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Carcinoma of the Urethra Histopathology Reporting Guide Urethrectomy Specimen

ICCR

Family/Last name | Date of birth DD – MM – YYYY

Given name(s)

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 (Note 1)

- ◯ Information not provided
- ◯ Information provided (select all that apply)
  - ☐ Previous history of urinary tract disease or distant metastasis
    - ☐ Carcinoma in situ, flat
    - ☐ Non-invasive papillary
    - ☐ Invasion into lamina propria
    - ☐ Invasion of muscularis propria or beyond
    - ☐ Distant metastasis
    - ☐ Other, *specify*
  - ☐ Previous therapy
    - ☐ Bacillus Calmette-Guerin (BCG)
    - ☐ Immunotherapy
    - ☐ Radiation therapy
    - ☐ Chemotherapy, systemic
    - ☐ Chemotherapy, intravesical, *specify*
    - ☐ Other, *specify*
  - ☐ Other clinical information, *specify*

OPERATIVE PROCEDURE (Note 2)

- ◯ Not specified
- ◯ Urethrectomy, partial
- ◯ Urethrectomy, complete
- ◯ Urethrectomy with cystectomy
- ◯ Urethrectomy with cystoprostatectomy
- ◯ Urethrectomy with penectomy
- ◯ Other, *specify*

ADDITIONAL SPECIMEN(S) SUBMITTED (Note 3)

- ◯ Not submitted
- ◯ Submitted, *specify*

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

- ◯ Not specified
- ◯ No macroscopically visible tumour

Male

- ☐ Penile
- ☐ Bulbomembranous
- ☐ Prostatic

Female

- ☐ Anterior
- ☐ Posterior

- ☐ Diverticula
- ☐ Other, *specify*

TUMOUR FOCALITY (Note 5)

- ◯ Unifocal
- ◯ Multifocal

TUMOUR DIMENSIONS (Note 6)

- ◯ No macroscopically visible tumour

Maximum tumour dimension (largest tumour) ____ mm

Additional dimensions (largest tumour) ____ mm X ____ mm

MACROSCOPIC EXTENT OF INVASION (select all that apply) (Note 7)

- ◯ No macroscopically visible tumour
- ◯ Non-invasive tumour visible
- ☐ Invasion into muscular wall
- ☐ Invasion into corpus spongiosum
- ☐ Invasion into corpus cavernosum
- ☐ Invasion into anterior vaginal wall
- ☐ Invasion into bladder wall
- ☐ Invasion into prostatic tissue
- ☐ Invasion into periprostatic tissue
- ☐ Involvement of other adjacent structures, *specify*

BLOCK IDENTIFICATION KEY (Note 8)

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

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HISTOLOGICAL TUMOUR TYPE (Note 9)

(Value list based on the World Health Organization Classification of Urinary and Male Genital Tumours, 5th Edition (2022))

- ◯ Urothelial carcinoma
- ◯ Squamous cell carcinoma
- ◯ Adenocarcinoma
- ◯ Tumours of Müllerian type
  - ◯ Clear cell adenocarcinoma
  - ◯ Endometrioid carcinoma
- ◯ Neuroendocrine carcinoma
  - ◯ Small cell neuroendocrine carcinoma
  - ◯ Large cell neuroendocrine carcinoma
  - ◯ Carcinoma mixed with neuroendocrine carcinoma
    - ____ %
- ◯ Other, *specify*

Histologic subtype and divergent differentiation (urothelial carcinoma)

- ◯ Not identified
- ◯ Present, *specify subtype and percentage* (select all that apply)
  - ☐ Squamous ____ %
  - ☐ Glandular ____ %
  - ☐ Nested ____ %
  - ☐ Micropapillary ____ %
  - ☐ Plasmacytoid ____ %
  - ☐ Sarcomatoid ____ %
  - ☐ Other, *specify* ____ %

Comments

NON-INVASIVE CARCINOMA[a] (select all that apply) (Note 10)

- ◯ Not identified
- ◯ Indeterminate
- ☐ Carcinoma in situ
  - ◯ Focal ◯ Multifocal
- ☐ Papillary urothelial carcinoma
- ☐ Other, *specify*

[a] *Core in cases of non-invasive carcinoma requiring cystectomy; non-core for all other.*

