# Urinary Tract Carcinoma Histopathology Reporting Guide
# Biopsy and Transurethral Resection 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**

- ○ Information not provided
- ○ No previous history
- ○ *Provide details, including site(s), if present*

**Previous therapy**

- ○ Information not provided
- ○ No previous therapy
- ○ *Provide type of therapy(s), if present*

**Cytoscopic appearance** (select all that apply)

- ○ Information not provided
- ☐ Papillary
- ☐ Polypoid
- ☐ Red (erythematous) area
- ☐ Other, *specify*
- ☐ Normal

**Other clinical information,** *specify*

## SPECIMEN SITE* (Note 2)

- ○ Renal pelvis
- ○ Ureter
- ○ Bladder, *specify site(s)*
- ○ Prostate/prostatic urethra
- ○ Urethra, *specify site(s)*
- ○ Other, *specify*

* *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 (TUR)
- ○ 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 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 6)

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


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**ASSOCIATED EPITHELIAL LESIONS** (Note 7)

- ◯ Present, *specify*
- ◯ Not identified

**HISTOLOGICAL TUMOUR GRADE** (Note 8)

- ◯ 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*

**STATUS OF MUSCULARIS PROPRIA** (Note 9)

- ◯ Present
- ◯ Not present/submitted

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

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

**SUBSTAGING T1 DISEASE** (Note 11)

Depth of invasion ____ 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

**LYMPHOVASCULAR INVASION** (Note 12)

- ◯ Not identified
- ◯ Present
- ◯ Indeterminate

**COEXISTENT PATHOLOGY** (Note 13)

- ◯ None identified
- ◯ Present, *specify*

**ANCILLARY STUDIES** (Note 14)

- ◯ Not performed
- ◯ Performed, *specify*


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## Scope

The dataset has been developed for the reporting of biopsy and transurethral resection (TUR) specimens of the bladder, urethra, ureter and renal pelvis. If biopsies are from different locations then a separate dataset should be completed for each tumour site. 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 Carcinoma of the penis and distal urethra dataset. Biopsy of the kidney is dealt with in a separate dataset.

## 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.[1-4] 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. 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. These can be associated with morphologic changes that have the potential for misdiagnosis if the pathologist is unaware of the prior treatment.[5,6] Radiation therapy (to the bladder or to adjacent organs) can be associated with pseudocarcinomatous hyperplasia that can be misdiagnosed as invasive carcinoma.[7,8] Nephrogenic adenoma can be seen following biopsy or TUR and can mimic recurrent tumour clinically and pathologically.[9,10] Knowledge of the cystoscopic appearance can also be helpful in some cases.[1,3] For example, when evaluating a biopsy for the presence or absence of papillary neoplasia, knowledge of the cystoscopic finding of a papillary lesion can inform the interpretation. 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.

⬆ **Back**

## Note 2 - Specimen site (Required)

**Reason/Evidentiary Support**

Since this dataset applies to the full breadth of the urinary tract the specific anatomic site is essential to the correct site identification and interpretation. The differential diagnostic considerations will have many site specific alternatives. Although the key staging landmarks have much overlap there are also several that will be site specific such as the renal stroma in renal pelvis tumours, prostatic

stroma in the prostatic urethra and corporal bodies in the penile urethra. Location within individual sites can also be important to interpretation. In the urinary bladder specimens from the dome/anterior wall will include urachal lesions in the differential diagnosis. In the posterior wall/trigone/bladder neck secondary tumours from adjacent organs become important considerations in differential diagnosis. The distribution of muscularis mucosae fibres also vary by location in the urinary bladder and so knowledge of location can assist in evaluation of smooth muscle in the context of staging parameters.[11] In males the urethra is divided into four regions, the preprostatic, prostatic, membranous and penile. Knowing the origin of a "urethral" biopsy or TUR is important as there are histologic differences between regions as well as different glandular elements that may be relevant to the interpretation of a given specimen.

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

⬆ **Back**

## **Note 3 - Operative procedure** (Required)

**Reason/Evidentiary Support**

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

⬆ **Back**

## **Note 4 - 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. 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).

⬆ **Back**

## Note 5 - Histological tumour type (Required)

**Reason/Evidentiary Support**

The 2016 World Health Organization (WHO) classification is utilized for assigning histological tumour type.[12] As in the 2004 WHO Classification,[13] 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 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%)*.

