Carcinoma of the Penis and Distal Urethra Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in **grey text** are RECOMMENDED.

CLINICAL INFORMATION (select all that apply) (Note 1)

- ◯ Not provided
- ☐ Previous history of penile or urethral cancer, *specify*
- ☐ Previous therapy, *specify*
- ☐ Other, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

- ☐ Partial penectomy
- ☐ Radical penectomy
- ☐ Glans resurfacing
- ☐ Glansectomy
- ☐ Lymphadenectomy
  - ☐ Sentinel
    - ☐ Left, *number of site(s)*
    - ☐ Right *number of site(s)*
  - ☐ Inguinal
    - ☐ Left
    - ☐ Right
  - ☐ Pelvic
    - ☐ Left, *specify site(s)*
    - ☐ Right, *specify site(s)*
  - ☐ Other, *specify*
    - ☐ Left, *specify site(s)*
    - ☐ Right, *specify site(s)*
- ☐ Other, *specify laterality and site(s)*
- ☐ Circumcision
- ☐ Incisional/punch biopsy
- ☐ Excisional biopsy
- ☐ Urethrectomy
- ◯ Not specified

TUMOUR FOCALITY (Note 3)

- ◯ Cannot be assessed
- ◯ Indeterminate
- ◯ Unifocal
- ◯ Multifocal, *specify number of tumours in specimen*

MACROSCOPIC TUMOUR SITE (select all that apply) (Note 4)

- ☐ Glans penis
- ☐ Sulcus
- ☐ Foreskin
- ☐ Distal penile urethra
- ◯ No macroscopically visible tumour
- ◯ Indeterminate

MACROSCOPIC MAXIMUM TUMOUR DIMENSIONS (Note 5)

width mm

thickness mm

- ◯ Cannot be assessed
- ◯ Not applicable

BLOCK IDENTIFICATION KEY (Note 6)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 7)

(Value list from the World Health Organisation Classification of tumours. Pathology and genetics of urinary system and male genital organs (2016))

- ☐ Squamous cell carcinoma of usual subtype (NOS)
- ☐ Basaloid squamous cell carcinoma
- ☐ Warty (condylomatous) squamous cell carcinoma
- ☐ Verrucous squamous cell carcinoma
- ☐ Papillary squamous cell carcinoma
- ☐ Mixed squamous cell carcinomas, *specify subtypes*
- ☐ Other, *specify**

*(*refer to extended list in WHO Classification 2016)*

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HISTOLOGICAL GRADE (Note 8)

- ◯ Not applicable
- ◯ G1: Well differentiated
- ◯ G2: Moderately differentiated
- ◯ G3: Poorly differentiated
- ◯ Sarcomatoid areas present

MICROSCOPIC MAXIMUM TUMOUR DIMENSIONS (Note 9)

width mm

thickness mm

- ◯ Cannot be assessed
- ◯ Not applicable

EXTENT OF INVASION (select all that apply) (Note 10)

Primary tumours of the penis and foreskin

- ◯ Cannot be assessed*
- ☐ Subepithelial/lamina propria invasion by tumour
- ☐ Invasion of corpus spongiosum of glans
- ☐ Invasion of corpus cavernosum
- ☐ Invasion of the penile urethra
- ☐ Invasion of adjacent structures, *specify*

Primary tumours of the distal urethra

- ◯ Cannot be assessed*
- ☐ Subepithelial/lamina propria invasion by tumour
- ☐ Invasion of corpus spongiosum
- ☐ Invasion of corpus cavernosum
- ☐ Invasion of adjacent structures, *specify*

** Only applicable to biopsy specimens and resection specimens with tumours at the margins.*

LYMPHOVASCULAR INVASION (Note 11)

◯ Not identified ◯ Present ◯ Indeterminate

PERINEURAL INVASION (Note 12)

◯ Not identified ◯ Present ◯ Indeterminate

ASSOCIATED PENILE INTRAEPITHELIAL NEOPLASIA (PeIN) (Note 13)

- ◯ Not identified ◯ Indeterminate
- ◯ Present
  - ◯ Undifferentiated (Warty and/or Basaloid)
  - ◯ Differentiated

MARGIN STATUS (Note 14)

Urethral margin *(primary tumours of the penis and foreskin (resections and excision biopsy only))*

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved by PeIN only
- ◯ Involved by invasive carcinoma
- ◯ Not involved
  - Distance to invasive tumour: mm OR ◯ >5 mm

