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Urinary Tract Carcinoma
Histopathology Reporting Guide
Biopsy and Transurethral Resection 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, *specify including site(s)*
- ☐ Previous therapy, *specify*
- ☐ Cytoscopic appearance
  - ☐ Polypoid
  - ☐ Papillary
  - ☐ Red (erythematous) area
  - ☐ Normal
  - ☐ Other, *specify*
- ☐ Other clinical information, *specify*

SPECIMEN SITE[a] (Note 2)

◯ Renal pelvis
- ☐ Left ☐ Right ◯ Laterality not specified

◯ Ureter
- ☐ Left ☐ Right ◯ Laterality not specified

◯ Prostate/prostatic urethra
◯ Bladder, *specify site(s)*
◯ Urethra, *specify site(s)*
◯ Other, *specify*

[a] *If biopsies are from different locations then a separate dataset should be completed for each specimen site.*

OPERATIVE PROCEDURE (Note 3)

◯ Not specified
◯ Transurethral resection
◯ Biopsy
◯ Other, *specify*

BLOCK IDENTIFICATION KEY (Note 4)

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

HISTOLOGICAL TUMOUR TYPE (Note 5)

(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*	%

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NON-INVASIVE CARCINOMA[b] (select all that apply) (Note 6)

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

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

ASSOCIATED EPITHELIAL LESIONS (Note 7)

- ◯ Not identified
- ◯ Present, *specify*

HISTOLOGICAL TUMOUR GRADE[c] (Note 8)

- ◯ Not applicable
- ◯ Cannot be assessed

Urothelial carcinoma[d]

- ◯ 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*

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

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

STATUS OF MUSCULARIS PROPRIA (Note 9)

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present

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

- ◯ Cannot be assessed
- ☐ Papillary urothelial carcinoma, non-invasive
- ☐ Carcinoma in situ, flat
- ☐ Tumour invades subepithelial connective tissue (lamina propria)
- ☐ Tumour invades muscularis propria (detrusor muscle)
- ☐ Tumour involves prostatic urethra
- ☐ Tumour involves prostatic ducts and acini
- ☐ Tumour invades prostatic stroma
- ☐ Tumour invades renal stroma
- ☐ Tumour invades periurethral muscle
- ☐ Tumour invades corpus spongiosum
- ☐ Tumour invades corpus cavernosum
- ☐ Tumour invades adjacent structures, *specify*

SUBSTAGING T1 DISEASE (Note 11)

Depth of invasion (measuring from the basement membrane of the urothelium) _____ mm

AND/OR

Total maximum dimension of invasive tumour _____ mm

AND/OR

- ◯ Invasion superficial to muscularis mucosae
- ◯ Invasion involving and/or deep to muscularis mucosae
- ◯ T1m
- ◯ T1e

LYMPHOVASCULAR INVASION (Note 12)

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present

COEXISTENT PATHOLOGY (select all that apply) (Note 13)

- ◯ None identified
- ☐ Adenocarcinoma of prostate
- ☐ Urothelial carcinoma involving urethra, prostatic ducts and acini with or without stromal invasion
- ☐ Inflammation/regenerative changes
- ☐ Therapy-related changes
- ☐ Cystitis cystica et glandularis
- ☐ Keratinising squamous metaplasia
- ☐ Squamous metaplasia
- ☐ Glandular metaplasia
- ☐ Nephrogenic adenoma
- ☐ Other, *specify*

ANCILLARY STUDIES (Note 14)

- ◯ 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*

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) recommends that some ancillary testing in ICCR Datasets is included as core elements. 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.

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Scope

The dataset has been developed for the pathology reporting of biopsy and transurethral resection (TUR) specimens of the bladder, urethra, ureter and renal pelvis. 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. The most distal portion of the penile urethra in the region of the glans penis is not included in this dataset; it is covered in the ICCR Carcinoma of the penis and distal urethra dataset.[2] Biopsy of the kidney is dealt with in a separate ICCR dataset.[3]

If biopsies are from different locations, then a separate dataset should be completed for each tumour site.

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.[4] The ICCR dataset includes 5th

edition Corrigenda, July 2024.[5] 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 critical in the accurate diagnosis of tumours throughout the urinary tract.[6-8] It is relevant to the specific diagnosis. This is a non-core rather than a core element 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 is important for the interpretation in subsequent specimens. Urothelial tumours in the urinary bladder and upper tract may have been treated with therapies such as bacillus Calmette-Guerin (BCG), mitomycin C, pembrolizumab and others.[9-12] Morphologic changes can be seen after treatment and without information the potential for misdiagnosis exists.[13-15] Radiation therapy (to the bladder or to adjacent organs) can be associated with pseudocarcinomatous hyperplasia that can be taken for an invasive carcinoma.[16,17] Nephrogenic adenoma can be seen following biopsy or TUR and can mimic recurrent tumour clinically and pathologically.[18] Therefore, it is extremely important for the pathologist to have a prior history of the patient, including whether the patient has had a clinical history of urinary tract disease and what kind of treatment has been provided.[19-21] Knowledge of the cystoscopic appearance can also be helpful in some cases. Finally, knowledge of a history of carcinoma elsewhere such as prostatic adenocarcinoma, colorectal adenocarcinoma, cervical squamous cell carcinoma, and others can greatly assist in the interpretation of biopsy/TUR specimens in the right circumstances.[22,23]

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Note 2 – Specimen site (Core)

Since this dataset applies to the complete urinary (urothelial) tract, the specific anatomic site is essential for accurate interpretation. The differential diagnostic considerations may be site-specific. Additionally, key staging issues may be site-specific, i.e., renal parenchymal involvement in renal pelvis tumours, prostatic parenchymal positivity in the prostatic urethra tumours and corporal body involvement in the penile urethral lesions. Location within individual sites may also be important to interpretation. For instance, in urinary bladder specimens from the dome urachal lesions could enter the differential diagnosis. In the posterior wall/trigone/bladder neck, secondary tumours from adjacent organs may be diagnostic considerations. The distribution of muscularis mucosae (MM) fibres also vary by location in the urinary bladder and so knowledge of location can assist in evaluation of smooth muscle for staging purposes.[24] Furthermore, the detrusor muscle in the bladder neck may be very close to the urothelial surface and may not necessarily form of discrete muscle bundles.

If biopsies are from multiple locations, separate datasets should be completed for each positive site.

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Note 3 – Operative procedure (Core)

Documentation of the specific procedure performed should be a standard part of any pathology report.

Some novel biopsy/resection techniques have emerged in recent years. A 2021 meta-analysis considered 17 prospective non-randomised and randomised controlled trials.[25] The authors demonstrated that tumour resection with photodynamic diagnosis and narrow band imaging exhibited lower recurrence rates and greater diagnostic sensitivity compared to white light cystoscopy alone.[25] Narrow band imaging demonstrated superior disease sensitivity and specificity as compared to white light cystoscopy and an overall greater hierarchical summary receiver operative characteristic.[25] Updated guidelines show the value of integrating these technologies as a part of the standard care for patients with suspected or confirmed non-muscle-invasive bladder cancer (NMIBC).[19]

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Note 4 – 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 5 – 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).[4] The ICCR dataset includes 5th edition Corrigenda, July 2024.[5] 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).[4] 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.[4] 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'.[4] 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.[26] The National Comprehensive Cancer Network (NCCN) includes tumours with any small cell component in the category of non-urothelial carcinoma.[26] The larger series in the literature include cases with only focal small cell neuroendocrine carcinoma.[26-30] A 2023 study found that patients with pure and mixed small cell bladder carcinoma have similar outcomes, which are correlated with pathological stage at radical cystectomy, and are best among patients with pathological downstaging after neoadjuvant chemotherapy.[31]

