Protocol for the Examination of Specimens From Patients With Carcinoma of the Urinary Bladder

Protocol applies primarily to invasive carcinomas and/or associated epithelial lesions, including carcinoma in situ.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2013

Procedures
• Bladder Biopsy, Transurethral Resection of Bladder Tumor (TURBT) Specimen
• Cystectomy (Partial, Total)
  - Radical Cystoprostatectomy
  - Pelvic Exenteration

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CAP Urinary Bladder Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: UrinaryBladder 3.2.1.0

Summary of Changes
The following changes have been made since the June 2012 release.

Biopsy and TURBT; Cystectomy, Partial, Total, or Radical; Anterior Exenteration

Tumor Type
A reporting element for tumor type was added, as follows:

Tumor Type
___ Invasive carcinoma
___ Noninvasive carcinoma
___ Carcinoma in situ
Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

URINARY BLADDER: Biopsy and Transurethral Resection of Bladder Tumor (TURBT)

Note: Use of case summary for biopsy specimens is optional

Select a single response unless otherwise indicated.

Procedure (required only for TURBT) (Note A)
___ Biopsy
___ TURBT
___ Other (specify): ____________________________
___ Not specified

Tumor Type
___ Invasive carcinoma
___ Noninvasive carcinoma
___ Carcinoma in situ

Histologic Type (Note B)
___ Urothelial (transitional cell) carcinoma
___ Urothelial (transitional cell) carcinoma with squamous differentiation
___ Urothelial (transitional cell) carcinoma with glandular differentiation
___ Urothelial (transitional cell) carcinoma with variant histology (specify): ____________________________
___ Squamous cell carcinoma, typical
___ Squamous cell carcinoma, variant histology (specify): ____________________________
___ Adenocarcinoma, typical
___ Adenocarcinoma, variant histology (specify): ____________________________
___ Small cell carcinoma
___ Undifferentiated carcinoma (specify): ____________________________
___ Mixed cell type (specify): ____________________________
___ Other (specify): ____________________________
___ Carcinoma, type cannot be determined

Associated Epithelial Lesions (select all that apply) (Note C)
___ None identified
___ Urothelial (transitional cell) papilloma (World Health Organization [WHO] 2004/ International Society of Urologic Pathology [ISUP])
___ Urothelial (transitional cell) papilloma, inverted type
___ Papillary urothelial (transitional cell) neoplasm, low malignant potential (WHO 2004/ISUP)
___ Cannot be determined

Histologic Grade (select all that apply) (Note C)
___ Not applicable
___ Cannot be determined
___ Urothelial carcinoma
   ___ Low-grade
   ___ High-grade
   ___ Other (specify): ____________________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
___ Squamous cell carcinoma or adenocarcinoma
   ___ GX: Cannot be assessed
   ___ G1: Well differentiated
   ___ G2: Moderately differentiated
   ___ G3: Poorly differentiated
   ___ Other (specify): ____________________________
___ Other carcinoma
   ___ Low-grade
   ___ High-grade
   ___ Other (specify): ____________________________

+ Tumor Configuration (select all that apply)
  + ___ Papillary
  + ___ Solid/nodule
  + ___ Flat
  + ___ Ulcerated
  + ___ Indeterminate
  + ___ Other (specify): _______________________

Adequacy of Material for Determining Muscularis Propria Invasion (Note D)
___ Muscularis propria (detrusor muscle) not identified
___ Muscularis propria (detrusor muscle) present
___ Presence of muscularis propria indeterminate

Lymph-Vascular Invasion (Note E)
___ Not identified
___ Present
___ Indeterminate

Microscopic Tumor Extension (select all that apply) (Note F)
___ Cannot be assessed
___ Noninvasive papillary carcinoma
___ Flat carcinoma in situ
___ Tumor invades subepithelial connective tissue (lamina propria)
___ Tumor invades muscularis propria (detrusor muscle)
___ Urothelial carcinoma involving prostatic urethra in prostatic chips sampled by TURBT
___ Urothelial carcinoma involving prostatic ducts and acini in prostatic chips sampled by TURBT
___ Urothelial carcinoma invasive into prostatic stroma in prostatic chips sampled by TURBT

