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

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

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

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

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

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

Previous therapy (select all that apply)

- ○ Information not provided
- ○ No previous therapy
- ☐ 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
  - ☐ Left ☐ Right ○ Laterality not specified
- ☐ Ovaries
  - ☐ Left ☐ Right ○ Laterality not specified
- ☐ Ureter
  - ☐ Left ☐ Right ○ Laterality not specified
- ☐ Prostate gland
- ☐ Seminal vesicles
- ☐ Penile urethra
- ☐ 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) mm

Additional dimensions (largest tumour) mm X mm

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) (Note7)

- ○ 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)

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HISTOLOGICAL TUMOUR TYPE (Note 9)
(Value list from the WHO Classification of Tumours of the Urinary System and Male Genital Organs (2016))

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

Histological sub-type/variant (urothelial carcinoma)

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

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

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

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

ASSOCIATED EPITHELIAL LESIONS (Note 11)

- ○ Present, *specify*
- ○ Not identified

HISTOLOGICAL TUMOUR GRADE (Note 12)

- ○ Not applicable
- ○ Cannot be determined

Urothelial carcinoma

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

Squamous cell carcinoma or adenocarcinoma

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

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

- ○ Cannot be assessed
- ○ No evidence of primary tumour
- ☐ 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*

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*

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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

Extranodal spread

○ Present ○ Not identified

Size of largest metastasis mm

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*

ANCILLARY STUDIES (Note 19)

- ○ Not performed
- ○ Performed, *specify*

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 20)

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

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

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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.

⬆ **Back**

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.

⬆ **Back**

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.

Back

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 some[11,12] 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]

Back

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]

Back

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.

Back

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[16] 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.

Back

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).

⬆ **Back**

Note 9 - Histological tumour type (Required)

Reason/Evidentiary Support

The 2016 WHO classification is utilized for assigning histological tumour type.[16] As in the 2004 WHO Classification,[17] 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.[18] 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.”[16,19] 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.[16] Because urothelial carcinoma has a remarkable capacity for morphologic variation the number of histologic variants that have been described in the literature is extensive.[40,41] 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.[42,43] 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.[1,44] There are an increasing number of therapeutic algorithms that incorporate variant histology as a significant factor.[45]

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[a16]

Descriptor	ICD-O codes
Urothelial tumours	
Infiltrating urothelial carcinoma	8120/3
Nested, including large nested	
Microcystic	
Micropapillary	8131/3
Lymphoepithelioma-like	8082/3
Plasmacytoid / signet ring cell / diffuse	
Sarcomatoid	8122/3

Descriptor	ICD-O codes
Giant cell	8031/3
Poorly differentiated	8020/3
Lipid-rich	
Clear cell	
Non-invasive urothelial lesions	
Urothelial carcinoma in situ	8120/2
Non-invasive papillary urothelial carcinoma, low-grade	8130/2
Non-invasive papillary urothelial carcinoma, high-grade	8130/2
Papillary urothelial neoplasm of low malignant potential	8130/1
Urothelial papilloma	8120/0
Inverted urothelial papilloma	8121/0
Urothelial proliferation of uncertain malignant potential	
Urothelial dysplasia	
Squamous cell neoplasms	
Pure squamous cell carcinoma	8070/3
Verrucous carcinoma	8051/3
Squamous cell papilloma	8052/0
Glandular neoplasms	
Adenocarcinoma, NOS	8140/3
Enteric	8144/3
Mucinous	8480/3
Mixed	8140/3
Villous adenoma	8261/0
Urachal carcinoma	8010/3
Tumours of Müllerian type	
Clear cell carcinoma	8310/3
Endometrioid carcinoma	8380/3
Neuroendocrine tumours	
Small cell neuroendocrine carcinoma	8041/3
Large call neuroendocrine carcinoma	8013/3
Well-differentiated neuroendocrine tumour	8240/3
Paraganglioma[b]	8693/1

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

b Paraganglioma is not an epithelial derived tumour.

Back

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.[46] Cystectomy is also recommended for patients with recurrent high grade papillary carcinomas refractory to BCG or recurring after completion of BCG maintenance.[46] 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.[47-50] 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.[51] 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.[48,49,52,53] 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.[10] 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.[11-13]

⬆ **Back**

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.

⬆ **Back**

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.[54] The system is now recommended by almost all major pathology and urology organizations as the preferred grading system.[2,4]

This is a 3-tiered system with the lowest category of papillary urothelial neoplasm of low malignant potential considered to represent a tumour without the capacity to invade or metastasize and as such is considered to be a benign neoplasm.[55] 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.[55,56] 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.[55,57] 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.[56] 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.[56] 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.[55] Tumours were evaluated based on predominant and secondary grades but secondary components were ignored if less than 5%.[55] In their study worst, predominant and average grade all were significant predictors of progression.[55] Progression was higher in pure high grade tumours (>95% high grade) than in mixed high/low grade tumours (5% to 95% high grade).[55] In another study tumours with less than 10% of high grade histology (5% of the cases) were compared with low and high-grade tumours.[58] 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.[58] 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.[2] 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,[4,46,59] while others provide for the 1973 grade to be included by institutional choice.[2,4,16] 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.[2,4,59,60] There is an extensive

literature based on the 1973 WHO system documenting its significance as a predictor of outcome for papillary urothelial carcinoma. These include many studies using material from phase III clinical trials. The current European Organisation for Treatment and Research of Cancer (EORTC) risk tables, developed from the data of 8 phase III clinical trials use the 1973 WHO grading system.[61] 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.[62-64] In studies using the 1998 ISUP/WHO 2004 grading system the vast majority of invasive tumours are high grade.[65,66] The conclusion of the International Consultation on Urologic Disease pathology group was that all invasive carcinomas should be considered high grade.[2,67] 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.[68-71] 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.[72] 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.[61,63,73,74] 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.