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.[32-34] TTF-1 is expressed in more than 50% of cases.[35-39] In cases with pure small cell morphology the possibility of direct spread from an adjacent organ or metastasis must be clinically excluded.[40] Recent research demonstrates that small cell bladder cancer microscopically resembles aggressive small cell lung cancer, shares DNA shares DNA abnormalities with small cell lung cancer and expresses a different gene profile than urothelial carcinoma of blabber, possibly explaining its aggressive behaviour.[40]

Biopsies/TURs that contain apparent pure adenocarcinoma need to be generously sampled to exclude the possibility of urothelial carcinoma with extensive divergent differentiation. The presence of keratinising squamous metaplasia particularly when there is dysplasia would support the diagnosis of primary squamous cell carcinoma.[41] There are no reliable immunohistochemical markers to distinguish with certainty in the individual case. In urothelial carcinoma with glandular differentiation, the glandular component may retain its 'urothelial' profile including expression of p63, GATA3 and high molecular weight keratin but often these are lost with the tumour showing an enteric immuno-histochemical profile. Markers of squamous differentiation such as CK5/6 and CK14 have not been proven to reliably separate pure squamous cell carcinoma from urothelial carcinoma with squamous differentiation.[32] Further, for both adenocarcinoma and squamous cell carcinoma the diagnosis of primary origin requires clinical correlation to exclude the possibility of origin at another site.

The 2022 WHO classification includes carcinomas arising in the urachus as a separate category.[4] These are defined as carcinomas arising from urachal remnants. Criteria for the diagnosis of urachal carcinoma include location in the bladder dome or anterior wall, an epicentre in the bladder wall or perivesical tissue.[42-47] The majority (over 80%) of urachal carcinomas are adenocarcinoma followed by urothelial carcinoma, squamous cell carcinoma, small cell neuroendocrine carcinoma and mixed carcinomas. If a diagnosis of urachal carcinoma is rendered the subtype must be specified. Adenocarcinomas of the urachus are most often mucinous and can be either solid or cystic. Subtypes such as enteric and signet ring-cell occur. The 2022 WHO also includes a category of 'mucinous cystic tumour of low malignant potential'.[4] There are no reliable immunohistochemical markers to distinguish adenocarcinomas (of urachal origin) from primary adenocarcinomas of the bladder proper or from secondary adenocarcinomas of gastrointestinal origin.[32,42,48,49] Molecular studies provide insights and show a close relation to colorectal cancers.[47]

Like the previous edition, the 2022 WHO classification includes the category of Müllerian tumours.[4] 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.[4] 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.[50] 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.[51-55] Clear cell adenocarcinoma must also be distinguished from urothelial carcinoma with clear aspects of the cytoplasm.[56] 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.[57]

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.[4] According to the 2022 WHO classification, all subtypes are considered high grade.[4] The urothelial carcinoma has a remarkable capacity for morphologic changes and the number of subtypes that have been described in the literature is extensive.[58] 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.[59]

The importance of subtypes in clinical management decisions has been receiving increasing clinical attention.[60,61] Some subtypes have been highlighted because of the high frequency of under staging.[6] There are an increasing number of therapeutic algorithms that incorporate subtypes as a significant factor.[62] For T1 urothelial carcinoma, the presence of a histological subtype is one feature that is used in determining whether to consider immediate cystectomy.[26]

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).[4] 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.[4]

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

Descriptor	ICD-O codes[a]
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).[63] 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.[5]

[b] Paraganglioma is not an epithelial derived tumour.

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Note 6 – Non-invasive carcinoma (Core)

Most patients with urothelial carcinoma present initially with non-muscle invasive disease, usually, a non-invasive papillary tumour and occasionally urothelial CIS. Non-invasive papillary tumours account for 70% to 75% of newly diagnosed cases with over one-half being in the lower grade categories (papillary urothelial neoplasm of low malignant potential, low grade papillary carcinoma).[64] Urothelial CIS in its pure form counts for 1% to 3% of newly diagnosed urothelial tumours and is always high grade.[65] More commonly, CIS coexists with high grade papillary urothelial carcinoma and is present in up to two thirds of invasive urothelial carcinoma cases.[66] Low grade papillary carcinoma and high grade papillary carcinoma (along with urothelial CIS) are thought to develop through different genetic pathways and have different biologic behaviours.[19,67]

