Protocol for the Examination of Specimens from Patients with Carcinoma of the Urinary Bladder

Protocol applies primarily to invasive and noninvasive carcinomas, including carcinoma in situ.

Version: UrinaryBladder 3.3.0.0 Protocol Posting Date: February 2017
Includes pTNM requirements from the 7th Edition, AJCC Staging Manual

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

Accreditation Requirements
This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- **Core data elements** are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is "not applicable" or "cannot be determined."
- **Conditional data elements** are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- **Optional data elements** are identified with "+" and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

Transurethral resection of a bladder tumor is NOT considered to be the definitive resection specimen, even though the entire cancer may be removed. A protocol is recommended for reporting TURBT specimens for clinical care purposes, but this is not required for accreditation purposes.

**CAP Laboratory Accreditation Program Protocol Required Use Date: November 2017***
* Beginning January 1, 2018, the 8th edition AJCC Staging Manual should be used for reporting pTNM. The CAP will offer a revised 8th edition version of this protocol by mid-year 2017.

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CAP Urinary Bladder Protocol Revision History

Summary of Changes
The following changes have been made since the October 2013 release.

Biopsy and TURBT
The following data elements have been modified:
- Histologic Type
- Muscularis Propria

The following data element has been added:
- Primary Tumor Site

The following data element has been deleted:
- Tumor Type

Cystectomy, Partial, Total, or Radical; Anterior Exenteration
The following data elements have been modified:
- Procedure
- Primary Tumor Site
- Tumor Size
- Histologic Type
- Associated Epithelial Lesions
- Microscopic Tumor Extension
- Margins

The following data element has been added:
- Lymph Node Dissection

The following data element has been deleted:
- Tumor Type
Surgical Pathology Cancer Case Summary

Protocol posting date: February 2017

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

Note: For patient care the use of this protocol is recommended for reporting biopsy and TURBT specimens but for accreditation purposes the use of case summary for these specimens is not required.

Select a single response unless otherwise indicated.

Procedure (Note A)
___ Biopsy
___ TURBT
___ 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

Histologic Type (select all that apply) (Note B)

Urothelial
___ Papillary urothelial carcinoma, noninvasive
___ Papillary urothelial carcinoma, invasive
___ Urothelial carcinoma in situ
___ Urothelial carcinoma, invasive
___ Urothelial carcinoma, nested (including large nested) variant
___ Urothelial carcinoma, micropapillary variant
___ Urothelial carcinoma, lymphoepithelioma-like variant
___ Urothelial carcinoma, plasmacytoid / signet ring / diffuse variant
___ Urothelial carcinoma, sarcomatoid variant
___ Urothelial carcinoma, giant cell variant
___ Urothelial carcinoma, poorly differentiated variant
___ Urothelial carcinoma, lipid-rich variant
___ Urothelial carcinoma, clear cell variant
___ Urothelial carcinoma with squamous differentiation
  + Specify percentage of squamous differentiation: _____%
___ Urothelial carcinoma with glandular differentiation
  + Specify percentage of glandular differentiation: _____%
___ Urothelial carcinoma with trophoblastic differentiation
  + Specify percentage of trophoblastic differentiation: _____%
___ Urothelial carcinoma with Müllerian differentiation
  + Specify percentage of Müllerian differentiation: _____%

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
Squamous
____ Pure squamous cell carcinoma
____ Verrucous carcinoma
____ Squamous cell carcinoma in situ (no invasive carcinoma identified)

Glandular
____ Adenocarcinoma
____ Adenocarcinoma, enteric
____ Adenocarcinoma, mucinous
____ Adenocarcinoma, mixed
____ Adenocarcinoma in situ (no invasive carcinoma identified)

Tumors of Müllerian Type
____ Clear cell carcinoma
____ Endometrioid carcinoma

Neuroendocrine Tumors
____ Small cell neuroendocrine carcinoma
    + Specify percentage of small cell neuroendocrine component: _____%
____ Large cell neuroendocrine carcinoma
    + Specify percentage of large cell neuroendocrine component: _____%
____ Well-differentiated neuroendocrine carcinoma
    + Specify percentage of well-differentiated neuroendocrine component: _____%
____ Other histologic type not listed (specify): ____________________________

+ Associated Epithelial Lesions (select all that apply) (Note C)
  + ____ None identified
  + ____ Urothelial papilloma
  + ____ Urothelial papilloma, inverted type
  + ____ Papillary urothelial neoplasm, low malignant potential (PUNLMP)
  + ____ Urothelial dysplasia
  + ____ Urothelial proliferation of uncertain malignant potential
  + ____ Cannot be determined

