loss of the p53 gene is a frequent event in penile SCC (42%) (27) and p53 expression has been linked to poor prognosis (28). Another element influencing lymph node metastasis is the metastasis suppressor protein KAI1/CD82; decreased expression of this protein favours lymph node metastasis (29).

### **Penile biopsy**

Often the diagnosis of penile cancer is without clinical doubt but in rare cases non-SCC penile carcinoma or inflammatory lesions may be misleading. Therefore, histological verification by biopsy should be mandatory before any local treatment is undertaken.

In cases, where definitive surgical treatment is planned, confirmatory frozen section excisional biopsy can be done before continuing with the ablative surgical procedure. In all cases where the diagnosis is clinically uncertain and/or when non-surgical treatment is planned, histological verification must be obtained before treatment.

In the management of penile cancer there is need for histological confirmation if:

- there is doubt about the exact nature of the lesion (e.g. CIS, metastasis or melanoma) and/or;
- treatment with topical agents, radiotherapy or laser surgery is planned;
- treatment of the lymph nodes is based on preoperative histological information (risk-adapted strategy).

When performing a biopsy, the size of the biopsy is important. Studies of biopsies with an average size of 0.1 cm found that there was difficulty in evaluating the extent of depth of invasion in 91% of biopsies, there was discordance between the grade at biopsy and in the final specimen in 30% of cases and that there was failure to detect cancer in 3.5% of cases (4). Also, vascular and lymphatic tumour emboli were detected in only 9-11% of cases. Thus, although a punch biopsy may be sufficient for superficial lesions, an excisional biopsy is preferable which should be deep enough to assess the degree of invasion and stage adequately.

### **Intraoperative frozen sections and surgical margins**

The aim of any surgical treatment must be the complete removal of the penile carcinoma and negative surgical margins must be achieved. The width of negative surgical margins should follow a risk-adapted strategy based on tumour grade. Negative surgical margins may be confirmed intraoperatively by frozen section (30). If surgical margins are studied following these criteria (including urethral and periurethral tissue), only 5 mm of tumour-free tissue is sufficient to consider the surgical margins to be negative (31).

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## 7. DIAGNOSIS AND STAGING

Penile cancer can be cured in over 80% of all cases but is a life-threatening disease with poor prognosis once metastatic spread has occurred. Furthermore, local treatment although potentially life-saving, can be mutilating and devastating for the psychological well-being of the patient. Therefore, the treatment of patients with penile cancer requires a careful diagnosis and adequate staging before treatment decisions can be made.

### 7.1 Primary lesion

Penile carcinoma is often a clinically obvious lesion but can be hidden under a phimosis. Physical examination of a patient with penile cancer should include palpation of the penis with a view to examining the extent of local invasion.

Ultrasound can give information about infiltration of the corpora (1,2). Magnetic resonance imaging (MRI) in combination with an artificial erection with prostaglandin E 1 can also be used for excluding tumour invasion of the corpora cavernosa if organ-preservation is planned and preoperative decisions are needed (3,4).

### 7.2 Regional lymph nodes

Careful palpation of both groins for the detection of enlarged inguinal lymph nodes must be part of the initial physical examination of patients with penile cancer.

#### 7.2.1 Non-palpable inguinal nodes

In the absence of palpable abnormalities, the likelihood of the presence of micro-metastatic disease is about 25%. However, current imaging techniques are not reliable in detecting micro-metastases.

Inguinal ultrasound (7.5 MHz) can reveal abnormal nodes with some enlargement. The longitudinal/transverse diameter ratio and the absence of the lymph node hilum have been reported to be findings with relatively high specificity (5). Conventional CT or MRI scans similarly cannot detect micrometastases reliably (6). <sup>18</sup>FDG-positron emission tomography (PET)/CT imaging does not detect lymph node metastases < 10 mm (7,8). Imaging studies are therefore not helpful in staging clinically normal inguinal regions. An exception can be patients with obesity in whom palpation is unreliable or not possible.

The further diagnostic management of patients with normal inguinal nodes should be guided by

pathological risk factors. Several series have identified lymphovascular invasion, local stage and grade as risk factors predicting the likelihood of lymphatic metastasis (9,10). Nomograms are unreliable as they cannot achieve an accuracy over 80%. Invasive lymph node staging is required in patients at intermediate- or high risk of lymphatic spread (see section 8.2).

### 7.2.2 Palpable inguinal nodes

Palpable lymph nodes are highly suspicious for the presence of lymph node metastases. Physical examination should note the number of palpable nodes on each side and whether these are fixed or mobile. Additional inguinal imaging does not alter management (see section 8) and is usually not required.

A pelvic CT scan can be performed in order to assess the pelvic lymph nodes. <sup>18</sup>FDG-PET/CT has been reported to have a high sensitivity of 88-100% with a specificity of 98-100% for confirming metastatic nodes in patients with palpable inguinal lymph nodes (8,11).

### 7.3 Distant metastases

An assessment of distant metastases should be performed in patients with positive inguinal nodes (12-14) (LE: 2b). Computed tomography of the abdomen and pelvis and a chest X-ray are recommended, a thoracic CT will be more sensitive than a chest X-ray. PET/CT has also been reported to be reliable in the identification of pelvic nodal and distant metastases in patients with positive inguinal nodes and is an option (15).

There is no established tumour marker for penile cancer. The squamous cell carcinoma antigen (SCC Ag) is increased in less than 25% of penile cancer patients. In one study, SCC Ag was not a predictor for occult metastatic disease but it was a prognostic indicator of disease-free survival in lymph-node positive patients (16).

### 7.4 Recommendations for the diagnosis and staging of penile cancer

	GR
<b>Primary tumour</b>	
Physical examination, recording morphology, extent and invasion of penile structures. MRI with artificial erection in selected cases with intended organ preserving surgery.	C
<b>Inguinal lymph nodes</b>	
Physical examination of both groins, recording number, laterality and characteristics of inguinal nodes • If nodes are not palpable, invasive lymph node staging in high-risk patients (see section 8). • If nodes are palpable, a pelvic CT may be indicated, PET/CT is an option.	C
<b>Distant metastases</b>	
In N+ patients, abdomino-pelvic CT scan and chest X-ray are required for systemic staging. PET/CT scan is an option.	C
In patients with systemic disease or with relevant symptoms, a bone scan may be indicated.	

CT = computed tomography; PET = positron emission tomography.

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## 8. TREATMENT

### 8.1 Treatment of the primary tumour

The aims of the treatment of the primary penile cancer lesion are complete tumour removal with as much organ preservation as possible while radicality of the treatment should not be compromised. A local recurrence in itself has little influence on long-term survival so that organ preservation strategies are justified (1).

There are no randomised controlled trials for any of the surgical management options of localised penile cancer, neither are there any observational studies comparing different surgical approaches or studies comparing surgical and non-surgical treatment modalities. The available studies all have one or more form of bias such as bias of selection, performance, detection, attrition, selective reporting or publication. Thus, the overall quality of the existing evidence must be regarded as low.

