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Pathology: the science behind the cure

Standards and Datasets for Reporting Cancers

Dataset for penile cancer histopathology reports

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**Coordinators: Dr Patricia Harnden, St James's University Hospital, Leeds;
Dr Catherine Corbishley, St George's Hospital, London;
Dr Alex Freeman, University College London.**

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The Royal College of Pathologists
2 Carlton House Terrace
London
SW1Y 5AF
Tel: 020 7451 6700
Fax: 020 7451 6701
Web: www.rcpath.org
Registered charity in England and Wales, no. 261035
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1 INTRODUCTION

Penile cancer is rare in the Europe and the USA, with an incidence rate of between 1 and 2 new patients per 100,000 population in the UK, representing less than 1% of all malignant diseases in men. Because of this low frequency, the NICE Guidance, Improving Outcomes in Urological Cancers (www.nice.org.uk), recommends the joint establishment by two to four neighbouring networks of specialised penis cancer multidisciplinary teams, serving a population base of 4 million or more and managing a minimum of 25 new patients a year. Patients with penile cancers diagnosed by local urological multidisciplinary cancer teams should be referred to the specialist supra-network team and the diagnostic slides made available for review. It is expected that pathologists reporting penile cancers participate in an external quality assurance scheme as recommended by the NICE Guidance.

Aspects of the epidemiology, clinical diagnosis and treatment of penile cancer have recently been reviewed.¹ Partial or total penectomy is still considered to be the gold standard of therapy but, because of the psychosexual consequences of this disfiguring treatment, there is an increasing trend towards more conservative therapies, including organ sparing surgery², laser surgery and radiation.

There are no published randomised clinical trials in penile cancer, and the pathological literature is also largely composed of retrospective studies based on relatively small numbers of selected patients. Because penile cancer is more common in developing countries³, many of the original papers on specimen examination and prognostic factors are not in English. These guidelines are therefore not based on a full evidence review but on selected papers from the English language literature. They reflect best clinical practice. Guidelines for the reporting of penile tumour specimens are required and should be adopted for the following reasons:

1. Staging and grading of tumours determine subsequent clinical management and follow-up.
2. Different subtypes of penile carcinomas have been defined, which appear to be associated with different outcomes and may also therefore justify the adoption of different treatment strategies.
3. Accurate characterisation of the tumour is important to assess the efficacy of conservative forms of treatment and compare patient outcomes stratified for stage and grade.
4. Adoption of a consistent approach to classification and risk assessment of penile cancers is essential for audit and epidemiological studies, particularly since data specific to the UK are relatively uncommon.

This document has been devised to include the data required for a careful assessment of a penile tumour. It is based on factors used in clinical management. It is recognised that some of these factors, such as the TNM staging system^{4,5}, were derived historically from consensus rather than an unbiased evidence base⁶, but they subsequently have received a degree of external validation.

The following organisations have been consulted in writing the dataset: BAUS/BAUS section of oncology, BAUS section of andrology, British Uro-oncology Group, Penile subsection of the NCRI Bladder Clinical Studies Group

2 CLINICAL INFORMATION REQUIRED ON THE SPECIMEN REQUEST FORM

This includes the type of specimen (punch, incisional or excisional biopsy, circumcision, wedge resection of glans, glansctomy, partial or total penectomy and/or lymph node sampling), the site of biopsies, the anatomical origin of lymph nodes and history of prior penile tumours and treatment.

3 PREPARATION OF SPECIMENS BEFORE DISSECTION

Circumcisions can be pinned flat for fixation as the number, size and location of tumours are more clearly seen. Except for large en bloc resections, it is generally not necessary to section the specimens to achieve optimum fixation. If sectioning is required, inking of margins should be performed at this stage.

4 SPECIMEN HANDLING AND BLOCK SELECTION

A synoptic reporting proforma (appendix B) has been added as an *aide memoire* for the main features of these neoplasms. The proforma extracts the dataset currently used in diagnosis and staging. This would usually be supplemented by a more detailed written report. Aspects of best practice in handling penile tumour specimens have recently been reviewed.⁷

4.1 Gross examination

Larger specimens should be orientated by identifying the glans, the coronal (balanopreputial) sulcus, which separates the glans from the shaft, and the foreskin (prepuce). The glans is essentially an extension of the urethral corpus spongiosum and the urethral meatus is a vertical cleft at the apex of the glans, connected to the foreskin by a triangular plicature of the mucosa, the frenulum. This identifies the ventral aspect of the penis. If the glans surface is distorted by tumour obscuring these structures, the underside (deep resection margin) may be less affected and the urethra, surrounded by spongiosum, still visible. It is then helpful to use different colours of ink to distinguish right and left sides and/or ventral and dorsal aspects of the skin limits and deep resection margin prior to sectioning. Specimens are measured in three dimensions.

