The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for penile and distal urethral cancer histopathology reports

August 2024

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Unique document number	G038
Document name	Dataset for penile and distral urethral cancer histopathology reports
Version number	4
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Date active	August 2024 **(to be implemented within 3 months)**
Date for full review	August 2027
Comments	This document will replace the 3rd edition of *Dataset for penile and distral urethral cancer histopathology reports*, published in July 2015. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 1 May to 29 May 2024. Responses and authors' comments are available to view on publication. **Dr Brian Rous** **Clinical Lead for Guideline Review**

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Registered charity in England and Wales, no. 261035

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Foreword

The cancer datasets published by The Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items (see Appendices D–I) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Dataset) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult for this document:

- British Association of Urological Pathologists (BAUP)
- British Association of Urological Surgeons (BAUS), including sections of oncology and andrology
- British Uro-oncology Group (BUG)
- European Association of Urology (EAU) Penile Guidelines Subgroup
- UK Association of Cancer Registries (UKACR)
- Penile Subgroup of National Cancer Intelligence Network (NCIN) Urology Clinical Reference Group
- British Association of Dermatopathologists.

No major organisational changes have been identified that would hinder the implementation of the dataset.

The information used to develop this dataset was obtained by undertaking a systematic search of PubMed. Key terms searched included penile squamous cell carcinoma, HPV-associated, HPV-related, histopathology, p16 immunohistochemistry and prognostic factors and dates searched were between January 2015 and January 2024. In addition, EAU-American Association of Clinical Oncology (ASCO) collaborative guidelines on penile cancer (2023),[1] EAU guidelines on primary urethral carcinoma,[2] College of American Pathologist (CAP) protocols[3] and International Collaboration for Cancer Reporting (ICCR) protocol[4] were considered for this review. Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence were identified by College members via feedback received during consultation.

A formal revision cycle for all cancer datasets takes place on a 3-yearly basis. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant sub-specialty adviser to the College, to consider whether the dataset needs to be revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website for 2 weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Professional Guidelines team, Working Group on Cancer Services and Lay Advisory Group and was placed on the College website for consultation with the membership from 1 May to 29 May 2024. All comments received from the Working Group and membership were addressed by the author to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest;

these are monitored by the Professional Guidelines team and are available on request. The authors have declared no conflicts of interest.

1 Introduction

This document is the 4th edition of the *Dataset for penile and distal urethral cancer histopathology*, first published in 2006, and includes guidelines on the handling and reporting of tumours of the distal penile urethra.

1.1 Target users and health benefits of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons and oncologists, cancer registries and the NCIN. Standardised cancer reporting and multidisciplinary team (MDT) working reduce the risk of histological misdiagnosis and help to ensure that clinicians have all the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer specific data also provides information for healthcare providers and epidemiologists and facilitates international benchmarking and research.

1.2 Primary penile squamous carcinoma

Penile cancer is rare in Europe and the USA, with an incidence rate of 2.4 new patients per 100,000 population in the UK (approximately 700 new cases per year).[5] Because of this low frequency, the National Institute for Health and Care Excellence (NICE) guidance on Improving Outcomes in Urological Cancers,[6] recommended the joint establishment of specialist penile supranetworks with cancer multidisciplinary teams serving a population base of 4 million or more and managing a minimum of 25 new patients a year.[7]

In England and Wales, 10 such networks have now been established. Patients with penile cancers diagnosed by local urological, genitourinary, plastic surgery or dermatology teams should be referred to the specialist supranetwork team, with any diagnostic slides and/or blocks made available for review prior to subsequent treatment planning by the specialist team.[7]

Treatment of penile carcinoma is primarily surgical. The development of supranetworks has made organ-sparing techniques associated with reconstruction widely available and radical or partial penectomy is no longer the standard treatment for this disease except in advanced cases.[1,7–9]

There are few randomised clinical trials in penile cancer and the pathological literature is also largely composed of retrospective studies of selected patients. These guidelines cannot therefore be based on a full evidence review but on selected papers and guidelines with evidence being only level C or D, with occasional larger cohort studies reaching level B (see Appendix I). They reflect best clinical practice and the application of general principles of cancer management applied to this area of practice. Although some of the literature comes from series in higher incidence countries, the subtypes and associations of diseases in those areas appear to be the same as those seen in lower incidence countries such as the UK.[10,11]

Accurate staging and grading of tumours are used to determine subsequent clinical management and follow up. 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.[10] A major change from previous datasets has been the recognition of the importance of human papillomavirus (HPV) in penile neoplasms; this has been reflected in a new classification for PeIN (Penile intraepithelial neoplasia) and invasive cancers.[12] It is recognised that the use of routine p16 immunohistochemistry as a surrogate for HPV positivity, may have financial implications for some departments, mitigated by its use in gynaecology pathology; otherwise, compared to the 2015 dataset, no other new major financial or work implications have arisen from this implementation. Adoption of a consistent approach to the new classification is essential for the definition of further changes in management and understanding of risk assessment of penile cancers, in addition to being fundamental for audit and epidemiological studies, particularly since data specific to the UK are relatively uncommon.

1.2.1 Non-squamous tumours of the penis and primary urethral tumours

Penectomy, glansectomy or distal urethrectomy may also be used as treatments for other primary tumours of these sites including malignant melanoma. Malignant melanoma of the penis or urethra should be assessed in conjunction with the specialist team for this tumour and it is more appropriate to use the RCPath's *Dataset for histopathological reporting of primary cutaneous malignant melanoma and regional lymph nodes* for reporting these cases, although the anatomical principles of specimen cut up are the same as in other tumours of the penis and urethra.[13–15]

Distal urethral tumours are most commonly squamous and are much less common than tumours of the glans penis or foreskin. However, surgical management is usually

undertaken by the specialist supraregional penile team, and it is therefore appropriate that these are handled by a specialist penile pathologist rather than a general pathologist. Tumours and PeIN of the glans may involve the urethra and vice versa.[16] The TNM staging also differs for these tumours (see Appendix B),[17] but the principles of handling specimens such as glansectomies and penectomies for primary distal urethral tumours is essentially the same as for other penile tumours.

The principles of reporting of distal urethral tumours are the same as for more conventional penile tumours with attention to anatomical landmarks and margins. Rarely urothelial tumours may occur in the distal urethra, but these are most common within the prostatic urethra rather than the penis itself. It was therefore agreed that this penile dataset will also cover distal urethral squamous tumours, which were not covered by the RCPath's recently revised *Dataset for tumours of the urinary collecting system (renal pelvis, ureter, urinary bladder and urethra) (3rd edition)*, published in 2021.[14]

1.3 Tumours of penile shaft skin and scrotum

Tumours of hair-bearing skin of the shaft and scrotum and appendage tumours should be reported using the RCPath guidelines and proformas for skin and appendage tumours, such as the *Dataset for histopathological reporting of primary cutaneous adnexal carcinomas and regional lymph nodes* and the *Dataset for histopathological reporting of primary cutaneous malignant melanoma and regional lymph nodes*.[13,15] Although primary basal cell carcinomas (BCC) of the penis have been reported, this diagnosis should be made with extreme caution as BCCs are tumours of hair-bearing skin and may be confused with basaloid carcinoma.[7,10] Extramammary Paget's disease, which is sometimes associated with invasive tumours of apocrine or appendage tumour type, is seen in the scrotum and may be managed by penile cancer specialist teams.[7] Extramammary Paget's disease of the glans penis and/or distal urethra is most often associated with urothelial carcinoma higher up the urinary tract.

1.4 Quality assurance

Pathologists reporting penile cancers are required to participate in an external quality assurance (EQA) scheme as recommended by NICE guidance. The UK-run Urological EQA includes penile cases in their slide-based EQA scheme.[18]

It is expected that cases of penile cancer and precancerous lesions diagnosed outside penile supraregional centres should have pathology sent for review to the network

specialist penile pathology team to ensure correct diagnosis, grading, subtyping and staging.[7] A second-opinion service provided by specialist penile pathologists for other difficult penile and distal urethral lesions should also be available via the penile supranetworks.

2 Specimen request form

The type and site of specimen(s) should be specified and will usually include 1 or more of the following specimen types:

- punch, incisional or excisional biopsy, circumcision, wedge excision of glans, glans resurfacing, glansectomy, partial or total penectomy
- lymph node biopsies, sampling, sentinel lymph nodes or dissections – anatomical origin of lymph nodes, iliac or pelvic, including laterality.

History should be given of prior penile tumours and treatments, including topical treatment, radiotherapy and chemotherapy, particularly if the patient has been treated elsewhere.

It is good clinical practice to transcribe all clinical information from the request form on to the pathology report.

3 Preparation of the specimens before dissection

Circumcision and glans resurfacing specimens should be pinned flat for fixation as the number, size and location of tumours are more clearly seen and distortion during fixation is minimised.[19]

Larger specimens such as glansectomies, partial and radical penectomies should be sliced longitudinally along the line of the urethra and between the corporal heads, separating the sample in right and left sides. Some pathologists may prefer to use transverse sections of the proximal shaft in radical penectomies. Transverse slices may be more appropriate for some urethral tumours in penectomy or urethrectomy specimens when no tumour is visible externally. A longitudinal slice at the proximal urethral resection margin may be appropriate to show proximity of tumour to this margin, depending on its location, but otherwise transverse blocks can show the extent of a urethral tumour better in some cases. Resection margins should be inked prior to slicing.[10,19]

Visualisation of the tumour may be difficult particularly if the penis is uncircumcised. Longitudinal sectioning along the urethra in the vertical plane, between the corporal heads

if present, allows easier visualisation of glans tumours as the foreskin may then be retracted for inspection.

Radioactive specimens can be sliced when fresh and handled fixed with suitable protocols and precautions after local radiation protection risk assessments have been undertaken.[20–22]

4 Specimen handling and blocking

Reporting proformas have been added as an aide mémoire for the main features of these neoplasms (see Appendices D and G for penile, Appendices E and H for distal urethral and Appendices F and I for lymph node specimens). For cut-up, an ink code description and block key to indicate sites of sampling should be standard practice and to help continue national standards. The proforma extracts the dataset currently used in diagnosis and staging. This can be supplemented by a more detailed written report or inclusion of a comment. Outline diagrams are included in Appendix J to aid appreciation of penile anatomy and dissection of more complex penile specimens. Further detailed diagrams are available in standard publications and literature.[10,23]

4.1 Gross examination

Specimens and tumour sizes are measured in 3 dimensions in millimetres.