+ Additional Pathologic Findings (select all that apply)
  + ___ Urothelial dysplasia (low-grade intraurothelial neoplasia)
  + ___ Inflammation/regenerative changes
  + ___ Therapy-related changes
  + ___ Cautery artifact
  + ___ Cystitis cystica et glandularis
  + ___ Keratinizing squamous metaplasia
  + ___ Intestinal metaplasia
  + ___ Other (specify): ____________________________

+ Comment(s)

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

URINARY BLADDER: Cystectomy, Partial, Total, or Radical; Anterior Exenteration

Select a single response unless otherwise indicated.

Specimen
___ Bladder
___ Other (specify): __________________________
___ Not specified

Procedure (Note G)
___ Partial cystectomy
___ Total cystectomy
___ Radical cystectomy
___ Radical cystoprostatectomy
___ Anterior exenteration
___ Other (specify): __________________________
___ Not specified

+ Tumor Site (select all that apply)
  + ___ Trigone
  + ___ Right lateral wall
  + ___ Left lateral wall
  + ___ Anterior wall
  + ___ Posterior wall
  + ___ Dome
  + ___ Other (specify): __________________________
  + ___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: __x___ cm
___ Cannot be determined (see Comment)

Tumor Type
___ Invasive carcinoma
___ Noninvasive carcinoma
___ Carcinoma in situ

+ Data elements preceded by this symbol are not required. However, these elements may be
clinically important but are not yet validated or regularly used in patient management.
Histologic Type (Note B)
___ Urothelial (transitional cell) carcinoma
___ Urothelial (transitional cell) carcinoma with squamous differentiation
___ Urothelial (transitional cell) carcinoma with glandular differentiation
___ Urothelial (transitional cell) carcinoma with variant histology (specify): __________________________
___ Squamous cell carcinoma, typical
___ Squamous cell carcinoma, variant histology (specify): __________________________
___ Adenocarcinoma, typical
___ Adenocarcinoma, variant histology (specify): __________________________
___ Small cell carcinoma
___ Undifferentiated carcinoma (specify): __________________________
___ Mixed cell type (specify): __________________________
___ Other (specify): __________________________
___ Carcinoma, type cannot be determined

Associated Epithelial Lesions (select all that apply) (Note C)
___ None identified
___ Urothelial (transitional cell) papilloma (World Health Organization [WHO] 2004/ International Society of Urologic Pathology [ISUP])
___ Urothelial (transitional cell) papilloma, inverted type
___ Papillary urothelial (transitional cell) neoplasm, low malignant potential (WHO 2004/ISUP)
___ Cannot be determined

Histologic Grade (select all that apply) (Note C)
___ 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): __________________________
___ Other carcinoma
    ___ Low-grade
    ___ High-grade
    ___ Other (specify): __________________________

+ Tumor Configuration (select all that apply)
+ ___ Papillary
+ ___ Solid/nodule
+ ___ Flat
+ ___ Ulcerated
+ ___ Indeterminate
+ ___ Other (specify): __________________________
### Microscopic Tumor Extension (select all that apply) (Note D)

- Cannot be assessed
- No evidence of primary tumor
- Noninvasive papillary carcinoma
- Carcinoma in situ: “flat tumor”
- Tumor invades lamina propria
- Tumor invades muscularis propria
  - Tumor invades superficial muscularis propria (inner half)
  - Tumor invades deep muscularis propria (outer half)
- Tumor invades perivesical tissue
  - Microscopically
  - Macroscopically (extravesical mass)
- Tumor invades adjacent structures
  - Prostatic stroma
  - Seminal vesicles
  - Uterus
  - Vagina
  - Adnexae
  - Pelvis wall
  - Abdominal wall
  - Rectum
- Other (specify): ______________________________

### Margins (select all that apply) (Note G)

- Cannot be assessed
- Margin(s) involved by invasive carcinoma
  - Ureteral margin
  - Distal urethral margin
  - Deep soft tissue margin
  - Other margin(s) (specify)*: ______________________________
- Margins(s) involved by carcinoma in situ/noninvasive high-grade urothelial carcinoma
  - Ureteral margin
  - Distal urethral margin
  - Other margin(s) (specify)*: ______________________________
- Margins uninvolved by invasive carcinoma/carcinoma in situ/noninvasive high-grade urothelial carcinoma
  + Distance of carcinoma from closest margin: ___ mm
    + Specify margin*:
  + Other significant changes at margin (specify margin)*: ______________________________
    + ___ Low-grade dysplasia
    + ___ Non-invasive low-grade urothelial carcinoma

* For partial cystectomies, if the specimen is received unoriented precluding identification of specific margins, it should be denoted here.

