Penile tumors: an overview

Christopher Blick, Manit Arya, Nilay Patel, Suks Minhas, Asif Muneer

University College Hospital, London and King's College Hospital, London (CB, MA, NP, SM, AM)

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Identity

Alias
Penile Cancer

Classification

Histologic types:
- Squamous cell carcinoma (90%)
- Adenocarcinoma (5%)
- Melanoma (2%)
- Basal cell carcinoma (2%)
- Sarcoma (1%)

The 1997/2002 TNM (Tumour, Node, Metastasis) classification of penile cancer:
- 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

Clinics and pathology

Disease
Penile Cancer

Epidemiology

Penile carcinoma is an uncommon malignant disease, with an incidence of 0.1-7.9 per 100,000 males. In Europe and the USA, the incidence is 0.1-0.9 per 100,000 rising to 19 per 100 000 in some areas of Asia, Africa and South America.

Penile cancer tends to be a disease of uncircumcised men, with an increase in incidence of men in their sixties; incidence peaks in men aged 80 years. The frequency of penile carcinoma varies according to hygienic practices, cultural and religious beliefs. Penile cancer has been associated with the presence of herpes virus infection and human papilloma viruses (HPV). HPV is thought to be strongly associated with the generation of insitu and invasive cancers of epithelial tumours (Walboomers et al., 1999). The prevalence of HPV DNA in penile carcinoma is 40-45%. HPV
infection also correlates with penile cancer basaloid subtypes, however verrucous tumours tend to be negative for HPV. HPV 16 and 18 are found in 60-75% of insitu and invasive carcinomas whereas HPV 6 and 11 are found in lower risk condylomas.

**Clinics**
Non healing ulcer, painless penile mass, phimosis.

**Pathology**
Grading and staging: graded by the degree of cellular atypia (G1->G3), Staged by TNM classification (see above).

**Treatment**
Non surgical treatments for premalignant lesions include laser therapy, Moh's micrographic surgery, topical 5-FU. Penis-preserving surgery is recommended for premalignant lesions such as carcinoma in situ and also Ta-T1 lesions. Penis preserving surgery is suitable for T2 lesions confined to the glans. More extensive lesions involving the corpus cavernosum or urethra require a partial or total amputation. Local disease recurrence may require partial or total amputation.

In those with a high risk of metastases and non palpable nodes, modified or radical lymphadenectomy is recommended, for those with an intermediate or low risk, the options include surveillance or dynamic sentinel node biopsy or modified inguinal lymphadenectomy. If patients have palpable pathological nodes then radical inguinal lymphadenectomy is the standard recommendation. Pelvic lymphadenectomy is performed in those patients with greater than two positive inguinal nodes.

**Evolution**
Penile carcinoma is one of the few solid tumours in which lymphadenectomy can provide a high cure rate even when lymph nodes are involved. Most relapses occur during the first 2 years; late recurrences, though uncommon, may occur.

**Prognosis**
The mean time until death from cancer is 66.6 months for those with CIS, 50.1 months for those with localized disease, 32.4 months for those with regional disease and 7.4 months for those with distant metastases.

The most powerful prognostic factor in patients with SCC of the penis is involvement of the lymph nodes in the groin. 5-year cancer-specific survival probabilities were 93% for N0 patients, 80% for N1, and 50% for N2 patients. Mutant p53 protein has been detected in 67.6% of patients with lymph node metastases, while only 39.6% of patients with metastases had the wild-type protein. Low levels of E-cadherin were present in 59.5% of patients with groin metastases, while high levels of the protein were detected in 61.7% of the patients without nodal involvement (P = 0.032). More interestingly, MMP-9 immunoreactivity was shown to be an independent predictor of disease recurrence as was the presence of urethral infiltration and lymph node metastasis, which had an important prognostic role.

**Cytogenetics**

**Cytogenetics Morphological**
A diploid population has been established in all verrucous carcinomas, aneuploidy varies according to grade of the tumour: well differentiated (5.5%), moderately differentiated (28.8%), and poorly differentiated (66.6%), there is a tendency towards high DNA index correlating with increased metastatic risk, detectable telomerase activity in has been found in 85.4% (41 of 48) of invasive penile tumours. Increased levels of activity were also identified in adjacent skin and corpus cavernosal tissue (Kayes et al., 2007). Unfortunately due to the rarity and small numbers involved complete analysis of aneuploidy and penile cancer cannot be completed.

The evidence linking P53 expression and presence of HPV DNA in penile cancer is contradictory and there is no adequately proven association.

**Amplifications:**
Common copy-number gains included 8q24, 16p11-12, 20q11-13, 22q, 19q13, and 5p15 (Gregoire et al., 1995).

**Losses:**
Deletions were seen in 13q21-22, 4q21-32, and along the X chromosome.

**Genes involved and proteins**

**Viral genes**
Note
E6 and E7
These viral genes are expressed in high risk types of HPV transformed cells (Castellsague et al., 2002).

**TP53**

**Location:** 17p13

**Note**
This gene is situated on chromosome 17p13 and a mutation in this gene can lead to either expression of a mutant protein (90%) or absence of the protein (Leis et al., 1998). Mutant P53 has been shown to fail to bind to MDM2, thus, resulting in the accumulation of the oncogenic protein in cells. There is also evidence that overexpression of MDM2 is important in aberrant P53 down-regulation in penile cancer (Ouban et al., 2003). There is no evidence of correlation with grade or stage of disease. In multivariate analysis P53 was assessed as an independent prognostic indicator and patients with a negative P53 had significantly better 5 and 10 year survival (Ornellas et al., 1998). Outcome was worst in patients who were P53 and HPV positive.
Serine protease inhibitors

Note
SERPINB1 and SERPINB4 (18q21.3)
These serine protease inhibitors have been assessed in several studies involving penile cancer, revealing that they can provide information for detecting lymph-node metastases in penile cancer, either at diagnosis (sensitivity 57%; specificity 100%) or for patients entered into surveillance programmes (Laniado et al., 2003).

Proapoptotic and antiapoptotic genes

Note
BAX (19q13) and BCL-2 (18q21)
BCL-2 concentrations are significantly (Masih et al., 1992) increased in low-grade disease compared with verrucous cancers, whereas BAX concentrations were comparable.

E-cadherin

Location
16q22

Note
There is evidence that low E-cadherin immunoreactivity is associated with a greater risk of lymph-node metastases (Campos et al., 2006).

MMP genes

Note
MMP-2 (16q12.2) and MMP-9 (20q13.12)
High MMP-9 expression was an independent risk factor for disease recurrence (Campos et al., 2006).

P16INK4a [A50]/cyclin D/retinoblastoma pathway

Note
This pathway can be disrupted by three independent mechanisms in penile cancer. Analysis of 52 cases of invasive penile cancer were scrutinised for P16INK4a and BMI1 using immunohistochemical techniques. HPV-16 E6 and E7 mRNA and P16INK4a methylation were assessed using polymerase chain reaction. HPV presence was also investigated using in-situ hybridisation (Ferreux et al., 2003). The authors described HPV-dependent and HPV-independent mechanisms affecting the normal functioning of this important signalling pathway. p16INK4a might act as a potential prognostic marker and that these results have strong implications on the potential effectiveness of prophylactic HPV vaccines for this tumour.

References


This article should be referenced as such: