# 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: [ ]

Scope of this dataset: [ ]

## Elements in black text are CORE. Elements in grey text are NON-CORE.

- Indicates multi-select values
- Indicates single select values

## CLINICAL INFORMATION (select all that apply) (Note 1)
- Information not provided
- Previous history of penile or urethral cancer, specify
- Previous therapy, specify
- Previous HPV infection, specify
- Other clinical information, specify

## OPERATIVE PROCEDURE (select all that apply) (Note 2)
- Not specified
- Partial penectomy
- Radical penectomy
- Glans preserving
- Lymphadenectomy
- Sentinel
- Glansectomy
- Circumcision (partial or complete)
- Incisional/punch biopsy
- Excisional biopsy
- Urethrectomy
- Left, number of site(s)
- Right, number of site(s)
- Inguinal
- Left
- Right
- Pelvic
- Left, specify site(s)
- Right, specify site(s)
- Other, specify site(s)

## TUMOUR SITE (select all that apply) (Note 3)
- No macroscopically visible tumour
- Glans penis
- Coronal sulcus
- Foreskin
- Distal penile urethra
- Body/shaft of penis

## TUMOUR FOCALITY (Note 4)
- Unifocal
- Multifocal
- Specify number of tumours

## TUMOUR DIMENSIONS (Note 5)
- Cannot be assessed
- Maximum tumour dimension
- Additional dimensions

## BLOCK IDENTIFICATION KEY (Note 6)
(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

## HISTOLOGICAL TUMOUR TYPE (Note 7)
(Value list based on the World Health Organization (WHO) Classification of Urinary and Male Genital Tumours (2022))
- Squamous cell carcinoma, HPV-associated
- Basaloid squamous cell carcinoma
- Warty carcinoma
- Clear cell squamous cell carcinoma
- Lymphoepithelial carcinoma
- Mixed squamous cell carcinomas, specify subtypes
- Squamous cell carcinoma, HPV-independent
- Squamous cell carcinoma, usual type
- Verrucous carcinoma (including carcinoma cuniculatum)
- Papillary squamous cell carcinoma
- Sarcomatoid squamous cell carcinoma
- Mixed squamous cell carcinomas, specify subtypes
- Squamous cell carcinoma, NOS
- Other, specify

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

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HISTOLOGICAL TUMOUR GRADE (Note 8)
(Applicable for resection specimens only)
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- Sarcomatoid areas present

EXTENT OF INVASION (select all that apply) (Note 9)
(Applicable to biopsy specimens and resection specimens with tumours at the margins)

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 tunica albuginea
- 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

Tumour thickness

Depth of invasion

TUMOUR PATTERN OF INVASION (Note 10)
(Applicable for partial or radical penectomy)
- Pushing (Broad base)
- Infiltrative (Jagged)
- Other, specify

LYMPHOVASCULAR INVASION (Note 11)
- Indeterminate
- Not identified
- Present

PERINEURAL INVASION (Note 12)
- Indeterminate
- Not identified
- Present

ASSOCIATED PENILE INTRAEPITHELIAL NEOPLASIA (PeIN) (Note 13)
- Not identified
- Present
- Warty and/or Basaloid
- Differentiated

MARGIN STATUS (Note 14)
Urethral margin
(Applicable to primary tumours of the penis and foreskin - resections and excision biopsy only)
- Cannot be assessed
- Not involved
  - Distance to invasive tumour
    - mm OR >5 mm
  - Involved by PeIN only
  - Involved by invasive carcinoma

Proximal urethral margin
(Applicable to primary tumours of the urethra)
- Cannot be assessed
- Not involved
  - Distance to invasive tumour
    - mm OR >5 mm
  - Involved by PeIN only
  - Involved by invasive carcinoma

Peri-urethral tissues
- Cannot be assessed
- Not involved
  - Distance to invasive tumour
    - mm OR >5 mm
  - Involved by invasive carcinoma

Corpus cavernosum
- Cannot be assessed
- Not involved
  - Distance to invasive tumour
    - mm OR >5 mm
  - Involved by PeIN only
  - Involved by invasive carcinoma

Circumferential shaft margin
- Cannot be assessed
- Not involved
  - Distance to invasive tumour
    - mm OR >5 mm
  - Involved by invasive carcinoma

