Carcinoma of the Bladder Histopathology Reporting Guide
Cystectomy, Cystoprostatectomy and Diverticulectomy Specimen

CLINICAL INFORMATION (Note 1)
Previous history of urinary tract disease or distant metastasis (select all that apply)
- Information not provided
- Non-invasive papillary
- Invasion into lamina propria
- Other, specify

Previous therapy (select all that apply)
- Information not provided
- Transurethral resection (TURBT)
- Bacillus Calmette-Guerin (BCG)
- Chemotherapy, intravesical, specify
- Chemotherapy, systemic
- Radiation therapy
- Other, specify

Other clinical information, specify

OPERATIVE PROCEDURE (Note 2)
- Not specified
- Cystectomy, partial
- Cystectomy, simple
- Cystectomy, radical (female)
- Cystoprostatectomy (male)
- Diverticulectomy
- Anterior extenteration (female)
- Urethrectomy
- Lymphadenectomy
- Other, specify

ADDITIONAL SPECIMENS SUBMITTED (select all that apply) (Note 3)
- Not submitted
- Uterus
- Vaginal cuff
- Fallopian tubes
- Ovaries
- Ureter
- Other, specify

TUMOUR FOCALITY (Note 4)
- Unifocal
- Multifocal
- Cannot be assessed, specify

MAXIMUM TUMOUR DIMENSION (Note 5)
- Cannot be assessed
- No macroscopically visible tumour

Maximum tumour dimension (largest tumour)

Additional dimensions (largest tumour)

MACROSCOPIC TUMOUR SITE (select all that apply) (Note 6)
- Indeterminate
- No macroscopically visible tumour
- Trigone
- Right lateral wall
- Left lateral wall
- Anterior wall
- Posterior wall
- Dome
- Other, specify

MACROSCOPIC EXTENT OF INVASION (select all that apply) (Note 7)
- Cannot be assessed
- No macroscopically visible tumour
- Non-invasive tumour visible
- Invasion into bladder wall
- Invasion into perivesical tissue
- Involvement of peritoneal surface
- Involvement of other adjacent structures, specify

BLOCK IDENTIFICATION KEY (Note 8)
(List overleaf or separately with an indication of the nature and origin of all tissue blocks)
### Microscopic Extent of Invasion (select all that apply)  
(Note 13)

- Cannot be assessed
- No evidence of primary tumour
- Non-invasive tumour present
- Tumour invades lamina propria
- Tumour invades muscularis propria
  - Tumour invades superficial muscularis propria (inner half)
  - Tumour invades deep muscularis propria (outer half)
- Tumour invades perivesical tissue
  - Microscopically
  - Macroscopically (extravesical mass)
- Tumour involves adjacent structures
  - Prostatic stroma
  - Seminal vesicles
  - Uterus
  - Vagina
  - Adnexae
  - Pelvis wall
  - Abdominal wall
  - Rectum
- Other, specify

### Histological Tumour Type (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) (select all that apply)

- Not identified
- Present, specify sub-type/variant and percentage
- Squamous
- Microcystic
- Glandular
- Micropapillary
- Other, specify

### Non-Invasive Carcinoma (select all that apply) (Note 10)

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

### Associated Epithelial Lesions (Note 11)

- Present, specify
- Not identified

### Histological Tumour Grade (Note 12)

- Not applicable
- Cannot be determined
- Urothelial carcinoma
  - Low-grade
  - High-grade
  - Other, specify
- Squamous cell carcinoma or adenocarcinoma
  - GX: Cannot be assessed
  - G1: Well differentiated
  - G2: Moderately differentiated
  - G3: Poorly differentiated
  - Other, specify

### Response to Pre-Operative Therapy (Note 14)

- Complete response (ypT0)
- Incomplete response
- No response
- No prior treatment
- Cannot be assessed, explain reasons

### Lymphovascular Invasion (Note 15)

- Not identified
- Present
- Indeterminate

### Margin Status (Note 16)

- Cannot be assessed
- Not involved
- Involved
  - Macroscopic, specify

- Microscopic
  - Invasive carcinoma (select all that apply)
    - Urethral
    - Ureteral, specify side
  - Soft tissue
  - Other, specify

- Carcinoma in situ/non-invasive high-grade
  - Urothelial carcinoma (select all that apply)
    - Urethral
    - Ureteral, specify side
    - Other, specify
  - Other, specify
### Ancillary Studies (Note 19)
- Not performed
- Performed, specify