Detailed protocols for the handling of small skin, mucosal and core biopsies are published elsewhere in RCPath cancer datasets and tissue pathways and it is not proposed to reiterate them here, except to state that information about orientation and margins should be retained by using differential inking and block keys as required.

Larger specimens should be orientated by identifying the glans, the coronal sulcus, which separates the glans from the shaft, and the foreskin (prepuce) if present. The urethral meatus lies towards the ventral side of the glans, as does the frenulum. If the glans surface is distorted by tumour obscuring these structures, it may still be possible to orientate the specimen from the underside using landmarks such as the urethra and corporal heads. Differential inking should be used to distinguish right and left sides and/or ventral and dorsal aspects of the skin limits and deep resection margins prior to sectioning.

Difficulties may be encountered in identifying the true circumferential margin of the larger penectomy and glansectomy specimens proximally where skin has been retracted distally

and surgical techniques vary between centres. In these cases, the surgeon may be able to assist in identifying the likely extent of a true margin.

The following features should be noted:

- the number of distinct tumours
- tumour size(s) including maximum width and thickness if assessable macroscopically
- tumour location and relationship to any identifiable structures such as the urethral meatus, corporal heads, the sulcus, or the penile urethra itself
- the relationship of the tumour(s), including invasive fronts, to the margins as far as can be assessed visually (deep/proximal cut margin, corporal, urethral, circumferential bare shaft (Buck's fascia), peripheral skin or glans surface margin)
- the presence of any other surface abnormalities such as white plaques, red patches, ulcers, or nodules.

A macroscopic photograph of the specimen en face and following sectioning is fundamental and should be used to supplement the block key. Measurement of actual macroscopic margin distances is a non-core item. The macroscopic growth pattern of the tumour, for example endo or exophytic, may also be noted as a non-core item.

4.2 Block selection

A block key transcribed onto the main report is essential.

The availability of large block technology is essential for larger specimens such as glansectomies and penectomies as it facilitates staging with easier identification of deep structures, in particular the urethra, corpus spongiosum and corpora cavernosa. [24]

Blocks are selected to represent:

- the tumour(s)
- the maximum extent, width, and depth of invasion
- the distance to the nearest margins
- the deep margin, including the corporal heads, urethra, and skin margins in larger resections
- uninvolved glans, skin, or foreskin.

4.3 Circumcision

In cases of known or suspected penile carcinoma or precancerous lesions (e.g. PeIN), it is advisable to block the entire specimen rather than sampling. Sections are taken perpendicular to the skin/mucosal surface. Differential inking should be used to indicate the glans/coronal margin and the peripheral skin/shaft margins. The foreskin is a cylindrical structure that is usually cut open into a rectangle during circumcision, therefore these cut ends are not resection margins, and orientation by the surgeon must be necessary.[19] See Appendix J, Figure 1.

4.4 Wedge excision of glans penis

These specimens may be elliptical or triangular in shape, usually with a segment of coronal sulcus at 1 edge and corpus spongiosum on the deep surface. Sections perpendicular to the surface are generally taken through the specimen after orientation and marking of margins. These relatively small specimens are usually all embedded.

4.5 Glans resurfacing specimens

This is a complex plastic surgery procedure used in some centres for indolent benign disease such as lichen sclerosus, as well as preinvasive disease (i.e. PeIN) and superficial low-grade tumours. These specimens should be sent pinned if possible and/or properly oriented with surgical notes by the surgeon. Sections perpendicular to the true peripheral coronal/foreskin margin should be taken. It must be noted that the edges of the glans surface segments would join together and are therefore not true margins. The peripheral, urethral and deep margins are inked and the entire specimen blocked. The surgeon should either mark the true urethral margin with a suture or preferably send it as a separate biopsy specimen.[25] See Appendix J, Figure 2.

4.6 Glansectomy

The specimen includes glans, meatus, distal urethra and coronal sulcus with or without foreskin. In some specimens, the tips of the corporal heads are included. Parasagittal sections from right and left of the centre of the specimen, in large block sections, if necessary, allow for the assessment of the relationship of the tumour with the urethra and the ventral and dorsal skin margins. The proximal urethral margin does not protrude from the deep surface, so it is not usually blocked separately. Coronal cruciate sections of right and left sides should be taken to include peripheral skin margins. See Appendix J, Figures 3–5.

4.7 Partial or total penectomy

The specimen should be orientated and differentially inked to indicate margins. An initial longitudinal section along the urethra can then be taken, separating right and left sections, followed by parasagittal incisions along the entire specimen. Some pathologists may prefer to use a probe to identify the urethra, but care must be taken not to dislodge superficial tumours or areas of PeIN.

It is useful to embed complete parasagittal sections of the glans and tumour, which should include the urethral meatus, in large blocks. It is important to sample the urethra adequately, as it can be a route for cancer spread and or site of primary for distal penile cancers. The surgical cut end of the urethra is often more distal than the corporal margins. For well-defined tumours well away from margins it may be appropriate to take shave or transverse margins of corporal heads, urethra and skin. If margins are close, it is better to try and include them in directed block taking, including large block parasagittal sections, which also with care can be taken to include large well-orientated extents of the urethra and corporal heads. Some pathologists may prefer to sample the proximal shaft using stepped transverse sections, particularly if it is well clear of macroscopic tumour. See Appendix J, Figures 3 and 6.

4.8 Urethral resections for distal urethral tumours

Tumours of the distal urethra are generally squamous cell carcinomas. The same subtypes are seen as in tumours arising on the glans, but basaloid tumours are more common at this site.[26,27] Surgical procedures include glansectomy and partial and radical penectomy, which can be dissected and sampled in the same way as primary penile tumours, although care must be taken to ensure proper preferential sampling of the urethra and its relationships to the adjacent structures. Urethral tumours often also involve the glans and vice versa and, in some cases, primary origin may be difficult to identify. The presence of adjacent precancerous epithelial lesions, either on the glans or urethra, may be useful in indicating the most likely primary site.[26]

For superficial urethral tumours and indolent lichen sclerosus, urethrectomy may be performed. The distal and proximal margins should be identified and marked, and the deep margins also inked. The specimens are usually relatively small and can be blocked in sequential transverse sections in their entirety.

4.9 Lymph node dissections

The superficial and deep inguinal nodes are often sent separately. Within the deep inguinal nodes, the most superior 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. The size of the largest and macroscopically involved nodes should be noted. Macroscopically uninvolved nodes should be embedded in their entirety but in most cases of large, grossly positive nodes, it is sufficient to measure and sample the node, taking care to include the capsule and surrounding tissue to assess for extracapsular spread. Blocking to show specimen surface involvement is necessary if the tumour has been surgically incised during the procedure. Selective inking of the margins of suspicious areas is advised. Less commonly, pelvic lymph node dissections can be done and should be processed in similar way to inguinal node dissections.

4.10 Sentinel lymph nodes

Dynamic sentinel node biopsy, [21,22] generally using a combination of a blue-dye technique with 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. Sometimes the true sentinel node is missed by the surgeon because of lymphatic blockage by tumour, leading to a false negative procedure.[28]

The radioactive isotopes used in this technique are low risk, but local assessments should be undertaken. The isotope decays to virtually undetectable levels by 24 hours after injection.[20]

The technique may identify 1 or more nodes from each basin, which are usually sent separately and labelled and numbered to indicate side and sequence. The nodes should be embedded in their entirety in 2 mm transverse slices. Multiple serial sections and levels are not required but may be requested if initial sections are not full face. The immunostaining protocol for sentinel nodes is detailed in section 5 below.

5 Core data items to be included in the report

5.1 Tumour type and subtype

Over 95% of penile cancers are squamous cell carcinomas, with rare instances of sarcomas, melanomas or neuroendocrine carcinomas (NECs) (including large cell and small cell NEC). The most common subtype is the usual squamous carcinoma, but several subtypes has been described.[10,12,29]

Taking into account the modern understanding of a biphasic model for penile carcinogenesis, mimicking other squamous cell carcinomas arising in the lower ano-genital tract,[12] the tumours should be classified as HPV-independent or HPV-associated (see below and Appendix A), using p16 immunohistochemistry as the preferred methodology to ascertain the causal aetiology. Guidelines for the interpretation of p16 immunohistochemistry in lower anogenital tract neoplasia have been published by the British Association of Gynaecological Pathologists (BAGP) and can be applied to penile lesions.[30]

Subtyping according to morphology is closely related to the HPV status (see Appendix A) with occasional exceptions, and is required as verruciform carcinomas (papillary, warty or verrucous carcinomas) have better outcomes. Basaloid, acantholytic and sarcomatoid carcinomas are always high grade with a worse prognosis than the usual type of squamous carcinoma and may more readily metastasise via the blood stream to distant sites such as the lung. Mixed patterns are frequently present and in these cases all subtypes identified should be recorded.[31–34]

Different patterns of growth can also be distinguished. Vertical growth/endophytic carcinomas are associated with a higher risk of metastases than superficial spreading/exophytic carcinomas,[10,34] although it is not clear whether this distinction offers superior prognostic power over tumour stage.

[Level of evidence – C.]