Penile preservation appears to be superior in functional and cosmetic outcomes and should be offered as the primary treatment modality to men with localised penile cancer. However, there are no randomized studies comparing organ-preserving and ablative treatment strategies. There are only retrospective studies with a level of evidence of 3 or less.

Histological diagnosis with local staging must be obtained in all cases, especially if non-surgical treatment modalities are considered (GR: C).

The treatment of the primary tumour and that of the regional nodes can be done as staged procedures. In both cases, it is essential to remove all malignant tissue with negative surgical margins. Patients must be counselled about all relevant treatment modalities.

There are a variety of local treatment modalities for small and localized penile cancer including excisional surgery, external beam radiotherapy, brachytherapy and laser ablation which are used to treat localized invasive disease.

#### **8.1.1 Treatment of superficial non-invasive disease (CIS)**

For penile CIS, topical chemotherapy with imiquimod or 5-FU is an effective first-line treatment. Toxicity and adverse events of these topical treatments are relatively low but the efficacy is limited. Complete responses have been reported in up to 57% of cases of CIS (2). For the reason of a high rate of persistence and/or recurrence, close and long-term surveillance of such patients is required. If topical treatment fails it should not be repeated.

Laser treatment can be used for CIS. Photodynamic control may be used in conjunction with CO<sub>2</sub> laser treatment (3).

Alternatively, total or partial glans resurfacing can be offered as a primary treatment modality for CIS and as a secondary treatment in case of treatment failure with topical chemotherapy or laser therapy. Glans resurfacing is a surgical technique which consists of complete abrasion of the glandular epithelium with covering by a split skin graft. With glans resurfacing for presumed non-invasive disease, up to 20% of patients are found to have superficial invasive disease (4).

#### **8.1.2 Treatment of invasive disease confined to the glans (category Ta/T1a)**

For small and localised invasive lesions (Ta/T1a), a penis-preserving strategy is recommended (GR: C).

Prior to conservative treatment modalities, it is mandatory to obtain histopathological diagnosis by biopsy (GR: C). All patients must be circumcised before considering conservative non-surgical treatment modalities. For tumours confined to the prepuce, radical circumcision alone may be curative, if negative surgical margins are confirmed by definitive histology.

For all surgical treatment options, the intra-operative assessment of surgical margins by frozen section is recommended (GR: C) as tumour-positive margins lead to local recurrence (5). Total removal of the glans (glansectomy) and prepuce does have the lowest recurrence rate among the treatment modalities for small penile lesions (2%) (5). Negative surgical margins are imperative when using penile-conserving treatments (GR: C) and a margin of 5 mm is considered oncologically safe (5,6).

Treatment choice should depend on tumour size, histology including stage and grade, localization especially relative to the meatus, as well as patient preference as there are no documented differences in the long term local recurrence rates between surgery, laser and radiation therapy.

##### **8.1.2.1 Results of different surgical organ-preserving treatment modalities**

Results of the different treatment modalities have been reported in retrospective cases series only. The results published are mostly reported in a very heterogeneous way so that the database for assessment is of limited quality. There have been no randomized trials on any of these treatment options.

#### **Laser therapy**

Laser ablation can be done with a Nd:YAG laser or a CO<sub>2</sub> laser (7-12), visualisation may be improved by photodynamic diagnosis.

The results of CO<sub>2</sub> laser treatment have been reported by three studies all from the same institution (7-9). Laser treatment was given in combination with radio- or chemotherapy and patients included had CIS or T1 penile cancers. Follow-up was 5 years (median) in all three studies. There is some overlap between the cohorts reported, in total 195 patients are included in these retrospective series.

No cancer-specific deaths were reported in any of these three studies. In one, an estimated cumulative risk of local recurrence at five years was given with 10% (106 patients with CIS) and 16% (78 patients with T1 tumour) (7). In all three series taken together, local recurrence ranged from 14% for CIS and T1 tumours (9) to 23% (T1 tumours) (8). The reported rate of inguinal nodal recurrence after local CO<sub>2</sub> laser treatment was 0% (0/11) (9) and 4% (2/56) (8). Secondary partial penectomy at 10 years was 3% and 10%, depending on the tumour (CIS vs T1) and whether combination treatment had been given or not (7).

The four studies on the results of Nd:YAG laser treatment (10-13) together report a total of 150 patients with a follow-up of at least 4 years. Local recurrence rates at last follow-up ranged across the four studies from 10% (3/29) (10) to 48% (21/44) (11). In one of these studies (12), recurrence-free survival rates were reported as 100%, 95% and 89% at one, two and five years. Inguinal nodal recurrence were reported in 21% (9/44) (10). Cancer-related deaths were reported in 2% (1/54) (13) and 9% of patients (4/44) (11),

respectively. Three studies from the same institution, probably including overlapping cohorts of patients, reported overall survival by censored or uncensored data which ranged from 100% at 4 years (10) and 95% (12) to 85% (14) at seven years. The rate of secondary partial penectomy after initial Nd:YAG laser treatment was reported to have been 4% (1/23) (12) and 45% (20/44) (11), respectively. Complications, urinary and sexual function outcomes were reported only by one study with 29 patients (10), which reported no complications and no change in urinary and sexual function after successful Nd:YAG laser treatment.

Other studies have reported data on a variety of laser treatments with either CO<sub>2</sub> laser, Nd:YAG laser, a combination of both, or a KTP laser (15-18), with a mean follow-up of 32-60 months and stages CIS up to T3 included. The four studies reported on a total of 138 patients.

The cancer-specific survival probability at 5 years was 95% in one study using the Kaplan-Meier method (16). This was consistent with the finding from another study in which the cancer-specific mortality rate was relatively low at 2% (1 of 44) at a mean follow-up of around 5 years (17). Local recurrence rates were 11% (5/44) (17), 19% (13/67) (16) and 26% (5/19) (18). In one study recurrence-free survival at 5 years was estimated to be 88% (16).

### ***Mohs micrographic surgery***

Mohs micrographic surgery is a technique by which histological margins are taken in a geometrical fashion around a cone of excision. This technique has not been widely used. Only two studies reported a total of 66 patients (19,20). The original description (19) consisted of 33 consecutive patients treated between 1936 and 1986 and reported on 29 patients with at least 5 years follow-up. One patient in each study received secondary penile amputation and one in each died of penile cancer. In Mohs series, 79% (23/29) were cured at 5 years (19). In the other series, 68% (17/25) were recurrence-free after a median of 37 months and 8% (2/25) had inguinal nodal recurrence and died of the disease (20). One cancer-specific death was reported in each series, local recurrence rate was 32% (8/25) in one series (20).

### ***Glans resurfacing***

Three studies have reported results of this technique (21-23) with a total of 71 patients with stages CIS or T1. Shabbir et al. report results of total and partial glans resurfacing (23). The range of the median duration of follow-up in the three studies was 21-30 months. No cancer-specific deaths were reported, the rates of local recurrence were 0% (0/10) (21) and 6% (2/33) (22) without reports of nodal recurrence. There were no reported complications in any of the three studies.

