London Cancer
Guidelines for referral, investigation and management of cancer of the penis
Supra-Network MDT for Penile Cancer Covering London Cancer, Surrey, West Sussex & Hampshire

MAY 2014
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1. Introduction

1.1. Incidence

Cancer of the penis is rare, accounting for 0.4-0.6% of male malignancies, and with an incidence of 1 in 100,000 and around 300 new cases/year in England and Wales.

The rarity of penile cancers means there are very few prospective clinical trials investigating the management of such tumours. Retrospective patient series provide important data on which to base management guidelines.

1.2. Histology

The majority of invasive cancer of the penis is squamous carcinoma. A substantial minority of penile cancers are of the verrucous subtype. This has a better prognosis and may be suitable for a more conservative management policy. Rarer histology includes basal cell carcinoma, melanoma and neuroendocrine cancer. Such tumours should be managed along guidelines described for those cutaneous tumours in other sites, with modifications accounting for location.

1.3. Aetiology

Human Papilloma virus (HPV) has a strong association with both invasive squamous carcinoma of the penis and with carcinoma-in-situ. Certain serotypes (notably HPV16) seem to exert transforming oncogenic potential. Research is ongoing and one subsidiary function for the supra-regional MDT is to support such work, where possible.

Cancer of the penis is less prevalent among populations most of whose males are circumcised. This is believed to be related to the carcinogenic properties of smegma. Skin diseases that are associated with cancer of the penis include Lichen Planus, Lichen Sclerosus, Balanitis xerotica obliterans and the frankly pre-malignant conditions Bowen’s Disease and Erythroplasia of Queyrat (collectively Carcinoma-in-Situ).

1.4. Staging

Two systems are in common usage: the TNM staging system (that will be used by the MDT) and Jackson’s Stage, an older classification used in many reports.

1.4.1. Jackson’s Staging

Stage I  Tumour confined to glans or prepuce
Stage II Invasion into shaft or corpora; no nodal or distant metastases
Stage III Tumour confined to penis; operable inguinal nodal metastases
Stage IV Tumour involves adjacent structures; inoperable inguinal nodes and/or distant metastatic disease

1.4.2. TNM Staging system for penile cancer primary tumour

Tx  Primary tumour cannot be assessed
To No evidence of primary tumour
Tis Carcinoma in situ
Ta Non-invasive verrucous type carcinoma
T1 Tumour invades sub-epithelial connective tissue
T2 Tumour invades corpus cavernosum and spongiosum
T3 Tumour invades urethra or prostate
T4 Tumour invades other adjacent structures

Regional lymph nodes
Nx Regional lymph nodes cannot be assessed
No No regional lymph node metastasis
N1 Metastasis in a single superficial inguinal node
N2 Metastasis in multiple or bilateral single superficial inguinal nodes
N3 Metastasis in deep inguinal or pelvic node(s), unilateral or bilateral

Distant metastasis
Mo No distant metastasis
M1 Distant metastasis

1.5. Prognostic factors

1.5.1. Histology

Several series have demonstrated a better outcome for verrucous histology compared to squamous differentiation, with lower rates of lymph node metastases, distant metastases and greater median survival.\(^2,3,20\)

Reports vary over the prognostic significance of grade. It fails to emerge as an independent prognostic factor, but poorer differentiation does predict for lymph node involvement (see below).\(^3,21-23\)

Vascular invasion has been reported as having prognostic significance, but this probably relates to its influence on lymph node disease.\(^23\)

1.5.2. T Stage

Both T stage and size are prognostic factors for lymph node involvement\(^23\) but do not remain as independent factors when N stage is taken into account.\(^21\) Similarly, depth of invasion has been described as a prognostic indicator, but this has not been separated from its influence on nodal metastases.\(^24\)

1.5.3. N Stage

Locoregional lymph node status is regarded as the single most significant prognostic factor for invasive squamous carcinoma.\(^25,26\) Univariate analyses overwhelmingly confirm the negative impact of lymph node disease and, unusually, it remains significant in multivariate analyses. Many factors which lose their significance in multivariate analyses do so because they influence the likelihood of lymph node diseases.\(^23,27\)
1.5.4. Molecular markers

HPV positivity does not seem to confer adverse prognosis, in spite of its pathogenic role. Immunoreactivity for p53 is an independent predictor of poor prognosis in multivariate analysis.

1.6. Management overview

Carcinoma-in-situ may be treated with topical agents (typically 5FU), by laser therapy, or by local excision (including Mohs micrographic surgery).

