GUIDELINES ON PENILE CANCER

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Introduction

Penile carcinoma is an uncommon malignant disease with an incidence ranging from 0.1 to 7.9 per 100,000 males. In Europe, the incidence is 0.1-0.9 and in the US, 0.7-0.9 per 100,000. In some areas, such as Asia, Africa and South America, penile carcinoma accounts for as many as 10% - 20% of male cancers.

Social and cultural habits seem to be important factors related to penile cancer, exemplified by the fact that 44-90% of patients suffer from phimosis at presentation and there is a documented association between human papilloma virus and penile carcinoma.

An overall 5-year survival rate of 52% has been reported: 66% in patients with negative lymphnodes and 27% in patients with positive nodes.

CLASSIFICATION

Pathology

Squamous cell carcinoma is by far the most common malignant disease of the penis, accounting for more than 95% of cases.

Premalignant lesions

1. Lesions sporadically associated with squamous cell carcinoma of the penis: Balanitis xerotica obliterans, cutaneous horn of the penis and Bowenoid papulosis of the penis.
2. Lesions at low risk of developing into squamous cell carcinoma of the penis: Penile intraepithelial neoplasia (Erythroplasia of Queyrat, Bowen's disease).

Penile neoplasias (Squamous cell carcinoma)

1. Types: Classic, Basaloid, Verrucous, Sarcomatoid, Adenosquamous.
2. Growth patterns: Superficial spread, Nodular or vertical-phase growth, Verrucous.
3. Differentiation grades: the Broders or the Maiche system score (the most suitable).

Mesenchymal tumours (less than 3%)

Kaposi's sarcoma, angiosarcoma, epitheliod hemagioendothelioma, etc.).

Metastatic disease (uncommon)

Prostate, rectal tumours are reported as primary tumours in cases of metastatic disease.

Tumour, nodes, metastasis (TNM) classification.

The 1997 TNM classification for penile cancer is shown in Table 1.

Table 1. 1997 TNM classification of penile cancer

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
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
Distant metastasis	
Mx	Distant metastases cannot be assessed
M0	No evidence of distant metastases
M1	Distant metastases

DIAGNOSIS

In order to establish a rational diagnostic approach to penile cancer, the primary lesion, regional lymph nodes and distant metastases should be taken into account initially and during follow-up. Patients with a suspicious penile lesion should undergo a detailed physical examination on primary tumour as well as inguinal regions in order to determine whether the presence or not of palpable nodes. In this examination record (mandatory):

- Diameter
- Location
- Number
- Morphology
- Colour

- Boundaries, mobile or fixed of lesions &
- Relationship of the primary tumor or/and palpable nodes with other structures.

Diagnostic Imaging can assist in identifying the depth of tumour invasion, particularly with regard to corpora cavernosa infiltration. However, penile ultrasound imaging is sometimes difficult to interpret and is an unreliable method with microscopic infiltration.

A diagnostic schedule for penile cancer is shown in Table 2.

Table 2. Diagnosis schedule for penile cancer

	Procedures		
Lesion level	Mandatory	Advisable	Optional
Primary tumour	Physical examination Cytological or histological diagnosis	Ultrasound (if invasion suspected)	MRI (if ultrasound inconclusive)
Regional disease			
Non-palpable nodes	Physical examination		Sentinel node biopsy[1] (inves-
Palpable nodes	Cytological or histological diagnosis		(tigational)
Distant metastases		Pelvic CT (if nodes +ve) Abdominal CT (if pelvic nodes +ve) Chest x-ray (if nodes +ve)	Bone scan (in symptomatic patients)

MRI = magnetic resonance imaging.

[1]Cabañas technique is no longer advisable. Isosulfan blue or 99m Tc-colloid sulfur are promising new investigational procedures.

TREATMENT

In penile carcinoma, the success of therapy is related to lymphnode status and treatment. Lymphadenectomy has been shown to be an effective therapy for patients with positive lymph nodes but this procedure is associated with a high morbidity rate of 30 - 50% , even with modern technical modifications.

A rational use of lymphadenectomy requires a careful groin assessment and awareness of predictive factors for positive lymph nodes In patients with non-palpable nodes three risk groups of patients can be defined using pathological predictive factors from primary tumour:

low risk, including patients with categories pTis, pTaG1-2 or pT1G1;
intermediate risk, includes categories pT1G2
high risk, includes categories pT(2 or G3 pT1G2 tumours.

According to these risk groups, surveillance is recommended in low risk, lymphadenectomy in high risk and in intermediate risk the decision-making process might be based on the presence of vascular or lymphatic invasion and growth pattern.

A therapeutic schedule for penile cancer is shown in Table 3.