### ***Glansectomy***

Results of another fairly new technique, glansectomy, were reported by three studies (5,24,25), whereby Li et al. also reports on glans-preserving surgery (25). A total of 68 patients with a follow-up of 114 months (24) and 63 months (25) were included. One patient (8%) had a local recurrence (24) and 6 patients (9%) had inguinal nodal metastases. There were no cancer-specific deaths reported. Another group reported 87 patients with 6 local (6.9%), 11 regional (12.6%) and 2 systemic recurrences (2.3%) during a mean follow-up of 42 months (5).

### ***Partial penectomy***

Results of partial penectomy were reported in eight rather heterogeneous studies (25-32) amounting to 184 included patients. Tumour stages included were T1-T3. Reported follow-up ranged from 40-194 months. 0-27% of patients were reported to have died of penile cancer, local recurrence rates ranged from 4-50% of patients. The 5-year overall survival rate was reported by three studies and ranged from 59 to 89% (28,29,32).

#### ***8.1.2.2 Summary of results of surgical techniques***

There is not sufficient evidence to suggest a difference regarding outcomes of different penis-sparing strategies which in general appear to show good oncological results. Although conservative surgery may improve quality of life, the risk of local recurrence is higher than after radical surgery e.g. partial penectomy (5-12% vs. 5%). In a large cohort of patients undergoing conservative surgery, isolated local recurrence was reported to be 8.9%, with a 5-year disease-specific survival rate of 91.7%. Tumour grade, stage and lymphovascular invasion appear to be predictors of local recurrence.

#### ***8.1.2.3 Results of radiotherapy for T1 and T2 disease***

Radiation treatment of the primary tumour is an alternative organ-preserving approach with good results in selected patients with T1-2 lesions < 4 cm in diameter (33-38) (LE: 2b). Radiotherapy may be given as external radiotherapy with a minimum dose of 60 Gy combined with a brachytherapy boost or brachytherapy on its own (34,36). The reported results of radiotherapy are best with penile brachytherapy with local control rates ranging from 70-90% (34,36). The American Brachytherapy Society and the Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement

for penile brachytherapy report good tumour control rates, acceptable morbidity and functional organ preservation for penile brachytherapy for T1 and T2 penile cancers (39). The rates of local recurrence after radiotherapy are higher than after partial penectomy. With local failure after radiotherapy, salvage surgery can achieve local control (40). Patients with lesions > 4 cm are not candidates for brachytherapy.

With radiotherapy, the following complications are common: urethral stenosis (20-35%), glans necrosis (10-20%) and late fibrosis of the corpora cavernosa (41) (LE: 3). With brachytherapy, meatal stenosis is a common complication occurring in > 40% of cases.

**Table 7: Summary of reported complications and oncological outcomes of local treatments\***

treatment	complications	local recurrence	nodal recurrence	cancer-specific deaths	references
Nd:YAG laser	none reported	10-48%	21%	2-9%	10-13
CO <sub>2</sub> -laser	bleeding, meatal stenosis (both < 1%)	14-23%	2-4%	none reported	7-9
Lasers (unspecified)	bleeding (8%), local infection 2%	11-26%	2%	2-3%	15-18
Moh's micrographic surgery	local infection 3%, meatal stenosis 6%	32%	8%	3-4%	19,20
Glans resurfacing	none reported	4-6%	not reported	not reported	21-23
Glansectomy	none reported	8%	9%	none reported	24,25
Partial penectomy	not reported	4-13%	14-19%	11-27%	28-32
Brachytherapy	meatal stenosis > 40%	10-30%	not reported	not reported	33,34,36
Radiotherapy	urethral stenosis 20-35%, glans necrosis 10-20%	not reported	not reported	not reported	35,38,39,40,41

\*The ranges given report the lowest and highest number of occurrences reported in the different series, respectively.

### **Summary of treatment recommendations for non-invasive and localized superficially invasive penile cancer**

#### **8.1.3 Treatment of invasive disease confined to the corpus spongiosum/glans (Category T2)**

Total glansectomy, with or without resurfacing of the corporeal heads, is recommended (42) (LE: 3; GR: C). Radiotherapy is an option (see below, section 8.1.7). Partial amputation should be considered in patients who are unfit for reconstructive surgery (40) (GR: C).

#### **8.1.4 Treatment of disease invading the corpora cavernosa and/or urethra (category T2/T3)**

Partial amputation with a tumour-free margin with reconstruction is standard treatment (37) (GR: C). A surgical margin of 5 mm is considered safe (5,6) but patients should remain under close follow-up. Radiotherapy is an option.

#### **8.1.5 Treatment of locally advanced disease invading adjacent structures (category T3/T4)**

These are relatively rare (Europe 5%, Brazil 13%) (6). Total penectomy with perineal urethrostomy is standard surgical treatment for T3 tumours (6) (GR: C).

In more advanced disease (T4) neoadjuvant chemotherapy may be advisable, followed by surgery in responders as in the treatment of patients with fixed enlarged inguinal nodes (see section 8.2.4) (GR: C). Otherwise, adjuvant chemotherapy or palliative radiotherapy may be an option (GR: C; see sections 8.2.4 and 8.1.7).

#### **8.1.6 Local recurrence after organ-conserving surgery**

A second organ-conserving procedure can be performed if there is no corpus cavernosum invasion (6,37,43,44) (GR: C). For large or high stage recurrence, partial or total amputation will be required (41) (GR: C). In patients undergoing total/subtotal amputation a total phallic reconstruction may be offered (45,46).

### 8.1.7 Recommendations for stage-dependent local treatment of penile carcinoma.

Primary tumour	Organ-preserving treatment is to be considered whenever possible	LE	GR
Tis	Topical treatment with 5-fluorouracil or imiquimod for superficial lesions with or without photodynamic control.	3	C
	Laser ablation with CO <sub>2</sub> or Nd:YAG laser.		
	Glans resurfacing.		
Ta, T1a (G1, G2)	Wide local excision with circumcision CO <sub>2</sub> or Nd:YAG laser surgery with circumcision.	3	C
	Laser ablation with CO <sub>2</sub> or Nd:YAG laser.		
	Glans resurfacing.		
	Glansectomy with reconstructive surgery, with or without skin grafting.	3	C
	Radiotherapy by external beam or as brachytherapy for lesions < 4 cm.		
T1b (G3) and T2 confined to the glans	Wide local excision plus reconstructive surgery, with or without skin grafting.	3	C
	Laser ablation with circumcision.		
	Glansectomy with circumcision, with reconstruction.		
	Radiotherapy by external beam or brachytherapy for lesions < 4 cm in diameter.		
T2 with invasion of the corpora cavernosa	Partial amputation and reconstruction.	3	C
	Radiotherapy by external beam or brachytherapy for lesions < 4 cm in diameter.		
T3 with invasion of the urethra	Partial penectomy or total penectomy with perineal urethrostomy.	3	C
T4 with invasion of other adjacent structures	Neoadjuvant chemotherapy followed by surgery in responders. Alternative: palliative external beam radiation.	3	C
Local recurrence after conservative treatment	Salvage surgery with penis-sparing treatment in small recurrences or partial amputation.	3	C
	Large or high stage recurrence: partial or total amputation.	3	C

CO<sub>2</sub>= carbon dioxide; Nd:YAG = neodymium:yttrium-aluminium-garnet.