Peripheral cutaneous margin
- Cannot be assessed
- Not involved
  - Distance to invasive tumour
    - mm OR >5 mm
  - Involved by PeIN only
  - Involved by invasive carcinoma
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**MARGIN STATUS** (Note 14) continued

**Peripheral glans margin**
- Cannot be assessed
- Not involved
  - Distance to invasive tumour
    - mm OR □ > 5 mm
- Involved by PeIN only
- Involved by invasive carcinoma

**Deep soft tissue margins (NOS)**
- Cannot be assessed
- Not involved
  - Distance to invasive tumour
    - mm OR □ > 5 mm
- Involved by PeIN only
- Involved by invasive carcinoma

**Other margin, specify**

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

**LYMPH NODE STATUS** (Note 15)

**Inguinal nodes - Sentinel**

**LEFT**
- No nodes submitted or found
- Number of lymph nodes examined
- Not involved
- Isolated tumour cells only
- Involved
  - Number of involved lymph nodes
- Number cannot be determined

**Maximum dimension of largest deposit**
- mm

**Extranodal extension**
- Indeterminate
- Not identified
- Present

**RIGHT**
- No nodes submitted or found
- Number of lymph nodes examined
- Not involved
- Isolated tumour cells only
- Involved
  - Number of involved lymph nodes
- Number cannot be determined

**Maximum dimension of largest deposit**
- mm

**Extranodal extension**
- Indeterminate
- Not identified
- Present

**Inguinal nodes - Non sentinel**

**LEFT**
- No nodes submitted or found
- Number of lymph nodes examined
- Not involved
- Isolated tumour cells only
- Involved
  - Number of involved lymph nodes
- Number cannot be determined

**Maximum dimension of largest deposit**
- mm

**Extranodal extension**
- Indeterminate
- Not identified
- Present

**RIGHT**
- No nodes submitted or found
- Number of lymph nodes examined
- Not involved
- Isolated tumour cells only
- Involved
  - Number of involved lymph nodes
- Number cannot be determined

**Maximum dimension of largest deposit**
- mm

**Extranodal extension**
- Indeterminate
- Not identified
- Present

*Extranodal extension is synonymous with extracapsular extension/spread.*
LYMPH NODE STATUS (Note 15) continued

Pelvic nodes

LEFT
- No nodes submitted or found
- Number of lymph nodes examined
- Not involved
- Isolated tumour cells only
- Involved
  - Number of involved lymph nodes
- Number cannot be determined
  - Maximum dimension of largest deposit
  - Extranodal extension
    - Indeterminate
    - Not identified
    - Present

RIGHT
- No nodes submitted or found
- Number of lymph nodes examined
- Not involved
- Isolated tumour cells only
- Involved
  - Number of involved lymph nodes
- Number cannot be determined
  - Maximum dimension of largest deposit
  - Extranodal extension
    - Indeterminate
    - Not identified
    - Present

Other node(s), specify laterality and site(s)
- Number of lymph nodes examined
- Not involved
- Isolated tumour cells only
- Involved
  - Number of involved lymph nodes
- Number cannot be determined
  - Maximum dimension of largest deposit
  - Extranodal extension
    - Indeterminate
    - Not identified
    - Present

COEXISTENT PATHOLOGY (select all that apply) (Note 16)
- None identified
- Lichen sclerosus
- Other, specify

ANCILLARY STUDIES (Note 17)
- Not performed
- Performed (select all that apply)
  - p16, specify test(s) and result(s)
  - p53, specify test(s) and result(s)
  - Ki-67 proliferation index
  - Cytokeratin and/or Epithelial Membrane Antigen (EMA), specify test(s) and result(s)
  - PD-L1, specify test(s) and result(s)
  - Other, record test(s), methodology and result(s)

Representative blocks for ancillary studies, specify those blocks best representing tumour and/or normal tissue for further study

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*Extranodal extension is synonymous with extracapsular extension/spread.*
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PATHOLOGICAL STAGING (UICC TNM 8th edition)\(^b\) (Note 18)

TNM Descriptors (only if applicable) (select all that apply)
- m - multiple primary tumours
- r - recurrent
- y - post-therapy

**PENIS AND FORESKIN**

**Primary tumour (pT)**
- TX\(^c\) Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma in situ (PeIN)
- Ta Non-invasive localised squamous cell carcinoma\(^d\)
- T1 Tumour invades subepithelial connective tissue\(^e\)
  - T1a Tumour invades subepithelial connective tissue without lymphovascular invasion or perineural invasion and is not poorly differentiated
  - 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

