Diagnosis and management of penile cancer

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Cancer of the penis is rare, but if caught early has a good prognosis. In this article the authors discuss the epidemiology, risk factors, presentation features and management of penile cancer.

Penile cancer is rare, representing less than 1% of all UK cancer diagnoses. It most commonly presents in the fifth decade and involves the glans or prepuce in over 80% of cases.[1] While squamous cell carcinoma (SCC) is the dominant pathology, other subtypes including basaloid, warty and adenosquamous also exist.[2] Human papillomavirus (HPV) and phimosis are the most important risk factors for the development of penile cancer.

The prognosis is highly dependent on stage at diagnosis, ranging from 90% five-year survival with localised disease, to 40% with more than two lymph nodes involved. Due to the rarity of the disease, there is limited level 1 evidence for the management of penile cancer, and guidelines are often based on retrospective, single-centre studies.

EPIDEMIOLOGY

Although penile cancer is rare, with approximately 620 cases diagnosed in the UK annually, the incidence is increasing. Over the last decade the incidence in the UK has increased by 25%, with the majority of cases diagnosed in those over 65 years.[3] The increased incidence is explained by changes in sexual practice (resulting in higher exposure to HPV), decreasing rates of circumcision and an ageing population.[4]

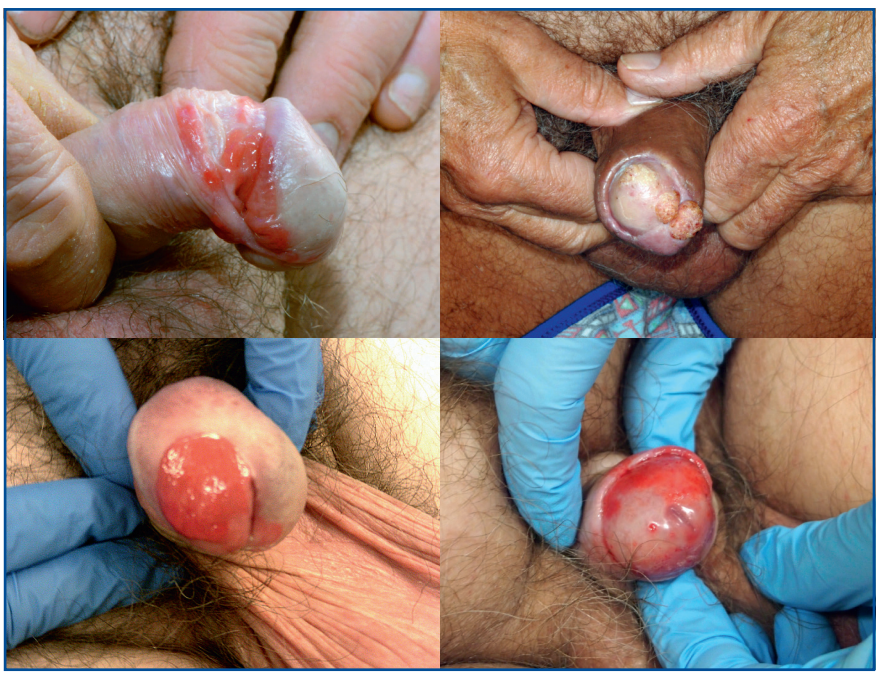

Figure 1. Presenting features of penile cancer. Any new lesion present on the penis for more than four weeks is suspicious and warrants an urgent referral for further investigation

RISK FACTORS

A number of risk factors for penile cancer have been identified, including HPV infection, smoking, circumcision state, phimosis, poor hygiene and low socio-economic status.[5] HPV infection, which is associated with an increased number of sexual partners, a history of genital warts and concomitant sexually transmitted diseases, is a strong risk factor for penile cancer. As many as 60–80% of penile cancers are associated with HPV infection,[5]

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although the link with HPV is dependent on cancer subtype, being highest in warty/basaloid cancers at around 70–100%, in comparison to 30% in other types of penile cancer. The predominant genotypes found are HPV16 and 18.[6] Concurrent infection with HIV or immunosuppression increases the rates of malignant transformation of HPV lesions.

