Carcinoma of the Urethra Histopathology Reporting Guide
Urethrectomy Specimen

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

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

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

Previous history of urinary tract disease or distant metastasis (select all that apply)

- ○ Information not provided
- ○ No previous history
- ☐ Non-invasive papillary
- ☐ Carcinoma in situ, flat
- ☐ Invasion into lamina propria
- ☐ Muscle invasive disease
- ☐ Other, *specify*
- ☐ Distant metastasis

Previous therapy (select all that apply)

- ○ Information not provided
- ○ No previous therapy
- ☐ Bacillus Calmette-Guerin (BCG)
- ☐ Chemotherapy, intravesical, *specify*
- ☐ Chemotherapy, systemic
- ☐ Radiation therapy
- ☐ 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 SPECIMENS SUBMITTED (Note 3)

- ○ Submitted, *specify*
- ○ Not submitted

TUMOUR FOCALITY (Note 4)

- ○ Unifocal
- ○ Multifocal
- ○ Cannot be assessed, *specify*

MAXIMUM TUMOUR DIMENSION (Note 5)

- ○ Cannot be assessed
- ○ No macroscopically visible tumour

Maximum tumour dimension (largest tumour)

mm

Additional dimensions (largest tumour)

mm x mm

MACROSCOPIC TUMOUR SITE (select all that apply) (Note 6)

- ○ Indeterminate
- ○ No macroscopically visible tumour

Male

- ☐ Penile
- ☐ Bulbomembranous
- ☐ Prostatic

Female

- ☐ Anterior
- ☐ Posterior

⇩

- ☐ Diverticula
- ☐ Other, *specify*

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

- ○ Cannot be assessed
- ○ 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 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 from the WHO Classification of Tumours of the Urinary System and Male Genital Organs (2016))

- ○ Urothelial carcinoma
- ○ Squamous cell carcinoma
- ○ Adenocarcinoma
- ○ Tumours of Müllerian type
  - ○ Clear cell carcinoma
  - ○ Endometrioid carcinoma
- ○ Neuroendocrine tumour
  - ○ Small cell neuroendocrine carcinoma
  - ○ Large cell neuroendocrine carcinoma
- ○ Other, *specify*

Histological sub-type/variant (urothelial carcinoma)

- ○ Not identified
- ○ Present, *specify sub-type/variant and percentage*
  (select all that apply)

☐ Squamous ⇒	%	☐ Micropapillary ⇒	%
☐ Glandular ⇒	%	☐ Plasmacytoid ⇒	%
☐ Nested ⇒	%	☐ Sarcomatoid ⇒	%
☐ Other, *specify*		⇒	%

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

- ○ Not identified
- ○ Indeterminate
- ☐ Carcinoma in situ, flat
  - ○ Focal
  - ○ Multifocal
- ☐ Papillary carcinoma, non-invasive
- ☐ Other, *specify*

ASSOCIATED EPITHELIAL LESIONS (Note 11)

- ○ Present, *specify*
- ○ Not identified

HISTOLOGICAL TUMOUR GRADE (Note 12)

- ○ Not applicable
- ○ Cannot be determined

Urothelial carcinoma

- ○ 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*

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
- ☐ Carcinoma in situ
- ☐ Tumour invades subepithelial connective tissue
- ☐ Tumour involves adjacent structures
  - ☐ Prostatic stroma
  - ☐ Corpus spongiosum
  - ☐ Periurethral muscle
  - ☐ Corpus cavernosum
  - ☐ Extra prostatic extension
  - ☐ Anterior vagina
  - ☐ Bladder neck
  - ☐ Bladder wall
  - ☐ Rectum
  - ☐ Other, *specify*

Urothelial carcinoma of the prostate

- ☐ Carcinoma in situ, involvement of the prostatic urethra
- ☐ Carcinoma in situ, involvement of the prostatic ducts
- ☐ Tumour invades urethral subepithelial connective tissue
- ☐ Tumour invades prostatic stroma
- ☐ Extra prostatic extension
- ☐ Tumour involves adjacent structures
  - ☐ Corpus spongiosum
  - ☐ Periurethral muscle
  - ☐ Corpus cavernosum
  - ☐ Bladder neck
  - ☐ Bladder wall
  - ☐ Rectum
  - ☐ Other, *specify*

