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

Version: 4.1.0.0
Protocol Posting Date: June 2021

The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

This protocol may be used for the following procedures AND tumor types:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>Includes specimens designated biopsy or transurethral resection</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)</td>
</tr>
</tbody>
</table>

The following should NOT be reported using this protocol:

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection (consider the Urethra Resection protocol)</td>
</tr>
<tr>
<td>Transurethral resection</td>
</tr>
<tr>
<td>Cytologic specimens</td>
</tr>
</tbody>
</table>

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>

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

* Denotes primary author.
Accreditation Requirements
The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Summary of Changes

v 4.1.0.0

- General Reformatting
- Added LVI section
- Elements that are recommended for clinical care purposes are designated as Core and Conditional (indicated by bolded text), while Non-core elements are now indicated with a plus (+) sign
### Reporting Template

Protocol Posting Date: June 2021  
Select a single response unless otherwise indicated.

**CASE SUMMARY: (URETHRA: Biopsy)**  
**Standard(s):** AJCC-UICC 8  
This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

### SPECIMEN (Note A)

**Specimen**  
- Urethra  
- Other (specify): ____________________  
- Not specified

### TUMOR

**Tumor Site (select all that apply)**  
- **Male**  
  - Penile urethra  
  - Bulbomembranous urethra  
  - Prostatic urethra  
- **Female**  
  - Anterior urethra  
  - Posterior urethra  
- **Other**  
  - Urethra, not otherwise specified: ____________________

**Histologic Type (Note B) (select all that apply)**  
- **Urothelial**  
  - Papillary urothelial carcinoma, noninvasive  
  - Papillary urothelial carcinoma, invasive  
  - Urothelial carcinoma in situ  
  - Urothelial carcinoma, invasive  
  - Urothelial carcinoma, nested (including large nested) variant  
  - Urothelial carcinoma, micropapillary variant  
  - Urothelial carcinoma, microcystic variant  
  - Urothelial carcinoma, lymphoepithelioma-like variant  
  - Urothelial carcinoma, plasmacytoid / signet ring cell / 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  

**+Percentage of Squamous Differentiation**  
- Specify percentage: ____________________ %  
- Other (specify): ____________________  
- Cannot be determined
___ Urothelial carcinoma with glandular differentiation

+Percentage of Glandular Differentiation
  ___ Specify percentage: _______________ %
  ___ Other (specify): _______________
  ___ Cannot be determined

___ Urothelial carcinoma with trophoblastic differentiation

+Percentage of Trophoblastic Differentiation
  ___ Specify percentage: _______________ %
  ___ Other (specify): _______________
  ___ Cannot be determined

___ Urothelial carcinoma with Müllerian differentiation

+Percentage of Müllerian Differentiation
  ___ Specify percentage: _______________ %
  ___ Other (specify): _______________
  ___ Cannot be determined

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

+Percentage of Small Cell Neuroendocrine Component
  ___ Specify percentage: _______________ %
  ___ Other (specify): _______________
  ___ Cannot be determined

___ Large cell neuroendocrine carcinoma

+Percentage of Large Cell Neuroendocrine Component
  ___ Specify percentage: _______________ %
  ___ Other (specify): _______________
  ___ Cannot be determined

___ Well-differentiated neuroendocrine tumor

+Percentage of Well-differentiated Neuroendocrine Component
  ___ Specify percentage: _______________ %
  ___ Other (specify): _______________
  ___ Cannot be determined

Other
  ___ Other histologic type not listed (specify): _______________
  ___ Carcinoma, type cannot be determined: _______________

+Histologic Type Comment: _______________
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
___ Other (specify): _________________
___ Cannot be determined: _________________
___ Not applicable: _________________

Tumor Extent (Note D)
Male
___ Carcinoma of penile and bulbomembranous urethra
___ Noninvasive urothelial papillary carcinoma
___ Carcinoma in situ
___ Invades subepithelial connective tissue
___ Invades adjacent structure(s)
   ___ Corpus spongiosum
   ___ Periurethral muscle
   ___ Corpus cavernosum
   ___ Bladder wall
   ___ Rectum
   ___ Other (specify): _________________
___ Carcinoma of the prostatic urethra
___ Carcinoma in situ, involving prostatic urethra
___ Carcinoma in situ, involving prostatic ducts
___ Invades urethral subepithelial connective tissue immediately underlying the urothelium
___ Invades prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts
   ___ Invades periprostatic fat
   ___ Invades adjacent structure(s)
   ___ Extraprostatic invasion of the bladder wall
   ___ Rectum
   ___ Other (specify): _________________
Female
___ Noninvasive urothelial papillary carcinoma
___ Carcinoma in situ
___ Invades subepithelial connective tissue
___ Invades adjacent structure(s)
   ___ Periurethral muscle (fibromuscular and adipose tissue)
   ___ Bladder wall
   ___ Rectum
   ___ Other (specify): _________________
Other
___ Cannot be determined: _________________
___ No evidence of primary tumor
+Lymphovascular Invasion
___ Not identified
___ Present
___ Cannot be determined: _________________

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

+Tumor Comment: _________________

ADDITIONAL FINDINGS

+Associated Epithelial Lesions (select all that apply)
___ 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
___ Other (specify): _________________
___ Cannot be determined: _________________

+Additional 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): _________________

COMMENTS

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. 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 periurethral 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

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

References

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. 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