

Penile cancer: an overview

R Hamid, I Shergill, M Arya, HRH Patel

Carcinoma of the penis affects 1 in 100 000 men per year in most developed countries. It accounts for less than 1% of adult malignancies in Europe and the USA. Survival is excellent if diagnosed early, but most men present up to 1 year after the initial lesion is noted. Unfortunately the treatment of metastatic disease is still disappointing.

Penile cancer is often overshadowed by other urological malignancies (prostate, bladder and testis). It does not usually present a diagnostic challenge but its management can be difficult. Surgery has always been the treatment of choice. However, with the advancement of chemoradiotherapy, and the severe psychological and physical consequences associated with extensive surgery, the emphasis has shifted to penile preservation.

EPIDEMIOLOGY

Penile cancer affects 1 in 100 000 men per year in the USA and Europe (Mobilio and Ficarra, 2001). In certain areas of Africa, Asia and South America the incidence may reach 19 in 100 000 men per year (Hakenberg and Wirth, 1999). It accounts for 0.4–0.6% of malignancies in the USA and Europe but may constitute up to 10% of malignancies in African and some South American countries (Gloeckler-Ries, 1990). Men over the age of 60 years are predominantly affected (Persky, 1977). However, a significant proportion (22%) of these tumours appear in males under 40 years of age (Dean, 1935).

RISK FACTORS

Poor hygiene

Poor hygiene has commonly been associated with penile cancer. It occurs with higher frequency in uncircumcised individuals with congenital phimosis and is rare in men circumcised at birth. In India, carcinoma of penis is almost non-existent in the neonatally circumcised Jewish population, present in prepubertal Muslims and relatively common in uncircumcised Hindus and Christians (Paymaster and Gangadharan, 1967). Adult circumcision offers little protection against penile cancer (Thomas and Small, 1963). It has been

suggested that chronic penile irritation secondary to smegma accumulation or balanitis with poor hygiene are contributory (Mobilio and Ficarra, 2001).

Human papilloma virus

Human papilloma virus infection with types 16 and 18 has also been implicated (Picconi et al, 2000). Interestingly, up to an eight-fold increase in the incidence of cervical cancer has been reported in partners of patients with carcinoma of the penis (Goldberg et al, 1979).

Venereal diseases and trauma

Although penile cancer has been documented in scarred penis after mutilating circumcision (Bissada et al, 1986) the correlation is thought to be incidental. Similarly no consistent relationship exists between penile cancer and venereal disease (Schrek and Lenowitz, 1947).

PATHOLOGY

Premalignant dermatological lesions

Balanitis xerotica obliterans (BXO), or newly termed lichen sclerosis atrophicus, is an idiopathic condition caused by abnormal collagen deposition and histiocytic infiltration (Layman and Freeman, 1944). There are reports documenting the development of penile cancer even after the excision of the BXO (Dore et al, 1990).

Leukoplakia appears as solitary or multiple whitish lesions. Histologically hyperkeratosis, parakeratosis and lymphocytic infiltration are seen. There is an association with squamous cell carcinoma in situ (Bain and Geronemus, 1989).

Virus-related dermatological lesions

Buschke–Lowenstein tumour (giant condylomata acuminata) are believed to be of viral origin, particularly human papilloma virus types 16, 18 and 31 (Smotkin, 1989). They are soft papillomatous growths and generally considered to be non-

Mr R Hamid is Clinical Research Fellow, **Mr I Shergill** is Clinical Research Fellow, **Mr M Arya** is Specialist Registrar and **Mr HRH Patel** is Honorary Clinical Lecturer in Urology, Institute of Urology, London W1W 7EY

Correspondence to:
Mr HRH Patel

metastatic, but have been associated with penile carcinoma (Rhatigan et al, 1972).

Kaposi's sarcoma was first described in 1972 as a tumour of the reticuloendothelial system (Kaposi, 1982). It is now closely linked with acquired immune deficiency syndrome (AIDS) when it is more aggressive. Penile involvement is more common in AIDS patients who are homosexual than in those who are intravenous drug abusers or haemophiliacs (Bayne and Wise, 1988).

