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

Version: 4.2.0.0
Protocol Posting Date: September 2023

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 subtypes, and other carcinoma such as squamous cell carcinoma, adenocarcinoma, Müllerian carcinoma, and neuroendocrine carcinoma*</td>
</tr>
</tbody>
</table>

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

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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* 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 4.2.0.0

- WHO 5th Edition update to content and Explanatory Notes
- LVI question update from "Lymphovascular Invasion" to “Lymphatic and/or Vascular Invasion"
Reporting Template
Protocol Posting Date: September 2023
Select a single response unless otherwise indicated.

CASE SUMMARY: (URETHRA: Biopsy)
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, NOS: ____________________

Histologic Type (Note B) (select all that apply)
Urothelial
___ Papillary urothelial carcinoma, noninvasive
___ Papillary urothelial carcinoma, invasive
___ Urothelial carcinoma in situ
___ Urothelial carcinoma, invasive (conventional)
___ Urothelial carcinoma, micropapillary
___ Urothelial carcinoma, nested
___ Urothelial carcinoma, tubular and microcystic
___ Urothelial carcinoma, lymphoepithelioma-like
___ Urothelial carcinoma, plasmacytoid
___ Urothelial carcinoma, sarcomatoid
___ Urothelial carcinoma, giant cell
___ Urothelial carcinoma, poorly differentiated
___ Urothelial carcinoma, lipid-rich
___ Urothelial carcinoma, clear cell (glycogen-rich)
___ Urothelial carcinoma with squamous differentiation
___ Urothelial carcinoma with glandular differentiation
___ Urothelial carcinoma with trophoblastic differentiation
___ Urothelial carcinoma with Müllerian differentiation
Squamous
___ Squamous cell carcinoma
___ Verrucous carcinoma
___ Squamous cell carcinoma in situ (no invasive carcinoma identified)
**Histologic Type Comment:**

1. **HPV-associated squamous cell carcinoma**
2. **Glandular**
   - Adenocarcinoma, NOS
   - Adenocarcinoma, enteric
   - Adenocarcinoma, mixed
   - Adenocarcinoma, mucinous
   - Adenocarcinoma, signet-ring cell
   - Adenocarcinoma in situ (no invasive carcinoma identified)
3. **Müllerian**
   - Clear cell adenocarcinoma
   - Endometrioid carcinoma
4. **Neuroendocrine**
   - Small cell neuroendocrine carcinoma
   - Large cell neuroendocrine carcinoma
   - Well-differentiated neuroendocrine tumor
5. **Other**
   - Littre gland adenocarcinoma
   - Skene gland adenocarcinoma
   - Cowper gland adenocarcinoma
   - Other histologic type not listed (specify): ____________________
   - Carcinoma, type cannot be determined: ____________________

**+Specify Percentages of Histologic Subtypes and Divergent Differentiations Present (totaling 100%)# (select all that apply)**

# Applicable for mixed subtypes, divergent differentiations, and other carcinomas

1. **Urothelial carcinoma, invasive (conventional):** ____________________ %
2. **Urothelial carcinoma, micropapillary:** ____________________ %
3. **Urothelial carcinoma, nested:** ____________________ %
4. **Urothelial carcinoma, large nested:** ____________________ %
5. **Urothelial carcinoma, tubular and microcystic:** ____________________ %
6. **Urothelial carcinoma, lymphoepithelioma-like:** ____________________ %
7. **Urothelial carcinoma, plasmacytoid:** ____________________ %
8. **Urothelial carcinoma, sarcomatoid:** ____________________ %
9. **Urothelial carcinoma, giant cell:** ____________________ %
10. **Urothelial carcinoma, poorly differentiated:** ____________________ %
11. **Urothelial carcinoma, lipid-rich:** ____________________ %
12. **Clear cell (glycogen-rich):** ____________________ %
13. **Squamous differentiation:** ____________________ %
14. **Glandular (adenocarcinoma) differentiation:** ____________________ %
15. **Trophoblastic differentiation:** ____________________ %
16. **Müllerian differentiation:** ____________________ %
17. **Small cell neuroendocrine carcinoma:** ____________________ %
18. **Large cell neuroendocrine carcinoma:** ____________________ %
19. **Other (specify):** ____________________

**Histologic Grade (Note C)**

For urothelial carcinoma, other variants, or divergent differentiation

1. **Low-grade**
2. **High-grade**

For squamous cell carcinoma or adenocarcinoma

1. **G1, well-differentiated**
___ G2, moderately differentiated
___ G3, poorly differentiated
___ GX, cannot be assessed: ____________________