**Regional lymph nodes (pN)**
- NX\(^c\) Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in one or two inguinal lymph nodes
- N2 Metastasis in more than two unilateral inguinal nodes or bilateral inguinal lymph nodes
- N3 Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of regional lymph node metastasis

**PENILE URETHRA**

**Primary tumour (pT)**
- TX\(^c\) Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Ta\(^f\) Non-invasive papillary, polypoid, or verrucous 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, beyond prostatic capsule, bladder neck (extraprostatic extension)
- T4 Tumour invades other adjacent organs (invasion of the bladder)

**Regional lymph nodes (pN)**
- NX\(^c\) Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single lymph node
- N2 Metastasis in multiple regional lymph nodes


\(c\) TX and NX should be used only if absolutely necessary.

\(d\) Including verrucous carcinoma.

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

\(f\) The consensus of the dataset authors is that the use of this category for verrucous carcinoma is to be avoided as it is not evidence based. This category includes non-invasive urothelial carcinomas but these are very rare in the distal urethra.
Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence\(^1\)). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

Non-morphological testing e.g., molecular or immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

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 in males.

The male urethra is divided into the anterior and posterior urethra. The anterior urethra extends from the perineal membrane to the urethral meatus and is divided into the penile urethra (surrounded by the corpus spongiosum urethra), which includes the fossa navicularis (surrounded by corpus spongiosum),\(^2\,^3\) The corpora cavernosa and the tunica albuginea extend only into the distal part of the glans penis. They generally do not extend around the fossa.\(^2\,^3\)
Squamous cell carcinomas (SCC) of the fossa navicularis are reported using this dataset, while those arising from the proximal anterior urethra are reported using the ICCR Carcinomas of the urethra dataset.4

Melanomas and other urethral carcinomas are not included in the scope of this dataset—separate ICCR datasets are available and should be used for these neoplasms.5

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours, Urinary and Male Genital Tumours, 5th edition, 2022.6 The ICCR dataset includes 5th edition Corrigenda, November 2022.7

Gross images are included in this dataset given the complexity of this carcinoma to improve consistency of recording data.

† Back

Note 1 – Clinical information (Non-core)

The provision of accurate clinical information and detail is important to provide context to the specimen. A history of any previous penile or urethral cancer, or precursor lesion is important. Information regarding a history of previous human papillomavirus (HPV) infection is important since penile cancer can develop along HPV-dependent and HPV-independent pathways.8

Knowledge of the previous history of any therapy (chemotherapy, radiotherapy, chemoradiation) is important because this can have a marked effect on the pathologic appearances of the penile tumour (gross and histologic).9

† Back

Note 2 – Operative procedure (Core)

Surgery forms the cornerstone of therapy for penile cancer. The most relevant advancement in surgery for penile cancer has been the principle of penile preservation and reconstructive techniques.10 Treatment of the primary tumour should include consideration for organ-sparing modalities. Lesions confined to the foreskin can be treated with circumcision alone and often any extension onto the penile coronal ridge can be excised at the same time. Small lesions on the distal penile skin or glans penis can be treated by wide local excision.11

Partial or complete glansectomy may be considered for patients with penile cancer invading the corpus spongiosum. For patients with involvement of the corpora cavernosa, partial or subtotal/total penectomy is the standard of care.12

† Back
Note 3 – Tumour site (Core)

The majority of penile SCCs originate in the glans penis (80%), foreskin (14%) or coronal/balanopreputial sulcus (4%). SCC arising in the skin of the penile shaft is exceptionally rare at around 2%. Detailing the anatomic site of penile SCC is important since tumour-site specific survival differences have been reported (see Figures 1 and 2). Carcinomas exclusively involving the foreskin are associated with a better prognosis than those arising on the glans penis, partly because foreskin tumours are limited to a pT1 stage. Patients with penile SCC invading into the corpus spongiosum (pT2 stage) and corpus cavernosum (pT3 stage) have a greater likelihood of metastases.

