# EAU Guidelines on

# Penile Cancer

O.W. Hakenberg (Chair), E. Compérat, S. Minhas,
A. Necchi, C. Protzel, N. Watkin (Vice-chair)
Guidelines Associate: R. Robinson



European
Association
of Urology

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# 1. INTRODUCTION

## 1.1 Aim and objectives

The European Association of Urology (EAU) Guidelines on Penile Cancer provides up-to-date information on the diagnosis and management of penile squamous cell carcinoma (SCC).

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

## 1.2 Panel composition

The EAU Penile Cancer Guidelines Panel consists of an international multi-disciplinary group of clinicians, including a pathologist and an oncologist. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of having penile cancer. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/penile-cancer/.

## 1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, the most recent dating back to 2014 [1], as are a number of translations of all versions of the Penile Cancer Guidelines. All documents are available through the EAU website Uroweb: http://uroweb.org/guideline/penile-cancer/.

## 1.4 Publication history

The EAU Penile Cancer Guidelines were first published in 2000; the current publication presents a limited update of the 2017 print.

## 1.5 Summary of changes

Key changes for the 2018 print:

Chapter 3 - Epidemiology, aetiology and pathology. New information has been added on the various histological subtypes of penile carcinomas, risk factors and human papilloma virus (HPV) association.

New and changed recommendations can be found in sections:

*3.4.8 Guidelines for the pathological assessment of tumour specimens*

| Recommendations | Strength rating |
|---|---|
| The pathological evaluation of penile carcinoma specimens must include an assessment of the human papilloma virus status. | Strong |
| The pathological evaluation of penile carcinoma specimens must include a diagnosis of the squamous cell carcinoma subtype. | Strong |
| The pathological evaluation of penile carcinoma surgical specimens must include an assessment of surgical margins including the width of the surgical margin. | Strong |

**4.2 Guidelines on staging and classification**

| Recommendation | Strength rating |
|---|---|
| The pathological evaluation of penile carcinoma specimens must include the pTNM stage and an assessment of tumour grade. | Strong |

**5.4 Guidelines for the diagnosis and staging of penile cancer**

| Recommendations | Strength rating |
|---|---|
| **Primary tumour** | |
| Perform a physical examination, record morphology, extent and invasion of penile structures. | Strong |

| | |
|---|---|
| Obtain a penile Doppler ultrasound or MRI with artificial erection in cases with intended organ-sparing surgery. | Weak |
| **Inguinal lymph nodes** | |
| Perform a physical examination of both groins, record the number, laterality and characteristics of inguinal nodes and:<br>• If nodes are not palpable, offer invasive lymph node staging in intermediate- and high-risk patients;<br>• If nodes are palpable, stage with a pelvic computed tomography (CT) or positron emission tomography (PET)/CT. | Strong |
| **Distant metastases** | |
| In N+ patients, obtain an abdominopelvic CT scan and chest X-ray/thoracic CT for systemic staging. Alternatively, stage with a PET/CT scan. | Strong |
| In patients with systemic disease or with relevant symptoms, obtain a bone scan. | |

*6.2.6* ***Guidelines for treatment strategies for nodal metastases***

| **Regional lymph nodes** | **Management of regional lymph nodes is fundamental in the treatment of penile cancer** | **Strength rating** |
|---|---|---|
| Radiotherapy<br>Radiotherapy | Not recommended for nodal disease except as a palliative option. | Strong |
| | > T1G2: invasive lymph node staging by either bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy. | Strong |
| Palpable inguinal nodes (cN1/cN2) | Radical inguinal lymphadenectomy. | Strong |
| Fixed inguinal lymph nodes (cN3) | Neoadjuvant chemotherapy followed by radical inguinal lymphade-nectomy in responders. | Weak |
| Pelvic<br>Lymph nodes | Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) or if extracapsular nodal metastasis (pN3) reported | Strong |
| Adjuvant chemotherapy | In pN2/pN3 patients after radical lymphadenectomy. | Strong |
| Radiotherapy | Not recommended for nodal disease except as a palliative option. | Strong |

*6.3.6* ***Guidelines for chemotherapy***

| **Recommendations** | **Strength rating** |
|---|---|
| Offer patients with pN2-3 tumours adjuvant chemotherapy after radical lymphadenectomy (three to four cycles of cisplatin, a taxane and 5-fluorouracil or ifosfamide). | Strong |
| Offer palliative chemotherapy to patients with systemic disease. | Weak |

A systematic review (SR) was performed by the Panel on 'Risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy in node-positive penile cancer' [2]. Even though not fully published, the review findings support the information presented in Section 6.2.2.3 Adjuvant treatment.

This review was performed using standard Cochrane SR methodology: http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html

# 2. METHODS

## 2.1 Data identification

For the 2018 Penile Cancer Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Penile Cancer Guidelines, was performed. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering the period between November 1st 2013 and September 20th 2016. All articles relating to penile cancer (n = 838) in the relevant literature databases were reviewed resulting in the inclusion of 29 new publication in this print.

Fully revised Guidelines were produced using the updated research base, together with several national and international guidelines on penile cancer (National Comprehensive Cancer Network [3], French Association of Urology [4] and the European Society of Medical Oncology [5]).

For the 2018 edition of the EAU Guidelines the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [6, 7]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [8];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation which is represented by the words 'strong' or 'weak' [9]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/.

A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

# 3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

## 3.1 Definition of penile cancer

Penile carcinoma is usually a SCC and there are several recognised subtypes of penile SCC with different clinical features and natural history (see Table 1). Penile SCC usually arises from the epithelium of the inner prepuce or the glans.

**Table 1: Histological subtypes of penile carcinomas, their frequency and outcome**

| Subtype | Frequency (% of cases) | Prognosis |
|---|---|---|
| Common squamous cell carcinoma (SCC) | 48-65 | Depends on location, stage and grade |
| Basaloid carcinoma | 4-10 | Poor prognosis, frequently early inguinal nodal metastasis [10] |
| 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 [11] (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 human papilloma virus, aggressive, early metastasis, poor prognosis, outcome is lesion-dependent, frequent lymphatic metastasis [12] |

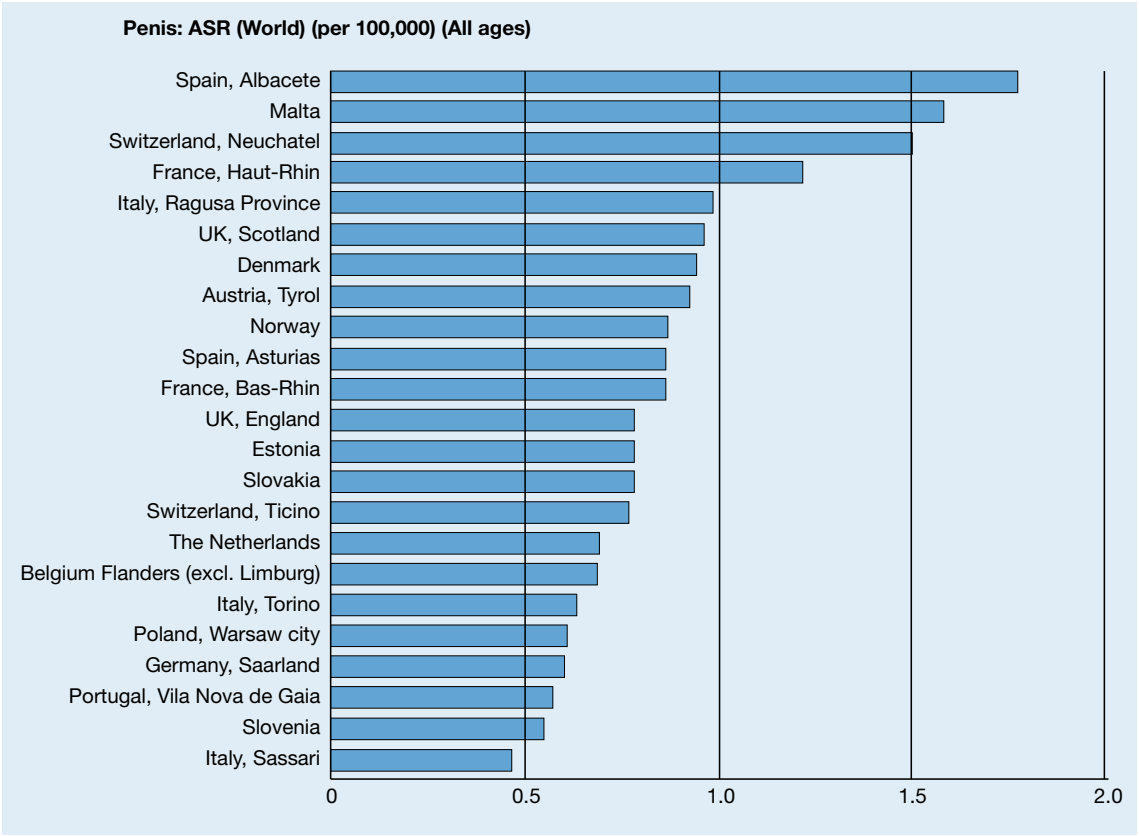
## 3.2 Epidemiology

In industrialised countries, penile cancer is uncommon, with an overall incidence of around 1/100,000 males in Europe and the USA [13, 14]. There are several areas in Europe with a higher incidence (Figure 1) [15]. Recent data from Scandinavia report an incidence of around 2/100,000 men. In the USA, the incidence of penile cancer is affected by race and ethnicity, with the highest incidence in white Hispanics (1.01), followed by Alaskans and Native American Indians (0.77), African Americans (0.62) 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 is much higher and can account for 1-2% of malignant diseases in men [15]. The annual age-adjusted incidence is 0.7-3.0 in India, 8.3 in Brazil (per 100,000, respectively) and even higher in Uganda, where it is the most commonly diagnosed male cancer [15, 16].