Proximal urethral margin *(primary tumours of the urethra only)*

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved by PeIN only
- ◯ Involved by invasive carcinoma
- ◯ Not involved
  - Distance to invasive tumour: mm OR ◯ >5 mm

Distal urethral margin *(primary tumours of the urethra only)*

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved by PeIN only
- ◯ Involved by invasive carcinoma
- ◯ Not involved
  - Distance to invasive tumour: mm OR ◯ >5 mm

Peri-urethral tissues

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved by invasive carcinoma
- ◯ Not involved
  - Distance to invasive tumour: mm OR ◯ >5 mm

Corpus cavernosum

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved by invasive carcinoma
- ◯ Not involved
  - Distance to invasive tumour: mm OR ◯ >5 mm

Circumferential shaft margin

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved by invasive carcinoma
- ◯ Not involved
  - Distance to invasive tumour: mm OR ◯ >5 mm

Peripheral cutaneous margin

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved by PeIN only
- ◯ Involved by invasive carcinoma
- ◯ Not involved
  - Distance to invasive tumour: mm OR ◯ >5 mm

Peripheral glans margin

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved by PeIN only
- ◯ Involved by invasive carcinoma
- ◯ Not involved

Distance to invasive tumour

mm OR ◯ >5 mm

Deep soft tissue margins (NOS)

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved by invasive carcinoma
- ◯ Not involved

Distance to invasive tumour

mm OR ◯ >5 mm

Other margin, *specify*

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved by PeIN only
- ◯ Involved by invasive carcinoma
- ◯ Not involved

Distance to invasive tumour

mm OR ◯ >5 mm

LYMPH NODE STATUS (select all that apply) (Note 15)

INGUINAL NODES - SENTINEL

RIGHT

- ◯ Not submitted

Number of lymph nodes examined

- ◯ Not involved
- ◯ Isolated tumour cells only
- ◯ Involved

Number of positive lymph nodes

OR ◯ Number cannot be determined

Maximum dimension of largest deposit

mm

Extracapsular spread

◯ Present ◯ Not identified

LEFT

- ◯ Not submitted

Number of lymph nodes examined

- ◯ Not involved
- ◯ Isolated tumour cells only
- ◯ Involved

Number of positive lymph nodes

OR ◯ Number cannot be determined

Maximum dimension of largest deposit

mm

Extracapsular spread

◯ Present ◯ Not identified

INGUINAL NODES - NON SENTINEL

RIGHT

- ◯ Not submitted

Number of lymph nodes examined

- ◯ Not involved
- ◯ Isolated tumour cells only
- ◯ Involved

Number of positive lymph nodes

OR ◯ Number cannot be determined

Maximum dimension of largest deposit

mm

Extracapsular spread

◯ Present ◯ Not identified

LEFT

- ◯ Not submitted

Number of lymph nodes examined

- ◯ Not involved
- ◯ Isolated tumour cells only
- ◯ Involved

Number of positive lymph nodes

OR ◯ Number cannot be determined

Maximum dimension of largest deposit

mm

Extracapsular spread

◯ Present ◯ Not identified

PELVIC NODES

RIGHT

◯ Not submitted

Number of lymph nodes examined ☐

◯ Not involved
◯ Isolated tumour cells only
◯ Involved

Number of positive lymph nodes ☐

OR ◯ Number cannot be determined

Maximum dimension of largest deposit ☐ mm

Extracapsular spread
◯ Present ◯ Not identified

LEFT

◯ Not submitted

Number of lymph nodes examined ☐

◯ Not involved
◯ Isolated tumour cells only
◯ Involved

Number of positive lymph nodes ☐

OR ◯ Number cannot be determined

Maximum dimension of largest deposit ☐ mm

Extracapsular spread
◯ Present ◯ Not identified

OTHER NODES *(specify laterality and site)*

☐

◯ Not submitted

Number of lymph nodes examined ☐

◯ Not involved
◯ Isolated tumour cells only
◯ Involved

Number of positive lymph nodes ☐

OR ◯ Number cannot be determined

Maximum dimension of largest deposit ☐ mm

Extracapsular spread
◯ Present ◯ Not identified

PATHOLOGICAL STAGING (AJCC TNM 8th edition)## (Note 16)

☐ m - multiple primary tumours
☐ r - recurrent
☐ y - post-therapy

PENIS AND FORESKIN

Primary tumour (pT)

