EAU-ASCO COLLABORATIVE GUIDELINES ON PENILE CANCER

(Limited text update March 2023)

O.R. Brouwer (co-chair), S.T. Tagawa (co-chair), M. Albersen, B. Ayres, J. Crook, M.S. van der Heijden, P.A.S. Johnstone, A. Necchi, P. Oliveira, L.C. Pagliaro, A. Parnham, C.A. Pettaway, C. Protzel, R.B. Rumble, D. Sánchez Martínez, P.E. Spiess
Patient Advocates: K. Manzie, J-D. Marcus, J. Osborne
Panel Associates: T. Antunes-Lopes, L. Barreto, R. Campi, S. Fernandez Pello, H.A. Garcia Perdomo, I. Greco, M. Kailavasan, A. Sachdeva, L. Zapała
Guidelines Office: C. Bezuidenhout

Introduction

Penile cancer has a significant impact on quality of life (QoL) in many ways and there remain many unmet needs to address. The Guideline Panel have chosen to stress the importance of QoL in penile cancer in the introduction to these guidelines to underline that the significant emotional, social, and physical needs are to be discussed and addressed early in a patient's pathway, through a holistic and multi-disciplinary approach.

Epidemiology

The incidence of penile cancer increases with age, with a peak in the sixth decade but it does occur in younger patients. Penile cancer is most common in regions with a high prevalence of human papillomavirus (HPV), and approximately one third to half of cancer cases are attributed to HPV-related carcinogenesis. A slight increase in incidence is seen in Western/developed countries, most likely caused by higher infection rates of HPV which is a trend also observed in other cancers.

Risk factors

HPV infection is the main risk factor for penile cancer. Several other risk factors for penile cancer have been identified, including phimosis, chronic penile inflammation, lichen sclerosus, smoking, ultraviolet A phototherapy, and low socio-economic status.

Pathology

Squamous cell carcinoma (SCC) accounts for over 95% of penile malignancies. Different histological subtypes of penile SCC with distinct growth patterns, clinical aggressiveness and HPV associations have been identified. Numerous mixed forms exist with warty-basaloid form the most common mixed form (50–60%). Penile Intraepithelial Neoplasia (PeIN) is considered the precursor lesion of the penile SCC.
Other malignant lesions of the penis include melanocytic and sarcomatoid lesions, mesenchymal tumours, lymphomas, and metastases, all of which are extremely rare in comparison to SCC.

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), urethral invasion, invasion of corpus spongiosum/cavernosum, surgical margins and p16 immunohistochemistry (IHC) results.

Recommendations for the pathological assessment of tumour specimens	Strength rating
The pathological evaluation of penile carcinoma specimens must include the pTNM 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.

Staging and classification systems

The 8th edition of the UICC/AJCC TNM should be used for the staging and classification system of penile cancer (Table 1).

Table 1: UICC/AJCC 8th edition TNM clinical and pathological classification of penile cancer

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 localised squamous cell 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 (unilateral)
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.*

Diagnosis and staging

Physical Examination

Physical examination should include inspection and palpation of the entire penis and both groins. The dimensions, anatomic location, and extent of local invasion should be noted. Physical examination is a reliable method for estimating penile tumour size and clinical T stage. Careful palpation of both groins for enlarged/pathologic inguinal lymph nodes (LNs) must be part of the initial physical examination of patients suspected of having penile cancer.

Penile biopsy

A biopsy of the primary tumour should be obtained when there is doubt about the exact nature of the lesion. Histological confirmation is necessary to guide management when treatment is planned with topical agents, radiotherapy, or laser surgery.

Imaging of the primary tumour

- Magnetic resonance imaging (MRI) can be helpful in case of uncertainty if the tumour invades the cavernosal bodies (cT3), and if organ-sparing treatment options are considered.
- Ultrasound (US) can be considered if MRI is not available.

Lymph node staging

The presence and extent of LN metastasis is the most important prognostic factor for survival of penile cancer. There are data showing that survival is better when LN metastases are removed in a micro-metastatic state (before they become palpable (cN0).