In the USA, the overall age-adjusted incidence rate decreased from 1973 to 2002 from 0.84 in 1973-1982 to 0.69 in 1983-1992, and to 0.58 in 1993-2002, per 100,000, respectively [13]. In Europe, the overall incidence has been stable from the 1980s until 2013 [14]. An increased incidence was observed in Denmark [17] and the UK (21% between 1979 and 2009) [18].

The incidence of penile cancer increases with age [14], with a peak in the sixth decade but it does occur in younger men [19]. Penile cancer is common in regions with a high prevalence of HPV and this may account for the worldwide variation in incidence [13]. About one third of cases are attributed to HPV-related carcinogenesis [20]. Penile cancer is not linked to HIV or AIDS.

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




*Adapted from [15].*

### 3.3 Risk factors and prevention

Several risk factors for penile cancer have been identified (Table 2) [21] (LE: 2a).

**Table 1: Recognised aetiological and epidemiological risk factors for penile cancer**

| Risk factors | Relevance | Ref |
|---|---|---|
| Phimosis | Odds ratio 11-16 vs. no phimosis | [22-24] |
| Chronic penile inflammation (balanoposthitis related to phimosis), lichen sclerosus | Risk | [25] |
| Sporalene and ultraviolet A phototherapy for various dermatological conditions such as psoriasis | Incidence rate ratio 9.51 with > 250 treatments | [26] |
| Smoking | Five-fold increased risk (95% Confidence interval (CI): 2.0-10.1) vs. non-smokers | [22, 23, 27] |
| HPV infection, condylomata acuminate | 22.4% in verrucous squamous cell carcinoma 36-66.3% in basaloid-warty | [13, 28] |
| Rural areas, low socio-economic status, unmarried | | [29-32] |
| Multiple sexual partners, early age of first intercourse | Three to five-fold increased risk of penile cancer | [21, 23, 33] |

Human papilloma virus infection is a risk factor for penile cancer [34]. Human papilloma virus DNA has been identified in 70-100% of intra-epithelial neoplasia and in 30-40% of invasive penile cancer tissue samples (LE: 2a). The HPV virus interacts with oncogenes and tumour suppressor genes (*p16, P53, Rb* genes) [28, 35]. The rate of HPV-positivity differs between different histological subtypes of penile SCC. Human papilloma virus is a cofactor in the carcinogenesis of some variants of penile SCC, while others are not related to HPV. The commonest HPV subtypes in penile cancer are types 16 and 18 [36]. The risk of penile cancer is increased in patients with condyloma acuminata [37] (LE: 2b).

A significantly better five-year disease-specific survival has been reported for HPV-positive vs. HPV-negative cases (93% vs. 78%) in one study [38], while no difference in lymph node metastases and ten-year survival was reported in another study [39] (Table 3). There is no association between the incidence of penile and cervical cancer, although both are linked to HPV [40, 41]. Female sexual partners of patients with penile cancer do not have an increased incidence of cervical cancer [42].

**Table 3: Outcomes for HPV and non-HPV penile carcinomas**

| Non HPV related | Prognosis | HPV related | Prognosis |
|---|---|---|---|
| SCC usual type/NOS | 30% DOD | Basaloid SCC | > 50% DOD |
| Pseudohyperplastic carcinoma | 0% | Papillary basaloid carcinoma | |
| Pseudoglandular carcinoma | > 50% | Warty carcinoma | Mortality low |
| Verrucous carcinoma | Good | Warty-basaloid carcinoma | 30% DOD |
| Carcinoma cuniculatum | Good | Clear-cell carcinoma | 20% |
| Papillary carcinoma NOS | Good | Lymphoepithelioma-like carcinoma | Not known |
| Adenosquamous carcinoma | Good | | |
| Sarcomatoid carcinoma | 75% DOD | | |

*DOD = died of disease; HPV = human papillomavirus; SCC = squamous cell carcinoma.*

At present, except for a few countries, there is no general recommendation for HPV vaccination in males because of the different HPV-associated risk patterns in penile- and cervical cancer. Furthermore, the epidemiological effects of HPV vaccination in girls still have to be assessed [43, 44].

Phimosis is strongly associated with invasive penile cancer [23, 29, 45, 46], due to associated chronic infection. However, smegma is not a carcinogen [45]. The incidence of lichen sclerosus is relatively high in penile cancer but is not associated with adverse histopathological features, including penile intraepithelial neoplasia (PeIN). Other epidemiological risk factors are cigarette smoking, low socioeconomic status and a low level of education [29, 46].

Neonatal circumcision reduces the incidence of penile cancer; however, it does not seem to reduce the risk of PeIN [23]. The lowest incidence of penile cancer is reported for Israeli Jews (0.3/100,000/year). One matched-pair, case-control study reported that the protective effect of neonatal circumcision against invasive penile cancer (OR 0.41) was much weaker when the analysis was restricted to men without a history of phimosis (OR 0.79, 95% CI: 0.29-2) [23]. Circumcision in adult life does not have any protective effect.

The controversial discussion about neonatal circumcision should take into account that circumcision removes approximately half the tissue that can develop into penile cancer.

## 3.4 Pathology

Squamous cell carcinoma accounts for over 95% of penile malignancies (see Table 1). It is not known how often SCC is preceded by premalignant lesions (see Table 4) [47-50].

Different histological types of penile SCC with different growth patterns, clinical aggressiveness and HPV associations have been identified (see Table 5). Numerous mixed forms exist such as the warty-basaloid form, with 50-60% the most common mixed form, the usual-verrucous (hybrid), usual-warty, usual-basaloid and the usual-papillary, as well as other rarer combinations.

Other malignant lesions of the penis, all much less common than penile SCC, are melanocytic lesions, mesenchymal tumours, lymphomas and metastases. Penile metastases are frequently of prostatic or colorectal origin. Different types of penile sarcoma have been reported.

**Table 4: Premalignant penile lesions (precursor lesions)**

| |
|---|
| Lesions sporadically associated with squamous cell carcinoma (SCC) of the penis:<br>• Bowenoid papulosis of the penis (HPV related)<br>• Lichen sclerosis |
| Premalignant lesions (up to one-third transform to invasive SCC):<br>• Penile intraepithelial lesions<br>• Giant condylomata (Buschke-Löwenstein)<br>• Bowen's disease<br>• Paget's disease (intradermal ADK) |

**Table 5: Classification of intra-epithelial neoplasia (PeIN)**

| |
|---|
| • **Non-HPV-related PeIN** |
| • o Differentiated PeIN |
| • **HPV-related PeIN** |
| • o Basaloid PeIN |
| • **Warty PeIN** |
| • **Warty-basaloid PeIN** |
| • **Other rare patterns of PeIN** (pleomorphic, spindle, clear cell, pagetoid) |

### *3.4.1 Gross handling of pathology specimens*

Tissue sections determine the accuracy of histological diagnosis. Small lesions should be fully included, bigger lesions should have at least 3-4 blocks. Lymph nodes must be included in their entirety after having been inked, in order to detect metastases. After having been inked, surgical margins have to be completely included [51]. Second-opinion pathology review is highly desirable for this rare tumour entity [52].

### *3.4.2 Pathology report*

The pathology report must include the anatomical site of the primary tumour, the histological type of SCC, grade, perineural invasion, depth of invasion, vascular invasion (venous/lymphatic), irregular growth and front of invasion, urethral invasion, invasion of corpus spongiosum/cavernosum, surgical margins and the *p16*/HPV status (Table 6) [53-56].

**Table 6: Outcomes for HPV and non-HPV penile carcinomas**

| Information to include in the pathology report | Recommended | required |
|---|---|---|
| **Clinical information**<br>• Prior treatments (topic, radiotherapy, chemotherapy) | x | |
| **Surgical procedure** | | x |
| **Tumour localisation** | x | |
| **Macroscopic tumour dimension**<br>• Depth of invasion<br>• Millimetres from basement membrane to deepest point of invasion<br>• Maximum thickness<br>• Size of tumour | | x |
| **Block identification** | x | |
| **Histological tumour type** | | x |
| **Histological grade** | | x |
| **Microscopic maximum dimensions**<br>• Combination of gross and microscopic if large tumours | | x |
| **Extent of invasion** | | x |
| **LVI** [58, 59] | | x |
| **Perineural invasion** | | x |
| **Margin status in mm** | | x |
| **Lymph node (LN) status**<br>• Size of largest nodal tumour deposit (not LN size)<br>• Number of LN+, extracapsular spread (ECS), inguinal or pelvic, to be reported in every site separately | | x |
| **TNM Stage** | | x |
| **p16/HPV status** | x | |

** See also www.ICCR-cancer.org. database.*

### *3.4.3 Grading*

The TNM classification for penile cancer includes tumour grade, due to its prognostic relevance (Table 9). Tumour grading in penile cancer has been shown to be highly observer-dependent and can be problematic, especially in heterogeneous tumours. Grading should use the categories specified by the WHO for penile cancer (Table 7).

