GUIDELINES ON PENILE CANCER

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Eur Urol 2002;42(3):199-203

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 of (f.i) Asia, Africa and South America, the incidence increases up to 19 per 100,000 males. (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, 27% in patients with positive nodes and from 0 to 38.4% for patients with pelvic node involvement.

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 carcino-

ma of the penis: cutaneous horn of the penis and Bowenoid papulosis of the penis.

2. Lesions at high (low) risk of developing into squamous cell carcinoma of the penis: penile intraepithelial neoplasia (Erythroplasia of Queyrat, Bowen's disease, Balanitis xerortica obliterans).

Penile neoplasias (Squamous cell carcinoma)

1. Types: Classic, Basaloid, Verrucous and its varieties (Warty, Verrucous carcinoma, Papillary carcinoma, Hybrid verrucous carcinoma), 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 2002 TNM classification for penile cancer is shown in Table 1.

Table 1. 2002 TNM classification of penile cancer

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 regional lymph node metastasis
N1	Metastasis in a single superficial inguinal lymphnode
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 metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

Table 2. Diagnosis schedule for penile cancer

Lesion level		
	Mandatory	
Primary tumour	Physical examination; Cytological or histological diagnosis	
Regional disease		
• Non-palpable nodes	Physical examination;	Cytological
• Palpable nodes	or histological diagnosis	
Distant metastases		

MRI = magnetic resonance imaging.

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. Cytology or histological diagnosis is absolutely necessary before making treatment decisions. In this examination record (mandatory):

- Diameter
- Location
- Number
- Morphology
- Colour
- Boundaries, mobile or fixed of lesions
- Relationship of the primary tumour or/and palpable nodes with other structures.

Procedures	
Advisable	Optional
Ultrasound (if corpora cavernosa invasion suspected)	MRI (if ultrasound inconclusive)
Dynamic sentinel node biopsy[1]	
Pelvic CT (if inguinal nodes +ve) Abdominal CT (if pelvic nodes +ve) Chest radiography (if nodes +ve)	Bone scan (in symptomatic patients)

[1] Cabanas technique (5) is no longer advisable. Isosulphan blue or 99mTc-colloid sulphur is a promising new procedure (7-13).

Diagnostic Imaging, ultrasounds and MRI can assist in identifying the depth of tumour invasion, particularly with regard to corpora cavernosa infiltration. Since penile ultrasound imaging results are sometimes difficult to interpret, when microscopic infiltration is present, this is an unreliable method of investigation.

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

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

Table 3. Therapeutic schedule for penile cancer

Recommendations		
Lesion therapy	Therapy	Strong
Primary tumour	Conservative therapy	Primary/recurrent Tis, Ta-1G1-2
	Total/partial amputation	Primary/recurrent T1G3, T 2
	Radiotherapy	T1-2 < 4cm
Regional (non-palpable nodes)	Surveillance	Tis, TaG1-2, T1G1, T1G2 Superficial growth, vascular (-ve) or negative dynamic sentinel node biopsy

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 pT2 or G3 pT1G2 tumours.

According to these risk groups, surveillance is recommended in low risk, lymphadenectomy in high risk. In intermediate risk groups, the decision-making process might be based on the presence of vascular or lymphatic invasion and growth pattern. In this risk group the current high reliability of dynamic sentinel node biopsy - demonstrated in recent reports - can replace the previous predictive factors in indicating a modified lymphadenectomy.

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

Optional	Investigational
T1G3, T 2 limited to < 50% of glans (fit patients for surveillance)	After chemotherapy, according to tumour response
Primary or recurrent Ta-1G1-2 (conservative therapy not feasible), amputation refusal	In combination with chemotherapy
T2G2-3 (Preference and fit patients for close follow-up)	

	Modified LND[1]	T1G2 nodular growth or vascular (+ve) or positive dynamic sentinel node biopsy, T1G3 or any T2
Regional (palpable nodes)	Radical LND[2]	Positive nodes at presentation Positive nodes after surveillance
	Chemotherapy +/- LND[3]	Fixed inguinal masses, pelvic nodes (fit patients for chemotherapy)
	Radiotherapy[4] +/- LND	
Distant metastases		

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 should be done for more than one positive inguinal node only.

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.

T1G2 vascular (-ve) flat growth or negative dynamic sentinel node biopsy (patients unfit for follow-up)
Plus adjuvant chemotherapy[3] or radiotherapy[4] (> 1 positive node) Unilateral LND on nodal site (disease-free interval > 6 months and < 3 positive nodes)
Fixed masses (patients unfit for chemotherapy)
Chemotherapy[3] or palliative therapy (according to performance status, age, etc.)

[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.

Technical aspects

- With the primary lesion, the simplicity and morbidity of the procedure and the 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.

Table 4. Follow-up schedule for penile cancer

		Interval	
Lesion level	Therapy	Years 1 and 2	Year 3
Primary tumour	Conservative therapy	2 months	3 months
	Partial/total penectomy	4 months	6 months
Regional approach	Surveillance	2 months	3 months
	LND (pN0)	4 months	6 months
	LND (pN+)	Institutional protocol[1]	Institutional protocol[1]

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

- 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.

	Examinations	
Years 4 and 5	Mandatory	Advisable
6 months	Physical/self exam/QOL	
Yearly	Physical/self exam/QOL	
6 months	Physical exam/QOL	Cytology or biopsy if unclear clinical findings
Not necessary	Physical/self exam/QOL	
Institutional protocol[1]	Physical/self exam/QOL/ CT scan/chest x-ray	Bone scan (symptoms)

[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.

Quality of life.

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

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 lymphnodes 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 48 and 49.

This short booklet is based on the more comprehensive EAU guidelines (ISBN 90-70244-19-5), available to all members of the European Association of Urology at their website - www.uroweb.org.

ISBN 90-70244-07-1
Printed and edited by drukkerij Gelderland Arnhem - the Netherlands.