COLLEGE of AMERICAN PATHOLOGISTS

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Protocol for the Examination of Specimens from Patients with Carcinoma of the Urethra and Periurethral Glands

Protocol applies to invasive carcinomas and carcinoma in situ.

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

Procedures
• Urethral Biopsy, Transurethral Resection Specimen
• Urethrectomy (Partial, Total)
- With Radical Cystoprostatectomy
- With Radical Cystectomy
- With Penectomy
- With 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 urethral tumor is NOT considered to be the definitive resection specimen, even though the entire cancer may be removed. A protocol is recommended for reporting such 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 Urethra Protocol Revision History

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

Biopsy

The following data elements have been modified:
- Primary Tumor Site
- Histologic Type
- Associated Epithelial Lesions
- Microscopic Tumor Extension

The following data elements have been deleted:
- Tumor Type
- Pathologic Staging (pTNM)

Total Urethrectomy; Cystectomy, Cystoprostatectomy; Anterior Exenteration

The following data elements have been modified:
- Primary Tumor Site
- Histologic Type
- Associated Epithelial Lesions
- Microscopic Tumor Extension
- Primary Tumor (pT)
- Regional Lymph Nodes (pN)

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

URETHRA: Biopsy (Note A)

Note: Use of case summary for biopsy specimens is optional.

Select a single response unless otherwise indicated.

+ Specimen
+ ___ Urethra
+ ___ Other (specify): _____
+ ___ Not specified

+ Primary Tumor Site (select all that apply)

+ Male
+ ___ Penile
+ ___ Bulbomembranous
+ ___ Prostatic
+ ___ Cannot be determined

+ Female
+ ___ Anterior
+ ___ Posterior
+ ___ Cannot be determined

+ 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
    + 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)

+ Tumours 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
+ ___ Condyloma
+ ___ Squamous dysplasia (low, intermediate, high grade)
+ ___ 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

+ For squamous cell carcinoma or adenocarcinoma
+ ___ GX: Cannot be assessed
+ ___ G1: Well-differentiated
+ ___ G2: Moderately differentiated
+ ___ G3: Poorly differentiated

+ ___ Other (specify): _____

+ Microscopic Tumor Extension (select all that apply) (Note D)
+ ___ Cannot be assessed
+ ___ No evidence of primary tumor
+ ___ Primary tumor involving male penile urethra and female urethra (for urothelial carcinoma involving prostatic urethra see "Urothelial carcinoma of the prostatic urethra" below)
    + ___ Papillary noninvasive carcinoma
    + ___ Carcinoma in situ
    + ___ Tumor invades subepithelial connective tissue
    + ___ Tumor invades adjacent structures
        + ___ Corpus spongiosum
        + ___ Periurethral muscle
        + ___ Corpus cavernosum
        + ___ Anterior vagina
        + ___ Rectum
        + ___ Other (specify): _____
+ ___ Urothelial carcinoma of the prostatic urethra
    + ___ Carcinoma in situ, involvement of the prostatic urethra
    + ___ Carcinoma in situ, involvement of the prostatic ducts
    + ___ Tumor invades urethral subepithelial connective tissue immediately underlying the urothelium
    + ___ Tumor invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts
    + ___ Tumor invades the periprostatic fat
    + ___ Tumor invades adjacent structures
        + ___ Extraprostatic invasion of the bladder wall
        +____Rectal wall
        + ___ Other (specify): _____

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

+ Additional Pathologic Findings (select all that apply)
+ ___ Keratinizing squamous metaplasia
+ ___ Inflammation/regenerative changes
+ ___ Therapy-related changes
+ ___ Cautery artifact
+ ___ Urethritis cystica et glandularis
+ ___ Intestinal metaplasia
+ ___ Other (specify): _____

+ Comment(s): _____

Surgical Pathology Cancer Case Summary

Protocol posting date: February 2017

URETHRA: Partial or Total Urethrectomy; Cystectomy, Cystoprostatectomy; Anterior Exenteration

Select a single response unless otherwise indicated.

Specimen
___ Urethra
___ Other (specify): _____
___ Not specified

Procedure
___ Partial urethrectomy
___ Total urethrectomy
___ Urethrectomy with cystectomy
___ Urethrectomy with cystoprostatectomy
___ Urethrectomy with penectomy
___ Anterior exenteration
___ Other (specify): _____
___ Not specified

+ Tumor Site (select all that apply)

+ Male
+ ___ Penile
+ ___ Bulbomembranous
+ ___ Prostatic
+ ___ Cannot be determined

+ Female
+ Distance from proximal margin: ____ cm
+ ___ Cannot be determined

+ Tumor Size
+ Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
+ ___ Cannot be determined

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
+ 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)

Tumours 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
+ ___ Condyloma
+ ___ Squamous dysplasia (low, intermediate, high grade)
+ ___ 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): _____

+ 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.

