University College London Hospitals NHS
NHS Foundation Trust

SUPRANETWORK MDT FOR PENILE CANCER

Network Clinical Guidelines
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Host site: UCLH

Member Networks:

London Cancer

Thames Valley Cancer Network (TVCN)

St Lukes Cancer Alliance

Guidelines have been agreed by the host network and member networks:

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1.0 Introduction

Penile cancer is a rare genitourinary malignancy and accounts for less than 1% of all male malignancies in the UK. The age standardised incidence is 1.2-1.5 per 100 000 population in England and Wales. [1] More than 95% of penile cancers are squamous cell carcinomas (SCC) with the remaining 5% comprising melanomas, sarcomas and basal cell carcinomas

There are approximately 500-600 cases of newly diagnosed penile cancer annually in the UK with University College London Hospital (UCLH) managing between 15-25% of the national workload at local, specialist and supranetwork levels. The catchment area that is currently served is approximately 10 million.

Referrals are received from referring centres listed in the Network Guidelines. The clinical management of penile cancer patients is undertaken by the core team which consists of three Consultant Urological Surgeons, namely Mr Asif Muneer, Professor Peter Malone and Mr Raj Nigam and a Clinical Oncologist Dr Anita Mitra. Professor Peter Malone is based at the Royal Berkshire Hospital, Reading and oversees referrals from the Thames Valley Cancer Network and undertakes surgery at UCLH. Mr Raj Nigam is based at Royal Surrey County Hospital, Guildford and oversees referrals from St Lukes Cancer Alliance and operates on all of the penile cancer cases at UCLH.

1.1 Facilities

The penile cancer service receives just under 100 new referrals annually, which are discussed at a weekly supranetwork MDT meeting held within the Macmillan Cancer Centre on Friday morning. Patients within the London Cancer Network are seen in the outpatient facility in the Macmillan Cancer Centre on Wednesday morning and introduced to their key worker Clare Akers (CNS).
Outpatient consultations are undertaken in parallel with the oncology clinic and there are dedicated radiology and preassessment appointments ringfenced for patients requiring urgent imaging or surgery. There are also facilities available to undertake a local anaesthetic diagnostic biopsy in the clinic. The Macmillan Cancer Centre also houses the UK's first hybrid MRI-PET scanner which is currently being used for penile cancer patients as a clinical trial at UCLH.
The Institute of Nuclear Medicine based at UCLH has multiple Gamma Cameras for lymphoscintigraphy and undertakes SPECT and SPEC-CT imaging for patients undergoing dynamic sentinel lymph node biopsies.
The Macmillan Cancer Centre also provides the venue for a monthly Penile Cancer Support Group which is open to all men diagnosed with penile cancer.
Patients within the Thames Valley Network undergo initial consultations at the Royal Berkshire Hospital with Professor Malone in a penile cancer clinic and those referred from the St Lukes Cancer Alliance have their initial consultation with Mr Nigam at Royal Surrey County Hospital. Any new patients or patients presenting with recurrent disease are then discussed at the Friday SNMDT. Surgery is then performed at the host trust (UCLH). Local follow up post operatively is organized at Royal Berkshire Hospital or Royal Surrey Hospital.

All patients undergo their primary penile and reconstructive surgery in addition to any inguinal/pelvic lymph node surgery within the host trust, University College London Hospital, under the direct clinical care of Mr Asif Muneer and two in-reach surgeons Mr Raj Nigam and Professor Peter Malone.

2.0 Referral Guidelines

2.1 Role of Diagnostic Penile Biopsy

Although not mandatory patients may have already undergone a penile biopsy at a local/network level; although not all patients are required to have this performed if there is a strong clinical suspicion of cancer in order to avoid a delay in referral.
Where there is an obvious penile malignancy, patients should be referred immediately without the need for a biopsy in order to avoid delay in the pathway.

2.2 Referral to the SNMDT

Referral to the Supranetwork Team (SNT) is made via either a standard pro-forma that is available to all referring MDTs or by using an urgent referral letter faxed to UCLH (contact details in Appendix A, page 26).