Stage I/pT1No tumours are suitable for conservative treatment with wide local excision. Laser therapy may be suitable for some tumours.

Tumours involving the corpora are usually treated by partial penectomy. Radiation therapy is an acceptable alternative for selected patients, although not routine treatment in this supra-network.

Locally advanced disease requires radical treatment, usually total or partial penectomy.

The management of clinically involved lymph nodes should be node dissection where possible. The investigation and management of clinically uninvolved lymph nodes may involve sentinel lymph node biopsy (the technique referred to as "dynamic sentinel lymph node biopsy" in some reports).

Distant metastatic disease is incurable. Patients may benefit from palliative chemotherapy. The most active agents studied are methotrexate and cisplatin.

Verrucous Carcinoma of the Penis is a distinct clinical entity with a favourable prognosis. It is suitable for conservative therapy including cryotherapy, laser therapy, interferon and local excision.

Management of all patients should be discussed in the forum of the MDT.
2. Referral

2.1. Sources of referral

It is envisaged that referral to the Supranetwork MDT will be via local network MDTs.

The majority of referrals will be from urologists, but other clinicians to whom patients with cancers of the penis may present include dermatologists, genitourinary physicians, plastic surgeons and general surgeons. Guidelines for referral will be distributed to all these specialties throughout the networks contributing to the supranetwork MDT.

The cancer services manual requires a named member of each contributing network to be designated as a core member of the supranetwork MDT.

The liaising members of London Cancer to the Supranetwork MDT will be Dr S Nicholson (Medical Oncology), Mr G Moir (Plastic Surgery), Mr A Muneer and Mr D Ralph (Urology/Andrology).

Liaising members of Surrey, West Sussex and Hampshire will be Mr R Nigam (Urology).

2.2. Referral procedure

Most patients will have undergone biopsy at a local/network level. Referral to the Supranetwork Team (SNT) should ideally be made via a standard pro-forma that will be made available to all referring MDTs. The referral form will be provided in both hard copy and electronic formats. Referral by fax or email is to be encouraged in order to expedite review.

Minimum data required for referral are as follows:

- NHS Number
- Name
- Hospital Number (for referring hospital) Birthdate
- Referring clinician and GP
- Histology (if biopsy has been performed) Imaging (if any)

The outcome of the SNT discussion and the management plan for the patient will be communicated to the referring clinician and to the GP, along with all other clinicians involved in the care of the patient where these are known.

Patients with suspected penile cancer may be referred directly to the SNT prior to biopsy. Initial biopsy of the lesion may be undertaken at local level before referral.

All patients with histologically-proven penile cancers must be reviewed at the SNT.
<table>
<thead>
<tr>
<th>THE SUPRANETWORK MDT Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Consultant Urologists</td>
</tr>
<tr>
<td>Consultant Pathologist</td>
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<tr>
<td>Consultant Radiologist</td>
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<tr>
<td>Consultant Clinical Oncologist</td>
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<tr>
<td>Consultant Medical Oncologist</td>
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<tr>
<td>Consultant Plastic Surgeon</td>
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<tr>
<td>Clinical Nurse Specialist</td>
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<tr>
<td>MDT Co-ordinator</td>
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</table>

The SNT will meet at least monthly. The venue will be UCLH. Corresponding members of all contributing networks will be notified one week prior to the meeting, with a list of patients to be discussed being circulated.
3. Staging Investigations

3.1. Examination

Physical Examination should include a record of the site and size of the primary tumour, the presence of satellite lesions and the presence or absence of palpable inguinal lymphadenopathy.

3.2. Biopsy

Biopsy of the primary lesion may be performed locally or at an agreed site after discussion at the SNT.

3.3. Imaging

A Chest X ray is required for all patients. The imaging modality of choice for staging of the primary lesion and loco-regional nodes will be MRI for this Supranetwork Team\textsuperscript{29,30} MRI of the penis following intra-cavernosal injection of prostaglandin E1 can be arranged via the SNT.

3.4. Staging of Locoregional Lymph Nodes

Sentinel Lymph Node Biopsy (also known as “dynamic sentinel lymph node biopsy) is an appropriate staging procedure for patients with intermediate and high-risk tumours as defined by the EUA guidelines.\textsuperscript{31}

This would include:

- All G3 tumours,
- G2 tumours that are T1 or greater
- G1 tumours that are T2 or greater

SNLB is available through the NELCN and can be performed at the time of Wide Local Excision.

