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SPECIAL ARTICLE

Penile cancer: ESMO—EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INCIDENCE AND EPIDEMIOLOGY

Penile cancer is a rare genital malignancy with an estimated global incidence of 36 068 new cases in 2020.[1] In Western Europe and the United States, the age-adjusted incidence of penile cancer is 0.3-2.1 per 100 000.[2] Conversely, in countries where circumcision is routine practice due to religious or cultural reasons,[3] penile cancer is almost non-existent, whereas areas within South America, South Asia and Sub-Saharan Africa have the highest prevalence in the world (3-7 per 100 000 men).[1,4]

A number of aetiological factors have been linked with penile cancer and its geographical distribution. Among them, ethnicity, human papilloma virus (HPV), population age, social and cultural habits and prevalence of neonatal circumcision are the most important.[3] HPV infection has been reported in up to 50.8% [95% confidence interval (CI) 44.8% to 56.7%] of penile cancer cases and in up to 79.8% (95% CI 69.3% to 88.6%) of patients with penile intraepithelial neoplasia (PeIN).[5] The predominant oncogenic HPV subtype in penile cancer is HPV 16, which is prevalent in up to 70% of HPV-positive penile cancers;[6] other common HPV subtypes include HPV 6, 11, 18, 31 and 33.[7]

Lichen sclerosus, a chronic inflammatory condition of unknown aetiology which mainly affects the anogenital area (85%-98%), has also been associated with the development of penile cancer. Lichen sclerosus is associated with up to 30% of penile cancer cases, and in particular those that are not HPV driven.[8,9] Other risk factors include smoking, poor penile hygiene and treatment with psoralen ultraviolet (UV)-A phototherapy (PUVA).

DIAGNOSIS, STAGING AND PATHOLOGY

Diagnosis

The most common tumour affecting the penis is squamous-cell carcinoma (SCC). SCCs are predominantly exophytic lesions originating from the mucosal surface of the glans and inner prepuce as opposed to the keratinised skin of the penile shaft. Incisional or excisional biopsies of suspected penile cancer should be carried out to confirm a histological diagnosis. Penile cancer has an accepted stepwise lymphatic dissemination whereby it initially drains to the inguinal lymph nodes (LNs) followed by the pelvic LNs.

A proposed algorithm for the diagnostic work-up of penile cancer is shown in Figure 1.

Assessment of the primary tumour. Clinical assessment of the primary tumour should record the size, morphology and relationship to adjacent structures in order to plan penile-preserving surgery where possible. Lesions on the glans penis should be assessed for invasion into the distal corpus cavernosum. Where there is uncertainty, magnetic resonance imaging (MRI) or penile ultrasound (US) combined with an intracavernosal injection of prostaglandin E1 to induce an artificial erection can be helpful to stage the primary lesion.[10-12]

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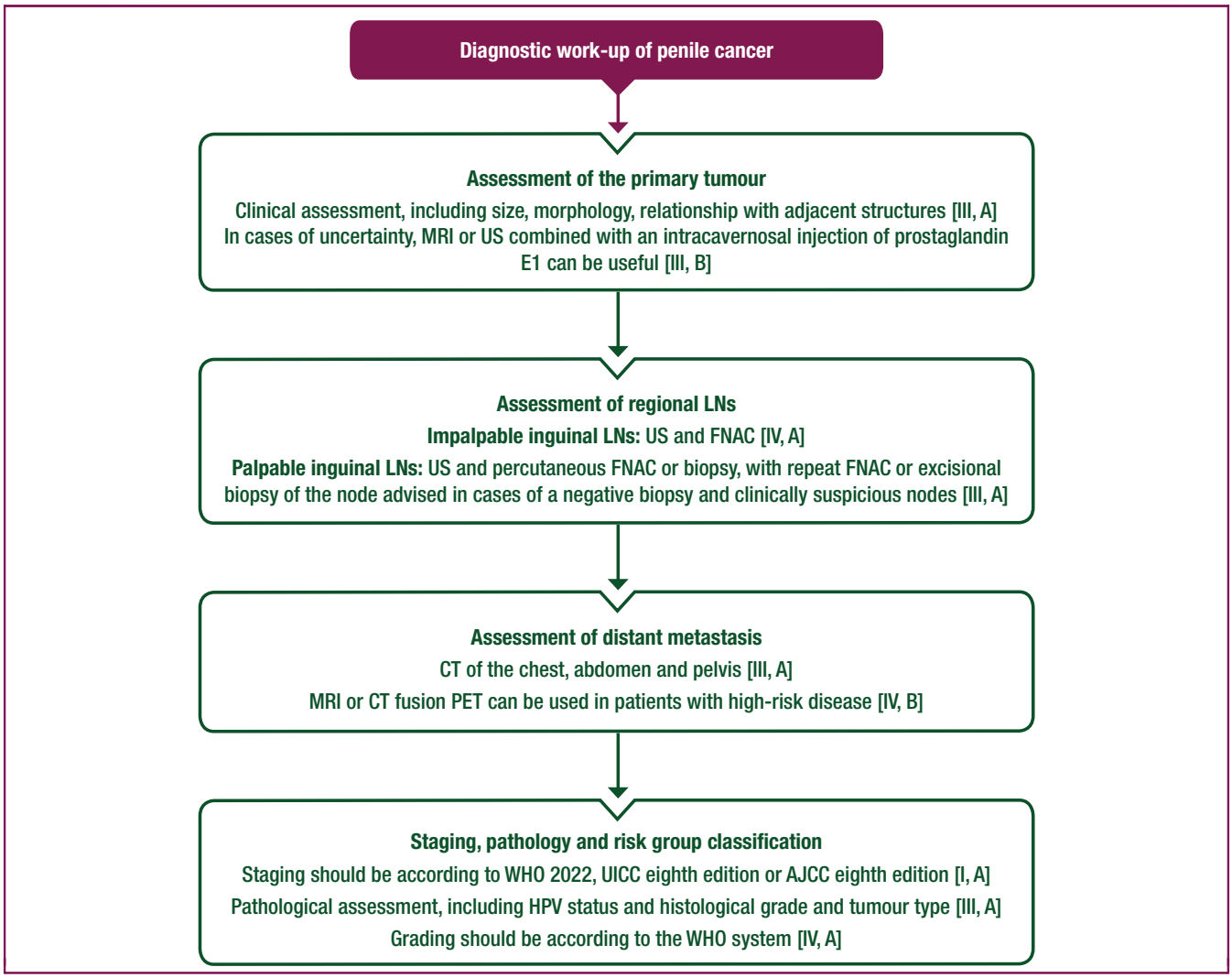

Figure 1. Proposed algorithm for the diagnostic work-up of penile cancer.
Purple: algorithm title; white: other aspects of management.
AJCC, American Joint Committee on Cancer; CT, computed tomography; FNAC, fine-needle aspiration cytology; HPV, human papillomavirus; LN, lymph node; MRI, magnetic resonance imaging; PET, positron emission tomography; UICC, Union for International Cancer Control; US, ultrasound; WHO, World Health Organization.