5.1.2 Tumour subtypes of squamous cell carcinoma (adapted from WHO Classification 5th edition)[12]

HPV-associated:

- basaloid squamous cell carcinoma[35]
- warty (condylomatous) squamous cell carcinoma[36,37]
- clear cell[38]
- lymphoepithelioma-like squamous cell carcinoma[39]

- mixed

HPV-independent:

- squamous cell carcinoma, usual (includes pseudohyperplastic[40] and pseudoglandular[41])
- verrucous carcinoma including cuniculatum carcinoma[42]
- papillary[43]
- sarcomatoid (spindle cell) carcinoma[44]
- mixed

Squamous cell carcinoma, not otherwise specified (NOS) (invasive keratinizing carcinoma without special features, for which evaluation of p16 is not available)

Adenosquamous carcinoma[45]

Mucoepidermoid carcinoma[46]

Others:

- high-grade NECs including large cell NECs and small cell carcinomas[47,48]
- malignant melanoma[49]
- soft tissue tumours
- urothelial carcinoma of urethra
- extramammary Paget's disease
- appendage tumours
- metastatic tumours

5.2 Tumour grade

There is no consensus concerning grading, but the most recent WHO classification (2022)[1] states that the World Health Organization/International Society of Urological Pathology (WHO/ISUP) 3-tiered grading scheme (grades 1, 2 and 3) may be used for reporting histological grade.[50]

The 'classical' method defines well-, moderately- and poorly differentiated carcinomas on the basis of the degree of cytological atypia, keratinisation, intercellular bridges and mitotic activity (see Table 1). Sarcomatoid change should be stated as a separate category, which

often combines with other tumour types and conveys a very poor prognosis.[44] These criteria are difficult to apply to some subtypes of penile carcinoma, e.g. verrucous carcinomas, which are well differentiated but often show little or no keratinisation.

Tumours are generally graded on their worst component. Although at one time a threshold of 50% of poorly differentiated cancer was suggested as the cut-off point most predictive of nodal metastases,[51] it has been shown that any component of high-grade tumour conveys a worse prognosis so should be included in the final grade.[52,53]

[Level of evidence – C.]

Table 1: Grading of penile squamous cell carcinoma (WHO/ISUP)[50]

Feature	Grade 1	Grade 2	Grade 3
Cytological atypia	Mild	Moderate	Anaplasia
Keratinisation	Usually abundant	Less prominent	May be absent
Intercellular bridges	Prominent	Occasional	Few or none
Mitotic activity	Rare	Increased	Abundant
Tumour margin	Pushing/ well-defined	Focally irregular	Infiltrative/ ill-defined

5.3 Staging

TNM UICC 8th edition[17] should be followed (see Appendix A).

The anatomy of the penis is complex, and difficulties often arise in distinguishing levels of invasion. 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 than those within the lamina propria, which are more variably sized and separated by loose connective tissue.

Staging of pT1 is subdivided in TNM into pT1a for low-risk tumours and pT1b for high-risk tumours, depending on the absence or presence of high-grade tumour (G3) and/ or lymphovascular/ perineural invasion, respectively. Metastatic tumour in regional lymph nodes with extranodal spread is now categorised as pN3.[17]

pT2 primary tumour classification implies invasion into the spongiosum and pT3 into the corpora cavernosa. Tumour invasion in the tunica albuginea (the fibrous envelope of the corpora cavernosa penis) is considered as pT3.

Invasion of urethra has been put aside in latest TNM edition as a criterion for staging penile tumours. Microscopic confirmation of invasion of adjacent structures other than urethra is recommended for staging pT4.

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, or the maximum thickness or size of the tumour may also give prognostic information as seen in squamous tumours of other sites such as skin.[34,54]

For penile and urethral tumours, particularly if the anatomy is distorted and as the mucosal surface is not flat, the measurement of tumour thickness is more readily undertaken than an estimation of tumour depth.

If deep structures are not sampled and/or the invasive tumour extends to the margins of excision, staging should still be attempted but designated as “pT1 at least”. The designation of “pTX (unstageable)” even in small biopsies should be avoided as far as possible, as it is clinically unhelpful.

The category of M0 should not be used in pathological staging.

[Level of evidence − C.]

5.4 Vascular and perineural invasion

Vascular invasion is recorded as a core data item as it is a predictor of nodal metastases.[50,53] Perineural invasion also has prognostic significance and the updated TNM8 recognises this, and is recorded as a core item.[52,55,56]

[Level of evidence − C.]

5.5 Surgical margins

Penile preserving techniques have led to closer surgical tumour resection margins and there is evidence that this does not significantly compromise local recurrence rates if tumour cells are not present at the margin itself.[57–59] Positive margins must be recorded by site and microscopic distance of tumour from close margins (if the distant to the margin is 5 mm or less) recorded in mm, otherwise recording “margins free of tumour is acceptable”. Some authors recommend considering a margin as positive when the tumour is less than 1 mm from the surgical margin.[59] Microscopic margin positivity may be identified unexpectedly in tumours that infiltrate widely without creating a mass effect. The presence of microscopic involvement of surgical margins, however, has implications for audit of pre-

operative staging and/or surgical technique. Actual measurement of lateral extent of individual margins is a non-core item but is valued by surgeons in assessing their techniques.

[Level of evidence – C.]

5.5.1 Margins of resection for penile specimens (except circumcision)

Urethral

Periurethral tissues including lamina propria and corpus spongiosum

Corpora cavernosa

Circumferential margins of bare penile shaft

Peripheral skin

Deep soft tissue margin.

5.5.2 Margins of resection of circumcision specimens

Coronal sulcus/glans margin

Peripheral cutaneous margin

Deep central soft tissue margin.

5.6 Reporting of PeIN

The pathological nomenclature and patterns of different forms of preinvasive lesions of the penis has been radically modified over the last few years, with the abandonment of clinical terms such as eythroplasia of Queyrat and Bowen's disease and the adoption of the encompassing term "penile intraepithelial neoplasia – PeIN" in pathological reports.[12,60]

Accompanying the recent bimodal aetiology in penile cancer carcinogenesis the classification of PeIN has changed.[12] The proposed classification mimics the one recently adopted for vulvar intra-epithelial lesions on the WHO Classification for Female Genital Tract Tumours 2020:[61] HPV-independent and HPV-associated lesions. Immunohistochemistry for p16 is needed to proper classify these lesions as p16 positivity has been shown as a reliable surrogate marker of HPV association.[62]

5.6.1 HPV-independent PeIN

Formerly known as "differentiated PeIN" is mainly associated with lichen sclerosus and most commonly observed in the foreskin and is negative for p16 immunohistochemistry.

5.6.2 HPV-associated PeIN

Previously called “undifferentiated PeIN” locates preferentially in the glans penis and includes 1) high-grade lesions associated mainly with HPV16 showing full thickness warty/basaloid histology and strong en-block staining for p16 on immunohistochemistry; and 2) atypical flat lesions with positive p16 labelling but without the characteristic warty/basaloid histology more akin to a squamous cell carcinoma in situ.

5.6.3 Condylomas

These lesions are regarded as low-grade associated HPV lesions (e.g. viral subtypes HPV6 and HPV11) and are negative for p16. They are not associated with malignant transformation and are not included in the PeIN category.[63]

5.6.4 Other precancerous lesions

Although in most cases the classification of PeIN in the 2 groups is straightforward, occasional cases show discordance between the morphological patterns and p16 immunolabelling. Unless genomic studies for HPV, allows a clear assignment to 1 of the subtypes, we recommend the use of the category “undetermined for HPV” with an explanatory comment as this will allow retrieval and future analysis of this cases in terms of epidemiological and clinical studies.

Precancerous lesions identical to PeIN are seen in the distal urethra but there is no guidance on how to report them. Rather than designating these as carcinoma in situ or severe dysplasia, it may be advisable to also use the term PeIN in this context.

A potential problem arises when there are cytological abnormalities not thought to be severe enough to be designated as PeIN in the HPV-independent subtype. Then a category such as “atypia falling short of PeIN” with a recommendation for follow up may be used, to avoid over treatment.

It is not necessary to report PeIN using the full dataset proformas, but written reports should indicate the subtype and extent of PeIN and whether or not there is margin involvement.

[Level of evidence − C and D.]

5.7 Lymph node dissections including sentinel lymph nodes

Nodal involvement is a recognised predictor of poor prognosis. 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. A minor change from the TNM7 occurred for pN status in TNM8: metastasis in 1 or 2 inguinal lymph nodes are designated as pN1 and more than 2 unilateral inguinal nodes or bilateral inguinal lymph nodes designated as pT2. TNM8 classifies any pelvic lymph node involvement or extracapsular extension of any regional lymph node (inguinal or pelvic) as pN3 in the penile but not in the urethral TNM.[17,64]

[Level of evidence – B.]

The number of nodes found within an individual specimen should be specified in the report. The size of the largest nodal tumour deposit (not the nodal size), together with presence of extranodal spread, must also be recorded as there is evidence that this may affect prognosis. If tumour is present at the surgical margins on the surface of the specimen, this should also be noted.

Sentinel nodes may single or multiple but are usually submitted separately and cut up as described in section 4.10. Immunohistochemistry is essential for the assessment of micrometastases in sentinel lymph nodes as small metastases under 2 mm or single isolated tumour cells may be easily missed. For squamous carcinomas CK5/6 alone, or in combination with AE1/3 or MNF116, to include broad spectrum and/or high molecular weight forms, is advised. Low molecular weight cytokeratins, such as CAM 5.2 and CK8/18 do not reliably stain squamous tumours and should not be used routinely. The use of 2 antibodies is most helpful in small tumour deposits (less than 2 mm) and sparse single tumour cell involvement by metastatic tumours for confirmation that staining is genuine and not due to artefact. For macroscopically normal sentinel nodes immunohistochemistry may be routinely requested at cut up or spares cut so that sections are sequential.

Tumour presence or absence, size of tumour deposit and presence or absence of extracapsular spread are reported separately for each individual node site. Occasionally individual tumour cells are identified in the peripheral sinus. The significance of these is uncertain but they should be described within reports.

The margin status of the lymph nodes should be recorded as involved or non-involved.

[Level of evidence – D.]

6 Core data items

6.1 Clinical

- Type of specimen(s) and procedure(s)
- Anatomic site, including laterality for node dissections
- Any history of previous treatment, including results of previous biopsies.

6.2 Pathological

Macroscopic items:

- Type of specimen
- Number, location and description of tumour(s)
- Maximum tumour width and thickness (mm)
- Block key indicating sites of individual blocks.