For biopsies and TURs that contain pure adenocarcinoma or pure squamous cell carcinoma, they should be diagnosed as such. Without evaluation of the entire lesion it is not however possible to exclude the possibility of a urothelial carcinoma with squamous or glandular differentiation and consider a comment explaining that should always be included. The presence of keratinizing squamous metaplasia particularly when there is dysplasia would support the diagnosis of primary squamous cell carcinoma.[14] Similarly the presence of intestinal metaplasia with dysplasia would support the diagnosis of primary adenocarcinoma. None the less a definitive diagnosis of either should be made with caution in biopsy or transurethral resection of bladder tumour (TURBT) material. There are no reliable immunohistochemical markers to distinguish these possibilities 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 cytokeratin but often these are lost with the tumour showing an enteric immuno-histochemical profile. Markers of squamous differentiation such as desmoglein 3, CK14 and MAC387 have not been proven to reliably separate pure squamous cell carcinoma from urothelial carcinoma with squamous differentiation.[15] Further for both adenocarcinoma and squamous cell carcinoma the diagnosis of primary origin in the urinary bladder requires clinical correlation to exclude the possibility of origin at another site.

The 2016 WHO classification now includes carcinomas arising in the urachus as a separate category.[12] These are defined as carcinomas arising from urachal remnants. In general it is not possible to diagnose these in biopsy and TURBT material based on the morphologic findings alone. 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, the absence of diffuse cystitis glandularis/ intestinal metaplasia outside of the dome/anterior wall region and the absence of a known primary elsewhere.[16] The majority (over 80%) of urachal carcinomas are adenocarcinoma followed by urothelial carcinoma, squamous cell carcinoma and small cell neuroendocrine carcinoma. If a diagnosis of urachal carcinoma is rendered the histologic type should be specified. Adenocarcinomas of the urachus are most often mucinous and can be either solid or cystic. Other variants of adenocarcinoma including enteric and signet ring-cell also occur. The WHO does include a category of “mucinous cystic tumour of low malignant potential” that could not be diagnosed with certainty

in biopsy/TURBT material.[12] 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.[15-17]

Also new in the 2016 WHO classification is the category of Müllerian tumours.[12] For the purposes of this 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. They are rare tumours and most often when clear cell adenocarcinoma presents as a primary bladder tumour it represents secondary involvement most often originating in a urethral diverticulum.[18] 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.[19-22] 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.[23] 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.[24] Müllerian type clear cell adenocarcinoma has similar immunohistochemical profile to primary tumours of the female genital tract and cannot be used to distinguish a primary from a secondary origin.[21,25-27]

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. About one-half of cases are pure and one-half are mixed with another component with urothelial carcinoma being most frequent. 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.[28-32] For example the National Comprehensive Cancer Network (NCCN) includes tumours with “any small-cell component in the category of non-urothelial cell carcinoma.[32,33] The diagnosis is defined by morphologic criteria but most cases do demonstrate evidence of neuroendocrine differentiation by immunohistochemistry. The most sensitive immunohistochemical markers are CD56 and synaptophysin.[15] TTF-1 is expressed in about 50% of cases.[34,35] In cases with pure small cell morphology the possibility of direct spread from an adjacent organ or metastasis must be excluded clinically.

Lastly there are carcinomas arising in the urinary bladder that have no specific differentiation and based on exclusion of metastasis from another site are considered to be primary in the urinary tract. In the 2004 WHO classification these were included as a variant of urothelial carcinoma but given that by definition they have no urothelial differentiation these should be reported using the “carcinoma, type cannot be determined” category.[13]

**Histologic subtype/variant**

The 2016 WHO classification includes a number of recognised morphologic variants as outlined in the table below.[12] Because urothelial carcinoma has a remarkable capacity for morphologic variation

the number of histologic variants that have been described in the literature is extensive.[36,37] In the development of the 2016 WHO classification not all of these are included.[12] 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.[38,39] Some variants have been highlighted because of the high frequency of under staging when present in biopsy or TURBT specimens.[2] There are an increasing number of therapeutic algorithms that incorporate variant histology as a significant factor.[40] For T1 urothelial carcinoma, the presence of variant histology is one feature that is used in determining whether to consider immediate cystectomy.[32,41]

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 recommended (this is recommended in the WHO 2016 monograph).[12] The data supporting this is very limited and only available for selected variants (micropapillary, sarcomatoid, lymphoepithelioma-like), with divergent differentiation (glandular, squamous). 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 and the estimated percentage of the tumour it makes up reported. For cases with more than one variant present, the percentage of each is recommended to be documented.

