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 CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

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
    - ☐ 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)*
    - ☐ Left, *specify site(s)*
    - ☐ Right, *specify site(s)*
- ☐ Other, *specify laterality and site(s)*
- ☐ Glansectomy
- ☐ Circumcision (partial or complete)
- ☐ Incisional/punch biopsy
- ☐ Excisional biopsy
- ☐ Urethrectomy

TUMOUR SITE (select all that apply) (Note 3)

- ◯ No macroscopically visible tumour
- ☐ Glans penis
- ☐ Coronal sulcus
- ☐ Foreskin
- ◯ Indeterminate
- ☐ 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 mm

Additional dimensions mm x mm

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*

DRAFT Version 2.0 Published XXXX ISBN: XXXX

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

____ mm

Depth of invasion

____ mm

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

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 invasive carcinoma

Other margin, *specify*

- ◯ 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**[a]
    - ◯ 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**[a]
    - ◯ 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**[a]
    - ◯ 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**[a]
    - ◯ Indeterminate
    - ◯ Not identified
    - ◯ Present

[a] *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 ____ mm

Extranodal extension[a]

- ◯ 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[a]

- ◯ 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 ____ mm

Extranodal extension[a]

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present

[a] *Extranodal extension is synonymous with extracapsular extension/spread.*

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)*
  - ☐ PDL1, *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*

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

[b] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 31st January 2024).*

[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.

⬆ **Back**

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).[13] 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.[14]

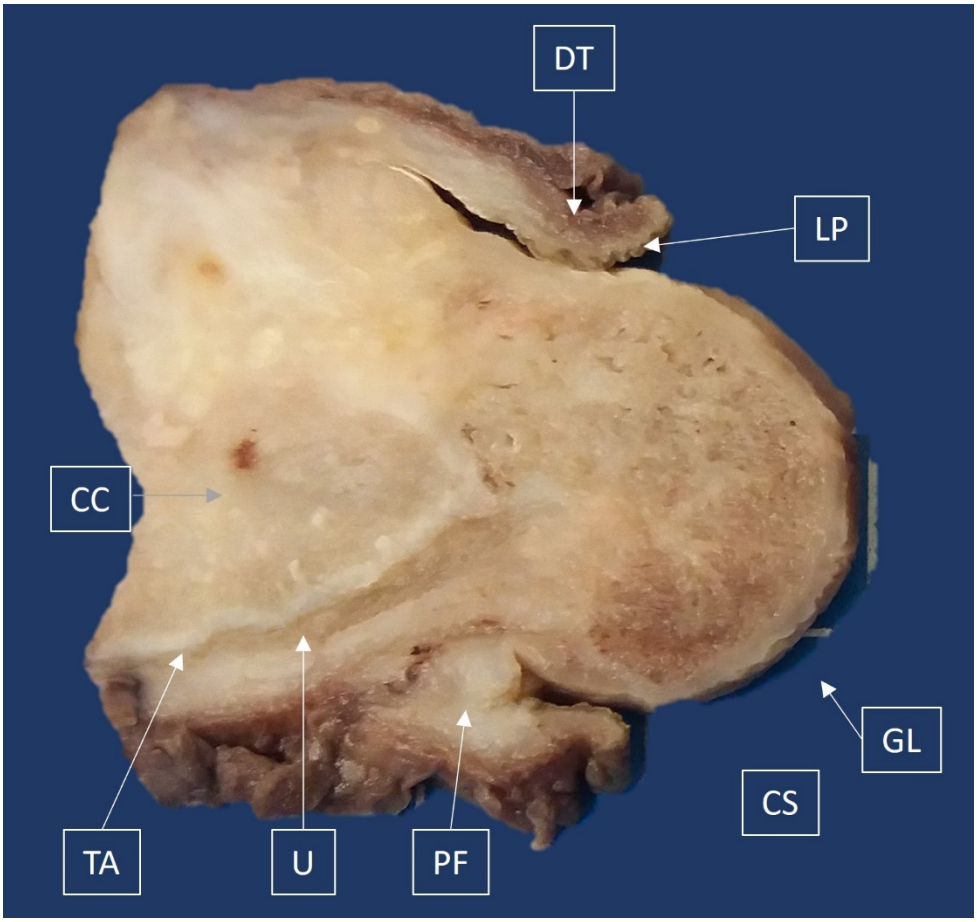

Figure 1: Gross appearance of the distal portion of the penis with a squamous cell carcinoma (CA), located in the coronal sulcus. (CS) which includes foreskin (FS) glans penis (GL), corpus spongiosum (CS), tunica albuginea (TA), corpus cavernosum (CC), dartos (DT), urethra (U) and skin (SK). *Permission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