ASSOCIATED EPITHELIAL LESIONS (Note 11)

- ◯ Not identified
- ◯ Present, *specify*

HISTOLOGICAL TUMOUR GRADE[b] (Note 12)

- ◯ Not applicable
- ◯ Cannot be assessed

Urothelial carcinoma[c]

- ◯ Low grade
- ◯ High grade
- ◯ Other, *specify*

Squamous cell carcinoma or adenocarcinoma

- ◯ GX: Cannot be assessed
- ◯ G1: Well differentiated
- ◯ G2: Moderately differentiated
- ◯ G3: Poorly differentiated
- ◯ Other, *specify*

[b] *If more than one foci with different grades, record the highest grade.*

[c] *In cases with heterogeneous grades, the cutoff for high grade is 5%.*

MICROSCOPIC EXTENT OF INVASION (select all that apply) (Note 13)

- ◯ Cannot be assessed
- ◯ No evidence of primary tumour

Primary tumour (male and female) (*excluding urothelial carcinoma of prostate*)

- ☐ Non-invasive papillary, polypoid or verrucous carcinoma
- ☐ Carcinoma in situ
- ☐ Invades subepithelial connective tissue
- ☐ Invades corpus spongiosum, prostate, periurethral muscle
- ☐ Invades corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck (extraprostatic extension)
- ☐ Invades other adjacent structures
  - ☐ Prostatic stroma
  - ☐ Corpus spongiosum
  - ☐ Periurethral muscle
  - ☐ Corpus cavernosum
  - ☐ Extraprostatic extension
  - ☐ Anterior vagina
  - ☐ Bladder wall
  - ☐ Rectum
  - ☐ Other, *specify*

Urothelial carcinoma of the prostate

- ☐ Carcinoma in situ, involvement of the prostatic urethra without stromal invasion
- ☐ Carcinoma in situ, involvement of the periurethral ducts without stromal invasion
- ☐ Carcinoma in situ, involvement of the prostatic ducts without stromal invasion
- ☐ Invades urethral subepithelial connective tissue
- ☐ Invades prostatic stroma, corpus spongiosum, periurethral muscle
- ☐ Invades corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
- ☐ Invades other adjacent structures
  - ☐ Bladder wall
  - ☐ Rectum
  - ☐ Other, *specify*

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LYMPHOVASCULAR INVASION (Note 14)

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present

MARGIN STATUS (Note 15)

- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved
  - ◯ Invasive carcinoma (select all that apply)
    - ☐ Distal[d]
    - ☐ Proximal[d]
    - ☐ Soft tissue
    - ☐ Other, *specify*
  - ◯ Carcinoma in situ/non-invasive papillary urothelial carcinoma (select all that apply)
    - ☐ Distal mucosa
    - ☐ Proximal mucosa
    - ☐ Other, *specify*

[d] *Relative to urinary bladder as reference point.*

LYMPH NODE STATUS (Note 16)

- ◯ No nodes submitted or found

Number of lymph nodes examined

- ◯ Not involved
- ◯ Involved

Number of involved lymph nodes

- ◯ Number cannot be determined

Location of involved lymph nodes, *specify*

Extranodal extension

- ◯ Not identified
- ◯ Present

COEXISTENT PATHOLOGY (Note 17)

- ◯ None identified
- ◯ Present, *specify*

ANCILLARY STUDIES (Note 18)

- ◯ Not performed
- ◯ Performed, *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*

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 19)

- ◯ Not identified
- ◯ Present (M1), *specify site(s)*

PATHOLOGICAL STAGING (UICC TNM 9th edition)[e] (Note 20)

TNM Descriptors (only if applicable) (select all that apply)

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

Primary tumour (pT)

- ◯ TX[f] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour

URETHRA (MALE AND FEMALE)

- ◯ Ta[g] 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, prostate or periurethral muscle
- ◯ T3 Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina or bladder neck (extraprostatic extension)
- ◯ T4 Tumour invades other adjacent organs (invasion of the bladder)

UROTHELIAL CARCINOMA OF THE PROSTATE

- ◯ Tis Carcinoma in situ, involving the prostatic urethra, periurethral or prostatic ducts without stromal invasion
- ◯ T1 Tumour invades subepithelial connective tissue (for tumours involving prostatic urethra only)
- ◯ T2 Tumour invades any of the following: prostatic stroma, corpus spongiosum or periurethral muscle
- ◯ T3 Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule or bladder neck (extraprostatic extension)
- ◯ T4 Tumour invades other adjacent organs (invasion of the bladder or rectum)