**Table 7: Grading recommendations for penile SCC**

| Feature | Grade 1 | Grade 2 | Grade 3 | Sarcomatoid |
|---|---|---|---|---|
| **Cytological atypia** | Mild | Moderate | Anaplasia | Sarcomatoid |
| **Keratinisation** | Usually abundant | Less prominent | May be present | Absent |
| **Intercellular bridges** | Prominent | Occasional | Few | Absent |
| **Mitotic activity** | Rare | Increased | Abundant | Abundant |
| **Tumour margin** | Pushing/well | Infiltrative/ill defined | Infiltrative/ill defined | Infiltrative/ill defined |

### *3.4.4 Pathological prognostic factors*

Pathological subtype, perineural invasion, lymphovascular invasion [58], depth of invasion and grade in the primary tumour are strong predictors of poor prognosis and high cancer-specific mortality [60]. Tumour grade is a predictor of metastatic spread, and lymphatic invasion is a predictor of metastasis. Venous embolism is often seen in advanced stages. The extent of lymph node metastasis and extracapsular spread are also strong predictors of prognosis.

The variants of penile SCC can be divided into three prognostically different groups (Table 8).

**Table 8: Prognosis of the variants of penile SCC**

| Penile SCC | Good prognosis | Intermediate prognosis | Poor prognosis |
|---|---|---|---|
| **Local growth** | Destructive | Destructive | Destructive |
| **Metastasis** | Rare | Intermediate | Common |
| **Risk of cancer-related mortality** | Very low | Intermediate | High |
| **SCC variants** | • Verrucous<br>• Papillary<br>• Warty<br>Pseudohyperplastic carcinoma cuniculatum | • Usual SCC<br>• Mixed forms<br>• Pleomorphic form of warty carcinoma | • Basaloid,<br>• Sarcomatoid adenosquamous |

There is discussion as to whether cases that show invasion of the distal urethra have a worse prognosis; however, there is no evidence to support this [61]. Nevertheless, invasion of the more proximal urethra signifies a highly aggressive SCC with a poor prognosis (see Table 9). pT3 denotes a worse prognosis than pT2 [62, 63] (LE: 2b). Capsular extension in even one single lymph node carries a poor prognosis and is denoted as pN3 [64-66].

Chaux *et al.* suggested a prognostic index which incorporates grade, anatomical level of infiltration and perineural invasion to predict the likelihood of inguinal lymph node metastases and 5-year survival [67].

### *3.4.5 Penile cancer and HPV*

The association between penile cancer and HPV is different for the different variants of penile SCC. A high prevalence of HPV infection is found in basaloid (76%), mixed warty-basaloid (82%) and warty penile (39%) SCCs. Verrucous and papillary penile SCCs are HPV-negative. The commonest HPV-types in penile SCC are HPV-16 (72%), HPV-6 (9%) and HPV-18 (6%). Overall, only one-third of penile SCCs show HPV infection, but those that do are usually infected by several HPV strains.

### *3.4.6 Penile biopsy*

Any doubtful penile lesion should be biopsied and, even in clinically obvious cases, histological verification must be obtained before local treatment. Before definitive surgical treatment, confirmatory frozen section excisional biopsy can be done. Histological confirmation is necessary to guide management when:

- there is doubt about the exact nature of the lesion (e.g. PeIN, metastasis or melanoma);
- treatment is planned with topical agents, radiotherapy or laser surgery.

The size of a biopsy is important. In one study, in biopsies with an average size of 0.1 cm it was difficult to evaluate the depth of invasion in 91% of cases. The grade at biopsy, and in the final specimen, may differ in up to 30% of cases, with failure to detect cancer in 3.5% of cases [47]. Furthermore, vascular and lymphatic tumour emboli were detected in only 9-11% of cases. Although a punch biopsy may be sufficient for superficial lesions, an excisional biopsy which is deep enough to properly assess the degree of invasion and stage is preferable.

### *3.4.7 Intra-operative frozen sections and surgical margins*

Surgical treatment must completely remove the penile carcinoma with negative surgical margins, which may be confirmed by intra-operative frozen section [68]. The width of negative surgical margins should follow a risk-adapted strategy based on tumour grade. Only 3 mm of tumour-free tissue is sufficient to consider the surgical margins to be negative [69].

### *3.4.8 Guidelines for the pathological assessment of tumour specimens*

| Recommendations | Strength rating |
|---|---|
| The pathological evaluation of penile carcinoma specimens must include an assessment of the human papilloma virus status. | Strong |
| The pathological evaluation of penile carcinoma specimens must include a diagnosis of the squamous cell carcinoma subtype. | Strong |
| The pathological evaluation of penile carcinoma surgical specimens must include an assessment of surgical margins including the width of the surgical margin. | Strong |

# 4. STAGING AND CLASSIFICATION SYSTEMS

## 4.1 TNM classification

The 2016 UICC TNM classification for penile cancer [51] introduced some changes in comparison to previous editions. The T1 category is stratified into two prognostically different risk groups, depending on the presence or absence of lymphovascular invasion and grading (Table 9). The classification T2 denotes invasion of the corpus spongiosum, while T3 is defined as invasion of the corpora cavernosa, due to the different prognosis of these two patterns [62, 63]. For penile cancer, unlike in other neoplasms, tumour grade is used for the TNM classification in the subdivision of the T1 stage (Table 9).

The current pN1 group consists of one or two ipsilateral inguinal lymph node metastases, pN2 is defined as more than two uni- or bilateral metastatic nodes and pN3 any pelvic nodes, uni- or bilateral, or any extranodal extension regardless of the number of lymph node metastases [51]. Retroperitoneal lymph node metastases are classified as extra-regional nodal and, therefore, distant metastases.

**Table 9: 2016 TNM clinical and pathological classification of penile cancer** [51]

| | |
|---|---|
| **Clinical classification** | |
| **T - Primary Tumour** | |
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| Tis | Carcinoma *in situ* |
| Ta | Non-invasive verrucous carcinoma* |
| T1 | Tumour invades subepithelial connective tissue |
| T1a | Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated |
| T1b | Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated |
| T2 | Tumour invades corpus spongiosum with or without invasion of the urethra |
| T3 | Tumour invades corpus cavernosum with or without invasion of the urethra |
| T4 | Tumour invades other adjacent structures |
| **N - Regional Lymph Nodes** | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No palpable or visibly enlarged inguinal lymph nodes |
| N1 | Palpable mobile unilateral inguinal lymph node |
| N2 | Palpable mobile multiple or bilateral inguinal lymph nodes |
| N3 | Fixed inguinal nodal mass *or* pelvic lymphadenopathy, unilateral or bilateral |
| **M - Distant Metastasis** | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| **Pathological classification** | |
| The pT categories correspond to the clinical T categories.<br>The pN categories are based upon biopsy or surgical excision | |
| **pN - Regional Lymph Nodes** | |
| pNX | Regional lymph nodes cannot be assessed |
| pN0 | No regional lymph node metastasis |
| pN1 | Metastasis in one or two inguinal lymph nodes |
| pN2 | Metastasis in more than two unilateral inguinal nodes or bilateral inguinal lymph nodes |
| pN3 | Metastasis in pelvic lymph node(s), unilateral *or* bilateral extranodal or extension of regional lymph node metastasis |
| **pM - Distant Metastasis** | |
| pM1 | Distant metastasis microscopically confirmed |
| **G - Histopathological Grading** | |
| GX | Grade of differentiation cannot be assessed |
| G1 | Well differentiated |
| G2 | Moderately differentiated |
| G3 | Poorly differentiated |
| G4 | Undifferentiated |

**Verrucous carcinoma not associated with destructive invasion.*

### 4.2 Guidelines on staging and classification

| Recommendation | Strength rating |
|---|---|
| The pathological evaluation of penile carcinoma specimens must include the pTNM stage and an assessment of tumour grade. | Strong |

# 5. DIAGNOSTIC EVALUATION AND STAGING

Penile cancer can be cured in over 80% of cases if diagnosed early, but is a life-threatening disease when lymphatic metastasis occurs. Local treatment can be mutilating, and devastating for the patient's psychological well-being.

## 5.1 Primary lesion

Penile carcinoma is usually a clinically obvious lesion but it may be hidden under a phimosis [24]. Physical examination should include palpation of the penis to assess the extent of local invasion and palpation of both groins to assess the lymph node status.