For squamous cell carcinoma or adenocarcinoma
___ GX: Cannot be assessed
___ G1: Well-differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated

___ Other (specify): _____

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

Tumor Extension (select all that apply) (Note D)
___ Cannot be assessed
___ No evidence of primary tumor
Male
___ Urothelial carcinoma of penile and bulbomembranous urethra
    ___ Noninvasive papillary carcinoma
    ___ Carcinoma in situ
    ___ Tumor invades subepithelial connective tissue
    ___ Tumor invades adjacent structures
        ___ Corpus spongiosum
        ___ Periurethral muscle
        ___ Corpus cavernosum
        ___ Bladder wall
        ___ Rectum
        ___ Other (specify): _____
___ Urothelial carcinoma of the prostatic urethra
    ___ Carcinoma in situ, involvement of the prostatic urethra
    ___ Carcinoma in situ, involvement of the prostatic ducts
    ___ Tumor invades urethral subepithelial connective tissue immediately underlying the urothelium
    ___ Tumor invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts
    ___ Tumor invades the periprostatic fat
    ___ Tumor invades adjacent structures
        ___ Extraprostatic invasion of the bladder wall
        ___ Rectum
        ___ Other (specify:) _____
Female
___ Noninvasive papillary carcinoma
___ Carcinoma in situ
___ Tumor invades subepithelial connective tissue
___ Tumor invades adjacent structures
    ___ Periurethral muscle (fibromuscular and adipose tissue)
    ___ Anterior vagina
    ___ Bladder wall
    ___ Rectum
    ___ Other (specify): _____

Margins (select all that apply) (Notes F and G)
___ Cannot be assessed
___ Involved by invasive carcinoma
    ___ Proximal mucosal margin
    ___ Distal mucosal margin
    ___ Deep soft tissue margin
    ___ Other margin(s) (specify)[#]: _____
___ Involved by carcinoma in situ/noninvasive high-grade urothelial carcinoma
    ___ Proximal mucosal margin
    ___ Distal mucosal margin
    ___ 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)[#]: _____
        + ___ Low-grade dysplasia
        + ___ Noninvasive low-grade urothelial carcinoma

[#] *If the specimen is received unoriented, precluding identification of margins as distal or proximal, it should be denoted here.*

+ Lymphovascular Invasion (Note H)
+ ___ 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

Pathologic Stage Classification (pTNM, AJCC 7th Edition) (Notes D and E)

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

Primary Tumor (pT) (male and female)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTa: Noninvasive papillary carcinoma
___ pTis: Carcinoma in situ
___ pT1: Tumor invades subepithelial connective tissue
___ pT2: Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
___ pT3: Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
___ pT4: Tumor invades other adjacent organs (invasion of the bladder)

Primary Tumor (pT) (urothelial [transitional cell] carcinoma of the prostate)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTa: Noninvasive papillary, polypoid, or verrucous carcinoma
___ pTis pu: Carcinoma in situ, involvement of prostatic urethra
___ pTis pd: Carcinoma in situ, involvement of prostatic ducts
___ pT1: Tumor invades subepithelial connective tissue (only applied to tumors invading from the urethral lumen)[#]
___ pT2: Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
___ pT3: Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
___ pT4: Tumor invades other adjacent organs (invasion of the bladder)

[#] *Tumors invading directly from prostatic ducts colonized by carcinoma in-situ are designated as at least pT2, regardless of depth or extent of invasion (ie, there is no pT1 category in that setting).*

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in a single lymph node 2 cm or less in greatest dimension
___ pN2: Metastasis in a single lymph node more than 2 cm in greatest dimension, or in multiple nodes

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

+ Additional Pathologic Findings (select all that apply)
+ ___ Keratinizing squamous metaplasia
+ ___ Inflammation/regenerative changes
+ ___ Therapy-related changes
+ ___ Urethritis cystica et glandularis
+ ___ Intestinal metaplasia
+ ___ Other (specify): _____

+ Comment(s)

Explanatory Notes

A. History

A relevant history is important for interpretation of urethral biopsies. A history of renal stones, recent urinary tract procedures, infections, obstruction, or prior therapy (intravesical or systemic chemotherapy, local radiation) can lead to reactive epithelial changes potentially mimicking malignancy. Any neoplasms previously diagnosed should be specified, including the histologic type, primary site, and histologic grade.