Referring hospitals linked with designated Specialist Centres in their Networks (Thames Valley Cancer Network and St Lukes Cancer Alliance) will refer to these centres in order to facilitate an urgent outpatient consultation and local follow-up arrangements.

Currently all referrals to the SNMDT occur via local network MDTs. The majority of referrals are from urologists, but allied specialties to whom patients with penile cancer may also present include dermatologists, genitourinary physicians, plastic surgeons and general surgeons. Guidelines for referral have been distributed to all of these specialties throughout the networks contributing to the SNMDT.

Referral by fax or email is sent to the SNMDT Coordinator or the Key Worker and Penile Cancer Nurse Specialist (Clare Akers). Other referrals are co-ordinated via the PA of the SNMDT Chair in order to expedite review. Contact details for all of these are added to the appendix.

2.3 Patient data and clinic booking

Both the penile cancer CNS and the SNMDT coordinator are responsible for co-ordinating the booking of patients into the dedicated penile cancer clinic, liaising with the referring network and patients and ensuring appropriate imaging and pathology is available to the SNMDT ready for review by the specialist pathologists and radiologists.

The minimum data required for referral are as follows:

- Demographics: Name, Date of Birth, Address, Patient Contact Telephone number (mobile number and landline)
- Hospital Number (for referring hospital)
- Name and contact of referring clinician and details of the patients' GP
- Histology result (if biopsy has been already performed)
- Imaging results (if any)

2.4 **Cases requiring SNMDT referral**

The histology and imaging if performed locally is sent to the SNT prior to discussion at the SNMDT meeting. All patients with histologically -proven penile cancers, suspected primary

distal urethral cancer and penile carcinoma *in situ* must be referred and reviewed at the SNMDT and the histology sent to the specialist uropathologists at UCLH for a formal review.

As the SNMDT for UCLH covers a large geographical network of hospitals, it has been agreed that in order to minimise travelling for patients and undue distress for family members, specific surgical procedures such as diagnostic biopsies may be carried out at the local referring hospital. The procedures can only be carried out if agreed at the SNMDT and the operating surgeon has the appropriate training and skills. Any complex case still requires surgery to be performed at UCLH:

3.0 Histological Subtypes of Penile Cancer

Most tumors affecting the penis are primary squamous cell carcinomas (SCC) arising in the epithelium lining the glans, coronal sulcus and prepuce. Glans tumors represent just over 80% of all cases, followed by those exclusive to the foreskin (15%) and coronal sulcus (5%)[2].

Other rare subtypes of penile primary tumours which may present on the glans or penile shaft include basal cell carcinoma, malignant melanoma and sarcomas. Metastatic disease, mainly from primary tumors originating in the genitourinary system (prostate and bladder) and lower digestive tract present infrequently.

The majority of invasive cancers of the penis are squamous cell carcinomas with SCC usual subtype comprising 55-65% and verruciform carcinomas, representing 19-28% of all penile SCC. These are further subdivided into good prognosis subtypes (eg verrucous, warty, papillary) and poor prognosis subtypes (eg basaloid, sarcomatoid)[2,3].

The rarer penile malignancies (melanoma, sarcoma and neuroendocrine cancer) [4-11] should be managed along guidelines described for cutaneous tumours in other sites, with modifications accounting for the location of the tumour. Sarcomas of the penis are managed jointly with the London Sarcoma Centre at UCLH and melanoma are discussed at the melanoma MDT at the Royal Free Hospital.

4.0 Aetiology of Penile Cancer

Penile cancer is uncommon amongst populations where male circumcision is routinely practiced confirming that the presence of a foreskin is a major risk factor for penile cancer. Human Papilloma virus (HPV) (high risk HPV subypes - HPV 16 and 18) has a strong association with both invasive squamous cell carcinoma of the penis and with carcinoma-in-situ [12-16]. The other HPV subtypes include low risk HPV 6, 11 which are associated with giant condylomata acuminate (GCA) or Buschke-Lowenstein tumours. . The risk factors for penile cancer and pre-malignant disease are listed in Table 1.