LYMPHOVASCULAR INVASION (Note 14)

- ○ Not identified
- ○ Present
- ○ Indeterminate

MARGIN STATUS (Note 15)

- ○ Cannot be assessed
- ○ Not involved
- ○ Involved
  - ○ Invasive carcinoma (select all that apply)
    - ☐ Distal
    - ☐ Proximal
    - ☐ Deep soft tissue
    - ☐ Other, *specify*
  - ○ Carcinoma in situ/non-invasive high-grade urothelial carcinoma (select all that apply)
    - ☐ Distal mucosal
    - ☐ Proximal mucosa
    - ☐ Other, *specify*

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REGIONAL LYMPH NODE STATUS (Note 16)

- ○ No regional nodes submitted
- ○ Not involved
  - Number of lymph nodes examined: ____
- ○ Involved
  - Number of lymph nodes examined: ____
  - Number of positive lymph nodes: ____
  - ○ Number cannot be determined
  - Extranodal spread
    - ○ Present ○ Not identified
  - Size of largest metastasis: ____ mm
  - Location of involved lymph nodes, *specify*: ____

COEXISTENT PATHOLOGY (Note 17)

- ○ Present, *specify* ○ None identified
  - ____

ANCILLARY STUDIES (Note 18)

- ○ Not performed
- ○ Performed, *specify*
  - ____

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 19)

- ○ Not identified
- ○ Indeterminate
- ○ Present, *specify site(s)*
  - ____

PATHOLOGICAL STAGING (AJCC TNM 8th edition)## (Note 20)

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

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

Primary tumour (pT)

Male penile urethra and female urethra

- ○ TX Primary tumour cannot be assessed
- ○ T0 No evidence of primary tumour
- ○ Ta Non-invasive papillary carcinoma
- ○ Tis Carcinoma in situ
- ○ T1 Tumour invades subepithelial connective tissue
- ○ T2 Tumour invades any of the following: corpus spongiosum, periurethral muscle
- ○ T3 Tumour invades any of the following: corpus cavernosum, anterior vagina
- ○ T4 Tumour invades adjacent organs (e.g. invasion of the bladder wall)

Prostatic urethra

- ○ Tis Carcinoma in situ involving the prostatic urethra or periurethral or prostatic ducts without stromal invasion
- ○ T1 Tumour invades urethral subepithelial connective tissue immediately underlying the urothelium
- ○ T2 Tumour invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts
- ○ T3 Tumour invades the periprostatic fat
- ○ T4 Tumour invades other adjacent organs (e.g. extraprostatic invasion of the bladder wall, rectal wall)

Regional lymph nodes (pN)

- ○ NX Regional lymph nodes cannot be assessed
- ○ N0 No regional lymph node metastasis
- ○ N1 Single regional lymph node metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric) and external iliac], or presacral lymph node
- ○ N2 Multiple regional lymph node metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric) and external iliac], or presacral lymph node

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Scope

The dataset has been developed for the reporting of resection specimens from patients with carcinoma of the urethra. The protocol applies to primary carcinomas (non-invasive and invasive), with or without associated epithelial lesions. Urothelial tumours diagnosed as papilloma or papillary urothelial neoplasm of low malignant potential are not carcinomas and this dataset does not apply to those diagnoses. Biopsy and transurethral resection specimens are dealt with in a separate dataset. Carcinomas arising in the distal penile urethra (glans region) are included in the Carcinoma of the penis and distal urethra dataset and are not to be reported using this dataset.[1] This dataset is to be used for adenocarcinoma arising in the accessory glands of the urethra (Skene, Littre, Cowper).[2] Most studies of primary urethral carcinoma exclude cases of urothelial carcinoma developing as a site of recurrence following cystectomy.[3] The latter is much more frequent than primary urothelial carcinomas arising "de novo".[4,5]

