GUIDELINES ON PENILE CANCER

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Introduction

The incidence of penile cancer increases with age, with an age peak 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 as this controversial.

Classification and pathology

The 2009, Tumour Node Metastasis (TNM) classification should be used (Table 1). 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 only is much better than for corpora cavernosa invasion.

Table 1: 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	Noninvasive verrucous carcinoma
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades corpus spongiosum or cavernosum
T3	Tumour invades urethra or prostate
T4	Tumour invades other adjacent structures
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single superficial inguinal lymph node
N2	Metastasis in multiple or bilateral superficial inguinal lymph nodes
N3	Metastasis in deep inguinal or pelvic lymph node(s), unilateral or bilateral
M - Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
pTNM Pathological Classification The pT, pN and pM categories correspond to the T, N, and M categories.	
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

Pathology

Squamous cell carcinoma (SCC)in different variants accounts for > 95% of cases of malignant penile disease. Table 2 lists premalignant lesions and Table 3 lists the pathological subtypes of penile carcinomas.

Table 2: Premalignant penile lesions (precursor lesions)
• 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)

Diagnosis and staging of penile cancer

Penile cancer can be cured in > 80% of cases but it is a life-threatening disease with poor prognosis once metastatic spread has occurred. Local treatment, although potentially life-saving, can be mutilating and devastating for the psychological well-being of the patient supporting the need for careful diagnosis and adequate staging before any treatment decisions can be made.

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) and/or;
- treatment with topical agents, radiotherapy or laser surgery is planned.

Table 3: Histological subtypes of penile carcinomas, their frequency and prognosis		
Subtype	**Frequency (%)**	**Prognosis**
common 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	heterogenous group
pseudohyper-plastic carcinoma	<1	foreskin, related to lichen sclerosus, good prognosis, metastasis not reported
carcinoma cuniculatum	<1	variant of verrucous carcinoma, good prognosis, metastasis not reported
pseudoglan-dular carcinoma	<1	high grade carcinoma, early metastasis, poor prognosis
warty-basaloid carcinoma	9-14	poor prognosis, high metastatic potential, (higher than warty, lower than 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 lesion dependent, frequent lymphatic metastasis

Physical Examination

Physical examination of a patient with penile cancer should include palpation of the penis to examine the extent of local invasion and careful examination of the groins for regional lymph node enlargement.

Imaging

- Ultrasound (US) can give information about infiltration of the corpora.
- Magnetic resonance imaging (MRI) in combination with an artificial erection with prostaglandin E1 may be used for excluding tumour invasion of the corpora cavernosa if organ-preservation is planned and preoperative decisions are needed.
- In case of non-palpable inguinal nodes current imaging techniques are not reliable in detecting micro-metastases.
- A pelvic CT scan can be performed 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	
Physical examination, recording morphology, extent and invasion of penile structures.	
MRI with artificial erection in selected cases with intended organ preserving surgery.	C
Inguinal lymph nodes	
Physical examination of both groins, recording number, laterality and characteristics of inguinal nodes • If nodes are not palpable, invasive lymph node staging in high-risk patients. • If nodes are palpable, a pelvic CT may be indicated, PET/CT is an option.	C
Distant metastases	
In N+ patients, abdomino-pelvic CT scan and chest X-ray are required for systemic staging. PET/CT scan is an option. In patients with systemic disease or with relevant symptoms, a bone scan may be indicated.	C

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

Treatment

The aims of the treatment of the primary penile cancer lesion are complete tumour removal with as much organ preservation as possible while radicality of the treatment should not be compromised.

Guidelines for stage-dependent local treatment of penile carcinoma			
Primary tumour	**Conservative treatment is to be considered 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 CO_2 or Nd:YAG laser		
	Glans resurfacing		
Ta, T1a (G1, G2)	Wide local excision with circumcision CO_2 or Nd:YAG laser surgery with circumcision	3	C
	Laser ablation with CO_2 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	3	C

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	3	C
	Radiotherapy by external beam or brachytherapy for lesions < 4 cm in diameter		
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.	3	C

CO_2 = carbon dioxide; Nd:YAG = neodymium:yttrium-aluminium-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 pT1G2 and higher.

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

DSNB = dynamic sentinel node biopsy.

Guidelines for chemotherapy in penile cancer patients	LE	GR
Adjuvant chemotherapy (3-4 cycles of TPF) is an option for patients with pN2-3 tumours.	2b	C
Neoadjuvant chemotherapy (4 cycles of a cis-platin and taxane-based regimen) followed by radical surgery is recommended in patients with non-resectable or recurrent lymph node metas-tases.	2a	B
Chemotherapy for systemic disease is an option in patients with limited metastatic load.	3	C

TPF = cisplatin, 5FU plus paclitaxel or docetaxel.

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.

Guidelines for follow-up in penile cancer		
	Interval of follow-up	
	Years 1-2	Years 3-5
Follow-up of the primary tumour		
Penile preserving treatment	3 months	6 months
Amputation	3 months	1 year
Follow-up of the inguinal lymph nodes		
Surveillance	3 months	6 months
pN0 at initial treatment	3 months	1 year
pN+ at initial treatment	3 months	6 months

CT = computed tomography; FNAC = fine-needle aspiration cytology;

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.

Examinations and investigations	Maximum duration of follow-up	GR
Regular physician or self-examination. Repeat biopsy after topical or laser treatment for CIS.	5 years	C
Regular physician or self-examination.	5 years	C
Regular physician or self-examination.	5 years	C
Regular physician or self-examination. US with FNAC optional	5 years	C
Regular physician or self-examination. US with FNAC optional CT/MRI optional.	5 years	C

US = ultrasound.

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-65-6), available to all members of the European Association of Urology at their website, http://www.uroweb.org.