Assessment of regional LNs. Evaluation of the LNs is critical as characteristics, such as the involvement of inguinal LNs, the number and site of metastatic nodes and extracapsular nodal involvement, provide the strongest prognostic factors for disease-specific survival (DSS).[13]

Impalpable inguinal nodes. Clinically impalpable inguinal LNs (cN0) should undergo US imaging and fine-needle aspiration cytology (FNAC) of morphologically abnormal inguinal nodes.

Palpable inguinal nodes. Palpable inguinal nodes are likely due to metastatic disease in >80% of cases; this can be confirmed by carrying out percutaneous FNAC or a biopsy of the LN. In cases of a negative biopsy and clinically suspicious nodes, a repeat FNAC or excisional biopsy of the node is advised.[14] In the presence of fungating primary lesions, lymphadenopathy can develop secondary to inflammatory changes. If nodes are palpable, US ± FNAC has a high sensitivity for detecting cancer, although it can still miss micrometastases in reactive nodes.[15]

MRI and computed tomography (CT) scanning can detect enlarged inguinal and pelvic LNs. CT is primarily used, despite the low sensitivity (36%). The use of [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)—positron emission tomography (PET)—CT remains uncertain, although the sensitivity is reported as 96% for palpable nodes.[16]

Assessment of distant metastases. MRI or CT fusion PET probably has the highest sensitivity for detecting distant metastasis and can be used in high-risk cases. For routine staging at diagnosis and follow-up, however, CT of the chest, abdomen and pelvis is sufficient.

Staging

Tumour staging must be carried out according to a recognised staging classification system—either the World Health Organization (WHO) 2022, the Union for International

Cancer Control (UICC) eighth edition or the American Joint Committee on Cancer (AJCC) eighth edition.[17-21] The TNM (tumour—node—metastasis) clinical and pathological classification of penile cancer according to the UICC eighth edition is shown in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103481.

Staging of the primary lesion and regional LNs requires accurate knowledge of the penile anatomy. In the distal penis, three different epithelial mucosal compartments exist: glans, coronal sulcus and inner prepuce of the foreskin.

Pathology

Precursor lesions. Premalignant disease of the penis is termed PeIN. Here, the basement membrane remains intact but intraepithelial changes occur. PeIN is a recognised precursor of invasive SCC; it was integrated into the WHO 2016 classification[22] and is maintained in the WHO 2022 classification.[21] Precursor lesions of SCC are outlined in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103481. Two major subgroups of PeIN can be distinguished, as shown in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103481.

Invasive carcinoma. WHO 2022 has retained the classification of invasive penile cancer based on the association with HPV,[23] in line with the classification of precursor lesions, giving due importance to the pathogenesis.[21]

Non-HPV-related penile cancer. The most common histological subtype in this group is SCC usual type, which also includes the well differentiated pseudo-hyperplastic form. Grading of these lesions should be according to the WHO system.[21] Other subtypes are verrucous carcinoma, which includes a low-grade entity called carcinoma cuniculatum,[24] papillary carcinoma, pseudoglandular carcinoma, mixed carcinoma, the rare sarcomatoid carcinoma and the extremely rare adenosquamous carcinoma (including mucoepidermoid carcinoma). The frequency and prognosis[25] for each histological subtype are summarised in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.103481.

HPV-related penile cancer. HPV-associated SCC is related to high-risk HPV, such as HPV 16 and 18, and demonstrates p16 expression. Histological subtypes include basaloid SCC,[26] warty carcinoma,[27,28] clear-cell carcinoma,[29] lymphoepithelioma-like carcinoma[30] and mixed (previously termed warty-basaloid) carcinoma. The frequency and prognosis[25] of each histological subtype are shown in Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.103481.

Others. *SCC not otherwise specified.* Invasive keratinising carcinoma without any special features and which cannot be tested for HPV is designated as SCC not otherwise specified (NOS). No established prognostic or treatment differences between HPV-associated and HPV-independent penile cancers currently exist. Some recent studies suggest, however, that HPV-associated SCC may respond better to radiotherapy (RT) or multimodality treatments.[31,32]

Mandatory and recommended information to include in the pathology report for penile cancers is provided in Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2024.103481.

Recommendations

- Clinical assessment of the primary tumour should record size, morphology and relationship to adjacent structures [III, A].
- The use of MRI or US combined with an intracavernosal injection of prostaglandin E1 is useful to assess the primary lesion [III, B].
- FNAC should be used in clinically impalpable inguinal nodes when they are detected as morphologically abnormal on US [IV, A].
- Clinicians should carry out percutaneous FNAC for palpable inguinal nodes and repeat the FNAC or carry out an excisional biopsy in case of negative findings for clinically suspicious nodes [III, A].
- CT is advised in all cases for the assessment of distant metastases [III, A]. MRI or CT fusion PET can be used in patients with high-risk disease [IV, B].
- The following are recommended for disease staging classification: WHO 2022, UICC eighth edition or AJCC eighth edition [I, A].
- Pathological assessment should include HPV status, histological grade and tumour type [III, A].
- The WHO system is recommended for disease grading [IV, A].

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE

Management of local disease according to stage

It is important to note that the treatment of penile cancer is based on non-randomised data largely derived from heterogeneous patient cohorts, typically from high-volume institutional series. No randomised studies have been undertaken in this disease that have suggested a survival benefit of one approach over another. The rarity of the disease makes large randomised trials unfeasible.

According to the AJCC eighth edition, localised penile cancer includes stage I (T1a N0 M0) and stage II (T1b-T3 N0 M0) disease. For both stages, treatment should be carried out with curative intent with surgical resection or RT which includes brachytherapy and/or external beam RT (EBRT) in selected cases. Although brachytherapy is not widely available, it is potentially suitable for selected cases when the lesion is located in the distal penis and the patient does not want to undergo surgical intervention. A proposed algorithm for the management of primary penile tumours is shown in Figure 2.

The primary aim of surgical intervention is to remove the tumour using penile-preserving techniques. Preservation of the aesthetic, sexual and urinary function is an important outcome to allow penetrative sexual intercourse and voiding standing up.

