



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

Version: 4.2.0.0

Protocol Posting Date: September 2023

CAP Laboratory Accreditation Program Protocol Required Use Date: June 2024

The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes specimens designated urethrectomy, radical cystectomy, radical cystoprostatectomy, penectomy, and pelvic exenteration
Tumor Type	Description
Carcinomas	Includes invasive carcinomas of the urinary tract, including urothelial carcinoma, its morphological subtypes, and other carcinoma such as squamous cell carcinoma, adenocarcinoma, Müllerian carcinoma, neuroendocrine carcinoma [#]

[#] This protocol is recommended for reporting noninvasive urothelial tumors (papillary and flat), but it is not required for accreditation purposes.

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy and Transurethral resection* (consider the Urethra Biopsy and TUR protocol)
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens
Penile mucosa / skin carcinoma (consider the Penile protocol)

*Transurethral resection of a urethral tumor is NOT considered to be the definitive resection specimen, even though the entire cancer may be removed. A protocol is recommended for reporting such specimens for clinical care purposes, but this is not required for accreditation purposes.

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)
Melanoma

Authors

Lara R. Harik, MD, FCAP*; Gladell P. Paner, MD, FCAP*; Hikmat A. Al-Ahmadie, MD; Robert W. Allan, MD; Donna E. Hansel, MD, PhD; Giovanna A. Giannico, MD; Jesse K. McKenney, MD; Philippe E. Spiess, MD; Pheroze Tamboli, MD; Toyonori Tsuzuki, MD; Matthew Wasco, MD.

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

* Denotes primary author.

Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is “not applicable” or “cannot be determined.”
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with “+” and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
 - Anatomic site or specimen, laterality, and procedure
 - Pathologic Stage Classification (pTNM) elements
 - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 4.2.0.0

- WHO 5th Edition update to content and Explanatory Notes
- pTNM Classification update
- LVI question update from “Lymphovascular Invasion” to “Lymphatic and/or Vascular Invasion”

RETIRED

Reporting Template**Protocol Posting Date: September 2023****Select a single response unless otherwise indicated.****CASE SUMMARY: (URETHRA: Resection)****Standard(s): AJCC-UICC 8****SPECIMEN****Procedure**

- Partial urethrectomy
 Total urethrectomy
 Urethrectomy with cystectomy
 Urethrectomy with cystoprostatectomy
 Urethrectomy with penectomy
 Anterior exenteration
 Other (specify): _____
 Not specified

TUMOR**+Tumor Site (select all that apply)***Male Genital Organs*

- Penile urethra
 Bulbomembranous urethra
 Prostatic urethra

Female Genital Organs

- Anterior urethra
 Posterior urethra

Other

- Urethra, NOS: _____

Histologic Type (Note [A](#)) (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 B)*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 Size** Greatest dimension in Centimeters (cm): _____ cm**+Additional Dimension in Centimeters (cm):** x cm Cannot be determined (explain): _____**Tumor Extent (Note C)***Male* Carcinoma of penile and bulbomembranous urethra Noninvasive papillary urothelial 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 Extraprostatic invasion of seminal vesicle Rectum 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 (Note D)

- Not identified
- Present
- Cannot be determined: _____

+Tumor Configuration (select all that apply)

- Papillary
- Solid / nodule
- Flat
- Ulcerated
- Other (specify): _____
- Cannot be determined: _____

+Tumor Comment: _____

MARGINS (Notes E,F)

Margin Status for Invasive Carcinoma

- All margins negative for invasive carcinoma

+Closest Margin(s) to Invasive Carcinoma (select all that apply)

- Proximal: _____
- Distal: _____
- Deep soft tissue: _____

If the specimen is received unoriented, precluding identification of margins as distal or proximal, it should be denoted here.

- Other (specify)#: _____
- Cannot be determined (explain): _____

+Distance from Invasive Carcinoma to Closest Margin

Specify in Millimeters (mm)

- Exact distance: _____ mm
- Greater than: _____ mm
- At least (specify): _____ mm
- Less than: _____ mm
- Less than 1 mm
- Other (specify): _____
- Cannot be determined: _____

- Invasive carcinoma present at margin

Margin(s) Involved by Invasive Carcinoma (select all that apply)

- Proximal: _____

Distal: _____
 Deep Soft Tissue: _____
If the specimen is received unoriented, precluding identification of margins as distal or proximal, it should be denoted here.
 Other (specify)#: _____
 Cannot be determined (explain): _____
 Other (specify): _____
 Cannot be determined (explain): _____
 Not applicable

Margin Status for Carcinoma in Situ / Noninvasive Urothelial Carcinoma

All margins negative for carcinoma in situ / noninvasive urothelial carcinoma
+Closest Margin(s) to Carcinoma in Situ / Noninvasive Urothelial Carcinoma (select all that apply)

Proximal: _____
 Distal: _____
If the specimen is received unoriented, precluding identification of margins as distal or proximal, it should be denoted here.
 Other (specify)#: _____
 Cannot be determined (explain): _____

+Distance from Carcinoma in Situ / Noninvasive Urothelial Carcinoma to Closest Margin

Specify in Millimeters (mm)
 Exact distance: _____ mm
 Greater than: _____ mm
 At least (specify): _____ mm
 Less than: _____ mm
 Less than 1 mm
 Other (specify): _____
 Cannot be determined: _____