Classification of non-invasive urothelial tumours into papillary and in situ categories has both prognostic and management implications. Furthermore, CIS coexisting with papillary carcinoma has therapeutic significance. In biopsy and TURBT specimens both diagnoses can be made when papillary carcinoma and CIS are present in different tissue fragments or in specimens from different sites. When a flat lesion is present immediately adjacent to and in continuity with a papillary tumour the question becomes whether the flat part represents a 'shoulder' of high grade papillary carcinoma. There are no generally accepted histological criteria for making this distinction, however, from a practical perspective, the DAC suggests making the diagnosis of CIS associated with papillary carcinoma when (i) there is a gap of normal urothelium between the papillary tumour and the flat lesion; or (ii) if the morphology of the flat lesion is different than that of the papillary lesion.

For patients presenting with invasive urothelial carcinoma the recognition and documentation of an associated non-invasive papillary carcinoma and/or CIS remains important. For patients with T1 disease the presence of CIS indicates a significantly increased risk of subsequent recurrence and progression to muscle invasive disease. For patients with CIS of the bladder unresponsive to BCG therapy this can be an indication for early cystectomy.[19,68,69] The presence of associated CIS in newly diagnosed high grade T1 disease may also be used to support early cystectomy.[19] For patients presenting with invasive urothelial carcinoma there are data that such cases arising through the 'papillary' pathway have a better prognosis that those developing via the 'flat' pathway.[70,71]

There is evidence that the extent of CIS is significant and distinguishing between a single focus and diffuse (or multifocal) disease is important.[72] For this dataset, diffuse is defined as the presence of CIS in more than one site as indicated by biopsies submitted separately or involving more than one tissue fragment in a TURBT specimen.

Lastly non-urothelial CIS can also occur in the urinary tract. Most frequently this is squamous cell CIS typically in association with keratinising squamous metaplasia. Urothelial CIS can show areas of squamous and glandular differentiation, and these should not be diagnosed as pure squamous or adenocarcinoma in situ, respectively.

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Note 7 – 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, papillary urothelial neoplasm of low malignant potential 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 may have diagnostic implications (e.g., the presence of keratinising squamous metaplasia supporting the diagnosis of primary squamous cell carcinoma) but do not have known 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 8 – 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 carcinoma. For non-invasive papillary tumours the 2022 WHO[4] remains the same as in the 2004 WHO and continues to be recommend the grading system, which was first put forward by the International Society of Urological Pathology (ISUP) in 1998.[73] The system is now recommended by almost all major pathology and urology organisations as the preferred grading system.[7,8]

In the 2022 WHO system, the lowest category is papillary urothelial neoplasm of low malignant potential (PUNLMP) which will not invade or metastasise.[4,74] This entity is rare (3.8% de novo), the risk of progression is minimal.[75] Papillary carcinomas are classified as low or high grade.[4] There are significant differences in the risk of progression to invasive carcinoma and death from bladder cancer between low and high grade categories.[76-78] The grade of non-invasive papillary carcinoma is the major variable in the choice of therapy in these patients.[19] Other features of importance in predicting outcome of patients with Ta papillary tumours are number of tumours/multifocality,[78-81] tumour size,[78,82-84] the presence of associated CIS,[78] and a history of prior recurrence.[78] It has also been suggested that for low grade papillary tumours the frequency of follow up cystoscopies can be reduced.[19]

Grade heterogeneity is not uncommon in papillary urothelial carcinoma being reported in up to 32% of cases.[85,86] The 2022 WHO recommends grading based on the highest grade component and recommends the cut of 5% for high grade tumours.[4] Tumours with up to 5% high grade component would be categorised as low grade and it may be useful to state the proportion of high grade disease.[4]

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.[4,7] 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.[4,7]

