EAU GUIDELINES ON PENILE CANCER

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

Introduction and epidemiology

The incidence of penile cancer increases with age, peaking during the sixth decade of life. However, the disease does occur in younger men. There are significant geographical variations within Europe as well as worldwide. Penile cancer is common in regions with a high prevalence of human Papilloma virus (HPV), which may account for the global incidence variation, as the worldwide HPV prevalence varies considerably. There is at present no recommendation for the use of HPV vaccination in boys.

Risk factors

Recognised aetiological and epidemiological risk factors for penile cancer are:

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

Pathology

Different variants of squamous cell carcinoma (SCC) accounts for more than 95% of cases of malignant penile disease. Table 1 lists premalignant lesions and Table 2 lists the pathological subtypes of penile carcinomas.

Table 1: Premalignant penile lesions (precursor lesions)

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

Table 2: Histological subtypes of penile carcinomas, their frequency and outcome

Subtype	Frequency (% of cases)	Prognosis
Common squamous cell carcinoma (SCC)	48-65	Depends on location, stage and grade
Basaloid carcinoma	4-10	Poor prognosis, frequently early inguinal nodal metastasis
Warty carcinoma	7-10	Good prognosis, metastasis rare
Verrucous carcinoma	3-8	Good prognosis, no metastasis
Papillary carcinoma	5-15	Good prognosis, metastasis rare
Sarcomatoid carcinoma	1-3	Very poor prognosis, early vascular metastasis
Mixed carcinoma	9-10	Heterogeneous group

Pseudohyperplastic carcinoma	< 1	Foreskin, related to lichen sclerosis, good prognosis, metastasis not reported
Carcinoma cuniculatum	< 1	Variant of verrucous carcinoma, good prognosis, metastasis not reported
Pseudoglandular carcinoma	< 1	High-grade carcinoma, early metastasis, poor prognosis
Warty-basaloid carcinoma	9-14	Poor prognosis, high metastatic potential (higher than in warty, lower than in basaloid SCC)
Adenosquamous carcinoma	< 1	Central and peri-meatal glans, high-grade carcinoma, high metastatic potential but low mortality
Mucoepidermoid carcinoma	< 1	Highly aggressive, poor prognosis
Clear cell variant of penile carcinoma	1-2	Exceedingly rare, associated with human papilloma virus, aggressive, early metastasis, poor prognosis, outcome is lesion-dependent, frequent lymphatic metastasis

Biopsy

Doubtful penile lesions should be biopsied and histological verification obtained before local treatment. Histological confirmation is necessary to guide management when:

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

Recommendations for the pathological assessment of tumour specimens	Strength rating
The pathological evaluation of penile carcinoma specimens must include an assessment of the HPV status.	Strong
The pathological evaluation of penile carcinoma specimens must include a diagnosis of the squamous cell carcinoma subtype.	Strong
The pathological evaluation of penile carcinoma surgical specimens must include an assessment of surgical margins including the width of the surgical margin.	Strong

Staging and classification systems

The 2016 UICC, Tumour Node Metastasis (TNM) classification should be used for staging and classification (Table 3). The T1 category is stratified into two prognostically different risk groups. The classification T2 denotes invasion of the corpus spongiosum and T3 invasion of the corpora cavernosa, recognising that these two invasion patterns differ prognostically. The current pN1 group consists of one or two inguinal lymph node metastases, pN2 is more than two uni- or bilateral metastatic nodes, and pN3 any pelvic nodes, uni- or bilateral and any extranodal extension.

Table 3: 2016 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*
Ta	Non-invasive verrucous carcinoma*
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated
T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated
T2	Tumour invades corpus spongiosum with or without invasion of the urethra
T3	Tumour invades corpus cavernosum with or without invasion of the urethra
T4	Tumour invades other adjacent structures
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph nodes
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass *or* pelvic lymphadenopathy, unilateral or bilateral
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

Pathological classification	
The pT categories correspond to the clinical T categories	
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

**Verrucous carcinoma not associated with destructive invasion.*

Diagnostic evaluation and staging

Penile cancer can be cured in over 80% of all cases if diagnosed early. Once metastatic spread has occurred, it is a life-threatening disease with poor prognosis. Local treatment, although potentially life-saving, can be mutilating and devastating for the patient's psychological well-being.

Physical Examination

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

Imaging

- Ultrasound (US) can give information about infiltration of the corpora.
- Magnetic resonance imaging (MRI) with an artificially induced erection can help to exclude tumour invasion of the corpora cavernosa if preservation of the penis is planned.
- In case of non-palpable inguinal nodes, current imaging techniques are not reliable in detecting micrometastases.
- A pelvic computed tomography (CT) scan can be used to assess pelvic lymph nodeIn case of positive inguinal nodes, CT of the abdomen and pelvis and a chest X-ray are recommended; a thoracic CT will be more sensitive than an X-ray.