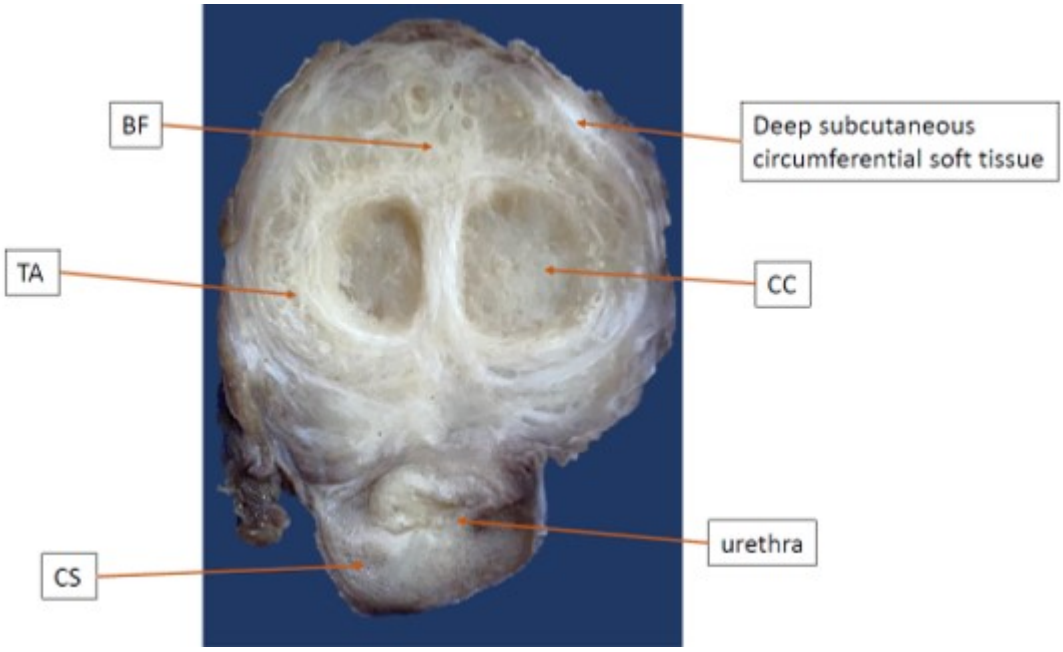

Figure 2: Gross picture of total penectomy (cross section) with a squamous cell carcinoma with extension to Buck Fascia (BF), illustrating deep subcutaneous circumferential soft tissue, tunica albuginea (TA), corpora cavernosa (CC), corpus spongiosum (S) and urethra (U). *Permission courtesy of Dr Isabel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

⬆ **Back**

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]

