Malignant and premalignant lesions of the penis

Manit Arya,1 Jas Kalsi,2 John Kelly,3 Asif Muneer3

Penile cancer can have devastating mutilating and psychological consequences for those affected. It is important for clinicians to be aware of the condition. Differentiation of benign genital dermatoses from premalignant penile lesions and early stage penile cancer, with prompt specialist referral, usually prevents progression, improves prognosis, and results in improved functional and cosmetic outcomes for affected men. A retrospective single centre study of all penile cancer cases in a specialist unit over five years found that general practitioners initiated most referrals, but that about 20% of patients were initially referred to specialties other than urology, such as genitourinary medicine, dermatology, or plastic surgery. This delay in diagnosis by up to six months and potentially adversely affected quality of life, prognosis, and survival. Our article, written for the non-specialist, aims to provide an evidence-based review of the causes and current trends in the diagnosis and management of premalignant and malignant penile lesions.

How common are penile cancer and premalignant lesions of the penis?

Current understanding of penile cancer is based mainly on small non-randomised retrospective case series. However, there is now a push for research into penile cancer by the International Rare Cancers Initiative (IRCI), a strategic collaboration between Cancer Research UK, the UK National Cancer Research Network (NCRN), the US National Cancer Institute (NCI), and the European Organisation for Research and Treatment of Cancer (EORTC).

The mean age at diagnosis of penile cancer is about 60 years. However, a prospective study of 100 consecutive patients from one institution in the United Kingdom suggested that 25% of men were under 50 years of age at diagnosis. The age standardised incidence is 0.3-1 per 100 000 men in European countries and the United States, according to European Association of Urology guidelines. Incidence is much higher in developing countries—3 per 100 000 in parts of India, 8.3 per 100 000 in Brazil, and even higher in Uganda. In Uganda it is the most commonly diagnosed cancer in men, accounting for 10-20% of all tumours. The incidence and prevalence of premalignant penile lesions and their geographical variation is not well established. However, as a European example, a retrospective analysis using two nationwide registries estimated the age specific incidence rate of premalignant penile conditions in Denmark to be 0.9 per 100 000 men in 2006-08. No similar robust data have been published from developing countries where the cancer is more common.

What are the risk factors for penile cancer?

An extensive systematic review of publications (case-control studies, cohort studies, ecological studies, cross sectional studies, case series, and case reports) from 1966 to 2000 and their citations found an association between the presence of a foreskin and tumour development. Researchers in North America observed this association in a population based case-control study. They found a 3.2 times greater risk in men who were never circumcised and a 3.0 times greater risk in men who were circumcised after the neonatal period compared with those circumcised as neonates. Adult circumcision seems to have no protective effect. In addition, penile cancer is rarer in countries with subpopulations who practise childhood circumcision, such as India and Nigeria. Early circumcision protects against phimosis, poor penile hygiene, and retention of smegma (desquamated epidermal cells and urinary products). These conditions are proposed to result in chronic inflammation of the glans and prepuce, which is thought to promote the development of penile cancer. However, well conducted longitudinal studies are needed to fully elucidate the protective role of early circumcision.

Human papillomavirus (HPV) infection also plays a role in the development of this tumour. A systematic review of the major penile cancer studies published from 1986 to 2008 established that about 50% of cancers were associated with HPV, with the main subtype being HPV-16 (involved in 60% of cases) followed by HPV-18 (13% of cases).

Table 1 summarises other risk factors for penile cancer.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td>Foreskin</td>
<td>Presence of foreskin increases risk</td>
</tr>
<tr>
<td>HPV infection</td>
<td>Human papillomavirus type 16 and 18</td>
</tr>
<tr>
<td>Circumcision</td>
<td>Circumcision protects against phimosis, poor hygiene, and retention of smegma</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>Chronic inflammation due to foreskin and glans increases risk</td>
</tr>
</tbody>
</table>

How does penile cancer present and what are the indications for specialist referral?