It is important to identify the four distinct anatomical levels⁸ of the penis as this allows accurate staging. They are best demonstrated by longitudinal sections. They consist of:

- the epithelium, normally no more than 1mm thick;
- the underlying lamina propria, usually approximately 2mm thick;
- the corpus spongiosum, a slightly red, spongy tissue surrounding the urethra and limited inferiorly by the thick (2mm approximately), white, tunica albuginea;
- the corpora cavernosa, surrounded by the tunica albuginea, and with its most distal, tapered portion often within the glans.

The following features are noted:

- the number of distinct tumours;
- their appearance (e.g. endo- or exo- phytic, papillary);
- tumour size(s);
- tumour location and relationship to any identifiable structures such as the urethral meatus, the sulcus or the penile urethra itself;
- the presence of identifiable invasion and its depth;
- the relationship of the tumour(s), including invasive fronts, to the margins;
- the presence of any other surface abnormalities such as white plaques, red patches, ulcers or nodules.

A photograph of the specimen *en face* and following sectioning is useful.

4.2 Block selection

The availability of large block technology is an advantage for specimens that can be orientated, as it is easier to assess the relationship of the tumour to adjacent and underlying structures.

Blocks are selected to represent:

- the tumour(s);
- the maximum depth of invasion;
- the distance to the nearest margin;

- the deep margin, including the erectile bodies and urethra, and skin limits in larger resections;
- uninvolved skin.

4.2.1 Circumcision

Sections are taken perpendicular to the skin surface. All specific lesions are sampled. Random sections allow the identification of multifocal carcinoma in situ and presence or absence of balanitis xerotica obliterans.

4.1.2 Wedge resection of glans penis

Sections perpendicular to the skin are generally taken through the specimen, and these relatively small specimens can often be all embedded.

4.2.3 Glansectomy

A semi- circular or cup-shaped piece of tissue is usually received, which includes the corona, skin limits, urethral meatus and occasionally the tunica. Parasagittal sections from right and left of the centre of the specimen allow for the assessment of the relationship of the tumour with the urethra and the ventral and dorsal skin limits. Coronal sections of right and left sides represent the lateral skin limits well. The tissue is generally all embedded.

4.1.4 Partial or total penectomy

After orientating and inking the specimen, it is useful to take shave sections to document the status of the urethral, spongiosus or cavernosal and skin margins. An initial longitudinal section along the urethra (a probe may be useful) can then be taken, separating right and left sections, followed by parasagittal incisions along the entire specimen. It is important to assess for the presence or absence of urethral involvement, as in the TNM system⁵ this upstages the tumour to pT3. It is useful for this purpose to embed a complete parasagittal section, which includes the urethral meatus, in a large block.

4.1.5 Lymph nodes

The superficial and deep inguinal nodes are often sent separately. Within the deep inguinal nodes, the superior-most node, called the Cloquet node, is located under the inguinal ligament, often at the medial aspect of the specimen. The placement of a suture mark by the surgeon for orientation is helpful. The fat can then be sampled for lymph nodes, starting from the Cloquet node and working systematically towards the opposite end of the specimen, and labelled in sequence. Alternatively, if investigations have been performed to identify the sentinel node, the nodes should be received labelled in the sequence they are identified radiologically, using a clear coding system agreed between radiologists, surgeons and pathologists. Macroscopically uninvolved nodes should be embedded in their entirety but in most cases of large, grossly positive nodes, it is sufficient to sample the node, taking care to include the capsule and surrounding tissue to assess for extracapsular spread.

Dynamic sentinel node biopsy, using either the blue dye technique or lymphoscintigraphy, refers to the intraoperative identification of the first node draining the tumour. It relies on the assumption that lymphatic spread is a stepwise process, so that, if the sentinel node is negative, further nodal dissection would yield negative results. This technique may be used in some centres for patients with no clinical signs of nodal involvement.