Other
___ Other (specify): ____________________
___ Cannot be assessed: ____________________
___ 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)

Select all that apply
___ Corpus spongiosum
___ Periurethral muscle
___ Tunica albuginea
___ Corpus cavernosum
___ Scrotum
___ Urinary bladder wall
___ Rectum
___ Other (specify): ____________________

___ Carcinoma of 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)

Select all that apply
___ Extraprostatic invasion of the bladder wall
___ Other (specify): ____________________

Female
___ Noninvasive urothelial papillary carcinoma
___ Carcinoma in situ
___ Invades subepithelial connective tissue
___ Invades adjacent structure(s)

Select all that apply
___ Periurethral muscle (fibromuscular and adipose tissue)
___ Anterior vagina
___ Urinary bladder wall
___ Rectum
___ Other (specify): ____________________

Other
___ Cannot be determined: ____________________
___ No evidence of primary tumor
**Lymphatic and / or Vascular 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 (Note C) (select all that apply)**
- None identified
- Condyloma acuminata
- Squamous dysplasia (low, intermediate, high grade)
- Urothelial papilloma
- Urothelial papilloma, inverted type
- Papillary urothelial neoplasm, low malignant potential (PUNLMP)
- 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 the 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. 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 should be made. The 2022 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.

2022 WHO Classification of Epithelial Tumors of the Urothelial Tract

**Urothelial tumors**

*Invasive urothelial carcinoma*
- Conventional urothelial carcinoma
- Urothelial carcinoma with squamous differentiation
- Urothelial carcinoma with glandular differentiation
- Urothelial carcinoma with trophoblastic differentiation
- Nested urothelial carcinoma
- Tubular and microcystic urothelial carcinomas
- Micropapillary urothelial carcinoma
- Lymphoepithelioma-like urothelial carcinoma
- Plasmacytoid urothelial carcinoma
- Giant cell urothelial carcinoma
- Lipid-rich urothelial carcinoma
- Clear cell (glycogen-rich) urothelial carcinoma
- Urothelial carcinoma, poorly differentiated

*Noninvasive urothelial lesions*
- Urothelial carcinoma in situ
- Noninvasive papillary urothelial carcinoma, high grade
- Noninvasive papillary urothelial carcinoma, low grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma
Squamous cell neoplasms
- Squamous cell carcinoma
- Verrucous carcinoma
- Squamous papilloma

Glandular neoplasms
- Adenocarcinoma, NOS
  - Enteric
  - Mucinous
  - Mixed
  - Signet-ring cell
  - Adenocarcinoma in situ
- Villous adenoma

Urical and diverticular neoplasms
- Urachal carcinoma
- Diverticular carcinoma

Tumors of Mullerian type
- Clear cell adenocarcinoma
- Endometrioid carcinoma

Neuroendocrine neoplasms
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Mixed neuroendocrine neoplasm
- Well-differentiated neuroendocrine tumor
- Paraganglioma

Urethral accessory glands
- Carcinoma of Littre glands
- Carcinoma of Skene glands
- Carcinoma of Cowper glands

References
C. Histologic Grade
Squamous cell carcinoma and adenocarcinoma are graded on a 3-tiered system that is based on tumor differentiation as well differentiated (grade 1), moderately differentiated (grade 2), or poorly differentiated (grade 3).\textsuperscript{1,2}

For urothelial neoplasia, flat intraepithelial lesions and papillary and invasive lesions are graded separately.\textsuperscript{1,3,4,5,6} A more universally acceptable system, the World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification, was proposed in 1998 by ISUP and has been adopted in the 2004 WHO classification system and has been validated by many studies to be prognostically significant. This grading system has also been upheld in the 2016 and 2022 WHO classifications with slight modifications. Other systems (that were being used previously) may still be used according to institutional preferences. Tumor grade according to both the 2004 WHO/ISUP system and the older 1973 WHO system may be concurrently used.

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.\textsuperscript{1} The surrounding anatomic structures vary by gender and location within the urethra and may include at least the subepithelial connective tissue, periurethral muscle, prostate, and corpus spongiosum in transurethral resection specimens. Identification of these anatomic landmarks and documentation of their tumor involvement is important. In the prostatic urethra, invasion may arise from a tumor lining the urethral lumen or from carcinoma in situ colonizing prostatic ducts. The T1 designation should only be applied to superficial invasion arising from the urethral lining; invasion arising from the prostatic ducts into the prostatic stroma is designated as T2. A urethral urothelial carcinoma may occur concurrently with bladder urothelial carcinoma, thus, prostatic tumor involvement in urethral transurethral resections should not be automatically considered as transmural bladder extension by bladder cancer.

References