◯ TX	Primary tumour cannot be assessed
◯ T0	No evidence of primary tumour
◯ Tis	Carcinoma in situ (Penile Intraepithelial Neoplasia [PeIN])
◯ Ta	Non invasive localised squamous cell carcinoma*
◯ T1	Tumour invades subepithelial connective tissue, dermis or lamina propria**
◯ T1a	Tumour is without lymphovascular invasion or perineural invasion and is not high grade
◯ T1b	Tumour exhibits lymphovascular invasion and/or perineural invasion or is high grade
◯ T2	Tumour invades into corpus spongiosum with or without urethral invasion
◯ T3	Tumour invades into corpora cavernosum with or without urethral invasion
◯ T4	Tumour invades other adjacent structures

* The authors do not recommend the use of the pTa category as it is not evidence based.

** Refer to section 16 for site specific guidance in TNM8.

Regional lymph nodes (pN)

◯ NX	Lymph node metastasis cannot be established
◯ N0	No lymph node metastasis
◯ N1	≤2 unilateral inguinal metastases, no ENE
◯ N2	≥3 unilateral inguinal metastases or bilateral metastases
◯ N3	Extranodal extension of lymph node metastasis or pelvic lymph node metastases

PENILE URETHRA

Primary tumour (pT)

◯ TX	Primary tumour cannot be assessed
◯ T0	No evidence of primary tumour
◯ Ta***	Non-invasive papillary carcinoma
◯ Tis****	Carcinoma in situ
◯ T1	Tumour invades subepithelial connective tissue
◯ T2	Tumour invades any of the following: corpus spongiosum, periurethral muscle
◯ T3	Tumour invades any of the following: corpus cavernosum
◯ T4	Tumour invades other adjacent organs

*** This category includes non-invasive papillary urothelial carcinomas but these are very rare in the distal urethra.

**** This category includes PeIN type changes within the urethra.

Regional lymph nodes (pN)

◯ NX	Regional lymph nodes cannot be assessed
◯ N0	No regional lymph node metastasis
◯ N1	Single regional lymph node metastasis
◯ N2	Multiple regional lymph node metastases

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Scope

The dataset has been developed for the reporting of specimens from patients with carcinoma of the penis, including resection, biopsy and lymphadenectomy. The protocol applies to primary carcinoma of the penis, as well as distal urethral squamous carcinomas.

Melanomas and other urethral carcinomas are not included in the scope of the dataset – separate datasets are available and should be used for these carcinomas.

Note 1 - Clinical information (Recommended)

Reason/Evidentiary Support

History of prior penile tumours and treatments, including topical treatment, radiotherapy and chemotherapy should be given 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.[1] This is a recommended rather than a required item as it is the responsibility of the clinician requesting the pathological examination of a specimen to provide information that will have an impact on the diagnostic process or affect its interpretation.

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Note 2 - Operative procedure[1-3] (Required)

Reason/Evidentiary Support

Treatment of penile carcinoma is primarily surgical. The development of supranetworks in some countries 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.[4,5]

Nodal involvement is a recognised predictor of poor prognosis. In node positive disease, the number of positive nodes, the presence of extracapsular spread (ECS) and the level of nodal involvement (pelvic versus inguinal) have been shown to influence survival by multivariate analysis and this is reflected in both TNM7[6,7] and TNM8[8] which classify 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.

Extent of inguinal node involvement and presence of ECS also predicts pelvic node involvement.[6,7,9,10]

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 lymph node size) together with presence of extranodal spread must also be recorded as there is evidence that this may affect prognosis.

Tumour presence or absence, size of tumour deposit and presence or absence of ECS 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.

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.

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Note 3 - Tumour focality (Recommended)

Reason/Evidentiary Support

Some types of penile squamous carcinoma may be multifocal particularly if associated with precancerous changes (differentiated or undifferentiated penile intraepithelial neoplasia (PeIN)). There are little data for this in the literature but one text reports up to 5% of tumours are multifocal.[11]

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Note 4 - Macroscopic tumour site[1,6,12-14] (Required)

Reason/Evidentiary Support

The site(s) of primary penile and urethral tumours should be noted macroscopically. The prognosis of equivalent tumours of the foreskin may be better than that of the glans. Tumours of the urethra have a worse prognosis than those of the penis or foreskin. The presence or absence of PeIN or urothelial carcinoma in situ can be helpful in differentiating primary penile or urethral squamous from urothelial carcinomas.

Penile and urethral melanomas and primary skin tumours of the shaft should be handled and reported using melanoma and skin tumour datasets respectively.