5 CORE DATA ITEMS

Over 95% of penile cancers are squamous cell carcinomas, with rare instances of sarcomas, melanomas or small cell carcinomas. In addition to the most common, usual type of squamous carcinoma and in order of frequency, papillary, basaloid, warty (condylomatous), verrucous and sarcomatoid subtypes are recognised.⁹ Subtyping is recommended as verruciform carcinomas (papillary, warty or verrucous carcinomas) have a better and basaloid or sarcomatoid carcinomas have a worse prognosis than the usual type of squamous

carcinoma.¹⁰ Different patterns of growth can also be distinguished, and vertical growth carcinomas are associated with a higher risk of metastases than superficial spreading carcinomas¹¹, although it is not clear whether this distinction offers superior prognostic power than tumour stage.

There is no consensus concerning grading, and the most recent WHO classification does not make a specific recommendation.⁹ The “classical” method⁷ defines well-, moderately-well and poorly differentiated carcinomas on the basis of the degree of cytological atypia, keratinisation, intercellular bridges and mitotic activity (see table 1). Sarcomatoid change is a separate category, which can be termed grade 4.⁷ Tumours are generally graded on their worst component, although a threshold of 50% of poorly differentiated cancer has been suggested as the cut-off point most predictive of nodal metastases.¹²

Table 1. Grading of penile squamous cell carcinoma

Feature	Grade 1	Grade 2	Grade 3
Cytological atypia	Mild	Moderate	Anaplasia
Keratinisation	Abundant keratin pearls	Focal /single cell	Absent
Intercellular bridges	Prominent	Occasional	Few or none
Mitotic activity	Rare	Increased	Abundant

The TNM system⁵ is internationally accepted, although it must be acknowledged that it was historically based on expert consensus, and a more rigorous method for continuous improvement has only recently been adopted.⁶ The distinction between lamina propria and corpus spongiosum is made on the basis of vascularity: vessels within erectile tissue are more angular and thin-walled with intervening fibromuscular tissue and those within the lamina propria are more variably sized and separated by loose connective tissue. It has been suggested that the pT2 primary tumour classification be subdivided to distinguish between invasion into the spongiosum and cavernosum, on the basis of a small number of reports showing that most patients with metastases have invasion of the cavernosa.¹³⁻¹⁶ This has not been adopted but it may be useful to record this data item in order to audit outcomes. It has also been suggested that measurement of the depth of invasion, measured in millimetres from the basement membrane of the adjacent epithelium to the deepest point of invasion, added prognostic information using a threshold of 6mm¹⁷ but not 3mm.¹² If deep structures are not sampled, and particularly if the tumour extends to the margins of excision, formal staging cannot be performed and the category pTx applies.

There do not appear to be any publications regarding the prognostic value of perineural invasion in penile cancer but personal experience of the authors suggests that it may be important as in other squamous cell carcinomas.¹⁸ It is recommended that the presence or absence of perineural invasion are recorded for audit in relationship to outcomes.

Because of the morbidity associated with lymphadenectomy, studies have investigated predictors of nodal metastases, which could be applied to patients with clinically negative nodes. A combination of grade and stage has been suggested as the optimum method to identify patients at high risk and who would therefore benefit from primary lymphadenectomy.^{14,19} The presence of vascular invasion has also been identified as a predictor of nodal metastases.^{12,15,20,21} The European Association of Urology Guidelines for the management of patients with penile cancer suggests a model combining primary tumour stage, grade, growth pattern (superficial versus nodular) and vascular invasion for the selection of a therapeutic schedule.²²

Traditionally, it was thought that a surgical margin of 15-25 mm was required for adequate disease control but recent studies have challenged this concept^{23,24}, whilst another study has further suggested that this should be related to grade.²⁵ Reducing the length of the clearance required allows more patients to have a partial rather than a total penectomy with better functional and cosmetic results. Margin status is recorded both macroscopically and microscopically. Microscopic margin positivity may be identified unexpectedly in tumours that infiltrate widely without creating a mass effect. The presence of macroscopic involvement of surgical margins, however, has implications for audit of pre-operative staging and/or surgical technique.

Nodal involvement is a recognised predictor of poor prognosis.^{16,22,26,27} In node positive disease, the number of positive nodes, the presence of extracapsular spread and the level of nodal involvement (pelvic versus inguinal) have been shown to influence survival by multivariate analysis.²⁸

Summary of core data items

5.1 Clinical

- Type of specimen and procedure;
- Anatomic site.

5.2 Pathological

5.2.1 Macroscopic items

- Number, location and description of tumour(s);
- Depth of invasion and anatomical structures involved;
- Margin status;
- Presence or absence of other surface abnormalities.

5.2.2. Microscopic items

- Tumour subtype;
- Tumour grade;
- Primary tumour category (pT stage);
- Vascular invasion;
- Margin status;
- Regional nodal status (pN stage) including number involved relative to total number, level of positive nodes and presence or absence of extracapsular spread.
- Presence or absence of carcinoma in situ.

