Modern management of penile cancer

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1. Introduction

Multidisciplinary management is the standard of care for common cancer subtypes, and it is particularly important for rare cancers such as penile cancer. Often clinical expertise may have to be concentrated into defined regional or supra-regional cancer centres; thus patients may have to be treated at centres distant from their home town. For comprehensive management of the needs of penile patients, close communication is needed between the specialist cancer teams and local medical services, including community support services, particularly in the aftercare of surgery, for follow-up and in the palliative management of end-stage disease.

2. Background (epidemiology, incidence, path and biology)

Penile cancer is relatively rare, representing about 0.5% of male cancers. It has an incidence in Western societies estimated at 1:100,000 [1]; a higher incidence is reported in non-Western societies such as South America, Africa (particularly Uganda) and Asia. Whilst it is more prevalent in older men, about 25% of cases are found in men younger than 40 years of age and about 10% in men under 30 years of age [2].

Predisposing factors include both cultural and religious practices as well as social and hygienic habits [3]. Of these, circumcision in newborns and before puberty, together with good hygiene, is associated with a reduced risk (by 3–4-fold) of penile cancer. Other risk factors include smoking [4], phimosis, inflammatory conditions such as lichen sclerosus or balanoposthitis, ultraviolet radiation [5] and the presence of human papilloma virus (HPV) that is related to sexual promiscuity. However, there is no clear evidence yet that the presence of HPV in penile cancer confers a worse prognosis [6], but rather that it may predict a favourable outcome [7].

The major histopathological subtype is squamous-cell carcinoma (SCC), and this entity represents 95% of penile cancers. Other subtypes include melanoma and basal-cell carcinoma. Herein we will concentrate on malignant SCC of the penis. It has been reported that penile SCC may demonstrate four different patterns of growth [8] differing in natural history and prognosis [9]: superficial spreading, vertical growth, verrucous growth and multicentric growth. This will be relevant to surgical management to ensure that any surgical resection adequately encompasses the potential patterns of spread.

3. TNM (primary tumour, regional nodes and metastasis) classification

The 2009 TNM classification listed in Table 1 has provided an update for the T1 category but still suffers from limitations in the T2 category, where corpus spongiosum involvement has been reported to be associated with a better prognosis than corpora cavernosa involvement [10]. Another limitation of the current TNM system is the lack of differentiation between T2 and T3 disease. One improvement is that the identification of retroperitoneal nodal disease is now accurately regarded as extra-regional disease or distant metastasis (M1).

4. Prognostic factors

Early diagnosis and adequate staging is crucial to ensure that management is organised appropriately. Full examination of the penis and particularly of the surrounding nodal drainage regions is needed, as the primary drainage of the penis is into the inguinal nodes. In the clinically negative inguinal the use of ultrasound may identify suspicious nodes suitable for fine-needle aspiration (FNA). Recent advances and improved techniques

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Table 1 – TNM classification of penile cancer.

T	**Primary tumour**
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 Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)
	T1b Tumour invades subepithelial connective tissue without with lymphovascular invasion or is poorly differentiated or 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 metastasis
pN	**Regional lymph nodes**
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node
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
G	**Histopathological grading**
GX	Grade of differentiation cannot be assessed
G1	Well-differentiated
G2	Moderately differentiated
G3–4	Poorly differentiated/undifferentiated

* Ref. [20]

for sentinel-node biopsy have provided better identification of the relevant inguinal node(s) and have permitted extraction of the node for full histological evaluation compared with the limitations of using FNA.

5. Clinical presentation and diagnosis

It is important to make a detailed examination of the penis with attention to the dimensions and location of the lesion and its relationship to the musculature of the penis. A deep biopsy is needed in equivocal cases, with dorsal slitting if there is a tight phimosis. Full assessment of the regional drainage regions, i.e., inguinal, is mandatory. If there are palpable nodes, then an FNA with or without ultrasound guidance should be undertaken. Further staging of the pelvis and abdomen will be needed using a computed tomography (CT) scan of the thorax, abdomen and pelvis. The role of magnetic resonance imaging (MRI) and positron emission tomography (PET) staging has not been fully established and remains under investigation. In clinical cases of negative inguinal nodes, where there is moderate to high risk of nodal involvement ($\geqslant$T1 G2), then dynamic sentinel node examination should be undertaken. The management schema described herein provides the policy guidelines followed within our supra-regional centre, one of the largest services within the United Kingdom.

6. Management of primary disease

Ta lesions are treated conservatively, usually with circumcision for lesions located over the prepuce, whilst lesions on the glans can be treated using a wide local excision for smaller lesions, or for larger lesions a total glans resurfacing or glansectomy.

