



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.

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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

___ 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

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___ 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