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

ICCR

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 CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

◯ Information not provided

◯ Information provided (select all that apply)

- ☐ Previous history of urinary tract disease or distant metastasis
  - ☐ Carcinoma in situ, flat
  - ☐ Non-invasive papillary
  - ☐ Invasion into lamina propria
  - ☐ Invasion of muscularis propria or beyond
  - ☐ Distant metastasis
  - ☐ Other, *specify*
- ☐ Previous therapy
  - ☐ Transurethral resection
  - ☐ Bacillus Calmette-Guerin (BCG)
  - ☐ Immunotherapy
  - ☐ Radiation therapy
  - ☐ Chemotherapy, systemic
  - ☐ Chemotherapy, intravesical, *specify*
  - ☐ Other, *specify*
- ☐ Other clinical information, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

◯ Not specified

☐ Cystectomy, partial

☐ Cystectomy, simple

☐ Cystectomy, radical (female)

☐ Cystoprostatectomy (male)

☐ Diverticulectomy

☐ Anterior exenteration (female)

☐ Urethrectomy

☐ Lymphadenectomy

☐ Other, *specify*

ADDITIONAL SPECIMEN(S) SUBMITTED (select all that apply) (Note 3)

◯ Not submitted

☐ Uterus

☐ Vaginal cuff

☐ Prostate gland

☐ Adnexa

☐ Seminal vesicles

☐ Penile urethra

☐ Ureter

☐ Left ☐ Right ◯ Laterality not specified

☐ Other, *specify*

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

◯ No macroscopically visible tumour

☐ Trigone

☐ Left lateral wall

☐ Right lateral wall

☐ Anterior wall

☐ Posterior wall

☐ Dome

☐ Urachal remnant

☐ Bladder diverticulum

☐ Other, *specify*

TUMOUR FOCALITY (Note 5)

◯ Unifocal

◯ Multifocal

TUMOUR DIMENSIONS (Note 6)

◯ No macroscopically visible tumour

Maximum tumour dimension (largest tumour)

mm

Additional dimensions (largest tumour)

mm X mm

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

- ○ 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)

HISTOLOGICAL TUMOUR TYPE (Note 9)

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

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

Histologic subtype and divergent differentiation (urothelial carcinoma)

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

Comments

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

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

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

ASSOCIATED EPITHELIAL LESIONS (Note 11)

- ○ Not identified
- ○ Present, *specify*

HISTOLOGICAL TUMOUR GRADE[b] (Note 12)

- ○ Not applicable
- ○ Cannot be assessed

Urothelial carcinoma[c]

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

Squamous cell carcinoma or adenocarcinoma

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

[b] *If more than one foci with different grades, record the highest grade.*
[c] *In cases with heterogeneous grades, the cutoff for high grade is 5%.*

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

- ○ Cannot be assessed
- ○ No evidence of primary tumour
- ☐ Non-invasive tumour present
- ☐ Tumour invades subepithelial connective tissue (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 invades adjacent structures
  - ☐ Prostatic stroma
  - ☐ Seminal vesicles
  - ☐ Uterus
  - ☐ Vagina
  - ☐ Adnexa
  - ☐ Pelvis wall
  - ☐ Abdominal wall
  - ☐ Other, *specify*

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RESPONSE TO PRE-OPERATIVE THERAPY (Note 14)

- ◯ No prior treatment
- ◯ No response
- ◯ Complete response (ypT0)
- ◯ Partial response
- ◯ Cannot be assessed, *explain reasons*

LYMPHOVASCULAR INVASION (Note 15)

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present

MARGIN STATUS (Note 16)

- ◯ Cannot be assessed
- Not involved
- ◯ Involved (select all that apply)
  - ☐ Macroscopic, *specify*
  - ☐ Microscopic
    - ◯ Invasive carcinoma
      - ☐ Urethral
      - ☐ Ureteral, *specify side*
      - ☐ Soft tissue
      - ☐ Other, *specify*
    - ◯ Carcinoma in situ/non-invasive papillary urothelial carcinoma
      - ☐ Urethral
      - ☐ Ureteral, *specify side*
      - ☐ Other, *specify*