Back

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.[75] 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.[3,76,77]

In contemporary cystectomy series there is no residual tumour identified in the radical cystectomy specimen in between 5% and 20% of specimens.[78-81] 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.[82] Ananthanarayanan and colleagues demonstrated the inconsistency among expert urologic pathologists in defining peri-vesical fat extension.[83] 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,[84,85] while others have found there to be a significant difference.[86] Distinction of pT3a from pT3b tumours is however consistently found to be significant.[84,85,87] In many of the larger cystectomy series the data compares pT2 and pT3 tumours without subdividing them.[48,49,81]

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.[88] 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.[89] In most series squamous cell carcinoma is more frequent than in the bladder proper.[88,90] 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.[91] 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.[92] In one report hypertrophic muscularis mucosae was found in 59% of diverticula resected for carcinoma.[93] Carcinomas arising in diverticula can be treated by diverticulectomy, partial cystectomy or radical cystectomy.[91,94]

Back

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.[35,95] 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.”[95] The recommendation was a “grade A” recommendation.[95]

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.[96-99] pT0 at cystectomy after TURBT is also associated with significantly improved survival but pT0 is more frequent in patients having neoadjuvant chemotherapy.[98]

Improved survival following neoadjuvant chemotherapy has also been studied for specific histologic types and generally had similar results.[100]

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.[101] 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.

⬆ **Back**

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.[9,48,50,53,102,103] These have included very large multi-institutional series (e.g. Kluth et al[48]), cases from phase 3 clinical trials (von Rundstedt et al[103] – SWOG4B951/NCT00005047) and in the generation of prognostic scores (Eisenberg et al[9] – SPARC Score) all of which have found LVI to be a highly significant independent predictor of outcome. This is therefore a required element.

⬆ **Back**

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.[48,104-108] 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.[106]

Positive soft tissue surgical margins have been an independent predictor of an increased risk of recurrence and decreased cancer specific survival.[48,53,106,107,109,110] 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.[106] 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.[111]

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.[112-114] 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,[113,115,116] while others have recommended against routine use of frozen section in general.[112,117,118] Overall subsequent recurrence in the ureter occurs in up to 13% of patients,[112] with most studies reporting upper tract recurrence in the 4% to 6% range[10,114] and with recurrence of invasive carcinoma at the uretero-ileal anastomosis in less than 1%.[113] Recurrence is significantly higher in patients with documented ureteric involvement.[10,112-114] This increased risk remains but is reduced if a negative margin is subsequently obtained with frozen section control.[114,119] The latter may in part be related to “skip lesions” that can be present in up to 4.8% of patients.[118,120]

Although urethral margins are positive in up to 10% of cases, frozen sections are less often performed for margin control.[116,121,122] 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.[121]

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

Back

Note 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[123-126] but this has not been uniform.[127] In a multi-institutional study of 748 cases with positive lymph nodes, extranodal extension was present in 50%.[126] In a multivariable analysis, the presence of extranodal extension was the most significant independent predictor of disease recurrence and cancer-specific mortality.[126]

Back

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.[128] When this occurs the prostatectomy dataset should be inserted in the pathology report and completed as appropriate.

Back

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.

Back

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 manual[129] 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.

Back

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.[135,137,139,140] 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.[129] 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.[139,140] Using this approach, prostatic stromal invasion would be pT2.[129]

References

1 Hansel DE, Amin MB, Comperat E, Cote RJ, Knuchel R, Montironi R, Reuter VE, Soloway MS, Umar SA and Van der Kwast TH (2013). A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. *Eur Urol* 63(2):321-332.

2 Amin MB, Smith SC, Reuter VE, Epstein JI, Grignon DJ, Hansel DE, Lin O, McKenney JK, Montironi R, Paner GP, Al-Ahmadie HA, Algaba F, Ali S, Alvarado-Cabrero I, Bubendorf L, Cheng L, Cheville JC, Kristiansen G, Cote RJ, Delahunt B, Eble JN, Genega EM, Gulmann C, Hartmann A, Langner C, Lopez-Beltran A, Magi-Galluzzi C, Merce J, Netto GJ, Oliva E, Rao P, Ro JY, Srigley JR, Tickoo SK, Tsuzuki T, Umar SA, Van der Kwast T, Young RH and Soloway MS (2015). Update for the practicing pathologist: The International Consultation On Urologic Disease-European association of urology consultation on bladder cancer. *Mod Pathol* 28(5):612-630.

3 Chandra A, Griffiths D and McWilliam LJ (2010). Best practice: gross examination and sampling of surgical specimens from the urinary bladder. *J Clin Pathol* 63(6):475-479.

4 CAP (College of American Pathologists) (2017). *Protocol for the Examination of Specimens from Patients with Carcinoma of the Urinary Bladder.* Available at: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution Folders/WebContent/pdf/urinary-17protocol-3300.pdf (Accessed 1st March 2017).

5 Lopez-Beltran A, Luque RJ, Mazzucchelli R, Scarpelli M and Montironi R (2002). Changes produced in the urothelium by traditional and newer therapeutic procedures for bladder cancer. *J Clin Pathol* 55(9):641-647.

6 Oxley JD, Cottrell AM, Adams S and Gillatt D (2009). Ketamine cystitis as a mimic of carcinoma in situ. *Histopathology* 55(6):705-708.

7 Baker PM and Young RH (2000). Radiation-induced pseudocarcinomatous proliferations of the urinary bladder: a report of 4 cases. *Hum Pathol* 31(6):678-683.

8 Chan TY and Epstein JI (2004). Radiation or chemotherapy cystitis with "pseudocarcinomatous" features. *Am J Surg Pathol* 28(7):909-913.

9 Eisenberg MS, Boorjian SA, Cheville JC, Thompson RH, Thapa P, Kaushik D and Frank I (2013). The SPARC score: a multifactorial outcome prediction model for patients undergoing radical cystectomy for bladder cancer. *J Urol* 190(6):2005-2010.

10 Picozzi S, Ricci C, Gaeta M, Ratti D, Macchi A, Casellato S, Bozzini G and Carmignani L (2012). Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. *J Urol* 188(6):2046-2054.

11 Huguet J, Monllau V, Sabate S, Rodriguez-Faba O, Algaba F, Palou J and Villavicencio H (2008). Diagnosis, risk factors, and outcome of urethral recurrences following radical cystectomy for bladder cancer in 729 male patients. *Eur Urol* 53(4):785-792 discussion 792-783.

