# GUIDELINES ON PENILE CANCER

*(Text updated March 2005)*

G. Pizzocaro (chairman), F. Algaba, S. Horenblas,
H. van der Poel, E. Solsona, S. Tana, N. Watkin

**Eur Urol 2004;46(1);1-8**

## 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 men. 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 91% has recently been reported in a specialized centre: 94% in patients with negative lymph nodes, 80% in patients with positive inguinal nodes and 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 carcinoma 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 xerotica 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 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 haemagioendothelioma, etc.

*Metastatic disease (uncommon)*

Prostate and rectal tumours are the most common 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 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 metastases cannot be assessed |
| M0 | No 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 penile lesion should undergo a detailed physical examination on primary tumour as well as on inguinal regions in order to assess the presence or absence of palpable nodes. Cytology or histological diagnosis is absolutely necessary before making treatment decisions.

In this examination record:

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

Diagnostic imaging, ultrasound and MRI can assist in identifying the depth of tumour invasion, particularly with regard to corpora cavernosa infiltration. A diagnostic schedule for penile cancer is shown in Table 2.

## Table 2: Diagnosis schedule for penile cancer

| Lesion level | Procedures | | |
|---|---|---|---|
| | Mandatory | Advisable | Optional |
| Primary tumour | Physical examination; Cytological or histological diagnosis | Ultrasound (if corpora cavernosa invasion suspected) | MRI (if ultrasound inconclusive) |
| Regional disease<br>• Non-palpable nodes<br>• Palpable nodes or histological diagnosis | Physical examination; Cytological | Dynamic sentinel node biopsy[1]<br><br>Pelvic CT (if inguinal nodes +ve) | |
| Distant metastases | Abdominal CT (if pelvic nodes +ve)<br>Chest radiography (if nodes +ve)<br>Bone scan (in symptomatic patients) | | |

[1] *Cabañas technique is no longer advisable. Identification of the sentinel node by isosulphan blue and $^{99m}$Tc-colloid sulphur is a promising new procedure.*

*MRI = magnetic resonance imaging.*

## Treatment

In penile carcinoma, the success of therapy is related to appropriate treatment of the primary tumour and the lymph node status. 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 (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 can be defined using pathological predictive factors from the primary tumour:

- **low risk**, includes patients with categories pTis, pTaG1-2 or pT1G1
- **intermediate risk**, includes categories pT1G2
- **high risk**, includes categories pT ≥ 2 or G3 pT1 tumours.

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

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

## Table 3: Therapeutic schedule for penile cancer

| Lesion site | Therapy | Strong |
|---|---|---|
| Primary tumour | Conservative therapy | Primary/recurrent Tis, Ta-1G1-2. |
| | Total/partial amputation | Primary/recurrent T1G3, T ≥ 2. |
| | Radiotherapy | T1-2 < 4 cm |
| Regional (non-palpable nodes) | Surveillance | Tis, TaG1-2, T1G1, T1G2. |
| | Dynamic sentinel node biopsy | T1G3,T ≥ 2 |
| | Inguinal LND | Positive dynamic sentinel node biopsy, or any T2. |
| Regional (palpable nodes) | Radical LND[1] | Positive nodes at presentation. Positive nodes after surveillance. |
| | Chemotherapy[2] + LND | Fixed inguinal masses, pelvic nodes. |
| | Radiotherapy[3] +/- LND | |
| Distant metastases | | |

[1] *Pelvic LND should be done for more than one positive inguinal node.*

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

[3] *Radiotherapy has high morbidity associated with surgery.*

*LND = lymphadenectomy.*

| | Recommendations | |
|---|---|---|
| | **Optional** | **Investigational** |
| | T1G3, T2 of glans<br>(fit patients for surveillance) | After chemotherapy, according to tumour response. |
| | Recurrent Ta-1G1-2<br>(conservative therapy not feasible) | |
| | | |
| | T1G3, T2<br>(fit patients for close follow-up) | |
| | T1G2 | |
| | T1G3 | |
| | Plus adjuvant chemotherapy[2] (> 1 positive node).<br>Unilateral LND on nodal site<br>(disease-free interval > 6 months and < 3 positive nodes). | |
| | | |
| | Fixed masses (patients unfit for chemotherapy). | |
| | Chemotherapy[2] or palliative therapy<br>(according to performance status, age, etc.). | |

## 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 surgery or radiotherapy when indicated according to the tumour response.

## 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 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-fluorouracil with appropriate doses and sequence.
- Adjuvant chemotherapy: two courses of cisplatin and 5-fluorouracil may be sufficient or 12 weekly courses of vincristine, methotrexate and bleomycin may be administered on an outpatient basis.

## Quality of life

A patient's 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 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.

*This short booklet text 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 - http://www.uroweb.org.*

## 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 nodes | Surveillance | 2 months | 3 months |
| | LND (pN0) | 4 months | 6 months |
| | LND (pN+) | Institutional protocol[1] | Institutional protocol[1] |

[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.*

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

| | | Examinations | |
|---|---|---|---|
| | **Years 4 and 5** | **Mandatory** | **Advisable** |
| | 6 months | Physical/self exam/QOL | |
| | Yearly | Physical/self exam/QOL | |
| | 6 months | Physical/self 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) |