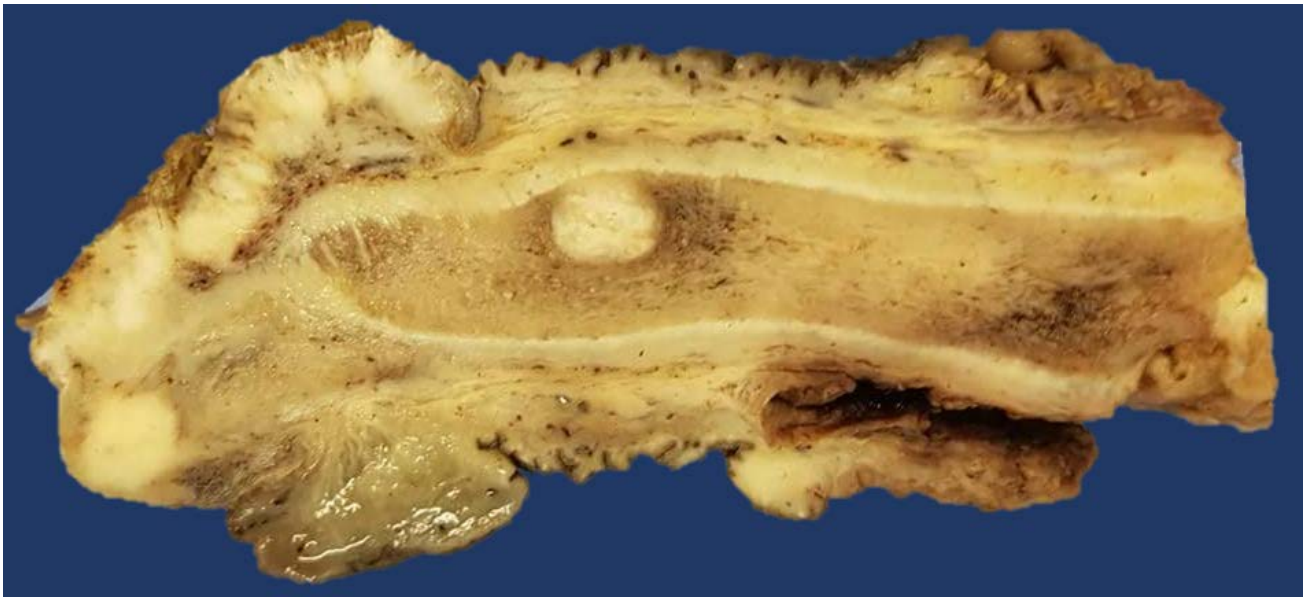

Figure 3: Total penectomy with a multicentric squamous cell carcinoma. *Permission courtesy of Dr Isabel Alvarado-Cabrero.*

Back

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]

Back

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.

Back

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).[6] The ICCR dataset includes the 5th edition Corrigenda, November 2022.[7]

Table 1: World Health Organization classification of tumours of the penis.[6]

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

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O).[17] 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.[7]

* 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 sclerosus. 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.[13] It is recommended that the type of penile SCC (HPV-associated or HPV-independent) be documented in the pathology report.[6,8] 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]

⬆ **Back**

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.

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

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]

⬆ **Back**

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.[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.[27,28] DOI also correlates with pT category, since tumours that invade deeper tend to be pT2 or pT3. DOI.[29]

⬆ Back

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.[30,31]

⬆ Back

Note 11 – Lymphovascular invasion (Core)

Vascular invasion, lymphatic or venous, adversely affects prognosis of penile cancer. The TNM8[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.[32]

⬆ Back

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.[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.[33]

⬆ Back

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.[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).[13] HPV-associated 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.[34]