Phimosis
HPV infection
Smoking
Age
PUVA photochemotherapy
HIV infection
Lichen sclerosus
Genital warts
Penile injury

Table 1 – Risk factors for penile cancer and pre-malignant disease

Genital skin disorders such as lichen sclerosus et atrophicus otherwise known as balanitis xerotica obliterans (BXO) is also associated with penile cancer although there is still debate as to whether it is an association or a pre-malignant condition.[17, 8, 19]. However, it does appear that a subset of invasive disease is either HPV driven and another subset is lichen sclerosus related.

Pre-malignant conditions are epononymously referred to as Bowen's Disease which is Carcinoma-in-Situ (CIS) limited to the penile shaft skin and Erythroplasia de Queyrat which is CIS limited to the glans penis and inner prepuce. Histologically these lesions are classified as diagnose PeIN III. The progression to invasive disease varies and occurs in up to 30% of CIS cases. Bowenoid papulosis is an HPV related premalignant condition which is limited to the penile shaft skin and infrapubic skin.

5.0 Staging

The following TNM staging system is currently used in the SNMDT:

5.1 TNM Staging system for penile cancer 2009

A Primary tumour

Tx: Primary tumour can not be assessed

Tis: Carcinoma in-situ

Ta: Non-invasive verrucous carcinoma, not associated with destructive invasion

T1: Invades subepithelial connective tissues

T1a: without lymphovascular invasion and is not poorly or undifferentiated

(T1G1/2)

T1b: with lymphovascular invasion or poorly or undifferentiated (T1G3/4)

T2: Invades corpus spongiosum/cavernosum

T3: Invades urethra

T4: Invades adjacent structures

B. Regional lymph nodes

Nx: Regional lymph nodes can not be assessed

N0: No regional lymph node metastasis

N1: Intra-nodal metastasis in single inguinal lymph node

N2: Metastasis in multiple or bilateral inguinal lymph nodes

N3: Metastasis in pelvic lymph node(s), unilateral or bilateral or extra-nodal extension of regional lymph node metastasis

C. Distant metastasis

Mx: Distant metastasis con not be assessed

M0: No distant metastasis

M1: Distant metastasis

Histopathological grading

Gx Grade of differentiation cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3-4 Poorly/undifferentiated

6.0 Prognostic Factors

6.1 Histology

The prognostic significance of the histological grade is still uncertain. Although grade in itself is not an independent prognostic indicator, poorly differentiated lesions are associated with an increased risk of metastatic disease in the lymph nodes as well as lymphovascular invasion (see below) [3, 21-23]. Although a number of predictive nomograms have been developed previously in order to predict inguinal lymph node involvement, these have been found to be unreliable and therefore have not been adopted universally.

6.2 T Stage

Both the T stage and the size of the primary tumour 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].

6.3 N Stage

Penile SCC is known to have a step-wise lymphogenic spread prior to haematogenous dissemination. The primary draining lymph nodes are located within the inguinal region and further dissemination continues to the pelvic nodes before distant sites. Locoregional lymph node status is regarded as the single most significant prognostic factor for invasive penile SCC [25,26].

6.4 Molecular Markers

The prevalence of HPV DNA in penile carcinoma ranges between 20-80% and varies depending on the methods utilised for the detection of HPV. Basaloid and warty subtypes are almost always associated with HPV as is carcinoma in situ (90%) which is in contrast to keratinising and verrucous tumours where only one third of the tumours are associated with HPV.

Studies have now shown that both HPV dependent and independent tumours occur with conflicting evidence regarding tumour progression and prognosis. A number of other molecular markers have been proposed and summarised in Table 1.

Marker	Lymph Node Status	Survival
HPV	Contradictory evidence. Probable link with high risk HPV	Majority of studies show no correlation
p53	Unclear relationship to lymph node status	Correlates with survival in T1 lesions only
$P16^{INK4a}$	Not established	Not established

SCC Antigen	Correlates with macroscopic lymph node involvement	No role
Ki-67	Predicts increased risk	No role
E-Cadherin	Low expression associated with lymph node involvement	Low expression predicts poorer survival
MMP-9	No role	High expression predicts recurrence