### 8.1.8 References

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## 8.2 Management of regional lymph nodes

The development of lymphatic metastases in penile cancer follows some anatomic rules. The inguinal and the pelvic lymph nodes are the regional drainage system of the penis. The superficial and deep inguinal lymph nodes are thereby the first regional nodal group reached by lymphatic metastatic spread. Spread to the inguinal lymph nodes can be uni- or bilateral from any primary penile cancer (1).

A single photon emission computed tomography (SPECT) study in penile cancer patients reported that all inguinal sentinel nodes were located in the superior and central inguinal zones, with most found in the medial superior zone (2). No lymphatic drainage was observed from the penis to the two inferior regions of the groin, and no direct drainage to the pelvic nodes was visualized. These findings confirm earlier studies (3,4).

The second regional lymph node groups are the ipsilateral pelvic lymph nodes. Pelvic nodal disease does not seem to occur without ipsilateral inguinal lymph node metastasis and cross-over metastatic spread from one inguinal side to the other pelvic side has never been reported in penile cancer. Further metastatic lymph node spread from the pelvic nodes to paraaortic and paracaval nodes is outside the regional lymph node drainage system of the penis and is therefore classified as systemic metastatic disease.

The management of regional lymph nodes is decisive for long-term patient survival. Cure can be achieved in metastatic disease confined to the regional lymph nodes. Lymphadenectomy is the treatment of choice for patients with inguinal lymph node metastases (GR: B) but multimodal treatment combining surgery and polychemotherapy is often indicated.

Management of the regional lymph nodes should be stage-dependent. In clinically node-negative patients (cN0), there is a definite risk of micro-metastatic lymph node involvement in about 25% of cases which is related to local tumour stage and grade. In clinically positive lymph nodes (cN1/cN2), metastatic disease is highly likely and no time should be wasted on antibiotic treatment before surgical treatment. With enlarged fixed inguinal lymph nodes (cN3), multimodal treatment by chemotherapy and surgery is indicated. Capsular penetration and extranodal extension in lymph node metastasis even if present in only one node carries a high risk of progression and is classified as pN3 which also requires multimodal treatment.

### 8.2.1 Management of patients with clinically normal inguinal lymph nodes (cN0)

Risk stratification for the management of patients with clinically normal lymph nodes depends on stage, grade and the presence or absence of lymphovascular invasion in the primary tumour (5). Tumours with low risk of metastatic disease are those with superficial penile cancer (pTa, pTis) and low grade. pT1 tumours represent a heterogeneous risk group: they can be considered low-risk if they are well differentiated (pT1G1), otherwise they represent an intermediate-risk group (pT1G2) (6) or must be considered high risk (pT1G3) together with all higher stages.

Several studies have shown that early inguinal lymphadenectomy in clinically node-negative patients is far superior concerning long-term patient survival compared to therapeutic lymphadenectomy when regional nodal recurrence occurs (7,8). One prospective study comparing bilateral lymphadenectomy, radiotherapy and surveillance in clinically node-negative patients reported that 5-year overall survival was significantly better with inguinal lymphadenectomy compared to immediate inguinal radiotherapy or that observed with a surveillance strategy (74% vs 66% and 63%, respectively) (9).

#### 8.2.1.1 Surveillance

Surveillance for the management of regional lymph nodes carries the risk of regional recurrence arising later from existing micrometastatic disease. Patient survival is over 90% with early lymphadenectomy and below 40% with lymphadenectomy for regional recurrence later (10,11). This definite risk must be taken into account when considering surveillance and the patient should be informed about this. Surveillance can only be recommended in patients with pTis and pTa penile cancer, and with the appropriate caveats in pT1G1 tumours (10,11,12). A prerequisite for surveillance is good patient information and compliance.

#### 8.2.1.2 Invasive nodal staging

Staging of the inguinal lymph nodes in cN0 penile cancer requires an invasive procedure since all imaging techniques (ultrasound, CT, MRI) are unreliable in excluding small and micro-metastatic lymph node involvement. While CT criteria other than size have been defined for the retrospective detection of lymph node metastases, these have not been validated prospectively (13). Nomograms are unreliable as their ability to predict the likelihood of lymph node involvement does not exceed 80% (10,14,15) (LE: 2b). Fine needle aspiration cytology does not reliably exclude micrometastatic disease (low specificity) and is not recommended. Therefore, the pathological risk factors have to be used to stratify node-negative patients (8,16) (LE: 2b).

There are two invasive diagnostic procedures whose efficacy is evidence-based: modified inguinal

lymphadenectomy and dynamic sentinel-node biopsy. Both are at present standard approaches for the invasive diagnosis of inguinal lymph nodes in node-negative patients.

Modified inguinal lymphadenectomy (mILND) is the standard surgical approach in this situation and defines a limited template whereby the superficial inguinal lymph nodes from at least the central and both superior Daseler's zones are removed bilaterally (1,17) (LE: 3) and the greater saphenous vein is left in place.

Dynamic sentinel node biopsy (DSNB) is a technique based on the assumption that primary lymphatic drainage from a penile cancer goes to only one inguinal lymph node on each side which may however be in different locations based on individual anatomy. Tc99m nanocolloid is injected around the penile cancer site the day before surgery and, additionally, patent blue can be injected before surgery. A  $\gamma$ -ray detection probe is used intraoperatively for the detection of the sentinel node which is possible in 97% of cases. The protocol has been standardized for routine use and the learning curve is relatively short (18) (GR: B). Some groups have reported a high sensitivity of the DSNB technique of 90-94% (18,19) (LE: 2b). In a pooled meta-analysis of 18 studies the pooled sensitivity was 88% and was improved to 90% with the additional use of patent blue (20).

With both methods of invasive regional lymph node staging in cN0 patients, missing existing micro-metastatic disease will lead to later regional recurrence with a dramatic deterioration in long-term survival (7). This false-negative rate has been reported to be as high as 12-15% for the DSNB technique even in experienced centres (11,12). The false-negative rate of mILND is not known. The risk of a false-negative result and its implications for the prognosis should be explained to the patient before deciding on which method to use.

If lymph node metastasis is found with either method, an ipsilateral radical inguinal lymphadenectomy is indicated.