It should be noted that primary carcinomas of the urethra are rare tumours and as such there are limited data regarding most parameters and their prognostic significance. As noted in the most recent European Association of Urology (EAU) guidelines on primary urethral carcinomas, "because primary urethral cancer belongs to the family of rare cancers, most studies are retrospective, and recommendations given in these guidelines are mainly based on level 3 evidence".[6] The same can be said for the pathologic features discussed in this dataset. The only study to date that has applied multivariate analysis to prognostic features is a study of urethral carcinomas in men using Surveillance, Epidemiology, and End Results Program (SEER) data with the limitations that such an analysis engenders.[3]

Note 1 - Clinical information (Recommended)

Reason/Evidentiary Support

Knowledge of any relevant history is critical in the accurate diagnosis of tumours throughout the urinary tract.[7-10] This may be relevant to the specific diagnosis being entertained. This is a recommended rather than a required item as it is the responsibility of the clinician requesting the pathological examination of a specimen to provide information that will have an impact on the diagnostic process or affect its interpretation. Patients with a history of urothelial neoplasia are at risk for urothelial tumours throughout the urinary tract and this may inform the interpretation in subsequent specimens. In males several predisposing factors can be found in the literature including urethral strictures,[11] chronic irritation[12] and radiation therapy.[13,14] There are isolated reports of high risk HPV infection being a risk factor for squamous cell carcinoma of the urethra.[15] In females reported risk factors have included urethral diverticula[16,17] and recurrent infections.[18]

Urothelial tumours in the urinary bladder and upper tract may have been treated with therapies such as Bacillus Calmette-Guerin (BCG), mitomycin C and others. BCG has also been used in the treatment of non-invasive urothelial carcinoma (Ta, Tis) of the prostatic urethra.[19,20] Particularly following intravesical therapy the urethra can show changes related to the treatment. These can be associated with morphologic changes that have the potential for misdiagnosis if the pathologist is unaware of the prior treatment.[21,22] Radiation therapy (to the bladder or to adjacent organs) can be

associated with pseudocarcinomatous hyperplasia that can be misdiagnosed as invasive carcinoma.[23,24]

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Note 2 - Operative procedure (Required)

Reason/Evidentiary Support

Documentation of the specific procedure performed 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 instances 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 tissues may not be readily apparent from the gross evaluation alone.

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Note 3 - Additional specimens submitted (Required)

Reason/Evidentiary Support

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

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Note 4 - Tumour focality (Recommended)

Reason/Evidentiary Support

Multifocality is a feature of urothelial neoplasms in particular and in total urethrectomy specimens in males it may be recognised. In such cases documentation of the multifocality is reasonable but there is no data regarding its significance in this setting.

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Note 5 - Maximum tumour dimension (Required and Recommended)

Reason/Evidentiary Support

Documentation of tumour size is considered a basic data element of the surgical pathology report. There are data that tumour size in cystectomy specimens may be a significant prognostic feature.[25] In one large study of primary urethral carcinoma in males, based on SEER data in the United States, tumour size was found to have prognostic significance.[3]

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Note 6 - Macroscopic tumour site (Required)

Reason/Evidentiary Support

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.[26-28] Urethral diverticula in particular are a typical location for clear cell adenocarcinomas in females.[27,29] In males squamous cell carcinoma accounts for the majority of tumours arising in the penile and bulbomembranous urethra[30,31] with urothelial carcinoma predominating in the prostatic urethra.[32,33] Adenocarcinomas in males occur predominantly in the bulbomembranous segment. The very rare adenocarcinomas of the accessory glands (Skene glands in females; Littre or Cowper glands in males) localize to the 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.[30,33,34] In one multi-institutional series proximal tumour location was associated with a significantly worse outcome.[35]

Finally the pathologic staging system for primary carcinomas of the urethra is location dependent with pT categories for tumours of the prostatic urethra and a second definition of pT categories for the male penile and female urethra.[36]

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Note 7 - Macroscopic extent of invasion (Required)

Reason/Evidentiary Support

Pathological staging is dependent on determining the involvement of structures that may be recognisable at gross examination. This can guide block selection to confirm the gross evaluation. Discrepant findings between the microscopic and gross examination may prompt additional section submission.

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Note 8 - Block identification key (Recommended)

Reason/Evidentiary Support

The origin/designation of all tissue blocks should be recorded and it is preferable to document this information in the final pathology report. This is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion or order ancillary studies. 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.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks, for example for further immunohistochemical or molecular analysis, research studies or clinical trials.