Figure 1: Gross appearance of the distal portion of the penis with a squamous cell carcinoma (CA), located in the coronal sulcus. (CS) which includes foreskin (FS) glans penis (GL), corpus spongiosum (CS), tunica albuginea (TA), corpus cavernosum (CC), dartos (DT), urethra (U) and skin (SK). Permission courtesy of Dr Isabel Alvarado-Cabrero.
Note 4 – Tumour focality (Non-core)

A solitary tumour is the most common clinical presentation. True multifocal or synchronous penile carcinomas are rare. Multifocal or synchronous penile squamous cell carcinomas (SCC) tend to be associated with HPV associated and HPV independent penile intraepithelial neoplasia (PeIN) (see Figure 3).15

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**Figure 2:** Gross picture of total penectomy (cross section) with a squamous cell carcinoma with extension to Buck Fascia (BF), illustrating deep subcutaneous circumferential soft tissue, tunica albuginea (TA), corpora cavernosa (CC), corpus spongiosum (S) and urethra (U). Permission courtesy of Dr Isabel Alvarado-Cabrero.
Figure 3: Total penectomy with a multicentric squamous cell carcinoma. Permission courtesy of Dr Isabel Alvarado-Cabrero.

Note 5 – Tumour dimensions (Core and Non-core)

Gross tumour measurement in penile carcinomas may be done in three dimensions but measuring the maximum diameter is considered as core. The size of the lesion correlates with overall and disease-specific survival.16

Note 6 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. 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. It may be useful to have a digital image of the gross specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials.
Note 7 – Histological tumour type (Core)

The WHO Classification of Tumours, Urinary and Male Genital Tumours, 5th edition, 2022, is used to classify and code malignant squamous epithelial tumours of the penis (Table 1). The ICCR dataset includes the 5th edition Corrigenda, November 2022.

Table 1: World Health Organization classification of tumours of the penis.

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>ICD-0-codes</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive squamous epithelial tumours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma, HPV-associated</td>
<td>8085/3</td>
<td></td>
</tr>
<tr>
<td>Basaloid squamous cell carcinoma</td>
<td>8083/3</td>
<td></td>
</tr>
<tr>
<td>Warty carcinoma</td>
<td>8054/3</td>
<td></td>
</tr>
<tr>
<td>Clear cell squamous cell carcinoma</td>
<td>8084/3</td>
<td></td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td>8082/3</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma, HPV-independent</td>
<td>8086/3</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma, usual type</td>
<td>8086/3</td>
<td></td>
</tr>
<tr>
<td>Verrucous carcinoma (including carcinoma cuniculatum)</td>
<td>8051/3</td>
<td></td>
</tr>
<tr>
<td>Papillary squamous cell carcinoma</td>
<td>8052/3</td>
<td></td>
</tr>
<tr>
<td>Sarcomatoid squamous cell carcinoma</td>
<td>8074/3</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma, NOS*</td>
<td>8070/3</td>
<td></td>
</tr>
<tr>
<td><strong>Other epithelial tumours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>8560/3</td>
<td></td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>8430/3</td>
<td></td>
</tr>
<tr>
<td>Paget disease, extramammary</td>
<td>8542/3</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma precursors, HPV-associated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High grade squamous intraepithelial lesion</td>
<td>8077/2</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma precursors, HPV-independent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiated penile intraepithelial neoplasia</td>
<td>8071/2</td>
<td></td>
</tr>
</tbody>
</table>

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; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Incorporates all relevant changes from the 5th edition Corrigenda, November, 2022.

* p16 immunohistochemistry not available.


There are two types of penile squamous cell carcinomas (SCCs), one is related to HPV infection while the other is likely related to chronic inflammation conditions, such as lichen sclerosis. Most HPV-associated SCCs have a warty or basaloid morphology, and the latter tumours tend to have a worse prognosis than the usual type of SCC. It is recommended that the type of penile SCC (HPV-associated or HPV-independent) be documented in the pathology report. In SCC where morphologic features on haematoxylin-eosin (H&E) do not allow the clear cut designation of a variant subtype and p16 is not available or is negative the tumour should be designated as SCC-NOS.

The proforma lists only the most common types/subtypes of established prognostic importance. Other tumours may be recorded under ‘other, specify’.
Emerging entities - Medullary carcinoma

Medullary carcinoma is a poorly differentiated carcinoma that grows in solid sheets composed of anaplastic large cells with prominent nucleoli. The tumour is characteristically rich in inflammatory cells.18

Note 8 – Histological tumour grade (Core)

Penile SCCs are graded using a three-tiered system based on WHO recommendations (Table 2).6 In this system, grade 1 tumours are well differentiated with minimal cell atypia, and grade 3 tumours are composed of anaplastic cells with little or no keratinisation. Tumours that do not meet the criteria for grades 1 or 3 belong to grade 2. Any proportion of grade 3 should be mentioned in the pathology report.19-22

Table 2: Grading of penile squamous cell carcinoma.