### **8.2.2 Management of patients with palpable inguinal nodes (cN1/cN2)**

With uni- or bilateral palpable inguinal lymph nodes (cN1/cN2), the likelihood is very high that metastatic lymph node disease is present. Therefore, the old clinical advice that antibiotic treatment should be given for several weeks because such lymph node enlargement might be related to infection no longer holds true. Instead, no time should be wasted with such unnecessary delays and appropriate oncological diagnosis and treatment should be undertaken before further metastatic spread occurs. In clinically doubtful cases, ultrasound-guided fine needle aspiration cytology can be an option (21).

With palpably enlarged inguinal lymph nodes, additional staging investigations are not useful. Imaging by ultrasound, CT or MRI do not provide additional information about the inguinal lymph nodes except in very obese patients. However, CT or MRI can provide information about the pelvic nodal status. 18F-FDG-PET/CT can identify additional metastases in lymph-node positive patients (22). Dynamic sentinel node biopsy is not reliable in patients with palpably enlarged and suspicious inguinal lymph nodes and should not be used (23) (LE: 3).

#### **8.2.2.1 Radical inguinal lymphadenectomy**

In clinically lymph-node positive patients, surgical staging by inguinal lymphadenectomy is indicated.

Intraoperative frozen sections may be used to confirm lymph node metastasis in which case an ipsilateral radical inguinal lymphadenectomy is required (7,8).

Radical inguinal lymphadenectomy carries a significant morbidity related to problems of lymph drainage from the legs and wound healing. While morbidity can be as high as 50% (24) with increased BMI and Sartorius muscle transposition being significant risk factors for complications, other centres have reported ranges around 25% in recent series (25,26) (LE: 2b). Therapeutic radical inguinal lymphadenectomy can be life-saving but it may be underused for fear of associated morbidity (27). Lymph-node density is a prognostic factor (28).

The surgical technique should be meticulous regarding tissue handling and should take into account the fact that the wall of lymphatic vessels does not contain smooth muscle. Therefore, lymphatic vessels cannot be closed by electric coagulation. Instead, ligation or possibly clips should be used liberally (16,29). Additional measures counteracting postoperative lymphatic stasis and leakage such as stockings, bandaging of legs, inguinal pressure dressings or vacuum suction (30) as well as prophylactic antibiotics can reduce postoperative morbidity. In advanced cases, reconstructive surgery is often necessary for primary wound closure.

The most commonly reported complications in recent series were wound infections (1.2-1.4%), skin necrosis (0.6-4.7%) lymphedema (5-13.9%) and lymphocele formation (2.1-4%) (25,26).

The feasibility of performing laparoscopic and robot-assisted inguinal lymphadenectomy has been reported by several groups. Whether this provides any advantage is unclear (31-34).

#### **8.2.2.2 Pelvic lymphadenectomy**

Patients with positive pelvic nodes have a worse prognosis compared to patients with only inguinal nodal metastasis (5-year CSS 71.0% vs. 33.2%) (35). In the same study with 142 node-positive patients, significant

risk factors for pelvic nodal metastasis were the number of positive inguinal nodes (cut-off 3), the diameter of inguinal metastatic nodes (cut-off 30 mm) and the presence of extra nodal extension whereby the proportion of pelvic nodal metastases was 0% in cases without any of these risk factors and 57.1% when all three risk factors were present (35).

If two or more positive lymph nodes or one node with extracapsular extension (pN3) are found on one side, an ipsilateral pelvic lymphadenectomy is indicated. There is no direct lymphatic drainage from penile tumours to the pelvic lymph nodes (2), therefore pelvic LAD is not indicated if there is no involvement of inguinal nodes on that side. This recommendation is based on a study in which the rate of positive pelvic nodes was found to be 23% in cases with more than two positive inguinal nodes and 56% in those with more than three positive inguinal nodes, or if there was extracapsular involvement in at least one inguinal node (8,36) (LE: 2b).

Pelvic lymphadenectomy may be performed simultaneously or as a secondary procedure following definitive histology. If bilateral pelvic dissection is indicated, it can be performed through a midline suprapubic extraperitoneal incision. It is important to avoid unnecessary delay if these procedures are indicated (37).

#### 8.2.2.3 *Adjuvant treatment*

In patients with pN2/pN3 disease, adjuvant chemotherapy is recommended (38) (GR: C) (see section 8.3.1). This recommendation is based on one retrospective study in which a long-term disease-free survival of 84% was reported for node-positive patients with adjuvant chemotherapy after radical lymph node surgery compared to historical controls without chemotherapy after lymphadenectomy with only 39% long-term disease-free survival (38).

Adjuvant radiotherapy has been used after inguinal lymphadenectomy. The published evidence for this is very limited and it is not generally recommended (see section 8.2.5). There have been no reported results of adjuvant radio-chemotherapy in this situation.

#### 8.2.3 **Management of patients with fixed inguinal nodes (cN3)**

The presence of metastatic disease in these cases is beyond doubt. Additional diagnostic measures do not alter the immediate management but staging by thoracic, abdominal and pelvic CT scan is indicated in order to assess the presence of further pelvic nodal disease and systemic metastatic disease. In clinically unequivocal cases, histological verification by biopsy is not required. In rare cases with reasonable doubt, an excisional or core needle biopsy may be done.

These patients have a poor prognosis and are unlikely to be cured by surgery alone. Upfront surgery is not generally recommended (GR: B) as this is non-curative and also usually quite destructive. Multimodal treatment with neoadjuvant chemotherapy followed by radical lymphadenectomy in clinically responsive cases is recommended (39–41). Responders to neoadjuvant chemotherapy with post-chemotherapy surgery have been reported to achieve long-term survival in 37% of cases (39). In some cases, there may be individualized reasons for upfront surgery followed by adjuvant treatment.

#### 8.2.4 **Management of lymph node recurrence**

Patients with regional recurrence after surveillance should be treated in the same way as patients with primary cN1 or cN2 disease (see section 8.2.2). Patients with regional recurrence following negative invasive staging by DSNB or modified inguinal lymphadenectomy already have a disordered inguinal lymphatic drainage anatomy and must be considered at a high risk of irregular metastatic progression. Patients with inguinal nodal recurrence after therapeutic radical inguinal lymphadenectomy have been reported to have a 5-year cancer-specific survival of 16% (42).

There is no evidence for the best management in such cases but multimodal treatment with neoadjuvant and/or adjuvant chemotherapy after radical lymph node surgery is advised.

#### 8.2.5 **The role of radiotherapy for the treatment of lymph node disease**

The use of radiotherapy for nodal disease varies in different European countries and seems to follow tradition and single institution policies rather than being evidence-based. Although radiotherapy is widely used in some countries in the management of regional lymph node metastasis in penile cancer, there is hardly any published evidence on its role.

Neither neoadjuvant nor adjuvant radiotherapy has been reported to improve oncological outcome in node-positive penile cancer (43). One prospective trial comparing inguinal radiotherapy with inguinal node-dissection reported superior results for surgery (9). Franks et al. reported poor long-term survival in patients with adjuvant inguinal and pelvic radiotherapy (44). Adjuvant chemotherapy has been reported to be far superior to adjuvant radiotherapy after radical inguinal lymphadenectomy in node-positive patients in one retrospective series (38). In an analysis of the National Cancer Institute Surveillance, Epidemiology and End

Results (SEER) Program database, treatment results of 2458 penile cancer patients treated either by surgery alone or surgery combined with EBRT were analysed. Multivariate analysis showed that the addition of adjuvant radiotherapy “had neither a harmful nor a beneficial effect on CSS” (45).