Regional lymph nodes (pN)

- ◯ NX[f] 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

[e] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 9th Edition, eds by James Brierley, Meredith Giuliani, Brian O'Sullivan, Brian Rous, Elizabeth Van Eycken. 2025, Publisher Wiley (incorporating errata published 12th October 2025).*

[f] *TX and NX should be used only if absolutely necessary.*

[g] *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.*

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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 by 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 DAC.

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Scope

The dataset has been developed for pathology reporting resection specimens from patients with primary carcinoma (non-invasive and invasive) of the urethra. Biopsy and transurethral resection specimens are dealt with in a separate ICCR dataset.[2] Carcinomas arising in the very distal penile urethra (fossa navicularis/merging with glans penis) are usually HPV-associated squamous cell carcinomas and are included in the ICCR Carcinoma of the penis and distal urethra dataset and are not to be reported using this dataset.[1] This dataset is also used for adenocarcinoma arising in the accessory urethral glands (Skene, Littre, Cowper). Most studies of primary urethral carcinoma exclude recurrence of urothelial carcinoma in the urethra following cystectomy.[3] The latter is considerably more common than ”de novo” urothelial carcinoma of urethra and should not be reported using this dataset.[4,5]

Primary carcinoma of the urethra is rare and as such there are limited data regarding the prognostic significance of descriptive pathologic parameters.

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Urinary and Male Genital Tumours, 5th edition, 2022.[3] The ICCR dataset includes 5th edition Corrigenda, July 2024.[4] In development of this dataset, the DAC considered evidence up until October 2025.

A list of changes in this dataset edition can be accessed here.

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Core and Non-core)

Presence or absence of clinical information is a core item, whereas details of the clinical information are non-core, since information may not be provided.

Knowledge of any relevant history is required for the accurate diagnosis of tumours throughout the urinary tract.[5-7] This may be relevant to the specific diagnosis being entertained. Clinical information is considered non-core since it is the responsibility of the clinician submitting the specimen to provide relevant information. The incidence rates of urethral cancer are highest in males, elderly patients and African Americans.[8,9] Patients with a history of urothelial neoplasia are at risk for urothelial tumours throughout the urinary tract. In males, predisposing factors include urethral strictures,[10] chronic irritation[11] and radiation therapy.[12,13] There are isolated reports of high risk human papillomavirus (HPV) infection being a risk factor for squamous cell carcinoma of urethra.[14] In females reported risk factors have included urethral diverticula[15,16] and recurrent infections.[17]

Urothelial tumours in the urinary bladder and upper tract may be treated with intravesical therapies such as bacillus Calmette-Guerin (BCG) mitomycin C and others. BCG has also been used to treat non-invasive urothelial carcinoma of prostatic urethra.[18,19] Intravesical treatment may produce morphologic changes leading to misdiagnosis if the pathologist is unaware of the prior treatment.[20] Additionally, radiation therapy involving bladder and/or adjacent organs can be associated with pseudocarcinomatous hyperplasia, a mimicker of invasive carcinoma.[21]

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Note 2 – Operative procedure (Core)

Documentation of the specific operative procedure should be a standard part of any pathology report. Knowledge of the procedure is crucial to the proper handling and reporting of a case. In some cases where there has been prior therapy (e.g., external beam radiation therapy for prostate cancer) or with a large invasive tumour, the presence of certain anatomic structures may not be readily apparent from the gross evaluation alone.

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Note 3 – Additional specimen(s) submitted (Core)

If any additional tissues are resected, documentation of these is a necessary part of the pathology report.