### Histologically Confirmed Distant Metastases (Note 20)
- Not identified
- Indeterminate
- Present, specify site(s)

### Regional Lymph Node Status (Note 17)
- No regional nodes submitted
- Not involved
  - Number of lymph nodes examined
- Involved
  - Number of lymph nodes examined
  - Number of positive lymph nodes
  - Number cannot be determined
  - Extramural spread
    - Present
    - Not identified
  - Size of largest metastasis
  - Location of involved lymph nodes, specify

### Coexistent Pathology (select all that apply) (Note 18)
- 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
- Keratinizing squamous metaplasia
- Intestinal metaplasia
- Other, specify

### Pathological Staging (AJCC TNM 8th edition)** (Note 21)
#### TNM Descriptors (only if applicable) (select all that apply)
- m - multiple primary tumours
- r - recurrent
- y - post-therapy

#### Primary Tumour (pT)
- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Ta Non-invasive papillary carcinoma
- Tis Urothelial carcinoma in situ: "flat tumour"
- T1 Tumour invades lamina propria (subepithelial connective tissue)
- T2 Tumour invades muscularis propria
  - T2a Tumour invades superficial muscularis propria (inner half)
  - T2b Tumour invades deep muscularis propria (outer half)
- T3 Tumour invades perivesical soft tissue
- T3a Tumour invades perivesical soft tissue microscopically
- T3b Tumour invades perivesical soft tissue macroscopically (extravesical mass)
- T4 Extravesical tumour directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
  - T4a Extravesical tumour invades directly into prostatic stroma, uterus, vagina
  - T4b Extravesical tumour invades pelvic wall, abdominal wall

#### Regional Lymph Nodes (pN)
- NX Lymph nodes cannot be assessed
- N0 No lymph node metastasis
- N1 Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
- N2 Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
- N3 Lymph node metastasis to the common iliac lymph nodes

Scope

The dataset has been developed for the reporting of cystectomy, cystoprostatectomy or diverticulectomy specimens from patients with carcinoma of the bladder. The protocol applies to primary carcinomas (non-invasive and invasive), with or without associated epithelial lesions. Urothelial tumours diagnosed as papilloma or papillary urothelial neoplasm of low malignant potential are not carcinomas and this dataset does not apply to those diagnoses. Biopsy and transurethral resection specimens are dealt with in a separate dataset.

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.\(^7\)\(^,\)\(^8\) Neoadjuvant chemotherapy may result in significant tumour response and necessitate very careful macroscopic and microscopic assessment for residual tumour.

Note 2 - Operative procedure (Required)

Reason/Evidentiary Support

Documentation of the specific procedure performed should be a standard part of any pathology report. Knowledge of the procedure is crucial to the proper handling and reporting of a case. In some instances where there has been prior therapy (e.g. external beam radiation therapy for prostate cancer) or with a large invasive tumour, the presence of certain tissues may not be readily apparent from the gross evaluation alone.
Note 3 - Additional specimens submitted (Required)

Reason/Evidentiary Support

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

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Note 4 - Tumour focality (Recommended)

Reason/Evidentiary Support

Multifocality is relatively common in urothelial carcinoma of the urinary bladder. This can include an invasive carcinoma associated with non-invasive papillary carcinomas or multifocal invasive tumours. The presence of multifocal invasive carcinoma is a component of the SPARC score for predicting outcome after radical cystectomy for bladder cancer.9 In a meta-analysis of 13,185 patients the presence of multifocal disease was a significant risk factor for subsequent upper tract recurrence.10 Multifocality has also been found to be a risk factor for urethral recurrence following cystectomy in some11,12 but not all reports.13 When more than one tumour is present, it is important to sample all tumours as significant differences in histology can be present.14

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Note 5 - Maximum tumour dimension (Required and Recommended)

Reason/Evidentiary Support

Some studies have demonstrated the maximum diameter of the residual tumour at the time of cystectomy as an independent predictor of recurrence and cancer specific survival. In one report residual tumour diameter ≥3 cm was an independent predictor of cancer specific survival.15

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Note 6 - Macroscopic tumour site (Recommended)

Reason/Evidentiary Support

Tumour location is important for several reasons including diagnosis and staging. Tumours arising in the dome and anterior wall region raise the possibility of an urachal origin. Most cases of secondary involvement of the urinary bladder are direct extension from adjacent organs. In males this is more often the prostate gland and in females the cervix and lower uterine segment. In both, colorectal adenocarcinoma is also a consideration. Depending on the histologic findings these possibilities may be raised and knowledge of location may be helpful.
For staging purposes location in the posterior wall and bladder neck region is particularly relevant. It is in this area that adjacent organs are most often involved (stage pT4a). In the case of the prostate gland involvement can be by direct invasion or by in situ disease involving the urethra and subsequently the prostate gland (see Note 21 - PATHOLOGICAL STAGING). Knowledge of the tumour location may be helpful in making this distinction and correctly assigning pathologic stage.