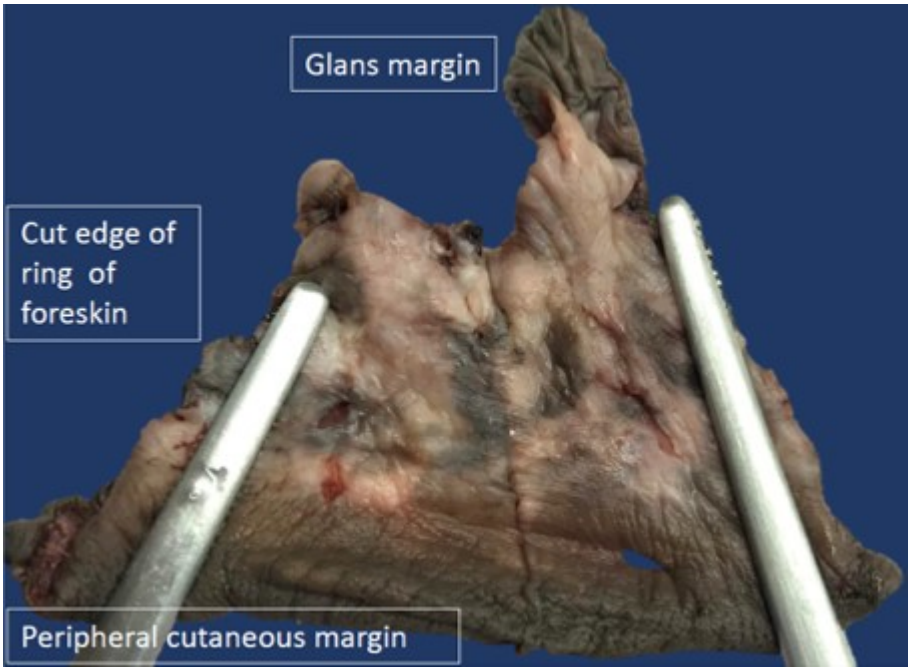

Figure 4: Gross picture of an opened radical circumcision specimen showing a lesion (differentiated penile intraepithelial neoplasia (PeIN)) on the inner mucosal surface. *Permission courtesy of Dr Isabel Alvarado-Cabrero.*

Back

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.[10]

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.[11] 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.[35,36]

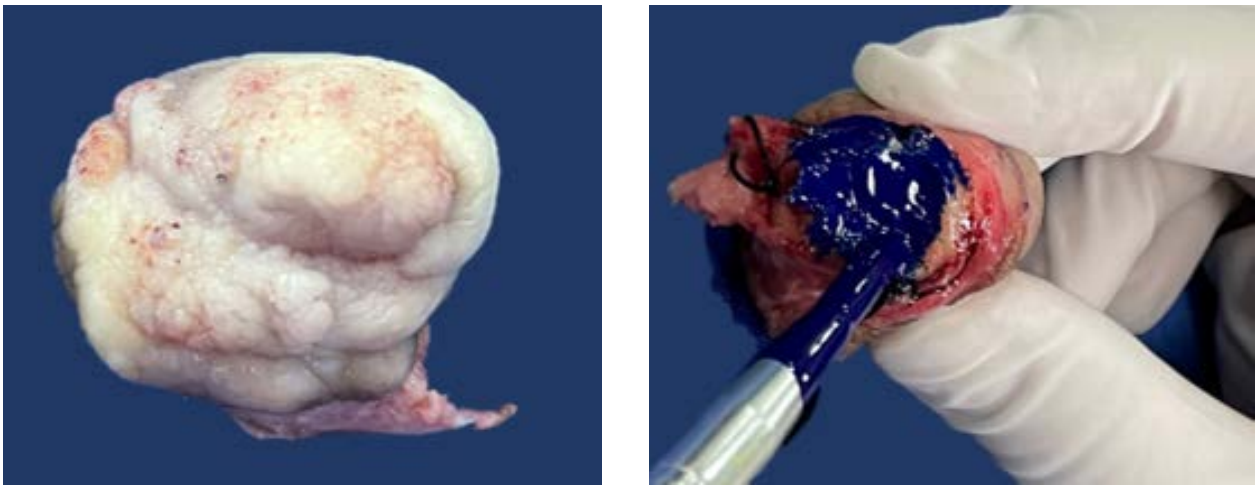

Figure 5. Glansectomy specimen with a verruciform lesion (Verrucous carcinoma) (A - left), and surgical margins (B - right). *Permission courtesy of Dr Isabel Alvarado-Cabrero.*

Back

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.[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.[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).[19,23] Laterality of lymph node metastasis further increases the accuracy of predicting the outcome, this is reflected in the 8th edition of the TNM.[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]

Back

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]

Back

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]

⬆ **Back**

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 edition[25,26] 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 edition[25,26] 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 TMN 8th edition[25,26] 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]

Back

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.

2 Abelson B, Sun D, Que L, Nebel RA, Baker D, Popiel P, Amundsen CL, Chai T, Close C, DiSanto M, Fraser MO, Kielb SJ, Kuchel G, Mueller ER, Palmer MH, Parker-Autry C, Wolfe AJ and Damaser MS (2018). Sex differences in lower urinary tract biology and physiology. *Biol Sex Differ* 9(1):45.

3 del Pozo-Jiménez G, Jara Rascón J, Aragón Chamizo J, Blaha I, Hernández Fernández C and Lledó García E (2014). [Anatomy and vascularization on the male urethra and penis]. *Arch Esp Urol* 67(1): 5-11.

4 International Collaboration on Cancer Reporting (2024). *Carcinoma of the urethra - urethrectomy specimen Histopathology Reporting Guide. 2nd edition*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/urethra-urethrectomy/ (Accessed TBC 2024).