Due to the lack of evidence, radiotherapy in the treatment of lymph node disease in penile cancer is not generally recommended. Prophylactic radiotherapy for cN0 disease is not indicated. Adjuvant inguinal radiotherapy may be considered as an option in selected patients with extracapsular nodal extension (cN3) or as a palliative treatment for surgically irresectable disease.

### 8.2.6 Recommendations for treatment strategies for nodal metastases

Regional lymph nodes	Management of regional lymph nodes is fundamental in the treatment of penile cancer	LE	GR
No palpable inguinal nodes (cN0)	Tis, Ta G1, T1G1: surveillance.	2a	B
	> T1G2: invasive lymph node staging by bilateral modified inguinal lymphadenectomy or DSNB.	2a	B
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.		
Fixed inguinal lymph nodes (cN3)	Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders.		
Pelvic lymphadenectomy	Ipsilateral pelvic lymphadenectomy is indicated if two or more inguinal nodes are involved on one side (pN2) and in extracapsular nodal metastasis (pN3).	2a	B
Adjuvant chemotherapy	Indicated in pN2/pN3 patients after radical lymphadenectomy	2b	B
Radiotherapy	Radiotherapy is not indicated for the treatment of nodal disease in penile cancer.		

DSNB = dynamic sentinel node biopsy.

### 8.2.7 References

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### 8.3 Chemotherapy

#### 8.3.1 **Adjuvant chemotherapy in node-positive patients after radical inguinal lymphadenectomy**

Multimodal treatment can improve patient outcome in many tumour entities. Adjuvant chemotherapy after resection of nodal metastases in penile carcinoma has been reported in a few small and heterogeneous series (1-5). Comparing different small scale clinical studies is fraught with difficulties.

The value of adjuvant chemotherapy after radical inguinal lymphadenectomy in node-positive penile cancer was demonstrated by an Italian group who reported long-term disease-free survival (DFS) of 84% in 25 consecutive patients treated with 12 adjuvant weekly courses of vincristine, bleomycin, and methotrexate (VBM) during the period 1979-1990 and compared this to a historical control group of 38 consecutive node-positive patients with radical lymphadenectomy (with or without adjuvant inguinal radiotherapy) who had achieved a DFS rate of only 39% (2).

This group has also published results of a chemotherapy regimen adjuvant to radical lymphadenectomy in stage pN2-3 patients receiving three courses of cisplatin and 5-FU which they had been using since 1991 with lower toxicity and even better results compared to VBM (4) (LE: 2b). The same group has been using an adjuvant taxane-based regimen since 2004 (cisplatin, 5FU plus paclitaxel or docetaxel (TPF)) in 19 node-positive patients receiving 3-4 cycles of TPF after resection of pN2-3 disease (5). Of those patients, 52.6% were disease-free after a median follow up of 42 months and tolerability was good. Results of adjuvant treatment with paclitaxel and cisplatin also improved outcome (6).

The use of adjuvant chemotherapy is recommended, in particular when the administration of the triple combination chemotherapy is feasible, and curative treatment is aimed for (LE: 2b).

No data for the adjuvant chemotherapeutic treatment of penile carcinoma in stage pN1 are available. The administration of an adjuvant treatment in pN1 disease is therefore recommended only in clinical trials.

#### 8.3.2 **Neoadjuvant chemotherapy in patients with fixed or relapsed inguinal nodes**

Bulky inguinal lymph node enlargement (cN3) signifies extensive lymphatic metastatic disease and therefore primary lymph node surgery is not generally recommended (GR: B), as complete surgical resection will be unlikely and therefore only a small portion of these patients will benefit from surgery as a monotherapy.

Neoadjuvant chemotherapy before inguinal lymph node surgery is an attractive treatment paradigm because it allows for early treatment of the likely systemic disease as well as down-staging of the inguinal lymph node disease. In cases with good clinical response, complete surgical treatment becomes feasible. However, there are very limited data available on this treatment modality.

Small retrospective studies of 5-20 patients have reported bleomycin-vincristine-methotrexate (BVM) and bleomycin-methotrexate-cisplatin (BMP) (7-9). Despite initially promising results, unacceptable toxicity with treatment-related mortality due to bleomycin and only modest results were reported with this regimen. In a confirmatory BMP-trial of the Southwest Oncology Group similar results with modest clinical efficacy coupled with high toxicity were reported for the BMP regimen in penile cancer (10).

Cisplatin/5FU (PF) chemotherapy has been reported with a response rate of 25-50% and a more acceptable tolerability (11,12). Leijte et al. reported 20 patients treated with five different neoadjuvant chemotherapy regimens, however, over a period of over 30 years (13). Responders underwent post-chemotherapy surgery and then achieved long-term survival in 37%. The EORTC study 30992 included 26 patients with locally advanced or metastatic disease who received irinotecan and cisplatin chemotherapy. This study did not meet its primary endpoint (response-rate) but pathologic complete remissions were reported in 3 cases (14).

A phase 2 trial evaluated the administration of 4 cycles of neoadjuvant paclitaxel, cisplatin, and ifosfamide (TIP) and an objective response was reported in half of the 30 patients, including 3 pathological complete responses (pCR), which was a marginally significant predictor of survival. The estimated median time to progression (TTP) in this study was 8.1 months and median overall survival was 17.1 months (15) (LE: 2a).

Based on histological and other similarities of penile SCC with head & neck SCC, it may be assumed that

clinical responses to systemic treatment might be similar. Therefore, chemotherapy regimens with efficacy in head & neck SCC were evaluated for penile cancer. Thus, some groups have introduced taxanes into penile cancer chemotherapy. The combination of cisplatin and 5-FU coupled with a taxane has been used in the neoadjuvant as well as an adjuvant setting (5). Overall, an objective response rate of 44% in 28 patients treated neoadjuvantly including 14% pCR (LE: 2b) has been reported.

Similarly, a Cancer Research UK phase 2 trial with TPF (using only docetaxel) reported an objective response of 38.5% in 29 locally advanced or metastatic patients, a rate not meeting the primary endpoint. However, the treatment was characterized by significant toxicity (16) (LE: 2a).

Taken together, these results support the use of neoadjuvant chemotherapy for patients with fixed, unresectable nodal disease, particularly with a triple combination including cisplatin and a taxane, whenever feasible (LE: 2a; GR: B).

There are hardly any data concerning radiochemotherapy together with lymph-node surgery in penile cancer. The existing literature is very old and refers to very few patients or case reports only. Radiochemotherapy is therefore not recommended except in clinical trials (17).