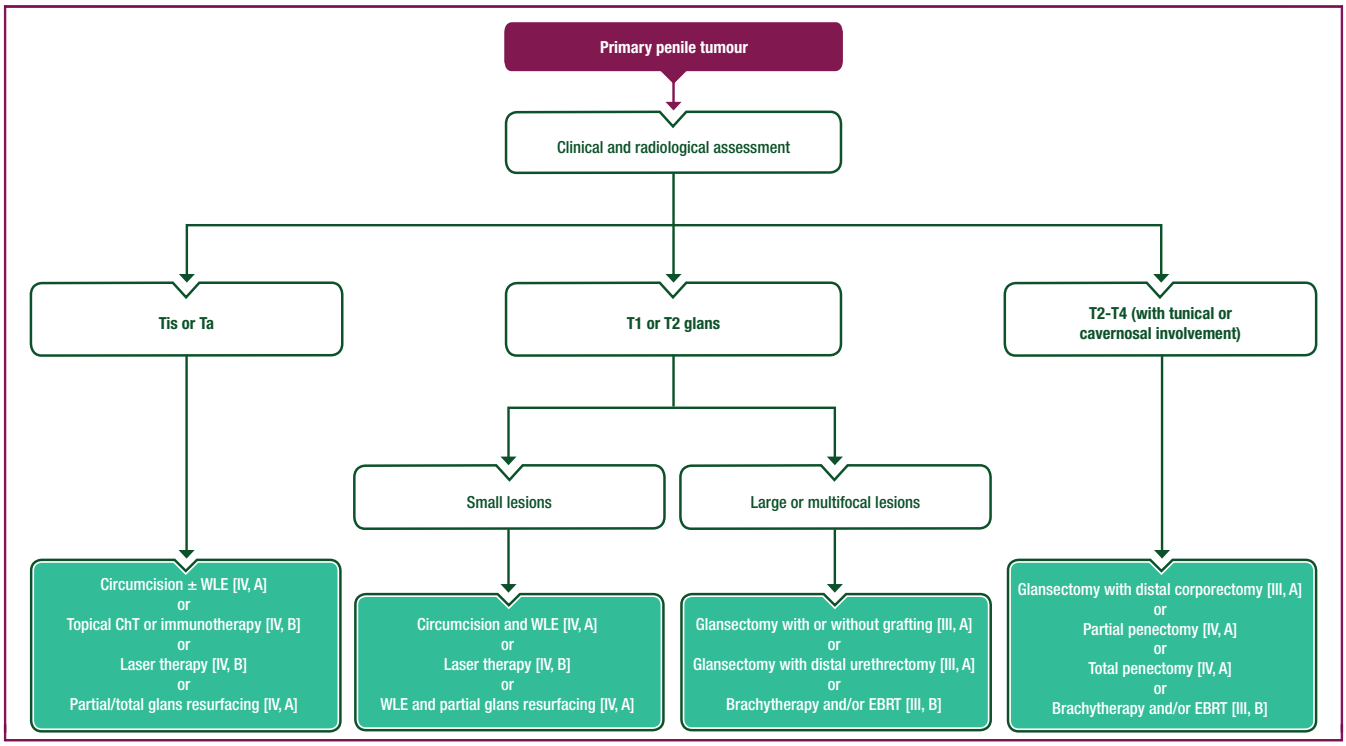

Figure 2. Proposed algorithm for the management of primary penile tumours.
Purple: algorithm title; turquoise: combination of treatments or treatment modalities; white: other aspects of management.
ChT, chemotherapy; EBRT, external beam radiotherapy; T, tumour; Tis, carcinoma *in situ*; WLE, wide local excision.

Several organ-sparing surgery (OSS) options have been described to manage the primary penile cancer. Nonetheless, no randomised controlled trials or comparative studies are available to define the best OSS in patients with localised penile cancer. Thus, surgical options should be tailored according to the disease stage, patient willingness for reconstruction and clear surgical margins.

Premalignant disease (PeIN). In cases of biopsy-proven PeIN located on the glans or prepuce, circumcision is mandatory as the initial management. Following circumcision, any residual PeIN can be treated using topical agents, such as 5-fluorouracil (5-FU)[33] or imiquimod. Alternatively, carbon dioxide (CO_2) laser ablation (penetration is 2-2.5 mm) can be used. Following topical treatment, the response should be assessed clinically or with a repeat biopsy of any new lesions which may indicate progression to invasive disease. If topical treatment fails, wide local excision or glans resurfacing, whereby the mucosal layer is removed and replaced with a split-thickness skin graft (SSG), should be considered. The 5-year local recurrence rate after laser treatment is ∼50%[34,35] which emphasises the importance of close clinical follow-up.[34] Vaccination against HPV in HPV-related PeIN has not been routinely used as the long-term efficacy is unclear, but in high-risk individuals, it is an option that can be discussed in unvaccinated men.[36] Therefore, concomitant use of local treatment and nonavalent vaccine in HPV-related PeIN is an option but requires further validation.

Ta-1 disease. Patients with tumour localised to the foreskin can undergo a circumcision, which is often therapeutic. Wide local excision of the lesion with reconstruction using an SSG or advancement flap using penile shaft skin is preferable for small tumours located on the glans penis. Long-term follow-up, depending on the tumour stage, is mandatory for both procedures as recurrence rates can reach 15.4% according to contemporary evidence.[37] Glans resurfacing is recommended for PeIN or T1a lesions with excellent oncological outcomes as well as aesthetic and functional outcomes.[38] The local recurrence rate is up to 4.5%,[39] but positive surgical margins (48%) and repeat surgery (28%) are common.[40] Mohs micrographic surgery can be used for small, low-grade penile lesions (T1) but again there is a high recurrence rate (32%)[41] and the need for a more complicated clinical set-up, including a pathologist.

T2 disease. Glansectomy, with or without distal urethrectomy, is the surgical treatment of choice for T2 tumours on the glans penis. An SSG is recommended to reconstruct a neo-glans from the preserved distal corporal tips. Surgical margins of >1 mm are now accepted, with the risk of local recurrence being low. According to a recent systematic review, local recurrence and positive surgical margin rates after glansectomy are 2.6%-16.7% and 2.9%-22.6%, respectively. The incidence of salvage penectomy for positive margins and/or recurrence is 1.2%-8.3%. The overall survival (OS) rate is 78.6%-91.9% and the DSS rate is 89%-96.6%. Good cosmetic outcomes are reported in 95%-100% and normal erectile function in 50%-100% of cases.[42] Partial or total penectomy still remain valid alternatives whenever adequate surgical margins cannot be guaranteed or when the patient is unfit for reconstruction after OSS.

T3 disease. Partial penectomy or total penectomy combined with a perineal urethrostomy are the treatments of choice when the cancer infiltrates proximally into the corpus cavernosum. The penile shaft length should be evaluated before surgery. In the presence of an adequate penile shaft length, partial penectomy with an SSG or urethral advancement[43] for neo-glans reconstruction are valid options. For shorter penile shaft lengths or where there is a buried penis, total penectomy with urinary diversion via a perineal urethrostomy is advised. Total phallic reconstruction can be considered following subtotal or total penectomy. Radial-artery free flaps[44] and latissimus dorsi flaps[45] are the preferred options in patients with penile cancer.

T4 disease. With more extensive disease, total penectomy with perineal urethrostomy is the recommended option. Toilet procedures with urinary diversion are also considered as palliative treatment in advanced cases when negative margins cannot be achieved. This allows easier wound management for patients in the community setting.

Inguinal LN disease

The inguinal LNs represent the initial site for metastatic disease in patients with penile cancer due to the stepwise lymphogenic spread before any haematogenic spread. The presence of metastatic disease in the inguinal LNs is the most important prognostic indicator in patients with penile cancer, with 5-year survival rates dropping from 90% in localised disease to 50% when there is regional LN involvement.[46] Thus, the clinical and pathological assessment of the inguinal LNs is pivotal in the management of patients diagnosed with penile cancer. A proposed algorithm for the management of inguinal LNs is shown in Figure 3.

The management of the inguinal LNs depends on the clinical stage, which is still classified according to whether they are palpable or not. Accordingly, patients with impalpable inguinal LNs are classified as cN0 and those with uni- or bilateral palpable disease are classified as cN1-2. Cases of grossly enlarged or fungating inguinal LNs are classified as cN3.