5 International Collaboration on Cancer Reporting (2024). *ICCR Datasets*. Available from https://www.iccr-cancer.org/datasets/published-datasets/ (Accessed 2nd April 2024).

6 WHO Classification of Tumours Editorial Board (2022). *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8*, IARC Publications, Lyon.

7 WHO Classification of Tumours Editorial Board (2022). *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8 - Corrigenda November 2022.* Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Urinary-And-Male-Genital-Tumours-2022 (Accessed 2nd April 2024).

8 Brouwer OR, Albersen M, Parnham A, Protzel C, Pettaway CA, Ayres B, Antunes-Lopes T, Barreto L, Campi R, Crook J, Fernández-Pello S, Greco I, van der Heijden MS, Johnstone PAS, Kailavasan M, Manzie K, Marcus JD, Necchi A, Oliveira P, Osborne J, Pagliaro LC, Garcia-Perdomo HA, Rumble RB, Sachdeva A, Sakalis VI, Zapala Ł, Sánchez Martínez DF, Spiess PE and Tagawa ST (2023). European Association of Urology-American Society of Clinical Oncology Collaborative Guideline on Penile Cancer: 2023 Update. *Eur Urol* 83(6):548-560.

9 Yi XY, Cao DH, You PH, Xiong XY, Zheng XN, Peng G, Liao DZ, Li H, Yang L and Ai JZ (2022). Neoadjuvant chemotherapy for patients with locally advanced penile cancer: an updated evidence. *Asian J Androl* 24(2):180-185.

10 Fang A and Ferguson J (2020). Penile Sparing Techniques For Penile Cancer. *Postgrad Med* 132(sup4):42-51.

11 Pang KH, Alnajjar HM and Muneer A (2022). Advances in penile-sparing surgical approaches. *Asian J Urol* 9(4):359-373.

12 Peyraud F, Allenet C, Gross-Goupil M, Domblides C, Lefort F, Daste A, Yacoub M, Haaser T, Ferretti L, Robert G and Ravaud A (2020). Current management and future perspectives of penile cancer: An updated review. *Cancer Treat Rev* 90:102087.

13 Epstein JI M-GC, Ming Zhou, Cubilla AL (2020). *Tumors of the Prostate Gland, Seminal Vesicles, Penis, and Scrotum AFIP Atlas of Tumor and Non-Tumor Pathology, Series 5*. American Registry of Pathology, Washington DC, United States.

14 Li K, Le X, Wang J, Fan C and Sun J (2022). Tumor Location May Independently Predict Survival in Patients With M0 Squamous Cell Carcinoma of the Penis. *Front Oncol* 12:927088.

15 Menon S, Moch H, Berney DM, Cree IA, Srigley JR, Tsuzuki T, Compérat E, Hartmann A, Netto G, Rubin MA, Gill AJ, Turajlic S, Tan PH, Raspollini MR, Tickoo SK and Amin MB (2023). WHO 2022 classification of penile and scrotal cancers: updates and evolution. *Histopathology* 82(4):508-520.

16 Longpre MJ, Lange PH, Kwon JS and Black PC (2013). Penile carcinoma: lessons learned from vulvar carcinoma. *J Urol* 189(1):17-24.

17 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM and Whelan S (eds) (2020). *International Classification of Diseases for Oncology, Third edition, Second revision ICD-O-3.2*. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577 (Accessed 16th December 2023).

18 Cañete-Portillo S, Clavero O, Sanchez DF, Silvero A, Abed F, Rodriguez IM, Ayala G, Alemany L, Munoz N, de Sanjose S, Quint W, Bosch FX and Cubilla AL (2017). Medullary Carcinoma of the Penis: A Distinctive HPV-related Neoplasm: A Report of 12 Cases. *Am J Surg Pathol* 41(4):535-540.

19 Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW and Amin MB (2018). Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. *Eur Urol* 73(4):560-569.

20 Velazquez EF, Ayala G, Liu H, Chaux A, Zanotti M, Torres J, Cho SI, Barreto JE, Soares F and Cubilla AL (2008). Histologic grade and perineural invasion are more important than tumor thickness as predictor of nodal metastasis in penile squamous cell carcinoma invading 5 to 10 mm. *Am J Surg Pathol* 32(7):974-979.