### Lymph-Vascular Invasion (Note E)

- Not identified
- Present
- Indeterminate

* Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Pathologic Staging (pTNM) (Note F)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pTa: Noninvasive papillary carcinoma
___ pTis: Carcinoma in situ: “flat tumor”
___ pT1: Tumor invades subepithelial connective tissue (lamina propria)
___ pT2: Tumor invades muscularis propria (detrusor muscle)
___ pT2a: Tumor invades superficial muscularis propria (inner half)
___ pT2b: Tumor invades deep muscularis propria (outer half)
___ pT3: Tumor invades perivesical tissue
___ pT3a: Microscopically
___ pT3b: Macroscopically (extravesicular mass)
___ pT4: Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
___ pT4a: Tumor invades prostatic stroma or uterus or vagina
___ pT4b: Tumor invades pelvic wall or abdominal wall

Regional Lymph Nodes (pN)
___ pNX: Lymph nodes cannot be assessed
___ pN0: No lymph node metastasis
___ pN1: Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node)
___ pN2: Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node metastasis)
___ pN3: Lymph node metastasis to the common iliac lymph nodes
___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ___
___ Number cannot be determined (explain): ______________________

Number of Lymph Nodes Involved (any size)
Specify: ___
___ Number cannot be determined (explain): ______________________

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
    + Specify site(s), if known: ______________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
+ Additional Pathologic Findings (select all that apply)
+ ___ Adenocarcinoma of prostate (use protocol for carcinoma of prostate)
+ ___ Urothelial (transitional cell) carcinoma involving urethra, prostatic ducts and acini with or without stromal invasion (use protocol for carcinoma of urethra)
+ ___ Urothelial dysplasia (low-grade intraurothelial neoplasia)
+ ___ Inflammation/regenerative changes
+ ___ Therapy-related changes
+ ___ Cystitis cystica et glandularis
+ ___ Keratinizing squamous metaplasia
+ ___ Intestinal metaplasia
+ ___ Other (specify): ____________________________

+ Comment(s)

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Explanatory Notes

A. History
A relevant history is important for interpretation of all bladder specimens.\textsuperscript{1-4} Cystoscopic visualization findings hold useful information on the nature and extent of bladder lesions in biopsy and TURBT specimens. A history of renal stones, recent urinary tract procedures, infections, or obstruction may influence the interpretation of random biopsies obtained on patients with hematuria. Any neoplasms previously diagnosed should be specified, including the histologic type, primary site, and histologic grade. If prior therapy has been given, it should be described (systemic or intravesical chemotherapy, immunotherapy, radiation, etc). The method of collection and date also should be specified in urine cytology specimens.

B. Histologic Type
The vast majority (more than 95\%) of carcinomas of the urinary bladder, renal pelvis, and ureter are urothelial or transitional cell in origin. A working histologic classification encompassing the wide histologic diversity and histologic range within the different types of carcinomas of the urothelial tract is tabulated in this note. Benign tumors are included in this classification because, within the same patient, a spectrum of differentiation from benign to malignant tumors may be seen in the bladder, either at the same time or over the clinical course of the disease. Also, clinicians stage most tumors irrespective of histologic grade.\textsuperscript{5-12} The distinction between a urothelial carcinoma with aberrant squamous or glandular differentiation and a primary squamous cell carcinoma or adenocarcinoma is rather arbitrary. Most authorities require a pure histology of squamous cell carcinoma or adenocarcinoma to designate a tumor as such, all others with recognizable papillary, invasive, or flat carcinoma in situ (CIS) urothelial component being considered as urothelial carcinoma with aberrant differentiation.