Microscopic items:

- Penile and urethral specimens:
  - tumour origin
  - HPV putative aetiology assessed by p16 immunohistochemistry (IHC)
  - tumour subtype(s)
  - tumour grade (based on the worst area irrespective of percentage)
  - maximum tumour width and thickness (mm)
  - tumour extent
  - pathological tumour stage category (pT)
  - lymphovascular invasion
  - perineural invasion
  - presence or absence of PeIN and subtype of PeIN
  - margin status of both invasive tumour and PeIN, including distance for invasive component if 5 mm or less from margin.
- Nodal specimens:
  - regional nodal status (pN)
  - number and site(s) of involved nodes
  - size of largest nodal tumour deposit(s) at each site sampled

- presence or absence of extracapsular spread
- presence or absence of tumour at the margins of nodal specimens.

SNOMED code to include site, tumour type and procedure codes.

7 Non-core data items

- Macroscopic measurement of margins
- Pattern of growth (endo or exophytic)
- Infiltrating or pushing tumour margin
- Percentage of poorly differentiated cancer
- Presence or absence of associated epithelial lesions (e.g. Lichen sclerosus/BXO)
- Involvement of dartos muscle or external skin in foreskin tumours
- Actual numeric measurements of extent of individual positive surgical margins
- Representative block of tumour slide/block code number (for research or review purposes).

8 Diagnostic coding and staging

8.1 TNM classification (see Appendix B)

The UICC 8th edition of TNM should be followed.[17]

NB: The TNM systems are separate for penile tumours or urethral tumours and only apply to epithelial tumours.

8.2 SNOMED coding (see Appendix C)

This should include both tumour site and type/subtype as well as a procedure code to comply with key performance indicators (KPIs).[65]

9 Special techniques including sentinel nodes

Immunohistochemistry for p16 is needed for the proper classification of penile cancers and pre-neoplastic intraepithelial lesions as studies have shown a high correlation with the

genomic HPV testing.[66-68] Criteria for positivity should follow the ones for gynaecological lesions.

[Level of evidence – C.]

HPV genomic subtyping is not routinely used in diagnostic practice on primary penile tumours and pre-invasive lesions. Immunohistochemical panels including high molecular weight cytokeratins are often necessary to confirm the underlying epithelial nature of sarcomatoid carcinomas and distinguish them from true sarcomas. GATA3 may be useful to distinguish urothelial tumours from squamous carcinomas.[69]

[Level of evidence – D.]

Immunohistochemistry is essential for the assessment of micrometastases in sentinel lymph nodes as small metastases under 2 mm or single isolated tumour cells may be easily missed (see section 5.7).

10 Frozen section diagnosis

These are only performed in specific cases, usually to assess excision margin status, to examine suspicious lymph nodes or in the presence of unexpected intraoperative findings. Specimens should be orientated by the surgeon, if necessary, to identify the relevant margin(s) or separate small samples of specific areas of interest submitted. Frozen sections can be safely performed on radioactive specimens following proper risk assessments as the radioactive load is low.[20] However, the authors believe that frozen sections are not appropriate in the assessment of sentinel nodes, unless the macroscopic findings are highly suggestive for a metastatic deposit and an immediate lymphadenectomy is considered by the surgeon.

[Level of evidence – C.]

11 Criteria for audit

The following are recommended by the College as key assurance indicators and key performance indicators:[70]

- cancer resections should be reported using a template or proforma, including items listed in the English COSD, which are, by definition, core data items in RCPath cancer

datasets. English trusts were required to implement the structured recording of core pathology data in the COSD

  - standard: 95% of reports must contain structured data

- histopathology cases that are reported, confirmed and authorised within 7 and 10 calendar days of the procedure

  - standard: 80% of cases must be reported within 7 calendar days and 90% within 10 calendar days.

Audits of the availability of pathology reports and data at MDT meetings (National Cancer standards)[71] are as follows:

- standard: 90% of cases discussed at MDT meetings where biopsies or resections have been taken should have pathology reports/core data available for discussion at the time of the meeting
- standard: 90% of cases where pathology has been reviewed for the MDT meeting should have the process of review recorded.

The following criteria may be assessed in periodic reviews of histological reports on penile and urethral cancers:

- surgical margin status of penile and/or nodal specimens
- tumour subtyping and distribution of tumour subtypes
- numbers of lymph nodes retrieved from inguinal dissections.

12 Acknowledgements

The authors thank the following individual who has contributed to the updating of this dataset and who has willingly reviewed its various versions:

- Dr Diego F Sanchez, Instituto de Patología e Investigación, Asunción, Paraguay.

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Appendix A WHO classification of tumours of the penis and scrotum

The new WHO classification[12] is based on the association or independence of the tumour with the Human papillomavirus, following similar schemas in the morphology of the different penile carcinoma subtypes identified are associated with the presence of HPV.

- Precursor lesions:
  - penile Intraepithelial Neoplasia (PeIN), HPV-associated
  - differentiated Penile Intraepithelial Neoplasia (PeIN), HPV-independent.
- **Invasive squamous cell carcinoma**:

HPV-associated	**HPV-independent**
• Basaloid. • Warty. • Clear cell. • Lymphoepithelioma-like. • Mixed.	• Usual type. • Also includes: – pseudohyperplastic – pseudoglandular – verrucous carcinoma. • Also includes: – cuniculatum – papillary – sarcomatoid – mixed.

3 special categories do not fit to the previous model related to HPV presence:

1. squamous cell carcinoma NOS: invasive squamous carcinoma without special features, for which p16 evaluation is not available.
2. adenosquamous carcinoma
3. mucoepidermoid carcinoma.

Appendix B Staging for penile tumours

TNM pathological staging of penile tumours (8th edition, UICC)[15]

The primary tumour classification has changed since TNM7, with the redefinition of pT2 and pT3 based on the erectile corpora involvement, and the subdivision of stage pT1 into 1a and 1b adding perineural invasion and/or poorly differentiated as additional discriminative features. Urethral involvement is not relevant for pT classification anymore. In addition, any inguinal node with extranodal extension or positive pelvic nodes becomes pN3, irrespective of size.

Although there is a category of non-invasive verrucous carcinoma in the primary tumour classifications (Ta), the criteria for the diagnosis of this entity and its distinction from verrucous hyperplasia are unclear to the authors of this dataset and use of this category is not recommended. Although verrucous carcinomas have a pushing rather than infiltrative margin, they are nevertheless invasive. Invasion is often only superficial but more deeply invasive tumours may be observed.

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).

Use of the category TX is to be avoided and the designation “T… at least” is preferable if full staging is not possible because of the nature of the specimen (e.g. small incision biopsies) or the presence of positive margins.

Urethral invasion is irrelevant for staging on TNM8 and extension to the corpora cavernosum (including albuginea) implies a pT3 tumour.

a) Tumours of the penis and foreskin

Primary tumour (T)

(Changes between TNM8 and TNM7 are highlighted in **bold**.)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ (PeIN)

Ta* Non-invasive localized squamous cell carcinoma including verrucous carcinoma*

T1 Tumour invades subepithelial connective tissue (Glans: lamina propria; Foreskin: invades dermis, lamina propria or dartos fascia; Shaft: invades connective tissue between epidermis and corpora and regardless of location)

T1a Tumour invades subepithelial connective tissue without lymphovascular invasion or perineural invasion and is not poorly differentiated (i.e. grade 3)

T1b Tumour invades subepithelial connective tissue with lymphovascular invasion or perineural invasion or is poorly differentiated

T2 Tumour invades corpus spongiosum with or without invasion of the urethra

T3 Tumour invades corpus cavernosum with or without invasion of the urethra

T4 Tumour invades other adjacent structures

* The dataset authors' view is that the use of this category is to be avoided as it is not evidence based.

Regional lymph nodes (N)

Clinical stage definition

cNX Regional lymph nodes cannot be assessed.

cN0 No palpable or visibly enlarged inguinal lymph nodes.

cN1 Palpable mobile unilateral inguinal lymph node.

cN2 Palpable mobile multiple or bilateral inguinal lymph nodes.

cN3 Fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral.

Pathologic stage definition

pNX Regional lymph nodes cannot be assessed.

pN0 No regional lymph node metastasis.

pN1 Metastasis in 1 or 2 unilateral inguinal lymph nodes.

pN2 Metastases in more than 2 unilateral inguinal nodes or bilateral inguinal lymph nodes.

pN3 Metastasis in pelvic lymph node(s), unilateral or bilateral, or extranodal extension of regional lymph node metastasis

Distant metastasis (M)

M0 No distant metastasis (clinical category only).

M1 Distant metastasis.

Includes lymph node metastasis outside the regional lymph nodes (superficial and deep inguinal and the pelvic nodes) in addition to visceral or bone sites.

Anatomic stage/prognostic groups

Stage	T	N	M
0	Tis	N0	M0
	Ta	N0	M0
I	T1a	N0	M0
IIA	T1b,T2	N0	M0
IIB	T3	N0	M0
IIIA	T1–3	N1	M0
IIIB	T1–3	N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

b) Tumours of the distal urethra

It should be noted that the N categories differ considerably between urethral and penile tumours and extranodal spread is not a feature of the urethral N staging (i.e. there is no N3 category).

Primary tumour (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Ta Non-invasive papillary, polypoid, or verrucous carcinoma*

Tis Carcinoma in situ (PeIN)** or urothelial carcinoma in situ

T1 Tumour invades subepithelial connective tissue

T2 Tumour invades any of the following: corpus spongiosum, prostate, periurethral muscle

T3 Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck

T4 Tumour invades other adjacent organs (including bladder wall)

* The dataset authors' view is that the use of this category for verrucous carcinoma is the be avoided as it not evidence based. This category includes non-invasive urothelial carcinomas but these are very rare in the distal urethra.

** The dataset authors recommend the use of the same terminology (PeIN) for squamous precancerous lesions of the distal urethra as in the penis.

Regional lymph nodes

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph node metastasis.

N1 Metastasis in a single lymph node

N2 Metastases in multiple nodes.

Distant metastasis

M0 No distant metastasis*

M1 Distant metastasis.

* This is a clinical category, not to be used in pathological reporting.

Adapted from Penis, pp 188–190; Urethra, pp 208–210. *In:* Brierley JD, Gospodarowicz, MK, Wittekind C. *TNM Classification of Malignant Tumours (8th edition)*. Oxford, UK: Wiley, 2017.