**Note 7 - Macroscopic extent of invasion** (Required)

**Reason/Evidentiary Support**

The staging of bladder cancer requires documentation of the gross extent of tumour (specifically for separation of pT3a from pT3b). It is also important for determination of the appropriateness of sampling of the tumour. Sites of prior transurethral resections of bladder tumours (TURBT) typically appear as scarred areas with fibrosis and a depressed mucosal surface. Calcifications are often present. Grossly the appearance mimics tumour and the fibrosis can extend into the perivesical fat mimicking a pT3b tumour. Correlating the gross and microscopic findings is necessary to accurately assign the pathologic stage.

Prostatic involvement by tumour can occur by direct invasion or by in situ involvement of the urethra with subsequent invasion of the prostate gland. These two mechanisms are staged differently and so the gross evaluation is critical in making the distinction. For invasive carcinomas located towards the bladder neck region of the urinary bladder submission of sections to include the invasive tumour and the adjacent prostate gland are important. Further, invasive tumours that are located posteriorly can directly invade the seminal vesicles and sections should be submitted to demonstrate the relationship between the invasive carcinoma and the seminal vesicles.

For tumours located in the dome the gross evaluation can be important in distinguishing tumours originating in the urachus from the urinary bladder proper. The current World Health Organization (WHO) classification system\(^6\) includes urachal tumours as a separate category irrespective of the histologic type of tumour. Although most urachal tumours are adenocarcinoma, all other histologic types are represented and an urothelial carcinoma in the dome area may also be of urachal origin.

**Note 8 - Block identification key** (Recommended)

**Reason/Evidentiary Support**

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

Note 9 - Histological tumour type (Required)

Reason/Evidentiary Support

The 2016 WHO classification is utilized for assigning histological tumour type. As in the 2004 WHO Classification, 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. Subsequent evaluation of the entire lesion in the cystectomy specimen should allow for definitive classification. It is not unusual for a tumour with pure squamous or glandular differentiation on biopsy/TURBT to prove to represent a urothelial carcinoma with squamous or glandular differentiation. It is for this reason that a definitive diagnosis of either should be made with caution in biopsy or TURBT material.

The 2016 WHO classification now includes carcinomas arising in the urachus as a separate category. These are defined as carcinomas arising from urachal remnants. It is generally 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. 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.” 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.\(^{18-20}\) The gross examination is an important parameter in making this distinction in the resection specimen.

Also new in the 2016 WHO classification is the category of Müllerian tumours. For the purposes of this dataset this consists primarily of clear cell adenocarcinoma 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.\(^{21}\) 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.\(^{22-25}\) 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.\(^{26}\) Markers such as p63, GATA3 and high molecular weight cytokeratin are not expressed by clear cell adenocarcinoma and expression of these markers even in the absence of a recognisable urothelial component would suggest this possibility.\(^{27}\) 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.\(^{24,28-30}\)

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. In some cases the biopsy/TURBT specimen does not include a small cell neuroendocrine component and it is only discovered in the resection specimen. 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.\(^{31-34}\) For example the National Comprehensive Cancer Network (NCCN) includes tumours with “any small-cell component” in the category of non-urothelial cell carcinoma.\(^{35,36}\) 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.\(^{37}\) TTF-1 is expressed in about 50% of cases and hence would not be indicative of metastasis from the lung.\(^{38,39}\) 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.\(^{17}\)
Histologic subtype/variant

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

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

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 as in the WHO 2016 monograph. The data supporting this is very limited and only available for selected variants (micropapillary, sarcomatoid, lymphoepithelioma-like), with divergent differentiation (glandular, squamous). 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 approximate 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**

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>ICD-O codes</th>
</tr>
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<tbody>
<tr>
<td><strong>Urothelial tumours</strong></td>
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<tr>
<td>Infiltrating urothelial carcinoma</td>
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<tr>
<td>Nested, including large nested</td>
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<td>Microcystic</td>
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<td>Micropapillary</td>
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<td>Lymphoepithelioma-like</td>
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<td>Sarcomatoid</td>
<td>8122/3</td>
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<tr>
<td>Descriptor</td>
<td>ICD-O codes</td>
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<td>-------------</td>
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<td>Giant cell</td>
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<tr>
<td>Poorly differentiated</td>
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\(^{a}\) The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.