12 Boorjian SA, Kim SP, Weight CJ, Cheville JC, Thapa P and Frank I (2011). Risk factors and outcomes of urethral recurrence following radical cystectomy. *Eur Urol* 60(6):1266-1272.

13 Stein JP, Clark P, Miranda G, Cai J, Groshen S and Skinner DG (2005). Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. *J Urol* 173(4):1163-1168.

14 Davili Z, Makhuli Z, Hartman C and Rong R (2011). Presentation of bladder leiomyoma concurrent with transitional cell carcinoma. *Can J Urol* 18(1):5559-5563.

15 Soave A, John LM, Dahlem R, Minner S, Engel O, Schmidt S, Kluth LA, Fisch M and Rink M (2015). The Impact of Tumor Diameter and Tumor Necrosis on Oncologic Outcomes in Patients With Urothelial Carcinoma of the Bladder Treated With Radical Cystectomy. *Urology* 86(1):92-98.

16 World Health Organization (2016). *World Health Organization (WHO) Classification of tumours. Pathology and genetics of the urinary system and male genital organs*. Moch H, Humphrey PA, Reuter VE, Ulbright TM. IARC Press, Lyon, France.

17 WHO (World Health Organization) (2004). *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organ*. Eble JN, Sauter G, Epstein JI and Sesterhenn IA. IARC Press, Lyon, France.

18 Gopalan A, Sharp DS, Fine SW, Tickoo SK, Herr HW, Reuter VE and Olgac S (2009). Urachal carcinoma: a clinicopathologic analysis of 24 cases with outcome correlation. *Am J Surg Pathol* 33(5):659-668.

19 Amin MB, Smith SC, Eble JN, Rao P, Choi WW, Tamboli P and Young RH (2014). Glandular neoplasms of the urachus: a report of 55 cases emphasizing mucinous cystic tumors with proposed classification. *Am J Surg Pathol* 38(8):1033-1045.

20 Paner GP, McKenney JK, Barkan GA, Yao JL, Frankel WL, Sebo TJ, Shen SS and Jimenez RE (2011). Immunohistochemical analysis in a morphologic spectrum of urachal epithelial neoplasms: diagnostic implications and pitfalls. *Am J Surg Pathol* 35(6):787-798.

21 Kosem M and Sengul E (2005). Clear cell adenocarcinoma of the urinary bladder. *Scand J Urol Nephrol* 39(1):89-92.

22 al-Izzi MS, Horton LW, Kelleher J and Fawcett D (1989). Malignant transformation in endometriosis of the urinary bladder. *Histopathology* 14(2):191-198.

23 Allen D, O'Brien T, Pingle P and Chandra A (2005). Endometrioid adenocarcinoma of the bladder. *Histopathology* 46(2):232-233.

24 Drew PA, Murphy WM, Civantos F and Speights VO (1996). The histogenesis of clear cell adenocarcinoma of the lower urinary tract. Case series and review of the literature. *Hum Pathol* 27(3):248-252.

25 Lah K, Desai D, Hadway P, Perry-Keene J and Coughlin G (2013). Primary vesical clear cell adenocarcinoma arising in endometriosis: a rare case of mullerian origin. *Anticancer Res* 33(2):615-617.

26 Sung MT, Zhang S, MacLennan GT, Lopez-Beltran A, Montironi R, Wang M, Tan PH and Cheng L (2008). Histogenesis of clear cell adenocarcinoma in the urinary tract: evidence of urothelial origin. *Clin Cancer Res* 14(7):1947-1955.

27 Gilcrease MZ, Delgado R, Vuitch F and Albores-Saavedra J (1998). Clear cell adenocarcinoma and nephrogenic adenoma of the urethra and urinary bladder: a histopathologic and immunohistochemical comparison. *Hum Pathol* 29(12):1451-1456.

28 Oliva E, Amin MB, Jimenez R and Young RH (2002). Clear cell carcinoma of the urinary bladder: a report and comparison of four tumors of mullerian origin and nine of probable urothelial origin with discussion of histogenesis and diagnostic problems. *Am J Surg Pathol* 26(2):190-197.

29 Tong GX, Weeden EM, Hamele-Bena D, Huan Y, Unger P, Memeo L and O'Toole K (2008). Expression of PAX8 in nephrogenic adenoma and clear cell adenocarcinoma of the lower urinary tract: evidence of related histogenesis? *Am J Surg Pathol* 32(9):1380-1387.

30 Vang R, Whitaker BP, Farhood AI, Silva EG, Ro JY and Deavers MT (2001). Immunohistochemical analysis of clear cell carcinoma of the gynecologic tract. *Int J Gynecol Pathol* 20(3):252-259.

31 Choong NW, Quevedo JF and Kaur JS (2005). Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. *Cancer* 103(6):1172-1178.

32 Siefker-Radtke AO, Dinney CP, Abrahams NA, Moran C, Shen Y, Pisters LL, Grossman HB, Swanson DA and Millikan RE (2004). Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: a retrospective review of the M. D. Anderson cancer experience. *J Urol* 172(2):481-484.

33 Mackey JR, Au HJ, Hugh J and Venner P (1998). Genitourinary small cell carcinoma: determination of clinical and therapeutic factors associated with survival. *J Urol* 159(5):1624-1629.

34 Lynch SP, Shen Y, Kamat A, Grossman HB, Shah JB, Millikan RE, Dinney CP and Siefker-Radtke A (2013). Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: results from a retrospective study at the MD Anderson Cancer Center. *Eur Urol* 64(2):307-313.

35 Clark PE, Agarwal N, Biagioli MC, Eisenberger MA, Greenberg RE, Herr HW, Inman BA, Kuban DA, Kuzel TM, Lele SM, Michalski J, Pagliaro LC, Pal SK, Patterson A, Plimack ER, Pohar KS, Porter MP, Richie JP, Sexton WJ, Shipley WU, Small EJ, Spiess PE, Trump DL, Wile G, Wilson TG, Dwyer M and Ho M (2013). Bladder cancer. *J Natl Compr Canc Netw* 11(4):446-475.

36 National Comprehensive Cancer Network (NCCN). *NCCN Guidelines*. Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp (Accessed 1st March 2017).