For pure squamous and adenocarcinomas, a three tier system 'well differentiated', 'moderately differentiated' or 'poorly differentiated' is recommended.[4]

The ICCR dataset recommends the use of the 5th edition WHO grade as a core element.[87,4] 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,[19,88,89] while others allow for the 1973 grade to be provided by institutional choice.[4,6,8] 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.[90-92]

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Note 9 – Status of muscularis propria (Core)

The presence or absence of muscularis propria (MP) is a vital piece of information in determining the adequacy of a biopsy or TUR specimen that contains an invasive carcinoma.[6,19,88,93] The absence of MP in a TURBT is generally an indication for a repeat TUR if treatment other than cystectomy is being considered. It is well documented that absence of MP in a TURBT specimen is associated with an increased risk of residual

disease and early recurrence.[94] The current European Association of Urology (EAU) guidelines recommend repeat TUR (i) after an incomplete initial TURBT; (ii) if there is no muscle in the specimen after initial resection with the exception of Ta, low grade/grade 1 tumours and primary CIS; (iii) in all T1 tumours; and (iv) in all high grade/grade 3 tumours except primary CIS.[95] It is also considered prudent to comment on the presence or absence of MP in a biopsy or TUR specimen, irrespective of the presence or absence of invasive carcinoma. According to the EAU guidelines, it is not required to have detrusor muscle if the tumour is a pTa low grade tumour or a PUNLMP.[19]

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Note 10 – Extent of invasion (Core)

Reporting the extent of invasion is a critical part of the assessment of carcinomas arising in the urinary tract. The elements included reflect the anatomic landmarks that are essential to the pathologic staging of each tumour and vary by site within the urinary tract.[96,97] It is not appropriate to assign pathologic stage on biopsy or TUR specimens and pathologic stage is not an element within this dataset. However, it is possible, based on the assessment of extent of invasion, to recognise the least pathological stage possible in each case.

The diagnosis of invasion can be challenging. Throughout the urothelial tract histologic features that are indicative of stromal invasion include individual tumour cells, irregular nests or cords of cells, retraction artefact around nests, increased cytoplasmic eosinophilia, and a myxoid or desmoplastic stromal response.[98] Inverted lesions can also be problematic, especially aspects with pushing borders.[99] Several studies have documented the difficulty with the diagnosis of invasion.[100,101] Two large studies based on central review of patients being entered on clinical trials have demonstrated the over diagnosis of invasion in 35% to 53% of cases.[102] Studies have also demonstrated lack of agreement among pathologists with special interest in urologic pathology.[101] In some cases immunohistochemistry with a pan keratin marker is helpful in identifying individual cells particularly when there is a heavy inflammatory infiltrate present. Following the principles of the 9th edition Union for International Cancer Control (UICC)/8th edition American Joint Committee on Cancer (AJCC) Cancer Staging Manuals, the diagnosis of invasion should be limited to cases with unequivocal invasion.[96,97]

Identification of invasion of smooth muscle fibres in specimens from the renal pelvis, ureter and urethra all indicate T2 disease. In the urinary bladder, the presence of the MM complicates the interpretation as involvement of this structure represents a T1 tumour.[96,97] MM fibres can be present throughout the bladder.[24] In the trigone/bladder neck region, MM fibres are often not found and from a practical perspective involvement of smooth muscle generally indicates MP invasion. MM fibres are typically thin and wispy forming small bundles, they lack the dense eosinophilic cytoplasm characteristic of MP. Often the fibres are seen in association with a layer of thick-walled blood vessels (plexus vascularis). The MM can however occasionally be thickened and better defined, more closely mimicking MP, especially after treatment. In some cases, it is not possible to be certain if the smooth muscle involvement represents MM or MP. In those cases, the uncertainty should be explicitly commented on. Repeat TUR on these cases can sometimes help to determine the true depth of involvement.[103] Another challenge in staging are inverted lesions of the bladder. In this situation deeper cuts can be helpful.[99]