\(^{b}\) Paraganglioma is not an epithelial derived tumour.

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**Note 10 - Non-invasive carcinoma** (Required)

**Reason/Evidentiary Support**

The majority of surgical resections of bladder tumours are performed for invasive carcinoma, however patients with carcinoma in situ that fail intra-vesical therapy are also usually managed by cystectomy. Cystectomy is also recommended for patients with recurrent high grade papillary carcinomas refractory to BCG or recurring after completion of BCG maintenance. For patients that are BCG intolerant this may also be an indication for cystectomy. Occasionally patients have such large and extensive non-invasive papillary tumours that cystectomy also becomes necessary. In those cases this category will represent the tumour that was the indication for the procedure.

For patients undergoing cystectomy for invasive carcinoma, it may sometimes be important to document non-invasive carcinoma if present. In large cystectomy series concomitant carcinoma in situ is found in 19% to 54% of cases with most series at the higher end of this range. The presence of urothelial carcinoma in situ in these cases has been associated with an increased risk of recurrence in a limited number of studies. However, in the majority of reports the presence of carcinoma in situ has not been found to be associated with either recurrence or cancer specific survival. In a meta-analysis of 13,185 patients undergoing radical cystectomy, the presence of carcinoma in situ was not a significant risk factor for subsequent upper tract recurrence. Similarly most reports have not found carcinoma in situ in the bladder to be associated with a higher likelihood of urethral recurrence in contrast to prostatic involvement by in situ carcinoma which is a major risk factor of urethral recurrence in men.

**Note 11 - Associated epithelial lesions** (Recommended)

**Reason/Evidentiary Support**

A variety of neoplastic lesions that fall short of carcinoma are recognised in the urinary tract. These include 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.
**Note 12 - Histological tumour grade** (Required)

**Reason/Evidentiary Support**

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

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. This lesion represents up to one-third of newly diagnosed non-invasive papillary tumours. Papillary urothelial neoplasm of low malignant potential is not reported using this dataset. It is nonetheless a significant diagnosis and does indicate an increased risk for the development of other neoplasms in the urinary tract.

Grade heterogeneity is not uncommon in papillary urothelial carcinoma being reported in up to 32% of cases. 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. Using the 1999 WHO grading system, Billis et al found that pure grade 3 tumours were more often muscle invasive than tumours with mixed grades 2 and 3. 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. 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. Tumours were evaluated based on predominant and secondary grades but secondary components were ignored if less than 5%. In their study worst, predominant and average grade all were significant predictors of progression. Progression was higher in pure high grade tumours (>95% high grade) than in mixed high/low grade tumours (5% to 95% high grade). In another study tumours with less than 10% of high grade histology (5% of the cases) were compared with low and high-grade tumours. The progression free and cancer specific survival of the mixed cases was similar to low grade tumours and significantly better than that of high grade cases. The limited data does not allow for a definitive statement regarding reporting of cases with a small volume of high grade tumour or to determine what percentage of high grade tumour is necessary to indicate a significantly worse prognosis. The International Consultation on Urologic Disease recommended against the application of an arbitrary percentage of high grade tumour to ignore when assigning grade. 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 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, while others provide for the 1973 grade to be included by institutional choice. 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.
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. The ICCR dataset follows the WHO 2016 approach with reporting of the WHO 2016 grade as a required element and the inclusion of other grading systems as optional.

The grading of invasive urothelial carcinoma is another area of controversy. In North America the vast majority of invasive urothelial carcinomas have been diagnosed as high grade in contrast to European studies where a substantial percentage of invasive tumours have been graded as 2 or even 1. Currently there is general agreement that grade 1 tumours (WHO 1973), largely corresponding to papillary urothelial neoplasm of low malignant potential, lack the capacity to invade. In studies using the 1998 ISUP/WHO 2004 grading system the vast majority of invasive tumours are high grade. The conclusion of the International Consultation on Urologic Disease pathology group was that all invasive carcinomas should be considered high grade. It has been noted that there are variants of urothelial carcinoma with low grade cytologic features, such as the nested variant, that appear to behave stage for stage like usual high grade carcinoma. 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. 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. We recommend the 2016 WHO approach of continuing to grade invasive carcinoma using the WHO 2004 system while recognising that the vast majority of tumours will be high grade. If invasive tumours are graded using an alternative grading system this should be indicated.