Presentation is often delayed because of embarrassment about the lesion. A retrospective UK study suggested a delay...
Relative increased risk of penile cancer

Table 1 | Risk factors for penile cancer

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative increased risk of penile cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not circumcised (associated with phimosis, poor penile hygiene, smegma retention)</td>
<td>× 3.2 relative to neonatal circumcision¹</td>
</tr>
<tr>
<td>HPV infection (most commonly types 16 and 18)†</td>
<td>—</td>
</tr>
<tr>
<td>Genital warts</td>
<td>5.9 times²</td>
</tr>
<tr>
<td>Multiple sexual partners and early age of first intercourse</td>
<td>3-5 times³</td>
</tr>
<tr>
<td>HIV infection</td>
<td>8 times⁴</td>
</tr>
<tr>
<td>Smoking (dose dependent effect)</td>
<td>×2.8 relative to non-smokers⁵</td>
</tr>
<tr>
<td>Psoralen plus ultraviolet light A (PUVA) treatment for psoriasis</td>
<td>×58.8 times⁶</td>
</tr>
<tr>
<td>Penile injury (small tears or abrasions)</td>
<td>3.9 times⁷</td>
</tr>
</tbody>
</table>

*A retrospective review of a cancer database over 18 years in patients with HIV/AIDS. †A 12.3 year prospective cohort study in a single centre of men with psoriasis treated with PUVA. HPV=human papillomavirus.

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- Postpartum management of hypertension (BMJ 2013;346:f894)
- Diagnosis and management of pulmonary embolism (BMJ 2013;346:f757)
- Anaphylaxis: the acute episode and beyond (BMJ 2013;346:f602)
- Ulcerative colitis (BMJ 2013;346:f432)
- Prostate cancer screening and the management of clinically localized disease (BMJ 2013;346:f325)
- Bed bug infestation (BMJ 2013;346:f138)

of 5.8 months from the onset of symptoms to presentation to a medical professional.¹ Most men present with a lump (47%), ulcer (35%), or erythematous lesion (17%). Men may also present with bleeding or discharge from a lesion concealed by a phimotic foreskin.

The diagnosis of penile cancer is therefore often obvious because lesions are directly visible or palpable under a phimotic foreskin. If penile cancer is suspected, urgently refer the man to a urology department, ideally a supraregional referral centre for penile cancer. Arrange an emergency admission if there are coexistent complications—such as voiding dysfunction, urinary retention, or extensive metastatic disease—so that adequate urinary drainage and investigations can be instigated without delay.

How can premalignant lesions be differentiated from benign genital dermatoses?

Differentiating erythematous premalignant lesions from benign genital dermatoses is a challenge. Maintain a high index of suspicion and remember that follow-up is extremely important. Benign lesions such as eczema, psoriasis, lichen planus, and Zoon’s balanitis are common and normally respond to treatment with a combination of topical steroids and emollients. However, patients treated for these benign conditions must be closely followed up to ensure that the lesions resolve completely. If an erythematous area or ulcer does not heal after two to three weeks of conservative treatment with steroids or antifungals, urgent referral to a urologist or dermatologist with an interest in genital dermatology is essential because a diagnostic biopsy is mandatory to exclude premalignant disease. However, if the initial lesion is exophytic or raised and irregular, prompt urological referral from the outset is preferable because this may be an invasive carcinoma.

What are the histological subtypes of penile cancer and staging system?

Table 2 summarises the histological subtypes of penile cancer. Squamous cell carcinoma accounts for most cases and is the main focus of this article. Sarcomatoid and basaloid subtypes are rarer, more aggressive, and have a poorer prognosis. The box (see bmj.com) shows the TNM staging of this cancer.²³

What premalignant conditions are associated with penile cancer?

Several premalignant lesions of the penis have been described (tables 3 and 4), although the risk of progression to invasive penile cancer depends on the site and type of lesion. Penile intraepithelial neoplasia (PIN), classified as PIN I-III, is commonly associated with high risk HPV types 16 and 18.⁷ The pathological features of PIN II are similar to Bowenoid papulosis and those of PIN III are synonymous with erythroplasia of Queyrat (fig 1) and Bowen’s disease, both of which are also referred to as carcinoma in situ (CIS). Bowenoid papulosis is mainly located on the penile shaft and presents as multiple red velvety papillary areas. Erythroplasia of Queyrat presents as velvety bright red patches located on the mucosal surfaces of the penis, whereas lesions in Bowen’s disease are solitary well defined red plaques located on the penile shaft, often with areas of crusting or ulceration.
**CLINICAL REVIEW**