### 8.3.3 **Palliative chemotherapy in advanced and relapsed disease**

A recent retrospective study of individual patient data of 140 men with advanced penile SCC reported that the presence of visceral metastases and an ECOG-Performance status  $\geq 1$  were independent prognostic factors, and that patients receiving cisplatin-based regimens had better outcomes than those who received non-cisplatin based regimens after adjusting for prognostic factors (18) (LE: 3).

In clinical practice, however, there is substantial variability of first-line chemotherapy regimens used. Before the introduction of taxanes, the data reported are limited by small numbers, the heterogeneity of patients included and the retrospective nature of the studies (except for the EORTC trial (14)) and this limits the interpretation and comparability of the reported results. Initial response rates ranged from 25 to 100% across the series, with, however, very few sustained responses and very few long-term survivors. It seems that the introduction of taxanes into penile cancer chemotherapy has enhanced the activity and efficacy of the regimens used (6-16,19).

There is virtually no data on second-line chemotherapy in penile cancer. One report using second-line paclitaxel monotherapy reported an initial response rate under 30% which therefore may be a reasonable option. However, no patient survived (20) (LE: 2a; GR: B). Anecdotally, a benefit has been observed by combining cisplatin with gemcitabine (21) (LE: 4).

### 8.3.4 **Intraarterial chemotherapy**

Clinical responses have been reported with the use of intraarterial chemotherapy in locally advanced cases with the use of several agents, especially cisplatin and gemcitabine in small case series (22-25). Apart from limited clinical response there is no further evidence that outcome is significantly improved.

### 8.3.5 **Targeted therapy**

Targeted drugs have been used in some cases as second-line treatment. Based on the observation that epidermal growth factor receptor (EGFR) is almost invariably expressed in penile SCC (22,26) and again assuming similarities with head & neck SCC, anti-EGFR targeted monotherapy has been investigated in pilot trials (23,24). Some activity, particularly with the use of the anti-EGFR monoclonal antibodies panitumumab and cetuximab, has been reported but results are not yet beyond the proof-of-principle stage and further clinical investigations will be needed (LE: 4). Some activity of tyrosine kinase inhibitors has been reported as well (25). These targeted drugs could be considered as single-agent treatment in refractory cases.

### 8.3.6 **Recommendations for chemotherapy in penile cancer patients**

	LE	GR
Adjuvant chemotherapy (3-4 cycles of TPF) is an option for patients with pN2-3 tumours (5).	2b	C
Neoadjuvant chemotherapy (4 cycles of a cisplatin and taxane-based regimen) followed by radical surgery is recommended in patients with non-resectable or recurrent lymph node metastases (5,14).	2a	B
Chemotherapy for systemic disease is an option in patients with limited metastatic load.	3	C

*TPF = cisplatin, 5FU plus paclitaxel or docetaxel.*

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## 9. FOLLOW-UP

Follow-up after curative treatment in penile carcinoma as in any malignant disease is important for two reasons:

- early detection of recurrence allows for potentially curative treatment. Local recurrence does not significantly reduce long-term survival if successfully treated while inguinal nodal recurrence leads to a drastic reduction in the probability of long-term disease-specific survival.
- the detection and management of treatment-related complications.

Local recurrence and regional nodal recurrence most frequently occur within two years of primary treatment. The follow-up interval and strategies for patients with penile cancer are directed by the initial treatment of the primary lesion and regional lymph nodes. In a multicentre study (1), during the first two years 74.3% of all recurrences, 66.4% of local recurrences, 86.1% of regional recurrences and 100% of distant recurrences were detected. In the same study, 92.2% of all recurrences occurred within the first 5 years and all recurrences seen after 5 years were local recurrences or new primary lesions (1).

Therefore, an intensive follow-up regimen during the first 2 years is rational, with less intensive follow-up needed thereafter for a minimum of 5 years. Generally, follow-up should continue thereafter but may be omitted in well-educated and motivated patients who reliably continue to carry out regular self-examination (1).

### 9.1 When and how to follow-up

In patients with negative inguinal nodes after local treatment, follow-up should include physical examination of the penis and the groins for the detection of local and/or regional recurrence. The value of additional imaging has not been proven.

Follow-up should also be dependent on the primary treatment modality that was used. After laser ablation or topical chemotherapy, histology may need to be obtained from the glans to ascertain a disease-free status.

After potentially curative treatment for inguinal nodal metastases, imaging by CT or MRI scanning

for the detection of systemic disease is advised at three-monthly intervals during the first two years as these patients may benefit from chemotherapy.

Despite the fact that late local recurrences occur and are well documented, it is reasonable to discontinue regular follow-up after 5 years, provided the patient will report local changes immediately (2). This approach is advisable because the likelihood of life-threatening regional and distant metastases becomes very low after 5 years. In patients who are unlikely to self-examine, long-term follow-up may be necessary.

## 9.2 Recurrence of the primary tumour

Local recurrence is more likely with all types of local organ-preserving treatment, i.e. after local excision, laser treatment, brachytherapy and associated therapies but has little influence on disease-specific survival, in contrast to regional recurrence (1,3). Local recurrence has been reported to occur during the first two years in up to 27% of patients treated with penis-preserving modalities (4). After partial penectomy, the risk of local recurrence is lower, about 4-5% (1,3,4).

Local recurrence is easily detected by careful self-examination or physical examination. Patient education is therefore an important aspect of follow-up. The patient should be urged to visit a specialist if any changes are seen.

## 9.3 Regional recurrence

Follow-up after treatment of regional nodal disease should be stringent during the first two years as most regional recurrences occur within that time period irrespective of whether a surveillance strategy, a sentinel-node based management or modified inguinal lymphadenectomy has been used. Regional recurrence can also occur later, however rarely, so that continuation of close follow-up in these patients is nevertheless advisable. Regional recurrence can show up unexpectedly during follow-up and again self-examination by the patient is very important (5).

The highest rate of regional recurrence (9%) occurs in patients managed by a surveillance strategy for the regional lymph nodes, the lowest in patients who underwent invasive nodal staging by modified inguinal lymphadenectomy or DSNB and had negative nodes at the time (2.3%).

The use of ultrasound and fine needle aspiration cytology (FNAC) in case of suspicious findings has been reported to improve early detection of regional recurrence (5,6,7). There are no data indicating that CT or MRI use for follow-up of regional nodes is routinely advisable.

Patients who had surgical treatment for lymph node metastases without adjuvant treatment have an increased risk of regional recurrence of 19% (1). Regional recurrence requires timely treatment by radical inguinal lymphadenectomy and adjuvant therapy (see Chapter 8).

