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

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| **Version:** Urethra Biopsy 4.0.2.0 | **Protocol Posting Date:** August 2019 |
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| **Accreditation Requirements** |
| 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 variants (squamous cell carcinoma, adenocarcinoma, Mϋllerian carcinoma, neuroendocrine carcinoma, and sarcomatoid carcinoma) |

**The following should NOT be reported using this protocol:**

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| --- |
| **Procedure** |
| Resection (consider the Urethra Resection protocol) |
| Transurethral resection |
| Cytologic specimens |

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

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| --- |
| **Tumor Type** |
| Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols) |
| Sarcoma (consider the Soft Tissue protocol) |

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Summary of Changes

**Version 4.0.2.0**

Separated resection and biopsy case summaries into discrete cancer protocols

**The following was modified:**

Histologic Type

Tumor Extension

Surgical Pathology Cancer Case Summary

Protocol posting date: August 2019

# URETHRA: Biopsy

**Note: This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes. Core data elements are bolded to help identify routinely reported elements.**

## Select a single response unless otherwise indicated.

**Specimen (Note A)**

\_\_\_ Urethra

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not specified

## Tumor Site (select all that apply)

Male

\_\_\_ Penile urethra

\_\_\_ Bulbomembranous urethra

\_\_\_ Prostatic urethra

Female

\_\_\_ Anterior urethra

\_\_\_ Posterior urethra

\_\_\_ Urethra, not otherwise specified

**Histologic Type (select all that apply) (Note B)**

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 / 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

Specify percentage of squamous differentiation: \_\_\_\_\_%

\_\_\_ Urothelial carcinoma with glandular differentiation

Specify percentage of glandular differentiation: \_\_\_\_\_%

\_\_\_ Urothelial carcinoma with trophoblastic differentiation

Specify percentage of trophoblastic differentiation: \_\_\_\_\_%

\_\_\_ Urothelial carcinoma with Mϋllerian differentiation

Specify percentage of Mϋllerian differentiation: \_\_\_\_\_%

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 Mϋllerian Type

\_\_\_ Clear cell carcinoma

\_\_\_ Endometrioid carcinoma

Neuroendocrine Tumors

\_\_\_ Small cell neuroendocrine carcinoma

Specify percentage of small cell neuroendocrine component: \_\_\_\_\_%

\_\_\_ Large cell neuroendocrine carcinoma

Specify percentage of large cell neuroendocrine component: \_\_\_\_\_%

\_\_\_ Well-differentiated neuroendocrine carcinoma

Specify percentage of well-differentiated neuroendocrine component: \_\_\_\_\_%

\_\_\_ Other histologic type not listed (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

## Associated Epithelial Lesions (select all that apply) (Note C)

\_\_\_ 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

\_\_\_ Cannot be determined

## 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 (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be assessed

\_\_\_ Not applicable

**Tumor Extension (select all that apply) (Note D)**

\_\_\_ No evidence of primary tumor

Male

\_\_\_ Carcinoma of penile and bulbomembranous urethra

\_\_\_ Noninvasive urothelial papillary carcinoma

\_\_\_ Carcinoma in situ

\_\_\_ Tumor invades subepithelial connective tissue

\_\_\_ Tumor invades adjacent structures

\_\_\_ Corpus spongiosum

\_\_\_ Periurethral muscle

\_\_\_ Corpus cavernosum

\_\_\_ Bladder wall

\_\_\_ Rectum

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Carcinoma of the prostatic urethra

\_\_\_ Carcinoma in situ*,* involvement of the prostatic urethra

\_\_\_ Carcinoma in situ*,* involvement of the prostatic ducts

\_\_\_ Tumor invades urethral subepithelial connective tissue immediately underlying the urothelium

\_\_\_ Tumor invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts

\_\_\_ Tumor invades the periprostatic fat

\_\_\_ Tumor invades adjacent structures

\_\_\_ Extraprostatic invasion of the bladder wall

\_\_\_ Rectum

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Female

\_\_\_ Noninvasive urothelial papillary carcinoma

\_\_\_ Carcinoma in situ

\_\_\_ Tumor invades subepithelial connective tissue

\_\_\_ Tumor invades adjacent structures

\_\_ Periurethral muscle (fibromuscular and adipose tissue)

\_\_\_ Anterior vagina

\_\_\_ Bladder wall

\_\_\_ Rectum

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Cannot be assessed

## Tumor Configuration (select all that apply)

\_\_\_ Papillary

\_\_\_ Solid/nodule

\_\_\_ Flat

\_\_\_ Ulcerated

\_\_\_ Cannot be determined

\_\_\_ Other (specify): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

## Additional Pathologic 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): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

## 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 histologicgrade.

## B. Histologic Type

Carcinomas of the urethra vary in histologic type, depending on type of epithelium lining the urethra in a given anatomic location.1-4 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.5 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.4 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.6

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

1. Amin MB, Young RH. Primary carcinomas of the urethra. *Semin Diag Pathol.* 1997;14(2):147-160.
2. Reuter V.E. Urethra. In: Bostwick DG, Eble JN, eds. *Urologic Surgical Pathology.* St. Louis, MO: Mosby Year Book, Inc; 1997:223-230.
3. Reuter VE. The urothelial tract: renal pelvis, ureter, urinary bladder and urethra. In: Mills SE, Carter D, Greenson JK, Oberman HA, Reuter VE, Stoler MH, eds. *Sternberg’s Diagnostic Surgical Pathology.* 4th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2004:2035-2081.
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.
5. Oliva E, Young RH. Clear cell adenocarcinoma of the urethra: a clinicopathologic analysis of 19 cases. *Mod Pathol.* 1996;9:513-520.
6. 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.

## 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 proposed7 and has been adopted in the 2016 WHO classification1,2 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.3,4

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

References

1. 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
2. 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.
3. 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.
4. 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 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 pT2.2 In papillary urothelial tumors, invasion occurs most often at the base of the tumor and less frequently in the stalk.

References

1. Mostofi FK. Histological typing of urinary bladder tumours. In: *WHO Histological Classification of Tumours. No. 10.* Geneva, Switzerland: World Health Organization; 1973.
2. 11. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017