LYMPH NODE STATUS (Note 17)

- ◯ No nodes submitted or found

Number of lymph nodes examined

- ◯ Not involved
- ◯ Involved

Number of involved lymph nodes

- ◯ Number cannot be determined

Location of involved lymph nodes, *specify*

Maximum dimension of largest deposit ____ mm

Extranodal extension

- ◯ Not identified
- ◯ Present

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
- ☐ Keratinising squamous metaplasia
- ☐ Squamous metaplasia
- ☐ Glandular metaplasia
- ☐ Nephrogenic adenoma
- ☐ Other, *specify*

ANCILLARY STUDIES (Note 19)

- ◯ Not performed
- ◯ Performed, *record test(s), methodology and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 20)

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

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PATHOLOGICAL STAGING (UICC TNM 9th edition)[d] (Note 21)

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

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

Primary tumour (pT)

- ◯ TX[e] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ Ta Non-invasive papillary carcinoma
- ◯ Tis Carcinoma in situ: 'flat tumour'
- ◯ T1 Tumour invades 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 tissue:
  - ◯ T3a Microscopically
  - ◯ T3b Macroscopically (extravesical mass)
- ◯ T4 Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall or abdominal wall
  - ◯ T4a Tumour invades prostate stroma, seminal vesicles, uterus or vagina
  - ◯ T4b Tumour invades pelvic wall or abdominal wall

Regional lymph nodes (pN)

- ◯ NX[e] Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral)
- ◯ N2 Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
- ◯ N3 Metastasis in a common iliac lymph node(s)

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

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

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Definitions

CORE elements

Core elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a core element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system, e.g., Pathological TNM staging, would normally be included as a core element.

Non-morphological testing e.g., molecular or immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) recommends that some ancillary testing in ICCR Datasets is included as core elements. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as non-core items.

The summation of all core elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

Non-core elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either core or non-core elements by consensus of the DAC.

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Scope

The dataset has been developed for the pathology reporting of cystectomy, cystoprostatectomy or diverticulectomy specimens from patients with carcinoma of the bladder. The dataset applies to primary carcinomas (non-invasive and invasive), with or without associated epithelial lesions. The dataset also applies to urachal tumours. Biopsy and transurethral resection specimens are dealt with in a separate ICCR dataset.[2]

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

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

The authors of this dataset can be accessed here.

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

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

Knowledge of any relevant history is critical in the accurate diagnosis of tumours throughout the urinary tract.[5-7] This may be relevant to the specific diagnosis being entertained. This is a non-core rather than a core element as it is the responsibility of the clinician requesting the pathological examination of a specimen to provide information that will have an impact on the diagnostic process or affect its interpretation. Patients with a history of urothelial neoplasia are at risk for urothelial tumours throughout the urinary tract and this 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.[8,9] Radiation therapy (to the bladder or to adjacent organs) can be associated with pseudocarcinomatous hyperplasia that can be misdiagnosed as invasive carcinoma.[10] Neoadjuvant chemotherapy may result in significant tumour response and necessitate very careful macroscopic and microscopic assessment for residual tumour.[11]

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Note 2 – Operative procedure (Core)

The operative 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, neoadjuvant chemotherapy) or if a large invasive tumour is present, some aspects may not be readily apparent from the gross evaluation alone.

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

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

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Note 4 – Tumour site (Non-core)

Tumour location is important to document for several reasons. Tumours arising in the trigone are more likely to develop nodal metastasis.[12] A localisation in the dome or anterosuperior raises the possibility of urachal origin, confirmation of which may require additional imaging and clinical information. Most cases of secondary involvement of the urinary bladder represent direct extension from tumours in adjacent organs such as the prostate gland and cervix/uterine segment. Colorectal adenocarcinoma is also an important consideration. It is important to rule out secondary involvement of the bladder especially when dealing with adenocarcinoma where a distinction based on histology and immunohistochemistry may be impossible.[13]

For staging purposes location in the posterior wall and bladder neck region is particularly relevant. In these areas adjacent organs are more often involved (stage pT4a). In the case of the prostate gland involvement, direct invasion and/or in situ disease involving the urethra and prostatic ducts are possible (refer to **Note 21 – PATHOLOGICAL STAGING**). Knowledge of the specific type of prostatic involvement is important to correctly assign pathologic stage.