37 Amin MB, Trpkov K, Lopez-Beltran A and Grignon D (2014). Best practices recommendations in the application of immunohistochemistry in the bladder lesions: report from the International Society of Urologic Pathology consensus conference. *Am J Surg Pathol* 38(8):e20-34.

38 Agoff SN, Lamps LW, Philip AT, Amin MB, Schmidt RA, True LD and Folpe AL (2000). Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. *Mod Pathol* 13(3):238-242.

39 Jones TD, Kernek KM, Yang XJ, Lopez-Beltran A, MacLennan GT, Eble JN, Lin H, Pan CX, Tretiakova M, Baldridge LA and Cheng L (2005). Thyroid transcription factor 1 expression in small cell carcinoma of the urinary bladder: an immunohistochemical profile of 44 cases. *Hum Pathol* 36(7):718-723.

40 Amin MB (2009). Histological variants of urothelial carcinoma: diagnostic, therapeutic and prognostic implications. *Mod Pathol* 22 Suppl 2:S96-s118.

41 Lopez-Beltran A and Cheng L (2006). Histologic variants of urothelial carcinoma: differential diagnosis and clinical implications. *Hum Pathol* 37(11):1371-1388.

42 Xylinas E, Rink M, Robinson BD, Lotan Y, Babjuk M, Brisuda A, Green DA, Kluth LA, Pycha A, Fradet Y, Faison T, Lee RK, Karakiewicz PI, Zerbib M, Scherr DS and Shariat SF (2013). Impact of histological variants on oncological outcomes of patients with urothelial carcinoma of the bladder treated with radical cystectomy. *Eur J Cancer* 49(8):1889-1897.

43 Kim SP, Frank I, Cheville JC, Thompson RH, Weight CJ, Thapa P and Boorjian SA (2012). The impact of squamous and glandular differentiation on survival after radical cystectomy for urothelial carcinoma. *J Urol* 188(2):405-409.

44 International Collaboration on Cancer Reporting (ICCR) (2017). Urinary tract carcinoma - Biopsy and transurethral resection specimen dataset. Available at: http://www.iccr-cancer.org/datasets (Accessed 31st May 2018).

45 Shah JB, McConkey DJ and Dinney CP (2011). New strategies in muscle-invasive bladder cancer: on the road to personalized medicine. *Clin Cancer Res* 17(9):2608-2612.

46 Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Comperat E, Sylvester RJ, Kaasinen E, Bohle A, Palou Redorta J and Roupret M (2013). EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol* 64(4):639-653.

47 Moschini M, Sharma V, Dell'oglio P, Cucchiara V, Gandaglia G, Cantiello F, Zattoni F, Pellucchi F, Briganti A, Damiano R, Montorsi F, Salonia A and Colombo R (2016). Comparing long-term outcomes of primary and progressive carcinoma invading bladder muscle after radical cystectomy. *BJU Int* 117(4):604-610.

48 Kluth LA, Rieken M, Xylinas E, Kent M, Rink M, Roupret M, Sharifi N, Jamzadeh A, Kassouf W, Kaushik D, Boorjian SA, Roghmann F, Noldus J, Masson-Lecomte A, Vordos D, Ikeda M, Matsumoto K, Hagiwara M, Kikuchi E, Fradet Y, Izawa J, Rendon R, Fairey A, Lotan Y, Bachmann A, Zerbib M, Fisch M, Scherr DS, Vickers A and Shariat SF (2014). Gender-specific differences in clinicopathologic outcomes following radical cystectomy: an international multi-institutional study of more than 8000 patients. *Eur Urol* 66(5):913-919.

49 Karakiewicz PI, Shariat SF, Palapattu GS, Gilad AE, Lotan Y, Rogers CG, Vazina A, Gupta A, Bastian PJ, Perrotte P, Sagalowsky AI, Schoenberg M and Lerner SP (2006). Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. *J Urol* 176(4 Pt 1):1354-1361; discussion 1361-1352.

50 Fritsche HM, Burger M, Svatek RS, Jeldres C, Karakiewicz PI, Novara G, Skinner E, Denzinger S, Fradet Y, Isbarn H, Bastian PJ, Volkmer BG, Montorsi F, Kassouf W, Tilki D, Otto W, Capitanio U, Izawa JI, Ficarra V, Lerner S, Sagalowsky AI, Schoenberg M, Kamat A, Dinney CP, Lotan Y and Shariat SF (2010). Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. *Eur Urol* 57(2):300-309.

51 Buchner A, May M, Burger M, Bolenz C, Herrmann E, Fritsche HM, Ellinger J, Hofner T, Nuhn P, Gratzke C, Brookman-May S, Melchior S, Peter J, Moritz R, Tilki D, Gilfrich C, Roigas J, Zacharias M, Hohenfellner M, Haferkamp A, Trojan L, Wieland WF, Muller SC, Stief CG and Bastian PJ (2013). Prediction of outcome in patients with urothelial carcinoma of the bladder following radical cystectomy using artificial neural networks. *Eur J Surg Oncol* 39(4):372-379.

52 Catto JW, Abbod MF, Linkens DA, Larre S, Rosario DJ and Hamdy FC (2009). Neurofuzzy modeling to determine recurrence risk following radical cystectomy for nonmetastatic urothelial carcinoma of the bladder. *Clin Cancer Res* 15(9):3150-3155.

53 Shariat SF, Svatek RS, Tilki D, Skinner E, Karakiewicz PI, Capitanio U, Bastian PJ, Volkmer BG, Kassouf W, Novara G, Fritsche HM, Izawa JI, Ficarra V, Lerner SP, Sagalowsky AI, Schoenberg MP, Kamat AM, Dinney CP, Lotan Y, Marberger MJ and Fradet Y (2010). International validation of the prognostic value of lymphovascular invasion in patients treated with radical cystectomy. *BJU Int* 105(10):1402-1412.

54 Epstein JI, Amin MB, Reuter VR and Mostofi FK (1998). The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. *Am J Surg Pathol* 22(12):1435-1448.

55 Cheng L, Neumann RM, Nehra A, Spotts BE, Weaver AL and Bostwick DG (2000). Cancer heterogeneity and its biologic implications in the grading of urothelial carcinoma. *Cancer* 88(7):1663-1670.