7.0 Management of Penile Cancer

7.1 Staging Investigations

7.1.1 Examination

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

7.1.2 Biopsy

Biopsy of the primary lesion may be performed locally or at an agreed site after discussion at the SNMDT. However, where there is a clinically obvious penile tumour, patients should be referred directly to the SNT without a biopsy in order to avoid any delay in the treatment pathway. (see 2.1)

7.1.3 Imaging

All newly diagnosed cases of penile cancer require a staging CT to include the chest, abdomen and pelvis. The imaging modality for staging of the primary lesion is MRI or USS (with the use of intracavernosal injection of alprostadil)[29,30]. MRI of the penis following intra-cavernosal injection of prostaglandin E1 (alprostadil) can be arranged via the SNT. Alternatively an ultrasound of the penis following alprostadil injection can be performed for lesions which are clinically confined to the glans penis in order to exclude involvement of the distal corpus cavernosum and assists in the planning of surgery.

Patients requiring imaging of the penis include those with extensive corpus cavernosum involvement in order to detect skip lesions proximally, those with suspected primary urethral tumours, and those with extensive glans tumours in order to exclude distal corpus cavernosum involvement.

Tumours limited to the foreskin or small glans lesions do not require MRI or USS imaging of the penis.
Patients with clinically impalpable inguinal lymph nodes(cN0 disease) also undergo a preoperative ultrasound of the inguinal lymph nodes and a fine needle aspiration (FNA) of morphologically abnormal lymph nodes.

The cytology result is reviewed before deciding on the management of the inguinal lymph nodes in order to identify those patients suitable for dynamic sentinel lymph node biopsy where the FNA is negative or those requiring a radical inguinal lymphadenectomy where the FNA is positive for SCC.

7.2 Management of carcinoma *in situ*

- Carcinoma *in situ* is a significant risk factor for invasive SCC. There is a risk that 28% of patients will be understaged due to inadequate biopsies being performed. Therefore patients with carcinoma *in situ* should be referred and reviewed at the SNMDT and recommendations recorded on the proforma. Guidance on the management of CIS will be made on a case-by-case basis and the medical treatment is supervised by Professor Chris Bunker.

- Patients with premalignant lesions should undergo a diagnostic biopsy from multiple sites ensuring that the biopsy is deep enough to include the lamina propria. This should be combined with a circumcision if this has not already been performed.

- Biopsies confirming carcinoma *in situ* should be reviewed by the specialist uropathologists at the SNMDT

- Carcinoma-*in-situ* may be treated with topical therapy (typically using topical 5-FU or imiquimod), salicylic acid or curettage and cautery or cryotherapy or by surgical excision of the area combined with circumcision. 5-fluoruracil (5-FU) has been employed in the treatment of penile CIS for a number of years[35].

- Imiquimod is an alternative topical immunotherapy and is used as second line treatment if topical 5-FU has failed. The combination of 5FU and imiquimod has been employed in the management of cutaneous (including perianal) CIS in immunosuppressed individuals[39,40].

- Although laser therapy with rigorous follow-up has been used for CIS in a small number of centres, this is not routinely offered as standard management at UCLH due to the high recurrence rates and the possibility of patients harbouring an invasive lesion. Previous reports from Windahl and Anderson reported a recurrence in 3 of 21 patients (14%) with CIS treated with neodymium YAG laser, 2 recurring with CIS and one with pT1 disease[33]. Van Benzooijen et al reported recurrence in 5 of 19 patients (26%) again only 1 having pT1 disease[34].

- Treatment failures using topical 5-FU or Imiquimod can undergo surgical excision of the lesion by undergoing a glans resurfacing procedure. The cosmetic results are excellent and the procedure also allows histological analysis of the tissue in order to exclude an invasive component.

7.3 Management of primary penile tumours

The surgical management of primary penile tumours and distal urethral tumours involves excision of the tumour for oncological control whilst minimising anatomical and functional disruption. Maintaining erectile function and the ability to stand up and void can be maintained using penile preserving techniques.

Previous studies reported that well-differentiated lesions less than 40mm in diameter may be suitable for penile preserving surgery[53]. Following this a surgical margin of 10mm was deemed sufficient for G1 and G2 lesions, whilst a 15mm margin was recommended for G3 lesions[54].

