EAU-ASCO Collaborative Guidelines on

Penile Cancer

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) – American Society of Clinical Oncology (ASCO) Guidelines on Penile Cancer provide 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 level of evidence available to the experts, but following guideline recommendations will not necessarily result in the best treatment-related outcomes for a given patient. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather, help to focus decisions. Taking patient's personal values and preferences/individual circumstances into account is of paramount importance. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU-ASCO Penile Cancer Guidelines Panel consists of an international, multidisciplinary group of clinicians, including urologists, pathologists, oncologists, radiation oncologists and patient advocates. The members of this Panel have been selected based on their expertise and to represent the multidisciplinary professionals caring for patients with 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 in print and on the EAU website. The Pocket Guidelines are an abridged version of the full-text Guidelines, which may require consultation together with the full text version. This updated 2026 document presents a complete revision of the prior (2023) publication. All prior versions can be viewed at the EAU website: https://uroweb.org/guidelines/archive/penile-cancer.

An EAU Guidelines App is also available for iOS and Android devices containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, guidelines cheat sheets and links to the extended guidelines.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU Penile Cancer Guidelines were first published in 2000. The 2023 EAU-ASCO publication was a complete revision of the prior print, and the 2026 version represents another major update.

1.4.2 Summary of changes

The literature for the complete document has been assessed, and all Chapters of the 2026 Penile Cancer Guidelines have been updated. New data have been included in the following Sections, resulting in new Sections, and new and revised guidelines:

- New text additions and references throughout Chapter 3.
- Incorporation of new text and references throughout Chapter 5, including a new Section 5.3 on genomic testing, as well as a new Figure 5.1 providing information on clinical cN0 management.
- New text additions and references throughout Chapter 6, with an updated summary of evidence in Section 6.1.5 on local treatment of penile carcinoma. A new figure is provided in Section 6.2: Figure 6.1, which provides information on regional lymph node management: clinically evident disease (cN1–cN3). Section 6.5.2.a on immunotherapy has also been restructured.
- A new figure in Section 6.5, Figure 6.2, provides information on systemic and palliative therapies for advanced disease.
- Substantial text additions have been made to Section 7, and the Section has been restructured, including the new Section 7.4.1 on the advantages of centralised care, Section 7.4.2 on Guidelines adherence, Section 7.4.3 on survival, and Section 7.4.4 on the disadvantages of centralised care.
- Updated summary of evidence and new guideline in Chapter 7 regarding follow-up and quality of life.

1.5 Preface

Penile cancer has a significant impact on quality of life (QoL) in many ways. Patients are not only exposed to the psychological and emotional stress of a cancer diagnosis and what that means for the rest of their lives, but also the psychological impact and stigma of cancer on an intimate part of the body. The treatments also cause significant physical and emotional changes, resulting in feelings of mutilation, loss of masculinity and coping with

the impact on voiding and sexual function, which in turn can result in relationship breakdowns and withdrawal from society. Long-term management of lymphoedema also presents a challenge for many of these men.

As a Guidelines Panel, we have chosen to stress the importance of QoL in penile cancer at the beginning of these Guidelines.We believe strongly that these significant emotional, social and physical needs must be discussed and addressed early in the patient pathway, through a holistic and multidisciplinary approach. An important part of a holistic approach is access to palliative care. The World Health Organization (WHO) definition of palliative care states it: 'is a crucial part of integrated, people-centred health services. Relieving serious health-related suffering, be it physical, psychological, social, or spiritual, is a global ethical responsibility' [1]. As a result, access to palliative care should be available to patients throughout their cancer pathway.

It is important to recognise the evolving needs of a patient with a diagnosis of penile cancer, even many months following the completion of treatment, and therefore appropriate follow-up and patient support services are also a critical aspect of penile cancer care.

The reality is that much of the literature on this rare cancer over the last two decades has focused on oncological outcomes rather than functional and QoL outcomes. So much more needs to be done to investigate these issues and address the many unmet needs of patients diagnosed with penile cancer, some of which are described in Table 1.1 [2].

Table 1.1: Unmet needs of patients with penile cancer

Emotional needs	Relational needs	Medical needs
Loss of masculinity	Impact on relationship with partner	Lack of advice on how to cope
Shock/disbelief	Sexual	Lymphoedema
Depression/sadness	Performance anxiety/cannot satisfy partner	Lack of information on what to expect after surgery
Fear	Concerns on how to tell family	Sit down to urinate/cleanliness of toilets
Anxiety	Relationships damaged or lost	Lack of rehabilitation/supportive care
Embarrassment/stigma	Avoiding meeting friends/new relationships	Missed/incorrect diagnosis

2. METHODS

2.1 Data identification

For the 2026 Penile Cancer Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. Comprehensive literature searches were carried out for all Sections. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between 1 February 2022 and 1 May 2025. A total of 1,696 unique records were identified, retrieved and screened for relevance. A total of 55 new references were added to the 2026 Penile Cancer Guidelines. A detailed search strategy is available online: https://uroweb.org/guidelines/penile-cancer/publications-appendices.

Recommendations within the Guidelines are developed by the Panels to prioritise clinically important care decisions. 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 the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms that accompany each Guidelines recommendation, addresses a number of key elements:

1. the overall quality of the evidence that exists for the recommendation [5];
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; and
6. the certainty of those patient values and preferences.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [6].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review and future goals

The 2023 Guidelines document was subjected to peer-review prior to publication. The next peer-review is scheduled for 2028. Publications ensuing from published systematic reviews have all been peer reviewed.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Definition of penile cancer

More than 95% of penile cancers are SCCs. There are several recognised subtypes of penile SCC with various clinical features and natural history (see Table 3.1). Penile SCC usually arises from the epithelium of the inner prepuce or the glans.

Table 3.1: Histological subtypes of penile carcinomas according to the 2022 WHO Classification [7, 8], **frequency and outcomes** (Modified from [9])

Subtype	Frequency (% of cases)	Mortality (%)	Other features
HPV-independent SCC			
Usual	45–75	20–38	Diagnosis of exclusion. Various degrees of differentiation.
Pseudohyperplastic*	< 1	0	Well-differentiated, superficially spreading simulating pseudoepitheliomatous hyperplasia.
Pseudoglandular*	< 1	30	Poorly-differentiated carcinoma with acantholytic pseudolumina simulating glands.
Verrucous	3–8	0	Extremely well-differentiated, broad-based, and pushing tumour front. No metastasis reported.
Cuniculatum**	< 1	0	Endophytic labyrinthine growth pattern with broad-based pushing margins.
Papillary	2–15	0–6	Papillae covered by well- to moderately differentiated cells without koilocytes.
Sarcomatoid	1–7	45–90	Biphasic epithelial and spindle cell neoplasia. Most aggressive and worse prognosis.
Mixed	10–19	3–7	Two or more subtypes in the same specimen. Prognosis is related to the subtypes involved.
HPV-associated			
Basaloid	4–10	21–67	Uniform basaloid cells in nests or sheets, with comedonecrosis or abrupt keratinisation.
Warty	5–10	0–10	Condylomatous papillae with central fibrovascular cores and koilocytes.
Clear cell	< 1	20–30	Nests or sheets of cells with ample, clear cytoplasm with central of geographical necrosis.

Lymphoepithelioma-like	< 1	Unknown	Poorly differentiated cells intermixed with dense lymphoplasmacytic and eosinophilic infiltrate.
Mixed	4–10	30–50	Mainly warty-basaloid carcinoma according to the WHO 2022.
Others			
SCC NOS	Unknown	Unknown	Keratinising carcinoma. This must be used only when evaluation of p16 is not available.
Adenosquamous	1–2	0–14	Squamous tumour nests intermixed with a minor mucinous glandular component.
Mucoepidermoid	Unknown	Unknown	Clear separation between adenosquamous and mucoepidermoid is not provided in the WHO classification. Salivary glands criteria can be applied but there is no consensus.

HPV = human papillomavirus; NOS = not otherwise specified; SCC = squamous cell carcinoma; WHO = World Health Organization.
** WHO 2022 classification consider these subtypes part of usual SCC.*
*** Cuniculatum carcinoma is considered a variant of verrucous carcinoma by the WHO 2022.*

3.2 Epidemiology

Penile cancer incidence varies across the world (Figure 3.1). In industrialised countries, penile cancer is uncommon, with an overall incidence of approximately 0.94/100,000 males in Europe and 0.5 in the United States of America (USA) [10, 11]. In contrast, in South America, Southeast Asia and parts of Africa, the incidence is much higher and can account for 1–2% of malignant disease in men [11]. The annual age-adjusted incidence is 0.7–3.0 in India and 8.3 in Brazil (per 100,000, respectively), and is higher in parts of Africa, such as Uganda [11, 12]. Interestingly, some current data from South Korea demonstrate a decline in age-standardised rates, despite population aging [13].

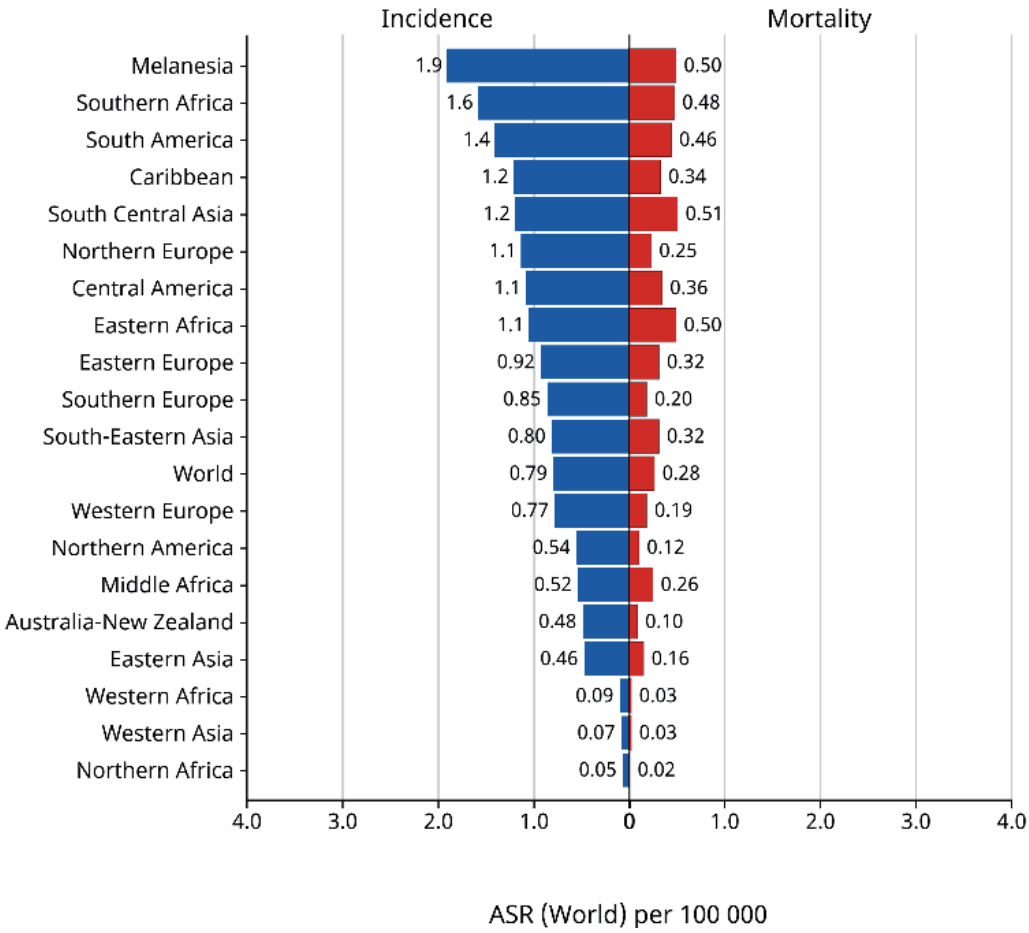
In Europe, there is considerable variation across countries. Recent registry-based analyses across 27 European countries [14] confirm substantial heterogeneity in incidence and mortality trends. According to incidence, four groups were reported: the highest incidence in Lithuania, Latvia and Ireland; intermediate incidence for Czechia, Belgium, Germany and Estonia; low incidence for Switzerland, the Netherlands, Slovenia, Poland and Finland; and the lowest incidence was recorded for Austria. Data from Norway showed an increase in the age-standardised incidence rates in five-year periods from 2001–2015 compared to the previous periods (0.65/100,000 in 1956–1960 vs. 0.91/100,000 in 2011–2015) with an estimated annual percent change of +0.80% [15]; as well as a significant rise in the proportion of human papillomavirus (HPV)-related penile cancers (from < 30% in the 1970s to nearly 50% in the 2010s) [16]. The NORDCAN initiative, covering Denmark, Finland, Iceland, Norway and Sweden showed an increase in the incidence of penile SCC from 2000 to 2022, while survival remained unchanged [17]. In Germany, registry-based data from Saxony reported a significant rise in incidence from 0.86 in 2000 to 2.67 per 100,000 in 2018, corresponding to an annual percent change of +3.6% [18]. A study from the Netherlands [19], based on data from a nationwide cancer registry, reported an increase in incidence from 0.92 to 1.83 per 100,000 per year between 1990 and 2020. In the United Kingdom (UK), the age-standardised incidence rate increased 28% between 1993 and 2018. This trend was seen in age groups from 50 to 79 years old. Incidence rates remained unchanged for both age extremes (< 50 and > 79 years) [20]. Based on 16 cancer registries in France, incidence rates between 2009 and 2011 were 0.59 per 100,000 men (95% confidence interval [CI]: 0.50–0.68) and these rates have remained stable since 1989 [21].

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 males, respectively. The overall age-adjusted incidence rate decreased between 1973 and 2002 per decade from 0.84 (1973–1982) to 0.69 (1983–1992) and 0.58 (1993–2002) per 100,000 males, respectively [22]. An increasing trend, slightly surpassing the previous incidence rates, was described using the Surveillance, Epidemiology and End Result (SEER) 2000–2016 data [23], showing an estimated annual percent change of +3.5% from 2004 to 2016 [24].

The incidence increases with age [20, 25], with a peak in the sixth decade, but does occur in younger men [26]. Penile cancer is common in regions with a high prevalence of HPV, and approximately one-third to half of cancer cases are attributed to HPV-associated carcinogenesis [27, 28]. There are no reports linking this cancer to human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS).

Despite the lack of consistent primary epidemiological data on penile cancer worldwide, current evidence suggest an increase in incidence in Western/developed countries, most likely driven by higher infection rates of HPV, which is a trend also observed in oropharynx carcinoma [29]. There is a critical need to improve the reporting and standardisation of penile cancer epidemiological data globally to evaluate the effectiveness of interventions.

Figure 3.1: Annual incidence rate (world standardised) by world area [30]



3.3 Risk factors, prognosis and prevention

Several risk factors for penile cancer have been identified, such as phimosis, chronic penile inflammation, lichen sclerosus, smoking, ultraviolet A phototherapy and low socioeconomic status, amongst others [31].

Patient outcome is influenced by clinical and histologic features. United States SEER data from 18 cancer registries indicated an overall five-year relative survival of 67%, with no significant changes when comparing five-year spans between 2000 and 2014. Patients with localised disease showed the best outcome with up to 81% five-year relative survival. Patients with distant metastases have the worst outcomes with only 16% five-year relative survival [32].

Human papillomavirus infection is the main risk factor for penile cancer [33]. Human papillomavirus deoxyribonucleic acid (DNA) has been identified in intraepithelial neoplasia and invasive penile cancer tissue samples. The HPV virus interacts with oncogenes and tumour suppressor genes *(p16, P53, Rb genes)* [34, 35]. The rate of HPV-positivity differs among various histological subtypes of penile SCC. Human papillomavirus is a co-factor in the carcinogenesis of some subtypes of penile SCC, while others are not related to HPV. The risk of penile cancer is increased in patients with condyloma acuminata [36]. A systematic review of 52 studies concluded that the overall HPV prevalence in penile cancer is 50.8% (95% CI: 44.8–56.7). Among HPV-associated carcinomas, basaloid carcinoma showed the highest prevalence (84%), followed by warty-basaloid carcinoma (75.7%) and warty carcinomas (58.7%). In histologically HPV-independent carcinomas, HPV prevalence was 19.4%. The most frequent HPV genotypes were HPV16 (68.3%, 95% CI: 58.9–77.1), followed by the low-risk HPV6 genotype (8.1%, 95% CI: 4.0–13.7) [28].

In early studies, HPV has shown an inconsistent association with prognosis. In one study, a significantly better five-year disease-specific survival (DSS) was reported for HPV-positive versus HPV-negative cases (93% vs. 78%) [37], while no difference in lymph node (LN) metastases and ten-year survival was reported in another study [38]. This variable relationship with outcome remains unexplained, but some studies suggested that it can be related to specific treatment [39] and linked to various histologic subtypes [40]. A meta-analysis published in 2018 [41] reported a pooled hazard ratio (HR) of 0.61 for penile cancer HPV-positive cases, which is in line with head, neck [42] and anal cancers [43], with an HR of 0.34 and 0.54, respectively. Positivity for p16 immunohistochemistry (IHC), a surrogate for HPV activity (see Section 3.4.5), has emerged as an independent prognostic marker for penile SCC (DSS HR: 0.45) based on two meta-analyses [41, 44]. It positively outperforms HPV status in predicting DSS, with five-year DSS approaching 88% in p16-positive versus 58% in negative tumours [45]. One study from Norway showed better prognosis for HPV-positive cases in patients with positive LNs [16]. Similar trends were reported in vulvar and anal cancers [43, 46].

There is no significant association between the incidence of penile and cervical cancer, although half of penile cancer and virtually all cervical cancer cases are linked to HPV [47]. Female sexual partners of patients with penile cancer have not been found to have an increased incidence of cervical cancer [48].

Aberrant p53 immunostaining, as a surrogate for TP53 mutation, independently predicts worse overall survival (OS) and cancer-specific survival (CSS) [49, 50]. TP53 alterations may be more common in HPV-negative tumours and emerging datasets have described the genomic landscape of penile carcinoma, some of which may have prognostic implications [49-60]. High expression of Ki67 – another immunohistochemical marker used in penile SCC – was associated with marginal decrease in CSS [50].

At present, except in a limited number of countries, there is no general recommendation for HPV vaccination in males due to the various HPV-associated risk patterns in penile and cervical cancer. A meta-analysis showed that the incidence of anal (risk ratio [RR]: 0.42), oral (RR: 0.16) and cervical HPV infections (RR: 0.22) were reduced in vaccinated groups when compared against control groups, indicating that HPV vaccination leads to the prevention of HPV infection [61]. Human papillomavirus vaccination in males showed more than 50% efficacy against anal intraepithelial lesions, but no meaningful estimates were obtained for penile, anal and head and neck-invasive carcinomas [62]. An annual increase from 1.8% to 2.7% in HPV-associated cancers at other anatomical sites in males have been reported [63]. This trend is expected to continue over the coming decades, due to the late peak in incidence and the recent adoption of gender-neutral HPV vaccination programmes. Since up to 50% of invasive penile carcinomas and 80% of preneoplastic lesions are HPV-associated, HPV vaccination for this at-risk population is encouraged [64].

Phimosis is strongly associated with invasive penile cancer [65-68] due to associated chronic infections. However, smegma is not a carcinogen [67]. The incidence of lichen sclerosus is relatively high in patients with 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 [66, 68].

Neonatal circumcision reduces the incidence of penile cancer. However, it does not appear to reduce the risk of PeIN [65]. The lowest incidence of penile cancer is reported in 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 (odds ratio [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) [65].

3.4 Pathology

Squamous cell carcinoma accounts for over 95% of penile malignancies. It is not known how often SCC is preceded by premalignant lesions [69-72]. Recent multi-institutional data from North America showed that isolated PeIN, while highly recurrent (±30–48% after excision), rarely progresses to invasive carcinoma (±2%) even with frequent positive margins, supporting an indolent natural history in many cases [73]. Penile intraepithelial neoplasia is considered the precursor lesion of penile SCC; PeINs are classified into HPV-independent, known as differentiated PeIN, and HPV-associated, following the same scheme as the invasive counterparts, in line with WHO 2022 and the recent ISUP consensus [74] (see Table 3.2). Clinical terms such as 'Erythroplasia of Queyrat, Bowenoid papulosis and Bowen's disease' are discouraged, based on the 2022 WHO classification [7, 75].

