EAU GUIDELINES ON PENILE CANCER

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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	OR 11-16 vs. no phimosis
Chronic penile inflammation (balanoposthitis related to phimosis) Balanitis xerotica obliterans (lichen sclerosus)	Risk
Sporalene and UVA phototherapy for various dermatological conditions such as psoriasis	Incidence rate ratio 9.51 with > 250 treatments
Smoking	5-fold increased risk (95% CI: 2.0-10.1) vs. non-smokers
HPV infection condylomata acuminata	22.4% in verrucous SCC 36-66.3% in basaloid-warty
Rural areas, low socioeconomic status, unmarried	
Multiple sexual partners, early age of first intercourse	3-5-fold increased risk of penile cancer

HPV = human papilloma virus; OR = odds ratio; SCC = squamous cell carcinoma; UVA = ultraviolet A.

Pathology

Squamous cell carcinoma (SCC) in different variants 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 SCC of the penis • Cutaneous horn of the penis • Bowenoid papulosis of the penis • Lichen sclerosus (balanitis xerotica obliterans)
Premalignant lesions (up to one-third transform to invasive SCC) • Intraepithelial neoplasia grade III • Giant condylomata (Buschke-Löwenstein) • Erythroplasia of Queyrat • 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 SCC	48-65	Depends on location, stage and grade
Basaloid carcinoma	4-10	Poor prognosis, frequently early inguinal nodal metastasis [40]
Warty carcinoma	7-10	Good prognosis, metastasis rare
Verrucous carcinoma	3-8	Good prognosis, no metastasis
Papillary carcinoma	5-15	Good prognosis, metastasis rare
Sarcomatoid carcinoma	1-3	Very poor prognosis, early vascular metastasis
Mixed carcinoma	9-10	Heterogeneous group

Pseudohyperplastic carcinoma	< 1	Foreskin, related to lichen sclerosus, good prognosis, metastasis not reported
Carcinoma cuniculatum	< 1	Variant of verrucous carcinoma, good prognosis, metastasis not reported
Pseudoglandular carcinoma	< 1	High-grade carcinoma, early metastasis, poor prognosis
Warty-basaloid carcinoma	9-14	Poor prognosis, high metastatic potential [41] (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 HPV, aggressive, early metastasis, poor prognosis, outcome is lesion-dependent, frequent lymphatic metastasis

Biopsy

In the management of penile cancer there is need for histological confirmation if:

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

Staging and classification systems

The 2009, Tumour Node Metastasis (TNM) classification should be used (Table 3). A subclassification of the T2 category regarding invasion of the corpus spongiosum only, or the corpora cavernosa as well, would be desirable as it has been shown that the prognosis for corpus spongiosum invasion alone is much better than for corpora cavernosa invasion.

Table 3: 2009 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 carcinoma	
T1	Tumour invades subepithelial connective tissue	
	T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)
	T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)

T2	Tumour invades corpus spongiosum and/or corpora cavernosa
T3	Tumour invades 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 node
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple unilateral 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	Intranodal metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of any regional lymph node metastasis
pM - Distant Metastasis	
pM0	No distant metastasis
pM1	Distant metastasis

G - Histopathological Grading	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated/undifferentiated

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 nodes.
- In 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	GR
Primary tumour	
Perform a physical examination, record morphology, extent and invasion of penile structures.	C
Obtain MRI with artificial erection in cases for which organ-preserving surgery is intended.	
Inguinal lymph nodes	
For physical examination of both groins, record number, laterality and characteristics of inguinal nodes and: • If nodes are not palpable, offer invasive lymph node staging in high-risk patients. • If nodes are palpable, stage with a pelvic CT or PET/CT.	C
Distant metastases	
In N+ patients, obtain an abdominopelvic CT scan and chest X-ray for systemic staging. Alternatively, stage with a PET/CT scan.	C
In patients with systemic disease or with relevant symptoms, obtain a bone scan.	

CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging.