## WHO classification of tumours of the urothelial tract[a12]

| 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 | |

| Descriptor | ICD-O codes |
|---|---|
| *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.



**Back**

## Note 6 - Non-invasive carcinoma (Required)

**Reason/Evidentiary Support**

The majority of patients with urothelial carcinoma present initially with non-invasive disease. Most of these have a non-invasive papillary tumour and much less frequently have urothelial CIS as the initial diagnosis. 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).[42,43] Urothelial CIS in its pure form counts for 1% to 3% of newly diagnosed urothelial tumours and is by definition high grade.[44] Much more often it coexists with high grade papillary urothelial carcinoma and is found in association with invasive urothelial carcinoma in up to 65% of cases.[44-46] Papillary tumours range from benign (papilloma, papillary urothelial neoplasm of low malignant potential) to low and high grade carcinomas. CIS and papillary carcinoma develop by different genetic pathways and have different biologic behaviour and so are considered as different entities within the non-invasive category.[47]

Classification of non-invasive urothelial tumours into the papillary and in situ categories has both prognostic and management implications. Further the identification of CIS coexisting with papillary carcinoma also has significance for prognosis and treatment. In biopsy and TURBT specimens both diagnoses can be rendered when the papillary carcinoma and the CIS are present on different tissue fragments or in specimens submitted from different sites. When flat lesion is present adjacent to and in continuity with a papillary tumour the question becomes whether the flat part represents a "shoulder" of the papillary tumour or coexisting CIS. There are no generally accepted criteria for making this decision even though the diagnosis does have clinical significance. We would recommend making the diagnosis of associated CIS in this situation if (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 epithelium on the surface of papillary fronds.

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 of progression to muscle invasive disease. For patients with CIS of the bladder unresponsive to BCG therapy this is an indication for early cystectomy.[41,48,49] The presence of associated CIS in newly diagnosed high grade T1 disease may also be used to support early cystectomy.[41,50] For patients presenting with invasive urothelial carcinoma there are data that such cases arising through the "papillary" pathway have stage for stage a better prognosis that those developing via the "flat" pathway.[51,52]

There is also evidence that the extensiveness of the CIS is significant and so distinguishing between a single focus and diffuse (or multifocal) disease is important. For the purpose of 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 keratinizing squamous metaplasia. This can be identified in patients with invasive squamous cell carcinoma but also can be diagnosed in the absence of invasive disease. Adenocarcinoma in situ is not a well-defined lesion in the urinary tract. In cases of intestinal metaplasia varying degrees of atypia can be seen up to high grade dysplasia, a term we would prefer rather than adenocarcinoma in situ. Urothelial CIS can show areas of squamous and glandular differentiation and these should not be diagnosed as squamous or adenocarcinoma in situ respectively.

**Back**

## Note 7 - 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 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.

**Back**

## Note 8 - 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.[53] The system is now recommended by almost all major pathology and urology organizations as the preferred grading system.[2,4]

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.[54] This lesion represents 21% to 36% of newly diagnosed non-invasive (Ta) papillary tumours[55,56] and overall between 11% and 21% of newly diagnosed non-invasive papillary bladder tumours.[57,58] 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. In one large study that included 1,006 non-invasive papillary tumours (papillary urothelial neoplasm of low malignant potential, 212 [21%]; low grade papillary carcinoma, 603 [60%]; high grade papillary carcinoma, 191 [19%]), treated by TUR with or without intravesical therapy, recurrence occurred in 18%, 35% and 34% of each respectively and progression in 2%, 7% and 29% respectively.[55] The majority of studies have had similar results with no or minimal risk of progression in grade or stage for papillary urothelial neoplasm of low malignant potential.[55,57,59,60]

There are significant differences in the risk of progression to invasive carcinoma and death from bladder cancer between low and high grade papillary urothelial carcinoma.[55,61,62] The grade of non-invasive papillary carcinoma is the major variable in the choice of therapy in these patients.[41] Other features of importance in predicting outcome of patients with Ta papillary tumours are number of tumours/multifocality,[62-65] tumour size,[62,66-68] the presence of associated CIS,[62] and a history of prior

recurrence.[62] It has also been suggested that for low grade papillary tumours the frequency of follow up cystoscopies can be reduced.[69]

Grade heterogeneity is not uncommon in papillary urothelial carcinoma being reported in up to 32% of cases.[54,70] 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.[54,71] 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.[54] Tumours were evaluated based on predominant and secondary grades but ignored secondary components if less than 5%.[54] In their study worst, predominant and average grade all were significant predictors of progression.[54] Progression was higher in pure high grade tumours (>95% high grade) than in mixed high/low grade tumours (5% to 95% high grade).[54] 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 that 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 (ICUD) recommended against the application of an arbitrary percentage of high grade tumour when assigning grade.[1] 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.”