Ultrasound (US) can provide information about infiltration of the corpora [70, 71]. Magnetic resonance imaging (MRI) with an artificially induced erection can be used to exclude corporal invasion but is very unpleasant for the patient [72, 73]. The sensitivity and specificity of MRI in predicting corporal or urethral invasion was reported as 82.1% and 73.6%, and 62.5% and 82.1%, respectively [74]. Penile Doppler US has been reported to have a higher staging accuracy than an MRI in detecting corporal infiltration [75].

## 5.2 Regional lymph nodes

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

### *5.2.1 Non-palpable inguinal nodes*

If there are no palpable lymph nodes, the likelihood of micro-metastatic disease is about 25%. Imaging studies are not helpful in staging clinically normal inguinal regions, although may be used in obese patients in whom palpation is unreliable:

- Inguinal US (7.5 MHz) can detect abnormal, enlarged nodes. The longitudinal/transverse diameter ratio and absence of the lymph node hilum are findings with relatively high specificity [76].
- Conventional computed tomography (CT) or MRI cannot detect micro-metastases reliably [77].
- $^{18}$FDG-positron emission tomography (PET/CT) does not detect lymph node metastases < 10 mm [78, 79].

Further management of patients with normal inguinal nodes should be guided by pathological risk factors of the primary tumour. Lymphovascular invasion, local stage and grade are predictive of lymphatic metastasis [80, 81]. Existing nomograms are not accurate. Invasive lymph node staging is required in patients at intermediate- or high risk of lymphatic spread (see Section 6.2).

### *5.2.2 Palpable inguinal nodes*

Palpably enlarged lymph nodes are highly indicative of lymph node metastases. Physical examination should note the number of palpable nodes on each side and whether these are fixed or mobile. Additional imaging does not alter management and is not required (see Section 6).

A pelvic CT scan can be used to assess the pelvic lymph nodes. Imaging with $^{18}$FDG-PET/CT has shown high sensitivity (88-100%) and specificity (98-100%) for confirming metastatic nodes in patients with palpable inguinal lymph nodes [79, 82].

## 5.3 Distant metastases

Staging for systemic metastases should be performed in patients with positive inguinal nodes [83-85] (LE: 2b). Abdominal and pelvic CT should be done plus a chest X-ray, although a thoracic CT is more sensitive. PET/CT is an option [81].

There is no tumour marker for penile cancer. The SCC antigen (SCC Ag) is increased in less than 25% of penile cancer patients. One study reported that SCC Ag did not predict occult metastatic disease, but was an indicator of disease-free survival (DFS) in lymph-node-positive patients [86].

### 5.4 Guidelines for the diagnosis and staging of penile cancer

| Recommendations | Strength rating |
|---|---|
| **Primary tumour** | |
| Perform a physical examination, record morphology, extent and invasion of penile structures. | Strong |
| Obtain a penile Doppler ultrasound or MRI with artificial erection in cases with intended organ-sparing surgery. | Weak |
| **Inguinal lymph nodes** | |
| Perform a physical examination of both groins, record the number, laterality and characteristics of inguinal nodes and:<br>• If nodes are not palpable, offer invasive lymph node staging in intermediate- and high-risk patients;<br>• If nodes are palpable, stage with a pelvic computed tomography (CT) or positron emission tomography (PET)/CT. | Strong |
| **Distant metastases** | |
| In N+ patients, obtain an abdominopelvic CT scan and chest X-ray/thoracic CT for systemic staging. Alternatively, stage with a PET/CT scan. | Strong |
| In patients with systemic disease or with relevant symptoms, obtain a bone scan. | |

# 6. DISEASE MANAGEMENT

### 6.1 Treatment of the primary tumour

The aims of the treatment of the primary tumour are complete tumour removal with as much organ preservation as possible, without compromising oncological control. Local recurrence has little influence on long-term survival, so organ preservation strategies are justified [87].

There are no randomised controlled trials (RCTs) or observational comparative studies for any of the treatment options for localised penile cancer. Penile preservation appears to be superior in functional and cosmetic outcomes to partial or total penectomy, and is considered to be the primary treatment method for localised penile cancer. However, there are no RCTs comparing organ-preserving and ablative treatment strategies.

Histological diagnosis with local staging must be obtained before using non-surgical treatments. With surgical treatment, negative surgical margins must be obtained. Treatment of the primary tumour and of the regional nodes can be staged.

Local treatment modalities for small and localised penile cancer include excisional surgery, external beam radiotherapy (EBRT), brachytherapy and laser ablation. Patients should be counselled about all relevant treatment options.

#### *6.1.1 Treatment of superficial non-invasive disease (PeIN)*

Topical chemotherapy with imiquimod or 5-fluorouracil (5-FU) is an effective first-line treatment. Circumcision is advisable prior to the use of topical agents. Due to high persistence/recurrence rates, treatment must be assessed by biopsy and long-term surveillance is warranted. An insufficient response may signify underlying invasive disease. Significant inflammatory responses may occur [88, 89]. Complete responses have been reported in up to 57% of PeIN cases [90] and in 74% of cases treated by circumcision and 5-FU without relapse. If topical treatment fails, it should not be repeated.

Laser treatment with a neodymium:yttrium-aluminium-garnet (Nd:YAG) or Carbon dioxide ($CO_2$) laser is an effective treatment option [91-96]. Visualisation may be improved by photodynamic diagnosis with the $CO_2$ laser [97]. Rebiopsy for treatment control is mandatory.

Glans resurfacing, total or partial, can be a primary treatment for PeIN or a secondary option in case of failure of topical chemotherapy or laser therapy. Glans resurfacing consists of complete removal of the glandular epithelium followed by reconstruction with a graft (split skin or buccal mucosa). However, in one study in cases of glans resurfacing for presumed PeIN, up to 20% of patients were found to have invasive disease on histopathological examination [88].

### 6.1.2 *Treatment of invasive disease confined to the glans (category T1/T2)*

Small and localised invasive lesions should receive organ-sparing treatment. Additional circumcision is advisable for glandular tumours. Foreskin tumours are treated by 'radical circumcision'. Local excision, partial glansectomy or total glansectomy with reconstruction are surgical options. External beam radiotherapy or brachytherapy are radiotherapeutic options. Small lesions can also be treated by laser therapy but the risk of more invasive disease must be recognised.

Treatment choice depends on tumour size, histology, stage and grade, localisation (especially relative to the meatus) and patient preference.

#### 6.1.2.1 *Intra-operative frozen section*

Many authors recommend intraoperative frozen sections to assess surgical margins. Others have suggested that frozen sections are only needed if there are definite concerns [98]. For glans resurfacing, some advocate the use of acetic acid staining to delineate abnormal areas [99]. Data from one multi-centre study suggests that differentiated penile intraepithelial neoplasia, squamous hyperplasia and lichen sclerosis present at the surgical margins are frequent findings and are not relevant for cancer-specific survival [65].

#### 6.1.2.2 *Width of negative surgical margins*

There is no clear evidence as to the required width of negative surgical margins. With organ-sparing these can be minimal. For a general recommendation, 3-5 mm can be considered a safe maximum [100, 101]. A grade-based differentiated approach can also be used, with 3 mm for grade one, 5 mm for grade two and 8 mm for grade three. This approach has its limitations due to the difficulties with penile cancer grading.

### 6.1.3 *Results of different surgical organ-preserving treatments*

#### 6.1.3.1 *Laser therapy*

The results of $CO_2$ laser treatment have been reported by three retrospective studies from the same institution with a median follow-up of five years and a total of 195 patients [91-93]. Laser treatment was given in combination with radiotherapy or chemotherapy for PeIN or T1 penile cancers. No cancer-specific deaths were reported. Local recurrence ranged from 14% for PeIN [93] to 23% for T1 tumours [92], with an estimated cumulative risk of local recurrence at five years of 10% for PeIN (n = 106) and 16% for T1 (n = 78) tumours [91]. The reported rate of inguinal nodal recurrence was between 0% [93] and 4% [92]. The rate of secondary partial penectomy at ten years was 3% for PeIN and 10% for T1 tumours [91].

Four studies, three from the same institution, reported results of Nd:YAG laser treatment for a total of 150 patients with a follow-up of at least four years [94-96, 102]. Local recurrence rates ranged from 10% to 48% [94, 95]. One study [96] reported recurrence-free survival rates of 100%, 95% and 89% at one, two and five years, respectively. Inguinal nodal recurrence was reported in 21% of patients [94] and cancer-specific mortality was reported as 2% [102] and 9% [95]. The three studies from the same institution reported overall survival (OS) rates of 100% at four years [94] and 85-95% [96, 103] at seven years. The rate of secondary partial penectomy was highly divergent, with 4% in one study [96] and 45% in another [95]. One study reported that no complications and no adverse effects on urinary or sexual function were observed [94].

Other studies have presented data on a variety of laser treatments with either a $CO_2$ or a Nd:YAG laser, a combination of both, or a potassium titanyl phosphate (KTP) laser [104-107], with a mean follow-up of 32-60 months with stages PeIN to T3 included. These studies reported on a total of 138 patients, with local recurrence rates of 11% [92], 19% [105] and 26% [107]. In one study, recurrence-free survival at five years was 88% [105]. The cancer-specific survival (CSS) probability at five years was 95% in one study [105], and 2% at five years in another [105].