Different histological types of penile SCC with different growth patterns, clinical aggressiveness and HPV associations have been identified (see Table 3.1). Numerous mixed forms exist, such as the warty-basaloid form, the most common mixed form (50-60%), 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, urinary bladder or colorectal origin [76]. Various types of penile sarcoma have been reported [7].

Table 3.2: Classification of penile intraepithelial neoplasia [7]

• **HPV-independent**
• Differentiated PeIN
• **HPV-associated PeIN**
• Common patterns: basaloid (undifferentiated), warty (condylomatous) and mixed
• Other (less frequent) patterns: pagetoid, clear cell and spindle cell histology

3.4.1 Gross handling of pathology specimens

Tissue sections determine the accuracy of histological diagnosis. Small lesions should be fully included – larger lesions should have at least 3–4 blocks of tumour with the anatomical landmarks. Specimens should be properly oriented by the surgeons and, in case of circumcision or glans resurfacing, properly pinned to allow clear evaluation of the resection margins. Penectomy specimens must be canalised through the urethra and cut longitudinally in two halves for the evaluation of invasion of the penile structures. In larger tumours, identification of distal urethra on gross (as also microscopy) may be difficult. Whole-mount inclusion and sections are recommended, as they provide a better background for the appropriate identification of anatomical structures that can improve accurate staging, with a minimal increase in cost [77]. Sentinel LN should be evaluated according to a standardised IHC protocol [78] for detection of micrometastases. Lymphadenectomy/ lymph node dissection (LND) specimens should be inked and the LNs evaluated properly, since extracapsular extension profoundly influences nodal staging and treatment decisions. Second-opinion pathology review is highly desirable for this rare tumour entity [79], as is setting up comprehensive referral centres for penile cancer management on a national level [79, 80].

3.4.2 Pathology report

For standardisation and data collection purposes, the dataset template from the International Collaboration on Cancer Reporting (ICCR) should be used when possible. 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), pattern of invasion, urethral invasion, invasion of corpus spongiosum/corpora cavernosa, surgical margins and p16 IHC results [81-84] (Table 3.3). The confirmation of the presence of HPV in the specimen (e.g. polymerase chain reaction, *in situ* hybridisation [ISH] for viral DNA/ribonucleic acid [RNA]) is desirable, but currently only carried out in research settings.

Table 3.3: Information to include in pathology reports for penile carcinomas

Type of information*	Recommended	Required
Clinical information • Prior treatments (topic, radiotherapy, chemotherapy)	x	
Surgical procedure		x
Tumour localisation • Anatomic structures involved externally (e.g. foreskin, glans, etc.) and in depth (e.g. dartos, corpus spongiosum, etc.)		x
Macroscopic tumour dimension • Size of tumour • Maximum thickness		x
Photographic documentation	x	
Block identification with description of the localisation of the samples		x
Histological tumour type		x
Histological grade		x
Microscopic maximum dimensions • Depth of invasion (i.e. millimetres from basement membrane to deepest point of invasion) • Combination of gross and microscopic if large tumours		x

Extent of invasion (microscopic confirmation of all the involved anatomic structures)		x
Tumour invasion front (Broadly-based pushing, destructive but well-delineated, destructive irregular/finger-like invasion/tumour budding) [85-87]	x	
Lymphovascular invasion [88, 89]		x
Perineural invasion		x
Margin status in mm (margins as per specimen)		x
Lymph node status • Size of largest nodal tumour deposit (not LN size), total number of LNs, number of positive LNs, extra-capsular spread, inguinal or pelvic, to be reported in every site separately		x
pTNM Stage		x
HPV assessment (at least p16 IHC based)		x

** See also ICCR dataset: https://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/penis/.*

3.4.3 Grading

The tumour, node, metastasis (TNM) classification for penile cancer includes tumour grade, based on its prognostic relevance. Tumour grading in penile cancer has been shown to be highly observer-dependent and can be problematic, especially in large tumours, which may be heterogeneous. This may have implications on the clinical management, because there may be discordance between biopsy and resection grading [69]. Interobserver agreement varies according to the experience and specialisation of the pathologist. In general, interobserver agreement is poor to moderate (Fleiss' kappa 0.07–0.55) [90]. Alternatives or complementary approaches for grading, such as the tumour infiltration pattern [86, 91], have been suggested. A population-based Swedish study proposed a new histological risk grading system based on objective parameters – worst pattern of invasion, lymphocytic host response, lymphovascular invasion and perineural invasion. This model, which excludes subjective grading, identified a large cohort of patients as low risk (98.2% node-negative), suggesting many could safely avoid LN surgery [92]. Although some registries and studies have proposed grading PeIN into low and high-grade, the International Society of Urological Pathology (ISUP) 2025 consensus advises that PeIN should not be graded in routine practice [74]. Nevertheless, until a new methodology to grade penile SCC is developed, grading based on the WHO/ISUP classification is recommended (see Table 3.4), with grade 3 and sarcomatoid being considered to be poorly differentiated.

Table 3.4: Grading recommendations for penile squamous cell carcinoma

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-defined	Infiltrative/ill-defined	Infiltrative/ill-defined	Infiltrative/ill-defined

3.4.4 Pathological prognostic factors

Pathological subtype, perineural invasion, lymphovascular invasion [88], depth of invasion and grade in the primary tumour are strong predictors of poor prognosis and high cancer-specific mortality [93]. Higher grade and lymphovascular invasion are predictors of metastatic spread. Lymphovascular space involvement/invasion is often seen in advanced stages but may also be seen in early invasive tumours of high grade and some histologic subtypes [94, 95]. The extent of LN metastasis and extracapsular spread are also strong predictors of prognosis.

Urethral invasion is not considered a prognostic factor (Union for International Cancer Control [UICC], 9th Edn.) [96]. Nevertheless, invasion of the more proximal urethra can signify a highly aggressive SCC with a poor prognosis, probably due to the invasion of subjacent erectile corpora (see Table 4.1). A systematic review found that invasion of the corpus spongiosum (pT2) showed better CSS, but no OS benefit compared to invasion of the corpora cavernosa [97]. A modified pT2/T3 has been proposed, taking into consideration high-grade, lymphovascular and perineural invasion features in response to this inconsistency [98]. Extracapsular extension in even one single LN carries a poor prognosis and is denoted as pN3 [99-101].

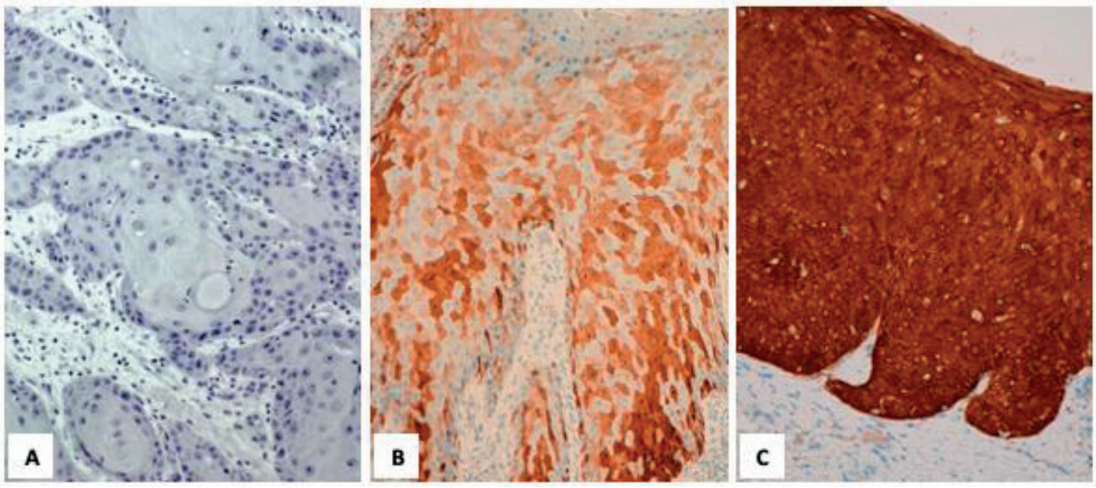
Chaux *et al.*, suggested a prognostic index which incorporates grade, anatomical level of infiltration and perineural invasion to predict the likelihood of inguinal LN metastases and five-year survival [79, 102]. Sali *et al.,* proposed a histopathological risk scoring incorporating grade and anatomical level of involvement, but replaced perineural invasion with pattern of infiltration [87]. Other clinical, pathological and radiological scores, as well as nomograms have been described, but none of these have been comparatively validated, which precludes making a recommendation.

3.4.5 ***Penile cancer and HPV***

In the 2022 WHO classification, the presence of HPV is a key determinant for the broad classification of penile SCC [7]. However, in most clinical settings, standard molecular assessment of HPV status is not available.

The p16 IHC is used as a surrogate for high-risk HPV genotype presence and as a marker of oncogenic activity. In the absence of more-advanced techniques, it is helpful in assigning penile SCC to HPV-associated subtypes. The p16 IHC overall positivity in penile cancer was 41.6% [28]. Higher positivity was seen in morphological HPV-associated SCCs (85.8%) as compared with HPV-independent SCCs (17.1%) [28]. Compared with RNA ISH, p16 IHC showed a sensitivity of 100% and a specificity of 71%, the latter improved to 89% when considering a high intensity for p16 IHC positivity [103]. These data indicate that sensitivity, specificity and predictive values for HPV positivity can be improved using the stringent p16 IHC cut-off suggested by Cubilla *et al.* [104] (Figure 3.2). The ISUP reported that 80% of their respondents during a consultation conference on molecular pathology of urogenital cancers used p16 IHC to separate HPV-associated from HPV-independent PeIN and SCCs and made recommendations on the use of p16 IHC [105].

Figure 3.2: Patterns of p16 expression - (A) no staining; (B) mosaic staining pattern; (C) *en-bloc* staining pattern. Only (C) is considered positive for p16



3.4.6 ***Penile biopsy: pathological and technical considerations***

The quality of biopsy is important [69]. In most cases, acquiring a punch biopsy (e.g. 2–3mm) under local anaesthesia is sufficient to confirm the diagnosis. In biopsies with an average size of 1mm, it was difficult to evaluate the depth of invasion in 91% of cases [69]. Moreover, vascular and lymphatic tumour emboli were detected in only 9–11% of cases [69]. Therefore, in cases in which assessment of depth of invasion is necessary, an incisional biopsy that is deep enough to properly assess the degree of invasion and stage is preferable.

3.4.7 ***Summary of evidence and guidelines for the pathological assessment of tumour specimens***

Summary of evidence	**LE**
Incidence of penile cancer varies according to geographical location, race and ethnicity.	2a
Western-developed countries have seen an increase in incidence, which may be caused by higher HPV infection rates.	2a
In analogy to other HPV-associated cancers, HPV status may influence DSS of penile cancer, but more data are needed, underlining the importance of routine assessment of HPV status in all patients with penile cancer.	2b

Recommendations	Strength rating
The pathological evaluation of penile carcinoma specimens must include the pTNM (see Chapter 4) stage and an assessment of tumour grade.	Strong
The pathological evaluation of penile carcinoma specimens must include an assessment of p16 by immunohistochemistry.	Strong
The pathological evaluation of penile carcinoma specimens should follow the ICCR dataset synoptic report.	Strong

ICCR = International Collaboration on Cancer Reporting; TNM = Tumour, Node, Metastasis.

4. CLASSIFICATION SYSTEMS

4.1 Tumour, Node, Metastasis classification

The 9th edition of the UICC/American Joint Committee on Cancer (AJCC) TNM classification published in 2025 does not differ from the 8th edition [96, 106]. Some changes were introduced compared to the 7th edition. The T1 category is stratified into two different risk groups, depending on the absence or presence of lymphovascular invasion, perineural invasion or poor differentiation (T1a vs. T1b, respectively, see Table 4.1) [107]. Furthermore, invasion into the urethra was previously classified as T3 disease. However, a tumour near the meatus may directly invade into the distal urethra through the corpus spongiosum, which is not associated with worse outcome. In addition, previous studies have shown that corpus spongiosum invasion is associated with a lower incidence of inguinal LN metastasis and has better survival compared to corpus cavernosum invasion. Therefore, invasion into the corpus spongiosum and corpus cavernosum is classified into T2 and T3, respectively [108, 109]. Patients with T4 tumours have extension into adjacent tissues (e.g. prepubic fat, scrotum, spermatic cord, pubic bone, prostate).

The pN1 category was modified to include up to two unilateral inguinal LN metastases, while the pN2 category was modified to be three or more unilateral, or any bilateral LN metastases. This was based on data showing poor outcomes in cases involving three or more unilateral or bilateral LNs compared with those involving one or two unilateral LNs [109, 110]. pN3 stage is defined as pelvic nodes (unilateral or bilateral) or presence of extranodal extension (ENE) (inguinal or pelvic, regardless of the number of LN metastases) [96, 106]. Further retroperitoneal LN spread cranial to the pelvic template is classified as extraregional and therefore as distant metastases.

Table 4.1: UICC/AJCC 8th and 9th editions TNM clinical and pathological classification of penile cancer [96, 106]

Clinical classification		
T – Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Tis	Carcinoma *in situ* (penile intraepithelial neoplasia – PeIN)	
Ta	Non-invasive verrucous carcinoma*	
T1	Tumour invades subepithelial connective tissue	
	T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion or perineural invasion and is not poorly differentiated
	T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or perineural 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	
cNX	Regional lymph nodes cannot be assessed
cN0	No palpable or visibly enlarged inguinal lymph nodes
cN1	Palpable mobile unilateral inguinal lymph node
cN2	Palpable mobile multiple or bilateral inguinal lymph nodes
cN3	Fixed inguinal nodal mass *or* pelvic lymphadenopathy, unilateral or bilateral
M – Distant metastasis	
cM0	No distant metastasis
cM1	Distant metastasis
Pathological classification	
The pT categories correspond to the clinical T categories. 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 or extranodal 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

**Including verrucous carcinoma.*

4.2 Cancer stage grouping

In the UICC TNM 8th edition, stage II was newly subdivided into Stage IIA and Stage IIB based on T categories. Stage IIA is defined as T1b–2N0M0, while Stage IIB is defined as T3N0M0 [96] (Table 4.2).

Table 4.2: UICC TNM stage/Prognostic groups [96]

Stage	T	N	M
0	Tis	N0	M0
	Ta	N0	M0
I	T1a	N0	M0
IIA	T1b	N0	M0
	T2	N0	M0
IIB	T3	N0	M0
IIIA	T1–3	N1	M0
IIIB	T1–3	N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

5. DIAGNOSTIC EVALUATION AND STAGING

5.1 Primary lesion

5.1.1 Physical examination

Primary penile carcinoma are usually clinically evident lesions, often presenting as raised or ulcerous lesions, which can be locally destructive [111]. It is critically important to note that the appearance of penile tumours can be heterogeneous and can sometimes be hidden under the foreskin in case of phimosis. Physical examination should include inspection and palpation of the entire penis (to identify potential skip lesions). The dimensions, anatomic location and extent of local invasion should be noted, and assessment of stretched penile length is recommended.

5.1.2 Imaging of the primary tumour

Physical examination is a reliable method for estimating penile tumour size and clinical T stage [112]. For distinguishing T1 from T2 disease, magnetic resonance imaging (MRI) does not outperform physical examination. However, when there is uncertainty regarding whether the tumour invades the cavernosal bodies (cT3), and if organ-sparing treatment options (e.g. glansectomy) are considered, MRI can be helpful [113, 114]. A systematic review showed a sensitivity and specificity of MRI in predicting corporal invasion of 80% (95% CI: 70–87%) and 96% (95% CI: 85–99%), respectively [115, 116]. Magnetic resonance imaging can also provide useful information regarding resectability in case of large (T4) tumours with invasion in adjacent structures. Magnetic resonance imaging with and without artificial erection showed similar accuracy in local staging [116]. If MRI is not available, penile ultrasound (US) can be considered [117].

5.1.3 Penile biopsy: indications

A biopsy of the penile tumour should be obtained when there is doubt regarding the exact nature of the lesion. However, even in clinically obvious cases, histological information from a biopsy can facilitate treatment decisions (such as indications for surgical staging). Histological confirmation is also necessary to guide management when treatment is planned with topical agents, radiotherapy or laser surgery [111]. For technical and histopathological considerations for penile biopsy, see Section 3.4.6.

5.2 Lymph node staging

Penile cancer metastasises in a stepwise manner through the lymphatic system, initially to the inguinal nodes, the pelvic nodes and finally to distant nodes [118]. Fewer than 5% of patients will present with distant metastases and these are generally accompanied by regional LN involvement. As a result, the most important prognostic factor for survival of penile cancer is the presence and extent of nodal metastases, with a five-year CSS of approximately 95%, 80%, 65% and 35% for N0, N1, N2 or N3 disease, respectively [119, 120].

In patients with clinically node-negative groins (no suspicious palpable nodes, cN0), a non-randomised controlled trial (RCT) observed that early LN surgery led to a three-year survival rate of 84% compared to 35% in those receiving delayed LN surgery, with an ENE incidence of 20% compared to 95% in the early versus delayed surgery groups, respectively [121]. Therefore, detecting lymphatic spread as early as possible is a crucial element in penile cancer management. Since penile cancer disseminates to the inguinal LNs first, initial LN staging is focused on identifying (micro)metastatic disease in the inguinal LNs as early as possible, and imaging for distant metastases is only indicated in clinically node-positive patients.

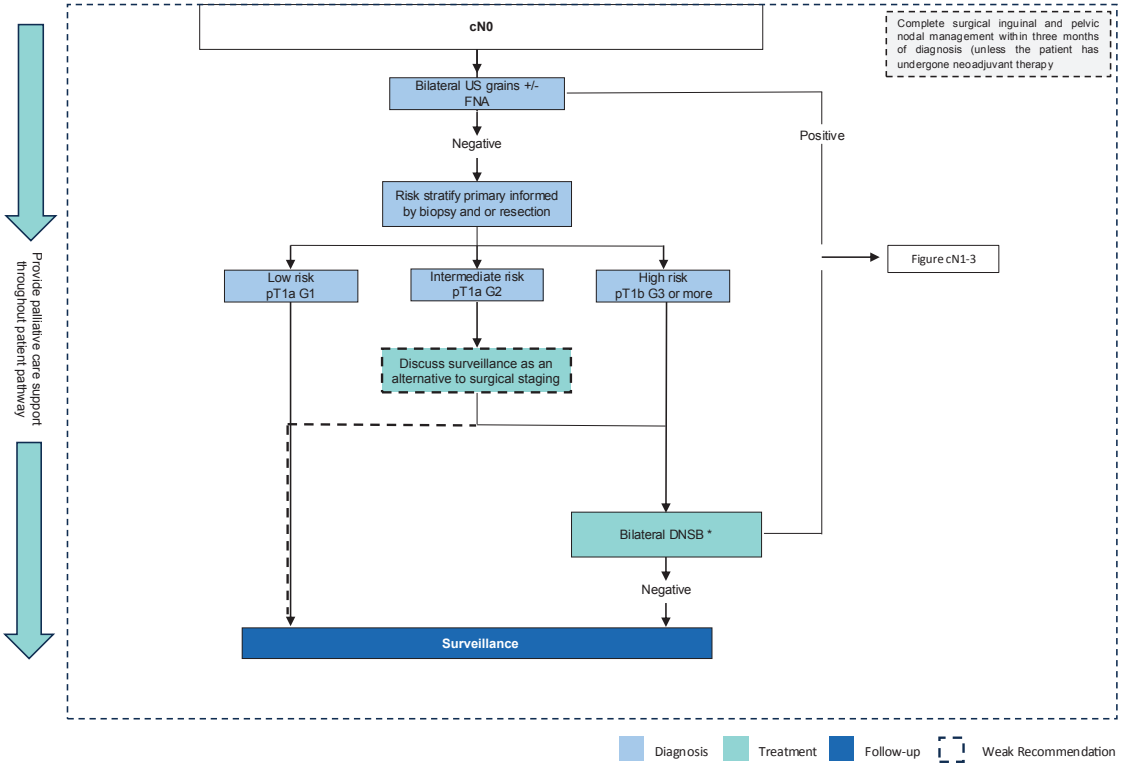
5.2.1 Physical examination

Careful palpation of both groins for enlarged/pathologic inguinal LNs must be part of the initial physical examination of patients suspected of having penile cancer. However, reliable physical examination can be challenging in case of obesity and in patients with previous inguinal surgery. Additionally, enlarged LNs secondary to infection of the primary tumour (rather than metastasis) can occur. The use of antibiotics with the aim to resolve enlarged nodes may delay further staging and treatment and is not recommended [122]. Based on physical examination, patients can be divided into those without suspicious nodes at physical examination (clinically node-negative, cN0), and those with suspicious palpable nodes (clinically node-positive, cN+). In case of suspected pathologic LNs at palpation, the number, location, size and whether the node is fixed or mobile should be noted.