In patients with cN0 disease, no imaging technique has the desired sensitivity to detect micrometastatic disease. As such, the clinical management is often based on the disease characteristics of the primary tumour, such as pT stage, histological grade and the presence of lymphovascular invasion. Accordingly, cN0 patients are classified into low-, intermediate- and high-risk groups based on the aforementioned characteristics,[47] as shown in Supplementary

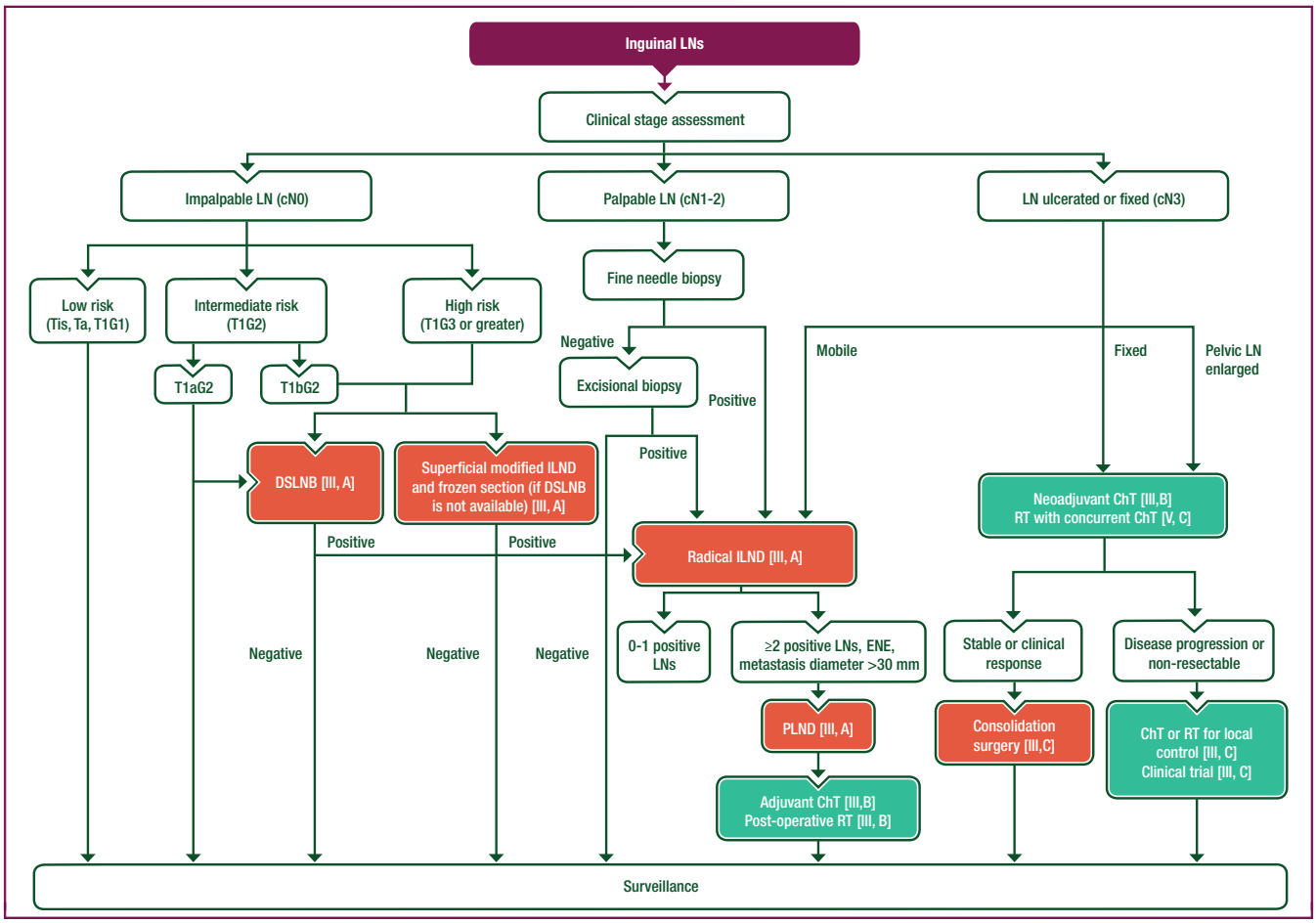

Figure 3. Proposed algorithm for the management of inguinal LNs.
Purple: algorithm title; orange: surgery; turquoise: combination of treatments or treatment modalities; white: other aspects of management.
c, clinical; ChT, chemotherapy; DSLNB, dynamic sentinel lymph node biopsy; ENE, extranodal extension; G, grade; ILND, inguinal lymph node dissection; LN, lymph node; N, node; PLND, pelvic lymph node dissection; RT, radiotherapy; T, tumour; Tis, carcinoma *in situ*.

Table S7, available at https://doi.org/10.1016/j.esmoop.2024.103481.

Management of cN0 disease. Treatment options for patients with cN0 disease include clinical surveillance, dynamic sentinel LN biopsy (DSLNB) followed by radical inguinal lymphadenectomy where there is micrometastatic disease detected in the sentinel node or a superficial modified inguinal lymphadenectomy with frozen section or modified inguinal lymphadenectomy when DSLNB is unavailable. As the risk of micrometastatic disease is up to 25%, subjecting all patients with cN0 disease to an open lymphadenectomy procedure would be deemed as overtreatment. In patients with low-risk disease following observation, the 5-year crude inguinal relapse-free survival is 90%.[48] Given these considerations, patients with cN0 low-risk disease should be managed with clinical surveillance, whereas active treatment is recommended for patients with intermediate- and high-risk disease.[49]

DSLNB followed by radical inguinal lymphadenectomy is an option for patients with intermediate- or high-risk metastatic disease.[50] A proven protocol which relies on preoperative US combined with FNAC for morphologically abnormal LNs followed by sentinel node localisation using a combination of technetium-99m (^{99m}TC) nanocolloid and patent blue dye has a false-negative rate of 10%.[51] Colocalisation of the sentinel node with indocyanine green (ICG) has also been used.[52,53]

The most comprehensive meta-analysis on DSLNB in patients with cN0 disease pooled 28 studies and reported a sensitivity of 87%.[54]

Modified inguinal LN dissection (ILND) aims to decrease the morbidity associated with radical inguinal lymphadenectomy by limiting the surgical dissection to the superficial LNs above the fascia lata and reducing the boundaries of the femoral triangle. Despite the promising results and the lower morbidity rate, no randomised controlled trial has compared the false-negative rate of modified and radical ILNDs. Similarly, no randomised trial has compared modified ILND and DSLNB.

Superficial modified inguinal lymphadenectomy reduces the boundary of dissection and requires intraoperative frozen section analysis before proceeding to a radical inguinal lymphadenectomy in the presence of metastatic nodes. Again, this is an alternative surgical option to reduce the post-operative morbidity.

DSLNB is recommended in all patients with intermediate- or high-risk cN0 disease. Modified ILND in patients with intermediate- and high-risk disease, which can be combined with an on-table frozen section, can be carried out when DSLNB is not available.

