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>

**Authors**

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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, microcystic variant
___ Urothelial carcinoma, micropapillary 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*

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>___ Low-grade</td>
<td></td>
</tr>
<tr>
<td>___ High-grade</td>
<td></td>
</tr>
</tbody>
</table>

*For squamous cell carcinoma or adenocarcinoma*

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>___ G1, well differentiated</td>
<td></td>
</tr>
<tr>
<td>___ G2, moderately differentiated</td>
<td></td>
</tr>
<tr>
<td>___ G3, poorly differentiated</td>
<td></td>
</tr>
<tr>
<td>___ GX, cannot be assessed:</td>
<td></td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>___ Other (specify):</td>
<td></td>
</tr>
<tr>
<td>___ Cannot be determined:</td>
<td></td>
</tr>
<tr>
<td>___ Not applicable:</td>
<td></td>
</tr>
</tbody>
</table>

### Tumor Extent (Note D)

**Male**

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>___ Carcinoma of penile and bulbomembranous urethra</td>
<td></td>
</tr>
<tr>
<td>___ Noninvasive urothelial papillary carcinoma</td>
<td></td>
</tr>
<tr>
<td>___ Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>___ Invades subepithelial connective tissue</td>
<td></td>
</tr>
<tr>
<td>___ Invades adjacent structure(s)</td>
<td></td>
</tr>
<tr>
<td>___ Corpus spongiosum</td>
<td></td>
</tr>
<tr>
<td>___ Periurethral muscle</td>
<td></td>
</tr>
<tr>
<td>___ Corpus cavernosum</td>
<td></td>
</tr>
<tr>
<td>___ Bladder wall</td>
<td></td>
</tr>
<tr>
<td>___ Rectum</td>
<td></td>
</tr>
<tr>
<td>___ Other (specify):</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>___ Carcinoma of the prostatic urethra</td>
<td></td>
</tr>
<tr>
<td>___ Carcinoma in situ, involving prostatic urethra</td>
<td></td>
</tr>
<tr>
<td>___ Carcinoma in situ, involving prostatic ducts</td>
<td></td>
</tr>
<tr>
<td>___ Invades urethral subepithelial connective tissue immediately underlying the urothelium</td>
<td></td>
</tr>
<tr>
<td>___ Invades prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts</td>
<td></td>
</tr>
<tr>
<td>___ Invades periprostatic fat</td>
<td></td>
</tr>
<tr>
<td>___ Invades adjacent structure(s)</td>
<td></td>
</tr>
<tr>
<td>___ Extraprostatic invasion of the bladder wall</td>
<td></td>
</tr>
<tr>
<td>___ Rectum</td>
<td></td>
</tr>
<tr>
<td>___ Other (specify):</td>
<td></td>
</tr>
</tbody>
</table>

**Female**

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>___ Noninvasive urothelial papillary carcinoma</td>
<td></td>
</tr>
<tr>
<td>___ Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>___ Invades subepithelial connective tissue</td>
<td></td>
</tr>
<tr>
<td>___ Invades adjacent structure(s)</td>
<td></td>
</tr>
<tr>
<td>___ Periurethral muscle (fibromuscular and adipose tissue)</td>
<td></td>
</tr>
<tr>
<td>___ Bladder wall</td>
<td></td>
</tr>
<tr>
<td>___ Rectum</td>
<td></td>
</tr>
<tr>
<td>___ Other (specify):</td>
<td></td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>___ Cannot be determined:</td>
<td></td>
</tr>
<tr>
<td>___ No evidence of primary tumor</td>
<td></td>
</tr>
</tbody>
</table>
+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 bulbo-urinary system 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
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.34

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