Histologic Grade (Note C)
____ Not applicable
____ Cannot be determined

For urothelial carcinoma, other variants, or divergent differentiation
____ Low-grade
____ High-grade
____ Other (specify): ____________________________

For squamous cell carcinoma or adenocarcinoma
____ GX: Cannot be assessed
____ G1: Well-differentiated
____ G2: Moderately differentiated
____ G3: Poorly differentiated
____ Other (specify): ____________________________

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
+ Tumor Configuration (select all that apply)
+ ___ Papillary
+ ___ Solid/nodule
+ ___ Flat
+ ___ Ulcerated
+ ___ Cannot be determined
+ ___ Other (specify): ____________________________

Muscularis Propria Presence (Note D)
___ No muscularis propria (detrusor muscle) identified
___ Muscularis propria (detrusor muscle) present
___ Cannot be determined (explain): _________________________

Lymphovascular Invasion (Note E)
___ Not identified
___ Present
___ Cannot be determined

Microscopic Tumor Extension (select all that apply) (Note F)
___ Cannot be assessed
___ Noninvasive papillary carcinoma
___ Flat carcinoma in situ
___ Tumor invades lamina propria (subepithelial connective tissue)
___ Tumor invades muscularis propria
___ 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)
+ ___ 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 for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
Surgical Pathology Cancer Case Summary

Protocol posting date: February 2017

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): __________________________
___Cannot be determined

Tumor Site (select all that apply)
___ Trigone
___ Right lateral wall
___ Left lateral wall
___ Anterior wall
___ Posterior wall
___ Dome
___ Other (specify): __________________________
___Cannot be determined

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (explain): __________________________

Histologic Type (select all that apply) (Note B)

Urothelial
___ Papillary urothelial carcinoma, noninvasive
___ Papillary urothelial carcinoma, invasive
___ Urothelial carcinoma in situ
___ Urothelial carcinoma, invasive
___ Urothelial carcinoma, nested (including large nested) variant
___ Urothelial carcinoma, microcystic variant
___ Urothelial carcinoma, micropapillary variant
___ Urothelial carcinoma, lymphoepithelioma-like variant
___ Urothelial carcinoma, plasmacytoid / signet ring / diffuse variant
___ Urothelial carcinoma, sarcomatoid variant
___ Urothelial carcinoma, giant cell variant
___ Urothelial carcinoma, poorly differentiated variant
___ Urothelial carcinoma, lipid-rich variant
___ Urothelial carcinoma, clear cell variant
___ Urothelial carcinoma with squamous differentiation

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
+ Specify percentage of squamous differentiation: _____%

__ Urothelial carcinoma with glandular differentiation
  + Specify percentage of glandular differentiation: _____%

__ Urothelial carcinoma with trophoblastic differentiation
  + Specify percentage of trophoblastic differentiation: _____%

__ Urothelial carcinoma with Müllerian differentiation
  + Specify percentage of Müllerian differentiation: _____%

Squamous
__ Pure squamous cell carcinoma
__ Verrucous carcinoma
__ Squamous cell carcinoma in situ (no invasive carcinoma identified)

Glandular
__ Adenocarcinoma
__ Adenocarcinoma, enteric
__ Adenocarcinoma, mucinous
__ Adenocarcinoma, mixed
__ Adenocarcinoma in situ (no invasive carcinoma identified)

Tumors of Müllerian Type
__ Clear cell carcinoma
__ Endometrioid carcinoma

Neuroendocrine Tumors
__ Small cell neuroendocrine carcinoma
  + Specify percentage of small cell neuroendocrine component: _____%
__ Large cell neuroendocrine carcinoma
  + Specify percentage of large cell neuroendocrine component: _____%
__ Well-differentiated neuroendocrine carcinoma
  + Specify percentage of well-differentiated neuroendocrine component: _____%
__ Other histologic type not listed (specify): ________________________________

+ Associated Epithelial Lesions (select all that apply) (Note C)
  + None identified
  + Urothelial papilloma
  + Urothelial papilloma, inverted type
  + Papillary urothelial neoplasm, low malignant potential (PUNLMP)
  + Urothelial proliferation of uncertain malignant potential
  + Urothelial dysplasia
  + Cannot be determined

Histologic Grade (Note C)
__ Not applicable
__ Cannot be determined

For urothelial carcinoma, other variants, or divergent differentiation:
__ Low-grade
__ High-grade
__ Other (specify): ________________________________