Management of cN1-2 disease. Each groin should be considered as a separate unit since the lymphatic drainage from the penis travels bilaterally. In patients with clinically doubtful inguinal LN disease, FNAC or an excisional biopsy of the LN is recommended to confirm the diagnosis followed by radical inguinal lymphadenectomy if metastatic disease is confirmed.

Radical inguinal lymphadenectomy removes the superficial and deep inguinal LNs with preservation of the long saphenous vein and fascia lata where possible. This is the recommended procedure where there are confirmed metastatic inguinal LNs.

The morbidity associated with inguinal lymphadenectomy is high, with complication rates of up to 55% reported.[55] Where there is extensive skin involvement, myocutaneous flap reconstruction[56] is an option to cover the groin defect. Epidermal vacuum-assisted wound closure[57] has not shown a net benefit for preventing post-operative complications and so is not currently recommended. The outcomes from using a fascial-sparing approach for radical inguinal lymphadenectomy, however, appear to reduce the wound complication rates.[58]

Minimally invasive approaches (robotic or laparoscopic) have demonstrated similar oncological outcomes but with less intraoperative blood loss, shorter hospital stay, reduced wound infection rates and reduced skin necrosis rates.[59] The number of patients in these series, however, is too small to conclude if there are any benefits in terms of oncological outcomes or lymphocele and lymphoedema rates.

Management of cN3 disease. Bulky or ulcerated disease requires imaging with CT and MRI scans followed by multimodal treatment.

Neoadjuvant chemotherapy (ChT) followed by ipsilateral radical inguinal and pelvic lymphadenectomy in responders is recommended. Contralateral procedures should be evaluated according to the clinical and pathological assessment.

Pelvic LN dissection. Patients with pelvic LN metastases have a poorer 5-year cancer-specific survival than those with only inguinal LN metastases (33.2% versus 71.0%, respectively).[60]

Ipsilateral pelvic LN metastases are more common in patients with two or more inguinal LN metastases, extranodal extension and metastasis with a diameter of $\geq$30 mm.[60,61] A recent series also highlighted the importance of local tumour stage as pelvic LN metastases were present in 44.2%, 59.0% and 58.3% of patients with pT2, pT3 and pT4 disease, respectively.[62] More than four bilateral inguinal LN metastases are associated with a significantly higher risk of bilateral pelvic LN metastases compared with a lower number of inguinal LN metastases [odds ratio (OR) 14.0, CI 1.71-115].[63] Additionally, the belief that contralateral pelvic LN metastases do not occur when the inguinal LNs are negative on the same side has now been challenged. An LN yield of nine or more pelvic LNs at the time of pelvic LN dissection (PLND) seems to improve recurrence-free survival.[64]

The authors recommend unilateral pelvic lymphadenectomy in patients with two or more ipsilateral inguinal metastases, metastasis diameter $\geq$30 mm or extranodal extension.

Salvage ILND. After primary inguinal lymphadenectomy, the presence of cN3 disease, three or more pathologically

involved LNs and extranodal extension are associated with a higher risk of inguinal recurrence. Salvage inguinal lymphadenectomy with myocutaneous flap reconstruction is an option in patients with recurrent inguinal disease without distant metastases. Surgical intervention is challenging and is associated with a risk of wound infection and debilitating lymphoedema; the reported 5-year cancer-specific survival was 20.9 months in the myocutaneous flap group.[65] Multimodal treatment with neoadjuvant or adjuvant ChT is therefore advised.

RT for primary disease

The optimal tumour characteristics which render a penile cancer best suitable for RT are superficial or exophytic lesions measuring <4 cm and located on the glans or coronal sulcus.[66]

External beam RT. Although EBRT has the advantage of being widely available,[66] the use of RT to treat the primary lesion is reserved for selected cases. Localised lesions can be treated using orthovoltage beams or electrons of 9 MeV with a total dose in the range of 35 Gy delivered in 10 fractions over 2 weeks.[67] Most patients with penile cancer referred to the radiation oncology department, however, present with advanced disease requiring external megavoltage RT as a palliative option. A tissue-equivalent bolus is often required to provide sufficient dose build-up to the surface of the lesion and three-dimensional printers are currently used to custom design immobilisation devices.[67] A typical radical external beam course consists of one daily fraction of about 2 Gy given as five fractions per week for 6-7 weeks to a total dose of 66-74 Gy.[66] Of interest, fractions of <2 Gy are suboptimal, possibly due to the prolongation of treatment time, and hypofractionation, e.g. 50-55 Gy delivered in 16 fractions is associated with more severe long-term sequelae.[66,67]

According to findings from a literature review, which included an analysis of data from 19 retrospective studies, EBRT had a significantly worse local control rate (50%) compared with penectomy and brachytherapy ($P < 0.001$). This analysis, however, was limited by the retrospective nature of the studies and inherent selection bias of the data.[68] In a literature review reported by Patel and colleagues,[66] EBRT was associated with a local control rate of 60% (range: 41%-69%).

Acute side-effects following EBRT are penile oedema, radiation dermatitis and moist desquamation.[67]

Long-term toxicities include penile necrosis (1%-3%), meatal stenosis (10%) and urethral stenosis (17%) with normofractionation (2 Gy per fraction), which increase when hypofractionation is used.[66-68]

Brachytherapy. Optimal candidates for brachytherapy are those with disease limited to the glans that is <4 cm in diameter.[66] In general, brachytherapy results in 5-year local control rates varying between 70% and 90%, with T stage and tumour size being important predictors, with modest impact on functional outcomes and quality of life.[66,69]

There are two distinct methods to carry out brachytherapy for penile cancer:

- Low-dose-rate (LDR) or pulse-dose-rate (PDR) brachytherapy. This treatment type should be reserved for tumours confined to the glans that are <4 cm in diameter. In case of high-grade tumours, surgical nodal staging is necessary.[67] The usual dose is 60-65 Gy delivered continuously (LDR) or in hourly pulses (PDR) over 5 days. Local control rates achieved are 85% at 5 years and 70% at 10 years.[70]
- High-dose-rate (HDR) brachytherapy. Patient selection is the same as for LDR.[67] Dose prescription varies between different series as well as the number of treatments,[67,71] but the most frequently proposed schedule is 42-45 Gy in 12-14 fractions.[72] In one of the largest series ($N = 76$), actuarial local control rate at 5 years was 66%.[73] Smaller series with mostly shorter follow-up have reported 5-year local control rates of 60%-100%.[67] Findings from a single-institution study from France evaluating clinical outcomes following HDR brachytherapy (35 Gy in nine fractions over 5 days) in 29 patients showed that after a median follow-up of 72 months, the 5-year local relapse-free survival rate was 82% and the median time to local recurrence was 29 months.[71] HDR brachytherapy has become the preferred option due to less radiation exposure to health care staff and family along with greater patient convenience.[66]

In the literature review published in 2015,[68] brachytherapy had a 5% higher local relapse rate compared with penectomy but this was significantly lower compared with EBRT. Of interest, when the comparison between brachytherapy and penectomy was limited to patients presenting with Tis, T1 or T2 disease, there was no significant difference in terms of local control or OS. Overall, the 5-year penile preservation rate after brachytherapy was 74%.

