

GUIDELINES ON PENILE CANCER

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G. Pizzocaro, F. Algaba, S. Horenblas, E. Solsona, S. Tana,
H. Van Der Poel, N. Watkin

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Introduction

Over recent years, the cure rate for penile cancer has risen to 80% because of improved knowledge of the disease, earlier diagnosis, technological advances, and specialist treatment in centres of excellence.

In Western countries, primary malignant penile cancer is uncommon, with an overall incidence of less than 1.00 per 100,000 males in Europe and the United States of America (USA). Incidence also varies according to racial group, ethnicity, and geographical location. Social and cultural habits, hygienic and religious practices interfere significantly with risk factors.

Since a few years, there has been a well-documented association between human papillomavirus (HPV) and squamous cell carcinoma (SCC). Vaccination is available for very young females against HPV strains responsible for most cases of cervical cancer. Vaccination will be considered in males according to the results in females.

Classification and pathology

The new, 2009, Tumour Node Metastasis (TNM) classification for penile cancer includes a change for the T1 category (Table 1). This classification needs a further update for the definition of the T2 category*.

Table 1: 2009 TNM staging classification**T - Primary tumour**

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i>
Ta	Non-invasive verrucous carcinoma, not associated with destructive invasion
T1	Tumour invades subepithelial connective tissue
T1a	without lymphovascular invasion and well or moderately differentiated (T1G1-2)
T1b	with lymphovascular invasion or poorly differentiated/undifferentiated (T1G3-4)
T2*	Tumour invades corpus spongiosum/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 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

TNM pathological classification

The pT categories correspond to the T categories. The pN categories are based upon biopsy, or surgical excision.

Table 2: 2009 TNM pathological classification	
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 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 accounts for more than 95% of cases of malignant penile disease. Table 3 lists premalignant lesions and Table 4 lists the different types of penile SCC neoplasia.

Table 3: Premalignant lesions	
Lesions sporadically associated with SCC of the penis	
<ul style="list-style-type: none"> • Cutaneous horn of the penis • Bowenoid papulosis of the penis 	
Lesion at intermediate risk	
<ul style="list-style-type: none"> • Balanitis xerotica obliterans (lichen sclerosus et atrophicus) 	

Lesions at high risk of developing SCC of the penis (up to one-third transform to invasive SCC)

- Penile intraepithelial neoplasia (carcinoma *in situ*)
- Erythroplasia of Queyrat and Bowen's disease

Table 4: Pathologic classification of SCC of the penis**Types of SCC**

- Classic
- Basaloid
- Verrucous and its varieties: warty (condylomatous) carcinoma; verrucous carcinoma; papillary carcinoma; hybrid verrucous carcinoma; and mixed carcinomas (warty basaloid, adenobasaloid carcinoma)
- Sarcomatoid
- Adenosquamous

Growth patterns of SCC

- Superficial spread
- Nodular or vertical-phase growth
- Verrucous

Differentiation grading systems for SCC

- Broder's grading system
- Maiche's system score

Diagnosis

Accurate histological diagnosis and staging of both the primary tumour and regional nodes are a prerequisite before making treatment decisions (Table 5).

Biopsy

The need for histological confirmation is dependent on:

- doubt about the exact nature of the lesion;
- treatment of the lymph nodes based on pre-operative histology.

In these cases an adequate biopsy is advised. Although a punch biopsy may be sufficient for superficial lesions, but an excisional one is preferred. There is no need for biopsy if:

- there is no doubt about the diagnosis;
- treatment of the lymph nodes is postponed after treatment of the primary tumour and/or after histological examinations of the sentinel node(s).

Physical examination

The physical examination of suspected penile cancer must record:

- diameter of the penile lesion(s) or suspicious areas;
- location of lesion(s) on the penis;
- number of lesions;
- morphology of lesion(s): papillary, nodular, ulcerous or flat;
- relationship of lesion(s) to other structures, e.g. submucosa, tunica albuginea, urethra, corpus spongiosum and corpus cavernosum;
- colour and boundaries of lesion(s);
- penile length.

Imaging

Physical examination is reliable in determining infiltration into the corpora. If doubt exists on depth of infiltration or proximal extension, magnetic resonance imaging (MRI) may be helpful on erect penis (\pm prostaglandin E1 injection).

Table 5: Guidelines for the diagnosis of penile cancer	GR
Primary tumour <ul style="list-style-type: none"> Physical examination, recording morphological and physical characteristics of the lesion. Cytological and/or histological diagnosis. 	C
Inguinal lymph nodes <ul style="list-style-type: none"> Physical examination of both groins, recording nodal morphological and physical characteristics. If nodes are non-palpable, DSNB is indicated; if DSNB is not available, ultrasound-guided FNAC/risk factors. If nodes are palpable, FNAC for cytological diagnosis. 	C
Regional metastases (inguinal and pelvic nodes) <ul style="list-style-type: none"> A pelvic CT, PET/CT is indicated in patients with metastatic inguinal nodes. 	C
Distant metastases (beside inguinal and pelvic nodes) <ul style="list-style-type: none"> PET/CT also allows evidence of distant metastasis. If PET/CT is not available, abdominal CT and plain radiography chest are advisable, and in symptomatic M1 patients a bone scan is also advisable. Biological laboratory determinations for penile cancer are investigational and not for clinical use. 	C

CT = computed tomography; DSNB = dynamic sentinel node biopsy; GR = grade of recommendation; FNAC = fine-needle aspiration cytology; PET = positron emission tomography.