**Table 3** | HPV related premalignant penile lesions
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<table>
<thead>
<tr>
<th>Lesion</th>
<th>Location and appearance</th>
<th>Progression rate to invasive cancer (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroplasia of Queyrat (PIN III; non-keratinising CIS)</td>
<td>Velvety red plaques on the glans penis and inner prepuce</td>
<td>30</td>
</tr>
<tr>
<td>Bowen’s disease (PIN III; keratinising CIS)</td>
<td>Pigmented lesions affecting follicle bearing areas of the penis shaft and scrotum</td>
<td>5</td>
</tr>
<tr>
<td>Bowenoid papulosis</td>
<td>Multiple brown-red maculopapular areas</td>
<td>1</td>
</tr>
<tr>
<td>Buscike-Löwenstein “tumour” (giant condyloma acuminatum)</td>
<td>Confluence of wart-like cauliflower-like growths</td>
<td>30</td>
</tr>
</tbody>
</table>

*Progression rates are not well documented and are based on small retrospective case series.

**Table 4** | Non-HPV related premalignant lesions
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<tr>
<th>Lesion</th>
<th>Location and appearance</th>
<th>Progression rate to invasive cancer (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen sclerosus et atrophicus (also known as balanitis xerotica obliterans)</td>
<td>White sclerotic patches affecting the prepuce, glans, or meatus; often result in phimosis</td>
<td>Not known</td>
</tr>
<tr>
<td>Leucoplaque</td>
<td>White verrucous plaques on mucosal surfaces</td>
<td>Not known</td>
</tr>
<tr>
<td>Cutaneous penile horn</td>
<td>Conical and exophytic lesion associated with areas of chronic inflammation</td>
<td>(mostly low grade)</td>
</tr>
</tbody>
</table>

*Progression rates are not well documented and are based on small retrospective case series.

The most common non-HPV related premalignant condition is lichen sclerosus et atrophicus, otherwise known as balanitis xerotica obliterans (fig 2). Lichen sclerosus is seen in uncircumcised men and is secondary to a chronic inflammatory process affecting the glans and prepuce. A pathological phimosis normally develops, and in severe cases both the meatus and urethra can be affected. The largest published series (retrospective study of 522 patients in a single centre) reported that 2.3% of patients diagnosed with lichen sclerosus had squamous cell carcinoma of the penis, whereas synchronous lichen sclerosus is found in 28-50% of patients treated for penile cancer. Lichen sclerosus can therefore be considered a risk factor for the development of penile cancer, albeit with a latency time of 12-17 years. Other non-HPV related premalignant lesions include leucoplaque and cutaneous penile horn (table 4).

**What treatments are available for premalignant and malignant disease of the penis?**

**Treatment of premalignant disease**

All men with suspected premalignant disease of the penis will have undergone a diagnostic biopsy. If this was an excisional biopsy and histological analysis indicates that the lesion was excised completely, the patient is placed under close surveillance after circumcision (which is strongly recommended internationally). If incisional biopsy was performed rather than excision, after circumcision further treatment will be needed to completely eradicate the lesion. Not only does circumcision remove a preputial lesion, it also aids surveillance (including self examination) and allows topical treatment to be applied. The most common first line topical treatment for CIS or PIN of the penis is 5% 5-fluorouracil, an antimetabolite chemotherapeutic agent. Treatment protocols vary, but it is generally applied to the lesion on alternate days for four to six weeks. In the largest study to date—a single centre retrospective review of 42 cases of penile CIS treated with 5-fluorouracil identified from a prospective database over 10 years—50% achieved a disease-free interval of seven patients with penile carcinoma. However, use of these nanoparticles is currently not authorised in Europe. Bilateral dynamic sentinel lymph node biopsy (fig 4; see below) is used in some specialist centres in Europe and North America for detecting lymph node metastases in a case series of seven patients with penile carcinoma. MRI with lymphotrophic nanoparticles using intravenous ferumoxtran-10 showed promising results in detecting occult metastases in a case series of seven patients with penile carcinoma. However, use of these nanoparticles is currently not authorised in Europe. Bilateral dynamic sentinel lymph node biopsy (fig 4; see below) is used in some specialist centres in Europe and North America for detecting lymph node metastasis in cN0 disease, but the technique is not yet standard in many countries.