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Note 5 – Tumour focality (Non-core)

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. Multifocality has been found to be a risk factor for urethral recurrence following cystectomy in some,[14-16] but not all reports.[15,16] When more than one tumour is present, it is important to sample all tumours as significant histological and molecular differences can be present.[17]

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Note 6 – Tumour dimensions (Non-core)

Some studies have demonstrated the maximum diameter of the residual tumour at the time of cystectomy to be an independent predictor of recurrence and cancer specific survival, especially in the neoadjuvant setting. Some authors even start claiming bladder preservation if a total downstaging after neoadjuvant chemotherapy is seen.[11,18]

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

The staging of bladder cancer requires documentation of the gross extent of tumour (specifically for separation of pT3a from pT3b). No consensus exists in cases of multiple synchronous tumours, but at least the largest and most deeply invasive carcinomas should be reported. The extent of tumour sampling is a significant consideration, but no consensus grossing protocol exists, although some attempts have been made.[19] Sites of prior transurethral resections of bladder tumours (TURBT) can appear as mucosal depressions and scarring. Calcifications may also be present. Fibrosis and inflammatory changes may extend into the perivesical fat, mimicking a pT3 tumour. Correlating the gross and microscopic findings is essential to accurately assign the pathologic stage.

Prostatic involvement by tumour can occur by direct invasion through the bladder wall, invasion from outside via the perivesical fat, or by in situ involvement of the urethra and prostatic ducts with associated invasion of prostatic tissue.[20] The latter situation is staged differently and has a different prognosis.[21,22] For invasive carcinomas located towards the bladder neck region of the urinary bladder, submission of sections to include the invasive tumour and adjacent prostate gland is 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.[3]

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 WHO Classification[3] includes urachal tumours as a separate category irrespective of the histologic type of tumour. Although most urachal tumours are adenocarcinomas, other histologic types are represented and a pure urothelial carcinoma in the dome may also be of urachal origin.

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Note 8 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

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

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

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

Well differentiated neuroendocrine tumours (formerly 'carcinoids') and paraganglioma are described in separate chapters in the 2022 WHO 'Blue book'.[3] In the carcinoma group, the small cell neuroendocrine carcinoma is the most common. About one-half of cases are pure and one-half are mixed with another component with urothelial carcinoma being most frequent. Therefore, cases with mixed differentiation are included in this category. There does remain some controversy regarding the percentage of the neuroendocrine component required to classify a tumour as a neuroendocrine carcinoma. From a practical standpoint, cases with a small cell neuroendocrine carcinoma component irrespective of the amount are managed as small cell neuroendocrine carcinoma.[23] The National Comprehensive Cancer Network (NCCN) includes tumours with any small cell component in the category of non-urothelial carcinoma.[23] The larger series in the literature include cases with only focal small cell neuroendocrine carcinoma.[23-27] A 2023 study found that patients with pure and mixed small cell bladder carcinoma have similar outcomes, which are

correlated with pathological stage at radical cystectomy, and are best among patients with pathological downstaging after neoadjuvant chemotherapy.[28]

The diagnosis is defined by morphologic criteria and most cases demonstrate evidence of neuroendocrine differentiation by immunohistochemistry. The most specific immunohistochemical markers are chromogranin A and synaptophysin, while CD56 although sensitive is not very specific.[29-31] TTF-1 is expressed in more than 50% of cases.[32-36] In cases with pure small cell morphology the possibility of direct spread from an adjacent organ or metastasis must be clinically excluded.[37] Recent research could demonstrate that small cell bladder cancer microscopically resembles aggressive small cell lung cancer, shares DNA changes similar to small cell lung cancer and expresses many genes that urothelial bladder cancer does not, possibly explaining aggressive activity.[37]

Radical resections that contain apparent pure adenocarcinoma need to be generously sampled to exclude the possibility of urothelial carcinoma with extensive divergent differentiation. The presence of keratinising squamous metaplasia particularly when there is dysplasia would support the diagnosis of primary squamous cell carcinoma.[38] There are no reliable immunohistochemical markers to distinguish with certainty in the individual case. In urothelial carcinoma with glandular differentiation, the glandular component may retain its 'urothelial' profile including expression of p63, GATA3 and high molecular weight keratin but often these are lost with the tumour showing an enteric immuno-histochemical profile. Markers of squamous differentiation such as CK5/6 and CK14 have not been proven to reliably separate pure squamous cell carcinoma from urothelial carcinoma with squamous differentiation.[29] Further, for both adenocarcinoma and squamous cell carcinoma the diagnosis of primary origin requires clinical correlation to exclude the possibility of origin at another site.