56 Billis A, Carvalho RB, Mattos AC, Negretti F, Nogueira CR, Oliveira MC, Valenca JT, Jr., Adam RL, Cotta AC, Nunes MS and Dinamarco PV (2001). Tumor grade heterogeneity in urothelial bladder carcinoma--proposal of a system using combined numbers. *Scand J Urol Nephrol* 35(4):275-279.

57 May M, Brookman-Amissah S, Roigas J, Hartmann A, Storkel S, Kristiansen G, Gilfrich C, Borchardt R, Hoschke B, Kaufmann O and Gunia S (2010). Prognostic accuracy of individual uropathologists in noninvasive urinary bladder carcinoma: a multicentre study comparing the 1973 and 2004 World Health Organisation classifications. *Eur Urol* 57(5):850-858.

58 Gofrit ON, Pizov G, Shapiro A, Duvdevani M, Yutkin V, Landau EH, Zorn KC, Hidas G and Pode D (2014). Mixed high and low grade bladder tumors--are they clinically high or low grade? *J Urol* 191(6):1693-1696.

59 Lopez-Beltran A, Bassi PF, Pavone-Macaluso M and Montironi R (2004). Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. A joint proposal of the European Society of Uropathology and the Uropathology Working Group. *Virchows Arch* 445(2):103-110.

60 Harnden P (2007). A critical appraisal of the classification of urothelial tumours: time for a review of the evidence and a radical change? *BJU Int* 99(4):723-725.

61 Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DW and Kurth K (2006). Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 49(3):466-465; discussion 475-467.

62 Mikulowski P and Hellsten S (2005). T1 G1 urinary bladder carcinoma: fact or fiction? *Scand J Urol Nephrol* 39(2):135-137.

63 van Rhijn BW, Musquera M, Liu L, Vis AN, Zuiverloon TC, van Leenders GJ, Kirkels WJ, Zwarthoff EC, Boeve ER, Jobsis AC, Bapat B, Jewett MA, Zlotta AR and van der Kwast TH (2015). Molecular and clinical support for a four-tiered grading system for bladder cancer based on the WHO 1973 and 2004 classifications. *Mod Pathol* 28(5):695-705.

64 Kruger S, Thorns C, Bohle A and Feller AC (2003). Prognostic significance of a grading system considering tumor heterogeneity in muscle-invasive urothelial carcinoma of the urinary bladder. *Int Urol Nephrol* 35(2):169-173.

65 Cao D, Vollmer RT, Luly J, Jain S, Roytman TM, Ferris CW and Hudson MA (2010). Comparison of 2004 and 1973 World Health Organization grading systems and their relationship to pathologic staging for predicting long-term prognosis in patients with urothelial carcinoma. *Urology* 76(3):593-599.

66 Otto W, Denzinger S, Fritsche HM, Burger M, Wieland WF, Hofstadter F, Hartmann A and Bertz S (2011). The WHO classification of 1973 is more suitable than the WHO classification of 2004 for predicting survival in pT1 urothelial bladder cancer. *BJU Int* 107(3):404-408.

67 Amin MB, McKenney JK, Paner GP, Hansel DE, Grignon DJ, Montironi R, Lin O, Jorda M, Jenkins LC, Soloway M, Epstein JI and Reuter VE (2013). ICUD-EAU International Consultation on Bladder Cancer 2012: Pathology. *Eur Urol* 63(1):16-35.

68 Linder BJ, Frank I, Cheville JC, Thompson RH, Thapa P, Tarrell RF and Boorjian SA (2013). Outcomes following radical cystectomy for nested variant of urothelial carcinoma: a matched cohort analysis. *J Urol* 189(5):1670-1675.

69 Lopez-Beltran A, Cheng L, Montironi R, Blanca A, Leva M, Roupret M, Fonseca J, Vidal A, Menendez CL, Pallares J, Bollito E, Reymundo C, Luque RJ and Comperat E (2014). Clinicopathological characteristics and outcome of nested carcinoma of the urinary bladder. *Virchows Arch* 465(2):199-205.

70 Wasco MJ, Daignault S, Bradley D and Shah RB (2010). Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases. *Hum Pathol* 41(2):163-171.

71 Cox R and Epstein JI (2011). Large nested variant of urothelial carcinoma: 23 cases mimicking von Brunn nests and inverted growth pattern of noninvasive papillary urothelial carcinoma. *Am J Surg Pathol* 35(9):1337-1342.

72 Amin MB et al (2012). *Bladder Cancer*. Pathology Consensus Guidelines by the Pathology of Bladder Cancer Work Group. Soloway S, Khoury A (Eds). ICUD-EAU, Paris, France.

73 Nishiyama N, Kitamura H, Maeda T, Takahashi S, Masumori N, Hasegawa T and Tsukamoto T (2013). Clinicopathological analysis of patients with non-muscle-invasive bladder cancer: prognostic value and clinical reliability of the 2004 WHO classification system. *Jpn J Clin Oncol* 43(11):1124-1131.

74 Patschan O, Sjodahl G, Chebil G, Lovgren K, Lauss M, Gudjonsson S, Kollberg P, Eriksson P, Aine M, Mansson W, Ferno M, Liedberg F and Hoglund M (2015). A Molecular Pathologic Framework for Risk Stratification of Stage T1 Urothelial Carcinoma. *Eur Urol* 68(5):824-832.

75 Edge SE, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A (2010). *General rules for TNM staging. Pages 9-12 from AJCC Cancer Staging Manual 7th edition*. New York, NY.: Springer.

76 Lopez-Beltran A, Bassi P, Pavone-Macaluso M and Montironi R (2004). Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. *Eur Urol* 45(3):257-266.

77 Grignon D (2014). Bladder tumors. In: *Urological Pathology*, Amin MB, Grignon DJ, Srigley JR, Eble JN (Eds), Wolters Kluwer, Philadelphia.

78 Palapattu GS, Shariat SF, Karakiewicz PI, Bastian PJ, Rogers CG, Amiel G, Lotan Y, Vazina A, Gupta A, Sagalowsky AI, Lerner SP and Schoenberg MP (2006). Cancer specific outcomes in patients with pT0 disease following radical cystectomy. *J Urol* 175(5):1645-1649; discussion 1649.