Assessment of the presence or absence of MP invasion can also be hampered by cautery artefact. This can result in stromal changes mimicking smooth muscle leading to over-staging or making MP unrecognisable leading to under-staging.[6]

Urothelial carcinoma can be primary in the prostatic urethra, but in the most cases involvement is seen in association with a bladder tumour.[104] Among all male patients with bladder cancer the prostate is involved in

approximately 4% of cases.[105] Prostatic involvement is found in 15% to 48% of patients undergoing cystoprostatectomy for urothelial carcinoma of the bladder.[106-108] Involvement is usually by urothelial CIS, but occasionally papillary tumours are seen. Extension into the prostatic ducts is frequently present in these cases and should not be mistaken for invasion. Inflammation can be present around the ducts in the absence of invasion. Frequently invasion of the subepithelial connective tissue or the prostatic stroma elicits a desmoplastic response. Immunohistochemistry may be required to distinguish urothelial carcinoma from high grade prostatic carcinoma.[32] Glandular and or squamous differentiation may be seen as with urothelial carcinoma elsewhere.

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Note 11 – Substaging T1 disease (Non-core)

There have been many efforts to establish the optimum method of identifying T1 tumours with low and high risk for recurrence, progression and death from bladder cancer. One focus of many of these reports has been to 'substage' T1 tumours. This has been recommended by the WHO 2016, but no method was stated.[109] The two methods most used can be divided into histoanatomical and quantitative.[4] An ideal T1 subcategorisation method must be reproducible and broadly feasible, especially in TUR fragments, and predictive of outcome (i.e., able to discriminate tumours with the highest risk for recurrence and progression).[110]

A large volume of literature has tried to use the MM as a landmark to subdivide T1 tumours into 2 or 3 subgroups. The first study of this type is the report of Younes et al (1990) who divided tumours into T1a (invasion superficial to MM), T1b (to the MM) and T1c (deep to the MM).[111] They found that the T1b/T1c tumours were associated with a worse progression free and cancer specific survival. On a long term, dividing into three groups was considered as too complicated, therefore only pT1a and b were retained in the histoanatomic category. The largest study to date is that of Rouprêt et al (2013) that evaluated 587 cases.[112] On multivariable analysis, pT1b (involving or deep to MM) tumours had a significantly worse recurrence, progression and cancer specific survival.[112] These authors also provide a comprehensive literature review. Based on this review a few observations can be made: (i) the ability to assess MM ranged from 58% to 100%; (ii) on univariate analysis invasion of MM or deeper was a significant predictor of recurrence free survival in four of 12 reports, progression free survival in 15 of 17 reports and of cancer specific survival in four of seven reports; and (iii) on multivariate analysis MM involvement was significant for recurrence free survival in three of 12 reports, progression free survival in 13 of 16 reports and cancer specific survival in three of six publications.[112] Additional studies have been published subsequently.[113-115] One prospective study of 200 patients by Orsola et al (2015) sub-staged based on invasion superficial to the MM (T1a) versus involving or deep to MM (T1b) to stratify patient treatment. Although the follow up was limited, substage was a highly significant predictor of tumour progression on multivariable analysis.[115] The conclusion was that high grade T1 bladder cancers only need a repeat TUR in T1b cases. Tumours deeply invading the lamina propria (high grade T1b) showed a three-fold increase in risk of progression.

The second major approach to substaging is micrometric. Microscopic invasion (T1m) corresponds to no more than one high power field (HPF) of invasive growth, and extensive (T1e) corresponds to more than one HPF and/or multifocal growth.[116] A review of several studies[114,117-122] demonstrates that this approach has also merit. Furthermore, the micrometric approach seems to be more feasible and better predicts outcome.[123]

Most studies were retrospective in design, and none of the prospective studies applied micrometric techniques. The latest WHO Classification recommends the use of sub-staging, without specifying a preferred method,[4,110] similar to the 2016 Classification.

Due to the potential for additional information in T1 tumours to directly impact clinical decision making, the ICCR dataset has included substaging of TI disease as a non-core element. The dataset also provides for alternative methods for reporting as there is insufficient data to recommend one method.