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,[41,73,74] while others provide for the 1973 to be provided by institutional choice.[2,4,12] 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.[1,73-75] 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.[62] The International Collaboration on 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.[12]

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.[76-78] In studies using the 1998 ISUP/WHO 2004 grading system the vast majority of invasive tumours are high

grade.[79,80] The conclusion of the ICUD pathology group was that all invasive carcinomas should be considered high grade.[1,81] 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.[82-85] 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.[86] 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.[62,77,87,88] 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.[12] If invasive tumours are graded using an alternative grading system this should be indicated.

**Back**

## Note 9 - Status of muscularis propria (Required)

The presence or absence of muscularis propria is a vital piece of information in determining the adequacy of a biopsy or TUR specimen that contains an invasive carcinoma.[2,41,73] For such patients, the absence of muscularis propria in a TURBT would be an indication for a repeat TUR to be performed if treatment is other than cystectomy. It is well documented that absence of muscularis propria in a TURBT specimen is associated with a significantly increased risk of residual disease and early recurrence.[110] The current European Association of Urology (EAU) guidelines recommend repeat TUR (i) after an incomplete initial TUR, (ii) if there is no muscle in the specimen after initial resection with the exception of Ta, LG/G1 tumours and primary CIS, (iii) in all T1 tumours and (iv) in all HG/G3 tumours except primary CIS.[41] It generally is also considered appropriate to comment on the presence or absence of muscularis propria in a biopsy or TUR specimen, irrespective of the presence or absence of invasive carcinoma.

**Back**

## Note 10 - Extent of invasion (Required)

**Reason/Evidentiary Support**

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.[89] It is not appropriate to assign pathologic stage on biopsy or TUR specimens and pathologic stage is not an element within this dataset. It is however possible, based on the assessment of the extent of invasion to recognise the least pathological stage possible in a given 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.[90,91] Several studies have documented the difficulty with the diagnosis of

invasion.[92-94] 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.[95,96] Studies have also demonstrated lack of agreement among pathologists with special interest in urologic pathology.[97] In some cases immunohistochemistry with a pan cytokeratin marker is helpful in identifying individual cells particularly when there is a heavy inflammatory infiltrate present. Following the principles of the American Joint Committee on Cancer (AJCC) TNM staging system the diagnosis of invasion should be limited to cases with unequivocal invasion.[89]

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 muscularis mucosae complicates the interpretation as involvement of these fibres still represents a T1 tumour.[98] Muscularis mucosae fibres can be present throughout the bladder.[11] The trigone/bladder neck region least often has recognisable muscularis mucosae fibres and from a practical perspective involvement of smooth muscle in this location essentially always indicates muscularis propria invasion. Muscularis mucosae fibres are typically thin and wispy forming small bundles that taper at the ends and usually are only a few cells thick. They lack the dense eosinophilic cytoplasm characteristic of muscularis propria. Often the fibres are seen in association with a layer of thick walled blood vessels. The muscularis mucosae can however occasionally be thickened and better defined, more closely mimicking muscularis propria. Smoothelin, a cytoskeletal protein is differentially expressed in the muscularis propria and not the muscularis mucosae.[99] Application in challenging cases can be helpful but for the most part the marker has not gained widespread application.[100,101] Regarding the use of smoothelin for staging, the ISUP states “limited experience and conflicting data preclude smoothelin or vimentin to be recommended routinely for subclassifying muscle type at this time.”[15] In some cases it is not possible to be certain if the smooth muscle involvement represents muscularis mucosae or muscularis propria. In those cases this should be specifically commented upon. Repeat TUR on these cases is necessary to determine the true depth of involvement.[101]

Assessment of the presence or absence of muscularis propria invasion can also be hampered by cautery artefact. This can result in stromal changes that mimic smooth muscle leading to over staging or make muscularis propria unrecognisable leading to under staging.[2] Pathologists have used histochemistry (trichrome stain) or immunohistochemistry (desmin) to help determine if muscle is represented in cauterized tissue but no controlled studies of the reliability of these approaches is available.