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Note 13 - Microscopic extent of invasion (Required)

Reason/Evidentiary Support

Determining the extent of invasion is the key feature for the assignment of pathologic stage. In most cases this determination is relatively straightforward but a few situations are worth specific discussion. There are several publications providing guidelines for the optimal gross examination and sampling of radical cystectomy specimens.

In contemporary cystectomy series there is no residual tumour identified in the radical cystectomy specimen in between 5% and 20% of specimens. It is likely that this frequency will continue to increase with the more frequent treatment of T1 tumours by radical cystectomy and the increased use of neoadjuvant chemotherapy. In most cases the site of the prior TURBT is evident grossly and this area can be completely submitted for microscopic examination (or if large extensively sampled). In cases with no grossly apparent lesion the clinical information including radiologic findings may be helpful in guiding sampling. Sampling of areas with mucosal lesions such as erythema may identify foci of carcinoma in situ as may random samples of apparently normal mucosa. As long as the site of
the prior TURBT is identified microscopically the case can be reported as “no residual tumour” without resorting to extensive sampling of grossly normal bladder tissue.

Determination of peri-vesical fat invasion seems on the face of it to be relatively straightforward. However, unlike in the colon, the junction between the muscle of the muscularis propria and the perivesical fat is not well defined. Adipose tissue is present throughout the bladder wall and at the deep aspect of the muscularis propria typically results in haphazardly separated muscle bundles forming a poorly formed demarcation. Ananthanarayanan and colleagues demonstrated the inconsistency among expert urologic pathologists in defining peri-vesical fat extension. We are unaware of a definition that has been validated with outcome data to provide guidance. It may be that this variability in part explains the variation in prognostic differences between pT2b and pT3a tumours in different reports. Some reports have found no significant difference between pT2b and pT3a carcinomas, while others have found there to be a significant difference. Distinction of pT3a from pT3b tumours is however consistently found to be significant. In many of the larger cystectomy series the data compares pT2 and pT3 tumours without subdividing them.

Documentation of invasion into adjacent structures represents pT4 disease and is important to document. Involvement of the prostate gland represents a unique group in that the invasion can occur by two routes: direct invasion by the invasive tumour from the bladder or invasion by in situ disease involving the prostatic urethra and/or prostatic ducts. The significance of this is discussed in detail in Note 21 - PATHOLOGICAL STAGING.

Carcinoma arising in diverticula represent less than 2% of urothelial carcinomas of the bladder. The urothelium in diverticula is however known to be at significantly higher risk for the development of carcinoma than that of the urinary bladder. The majority of carcinomas arising in diverticula are urothelial carcinoma but all histologic types can occur. In most series squamous cell carcinoma is more frequent than in the bladder proper. Most diverticula in adults are acquired and by definition do not have a muscularis propria therefore there are no pT2 tumours. Invasive carcinomas are staged as either pT1, pT3a or pT3b only. It should be noted that acquired diverticula usually have fibres of the muscularis mucosae and these can be hypertrophic and should not be confused with muscularis propria. In one report hypertrophic muscularis mucosae was found in 59% of diverticula resected for carcinoma. Carcinomas arising in diverticula can be treated by diverticulectomy, partial cystectomy or radical cystectomy.

Note 14 - Response to pre-operative therapy (Recommended)

Reason/Evidentiary Support

Neoadjuvant chemotherapy is commonly part of the management of patient with high risk bladder cancer prior to cystectomy. In the 2013 European Association of Urology (EAU) guidelines neoadjuvant chemotherapy was “recommended for T2-T4a cN0 M0 bladder cancer and should always be cisplatinum-based combination therapy.” The recommendation was a “grade A” recommendation.
At cystectomy patients treated with neoadjuvant chemotherapy are often down staged and may be pT0. This has been demonstrated to be associated with improved survival. pT0 at cystectomy after TURBT is also associated with significantly improved survival but pT0 is more frequent in patients having neoadjuvant chemotherapy.

Improved survival following neoadjuvant chemotherapy has also been studied for specific histologic types and generally had similar results.