Appendix C SNOMED coding

SNOMED 'T' codes

Topographical item	SNOMED 2	SNOMED 3	SNOMED CT description	SNOMED CT code
Foreskin	T-76330	T-91330	Preputial structure (body structure)	17880006
Penis	T-76000	T-91000	Penile structure (body structure)	18911002
Urethra	T-75000	T-75000	Urethral structure (body structure)	13648007
Lymph node	T-08000	T-C4000	Entire lymph node (body structure)	181756000

SNOMED 'M' codes

Morpohological item	SNOMED 2	SNOMED 3	SNOMED CT description	SNOMED CT code
Balanitis xerotica obliterans Lichen sclerosus	M-58240	D0-40200	Balanitis xerotica obliterans (disorder)	198033005
Squamous cell carcinoma in situ (Differentiated and undifferentiated PeIN)	M-80702	M-80702	Squamous cell carcinoma in situ, no ICD-O subtype (morphologic abnormality)	1162893000
Squamous carcinoma (NOS)	M-80703	M-80703	Squamous cell carcinoma, no ICD-O subtype (morphologic abnormality)	1162767002
Metastatic squamous cell	M-80706	M-80706	Metastatic squamous cell carcinoma (morphologic abnormality)	64204000

carcinoma				
Basaloid carcinoma	M-80833	M-80833	Basaloid squamous cell carcinoma (morphologic abnormality)	128634009
Warty/ condylomatous carcinoma	M-80513	R-100C8	Warty (condylomatous) carcinoma (morphologic abnormality)	399408005
Verrucous carcinoma	M-80513	M-80513	Verrucous carcinoma (morphologic abnormality)	89906000
Urothelial carcinoma (transitional cell carcinoma)	M-81203	M-81203	Transitional cell carcinoma (morphologic abnormality)	27090000
Malignant melanoma	M-87203	M-87203	Malignant melanoma, no ICD-O subtype (morphologic abnormality)	1162635006
Malignant melanoma in situ	M-87202	M-87202	Melanoma in situ (morphologic abnormality)	77986002

Morpohological item	**SNOMED 2**	**SNOMED 3**	**SNOMED CT description**	**SNOMED CT**
Adenosquamous carcinoma	M-85603	M-85603	Adenosquamous carcinoma (morphologic abnormality)	59367005
Sarcomatoid/spindle cell carcinoma	M-80743	M-80743	Squamous cell carcinoma, spindle cell (morphologic abnormality)	10288008
Extramammary Paget’s disease	M-85423	M-85423	Paget's disease, extramammary (except Paget's disease of bone)	71447003

			(morphologic abnormality)	
Large cell NEC	M-80133	M-80133	Large cell NEC (morphologic abnormality)	128628002
Small cell carcinoma	M-80413	M-80413	Small cell carcinoma (morphologic abnormality)	74364000
Adenocarcinoma	M-81403	M-81403	Adenocarcinoma, no subtype (morphologic abnormality)	1187332001

Procedural codes

Procedural codes	SNOMED code 2	SNOMED code 3	SNOMED description	SNOMED CT code
Small biopsy or small excision/incision biopsy, single lymph node biopsy (biopsy)	P-1140	P1-03100	Biopsy (procedure)	86273004
Wedge excision biopsy, radical circumcision, glans resurfacing, lymph node dissections (excisions)	P-1141	P1-03101	Excisional biopsy (procedure)	8889005
Glansectomy (resection)	P-1100	P1-77338	Amputation of glans penis (procedure)	32638005
Partial or radical penectomy (resections)		P1-77340	Amputation of penis (procedure)	80855002

Procedure codes (P)

These are used in SNOMED 2 and SNOMED 3 to distinguish biopsies, partial resections and radical resections to indicate the nature of the procedure.

Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

Appendix D Reporting proforma for penile tumours

Surname…… Forenames…… Date of birth…….. Sex…….
Hospital…….…….…… Hospital no…….…….. NHS/CHI no……
Date of receipt…….…….. Date of reporting……..…….. Report no……
Pathologist…….…… Surgeon…….…….

Relevant clinical information/associated or previous specimens (histology and/or cytology)

Macroscopy

Nature of specimen/procedure

Small incision/punch biopsy □

Excision biopsy □

Circumcision □

Glans resurfacing □

Glansectomy □

Partial penectomy □

Radical penectomy □

Site not specified □

Other (specify) ……..

Other tissues/organs included…….....

Tumour location (tick all that apply)

Glans penis□ Sulcus□ Foreskin□

Maximum tumour width…..... mm Not assessable□

Tumour thickness…….. mm Not assessable□

Number of tumours…….

or

No obvious tumour visible macroscopically□□

Microscopy

Tumour subtypes (specify all subtypes present if tumour is mixed)

HPV-independent Squamous cell carcinoma□

HPV-associated Squamous cell carcinoma □

Squamous cell carcinoma NOS □

Adenosquamous carcinoma □

Mucinous carcinoma □

Specify subtype……

Other (specify) ……

Degree of differentiation (by worst area)

Well differentiated (Grade 1) □

Moderately differentiated (Grade 2) □

Poorly differentiated (Grade 3) □

Sarcomatoid areas present □

Maximum tumour width……..mm Not assessable□

Maximum tumour thickness……...mm Not assessable□

Associated PeIN	Present □		Not identified□	Cannot be assessed □
Subtype of PeIN	HPV-independent □		HPV-associated □	Not applicable □

Lymphovascular invasion	Present □	Not identified□
Perineural invasion	Present □	Not identified□

Tumour extent, penile and foreskin tumours (tick all that apply)

Subepithelial invasion by tumour	Yes□	No□
Invasion of corpus spongiosum	Yes□	No□
Invasion of corpus cavernosum	Yes□	No□
Urethral invasion	Yes□	No□
Invasion of adjacent structures	Yes□	No□

Resection margins

Indicate sites of positive margins and distance from margins when invasive tumour clearance is 5 mm or less.

Urethral margin Distance from margin…… mm	Involved□	Not involved□	Not assessable/applicable □
Peri-urethral tissues Distance from margin…… mm	Involved□	Not involved□	Not assessable/applicable □
Corpus cavernosum Distance from margin…… mm	Involved□	Not involved□	Not assessable/applicable □
Circumferential shaft margin Distance from margin…… mm	Involved□	Not involved□	Not assessable/applicable □
Peripheral cutaneous margin Distance from margin……. mm	Involved□	Not involved□	Not assessable/applicable □
Peripheral glans margin Distance from margin…… mm	Involved□	Not involved□	Not assessable/applicable □
Deep margin (NOS) Distance from margin…… mm	Involved□	Not involved□	Not assessable/applicable □
Other (specify) …… Distance from margin……. mm	Involved□	Not involved□	Not assessable/applicable □

PeIN at margin Yes□□ No□□ Cannot be assessed□□□

Site(s) of PeIN positive margins…….

Specimen TNM classification and SNOMED coding (foreskin and penile tumours)

pTNM classification (TNM 8, 2016) pT……

SNOMED codes including procedure code (see Appendix C)

T……. M……. P .....

Comments:

Pathologist……..... Date……..

Notes on staging

The use of TX is to be avoided if possible and the term ‘at least’ may be added to the stage where it is not possible to fully stage the tumour as in some biopsies and margin positive cases.

N stage differs between penile and urethral TNM staging systems (see Appendix B).

Appendix E Reporting proforma for distal urethral tumours

Surname…… Forenames……..…Date of birth…….. Sex…...

Hospital…….…….…… Hospital no…….…….. NHS/CHI no……

Date of receipt…….…….. Date of reporting……..…….. Report no……

Pathologist…….…… Surgeon…….……

Relevant clinical information/associated or previous specimens (histology and/or cytology)

Macroscopy

Nature of specimen/procedure

Small incision/punch biopsy □

Excision biopsy □

Urethrectomy □

Glansectomy □

Partial penectomy □

Radical penectomy □

Site not specified □

Other (specify) ……

Tumour location

Distal urethra□ Mid urethra□ Not assessable□

Maximum tumour width..... mm Not assessable□

Maximum tumour thickness..…mm Not assessable□

Number of tumours……...

or

No obvious tumour visible macroscopically □

Other tissues/organs included…….....

Microscopy

Tumour subtypes (specify all subtypes present if tumour is mixed)

HPV-independent Squamous cell carcinoma□

HPV-independent Squamous cell carcinoma□

Squamous cell carcinoma NOS □

Adenosquamous carcinoma □

Mucinous carcinoma □

Urothelial carcinoma □

Specify subtype……

Other (specify) ……

Degree of differentiation (squamous tumours) (by worst area)

Well differentiated (Grade 1) □
Moderately differentiated (Grade 2) □
Poorly differentiated (Grade 3) □
Sarcomatoid areas present □
Maximum tumour width……..mm Not assessable□
Maximum tumour thickness……...mm Not assessable□□

Associated PeIN Present □ Not identified□ Cannot be assessed □
Subtype of PeIN HPV-independent□ HPV-associated□ Not applicable □

Lymphovascular invasion Present □ Not identified□
Perineural invasion Present □ Not identified□

Tumour extent, urethral tumours (tick all that apply)

Subepithelial invasion by tumour Yes□ No□
Invasion of corpus spongiosum Yes□ No□
Invasion of corpus cavernosum Yes□ No□
Invasion of adjacent structures Yes□ No□

Resection margins:

Indicate sites of positive margins and distance from margins when invasive tumour clearance is 5 mm or less.

Proximal urethral margin Distance from margin…… mm	Involved□	Not involved□	Not assessable/applicable □
Distance urethral margin Distance from margin…… mm	Involved□	Not involved□	Not assessable/applicable □
Peri-urethral tissues Distance from margin…… mm	Involved□	Not involved□	Not assessable/applicable □

Corpus cavernosum Distance from margin…… mm	Involved□	Not involved□ Not assessable/applicable □
Circumferential shaft margin Distance from margin……. mm	Involved□	Not involved□ Not assessable/applicable □
Peripheral cutaneous margin Distance from margin…… mm	Involved□	Not involved□ Not assessable/applicable □
Peripheral glas margin Distance from margin…… mm	Involved□	Not involved□ Not assessable/applicable □
Deep margin (NOS) Distance from margin…… mm	Involved□	Not involved□ Not assessable/applicable □
Other (specify) …… Distance from margin……. mm	Involved□	Not involved□ Not assessable/applicable □

PeIN at margin Yes□ No□ Cannot be assessed □

Site(s) of PeIN positive margins…….