In organ-preserving surgery smaller margins have been shown to be safe provided that patients are monitored closely due to the higher local recurrence rate. However, in the presence of a local recurrence, further surgery for recurrent lesions does not change the long term prognosis.

Distal primary urethral tumours are invariably SCC histologically and are managed using a similar protocol to primary penile SCC. However, proximal urethral tumours are rare and may be adenocarcinomas or SCC and require more extensive surgery together with neoadjuvant and adjuvant chemotherapy regimes which are discussed on a case by case basis.

7.4 Management of early invasive penile cancer

This includes any invasive lesion confined to the glans, foreskin and penile shaft skin without palpable inguinal lymph nodes.

7.4.1 Management of T1 lesions

- T1 tumours are suitable for penile preserving surgery. Depending on the size of the lesion and the location of the lesion, a wide local excision or glansectomy combined with a split skin grafting can be performed both of which also require removal of the foreskin. If the lesion is confined to the foreskin then a radical circumcision can be performed ensuring clear margins.

7.4.2 Management of T2 lesions

- T2 tumours with invasion into the corpus spongiosum and limited to the glans penis can be treated by performing a glansectomy and split skin graft. If the tumour is limited to the coronal margin then a partial glans excision followed by close surveillance can also be offered.

- Tumours invading the distal corpus cavernosum are usually treated by glansectomy and distal corporectomy although more proximal involvement requires a partial penectomy. Where there is a suspicion of distal corpus cavernosum involvement, on table frozen section analysis of the proximal margin should be undertaken.

7.5 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).

7.5.1 Surgical Management of the Primary Tumour

- Tumours invading the proximal corpus cavernosum are treated either by performing a partial penectomy (with or without a split thickness skin graft) if there is enough penile shaft to allow voiding standing up. More extensive lesions should undergo a total penectomy and perineal urethrostomy.

- Rare tumours of the anterior urethra can invade into the glans penis and are managed surgically by performing a glansectomy and surgical excision of the anterior urethra. The inguinal lymph nodes are managed using the same protocol as for penile cancer. Primary urethral SCC which is not invading into the glans penis can be managed by performing a distal urethrectomy and either primary glans closure with the formation of a hypospadiac urethral opening or by leaving the glans bed open and using a buccal mucosal graft which can be closed after 6 months.

- Posterior urethral tumours are rare and carry a poor prognosis. Histologically they may be a squamous cell carcinoma, transitional cell carcinoma or an adenocarcinoma. These are discussed at the SNMDT with the management planned on a case by case basis. The management of posterior urethral tumours includes neoadjuvant chemotherapy followed by surgical excision of the tumour which may involve a pan-urethrectomy, prostatectomy and bladder neck closure followed by reconstruction using a Mitrofanoff procedure to allow self catheterisation.

7.5.2 Penile Reconstruction

Patients who have undergone total/subtotal penile amputation are offered reconstructive surgery using a radial artery forearm free flap or ALT flap to create a neophallus. Patients are assessed for this procedure by the extended team (under the supervision of Mr David Ralph) after a period of close surveillance provided that there is no evidence of disease recurrence.

7.5.3 Advanced or inoperable T4 penile lesions

Radical penectomy and formation of perineal urethrostomy is usually the only option. Down staging with neoadjuvant chemotherapy should be considered on a case by case basis. The standard regimen is cisplatin and 5-FU (see appendix for details). In selected cases radiotherapy can be considered for local control after discussion between the Clinical Oncologist and Urologists in the SNMDT.

7.6 Management of Inguinal Lymph Nodes

7.6.1 Management of clinically impalpable inguinal lymph nodes

In patients with ≥ T1G2 disease and clinically impalpable inguinal lymph nodes (cN0), Dynamic Sentinel Lymph Node biopsy (DSNB) is undertaken.