In a prospective study, 31 patients with Tis or T1 penile cancer were treated with HDR brachytherapy to a cumulative dose of 54 Gy in 18 fractions (two fractions per day). Most patients had low-grade disease. After a median follow-up of 117.5 months, local control rates at 5 and 10 years were 80.7% and 68.3%, respectively. Median time to local recurrence was 47 months. Salvage therapy resulted in a local disease control rate of 100%.[74]

Penile necrosis and urethral stenosis are reported side-effects,[67] with a mean occurrence rate of up to 33% in some series,[68] although other series report a much lower incidence.[74] Telangiectasia has been described in 17%[71] and sexual dysfunction has been reported in <20% of patients.[68] In all cases, a circumcision should be carried out before brachytherapy.

Neoadjuvant or adjuvant therapy for locally advanced disease

Cytotoxic ChT has been used as palliative treatment to prolong life and improve symptoms in patients with metastatic, inoperable penile cancer. More recently, it has moved

forward in the therapeutic algorithm as an important perioperative treatment for patients with high-risk, locally advanced or node-positive disease.[75]

In many other genitourinary (GU) malignancies, there is a clear mandate for intervention with systemic therapy in node-positive and/or locally advanced disease. In penile cancer, multimodality treatment to manage positive regional LNs has been controversial. Men who present with high-risk nodal disease, i.e. with bulky >4 cm or fixed regional LNs, are highly unlikely to be cured by surgery alone, and both ChT and RT have been considered as perioperative treatments to improve the chances of local control and to reduce the chance of metastatic progression. No randomised data exist currently, however, to guide the clinician. The InPACT trial, a multicentre international collaboration using a randomised Bayesian trial design, is currently recruiting and will establish the standard of care for patients with locally advanced penile cancer.[76]

Several non-randomised studies have explored the efficacy of combination ChT as neoadjuvant treatment before surgery for bulky >4 cm, fixed or cN3 LN disease.[77,78] A key phase II study demonstrating the ability to achieve a meaningful response with ChT in this setting utilised cisplatin—paclitaxel—ifosfamide (TIP) in a 3-day regimen every 21 days as neoadjuvant treatment of locally advanced, inoperable disease.[78] This study reported a response rate of ∼50% with an acceptable toxicity profile, and importantly, ∼30% of patients were free of disease having undergone radical surgery at a median follow-up of 34 months. Complete responses and surgical downstaging with some long-term responders were also reported, with a complete pathological response rate of 13% achieved among patients who underwent surgery. Other non-randomised studies have also shown an OS benefit in patients undergoing neoadjuvant ChT for cN2 and cN3 disease.[79]

Therefore, neoadjuvant ChT with up to four cycles of a triplet regimen, such as TIP or docetaxel—cisplatin—fluorouracil (TPF), in all eligible patients with locally advanced (T4), inoperable, primary penile or urethral SCC,[80] or those patients presenting with fixed inoperable regional nodes (cN3),[81,82] should be discussed. Most physicians have continued to advocate the importance of this intervention through the COVID-19 pandemic, which was also reflected in a European Reference Network Urogenital-Diseases section (eUROGEN) consensus statement.[83]

For patients with high-risk disease (pN2-pN3), i.e. more than two bilateral involved inguinal LNs, the presence of positive pelvic LNs or extranodal extension seen on histopathology, who have undergone radical inguinal lymphadenectomy but have not received neoadjuvant ChT, the data are less clear.

Some centres have extrapolated neoadjuvant data to use adjuvant ChT with four cycles TIP or platinum—taxane—5-FU. Published data showing the benefit of adjuvant treatment in patients with high-risk, node-positive disease following inguinal lymphadenectomy are limited to small retrospective cohort studies.[84-87] Multicentre studies have shown improvements in OS in patients with highest-risk disease, including those with pelvic LN involvement.[88] Conversely, a study from a United States National registry[89] suggested that receipt of adjuvant ChT in node-positive disease was not associated with improved OS on multivariate analysis. Although there continues to be a lack of prospective published data, adjuvant ChT with four cycles of TIP or TPF should be discussed in eligible patients with high-risk, node-positive penile cancer following radical lymphadenectomy who have not received neoadjuvant ChT before surgery.

Adjuvant post-operative RT for the management of regional LN metastases

The role of adjuvant post-operative RT is still considered controversial and there is a lack of prospective studies to guide its use.[66] A recent meta-analysis of published studies evaluating adjuvant RT in penile cancer concluded that there was no OS benefit or reduction in relapse rate afforded by the addition of adjuvant RT and therefore no good evidence to support its use in routine practice. The data reported in this meta-analysis, however, were heterogenous in terms of radiation dosage and indication and may not reflect current standards. Moreover, there has been some positive evidence reported supporting the use of adjuvant RT in high-risk node-positive disease.[90]

An analysis of the United States National Cancer Database demonstrated an OS benefit, both at 3 and 5 years, in favour of adjuvant RT [hazard ratio (HR) 0.58]. This benefit was driven by patients presenting with N2 disease and was absent in patients presenting with N1 disease.[91] This benefit was confirmed by Tang et al.,[92] who demonstrated a significant OS benefit of 4 months when adjuvant pelvic RT was applied in patients presenting with positive pelvic LNs after PLND. HPV-positive patients receiving post-operative RT to the LNs had a significantly longer OS compared with those with an HPV-negative status. This difference amounted to 23 months and 32 months at 5 and 7 years of follow-up, respectively.[32] These differences in OS also held true after propensity score-matching ($P = 0.006$).

The recommended dose is 50 Gy in 2 Gy fractions[86,92] or a biological equivalent dose at 1.8 Gy fractions. This dose has been questioned by Johnstone et al.,[93] however, who suggested that a dose of up to 66 Gy (2 Gy per fraction) might be necessary to achieve sufficiently high local control rates. This dose-response relationship was also suggested by Ager at al.,[94] who concluded that a dose ≤50 Gy resulted in more in-field recurrences compared with >50 Gy (31% versus 14%). There are no arguments to support hypofractionation. Although studies in other SCCs of the perineal area, e.g. vulvar and anal cancer, have demonstrated the efficacy of chemoradiotherapy (CRT) regimens, prospective studies of such strategies are unavailable in penile cancer.

In patients presenting with pN3 disease, defined in this particular study as those having positive inguinal LNs with extracapsular extension, adjuvant CRT significantly improved 3-year cause-specific survival (CSS) compared with adjuvant ChT alone (29% versus 16%; $P = 0.036$), corresponding to a CSS benefit of nearly 8 months. In a multivariate analysis, the

use of CRT was the only significant predictor for CSS.[95] These results were confirmed in a single-institution study from India,[86] where adjuvant multimodality treatment with CRT resulted in the highest 2-year OS rate compared with single-modality treatment or no treatment (75% versus 67% and 28%, respectively). Similar differences were observed for 2-year disease-free survival (DFS; 73% versus 54% and 16%, respectively). Of note, single-modality RT resulted in a superior 2-year OS and DFS compared with single-modality cisplatin-based ChT (81% versus 57% and 68% versus 44%, respectively).