The block identification is not a required element within the synoptic report but we would consider it required within the report text (most often is included in the gross description section).

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Note 9 - Histological tumour type (Required)

Reason/Evidentiary Support

The 2016 World Health Organization (WHO) classification is used for assigning histological tumour type.[37] As in the 2004 WHO Classification,[38] a tumour is classified as a urothelial carcinoma if there is any identifiable urothelial component no matter how small and including urothelial carcinoma in situ (CIS). The one exception to this rule is for cases with a neuroendocrine component (small cell neuroendocrine carcinoma or large cell neuroendocrine carcinoma) where classification is now in the neuroendocrine tumour category. For those cases that are mixed, the other elements should be reported with an estimated percentage. In the above scheme, 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 tumour (small cell neuroendocrine carcinoma)* and then under histological tumour type – Other, specify - *urothelial carcinoma (30%)*.

Also new in the 2016 WHO classification is the category of Müllerian tumours. For the purposes of this dataset this consists primarily of clear cell adenocarcinoma. Clear cell adenocarcinoma must also be distinguished from urothelial carcinoma with divergent differentiation along Müllerian lines in which case it would be classified under urothelial carcinoma.[39] Expression of markers such as p63, GATA3 and high molecular weight cytokeratin are not present in clear cell adenocarcinoma and in the absence of a recognisable urothelial component would suggest this possibility.[40] Müllerian type clear cell adenocarcinoma has a similar immunohistochemical profile to primary tumours of the female genital tract and cannot be used to distinguish a primary from a secondary origin.[41-44]

Primary adenocarcinomas of the urethra have some unique features to the other datasets in this series. Most primary adenocarcinomas of the urethra are considered to be of a not otherwise

specified type. This group would include enteric type adenocarcinomas,[27,45] mucinous (colloid) adenocarcinomas[46,47] and signet ring cell carcinomas[48] Clear cell adenocarcinoma (discussed above) is relatively common in the urethra in contrast to elsewhere in the urinary tract.[27,29,49,50] Primary adenocarcinoma and adenoid cystic carcinoma arising in the accessory glands are also included in this dataset.[2,51,52]

The neuroendocrine tumour category includes small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, well-differentiated neuroendocrine tumour and paraganglioma. Small cell neuroendocrine carcinoma is by far the most common of these. By definition this is a malignant neoplasm with neuroendocrine differentiation. 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 with the larger series in the literature including cases with only a focal component of small cell carcinoma.[53-56] For example the National Comprehensive Cancer Network (NCCN) includes tumours with "any small-cell component in the category of non-urothelial cell carcinoma.[57,58] Primary neuroendocrine tumours are exceedingly rare in the urethra and essentially are limited to case reports.[59,60]

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.[26-28] Urethral diverticula in particular are a typical location for clear cell adenocarcinomas in females although other histologic types may arise from these structures.[27,29,61] In males squamous cell carcinoma accounts for the majority of tumours arising in the penile and bulbomembranous urethra[30,31] with urothelial carcinoma predominating in the prostatic urethra.[32,33] Adenocarcinomas in males occur predominantly in the bulbomembranous segment. The very rare adenocarcinomas of the accessory glands (Skene glands in females; Littre or Cowper glands in males) localize to the sites of those glands.

Histologic subtype/variant

The 2016 WHO classification includes a number of recognised morphologic variants as outlined in the table below.[37] Because urothelial carcinoma has a remarkable capacity for morphologic variation the number of histologic variants that have been described in the literature is extensive.[62,63] In the development of the 2016 WHO classification not all of these are included. In general the variants that have been specifically recognised fall into three broad categories. Variants that have a deceptively bland morphology, such as the nested variant, could be misdiagnosed as benign or considered low grade although their behaviour is the same as for high grade tumours. 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.