#### 6.1.3.2 *Moh's micrographic surgery*

Moh's micrographic surgery is a historical technique by which histological margins are taken in a geometrical fashion around a conus of excision. The original description [108] consisted of 33 consecutive patients treated between 1936 and 1986 with 79% cured at five years [108]. The second study reported 68% recurrence-free survival at three years, 32% local recurrences and 8% inguinal nodal recurrence [109]. In both studies, one partial amputation and one cancer-specific death occurred. In a contemporary series of 48 cases, there were no recurrences among 10 primary invasive SCCs with a cure rate of 100% (mean follow-up, 161 months, median follow-up, 177 months), but one recurrence in 19 cases of penile intraepithelial neoplasia (cure rate 94.7%) [110].

#### 6.1.3.3 *Glans resurfacing*

Three studies have reported results of glans resurfacing in a total of 71 patients with PeIN or T1 with a median follow-up of 21-30 months [88, 111, 112]. No cancer-specific deaths were reported, the rates of local recurrence were 0% [111] and 6% [112], without reports of nodal recurrence or complications.

#### *6.1.3.4* ***Glansectomy***

Results of glansectomy were reported in three studies [100, 113, 114], while a fourth also reported on glans-preserving surgery [114]. One study reported 87 patients with six local (6.9%), eleven regional (12.6%) and two systemic recurrences (2.3%) with a mean follow-up of 42 months [100]. The other two studies reported on a total of 68 patients with a follow-up of 63 [114] and 114 months [113], respectively, in which there was one patient (8%) with local recurrence [113], six (9%) with inguinal nodal recurrence, and no cancer-specific deaths.

#### *6.1.3.5* ***Partial penectomy***

Results of partial penectomy were reported in rather heterogeneous studies with a total of 184 patients with T1-T3 tumours and a follow-up of 40-194 months [93, 114-119]. The rate of local recurrence ranged from 4-50% and cancer-specific mortality from 0-27%. The reported five-year OS ranged from 59-89% [117, 119, 120].

#### *6.1.3.6* ***Summary of results of surgical techniques***

Although conservative, organ-sparing surgery may improve quality of life (QoL), local recurrence is more likely than after amputation surgery for penile cancer. In one study the local recurrence rate after organ-sparing surgery was 18%, most of these occurred within 36 months [121], and amputation was necessary in 17% of the recurrences. Compared to this, the local recurrence rate after amputation surgery (partial or radical) was lower (4%). Glansectomy with circumcision for the treatment of small penile lesions has a very low rate of local recurrence (2%) [100].

In one large cohort of patients undergoing organ-sparing surgery, isolated local recurrence was 8.9% and five-year disease-specific survival (DSS) 91.7%. Tumour grade, stage and lymphovascular invasion were predictors of local recurrence. In the largest cohort of penile surgery, the 5-year cumulative incidence of local recurrence after organ-sparing (including laser treatment) was 27% while it was only 3.8% in the amputation group [98]. Of the 451 patients treated by organ-sparing surgery, 16% eventually underwent amputation. However, there was no significant difference in survival between the organ-sparing and the amputation groups. These results suggest that the local recurrence rates following penile preserving surgery are higher than with partial penectomy, although survival appears to be unaffected.

### *6.1.4* ***Summary of results of radiotherapy for T1 and T2 disease***

Radiotherapy is an organ-preserving approach with good results in selected patients with T1-2 lesions < 4 cm in diameter [122-127] (LE: 2b). It can be given as external radiotherapy with a minimum dose of 60 Gy combined with a brachytherapy boost or as brachytherapy alone [123, 125]. Reported results are best with brachytherapy with local control rates ranging from 70-90% [123, 125]. The American Brachytherapy Society and the Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology consensus statement for penile brachytherapy also reported good tumour control rates, acceptable morbidity and functional organ preservation for penile brachytherapy for stages T1 and T2 [128]. Penile preservation rates of 70-88% have been reported [129], with overall penile conservation rates of 87% and 70% at five and ten years. Pulsed-dose-rate brachytherapy has been introduced as a new modality and 15% local recurrences have been reported in one series [130].

In the few comparisons of surgical treatment and radiotherapy, results of surgery were slightly better. In a meta-analysis comparing surgery and brachytherapy, 5-year OS and local control rates with surgery were 76%/84% for surgery and 73%/79% for brachytherapy, respectively [131]. The organ preservation rate for brachytherapy was 74% and there was no difference in survival. Local recurrence after radiotherapy can be salvaged by surgery [132].

Specific complications of radiotherapy for penile cancer are urethral stenosis (20-35%), glans necrosis (10-20%) and late fibrosis of the corpora cavernosa [133] (LE: 3). With brachytherapy, meatal stenosis has been reported to occur in 40% of cases, but was much lower in a contemporary series of 73 patients with only 6.6%. In that series, 2.6% reported pain with sexual intercourse and 5.3% dysuria over a follow-up of 5 years. Penile amputation for necrosis was necessary in 6.8 % of patients [134].

Functional outcome after radiotherapy has not often been reported. In one report, 17/18 patients with normal erections before treatment maintained these after treatment [129].

Table 10 provides an overview of the complications and outcomes of primary local treatments.

**Table 10: Summary of reported complications and oncological outcomes of local treatments***

| Treatment | Complications | Local recurrence | Nodal recurrence | Cancer-specific deaths | References |
|---|---|---|---|---|---|
| ND:YAG laser | n.r. | 10-48% | 21% | 2-9% | [94-96, 102] |
| C02 laser | Bleeding, meatal stenosis, both < 1% | 14-23% | 2-4% | n.r. | [91-93] |
| Lasers (unspecified) | Bleeding 8%, local infection 2% | 11-26% | 2% | 2-3% | [104-107] |
| Moh's micrographic surgery | Local infection 3%, Meatal stenosis 6% | 32% | 8% | 3-4% | [108-110] |
| Glans resurfacing | n.r. | 4-6% | n.r. | n.r. | [88, 111, 112, 135] |
| Glansectomy | n.r. | 8% | 9% | n.r. | [113, 114] |
| Partial penectomy | n.r. | 4-13% | 14-19% | 11-27% | [93, 117, 119, 120] |
| Brachytherapy | Meatal stenosis > 40% | 10-30% | n.r. | n.r. | [122, 123, 125] |
| External beam radiotherapy | Urethral stenosis 20-35%, Glans necrosis 10-20% | n.r. | n.r. | n.r. | [123, 127, 128, 132, 133] |

**The ranges are the lowest and highest number of occurrences reported in different series.*

### *6.1.5 **Treatment recommendations for invasive penile cancer (T2-T4)***

#### *6.1.5.1 Treatment of invasive disease confined to the glans with or without urethral involvement (T2)*

Total glansectomy, with or without resurfacing of the corporeal heads, is recommended [115] (LE: 3). Radiotherapy is an option (see Section 6.1.6). Partial amputation should be considered in patients unfit for reconstructive surgery [132].

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

Glansectomy with distal corporectomy and reconstruction or partial amputation with reconstruction are standard [100, 101, 126]. Radiation therapy is an option.

#### *6.1.5.3 Treatment of locally advanced disease invading adjacent structures (T4)*

Extensive partial amputation or total penectomy with perineal urethrostomy is the standard advisable treatment [101]. For locally advanced and ulcerated cases, neoadjuvant chemotherapy may be an option. Otherwise, adjuvant chemotherapy or palliative radiotherapy are options (see Sections 6.2.4 and 6.1.6).

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

A second organ-conserving procedure can be performed if there is no corpus cavernosum invasion [97, 101, 121, 126, 136]. For large or high-stage recurrence, partial or total amputation is required [133]. A total phallic reconstruction may be offered to patients undergoing total/subtotal amputation [137, 138].

### *6.1.6 **Guidelines for stage-dependent local treatment of penile carcinoma***

| Primary tumour | Use organ-preserving treatment whenever possible | Strength rating |
|---|---|---|
| Tis | Topical treatment with 5-fluorouracil (5-FU) or imiquimod for superficial lesions with or without photodynamic control. | Strong |
| | Laser ablation with carbon dioxide ($CO_2$) or neodymium:yttrium-aluminium-garnet (Nd:YAG) laser. | |
| | Glans resurfacing. | |
| Ta, T1a (G1, G2) | Wide local excision with circumcision, $CO_2$ or Nd:YAG laser with circumcision. | Strong |
| | Laser ablation with $CO_2$ or Nd:YAG laser. | |
| | Glans resurfacing. | |
| | Glansectomy with reconstruction. | |
| | Radiotherapy for lesions < 4 cm. | |

| | | |
|---|---|---|
| T1b (G3) and T2 | Wide local excision plus reconstruction. | Strong |
| | Glansectomy with circumcision and reconstruction. | |
| | Radiotherapy for lesions < 4 cm in diameter. | |
| T3 | Partial amputation with reconstruction or radiotherapy for lesions < 4 cm in diameter. | Strong |
| T3 with invasion of the urethra | Partial penectomy or total penectomy with perineal urethrostomy. | Strong |
| T4 | Neoadjuvant chemotherapy followed by surgery in responders or palliative radiotherapy. | Weak |
| Local recurrence | Salvage surgery with penis-sparing in small recurrences or partial amputation. | Weak |
| | Large or high-stage recurrence: partial or total amputation. | |

## 6.2 Management of regional lymph nodes

The development of lymphatic metastases in penile cancer follows the route of anatomical drainage. The inguinal lymph nodes, followed by the pelvic lymph nodes, provide the regional drainage system of penis. The superficial and deep inguinal lymph nodes are the first regional node group to be affected, which can be uni- or bilateral [87].