As current non-invasive staging options such as CT or PET/CT are not reliable enough to detect micro-metastatic disease (and should not be routinely performed in cN0 patients), surgical staging is recommended in cN0 patients at high risk of having occult LN involvement (≥ pT1b). pT1a G2 tumours are considered intermediate-risk. In patients with low-risk tumours (pT1a G1), the risk of metastates is too low to justify surgical staging.

Inguinal lymph node dissection (ILND) is the most reliable surgical staging procedure, but is associated with the highest morbidity. Dynamic sentinel node biopsy (DSNB) has shown high diagnostic accuracy and low morbidity, especially in high-volume centres. Inguinal US + fine needle aspiration cytology (FNAC) of sonographically abnormal nodes can reduce the need of DSNB when tumour positive, allowing for earlier therapeutic treatment of node-positive disease.

In cN+ patients, obtaining pathological confirmation (by biopsy) and additional imaging for staging pelvic LNs and distant sites is recommended. Imaging with ^{18}FDG-PET/CT showed higher sensitivity/specificity than CT alone.

Recommendations for the diagnosis and staging	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 alternative option.	Weak
Obtain a pre-treatment 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 (LNs)	
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 micro-metastatic disease (T1b or higher).	Strong

In case of T1a G2 disease, also discuss surveillance as an alternative to surgical staging in 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 preferred by the patient after being well informed, offer inguinal lymph node dissection (ILND) (open or video-endoscopic).	Strong
If DSNB is planned, perform inguinal US first, with fine needle aspiration cytology (FNAC) 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}FDG-PET/CT or CT of the chest and abdomen before initiating treatment.	Strong

Disease management

Treatment of the primary tumour

Main aims of treatment of the primary tumour are complete tumour removal, which has to be balanced against optimal organ preservation without compromising oncological control.

Superficial non-invasive disease (PeIN, Ta)

Circumcision should be the primary surgical option and close monitoring before starting additional treatment is advocated.

Topical therapies
Topical therapy with imiquimod (IQ) or 5-fluorouracil (5-FU) are effective non-invasive first-line treatment options.

Laser ablation
Laser ablation is an alternative treatment option.

Surgery
Extensive PeIN, residual PeIN in resection margins or recurrent disease after ablative or topical therapy, can be treated by surgical excision/glans resurfacing.

Invasive disease confined to the glans (cT1/T2)
Treatment choice depends on tumour size, histology, stage, grade, localisation, and patient preference. Minimal resection margins (> 1 mm) were shown to be oncologically safe. Therefore, organ-sparing treatment (circumcision, wide local excision, glans resurfacing, glansectomy) should be offered, when feasible. Although organ-sparing treatments have been associated with higher recurrence rates compared to amputative surgery, there is little impact on long-term survival. The higher recurrence-free survival rates observed after amputative surgery need to be weighed against the negative impact on patients' sexual function and QoL.

Glansectomy
Patients with tumours confined to the glans and prepuce 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.

Partial penectomy
Partial amputative surgery is generally reserved for more

advanced disease (≥ T3). Data suggest that recurrence-free rates after amputative surgery were superior to penile-sparing surgery, indicating that a wider resection is protective against local recurrence and should always be discussed as an alternative option.

Radiotherapy

Radiotherapy, either external beam radiotherapy (EBRT) (min dose 60 Gy) or brachytherapy (the latter for lesions < 4 cm in diameter), is an alternative organ-preserving approach in selected patients with T1–2 lesions. Reported results are best with brachytherapy.

Local recurrence after organ-sparing surgery

A second organ-sparing procedure can be performed in the absence of corpus cavernosum invasion. In large or high-stage recurrence, partial or total amputation is required, unless the lesion cannot be resected, or concurrent nodal- or distant metastases were diagnosed.