5.2.2 Clinically node-negative (cN0)

If no suspicious nodes are present at palpation (cN0), approximately 20–25% of patients may still harbour occult metastases; therefore, additional staging is warranted [123].

Figure 5.1 : Clinically cN0 management



** If DSNB is not available, perform ILND (open or videoendoscopic).*
DSNB = dynamic sentinel node biopsy; FNA = fine-needle aspiration; G = grade; ILND = inguinal lymph node dissection; US = ultrasound.

5.2.2.a Non-surgical staging options

No validated nomograms or tumour markers can reliably predict LN involvement. Conventional imaging modalities such as US, computed tomography (CT) or MRI cannot detect micrometastases, and ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG-PET) does not reliable detect LN metastases < 10mm [124-126]. Therefore, these imaging modalities are of limited value and are not recommended for routine use in clinically node-negative patients, in which the aim is to identify small, subclinical, LN metastasis [127, 128]. However, these imaging modalities can be of value to detect enlarged/abnormal nodes in patients when physical examination is challenging (e.g. due to obesity).

In centres that offer dynamic sentinel node biopsy (DSNB) as a surgical staging option (see Section 5.2.2.c), inguinal US is obtained prior to DSNB. If sonographically suspicious nodes are detected, fine-needle aspiration cytology (FNAC) can easily be performed in the same session to confirm the diagnosis of inguinal LN metastasis [129]. Studies incorporating US + FNAC as an initial investigation in clinically node-negative patients prior to surgical staging, reported a sensitivity and specificity of 39% and 100%, respectively. Hence, a negative US is unreliable to exclude LN metastasis in clinically node-negative patients and US should be combined with surgical staging when indicated. However, if US + FNAC is positive, it can reduce the need for DSNB by 10–13%, allowing for additional staging and therapeutic LND at an earlier stage [130, 131]. Therefore, it is recommended to perform US + FNAC in clinically node-negative patients before surgical staging with DSNB.

5.2.2.b Indications for surgical staging

Since delayed treatment of occult LN metastasis results in a lower CSS rate and current non-invasive staging options (nomograms, imaging) are not sufficiently reliable to detect micrometastatic disease, invasive/surgical staging remains indispensable to identify micrometastasis before nodal metastases become palpable/visible [121]. However, surgical staging is over-treatment in the majority of patients, since only 20–25% of all clinically node-negative patients harbour occult metastasis.

To select patients that are particularly at risk of nodal metastases, risk categories have been established based on T stage, grade of differentiation and the presence of lymphovascular/perineural invasion in the primary tumour. Well-differentiated (G1) pTa, pTis and pT1 tumours without lymphovascular/perineural invasion

(pT1a) are considered low-risk tumours. In patients with low-risk tumours, the risk of metastases is too low to justify surgical staging. Moderately differentiated (G2) pT1a tumours are considered intermediate-risk and are associated with a 6–8% probability of (micro-)metastatic LN disease, whereas in pT1b G2 tumours, the risk is 22–30%. Therefore, all tumours that are stage T1b or higher are considered high-risk tumours [95, 132].

Based on these predictors, surgical staging is recommended in all high-risk tumours (T1 with presence of lymphovascular invasion, perineural invasion or poorly differentiated, and T2–T4 with any grade). In intermediate-risk tumours (pT1a G2), the risk of LN metastasis should be balanced against the morbidity of surgical staging on a case-by-case basis.

5.2.2.c Surgical staging options

By definition, radical inguinal LND (ILND) is the most accurate surgical staging method. However, ILND is also associated with the highest complication rates (see Section 6.2). To lower morbidity while maintaining sufficient sensitivity, modified ILND templates were developed (consisting of a shorter skin incision, with no dissection lateral to the femoral artery or caudal to the fossa ovalis and preservation of the saphenous vein) [133]. However, modified ILND is still associated with considerable complication rates of 35–49% and false-negative rates of 15–20% [134, 135]. More recently, videoendoscopic/robot-assisted radical LND was introduced (see Section 6.2, LN management). Initial reports indicate a reduction mainly in wound-related complications compared to open ILND [136]. However, a significant reduction of lymphatic complications is not to be expected, since the main predictor of lymphatic complications was shown to be the number of removed LNs [137-139], and the LN yield (LNY) of the videoendoscopic approach is comparable to open ILND [140].

To avoid resecting unnecessary LNs and thereby minimising the morbidity of surgical staging, DSNB was developed [141]. A sentinel node (SN) is defined as the first LN on a direct drainage pathway from the primary tumour. Based on this concept, it is assumed that if the SN is negative, it indicates the absence of lymphatic tumour spread in the corresponding inguinal basin. If histopathology identifies SN (micro)metastasis, ipsilateral completion ILND is indicated (see Section 6.2.2) [142]. Dynamic SN biopsy is typically performed using a combination of a radioactive tracer and patent blue dye to achieve optimal visualisation of the lymphatic drainage system prior to and during surgery. Recent innovations include the incorporation of single-photon emission CT/CT (SPECT/CT) and hybrid radioactive and fluorescent tracers [143]. Throughout the years, the procedure has matured into a reliable staging technique with high diagnostic accuracy and low complication rates, especially when performed in experienced centres (sensitivity 92–96%, false-negative rates 4–8%, complication rate 6–14%) [131, 137, 144]. A meta-analysis reported a higher pooled false-negative rate of 12% and showed that the false-negative rate was lower in high-volume centres [145]. This might indicate a potential learning curve and supports the call for centralisation of penile cancer care.

If DSNB is not available, and referral to a centre with experience with DSNB is not feasible, or if the patient does not want to run the risk of a false-negative procedure, ILND (modified/superficial/videoendoscopic) can be considered after informing the patient of the inherent risk of higher morbidity associated with these procedures.

5.2.3 Clinically node-positive (cN+)

In patients with palpable nodes, nodal metastases are present in approximately 45–80% of cases [146]. Lymph node metastasis should preferably be histopathologically confirmed by image-guided biopsy (e.g. US or CT). While in cN0 patients further abdominal and thoracic imaging is not recommended (See Section 5.2.2.1), it is of value in cN+ patients to clinically stage the pelvis and exclude distant metastases. Computed tomography of the chest/abdomen is broadly available. However, CT has a sensitivity of only 20–38% for the detection of pelvic LNs. Magnetic resonance imaging constitutes another diagnostic staging modality, in particular in those patients with a contra-indication to iodine-based contrast agents who cannot be staged by CT. A meta-analysis comparing CT and MRI showed comparable results with a pooled sensitivity of 42% for CT and 39% for MRI and pooled specificity was 82% for both [147]. Imaging with ^{18}FDG-PET/CT is likely to be more accurate than CT alone in the preoperative staging of pelvic LNs, as shown in other malignancies [148]. In penile cancer, ^{18}FDG-PET/CT showed a sensitivity and specificity of 91% and specificity of 100%, respectively, for the detection of pelvic metastases in patients with an US + FNAC-confirmed positive inguinal LN [149]. In patients initially staged as cN0 and who are subsequently upstaged to pN+ at surgical staging, additional imaging of the chest/abdomen should also be considered. Treatment of node-positive disease is discussed further in Section 6.2.

5.3 Genomic testing

In other cancers, genomic tumour testing has provided prognostic and predictive data upon which treatment regimens may be based. The only genomic test so far reported in penile cancer is the Radiosensitivity Index (RSI)/Genomic-Adjusted Radiation Dose (GARD) [150]. Genomic-Adjusted Radiation Dose may be predictive of

radiotherapy benefit while the physical dose of radiation delivered to a lesion has not. In patients treated with radiation, GARD is significantly associated with OS and time to first recurrence across various cancer types [151]. Specific analysis of penile cancer patient data reveals that the radiation doses delivered in patients treated to date likely may have been too low. For patients with advanced disease, certain subsets may have access to systemic therapeutic agents based upon genomic or proteomic analysis, as described in Chapter 6.

5.4 Summary of evidence and guidelines for the diagnosis and staging of penile cancer

Summary of evidence	LE
For distinguishing T1 from T2 disease, MRI does not outperform clinical staging.	2b
For predicting corporal invasion (T3 disease), MRI showed a pooled sensitivity and of 80% (95% CI: 70–87%) and 96% (95% CI: 85–99%), respectively.	2b
Magnetic resonance imaging with and without artificial erection showed similar accuracy in local staging.	2b
Computed tomography, PET/CT and MRI imaging cannot detect micro-metastases and are therefore of limited value in clinically node-negative patients in which the aim is to identify small sub-clinical LN metastasis.	2a
Inguinal US + FNAC of sonographically abnormal nodes can reduce the need for DSNB when tumour positive, allowing for earlier therapeutic treatment of node-positive disease.	2a
For surgical staging of cN0 patients, DSNB has shown a high diagnostic accuracy.	2a
Sentinel node biopsy has been shown to lower complication rates compared to modified-, superficial-, or videoendoscopic ILND.	2b
Imaging with ^{18}FDG-PET/CT in clinically node-positive patients showed higher sensitivity/specificity than CT alone in the preoperative staging of the pelvic LNs and distant metastasis.	2b

Recommendations	Strength rating
Primary tumour	
Perform a detailed physical examination of the penis and external genitalia, recording morphology, size and location of the penile lesion, including extent and invasion of penile (adjacent) structures.	Strong
Perform magnetic resonance imaging (MRI) of the penis/primary tumour (artificial erection not mandatory) when there is uncertainty regarding corporal invasion and/or the feasibility of (organ-sparing) surgery. If MRI is not available, offer ultrasound (US) as an alternative option.	Weak
Obtain a pretreatment biopsy of the primary lesion when malignancy is not clinically obvious, or when non-surgical treatment of the primary lesion is planned (e.g. topical agents, laser, radiotherapy).	Strong
Inguinal lymph nodes (LN)	
Perform a physical examination of both groins. Record the number, laterality and characteristics of any palpable/suspicious inguinal nodes.	Strong
Clinically node-negative (cN0)	
If there are no palpable/suspicious nodes (cN0) at physical examination, offer surgical LN staging to all patients at high risk of having micrometastatic disease (T1b or higher).	Strong
In case of T1a G2 disease, also discuss surveillance as an alternative to surgical staging in (frail) patients willing to comply with strict follow-up.	Weak
When surgical staging is indicated, offer dynamic sentinel node biopsy (DSNB). If DSNB is not available and referral is not feasible, or if the patient prefers after being well informed, offer inguinal LN dissection (ILND) (open or videoendoscopic).	Strong
If DSNB is planned, perform inguinal US first, with fine-needle aspiration cytology of sonographically abnormal LNs.	Strong
Clinically node-positive (cN+)	
If there is a palpable/suspicious node at physical examination (cN+), obtain (image-guided) biopsy to confirm nodal metastasis before initiating treatment.	Strong
In cN+ patients, stage the pelvis and exclude distant metastases with ^{18}F-fluoro-2-deoxyD-glucose positron emission tomography computed tomography (CT) or CT of the chest and abdomen before initiating treatment.	Strong

6. DISEASE MANAGEMENT

6.1 Treatment of the primary tumour

Along with its role in sexual functioning and urination, a fully functional penis is central to a patient's sense of wholeness, desirability and masculinity. For that reason, the aims of the treatment of the primary tumour are complete tumour removal with as much organ preservation as possible, without compromising oncological control.

There are no 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 as compared to partial or total penectomy and is considered to be the primary treatment method for localised penile cancer, based on retrospective studies.

Histological diagnosis and local staging must be obtained before non-surgical treatments can be considered. For small tumours, excisional biopsy can equal treatment, while for larger lesions which necessitate more complex or mutilating surgery, an incisional biopsy is advised (see Section 3.4.6). Histology provides confirmation of the diagnosis before treatment and informs on the risk group of the primary tumour which has important consequences for invasive staging of the groins. With surgical treatment, negative surgical margins for invasive carcinoma must be obtained. Treatment of the primary tumour and of the regional nodes can either be simultaneous or staged.

Local treatment modalities for small and localised penile cancer include topical therapy, laser ablation, excisional surgery, external beam radiotherapy (EBRT) and brachytherapy. The systematic review of this Panel revealed a complete absence of both RCTs and prospective trials assessing and comparing the effectiveness of interventions for managing the primary tumour [152]. Treatment recommendations can therefore only be based on retrospective data and expert opinion. In the absence of comparative evidence supporting treatment modalities, patients should be informed of all appropriate treatment options for their specific tumour and situation, together with the potential advantages and disadvantages for each technique. These are discussed per disease stage in the following Sections.

6.1.1 Treatment of superficial non-invasive disease (PeIN, Ta)

Despite treatment, PeIN can progress to invasive lesions in 2.6–13% of patients. Therefore, definitive eradication and diligent follow-up monitoring are important [153-155]. Most PeIN lesions are located on the mucosal surfaces of the glans or prepuce, whilst lichen sclerosus also affects the prepuce [154]. Therefore, circumcision should be the primary surgical option [155]. Following circumcision, the glans mucosa keratinises over a period of three to six months and any residual PeIN or lichen sclerosus may resolve. Close monitoring before starting additional therapy has been advocated, but to date, data supporting this concept are limited [155]. Considering a median time to progression to malignancy of 13 months [154], this approach seems reasonable to test in future clinical trials.

6.1.1.a Topical therapies

Topical therapy with imiquimod (IQ) or 5-fluorouracil (5-FU) are effective non-invasive first-line treatment options whose use is increasingly reported [156]. 5-Fluorouracil exerts its effects through inhibition of the enzyme thymidylate synthase. Although no standard protocol exists, leaving the 5-FU ointment on for 12 hours every 48 hours during a four to six week treatment course is often recommended in reported series of PeIN therapy [157]. Imiquimod acts through several pathways, including activation of immune cells via toll-like receptor 7, creating an inflammatory response, and is commonly used three times per week for 12 weeks. There is no consensus or comparative data on the optimal treatment schedules for these therapies, and the evidence for these treatments is heterogenous as it only relies on retrospective studies. A systematic review based on the aforementioned low-quality data illustrated that topical agents showed response and recurrence rates of 40–100% and 20% for IQ, versus 48–74% and 11% for 5-FU, respectively [158]. Because the use of 5-FU typically results in marked erythema, erosions and crust lasting for a month or longer, decreased patient compliance with treatment regimens may result in diminished effectiveness. Similarly, IQ use is complicated by the resultant tissue effects, including erythema, oedema, erosions, ulceration and crust, that are not consistent from one individual to the next [159]. Discontinuation of topical agents due to side effects was observed in 12% of cases [158]. It is advised that treatment effects must be clinically assessed, and in cases of doubt, evaluated by biopsy; long-term surveillance is warranted. Insufficient responses and recurrences may signify underlying invasive disease. Therefore, if topical treatment fails, it should not be repeated.

6.1.1.b Laser ablation

Laser ablation is an alternative treatment option. Energy-based therapies discussed in the literature include neodymium: yttrium-aluminium-garnet (Nd:YAG, penetration 4–6mm, wavelength 1064nm) or carbon dioxide (CO_2, penetration < 1mm, wavelength 10600nm) lasers and photodynamic therapy [160]. Laser treatment has shown total response rates of 52–100%, with recurrence reported in 7–48% of patients [158]. Altered penile sensitivity following laser treatment has been described, including increased sensitivity in 50% and decreased sensitivity in 15% of patients. Reports show relatively high rates of local recurrence, possibly owing to inadequate penetration, difficulties in assessing borders of affected areas and missing lesions that have invaded the subepithelial tissue [9, 161, 162]. Repeat laser treatment for recurrence has been described in some series without compromising long-term oncological outcomes, which is likely a result of the low risk of the lesions treated in those series [163, 164]. For cryotherapy, with or without topical therapy, and photodynamic therapy, which induces photo-selective cell death, only limited data are available for the treatment of PeIN.

6.1.1.c Surgery

Extensive PeIN – residual PeIN in resection margins or recurrent disease after ablative or topical therapy – can be treated by surgical excision. Glans resurfacing consists of full thickness removal of the glandular epithelium, followed by reconstruction with a graft (split skin [165] or buccal mucosa for urethral reconstruction [166]). Grafts tend to have excellent engraftment rates on this well-vascularised wound bed [167]. Recurrences are reported to be low (0–20%) and cosmesis is acceptable [165, 167, 168]. If feasible, preservation of the coronal ridge helps maintain sexual function and provides excellent cosmetic outcomes as shown by a small retrospective report [169]. Resection, as opposed to ablative or topical treatments, provides the advantage of complete histopathological local staging and detection of areas of invasion. 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 [165]. Surgeons and pathologists are urged to discuss appropriate specimen handling (e.g. pinning down the skin as resected) and pathological reporting of these cases to aid further management and avoid over-reporting of positive margins [170].

6.1.2 Treatment of invasive disease confined to the glans (cT1/T2)

When feasible, small and localised invasive lesions should receive organ-sparing treatment. Resection of the primary lesion not only eradicates all disease in localised invasive tumours, but also provides definitive pathological staging without the risk of understaging or of missing intratumour heterogeneity encountered with incisional or punch biopsy [9]. Foreskin tumours are treated by 'radical' circumcision. For glandular and coronal lesions, wide local excision, partial glansectomy or total glansectomy with reconstruction are surgical options, while additional circumcision is advised in glandular tumours. External beam radiotherapy and brachytherapy are radiotherapeutic options for these patients. Laser therapy of small lesions has been reported, but the risk of invasive disease must be recognised, and the recurrence risk is high, possibly due to the limited tissue penetration depth of laser ablation. Further research is needed to better establish the comparative safety and effectiveness of surgical and non-surgical therapies for penile cancer.

Treatment choice depends on tumour size, histology, stage and grade, localisation and patient preference. Over the recent decades, a shift towards organ-sparing surgery has been observed, based on the assumption that local recurrence has little influence on long-term survival. Over recent decades, organ-sparing surgery has become increasingly adopted, based on the assumption that local recurrence has limited impact on long-term survival. Preservation of large areas of epithelium, however, carries a risk of metachronous recurrence in the residual, predisposed tissue. In a multi-institutional series by Elst *et al.*, including a cohort enriched for lower-risk tumours (80% T1, 20% G3), local recurrence rates were high (30%), but did not adversely affect survival [171].

Conversely, in a large series looking at higher-risk (26% T1, 41% G3) tumours treated with glansectomy [172] or partial penectomy by resection of only the corporeal tips [173], it was observed that fewer patients experienced local recurrence, yet had poorer survival, including in multivariate analysis correcting for poor prognosticators. This, however, does not indicate that these patients may have fared better with more radical excision, as local recurrence in those cases may be a display of a more aggressive disease biology in general. On the other hand, large series are available showing lower local recurrence rates after amputative surgery despite more aggressive tumours, supporting a wider resection [174].

The systematic review by this Panel found a cumulative five-year recurrence-free rate (RFR) of 82% in case series and 76.7% in non-RCTs for organ-sparing surgery. Similarly, the cumulative five-year RFR of amputative surgery was reported 83.9% in case series and 93.3% in controlled studies. These variations reflect the differences of study designs as well as the various cohorts analysed at each instance. A larger proportion of patients treated with amputative surgery typically present with advanced disease (> T3: 29.4% vs. < T3: 7.8%). The higher RFRs observed after amputative surgery must be weighed against the impact on sexual function and QoL. Hence, the limits of organ-sparing surgery are not completely clear, and the higher risks of local recurrence should be discussed with the patient when making a treatment plan.

