COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Carcinoma of the Urethra and Periurethral Glands

Version: Urethra 4.0.1.1 **Protocol Posting Date:** June 2017
Includes pTNM requirements from the 8th Edition, AJCC Staging Manual

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes specimens designated urethrectomy, radical cystectomy, radical cystoprostatectomy, penectomy, and pelvic exenteration
Tumor Type	**Description**
Carcinomas	Includes invasive carcinomas of the urinary tract, including urothelial carcinoma and its morphological variants (squamous cell carcinoma, adenocarcinoma, Müllerian carcinoma, neuroendocrine carcinoma, and sarcomatoid carcinoma)#

 # This protocol is recommended for reporting noninvasive urothelial tumors (papillary and flat), but it is not required for accreditation purposes.

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Transurethral resection#
Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)
Cytologic specimens

**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.*

The following tumor types should NOT be reported using this protocol:

Tumor Type
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)
Sarcoma (consider the Soft Tissue protocol)

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

** Denotes primary author. All other contributing authors are listed alphabetically.*

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).

Synoptic Reporting
All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired "Data element: Response" format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e. all required elements must be in the synoptic portion of the report in the format defined above.

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2018*

** Beginning January 1, 2018, the 8th edition AJCC Staging Manual should be used for reporting pTNM.*

CAP Urethra Protocol Summary of Changes

Version 4.1.0.0
Biopsy
Tumor Extension

- **MODIFIED** to match resection format

Resection
Size of Largest Metastatic Deposit

- **MODIFIED** Unit of measure from millimeters to centimeters

Version 4.0.0.0:
The following data elements were modified:
Pathologic Stage Classification (pTNM, AJCC 8th Edition)

Surgical Pathology Cancer Case Summary

Protocol posting date: June 2017

URETHRA: Biopsy

Note: This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

Select a single response unless otherwise indicated.

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

+ Tumor Site (select all that apply)

+ Male
+ ___ Penile urethra
+ ___ Bulbomembranous urethra
+ ___ Prostatic urethra

+ Female
+ ___ Anterior urethra
+ ___ Posterior urethra

+ ___ Urethra, not otherwise 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, 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)

+ 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
+ ___ 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)

+ *For urothelial carcinoma, other variants, or divergent differentiation*
+ ___ Low grade
+ ___ High grade

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

+ ___ Other (specify): _____
+ ___ Cannot be assessed
+ ___ Not applicable

+ Tumor Extension (select all that apply) (Note D)
+ ___ 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): _____

+ ___ Cannot be assessed

+ 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 (specify): _____
+ ___ Cautery artifact
+ ___ Urethritis cystica et glandularis
+ ___ Intestinal metaplasia
+ ___ Other (specify): _____

+ Comment(s)

Surgical Pathology Cancer Case Summary

Protocol posting date: June 2017

URETHRA: Resection

Select a single response unless otherwise indicated.

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 urethra
+ ___ Bulbomembranous urethra
+ ___ Prostatic urethra

+ Female
+ ___ Anterior urethra
+ ___ Posterior urethra

+ ___ Urethra, not otherwise specified

+ Tumor Size
+ Greatest dimension (centimeters): ___ cm
+ Additional dimensions (centimeters): ___ 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: _____%

+ 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.

___ 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
+ ___ 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)

For urothelial carcinoma, other variants, or divergent differentiation
___ Low grade
___ High grade
___ Other (specify): _____

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

+ 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 (specify): _____
___ Cannot be assessed
___ Not applicable

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

Tumor Extension (select all that apply) (Note D)
___ 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): _____

___ Cannot be assessed

Margins (select all that apply) (Notes F and G)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma and carcinoma in situ/ noninvasive urothelial carcinoma
___ Uninvolved by invasive carcinoma

+ 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.

___ 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)[#]: _____
___ Involved by noninvasive low-grade urothelial carcinoma/urothelial dysplasia
___ Proximal mucosal margin
___ Distal mucosal margin
___ Other margin(s) (specify)[#]: _____

[#] *Note: 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 (centimeters): ___ cm
+ Specify Site: _____

+ Size of Largest Lymph Node Involved (centimeters): ___ cm
+ Specify Site: _____

+ Extranodal Extension
+ ___ Not identified
+ ___ Present
+ ___ Cannot be determined

Pathologic Stage Classification (pTNM, AJCC 8th Edition) (Notes D and E)

Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.

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

Primary Tumor (pT)

For the Male Penile Urethra and Female Urethra
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pTa: Non-invasive papillary carcinoma
___ pTis: Carcinoma in situ
___ pT1: Tumor invades subepithelial connective tissue
___ pT2: Tumor invades any of the following: corpus spongiosum, periurethral muscle
___ pT3: Tumor invades any of the following: corpus cavernosum, anterior vagina
___ pT4: Tumor invades other adjacent organs (eg, invasion of the bladder wall)

For the Prostatic Urethra
___ pT0: No evidence of primary tumor
___ pTa: Non-invasive papillary carcinoma
___ pTis: Carcinoma in situ involving the prostatic urethra or periurethral or prostatic ducts without stromal invasion
___ pT1: Tumor invades urethral subepithelial connective tissue immediately underlying the urothelium
___ pT2: Tumor invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts
___ pT3: Tumor invades the periprostatic fat
___ pT4: Tumor invades other adjacent organs (eg, extraprostatic invasion of the bladder wall, rectal wall)

Regional Lymph Nodes (pN)
___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Single regional lymph node metastasis in the inguinal region or true pelvis (perivesical, obturator, internal [hypogastric] and external iliac), or presacral lymph node
___ pN2: Multiple regional lymph node metastasis in the inguinal region or true pelvis (perivesical, hypogastric, obturator, internal and external iliac, or presacral lymph node)

Distant Metastasis (pM) (required only if confirmed pathologically in this case)
___ pM1: Distant metastasis
Specify site(s), if known: _____

+ Additional Pathologic Findings (select all that apply)
+ ___ Keratinizing squamous metaplasia
+ ___ Inflammation/regenerative changes
+ ___ Therapy-related changes (specify): _____
+ ___ 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.[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
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. Lymphovascular 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]

References
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