The 'sentinel' inguinal nodes, i.e. those first affected by lymphatic spread, appear to be located in the medial superior zone followed by the central inguinal zones [90]. No solitary lymphatic spread has been observed from the penis to the two inferior groin regions and no direct drainage to the pelvic nodes, either [88, 97]. These findings confirm earlier studies.

Pelvic nodal disease does not occur without ipsilateral inguinal lymph node metastasis. Also, crossover metastatic spread, from one groin to the contralateral pelvis, has never been reported. Further lymphatic spread from the pelvic nodes to retroperitoneal nodes (para-aortic, para-caval) is classified as systemic metastatic disease.

The management of regional lymph nodes is decisive for patient survival. Cure can be achieved in limited lymph node disease confined to the regional lymph nodes. Radical lymphadenectomy is the treatment of choice. Multimodal treatment combining surgery and chemotherapy is often indicated.

The management of regional lymph nodes is dependent on the clinical inguinal lymph node status. There are three possible scenarios. First, the clinical lymph nodes appear normal on palpation and are not enlarged. Secondly, the inguinal lymph nodes are palpably enlarged, either uni- or bilaterally. Thirdly, there are grossly enlarged and sometimes ulcerated inguinal lymph nodes, uni- or bilaterally.

In clinically node-negative patients (cN0), micro-metastatic disease occurs in up to 25% of cases and invasive lymph node staging is required since no imaging technique can reliably detect or exclude micro-metastatic disease. In clinically positive lymph nodes (cN1/cN2), metastatic disease is highly likely and lymph node surgery with histology is required. Enlarged fixed inguinal lymph nodes (cN3) require multimodal treatment by (neoadjuvant) chemotherapy and surgery. Even if present in only one node, capsular penetration/extra-nodal extension in lymph node metastasis carries a high risk of progression and is classified as pN3, which also requires multimodal treatment.

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

Risk stratification for the micro-metastatic inguinal lymph node disease depends on stage, grade and the presence/absence of lymphovascular invasion in the primary tumour [100]. pTa/pTis tumours and those with low grade have a comparatively low risk of lymphatic spread. Well-differentiated G1 pT1 tumours are considered low risk, pT1G2 intermediate risk and pT1G3 and all higher stage tumours are considered high risk for lymphatic spread [101].

For these patients, three management strategies are possible: surveillance, invasive nodal staging or radical lymphadenectomy. Early inguinal lymphadenectomy in clinically node-negative patients is superior for long-term patient survival compared to later lymphadenectomy with regional nodal recurrence [91, 92]. One prospective study comparing bilateral lymphadenectomy, radiotherapy and surveillance in such patients reported significantly better five-year OS lymphadenectomy vs. inguinal radiotherapy or surveillance (74% vs. 66% and 63%, respectively) [93].

#### *6.2.1.1 Surveillance*

Surveillance of regional lymph nodes carries the risk of regional recurrence arising later from existing micro-metastatic disease. Patient survival is over 90% with early lymphadenectomy and below 40% with lymphadenectomy for regional recurrence [94, 95]. Patients considering surveillance must be informed about this risk. Surveillance is only recommended in patients with pTis/pTa tumours and with the appropriate caveats in low risk G1 pT1 tumours [94-96]. Compliance is required for surveillance.

#### 6.2.1.2 *Invasive nodal staging*

Since no imaging technique can detect micro-metastatic disease, invasive lymph node staging is recommended for pT1 tumours of intermediate and high risk, as well as for T2-T4 tumours [92, 105] (LE: 2b). Fine-needle aspiration cytology also does not reliably exclude micro-metastatic disease and is not recommended.

Invasive nodal staging can be done by either dynamic sentinel-node biopsy (DSNB) or by modified inguinal lymphadenectomy (mILND), both of which are standard techniques [139]. Dynamic sentinel-node biopsy aims to detect affected sentinel nodes in both groins. Technetium-99m ($^{99m}$Tc) nanocolloid is injected around the penile cancer site on the day before surgery often combined with patent blue. A gamma-ray probe is used intra-operatively to detect the sentinel nodes, which is possible in 97% of cases. The protocol has been standardised for routine use [107]. Dynamic sentinel-node biopsy has a reported high sensitivity in some centres (90-94%) [107, 108] (LE: 2b). In a meta-analysis of eighteen studies, the pooled sensitivity was 88%, which improved to 90% with the addition of patent blue [109].

Modified ILND is an alternative option, whereby the medial superficial inguinal lymph nodes and those from the central zone are removed bilaterally [87, 106] (LE: 3), leaving the greater saphenous vein untouched.

Both methods of invasive lymph node staging may miss micro-metastatic disease leading to regional recurrence [91]. The false-negative rate may be as high as 12-15% for DSNB, even in experienced centres [95, 96]. The false-negative rate of mILND is unknown. If lymph node metastasis is found, ipsilateral radical inguinal lymphadenectomy is indicated.

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

With uni- or bilateral palpable inguinal lymph nodes (cN1/cN2), metastatic lymph node disease is highly likely. The notion that these may be inflammatory and that antibiotic treatment should first be used is unfounded and dangerous as it delays curative treatment.

Palpably enlarged groin lymph nodes should be surgically removed, pathologically assessed (by frozen section) and, if positive, a radical inguinal lymphadenectomy should be performed. In clinically doubtful cases, US-guided fine needle aspiration cytology is an option [140].

In such cases, CT or MRI can provide staging information about the pelvic nodal status and $^{18}$F-FDGPET/CT can identify additional metastases [141]. Dynamic sentinel-node biopsy is not indicated in patients with palpably enlarged lymph nodes [142] (LE: 3).

#### 6.2.2.1 *Radical inguinal lymphadenectomy*

Radical inguinal lymphadenectomy carries a significant morbidity due to impaired lymph drainage from the legs and scrotum. Morbidity can be as high as 50% [143] in the presence of significant risk factors such as increased body mass index (BMI). Recent series have reported lower morbidity in about 25% of cases [144, 145] (LE: 2b). Therapeutic radical inguinal lymphadenectomy can be life-saving and should not be underused for fear of associated morbidity [146].

Tissue handling must be meticulous in order to minimise post-operative morbidity. Lymphatic vessel walls do not contain smooth muscle and are therefore not reliably closed by electrocautery. Numerous metal clips may also cause post-operative problems so that ligation of all lymphatic vessels is advisable [147, 148]. Post-operative morbidity may be reduced by preserving the saphenous vein and post-operative measures to improve drainage, such as stockings, bandaging, inguinal pressure dressings or vacuum suction and prophylactic antibiotics [149]. Transposition of the Sartorius muscle is not recommended. There is no benefit from using fibrin glue intraoperatively [150]. Advanced cases may require reconstructive surgery for wound closure. The most commonly reported complications in recent series were wound infections (1.2-1.4%), skin necrosis (0.6-4.7%), lymphoedema (5-13.9%) and lymphocele formation (2.1-4%) [144, 145].

Minimally-invasive surgical techniques (laparoscopic, robot-assisted) for inguinal lymphadenectomy are technically feasible and, in small series, have been reported to significantly reduce post-operative morbidity except for the rate of lymphoceles [144, 150-153].

#### 6.2.2.2 *Pelvic lymphadenectomy*

Patients with two or more inguinal lymph node metastases on one side and/or extracapsular lymph node extension need to undergo ipsilateral pelvic lymphadenectomy. 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 extracapsular extension [101, 154] (LE: 2b).

Positive pelvic nodes carry a worse prognosis than only inguinal nodal metastasis (five-year CSS 71.0% vs. 33.2%) [155]. In a study of 142 groin node-positive patients, significant risk factors for pelvic nodal metastasis were the number of positive inguinal nodes (cut-off three), the diameter of inguinal metastatic nodes (cut-off 30 mm) and extra-nodal extension. The percentage of pelvic nodal metastases was 0% without any of these risk factors and 57.1% with all three risk factors present [155].

Pelvic lymphadenectomy may be performed simultaneously with inguinal lymphadenectomy or as a secondary procedure. 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 [156].

#### *6.2.2.3 Adjuvant treatment*

In patients with pN2/pN3 disease, adjuvant chemotherapy is recommended after lymphadenectomy [157] (see Section 6.3.1). One retrospective study reported long-term DFS of 84% in node-positive patients with adjuvant chemotherapy after radical lymph node surgery vs. 39% in historical controls without adjuvant chemotherapy after lymphadenectomy [157]. More recent studies have confirmed the survival benefit of adjuvant chemotherapy after radical inguinal lymphadenectomy [158-160].

