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

Version: Urethra Resection 4.0.3.0  Protocol Posting Date: February 2020
CAP Laboratory Accreditation Program Protocol Required Use Date: November 2020
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:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td>Includes specimens designated urethrectomy, radical cystectomy, radical cystoprostatectomy, penectomy, and pelvic exenteration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinomas</td>
<td>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)¹</td>
</tr>
</tbody>
</table>

¹ 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:

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy (consider the Urethra Biopsy protocol)</td>
</tr>
<tr>
<td>Transurethral resection²</td>
</tr>
<tr>
<td>Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)</td>
</tr>
<tr>
<td>Cytologic specimens</td>
</tr>
</tbody>
</table>

² 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:

<table>
<thead>
<tr>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)</td>
</tr>
<tr>
<td>Sarcoma (consider the Soft Tissue protocol)</td>
</tr>
</tbody>
</table>

Authors
Gladell P. Paner, MD*, Jesse K. McKenney, MD*; Ming Zhou, MD, PhD*; Robert Allan, MD; Mahul B. Amin, MD; Jonathan I. Epstein, MD; David J. Grignon, MD; Peter A. Humphrey, MD, PhD; Esther Oliva, MD; Jason Pettus, MD; Victor E. Reuter, MD; John R. Srigley, MD
With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

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

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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 (i.e., 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.

Summary of Changes
**Version 4.0.3.0**
Added pTX to pT for Prostatic Urethra
### Surgical Pathology Cancer Case Summary

Protocol posting date: February 2020

**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 A)

**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
___ 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 B)
+ ___ 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 B)

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 C)
___ No evidence of primary tumor

Male
___ Carcinoma of penile and bulbomembranous urethra
   ___ Noninvasive papillary urothelial carcinoma
   ___ Carcinoma in situ
   ___ Tumor invades subepithelial connective tissue
   ___ Tumor invades adjacent structures
      ___ Corpus spongiosum
      ___ Periurethral muscle
      ___ Corpus cavernosum
      ___ Bladder wall
      ___ Rectum
      ___ Other (specify): ____________________________
___ 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 urothelial 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 D and E)
___ 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 F)
+ ___ 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) (Note G)

*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

___ pTX: Primary tumor cannot be assessed
___ 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)
A. Histologic Type
Carcinomas of the urethra vary in histologic type, depending on type of epithelium lining the urethra in a given anatomic location. 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. 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 perirectal Skene's (female) or Littre's (male) glands. 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.

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
- 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

References

**B. 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 and has been adopted in the 2016 WHO classification 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.

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

References

**C. Extent of Invasion**
A critical role of the surgical pathologist is to diagnose the depth/extent of invasion into the tissues surrounding the urethra. 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. In papillary urothelial tumors, invasion occurs most often at the base of the tumor and less frequently in the stalk.

References

D. 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.

E. Margins
Resection margins, including those mentioned in Note D, 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.

F. Lymphovascular Invasion
Urethral carcinomas may invade blood vessels or lymphatic channels. In suspicious cases, surrounding endothelial cells may be highlighted by immunohistochemical staining for CD31 or CD34 and lymphatic vessel invasion by D2-40. Retraction artifact is prominent in invasive urothelial carcinoma, particularly the micropapillary variant, and should be distinguished from vascular space invasion.

References
Background Documentation


G. Pathologic Stage Classification

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.¹

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 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.

References