For squamous cell carcinoma or adenocarcinoma:
__ GX: Cannot be assessed
__ G1: Well-differentiated
__ G2: Moderately differentiated

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
___ G3: Poorly differentiated
___ Other (specify): ____________________________

+ Tumor Configuration (select all that apply)
  + ___ Papillary
  + ___ Solid/nodule
  + ___ Flat
  + ___ Ulcerated
  + ___ Cannot be determined
  + ___ Other (specify): ___________________________

Microscopic Tumor Extension (select all that apply) (Note D)
___ Cannot be assessed
___ No evidence of primary tumor
___ Noninvasive papillary carcinoma
___ Flat carcinoma in situ
___ Tumor invades lamina propria (subepithelial connective tissue)
___ 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#
   Male
   ___ Prostate (transmural invasion from the bladder tumor)##
   ___ Seminal vesicles
   Female
   ___ Uterus
   ___ Vagina
   ___ Adnexae
   Male/Female
   ___ Pelvis wall
   ___ Abdominal wall
   ___ Rectum
   ___ Other (specify): ____________________________

# Use the Urethral protocol for tumors that involve the urethral mucosa without invasion, or tumors that involve the urethral mucosa with invasion of subepithelial connective tissue/prostate stroma, tumors that involve prostatic ducts and acini with or without stromal invasion.
## See Note D, Figure 1.

Margins (select all that apply) (Note G)
___ Cannot be assessed
___ Involved by invasive carcinoma
   ___ Right ureteral margin
   ___ Left ureteral margin
   ___ Urethral margin
   ___ Soft tissue margin
   ___ Other margin(s) (specify): _______________________
___ Involved by carcinoma in situ/noninvasive high-grade urothelial carcinoma
   ___ Right ureteral margin
   ___ Left ureteral margin
   ___ Urethral margin
   ___ Soft tissue margin

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.
Other margin(s) (specify): _______________________
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)#: ________________________
    + Urothelial dysplasia
    + Noninvasive low-grade urothelial carcinoma

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

Lymphovascular Invasion (Note E)
  ___ Not identified
  ___ Present
  ___ Cannot be determined

Regional Lymph Nodes
  ___ No lymph nodes submitted or found

Lymph Node Examination (required only if lymph nodes are present in the specimen)
Number of Lymph Nodes Involved: ______
  ___ Number cannot be determined (explain): ____________________
Number of Lymph Nodes Examined: ______
  ___ Number cannot be determined (explain): ____________________
+ Size of Largest Metastatic Deposit (millimeter): ___ mm
  + Specify Location: ____________
+ Size of Largest Lymph Node Involved (centimeter): ___ cm
  + Specify Location: ____________
+ Extranodal Extension
+ ___ Not identified
+ ___ Present
+ ___ Cannot be determined

+ Additional Pathologic Findings (select all that apply)
  + ___ Adenocarcinoma of prostate (use protocol for carcinoma of prostate)
  + ___ Inflammation/regenerative changes
  + ___ Therapy-related changes, specify: _________________________
  + ___ Cystitis cystica et glandularis
  + ___ Keratinizing squamous metaplasia
  + ___ Intestinal metaplasia
  + ___ Other (specify): ____________________________

Pathologic Stage Classification (pTNM, AJCC 7th Edition) (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 lamina propria (subepithelial connective tissue)

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: Extravesical tumor invades directly into prostatic stroma, uterus, or vagina
___ pT4b: Extravesical 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

Distant Metastasis (pM) (required only if applicable)
___ pM1: Distant metastasis
 Specify site(s), if known: ____________________________

+ Comment(s)
Explanatory Notes

A. History
A relevant history is important for interpretation of all bladder specimens.\(^1\)\(^-\)\(^4\) 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 cell in origin. The most recent 2016 World Health Organization (WHO) classification of tumors of the urothelial tract, including urethra, urinary bladder, ureter, and renal pelvis, is provided 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.\(^5\)\(^-\)\(^13\) The distinction between a urothelial carcinoma with divergent squamous, glandular, or Müllerian differentiation and a pure squamous cell carcinoma, adenocarcinoma or Müllerian is rather arbitrary. Most authorities, including the 2016 WHO classification, require a pure histology of squamous cell carcinoma, adenocarcinoma or Müllerian 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 divergent differentiation. A malignant neoplasm with small cell neuroendocrine carcinoma component arising in the urinary tract is designated as small cell carcinoma.