79 Kassouf W, Spiess PE, Brown GA, Munsell MF, Grossman HB, Siefker-Radtke A, Dinney CP and Kamat AM (2007). P0 stage at radical cystectomy for bladder cancer is associated with improved outcome independent of traditional clinical risk factors. *Eur Urol* 52(3):769-774.

80 Tilki D, Svatek RS, Novara G, Seitz M, Godoy G, Karakiewicz PI, Kassouf W, Fradet Y, Fritsche HM, Sonpavde G, Izawa JI, Ficarra V, Lerner SP, Schoenberg M, Stief CG, Dinney CP, Skinner E, Lotan Y, Sagalowsky AI, Reich O and Shariat SF (2010). Stage pT0 at radical cystectomy confers improved survival: an international study of 4,430 patients. *J Urol* 184(3):888-894.

81 Hautmann RE, de Petriconi RC, Pfeiffer C and Volkmer BG (2012). Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. *Eur Urol* 61(5):1039-1047.

82 Philip AT, Amin MB, Tamboli P, Lee TJ, Hill CE and Ro JY (2000). Intravesical adipose tissue: a quantitative study of its presence and location with implications for therapy and prognosis. *Am J Surg Pathol* 24(9):1286-1290.

83 Ananthanarayanan V, Pan Y, Tretiakova M, Amin MB, Cheng L, Epstein JI, Grignon DJ, Hansel DE, Jimenez RE, McKenney JK, Montironi R, Oliva E, Osunkoya AO, Rao P, Reuter VE, Ro JY, Shen SS, Srigley JR, Tsuzuki T, Yao JL, Antic T, Haber M, Taxy JB and Paner GP (2014). Influence of histologic criteria and confounding factors in staging equivocal cases for microscopic perivesical tissue invasion (pT3a): an interobserver study among genitourinary pathologists. *Am J Surg Pathol* 38(2):167-175.

84 Bastian PJ, Hutterer GC, Shariat SF, Rogers CG, Palapattu GS, Lotan Y, Vazina A, Amiel GE, Gupta A, Sagalowsky AI, Lerner SP, Schoenberg MP and Karakiewicz PI (2008). Macroscopic, but not microscopic, perivesical fat invasion at radical cystectomy is an adverse predictor of recurrence and survival. *BJU Int* 101(4):450-454.

85 Neuzillet Y, Lebret T, Molinie V, Yonneau L, Herve JM, Theodore C and Botto H (2012). Perivesical fat invasion in bladder cancer: implications for prognosis comparing pT2b, pT3a and pT3b stages and consequences for adjuvant chemotherapy indications. *BJU Int* 110(11):1736-1741.

86 Scosyrev E, Yao J and Messing E (2010). Microscopic invasion of perivesical fat by urothelial carcinoma: implications for prognosis and pathology practice. *Urology* 76(4):908-913; discussion 914.

87 Tilki D, Svatek RS, Karakiewicz PI, Novara G, Seitz M, Sonpavde G, Gupta A, Kassouf W, Fradet Y, Ficarra V, Skinner E, Lotan Y, Sagalowsky AI, Stief CG, Reich O and Shariat SF (2010). pT3 Substaging is a prognostic indicator for lymph node negative urothelial carcinoma of the bladder. *J Urol* 184(2):470-474.

88 Baniel J and Vishna T (1997). Primary transitional cell carcinoma in vesical diverticula. *Urology* 50(5):697-699.

89 Tamas EF, Stephenson AJ, Campbell SC, Montague DK, Trusty DC and Hansel DE (2009). Histopathologic features and clinical outcomes in 71 cases of bladder diverticula. *Arch Pathol Lab Med* 133(5):791-796.

90 Micic S and Ilic V (1983). Incidence of neoplasm in vesical diverticula. *J Urol* 129(4):734-735.

91 Walker NF, Gan C, Olsburgh J and Khan MS (2014). Diagnosis and management of intradiverticular bladder tumours. *Nat Rev Urol* 11(7):383-390.

92 Idrees MT, Alexander RE, Kum JB and Cheng L (2013). The spectrum of histopathologic findings in vesical diverticulum: implications for pathogenesis and staging. *Hum Pathol* 44(7):1223-1232.

93 Zhong H, George S, Kauffman E, Guru K, Azabdaftari G and Xu B (2014). Clinicopathologic characterization of intradiverticular carcinoma of urinary bladder - a study of 22 cases from a single cancer center. *Diagn Pathol* 9:222.

94 Neuzillet Y, Comperat E, Roupret M, Larre S, Roy C, Quintens H, Houede N, Pignot G, Wallerand H, Soulie M and Pfister C (2012). [Intradiverticular bladder tumours: review of the Cancer Committee of the French Association of Urology]. *Prog Urol* 22(9):495-502.

95 Witjes JA, Comperat E, Cowan NC, De Santis M, Gakis G, Lebret T, Ribal MJ, Van der Heijden AG and Sherif A (2014). EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. *Eur Urol* 65(4):778-792.

96 Rosenblatt R, Sherif A, Rintala E, Wahlqvist R, Ullen A, Nilsson S and Malmstrom PU (2012). Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. *Eur Urol* 61(6):1229-1238.

97 Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, deVere White RW, Sarosdy MF, Wood DP, Jr., Raghavan D and Crawford ED (2003). Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 349(9):859-866.

98 Lavery HJ, Stensland KD, Niegisch G, Albers P and Droller MJ (2014). Pathological T0 following radical cystectomy with or without neoadjuvant chemotherapy: a useful surrogate. *J Urol* 191(4):898-906.

99 Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Vavassori I and Barni S (2014). Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. *Eur Urol* 65(2):350-357.

100 Meeks JJ, Taylor JM, Matsushita K, Herr HW, Donat SM, Bochner BH and Dalbagni G (2013). Pathological response to neoadjuvant chemotherapy for muscle-invasive micropapillary bladder cancer. *BJU Int* 111(8):E325-330.

101 Fleischmann A, Thalmann GN, Perren A and Seiler R (2014). Tumor regression grade of urothelial bladder cancer after neoadjuvant chemotherapy: a novel and successful strategy to predict survival. *Am J Surg Pathol* 38(3):325-332.

