**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:**

|  |  |
| --- | --- |
| **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:**

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

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

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

**Authors**

Gladell P. Paner, MD\*; Jesse K. McKenney, MD\*; Ming Zhou, MD, PhD\*; Lara R. Harik, MD; Robert Allan, MD; Mahul B. Amin, MD; Jonathan I. Epstein, MD; David J. Grignon, MD; Peter A. Humphrey, MD, PhD; Esther Oliva, MD; Jason Pettus, MD; Victor E. Reuter, MD; John R. Srigley, MD.

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**](#2197)**)**

**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**](#2198)**) (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**](#2199)**)**

*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 determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ Not applicable: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Tumor Extent (Note** [**D**](#2200)**)**

*Male*

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

\_\_\_ Noninvasive urothelial papillary carcinoma

\_\_\_ Carcinoma in situ

\_\_\_ Invades subepithelial connective tissue

\_\_\_ Invades adjacent structure(s)

\_\_\_ Corpus spongiosum

\_\_\_ Periurethral muscle

\_\_\_ Corpus cavernosum

\_\_\_ Bladder wall

\_\_\_ Rectum

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

\_\_\_ Carcinoma of the 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)

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

\_\_\_ Rectum

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

*Female*

\_\_\_ Noninvasive urothelial papillary carcinoma

\_\_\_ Carcinoma in situ

\_\_\_ Invades subepithelial connective tissue

\_\_\_ Invades adjacent structure(s)

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

\_\_\_ Bladder wall

\_\_\_ Rectum

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

*Other*

\_\_\_ Cannot be determined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_ No evidence of primary tumor

**+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 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,](#8568)[2,](#8569)[3,](#8570)[4](#8571) 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](#8572) 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](#8571) 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](#8573)

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 proposed and has been adopted in the 2016 WHO classification[1,](#8574)[2](#8575) 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,](#8576)[4](#8577)

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](#8578) 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](#8579) 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. Amin MB, Edge SB, Greene FL, et al., eds. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017