Carcinoma in situ

Erythroplasia of Queyrat, or Bowen's disease, is eponymous with carcinoma in situ of the penis and surrounding genital region. Lesions involving the glans, prepuce and shaft are called erythroplasia, while those affecting the remainder of the genitalia and perineal area are referred to as Bowen's disease. Clinically, these lesions present as erythematous plaques. Microscopically, they reveal hyperplastic cells with mitotic figures and vacuolated cytoplasm. If left untreated, carcinoma in situ of the penis may regress. However, up to a third of these patients will develop invasive carcinoma (Mikhail, 1980).

INVASIVE CARCINOMA

Squamous cell carcinoma accounts for 95% of all penile cancer, with approximately 40% of patients presenting with superficial disease at diagnosis. Squamous cell carcinoma is slow to metastasize to inguinal and subsequently pelvic lymph nodes. Haematogenous spread to lungs, liver and bone occurs in <10% of patients (Puras et al, 1978).

Verrucous carcinoma constitutes approximately 5% of penile cancer (Adriazola-Semino et al, 1990). Although the histological picture appears benign, the lesion behaves as a low-grade squamous cell carcinoma with invasion through the basement membrane occurring late in its evolution. Metastasis is extremely rare (Lopez Alcina et al, 1996).

Very rarely penile basal cell carcinoma may occur.

PRESENTATION

Presenting symptoms and signs are shown in *Table 1*.

The majority of lesions are not painful, which may explain why up to 50% of patients delay a medical opinion for at least 1 year from the time of initial awareness of the lesion (Dean, 1935). At presentation approximately 50% of patients have palpable inguinal nodes but these usually represent an inflammatory response rather than metastasis.

The exposure to smegma may explain the observed tumour distribution: glans (48%), prepuce (21%), both glans and prepuce (9%), coronal sulcus (6%), shaft (<2%) and a combination in 14% (Sufrin and Huben, 1991).

DIAGNOSIS

Diagnosis is confirmed by an incisional biopsy. A pelvic magnetic resonance imaging (MRI) scan is the investigation of choice to assess the extent of local invasion. If locally advanced, further clinical staging should include a computed tomography (CT) scan of the abdomen, chest X-ray and isotope bone scan. Less than 10% of patients present with metastasis. In the absence of osseous metastasis, hypercalcaemia is seen in up to 20% of cases correlating with the volume of the disease (Sklaroff and Yagoda, 1982).

STAGING

The most commonly used staging system is the tumour, node, metastasis (TNM) classification of the American Joint Committee on Cancer (1997) shown in *Table 2*.

TREATMENT

Treatment options for carcinoma in situ, verrucous carcinoma and the primary lesion in squamous carcinoma are shown in *Table 3* (Hakenberg and Wirth, 1999; Agrawal et al, 2000).

Other penile tumours

Although more than 95% of cases are squamous cell carcinomas, cases of basal cell carcinoma, Paget's disease and melanoma have been reported. The increase in human immunodeficiency virus (HIV) infection has led to an increased incidence of Kaposi's sarcoma. This tumour is highly radiosensitive.

Palpable nodes

Inguinal lymph nodes represent the first site of distant dissemination of penile carcinoma. Their involvement and the manner in which

TABLE 1.
Presenting symptoms and signs

Epithelial thickening on glans or inner prepuce
Ulcerative or exophytic growth
Penile discharge or dysuria
Bleeding
Palpable inguinal nodes

they are managed are the most important determinants of patient survival in penile cancer. Approximately 50% of patients will have palpable lymph nodes at presentation. Of this group only 15–45% will actually have metastatic involvement by tumour while in the remainder lymphadenopathy is caused by inflammation of the penis. A 4–5-week course of antibiotics will usually cause a complete regression of lymphadenopathy in the latter group. If lymphadenopathy persists after antibiotic treatment

bilateral lymphadenectomy is advised, provided chest X-ray and abdomino-pelvic CT or MRI scans are normal, as this may be curative. If the patient is not fit for this procedure radiotherapy to the nodes is an alternative.