Palpable lymphadenopathy is traditionally investigated after 6 weeks of treatment with broad-spectrum antibiotics, although this has been questioned.\textsuperscript{32} Acceptable investigations thereafter are Fine Needle Aspiration or intraoperative frozen section biopsy immediately prior to planned radical lymphadenectomy.
4. Management guidelines

4.1. Carcinoma-in-Situ

4.1.1. Laser therapy

Windahl and Anderson reported recurrence in 3 of 21 patients (14%) with pTis treated with neodymium YAG laser, 2 recurring with pTis and one with pT1 disease. Van Benzooijen et al reported recurrence in 5 of 19 patients (26%) again only 1 having pT1 disease. Laser therapy with rigorous follow-up is an acceptable treatment for CIS with excellent cosmetic and functional results.

4.1.2. Topical agents

5-fluoruracil (5FU) has been employed in the treatment of penile CIS for nearly 30 years. Concerns exist with regard to its lack of penetration and its limited efficacy.

Imiquimod is a topical immune stimulant. Its efficacy in the treatment of viral genital warts led to its successful use in Penile Intraepithelial Neoplasia and Carcinoma-in-situ.

The combination of 5FU and imiquimod has been employed in the management of cutaneous (including perianal) CIS in immunosuppressed individuals. Response rates were high and relapse rates low.

There are no randomised studies on which to base guidelines for the topical management of CIS of the penis, but imiquimod alone or in combination would seem to be the agent of choice at present.

4.1.3. Surgery

Mohs micrographic surgery has been the most successful surgical technique. It allows confirmed clear resection margins and reported relapse rates are low. There may be concerns regarding cosmetic results.

4.1.4. Systemic therapy

Interferon-α administered subcutaneously has activity in PIN and verrucous penile cancer. It is not in routine use for CIS.

4.1.5. Combined modality

A large trial on the use of combined modalities in the treatment of PIN demonstrated superiority of laser ablation plus topical 5FU plus systemic interferon, with complete remission in 96% of patients.

Guidance on the management of CIS will be made on a case-by-case basis. Clinical trials are needed and entry into trial protocols will be encouraged (where available).
4.2. Verrucous Carcinoma of the Penis

4.2.1. Introduction

Verrucous carcinoma (also known by the eponym “Buschke-Lowenstein tumour”) is a less common, well-differentiated subtype of penile cancer. HPV infection is found less frequently than in CIS or invasive squamous carcinomas \(^{15,45}\) and p53 mutation is not a feature. \(^{46}\) It has a low rate of lymph node invasion and, consequently, an excellent prognosis. Occasional tumours will contain micro-foci of invasive squamous carcinoma \(^{20}\) and an invasive variant associated with HPV type 11 has been described, \(^{47}\) but these are extremely uncommon. Conservative approaches to management are therefore indicated.

4.2.2. Treatment options

- **Wide Local Excision**
- **Cryosurgery** - Debulking of tumour followed by liquid nitrogen cautery has been described since the 1970s. \(^{48}\) It may be combined with topical 5FU application. \(^{49}\)
- **Interferon-α** - intralesional and combined with local excision \(^{42,43,50}\) Methotrexate-based chemotherapy. \(^{51}\)

Treatment options should be discussed with the patient and in the SNT. Sentinel node biopsy is not indicated.

4.3. Early Invasive Squamous Carcinoma of the Penis

This encompasses Ta, T1 and T2 tumours without lymph node involvement.

4.3.1. General considerations

Early invasive cancer may be upstaged either on imaging or on sentinel lymph node biopsy (indicated for pTa tumours that are G3, pT1 tumours that are G2 or above and all pT2 tumours).

All treatment options may involve cosmetic changes, psychological morbidity and loss of sexual function. \(^{52}\)

All patients must be counselled by a dedicated Clinical Nurse Specialist before treatment.

4.3.2. Surgical options

Erectile function and cosmesis can be maintained using organ-sparing techniques, without subjecting individuals to more extensive surgery. It has been suggested that well-differentiated lesions less than 40mm in diameter may be suitable for organ conservation. \(^{53}\) A surgical margin of 10mm has been recommended as sufficient for G1 and G2 lesions, while 15mm is recommended for G3 lesions \(^{54}\)

Tumours confined to the prepuce may be treated by circumcision alone. Lesions confined to the glans may be treated by glans excision and split thickness skin grafting.
Tumours invading the corpus cavernosum or corpus spongiosum (T2) must be treated by partial penectomy combined with penile reconstruction using split thickness skin grafting. Tumours that are more proximal may require total penectomy.