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Note 4 – Tumour site (Core)

In males, the urethra is divided into four regions, the preprostatic, prostatic, membranous and penile.[22] In females, the urethra is divided into an anterior segment (distal one-third) and a posterior segment (proximal two-thirds).[23] Documentation of the tumour location, when possible, is important. There is a significant relationship between tumour location and histologic type. In females, squamous cell carcinoma is the predominant type in the distal and meatal region with urothelial carcinoma and adenocarcinoma being found in the more proximal portion.[8,24,25] Urethral diverticula in particular are a typical location for clear cell adenocarcinomas in females.[8,24,25] In males, squamous cell carcinoma accounts for the majority of tumours arising in the penile and bulbomembranous urethra,[8,26] with urothelial carcinoma predominating in the prostatic urethra.[8,26] Adenocarcinomas in males occur predominantly in the bulbomembranous segment. Very rare adenocarcinomas of the accessory glands (Skene glands in females; Littre or Cowper glands in males) localise to the urethral sites of those glands.

Tumour site has been reported to be a significant prognostic parameter in a number of studies of urethral carcinoma in men.[27,28]

Finally, the pathologic staging system for primary carcinomas of the urethra is location dependent with different rules for pT categorisation of tumours of the prostatic urethra and those arising in the male bulbomembranous/penile urethra and female urethra.[19,26,29-31]

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Note 5 – Tumour focality (Non-core)

Multifocality is a common feature of urothelial neoplasms that may be seen in urethral specimens, especially in total urethrectomy specimens in males. In such cases, documentation of the multifocality is reasonable although there is no data regarding its significance in this setting.

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Note 6 – Tumour dimensions (Non-core)

There are limited data showing tumour size in cystectomy specimens to be a significant prognostic feature,[32] but this has not been established in urethrectomy specimens. Documentation of tumour size in the latter is considered a non-core element.

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Note 7 – Macroscopic extent of invasion (Non-core)

Pathological staging is dependent on determining involvement of structures that may be recognisable at gross examination. Block selection is also guided by the gross evaluation. Discrepant findings between the microscopic and gross examination may prompt additional block submission.

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Note 8 – 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 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 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.

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Note 9 – Histological tumour type (Core and Non-core)

The WHO Classification of Urinary and Male Genital Tumours, 5th edition, 2022, is utilised for assigning histological tumour type (Table 1).[3] The ICCR dataset includes 5th edition Corrigenda, July 2024.[4] Like in the previous edition, in the 2022 WHO a tumour is classified as a urothelial carcinoma if there is any identifiable urothelial component, including urothelial carcinoma in situ (CIS).[3] An exception to this rule is for neuroendocrine carcinomas (small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma and mixed neuroendocrine neoplasms). The 5th edition WHO has created a separate chapter for all tumours with neuroendocrine differentiation.[3] For mixed neuroendocrine cases, the other elements should be reported with an estimated percentage. This would be managed by placing the other component in the histological tumour type element. For example, a mixed tumour with 70% small cell neuroendocrine carcinoma and 30% urothelial carcinoma would be reported under the histological tumour type as *Neuroendocrine mixed neoplasm* and then under histological tumour type – Other, specify - *urothelial carcinoma (30%)*.

Well differentiated neuroendocrine tumours (formerly 'carcinoids') and paraganglioma are described in separate chapters in the 2022 WHO 'Blue book'. In the carcinoma group, the small cell neuroendocrine carcinoma is the most common. About one-half of cases are pure and one-half are mixed with another component with urothelial carcinoma being most frequent. Therefore, cases with mixed differentiation are included in this category. There does remain some controversy regarding the percentage of the neuroendocrine component required to classify a tumour as a neuroendocrine carcinoma. From a practical standpoint, cases with a small cell neuroendocrine carcinoma component irrespective of the amount are managed as small cell neuroendocrine carcinoma.[33] The National Comprehensive Cancer Network (NCCN) includes tumours with any small cell component in the category of non-urothelial carcinoma.[33] The larger series in the literature include cases with only focal small cell neuroendocrine carcinoma.[33-37]

The diagnosis is defined by morphologic criteria and most cases demonstrate evidence of neuroendocrine differentiation by immunohistochemistry. The most specific immunohistochemical markers are chromogranin A and synaptophysin, while CD56 although sensitive is not very specific.[38-40] TTF-1 is expressed in more than 50% of cases.[41-45] In cases with pure small cell morphology the possibility of direct spread from an adjacent organ or metastasis must be clinically excluded.[46] Recent research could demonstrate that small cell bladder cancer microscopically resembles aggressive small cell lung cancer, shares DNA changes similar to small cell lung cancer and expresses many genes that urothelial bladder cancer does not, possibly explaining aggressive activity.[46]