6.1.2.a Width of negative surgical margins

The concept of organ-preserving surgery is based on observations of how the distance between tumour and resection margin affects local recurrence. A study found that most lesions do not spread > 5mm beyond the macroscopic margin and, in line with this finding, subsequent reports show that an excision margin of between 5mm and 10mm results in acceptably low recurrence rates [175-177]. Another study from a supraregional referral centre found that local recurrence rates only increased considerably when the distance from tumour to margin was < 1mm [178]. However, comparative evidence is lacking for this topic and there is no clear evidence as to what constitutes an oncologically safe width of macroscopic negative surgical margins. Based on the observation that in lower-risk tumours (1) a local recurrence does not impact survival and (2) minimal section margins > 1mm do not result in a higher risk for local recurrence, macroscopic margins can indeed be minimal, specifically in smaller and less-aggressive lesions. Hence, to ensure complete removal with histologically negative margins, standard excision must include a margin of clinically normal-appearing skin around the tumour and surrounding erythema. However, for bulky or higher-grade lesions where local recurrence may have an impact on survival, adoption of a wider margin or partial penectomy may be prudent and should be discussed with the patient [172, 177]. The presence of PeIN at the surgical margin after organ-sparing surgery represents a challenging clinical situation. Current evidence is heterogeneous regarding the impact of PeIN-positive margins on local recurrence, and it remains unclear whether immediate re-resection, as opposed to delayed resection at recurrence, improves long-term oncological outcomes [179, 180]. Re-resection, however, may adversely affect penile function and QoL. By analogy with PeIN at the margin following circumcision, a strategy of active surveillance with or without topical therapy appears reasonable. These options should be discussed with the patient as part of a shared decision-making process.

6.1.2.b The use of intraoperative frozen section assessment

The role of frozen section and its value in the interpretation of excision margins remains uncertain. The potential benefits of adopting frozen section assessment include a decreased risk of local recurrence and a smaller safety margin, allowing maximum preservation of penile tissue. A study of 169 patients treated in a tertiary referral centre in the UK showed that frozen section use during organ-sparing surgery contributed to a very low definitive positive margin rate of 0.6% and a local recurrence rate of 5.3% [181, 182]. These data, however, are contradicted by a large contemporary series – also from a tertiary referral centre in the UK – showing similarly low local recurrence rates of 4% without routine intraoperative frozen section analysis [178]. A systematic review conducted in 2017 stated that routine frozen section analysis results in lower rates of local recurrence but failed to correct for patient selection. As a result, a causal relationship between frozen section analysis and low local recurrence rates is lacking, as is comparative research. Data from one multicentre study suggest that differentiated PeIN, squamous hyperplasia and lichen sclerosis present at the surgical margins are frequent findings and are not relevant for CSS [100]. As negative surgical margins are aimed for, in cases of doubt on the radicality of the resection, it is the Panel's opinion that frozen section analysis is a helpful tool to achieve definitive tumour-free margins, whereas it is not recommended for routine use.

6.1.2.c Laser ablation

In line with results achieved in non-invasive and superficially invasive penile lesions, laser ablation has been proposed as an option for smaller invasive lesions. Typically, a CO_2 laser can resect the tumour with ample millimetres of margin, while for coagulation of the tumour bed, an Nd:YAG laser is the better option, as it provides deeper uniform tissue coagulation. Healing time is fastest after CO_2 laser treatment, with re-epithelisation nearly complete by three to six weeks post-treatment. Because of the greater depth of tissue coagulation, the healing time for Nd:YAG laser treatment is longer; often up to six weeks [160]. Penetration depth depends on laser type and settings and the most commonly used settings are 15–20W for CO_2 and 15–25W for Nd:YAG lasers, but very few publications provide technical details [160].

In the Panel's systematic review, seven studies reported outcomes of laser therapy for invasive penile cancer limited to T1 (81.2%) or T2 (18.5%) disease in a total of 389 patients [152]. Five-year RFR ranged from 34.2 to 94%. The cumulative mean five-year RFR was 69.4% (270/389). Three studies reported a five-year RFR per

disease stage of 42.9–73.9% for T1 and 23.5%–84.2% for T2 disease. In nine studies (n = 512), the penile preservation rate following laser therapy was 50–100% (mean 89.2%), indicating that a large proportion of recurrences had to be managed with total amputation, which recommends caution on the use of such technique and its use is likely best limited to T1 tumours. Tang *et al.,* demonstrated that nodal recurrence was high in a multi-institutional cohort of patients treated with laser ablation as monotherapy, illustrating the importance of pre-ablation biopsy for risk stratification and nodal staging. Clinicians should be aware of the risk of understaging as a result of incision biopsy followed by ablation versus complete resection [9, 183], and it is advised that patients be informed that laser therapy may result in higher local recurrence rates when compared to surgical excision.

Three studies reported on laser-related complications, with preputial oedema and dysuria reported most frequently. Meatal stenosis was reported in 7.4% and postoperative bleeding in 1–7% of patients. Three studies assessed the sexual function after laser treatment and 46.0–56.5% of men report an impact on their sexual life. A single trial including 46 men found that 72% reported no change in erectile function, 22% reported decreased erectile function and 6% reported improvement [184].

6.1.2.d Moh's micrographic surgery

Moh's micrographic surgery is a surgical technique by which tissue is excised and processed with *en face* histological margins in real time to give a complete circumferential and deep margin. It aims at maximal organ preservation by adopting margin-guided excision. Three studies reported the five-year RFR in 51 men, most with T1 disease. Recurrence-free rates ranged from 71.4 to 100% with a cumulative mean five-year RFR of 88.2% (45/51) [152]. As data are very limited, it is not routinely recommended, and the Panel feels it is important to involve a clinician experienced in penile cancer management before referral for Moh's surgery.

6.1.2.e Wide local excision and circumcision

In addition to treating preputial penile cancer, circumcision combined with topical treatment, laser therapy or brachytherapy, facilitates follow-up examinations [182]. For small, distal preputial penile cancer, circumcision alone usually presents adequate treatment. However, lesions located on the corona or glans and limited in size, may be treated with wide local excision, which should include a margin of clinically normal-appearing skin around the tumour and surrounding erythema (see Section 6.1.2.a). Few data on wide local excision are available. The technique has, thus far, only been described in retrospective series combining various types of organ-sparing treatments.

6.1.2.f Glans resurfacing

Besides its established effects in the therapy of PeIN, total or partial glans resurfacing has been reported to be employed for superficially invasive lesions, combined with deeper resection at the site of invasion. The literature is heterogeneous, with many studies reporting miscellaneous techniques of organ-sparing surgery including glans resurfacing without specification of tumour invasiveness in these patients specifically. Five studies have reported results of glans resurfacing, specifically in invasive penile cancer, in a total of 68 patients, with most being pT1 and a few instances of T2 lesions displaying RFR ranging from 75 to 96.6% [169, 178, 185-187]. Similar to glans resurfacing as applied to carcinoma *in situ*, graft-related complications are scarce and cosmesis, as assessed by patients, is generally good. Cakir *et al.*, have described a small series using a technique for glans resurfacing with preservation of the coronal sulcus for distal tumours not invading the sulcus and show that this option can be considered when aiming for maximally preserved erogenous sensation [169].

6.1.2.g Glansectomy

Patients with tumours confined to the glans and prepuce that are not eligible for wide local excision or glans resurfacing are good candidates for glansectomy. Patients with poor vascular function, diabetes, immunosuppression or previous radiation to the groin area are less suitable for graft application due to higher failure rates, which should be discussed with the patient when making the decision between graft application for primary closure. For cases in which the lesion is confined to the glans and is clearly away from the corporal tips according to imaging or clinical examination, an approach that uses dissection over Bucks' fascia can be used to excise the glans, while in cases of doubt, a plane under the Bucks fascia can be used. In the Panel's systematic review, glansectomy with or without resection of the outermost tips of the corpora cavernosa was assessed in six studies including 1,681 men, 86.4% of whom with T1–T2 disease. The five-year RFR ranged from 78.0–95.8% [152]. A split-thickness skin graft is commonly used to reconstruct a neoglans and the graft loss rate was 1.5–23.5%. The incidence of meatal stenosis in a recent systematic review was 2.8–14.3%. Good cosmetic outcomes and normal erections were reported in 95–100% and 50–100% of cases, respectively [188]. In a large retrospective study by Roussel *et al.,* describing a multicentre cohort, including 230 pT1, 534

pT2 and 108 pT3 patients treated in high-volume centres, the authors found high-grade disease and pT3 to be independent risk factors predicting local recurrence. Three-year local RFS rates were 94.8%, 87.3% and 69.7% in patients with no, one or both risk factors, respectively. Moreover, in this population, local recurrence remained a significant predictor of decreased OS and CSS, even when excluding margin-positive cases, patients with pT3 disease and patients with clinical LN involvement. Hence, these issues should be discussed with the patient prior to surgical intervention when choosing between glansectomy and the more aggressive partial penectomy.

6.1.2.h Partial penectomy

Amputative and partial amputative surgery is reserved for more advanced disease. Results of partial or total penectomy were reported in five heterogeneous studies with a total of 243 patients. Among the cohort, 71.6% of men were staged as T1–T2 and the five-year RFR was 75.8-95.4%. The cumulative mean five-year RFR was 83.9% (204/243). Two case series including T1 and T2 men reported 92% and 95.4% five-year RFRs after partial penectomy [152]. There is no comparative evidence between partial penectomy and glansectomy for T1–T2 lesions, however, most case series report similar RFRs between penile-sparing surgery and amputative surgery. In a series of T1 and T2-only disease, five-year RFR after amputative surgery was superior to penile-sparing surgery, indicating that a wider resection is protective against local recurrence and should always be discussed as an alternative option, although the higher RFRs observed after amputative surgery needs to be weighed against the impact on sexual function and QoL.

6.1.2.i Radiotherapy for T1 and T2 disease

Radiotherapy is an organ-preserving approach with good results in selected patients with T1–2 lesions [152]. Radiotherapy can be given as external radiotherapy with a minimum dose of 60Gy EQD2, combined with a brachytherapy boost or as brachytherapy alone [189, 190]. Brachytherapy has been studied only for lesions < 4cm, therefore, its use should be limited to tumours not exceeding this size. Reported results are best with brachytherapy with local control rates ranging from 70 to 90% [189, 190]. 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 disease [189]. Penile preservation rates of 70–88% have been reported [191], with overall penile conservation rates of 87% and 70% at five and ten years, respectively. Pulse dose-rate brachytherapy can be used interchangeably with traditional low-dose rate, and 15% local recurrences have been reported in one series [192]. High dose-rate brachytherapy has been introduced, but experience is still limited [193-198].

The Panel's systematic review identified 21 studies evaluating the efficacy of radiotherapy for the management of primary tumour in men with penile cancer. A total of 1,222 men had low, pulse or high dose-rate brachytherapy after circumcision [152]. The cumulative mean five-year RFRs were 78.6% (861/1,096) after brachytherapy and 55.2% (37/67) after EBRT. Four studies (including some EBRT and some brachytherapy cohorts) reported RFRs per disease stage, with five-year RFRs for T1 ranging from 59 to 94%, 50 to 67% in T2, and 17 to 77% in T3 disease [196, 199-201].

In the few studies comparing surgical treatment and radiotherapy, results of surgery were slightly better. In a meta-analysis comparing surgery and brachytherapy, five-year OS and local control rates were 76–84% for surgery and 73–79% for brachytherapy, respectively [202]. The organ preservation rate for brachytherapy was 74% and there was no difference in survival. Local recurrence after radiotherapy can be salvaged by surgery [199].

Specific complications of radiotherapy for penile cancer are urethral stenosis (20–35%), glans necrosis (10–20%) and late fibrosis of the corpora cavernosa [203]. With brachytherapy, meatal stenosis has been reported to occur in up to 40% of cases but was much lower in a contemporary series of 73 patients with only 6.6%. In that series, 2.6% of patients reported pain with sexual intercourse and 5.3% dysuria over a follow-up of five years. Penile amputation for necrosis was necessary in 6.8% of patients [204].

Functional outcome after radiotherapy has not often been reported. In one report, 17/18 patients with normal erections before treatment maintained these after treatment [205]. After a minimum of three-years (median 5.9) follow-up after brachytherapy treatment, 29/34 patients (median age 63 years) answered a self-reporting questionnaire. Urethral dilatation had been necessary in 30% of patients and self-catheterisation in 13%. Erectile dysfunction was mild and 70% continued to maintain sexual activity, and QoL was good.

6.1.3 Locally advanced disease (T3–T4)

6.1.3.a Resectable disease

In cT2 disease in which there is doubt of corporeal or tunica albuginea invasion, rather than continuing the dissection over Buck's fascia to perform glansectomy combined with distal corporectomy, dissection superficial to the tunica albuginea can be adopted after dividing the neurovascular bundle. In these instances, frozen sections of the corporeal tips and urethra may be helpful in assessing the radicality of the procedure perioperatively. Preoperative MRI or US can assist in surgical planning, as discussed in Chapter 5. For cT3 patients with obvious involvement of the corpora cavernosa, partial amputation is standard. Patients can be offered reconstructive options such as urethral centralisation and/or neoglans formation with the use of a graft. Two studies in higher-risk patients treated with radical glansectomy or partial penectomy show that local recurrence in these instances is associated with poor survival. Patients should be informed that a wider resection (i.e. partial or radical penectomy) provides a lower risk of local recurrence at the cost of functionality of the penis [172, 206]. Radical amputation and diversion of urination with a perineal urethrostomy is reserved for those patients in whom a resection with a safe margin would result in the inability to void standing upright or without wetting the scrotum. Radiotherapy for locally advanced penile lesions should be undertaken with concurrent chemotherapy. As with disease in the LNs, traditional radiotherapy dosing recommendations are being reconsidered [150]. Complex treatment planning will be necessary in most cases of T3–T4 primary lesions, with patient-unique immobilisation to spare testes and scrotum. A total phallic reconstruction may be offered to patients undergoing total/subtotal amputation. Extensive partial amputation with wide margins or total penectomy with perineal urethrostomy is the standard advisable treatment. In case of locally advanced and ulcerated cases which are resectable, composite myocutaneous flaps or advancement flaps may be needed to cover the surgical defect [207].

6.1.3.b Non-resectable disease

In non-resectable disease, induction chemotherapy offers the ability to downstage disease and thereby enable surgical resection among responders, even among men with advanced penile cancer. Several retrospective and prospective series have evaluated the effects of combination regimens using paclitaxel or docetaxel with cisplatin and ifosfamide or 5-FU. The combination of irinotecan and cisplatinum, with vinflunine as monotherapy, have also been investigated. Although there is considerable heterogeneity in the regimens and cohorts combining advanced nodal disease and unresectable primary tumours, objective responses are observed in 29–60% of patients [206, 208-214]. In two recent systematic reviews, pooled objective response rate (ORR) were 53–57% [215]; with pooled ORR of 57% (95% CI: 46–67%) for taxane-platinum combinations and 54% (95% CI: 31–76%) for non-taxane platinum combinations [216], and pathological complete responses in 4–10% [216], at the cost of considerable toxicity. This approach is discussed in more detail in Section 6.4.1.a. In case of not obtaining a response sufficient for resection, palliative chemoradiotherapy is an option.

Accumulated evidence in anal and vulvar cancer supports the notion that definitive chemoradiotherapy is an effective treatment for anogenital SCC [217]. In a single study in six node-positive SCC penile cancer patients, four of the six patients were recurrence-free and two had developed recurrence, one of whom died [217].

In an observational cohort study in 40 locoregionally advanced penile cancer patients fit for chemoradiotherapy and treated with curative intent, Ottenhof *et al.,* observed that the response rate was 73%, with complete response seen in 39% [218]. Among the cohort, 52% had subsequent surgery: 27% for residual disease and 25% for later salvage. One- and two-year PFS was 34% and 31%, with a 33% grade 3 toxicity rate but no grade 4 or 5 [219]. Their regimen consisted of integrated boost intensity modulated radiotherapy with a dose of 59.5Gy to the primary tumour in fractions of 1.8Gy with mitomycin C on day one and capecitabin on radiation days. In comparison to perioperative chemotherapy studies, the omission of surgery is a potential advantage of chemoradiotherapy. As this strategy has only been evaluated in a single observational study, no recommendation can be made supporting this approach in patients suitable for other options.

6.1.4 Local recurrence after organ-sparing surgery

A second organ-sparing procedure can be performed if there is no corpus cavernosum invasion [162, 176, 220-222]. For large or high-stage recurrence, partial or total amputation is required, unless unresectable or concurrent with nodal or distant metastatic recurrence (see respective Sections).

6.1.5 Summary of evidence and guidelines for local treatment of penile carcinoma

Summary of evidence	LE
Penile intraepithelial neoplasia progresses to invasive lesions in 2.6–13% despite treatment.	3
Response and recurrence rates of topical therapies for PeIN are 40–100% and 20% for IQ, and 48–74% and 11% for 5-FU, respetively. For laser therapy, response rates are 52–100% and recurrence rates 7–48%. For glans resurfacing, recurrence rates are as low as 4%.	3

A systematic review including retrospective studies on organ-sparing surgical treatment of the primary lesion shows that cumulative mean five-year RFRs are 82% in case series and 76.7% in non-RCTs. For (partial) amputative surgery, cumulative mean five-year RFRs are 83.9% in case series and 93.3% in non-controlled studies. The cumulative mean five-year RFR was 69.4% for patients treated with laser therapy for invasive disease.	3
Current literature on frozen section analysis in organ-sparing surgery is heterogeneous and conflicting.	3
Tumour distance to the resection margin < 1mm resulted in higher local recurrence rates in a recent large retrospective case series from a tertiary referral centre.	3
In lower-risk tumours (predominantly T1, few G3), organ-sparing surgery results in high local recurrence rates of approximately 30%, but without impact on survival in available series.	3
In higher-risk cohorts (more frequent ≥ T2 or G3) treated with organ-sparing surgery, local recurrence after organ-sparing surgery is associated with poorer survival.	3
The cumulative mean five-year RFRs are 78.6% after brachytherapy and 55.2% after EBRT.	3
For neoadjuvant chemotherapy, pooled ORR was 53% (95% CI: 42–64%) and the pathological complete response rate in prospective studies was 4–10% (95% CI: 5–30%) in a recent systematic review and meta-analysis.	2a

Recommendations	**Strength rating**
Offer a balanced and individualised discussion on benefits and harms of possible treatments options with the goal of shared decision-making.	Strong
Inform patients that organ-sparing procedures and glanulopreputial epithelium-preserving techniques are associated with a higher risk of local recurrence compared to amputative surgery.	Strong
Topical therapy	
Offer topical therapy with 5-fluorouracil or imiquimod to patients with biopsy-confirmed penile intra-epithelial neoplasia (PeIN).	Weak
Clinically assess treatment effects after a treatment-free interval, and in cases of doubt, perform a biopsy. If topical treatment fails, it should not be repeated.	Weak
Laser ablation	
Offer laser ablation using carbon dioxide or Neodymium:Yttrium-Aluminium-Garnet laser to patients with biopsy-confirmed PeIN, Ta or T1 lesions.	Weak
Organ-sparing treatment: surgery (circumcision, wide local excision, glansectomy and glans resurfacing)	
Offer organ-sparing surgery and reconstructive techniques to patients with lesions confined to the glans and prepuce (PeIN, Ta, T1–T2) and who are willing to comply with strict follow-up.	Strong
Perform intraoperative frozen section analysis of resection margins in cases of doubt on the completeness of resection.	Weak
Offer salvage organ-sparing surgery to patients with small recurrences not involving the corpora cavernosa.	Weak
Organ-sparing treatment: radiotherapy (external beam radiotherapy and brachytherapy)	
Offer radiotherapy to selected patients with biopsy-confirmed T1 or T2 lesions.	Strong
Amputative surgery (partial and total penectomy)	
Offer partial penectomy – with or without reconstruction – to patients with invasion of the corpora cavernosa (T3) and those not willing to undergo organ-sparing surgery or not willing to comply with strict follow-up.	Strong
Offer total penectomy with perineal urethrostomy to patients with large invasive tumours not amenable to partial amputation.	Strong
Offer amputative surgery to patients with large local recurrences or corpora cavernosa involvement.	Weak
Multimodal therapy	
Offer induction chemotherapy followed by surgery to responders, or chemoradiotherapy to patients with non-resectable advanced primary lesions, or to patients with locally advanced-disease who refuse surgical management.	Weak

6.2 Regional lymph node management: clinically evident disease (cN1–cN3)

6.2.1 ***Introduction***

The development of lymphatic metastases in penile cancer follows the route of anatomical drainage from the primary tumour to the superficial and then deep inguinal LNs (which can occur on both or either side), followed by the ipsilateral pelvic LNs. The superficial nodes are located under the subcutaneous fascia and above the fascia lata within Scarpa's triangle. The deep nodes lie within the region of the fossa ovalis where the superficial saphenous veins anastomose with the femoral vein at the saphenofemoral junction. The Cloquet's node (or Rosenmuller's node) is located medial to the femoral vein around the entrance to the femoral canal and marks the transition between inguinal and pelvic regions. Daseler *et al.,* divided the superficial inguinal LNs into five regions centred around the saphenofemoral junction: central, lateral superior, lateral inferior, medial superior and medial inferior [223]. Studies of radical ILND (rILND) as well as SPECT imaging suggest that 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 [223-225]. No solitary lymphatic spread has been observed from the penis to the two inferior groin regions, nor has direct drainage to the pelvic nodes [223-225].