6 NON-CORE DATA ITEMS

- Pattern of growth;
- Percentage of poorly differentiated cancer;
- Depth of invasion (mm);
- Involvement of corpus cavernosum versus corpus spongiosum;
- Presence or absence of perineural invasion;
- Presence or absence of associated skin lesions (e.g. balanitis xerotica obliterans).

7 DIAGNOSTIC CODING

7.1 TNM classification

The 6th edition of TNM⁵ is recommended.

7.2 SNOMED coding

Foreskin	T76330	
Penectomy	T76000	Add P1140 if biopsy, P1104 if partial penectomy
Squamous carcinoma	M80703	

8 REPORTING OF SMALL BIOPSY SPECIMENS

8.1 Macroscopic items

The specimens are measured in three dimensions and features of the skin surface, including colour, texture and the presence of lesion or ulcer are noted.

8.1.1 Punch biopsy

The 4mm punch biopsies can be embedded whole if it is a 4mm punch, whereas the 6mm biopsies can be bisected. At least three levels are generally performed.

8.1.2 . Incisional biopsy

They can be bisected longitudinally and the entire specimen embedded.

8.1.3 Excisional biopsy

Additional comments should be recorded on the size of the lesion(s), the presence of multifocality and the proximity of the lesion(s) to the margins. The specimen is inked prior to sectioning and both circumferential and deep margins are sampled. The circumferential margins can be sampled in one of two ways:

- circumferential shaves of the entire specimen edge;
- cruciate sections from the central lesion out towards the specimen edge.

It is important to adequately sample the deep margin and multiple blocks are required for multifocal or extensive lesions.

8.2 Microscopic items

The data items are the same as for larger specimens although in most cases of punch and incisional biopsies, assessment of the margins is limited and it will not be possible to stage the tumour accurately as deep tissues are often not sampled. This should be clearly indicated in the report, and the tumour should be categorised as pTx. Biopsy material may also underestimate the grade as assessed in the penectomy specimen.²⁹

9 REPORTING OF FROZEN SECTIONS

These are only performed in specific cases, usually to assess excision margin status or to examine lymph nodes. Specimens should be orientated by the surgeon if necessary to identify the relevant margin(s).

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APPENDIX A TNM PATHOLOGICAL STAGING (6TH EDITION, UICC⁵)

The primary tumour classification has not been changed compared with the previous edition.⁴ The major change affects the assessment of nodes and applies to all cancer sites. A tumour nodule in the connective tissue of the lymph drainage area is classified as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node, even in the absence of histologically proven residual lymph node tissue.

Although there is a category of non-invasive verrucous carcinoma in the primary tumour classification, the criteria for the diagnosis of this entity and its distinction from verrucous hyperplasia are unclear and use of this category is not recommended. Although verrucous carcinomas have a pushing rather than infiltrative margin, they are nevertheless invasive. Invasion is generally limited to the lamina propria (pT1) but more deeply invasive tumours can be observed.

pT - Primary Tumour

pTX	Primary tumour cannot be assessed.
pT0	No evidence of primary tumour.
pTis	Carcinoma in situ.
pTa	Non-invasive verrucous carcinoma.
pT1	Tumour invades subepithelial connective tissue.
pT2	Tumour invades corpus spongiosum or cavernosum.
pT3	Tumour invades urethra or prostate.
pT4	Tumour invades other adjacent structures.

In the case of multiple tumours, the tumour with the highest T category should be classified and the multiplicity or number of tumours should be indicated in parentheses, e.g. pT2 (m) or pT2 (5).

pN - Regional Lymph Nodes

pNX	Regional lymph nodes cannot be assessed.
pN0	No regional lymph node metastasis.
pN1	Metastasis in a single superficial inguinal lymph node.
pN2	Metastasis in multiple all bilateral superficial inguinal lymph nodes.
pN3	Metastasis in deep inguinal or pelvic lymph node(s), unilateral or bilateral.

pM - Distant Metastasis

pMX	Distant metastasis cannot be assessed.
pM0	No distant metastasis.
pM1	Distant metastasis.

Stage Grouping

Stage 0	Tis Ta	N0 N0	M0 M0
Stage I	T1	N0	M0
Stage II	T1 T2	N1 N0, N1	M0 M0
Stage III	T1, T2 T3	N2 N0, N1, N2	M0 M0
Stage IV	T4	Any N	M0

Any T
Any T

N3
Any N

M0
M1