If nodes are fixed to the superficial and deep layers, inguinal lymphadenectomy is not advised as surgical excision may be difficult and incomplete, resulting in a high rate of morbidity. These patients should be treated with chemotherapy and, if there is a response, lymphadenectomy may be performed.

TABLE 2.
Tumour, node, metastasis (TNM) classification of penile cancer

Primary tumour (T) TX	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
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastases
	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
Distant metastasis (M)	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis

From American Joint Committee on Cancer (1997)

TABLE 3.
Treatment options for localized penile cancer

Carcinoma in situ	Laser ablation	
	Local excision	
	Topical chemotherapy (5-fluorouracil)	
	External beam radiotherapy	
Verrucous carcinoma	Partial penectomy	
	Total penectomy	
Squamous cell carcinoma	T1/T2 tumours*	Partial penectomy
		Laser ablation
		Yttrium aluminium garnet (YAG) or carbon dioxide laser
	T3 Total penectomy†	
	T4 Emasculation	

*Recently, more conservative surgery with maximum preservation of penile length and function has been increasingly used for the management for T1 tumours confined to the glans (Mobilio and Ficarra, 2001). These penile-sparing treatments result in less emotional impact than radical surgery but have been shown by some studies to have a high rate of local recurrence ranging from 32% to 50% (Mobilio and Ficarra, 2001). †External beam radiotherapy for T3 neoplasms has been reported to have high risk of recurrence (Fossa et al, 1987).

Non-palpable nodes

The most controversial issue is that of inguinal lymphadenectomy in patients with clinically negative nodes. Up to 20% of these patients have nodal micrometastasis and would benefit from early lymph node dissection (Mobilio and Ficarra, 2001). However, prophylactic lymph node dissection in the remaining 80% renders them liable to significant complications, including mortality in up to 3%, skin necrosis in up to 60% and lower limb lymphoedema in up to 25% (Hakenberg and Wirth, 1999). Thus in patients with clinically negative nodes the decision of prophylactic lymph node dissection is based on the pathological stage and grade of the primary tumour.

Patients with well differentiated pT1 tumours and clinically impalpable nodes have a low risk of micrometastatic node involvement and may be managed by active surveillance without lymphadenectomy. Patients with poorly differentiated and pT2–4 neoplasms have nodal micrometastases in up to 83% of cases and thus bilateral inguinal lymphadenectomy is recommended (Bouchot et al, 1997).

Metastatic disease

Success rates for metastatic disease are poor. Most treatment protocols rely on chemotherapeutic agents such as bleomycin, cisplatin and methotrexate. This may result in a 60% response rate although this is usually short-lived with a mean duration of response being 6 months (Hakenberg and Wirth, 1999).

Prognosis

The 5-year survival values are shown in *Table 4*.

FOLLOW UP

Specialist centres follow these patients according to the grade and stage of the tumour, in a multidisciplinary setting. It should include a physical examination, which in turn will dictate

TABLE 4
5-year survival figures for penile cancer

Stage at diagnosis	5-year survival
Node negative squamous cell carcinoma	65–90%
Inguinal node metastases	30–50%
Iliac node metastases	<20%
Soft tissue or bony metastases	0%

From Algaba et al (2000)

the need to perform an abdominal CT scan, inguinal MRI or a chest X-ray.

CONCLUSIONS

A better understanding of progression of penile carcinoma has led to improved survival in organ-confined disease and preservation of the penis. Unfortunately similar results have not been achieved in metastatic disease. It is expected that with advancement in chemoradiotherapy, improved survival for advanced disease will be achieved. **HM**

Conflict of interest: none.

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KEY POINTS

- Carcinoma of the penis presents as an obvious lesion, however, 50% of patients may delay seeking medical opinion up to a year from the time of initial awareness.
- Neonatal circumcision and good hygiene afford protection against penile cancer.
- Diagnosis has to be confirmed by biopsy.
- Surgery offers the best chance of cure in localized penile carcinoma.
- The rise in incidence of human immunodeficiency virus has resulted in increased cases of Kaposi's sarcoma, especially in homosexuals.
- Chemoradiation is increasingly being used to control localized disease in order to preserve organ function.
- The advancement in chemoradiation therapies is expected to result in better prognosis for patients with carcinoma of the penis.