There is minimal data however on morphologic alterations in the tumour itself following neoadjuvant chemotherapy and what the significance of such alterations might be. Fleischmann et al developed a “tumour regression grade” by comparing the tumour in the TURBT with residual tumour in the cystectomy following neoadjuvant chemotherapy. The grade was based on the amount of residual tumour with respect to the size of the TURBT site scar. Three grades were assigned: TRG1 – no identifiable residual tumour complete response), TRG2 – residual tumour occupying <50% of the area of fibrosis and TRG3 – residual tumour overgrowing or occupying ≥50% of the fibrotic area. The TRG correlated significantly with overall survival. The study is limited by small numbers and many other issues but this is one of the first efforts to come up with some measurement of response. Of note is that the TRG2 group did better than the TRG3 group.

Note 15 - Lymphovascular invasion (Required)

Reason/Evidentiary Support

The data on lymphovascular invasion (LVI) in urothelial carcinoma in the urinary bladder has continued to grow with very large series now reported. These have included very large multi-institutional series (e.g. Kluth et al), cases from phase 3 clinical trials (von Rundstedt et al – SWOG4B951/NCT00005047) and in the generation of prognostic scores (Eisenberg et al – SPARC Score) all of which have found LVI to be a highly significant independent predictor of outcome. This is therefore a required element.

Note 16 - Margin status (Required)

Reason/Evidentiary Support

Evaluation of surgical margin status is a core component of evaluation of resection specimens in most areas of surgical oncology. The prognostic significance of this finding in resection specimens for urinary bladder carcinoma has had variable significance in studies in the literature. Gross evaluation of the surgical margins is important primarily to ensure that tissue sections are taken at the locations that are most likely to have involvement confirmed histologically. For cases where the gross examination suggests a positive surgical margin and the histological sections do not reflect this
submission of additional sections may be appropriate. Confirmation by microscopic examination is necessary as the stromal response to invasive tumour or a prior TURBT may mimic a positive margin. Studies have reported positive surgical margins to be present in 4% to 15% of radical cystectomy specimens. Positive margins are generally placed in three categories: urethral, ureteral and soft tissue. Urethral and ureteral margins can be involved by in situ carcinoma and/or invasive carcinoma. Ureteric margins are frequently evaluated by frozen section as is the urethral margin to a lesser extent. For this reason in most studies of radical cystectomy specimens positive margins most frequently involve the soft tissues followed by the urethra and then the ureters.

Positive soft tissue surgical margins have been an independent predictor of an increased risk of recurrence and decreased cancer specific survival. In a multi-institutional case control study, Neuzillet et al (2013) showed a significantly higher recurrence rate and decreased cancer specific survival for patients with positive urethral and soft tissue surgical margins but not for ureteral margins. In the multivariable analysis both urethral and soft tissue margins remained significant for recurrence with only soft tissue margins being significant for cancer specific survival. It has also been reported that patients with positive soft tissue margins (as well as positive lymph nodes) have greater benefit from adjuvant chemotherapy than those without.

Ureter margins are typically controlled for by frozen section evaluation at the time of cystectomy. Frozen section interpretation is reliable with low false positive and false negative rates. Several studies have evaluated the utility of routine frozen sections with varying conclusions. In larger series ureteral involvement by carcinoma in situ is present in up to 9% of cases. In most cases with ureteric involvement there is carcinoma in situ in the urinary bladder leading some to recommend performing frozen sections only in those cases, while others have recommended against routine use of frozen section in general. Overall subsequent recurrence in the ureter occurs in up to 13% of patients, with most studies reporting upper tract recurrence in the 4% to 6% range and with recurrence of invasive carcinoma at the uretero-ileal anastomosis in less than 1%. Recurrence is significantly higher in patients with documented ureteric involvement. This increased risk remains but is reduced if a negative margin is subsequently obtained with frozen section control. The latter may in part be related to “skip lesions” that can be present in up to 4.8% of patients.

Although urethral margins are positive in up to 10% of cases, frozen sections are less often performed for margin control. It is most often used in the setting of orthotopic diversions and/or when there has been documented prostatic urethral involvement. Patients with positive urethral margins are at increased risk of the development of recurrence in the urethra. Limited data suggests that documentation of a negative urethral margin at frozen section is associated with a low likelihood of urethral recurrence.