**How is penile cancer investigated?**

Penile cancer should be managed in high volume supraglottal referral centres. Premalignant conditions need only an incisional or excisional biopsy to confirm the diagnosis and exclude invasive elements. However, invasive tumours require staging of the primary penile lesion and inguinal and pelvic lymph nodes. Tumours are most commonly seen on the glans (48%) or prepuce (21%) (fig 3). Such tumours require no further imaging unless it is unclear whether the tumour is limited to the corpus spongiosum or extends into the corpus cavernosum. Local staging can be performed by using intracavernosum prostaglandin (PGE1) to induce an artificial erection after magnetic resonance imaging (MRI) using T2 and T1 precontrast and postcontrast sequences. The largest study on the use of MRI retroactively analysed the correlation between MRI and the final histological findings in 55 patients in a single tertiary referral centre. Although corpus cavernosum involvement was correctly predicted in two cases, the technique over-staged six cases of T1 tumour as T2. Ultrasound of the glans penis can also be used to identify involvement of the corpus cavernosum.

Clinical examination of the inguinal region will detect enlarged inguinal lymph nodes as a result of metastatic disease (cN+) and staging computed tomography (CT) is performed to detect further abnormal lymphadenopathy in the inguinal and pelvic region, together with any distant metastatic disease. However, the sensitivity of both conventional CT and MRI for clinically impalpable disease (cN0) is poor because these techniques classify abnormal lymphadenopathy on the basis of size and morphology criteria. Alternative imaging modalities for cN0 and cN+ disease include ultrasonography combined with fine needle aspiration cytology and positron emission tomography-CT with fluorine-18 labelled FDG. A recent meta-analysis reported that this last technique had a pooled sensitivity of 96.4% for cN+ disease and 56.5% for cN0 disease. MRI with lymphotrophic nanoparticles using intravenous ferumoxtran-10 showed promising results in detecting occult metastases in a case series of seven patients with penile carcinoma. However, use of these nanoparticles is currently not authorised in Europe. Bilateral dynamic sentinel lymph node biopsy (fig 4; see below) is used in some specialist centres in Europe and North America for detecting lymph node metastasis in cN0 disease, but the technique is not yet standard in many countries.

**Fig 3** | Penile tumour on glans penis
The tumour while maintaining penile length and minimising penile preserving surgery, which allows surgical excision of conventional 2 cm resection margin from the primary tumour showed that the most important prognostic indicator. A retrospective analysis of a case series of 72 consecutive patients undergoing glansectomy and reconstruction reported a local recurrence rate of 6% after a mean follow-up of 27 months. Provided that local recurrences are excised, the long term prognosis remains unchanged for this group of patients.

**Surgery for advanced tumours (T2, T3, T4)**

The management of stage T4, high grade stage T3, or advanced stage T2 disease requires radical surgery in the form of a partial penectomy or total penectomy, with formation of a perineal urethrostomy (a form of urine diversion).

**Radiotherapy and chemotherapy**

The use of radiotherapy (external beam radiotherapy or brachytherapy) is now uncommon for penile carcinoma and is most appropriate for small T1 or T2 lesions in patients unfit or unwilling to undergo surgery.

Unlike other squamous cell carcinomas, penile cancer is an aggressive cancer with a limited response to chemotherapy regimens. Data on the use of chemotherapy in penile cancer are lacking, so evidence based recommendations are limited and the optimal chemotherapy regimen has yet to be defined.

**How important is lymph node disease?**

Anatomical and lymphoscintigraphic studies have shown that lymph from the penis drains bilaterally to the inguinal lymph nodes in most patients. Once metastatic disease involves the inguinal lymph nodes, further spread of metastatic cells occurs in a stepwise manner to the pelvic lymph nodes, then distant sites such as the lungs, bone, and para-aortic lymph nodes. A separate retrospective analysis of 201 patients over a 24 years period reported that extension of metastatic disease into the pelvic nodes was associated with a five year survival rate of only 80%. A separate retrospective analysis of 201 patients over a 24 years period reported that extension of metastatic disease into the pelvic nodes was associated with a five year survival rate of only 80%.

**Management of cN+ disease (clinically node positive)**

About 20% of patients in Western countries present with palpable inguinal lymph nodes, which almost always signify metastatic disease and will require a radical inguinal lymphadenectomy (a procedure associated with high morbidity).

**Management of cN0 disease (clinically node negative)**

About 80% of patients present with clinically impalpable inguinal lymph nodes. However, 20-25% of these patients will have occult metastasis, and it is this group of men who need accurate nodal staging. To avoid overtreatment of these patients, alternative options such as close surveillance, modified superficial inguinal lymphadenectomy, or bilateral dynamic sentinel lymph node biopsy (fig 4) can be offered.