Specimen TNM classification and SNOMED coding (urethral tumours)

pTNM classification (TNM 8, 2016) pT……

SNOMED codes including procedure code (see Appendix B)

T…….. M…… P ……..

Comments:

Pathologist……..... **Date……..**

Notes on staging

The use of TX is to be avoided if possible, and the term ‘at least’ may be added to the stage where it is not possible to fully stage the tumour as in some biopsies and margin positive cases.

N stage differs between penile and urethral TNM staging systems (see Appendix B).

Appendix F Reporting proforma for lymph node specimens from patients with penile or urethral carcinoma

Surname…… Forenames……..… Date of birth…….. Sex…...

Hospital……..…….…… Hospital no……..…….. NHS/CHI no……

Date of receipt……..…… Date of reporting……..…….. Report no……

Pathologist……..…… Surgeon……..…….

Relevant clinical information/associated or previous specimens (histology and/or cytology) including site of primary tumour (penile or urethral)

Macroscopy

Sentinel lymph nodes present

Yes☐ Left (number of sites)……..

No☐ Right (number of sites)……..

Inguinal lymph nodes present

Yes☐ Specify site(s) Left☐

No☐ Right☐

Other lymph nodes (Pelvic or other)

Yes☐ Specify site(s) Left☐

No☐ Right☐

Microscopy

Sentinel lymph nodes: Present ☐ Not applicable ☐

Right Total…… Left Total…….

Number involved……... Number involved…….…….

Size of largest deposit……..…. Size of largest deposit……..

Extracapsular spread: Extracapsular spread:

Present☐ Not identified☐ Present☐ Not identified☐

Tumour present at margins: Tumour present at margins:

Present☐ Not identified☐ Present☐ Not identified☐

Inguinal lymph nodes: Present ☐ Not applicable ☐

Right Total……	Left Total…….
Number involved……...	Number involved……..…….…….
Size of largest deposit…….….	Size of largest deposit……..
Extracapsular spread:	Extracapsular spread:
Present□ Not identified□	Present□ Not identified□
Tumour present at margins:	Tumour present at margins:
Present□ Not identified□	Present□ Not identified□

Other lymph nodes: Present □ Not applicable □

Site(s)……..……

Right Total……...…	Left Total.…….……..
Number involved……...	Number involved……..…….…….
Size of largest deposit…….….	Size of largest deposit……..
Extracapsular spread:	Extracapsular spread:
Present□ Not identified□	Present□ Not identified□
Tumour present at margins:	Tumour present at margins:
Present□ Not identified□	Present□ Not identified□

pTNM classification (TNM 8,2016) **pN**

Patient has primary penile tumour □

primary urethral tumour □

unknown primary site □

SNOMED codes including procedure code (see Appendix C)

T……M……. **P ……..**

Comments:

Pathologist……..... **Date……..**

Notes on staging

N stage differs between penile and urethral TNM staging systems (Appendix B).

Appendix G Reporting proforma for penile tumours in list format

Element name	Values	Implementation notes
Nature of specimen/procedure	Single selection value list: • small incision/punch biopsy • excision biopsy • circumcision • glans resurfacing • glansectomy • partial penectomy • radical penectomy • site not specified • other	
Nature of specimen/procedure, other (specify)	Free text	Only applicable if 'Nature of specimen/procedure: other' selected
Other tissues/organs included	Free text	
Tumour location	Multiple select value list: • glans penis • sulcus • foreskin	
Maximum tumour width, macroscopic	Size in mm	
Maximum tumour width, macroscopic, not assessable	Single selection value list: • yes • no	If 'Maximum tumour width, macroscopic size' is given, value is 'No'

Tumour thickness, macroscopic	Size in mm	
Tumour thickness, macroscopic, not assessable	Single selection value list: • yes • no	If ‘Tumour thickness, macroscopic’ is given, value is ‘No’
Number of tumours	Integer	If ‘Number of tumours’ is >0, value is ‘No’
Tumour subtypes	Multiple select value list: • HPV-independent squamous cell carcinoma • HPV-associated squamous cell carcinoma • Squamous cell carcinoma NOS • Adenosquamous carcinoma • Mucinous carcinoma • Specify	
Tumour subtypes, other	Free text	

Degree of differentiation	Single selection value list: • well differentiated (Grade 1) • moderately differentiated (Grade 2) • poorly differentiated (Grade 3) • sarcomatoid areas present	

Maximum tumour width, microscopic	Size in mm	
Maximum tumour width, macroscopic, not assessable	Single selection value list: • yes • no	If ‘Maximum tumour width, macroscopic size’ is given, value is ‘No’
Maximum tumour thickness, microscopic	Size in mm	
Maximum tumour thickness, microscopic, not assessable	Single selection value list: • yes • no	If ‘Maximum tumour thickness, microscopic’ is given, value is ‘No’
Associated PeIN	Single selection value list: • present • not identified • cannot be assessed	
Subtype of PeIN	Single selection value list: • HPV-independent • HPV-associated • not applicable	Not applicable if ‘Associated PeIN is not identified or cannot be assessed’
Lymphovascular invasion	Single selection value list: • present • not identified	
Perineural invasion	Single selection value list: • present • not identified	
Subepithelial invasion by tumour	Single selection value list: • yes • no	
Invasion of corpus spongiosum	Single selection value list: • yes • no	

Invasion of corpus cavernosum	Single selection value list: • yes • no	
Urethral invasion	Single selection value list: • yes • no	
Invasion of adjacent structures	Single selection value list: • yes • no	

Urethral margin	Single selection value list: • involved • not involved • not assessable/applicable	
Distance from urethral margin	Size in mm	Only recorded when distance is 5 mm or less
Periurethral tissue margin	Single selection value list: • involved • not involved • not assessable/applicable	
Distance from periurethral tissue margin	Size in mm	Only recorded when distance is 5 mm or less
Corpus cavernosum margin	Single selection value list: • involved • not involved • not assessable/applicable	

Distance from corpus cavernosum margin	Size in mm	Only recorded when distance is 5 mm or less
Circumferential shaft margin	Single selection value list: • involved • not involved • not assessable/applicable	
Distance form circumferential shaft margin	Size in mm	Only recorded when distance is 5 mm or less
Peripheral cutaneous margin	Single selection value list: • involved • not involved • not assessable/applicable	
Distance from peripheral cutaneous margin	Size in mm	Only recorded when distance is 5 mm or less
Peripheral glans margin	Single selection value list: • involved • not involved • not assessable/applicable	
Distance from peripheral glans margin	Size in mm	Only recorded when distance is 5 mm or less
Deep margin (NOS)	Single selection value list: • involved • not involved • not assessable/applicable	
Distance from deep margin (NOS)	Size in mm	Only recorded when distance is 5 mm or less
Other margin	Single selection value list:	

	• involved • not involved • not assessable/applicable	
Other margin, specify	Free text	
Distance from other margin	Size in mm	Only recorded when distance is 5 mm or less

PeIN at margin	Single selection value list: • yes • no • cannot be assessed	
Site of PeIN positive margins	Free text	
Modified UICC TNM version 8 pT stage	Single selection value list: • pTX • pT0 • pTis • pTa • pT1a • pT1b • pT2 • pT3 • pT4	pTis is used for PeIN.
SNOMED topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED morphology code	May have multiple codes. Look up from SNOMED tables.	
SNOMED procedure code	May have multiple codes.	

	Look up from SNOMED tables.	

Appendix H Reporting proforma for distal urethral tumours in list format

Element name	Values	Implementation notes
Nature of specimen/procedure	Single selection value list: • small incision/punch biopsy • excision biopsy • circumcision • glans resurfacing • glansectomy • partial penectomy • radical penectomy • site not specified • other	
Nature of specimen/procedure, other (specify)	Free text	Only applicable if 'Nature of specimen/procedure: other' selected
Other tissues/organs included	Free text	
Tumour location	Multiple select value list: • distal urethra • mid urethra • not assessable	
Maximum tumour width, macroscopic	Size in mm	

Maximum tumour width, macroscopic, not assessable	Single selection value list: • yes • no	If ‘Maximum tumour width, macroscopic size’ is given, value is ‘No’
Tumour thickness, macroscopic	Size in mm	
Tumour thickness, macroscopic, not assessable	Single selection value list: • yes • no	If ‘Tumour thickness, macroscopic’ is given, value is ‘No’
Number of tumours	Integer	If ‘Number of tumours’ is >0, value is ‘No’
Tumour subtypes	Multiple selection value list: • HPV-independent squamous cell carcinoma • HPV-associated squamous cell carcinoma • Squamous cell carcinoma NOS • Adenosquamous carcinoma • Mucinous carcinoma • Urothelial carcinoma • Specify	
Tumour subtypes, other	Free text	

Degree of differentiation	Single selection value list: • well differentiated (Grade 1)	

	• moderately differentiated (Grade 2) • poorly differentiated (Grade 3) • sarcomatoid areas present	
Maximum tumour width, microscopic	Size in mm	
Maximum tumour width, macroscopic, not assessable	Single selection value list: • yes • no	If 'Maximum tumour width, macroscopic size' is given, value is 'No'
Maximum tumour thickness, microscopic	Size in mm	
Maximum tumour thickness, microscopic, not assessable	Single selection value list: • yes • no	
Associated PeIN	Single selection value list: • present • not identified • cannot be assessed	
Subtype of PeIN	Single selection value list: • HPV-independent • HPV-associated • not applicable	Not applicable if 'Associated PeIN is not identified or cannot be assessed'
Lymphovascular invasion	Single selection value list: • present • not identified	
Perineural invasion	Single selection value list: • present	

	• not identified	
Subepithelial invasion by tumour	Single selection value list: • yes • no	
Invasion of corpus spongiosum	Single selection value list: • yes • no	
Invasion of corpus cavernosum	Single selection value list: • yes • no	
Invasion of adjacent structures	Single selection value list: • yes • no	