21 Chaux A, Torres J, Pfannl R, Barreto J, Rodriguez I, Velazquez EF and Cubilla AL (2009). Histologic grade in penile squamous cell carcinoma: visual estimation versus digital measurement of proportions of grades, adverse prognosis with any proportion of grade 3 and correlation of a Gleason-like system with nodal metastasis. *Am J Surg Pathol* 33(7):1042-1048.

22 Sanchez DF, Soares F, Alvarado-Cabrero I, Cañete S, Fernández-Nestosa MJ, Rodríguez IM, Barreto J and Cubilla AL (2015). Pathological factors, behavior, and histological prognostic risk groups in subtypes of penile squamous cell carcinomas (SCC). *Semin Diagn Pathol* 32(3):222-231.

23 Sun M, Djajadiningrat RS, Alnajjar HM, Trinh QD, Graafland NM, Watkin N, Karakiewicz PI and Horenblas S (2015). Development and external validation of a prognostic tool for prediction of cancer-specific mortality after complete loco-regional pathological staging for squamous cell carcinoma of the penis. *BJU Int* 116(5):734-743.

24 Li Z, Li X, Lam W, Cao Y, Geng J, Ornellas AA, Zhou F and Han H (2021). Corpora Cavernos invasion vs. Corpus Spongiosum invasion in Penile Cancer: A systematic review and meta-analysis. *J Cancer* 12(7):1960-1966.

25 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control. TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.

26 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.

27 Li K, Wu G, Fan C and Yuan H (2021). The prognostic significance of primary tumor size in squamous cell carcinoma of the penis. *Discov Oncol* 12(1):22.

28 Hakenberg OW, Compérat E, Minhas A, Necchi A, Protzet C and Watkin N (2022). *EAU Guidelines on Penile Cancer*, European Association of Urology. ISBN 978-94-92671-16-5.

29 Sanchez DF, Fernandez-Nestosa MJ, Canete-Portillo S, Rodriguez I and Cubilla AL (2021). What Is New in the Pathologic Staging of Penile Carcinoma in the 8th Edition of AJCC TNM Model: Rationale for Changes With Practical Stage-by-stage Category Diagnostic Considerations. *Adv Anat Pathol* 28(4):209-227.

30 Guimarães GC, Lopes A, Campos RS, Zequi Sde C, Leal ML, Carvalho AL, da Cunha IW and Soares FA (2006). Front pattern of invasion in squamous cell carcinoma of the penis: new prognostic factor for predicting risk of lymph node metastases. *Urology* 68(1):148-153.

31 Aita G, da Costa WH, de Cassio Zequi S, da Cunha IW, Soares F, Guimaraes GC and Lopes A (2015). Pattern of invasion is the most important prognostic factor in patients with penile cancer submitted to lymph node dissection and pathological absence of lymph node metastasis. *BJU Int* 116(4):584-589.

32 Fankhauser CD, de Vries HM, Roussel E, Jakobsen JK, Issa A, Lee EWC, Schifano N, Alnajjar H, Castiglione F, Antonelli L, Oliveira P, Lau M, Parnham A, Albersen M, Watkin NA, Muneer A, Ayres BE, Brouwer OR and Sangar V (2022). Lymphovascular and perineural invasion are risk factors for inguinal lymph node metastases in men with T1G2 penile cancer. *J Cancer Res Clin Oncol* 148(9):2231-2234.

33 Chaux A, Caballero C, Soares F, Guimarães GC, Cunha IW, Reuter V, Barreto J, Rodríguez I and Cubilla AL (2009). The prognostic index: a useful pathologic guide for prediction of nodal metastases and survival in penile squamous cell carcinoma. *Am J Surg Pathol* 33(7):1049-1057.

34 Gianicco GA and AL Cubilla (2023). Updates in the pathology of penile intraepithelial neoplasia. *Diagnostic Histopathology* 29;6:276-282.

35 Anderson E, Yao HH and Chee J (2021). Optimal surgical margin for penile-sparing surgery in management of penile cancer-Is 2 cm really necessary? *BJUI Compass* 2(4):281-285.