Like the previous edition, the 2022 WHO classification includes the category of Müllerian tumours.[3] For the purposes of the dataset this consists primarily of clear cell adenocarcinoma and rare examples of endometrioid carcinoma. These tumours are morphologically the same as their counterparts in the female genital tract, although their histogenesis of clear cell adenocarcinoma is controversial.[3] They are rare tumours and when clear cell adenocarcinoma presents as a primary bladder tumour it represents secondary involvement most often originating in a urethral diverticulum.[47] Diagnosis therefore requires clinical correlation to support diagnosis as a primary bladder tumour. Clear cell adenocarcinoma and endometrioid carcinoma may arise from endometriosis or rarely Müllerianosis.[48-52] Clear cell adenocarcinoma must also be distinguished from urothelial carcinoma with clear aspects of the cytoplasm.[53] Müllerian type clear cell adenocarcinoma has similar immunohistochemical profile to primary tumours of the female genital tract so immunohistochemistry cannot be used to distinguish a primary from a secondary origin.[54]

Histological subtypes and divergent differentiation (urothelial carcinoma)

The 2022 WHO classification includes a number of recognised morphologic subtypes of urothelial carcinoma as outlined in Table 1.[3] According to the 2022 WHO classification, all subtypes are considered high grade.[3] The urothelial carcinoma has a remarkable capacity for morphologic changes and the number of subtypes that have been described in the literature is extensive.[55] In general the subtypes that have been specifically recognised fall into three broad categories. Those with a deceptively bland morphology, such as the nested subtype, which could be misdiagnosed as benign. In the second category are tumours that have a morphology that mimics other tumours. Lastly are those tumours that have important prognostic or therapeutic implications.[56]

The importance of subtypes in clinical management decisions has been receiving increasing clinical attention.[57,58] Some subtypes have been highlighted because of the high frequency of under staging.[5] There are an increasing number of therapeutic algorithms that incorporate subtypes as a significant factor.[59] For T1 urothelial carcinoma, the presence of a histological subtype is one feature that is used in determining whether to consider immediate cystectomy.[33]

Rather than making reporting of specific subtypes that have some supporting data core and others lacking data non-core, the consensus of the DAC was to make the entire category a core element.

Reporting the percentage of subtypes when present is non-core (this is recommended in the WHO 2022 monograph).[3] The data supporting this is very limited and only available for selected subtypes (micropapillary, sarcomatoid and lymphoepithelioma-like), with divergent differentiation (glandular, squamous). There is also insufficient data available for setting specific amounts of each specific subtype in order for it to be clinically significant. Given the lack of data, if subtypes are identified, it should be reported and the estimated percentage of the tumour made up by each subtype reported (non-core).

Table 1: 5th edition of the World Health Organization classification of tumours of the urothelial tract.[3]

Descriptor	ICD-O codes[a]
Urothelial tumours	
Non-invasive urothelial neoplasms	
Papillary urothelial neoplasm of low malignant potential	8130/1
Non-invasive papillary urothelial carcinoma, low grade	8130/2
Non-invasive papillary urothelial carcinoma, high grade	8130/2
Urothelial carcinoma in situ	8120/2
Dysplasia	
Invasive urothelial carcinoma	8120/3
Nested	
Tubular microcystic	
Micropapillary	8131/3
Lymphoepithelioma-like	8082/3
Plasmacytoid	
Sarcomatoid	8122/3
Giant cell	8031/3
Poorly differentiated	8020/3
Lipid-rich	
Clear cell	
Squamous cell neoplasms	
Pure squamous cell carcinoma	8070/3
Verrucous carcinoma	8051/3
Glandular neoplasms	
Adenocarcinoma, not otherwise specified (NOS)	8140/3
Enteric	8144/3
Mucinous	8480/3
Mixed	8140/3
Tumours of Müllerian type	
Clear cell adenocarcinoma	8310/3
Endometrioid carcinoma	8380/3
Neuroendocrine tumours	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Mixed neuroendocrine neoplasms	
Well differentiated neuroendocrine tumour	8240/3
Paraganglioma[b]	8693/3

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O).[60] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. Subtype labels are indented. Incorporates all relevant changes from the 5th edition Corrigenda, July 2024.[4]

[b] Paraganglioma is not an epithelial derived tumour.