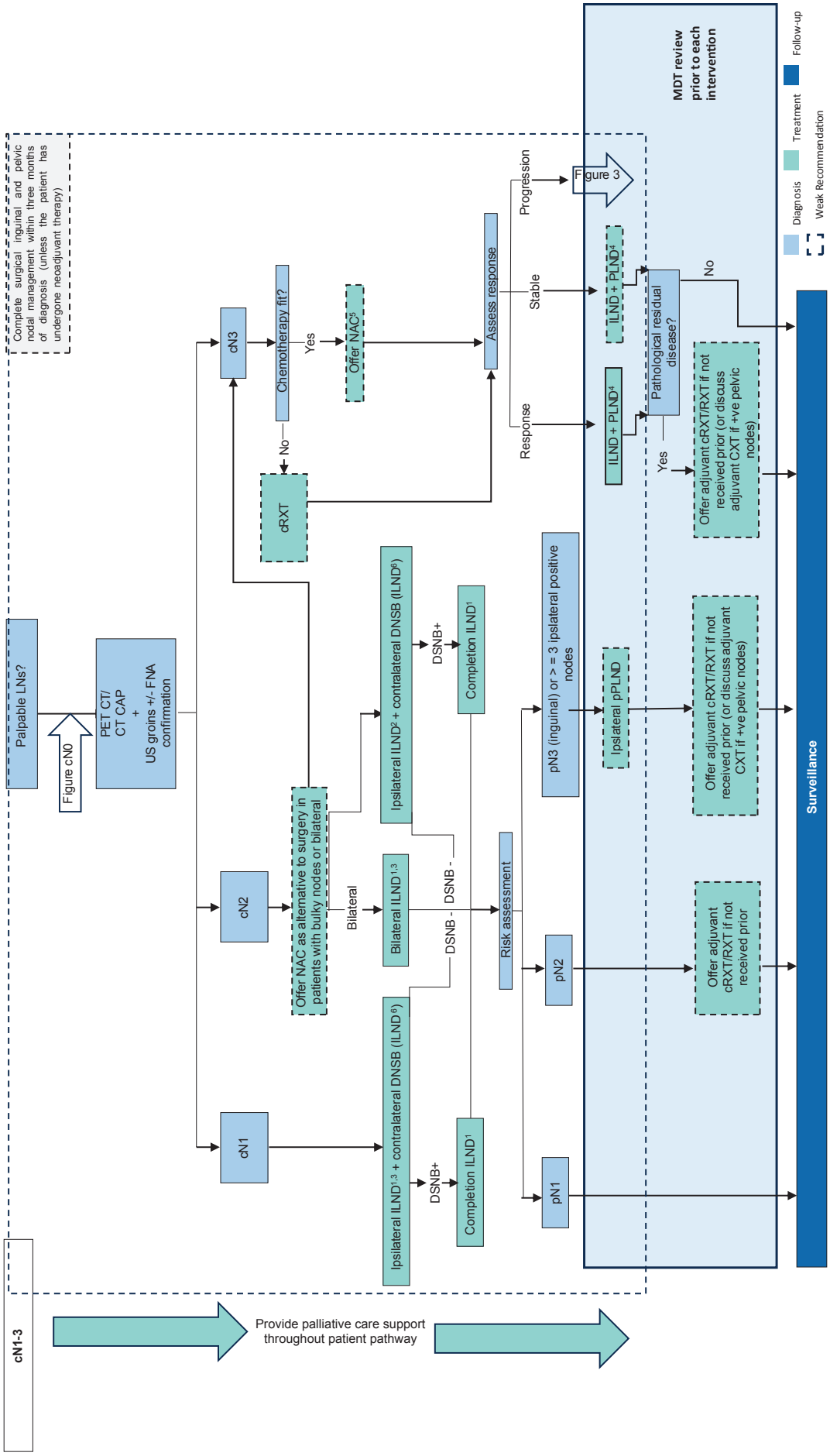
Pelvic nodal disease does not occur without ipsilateral inguinal LN metastasis. In addition, crossover metastatic spread, from one groin to the contralateral pelvis, is rare [226]. Further lymphatic spread from the pelvic nodes to retroperitoneal nodes (para-aortic, paracaval) is classified as systemic metastatic disease [227].

The management of regional LNs is decisive for patient survival. The presence and extent of nodal involvement is singularly the most important prognostic factor in patients with penile cancer. Cure can be achieved in limited LN-disease confined to the regional LNs. Radical LND is the treatment of choice. Multimodal treatment combining surgery, chemotherapy or radiotherapy is often indicated for more advanced disease.

In clinically positive LNs (cN1/cN2), more extensive LN metastasis is highly likely and LN surgery with histology is required. Given the very high chance of recurrence, enlarged fixed inguinal LNs (cN3) or clinically evident pelvic metastases require multimodal treatment by induction chemotherapy and consolidative surgery in responding patients. Even if present in only one node, extracapsular extension/ENE, or pelvic LN metastasis found at surgery carries a high risk of progression and is classified as pN3 and requires multimodal treatment.

Given the complexities of regional node management, the intent of the Panel in the following Sections (Sections 6.2–6.4) is to describe the available evidence-based strategies in the management of clinically evident LN metastases (i.e. cN1–cN3). These strategies include ILND/pelvic LND (PLND), chemotherapy, radiotherapy ± chemotherapy and integrated strategies such as neoadjuvant and adjuvant therapies combined with surgery. The reader is encouraged to review the text Sections, summaries of evidence, and recommendation tables collectively to better understand recommendations for single versus multimodal treatment and currently available data utilising various strategies.

Figure 6.1: Regional lymph node management: clinically evident disease (cN1–cN3)



CAP = chest, abdomen and pelvis; cRXT = chemoradiotherapy; CXT = chemotherapy; CT = computed tomography; DSNB = dynamic sentinel node biopsy; ENE = extranodal extension; FNA = fine-needle aspiration; (r)ILND = (radical) inguinal lymphadenectomy; LNs = lymph nodes; MDT = multidisciplinary team meeting; NAC = neoadjuvant chemotherapy; PET = positron emission tomography; (p)PLND = (prophylactic) pelvic lymph node dissection; RXT = radiotherapy; US = ultrasound.
[1] Fascial-sparing ILND dissection or open rILND, sparing the saphenous if possible.
[2] Ipsilateral open rILND, sparing the saphenous vein, if possible.
[3] Offer minimal-invasive ILND to patients with cN1–2 disease only as part of a clinical trial.
[4] Do not offer videoendoscopic ILND.
[5] Cisplatin and taxane-based chemotherapy.
[6] ILND is an option in cases in which DSNB is not feasible or preferred by the patient.
[7] The term 'bulky' is generally used to indicate a high suspicion of ENE.

6.2.2 *cN1–N2 disease: radical inguinal lymph node dissection*

6.2.2.a Indication for radical inguinal lymph node dissection

Radical ILND remains the standard of care for patients with cN1–2. In low-volume disease (pN1), rILND is curative with a suggestion of equivalent outcomes in those patients without nodal disease [228-230].

Nevertheless, several studies have demonstrated continuing non-adherence to accepted international guidance [231-234]. Cindolo *et al.*, evaluated adherence of 12 European and American centres to the EAU recommendations [234]. They reported a 26.3% rate of non-adherence in terms of LN management. For those patients managed as per guidance with LND, there was a statistically significant association with OS (adjusted HR: 0.48; 95% CI: 0.24–0.96, p = 0.038) [234].

6.2.2.b What is an acceptable definition?

Daseler's original description in 1948 is still considered the classical description of a rILND (see Table 6.1) [223]. Despite this, considerable variation exists across high-volume centres. In an international survey of surgeons' practice in European high-volume centres, consensus was not found on the definition of the superior and lateral borders of the dissection, and whether the fascia lata and saphenous should be preserved [235]. This variation in practice is likely a reflection of the desire on the part of clinicians and patients to reduce the significant burden of morbidity acknowledged in the literature associated with rILND (see Section 6.2.2.d on complications). A systematic review of the literature by the Panel identified only one other description of a modified template used in clinical N1–2 disease by Yao *et al.* [236] (see Table 6.1). This retrospective cohort study of 201 fascial-sparing ILNDs (fsILND) with < N2 disease demonstrated comparable oncological outcomes to rILND with three-year DFS of 92.1% (100% for pN0, 91.3% for pN1, 80% for pN2, and 33.3% for pN3 disease, respectively) and a complication rate of 29.3%. In a retrospective multicentre series of 421 patients (660 procedures), Schifano *et al.* described outcomes from fsILND. This approach achieved a three-year CSS of 86% for pN1 and 83% for pN2 disease with an overall complication rate of 36%, suggesting comparable oncological control to classical rILND with reduced morbidity [237]. To date, however, no direct comparison exists between rILND and fsILND in this group of patients (Table 6.1).

Table 6.1: Variations in radical inguinal ymph node dissection

Superior		Lateral	Medial	Inferior	Base	Fascia preserved	Saphenous spared	Sartorius transposition
rILND [223]	Superior margin of external ring to the anterior superior iliac spine	Anterior superior iliac spine inferiorly 20cm	15cm downwards from the pubic tubercle	Apex of femoral triangle	Sartorius, femoral vessels, adductor longus	No	No	Yes

fsILND [236]	Superior margin of external ring to the anterior superior iliac spine	Anterior superior iliac spine inferiorly 20cm	15cm downwards from the pubic tubercle	Apex of femoral triangle	Fascia	Yes. Deep inguinal LNs, medial to the femoral vein, dissected just distal to the fossa ovalis	Yes	No

fsILND = fascia-sparing inguinal lymph node dissection; LNs = lymph nodes; rILND = radical inguinal lymph node dissection.

6.2.2.c Quality metrics

To standardise the quality of resections, several studies have attempted to look for surrogate markers to infer complete oncological resection, including LNY, LN density (LNDen) and time to completion of surgery.

6.2.2.c.1 Lymph node yield and density

In a systematic review commissioned by the Panel, several studies were identified examining the association between LNY/LNDen and survival as a surrogate marker of adequate dissection in penile cancer [232, 238-242]. However, LNY varied from > 8 to > 15–16 and LNDen < 6.7 to < 22%. The variance in accepted values is likely due to different surgical templates, variable pathological assessment and stage migration. Consequently, widespread adoption of LNY and LNDen as a predictor of survival and as quality markers cannot be recommended.

6.2.2.c.2 Timing of surgery

Several studies have highlighted the importance of expedient LN management in patients with cN0 disease versus surveillance with LND on presentation of clinical disease. Two non-RCTs have demonstrated a survival benefit in patients who underwent early ILND compared with delayed ILND (within six weeks of primary surgical treatment vs. surgery following identification of positive nodes during surveillance), showing three-year CSS 84% vs. 35% (p = 0.0017) and three-year CSS 71% vs. 50%, respectively [121, 243].

The evidence in pN1–2 regarding optimal timing of LN management is limited. Chipollini *et al.*, examined the effects of early versus late ILND (> three months following primary surgery) in 84 patients with cN0 and cN+ disease. Overall, those patients undergoing early ILND demonstrated a five-year DSS of 64.1% versus 39.5% for late dissection with an unadjusted HR of 0.66 (0.32–1.37). However, when subanalysis was performed in cN+ patients, the five-year DSS for early versus late dissections failed to delineate a statistically significant benefit (31.8% vs. 35.3%, respectively) [244].

Gulia *et al.*, examined 28 patients undergoing rILND stratified by < six months (group 1) and > six months (group 2) from treatment of the primary tumour (70% and 50% palpable at presentation, respectively). The five-year CSS was 91 and 13%, respectively (p = 0.007) [245].

6.2.2.d Complications

Radical ILND carries a significant morbidity due to impaired lymph drainage from the legs and scrotum. However, it can be lifesaving and therefore should not be avoided [246].

Historical morbidity of the procedure has been as high as 61% [247]. Contemporary large series of rILND suggest between 21–55% of men will suffer a complication [138, 248, 249]. The reduction in morbidity is likely due to a better understanding of pre-, intra-, and postoperative management (see Table 6.2). In a systematic review commissioned by the Panel, the most reported complications were wound infections (2–43%), skin necrosis (3–50%), lymphoedema (3.1–30%), lymphocele formation (1.8–26%) and seroma (2.4–60%) [138, 228, 245, 248-255]. An international consensus group (CALI) has recently proposed a standardised classification system for ILND complications in melanoma, penile and vulval cancer. Through a three-round Delphi process involving 47 global experts, agreement was reached on intraoperative and postoperative complication categories, including infections, cutaneous, lymphatic, vascular and musculoskeletal domains. This framework is intended to harmonise reporting, enhance comparability between series and guide strategies to reduce morbidity [256]. Table 6.2 lists several strategies and conditions associated with increased, decreased or uncertain effects on morbidity outcomes reported in penile cancer, urologic or in other cancers. Future studies specific to ILND and strategies to decrease morbidity are needed.

Table 6.2: Impact of pre- intra- and postoperative factors on morbidity following radical inguinal lymph node dissection

Positive impact	Negative impact	Uncertain benefit
Linear transverse incision [257, 258]	S-shaped incision, vertical incision [247, 257, 259]	Vacuum dressings [260]
Saphenous sparing [258, 261, 262]	Time-controlled drainage [263]	Fibrin glue [264]
Volume-controlled drainage [263]	Ultrasonic device [265]	Advanced bipolar device [266]
Fascial-sparing [207, 236]	Sartorius transposition [219, 249]	
Minimally invasive techniques [267-269]	Raised body mass index [249]	
Lymphoedema prevention, e.g. massage, skin care, saphenous vein-sparing surgery [258, 270]	Increased disease burden [138]	
Deep venous thrombosis prophylaxis [271]	Sarcopenia [250]	
Prevention of surgical site infections, e.g. prophylactic antibiotics, shaving, skin prep [272]		

6.2.2.e Open versus minimally invasive approach

In recognition of the significant morbidity associated with rILND, clinicians have sought to reduce these through technical modifications. Expanding interest and experience in minimally invasive techniques have led to the introduction of videoendoscopic ILND (VEIL) and subsequently robot-assisted videoendoscopic ILND (RAVEIL), using rILND or fsILND templates.

Ports are generally placed at the apex of the femoral triangle, although variations include lateral and hypogastric approaches, allowing PLND through the same incisions [273-275].

A review of the literature commissioned by the Panel identified a single incomplete RCT in 2012, which closed prematurely due to poor accrual, with patients preferentially choosing minimally invasive approaches over open approaches [276]. The remaining studies identified were either retrospective cohort- or comparative series. Narrative review would suggest that, although operative time is longer, LNYs can be similar to open ILND: shorter length of hospital stay in VEIL/RAVEIL and fewer wound complications, although lymphocele and readmission rates were equivalent [136, 267, 269, 277-279].

A contemporary systematic review and meta-analysis of 16 comparative studies (n = 1,054) confirmed these observations, reporting comparable LNYs and node positivity, but with significantly fewer complications (minor RR: 0.65; major RR: 0.25), reduced wound infection rates (RR: 0.43), and a shorter length of stay (± four days), albeit with longer operative times, particularly with robotic approaches. Oncological outcomes appeared equivalent, with no excess in groin or overall recurrence, although the certainty of evidence was limited by retrospective designs and heterogeneity [280].

Follow-up for the minimally invasive approaches were short, and there was a high proportion of patients receiving VEIL or RAVEIL as prophylaxis as opposed to clinically node-positive disease, precluding incorporation in the current recommendations. In addition, some studies in which open rILND was used as a comparator involved more morbid manoeuvres when using an open approach, such as Sartorius transposition and saphenous vein sacrifice, which were not replicated in minimally invasive procedures.

A multicentre feasibility RCT (VELRAD) is currently underway in the UK to assess the acceptability of randomising men to VEIL versus open ILND, with primary outcomes of recruitment feasibility and loss-to-follow-up, alongside early complication, patient-centred and health-economic endpoints. The results are expected to inform a definitive randomised trial [281].

6.2.2.f Summary of evidence and guidelines for radical inguinal lymph node dissection in cN1–2 disease

Summary of evidence	LE
Open rILND is the standard for cN1–2 disease.	2a
Radical rILND carries a significant risk of complications (21–55%).	2a
Two studies reported on fsILND, and in cN1–2 disease, it appears to offer similar oncological outcomes and reduced complications.	2b
Lymph node yield and LNDen appear related to survival, however, variance in accepted values, pathological assessment and stage migration prevent recommendation of a specific LN count.	2a
Delay in nodal management of more than three to six months may affect DFS.	3
Minimally invasive approaches for ILND (VEIL/RAVEIL) generally have longer operative times, equivalent LNYs, shorter length of hospital stay and fewer wound complications when compared with open ILND. However, since current evidence is very limited in cN1–2 patients, no recommendation for minimally invasive approaches can be provided.	2b

Recommendations	Strength rating
In patients with cN1 disease, offer either ipsilateral: • fascial-sparing inguinal lymph node dissection (ILND) • open radical ILND (rILND), sparing the saphenous vein, if possible.	Strong
In patients with cN2 disease offer ipsilateral open rILND, sparing the saphenous vein, if possible.	Strong
Offer minimally invasive ILND to patients with cN1–2 disease only as part of a clinical trial.	Strong
Offer neoadjuvant chemotherapy (NAC) as an alternative approach to upfront surgery to selected patients with bulky mobile inguinal nodes or bilateral disease (cN2) who are candidates for cisplatin and taxane-based chemotherapy (see Section 6.4.1).	Weak
Complete surgical inguinal and pelvic nodal management within three months of diagnosis (unless the patient has undergone prior NAC).	Weak

6.2.3 Prophylactic pelvic lymph node dissection

Prophylactic PLND (pPLND) in most cases represents a staging procedure that can thus identify candidates for early adjuvant therapy, although in select patients may also provide a therapeutic benefit.

6.2.3.a Indications for prophylactic pelvic lymph node dissection

6.2.3.a.1 Risk factors for pelvic nodal metastasis

To identify patients with pelvic LN metastasis in the absence of radiological evidence for LN involvement, several studies have tried to develop generalised estimating models based on inguinal characteristics using logistic regression and multivariate analysis. Among various predictors, the number of positive inguinal LNs (1–2 vs. 3 or more, with no extracapsular extension) was associated with positive pelvic LNs in 0–6.5% of patients versus 33–67% of patients [282, 283]. The presence of extracapsular spread was also consistently significantly associated with positive ipsilateral pelvic LN metastasis in four studies [282-285]. Strong immunoreactivity of p53, LNDen > 30% and primary tumour grade are also reported as predictors of pelvic LN involvement [283].

6.2.3.b What is an acceptable dissection?

In a study by Yao *et al.*, the authors prospectively mapped the distribution of positive pelvic LNs at the time of PLND in 128 patients [226]. Most patients underwent bilateral PLND (86.7%). The median number of nodes retrieved per groin was 18 (interquartile range 10–30), with the distribution of positive nodes in the external iliac, obturator, common iliac, internal iliac and presacral packages being 50%, 36.6%, 7%, 6.4% and 0%, respectively. Notably, two patients were observed to have crossover metastasis from one inguinal region to the contralateral pelvic region, defying the accepted understanding of the historical literature. When the extent of dissection was considered in context of OS and RFS, there was no statistically significant difference [226]. Similar data were seen in a study by Zhu *et al.*, with the external iliac package being more commonly involved than the obturator and common iliac packages [286].

To evaluate the prognostic impact of LNY on survival outcomes for penile SCC, Chipollini *et al.*, examined 198 patients undergoing PLND [238]. In their cohort, they found that an LNY of > nine was a predictor of RFS (HR: 0.53, p = 0.032).