It has been suggested that HPV status may have both a prognostic and predictive role in determining treatment response, although the results are conflicting. While some studies have demonstrated a clear beneficial effect for HPV positivity on prognosis, others have been unable to confirm this.[7] Expression of HPV predicts treatment response in other HPV-related cancers, such as head and neck cancer, although it remains to be seen whether this is the case in penile cancer.

Phimosis and poor hygiene are important risk factors for penile cancer. Both lead to the accumulation of smegma, leading to chronic inflammation and irritation. As many as 90% of patients with penile cancer have a history of phimosis.[4,5] Other conditions causing inflammation, such as balanitis, paraphimosis and lichen sclerosis, also increase the risk of penile cancer, as do iatrogenic causes such as treatment with PUVA and psoralen for psoriasis.[4] Other risk factors known to increase the risk of penile cancer include tobacco use (2.8–4.5% increase), and low socio-economic and educational status.[5,8]

PATHOLOGY

SCC is the most common type of penile cancer, representing 90% of cases.[9] SCC normally develops on the foreskin or the head of the penis, and can be further classified based on appearance, *eg* basaloid, warty, mixed warty-basaloid, verrucous and papillary. Less common subtypes include adenocarcinomas, which arise from the sweat glands in the skin of the penis, melanoma, basal cell cancers and sarcoma.

PRESENTING FEATURES AND INVESTIGATIONS

The initial signs of penile cancer are often a thickening or a change in colour of an area of the penis or foreskin. This then develops into a non-healing rash, lump or ulcer. Lesions may present as a flat growth with a bluish-brown colour or red rash, a wart or small crusty bumps or an ulcer or blister (Figure 1). These changes are often painless and may only be visible when the foreskin is pulled back. Any new lesion present on the penis for more than four weeks is suspicious and warrants an urgent referral for further investigation. Later symptoms include bleeding or discharge, which is often malodorant. Alternatively, penile cancer may present with new onset phimosis. Occasionally, patients present with non-specific symptoms due to metastatic disease, such as fatigue, weight loss, abdominal pain or symptoms of bony metastases, such as pain.

INVESTIGATIONS

Initial investigations include physical examination with recording of the morphological and physical characteristics of the lesion and examination of both groins. Cytological and/or histological diagnosis is required and any palpable lymph nodes should also be biopsied. Pelvic imaging should be performed and a PET-CT (or standard CT if PET-CT is not available) in those with evidence of metastatic inguinal lymph nodes. A bone scan should be performed in patients with symptoms suggestive of bony metastatic disease.

STAGING AND PROGNOSIS

Penile cancer should be staged according to the American Joint Committee on Cancer (AJCC) tissue, nodes and metastases (TNM) classification (Table 1), with presenting stage important for prognosis.[10] Broadly, patients are divided into those with localised or metastatic disease. Localised disease is highly curable and further subdivided into Stage 0, 1 or 2. Stage 0 represents cancer on the surface of the skin only, Stage 1 where the cancer has invaded connective tissue but not lymph nodes or blood vessels, and Stage 2 where the cancer has spread to local connective

Stage	Prognosis (five-year survival)
Stage 0 (Tis, Ta, N0, M0: carcinoma *in situ* or non-invasive verrucous carcinoma)	90–100%
Stage 1 (T1a, N0, M0: no evidence of LVI)	90–100%
Stage 2 (T1b/T2/T3, N0, M0: LVI/poorly differentiated/undifferentiated/tumour invades corpus spongiosum/corpora cavernosa or urethra)	90–100%
Stage 3A (T1–3, N1, M0) Single, unilateral lymph node	80%
Stage 3B (T1–3, N2, M0) Multiple unilateral or bilateral inguinal lymph nodes	40%
Stage 4 (any T4, any N3, any M1) T4 – invades adjacent structures, N3 – fixed inguinal or pelvic lymph nodes, or metastatic disease	11%
Tis, tumour *in situ;* Ta, verrucous (wart-like) carcinoma that is only in the top layers of skin (non-invasive); LVI, lymphovascular invasion.	