Classification of Neoplasms of the Urinary Bladder, Including Urothelial (Transitional Cell) Carcinoma and Its Variants*

Urothelial (Transitional Cell) Neoplasia
Benign
Inverted papilloma
Papillary urothelial neoplasm of low malignant potential (WHO 2004/ISUP); WHO, 1973, grade I
Malignant
Papillary##
Typical, noninvasive
Typical, with invasion
Variant
With squamous or glandular differentiation
Micropapillary
Nonpapillary
Carcinoma in situ
Invasive carcinoma
Variants containing or exhibiting
Deceptively benign features
Nested pattern (resembling von Brunn’s nests)
Small tubular pattern
Microcystic pattern
Inverted pattern
Squamous differentiation
Glandular differentiation
Micropapillary histology

Sarcomatoid foci (“sarcomatoid carcinoma”)

Urothelial carcinoma with unusual cytoplasmic features

- Clear cell (glycogen rich)
- Plasmacytoid
- Rhabdoid
- Lipoid rich

Urothelial carcinoma with syncytiotrophoblasts

Unusual stromal reactions

- Pseudosarcomatous stroma
- Stromal osseous or cartilaginous metaplasia
- Osteoclast-type giant cells
- With prominent lymphoid infiltrate

Squamous Cell Carcinoma

Typical

Variant

- Verrucous carcinoma
- Basaloid squamous cell carcinoma
- Sarcomatoid carcinoma

Adenocarcinoma

Anatomic variants

- Bladder mucosa
- Urachal
- With exstrophy
- From endometriosis

Histologic variants

- Typical intestinal type
- Mucinous (including colloid)
- Signet-ring cell
- Clear cell
- Hepatoid
- Mixture of above patterns – adenocarcinoma not otherwise specified (NOS)

Tumors of Mixed Cell Types

Undifferentiated Carcinoma###

- Small cell carcinoma
- Large cell neuroendocrine carcinoma
- Lymphoepithelioma-like carcinoma
- Osteoclast-rich carcinoma
- Giant cell carcinoma
- Not otherwise specified

Metastatic Carcinoma

# Modified from Amin et al.5

## Papillary tumors may be invasive or noninvasive, and when invasive may be microinvasive (invasive to a depth of 2 mm or less) or frankly invasive (like nonpapillary tumors).

### Refers to tumors that are undifferentiated by light microscopy.

C. Histologic Grade

Flat intraepithelial lesions and papillary and invasive lesions are graded separately.10-16 There has been significant controversy in the classification of these lesions. Flat lesions were graded as mild, moderate,
and severe dysplasia and carcinoma in situ; or atypical hyperplasia and carcinoma in situ; or dysplasia and carcinoma in situ.\textsuperscript{5,7} Papillary lesions were classified as papillomas (grade 0) and transitional cell carcinomas, grades I, II and III; or as papillomas, low-grade and high-grade transitional cell carcinomas.\textsuperscript{12-14} Due to variable classification systems and the need for a universally acceptable system, the World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification was proposed.\textsuperscript{12} This system is adopted in the WHO 2004 “blue book”\textsuperscript{10} and 2004 AFIP fascicle.\textsuperscript{11} Other systems (that were being used previously) may still be used according to institutional preference. Until the WHO/ISUP system is clinically and prognostically validated, tumor grade according to both the WHO/ISUP (1998)\textsuperscript{12} / WHO (2004)\textsuperscript{10} system and the older WHO (1973)\textsuperscript{14} system, eg, papillary urothelial neoplasm of low malignant potential (WHO/ISUP, 1998)/transitional cell carcinoma, grade I (WHO, 1973), may be concurrently used.

The WHO (1999) classification of bladder tumors\textsuperscript{9} differs only slightly from the WHO/ISUP (1998)\textsuperscript{12} and WHO (2004)\textsuperscript{10} system\textsuperscript{12} in that carcinomas are graded on a I to III scale in the former and low-grade and high-grade in the latter. Most cases designated as grade II and III by the WHO (1999) system correspond to high-grade carcinomas in the WHO/ISUP (1998) and WHO (2004) Consensus Classification.