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Note 5 - Macroscopic maximum tumour dimensions[15-17] (Required)

Reason/Evidentiary Support

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. Minimal risk for metastasis is reported for tumours measuring less than 5 mm in thickness. Tumours invading deeper into penile anatomical levels are usually associated with a higher risk of nodal involvement (see **Note 9 - MICROSCOPIC MAXIMUM TUMOUR DIMENSIONS**). Thickness of penile tumours rather than depth of invasion is more readily assessed, especially in large tumours, because of the anatomical complexity of the organ.

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Note 6 - Block identification key[1,18-20] (Recommended)

Reason/Evidentiary Support

The origin/designation of all tissue blocks should be recorded and it is preferable to document this information in the final pathology report. This is particularly important should the need for internal or external review arise and in larger more complex specimens and/or those with orientation markings. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion including accurate staging. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist.

Specimen photographs and/or annotated diagrams may be of assistance in clarification of block keys. These documents should also be retrievable as part of the pathology record.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks, for example for further immunohistochemical or molecular analysis, research studies or clinical trials.
The availability of large block technology is strongly recommended 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.

It is recommended that a record is kept of a good representative paraffin block of tumour and if frozen tissue is stored.

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Note 7 - Histological tumour type[21-27] (Required)

Reason/Evidentiary Support

The most recent World Health Organisation (WHO) book (2016)[28] classifies and codes malignant squamous epithelial tumours of the penis as follows:

WHO classification of tumours of the penis[a28]

Descriptor	ICD-O codes
Malignant epithelial tumours	
Squamous cell carcinoma, NOS	8070/3
Verrucous carcinoma	8051/3
Adenosquamous carcinoma	8560/3
Sarcomatoid squamous carcinoma	8074/3
Mixed squamous cell carcinoma	8070/3
Basaloid squamous carcinoma	8083/3
Warty (condylomatous) carcinoma	8054/3
Papillary carcinoma (NOS)	8050/3
Lymphoepithelioma-like carcinoma	8082/2
Precursor lesions	
Penile intraepithelial neoplasia	
Low grade	8077/0
High grade	8077/2
Warty PeIN/Basaloid PeIN/Wart-basaloid PeIN	
PeIN differentiated	8071/2
Paget disease	8542/3

a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.

The tumours are further subclassified in the recent WHO publication into non- HPV related and HPV related tumours, however there is some group crossover particularly in Usual type squamous cell carcinomas a proportion of which are HPV positive. Mixed carcinomas may also show heterogeneity and sometimes include both HPV and non HPV associated tumour types.

A. Non–HPV-related penile squamous cell carcinomas (SCCs)
1. SCC
Usual carcinoma
Pseudohyperplastic carcinoma
Pseudoglandular carcinoma
2. Verrucous carcinoma
Pure verrucous carcinoma
Carcinoma cuniculatum
3. Papillary carcinoma, NOS

4. Adenosquamous carcinoma
5. Sarcomatoid squamous carcinoma
6. Mixed carcinoma
B. HPV-related penile SCCs
7. Basaloid carcinoma
Papillary–basaloid carcinoma
8. Warty carcinoma
Warty–basaloid carcinoma
Clear cell carcinoma
9. Lymphoepithelioma-like carcinoma
C. Other rare carcinomas

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.

Over 95% of penile cancers are squamous cell carcinomas, with rare instances of sarcomas, melanomas or neuroendocrine carcinomas (including large cell and small cell neuroendocrine carcinomas). In addition to the most common, usual type of squamous carcinoma, subtypes include papillary, basaloid, warty (condylomatous), verrucous and sarcomatoid subtypes.

Subtyping is required as verruciform carcinomas (papillary, warty or verrucous carcinomas) have better outcomes. Basaloid, pseudoglandular/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.

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 although it is not clear whether this distinction offers superior prognostic power over tumour stage.

p16 staining or assessment of HPV subtypes may also be of help in subtyping squamous tumours but are not mandatory.