6.2.3.c Survival and recurrence

The evidence that pPLND has an additional therapeutic effect over surveillance or adjuvant radiotherapy (see Section 6.4.2.b) is limited and significant controversy remains. Djajadiningrat *et al.* estimated the five-year DSS in all patients treated with pPLND was 51%. Patients with positive pelvic nodes had a significantly worse five-year DSS than those without pelvic involvement (17%, 95% CI: 6–47 vs. 62%, 95% CI: 50–76, $p < 0.001$) [284]. A retrospective multicentre study compared the outcomes of bilateral pPLND for N2 or N3 disease versus no surgery and reported better five-year OS in the pPLND group (35% vs. 25%) without reaching statistical significance [287, 254]. In N2 patients, three-year OS was significantly better in the PLND group as compared to the no-surgery group (83.3% vs. 50.2%, $p = 0.03$) [287]. This difference was not evident in N3 patients.

6.2.3.d Complications

Limited data are available regarding the reporting of complications from PLND. This is complicated by the fact that most patients will have already undergone an rILND, which carries a significant morbidity risk, as discussed above. A single-centre experience of 89 patients undergoing open PLND for penile cancer reported an overall complication rate of 18%. Nine patients had wound complications including infection, seroma and dehiscence. The remaining five patients had non-wound-related complications such as pneumonia, delirium and ileus [284].

6.2.3.e Minimally invasive versus open pelvic lymph node dissection

In a systematic review commissioned by the Panel, there were no reported studies that examined the role of minimally invasive pPLND in the setting of penile cancer and PLND. There is, however, a significant body of evidence that exists in other common urological malignancies that demonstrates equivalent oncological outcomes, as well as improved morbidity profile and recovery profile.

6.2.3.f Summary of evidence and guidelines for prophylactic pelvic lymph node dissection

Summary of evidence	LE
In most cases, pPLND represents a staging procedure that can thus identify candidates for early adjuvant therapy, although in select patients it may also provide a therapeutic benefit.	3
Three or more positive inguinal nodes or ENE of cancer in inguinal nodes are associated with a significantly higher incidence of pelvic LN metastases.	3

Recommendations	Strength rating
Offer open or minimally-invasive prophylactic ipsilateral pelvic lymphadenectomy to patients if: • three or more inguinal nodes are involved on one side on pathological examination; • extranodal extension is reported on pathological examination.	Weak
Complete surgical inguinal and pelvic nodal management within three months of diagnosis (unless the patient has undergone neoadjuvant chemotherapy).	Weak

6.3 Clinical N3 disease (cN3)

6.3.1 Diagnostic evaluation

Patients with clinical N3 disease, as defined by the presence of a fixed inguinal mass (i.e. to skin or underlying structures) or pelvic lymphadenopathy based upon imaging, should undergo a complete staging evaluation, including cross-sectional imaging (i.e. PET/CT or CT, see Section 5.2.3), if not already performed [288]. Biopsy of the inguinal mass in the setting of a patient with a known diagnosis of penile cancer is not required but should be performed in a previously undiagnosed patient, as needed, to establish the diagnosis and facilitate accurate staging.

6.3.2 Management strategy

Neoadjuvant chemotherapy (NAC) is a reasonable strategy among patients with cN3 disease based on the results of a systematic review which reported radiological response rates of approximately 53% and pathological complete response in approximately 12.8% of patients [215, 289]. This review consisted mostly of retrospective series – complete response rates in the intention-to-treat population were 10% (paclitaxel, ifosfamide and cisplatin [TIP]) and 4% (docetaxel, cisplatin and fluorouracil [TPF]) in prospective trials [206, 208]. In responding patients, and those with no evidence of disease progression, surgical resection to remove all residual disease utilising rILND and PLND techniques is the preferred strategy. For a detailed examination of perioperative chemotherapy, see Section 6.4.1.

Preoperative radiotherapy was used in a single study among a cN3 cohort of 12 patients and reported an objective response in only two patients, with seven of 12 patients subsequently undergoing ILND. Only two patients (17%) survived for five years [290]. It is worth recognising that these data, however, utilise historical radiotherapy techniques precluding meaningful extrapolation to modern practice (see Section 6.4.2 for further details).

Surgery as the initial treatment in patients with a fixed inguinal mass or clinically evident pelvic adenopathy (cN3) at presentation or recurrence is discouraged in routine management. While often technically feasible, a 'surgery first approach' often results in large skin/soft tissue defects, the need for myocutaneous flap reconstruction, prolonged hospital stays (mean or median 8.5–23 days) and is associated with high overall complication rates (65–77%) [291, 292]. In a single-centre study among 24 patients treated with surgical debulking alone in the advanced disease setting, the median CSS and DFS were only six and three months, respectively [292]. In the same study, 17.5% of patients exhibited rapid progression of disease post-surgery and never received adjuvant therapy [292].

6.3.3 ***Patient selection for consolidative radical inguinal/pelvic lymph node dissection***

According to a systematic review, patients whose tumours respond to NAC and subsequently undergo surgical consolidation represent a favourable subgroup of patients with a mean five-year survival of 56.9% [289]. Among cN3 patients who are not candidates for conventional multi-agent chemotherapy, preoperative chemo-radiation/radiation can be offered in an attempt to downsize tumours to improve resectability. The evidence for this, however, is recognised to be weak but is being prospectively investigated in the InPACT study [293].

6.3.4 ***Surgical technique***

6.3.4.a Inguinal lymph node dissection

Surgical resection should proceed five to eight weeks after completion of chemotherapy to provide time for haematologic recovery and to allow other therapy-related symptoms to improve. Preoperative planning to remove all residual disease taking into consideration the size of the mass, involvement of surrounding structures and the anticipated skin and soft tissue defects, as well as plastic surgical consultation (as appropriate), is required for successful outcomes.

6.3.4.b Lymph node dissection boundaries

Surgical boundaries should follow that of a 'radical inguinal lymph node' dissection (described in Table 6.1). Wide resection of involved skin is often required with *en bloc* ILND. Considering the extent of inguinal metastases, along with fixation to adjacent structures, minimally invasive techniques (i.e. robotic and laparoscopic ILND) are considered inappropriate in cN3 inguinal metastases.

6.3.4.c Pelvic lymph node dissection

If pelvic LN metastases were clinically evident at diagnosis, simultaneous PLND should be performed at the time of ILND. Ipsilateral PLND should also be performed in a simultaneous (preferred) or delayed fashion in the setting of advanced bulky inguinal metastases without clinically evident pelvic metastases (i.e. prophylactic). In the latter setting, microscopic pelvic metastases were noted quite frequently (44–100%) in the setting of extracapsular disease and especially when an inguinal mass was present in one series [282].

6.3.4.d Surgical complications in cN3 disease

Resection of bulky/fixed inguinal masses with or without prior chemotherapy is associated with a variety of complications. Minor complications not requiring hospitalisation or surgical intervention are common and tolerable when cure or significant palliation can be achieved. In several series, major post-surgical complications requiring medical or surgical intervention, or associated with disability or death, included infection/sepsis (1.5–4.5%), lymphocele requiring drainage (0–3.8%), wound dehiscence or necrosis requiring debridement (1.5–5.6%), pneumonia (0–2.9%), deep venous thrombosis/pulmonary embolus (0–8.7%), and death (0–5.6%) [208, 291, 292]. Overall, in the three selected series of patients treated at experienced centres, the incidence of major complications as described above was less than one in ten patients, with 3/82 (3.9%) patients succumbing to sepsis or other early perioperative complications.

6.3.5 *Summary of evidence and guidelines for the surgical management of cN3 disease*

Summary of evidence	LE
Surgery alone will rarely cure patients with cN3 disease.	3
Even when technically feasible, upfront surgery is associated with significant complications that may delay or prevent delivery of adjuvant therapy.	3
Approximately half of the patients with advanced (cN2–cN3) penile cancer respond to combination chemotherapy. Responders that subsequently undergo consolidative ILND/PLND have an OS chance of about 50% at five years.	2a
Inguinal LND in cN3 patients often requires resection of overlying skin to effectively remove a fixed bulky nodal mass.	4
The available literature includes virtually no cN3 patients to assess the efficacy or safety of minimally-invasive ILND.	4

Recommendations	Strength rating
Offer neoadjuvant chemotherapy (NAC) using a cisplatin- and taxane-based combination to chemotherapy-fit patients with pelvic lymph node involvement or those with extensive inguinal involvement (cN3), in preference to upfront surgery. (see Section 6.4.1).	Weak
Offer surgery to patients responding to NAC in whom resection is feasible.	Strong
Offer surgery to patients who have not progressed during NAC, but resection is feasible. See also (chemo)radiation.	Weak
Do not offer videoendoscopic inguinal lymphadenectomy.	Strong

6.4 Role of multimodal chemotherapy/radiotherapy in the management of (regional) lymph nodes

6.4.1 *Systemic therapy*

6.4.1.a Neoadjuvant chemotherapy

Bulky inguinal LN enlargement indicates extensive lymphatic metastatic disease, for which few patients will benefit from surgery alone. Neoadjuvant chemotherapy before inguinal LN surgery allows for early treatment of systemic disease and downsizing of the inguinal LN metastases. In responders, complete surgical treatment is possible with reasonable clinical outcome.

Cisplatin/5-FU (PF) chemotherapy achieved response rates of 25–50%, with mostly low-grade toxicity [294, 295]. Over a period of 30 years, five different NAC regimens including PF were used in 20 patients, with long-term survival in 37% of responders who underwent radical LN surgery after NAC [296]. In the European Organisation for Research and Treatment of Cancer (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 remission (pCRs) [214].

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. A phase II trial evaluated treatment with four cycles of neoadjuvant TIP in patients with clinical N2 or N3 LN metastases [208]. An ORR of 50% was reported in 30 patients, including three (10%) pCRs. The estimated median time to progression was 8.1 months and the median OS was 17.1 months. Long-term DFS was observed in 67% of responding patients and 7% of non-responding patients.

The combination of PF plus a taxane has been used in neoadjuvant and adjuvant settings [211, 212, 297, 298]. A phase II trial with TPF reported an objective response of 38.5% in 29 locally advanced or metastatic patients, although the study did not meet its primary endpoint and there was significant toxicity [212]. A prospective study testing neoadjuvant TPF in 26 patients with locoregionally advanced penile cancer showed a pathologic complete response in one (4%) patient, with a two-year PFS and DSS probability of 12% and 28%, respectively [206]. Treatment was discontinued in 23% of patients because of toxicity. In a meta-analysis analysing ten studies (n = 182 mostly retrospective), the pooled ORR was 53% (95% CI: 42–64), and the overall mortality was 55% (95% CI: 40–70) [215]. A retrospective study of perioperative chemotherapy regimens (99% doublets) concluded that carboplatin and paclitaxel was the most efficacious regimen (over cisplatin and paclitaxel or PF), but carboplatin was only used in the postoperative setting [299].

In a single-arm, phase II trial (NCT04475016) conducted in China, a neoadjuvant regimen of four cycles of toripalimab (anti-PD-1 antibody), nimotuzumab (anti-EGFR antibody) and triplet chemotherapy (nab TIP), followed by consolidative surgery was evaluated in 29 patients with locally advanced penile SCC. Of 24 patients who underwent consolidative surgery, 14 had a pCR. Two-year OS and PFS were 72.4% and 65.5%, respectively [300]. While these data are encouraging, the contribution of individual therapeutic components is difficult to assess.

Overall, these results support the activity of preoperative chemotherapy in patients with clinically involved regional LNs from penile SCC. However, randomised studies are lacking, and substantial concerns remain regarding the selection of patients who are best suited for a systemic therapy approach upfront. A large retrospective study from several international institutions including 743 patients who received an LND, suggested patients with a clinical N3 stage constituted the cohort with the most appreciable benefit from NAC use compared to LND alone [301]. Bilateral inguinal LN involvement emerged as a strong negative predictor of clinical outcome in patients with penile SCC, together with pelvic nodal involvement.

In summary, given the poor outcome of upfront surgery, NAC is a potentially suitable approach for fit patients having pelvic LN (cN3) metastases, fixed inguinal LN involvement (cN3), or bulky or bilateral involvement (cN2). The limited available evidence favours a cisplatin- and taxane-based combination (doublet or triplet) as the preferred preoperative approach. In non-responding patients, the potential benefits of surgery should be re-evaluated, as prognosis is poor in these patients. See also Section 6.4 on chemoradiotherapy.

6.4.1.b Adjuvant chemotherapy

There are known poor prognostic characteristics for a subset of patients with resected high-risk disease (such as involved pelvic LNs), indicating the likely presence of micrometastatic disease. Data exist on response rates for those with metastatic disease, and there is possible benefit for preoperative chemotherapy for those with unresectable locally advanced disease, as described above. With extrapolation from other diseases, it stands to reason that systemic therapy following resection (i.e. adjuvant therapy) may improve outcomes.

A retrospective multicentre analysis of patients with resected pathologically involved pelvic LNs suggested a potential benefit of adjuvant chemotherapy [264]. In this series, 84 patients were analysed. Patients who received chemotherapy for relapsed disease were excluded. Compared to those not receiving adjuvant chemotherapy, patients who received adjuvant chemotherapy were younger, had lower T stage, were more likely to have unilateral (rather than bilateral) LN involvement, and were less likely to receive adjuvant radiation. On multivariable analysis, receipt of adjuvant chemotherapy was associated with improved OS (HR: 0.40, 95% CI: 0.19–0.87, p = 0.021). Additional series have also been reported, including a series of 611 patients from the National Cancer Database reported in abstract form [302]. After adjusting for covariates, there was no difference in survival for those receiving adjuvant chemotherapy.

A recent meta-analysis examined this issue. After a systematic search, seven studies were identified examining the use of perioperative chemotherapy, four of which examined adjuvant chemotherapy (n = 771) [303]. There was no difference in survival for those receiving adjuvant chemotherapy versus observation (HR: 0.95, 95% CI: 0.48–1.80).

Upon examination of the overall data, there is no strong data supporting the use of adjuvant chemotherapy to improve OS following surgical resection of the primary tumour and involved LNs. However, given the fact that RFS is a relevant endpoint that has been suboptimally studied and there is a subset of patients at very high risk of recurrence, the Panel recommends a balanced discussion of risks and benefits of adjuvant chemotherapy in those thought to be healthy candidates. As previously stated for the neoadjuvant setting, the benefit from adjuvant chemotherapy is expected to be highest in the population of patients with pathological N3 stage, in particular for those patients with pelvic nodal involvement [301]. See also Section 6.4.1.b on adjuvant radiation and chemoradiotherapy.

6.4.1.c Summary of evidence and guidelines for neoadjuvant and adjuvant chemotherapy

Summary of evidence	LE
Results support the activity of NAC in patients with clinically involved regional LNs from penile SCC. However, randomised studies are lacking and substantial concerns remain regarding the selection of patients who are best suited for a systemic therapy approach upfront.	2b

The available evidence favours a cisplatin- and taxane-based combination (doublet or triplet) as the preferred approach.	2b
Limited data support the use of adjuvant chemotherapy to improve OS following surgical resection. However, it could be offered to patients with pN3 disease post-LND if NAC has not been received, upon careful consideration of risks and benefits with the patient.	4

Recommendations	Strength rating
Offer neoadjuvant chemotherapy using a cisplatin- and taxane-based combination to chemotherapy-fit patients with pelvic lymph node (LN) involvement or those with extensive inguinal involvement (cN3), in preference to upfront surgery.	Weak
Offer chemotherapy as an alternative approach to upfront surgery to selected patients with bulky mobile inguinal nodes or bilateral disease (cN2) who are candidates for cisplatin and taxane-based chemotherapy.	Weak
Have a balanced discussion of risks and benefits of adjuvant chemotherapy with high-risk patients with surgically resected disease, in particular with those with pathological pelvic LN involvement (pN3). See also Section on postoperative radiotherapy.	Weak

6.4.2 Radiotherapy

6.4.2.a Preoperative radiation therapy

The role of preoperative chemoradiotherapy is being investigated in the ongoing InPACT trial [293]. A prospective trial of chemoradiotherapy in 33 patients with (T4 any-N M0 and/or any-T N3 M0) revealed responses in 73% based upon FDG-PET/CT criteria. Ten patients (30%) remained progression- or recurrence-free at follow-up without additional surgery, while approximately 50% of the patient cohort received salvage surgical procedures. The two-year progression-free survival (PFS) and OS was 31 and 46%, respectively, but the toxicity was lower than the NAC + surgery approach. Should a patient who is otherwise unfit for chemotherapy require treatment for LNs while awaiting surgery, radiotherapy alone may be considered using conventional daily fractionation of up to 45–50Gy. Radiotherapy to the groins in penile cancer may benefit from inclusion of the prepubic fat to cover in transit lymphatics [304]. Since surgical therapy of enlarged LNs is of paramount importance, it is unlikely that preoperative radiotherapy alone would provide sufficient benefit. Should a patient who is otherwise unfit for chemotherapy require treatment to LNs while awaiting surgery, radiotherapy alone may be considered using conventional daily fractionation to 45–50Gy [218, 304].

6.4.2.b Postoperative radiation therapy

Adjuvant radiation therapy for node-positive penile cancer remains controversial. Since there is no level 1 evidence to support the benefit of radiation therapy in terms of disease recurrence and survival, it is not recommended by prior Guidelines [305, 306]. Radiotherapy is being used in some institutions in the management of regional LNs for penile SCC, based on evidence and experience with other SCC sites (such as head/neck and vulvar carcinomas) [203, 307, 308].

Jaipuria *et al.*, reported that following ILND and PLND, patients with > two positive LNs but negative pelvic nodes (n = 32) had increased OS with adjuvant radiation therapy compared to adjuvant chemotherapy (48 months vs. 14 months, $p < 0.0001$) [309]. Although 68% of patients had ENE, there were no in-field failures. The radiation dose was higher than that commonly used under these circumstances, 54Gy for ENE and up to 57–60Gy for gross residual disease. With a lower radiation dose of 50Gy, Johnstone *et al.* reported a high rate of in-field failures (32/39) [310]. At this dose, adjuvant radiation therapy (either groin: $p = 0.016$ or inguinal pelvic: $p = 0.006$) improved RFS only for patients without ENE. Ager *et al.* reporting on the experience with pN3 disease (either ENE or pelvic LN+) in two tertiary referral centres in the UK also found dose to be critically important [311]. A total of 121 of 146 patients received adjuvant radiotherapy. The five-year RFS was 51%. Twenty-six of 55 recurrences were in-field, but the risk of in-field failure was twice as high for lower doses (< 50Gy).

For 92 patients with positive pelvic LN from four international centres, adjuvant radiation was found to prolong DSS by six months and delay the time to recurrence [312].

The data collated in Table 6.3 reveal variable results with conventional radiotherapy delivered in the adjuvant setting, potentially impacted by HPV status and presence/absence of ENE. Also notable in the data is the fact that traditional radiotherapy doses delivered to microscopic disease may be insufficient. Genomic data analyses have modelled that a higher radiation dose may be necessary for management of penile cancer primary lesions and nodal basins [313, 314].

Table 6.3: Adjuvant conventional radiotherapy for node-positive penile cancer

Author	n	stage	aRT	Adj CT	RT	LR	OS	Study type
Jaipuria 2020 [309]	45	anyT pN2-3 pelvis pN-	25	7	VMAT/IMRT, 45Gy basic, 54Gy ENE, 57-60 macro	No InF	47 mo. RT vs. 14 mo. CT	Prosp registry
Johnstone 2019 [310]	93	anyTpN3 ENE- ENE+			50Gy/25 no details		↑OS aRT p = 0.037 or aCT p = 0.038 ↑DSS aRT p = 0.04	4 centres
Winters 2018 [315]	136	pT1-3 pN1-2			45Gy + boost 45%		↑OS aRT 5 yr. 64% vs. 53%	NCDB
Tang 2017 [312]	92	N3 + pelvis	40		63% 50Gy/25, 13% > 50Gy		↑OS aRT 12.2 vs.8 p = 0.04 ↑DSS 14.4 vs.8 p = 0.02	4 centres
Ager 2021 [311]	146	pN3 (ENE or pelvis+)	121		45Gy/20 to 54Gy/25 2X↑LR if < 50	26 inF	OS 44% RFS 5-y 51%	2 centres UK
Bandini 2021 [39]	507	ILND	86 HPV+ 40 aRT				↑OS aRT p = 0.015 Also propensity-matched analysis	11 centres

aCT = adjuvant chemotherapy; Adj = adjuvant; aRT = adjuvant radiotherapy; CT = chemotherapy; DSS = disease-specific survival; ENE = extra-nodal extension; Gy = gray; HPV = human papillomavirus; ILND = inguinal lymph node dissection; IMRT = intensity-modulated radiotherapy; InF = inguinal failure; LR = local recurrence; mo. = month; n = number of patients; NCDB = National Cancer Database; OS = overall survival; RFS = recurrence free survival; RT = radiotherapy; UK = United Kingdom; VMAT = volumetric modulated arc therapy; vs. = versus; yr. = year.