Table 1. Staging of penile cancer[10]

tissue, lymphatics or blood vessels, or to the erectile tissue or urethra. Metastatic disease includes Stage 3A, which involves a single unilateral groin node, Stage 3B where ≥1 lymph node is involved (including bilateral groin nodal disease) and Stage 4, which can represent invasion of local structures such as the prostate, pelvic lymph node involvement or distant metastatic disease.[11] The overall survival of patients with metastatic disease (beyond the pelvic nodes) is 0% at five years and <10% at two years.[11]

MANAGEMENT

Treatment is dependent on tumour stage, size and location. Treatment options include surgery, radiotherapy, chemotherapy and novel therapies. Surgical resection is an important part of treatment. For localised disease, conservative treatment such as cryotherapy, laser surgery and Mohs microsurgery can be considered. Mohs microsurgery is a technique where the tumour is cut from the skin in thin layers and examined microscopically during surgery to ensure clear margins. For more extensive disease, a partial or total penectomy is required, which may also include surgical removal of the lymph nodes in the groin for high-risk tumours. Radical iliac lymph node dissection is recommended for involved nodes. In the presence of metastatic inguinal node disease, superficial dissection of the contralateral side is also required, with complete dissection performed in the presence of positive nodes on frozen section.

Radiotherapy has the advantage of providing durable local control with the preservation of functional anatomy. External beam radiotherapy and brachytherapy can be used alone or in combination to treat the primary tumour. Radiotherapy is not without toxicity; this includes skin toxicity, soft-tissue ulceration and meatal stenosis, and less commonly urethral fistulae, penile necrosis and oedema. Any slow-healing ulcer following radiotherapy should be biopsied to exclude recurrent disease. Circumcision is routinely performed prior to radiotherapy treatment.

Chemotherapy is used in metastatic disease and in conjunction with surgery for those with local-regional disease, either in a neoadjuvant setting or postoperatively.[11] The evidence for chemotherapy in penile cancer is limited to small studies and retrospective analysis, which makes it difficult to draw any definite conclusions regarding optimal regimes. Chemotherapy regimes commonly combine two or three chemotherapy drugs due to the relative resistance of penile cancer to chemotherapy and the majority contain a cisplatin backbone. Neoadjuvant chemotherapy followed by surgery is recommended for patients with unresectable inguinal lymph nodes.[11] Adjuvant therapy is recommended for those with N2 or N3 disease. Combination therapy such as cisplatin/fluorouracil or paclitaxel/carboplatin is used for metastatic disease. Due to the rarity of penile cancer, few studies have examined the effects of novel targeted or biological therapies for its management, although the association with HPV suggests that immunotherapy may represent a promising treatment option.

KEY POINTS

- **Penile cancer is a rare cancer**
- **Incidence is increasing in the UK**
- **Prognosis is highly dependent on stage at diagnosis**
- **Most tumours are squamous cell cancers and can be cured if detected early enough**
- **Early diagnosis is essential**
- **Early signs to recognise include a new rash or lesion on the penis present for four weeks or longer**
- **Some lesions may be painless and may not be visible unless the foreskin is retracted**
- **New bleeding or discharge and new onset phimosis are warning signs**

CONCLUSIONS

Due to the rarity of penile cancer, treatment should be managed in a tertiary centre using a multidisciplinary approach. Early diagnosis gives the best chance of long-term survival and maintenance of function. In order to improve outcomes for patients, concerted efforts are required for multicentre, international collaborations to increase our understanding of this rare disease.

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