Proximal urethral margin	Single selection value list: • involved • not involved • not assessed/applicable	
Distance from proximal urethral margin	Size in mm	Only recorded when distance is 5 mm or less
Distal urethral margin	Single selection value list: • involved • not involved • not assessed/applicable	
Distance from distal urethral margin	Size in mm	Only recorded when distance is 5 mm or less
Corpus cavernosum margin	Single selection value list: • involved	

	• not involved • not assessed/applicable	
Distance from corpus cavernosum margin	Size in mm	Only recorded when distance is 5 mm or less
Circumferential shaft margin	Single selection value list: • involved • not involved • not assessed/applicable	
Distance from circumferential shaft margin	Size in mm	Only recorded when distance is 5 mm or less
Peripheral cutaneous margin	Single selection value list: • involved • not involved • not assessed/applicable	
Distance from peripheral cutaneous margin	Size in mm	Only recorded when distance is 5 mm or less
Peripheral glans margin	Single selection value list: • involved • not involved • not assessed/applicable	
Distance from peripheral glans margin	Size in mm	Only recorded when distance is 5 mm or less
Deep margin (NOS)	Single selection value list: • involved • not involved • not assessed/applicable	
Distance from deep margin (NOS)	Size in mm	Only recorded when distance is 5 mm or less

Other margin	Single selection value list: • involved • not involved • not assessed/applicable	
Other margin, specify	Free text	
Distance from other margin	Size in mm	Only recorded when distance is 5 mm or less
PeIN at margin	Single selection value list: • yes • no • cannot be assessed	
Site of PeIN positive margins	Free text	
UICC TNM version 8 pT stage	• pTX • pT0 • pTis • pTa • pT1 • pT2 • pT3 • pT4	
SNOMED topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED morphology code	May have multiple codes. Look up from SNOMED tables.	

SNOMED procedure code	May have multiple codes. Look up from SNOMED tables.	

Appendix I Reporting proforma for lymph node specimens from patients with penile or urethral carcinoma in list format

Element name	Values	Implementation notes
Sentinel lymph nodes present	Single selection value list: • yes • no	
Sentinel lymph nodes, left (number of sites)	Integer	
Sentinel lymph nodes, right (number of sites)	Integer	
Inguinal lymph nodes present	Single selection value list: • yes • no	
Inguinal lymph nodes, specify site(s)	Free text	
Inguinal lymph nodes, laterality	Single selection value list: • left • right • left and right • not applicable	Not applicable if 'Inguinal lymph nodes present' is 'No'
Other lymph nodes (pelvic or other) present	Single selection value list: • yes • no	

Other lymph nodes (pelvic or other), specify sites(s) macroscopic	Free text	
Other lymph nodes (pelvic or other), laterality	Single selection value list: • left • right • left and right • not applicable	No applicable if 'Other lymph nodes (pelvic or other) present' is 'No'
Sentinel lymph nodes present, microscopic	Single selection value list: • present • not applicable	
Sentinel lymph nodes right, total	Integer	
Sentinel lymph nodes right, number involved	Integer	
Sentinel lymph nodes right, size of largest deposit	Size in mm	
Sentinel lymph nodes right, extracapsular spread	Single selection value list: • present • not applicable	
Sentinel lymph nodes right, tumour present at margin	Single selection value list: • present • not identified	
Sentinel lymph nodes left, total	Integer	
Sentinel lymph nodes left, number involved	Integer	
Sentinel lymph nodes left, size of largest deposit	Size in mm	
Sentinel lymph nodes left, extracapsular spread	Single selection value list: • present	

	• not identified	
Sentinel lymph nodes left, tumour present at margin	Single selection value list: • present • not identified	
Inguinal lymph nodes present, microscopic	Single selection value list: • present • not applicable	
Inguinal lymph nodes, total	Integer	
Inguinal lymph nodes right, number involved	Integer	
Inguinal lymph nodes right, size of largest deposit	Size in mm	
Inguinal lymph nodes right, extracapsular spread	Single selection value list: • present • not identified	
Inguinal lymph nodes right, tumour present at margin	Single selection value list: • present • not identified	
Inguinal lymph nodes left, total	Integer	
Inguinal lymph nodes left, number involved	Integer	
Inguinal lymph nodes left, size of largest deposit	Size in mm	
Inguinal lymph nodes left, extracapsular spread	Single selection value list: • present • not identified	
Inguinal lymph nodes left, tumour present at margin	Single selection value list: • present • not identified	
Other lymph nodes present,	Single selection value list:	

microscopic	• present • not applicable	
Other lymph nodes, site microscopic	Free text	
Other lymph nodes right, total	Integer	
Other lymph nodes right, number involved	Integer	
Other lymph nodes right, size of largest deposit	Size in mm	
Other lymph nodes right, extracapsular spread	Single selection value list: • present • not identified	
Other lymph nodes right, tumour present at margin	Single selection value list: • present • not identified	
Other lymph nodes left, total	Integer	
Other lymph nodes left, number involved	Integer	
Other lymph nodes left, size of largest deposit	Size in mm	
Other lymph nodes left, extracapsular spread	Single selection value list: • present • not identified	
Other lymph nodes left, tumour present at margin	Single selection value list: • present • not identified	
UICC TNM version 8 pT stage	Single selection value list: • pNX • pN0	

	• pN1 • pN2 • pN3	
Primary tumour type	Primary penile tumour Primary urethral tumour Unknown primary site	
SNOMED topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED morphology code	May have multiple codes. Look up from SNOMED tables.	
SNOMED procedure code	May have multiple codes. Look up from SNOMED tables.	

Appendix J Diagrammatic representations of penile anatomy and specimen types

Figure 1: Opened radical circumcision specimen showing tumour on inner mucosal surface. Vertical bars indicate orientation for block taking. Original artwork by Dr Brendan Tinwell.

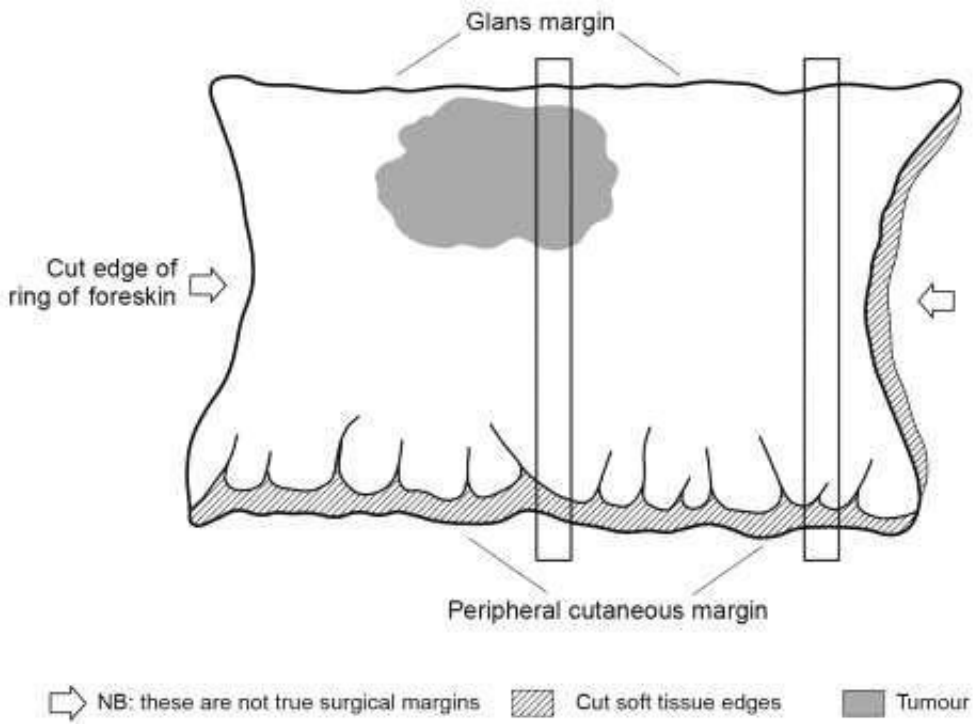
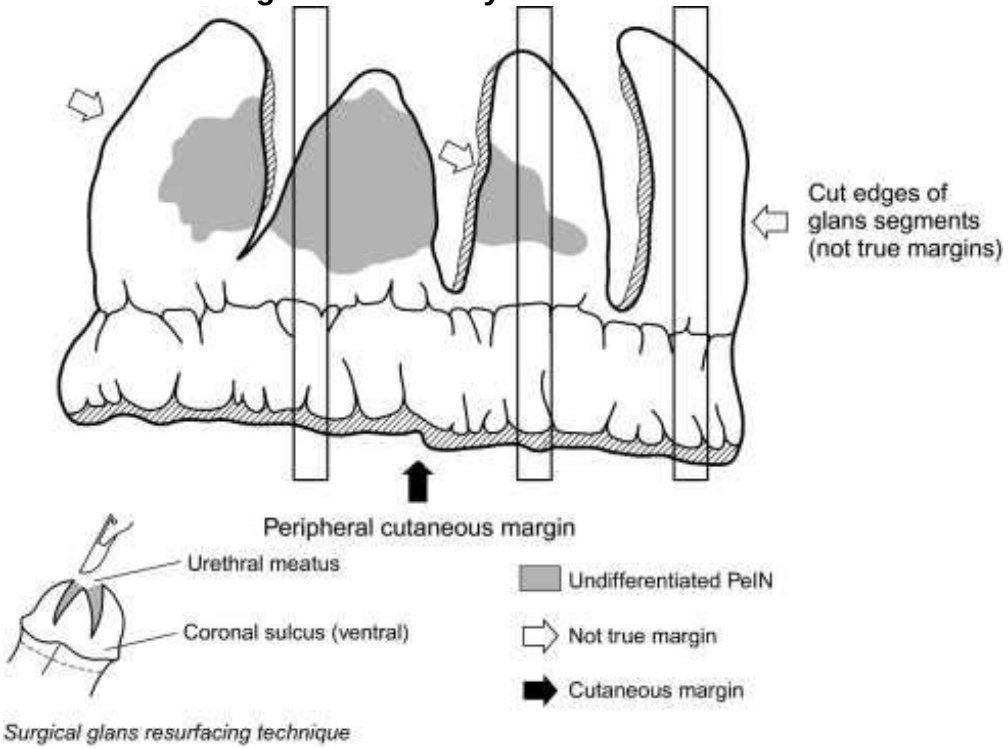


Figure 2: Glans resurfacing specimen with direction of block taking indicated by vertical bars. Original artwork by Dr Brendan Tinwell.