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Note 10 – Non-invasive carcinoma (Core)

Most urethrectomy specimens will be in patients with an invasive carcinoma. In such cases, documentation of an associated non-invasive component is considered part of a complete surgical pathology report. In contrast to other urinary tract sites, there is insufficient data in urethra to know whether such a finding has clinical significance. In some cases, urethrectomy may be performed following a diagnosis of carcinoma irrespective of documented invasion. This is most frequent in patients with urothelial carcinoma of urinary bladder and coexisting CIS of urethra. In those cases, this data element will be the primary diagnosis for the case.

There is evidence that the extent of CIS is significant and distinguishing between a single focus and diffuse (or multifocal) disease is important.[61]

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Note 11 – Associated epithelial lesions (Non-core)

A variety of neoplastic lesions that fall short of carcinoma are recognised in the urinary tract. These include papillary lesions such as urothelial papilloma and inverted urothelial papilloma. Similarly flat lesions such as urothelial dysplasia, keratinising squamous metaplasia with dysplasia and intestinal metaplasia with dysplasia can be seen. Identification of these lesions may have diagnostic implications (e.g., the presence of keratinising squamous metaplasia with dysplasia supporting the diagnosis of primary squamous cell carcinoma) but they have no proven prognostic or clinical significance. Therefore, the reporting of such findings, is considered non-core in the context of a carcinoma diagnosis.

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Note 12 – Histological tumour grade (Core)

Please note that this commentary is generic and most of the data is derived from studies of urothelial carcinoma of the bladder and to a less extent urothelial carcinoma in other anatomic sites.

Histologic grading of urothelial tumours is best considered in two categories, non-invasive papillary tumours and invasive carcinomas. For non-invasive papillary tumours, the 2022 WHO[3] remains the same as in the 2004 and 2016 WHO and continues to be recommend the grading system, which was first put forward by the International Society of Urological Pathology (ISUP) in 1998.[62] The system is now recommended by almost all major pathology and urology organisations as the preferred grading system.[6,63]

In the 2022 WHO system, the lowest category is papillary urothelial neoplasm of low malignant potential (PUNLMP) which will not invade or metastasise.[3,64] This entity is rare (3.8% de novo), the risk of progression is minimal.[65] Papillary carcinomas are classified as low or high grade.[3] There are significant differences in the

risk of progression to invasive carcinoma and death from bladder cancer between low and high grade categories.[66-68] The grade of non-invasive papillary carcinoma is the major variable in the choice of therapy in these patients.[69] Other features of importance in predicting outcome of patients with Ta papillary tumours are number of tumours/multifocality,[68,70-72] tumour size,[68,73-75] the presence of associated CIS,[68] and a history of prior recurrence.[68] It has also been suggested that for low grade papillary tumours the frequency of follow up cystoscopies can be reduced.[69]

The great majority of invasive urothelial carcinomas are high grade. According to the 2022 'Blue book', rare low grade invasive urothelial carcinomas lacking marked nuclear atypia are recognised but no standard criteria have been established to diagnose these as low grade.[3,6] Some authors have suggested that such low grade tumours have a more favourable outcome and therefore it is recommended that all invasive urothelial carcinomas be assigned a grade.[3,6]

For pure squamous and adenocarcinomas, a three tier system 'well differentiated', 'moderately differentiated' or 'poorly differentiated' is recommended.[3]

The ICCR dataset recommends the use of the 5th edition WHO grade as a core element.[3,76] The use of the 1973 WHO grading system for papillary tumours remains in use in some regions and one published guideline specifically recommends the reporting of both the current WHO grade with the 1973 grade,[69,77,78] while others allow for the 1973 grade to be provided by institutional choice.[3,5,63] It is beyond the scope of this commentary to provide a detailed argument for or against the 1973 WHO. Interested readers can review those discussions elsewhere.[77-79]

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Note 13 – Microscopic extent of invasion (Core)