The importance of variant histology in clinical management decisions has been receiving increasing clinical attention.[64,65] Some variants have been highlighted because of the high frequency of under staging when present in biopsy or transurethral resection of bladder tumour (TURBT) specimens, as discussed in the Urinary tract carcinoma – Biopsy and transurethral resection specimen dataset.[7,66] There are an increasing number of therapeutic algorithms that incorporate variant histology as a significant factor.[67]

The level of evidence for specific variants having independent prognostic information varies from the variant having no clinical significance but being important diagnostically (e.g. nested, microcystic, etc), to no data, to data indicating the variant has prognostic significance (e.g. micropapillary, plasmacytoid, sarcomatoid). Rather than making reporting of specific subtypes that have some supporting data mandatory and others lacking data recommended it is considered best to make the entire category a required element.

Reporting the percentage of variant histology when present is required (this is recommended in the WHO 2016 monograph). The data supporting this is very limited and only available for selected variants (micropapillary, sarcomatoid, lymphoepithelioma-like), with divergent differentiation (glandular, squamous) largely from tumours arising in the urinary bladder. There is also insufficient data available for setting specific amounts of each specific variant in order for it to be clinically significant. Given the lack of data, if variant histology is identified, it should be reported together with the estimated percentage of this component. For cases with more than one variant present, the percentage of each is required to be documented.

WHO classification of tumours of the urothelial tract[a37]

Descriptor	ICD-O codes
Urothelial tumours	
Infiltrating urothelial carcinoma	8120/3
Nested, including large nested	
Microcystic	
Micropapillary	8131/3
Lymphoepithelioma-like	8082/3
Plasmacytoid / signet ring cell / diffuse	
Sarcomatoid	8122/3
Giant cell	8031/3
Poorly differentiated	8020/3
Lipid-rich	
Clear cell	
Non-invasive urothelial lesions	
Urothelial carcinoma in situ	8120/2
Non-invasive papillary urothelial carcinoma, low-grade	8130/2
Non-invasive papillary urothelial carcinoma, high-grade	8130/2
Papillary urothelial neoplasm of low malignant potential	8130/1
Urothelial papilloma	8120/0
Inverted urothelial papilloma	8121/0
Urothelial proliferation of uncertain malignant potential	
Urothelial dysplasia	
Squamous cell neoplasms	
Pure squamous cell carcinoma	8070/3
Verrucous carcinoma	8051/3
Squamous cell papilloma	8052/0

Glandular neoplasms	
Adenocarcinoma, NOS	8140/3
Enteric	8144/3
Mucinous	8480/3
Mixed	8140/3
Villous adenoma	8261/0
Urachal carcinoma	8010/3
Tumours of Müllerian type	
Clear cell carcinoma	8310/3
Endometrioid carcinoma	8380/3
Neuroendocrine tumours	
Small cell neuroendocrine carcinoma	8041/3
Large call neuroendocrine carcinoma	8013/3
Well-differentiated neuroendocrine tumour	8240/3
Paraganglioma[b]	8693/1

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

b Paraganglioma is not an epithelial derived tumour.

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Note 10 - Non-invasive carcinoma (Required)

Reason/Evidentiary Support

Most urethrectomy specimens will be in patients with a diagnosis of 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 locations in the urinary tract there is insufficient data to know whether such a finding has any clinical significance. In some cases urethrectomy will be performed following a diagnosis of carcinoma irrespective of the documentation of invasion. In those cases this data element will be the primary diagnosis for the case. This is most frequent in patients with urothelial carcinoma of the urinary bladder found to have a co-existing carcinoma in situ of the urethra.

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Note 11 - Associated epithelial lesions (Recommended)

Reason/Evidentiary Support

A variety of neoplastic lesions that fall short of carcinoma are recognised in the urinary tract. These include benign papillary lesions such as urothelial papilloma, papillary urothelial neoplasm of low

malignant potential and inverted urothelial papilloma. Similarly flat lesions such as urothelial dysplasia, keratinizing squamous metaplasia with dysplasia and intestinal metaplasia with dysplasia can be seen. Identification of these may have diagnostic implications (e.g. the presence of keratinizing squamous metaplasia with dysplasia supporting the diagnosis of primary squamous cell carcinoma) but do not have known proven prognostic or clinical significance otherwise. While for completeness it may be useful to report such findings, it is not considered to be a required element in the context of a carcinoma diagnosis.