Table 3. Therapeutic schedule for penile cancer

Recommendations				
Lesion level	Therapy	Strong	Optional	Investigational
Primary tumour	Conservative therapy	Primary/recurrent Tis, Ta-1G1-2	T1G3, T ≥ 2 (fit patients for surveillance with < 0.5 glans)	After chemotherapy in patients Unfit for conservative therapy
	Total/partial amputation	Primary/recurrent T1G3, T ≥ 2	Primary or recurrent Ta-1G1-2 (conservative therapy not feasible)	
Regional (non-palpable nodes)	Surveillance	Tis, TaG1-2, T1G1, T1G2 Superficial growth, vascular (-)	T2G2-3 (preference and fit patients for follow-up)	Negative sentinel node
	Modified LND[1]	T1G2 nodular growth or vascular (+), T1G3 or any T2	T1G2 vascular (-) flat growth (unfit patients for follow-up)	Positive sentinel node

Regional (palpable nodes)	Radical LND[2]	Positive nodes at presentation Positive nodes after surveillance	Plus adjuvant chemotherapy[3] or radiotherapy[4] (> 1 positive node) Unilateral LND on nodal site (disease-free interval > 3-6 months)
	Chemotherapy +/- LND[3]	Fixed inguinal masses, > 2 cm pelvic nodes (fit patients for chemotherapy)	
	Radiotherapy[4] +/- LND		Fixed masses (unfit patients for chemotherapy)
Distant metastases			Chemotherapy[3] or palliative therapy (according to performance status, age, etc.)

LND = lymphadenectomy.

[1]Modified LND can be extended to radical in cases where there are positive nodes.

[2]If unilateral non-palpable nodes on the opposite side, modified LND can be carried out. Pelvic LND for more than one positive inguinal node only.

[3]Chemotherapy should be discussed with medical oncologist and preferably be given in the context of clinical trials.

[4]Radiotherapy has inconsistent results and high morbidity associated with surgery.

Integrated therapy

In patients presenting with a primary tumour together with positive nodes, both problems should be managed simultaneously. In patients presenting initially with positive pelvic nodes, induction chemotherapy could be administered first and radical or palliative surgery or radiotherapy when indicated according to the tumour response.

Technical aspects

- With the primary lesion, the simplicity and morbidity of the procedure and surgeon's experience play a more important role in the choice of conservative strategy than anything else. Formal circumcision should be advised before brachytherapy.
- Partial amputation does not require removal of 2 cm of the penis in order to achieve macroscopically free margins. Although this is probably more than necessary, it is essential to achieve negative margins with pathological confirmation.
- Radical inguinal lymphadenectomy should include the following anatomical landmarks: inguinal ligament, adductor muscle, sartorius muscle with the femoral vein and artery as the floor of dissection.
- 'Modified' inguinal lymphadenectomy, implies preservation of the saphenous vein and 1-2 cm reduction of external and

inferior boundaries.

- Pelvic lymphadenectomy includes the external iliac lymphatic chain and the ilio-obturator chain.

Chemotherapy.

The chemotherapy regimen should be discussed with the medical oncologist. However, the following can be used as guidelines:

- Induction chemotherapy: three to four courses of cisplatin and 5-fluor-uracil with appropriate doses and sequence.
- Adjuvant chemotherapy: two courses of cisplatin and 5-fluor-uracil may be sufficient or
  12 weekly courses of vincristine, methotrexate and bleomycin may be administered on an outpatient basis.

Quality of life.

Patients' age, performance status, socio-economic status, sexual function, patient motivation and morbidity of different procedures should be considered in the decision-making process.

Table 4. Follow-up schedule for penile cancer

		Interval			Examinations	
Lesion level	Therapy	Years 1 and 2	Year 3	Years 4 and 5	Mandatory	Advisable
Primary tumour	Conservative therapy	2 months	3 months	6 months	Physical/self exam/QOL	
	Partial/total penectomy	4 months	6 months	Yearly	Physical/self exam/QOL	
Regional approach	Surveillance	2 months	3 months	6 months	Physical exam/QOL	Cytology or biopsy if unclear clinical findings
	LND (pN0)	4 months	6 months	Not necessary	Physical/self exam/QOL	
	LND (pN+)	Institutional protocol[1]	Institutional protocol[1]	Institutional protocol[1]	Physical/self exam/QOL/CT scan/chest x-ray	Bone scan (symptoms)

LND = lymphadenectomy; QOL = quality of life (physical and sexual); CT = computed tomography.

[1] Based on the therapeutic approach applied. It is advisable, however, to carry out follow-up every 2-3 months for 2 years, then every 4-6 months during the third year and every 6-12 months thereafter.

FOLLOW-UP IN PENILE CANCER

Penile carcinoma is one of the few solid tumours in which lymphadenectomy can provide a high cure rate even if lymph-nodes are involved. Urologists are faced with the dilemma of reaching an appropriate balance between decreasing the morbidity with conservative procedures and disease control. In this context, follow-up is crucial in order to achieve similar survival rates with early or delayed lymphadenectomy.

The follow-up interval and strategies for patients with penile cancer are directly related to the initial treatment of the primary lesion and regional lymph nodes. See table 4, pages 10 and 11.

This short booklet is based on the more comprehensive EAU guidelines (ISBN 90-806179-8-9), available to all members of the European Association of Urology at their website - www.uroweb.org.

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