Locally advanced disease (T3–T4)

For patients staged ≥ cT3, (partial or total) amputative surgery is standard. Radical amputation and urinary diversion by perineal urethrostomy is reserved for those patients in whom a resection with tumour-free margins would result in the inability to void standing upright or without wetting the scrotum.

Recommendations for PeIN, Ta–cT1/T2 and T3–T4 disease	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 of the higher risk of local recurrence when using organ-sparing treatments 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 CO_2 or Nd:YAG 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 intra-operative 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 (EBRT 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 chemo-radiotherapy to patients with non-resectable advanced primary lesions or to patients with locally-advanced disease who refuse surgical management.	Weak

Treatment of cN1–2 disease

The management of regional LNs is decisive for patient survival. The presence and extent of nodal involvement is singulary the most important prognostic factor in patients with penile cancer.

Radical inguinal lymph node dissection

Open radical ILND remains the standard of care for patients with cN1–2 disease (including patients after positive DSNB). Radical ILND carries significant morbidity due to impaired lymph drainage from the legs and scrotum. Minimally-invasive (video-endoscopic) approaches have emerged, although

largely confined to cN0 patients with short follow-up data precluding incorporation in the current guideline.

Recommendations for cN1-2 disease	Strength rating
In patients with cN1 disease offer either ipsilateral: • fascial-sparing ILND • open radical ILND; sparing the saphenous vein, if possible.	Strong
In patients with cN2 disease offer ipsilateral open radical ILND; 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 chemotherapy as an alternative approach to upfront surgery in selected patients with bulky mobile inguinal nodes or bilateral disease (cN2) who are candidates for cisplatin and taxane-based chemotherapy.	Weak
Complete surgical inguinal and pelvic nodal management within three months of diagnosis (unless the patient has undergone prior neoadjuvant chemotherapy).	Weak

Prophylactic pelvic lymph node dissection (PLND)

Prophylactic PLND in most cases represents a staging procedure that can identify candidates for early adjuvant therapy, although in select patients it may also provide a therapeutic benefit. Among various predictors, the number of positive inguinal LNs and presence of extranodal extension is associated with positive ipsilateral pelvic LN metastasis.

Recommendations for prophylactic PLND	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

Clinical N3 disease

Patients with a fixed inguinal mass (i.e., to the skin or underlying structures) or pelvic lymphadenopathy are defined as cN3.

- Surgery alone will rarely cure patients with cN3 disease.
- Even when technically feasible, upfront surgery is associated with significant complications which may delay or prevent delivery of adjuvant therapy.
- About half of cN2–3 patients respond to combination chemotherapy. Responders that subsequently undergo consolidative inguinal/pelvic LND have an overall survival (OS) of about 50% at 5 years.
- Inguinal LND in cN3 patients often requires resection of overlying skin to effectively remove a fixed bulky nodal mass.
- The available literature includes virtually no cN3 patients to assess the efficacy or safety of minimally-invasive ILND.

Recommendations for cN3 disease	Strength rating
Offer neoadjuvant chemotherapy 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 up-front surgery.	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 video-endoscopic inguinal lymphadenectomy.	Strong

Multimodal chemotherapy/radiotherapy in management of (regional) lymph nodes

Systemic therapy

Neoadjuvant chemotherapy (NAC)

Given the poor outcome of upfront surgery, NAC is a potentially-suitable approach for patients with pelvic- and/or extensive/fixed inguinal LN involvement (cN3), or selected patients with (bulky) bilateral involvement (cN2). In non-responding patients, the potential benefits of surgery should be re-evaluated as prognosis is poor in these patients.

Adjuvant chemotherapy

There are no strong data supporting the use of adjuvant chemotherapy to improve OS following surgical resection of the primary tumour and involved LNs. However, in a subset of healthy patients at very high risk of recurrence, after a balanced discussion of risks and benefits of adjuvant chemotherapy, it can be offered.