Human papillomavirus status could be a suitable selection factor for patients who will benefit from adjuvant radiotherapy after ILND (in analogy to other HPV-related cancers). Bandini *et al.* reported on 507 patients from 11 centres, 86 of whom were HPV+. Among patients receiving adjuvant radiotherapy, those harbouring HPV-positive tumours appeared to have an increased OS relative to HPV-negative patients. However, more (prospective) studies are needed to validate these findings [39].

As in other SCC sites such as head and neck cancer, HPV status may also predict for increased responsiveness to combined chemoradiotherapy. Yuan *et al.* reported improved locoregional control (LRC) of 83% over 38% (p = 0.038) for node-positive p16+ patients receiving chemoradiotherapy following LND [308]. Twenty-eight of 51 patients were LN+, of whom 14 received chemoradiotherapy, seven of whom were HPV-positive. Overall, regardless of HPV status, two-year LRC was 54% for those receiving adjuvant chemoradiotherapy versus 13% (p = 0.006). Choo *et al.* found similar efficacy of adjuvant chemoradiotherapy with improved CSS at one and two years, even though the patients selected for adjuvant chemoradiotherapy had a higher number of positive LNs (64% > 5 vs. 8%), more pN3 disease (72% vs. 17%) and more ENE (45% vs. 17%) [316]. The OS was the same for the unfavourable group receiving adjuvant chemoradiotherapy as it was for the more favourable earlier-stage patients not receiving chemoradiotherapy.

Although PLND is recommended for patients with high-risk groin pathology (N2–N3), this is not the practice in all jurisdictions. Maibom et al. reported from Denmark on the use of inguinal-pelvic chemoradiotherapy for 21 patients with a median follow-up of 74 months [317]. All patients had ENE and two-thirds had bilateral groin disease, with a median OS of 84 months and 57% five-year survival. This concept is being tested in the currently accruing InPACT trial, in which men with high-risk groin pathology can be randomised to chemoradiotherapy or PLND followed by chemoradiotherapy [293].

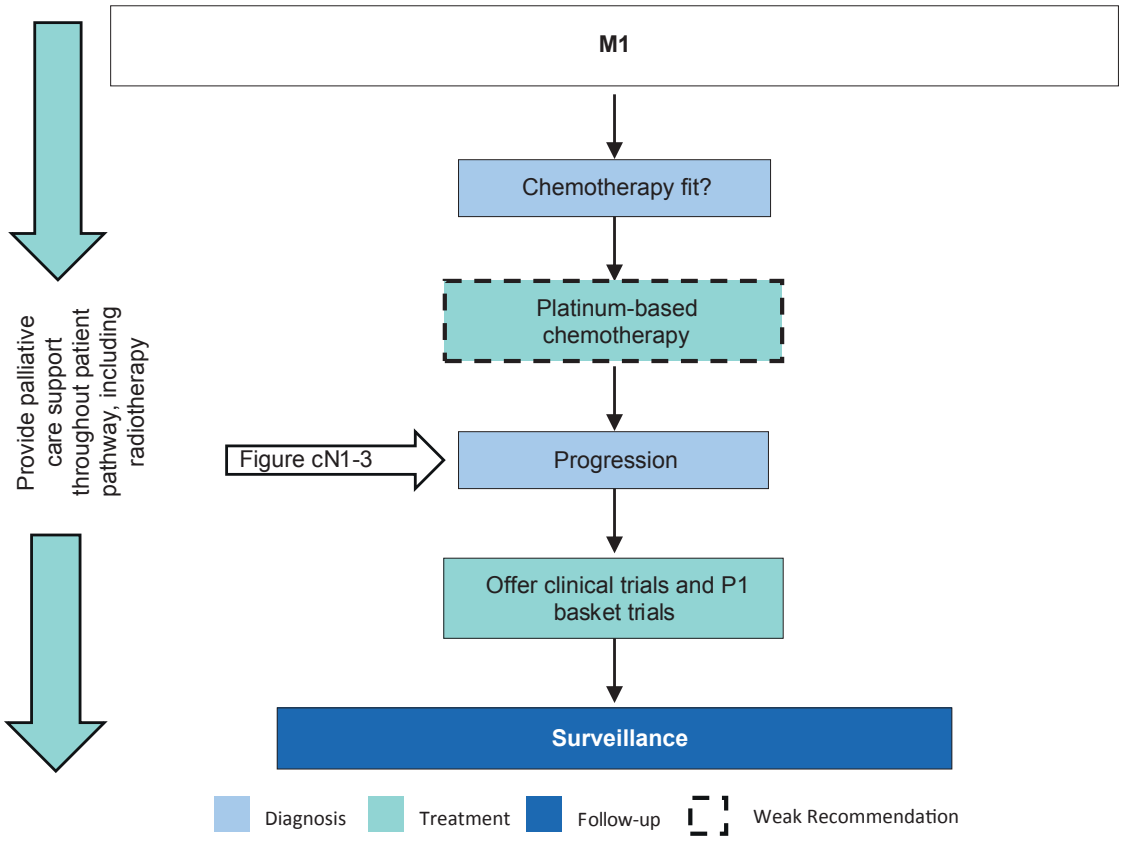
6.4.2.c Summary of evidence and guidelines for pre- and postoperative radiotherapy

Summary of evidence	LE
Adjuvant radiotherapy results in increased OS if greater than two inguinal LN-positive and PLND-dissection negative.	2b
Adjuvant conventional radiotherapy doses are often insufficient for durable control. Increased DSS and RFS in penile cancer requires 54Gy for ENE and 57–60Gy for positive margins.	3
Perioperative chemoradiotherapy	
Chemoradiotherapy significantly improves LRC over radiotherapy alone for other SCC originating in the anal canal or head and neck, whilst in vulvar cancers, chemoradiotherapy improves OS. The evidence, however, is sparse in penile cancer.	1b

Recommendations	Strength rating
Offer adjuvant radiotherapy (with or without chemosensitisation) to patients with pN2/N3 disease, including those who received prior neoadjuvant chemotherapy.	Weak
Offer definitive radiotherapy (with or without chemosensitisation) to patients unwilling or unable to undergo surgery.	Weak
Offer radiotherapy (with or without chemosensitisation) to cN3 patients who are not candidates for multiagent chemotherapy.	Weak

6.5 Systemic and palliative therapies for advanced disease

Figure 6.2: Systemic and palliative therapies for advanced disease



P1 = Phase I studies.

6.5.1 Introduction

Much of our current standard of care for this rare disease has evolved based upon extrapolated experience with similar cancers. The most common regimens utilised today for advanced disease are similar to those routinely used in the perioperative setting, consisting of platinum-based regimens. Most data come from institutional or retrospective studies, but cooperative groups have occasionally studied this disease via prospective phase II studies.

6.5.2 Chemotherapy

Phase II cooperative group studies with bleomycin, methotrexate and cisplatin (BMP) and irinotecan cisplatin yielded response rates of 31–33% [214, 318]. The median OS for BMP was 28 weeks. Toxicity was a concern with both regimens, particularly pulmonary toxicity from bleomycin.

A retrospective study of PF presented a response rate of 32% and median OS of eight months. Toxicity was manageable for this patient population [319].

Addition of taxanes to cisplatin-based regimens was associated with promising activity, including complete responses. Docetaxel, cisplatin and fluorouracil was prospectively studied in a cohort with distant metastasis (28%) or locally advanced disease (72%). The response rate was 38.5% and median OS of 14 months; 2/26 patients had complete response [212]. The study did not meet its efficacy endpoint and toxicity of TPF was a concern. Another prospective study of TPF in exclusively metastatic (M1) disease showed an objective response rate of 38.5% and median OS of seven months [320]. The latter study did meet its efficacy endpoint, and toxicity was interpreted as acceptable.

Paclitaxel, ifosfamide and cisplatin was prospectively studied in patients with metastases confined to LNs (N2–3, M0), having a response rate of 50% in this select population and 3/30 with surgically verified complete responses [208]. Toxicity was manageable in this setting, but limited data are available for TIP in distant metastatic disease.

A systematic review of cisplatin-based chemotherapy outcomes with and without taxanes suggested a higher toxicity rate with taxanes, 49% versus 26% [215].

Vinflunine single-agent chemotherapy was prospectively studied in patients with advanced disease who were not eligible for curative surgery or NAC. Patients were required to have ECOG performance status < 2 and estimated glomerular filtration rate (GFR) > 60mL/min. Median age was 70 years, with a 27% response rate and median OS of 8.4 months. Toxicity was manageable. A retrospective study of paclitaxel single-agent chemotherapy as second line reported a response rate of 20% and median OS of 23 weeks [321]. Two studies of various second-line systemic therapy regimens found median OS of 4.5–5.6 months [322, 323].

A retrospective study of 101 patients looked at the efficacy of chemotherapy as first-, second- and third-line treatment [322]. The median OS for first-line chemotherapy was 7.2 months, and two months with best supportive care. The second-line regimens in 17 patients included paclitaxel/carboplatin (41%), cisplatin/capecitabine (12%), paclitaxel (12%) or other (36%). There were two objective responses (12%), three stable disease (18%) and 17 with progressive disease (71%) as best response. Paclitaxel/carboplatin was also reported in adjuvant and neoadjuvant case series and was well tolerated [324, 325].

These data support the recommendation of platinum-based chemotherapy as the preferred approach to first-line palliative systemic therapy. Choices include triplet regimens (TPF, TIP) and doublets (PF, paclitaxel/carboplatin), where doublets appear to have less toxicity. Both TPF and TIP combine two neurotoxic drugs and are not appropriate for patients with pre-existing neuropathy or low GFR. Other comorbidities and functional status should be carefully considered when selecting a regimen. While data for paclitaxel/carboplatin in advanced penile cancer are limited, it is reasonable to extrapolate from its use as palliative treatment of SCC from other sites. An alternative approach is single-agent chemotherapy with vinflunine or a taxane.

Effective second-line palliative chemotherapy regimens are lacking. Second-line chemotherapy in multiple studies was associated with median OS of six months or less. This is an unmet need that also applies to patients with tumour recurrence after adjuvant or neoadjuvant chemotherapy.

6.5.2.a Immunotherapy

Immune-based therapies such as immune-checkpoint blockade (ICB), HPV-directed vaccines and adoptive T-cell therapies have emerged as potential treatment options for advanced penile cancer [326]. Given the relatively high expression of PD-L1 in penile SCC, several studies have retrospectively assessed checkpoint inhibition with or without chemotherapy in advanced disease with mixed results [327-331].

Basket studies testing combination therapies have included patients with penile SCC. In a phase I–II study of nivolumab combined with cabozantinib, with or without ipilimumab, nine patients with penile SCC were included: four with partial response and five with stable disease were reported [332]. In another study testing the combination of ipilimumab and nivolumab, five penile SCC were included reporting two patients having stable disease [333].

Prospective trials have been reported. The PERICLES trial assessed atezolizumab (anti-PD-L1), with or without locoregional radiotherapy, in advanced (stage IV) penile cancer and reported a one-year PFS of 12.5% with several patients having a durable response; median OS was 11.3 months [334]. In the response-evaluable population, confirmed ORR was 16.7%. The addition of radiation did not seem to confer additional benefit. Similarly, 18 patients with or without prior chemotherapy exposure were treated with retifanlimab (anti-PD-1) in the ORPHEUS trial; the ORR was 16.7% [335]. Median PFS was 2.0 months, and median OS was 7.2 months. Biomarkers such as HPV, tumour mutational burden, and PD-L1 status are being explored. However, the current level of data are insufficient to support their use as biomarkers to select patients for immune checkpoint inhibition.

In the HERCULES trial, 33 patients with advanced penile cancer were treated with cisplatin, 5-FU and pembrolizumab. The ORR was 39.4%, median PFS was 5.4 months, and median OS was 9.6 months [336]. These results suggest that the combination of chemotherapy with ICB raises response rates, although it may not improve long-term clinical benefit compared with ICB alone.

In conclusion, response rates to immune checkpoint inhibition are low, but some responses may be durable. This Panel highly recommends that all patients with advanced penile SCC enrol in clinical trials if possible. If a penile SCC trial is not available, enrolment into an early-phase basket trial is recommended.

6.5.2.b Targeted and molecularly selected therapies

Beyond chemotherapy, limited additional systemic options currently exist. Specific, actionable, genetic alterations appear rare in this disease. Targeted therapy against epidermal growth factor receptor (EGFR) has been tested, similar to SCCs originating from other anatomical regions.

Evidence of sporadic activity of several EGFR inhibitors have been reported from a few small clinical studies or case series [337-339]. Dacomitinib, an orally-available pan-HER inhibitor, was tested as monotherapy in a phase II study including patients with locally advanced and distant metastatic penile SCC. In this study, 28 patients were included and the ORR was 32.1%, with one patient benefiting with a complete response [340]. While enrolment into clinical trials is preferred, in some jurisdictions, tumour-agnostic, molecularly-selected therapy is available, such as pembrolizumab or dostarlimab for mismatch repair-deficient tumours (or high tumour mutational burden) or trastuzumab deruxtecan for HER2-positive solid tumours.

Despite PIK3CA, gene alterations have been reported as the most frequently identified potentially 'actionable' genomic alterations in SCC of the pelvic region. No data currently support the use of selected targeted agents in this disease [341].

6.5.3 Role of radiotherapy in palliation

Radiotherapy is frequently necessary for palliation of penile cancer and should be customised for unique presentations as necessary: for example, ulcerative fixed LNs or dermal lymphatic spread. While standard palliative regimens should be readily employed, providers should be aware that retreatment may be necessary for durable disease control [342]. This radioresistance in some cases has been noted [150].

6.5.4 Summary of evidence and guidelines for systemic and palliative therapies for advanced penile cancer

Summary of evidence	LE
Low-level data support the use of platinum-based chemotherapy as first-line systemic therapy in advanced disease.	3
Effective second-line palliative chemotherapy regimens are lacking. Second-line chemotherapy in multiple studies was associated with median OS of six months or less.	3
Initial phase II or basket studies assessed anti-EGFR therapy or checkpoint inhibition, as monotherapy or combination therapy, in advanced disease. Early evidence of promising clinical activity has been reported in patients with penile cancer.	2b

Recommendations	Strength rating
Systemic therapies	
Offer patients with distant metastatic disease platinum-based chemotherapy as the preferred approach to first-line palliative systemic therapy.	Weak
Do not offer bleomycin due to the pulmonary toxicity risk.	Strong
Offer patients with progressive disease under platinum chemotherapy the opportunity to enrol in clinical trials, including experimental therapies within phase I or basket trials.	Strong
Radiotherapy	
Offer radiotherapy for symptom control (palliation) in advanced disease.	Strong

7. FOLLOW-UP AND QUALITY OF LIFE

7.1 Unmet needs

Penile cancer has a significant impact on QoL and unfortunately there remain many unmet needs to address (see Table 1.1 in Chapter 1) [2]. The physical changes, along with the psychological and emotional stress that men with penile cancer suffer, requires recognition and professional support before, during and after treatment. Holistic patient support services delivered by a multidisciplinary team as a routine part of surveillance and follow-up should be standard of care. Patients with cancer endorse of the need for 'adjustment' and dealing with the 'new normal' as part of survivorship [343]. The extent of this and the time it takes varies from person to person and it is important to realise that some unmet needs may not become an issue until much later on.

7.2 Rationale for follow-up

From an oncological perspective, surveillance is important as early detection of recurrence may increase the likelihood of curative treatment. Some studies suggest that local recurrence does not significantly reduce long-term survival if successfully treated [174, 344]. However, a multicentre study reported an increased risk of recurrence following glansectomy in men with more-aggressive disease (T3 and/or high grade), which in turn resulted in poorer OS and CSS [172]. Disease that has spread to the inguinal LNs greatly reduces the rate of long-term CSS. Follow-up is also important for survivorship, allowing for the detection and management of the physical and psychological impact of treatments. The use of Patient Reported Outcome Measures (PROMs) related to body image (Male Genital Self-Image Scale [MGSIS-5]) and lymphoedema (Groin and Lower Limb Lymphoedema questionnaire [G3L-20]) have been proposed as tools to help patients and their healthcare team raise and discuss embarrassing topics during consultations [345]. In penile cancer, PROMs sent out to patients digitally (ePROMs) prior to consultations have been trialled. Non-responders tended to be older and have a poorer performance status. The study also found that patients initially engaged with the PROMs, but that this was not maintained over time. Fifty percent of clinicians were positive about the use of these tools, although they may lead to increased consultation times [346].

Local or regional nodal recurrences usually occur within two to three years of primary treatment [174, 347-349]. A study of 509 patients reported 52.3% of local recurrences occurred within two years and 79.5% within three years [348]. Fewer than 5% of regional or distant recurrences occur after two years, with the majority occurring within the first year after treatment [347, 348]. After five years, all recurrences were either local or new primary lesions [174]. 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 reliably undertake regular self-examination [174].

7.2.1 When and how to follow-up

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 local treatment with negative inguinal nodes, follow-up should include physical examination of the penis and groins for local and/or regional recurrence. A recent study reported that including three-monthly inguinal USs to this regime, following a negative inguinal SN procedure, detected nodal recurrence in 2% of intermediate and high-risk tumours. This was based on data from 201 patients, and the recommendation was that US groin surveillance could be diminished by 50% (stopped after year two) [350]. Using US to survey node-negative groins should also be considered in patients with high body mass index as clinical examination will be less accurate.

After potentially curative treatment for inguinal nodal metastases, CT imaging for the detection of systemic disease (imaging of thorax, abdomen and pelvis) should be performed at three-monthly intervals for the first two years. Following this, the frequency is usually reduced to six-monthly for a total of five years of follow-up. However, one study of 224 node-positive patients reported only two recurrences in years three to five of follow-up, and both of these were pN3 patients [347]. In penile cancer, ^{18}FDG-PET/CT has been shown to play a role in staging nodal and distant disease, with approximately 85% sensitivity, and so may have a role in surveillance in selected cases [127, 288]. It is important to acknowledge the anxiety patients face waiting for scan results and services should be designed to deliver prompt reporting and communication to patients.

Although rare, late local recurrence may occur. Therefore, regular follow-up can be stopped after five years, provided the patient understands the need to report any local changes immediately [121]. In patients unlikely to self-examine, long-term follow-up may be necessary (Table 7.1).

A recent study reported that early check-in with patients after ILND, with telemedicine appointments within one week of discharge, reduced 30-day Clavien-Dindo complications scores and reduced readmission rates [351].

Rarer, more aggressive penile cancers, such as those with sarcomatoid differentiation, have a poorer outcome with regional and distant recurrence more likely [352]. As a result, these patients should be managed by a multidisciplinary team in a specialist penile cancer centre with CT surveillance, even when they are node-negative.

7.2.2 ***Recurrence of the primary tumour***

Local recurrence is more likely with all types of local organ-sparing treatment. Until recently, local recurrence was not believed to influence the CSS rate, although one study challenged this showing a reduction in OS and CSS following local recurrence after glansectomy [172]. Large series of glansectomies have reported local recurrence rates around 10% [172, 353], although others have reported recurrence in up to 27% of patients treated with penis-preserving modalities, usually occurring within the first two years [173]. After partial penectomy, the risk of local recurrence is approximately 4–5% [173, 174, 344]. Local recurrence is easily detected by physical examination by the patient themselves or their 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.

7.2.3 ***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 [121]. 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 ILND or DSNB, and whose LNs were negative (2.3%). The use of US and FNAC in suspicious cases has improved the early detection rate of regional recurrence [129, 130, 354]. Patients who have had surgery for LN metastases without adjuvant treatment have an increased risk of regional recurrence of 19% [174]. Regional recurrence requires timely treatment by rILND with (neo)adjuvant chemotherapy/chemoradiotherapy.