Complete response and 31% a partial response. Persistent lesions can be treated with second line immunotherapy using topical 5% imiquimod, although its use is supported only by uncontrolled cohort studies and case reports, so its effectiveness is unclear. Topical chemotheraphy is most effective for solitary lesions in immunocompetent patients, but clinicians must be alert to recurrence in partial responders.

Premalignant lesions have also been treated using lasers (carbon dioxide; Nd:YAG (neodymium-doped yttrium aluminium garnet; Nd,Y,Al,O,); and KTP (potassium titanyl phosphate)) with good functional and cosmetic results. Published studies have included only modest numbers, but in one study 19 patients with premalignant penile disease who were treated with lasers were free from cancer after two years.

Surgical excision is reserved for refractory cases or for patients who have developed extensive CIS of the glans penis. Both intractable in situ disease and non-invasive verrucous disease can be effectively treated by excising the diseased area. This involves excision of the epithelial and subepithelial tissues of the glans penis with preservation of the underlying corpus spongiosum, followed by coverage of the denuded glans penis with a split thickness skin graft. This surgical technique is called glans resurfacing.

**Penile preserving surgery**

Single centre case series that retrospectively analysed resection margins after partial and total penectomy showed that the conventional 2 cm resection margin from the primary tumour is not needed to achieve long term oncological control and disease specific survival. This finding has formed the basis of penile preserving surgery, which allows surgical excision of the tumour while maintaining penile length and minimising anatomical, functional, and psychological disruption.

**T1-T2 lesions confined to the glans penis**

Wide local excision of the cancer followed by primary closure may be possible if the lesion is small. For larger tumours, a partial or total excision of the penile glans combined with reconstruction using a split skin graft can be performed. A retrospective study of 72 consecutive patients undergoing glansectomy and reconstruction reported a local recurrence rate of 6% after a mean follow-up of 27 months. Provided that local recurrences are excised, the long term prognosis remains unchanged for this group of patients.

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In the same study, patients with metastatic disease in one or two inguinal lymph nodes had a five year survival rate of about 80%. A separate retrospective analysis of 201 patients over a 24 years period reported that extension of metastatic disease into the pelvic nodes was associated with a five year survival of 0-21%.

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What are the psychological effects of penile cancer?
The penis is functionally important for micturition and sexual purposes. The effects of any disfiguring surgery to this organ can have a psychological impact on self-image and self-esteem, but research in this area is lacking. Embarrassment, anxiety, and fear may result in delayed presentation. In a retrospective study of 30 patients followed up for a median of 80 months after treatment for penile cancer, 50% had mental health symptoms, most commonly anxiety related conditions. These patients were also less satisfied with regard to subjective wellbeing and showed decreased social activity. Another systematic focused review of the literature on quality of life after penile cancer surgery identified 128 men from six studies. It found that treatment for penile cancer had negative effects on wellbeing in 37.5-40%, with psychiatric symptoms in about 50% and 36-67% of patients reporting a decrease in sexual function. In dedicated units in the UK, penile cancer nurse specialists are available to provide patient support and guidance and to arrange psychosocial services as needed.

Preventive strategies
Public health education on the risks of smoking, poor genital hygiene, and sexually transmitted diseases in relation to penile cancer is essential. Since 2005, three well designed randomised control trials of more than 10 000 men conducted in South Africa, Kenya, and Uganda have evaluated male circumcision for prevention of sexually transmitted infections. The trials found that circumcision decreases HIV infection by 53-60% and the prevalence of oncogenic high risk HPV by 32-35%. Although these trials were not designed to investigate the potential for circumcision programmes to reduce the incidence of penile cancer, it may be possible in future to assess whether circumcision has affected penile cancer rates in these regions.

Another potential preventive strategy is HPV vaccination, which has been introduced for girls to prevent cervical cancer. HPV vaccination has also been proposed for boys to reduce the total HPV burden in the population (herd effect) and to prevent HPV related cancers. Currently, decisions on routine vaccination in boys are awaiting the results of the female HPV vaccination programme.

The 2009 International Consultation on Urologic Disease Consensus Publishing Group suggested that circumcision and early treatment of phimosis, together with important changes in global health policy, were the most useful measures to prevent penile cancer. MA would like to thank Orchid (male cancer charity) (www.orchid-cancer.org.uk) and the Barts and the London Charity. JK would like to thank the UCLH Biomedical Research Centre. Funding: No special funding received. Competing interests: None declared. Patient consent obtained. Provenance and peer review: Not commissioned; externally peer reviewed. Reference: In the version on bmj.com.

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