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Note 12 - Histological tumour grade (Required)

Reason/Evidentiary Support

Histologic grading of urothelial tumours is best considered in two categories, non-invasive papillary tumours and invasive carcinoma. For non-invasive papillary tumours the 2016 WHO remains the same as in the 2004 WHO and continues to recommend the grading system first put forward by the International Society of Urological Pathology (ISUP) in 1997.[68] The system is now recommended by almost all major pathology and urology organizations as the preferred grading system.[8,10]

This is a 3-tiered system with the lowest category of papillary urothelial neoplasm of low malignant potential considered to represent a tumour without the capacity to invade or metastasize and as such is considered to be a benign neoplasm.[69] This lesion represents up to one-third of newly diagnosed non-invasive papillary tumours in the urinary tract. Papillary urothelial neoplasm of low malignant potential is not reported using this dataset. It is nonetheless a significant diagnosis and does indicate an increased risk for the development of other neoplasms in the urinary tract. Grade heterogeneity is relatively common in papillary urothelial carcinoma being reported in up to 32% of cases.[69,70] It is currently recommended that tumour grade be assigned based on the highest grade present. Some authors have recommended considering a tumour low grade if the high grade component accounts for less than 5% of the tumour volume.[69,71] Using the 1999 WHO grading system, Billis et al found that pure grade 3 tumours were more often muscle invasive than tumours with mixed grade 2 and 3 cases.[70] They also reported that pure grade 1 tumours were invasive in 25% of cases compared to 66% of predominantly grade 1 tumours with a grade 2 component.[70] Specific percentages of the grades in the mixed grade cases were not provided. In another study Cheng et al studied grade heterogeneity in non-invasive papillary neoplasms using the 1998 ISUP grading system.[69] Tumours were evaluated based on predominant and secondary grades but ignored secondary components if less than 5%.[69] In their study worst, predominant and average grade all were significant predictors of progression.[69] Progression was higher in pure high grade tumours (>95% high grade) than in mixed high/low grade tumours (5% to 95% high grade).[69] In another study tumours with less than 10% of high grade histology (5% of the cases) were compared with low and high-grade tumours.[72] The progression free and cancer specific survival of the mixed cases was similar to low grade tumours and significantly better than the high grade cases.[72] The limited data does not allow for a definitive statement regarding reporting of cases with a small volume of high grade tumour or to determine what percentage of high grade tumour is necessary to indicate a significantly worse prognosis. The International Consultation on Urologic Disease recommended

against the application of an arbitrary percentage of high grade tumour when assigning grade.[8] The 2016 WHO recommends grading based on the highest grade component and acknowledges the uncertainty of how to approach cases with a small proportion of high grade tumour. It does indicate that "it may be prudent to state the proportion of high-grade disease." We would recommend grading based on the highest grade present and in those cases where the high grade component is estimated to be less than 10%, a comment should be included providing this information.

The use of the 1973 WHO grading system for papillary tumours remains in use in many regions and some published guidelines specifically recommend the reporting of both the current WHO grade with the 1973 grade,[73-75] while others suggest that the 1973 to be provided is based on institutional choice.[8,10,37] 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.[8,73,75,76] There is an extensive literature based on the 1973 WHO system documenting its significance as a predictor of outcome for papillary urothelial carcinoma. These include many studies using material from phase III clinical trials. The current European Organisation for Treatment and Research of Cancer (EORTC) risk tables, developed from the data of 8 phase III clinical trials use the 1973 WHO grading system.[77] The International Collaboration of Cancer Reporting (ICCR) dataset follows the WHO 2016 approach with reporting of the WHO 2016 grade as a required element and the inclusion of other grading systems as optional.