If the histopathological examination of the sentinel lymph node shows the presence of metastatic disease then the patient must undergo a radical inguinal lymphadenectomy on the side where the sentinel lymph node contains metastatic disease. Where possible the sentinel lymph node biopsy should be performed at the same time as the surgery for the primary penile cancer.
In cases where there are impalpable inguinal lymph nodes and the patient is unsuitable for DSNB or has had previous non visualisation following a previous DSNB then a superficial modified inguinal lymphadenectomy is performed with an on table frozen section analysis. If the frozen section reveals metastatic disease then the patient should undergo a radical inguinal lymphadenectomy.
DSNB, is an appropriate staging procedure for patients with intermediate and high-risk tumours as defined by the EAU guidelines[31,] This would include:

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

DSNB is performed at UCLH radionuclide injection and preoperative imaging located in the Institute of Nuclear Medicine (Tower 5^{tth} Floor) . Although the procedure may be performed as a delayed procedure in patients who have already undergone the primary penile surgery, it is our policy to offer the procedure at the time as the surgery for the primary lesion. Injection of 99mTc nanocolloid radioisotope is normally performed on the morning of surgery and the operation performed on the afternoon of the same day. The injection can also be performed the day before surgery (double dose of radioisotope) with the operation taking place early the next day

7.6.2 Management of palpable inguinal lymph nodes

Patients with palpable inguinal lymph nodes (cN+) require a radical inguinal lymphadenectomy provided that the radiological features support metastatic disease and an FNAC/TRU-CUT or excisional biopsy has been performed for confirmation. Palpable lymphadenopathy in the absence of SCC on FNAC or biopsy can be treated with a 4 week course of broad-spectrum antibiotics but should then be reevaluated to ensure resolution and a repeat biopsy undertaken or DSNB if the lymph nodes are now impalpable[32].
Palpable lymphadenopathy arising during follow-up of penile cancer patients is invariably malignant and necessitates radical inguinal lymphadenectomy. Again patients can be offered an ultrasound guided FNAC or open biopsy for confirmation before proceeding to a radical inguinal lymphadenectomy.

7.7 Surgical Techniques for Inguinal Lymph Node Management

7.7.1 Sentinel Lymph Node Biopsy

The technique of localising sentinel node(s) by infiltrating proximal and around the site of the primary tumour with patent blue dye and ^{99m} technetium- radionanocolloid is distinct to the concept of “blind” excision of the likely sentinel node (superomedial to the sapheno-femoral junction) as popularised by Cabanas[63].
Although initial false negative rates reported were 18%[32, 64-67]. addition of a preoperative ultrasound scan of the inguinal regions with FNAC of morphologically abnormal lymph nodes and changes in the histological sectioning have reduced the false negative rates to 4%.-7%

7.7.2 Superficial modified inguinal lymph node dissection

Patients with cN0 disease who are deemed unsuitable for DSNB either due to non-visualisation or the absence of an injection site on the penis due to previous surgery in the form of a total penectomy are suitable for a superficial modified inguinal lymphadenectomy. This procedure uses smaller boundaries for dissection with skeletonisation of the saphenofemoral junction and fossa ovalis thus minimising the morbidity.

This is combined with a peri-operative frozen section on all lymph nodes sampled. Those patients with positive lymph nodes on frozen section must undergo immediate radical inguinal lymph node dissection.

7.7.3 Radical inguinal lymph node dissection

Unilateral radical inguinal lymph node dissection is performed where positive unilateral inguinal nodes are identified either by FNAC, excisional biopsy, sentinel lymph node biopsy (DSNB) or by frozen section during a superficial modified inguinal lymph node dissection.

Either a DSNB or a superficial modified inguinal lymph node dissection with frozen section analysis is recommended on the contralateral side if there are clinically impalpable lymph nodes (cN0 disease).

For small volume palpable inguinal node disease, this procedure has been performed as an open surgical procedure although the unit is developing a program to offer this as a laparoscopic procedure.

7.7.4 Advanced inguinal node disease

In patients with radiologically advanced disease in the inguinal region, surgical resection may still be feasible prior to undergoing adjuvant chemotherapy or radiotherapy. This includes planning the procedure with a vascular surgeon (extended team member Mr Toby Richards) and the reconstructive plastic surgery team (extended member Mr Ash Mosahebi). Cases are discussed on an individual basis and managed according to the performance status of the patient and the presence of distant metastatic disease. This is normally undertaken for palliative purposes.