Urothelial carcinoma can be primary in the prostatic urethra but in the majority of cases involvement is seen in association with a bladder tumour.[102-104] 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.[106-109] 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. Usually invasion of the subepithelial connective tissue or the prostatic stroma elicits a desmoplastic response. Immunohistochemistry is frequently required to distinguish urothelial carcinoma from high grade prostatic carcinoma.[15] Glandular and or squamous differentiation can be present as with urothelial carcinoma elsewhere.

## **Note 11 - Substaging T1 disease** (Recommended)

**Reason/Evidentiary Support**

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. The two methods most used can be divided into quantitative and anatomical.

The largest volume of literature has tried to use the muscularis mucosae (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 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. Since that report numerous groups have reported their experience with this approach.[111] The largest study to date is that of Rouprêt et al (2013) that evaluated 587 cases from multiple institutions in France.[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 that included 21 prior publications.[112] 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 use of MM was a significant predictor of recurrence free survival in 4/12 reports, progression free survival in 15/17 reports and of cancer specific survival in 4 of 7 reports and (iii) on multivariable analysis it was significant for recurrence free survival in 3/12, for progression free survival in 13/16 and for cancer specific survival in 3/6 publications.[112] Additional studies have been published subsequently.[113-115] The study by Orsolo et al (2015) is significant in that this is a prospective study that used substaging based on invasion superficial to the MM (T1a) versus involving or deep to MM (T1b) to stratify patient treatment.[115] The publication reports on the first 200 patients entered into the protocol.[115] Although the follow up is limited in this initial report, substage was a highly significant predictor of tumour progression on multivariable analysis.[115] These authors concluded: "In HGT1 bladder cancer, the strategy of performing a second TUR only in T1b cases results in a global low progression rate of 15.5%. Tumours deeply invading the lamina propria (HGT1b) showed a three-fold increase in risk of progression. Substaging should be routinely evaluated, with HGT1b cases being thoroughly evaluated for cystectomy. Inclusion in the TNM system should also be carefully considered."[115]

The second major approach to substaging has used quantitation of the depth or volume of the invasive carcinoma. The literature here is less robust than for utilising MM. A review of several studies[114,116-121] demonstrates that this approach also has merit. In two of these studies the authors measure the maximum depth of invasion perpendicular to the mucosal surface.[116,121] This method has the difficulty of orientation of the fragments and identification of the mucosal surface or basement membrane. In other studies the measurement is based on the maximum linear length of the invasive tumour, irrespective of the orientation.[114,117-121] Cut points have been 0.5 mm or 1.0 mm. The largest series (509 patients) that also had the longest follow up (median 81 months) utilized the 1.0 mm cut point (based on the sum of the maximum dimension of all invasive foci) and showed a strong correlation with recurrence free-, progression free- and cancer specific-survival.[118]

Recent guidelines have generally recommended that pathologists provide some indication of volume or depth of invasion without specifying a preferred method.[4] In the ICUD recommendations for quantitation, Amin et al stated "It is recommended that pathologists provide some form of estimate of the lamina propria invasion in pT1 tumours (e.g. focal, multifocal, extensive, etc)" and "Involvement of the MM may be included in a comment to provide information on the depth/extent of invasion." The 2016 WHO follows this recommendation as do the recently released College of American Pathologists reporting guidelines.[4,12]

Clinical guidelines have also noted the importance of depth of invasion. In the ICUD section on treatment of high grade Ta, CIS and T1 urothelial carcinoma, the author's first recommendation is "The assessment of T1 urothelial carcinoma should be based on tumour grade, early recurrence, multiplicity, tumour size, concomitant CIS, urothelial carcinoma involving the prostatic mucosa or ducts, and depth of invasion."[122]

Because of the potential for additional information in T1 tumours to directly impact clinical decision making the ICCR guidelines have included substaging of TI disease as a non-required element. The dataset also provides for alternative methods for reporting as there is insufficient data to recommend one alternative over the others.