<u>Tumour subtypes of squamous cell carcinoma</u>

- Squamous cell carcinoma of usual subtype (NOS).[11,29]
- Basaloid squamous cell carcinoma.[30]
- Warty (condylomatous) squamous cell carcinoma.[31,32]
- Verrucous squamous cell carcinoma.[26]
- Papillary squamous cell carcinoma.[33]
- Mixed squamous cell carcinomas (specify subtypes).[26]

<u>Other rare tumour subtypes</u>

Squamous cell carcinoma variants

- Pseudohyperplastic squamous cell carcinoma.[26,34,35]
- Verrucous carcinoma variant
    - Carcinoma cuniculatum.[34,36]

- Sarcomatoid (Spindle cell) squamous cell carcinoma.[37]
- Pseudoglandular (Acantholytic adenoid) squamous cell carcinoma.[34,38]
- Lymphoepithelioma like squamous cell carcinoma.[39]
- Warty carcinoma variants
    - Clear cell carcinoma.[34]
    - Warty basaloid squamous cell carcinoma.[40]
- Adenosquamous carcinoma.[41]

Non squamous tumours

- High grade neuroendocrine carcinomas including large cell neuroendocrine carcinoma and small cell carcinoma.[34,42,43]
- Malignant melanoma.[44]
- Mesenchymal tumours.[11]
- Urothelial carcinoma of urethra.[11]
- Extramammary Paget's disease.[11]
- Appendage tumours.[11]
- Metastatic tumours.[28]
- Lymphomas and haematological tumours.[11]

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Note 8 - Histological grade[11,16,28,37,45,46] (Required)

Reason/Evidentiary Support

Accurate staging and grading of tumours are used to determine subsequent clinical management and follow-up. Different subtypes of penile carcinoma have been defined, which appear to be associated with different outcomes and may also therefore justify the adoption of different treatment strategies.

There is no consensus concerning grading, and the most recent WHO classification (2016)[28] recommends a three step grading system based on degree of pleomorphism and keratinisation with the overall grade determined by the worst area no matter how small the percentage of the tumour. The most recent College of American Pathologists (CAP) guidelines[47] offer some outline global guidance which is applicable to usual type squamous carcinomas.

The "classical" method 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). These criteria are difficult to apply to some subtypes of penile carcinoma, for example verrucous carcinomas which are well differentiated but often show little or no keratinisation. Sarcomatoid change is a separate category, which is often combined with other tumour types and which conveys a very poor prognosis. All tumours with sarcomatoid areas should be graded as Grade 3 but this finding also needs to be noted separately as tumours with sarcomatoid areas have a worse prognosis than Grade 3 tumours generally.[8]

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, it has recently been shown that any component of high-grade tumour conveys a worse prognosis so should be included in the final grade.[46] Every effort should be made to assign a final grade as this is an important prognostic factor and this grade must be based on the most poorly-differentiated component, no matter how small.

Table 1: Grading of penile squamous cell carcinoma*

Feature	**Grade 1**	**Grade 2**	**Grade 3**	**Sarcomatoid areas present (Grade 3)**
Cytological atypia	Mild	Moderate	Anaplasia	Sarcomatoid
Keratinisation	Usually abundant	Less prominent	May be present	Absent
Intercellular bridges	Prominent	Occasional	Few	Absent
Mitotic activity	Rare	Increased	Abundant	Abundant
Tumour margin	Pushing/well defined	Infiltrative/ill defined	Infiltrative/ill defined	Infiltrative/ill defined

*Table modified from The Royal College of Pathologists (RCPath) Dataset for penile and distal urethral cancer histopathology reports, 2nd Edition 2015

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Note 9 - Microscopic maximum tumour dimensions (Required)

Reason/Evidentiary Support

Note: Tumour dimensions have to be determined through a combination of macroscopic and microscopic assessment, particularly if tumours are very large.

For evidence see **Note 5 - MACROSCOPIC MAXIMUM TUMOUR DIMENSIONS**.

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Note 10 - Extent of invasion[6,17,48,49] (Required)

Reason/Evidentiary Support

Tumours invading deeper into penile anatomical levels are usually associated with a higher risk of nodal involvement. There is also a correlation between deeper infiltration and higher histological grade, although some exceptions do occur. Tumours invading corpus cavernosum are at higher risk for presenting nodal metastases than those invading only corpus spongiosum and although these are both staged as T2 in Union for International Cancer Control (UICC)[6] and American Joint Committee on Cancer (AJCC)[7] TNM7, TNM8[8] now stages corpus cavernosum invasion as T3 irrespective of urethral involvement. The tunica albuginea , which separates corpus spongiosum from corpus cavernosum is considered part of the corpora cavernosa.[7]

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.

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Note 11 - Lymphovascular invasion[45,50] (Required)

Reason/Evidentiary Support

Vascular invasion, lymphatic or venous, adversely affects prognosis of penile cancer. The TNM staging classification in the seventh edition of the *AJCC Cancer Staging* Manual[7] subdivides T1 tumours into T1a and T1b based on the absence or presence of lymphovascular invasion (LVI) or poorly-differentiated tumours. This is also included in the 8th edition (TNM8)[8] which also includes the additional stratifier of perineural invasion (see **Note 12 - PERINEURAL INVASION**).