7.7.5 Pelvic lymph node dissection

The risk of pelvic nodal involvement is approximately 30% if two or more inguinal lymph nodes are involved[26, 68, 69]. Patients who have a single nodal metastasis in Cloquet's node or a single node with extracapsular spread may be offered an ipsilateral pelvic lymph node dissection., subject to discussion in the SNMDT. This is offered as either an open or laparoscopic/robotic assisted procedure. Alternatively patients with disease in a single inguinal lymph node with extracapsular spread may be offered radiotherapy to the inguinal region and the ipsilateral pelvic lymph nodes provided that the imaging does not detect any enlarged or suspicious pelvic lymph nodes.

8.0 Radiotherapy and Chemotherapy for Penile Cancer

Due to the rarity of penile cancer, the literature related to the value of chemotherapy and radiotherapy treatment options is fragmented and the optimal regimens have yet to the determined as studies are generally limited to small single centre retrospective studies.

8.1 Radiotherapy as a Primary Treatment for Penile Cancer

Radiotherapy has been used as an alternative to conservative 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]. The morbidity related to primary radiotherapy includes urethral stenosis and radionecrosis.

Due to the high local recurrence rate it is not the policy of this SNMDT to offer radiotherapy as a primary therapy for primary SCC of the penis.

8.2 Chemotherapy

The exact role of neoadjuvant and/or adjuvant chemotherapy remains to be determined. High response rates in small series have been reported for neoadjuvant Cisplatin/5FU[60] and this is the recommendation of the EAU guidelines [54].

The Supranetwork team will support trials related to adjuvant and neoadjuvant chemotherapy. No routine neoadjuvant chemotherapy is currently recommended by the MDT outside of a clinical trial although advanced cases are discussed on a case by case basis and included in ongoing clinical trials.

8.2.1 Neoadjuvant chemotherapy

The data for neoadjuvant chemotherapy is limited. There are a few studies which have shown responses using platinum based regimens. Cases are only considered after careful discussion at the SNMDT.

Neoadjuvant chemotherapy may be considered in the following circumstances:

1. Primary urethral squamous cell carcinomas. [71]
2. Advanced and inoperable squamous cell carcinomas of the penis where down staging may make the disease operable [72]

8.2.2 Adjuvant chemotherapy

The 2009 EAU guidelines support the use of adjuvant chemotherapy in pathological N2 and N3 disease. However, this is a single centre experience. [74, 75]

The SNMDT will consider adjuvant chemotherapy after careful discussion of individual cases. All patients should be offered neoadjuvant and adjuvant chemotherapy and chemoradiotherapy as part of a clinical trial whenever possible.

8.2.3 Chemoradiotherapy

In men who have a good performance status with disease localised to the pelvis concomitant chemoradiotherapy may be considered. Weekly cisplatin 40mg/m2 may be used to a maximum of 5 cycles. The GFR must be above 45ml/min. Radiotherapy will be given as documented in the radiotherapy work instructions. There is little data to support this modality

and the patients should be informed of this. However, this is a recognised modality used within the UK and US. These men must be discussed in the SNMDT but men with disease which is encompassable within a radical radiotherapy field with no contra-indications to chemotherapy may be considered.

8.3 Adjuvant pelvic and inguinal radiotherapy

Patients with a single positive inguinal lymph node with extra-capsular extension should be offered adjuvant radiotherapy to the ipsilateral groin. Patients with multiple or bilateral nodal disease should be considered for bilateral pelvic lymphadenectomy with adjuvant radiotherapy to the inguinal and pelvic regions. The evidence base for adjuvant pelvic and inguinal radiotherapy in penile cancer is limited. The EAU guidelines of 2002 and 2004 recommended it as an optional treatment[73, 74] More recent guidelines have implied that there may be an improvement in local control although there is no evidence for this.

The 2009 EAU guidelines support the use of adjuvant chemotherapy in N2 and N3 disease and this may be considered outside of a trial after careful discussion of individual cases in the SNMDT [75].

Where there are metastasis in the deep inguinal or pelvic lymph node(s) unilateral or bilateral (N3 disease) adjuvant radiotherapy should be considered. In unilateral disease, ipsilateral pelvic node dissection coupled with adjuvant radiotherapy to the groin and pelvis is recommended. Adjuvant chemotherapy may also be considered as above.