Jaipuria et al. conducted a retrospective analysis based on 45 patients presenting with positive inguinal LNs after LN dissection.[96] Most patients had pN3 disease (extracapsular extension) and 13 also presented with positive pelvic LNs. In patients with positive groin but negative pelvic LNs, adjuvant RT resulted in a better OS compared with adjuvant ChT. This advantage disappeared, however, in the presence of positive pelvic LNs.

Adjuvant RT is associated with the development of lower limb lymphoedema in approximately half of patients undergoing treatment. This can also impact ambulation in a significant proportion of patients.[96]

Thus, although contradictory evidence exists for the efficacy of adjuvant RT, for patients with involved inguinal and/or pelvic LNs, it remains a reasonable approach and should be considered as a tool in the post-operative management of patients with high-risk node-positive disease. There remains a lack of consensus as to which patients benefit the most from this approach and prospective clinical trial data are needed to inform decision making for both clinicians and patients.

Recommendations

PeIN

- Circumcision is recommended as the initial treatment in any biopsy-proven PeIN located on the glans or prepuce [IV, A].
- Following circumcision, any residual PeIN can be treated using topical agents, such as 5-FU or imiquimod. Alternatively, CO_2 laser ablation can be used [IV, B].

Ta-1 disease

- Wide local excision of lesions involving the glans or a glans resurfacing procedure is recommended, with reconstruction using SSG or penile shaft skin [IV, A].
- Clinicians may carry out Mohs micrographic surgery for low-grade penile lesions (T1) but only if the right clinical set-up, including a pathologist, is available [IV, C].
- Brachytherapy is an alternative to surgery in pT1 disease and patients should be referred to specialist centres for multidisciplinary consideration of the suitability of surgery or brachytherapy in this context [III, A].

T2-4 disease

- In T2 tumours of the glans penis, glansectomy with or without distal urethrectomy and SSG reconstruction is recommended [III, A].
- In selected patients with low-volume T1-T2 disease, brachytherapy is an option in specialist centres [III, B].
- Partial or total penectomy with perineal urethrostomy is recommended where the cancer infiltrates proximally into the corpus cavernosum (T3-T4) [IV, A].

cN0 disease

- Clinical surveillance of the inguinal nodes is recommended in patients presenting with cN0 tumours with low-risk features (pTa/pTis and pT1G1) [III, A].
- For patients with cN0 intermediate or high-risk disease (pT1G2, pT1-4G3/G4 or lymphovascular invasion), DSLNB should be carried out before proceeding to a radical inguinal lymphadenectomy in the presence of metastatic nodes [III, A].

cN1-2 disease

- In patients with cN1-2 disease, radical inguinal lymphadenectomy is recommended to remove the superficial and deep inguinal LNs with preservation of the long saphenous vein and the fascia lata where possible [III, A].

cN3 disease

- For bulky or ulcerated disease (cN3), neoadjuvant ChT followed by ipsilateral radical inguinal lymphadenectomy, with or without pelvic lymphadenectomy in responders, should be discussed for eligible patients [II, B].

PLND

- Unilateral pelvic lymphadenectomy is recommended in patients with two or more ipsilateral inguinal metastases, metastasis with a diameter of $\geq$30 mm or extranodal extension [III, A].

Salvage ILND

- Clinicians may recommend salvage inguinal lymphadenectomy with myocutaneous flap reconstruction in recurrent inguinal disease [IV, B]. Salvage ILND should be considered as part of multimodal treatment which should also include neoadjuvant or adjuvant ChT [III, A].

RT for primary disease

- A typical EBRT course is 66-74 Gy in 2 Gy fractions, five times per week [III, C].
- Physicians in specialist centres may recommend LDR or HDR brachytherapy for the treatment of penile cancer, especially if surgery is not an option [III, C].
  - The usual dose is 60-65 Gy delivered continuously (LDR) or in hourly pulses (PDR) over 5 days and 35 Gy in nine fractions over 5 days for HDR brachytherapy [III, B].
  - Low-volume residual disease can be treated with 38.4 Gy in 12 fractions but for intact tumours, the most frequently proposed schedule is 42-45 Gy in 12-14 fractions [III, C].

Systemic therapy for locally advanced disease

- Patients with cN3 fixed nodes should be considered for neoadjuvant ChT with triplet regimens such as TIP or TPF [III, B].

- Responders should be considered for consolidation surgery (bilateral and deep ILND and ipsilateral PLND if possible) [III, C].
- Patients with disease progression or unresectable LNs may consider additional systemic ChT, local-field RT or participation in a clinical trial [III, C].
- Patients with pN2 and pN3 disease following LND should be considered for adjuvant ChT following surgery [III, B].

Adjuvant post-operative RT for regional LN metastases

- Clinicians may consider the use of adjuvant RT with at least 50 Gy in 2 Gy fractions or a biological equivalent dose in 1.8 Gy fractions in combination with adjuvant ChT in patients with pN3 disease [III, B]. Higher doses up to 66 Gy have also been recommended.

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

Recurrent disease

Patients can develop recurrent disease at the site of the primary tumour or within the inguinal areas. When feasible, further surgery can help palliate these patients and allow easier wound management. Inoperable cases, however, present a challenge. Recurrent disease on the glans without corpus cavernosum invasion can be managed with wide local excision, distal corporectomy, or in selected cases, brachytherapy may be an option. More extensive disease involving the corpus cavernosum may require a partial or total penectomy.

Palliative ChT for metastatic disease

In the presence of metastatic inoperable disease, ChT has been used as a palliative intervention to improve symptoms and prolong life. Platinum-based ChT is the classical backbone of therapy for metastatic disease, with regimens often utilised that have demonstrated activity in other GU cancers or SCCs. Older regimens, such as methotrexate—bleomycin—cisplatin,[85] have been largely superseded due to concerns over toxicity.[97] The most commonly utilised approaches include cisplatin—5-FU, with a median progression-free survival (PFS) of 20 weeks and an OS of 8 months,[98] and platinum—taxane.[99] The use of such regimens in penile cancer have been associated with partial response or clinical benefit rates of 20%-40%, and rarely, profound durable responses have also been reported. There is also evidence for the efficacy of triplet regimens. A UK study of the regimen TPF reported a response rate of 38% and a grade 3-4 toxicity rate of 63%.[100] As mentioned earlier, a study which used TIP as a 3-day regimen every 21 days for the neoadjuvant treatment of inoperable disease reported a response rate of ∼50% and an acceptable toxicity profile.[78] Newer first-line studies have included the vinca alkaloid vinflunine, with an overall clinical benefit rate of 45% and a response rate of 27% reported in this setting.[101] A phase II study of the pan-human epidermal growth factor receptor (HER) tyrosine kinase inhibitor dacomitinib reported a response rate of 33% with an acceptable toxicity profile and a median 12-month PFS of 26%.[102] The phase II or retrospective nature of the studies reported to-date, along with their small sample sizes, and the lack of any randomised clinical trials comparing different regimens, however, preclude the identification of a superior drug regimen for the first-line treatment of patients with distant metastatic disease.