Recommendations for the diagnosis and staging of penile cancer	**Strength rating**
Primary tumour	
Perform a physical examination, record morphology, extent and invasion of penile structures.	Strong
Obtain a penile Doppler ultrasound or MRI with artificial erection in cases with intended organ-sparing surgery.	Weak

Inguinal lymph nodes	
Perform a physical examination of both groins, record the number, laterality and characteristics of inguinal nodes and: • If nodes are not palpable, offer invasive lymph node staging in intermediate- and high-risk patients; • If nodes are palpable, stage with a pelvic computed tomography (CT) or positron emission tomography (PET)/CT.	Strong
Distant metastases	
In N+ patients, obtain an abdominopelvic CT scan and chest X-ray/thoracic CT for systemic staging. Alternatively, stage with a PET/CT scan.	Strong
In patients with systemic disease or with relevant symptoms, obtain a bone scan.	

Disease management

Treatment of the primary penile cancer lesion aims to remove the tumour completely while preserving as much of the penis as possible without compromising radicality.

Recommendations for stage-dependent local treatment of penile carcinoma		
Primary tumour	**Use organ-preserving treatment whenever possible**	**Strength rating**
Tis	Topical treatment with 5-fluorouracil or imiquimod for superficial lesions with or without photodynamic control.	Strong
	Laser ablation with carbon dioxide (CO_2) or neodymium: yttrium-aluminium-garnet (Nd:YAG) laser.	
	Glans resurfacing.	
Ta, T1a (G1, G2)	Wide local excision with circumcision, CO_2 or Nd:YAG laser with circumcision.	Strong
	Laser ablation with CO_2 or Nd:YAG laser.	
	Glans resurfacing.	
	Glansectomy with reconstruction.	
	Radiotherapy for lesions < 4 cm.	
T1b (G3) and T2	Wide local excision plus reconstruction.	Strong
	Glansectomy with circumcision and reconstruction.	
	Radiotherapy for lesions < 4 cm in diameter.	
T3	Partial amputation with reconstruction or radiotherapy for lesions < 4 cm in diameter.	Strong

T3 with invasion of the urethra	Partial penectomy or total penectomy with perineal urethrostomy.	Strong
T4	Neoadjuvant chemotherapy followed by surgery in responders or palliative radiotherapy.	Weak
Local recurrence	Salvage surgery with penis-sparing in small recurrences or partial amputation.	Weak
	Large or high-stage recurrence: partial or total amputation.	

Management of inguinal lymph nodes

The treatment of regional lymph nodes is crucial for the survival of the patient. A surveillance strategy carries considerable risk as regional lymph node recurrence dramatically reduces the chance of long-term survival. Invasive staging by modified inguinal lymphadenectomy or dynamic sentinel node biopsy is recommended for penile cancers pT1G1 and higher.

Recommendations for treatment strategies for nodal metastases		
Regional lymph nodes	**Management of regional lymph nodes is fundamental in the treatment of penile cancer**	**Strength rating**
No palpable inguinal nodes (cN0)	Tis, Ta G1, T1G1: surveillance.	Strong
	> T1G2: invasive lymph node staging by either bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy.	Strong
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.	Strong
Fixed inguinal lymph nodes (cN3)	Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders.	Weak
Pelvic Lymph nodes	Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) or if extracapsular nodal metastasis (pN3) reported.	Strong
Adjuvant chemotherapy	In pN2/pN3 patients after radical lymphadenectomy.	Strong
Radiotherapy	Not recommended for nodal disease except as a palliative option.	Strong

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

Follow-up

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

- early detection of recurrence allows for potentially curative treatment;
- the detection and management of treatment-related complications.

Local recurrence does not significantly reduce long-term survival if successfully treated, while inguinal nodal recurrence leads to a drastic reduction in the probability of long-term disease-specific survival.

Recommendations for follow-up in penile cancer					
	Interval of follow-up		Examinations and investigations	Minimum duration of follow-up	Strength rating
	Years one to two	Years three to five			
Recommendations for follow-up of the primary tumour					
Penile-preserving treatment	Three months	Six months	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for penile intraepithelial neoplasia.	Five years	Strong
Amputation	Three months	One year	Regular physician or self-examination.	Five years	Strong
Recommendations for follow-up of the inguinal lymph nodes					
Surveillance	Three months	Six months	Regular physician or self-examination.	Five years	Strong
pN0 at initial treatment	Three months	One year	Regular physician or self-examination. Ultrasound with fine-needle aspiration biopsy optional.	Five years	Strong
pN+ at initial treatment	Three months	Six months	Regular physician or self-examination. Ultrasound with fine-needle aspiration cytology optional, computed tomography/magnetic resonance imaging optional.	Five years	Strong

Quality of life

Overall, nearly 80% of penile cancer patients of all stages can be cured. Partial penectomy has negative consequences for the patients' self-esteem and sexual function. Organ preserving treatment allows for better quality of life and sexual function and should be offered to all patients whenever feasible. Referral to centres with experience is recommended and psychological support is very important for penile cancer patients.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-01-1), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.