Table 7.1: Follow-up regime for penile cancer

	Interval of surveillance		**Examinations and investigations**	**Minimum duration of follow-up**
	Years 1–2	Years 3–5		
Recommendations for follow-up of the primary tumour				
Penile-preserving treatment*	3-monthly	6-monthly	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for PeIN (optional).	5 years
Amputation*	3-monthly	Annually	Regular physician or self-examination.	5 years

Recommendations for follow-up of the inguinal lymph nodes				
Surveillance*	3-monthly the first year, 6-monthly the second year	6-monthly	Regular physician or self-examination. Consider 3-monthly US ± FNAC during first year.	5 years
pN0*	3-monthly the first year, 6-monthly the second year	No lymph node follow-up required	Regular physician or self-examination. Consider 3-monthly US ± FNAC during first year, 6-monthly the second year and end follow-up thereafter in patients capable of self-examination of the penis.	5 years
pN+	3-monthly	6-monthly	Regular physician or self-examination. CT chest/abdomen/pelvis or ^{18}FDG-PET/CT if available.	5 years

CT = computed tomography; ^{18}FDG = ^{18}F-fluoro-2-deoxy-D-glucose; FNAC = fine-needle aspiration cytology; PeIN = penile intraepithelial neoplasia; PET = positron emission tomography; US = ultrasound.
**Self-examination can be considered in capable patients for penile preserving, amputation, surveillance and pN0 after two years with easy access back to clinic if needed.*

7.3 Patient support services

Surveillance is not just about assessing for recurrent disease and men may require more frequent appointments than suggested above with different members of the multidisciplinary team to deliver patient support services and address QoL challenges. In fact, the latter starts at the first preoperative consultation, where a needs assessment can identify areas that will be individually more challenging for that patient, be it physical, psychological, emotional, social or financial. Many men with penile cancer reflect that, whilst the knowledge of potential functional and psychological impacts of treatment would not have stopped them proceeding with it, they wish they had a better understanding before embarking on the surgery. Prehabilitation programmes can also help with this. A qualitative study highlighted that men with penile cancer would appreciate more focus on the following themes: 'early signs and seeking help,' 'disclosure of a personal cancer' and 'urological (dys) function' [355].

Not all men survive penile cancer, and some present with, or recur with, advanced disease, some with extremely challenging symptoms to manage, including pain, odour and discharge. In addition to medical treatments outlined in other parts of these Guidelines, early involvement of palliative care services for symptom control can make a substantial difference to these patients.

7.3.1 Psychological support

Access to psychological support, counselling and psychosexual therapy are critical components of a holistic and multidisciplinary survivorship service. Men will often think 'why me?' and need help to process their thoughts and try to adjust to their changing situation. Areas for discussion might include identity and self-esteem (lifestyle and role adjustments); being a perceived burden; illness beliefs and perceptions; levels of social support; relationship quality and intimacy; body and self-image; and concerns relating to mortality [356]. Despite these significant psychological challenges, the rate of suicide, based on the SEER database (1973–2013), is amongst the lowest of all urological malignancies: 13 out of 6,155 men [357].

7.3.2 Quality of life

Very little data is available on 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 PROMS for penile cancer. Some validated questionnaires have been used, but none of them were validated in men with penile cancer. Tools used include LYMQOL (lymphoedema) [358]; International Index of Erectile Function (IIEF) (erectile dysfunction) [359]; SF-36 [360]; EORTC QLQ-C30 [361]; Quality of Life Questionnaire-Penile Cancer-Rostock (HRO-PE29) [362]; Hospital Anxiety and Depression Scale [363]; EQ-5D (Euro QoL tool); Bigelow's questionnaire [364]; Male Genital Self-Image Scale MGSIS-5; and Groin and Lower Limb lymphoedema questionnaire G3L-20 [365].

Not surprisingly, published studies and discussions with patient groups demonstrate that penile cancer and its treatments have a significant impact on overall QoL, both physical and psychological. However, as discussed below, there is discrepancy in the literature as to whether partial penectomy impacts QoL more than penile-

preserving surgical techniques. Erectile dysfunction, reduced frequency of sexual intercourse and reduced satisfaction with intercourse are reported in some studies [366, 367]. Urinary spraying [368] is another potential significant consequence of penile cancer surgery. Significant anxiety (31%) and depression (6%) have also been reported [369].

A German study reported on 76 patients following primary penile surgery. The researchers reported a global QoL score well below the national average for age-standardised German patients, with voiding, sexuality, body image and lymphoedema all reported as areas of concern [362].

A Dutch study, in which 90 patients returned their questionnaires (a return rate of 62%) found that orgasm, appearance concerns, life interference and urinary function were all significantly poorer following partial penectomy compared with a penile-preserving approach. In the same study, LND had a significant impact on life interference. Interestingly, when compared to an age- and gender-matched normative sample from the general population, the patients reported better outcomes for the SF-36 physical domain and bodily pain subscale [368].

A systematic review [152] reported on post-treatment QoL from ten studies involving 346 men [186, 205, 362, 368, 370-375]. Two studies evaluated QoL as the primary endpoint and compared the outcomes among various treatment modalities [370, 374]. One of these studies used EORTC QLQ C-30 and reported on the QoL of men after penile cancer management with different treatment modalities. The researchers observed that the treatment itself was not related to overall wellbeing or to social contact and activity. However, half of the individuals had psychological symptoms at follow-up [374]. In contrast, a retrospective study of men who underwent penile-preserving surgery reported a significant impact of surgery in every domain of EORTC QLQ-C30 questionnaire [362].

Another study used Bigelow's questionnaire and compared the postoperative QoL score to that at two weeks before surgery [375]. The researchers reported that the scores relating to unpleasant feeling, sexual pleasure and familial/partner relations improved significantly ($p < 0.01$), whereas the domains relating to friend relationships and professional quality were unchanged.

Two non-randomised comparative studies used EORTC QLQ-C30 to assess QoL after penile-preserving surgery or amputative surgery [370, 371]. The first trial on 51 men reported a statistically significant negative correlation between aggressiveness of surgery and global health status and physical functioning [370], whereas the other trial reported no significant differences between penile-preserving surgery or partial penectomy in functional scale, symptom scale and in the global health status [371]. A comparison between glans resurfacing, glansectomy and partial penectomy using the EQ-5D tool showed no difference between groups, with comparable health status scores of 82.5, 85.0 and 87.5, respectively [186].

Another non-randomised comparative study compared penile-preserving surgery to partial penectomy and reported no difference in QoL using the SF-36 scores [368]. Those who underwent amputative surgery had significantly more appearance concerns ($p = 0.008$) and they reported more life interference ($p = 0.032$), depending on the degree of disfigurement caused by the procedure.

7.3.3 ***Urinary function***

Urinary function is an important topic to discuss with men before penile cancer treatment. Some will already be experiencing difficulty voiding due to their tumour causing urethral obstruction, and many report they sit down to pass urine due to the spraying caused by the tumour. As a result, some report improved function following surgery, often in terms of flow, but spraying and needing to sit down to void or use a funnel/bottle can be debilitating for many men.

Urinary function has been objectively assessed in only a few studies. Two case series reported improvement in postoperative urinary function and high satisfaction after penile surgery [373, 376]. Two non-randomised comparative studies reported no difference in urination between penile-preserving surgery or amputation. One demonstrated similar maximum flow rates following surgery (19.5mL/s vs. 20.8mL/s) [371], the other reported that urinary function was comparable across the study groups (glans resurfacing, glansectomy and partial penectomy) using the ICIQ-MLUTS score [186]. However, a different study found that urine spraying is more common after partial penectomy as compared to penile-preserving surgery (83% vs. 43%) [368]. Two case series reported no significant changes in urinary function following brachytherapy [195, 205]. A single trial on Moh's micrographic surgery reported no post-treatment change (66% response rate) [377].

7.3.4 ***Sexual function***

Sexual and erectile function after penile cancer varies between studies and between treatments. Generally, penile-preserving surgery preserves erectile function, although glans sensation and orgasm can be affected. Overall, partial penectomy is associated with poorer sexual outcomes.

A systematic review [152] reported on the sexual and erectile function from 27 studies that involve 991 men. The five- or 15-question IIEF scores were used by most studies. Other tools used were the Erectile Dysfunction Inventory of treatment satisfaction (EDITS) score, the index of male genitalia image (IM-GI), the Life Satisfaction of sexual life, the Self-Esteem and Relationship (SEAR) or a combination of tools to assess overall sexual function [152, 205, 371, 372, 374, 378]. It is important to acknowledge that only a few studies assessed baseline function and are therefore able to report the difference between pre- and post-treatment. Most studies reported only the post-treatment scores or the mean difference for retrospectively completed pre-treatment scores.

Three non-randomised comparative studies and one case series assessed the impact of penile-preserving surgery versus amputation on sexual function of 202 men [368, 371, 374, 379]. Two studies that used the 15-question IIEF questionnaire reported significant post-treatment changes in the orgasmic function domain in favour of penile-preserving surgery ($p = 0.033$ and $p = 0.033$), while the other domains remained comparable between the treatment arms [368, 371]. However, in other studies using the five-question IIEF score, no difference was identified between treatments [186, 369]. An older study that compared the impact of penile-preserving surgery, amputative surgery and radiotherapy on sexual function reported that those treated with amputation had worse sexual outcome [374]. Three trials retrospectively compared penile-preserving surgery techniques using the IIEF questionnaire [373, 380, 381]. Wide local excision was superior to glansectomy in all IIEF domains [380]. The impact of primary closure versus preputial flap reconstruction after glans-preserving surgery was similar as seen by IIEF results at six months or by rigid-scan parameters [381]. Partial glansectomy was not superior to total glansectomy [373].

Cohort studies have reported similar findings on sexual function. Five studies on patients who underwent penile-preserving surgery and reconstruction reported that 85–100% of men were able to achieve erection and maintain their sexual function [187, 382-385]. However, all patients reported reduced glans sensitivity. Following glans resurfacing for penile cancer ($n = 21$) or lichen sclerosis ($n = 16$), one study reported no significant change in urinary or sexual function (using IPPS and IIEF questionnaires), with glans sensitivity preserved in 89.2% of men [386].

Four studies of 167 men who have had partial penectomy reported significant changes in 15-question IIEF score with negative impact in every domain [366, 376, 378, 387]. A single trial reported that, after partial penectomy, 61.7% of men report erectile dysfunction [387]. However, a study from Brazil assessing 14 patients following partial penectomy found that, for 64%, overall sexual function was normal or slightly decreased, and frequency of sexual intercourse was unchanged or slightly decreased [367].

The sexual function after brachytherapy has been assessed in five cohort studies [191, 195, 205, 388, 389]. Among men who were sexually active before treatment, 58.8–70.0% remained sexually active after treatment [191, 205]. Potency was maintained in 81.5–100% of men [191, 195, 205, 388, 389]. Altered glans sensitivity is reported in 52.6% [191].

Three studies assessed sexual function after laser treatment [184, 372, 390] and 46–56.5% of men report an impact of treatment on their sexual life [372, 390]. A single trial on 46 men found that 72% reported no change in erectile function, 22% reported decreased erectile function and 6% reported improvement [184].

One trial on patients who underwent Moh's micrographic surgery reported no change in sexual function after treatment (57.5% response rate) [377].

7.3.5 ***Lymphoedema***

Lymphoedema significantly impacted functional domains in one study of patients 25 months following penile cancer nodal surgical treatment, with ILND and PLND having a much higher impact than ILND alone. Patients who had ILND and PLND also had a much poorer mood score (38% vs. 0%) [391]. Due to the significant morbidity associated with ILND, many patients are not offered the operation or choose not to undergo the operation. An analysis of the USA SEER database reported that only 233 out of 943 non-metastatic penile cancer patients (24.7%) had ILND between 1998 and 2015 [253]. This did not change over time. A similar proportion of men, 606 out of 2,224 (27.2%), underwent the surgery between 2004 and 2014, as recorded by the National Cancer Database [392].

Men should be assessed for genital and lower-limb lymphoedema at each outpatient clinic appointment and advised regarding proper skin care, compression, exercise, massage and elevation when resting as the mainstay of treatment. Following nodal surgery, ideally, these men would be referred to specialist lymphoedema services for assessment and management before any significant lymphoedema occurs.

Specialist lymphoedema services offer a range of made-to-measure compression garments or multilayer lymphoedema bandaging for lower-limb and genital lymphoedema. The latter not only compress the scrotal lymphoedema but also aim to lift it to aid drainage. For lower limb compression, adjustable Velcro garments are available. Proper skin care is critical to prevent infection that can damage remaining lymphatic channels. Prophylactic antibiotics should be used following any episode of cellulitis, with penicillin V, erythromycin or clindamycin recommended, except in genital lymphoedema, for which prophylactic trimethoprim can be used [393].

Manual lymphatic drainage in the form of specialised massage techniques also helps to alleviate lymphoedema and encourages drainage. Following penile cancer treatments, manual lymphatic drainage is commonly used for stubborn mons, lower abdominal swelling and thickening of the scrotum and penile shaft.

Whilst regular exercise may temporarily increase lymphoedema due to the effect of gravity, exercise has an overall beneficial effect on lymphoedema by reducing abdominal fat (fat drains via lymphatic channels, as well) and using natural muscle pumps and changes in thoracic pressure to help lymphatic drainage. Strength training and stretching exercises to promote flexibility are also important.

Debulking surgery with scrotal reduction and penile shaft skin grafting can significantly improve issues related to significant genital lymphoedema. There is limited evidence for the benefit of other surgical interventions such as limb liposuction followed by compression and lymphaticovenous anastomosis in penile cancer although some evidence does exist for extremity lymphoedema due to various causes [394].

7.4 Centralisation of penile cancer services

Current large-volume centres offer specialist nursing support, psychological support and specialised lymphoedema services to their patients. However, even in centralised healthcare systems such as the UK, services vary and are not always available.

7.4.1 ***Advantages of centralised care***

Centralisation of penile cancer services has a number of advantages in addition to delivering these important supportive services to patients (Table 7.2) [395]. These advantages include provision of an environment in which multidisciplinary discussion of cases can occur along with specialist pathological review, and delivery of high volume penile-preserving and nodal surgery, which can lead to innovation, such as closer surgical margins [178], more accurate DSNB and minimally invasive surgery. In the UK, approximately 80% of penile cancers are treated with penile-preserving surgery. Several population-based and database studies have demonstrated that treatment in high-volume or academic centres is associated with improved oncological outcomes. Higher-volume hospitals and academic institutions perform more-appropriate inguinal staging and LND, achieve higher LNYs and report lower rates of positive surgical margins compared with low-volume centres [392, 396]. These centres also more frequently apply organ-sparing techniques and multimodal treatment when indicated, supporting centralisation to experienced facilities.

Centralisation can also reduce system delays [397] and result in better adherence to guidelines. In addition, patients should be able to access a larger team of specialists, including psychological and lymphoedema survivorship services. Centralisation of penile cancer services also creates opportunities for translational and clinical research in a rare disease.

7.4.2 ***Guideline adherence***

Organ-sparing surgery is likely underused when comparing stage at presentation with guideline recommendations. Reported adherence varies widely, from < 50% in series in the USA to > 70% in some European datasets [396, 398-400]. Centralisation increases adherence, with higher use of OSS in referral centres [19, 401].

Adherence to nodal staging is also highly variable, often between 20–50% in population-based studies [123, 402, 403]. Centralisation markedly improves practice: Belgian and Dutch series showed staging rates > 90% in eligible patients after implementation of structured referral pathways [19, 401]. Omission of guideline-recommended nodal staging is consistently associated with worse survival [234, 392].

Adherence to perioperative chemotherapy in node-positive disease remains low, often below 40% in large registries [231, 404]. In Sweden, national guidelines and centralisation increased use from ± 30% to > 60%, with a significant reduction in penile cancer-specific mortality [405].

7.4.3 ***Survival***

In one hospital in the UK, five-year CSS rates improved by up to 12% (to 85%) following centralisation, which is likely due to several factors, including the impact of early and complete pathological LN staging, regular multidisciplinary patient reviews, and the use of adjuvant chemotherapy and chemoradiotherapy in most patients where indicated [406]. Evidence from the Netherlands also shows that centralisation can translate into improved survival. In a nationwide registry of 3,160 patients, five-year relative survival was significantly higher in the national reference centre compared to regional hospitals (86% vs. 76%, $p < 0.001$), despite a higher proportion of advanced-stage and node-positive disease at the centralised centre. After adjustment for tumour stage, grade, nodal status, age and year of diagnosis, treatment at regional centres remained an independent predictor of worse survival (HR: 1.22, 95% CI: 1.05–1.39) [19].

7.4.4 ***Disadvantages of centralised care***

Disadvantages of centralisation include deskilling of medical teams not involved with regularly looking after penile cancer and making patients travel long distances for treatment. This can be a significant financial burden, particularly as many patients are in a lower socioeconomic group. However, the recent increase in virtual healthcare and video consultation may reduce this burden, as does the provision of outreach clinics and services. In addition, educational sessions within cancer networks can help keep local teams up to date, enabling them to help support the patient when back at home (Table 7.2).

Table 7.2: Advantages and disadvantages of centralisation

Advantages	Disadvantages
Multidisciplinary team and holistic approach to penile cancer care	Deskilling of urologists and their teams
Opportunities for research, clinical trials and innovation	Distance patients need to travel
Improved survival	Financial burden of travel
High rates of penile-preserving surgery	Lack of local support for patients
High rates of surgical nodal staging	
Specialist lymphoedema services	
Specialist uroradiology/nuclear medicine	
Specialist pathology reporting/review	
Psychological support	
Adherence to guidelines	
Clear referral pathway/reduced system delays	

7.5 Summary of evidence and guidelines for follow-up and quality of life

Summary of evidence	LE
Follow-up surveillance is important, as early detection of recurrence may increase the likelihood of curative treatment.	3
Local or regional nodal recurrences usually occur within two years of primary treatment.	3
Penile cancer has a significant impact on QoL in many ways and there remain many unmet needs to address.	4
Very little data are available regarding 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 PROMS for penile cancer.	3
Penile-preserving surgery generally preserves erectile function, although glans sensation and orgasm can be affected. Overall, partial penectomy is associated with poorer sexual outcomes.	2b
Access to psychological support, counselling and psychosexual therapy are critical components of a holistic and multidisciplinary patient support service.	4

Ideally, following nodal surgery, patients would be referred to specialist lymphoedema services for assessment and management before any significant lymphoedema occurs.	4
A volume-outcome relationship exists in penile cancer: high-volume and centralised centres show higher adherence to guidelines for organ-sparing surgery, nodal staging and perioperative multimodal therapies.	3
Centralisation is associated with improved survival, with population-based data showing higher relative survival in national referral centres compared to regional hospitals, even after adjustment for adverse case mix.	3

Recommendations	**Strength rating**
Deliver penile cancer care as part of an extended multidisciplinary team consisting of urologists specialising in penile cancer, specialist nurses, pathologists, uroradiologists, nuclear medicine specialists, medical and radiation oncologists, lymphoedema therapists, psychologists, counsellors, palliative care teams for early symptom control, reconstructive surgeons, vascular surgeons and sex therapists.	Strong
Refer all patients with suspected or confirmed penile cancer to a high-volume expert centre for multidisciplinary evaluation and management. If direct referral is not feasible, ensure pretreatment discussion with such a centre, including the use of European Reference Networks where available.	Strong
Follow-up with men after penile cancer treatment, initially three-monthly for two years then less frequently to assess for recurrent disease and to offer patient support services through the extended multidisciplinary team. At discharge, recommend self-examination with easy access back to the clinic, as local recurrence can occur late.	Strong
Discuss the psychological impact of penile cancer and its treatments with the patient and offer psychological support and counselling services.	Strong
Discuss the negative impact of treatments for the primary tumour on penile appearance, sensation, and urinary and sexual function, so that the patient is better prepared for the challenges they may face.	Strong
Discuss the potential impact of lymphoedema as a consequence of inguinal and pelvic lymph node treatment with the patient, assess patients for lymphoedema at follow-up, and refer to lymphoedema therapists early.	Strong

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9. CONFLICT OF INTEREST

All members of the EAU-ASCO 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 provided below and is also publicly available on the EAU website: http://uroweb.org/guideline/penile-cancer/.

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