The 2022 WHO classification includes carcinomas arising in the urachus as a separate category.[3] These are defined as carcinomas arising from urachal remnants. Criteria for the diagnosis of urachal carcinoma include location in the bladder dome or anterior wall, an epicentre in the bladder wall or perivesical tissue.[39-44] The majority (over 80%) of urachal carcinomas are adenocarcinoma followed by urothelial carcinoma, squamous cell carcinoma, small cell neuroendocrine carcinoma and mixed carcinomas. If a diagnosis of urachal carcinoma is rendered the subtype must be specified. Adenocarcinomas of the urachus are most often mucinous and can be either solid or cystic. Subtypes such as enteric and signet ring-cell occur. The 2022 WHO also includes a category of 'mucinous cystic tumour of low malignant potential'.[3] 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.[29,39,45,46] Molecular studies could provide insights and show a close relation to colorectal cancers.[44]

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

Lastly there are carcinomas arising in the urinary bladder that have no specific differentiation and based on exclusion of metastasis are considered primary in the urinary tract.

Histological subtypes and divergent differentiation (urothelial carcinoma)

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

The importance of subtypes in clinical management decisions has been receiving increasing clinical attention.[57,58] Some subtypes have been highlighted because of the high frequency of under staging.[5] There are an increasing number of therapeutic algorithms that incorporate subtypes as a significant factor.[59] For T1 urothelial carcinoma, the presence of a histological subtype is one feature that is used in determining whether to consider immediate cystectomy.[23]

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

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

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

Descriptor	ICD-O codes[a]
Urothelial tumours	
Non-invasive urothelial neoplasms	
Papillary urothelial neoplasm of low malignant potential	8130/1
Non-invasive papillary urothelial carcinoma, low grade	8130/2
Non-invasive papillary urothelial carcinoma, high grade	8130/2
Urothelial carcinoma in situ	8120/2
Dysplasia	
Invasive urothelial carcinoma	8120/3
Nested	
Tubular microcystic	
Micropapillary	8131/3
Lymphoepithelioma-like	8082/3
Plasmacytoid	
Sarcomatoid	8122/3
Giant cell	8031/3
Poorly differentiated	8020/3
Lipid-rich	

Descriptor	ICD-O codes[a]
Clear cell	
Squamous cell neoplasms	
Pure squamous cell carcinoma	8070/3
Verrucous carcinoma	8051/3
Glandular neoplasms	
Adenocarcinoma, not otherwise specified (NOS)	8140/3
Enteric	8144/3
Mucinous	8480/3
Mixed	8140/3
Tumours of Müllerian type	
Clear cell adenocarcinoma	8310/3
Endometrioid carcinoma	8380/3
Neuroendocrine tumours	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Mixed neuroendocrine neoplasms	
Well differentiated neuroendocrine tumour	8240/3
Paraganglioma[b]	8693/3

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

[b] Paraganglioma is not an epithelial derived tumour.

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Note 10 – Non-invasive carcinoma (Core)

The majority of surgical resections of bladder tumours are performed for detrusor muscle invasive carcinoma, however patients with CIS that fail intra-vesical therapy can according to some guidelines be also managed by cystectomy.[61,62] Cystectomy is also recommended for patients with recurrent high grade papillary carcinomas refractory to BCG or recurring after completion of BCG maintenance.[62] Patients who are BCG intolerant may also undergo cystectomy. Occasionally patients have such large and extensive non-invasive low grade and/or high grade papillary tumours that cystectomy also becomes necessary. This element is core in the above scenarios in the absence of invasive disease.