Surgical glans resurfacing technique

Figure 3: Partial penectomy/glansectomy specimen showing deep margins including periurethral corpus spongiosum, corporal heads and deep subcutaneous circumferential soft tissue. Original artwork by Dr Brendan Tinwell.

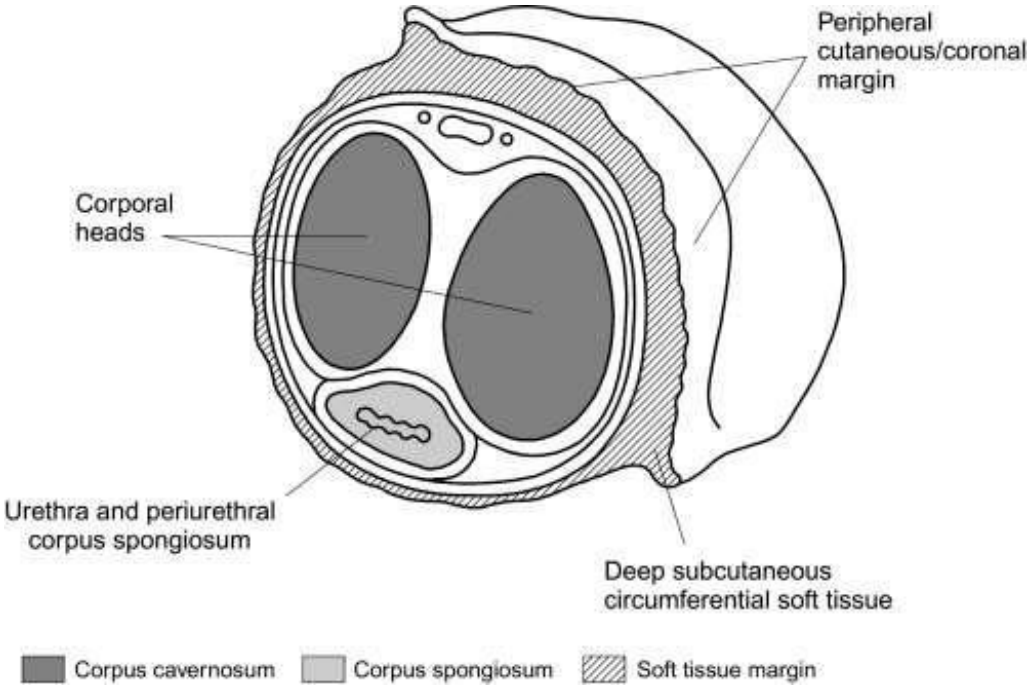


Figure 4: Longitudinal section of partial penectomy showing distribution of corpus spongiosum within glans and periurethral tissues and resection margins. Original artwork by Dr Brendan Tinwell.

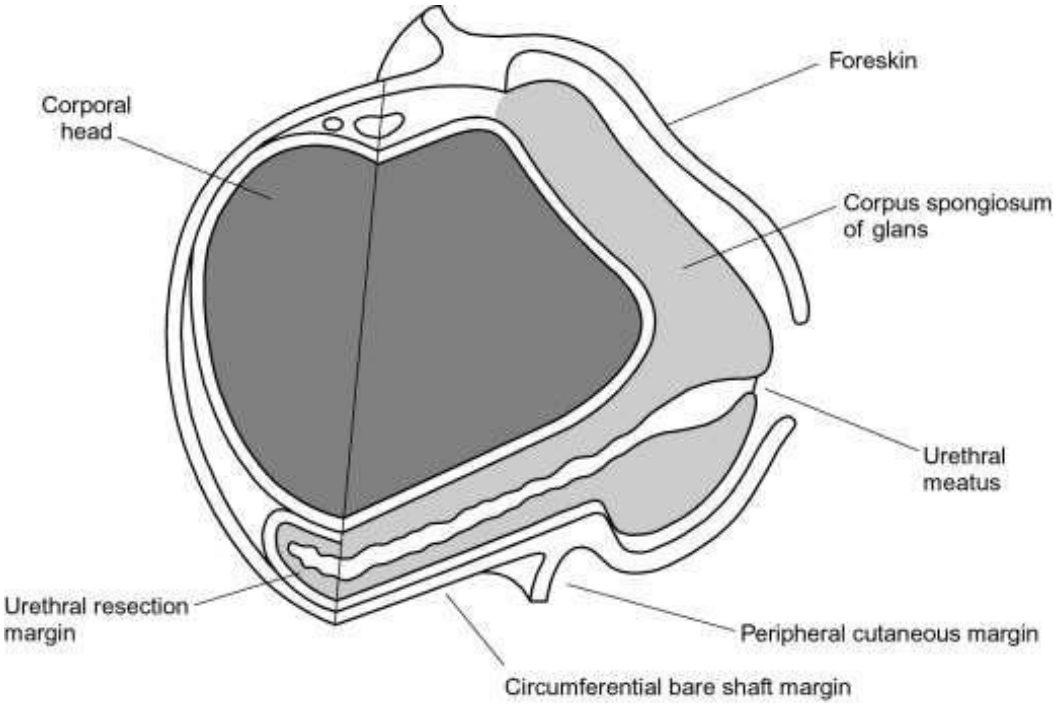


Figure 5: Trimmed parasagittal LS of partial penectomy for large block format processing. Original artwork by Dr Brendan Tinwell.

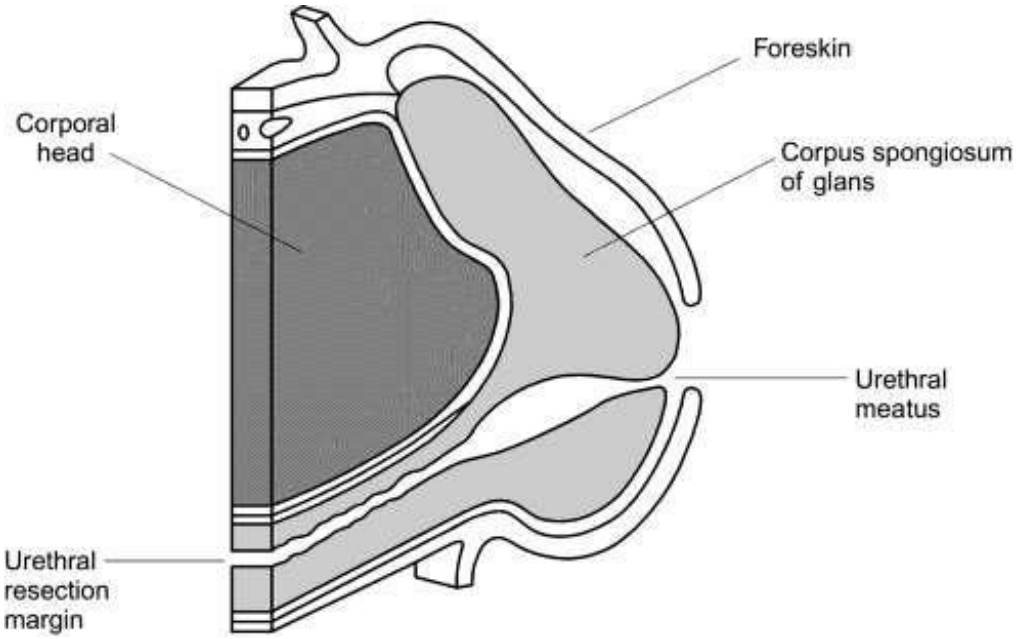
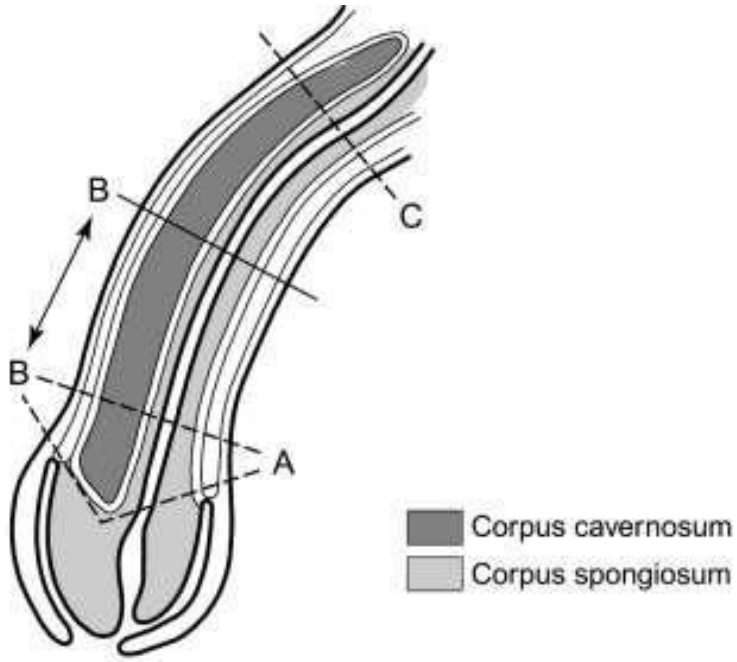


Figure 6: Longitudinal section of penis indicating sites of surgical planes for distal partial and radical penectomy and glansectomy. Original artwork by Dr Brendan Tinwell.



Approximate surgical plane of incision for:

A – glansectomy (corporal heads may be included)
B – partial penectomy
C – radical penectomy

Appendix K Summary table – Explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	**Nature of evidence**
Grade A	At least 1 high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high- quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix L AGREE II guideline monitoring sheet

The guidelines of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this guideline that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Foreword, 1
2 The health question(s) covered by the guideline is (are) specifically described	1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword, 1
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword, 1
12 There is an explicit link between the recommendations and the supporting evidence	All sections
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–10
16 The different options for management of the condition or health issue are clearly presented	1,3,4,5,9
17 Key recommendations are easily identifiable	2–6, 8–10
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–J
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	11
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword