GUIDELINES ON PENILE CANCER

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Introduction

By 2008, the cure rate for penile cancer had risen to 80% because of improved knowledge of the disease, earlier diagnosis, technological advances, and specialist treatment in centres of excellence. These guidelines are to provide urologists with up-to-date information to aid their decision making during the diagnosis and management of patients with penile cancer.

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). However, in some undeveloped countries, the incidence rate of penile cancer is much higher, accounting for as many as 10% of malignant disease in men. 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. Vaccination is available for very young females

against HPV strains responsible for most cases of cervical cancer. Vaccination has also been recommended in males.

Classification and pathology

TNM classification

The TNM classification for penile cancer has remained unchanged since 1987 (Table 1).

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
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 evidence of lymph node metastasis
N1	Metastasis in a single inguinal lymph node
N2	Metastasis in multiple or bilateral superficial lymph nodes
N3	Metastasis in deep inguinal or pelvic lymph nodes, unilateral or bilateral
M - Distant metastases	
MX	Distant metastases cannot be assessed
M0	No evidence of distant metastases

M1	Distant metastases

A proposal (Table 2) has been made to update the 1987-2002 UICC Tumour Node Metastasis (TNM) classification for penile cancer particularly categories T2, T3, T4 and N2, N3. Further research is needed to confirm the new classification.

Table 2: Proposed modification to 1987-2002 TNM classification

T - Primary tumour	
TX, T0, Tis, Ta and T1	Unchanged
T2	Tumour invades corpus spongiosum
T3	Tumour invades corpus cavernosum
T4	Tumour invades adjacent structures (e.g. urethra, prostate)
N - Regional lymph nodes	
Nx, N0 and N1*	Unchanged
N2	Multiple mobile inguinal metastases
N3	Fixed inguinal metastases or metastases in pelvic lymph nodes

**N1 category is maintained unchanged because 'one single intranodal metastasis' does not need adjuvant chemotherapy nor pelvic lymph node dissection.*

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

	LE
Lesions sporadically associated with SCC of the penis	
• Cutaneous horn of the penis	2b
• Bowenoid papulosis of the penis	
Lesion at intermediate risk	
• Balanitis xerotica obliterans (lichen sclerosus et atrophicus)	2a
Lesions at high risk of developing SCC of the penis (up to one-third transform to invasive SCC)	2a
• Penile intraepithelial neoplasia (carcinoma *in situ*): erythroplasia of Queyrat and Bowen's disease	

LE = level of evidence; SCC = squamous cell carcinoma.

Table 4: Premalignant lesions

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 system
- Maiche's system score

SCC = squamous cell carcinoma.

Diagnosis

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

Biopsy

The need for histological confirmation is dependent on the following elements:
- doubt about the exact nature of the lesion (metastasis, melanoma, etc.)
- treatment of the lymph nodes based on pre-operative histological information.

In these cases an adequate biopsy is advised. Although a punch biopsy may be sufficient for superficial lesions, 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 (± prostaglandin E1 injection).

Table 5: Guidelines for the diagnosis of penile cancer

Primary tumour	GR
• Physical examination	B
• Cytological or histological diagnosis	B
• Imaging: not necessary. If in doubt about depth of infiltration or proximal extension MRI (± using PGE1 injection is useful)	B
Regional lymph nodes	
• Physical examination	B
• If nodes are non-palpable, ultrasound guided FNAC	B
• If FNAC is inconclusive, dynamic sentinel node biopsy* is indicated	B

• If nodes are palpable, FNAC for cytological diagnosis is mandatory	B
• **Distant metastasis (only in patients with metastatic inguinal nodes)**	B
• Pelvic CT scan if > 1 metastatic inguinal nodes	B
• Abdominal CT scan and chest X-ray are advisable if pelvic CT scan is positive	B
• Bone scan is advisable in M1 symptomatic patients	C

GR = grade of recommendation, MRI = magnetic resonance imaging; PGE1 = prostaglandin E1; FNAC = fine-needle aspiration cytology; CT = computed tomography.
**With the aid of Isosulphan blue and technetium-99m (^{99m}Tc) colloid sulphur.*

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		LE
Category Tis and Ta		
Superficial lesions	Penis-preserving techniques: laser therapy with carbon dioxide (CO_2) or neodymium-YAG laser is superior to topical 5-fluorouracil, imiquimod 5% cream, photodynamic therapy or Mohs' micrographic surgery	2a

Multifocal lesions and HPV infection	Total glans resurfacing and circumcision recommended	2a
Category T1G1	Wide local excision with circumcision. Assessment of surgical margins reduces the rate of local recurrence	2b
Category T1G2-3	Wide local (laser) excision plus reconstructive surgery or glansectomy. Treatment choice determined by tumour size and position	2a
	Assessment of surgical margins reduces rate of local recurrence	2b
	Generally, early diagnosis of local recurrence does not have an adverse impact on survival	3
Category T2 (of glans)	Total glansectomy, with or without resurfacing of corporeal heads	2a
	Partial glansectory is an alternative in selected patients with tumours less than half the glans	2b
	Consider partial amputation in patients unfit for more conservative reconstructive surgery	
Category T2 (of the corpora) and T3	Partial amputation for tumours involving tips of the corpora. An alternative is reconstructive surgery with negative margins upon frozen section	2b
	Partial or total amputation for large tumours involving more than the distal corpora	2a

	Traditionally, partial amputation has required removal of 2-cm tumour-free margins. A surgical margin of 5-10 mm is safe	2b
Category T4	In strictly locally advanced disease: neoadjuvant chemotherapy with surgery or chemoradiation.	3
Local disease recurrence after conservative therapy	Second conservative procedure is strongly advised in absence of corpora cavernosa invasion	2b
	Partial or total amputation for large or deep infiltrating recurrence	2a
Main uses of radiotherapy	Organ-preserving treatment in selected patients with T1-2 glans or coronal sulcus lesions (< 4 cm)	2b
	Palliation in advanced or metastatic disease	
Regional lymph nodes		
No palpable inguinal nodes	DSNB. With completion inguinal LAD if sentinel node is tumour-positive	2b
Palpable inguinal nodes		
	Ultrasound with FNAC is only reliable if tumour-positive. Repeat if tumour-negative. Do not use DSNB	3
	All tumour-positive patients should undergo LAD. Contralateral non-palpable lymph nodes should be surgically staged (DSNB)	2b

	Ipsilateral pelvic LAD if ≥ 2 inguinal nodes are involved and/or extracapsular extension on one side	2b
	Pelvic LAD may be necessary as a secondary procedure	
Adjuvant chemotherapy in node-positive patients after radical resection of nodal metastases	Adjuvant chemotherapy is recommended for any extranodal metastases or for more than 1 positive node. Two or three courses of adjuvant PF are to be given to pN2 or pN3 patients	3
Patients with fixed or relapsed inguinal nodes	Neo-adjuvant chemotherapy is mandatory. Four courses of PF or TPF are recommended and post-chemotherapy radical LAD is mandatory	2b
Radiotherapy	Prophylactic radiotherapy in clinical N0 patients is not recommended	
	Radiotherapy may give palliation after failure of chemotherapy and surgery. Chemoradiation has not yet been tested in SCC of the penis. It is routine in head and neck cancer	4

** The guidance given on the treatment of penile cancer has been given a level of evidence where this has been assessed.*
LE = level of evidence; LAD = lymphadenectomy; FNAB = fine-needle aspiration biopsy; DSNB = dynamic sentinel node biopsy; PF = cisplatin +5-fluorouracil; TPF= taxane + cisplatin + 5-fluorouracil.

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 ultrasound imaging is a useful adjunct. 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. Follow-up can stop after 5 years in well-educated and motivated patients able to self-examine.

Quality of life

Today, nearly 80% of penile cancer patients can be cured. 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.

Table 7: Follow-up schedule for penile cancer

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

GR = grade of recommendation; FNAB = fine-needle aspiration biopsy;

Examination/investigation	Maximum length of follow-up	GR
Regular self/physician examination	5 years	C
Regular self/physician examination	5 years	C
Regular self/physician examination US with FNAB	5 years	C
Regular self-examination US with FNAB	5 years	C
Regular self/physician examination US with FNAB	5 years	C

US = Ultrasound.

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-54-0), available to all members of the European Association of Urology at their website - http://www.uroweb.org.