Treatment

The primary tumour and regional lymph nodes are usually treated separately (Table 6). Correct staging is crucial for accurate treatment. Lymphadenectomy (LAD) is mandatory for patients with evidence of inguinal lymph node metastases.

Table 6: Guidance on treatment strategies for penile cancer			
Primary tumour	Conservative treatment is to be considered whenever possible	LE	GR
Category Tis, Ta, T1a (G1, G2)	CO ₂ or Nd:YAG laser surgery, wide local excision, glans resurfacing, or glans resection, depending on size and location of the tumour	2b	B
	Mohs' micrographic surgery or photodynamic therapy for well differentiated superficial lesions (Tis, G1, Ta)	3	C
Categories: T1b (G3) and T2 (glans only)	Glansectomy, with or without tips amputation or reconstruction	2b	B
Category T2 (invasion of the corpora)	Partial amputation	2b	B
Category T3 invasion of urethra	Total amputation with perineal urethrostomy	2b	B
Category T4 (other adj. structures)	Eligible patients: neoadjuvant chemotherapy followed by surgery in responders. Alternative: external radiation	3	C
Local disease recurrence after conservative therapy	Salvage surgery, consisting of penis-sparing treatment in small recurrences	3	C
	Larger recurrence: some form of amputation	2b	B

Radiotherapy	Organ-preserving treatment in selected patients with T1-2 of glans or coronal sulcus, lesions < 4 cm	2b	B
Chemotherapy	Neo adjuvant, before surgery	3	C
	Palliation in advanced or metastatic disease	3	C

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

Table 7: Guidance on treatment strategies for regional lymph nodes in penile cancer

Regional lymph nodes	Management of regional lymph nodes is fundamental	LE	GR
No palpable inguinal nodes	Tis, Ta G1, T1G1: surveillance	2a	B
	> T1G2: DSNB (NB: Inguinal LAD if histology is positive)	2a	B
	If DSNB not available: risk factors/nomogram decision-making	3	C
Palpable inguinal nodes	US-guided FNAB (DSNB is unsuitable for palpable nodes)	2a	B
	Negative biopsy: surveillance (repeat biopsy)		
	Positive biopsy: inguinal LAD on positive side		
	(NB: Modified LAD must include the central zone and both superior Daseler's zones)		

Pelvic nodes	Pelvic LAD if there is: extranodal metastasis; Cloquet node involved; > 2 inguinal node metastases	2a	B
	Unilateral pelvic LAD if unilateral lymph node metastases with prolonged inguinal incision	2b	B
	Bilateral pelvic LAD if bilateral inguinal metastases	2a	B
Adjuvant chemotherapy	In patients with > 1 intranodal metastasis (pN2 pN3) after radical LAD, survival is improved by adjuvant chemotherapy (3 courses of cisplatin, fluorouracil [PF] chemotherapy)	2b	B

Table 8: Follow-up schedule for penile cancer

	Interval of follow-up	
	Years 1 and 2	Years 3, 4 and 5
<i>Recommendations for follow-up of the primary tumour</i>		
Penile preserving treatment	3 months	6 months
Amputation	6 months	1 year
<i>Recommendations for follow-up of the inguinal lymph nodes</i>		
'Wait-and-see'	3 months	6 months
pN0	6 months	1 year
pN+	3 months	6 months

Patients with fixed or relapsed inguinal nodes	Neo-adjuvant chemotherapy is strongly recommended in patients with unresectable or recurrent lymph node metastases	2a	B
	Taxanes seem to improve the efficacy of standard PF chemotherapy (or carboplatin)		
Radiotherapy	Curative radiotherapy may be used for palliation in primary tumours of the glans penis and sulcus < 4 cm or	2a	B
	Prophylactic radiotherapy in clinical N0 patients is not indicated	2a	B

LAD = lymphadenectomy; FNAB = fine-needle aspiration biopsy; DSNB = sentinel node biopsy.

Examinations and investigations	Maximum duration of follow-up	GR
Regular physician or self-examination	5 years	C
Regular physician or self-examination	5 years	C
Regular physician or self-examination	5 years	C
Regular physician or self-examination Ultrasound with FNAB	5 years	C
Regular physician or self-examination Ultrasound with FNAB	5 years	C

Follow-up

The aim of follow-up is to detect local and/or regional recurrences at an early curable stage. Metastases at distant sites are fatal. Risk stratification for recurrence is helpful. Traditional follow-up methods have been inspection and physical evaluation.

Modern US or PET/CT are useful adjuncts. The follow-up interval and strategies for patients with penile cancer are guided by the initial treatment of the primary lesion and regional lymph nodes (Table 7). About 92% of all recurrences occur within 5 years and they may be neo-occurrences. Follow-up can stop after 5 years in well educated and motivated patients able to perform self-examination.

Quality of life

As more people achieve long-term survival after cancer, sexual dysfunction and infertility are increasingly recognised as negative consequences. Penile-sparing surgery allows a better quality of life than penectomy and must be considered whenever feasible. Psychological support should be offered at a low threshold.

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-70-0), available to all members of the European Association of Urology at their website, <http://www.uroweb.org>.