Embolic involvement of lymphatic vascular spaces occurs usually near the invasive tumour front, but it may also be found at a certain distance from the primary tumour in anatomical areas such as the lamina propria, penile fascia, and especially in the subepithelial connective tissues surrounding penile urethra. Venous invasion indicates a more advanced stage of the disease and is related to the compromise of the specialized erectile venous structures of corpora spongiosa and cavernosa.

Vascular invasion may be difficult to assess particularly in small biopsies and immunohistochemistry with vascular markers may be of assistance in some cases.

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Note 12 - Perineural invasion[16,17,49] (Required)

Reason/Evidentiary Support

Risk groups stratification systems are available to predict the likelihood of inguinal nodal involvement and therapeutic planning and are based on a combination of histological grade and pT stage. Strongest predictive power is given by the combination of histological grade, deepest anatomical level of infiltration, and presence of perineural invasion. These factors are used for constructing the Prognostic Index. TNM8 now includes perineural invasion as a stratifier between T1a and T1b tumours in addition to LVI.[8]

Perineural invasion may be difficult to assess, especially in small and/or superficial biopsies. Immunohistochemistry with neural markers may be helpful in some circumstances.

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Note 13 - Associated penile intraepithelial neoplasia (PeIN)[14,45,51-55] (Recommended)

Reason/Evidentiary Support

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 Erythroplasia of Queyrat and Bowen's disease and the adoption of the encompassing term Penile Intraepithelial Neoplasia (PeIN) in pathological reports.

The new WHO classification of Penile Intraepithelial Neoplasia distinguishes three groups: 1. Non HPV related (differentiated or simplex), 2. HPV related (undifferentiated) PeIN (basaloid, warty and warty-basaloid) and 3. Others (pleomorphic, spindle, clear cell, pagetoid).[28] Undifferentiated HPV related PeIN shows full thickness warty and/or basaloid features (previously designated severe dysplasia/carcinoma in situ*)*. Differentiated PeIN usually involves only the basal layer and is associated with architectural atypia and aberrant keratinisation with features similar to that seen in precancerous lesions of the vulva. Undifferentiated PeIN is associated with p16 positivity and warty/basaloid invasive tumours but differentiated PeIN is associated with lichen sclerosis (balanitis xerotica obliterans), more commonly seen with verrucous and pseudohyperplastic tumours, and is usually p16 negative. It should also be noted that PeIN of any type is often multifocal.

The presence and subtype of PeIN should be reported together with its margin status independent of associated invasive tumour. The splitting of PeIN into subgrades (for example I-III or low-grade/high-grade) is not recommended by the authors. Written reports should indicate the subtype and extent of PeIN and whether or not there is margin involvement.

Precancerous lesions identical to differentiated and undifferentiated PeIN are seen in the distal penile 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 of either 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 if it is the only abnormality present without invasive carcinoma.

Immunohistochemistry with p16 may be of help in subclassifying PeIN but is not regarded as mandatory. It may also be of use in identifying high-risk HPV in atypical condylomas.

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Note 14 - Margin status[56,57] (Required)

Reason/Evidentiary Support

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. Positive margins must be recorded by site and microscopic distance of tumour from close margins (5 mm or less) recorded in mm. 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 linear extent of individual involved margins is a non core item but is valued by surgeons in assessing their techniques.

Staging in the presence of positive margins needs to be undertaken but made clear to clinicians. The term 'at least', as in pT2 at least, may be used to indicate a positive margin. It is not helpful to clinicians not to stage if margins are positive.

The deep central soft tissue margin is defined as areas of intervening tissue not identified as periurethral tissue, corpus cavernosum or circumferential shaft margins or may be used if the specific site of the deep margin is indeterminate.