In rare cases of advanced disease where there are positive margins after total penectomy and where residual tumour is inoperable, radiotherapy can be used post operatively.

9.0 Metastatic Squamous Cell Carcinoma of the Penis

Combination chemotherapy is the standard of care for patients with symptomatic metastatic disease. There is no evidence of survival benefit for palliative chemotherapy, although studies are limited. Drugs with the highest response rates are taxanes and cisplatin in a variety of combinations.

The combination of cisplatin and 5-FU has been in use for the treatment of squamous cell carcinoma of the penis since 1990. Three reports, when pooled, define its activity in a total of 19 patients, with a response rate of 63% (three complete remissions and 9 partial remissions) [76-78]. The single-agent response rate to cisplatin is 23% and this is not dissimilar to the overall response rate seen in EORTC 30992, which used a combination of irinotecan and cisplatin. [79-82]

The regimen in current use within this network is as follows (Please see appendix chemotherapy):

Day 1: Cisplatin 80 mg/sq m
5 Fluorouracil 1g/sq m/day, by continuous infusion for 4 days
21 day cycle

There are currently no second line chemotherapy regimens in standard use. Taxanes have some response and docetaxol was used in the TPF study. Therefore, in fit patients who wish

to pursue further chemotherapy, this network will offer docetaxol or weekly paclitaxel as second line chemotherapy unless a second line trial is available.

9.1 Radiotherapy for distant metastatic disease

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

9.2 Adjuvant pelvic and inguinal radiotherapy

All patients are discussed in the penile cancer specialist MDT
Radiotherapy is offered where clinically appropriate in cases with

1. Extracapsular spread after inguinal lymph node dissection
2. Greater than 1 positive inguinal lymph node after inguinal lymph node dissection
3. Positive margins after treatment of the primary penile tumour
4. The cases of positive pelvic lymph nodes after surgical resection are discussed on an individual patient basis.

The Clinical Target Volume is decided on an individual patient basis depending on the outcome of surgical resection.

All patients have imaging of the pelvis with MRI scan and imaging of the abdomen and chest with CT scan prior to being referred for radiotherapy.

9.2.1 Dose and Fractionation

45Gy-50.4Gy in 25-28# using 10MV photons
A boost dose is given where appropriate of 15-10Gy in 1.8Gy fractions, ideally given concomitantly. Field borders will be individualised

9.3 Palliative Radiotherapy

All patients who are deemed suitable for palliative radiotherapy are discussed at the penile cancer specialist MDT at referred to Dr Mitra for planning and treatment. Each case is discussed on an individual patient basis.

9.4 Surgery

Surgery has a limited role in the management of loco-regional disease in the presence of distant metastases and is reserved for local disease control.
In patients with metastatic disease, the evidence is lacking on the use of metastatectomy as a therapeutic option for isolated distant metastases. Symptomatic metastatic disease which is amenable to local excision can still be resected to minimise problematic bleeding or wound issues. These are discussed on a case by case basis at the SNMDT.

9.5 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.

10 Protocol for patient follow-up

Follow up of patients following diagnosis and treatment of penile cancer should take place in the clinics of core members of the SNMDT. Usually patients are followed up at UCLH unless patients choose to be followed up locally. All histology is presented at the MDT following surgical intervention and further clinical/radiological follow up is planned in line with these guidelines.

The schedule for follow-up is a modified version of the EAU[31] recommendations as follows:

Management	Follow-up	Years 1 & 2	Year 3-5	
Local Management	Conservative Therapy	3 monthly	6 monthly	
	Partial/Total Penectomy	3 monthly	Annually	
Lymph Node Management	Surveillance	3 monthly	6 monthly	
	pNo	3 monthly	6 monthly	
	pN+	3 monthly	6 monthly	

Physical examination of the penis and inguinal region is required at each visit. The value of routine imaging (i.e. in the absence of symptoms) has not been established but a useful adjunct is the availability of inguinal ultrasound. Patients undergoing DSNB where the result is pN0 should undergo 4 monthly surveillance using USS of the inguinal region for 2 years followed by clinical follow up on a 6 monthly basis.

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