In choosing microscopic margin status, if both invasive carcinoma and carcinoma in situ are present, then invasive carcinoma should be selected. If low grade tumour or carcinoma in situ is present at the margin, this should be noted.
Note 17 - **Regional lymph node status** *(Required and Recommended)*

**Reason/Evidentiary Support**

Lymph node dissection is a standard procedure performed at the time of radical cystectomy for bladder cancer. The past decade has seen considerable expansion of the literature on this topic addressing such issues as the optimal extent of the lymph node dissection, the significance of the number of lymph nodes examined and the proportion of positive lymph nodes (lymph node density) in cases with metastases.

For cases with lymph node metastases, a number of studies have evaluated the significance of extranodal extension. Most of these have found the presence of extranodal extension to be associated with worse cancer specific survival\(^\text{123-126}\) but this has not been uniform.\(^\text{127}\) In a multi-institutional study of 748 cases with positive lymph nodes, extranodal extension was present in 50%.\(^\text{126}\) In a multivariable analysis, the presence of extranodal extension was the most significant independent predictor of disease recurrence and cancer-specific mortality.\(^\text{126}\)

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Note 18 - **Coexistent pathology** *(Recommended)*

**Reason/Evidentiary Support**

A wide range of non-neoplastic changes can be found in radical cystectomy specimens. These include those found in the urinary bladder as well as in other organs that are often removed as part of the radical cystectomy (prostate gland and seminal vesicles; uterus and cervix with and without fallopian tubes and ovaries). For the urinary bladder findings such as keratinizing squamous metaplasia and intestinal metaplasia may be relevant in cases of squamous cell carcinoma and adenocarcinoma but for the most part these findings are not critical and so this element is not required.

Significant pathology in other organs submitted would however be considered required for reporting. The topic of urothelial carcinoma involving the urethra and prostate gland is discussed in detail in the staging section. Prostate adenocarcinoma is a frequent incidental finding in cystoprostatectomy specimens.\(^\text{128}\) When this occurs the prostatectomy dataset should be inserted in the pathology report and completed as appropriate.

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Note 19 - Ancillary studies (Recommended)

Reason/Evidentiary Support

Currently there are no ancillary studies that are recommended for routine use in urothelial carcinoma. In cases where immunohistochemistry is used diagnostically these should be reported in this section.

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Note 20 - Histologically confirmed distant metastases (Required)

Reason/Evidentiary Support

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

In the 8th edition of the American Joint Committee on Cancer (AJCC)/TNM manual129 the M category has been revised. M1 is now subdivided into M1a for distant metastases limited to lymph nodes beyond the common iliac nodes and M1b for non-lymph node metastases.

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Note 21 - Pathological staging (Required)

Reason/Evidentiary Support

Pathologic stage remains the single most important prognostic parameter in patients treated by radical cystectomy. In prior sections several issues related to pathologic staging including cases with no residual tumour in the cystectomy specimen (Extent of invasion), separation of pT2b from pT3a disease (Extent of invasion) and the importance of various lymph node parameters (Regional lymph node status) have been reviewed.

An important issue that has not been covered in detail is the assignment of pathologic stage in cases with involvement of the prostatic urethra and prostate gland in cystoprostatectomy specimens. It has long been recognised that in patients with bladder cancer, involvement of the prostatic urethra can also be present.130,131 In contemporary cystoprostatectomy series involvement of the prostatic urethra with or without prostate gland involvement is reported in 16% to 48% of patients.128,132-134 Pagano et al reported that prostatic gland involvement in such cases could be classified as contiguous or non-contiguous with the latter having a significantly better prognosis.135 Similar results have been reported by others.136-140
The prostatic stroma can be invaded by two different mechanisms. The first is direct (transmural) extension of the invasive bladder cancer into the prostatic stroma. A second mechanism would be extension of urothelial carcinoma in situ into the prostatic urethra and/or prostatic ducts with subsequent prostatic stromal invasion. There are data that indicate that there are significant prognostic differences between these two groups with the former having a substantially worse prognosis. It is therefore critical that when assigning pathologic stage in cases where the prostate gland is involved the mechanism of involvement be determined. The current TNM has clarified the handling of prostatic involvement. For cases with direct extension of the invasive tumour into the prostate gland, a stage of pT4a is assigned. For cases where the involvement is related to carcinoma in situ involving the prostatic urethra and or prostatic ducts, stage is assigned using the urethra staging system. Using this approach, prostatic stromal invasion would be pT2.

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