Margins of resection for penile specimens (except circumcision)

Urethral

Periurethral tissues including lamina propria and corpus spongiosum

Corpus cavernosum

Circumferential margins of bare penile shaft

Peripheral skin

Deep central soft tissue margin (other than periurethral tissue, corpus cavernosum or circumferential shaft)

Margins of resection of circumcision specimens

Coronal sulcus/glans margin

Peripheral cutaneous margin

Deep central soft tissue margin

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Note 15 - Lymph node status[2-4,6,9,10,14,58] (Required)

Reason/Evidentiary Support

Nodal involvement is a recognised predictor of poor prognosis. In node positive disease, the number of positive nodes, the presence of ECS and the level of nodal involvement (pelvic versus inguinal) have been shown to influence survival by multivariate analysis and this is reflected in TNM7[6,7] and TNM8[8] which classify 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. However in penile TNM8[8] the number of nodes which stratifies the staging between N1 and N2 is two or more unilateral nodes rather than one or more in TNM7.[6,7] The extent of inguinal lymph node involvement including number of nodes involved and presence or absence of ECS is used to determine the need for pelvic node sampling or excision.

The size of the largest nodal tumour deposit (not the lymph node size) must also be recorded as there is evidence that this may affect prognosis in penile cancer. Both TNM7 and TNM8 classify very small amounts of tumour as micrometastases (up to 0.2 mm)[6-8,59] and isolated tumour cells as N0 (i+).[8] However there is no evidence for a prognostic cut-off point for lymph node metastasis size in penile cancer so it is recommended in that maximum dimension of largest tumour deposit is recorded and tumour deposits over 0.2 mm staged as N1.

For urethral cancer in TNM7[6,7] the size of metastasis in a single regional node, if greater than 2 cm, stratifies between N1 and N2 nodes or if there are multiple nodes involved, but in TNM8[8] there is no metastasis size specified and the only stratifier is between single and multiple regional nodes.

Tumour presence or absence, size of tumour deposit and presence or absence of ECS are reported separately for each individual node site in both nodal resections and sentinel nodes. Occasionally individual tumour cells are identified in the peripheral sinus. The significance of these is uncertain but they should be described within reports. Immunohistochemistry is essential for the assessment of sentinel lymph nodes. 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.

Although the N categories differ for P(p)enile and U(u)rethral primary tumours it is recommended that data items as specified in this section are recorded for tumours of both these primary sites as tumours of the distal, as opposed to proximal, urethra appear to spread in the same way to local lymph nodes as do those of the penis.

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Note 16 – Pathological staging (Required and Recommended)

Reason/Evidentiary Support

This dataset includes the AJCC TNM 8th edition[8] definitions. The implementation of AJCC TNM 8th edition has been deferred until January 2018 in some jurisdictions. UICC 7th edition[6] or AJCC 7th edition[7] may be useful in the interim. If TNM 7th edition is used the following points should be noted:

1) Perineural invasion is now included as a stratifier between T1a and T1b tumours of the penis in addition to lymphovascular invasion and high grade in TNM8.

2) The division between T2 and T3 in TNM8 of the penis is entirely dependent on whether there corpus spongiosum or corpus cavernosum invasion irrespective of urethral involvement. This is the most significant change between TNM7 and TNM8.

3) The number of unilateral nodes to indicate N2 rather than N1 of the penis has increased to 3 from 2.

4) The size of metastasis is no longer used as a stratifier between N1 and N2 in unilateral regional nodes in urethral cancer.

5) The use of TX is to be avoided if at all possible and MX is not to be used.

6) Pathological staging should not be reported if the specimen submitted is insufficient for definitive staging. This may occur with biopsies or other specimens where depth of invasion or the required anatomical features cannot be discerned/assessed.

7) Staging in the presence of positive margins needs to be undertaken but made clear to clinicians. The term ‘at least’, as in pT2 at least, may be used to indicate a positive margin. It is not helpful to clinicians omit the stage if margins are positive.

By convention, the designation T refers to a primary tumour that has not been previously treated. The symbol p refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumour or a biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesion. Pathologic staging is usually performed after surgical resection of the primary tumour.

Additional Descriptor

The m suffix indicates the presence of multiple primary tumours and is recorded in parentheses, e.g. pTa(m)N0.

Tumours of the Penis and Foreskin (TNM7 and TNM8)[1,6,17,48,49]

Primary Tumour (T)

Changes between TNM7 and TNM8 are indicated and/or highlighted in bold

TX Primary tumour cannot be assessed.

T0 No evidence of primary tumour.

Tis Carcinoma in situ (Penile intraepithelial neoplasia [PeIN]).

Ta TNM7* Non invasive verrucous carcinoma.