First-line cisplatin-based combination ChT, selected based on patient comorbidities and Eastern Cooperative Oncology Group (ECOG) performance status (PS), is recommended for the treatment of metastatic disease. Cisplatin plus 5-FU, carboplatin plus paclitaxel, TIP and TPF are reasonable choices for first-line systemic therapy in patients considered fit enough. Following failure of first-line ChT, median OS in patients with metastatic penile SCC is only 6-8 months. There are very limited data on the use of systemic therapies in the second-line setting. Single-agent paclitaxel has been used in the second-line setting as it is well tolerated and was associated with a median OS of 23 weeks in a small phase II study.[103] A retrospective review evaluating second-line treatment with epidermal growth factor receptor-targeted therapy (mostly cetuximab) reported a median OS of 29.6 weeks.[104]

Molecular profiling and immunotherapy

Although no immunotherapy is currently licensed in unselected patients with penile cancer, preclinical work has shown that penile SCC expresses programmed death-ligand 1 (PD-L1) and may be amenable to therapeutic intervention with PD-L1-targeted immunotherapies that have been successful in other GU cancers.[105] The anti-PD-L1 agent cemiplimab has been approved by the United States Food and Drug Administration (FDA) for patients with cutaneous, inoperable SCC following results from a phase II trial which reported a response rate of 47%. Although cutaneous SCC is a malignancy with a different aetiology and pathogenesis, these cancers have a high tumour mutational burden (TMB), which has been associated with a higher likelihood of response to immunotherapy.[106] The unselected phase II PERICLES trial, evaluating atezolizumab with or without RT in 32 patients with advanced penile SCC, reported a median PFS of 2.6 months (2.6 months in the atezolizumab monotherapy arm and 3.9 months in the atezolizumab—RT arm), a median OS of 11.3 months (8.9 months in the atezolizumab monotherapy arm and 12.0 months in the atezolizumab—RT arm) and a response rate of 16.7% in both treatment arms.[107] Responses to other immune checkpoint inhibitors (ICIs) have been observed in patients with metastatic penile cancer. Recent data from the Global Society of Rare Genitourinary Tumors (GSRGT) retrospective study[108] has reported response rates to immune checkpoint therapy in the first- and second-line setting in metastatic penile cancer. Among 66 assessable patients, the overall disease control rate was 35%, including seven complete and partial responses. Toxicity was comparable to that seen in other GU malignancies. Patients with penile cancer have also been included in basket trials of rare GU cancers. In one cohort, a

response was seen in one patient with a high TMB,[109] and in another, a response was seen in a patient with a microsatellite instability-high (MSI-H) tumour.[110] Pembrolizumab has an FDA approval in a tumour-agnostic setting based on the responses seen across tumour types in patients with unresectable or metastatic MSI-H or mismatch repair deficient (dMMR) solid tumours as well as those with a high TMB status.[111] Ongoing trials will elucidate the role of immunotherapy in an unselected penile cancer patient population and its utility in combination with ChT. Early data therefore suggest that although the response rate to immunotherapy in an unselected population is not high, it may be a useful strategy, even in chemo-resistant disease, as a potential option in patients whose tumours have the genomic characteristics of TMB high, MSI-H or dMMR.

In health care settings where there is coverage for genomic testing and the provision of licensed tumour-agnostic therapies, such therapies may be considered for eligible patients whose tumours are resistant to standard therapies (see Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2024.103481). Without insurance coverage, however, these treatments are very expensive and may be financially challenging to the patient and their family.

Histopathological subtypes

There is some evidence to suggest that poorer outcomes are seen in certain subtypes of penile SCC. Across various GU malignancies, sarcomatoid SCC has been associated with a more aggressive disease course and tempo, with a propensity for early metastatic disease. This aggressive behaviour has also been reported in penile SCC.[112] There is currently no evidence to suggest that the earlier use of systemic therapy for the management of these tumour subtypes provides a benefit, but given the poor outcome if left untreated, it remains reasonable to consider ChT in this rare group of patients.

Recommendations

Recurrent disease

- For recurrences without invasion of the corpora cavernosa, salvage penile-sparing options can be considered [IV, C].
- Invasion of the corpora cavernosa warrants partial or total penectomy [IV, B].
- For regional recurrences in the inguinal and pelvic LNs, consider systemic ChT, EBRT, surgery or a combination [III, C].

Metastatic penile cancer

- Treatment options for patients with metastatic penile cancer include systemic ChT with platinum-based combination regimens e.g. cisplatin—5FU, carboplatin—paclitaxel, TIP or TPF, depending on the patient's comorbidities, fitness and ECOG PS. Clinical trial enrolment is strongly recommended [III, C].
  - o For those with no response or disease progression, second-line systemic ChT or RT for local control and/or best supportive care or a clinical trial may be considered [IV, C].
- Palliative RT or RT with concurrent ChT for sites requiring local control should be considered [V, C].

Molecular profiling

- Biomarker-selected clinical trials should be considered where available [V, C].
- In selected patients whose tumours have a high TMB, MSI-H or dMMR, the use of anti-PD-L1 immunotherapy can be considered [V, C].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

The aim of follow-up of patients with penile cancer after treatment is to detect local, regional and/or distant recurrence. Most recurrences develop within 5 years of primary treatment, with the majority detected within 2 years. Published data from a retrospective study of 700 patients showed that 66% of local recurrences, 86% of regional recurrence and all distant recurrences were detected within the first 2 years.[113] Thus, close clinical follow-up is required for the first 2 years after surgery.

As penile-preserving techniques have now become standard of care, close clinical follow-up is required as recurrence rates are 20%-50%. If detected early, further surgery does not impact on the DSS.

The risk of regional recurrence is largely dependent on whether the patient's disease is staged as pN0 or pN+, as well as the surgical technique used to remove the LNs. DSLNB removes very few inguinal LNs and the false-negative rate is ∼10%. pN+ disease can have a recurrence rate of 20%-40%,[114] however, and requires close surveillance. Unlike recurrent disease at the site of the primary tumour, regional recurrence does have a negative impact on DSS.

Risk of distant recurrence is largely dependent on the primary tumour histological subtype and the presence of pathological LNs in the inguinal region. The presence of distant disease in penile cancer is a poor prognostic indicator due to the poor response to adjuvant treatment.

Regular follow-up also allows patients to access psychological support and address urinary and sexual dysfunction as a result of the surgical interventions. Inguinal and pelvic lymphadenectomy is also associated with lower limb lymphoedema. Thus, dedicated lymphoedema teams can help reduce the risk of recurrent cellulitis, help with mobility and reduce the extent of lower limb and genital swelling.

Recommendations

- Close follow-up every 3-4 months for the first 2 years following primary surgery is required to detect local recurrence [IV, A].

- Follow-up should include clinical examination as well as imaging, which may include US of the inguinal LNs if the patient has undergone DSLNB or regular CT surveillance if the patient has undergone radical inguinal lymphadenectomy for pN+ disease [IV, A].
- Regular follow-up can provide psychological support and address sexual and urinary dysfunction as well as lymphoedema-related complications [IV, A].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2024.103481.[115] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/genitourinary-cancers/penile-cancer.

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