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Note 12 – Lymphovascular invasion (Core)

The data on lymphovascular invasion (LVI) in urothelial carcinoma in the urinary bladder has grown with many series now reported.[124-129] These have included very large multi-institutional series (e.g., Kluth et al[127] – 8,102 patients), cases from phase 3 clinical trials (von Rundstedt et al[128] – SWOG4B951/NCT00005047) and in the generation of prognostic scores (Eisenberg et al[126] – SPARC Score) all of which have found LVI to be a highly significant predictor of outcome.

Studies that have evaluated the significance of LVI on biopsy or transurethral resections of bladder tumours (TURBT) material specifically are more limited.[122,130-137] These have almost all been based on haematoxylin-eosin (H&E) evaluation with limited utilisation of immunohistochemistry. The frequency of identifying LVI has ranged from <10% to as high as 67%. Some authors identified LVI in 8% of cases and also included an indeterminate category (22% of cases).[137] LVI was an independent predictor of recurrence free-, progression free- and cancer specific survival.[137] Interestingly, one prospective study did not find any significant association with progression-free or cancer specific survival, but follow-up was short.[138] Overall, most studies have found LVI to be a predictor of outcome. Some authors even tried to improve the recognition of LVI with the help of imaging and the results seem promising.[139]

Specific data on LVI determination in biopsy/TUR specimens of the upper tract and urethra are not available. There are several reports that have found LVI to be significant (various endpoints) in resection specimens for upper tract urothelial carcinoma.[140-143]

For urethral carcinoma there is no substantive literature available. In the 2025 guidelines on urethral carcinoma by the EAU, LVI is not recognised as a prognostic indicator.[144]

Although the data on LVI in biopsy/TUR specimens is limited, the compelling evidence from studies of urothelial carcinoma of urinary bladder in large resections support its inclusion as a core element in this dataset.[145-147]

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Note 13 – Coexistent pathology (Non-core)

Biopsy and endoscopic resection specimens from throughout the urinary tract that are diagnosed with carcinoma can also show several non-neoplastic conditions. Frequent findings are (keratinising) squamous metaplasia and (diffuse) glandular/intestinal metaplasia. While these may be relevant in selected cases, they are not considered core elements. Keratinising squamous metaplasia should be mentioned since it is a significant risk factor for vesical squamous cell carcinoma and associated complications, such as bladder contracture and ureteral obstruction. Glandular metaplasia which frequently has an intestinal morphology may enter the differential diagnosis of well-differentiated adenocarcinoma. Cystitis cystica and/or glandularis can also be associated with intestinal metaplasia and may present cystoscopically as a tumour-like mass. However, no cytological atypia, necrosis, signet-ring cells and brisk or atypical mitotic activity are present. Mucus extravasation can be seen in these cases and this finding does not point to a diagnosis of

adenocarcinoma. Nephrogenic adenoma (formerly nephrogenic metaplasia) is a relatively common lesion that may enter the differential diagnosis of adenocarcinoma. This lesion can have a variety of growth patterns, the discussion of which is beyond the scope of this commentary.[148] A variety of inflammatory changes including treatment-associated effects such as BCG granulomas and post-TUR necrobiotic granulomas may be seen along with non-specific inflammatory reactions and fibrosis. Occasionally, pseudocarcinomatous epithelial hyperplasia, a mimicker of urothelial carcinoma, associated with prior radiation and rarely chemotherapy, may be confused with urothelial carcinoma.

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Note 14 – Ancillary studies (Non-core)

Currently there are no ancillary studies that are recommended for routine use in carcinoma of the urothelial tract. If immunohistochemical studies are performed for differential diagnosis or to assist in staging or detection of LVI they can be listed in this section. If ancillary studies are performed at the request of the clinician or to follow an institutional policy or for any other reason, these should also be included in the report. It is also useful to select a representative tissue block which is used for ancillary testing. Ideally the block should include both tumour and non-tumoral tissue.

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