TNM8* Non invasive localised squamous cell carcinoma

T1 TNM7 Tumour invades subepithelial connective tissue

TNM8 Glans: Tumour invades lamina propria

Foreskin: Tumour invades dermis, lamina propria or dartos fascia

Shaft: Tumour invades connective tissue between epidermis and corpora regardless of location

All sites with or without LVI or perineural invasion and is or is not high grade

T1a **Tumour invades lamina propria or subepithelial connective tissue and is without lymphovascular or perineural invasion and is not high grade (i.e. grade 3 or sarcomatoid)

T1b ** Tumour invades lamina propria or subepithelial connective tissue and exhibits lymphovascular or perineural invasion and or is high grade (i.e. grade 3 or sarcomatoid)

T2 TNM7 Tumour invades corpus spongiosum or cavernosum.

TNM8 Tumour invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion

T3 TNM7 Tumour invades urethra.

TNM8 T3 Tumour invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion

T4 Tumour invades other adjacent structures.

*The dataset authors' view is that the category of non invasive verrucous carcinoma in TNM7 and non invasive localised squamous cell carcinoma in AJCC TNM8 is to be avoided as it is not evidence based.

** AJCC TNM8 introduces Perineural invasion into the pT1 category but UICC and AJCC TNM7 do not include perineural invasion as a stratifier in the pT1 category.

Regional Lymph Nodes (N)

pNX Lymph node metastasis cannot be established.

pN0 No lymph node metastasis.

pN1 TNM7 Metastasis in a single inguinal lymph node.

TNM8 Two or more inguinal metastases without extranodal extension (ENE)

pN2 TNM7 Metastases in multiple or bilateral inguinal lymph nodes.

TMN8 Three or more unilateral inguinal metastases or bilateral metastases

pN3 ENE of lymph node metastases or pelvic lymph node metastases.

Distant Metastasis (M)

M0 No distant metastasis (clinical category only).

M1 Distant metastasis present.

M1 includes lymph node metastasis outside of the true pelvis in addition to visceral or bone sites.

Accurate staging and grading of tumours are used to determine subsequent clinical management and follow-up.

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.

Although there is a category of non-invasive verrucous carcinoma in the primary tumour classifications (Ta) in TNM7, 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. Non invasive localised tumours of the penis of any subtype are exceptionally rare in the authors experience.

Staging of pT1 is subdivided in TNM7 into pT1a for low-risk tumours and pT1b for high-risk tumours depending on the absence or presence of high-grade tumour and/or LVI. TNM8 also includes perineural invasion as a stratifier between T1a and T1b. The number of unilateral nodes needed upstage from pN1 to N2 has increased from two to three in TNM8. Metastatic tumour in regional lymph nodes with extranodal spread is categorised as pN3.

It was initially proposed that the pT2 primary tumour classification be subdivided to distinguish between invasion into the spongiosum and cavernosum, as some reports show that risk of metastases in increased in patients with invasion of the cavernosa. The RCPath dataset published in 2015 recommend substaging of T2 penile tumours into T2a (corpus spongiosum invasion) and T2b (corpus cavernosum invasion) as this is evidence based.[1] TNM8 now recommends that involvement of the corpus spongiosum is classified as T2 and involvement of corpora cavernosa is T3 irrespective of urethral involvement. The RCPath dataset is also being updated in 2017 to reflect TNM8.

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.

Use of the category TX is to be avoided and the designation e.g. 'T (numerical value) 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.

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 M0 should not be used in pathological staging. The term MX is no longer in use.

Tumours of the Distal Penile Urethra (TNM7 and TNM8)[6,14]

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). There are only minimal changes between TNM7 and TNM8.

Primary Tumour (T) of the Male Penile Urethra

TX Primary tumour cannot be assessed.

T0 No evidence of primary tumour.

Ta Non-invasive papillary carcinoma*.

Tis Carcinoma in situ**.

T1 Tumour invades subepithelial connective tissue.

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

T3 Tumour invades any of the following: corpus cavernosum.

T4 Tumour invades other adjacent organs.

* The dataset authors' view is that the use of this category for non invasive squamous localised squamous cell carcinoma is to be avoided as it is not evidence based. This category includes non-invasive papillary 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 (N)

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph node metastasis.

N1 TNM7 Metastasis measuring up to 2 cm or less in greatest dimension in a single lymph node.

TNM8 Single regional lymph node metastasis

N2 TNM7 Metastasis more than 2 cm in greatest dimension in a single node, or metastases of any size in multiple nodes.

TNM8 Multiple regional lymph node metastases

There are no different cN or pN categories in the Urethral tumour TNM which contrasts with the penile TNM.

Distant Metastasis (M)

M0 No distant metastasis*

M1 Distant metastasis.

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

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