Recommendation for neoadjuvant and adjuvant chemotherapy	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 up-front 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 post-operative radiotherapy.	Weak

Radiotherapy

Primary (definitive) and adjuvant radiotherapy for node-positive penile cancer remains controversial since there is no level 1 evidence. 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). As in other SCC sites, HPV status may also predict for increased responsiveness to combined chemo-radiotherapy.

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

Palliative therapies for advanced disease

Systemic therapy

- Low-level data support the use of platinum-based chemotherapy as the preferred approach in first-line palliative systemic therapy. Choices include triplet regimens (docetaxel, cisplatin & 5-FU [TPF], paclitaxel, ifosfamide, & cisplatin [TIP]) and doublets (PF, paclitaxel/ carboplatin), where doublets appear to have less toxicity.
- Effective second-line palliative chemotherapy regimens are lacking. Second-line chemotherapy in multiple studies was associated with a median OS of ≤ 6 months.
- Initial phase II or basket studies assessed anti-epidermal growth factor receptor (EGFR) therapy or checkpoint inhibition in advanced disease with mixed results, so not enough data is available for incorporation in the current guideline. Therefore, inclusion of patients with advanced penile SCC after chemotherapy exposure into trials is highly recommended.

Role of radiotherapy in palliation

Radiotherapy is frequently necessary for palliation of penile cancer, and should be customised for unique presentations as necessary: e.g., ulcerative fixed LNs or dermal lymphatic spread. While standard palliative regimens should be readily employed, providers should be aware that re-treatment may be necessary.

Recommendations for systemic and palliative therapies for advanced penile cancer	**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 because of 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 1 or basket trials.	Strong
Radiotherapy	
Offer radiotherapy for symptom control (palliation) in advanced disease.	Strong

Follow-up and quality of life

Follow-up

From an oncological perspective, surveillance is important as early detection of recurrence may increase the likelihood of curative treatment. Local or regional nodal recurrences usually occur within two years of primary treatment.
A suggested schedule is provided in Table 2.

Table 2: 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 nodes				
Surveillance	3-monthly	6-monthly	Regular physician or self-examination. US ± FNAC optional.	5 years
pN0	3-monthly	Annually	Regular physician or self-examination. US ± FNAC optional.	5 years
pN+	3-monthly	6-monthly	Regular physician or self-examination. US ± FNAC, CT chest/abdomen or PET/CT optional.	5 years

CT = computed tomography; FNAC = fine needle aspiration cytology; PET = positron emission tomography; US = ultrasound.

Quality of life and patient support services

Penile cancer has a significant impact on QoL in many ways and there remain many unmet needs to address. Surveillance is not just about assessing for recurrent disease and men may require more frequent appointments than suggested above, with different members of the multi-disciplinary team to deliver patient support services and address QoL challenges. Access to psychological support, counselling and psychosexual therapy are critical components of a holistic and multi-disciplinary patient support service.

Ideally, following nodal surgery, patients would be referred to specialist lymphoedema services for assessment and management before any significant lymphoedema occurs.

Centralisation of penile cancer services

Centralisation of penile cancer services has a number of advantages in addition to delivering these important supportive services to patients. These include provision of an environment where multi-disciplinary discussion of cases can occur along with specialist pathological review, delivery of high-volume penile-preserving- and nodal surgery, more accurate DSNB and minimally-invasive surgery. 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 research and running clinical trials with a larger number of patients in a rare disease.

Recommendations for follow-up and quality of life	Strength rating
Deliver penile cancer care as part of an extended multi-disciplinary team comprising of urologists specialising in penile cancer, specialist nurses, pathologists, uro-radiologists, 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
Follow-up 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 multi-disciplinary 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, urinary and sexual function so that the patient is better prepared for the challenges he may face.	Strong

Discuss the potential impact of lymphoedema as a consequence of inguinal and pelvic lymph node treatment with the patient and assess patients for it at follow-up and refer to lymphoedema therapists early.	Strong

This short booklet text is based on the more comprehensive EAU-ASCO Guidelines (ISBN 978-94-92671-29-5), available at: http://www.uroweb.org/guidelines/.