For patients undergoing cystectomy for invasive carcinoma, it may be important to document non-invasive carcinoma, especially CIS if present. In large cystectomy series concomitant CIS is found in 19% to 54% of cases with most series at the higher end of this range.[63-66] The presence of urothelial CIS in these cases has been associated with an increased risk of upper tract recurrence in a limited number of studies.[67] However, in most reports the presence of CIS has not been found to be associated with either recurrence or cancer

specific survival.[64,68,69] In a meta-analysis of 13,185 patients undergoing radical cystectomy, the presence of CIS was not a significant risk factor for subsequent upper tract recurrence.[70] Similarly most reports have not found CIS in the bladder to be associated with a higher likelihood of urethral recurrence in contrast to prostatic involvement by CIS which is a significant risk factor of urethral recurrence in men.[14,71,72]

There is evidence that the extent of CIS is significant and distinguishing between a single focus and diffuse (or multifocal) disease is important.[73]

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Note 11 – Associated epithelial lesions (Non-core)

A variety of neoplastic lesions that fall short of carcinoma are recognised in the urinary tract. These include papillary lesions such as urothelial papilloma, papillary urothelial neoplasm of low malignant potential and inverted urothelial papilloma. Similarly, flat lesions such as urothelial dysplasia, (keratinising) squamous metaplasia (with dysplasia) and intestinal metaplasia (with dysplasia) can be seen. Identification of these may have diagnostic implications (e.g., the presence of keratinising squamous metaplasia supporting the diagnosis of primary squamous cell carcinoma) but do not have known proven prognostic or clinical significance. Therefore, the reporting of such findings, is considered non-core in the context of a carcinoma diagnosis.

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Note 12 – Histological tumour grade (Core)

Histologic grading of urothelial tumours is best considered in two categories, non-invasive papillary tumours and invasive carcinomas. For non-invasive papillary tumours the 2022 WHO[3] remains the same as in the 2004 and 2016 WHO and continues to be recommend the grading system, which was first put forward by the International Society of Urological Pathology (ISUP) in 1998.[74] The system is now recommended by almost all major pathology and urology organisations as the preferred grading system.[6,7]

In the 2022 WHO system, the lowest category is papillary urothelial neoplasm of low malignant potential (PUNLMP) which will not invade or metastasise.[3,75] This entity is rare (3.8% de novo), the risk of progression is minimal.[76] Papillary carcinomas are classified as low or high grade.[3] There are significant differences in the risk of progression to invasive carcinoma and death from bladder cancer between low and high grade categories.[77-79] The grade of non-invasive papillary carcinoma is the major variable in the choice of therapy in these patients.[62] Other features of importance in predicting outcome of patients with Ta papillary tumours are number of tumours/multifocality,[79-82] tumour size,[79,83-85] the presence of associated CIS,[79] and a history of prior recurrence.[79] It has also been suggested that for low grade papillary tumours the frequency of follow up cystoscopies can be reduced.[62]

Grade heterogeneity is not uncommon in papillary urothelial carcinoma being reported in up to 32% of cases.[86,87] The 2022 WHO recommends grading based on the highest grade component and recommends the cut of 5% for high grade tumours.[3] Tumours with up to 5% high grade component would be categorised as low grade and it may be useful to state the proportion of high grade disease.[3]

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

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

The ICCR dataset recommends the use of the 5th edition WHO grade as a core element.[3,88] The use of the 1973 WHO grading system for papillary tumours remains in use in some regions and one published guideline specifically recommends the reporting of both the current WHO grade with the 1973 grade,[62,89,90] while others allow for the 1973 grade to be provided by institutional choice.[3,5,7] 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.[91-93]

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Note 13 – Microscopic extent of invasion (Core)

Determining the extent of invasion is the key feature for the assignment of pathologic stage.[21,22] 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.[94-96] 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.