36 Roussel E, Peeters E, Vanthoor J, Bozzini G, Muneer A, Ayres B, Sri D, Watkin N, Bhattar R, Parnham A, Sangar V, Lau M, Joice G, Bivalacqua TJ, Chipollini J, Spiess PE, Hatzichristodoulou G, de Vries L, Brouwer O and Albersen M (2021). Predictors of local recurrence and its impact on survival after glansectomy for penile cancer: time to challenge the dogma? *BJU Int* 127(5):606-613.

37 Zekan DS, Dahman A, Hajiran AJ, Luchey AM, Chahoud J and Spiess PE (2021). Prognostic predictors of lymph node metastasis in penile cancer: a systematic review. *Int Braz J Urol* 47(5):943-956.

38 Malik K, Chandrasekaran D, Kathiresan N and Raja A (2022). Factors Predicting Nodal Metastasis in Penile Cancer: Analysis from a Tertiary Center. *Urol Int* 106(7):716-721.

39 Kawase M, Takagi K, Kawada K, Ishida T, Tomioka M, Enomoto T, Fujimoto S, Taniguchi T, Ito H, Kameyama K, Yamada T, Kawase K, Kato D, Takai M, Iinuma K, Nakane K and Koie T (2022). Clinical Lymph Node Involvement as a Predictor for Cancer-Specific Survival in Patients with Penile Squamous Cell Cancer. *Curr Oncol* 29(8):5466-5474.

40 O'Brien JS, Teh J, Chen K, Kelly BD, Chee J and Lawrentschuk N (2022). Dynamic Sentinel Lymph Node Biopsy for Penile Cancer: Accuracy is in the Technique. *Urology* 164:e308.

41 Fallara G, Pozzi E, Onur Cakir O, Tandogdu Z, Castiglione F, Salonia A, Alnajjar HM and Muneer A (2023). Diagnostic Accuracy of Dynamic Sentinel Lymph Node Biopsy for Penile Cancer: A Systematic Review and Meta-analysis. *Eur Urol Focus* 9(3):500-512.

42 Cañete-Portillo S, Sanchez DF, Fernández-Nestosa MJ, Piris A, Zarza P, Oneto S, Gonzalez Stark L, Lezcano C, Ayala G, Rodriguez I, Hoang MP, Mihm MC and Cubilla AL (2019). Continuous Spatial Sequences of Lichen Sclerosus, Penile Intraepithelial Neoplasia, and Invasive Carcinomas: A Study of 109 Cases. *Int J Surg Pathol* 27(5):477-482.

43 Sewel A and Oxley J (2019). An overview of benign and premalignant lesions of the foreskin. *Diagnostic Histopathology* 25: 390-397.

44 Canete-Portillo S, Velazquez EF, Kristiansen G, Egevad L, Grignon D, Chaux A and Cubilla AL (2020). Report From the International Society of Urological Pathology (ISUP) Consultation Conference on Molecular Pathology of Urogenital Cancers V: Recommendations on the Use of Immunohistochemical and Molecular Biomarkers in Penile Cancer. *Am J Surg Pathol* 44(7):e80-e86.

45 Olesen TB, Sand FL, Rasmussen CL, Albieri V, Toft BG, Norrild B, Munk C and Kjær SK (2019). Prevalence of human papillomavirus DNA and p16(INK4a) in penile cancer and penile intraepithelial neoplasia: a systematic review and meta-analysis. *Lancet Oncol* 20(1):145-158.

46 Chahoud J, Zacharias NM, Pham R, Qiao W, Guo M, Lu X, Alaniz A, Segarra L, Martinez-Ferrer M, Gleber-Netto FO, Pickering CR, Rao P and Pettaway CA (2022). Prognostic Significance of p16 and Its Relationship with Human Papillomavirus Status in Patients with Penile Squamous Cell Carcinoma: Results of 5 Years Follow-Up. *Cancers (Basel)* 14(24):6024.

47 Sand FL, Rasmussen CL, Frederiksen MH, Andersen KK and Kjaer SK (2018). Prognostic Significance of HPV and p16 Status in Men Diagnosed with Penile Cancer: A Systematic Review and Meta-analysis. *Cancer Epidemiol Biomarkers Prev* 27(10):1123-1132.