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

Adapted with permission from The Royal College of Pathologists (2015). Dataset for penile and distal urethral cancer histopathology reports. The Royal College of Pathologists.35

Note 9 – Extent of invasion (Core and Non-core)

There is a significant correlation between tumour involvement of anatomic levels and incidence of inguinal lymph node metastases. Superficial tumours (lamina propria invasive) are at low risk of metastases. Recent studies have suggested that corpus spongiosum and corpus cavernosum invasion should be separated into different pT categories owing to the differences in the potential for lymph node metastases and survival.23,24 The 8th edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM classifications (TNM8)25,26 redefine T2 as corpus spongiosum involvement and T3 as corpus cavernosum and/or tunica albuginea involvement (see Note 18 PATHOLOGICAL STAGING).
The depth of invasion (DOI) correlates with the risk of lymph node metastases. The DOI is measured from the epithelial-stromal junction of the adjacent epithelium to the deepest point of invasion.\textsuperscript{13} The DOI needs to be distinguished from tumour thickness, which is defined as the measurement from the tumour surface to the deepest point of tumour invasion. In the pathology report, both measurements can be mentioned. Penile SCC invading to a depth less than or equal to 5 millimetres (mm) have very low risk for regional lymph node metastases, whereas tumours with a depth of greater than 10 mm have a high metastatic potential.\textsuperscript{27,28} DOI also correlates with pT category, since tumours that invade deeper tend to be pT2 or pT3. DOI.\textsuperscript{29}

**Note 10 – Tumour pattern of invasion (Non-core)**

The front of invasion is the deepest part of an invasive carcinoma to the underlying stroma. It is important to evaluate the most complex area of tumour-stroma interface and consequently, assessment is meaningfully determined only in resection specimens. There are two patterns of tumour front invasion, infiltrative and pushing, both have proven prognostic value.\textsuperscript{30,31}

**Note 11 – Lymphovascular invasion (Core)**

Vascular invasion, lymphatic or venous, adversely affects prognosis of penile cancer. The TNM\textsuperscript{8,25,26} subcategorises T1 into T1a and T1b based on the absence or presence of LVI or poorly differentiated tumours. Venous invasion, which is less frequent, indicates a more advanced stage of the disease and is related to the compromise of the specialized erectile venous structures of corpus spongiosum and corpora cavernosa.\textsuperscript{32}

**Note 12 – Perineural invasion (Core)**

Perineural invasion is recognised as a predictor for regional lymph node metastases and is now added as another separation criterion for T1a and T1b tumours besides LVI and high grade histology.\textsuperscript{25-26} It is present in about one-third to one-half of patients with penile carcinomas. Risk group stratification systems that use perineural invasion as a component of the scoring methodology have validated its usefulness as a prognostic factor.\textsuperscript{33}

**Note 13 – Associated penile intraepithelial neoplasia (PeIN) (Non-core)**

Penile carcinomas show a bimodal pathway of carcinogenesis; therefore, precursor lesions can be broadly classified into PeIN HPV-associated and PeIN HPV-independent (see Figure 4). Differentiated PeIN is a HPV independent precursor characterised by dysplastic squamous epithelium primarily of basal and parabasal cells within an otherwise well-differentiated epithelium and intact basement membrane.\textsuperscript{6} Irrespective of
histological appearance, all PeIN including differentiated PeINs are considered high grade. Differentiated PeIN is commonly associated with lichen sclerosus, which is considered a risk factor for the development of penile cancer.

Human papillomavirus (HPV)-associated PeIN caused by HPV 16/18 can occur on the glans or foreskin (such cases in the past were sometimes referred to clinically as erythroplasia of Queyrat) or on the skin of the shaft of the penis (where it was called either Bowen’s disease which was usually a unifocal lesion or Bowenoid papulosis when multifocal). Differentiated PeIN shows multiple patterns, including basaloid (undifferentiated) and warty (condylomatous). HPV-associated PeINs are frequently seen adjacent to HPV-associated invasive carcinoma. Reports should mention the subtype and extent of PeIN and whether there is margin involvement.