T1 lesions of the prepuce are treated with circumcision, while lesions on the glans can be managed by either penis-preserving surgery or radiotherapy. Penis-preserving surgery may utilise a wide local excision that may include skin grafting or glansectomy and skin grafting. Radiotherapy may be delivered using external-beam irradiation or brachytherapy which is the implantation of radioactive wires within the vicinity of the extent of the lesion.

T2/T3 lesions of the penis can also be treated conservatively with surgery if there is only distal involvement of the glans and/or corporal heads, but frozen sections of the resection margins are needed to ensure adequacy of surgical clearance. The penis-preserving surgical methods include glansectomy and skin-graft reconstruction, or glansectomy and distal corporectomy and reconstruction. If clinically appropriate, penis preservation may also be considered for proximal lesions. In these cases, delayed reconstruction with a penile lengthening procedure may be considered. If penis preservation surgery is not possible, then another alternative

is to use radiotherapy as described above, or radical penectomy with perineal urethrostomy.

T4 lesions of the penis often require multimodal therapy for adequate local control. Down-staging with neo-adjuvant chemotherapy should be considered. The standard chemotherapy is usually a platinum-based regimen, often in combination 5-fluoro-uracil (5-FU) or capecitabine. The surgery is a penectomy with perineal urethrostomy. Alternatively, radiotherapy can be considered for local control in selected cases.

7. Management of the regional nodes

7.1. *Clinically node negative at presentation*

G1 Ta to T1 disease: in these cases, those patients with a negative ultrasound and FNA are at very low risk of nodal disease and they can safely be observed.

G2 T1 lesions and above or T2 lesions G1-3: those patients with both a negative ultrasound FNA and dynamic sentinel node study are managed with surveillance. The surveillance programme involves clinical 2-monthly follow-up for the first year, 3-monthly follow-up for the second year and 4-monthly follow-up for the third year. During each follow-up visit, a full physical examination of the region is conducted, with ultrasound examination of the inguinal regions. A CT scan is undertaken only where there are specific clinical indications. For patients in whom the ultrasound FNA or dynamic sentinel node study is possible, then a modified radical inguinal node dissection will be performed on the ipsilateral side, with observation of the contralateral inguinal region. In these cases, all patients should have a staging CT scan of the thorax, abdomen and pelvis as a baseline, and this should be repeated every 6 months for 3 years.

7.2. *Clinically node positive at presentation*

Those patients with clinically positive nodal disease should receive a modified radical inguinal-node dissection on the ipsilateral side and a dynamic sentinel-node study on the contralateral side. Baseline CT staging is also needed, with any other imaging based on clinical indications.

Those patients who have been found to have extracapsular disease involvement should be offered postoperative radiotherapy to the ipsilateral region. For patients with multiple or bilateral superficial nodes, then bilateral inguinal-node dissection should be performed with consideration of pelvic nodal dissection. Postoperative radiotherapy should be offered in the presence of extracapsular disease involvement of the inguinal or pelvic nodal regions. Alternatively, if pelvic-node dissection cannot be undertaken, then external-beam radiotherapy can be used to cover the regions of risk together with the inguinal regions of extracapsular disease involvement. If there is large-volume pelvic disease then consideration should be directed towards combination therapy using chemo-radiation to the pelvis followed by consolidation chemotherapy or initial chemotherapy followed by chemo-radiation to the pelvis. There are currently no evidence-based data on the most suitable management course or sequence of therapies in these cases.

Chemotherapy for node-positive or high-risk disease is not given routinely. Where possible, recruitment into clinical trials of adjuvant therapy is strongly encouraged.

7.3. *Fixed or fungating inguinal nodes*

In this situation, palliative inguinal-node dissection with appropriate covering flaps undertaken by a supporting plastic surgery team should be considered. External-beam radiotherapy may also be used postoperatively if there is extensive residual disease or as monotherapy for symptomatic palliative intent.

7.4. *Metastatic disease*

The common sites of metastatic penile cancer disease are in the lungs, liver or nodal regions outside of the pelvis. The aim of palliative chemotherapy is to limit disease progression and to improve symptoms with the aim of maintaining a good quality of life for a good duration. Chemotherapy regimens are usually platinum-based (cisplatin or carboplatin, depending on renal clearance) in combination with either capecitabine or 5-fluorouracil. Other regimens include the combinations of carboplatin, methotrexate and bleomycin if fluoropyrimidines are contraindicated for cardiovascular disease. Alternatively taxane-containing regimens have been used. For localised metastatic lesions, palliative radiotherapy is effective in reducing painful symptoms.

8. Palliative care

Palliative care is an important aspect of management that requires multidisciplinary input as outlined in the introduction. Integrated coordination between cancer teams and local support teams is vital and should be initiated early in the course of management.

9. Conflict of interest statement

The author has disclosed no conflict of interest for this body of work.

For further reading, please see references [11–19].

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