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.[97] Two large studies based on central review of patients being entered on clinical trials have demonstrated the overdiagnosis of invasion in 35% to 53% of cases.[98,99] In some cases immunohistochemistry with a pan keratin marker is helpful in identifying individual cells particularly when there is a heavy inflammatory infiltrate present. Following the principles of the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) TNM staging system the diagnosis of invasion should be limited to cases with unequivocal invasion.[21,22]

Identification of invasion of muscularis propria (MP) (of the detrusor muscle) in specimens indicate T2 disease. In the urinary bladder the presence of the muscularis mucosae (MM) can complicate the interpretation as involvement of this structure still represents a T1 tumour.[21,22] MM fibres can be present throughout the bladder.[100] The trigone/bladder neck region least often has recognisable MM fibres and from a practical perspective involvement of smooth muscle in this location essentially always indicates MP invasion. In this situation deeper cuts can be helpful.[101]

In contemporary radical cystectomy series no residual tumour is identified in between 5% and 20% of specimens after neoadjuvant chemotherapy.[102-105] In cases with no grossly apparent lesion the clinical information including radiologic findings and site of previous biopsy/transurethral resection (TUR) may be helpful in guiding sampling. Sampling of areas with mucosal lesions such as erythema may identify foci of CIS as may random samples of apparently normal mucosa. If 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.

Urothelial carcinoma can be primary in the prostatic urethra, but in the majority of cases involvement is seen in association with a bladder tumour.[106] Among all male patients with bladder cancer the prostate is involved in approximately 4% of cases. Involvement is usually by urothelial CIS, but occasionally papillary tumours are seen. Prostate cancer is found in approximatively 22% of patients undergoing cystoprostatectomy for urothelial carcinoma of the bladder.[107] Immunohistochemistry can be required to distinguish urothelial carcinoma from high grade prostatic carcinoma.[29] Glandular and or squamous differentiation can be present as with urothelial carcinoma elsewhere.

Determination of peri-vesical fat invasion is generally relatively straightforward. However, unlike in the colon, the junction between the muscle of the MP and the perivesical fat is not always well defined. Adipose tissue is present throughout the bladder wall and the deep aspect of the MP typically results in haphazardly separated muscle bundles forming a poorly formed demarcation.[108] Some authors demonstrated the inconsistency among expert urologic pathologists in defining peri-vesical fat extension.[109] 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,[110,111] while others have found there to be a significant difference.[112] Distinction of pT3a from pT3b tumours is however consistently found to be significant.[110,111,113] In many of the larger cystectomy series the data compares pT2 and pT3 tumours without subdividing them.[64,65,105]

It is important to document invasion into adjacent structures as this would represent pT4 disease. 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**.

A special case is carcinomas arising in diverticula. They represent less than 2% of urothelial carcinomas of the bladder.[114] 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.[115] In most series squamous cell carcinoma is more frequent than in the bladder proper.[116,117] Most diverticula in adults are acquired and by definition do not have a MP therefore there are no pT2 tumours. Invasive carcinomas in this location are staged as either pT1, pT3a or pT3b only.[97] It should be noted that acquired diverticula usually have fibres of the MM and these can be hypertrophic and should not be confused with muscularis propria.[118] In one report, hypertrophic MM was found in 59% of diverticula resected for carcinoma.[119] Carcinomas arising in diverticula can be treated by diverticulectomy, partial cystectomy or radical cystectomy.[97,120]

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Note 14 – Response to pre-operative therapy (Non-core)

Neoadjuvant chemotherapy is commonly part of the management of patient with high risk bladder cancer prior to cystectomy.[121,122] In the 2022 European Association of Urology (EAU) guidelines neoadjuvant chemotherapy was “recommended for T2-T4a cN0 M0 bladder cancers”. [62] The recommendation is a ‘grade A’ recommendation.[62]

At cystectomy patients treated with neoadjuvant chemotherapy are often down staged and may be ypT0. This has been demonstrated to be associated with improved survival.[123-125] pT0 at cystectomy after only TURBT is also associated with significantly improved survival but ypT0 is more frequent in patients having neoadjuvant chemotherapy.[124]

Improved survival following neoadjuvant chemotherapy has also been studied for specific histologic types and generally had similar results.[126]

There is minimal data however on morphologic alterations in the tumour itself following neoadjuvant chemotherapy and what the significance of such alterations might be. Some authors have developed a 'tumour regression grade' by comparing the tumour in the TURBT with residual tumour in the cystectomy following neoadjuvant chemotherapy.[127,128]