The grading of invasive urothelial carcinoma is another area of controversy. In North America the vast majority of invasive urothelial carcinomas have been diagnosed as high grade in contrast to European studies where a substantial percentage of invasive tumours have been graded as 2 or even 1. Currently there is general agreement that grade 1 tumours (WHO 1973), largely corresponding to papillary urothelial neoplasm of low malignant potential, lack the capacity to invade.[78-80] In studies using the 1998 ISUP/WHO 2004 grading system the vast majority of invasive tumours are high grade.[81,82] The conclusion of the International Consultation on Urologic Disease pathology group was that all invasive carcinomas should be considered high grade.[8,83] It has been noted that there are variants of urothelial carcinoma that have low grade cytologic features such the nested variant, but that appear to behave stage for stage like usual high grade carcinoma.[84-87] When variant histology such as this is present the tumours should be reported as high grade despite the bland cytology in order to reflect the biologic behaviour.[88] Nonetheless it is equally apparent that many pathologists have graded invasive urothelial carcinomas using the 1973 WHO and other systems and have demonstrated its prognostic significance.[77,79,89,90] The 2016 WHO recommends continuing to grade invasive carcinoma using the WHO 2004 system recognising that the vast majority of tumours will be high grade. If invasive tumours are graded using an alternative grading system this should be indicated.

Data regarding grade as a prognostic indicator in urethral carcinoma are limited and the relationship to stage is not clear in those reports.[3] Current treatment guidelines are essentially based on tumour location and stage.[6]

Back

Note 13 - Microscopic extent of invasion (Required)

Reason/Evidentiary Support

Tumour stage is generally accepted to be the most important prognostic parameter for primary carcinoma of the urethra.[3,6,91] In order to accurately assign pathologic stage careful evaluation of the extent of microscopic invasion is the most critical feature. 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 specialized 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 staged as pT2. Because of the prognostic significance, in cases with in situ disease in the 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. There is no definable muscularis mucosae in the urethra so any demonstrated involvement of smooth muscle fibres is staged as at least pT2.

Back

Note 14 - Lymphovascular invasion (Required)

Reason/Evidentiary Support

Lymphovascular invasion (LVI) has been well documented as an independent prognostic parameter for urothelial carcinoma arising in the urinary bladder and upper tract. Similar data does not exist for urethral carcinoma. None the less it seems reasonable to include it for tumours arising here as well. The routine use of immunohistochemistry to evaluate for the presence or absence of LVI is not recommended in other sites in the urinary tract and is not recommended here.

Back

Note 15 - Margin status (Required)

Reason/Evidentiary Support

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.

In choosing microscopic margin status, if both invasive carcinoma and carcinoma in situ are present, then invasive carcinoma should be selected. If low grade tumour or carcinoma in situ is present at the margin, this should be noted.

Back

Note 16 - Regional lymph node status (Required and Recommended)

Reason/Evidentiary Support

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.[3,33,91] A recent review article concluded that there was insufficient data to allow for a clear guidelines as to the role of lymph node dissection or the specific templates to be used.[92] 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."[6] 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 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual uses number of lymph nodes (one versus more than one) to define the pN1 and pN2 categories.[36]

Back

Note 17 - Coexistent pathology (Recommended)

Reason/Evidentiary Support

A wide range of non-neoplastic changes can be found in radical urethrectomy specimens. Findings such as keratinizing 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 so this element is not required.

Back

Note 18 - Ancillary studies (Recommended)

Reason/Evidentiary Support

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.

Back

Note 19 - Histologically confirmed distant metastases (Required)

Reason/Evidentiary Support

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.

Back

Note 20 - Pathological staging (Required)

Reason/Evidentiary Support

Pathologic staging is considered to be the most significant prognostic parameter for primary carcinoma of the urethra.[3,6,91] Throughout the entire length of the urethra, invasion of the subepithelial connective tissue denotes stage pT1 disease. More advanced T categories are dependent on the location, and whether the patient is male or female.

In the male patient, primary carcinoma of the prostatic urethra is accorded a distinct set of T category definitions.[36] This reflects the somewhat unique relationship between urothelial carcinoma of the urinary bladder and the prostate gland and the relationship between prostatic gland involvement in those cases and assignment of T-category. For primary urethral carcinomas, the frequent involvement of prostatic ducts by carcinoma in situ results in the occurrence of prostatic stromal invasion directly from within the ducts (pT2) without passing through a pT1 stage as occurs in invasion from the prostatic urethra. In the Seventh edition of the AJCC Cancer Staging Manual, carcinoma in situ involving the prostatic ducts (pTis pd) was recognized separately from urethral involvement (pTis pu).[93] That distinction is no longer applied in the Eighth edition of the AJCC Cancer Staging Manual.[36]

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