![Gross picture of an opened radical circumcision specimen showing a lesion (differentiated penile intraepithelial neoplasia (PeIN)) on the inner mucosal surface.](image)

**Figure 4:** Gross picture of an opened radical circumcision specimen showing a lesion (differentiated penile intraepithelial neoplasia (PeIN)) on the inner mucosal surface. Permission courtesy of Dr Isabel Alvarado-Cabrero.

**Note 14 – Margin status (Core)**

Penile preserving techniques have led to closer surgical tumour resection margins and there is evidence that these surgical techniques do not significantly compromise local recurrence rates if tumour cells are not present at the margin itself. Specific margins of the specimen can be identified by using colored inks (see Figure 5). Positive margins must be recorded by site and microscopic distance of the tumour from close margins (≤5 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 the audit of pre-operative staging and/or surgical technique. Actual measurement of the linear extent of individual involved margins is a non-core item but is valued by surgeons in assessing their techniques. A pT category should be
assigned even in the presence of a positive margin(s). The term ‘at least’ may be used (e.g., at least pT2 in the setting of invasion of corpus spongiosum and margin involvement of corpus spongiosum) Margins to be evaluated depend on the extent of surgery; these generally include the glans penis mucosa, lamina propria, corpus spongiosum, urethra, skin with underlying fascia (Buck's and Dartos) and corpora cavernosa with tunica albuginea.\textsuperscript{35,36}

![Glansectomy specimen with a verruciform lesion (Verrucous carcinoma) (A - left), and surgical margins (B - right). Permission courtesy of Dr Isabel Alvarado-Cabrero.](image)

**Figure 5.** Glansectomy specimen with a verruciform lesion (Verrucous carcinoma) (A - left), and surgical margins (B - right). Permission courtesy of Dr Isabel Alvarado-Cabrero.

**Note 15 – Lymph node status (Core)**

The regional lymph nodes are the superficial and deep inguinal and pelvic lymph nodes. Penile cancer metastasizes in a stepwise manner through the lymphatic system, initially to the inguinal lymph nodes, then the pelvic lymph nodes and finally to distant lymph nodes. The status of inguinal lymph node metastases is the most important prognostic factor in patients with penile cancer. Factors associated with a higher risk of lymph node metastases include LVI, higher histologic grade, higher pT category, increased DOI, and infiltrative invasion.\textsuperscript{37-39}

Prophylactic inguinal lymphadenectomy, while providing the best survival in clinical LN-negative patients, may be overtreatment in patients that do not have metastases due to the high morbidity associated with that surgery. Considering that, dynamic sentinel node biopsy is a minimally invasive reliable procedure for vital staging of cN0 patients, who are at lower risk of lymph node metastases. If positive lymph nodes are found on dynamic sentinel node biopsy, radical inguinal lymph node dissection is recommended.\textsuperscript{40,41}

Patients with metastasis involving three or more unilateral or bilateral inguinal lymph nodes have poorer outcomes compared with metastasis involving one or two unilateral inguinal lymph nodes (60.5% versus 90.7% 3-year cancer specific survival).\textsuperscript{19,23} Laterality of lymph node metastasis further increases the accuracy of predicting the outcome, this is reflected in the 8\textsuperscript{th} edition of the TNM.\textsuperscript{25,26} pN1 now includes up to two unilateral inguinal lymph node metastases, while pN2 is more than three unilateral or bilateral inguinal lymph node metastases. The prognostic value of extranodal extension of carcinoma has also been noted as an adverse prognostic factor (when present, it is now staged as pN3) (see Note 18 PATHOLOGICAL STAGING).
The pathology report should include separately for each lymph node site, and site in both sentinel lymph node and lymph node resections: total number of lymph nodes, tumour presence or absence, number of lymph nodes with tumour, size of tumour deposit, and presence or absence of extranodal extension.8

Note 16 – Coexistent pathology (Non-core)

Recording the presence of precursor lesions and coexistent pathology is important for penile SCC since this gives insight into the pathogenesis of the tumour, specifically whether it is HPV-associated or HPV-independent. For instance, lichen sclerosus affects the genital region and is frequently associated with precancerous and cancerous lesions. When present adjacent to invasive carcinoma lichen sclerosus is commonly associated with areas of epithelial hyperplasia and atypia.42,43

Note 17 – Ancillary studies (Core and Non-core)

Immunohistochemistry has a key role in the pathology of penile cancer. There is a growing list of available products (antibodies) or antigen retrieval techniques, which all contribute to the broader utility of immunohistochemistry for solving diagnostic problems or for determining prognosis and response to treatment in penile cancer.44

p16 (Core)