**World Health Organization (WHO) 2004/ International Society of Urologic Pathology (ISUP) Consensus Classification for Urothelial (Transitional Cell) Lesions**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal#</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>Flat hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Papillary hyperplasia</td>
</tr>
<tr>
<td>Flat Lesions with Atypia</td>
<td>Reactive (inflammatory) atypia</td>
</tr>
<tr>
<td></td>
<td>Atypia of unknown significance</td>
</tr>
<tr>
<td></td>
<td>Dysplasia (low-grade intraurothelial neoplasia)#</td>
</tr>
<tr>
<td></td>
<td>Carcinoma in situ (high-grade intraurothelial neoplasia)#**</td>
</tr>
<tr>
<td>Papillary Neoplasms</td>
<td>Papilloma</td>
</tr>
<tr>
<td></td>
<td>Inverted papilloma</td>
</tr>
<tr>
<td></td>
<td>Papillary neoplasm of low malignant potential</td>
</tr>
<tr>
<td></td>
<td>Papillary carcinoma, low-grade</td>
</tr>
<tr>
<td></td>
<td>Papillary carcinoma, high-grade***</td>
</tr>
<tr>
<td>Invasive Neoplasms</td>
<td>Lamina propria invasion</td>
</tr>
<tr>
<td></td>
<td>Muscularis propria (detrusor muscle) invasion</td>
</tr>
</tbody>
</table>

# May include cases formerly diagnosed as “mild dysplasia.”

## Includes cases with “severe dysplasia.”

### Option exists to add comment as to the presence of marked anaplasia.

Squamous carcinomas and adenocarcinomas may be graded as well differentiated, moderately differentiated, and poorly differentiated.

**D. Extent of Invasion**

A critical role of the surgical pathologist is to diagnose the depth and extent of invasion into the subepithelial connective tissue/lamina propria/submucosa (pT1), muscularis propria (pT2), or beyond (pT3 or pT4).\textsuperscript{17-19} In papillary tumors, invasion occurs most often at the base of the tumor and very
infrequently in the stalk. In the urinary bladder, a tumor infiltrating the lamina propria (pT1) is sometimes overdiagnosed as vascular invasion; hence, caution should be exercised when diagnosing this feature, which in some cases may be supported by performing immunohistochemical studies for endothelial markers. Although attempts at substaging bladder pT1 tumors have been made, the WHO/ISUP committee recommended that it is currently not necessary for the practice to be universally adopted. Pathologists are, however, encouraged to provide some assessment as to the extent of lamina propria invasion (ie, focal versus extensive, or depth in millimeters, or by level – above, at, or below muscularis mucosae). Designation of a tumor as merely muscle invasive is inappropriate, but the type of muscle invasion, ie, muscularis mucosae (pT1 tumors) versus muscularis propria (pT2 tumors) invasion, needs to be clearly stated. Descriptive terminology, such as “urothelial carcinoma with muscle invasion, indeterminate for type of muscle invasion,” may be used when it is not possible to be certain whether the type of muscle invaded by the tumor is hypertrophic muscularis mucosae or muscularis propria. A comment on thermocoagulation effect may be made, especially if its presence impedes diagnostic evaluation. In TURBT specimens invasive into muscularis propria, no attempt should be made to substage the depth of muscularis propria invasion. Since fat may be present in the lamina propria and muscularis propria, the presence of tumor in adipose tissue is not necessarily diagnostic of extravesical spread; this determination is reserved for cystectomy specimens.

Involvement of the prostate gland may occur in several different patterns. The prostatic urethra may be involved (flat carcinoma in situ, papillary or invasive carcinoma), or the prostate gland may be involved. Involvement of the prostate gland may be evident as involvement of prostatic ducts and acini without stromal invasion (carcinoma in situ involving prostate glands) or as urothelial carcinoma involving prostatic stroma (either from prostatic urethral carcinoma, carcinoma extending directly through the bladder wall, or carcinoma involving prostatic ducts and acini additionally with stromal invasion).