B. Histologic Type

Carcinomas of the urethra vary in histologic type, depending on type of epithelium lining the urethra in a given anatomic location.[1-4] In women, squamous cell carcinoma is the most common histologic subtype (approximately 75%) and is most common in the anterior urethra (distal third). Urothelial carcinoma is next in frequency, followed by adenocarcinoma (approximately 10% to 15% each). Clear cell adenocarcinomas comprise a significant proportion of adenocarcinomas in women but are quite rare in men.[5] In the male, most tumors involve the bulbomembranous urethra, followed by penile urethra and prostatic urethra. Most carcinomas of the male urethra (80%) are squamous cell carcinoma, followed by urothelial origin. As in women, urothelial carcinomas are typically more proximal. Primary urethral adenocarcinomas are rare in men. Adenocarcinomas may rarely arise from the periurethral Skene's (female) or Littre's (male) glands.[4] 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 World Health Organization (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.[6]

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

Mucinous
Mixed
Villous adenoma
Urachal carcinoma

Tumors of Mullerian type
Clear cell carcinoma
Endometrioid carcinoma

Neuroendocrine tumors
Small cell neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
Well differentiated neuroendocrine tumor
Paraganglioma

C. Histologic Grade
Squamous cell carcinoma and adenocarcinoma are graded on a 3-tiered system as well-differentiated (grade 1), moderately differentiated (grade 2), or poorly differentiated (grade 3).

For urothelial neoplasia, flat intraepithelial lesions and papillary and invasive lesions are graded separately. 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[7] and has been adopted in the 2016 WHO classification[8,9] and has been validated by many studies to be prognostically significant. Other systems (that were being used previously) may still be used according to institutional preferences Tumor grade according to both the WHO/ISUP (1998) system and the older WHO (1973) system may be concurrently used.[10]

Flat and papillary urothelial hyperplasia has been renamed as “urothelial proliferation of uncertain malignant potential” in the 2016 WHO classification.

D. Extent of Invasion
A critical role of the surgical pathologist is to diagnose the depth/extent of invasion into the tissues surrounding the urethra.[10] The surrounding anatomic structures vary by gender and location within the urethra but include the subepithelial connective tissue, corpus spongiosum, corpus cavernosum, prostate, periurethral muscle, extraprostatic soft tissue, anterior vagina, bladder neck, or other adjacent organs. In the prostatic urethra, invasion may arise from a tumor lining the urethral lumen or from carcinoma in-situ colonizing prostatic ducts. The pT1 designation should only be applied to superficial invasion arising from the urethral lining; invasion arising from the prostatic ducts is designated as at least pT2.[11] In papillary urothelial tumors, invasion occurs most often at the base of the tumor and less frequently in the stalk.

E. TNM and Stage Groupings
The TNM Staging System for carcinomas of the urethra of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended and shown below.[11]

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)
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

Stage 0a	Ta	N0	M0[#]
Stage 0is	Tis	N0	M0
	Tis pu	N0	M0
	Tis pd	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
Stage IV	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

 # 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).

F. Sections for Microscopic Evaluation

Urethra
In transurethral 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. In urethrectomy specimens, submit 1 section per centimeter of tumor, including the macroscopically deepest penetration. Documentation of tumor in relation to surrounding anatomic structures (such as corpus spongiosum, corpus cavernosum, prostate, periurethral muscle, vagina, and bladder) is critical to proper staging. The distal and proximal urethral margins should be submitted (or distal urethra and bilateral ureteral margins if bladder is included), if not evaluated intraoperatively by frozen section. These margins are typically submitted en face in order to see the entire urothelial lining; however, if the tumor is grossly in close proximity to the margin, a perpendicular section showing relationship to ink may be more appropriate. The surrounding radial soft tissue margins should also be submitted, guided by the closest approximation of the tumor to ink by gross evaluation.

Lymph Nodes
Submit 1 section from each grossly positive lymph node. The size of grossly positive lymph nodes should be carefully recorded, especially if only representative sections are submitted that do not account for the largest dimension. All other lymph nodes should be entirely submitted, as presence of nodal disease may be used as an indication for adjuvant therapy.

Other Tissues
Submit 1 or more sections of other organs included in the resection. If the tumor grossly appears to invade the prostate, uterus, bladder, or vagina, sections should be targeted, such that the relationship of the infiltrating tumor in the urethra and the adjacent viscus is clearly demonstrable. Submit several sections of the urinary bladder mucosa remote from the carcinoma, especially if abnormal, including the lateral wall(s), dome, and trigone, because urothelial neoplasia is frequently multifocal. One section from each ureteral margin should be submitted if not evaluated by frozen section. Representative sections of the peripheral zone, central zone, and seminal vesicles should be included because concomitant prostatic adenocarcinoma is not uncommon. The gross examination may help target sampling of selective abnormal-appearing areas.

G. Margins
Resection margins, including those mentioned in Note **F**, should be carefully specified. Whether the margin is submitted en face or perpendicular to the inked surface should be clearly stated in the block summary.

H. Venous/Lymphatic Vascular Invasion
Urethral carcinomas may invade blood vessels or lymphatic channels. In suspicious cases, surrounding endothelial cells can be highlighted by immunohistochemical staining for CD31 or CD34 and lymphatic vessel invasion by D2-40.[12,13] Retraction artifact is prominent in invasive urothelial carcinoma, particularly the micropapillary variant, and should be distinguished from vascular space invasion.[14]

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