

## 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 8<sup>th</sup> 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) <sup>#</sup>

*# 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 <sup>#</sup>
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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### 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

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### 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

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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: \_\_\_\_\_%

+ 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
- + \_\_\_ 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**

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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



- 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

- Involved by invasive carcinoma
  - Proximal mucosal margin
  - Distal mucosal margin
  - Deep soft tissue margin
  - Other margin(s) (specify)<sup>#</sup>: \_\_\_\_\_
- Involved by carcinoma in situ/noninvasive high-grade urothelial carcinoma
  - Proximal mucosal margin
  - Distal mucosal margin
  - Other margin(s) (specify)<sup>#</sup>: \_\_\_\_\_
- Involved by noninvasive low-grade urothelial carcinoma/urothelial dysplasia
  - Proximal mucosal margin
  - Distal mucosal margin
  - Other margin(s) (specify)<sup>#</sup>: \_\_\_\_\_

<sup>#</sup> 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 8<sup>th</sup> 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)

+ 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.

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

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### 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.<sup>1-4</sup> 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.<sup>5</sup> 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.<sup>4</sup> 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.<sup>6</sup>

#### 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<sup>7</sup> and has been adopted in the 2016 WHO classification<sup>8,9</sup> 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.<sup>10</sup>

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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>11</sup>

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 <sup>#</sup>
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
Stage IV	T3	N0	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

<sup>#</sup> 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.<sup>12,13</sup> Retraction artifact is prominent in invasive urothelial carcinoma, particularly the micropapillary variant, and should be distinguished from vascular space invasion.<sup>14</sup>

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