48 Mohanty SK, Mishra SK, Bhardwaj N, Sardana R, Jaiswal S, Pattnaik N, Pradhan D, Sharma S, Kaushal S, Baisakh MR, Das S, Pradhan MR, Satapathy K, Pattnaik A, Sharma SK, Khadenga CR, Das S, Rath D, Nanda B and Parwani AV (2021). p53 and p16(ink4a) As Predictive and Prognostic Biomarkers for Nodal metastasis and Survival in A Contemporary Cohort of Penile Squamous Cell Carcinoma. *Clin Genitourin Cancer* 19(6):510-520.

49 Prapiska FF and Warli SM (2019). P53 and Survival Rate in Penile Cancer. *Open Access Maced J Med Sci* 7(7):1170-1173.

50 Pekarek L, Ortega MA, Fraile-Martinez O, García-Montero C, Casanova C, Saez MA, García-Honduvilla N, Alvarez-Mon M, Buján J, Diez-Nicolas V, Burgos JF and Gomez Dos Santos V (2022). Clinical and Novel Biomarkers in Penile Carcinoma: A Prospective Review. *J Pers Med* 12(9):1364.

51 Bowie J, Singh S, O'Hanlon C, Shiatis V, Brunckhorst O, Muneer A and Ahmed K (2021). A systematic review of non-HPV prognostic biomarkers used in penile squamous cell carcinoma. *Turk J Urol* 47(5):358-365.

52 Rutgers EJ (2008). Sentinel node biopsy: interpretation and management of patients with immunohistochemistry-positive sentinel nodes and those with micrometastases. *J Clin Oncol* 26(5):698-702.

53 Jakobsen JK (2022). Sentinel Node Methods in Penile Cancer - a Historical Perspective on Development of Modern Concepts. *Semin Nucl Med* 52(4):486-497.

54 Udager AM, Liu TY, Skala SL, Magers MJ, McDaniel AS, Spratt DE, Feng FY, Siddiqui J, Cao X, Fields KL, Morgan TM, Palapattu GS, Weizer AZ, Chinnaiyan AM, Alva A, Montgomery JS, Tomlins SA, Jiang H and Mehra R (2016). Frequent PD-L1 expression in primary and metastatic penile squamous cell carcinoma: potential opportunities for immunotherapeutic approaches. *Ann Oncol* 27(9):1706-1712.

55 Davidsson S, Carlsson J, Giunchi F, Harlow A, Kirrander P, Rider J, Fiorentino M and Andrén O (2019). PD-L1 Expression in Men with Penile Cancer and its Association with Clinical Outcomes. *Eur Urol Oncol* 2(2):214-221.

56 Joshi VB, Spiess PE, Necchi A, Pettaway CA and Chahoud J (2022). Immune-based therapies in penile cancer. *Nat Rev Urol* 19(8):457-474.

57 Chahoud J, Pickering CR and Pettaway CA (2019). Genetics and penile cancer: recent developments and implications. *Curr Opin Urol* 29(4):364-370.

58 Stoehr R, Wendler O, Giedl J, Gaisa NT, Richter G, Campean V, Burger M, Wullich B, Bertz S and Hartmann A (2019). No Evidence of Microsatellite Instability and Loss of Mismatch-Repair-Protein Expression in Squamous Cell Carcinoma of the Penis. *Pathobiology* 86(2-3):145-151.

59 Chadha J, Chahoud J and Spiess PE (2022). An update on treatment of penile cancer. *Ther Adv Med Oncol* 14:17588359221127254.

60 Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA and Diaz LA, Jr. (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 357(6349):409-413.

61 Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, Chung HC, Kindler HL, Lopez-Martin JA, Miller WH, Jr., Italiano A, Kao S, Piha-Paul SA, Delord JP, McWilliams RR, Fabrizio DA, Aurora-Garg D, Xu L, Jin F, Norwood K and Bang YJ (2020). Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 21(10):1353-1365.

62 Wittekind C, Brierley JD, van Eycken AL and van Eycken E (eds) (2019). *TNM Supplement: A Commentary on Uniform Use, 5th Edition* Wiley, USA.