## 9.4 Recommendations for follow-up in penile cancer

	Interval of follow-up		Examinations and investigations	Minimum duration of follow-up	GR
	Years 1-2	Years 3-5			
<i>Recommendations for follow-up of the primary tumour</i>					
Penile preserving treatment	3 months	6 months	Regular physician or self-examination Repeat biopsy after topical or laser treatment for CIS.	5 years	C
Amputation	3 months	1 year	Regular physician or self-examination	5 years	C
<i>Recommendations for follow-up of the inguinal lymph nodes</i>					
Surveillance	3 months	6 months	Regular physician or self-examination	5 years	C
pN0 at initial treatment	3 months	1 year	Regular physician or self-examination. Ultrasound with FNAB optional.	5 years	C
pN+ at initial treatment	3 months	6 months	Regular physician or self-examination Ultrasound with FNAC optional, CT/MRI optional.	5 years	C

*CIS = carcinoma in situ; CT = computed tomography; FNAB = fine-needle aspiration biopsy; FNAC = fine-needle aspiration cytology; MRI = magnetic resonance imaging.*

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## 10. QUALITY OF LIFE

### 10.1 Consequences after penile cancer treatment

In patients with long-term survival after penile cancer treatment, sexual dysfunction, voiding problems and cosmetic penile appearance must be recognized as potentially negative treatment consequences that affect quality of life (1). Data available on the sexual function and QoL after treatment for penile cancer are sparse and studies are limited by their retrospective nature, lack of control groups and the use of non-validated questionnaires.

#### 10.1.1 *Sexual activity and quality of life after laser treatment*

A retrospective structured interview-based Swedish study after laser treatment for penile CIS (2) in 58/67 surviving patients with a mean age of 63 years of whom 46 participated, reported a marked decrease in some sexual practices, such as manual stimulation, caressing and fellatio but a general satisfaction with life overall and with other domains of life including their sex life similar to that of the general Swedish population. In a large study on CO<sub>2</sub> laser treatment of penile cancer in 224 patients, no patient reported problems with erectile capability or sexual function following treatment (3). In another study (4), no sexual dysfunction occurred in the 19 patients treated.

#### 10.1.2 *Sexual activity after glans resurfacing*

In one study with 10 patients (5), 7/10 completed questionnaires (International Index of Erectile Function [IIEF-5] and a non-validated 9-item questionnaire) at their 6-month follow-up visit. Median IIEF-5 score was 24, indicating no erectile dysfunction. All patients who were sexually active before treatment were active again within 3 to 5 months after treatment. According to the (non-validated) questionnaire, all 7 patients stated that the sensation at the tip of their penis was either no different or better after surgery, that they had erections within 2 to 3 weeks of surgery, 6/7 patients had had sexual intercourse within 3 months of surgery and 5/7 patients felt that their sex life had improved. Overall patient satisfaction was high.

#### 10.1.3 *Sexual activity after glansectomy*

Two studies reported sexual function after glansectomy (6,7). In one study with unclear methodology (6), 54/68 patients (79%) did not report any difference in spontaneous erection, rigidity and penetrative capacity before and after surgery, while orgasm recovery was reported by 51/68 patients (75%) patients. The other study

(7) reported that all 12 patients had returned to 'normal' sexual activity one month after surgery. The mean International Index of Erectile Function (IIEF) scores measured at one month after surgery indicated that, on average, patients returned to the level of sexual function and satisfaction they had reported before surgery.

#### 10.1.4 **Sexual function after partial penectomy**

Sexual function after partial penectomy was reported by three studies (8-10). The Brazilian interview-based study including the IIEF questionnaire with 18 patients with a mean age of 52 years (8) reported that 55.6% of patients had erectile function that allowed sexual intercourse. In patients that did not resume sexual intercourse after partial penectomy, the reasons given were ashamedness because of a small penis and absence of the glans in 50% of cases as well as surgical complications in 33.3% of cases. Of those who had resumed sexual intercourse, 66.7% sustained the same frequency and level of sexual activity as before surgery, and 72.2% continued to have ejaculation and orgasm every time they had sexual activity. However, overall only 33.3% maintained their preoperative frequency of sexual intercourse and were satisfied with their overall sex life. Thus, the preoperative and postoperative scores were statistically worse for all domains of sexual function after partial penectomy.

D'Ancona et al. (9) used an 'Overall Sexual Functioning Questionnaire' in 14/18 patients who agreed to participate with a median time since surgery of 11.5 months (range 6-72). Prior to surgery, all patients had normal erectile function and at least one intercourse per month. The summary results showed that in 9/14 patients overall sexual functioning was 'normal' or 'slightly decreased', while 3/14 patients had no sexual intercourse after surgery.

Alei et al. (10) reported mean IIEF scores of 15 and 19.7 at 1 and 40 months after partial penectomy in 10 patients, indicating an improvement in erectile function with time.

#### 10.1.5 **Quality of life after partial penectomy**

D'Ancona and colleagues also used a number of qualitative and quantitative instruments to assess 'psychological behaviour and adjustment' as well as 'social activity' as indicators of QoL (9). For 'psychological behaviour and adjustment', qualitative findings were reported indicating fear of mutilation, of loss of sexual pleasure and of dying and consequences for the family. Support from families and partners was indicated as having helped to overcome difficulties after surgery. No significant levels of anxiety and depression were found on the GHQ-12 (General Health Questionnaire) and HAD scale (Hospital Anxiety and Depression Scale) in this study and 'social activity' remained as it had been before surgery in terms of living conditions, family life and interactions with other people.

## 10.2 **Total phallic reconstruction**

After full- or near-total penile amputation, total phallic reconstruction can be an option in selected cases. There have been several case reports and small series of these complex procedures (11-13). While cosmetic acceptable results may be achieved, functional restoration is not possible with these techniques.

## 10.3 **Specialized care**

Overall, nearly 80% of penile cancer patients of all stages can be cured. Partial penectomy has negative consequences for the patients' self-esteem and sexual function. With increasing experience in the management of penile cancer, it is recognized that organ-preserving treatment allows for better QoL and sexual function and should be offered to all patients whenever feasible (14). Referral to centres with experience is recommended and psychological support is very important for penile cancer patients.

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## 11. ABBREVIATIONS USED IN THE TEXT

*This list is not comprehensive for the most common abbreviations.*

5-FU	5-fluorouracil
BMP	cisplatin, methotrexate and bleomycin
CT	computed tomography
CSS	cancer-specific survival
DFS	disease-free survival
DSNB	dynamic sentinel node biopsy
EAU	European Association of Urology
FDA	US Food and Drug Administration
FDG	fluorodeoxyglucose
FNAB	fine-needle aspiration biopsy
FNAC	fine-needle aspiration cytology
GR	grade of recommendation
HPV	human papilloma virus
LAD	lymphadenectomy
LE	level of evidence
mILND	modified inguinal lymphadenectomy
MRI	magnetic resonance imaging
Nd:YAG	neodymium:yttrium-aluminum-garnet
PET	positron emission tomography
PF	cisplatin and fluorouracil
QoL	quality of life
SCC	squamous cell carcinoma
SNB	sentinel node biopsy
TC99m	technetium 99m
TPF	cisplatin, 5FU plus paclitaxel or docetaxel
TNM	tumour, node, metastasis
VBM	vinblastine, bleomycin, methotrexate

### **Conflict of interest**

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