Although adjuvant radiotherapy has been used after inguinal lymphadenectomy, there are no data showing definite patient benefit. Adjuvant radiotherapy after inguinal lymphadenectomy should not be administered outside of clinical studies.

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

Patients with large and bulky, sometimes ulcerated, inguinal lymph nodes require staging by thoracic, abdominal and pelvic CT for pelvic nodes and systemic disease. In clinically unequivocal cases, histological verification by biopsy is not required.

These patients have a poor prognosis. Multimodal treatment with neoadjuvant chemotherapy followed by radical lymphadenectomy in responders is recommended [161-163]. Responders to neoadjuvant chemotherapy with post-chemotherapy surgery have been reported to achieve long-term survival in 37% of cases [161]. Contemporary studies have confirmed this patient benefit [162, 164, 165].

### *6.2.4 **Management of lymph node recurrence***

Patients with regional recurrence should be treated in the same way as patients with primary cN1/cN2 disease. However, patients with regional lymph node recurrence after DSNB or modified inguinal lymphadenectomy already have disordered inguinal lymphatic drainage and are at a high risk of irregular metastatic progression. Inguinal nodal recurrence after radical inguinal lymphadenectomy has a five-year CSS rate of 16% [166].

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

### *6.2.5 **The role of radiotherapy in lymph node disease***

Radiotherapy is used in some institutions for the treatment of inguinal lymph nodes. However, this is not evidence-based. One of the rare prospective trials in penile cancer found that inguinal radical lymphadenectomy is superior to inguinal radiotherapy for lymph-node positive penile cancer patients [167].

There is no evidence that adjuvant radiotherapy after radical inguinal lymphadenectomy improves oncological outcome [168]. One study reported poor long-term survival in patients with adjuvant inguinal and pelvic radiotherapy [169]. Other studies have likewise not demonstrated a patient benefit [168-174].

In one comparative retrospective study, adjuvant chemotherapy was far superior to adjuvant radiotherapy after radical inguinal lymphadenectomy in node-positive patients [157]. A large retrospective analysis of the SEER database (National Cancer Institute Surveillance, Epidemiology and End Results Program) of 2,458 penile cancer patients treated with either surgery alone or surgery plus EBRT concluded that the addition of adjuvant EBRT 'had neither a harmful nor a beneficial effect on CSS' [175].

Due to this lack of positive evidence, radiotherapy cannot be recommended outside of controlled trials for the treatment of lymph node disease in penile cancer. Prophylactic radiotherapy for cN0 disease is not indicated. Radiotherapy for advanced lymph node disease remains a palliative option.

### *6.2.6 **Guidelines for treatment strategies for nodal metastases***

| **Regional lymph nodes** | **Management of regional lymph nodes is fundamental in the treatment of penile cancer** | **Strength rating** |
|---|---|---|
| No palpable inguinal nodes (cN0) | Tis, Ta G1, T1G1: surveillance. | Strong |
| | > T1G2: invasive lymph node staging by either bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy. | Strong |
| Palpable inguinal nodes (cN1/cN2) | Radical inguinal lymphadenectomy. | Strong |
| Fixed inguinal lymph nodes (cN3) | Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders. | Weak |

| | | |
|---|---|---|
| Pelvic lymph nodes | Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) or if extracapsular nodal metastasis (pN3) reported. | Strong |
| Adjuvant chemotherapy | In pN2/pN3 patients after radical lymphadenectomy. | Strong |
| Radiotherapy | Not recommended for nodal disease except as a palliative option. | Strong |

## 6.3 Chemotherapy

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

Multimodal treatment can improve patient outcome. Adjuvant chemotherapy after radical lymphadenectomy in node-positive patients has been reported in a few small and heterogeneous series [158-160]. Comparing different small-scale clinical studies is fraught with difficulty.

The value of adjuvant chemotherapy after radical inguinal lymphadenectomy in node-positive penile cancer was first demonstrated by a study which reported long-term (DFS) of 84% in 25 consecutive patients treated with twelve adjuvant weekly courses of vincristine, bleomycin, and methotrexate (VBM) during 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% [161].

The same group also published results of an adjuvant chemotherapy regimen with three courses of cisplatin and 5-FU with lower toxicity and even better results compared to VBM [176] (LE: 2b). The same group has published results of adjuvant chemotherapy with cisplatin, 5-FU plus paclitaxel or docetaxel (TPF), with three to four cycles after resection of pN2-3 disease [177]. Of 19 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 [178].

Therefore, the use of adjuvant chemotherapy is recommended, in particular when the administration of the triple combination chemotherapy is feasible and there is curative intent (LE: 2b). There are no data concerning adjuvant chemotherapy in stage pN1 patients. Adjuvant chemotherapy in pN1 disease is, therefore, recommended only in clinical trials.

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

Bulky inguinal lymph node enlargement (cN3) indicates extensive lymphatic metastatic disease. Primary lymph node surgery is not generally recommended since complete surgical resection is unlikely and only a few patients will benefit from surgery alone.

Limited data is available on neoadjuvant chemotherapy before inguinal lymph node surgery. However, it allows for early treatment of systemic disease and down-sizing of the inguinal lymph node metastases. In responders, complete surgical treatment is possible with a good clinical response.

Results of neoadjuvant chemotherapy for bulky inguinal lymph node metastases were modest in retrospective studies including five to twenty patients treated with bleomycin-vincristine-methotrexate (BVM) or bleomycin-methotrexate-cisplatin (BMP) regimens [162, 163, 179], as well as in the confirmatory BMP trial of the Southwest Oncology Group [180]. However, treatment-related toxicity was unacceptable due to bleomycin-related mortality.

Cisplatin/5-FU (PF) chemotherapy achieved a response rate of 25-50% with more acceptable toxicity [181, 182]. Over a period of 30 years, five different neoadjuvant chemotherapy regimens were used in twenty patients [87], with long-term survival in 37% of responders who underwent radical lymph node surgery after neoadjuvant chemotherapy. In the EORTC cancer study 30992, 26 patients with locally advanced or metastatic disease received irinotecan and cisplatin chemotherapy. Although the study did not meet its primary endpoint (response rate), there were three cases of pathologically complete remissions [183].

A phase II trial evaluated treatment with four cycles of neoadjuvant paclitaxel, cisplatin, and ifosfamide (TIP). An objective response was reported in 15/30 patients, including three pathologically complete remissions (pCRs). The estimated median time to progression (TTP) was 8.1 months and the median OS was 17.1 months [164] (LE: 2a).

Hypothetical similarities between penile SCC and head and neck SCC led to the evaluation, in penile cancer, of chemotherapy regimens with an efficacy in head and neck SCC, including taxanes. The combination of cisplatin and 5-FU plus a taxane has been used in neoadjuvant and adjuvant settings [177]. An overall objective response rate of 44% was reported in 28 patients treated neoadjuvantly, including 14% pCR (LE: 2b). Similarly, a phase II trial with TPF using docetaxel instead of paclitaxel reported an objective response of 38.5% in 29 locally advanced or metastatic patients, although the study did not meet its primary endpoint. However, there was significant toxicity [184] (LE: 2a). Further evidence of the benefit of neoadjuvant chemotherapy was published recently [165].

Overall, these results support the recommendation that neoadjuvant chemotherapy using a cisplatin- and taxane-based triple combination should be used in patients with fixed, unresectable, nodal disease (LE: 2a).

There are hardly any data concerning the potential benefit of radiochemotherapy together with lymph node surgery in penile cancer. It should therefore only be used in controlled clinical trials [185].

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

A recent retrospective study of 140 patients with advanced penile SCC reported that visceral metastases and an > 1 ECOG-performance status were independent prognostic factors, and that cisplatin-based regimens had better outcomes than non-cisplatin-based regimens after adjusting for prognostic factors [186] (LE: 3).

Before taxanes were introduced, chemotherapy data in penile cancer were limited by small numbers, patient heterogeneity and retrospective design (except for the EORTC trial [183]). Initial response rates ranged from 25% to 100%, with very few sustained responses and very few long-term survivors. The introduction of taxanes into penile cancer chemotherapy has enhanced the activity and efficacy of the regimens used [87, 162-164, 178-184, 187].

There are virtually no data on second-line chemotherapy in penile cancer. One report using second-line paclitaxel monotherapy reported a response rate of < 30% and no patient survived [188] (LE: 2a). Anecdotally, a benefit of second-line cisplatin with gemcitabine has been observed [189] (LE: 4).

#### *6.3.4 **Intra-arterial chemotherapy***

Intra-arterial chemotherapy which refers to intra-aortic application has been trialled in locally advanced cases, especially of cisplatin and gemcitabine in small case series [190-193]. Apart from a limited clinical response, the outcome was not significantly improved.