Penile SCC is an uncommon and potentially lethal cancer, the biology of which is driven, at least in part, by high risk HPV status. After high risk HPV infection, the p16 protein is upregulated and can be detected in high risk HPV related malignancies by immunohistochemistry. The p16 protein is not only a surrogate for HPV expression but has become a reproducible, reliable, and cost-effective predictor of prognosis following a diagnosis of penile SCC.45-47

While this element is deemed core, consideration should be given to temporarily downgrading this to a non-core element until resources allow.

p53 (Non-core)

There is preliminary evidence of a significant association between p53 expression and mortality in penile cancer patients.48 p53 expression in penile cancer cells examined by immunohistochemistry may show prognostic values in the disease progression.49

Ki-67 (Non-core)

There is preliminary evidence of a correlation between Ki-67 immunohistochemical expression and the presence of lymph node metastasis.50 It has been reported that overexpression (>20% of nuclei) of the nuclear proliferative protein Ki-67 is associated with increased penile SCC metastases to inguinal lymph nodes independent of tumour stage and grade.51
Cytokeratin and/or Epithelial Membrane Antigen (EMA) (Non-core)

Cytokeratin and/or Epithelial Membrane Antigen (EMA) are useful for the assessment of micrometastases in sentinel lymph nodes as small metastases under 2 mm or single isolated tumour cells may be easily missed.52,53

PDL1 (Non-core)

Despite the current limited use of immune checkpoint inhibitors in penile cancer, several studies have been conducted to characterise PDL1 expression in this disease.54,55 In one study, 69% of patients with lymph node metastases demonstrated PDL1 positivity in the primary tumour.56 Whereas, results of another study demonstrated PDL1 positivity in 40% of the primary tumour samples analysed.57 Overall, the current literature suggests a PDL1 positivity between 40% and 69% among primary penile cancer samples.55-57

Emerging ancillary markers

The are a number of emerging markers in penile cancer, including microsatellite instability (MSI).58 The National Comprehensive Cancer Network (NCCN) guidelines in penile cancer do endorse the use of immunotherapy under subsequent-line systemic therapy for unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) tumour that has progressed following prior treatment and without alternative treatment options,58,59 or if tumour mutational burden-high (TMB-H), TMB ≥10 mutations per megabase (mut/Mb) in patients who have progressed on previously approved lines of therapy.60,61

Note 18 – Pathological staging (Core)

TNM staging should be assessed according to the agreed criteria of the UICC and AJCC 8th editions.25,26 Compared with the previous edition, TNM 8th edition25,26 includes changes to the primary tumour (T) such as: 1) broadening the Ta* definition to include non-invasive, localised SCC; 2) describing T1 by the histological level (e.g., lamina propria, dermis) depending on tumour location (glans, foreskin, or shaft); 3) perineural invasion is recognised as a predictor for regional lymph node metastases and is now added as another separation criterion besides LVI and high grade histology for T1a and T1b tumours; 4) T2 is now restricted to invasion into corpus spongiosum; 5) while invasion into corpus cavernosum and/or tunica albuginea is categorised as T3; and 6) urethral invasion, previously defined as T3 disease, can now be present in either T2 or T3 categories reflecting the prognostic significance of corporal invasion over urethral invasion.

In addition, the TNM 8th edition25,26 includes changes to the regional lymph node definitions, the most notable being pN1 defined as ≤2 unilateral inguinal metastases without extranodal extension, and pN2 as more than three, unilateral or bilateral inguinal metastases. The pN3 category remains defined as the presence of extranodal extension or positive pelvic lymph nodes.

* The Ta category is expanded in the TNM 8th edition25,26 and applies to both pure (well or completely sampled) verrucous carcinomas with no overt destructive invasion and non-invasive papillary, warty, basaloid, or mixed carcinomas.

Reporting of pathological staging categories (pT,pN,pM) is based on the evidence available to the pathologist at the time of reporting the resection specimen. A pT category is not assigned on biopsy. As indicated in UICC and AJCC TNM8,25,26 the final stage grouping of a patient’s tumour is based on a combination of pathological staging and other clinical and imaging information.
The reference document TNM Supplement: A commentary on uniform use, 5th edition (C Wittekind et al. editors) may be of assistance when staging.62

References

1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. BMC Med Res Methodol 9:34.