4.3.3. Laser therapy

Laser ablation provides excellent cosmetic results. There are no randomised trials comparing laser therapy with conservative surgery, but authors several series claim recurrence rates equivalent to those of conservative surgery.55 The overall relapse rate is of the order of 20% and the ideal treatment strategy probably incorporates CO₂ laser ablation of the tumour followed by Nd:YAG laser coagulation to the tumour bed.

Laser therapy should be reserved for tumours less than 3cm in diameter and G1 or G2 histology.

4.3.4. Radiotherapy

Radiotherapy is an alternative to conservation surgery, with iridium-192 wire brachytherapy probably superior to external beam irradiation in terms of outcome and complications.56-58 Overall survival for first-line RT and salvage surgery where indicated is comparable to first-line surgery, but local control is inferior in non-randomised series.59 Morbidity includes urethral stenosis.

It is not the policy of this supranetwork MDT to offer radiation therapy as primary therapy for penile tumours.

4.3.5. Chemotherapy

The exact role of neoadjuvant and/or adjuvant chemotherapy remains to be determined. High response rates in small series have been claimed for neoadjuvant Cisplatin/5FU and this is the recommendation of the EAU.54 The combination of Vincristine, Bleomycin and Methotrexate has been used in both the adjuvant and neoadjuvant setting with favourable reports in unrandomised series.61 Trials of chemotherapy in both circumstances are required.

Neoadjuvant chemotherapy is an option for all patients undergoing conservative local therapy for early disease, although this is based on limited evidence.

The Supranetwork team will support trials of adjuvant and neoadjuvant therapy.

4.4. Locally Advanced Squamous Carcinoma of the Penis

This comprises pT3 and pT4 primary lesions or any pT with operable lymph node involvement (clinically or microscopically as detected on sentinel lymph node biopsy).

4.4.1. Surgical Management of the Primary Tumour

Extripation of the primary tumour may require partial penectomy, total penectomy and anything up to hemi-pelvectomy for T4 lesions. The practice of demanding a clear margin of 2cm (which may be the difference between suitability for partial penectomy and the
necessity of total penectomy) has been questioned. The EAU guidelines stress only the need for clear margins and there is evidence that margins of 10mm may suffice for G1 and G2 tumours and 15mm for G3 lesions.

Tumours may be downstaged by neoadjuvant chemotherapy (see below).

All patients who have undergone penile amputation should be offered reconstructive penile surgery using a radial artery forearm free flap.

4.4.2. Surgical Management of Locoregional Lymph Nodes

Lymph node dissection is indicated for patients with proven clinical node involvement and for patients with a positive sentinel lymph node biopsy. The operations under consideration are:

- Sentinel Lymph Node Biopsy
- Modified Inguinal Lymph Node Dissection
- Radical Inguinal Lymph Node Dissection
- Pelvic Lymph Node Dissection

**Sentinel lymph node biopsy**

It is important to emphasise that the term “Sentinel Lymph Node Biopsy” as used in this document refers to the technique of lymphatic mapping and sentinel lymphadenectomy described by Morton in 1990 and now used extensively in the staging of malignant melanoma and breast cancer. The technique of localising sentinel node(s) by infiltrating around the primary with vital blue dye and technetium-99m radiocolloid is distinct to the concept of “blind” excision of the likely sentinel node (superomedial to the sapheno-femoral junction) as popularised by Cabanas. The term “Dynamic Sentinel Lymph Node Biopsy” is often used in the literature on penile malignancy to differentiate the current technique from the older practice.

The indications for SLNB are given under “Staging Investigations,” above. Horenblas’s group has reported extensively on this procedure, and has recorded a false-negative rate of 18%. They identified a number of sources of error, however, including inadequate histological examination. They also employed the technique where unilateral clinical node involvement was obvious, and this may have altered the results.

Sentinel Lymph Node Biopsy may be offered to all patients at high risk of nodal metastases, who are clinically node negative. The procedure is available through the Dept of Plastic Surgery, St Bartholomew’s Hospital. All sentinel nodes will be examined using the same protocol employed for melanoma sentinel nodes.

**Modified inguinal lymph node dissection**

The EAU guidance recommends prophylactic bilateral superficial modified inguinal lymph node dissection for patients who are at high risk of having micro-metastasis or metastatic spread.

- pT1 G2 lesions with vascular invasion or nodular/vertical growth pattern pT1 G3 lesions
- Any pT2 lesion
Peri-operative frozen section must be performed of all lymph nodes sampled. Those patients with positive nodes on frozen section must undergo immediate radical inguinal lymph node dissection.