#### *6.3.5 **Targeted therapy***

Targeted drugs have been used as second-line treatment and they could be considered as single-agent treatment in refractory cases. Anti-epidermal growth factor receptor (EGFR) targeted monotherapy has been trialled [194], as EGFR is expressed in penile SCC [190, 191] and there are assumed similarities with head and neck SCC [190, 191]. There have been other studies, particularly with the anti-EGFR monoclonal antibodies panitumumab and cetuximab, without long-term response, however [195]. Some activity of tyrosine kinase inhibitors has been reported as well [193]. Further clinical studies are needed (LE: 4).

#### *6.3.6 **Guidelines for chemotherapy***

| Recommendations | Strength rating |
|---|---|
| Offer patients with pN2-3 tumours adjuvant chemotherapy after radical lymphadenectomy (three to four cycles of cisplatin, a taxane and 5-fluorouracil or ifosfamide). | Strong |
| Offer patients with non-resectable or recurrent lymph node metastases neoadjuvant chemotherapy (four cycles of a cisplatin- and taxane-based regimen) followed by radical surgery. | Weak |
| Offer palliative chemotherapy to patients with systemic disease. | Weak |

# 7. FOLLOW-UP

## 7.1 Rationale for follow-up

Early detection of recurrence increases the likelihood of curative treatment since local recurrence does not significantly reduce long-term survival if successfully treated [87, 196]. In contrast, disease that has spread to the inguinal lymph nodes greatly reduces the rate of long-term DSS. Follow-up is also important in the detection and management of treatment-related complications.

Local or regional nodal recurrences usually occur within two years of primary treatment [87]. After five years, all recurrences were either local or new primary lesions [87]. This supports an intensive follow-up regimen during the first two years, with a less intensive follow up later for a total of at least five years. Follow-up after five years may be omitted in motivated patients who will undertake regular self-examination reliably [87].

### *7.1.1 When and how to follow-up*

After local treatment with negative inguinal nodes, follow-up should include physical examination of the penis and groins for local and/or regional recurrence. Additional imaging has no proven benefit. Follow-up also depends on the primary treatment modality. Histology from the glans should be obtained to confirm disease-free status following laser ablation or topical chemotherapy.

After potentially curative treatment for inguinal nodal metastases, CT or MRI imaging for the detection of systemic disease should be performed at three-monthly intervals for the first two years.

Although rare, late local recurrence may occur, with life-threatening metastases becoming very unusual after five years. Therefore, regular follow up can be stopped after five years, provided the patient understands the need to report any local changes immediately [197]. In patients unlikely to self-examine, long-term follow up may be necessary.

### *7.1.2 Recurrence of the primary tumour*

Local recurrence is more likely with all types of local organ-sparing treatment but does not influence the rate of cancer-specific survival in contrast to regional lymph node recurrence [87, 196]. Local recurrence occurred during the first two years in up to 27% of patients treated with penis-preserving modalities [98]. After partial penectomy, the risk of local recurrence is about 4-5% [87, 98, 196].

Local recurrence is easily detected by physical examination, by the patient himself or his physician. Patient education is an essential part of follow-up and the patient should be urged to visit a specialist if any changes are seen.

### *7.1.3 Regional recurrence*

Most regional recurrences occur during the first two years after treatment, irrespective of whether surveillance or invasive nodal staging were used. Although unlikely, regional recurrence can occur later than two years after treatment. It is therefore advisable to continue follow up in these patients [197]. The highest rate of regional recurrence (9%) occurs in patients managed by surveillance, while the lowest is in patients who have undergone invasive nodal staging by modified inguinal lymphadenectomy or DSNB and whose lymph nodes were negative (2.3%).

The use of US and fine needle aspiration cytology (FNAC) in suspicious cases has improved the early detection rate of regional recurrence [76, 198, 199]. There are no data to support the routine use of CT or MRI for the follow-up of inguinal nodes.

Patients who have had surgery for lymph node metastases without adjuvant treatment have an increased risk of regional recurrence of 19% [87]. Regional recurrence requires timely treatment by radical inguinal lymphadenectomy and adjuvant chemotherapy (see Section 6).

### *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 |

## 7.2 Quality of life

### *7.2.1 **Consequences after penile cancer treatment***

In patients with long-term survival after penile cancer treatment, sexual dysfunction, voiding problems and cosmetic penile appearance may adversely affect the patient's QoL [200]. However, there is very little data on sexual function and QoL after treatment for penile cancer. In particular, there is heterogeneity of the psychometric tools used to assess QoL outcomes and further research is needed to develop disease-specific patient reported outcome measures for penile cancer.

***Comparative studies***

There are only two comparative studies in the literature reporting on the health-related quality of life (HRQoL) outcomes following surgery for localised penile cancer. One study compared wide local excision with glansectomy [201]. Among 41 patients there was reduction in post-operative International Index of Erectile Function (IIEF) and the authors concluded that local excision led to better sexual outcomes than glansectomy. In another study of 147 patients, the IIEF-15, the SF36 Health Survey and the Impact of Cancer questionnaire were used [202].

Compared to an age-matched population sample, men after partial penectomy reported significantly more problems with orgasm, cosmesis, life interference and urinary function than those who had undergone penile-sparing surgery (83% vs. 43%, $p < 0.0001$). Interestingly, there were no differences in erectile function, sexual desire, intercourse satisfaction or overall sexual satisfaction.

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

A retrospective interview-based Swedish study after laser treatment for penile PeIN [104] in 58 out of 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 rate with life overall and sexuality which was similar to that of the general Swedish population.

A large study on $CO_2$ laser treatment of penile cancer in 224 patients reported no problems with erectile or sexual function following treatment [91]. In another study [107], no sexual dysfunction occurred in nineteen patients treated.

### *7.2.3 **Sexual activity after glans resurfacing***

In one study with ten patients [111], 7/10 completed questionnaires (IIEF-5 and a non-validated 9-item questionnaire) at six months. The median IIEF-5 score was 24 (no erectile dysfunction). All patients who were sexually active before treatment were active after three to five months, 7/7 stated that the sensation at the tip of their penis was either no different or better after surgery, and 5/7 patients felt that their sex life had improved. Overall patient satisfaction with glans resurfacing was high.

### *7.2.4 **Sexual activity after glansectomy***

Two studies reported sexual function after glansectomy [112, 113]. In one (n = 68) with unclear methodology [113], 79% did not report any decline in spontaneous erection, rigidity or penetrative capacity after surgery, and 75% reported recovery of orgasm. In the other study [114], all twelve patients had returned to 'normal' sexual activity one month after surgery.

### *7.2.5 **Sexual function after partial penectomy***

Sexual function after partial penectomy was reported by three studies [203-205]. In one with 18 patients with a mean age of 52 years, the IIEF scores were significantly worse for all domains of sexual function after surgery [203] and 55.6% of patients had erectile function that allowed sexual intercourse. In patients who did not resume sexual activity, 50% were ashamed of their small penis and missing glans, while another third blamed surgical complications. Of those who had resumed sexual intercourse, 66.7% reported the same frequency and level of sexual activity as before surgery, while 72.2% continued to have ejaculation and orgasm every time with sexual activity. Overall, only 33.3% maintained their pre-operative frequency of sexual intercourse and were satisfied with their sex life.

In another study, an 'Overall Sexual Functioning Questionnaire' was used in 14 patients with a median time of 11.5 months after surgery (range 6-72) [204]. Prior to surgery, all patients had had normal erectile function and intercourse at least once a month. In 9/14 patients, sexual function was 'normal' or 'slightly decreased', while 3/14 had had no sexual intercourse since surgery. Alei *et al.* reported an improvement in erectile function over time [205]. In a report of 25 patients after partial penectomy and neoglans formation, the IIEF-5, Quality of Erection Questionnaire (QEQ), Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) and Self-Esteem and Relationship (SEAR) were used. This study reported a high percentage of patient and partner satisfaction with surgical treatment and recovery of sexual function, self-esteem, and overall relationship satisfaction [206].

#### *7.2.6 **Quality of life and sexual function after total penectomy***

In ten patients with penile cancer evaluated after total amputation of the penis, there were significant effects on sexual life and overall QoL, although there were no negative implications in terms of partner relationships, self-assessment or the evaluation of masculinity [207].

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

Several qualitative and quantitative instruments have been used to assess 'psychological behaviour and adjustment' and 'social activity' as QoL indicators [204, 208]. Patient-reported fears were those of mutilation, loss of sexual pleasure and of cancer death and what this would mean for their families. The study reported no significant levels of anxiety and depression on the General Health Questionnaire-12 and the Hospital Anxiety and Depression Scale. 'Social activity' remained the same after surgery in terms of living conditions, family life and social interactions.

### 7.3 Total phallic reconstruction

There is very limited data about total phallic reconstruction following full or near-total penile amputation [137, 209, 210]. Although it is not possible to restore function without a penile prosthesis, cosmetically acceptable results can be obtained.

### 7.4 Specialised care

Since penile cancer is rare, patients should be referred to a centre with experience and expertise in local treatment, pathological diagnosis, chemotherapy and psychological support for penile cancer patients. Some countries have centralised the care of penile cancer patients (Sweden, Denmark, the Netherlands, the UK).

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# 9. CONFLICT OF INTEREST

All members of the Penile Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://uroweb.org/guideline/penile-cancer/.

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# 10. CITATION INFORMATION

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