Tumour stage is generally accepted to be the most important prognostic parameter for primary carcinoma of the urethra.[19,26,33] In order to accurately assign pathologic stage careful evaluation of the extent of microscopic invasion is the most critical feature.[29,30] The immediately adjacent structures that determine pathologic stage vary depending on the anatomic location of the tumour. At all sites invasion of the subepithelial connective tissue represents pT1 disease. The prostatic urethra represents a specialised location and has unique features. In situ carcinoma can involve the urethra, the prostatic ducts or both. Invasion of the subepithelial tissue beneath the urethral surface represents pT1 disease. Invasion of the prostatic stroma can develop either from the urethra or from tumour in the prostatic ducts; in either case this is classified as pT2. In cases with in situ involvement of prostatic ducts, extensive sampling should be undertaken to exclude the possibility of prostatic stromal invasion. Elsewhere in the urethra of both males and females pT2 is defined by invasion of smooth muscle fibres deep to the subepithelial connective tissue. No definable muscularis mucosae is present in the urethra so any involvement of smooth muscle fibres is considered at least pT2.

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Note 14 – Lymphovascular invasion (Core)

Lymphovascular invasion (LVI) has been repeatedly found to be an important prognostic indicator for urothelial carcinoma of the upper tracts. The most recent EAU guidelines conclude that it is an independent predictor of outcome in these tumours.[80] There are many other studies where it has been reported to be an independent predictor as well.[81,82]

As in other datasets the use of special stains and/or IHC to determine the presence or absence of LVI is considered optional. In the major studies referenced above, IHC was not routine part of the evaluation.

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Note 15 – Margin status (Core)

Assessment of surgical margin status is a standard part of any surgical pathology reported evaluating a resection performed with curative intent. As with other parameters the data specific to primary carcinomas of the urethra is extremely limited.

If both invasive carcinoma and CIS are present at a margin, then invasive carcinoma should be recorded. If a low grade papillary tumour or CIS is present at the margin, this should also be noted.

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Note 16 – Lymph node status (Core and Non-core)

There are relatively limited data regarding specifics of lymph node status and outcome in primary urethral carcinoma. Published series have consistently found that the presence of lymph node metastases is associated with a worse outcome.[19,26,83] A recent review article concluded that there was insufficient data to allow for a clear guideline as to the role of lymph node dissection or the specific templates to be used.[84] The most recent EAU guidelines on urethral carcinoma management concluded “no clear evidence supports prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with urethral cancers”.[19] Patients with clinically enlarged suspicious lymph nodes are however likely to undergo lymph node dissection. In such cases it seems reasonable to report the findings as in other resection specimens of primary carcinomas of the urinary tract. The 9th edition Union for International Cancer Control (UICC)/8th edition American Joint Committee on Cancer (AJCC) Cancer Staging Manuals use number of lymph nodes (one versus more than one) to define the pN1 and pN2 categories.[29,30]

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Note 17 – Coexistent pathology (Non-core)

A wide range of non-neoplastic changes can be found in radical urethrectomy specimens. Findings such as keratinising squamous metaplasia and intestinal metaplasia may be relevant in cases of squamous cell carcinoma and adenocarcinoma but for the most part these findings are not critical and considered non-core.

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Note 18 – Ancillary studies (Non-core)

Currently there are no ancillary studies that are recommended for routine use in primary urethral carcinoma. In cases where immunohistochemistry is used diagnostically these should be reported in this section. Refer to the ICCR Carcinoma of the bladder dataset for further details.[85]

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Note 19 – Histologically confirmed distant metastases (Core)

In some patients there will be metastases that have been confirmed histologically. When these are known they should be included in the report. It is helpful to include in the report the relevant pathology number as a reference to the metastases.

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Note 20 – Pathological staging (Core)

The pathologic staging information is a core element in this dataset. Staging data should be assessed according to the 9th edition UICC/8th edition AJCC Cancer Staging Manuals.[29,30] Staging is considered to be the most important prognostic parameter for primary carcinoma of the urethra.[19,26,83] Throughout the entire length of the urethra, invasion of the subepithelial connective tissue denotes pT1 disease.

In the male patient, primary carcinoma of prostatic urethra has a distinct set of T category definitions.[29,30] A carcinoma of prostatic urethra extending into subepithelial connective tissue is considered category pT1 and when it involves prostate tissue is considered pT2. However, when CIS involves periurethral prostatic ducts and is associated with invasion of prostate tissue, it is considered pT2 (no category pT1 exists in this situation).

More advanced T categories are dependent on the location, and whether the patient is male or female.

Reporting of pathological staging categories (pT,pN,pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM9 and AJCC TNM8,[29,30] the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

Back

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