102 Tilki D, Shariat SF, Lotan Y, Rink M, Karakiewicz PI, Schoenberg MP, Lerner SP, Sonpavde G, Sagalowsky AI and Gupta A (2013). Lymphovascular invasion is independently associated with bladder cancer recurrence and survival in patients with final stage T1 disease and negative lymph nodes after radical cystectomy. *BJU Int* 111(8):1215-1221.

103 von Rundstedt FC, Mata DA, Groshen S, Stein JP, Skinner DG, Stadler WM, Cote RJ, Kryvenko ON, Godoy G and Lerner SP (2015). Significance of lymphovascular invasion in organ-confined, node-negative urothelial cancer of the bladder: data from the prospective p53-MVAC trial. *BJU Int* 116(1):44-49.

104 Dotan ZA, Kavanagh K, Yossepowitch O, Kaag M, Olgac S, Donat M and Herr HW (2007). Positive surgical margins in soft tissue following radical cystectomy for bladder cancer and cancer specific survival. *J Urol* 178(6):2308-2312; discussion 2313.

105 Osman Y, El-Tabey N, Abdel-Latif M, Mosbah A, Moustafa N and Shaaban A (2007). The value of frozen-section analysis of ureteric margins on surgical decision-making in patients undergoing radical cystectomy for bladder cancer. *BJU Int* 99(1):81-84.

106 Neuzillet Y, Soulie M, Larre S, Roupret M, Defortescu G, Murez T, Pignot G, Descazeaud A, Patard JJ, Bigot P, Salomon L, Colin P, Rigaud J, Bastide C, Durand X, Valeri A, Kleinclauss F, Bruyere F and Pfister C (2013). Positive surgical margins and their locations in specimens are adverse prognosis features after radical cystectomy in non-metastatic carcinoma invading bladder muscle: results from a nationwide case-control study. *BJU Int* 111(8):1253-1260.

107 Raza SJ, Wilson T, Peabody JO, Wiklund P, Scherr DS, Al-Daghmin A, Dibaj S, Khan MS, Dasgupta P, Mottrie A, Menon M, Yuh B, Richstone L, Saar M, Stoeckle M, Hosseini A, Kaouk J, Mohler JL, Rha KH, Wilding G and Guru KA (2015). Long-term oncologic outcomes following robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. *Eur Urol* 68(4):721-728.

108 Albisinni S, Fossion L, Oderda M, Aboumarzouk OM, Aoun F, Tokas T, Varca V, Sanchez-Salas R, Cathelineau X, Chlosta P, Gaboardi F, Nagele U, Piechaud T, Rassweiler J, Rimington P, Salomon L and van Velthoven R (2016). Critical Analysis of Early Recurrence after Laparoscopic Radical Cystectomy in a Large Cohort by the ESUT. *J Urol* 195(6):1710-1717.

109 Canter D, Guzzo TJ, Resnick MJ, Bergey MR, Sonnad SS, Tomaszewski J, VanArsdalen K and Malkowicz SB (2009). A thorough pelvic lymph node dissection in presence of positive margins associated with better clinical outcomes in radical cystectomy patients. *Urology* 74(1):161-165.

110 Hadjizacharia P, Stein JP, Cai J and Miranda G (2009). The impact of positive soft tissue surgical margins following radical cystectomy for high-grade, invasive bladder cancer. *World J Urol* 27(1):33-38.

111 Booth CM, Siemens DR, Wei X, Peng Y, Berman DM and Mackillop WJ (2015). Pathological factors associated with survival benefit from adjuvant chemotherapy (ACT): a population-based study of bladder cancer. *BJU Int* 116(3):373-381.

112 Raj GV, Tal R, Vickers A, Bochner BH, Serio A, Donat SM, Herr H, Olgac S and Dalbagni G (2006). Significance of intraoperative ureteral evaluation at radical cystectomy for urothelial cancer. *Cancer* 107(9):2167-2172.

113 Schumacher MC, Scholz M, Weise ES, Fleischmann A, Thalmann GN and Studer UE (2006). Is there an indication for frozen section examination of the ureteral margins during cystectomy for transitional cell carcinoma of the bladder? *J Urol* 176(6 Pt 1):2409-2413; discussion 2413.

114 Tollefson MK, Blute ML, Farmer SA and Frank I (2010). Significance of distal ureteral margin at radical cystectomy for urothelial carcinoma. *J Urol* 183(1):81-86.

115 Johnson DE, Wishnow KI and Tenney D (1989). Are frozen-section examinations of ureteral margins required for all patients undergoing radical cystectomy for bladder cancer? *Urology* 33(6):451-454.

116 Zhou H, Ro JY, Truong LD, Ayala AG and Shen SS (2014). Intraoperative frozen section evaluation of ureteral and urethral margins: studies of 203 consecutive radical cystoprostatectomy for men with bladder urothelial carcinoma. *Am J Clin Exp Urol* 2(2):156-160.

117 Schoenberg MP, Carter HB and Epstein JI (1996). Ureteral frozen section analysis during cystectomy: a reassessment. *J Urol* 155(4):1218-1220.

118 Donat SM (2008). Argument against frozen section analysis of distal ureters in transitional cell bladder cancer. *Nat Clin Pract Urol* 5(10):538-539.

119 Lee SE, Byun SS, Hong SK, Chang IH, Kim YJ, Gill MC, Song SH and Kim KT (2006). Significance of cancer involvement at the ureteral margin detected on routine frozen section analysis during radical cystectomy. *Urol Int* 77(1):13-17.

120 Hoang AN, Agarwal PK, Walton-Diaz A, Wood CG, Metwalli AR, Kassouf W, Brown GA, Black PC, Urbauer DL, Grossman HB, Dinney CP and Kamat AM (2014). Clinical significance of ureteric 'skip lesions' at the time of radical cystectomy: the M.D. Anderson experience and literature review. *BJU Int* 113(5b):E28-33.

121 Osman Y, Mansour A, El-Tabey N, Abdel-Latif M, Mosbah A, Hekal I, El-kappany S, Moustafa N and Shaaban A (2012). Value of routine frozen section analysis of urethral margin in male patients undergoing radical cystectomy in predicting prostatic involvement. *Int Urol Nephrol* 44(6):1721-1725.