E. Lymph-Vascular Invasion
Urothelial carcinoma may invade blood vessels or lymphatic channels. Lymphovascular invasion has been shown to be an independent predictor of recurrence and decreased overall survival. Presence of lymph-vascular invasion in TURBT specimens is associated with higher nodal metastasis. In suspicious cases, blood vessels can be highlighted by immunohistochemical staining for factor VIII-related antigen, CD31 or CD34. Staining will not resolve the problem of differentiating lymphatic versus artifactual space entrapment by tumor cells, and as mentioned, this is frequently seen in urothelial tumors invading the lamina propria. Retraction artifact is also prominent in the “micropapillary variant” of urothelial carcinoma.

F. TNM and Stage Groupings
The TNM Staging System for carcinomas of the urinary bladder of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended. A cystoprostatectomy specimen may contain 3 separate primaries: carcinoma of the urinary bladder, carcinoma of the prostate and carcinoma of the urethra. Depending on the pathology in a given case, the number of protocols to be used in a cystoprostatectomy specimen will vary.

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.
Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

**Primary Tumor (T)** (Figure 1)

The suffix “m” should be added to the appropriate T category to indicate multiple tumors. The suffix “is” may be added to any T to indicate the presence of associated carcinoma in situ.


**TNM Stage Groupings**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0a</td>
<td>Ta</td>
<td>N0</td>
<td>M0*</td>
</tr>
<tr>
<td>Stage 0is</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
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<td>Stage I</td>
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<td>T3b</td>
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<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1,2,3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

* M0 is defined as no distant metastasis.
TNM Descriptors
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y” and “r” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

Additional Descriptors
Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

G. Sections for Microscopic Evaluation
Bladder
Sections of bladder for microscopic evaluation are as follows. In TURBT specimens, submit 1 section per centimeter of tumor diameter (up to 10 cassettes). If the tumor is noninvasive by the initial sampling, additional submission of tissue (including possibly submitting all tissue) is necessary to diagnose or rule out the presence of invasion. If tumor is invasive into lamina propria in the initial sampling, additional sections (including possibly submitting the entire specimen) may be necessary to diagnose or rule out the possibility of muscularis propria invasion. In cystectomy specimens, several representative sections of the tumor, including the macroscopically deepest penetration, should be sampled. Submit several sections of the mucosa remote from the carcinoma, especially if abnormal, including the lateral wall(s), dome, and trigone. Submit 1 section of ureteral margin, unless submitted separately as frozen section specimens, and 1 section of urethral margin. If a long segment of the ureter(s) is present, then additional sections from the mid-portion may be necessary, as urothelial cancer often is multifocal.
Prostate and Prostatic Urethra
Prostatic urethral involvement should be carefully investigated in cystectomy specimens. Sections should include the prostatic urethra, including at the margin and with the surrounding prostatic parenchyma. Representative sections of the peripheral zone, central zone, and seminal vesicles should be included. Close gross examination may help target sampling of selective abnormal-appearing areas.

Lymph Nodes
Submit 1 section from each grossly positive lymph node. All other lymph nodes should be entirely submitted, as presence of nodal disease may be used as an indication for adjuvant therapy. Lymph nodes may be grossly or microscopically detected in the perivesical fat.

Other Tissues
Submit 1 or more sections of uterus (as indicated) and 1 or more sections of vagina, seminal vesicles, and other organs (as indicated). If the tumor grossly appears to invade the prostate, uterus, or vagina, sections should be targeted, such that the relationship of the infiltrating tumor in the bladder wall and the adjacent viscus is clearly demonstrable.

H. Margins
Resection margins, including those mentioned in Note G, should be carefully specified. Statements about deep soft tissue margins should specify whether peritoneal surfaces are involved by tumor. In cases of urachal adenocarcinoma in which partial cystectomy with excision of the urachal tract and umbilicus is performed, the margins of the urachal tract, ie, the soft tissue surrounding the urachus and the skin around the umbilical margin, should be specified. In renal pelvis, ureter, and nephroureterectomy specimens, the margins may include radial hilar soft tissue margin; bladder cuff; and ureteral, renal parenchymal, and Gerota’s fascia margins, depending on the type of surgical specimen.

References