**Back**

## Note 12 - Lymphovascular invasion (Required)

**Reason/Evidentiary Support**

The data on lymphovascular invasion (LVI) in urothelial carcinoma in the urinary bladder has continued to grow with many large series now reported.[123-127] These have included very large multi-institutional series (e.g. Kluth et al[126] – 8102 patients), cases from phase 3 clinical trials (von Rundstedt et al[127] – SWOG4B951/NCT00005047) and in the generation of prognostic scores (Eisenberg et al[125] – 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 TURBT material specifically are much more limited.[121,128-137] These have almost all been based on H&E evaluation with limited utilisation of immunohistochemistry. The frequency of identification of LVI has ranged from <10% to as high as 67%. Among the better studies are the paper by Olsson et al (2013) which is population based [all newly diagnosed T1 tumours (N=211)] in the Southeastern region of Sweden with relatively uniform treatment.[137] These authors identified LVI in 8% of cases and also included an indeterminate category (22% of cases).[137] The presence of LVI was an independent predictor of recurrence free-, progression free- and cancer specific survival.[137] The prospective study by Orsola et al (2005) in contrast found no significant association with progression-free or cancer specific survival.[138] This study is limited by the short follow up. Overall the majority of these studies have found LVI to be important but, as indicated, data is limited.

Specific data on LVI determination in biopsy/TUR specimens of 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.[139-142] These large, contemporary series have consistently identified LVI as a significant parameter in upper tract urinary cancer. For example, the study by Cha et al (2012) was a multi-institutional retrospective analysis of 2244 patients treated by radical nephroureterectomy.[139] The cases were divided into a development and an external validation cohort. LVI (based on the pathology reports) was an independent predictor of recurrence free survival and cancer specific survival in both cohorts and was included in the 2-year and 5-year recurrence-free and cancer-specific survival nomograms.[139]

For urethral carcinoma there is no substantive literature available. In the 2013 Guidelines on Urethral Carcinoma by the EAU, LVI is not recognised as a prognostic indicator.[143]

The role of immunohistochemistry in determining the presence or absence of LVI has been limited. The problem with recognising LVI on H&E sections has been demonstrated for urothelial carcinoma. Algaba[144] and Lopez-Beltran[73] among others have pointed out the importance of utilising strict criteria and these should be followed. Criteria recommended by Algaba (2006) included tightly cohesive tumour cells with a smooth border and the cells at the periphery having a shell-like appearance, the tumour thrombus floating free in the lumen of a space with an unequivocal endothelial cell lining, the presence of fibrin and/or red blood cells around the thrombus, and the space preferably associated with an arteriole with the surrounding stroma appearing normal.[144]

The possibility of routinely performing immunohistochemistry on T1 cases is much discussed but with little data. In one report[130] immunohistochemistry for D2-40 and CD34 was performed on 25 TUR specimens and the H&E evaluation of LVI was changed in only one case. This contrasts with the report by Larsen et al (1990) who found that only 14% of cases diagnosed as LVI by H&E were confirmed by immunohistochemistry.[128] It is likely that the Larsen study overstates the problem of overcalling of LVI in current practice. The ICUD pathology committee noted that there is well documented value to using immunohistochemistry in other organs to maximize detection of LVI (e.g. breast, etc) but little for urothelial carcinoma. They concluded "The general use of immunohistochemistry in the routine setting cannot however be recommended since performing two immunohistochemical stains on even selected paraffin blocks with bladder cancer would be extremely time consuming and cost intensive."[86]

Although the data on LVI in biopsy/TUR specimens is limited, the compelling evidence in large resection studies of urothelial carcinoma of the urinary bladder and upper tract support inclusion as a required element in this dataset.

**Back**

## Note 13 - Coexistent pathology (Recommended)

**Reason/Evidentiary Support**

Biopsy and endoscopic resection specimens from throughout the urinary tract that are diagnosed with carcinoma can also show a number of non-neoplastic conditions. Although some findings such as keratinizing squamous metaplasia and diffuse intestinal metaplasia may be relevant in a specific case the reporting of these findings does not have sufficient significance to be considered a required element.

**Back**

## Note 14 - Ancillary studies (Recommended)

**Reason/Evidentiary Support**

Currently there are no ancillary studies that are recommended for routine use in urothelial carcinoma of the urinary tract. If immunohistochemical studies are performed for differential diagnosis or to assist in staging or the detection of LVI they could be listed in this section. If ancillary studies are performed at the request of the clinician or in following an institutional policy or for any other reason, these should be included in the report.

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