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Note 15 – Lymphovascular invasion (Core)

The data on lymphovascular invasion (LVI) in urothelial carcinoma in the urinary bladder has grown with many series now reported.[64,66,69,128-130] These have included very large multi-institutional series (e.g., Kluth et al[64] – 8,102 patients), cases from phase 3 clinical trials (von Rundstedt et al[130] – SWOG4B951/NCT00005047) and in the generation of prognostic scores (Eisenberg et al[129] – 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 more limited.[131-139] These have almost all been based on haematoxylin-eosin (H&E) evaluation with limited utilisation of immunohistochemistry. The frequency of identifying LVI has ranged from <10% to as high as 67%. Some authors identified LVI in 8% of cases and also included an indeterminate category (22% of cases).[139] LVI was an independent predictor of recurrence free-, progression free- and cancer specific survival.[139] Interestingly, one prospective study did not find any significant association with progression-free or cancer specific survival, but follow-up was short.[140] Overall, most studies have found LVI to be a predictor of outcome. Some authors even tried to improve the recognition of LVI with the help of imaging and the results seem promising.[141]

Although the data on LVI in biopsy/TUR specimens is limited, the compelling evidence from studies of urothelial carcinoma of urinary bladder in large resections support its inclusion as a core element in this dataset.[142-144]

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Note 16 – Margin status (Core)

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 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.[64,106,145-148] 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 can be evaluated by frozen section, the urethral margin to a lesser extent. The EAU

guidelines do not recommend frozen section on ureteral margins,[149] they allow frozen section on urethral margins if the section is sent oriented with regards to a neobladder. 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.[150] Nevertheless, biopsies before the cystectomy are recommended at the urethra.[61] In most studies of radical cystectomy specimens, positive margins most frequently involve the soft tissues followed by the urethra and then the ureters.[146]

Positive soft tissue surgical margins have been an independent predictor of an increased risk of recurrence and decreased cancer specific survival.[64,69,146,147,151,152] 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.[146] 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.[153]

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Note 17 – Lymph node status (Core and Non-core)

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, several 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,[154-157] but this has not been uniform.[158] In a multi-institutional study of 748 cases with positive lymph nodes, extranodal extension was present in 50%.[157] In a multivariable analysis, the presence of extranodal extension was the most significant independent predictor of disease recurrence and cancer-specific mortality.[157]

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Note 18 – Coexistent pathology (Non-core)

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 keratinising squamous metaplasia and intestinal metaplasia may support the diagnoses of squamous cell carcinoma and adenocarcinoma, respectively, but for the most part these findings are not critical and are considered non-core.

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.[159] 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 (Non-core)

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 (Core)

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.

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Note 21 – Pathological staging (Core)

Pathologic stage remains the single most important prognostic parameter in patients treated by radical cystectomy. Staging data should be assessed according to the 9th edition UICC/8th edition AJCC Cancer Staging Manuals.[21,22] For urachal carcinomas, in addition to TNM, other staging systems have been proposed.[160] In prior sections, several issues related to pathologic staging including cases with no residual tumour in the cystectomy specimen (refer to **Note 13 – MICROSCOPIC EXTENT OF INVASION**), separation of pT2b from pT3a disease (refer to **Note 13 – MICROSCOPIC EXTENT OF INVASION**) and the importance of various lymph node parameters (refer to **Note 17 – 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.[161,162] In contemporary cystoprostatectomy series involvement of the prostatic urethra with or without prostate gland involvement is reported in 11% to 33% of patients.[159,163] Pagano et al (1996) reported that prostatic gland involvement in such cases could be classified as contiguous or non-contiguous with the latter having a significantly better prognosis.[164] Similar results have been reported by others.[165-169]

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 CIS 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.[164,166,168,169] 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.[21,22] 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 CIS involving the prostatic urethra and or prostatic ducts, stage is assigned using the urethra staging system.[168,169] Using this approach, prostatic stromal invasion would be pT2.[21,22]

Reporting of pathological staging categories (pT,pN,pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM9/AJCC TNM8,[21,22] the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

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