# GUIDELINES ON PENILE CANCER

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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. 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 developing countries, the incidence rate of penile cancer is much higher, accounting for a maximum of 10% of malignant diseases in Uganda. 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 will be considered in males according to the results in females.

# Classification and pathology

The new, 2009, Tumor 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 *in situ* |
| 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 metastases** | |
| M0 | No distant metastasis |
| M1 | Distant metastases |

## Table 2: 2009 TNM Pathological Classification

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

| | |
|---|---|
| **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 metastases** | |
| 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** |
| • Cutaneous horn of the penis |
| • Bowenoid papulosis of the penis |
| **Lesion at intermediate risk** |
| • 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 |

*SCC = squamous cell carcinoma.*

## 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 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
- 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

| | GR |
|---|---|
| **Primary tumour** | C |
| • Physical examination, recording morphological and physical characteristics of the lesion | |
| • Cytological and/or histological diagnosis | |
| **Inguinal lymph nodes** | C |
| • Physical examination of both groins, recording nodal morphological and physical characteristics | |
| - If nodes are non-palpable, DSNB is indicated; if DSNB not available, ultrasound-guided FNAC/risk factors | |
| - If nodes are palpable, FNAC for cytological diagnosis | |
| **Regional metastases (inguinal and pelvic nodes)** | C |
| • A pelvic CT scan/PET-CT scan is indicated in patients with metastatic inguinal nodes | |
| **Distant metastases (beside inguinal and pelvic nodes)** | C |
| • PET-CT scan also allows evidence of distant metastasis | |
| • If PET-CT is not available, abdominal CT scan and chest x-ray 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; DNSB = 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 Tl-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 |

*$CO_2$ = carbon dioxide; Nd:YAG = neodymium:yttrium-aluminum-garnet*

## Table 7: Guidance on treatment strategies for regional lymphnodes in penile cancer

| Regional lymph nodes | Management of regional lymph nodes is fundamental in the treatment of penile cancer | 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** | Ultrasound-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 |

| | | | |
|---|---|---|---|
| **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 seems to improve the efficacy of standard PF chemotherapy (or carboplatin) | | |
| **Radiotherapy** | Curative radiotherapy may be used for primary tumours of the glans penis and sulcus < 4 cm or for palliation | 2a | B |
| | Prophylactic radiotherapy in clinical N0 patients is not indicated | 2a | B |

*LE = level of evidence; GR = grade of recommendation; LAD = lymphadenectomy; FNAB = fine-needle aspiration biopsy; DSNB = sentinel node biopsy.*

## 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 or PET.TC 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 recur-

rences 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 self-examination.

## Table 8: Follow-up schedule for penile cancer

| | Interval of follow-up | |
|---|---|---|
| | Years 1 and 2 | Years 3, 4 and 5 |
| *Recommendations for follow-up of the 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 |

## 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.

| 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<br>Ultrasound with FNAB | 5 years | C |
| Regular physician or self-examination<br>Ultrasound with FNAB | 5 years | C |

*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.*