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**	**LE**	**GR**
Tis	Topical treatment with 5-fluorouracil or imiquimod for superficial lesions with or without photodynamic control.	3	C
	Laser ablation with CO2 or Nd:YAG laser.		
	Glans resurfacing.		
Ta, T1a (G1, G2)	Wide local excision with circumcision CO2 or Nd:YAG laser surgery with circumcision.	3	C
	Laser ablation with CO2 or Nd:YAG laser.		
	Glans resurfacing.		
	Glansectomy with reconstructive surgery, with or without skin grafting.		
	Radiotherapy by external beam or as brachytherapy for lesions < 4 cm.		

T1b (G3) and T2 confined to the glans	Wide local excision plus reconstructive surgery, with or without skin grafting.	3	C
	Laser ablation with circumcision.		
	Glansectomy with circumcision, with reconstruction.		
	Radiotherapy by external beam or brachytherapy for lesions < 4 cm in diameter.		
T2 with invasion of the corpora cavernosa	Partial amputation and reconstruction or radiotherapy by external beam or brachytherapy for lesions <4 cm in diameter.	3	C
T3 with invasion of the urethra	Partial penectomy or total penectomy with perineal urethrostomy.	3	C
T4 with invasion of other adjacent structures	Neoadjuvant chemotherapy followed by surgery in responders. Alternative: palliative external beam radiation.	3	C
Local recurrence after conservative treatment	Salvage surgery with penis-sparing treatment in small recurrences or partial amputation.	3	C
	Large or high-stage recurrence: partial or total amputation.		

CO2 = carbon dioxide; Nd:YAG = neodymium:yttrium-aluminum-garnet.

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**	**LE**	**GR**
No palpable inguinal nodes (cN0)	Tis, Ta G1, T1G1: surveillance.	2a	B
	> T1G2: invasive lymph node staging by bilateral modified inguinal lymphadenectomy or DSNB.	2a	B
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.		
Fixed inguinal lymph nodes (cN3)	Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders.		

Pelvic lymphadenopathy	Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) and if extracapsular nodal metastasis (pN3) is confirmed.	2a	B
Adjuvant chemotherapy	In pN2/pN3 patients after radical lymphadenectomy.	2b	B
Radiotherapy	Do not use for the treatment of nodal disease in penile cancer.		

DSNB = dynamic sentinel node biopsy.

Recommendations for chemotherapy in penile cancer patients	**LE**	**GR**
Treat with adjuvant chemotherapy (3-4 cycles of TPF) in patients with pN2-3 tumours.	2b	C
Treat with neoadjuvant chemotherapy (four cycles of a cisplatin and taxane-based regimen) followed by radical surgery in patients with non-resectable or recurrent lymph node metastases.	2a	B
In patients with systemic disease and a limited metastatic load, treat with chemotherapy.	3	C

TPF = cisplatin, 5-fluorouracil paclitaxel.

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.

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.

Recommendations for follow-up in penile cancer					
	Interval of follow-up		Examinations and investigations	Minimum duration of follow-up	GR
	Years 1-2	Years 3-5			
Recommendations for follow-up of the primary tumour					
Penile-preserving treatment	3 months	6 months	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for CIS.	5 years	C
Amputation	3 months	1 year	Regular physician or self-examination.	5 years	C
Recommendations for follow-up of the inguinal lymph nodes					
Surveillance	3 months	6 months	Regular physician or self-examination.	5 years	C
pN0 at initial treatment	3 months	1 year	Regular physician or self-examination. Ultrasound with FNAB optional.	5 years	C
pN+ at initial treatment	3 months	6 months	Regular physician or self-examination Ultrasound with FNAC optional, CT/ MRI optional.	5 years	C

CIS = carcinoma in situ; CT = computed tomography; FNAB = fine-needle aspiration biopsy; FNAC = fine-needle aspiration cytology; MRI = magnetic resonance imaging.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-90-79754-98-4), available to all members of the European Association of Urology at their website, http://www.uroweb.org.