**Radical inguinal lymph node dissection**

Unilateral radical inguinal lymph node dissection is performed where positive unilateral inguinal nodes are identified either by Sentinel Lymph Nodes. Biopsy or by frozen section during Modified Inguinal Lymph Node Dissection. A superficial modified inguinal lymph node dissection with frozen section is recommended on the contra-lateral side.

If peri-operative frozen section of nodes is positive then a contra-lateral radical inguinal lymph node dissection must be performed.

**Pelvic lymph node dissection**

The risk of pelvic nodal involvement is approximately 30% if two or more inguinal nodes are involved. Patients who have a single nodal metastasis may be offered a pelvic lymph node dissection, subject to discussion in the supranetwork MDT.

Patients with 2 or more positive inguinal nodes should be advised to undergo pelvic lymph node dissection if medically fit.

### 4.4.3. Chemotherapy

Patients with T3 lesions, or N1 or N2 disease, are eligible for neoadjuvant chemotherapy (Cisplatin plus Irinotecan) as part of EORTC 30992. This trial is being run in London by the Dept of Medical Oncology, Barts Hospital (NELCN).

Patients with T4 or N3 lesions are eligible for the same trial, with the option of extended use of chemotherapy as the primary treatment modality.

Patients undergoing surgery without neoadjuvant chemotherapy should probably be offered adjuvant treatment, although the regimen, duration and absolute benefit have not been defined in any large clinical trial.

Neoadjuvant chemotherapy should be offered to patients with locally advanced disease. The Supranetwork team will actively support chemotherapy trials in this patient group.

### 4.5. Metastatic Squamous Carcinoma of the Penis

#### 4.5.1. Chemotherapy

Combination chemotherapy is the standard of care for patients with symptomatic metastatic disease. This is based on subjective improvements in quality of life that attend objective response. There is no good evidence of survival benefit for palliative chemotherapy, although studies are few.
Drugs with the highest response rates are Methotrexate and Cisplatin in a variety of combinations. \[60,70\]

Patients with metastatic disease will be offered chemotherapy as part of EORTC 30992 (Cisplatin + Irinotecan) where eligible.

Other combinations of chemotherapy will be offered as appropriate, recruiting to clinical trials where possible

4.5.2. **Radiotherapy**

External Beam Radiotherapy has a role in palliation of distant metastatic disease and for loco-regional control in the presence of distant metastases.

Radiotherapy will be co-ordinated through Dr H Payne, Consultant Clinical Oncologist, UCLH.

4.5.3. **Surgery**

Limited surgery may have a role in the management of loco-regional disease in the presence of distant metastases.

Reports are lacking on the use of metastatectomy as a therapeutic option for isolated distant metastases.

4.5.4. **Palliative care**

The Supranetwork MDT appreciates the importance of palliative care input, both in the community and as an inpatient. Palliative care arrangements will involve GPs, community (e.g. MacMillan) home care teams, social workers, district nurses and palliative care physicians. These will be co-ordinated by the Clinical Nurse Specialist(s) for the Supranetwork team.
5. Protocol for Patient Follow-Up

The schedule for follow-up recommended by the EAU is as follows:

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<thead>
<tr>
<th></th>
<th>Years 1 &amp; 2</th>
<th>Year 3</th>
<th>Years 4 &amp; 5</th>
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<tbody>
<tr>
<td><strong>local management</strong></td>
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<td></td>
<td></td>
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<tr>
<td>conservative therapy</td>
<td>2 monthly</td>
<td>3 monthly</td>
<td>6 monthly</td>
</tr>
<tr>
<td>partial/total penectomy</td>
<td>4 monthly</td>
<td>6 monthly</td>
<td>annual</td>
</tr>
<tr>
<td><strong>lymph node management</strong></td>
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<td></td>
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<tr>
<td>surveillance</td>
<td>2 monthly</td>
<td>3 monthly</td>
<td>6 monthly</td>
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<tr>
<td>pNo</td>
<td>4 monthly</td>
<td>6 monthly</td>
<td>none</td>
</tr>
<tr>
<td>pN+</td>
<td>2 monthly</td>
<td>4 monthly</td>
<td>6 monthly</td>
</tr>
</tbody>
</table>

Physical examination is required at each visit. The value of routine imaging (i.e. in the absence of symptoms) has not been established.

5.1. Audit and peer review

Audit of all cases will take place at least annually. One core member of each referring network will be required to review cases with at least one core member of the supranetwork team. This will ideally take place before peer review.
6. References