2016 WHO Classification of Tumors of the Urothelial Tract

Urothelial tumors
Infiltrating urothelial carcinoma
- Nested, including large nested
- Microcystic
- Micropapillary
- Lymphoepithelioma-like
- Plasmacytoid/signet ring cell/diffuse
- Sarcomatoid
- Giant cell
- Poorly differentiated
Noninvasive urothelial lesions
- Urothelial carcinoma in situ
- Noninvasive papillary urothelial carcinoma, low grade
- Noninvasive papillary urothelial carcinoma, high grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma
- Urothelial proliferation of uncertain malignant potential
- Urothelial dysplasia

Squamous cell neoplasms
- Pure squamous cell carcinoma
- Verrucous carcinoma
- Squamous cell papilloma

Glandular neoplasms
- Adenocarcinoma, NOS
  - Enteric
C. Histologic Grade

Flat intraepithelial lesions and papillary and invasive lesions are graded separately.\textsuperscript{10-17} 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{13-15} 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{13} This system is adopted in the WHO 2004 classification\textsuperscript{10} and 2004 Armed Forces Institute of Pathology (AFIP) fascicle,\textsuperscript{12} and has been validated by many studies to be prognostically significant. The 2016 WHO system used essentially the same classification with minor modification.\textsuperscript{11} Other systems (that were being used previously) may still be used according to institutional preference. Tumor grade according to both the WHO/ISUP (1998)\textsuperscript{13} / WHO (2004)\textsuperscript{10} system and the older WHO (1973)\textsuperscript{15} system may be concurrently used.

\textbf{2004 WHO / ISUP Consensus Classification for Urothelial Lesions}

\textbf{Normal}
- Normal\textsuperscript{#}

\textbf{Hyperplasia}
- Flat hyperplasia
- Papillary hyperplasia

\textbf{Flat Lesions with Atypia}
- Reactive (inflammatory) atypia
- Atypia of unknown significance
- Dysplasia (low-grade intraurothelial neoplasia)\textsuperscript{#}
- Carcinoma in situ (high-grade intraurothelial neoplasia)\textsuperscript{##}

\textbf{Papillary Neoplasms}
- Papilloma
- Inverted papilloma
- Papillary neoplasm of low malignant potential
- Papillary carcinoma, low-grade
- Papillary carcinoma, high-grade\textsuperscript{###}

\textbf{Invasive Neoplasms}
- Lamina propria invasion
- Muscularis propria (detrusor muscle) invasion

\textsuperscript{#} May include cases formerly diagnosed as “mild dysplasia.”

\textsuperscript{##} Includes cases with “severe dysplasia.”

\textsuperscript{###} Option exists to add comment as to the presence of marked anaplasia.
Flat and papillary urothelial hyperplasia has been renamed as “urothelial proliferation of uncertain malignant potential” in the 2016 WHO classification.

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). 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. Depth of invasion is a critical prognostic determinant in invasive urothelial carcinoma. In T1 disease, several substaging methods have been proposed but have been difficult to adopt due to the inherent lack of orientation of the specimen. Pathologists are, however, encouraged to provide some assessment as to the extent of lamina propria invasion (ie, maximum dimension of invasive focus, 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. Tumors (flat carcinoma in situ, papillary or invasive carcinoma) can first spread along the prostatic urethral mucosa and subsequently invade prostatic stroma (transurethral mucosal route) (Figure 1, B). Tumors may also invade through the bladder wall and the base of the prostate directly into the prostate gland (Figure 1, A, straight arrow). Tumors can also invade into extravesical fat and then extend back into the prostate gland (Figure 1, B, curved arrow). The latter two routes are considered direct transmural invasion. The American Joint Committee on Cancer (AJCC) 7th edition staging manual defines direct extension of urinary bladder cancer into the prostate gland as T4 disease and excludes transurethral mucosal prostatic stroma invasion from the pT4a staging status. However, there is limited data on the best methodology to stage urothelial carcinoma that concurrently involves the urinary bladder and the prostatic urethra. In patients who have a large urinary bladder carcinoma that has invaded through the full thickness of the bladder wall and thereby secondarily involves the prostatic stroma, a T4 stage should be assigned per urinary bladder staging. In other circumstances in which involvement by urothelial carcinoma is seen in both sites, separate urinary bladder and prostatic urethral staging should be assigned.
E. Lymphovascular 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 AJCC is recommended. A cystoprostatectomy specimen may contain three 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 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 2)
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

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<th>N</th>
<th>M</th>
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<td>Any</td>
<td>M1</td>
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</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 (e.g., 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 one 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 anterior and lateral walls, dome, and trigone. Submit one 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 one 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 one or more sections of uterus (as indicated) and one 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


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