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

Version: 4.2.0.1
Protocol Posting Date: June 2024
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:

Procedure	Description
Biopsy	Includes specimens designated biopsy or transurethral resection
Tumor Type	**Description**
Carcinomas	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#

 # 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:

Procedure
Resection (consider the Urethra Resection protocol)
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)
Sarcoma (consider the Soft Tissue protocol)

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

Replaced by version 4.3.0.0 on December 11, 2024, Obsolete as of September 2025 (8 months after newest release date)

Summary of Changes

v 4.2.0.1

- Cover page correction to Procedure table

Reporting Template

Protocol Posting Date: June 2024
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, 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

Replaced by version 4.3.0.0 on December 11, 2024, Obsolete as of September 2025 (8 months after newest release date)

___ Urothelial carcinoma with Müllerian differentiation
Squamous
___ Squamous cell carcinoma
___ Verrucous carcinoma
___ Squamous cell carcinoma in situ (no invasive carcinoma identified)
___ HPV-associated squamous cell carcinoma
Glandular
___ Adenocarcinoma, NOS
___ Adenocarcinoma, enteric
___ Adenocarcinoma, mixed
___ Adenocarcinoma, mucinous
___ Adenocarcinoma, signet-ring cell
___ Adenocarcinoma in situ (no invasive carcinoma identified)
Müllerian
___ Clear cell adenocarcinoma
___ Endometrioid carcinoma
Neuroendocrine
___ Small cell neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Well-differentiated neuroendocrine tumor
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

___ Urothelial carcinoma, invasive (conventional): _____ %
___ Urothelial carcinoma, micropapillary: _____ %
___ Urothelial carcinoma, nested: _____ %
___ Urothelial carcinoma, large 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: _____ %
___ Clear cell (glycogen-rich): _____ %
___ Squamous differentiation: _____ %
___ Glandular (adenocarcinoma) differentiation: _____ %
___ Trophoblastic differentiation: _____ %
___ Müllerian differentiation: _____ %
___ Small cell neuroendocrine carcinoma: _____ %
___ Large cell neuroendocrine carcinoma: _____ %

___ Other (specify): _____
+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 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.[1,2,3,4] 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 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

Urachal 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

1. WHO Classification of Tumours Editorial Board. Tumours of the urinary tract. In: WHO Classification of Tumours. *Urinary and male genital tumours*. 5th edition. Geneva, Switzerland: WHO Press; 2022.
2. Moch H, Humphrey PA, Ulbright TM, Reuter VE. *WHO Classification of Tumours of the Urinary System and Male Genital Organs.* Geneva, Switzerland: WHO Press; 2016.
3. Lopez-Beltran A, Sauter G, Gasser T, et al. Infiltrating urothelial carcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, eds. *World Health Organization Classification of Tumours:*

Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. Lyon, France: IARC Press; 2004:97.
4. Murphy WM, Grignon DJ, Perlman EJ. *Tumors of the kidney, bladder, and related urinary structures. In: Atlas of Tumor Pathology.* 4th series. Fascicle 1. Washington, DC: American Registry of Pathology; 2004.

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).[1,2]

For urothelial neoplasia, flat intraepithelial lesions and papillary and invasive lesions are graded separately.[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

1. WHO Classification of Tumours Editorial Board. Tumours of the urinary tract. In: *WHO Classification of Tumours. Urinary and male genital tumours*. 5th edition. Geneva, Switzerland: WHO Press; 2022.
2. Paner GP, Kamat, Netto GJ, et al. International Society of Urological Pathology (ISUP) Consensus Conference on Current Issues in Bladder Cancer. Working Group 2: grading of mixed grade, invasive urothelial carcinoma including histologic subtypes and divergent differentiations, and non-urothelial carcinomas. *Am J Surg Pathol.* 2023; online ahead of print.
3. Moch H, Humphrey PA, Ulbright TM, Reuter VE. *WHO Classification of Tumours of the Urinary System and Male Genital Organs*. Geneva, Switzerland: WHO Press; 2016.
4. Sauter G, Algaba F, Amin MB, et al. Non-invasive urothelial tumours. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs.* Lyon, France: IARC Press; 2004:110.
5. Epstein JI, Amin MB, Reuter VR, Mostofi FK, the Bladder Consensus Conference Committee. The World Health Organization/ International Society of Urological Pathology Consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. *Am J Surg Pathol*. 1998;22(12):1435-1448.
6. Mostofi FK. Histological typing of urinary bladder tumours. In: WHO Histological Classification of Tumours. No. 10. Geneva, Switzerland: World Health Organization; 1973.

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.[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

1. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017