COLLEGE of AMERICAN PATHOLOGISTS

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

Version: Urethra Biopsy 4.0.2.0 **Protocol Posting Date:** August 2019

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, Müllerian 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)

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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 Müllerian differentiation
    Specify percentage of Müllerian 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 Müllerian 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 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.[1-4] 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 proposed[7] and has been adopted in the 2016 WHO classification[1,2] 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