122 Gordetsky J, Bivalacqua T, Schoenberg M and Epstein JI (2014). Ureteral and urethral frozen sections during radical cystectomy or cystoprostatectomy: an analysis of denudation and atypia. *Urology* 84(3):619-623.

123 Fleischmann A, Thalmann GN, Markwalder R and Studer UE (2005). Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. *J Clin Oncol* 23(10):2358-2365.

124 Seiler R, von Gunten M, Thalmann GN and Fleischmann A (2011). Extracapsular extension but not the tumour burden of lymph node metastases is an independent adverse risk factor in lymph node-positive bladder cancer. *Histopathology* 58(4):571-578.

125 Masson-Lecomte A, Vordos D, Hoznek A, Yiou R, Allory Y, Abbou CC, de la Taille A and Salomon L (2013). External validation of extranodal extension and lymph node density as predictors of survival in node-positive bladder cancer after radical cystectomy. *Ann Surg Oncol* 20(4):1389-1394.

126 Fajkovic H, Cha EK, Jeldres C, Robinson BD, Rink M, Xylinas E, Chromecki TF, Breinl E, Svatek RS, Donner G, Tagawa ST, Tilki D, Bastian PJ, Karakiewicz PI, Volkmer BG, Novara G, Joual A, Faison T, Sonpavde G, Daneshmand S, Lotan Y, Scherr DS and Shariat SF (2013). Extranodal extension is a powerful prognostic factor in bladder cancer patients with lymph node metastasis. *Eur Urol* 64(5):837-845.

127 Fritsche HM, May M, Denzinger S, Otto W, Siegert S, Giedl C, Giedl J, Eder F, Agaimy A, Novotny V, Wirth M, Stief C, Brookman-May S, Hofstadter F, Gierth M, Aziz A, Kocot A, Riedmiller H, Bastian PJ, Toma M, Wieland WF, Hartmann A and Burger M (2013). Prognostic value of perinodal lymphovascular invasion following radical cystectomy for lymph node-positive urothelial carcinoma. *Eur Urol* 63(4):739-744.

128 Bruins HM, Djaladat H, Ahmadi H, Sherrod A, Cai J, Miranda G, Skinner EC and Daneshmand S (2013). Incidental prostate cancer in patients with bladder urothelial carcinoma: comprehensive analysis of 1,476 radical cystoprostatectomy specimens. *J Urol* 190(5):1704-1709.

129 Amin M.B., Edge, S., Greene, F.L., Byrd, D.R., Brookland, R.K., Washington, M.K., Gershenwald, J.E., Compton, C.C., Hess, K.R., Sullivan, D.C., Jessup, J.M., Brierley, J.D., Gaspar, L.E., Schilsky, R.L., Balch, C.M., Winchester, D.P., Asare, E.A., Madera, M., Gress, D.M., Meyer, L.R. (Eds.) (2017). *AJCC Cancer Staging Manual 8th ed.* Springer, New York.

130 Ortega LG, Whitmore WF, Jr. and Murphy AI (1953). In situ carcinoma of the prostate with intraepithelial extension into the urethra and bladder. *Cancer* 6(5):898-923.

131 Seemayer TA, Knaack J, Thelmo WL, Wang NS and Ahmed MN (1975). Further observations on carcinoma in situ of the urinary bladder: silent but extensive intraprostatic involvement. *Cancer* 36(2):514-520.

132 Revelo MP, Cookson MS, Chang SS, Shook MF, Smith JA, Jr. and Shappell SB (2004). Incidence and location of prostate and urothelial carcinoma in prostates from cystoprostatectomies: implications for possible apical sparing surgery. *J Urol* 171(2 Pt 1):646-651.

133 Nixon RG, Chang SS, Lafleur BJ, Smith JJ and Cookson MS (2002). Carcinoma in situ and tumor multifocality predict the risk of prostatic urethral involvement at radical cystectomy in men with transitional cell carcinoma of the bladder. *J Urol* 167(2 Pt 1):502-505.

134 Mazzucchelli R, Barbisan F, Santinelli A, Scarpelli M, Galosi AB, Lopez-Beltran A, Cheng L, Kirkali Z and Montironi R (2009). Prediction of prostatic involvement by urothelial carcinoma in radical cystoprostatectomy for bladder cancer. *Urology* 74(2):385-390.

135 Pagano F, Bassi P, Ferrante GL, Piazza N, Abatangelo G, Pappagallo GL and Garbeglio A (1996). Is stage pT4a (D1) reliable in assessing transitional cell carcinoma involvement of the prostate in patients with a concurrent bladder cancer? A necessary distinction for contiguous or noncontiguous involvement. *J Urol* 155(1):244-247.

136 Shen SS, Lerner SP, Muezzinoglu B, Truong LD, Amiel G and Wheeler TM (2006). Prostatic involvement by transitional cell carcinoma in patients with bladder cancer and its prognostic significance. *Hum Pathol* 37(6):726-734.

137 Esrig D, Freeman JA, Elmajian DA, Stein JP, Chen SC, Groshen S, Simoneau A, Skinner EC, Lieskovsky G, Boyd SD, Cote RJ and Skinner DG (1996). Transitional cell carcinoma involving the prostate with a proposed staging classification for stromal invasion. *J Urol* 156(3):1071-1076.

138 Ayyathurai R, Gomez P, Luongo T, Soloway MS and Manoharan M (2007). Prostatic involvement by urothelial carcinoma of the bladder: clinicopathological features and outcome after radical cystectomy. *BJU Int* 100(5):1021-1025.

139 Patel AR, Cohn JA, Abd El Latif A, Miocinovic R, Steinberg GD, Paner GP and Hansel DE (2013). Validation of new AJCC exclusion criteria for subepithelial prostatic stromal invasion from pT4a bladder urothelial carcinoma. *J Urol* 189(1):53-58.

140 Knoedler JJ, Boorjian SA, Tollefson MK, Cheville JC, Thapa P, Tarrell RF and Frank I (2014). Urothelial carcinoma involving the prostate: the association of revised tumour stage and coexistent bladder cancer with survival after radical cystectomy. *BJU Int* 114(6):832-836.