Carcinoma in situ / noninvasive urothelial carcinoma present at margin

Margin(s) Involved by Carcinoma in Situ / Noninvasive Urothelial Carcinoma (select all that apply)

Proximal: _____
 Distal: _____
If the specimen is received unoriented, precluding identification of margins as distal or proximal, it should be denoted here.
 Other (specify)#: _____
 Cannot be determined (explain): _____
 Other (specify): _____
 Cannot be determined (explain): _____
 Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status

Not applicable (no regional lymph nodes submitted or found)
 Regional lymph nodes present
 All regional lymph nodes negative for tumor
 Tumor present in regional lymph node(s)

Number of Lymph Nodes with Tumor

- Exact number (specify): _____
- At least (specify): _____
- Other (specify): _____
- Cannot be determined (explain): _____

+Size of Largest Nodal Metastatic Deposit

Specify in Centimeters (cm)

- Exact size: _____ cm
- At least (specify): _____ cm
- Greater than: _____ cm
- Less than: _____ cm
- Other (specify): _____
- Cannot be determined (explain): _____

+Nodal Site with Largest Metastatic Deposit (specify site): _____**+Size of Largest Lymph Node with Tumor**

Specify in Centimeters (cm)

- Exact size: _____ cm
- At least (specify): _____ cm
- Greater than: _____ cm
- Less than: _____ cm
- Other (specify): _____
- Cannot be determined (explain): _____

+Largest Lymph Node with Tumor (specify site): _____**+Extranodal Extension (ENE)**

- Not identified
- Present
- Cannot be determined: _____
- Other (specify): _____
- Cannot be determined (explain): _____

Number of Lymph Nodes Examined

- Exact number (specify): _____
- At least (specify): _____
- Other (specify): _____
- Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____**DISTANT METASTASIS****Distant Site(s) Involved, if applicable**

- Not applicable
- Specify site(s): _____
- Cannot be determined: _____

pTNM CLASSIFICATION (AJCC 8th Edition) (Note [G](#))

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Modified Classification (required only if applicable) (select all that apply)

- Not applicable

y (post-neoadjuvant therapy)

r (recurrence)

pT Category

For the Male Penile Urethra and Female Urethra

pT Category

pT not assigned (cannot be determined based on available pathological information)

pT0: No evidence of primary tumor

pTa: Non-invasive papillary carcinoma

pTis: Carcinoma *in situ*

pT1: Tumor invades subepithelial connective tissue

pT2: Tumor invades any of the following: corpus spongiosum, periurethral muscle

pT3: Tumor invades any of the following: corpus cavernosum, anterior vagina

pT4: Tumor invades other adjacent organs (invasion of the bladder)

For the Prostatic Urethra

pT Category

pT not assigned (cannot be determined based on available pathological information)

pT0: No evidence of primary tumor

pTa: Non-invasive papillary carcinoma

pTis: Carcinoma *in situ* involving the prostatic urethra or periurethral or prostatic ducts without stromal invasion

pT1: Tumor invades urethral subepithelial connective tissue immediately underlying the urothelium

pT2: Tumor invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts

pT3: Tumor invades the periprostatic fat

pT4: Tumor invades other adjacent organs (e.g., extraprostatic invasion of the bladder wall, rectal wall)

T Suffix (required only if applicable)

Not applicable

(m) multiple primary synchronous tumors in a single organ

pN Category

pN not assigned (no nodes submitted or found)

pN not assigned (cannot be determined based on available pathological information)

pN0: No regional lymph node metastasis

pN1: Single regional lymph node metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric) and external iliac], or presacral lymph node

pN2: Multiple regional lymph node metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric) and external iliac], or presacral lymph node

pM Category (required only if confirmed pathologically)

Not applicable - pM cannot be determined from the submitted specimen(s)

pM1: Distant metastasis

ADDITIONAL FINDINGS

+Associated Epithelial Lesions (Note B) (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): _____

RETIRED

Explanatory Notes

A. Histologic Type

Carcinomas of the urethra vary in histologic type, depending on the 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. 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.
4. 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.

B. 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.^{1,2,3,4,5,6} 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.

C. 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. Identification of these anatomic landmarks and documentation of their tumor involvement is important for accurate tumor staging. 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 into the prostatic stroma is designated as at least pT2. A urethral urothelial carcinoma may occur concurrently with a urinary bladder urothelial carcinoma and extent of invasion from the urethral carcinoma should be documented.

References

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

D. Lymphatic and/or Vascular Invasion

Urethral carcinomas may invade blood vessels or lymphatic channels.^{1,2} In suspicious cases, surrounding endothelial cells can be highlighted by immunohistochemical staining for CD31 or CD34 and lymphatic vessel invasion by D2-40. Retraction artifact is prominent in invasive urothelial carcinoma, particularly the micropapillary variant, and should be distinguished from vascular space invasion.

References

1. Wemtz RP, Smith ZL, Packiam VT, et al. The impact of lymphovascular invasion on risk of upstaging and lymph node metastasis at the time of radical cystectomy. *Eur Urol Focus* 2020;15:292-297.
2. Mari A, Kimura S, Foerster B, et al. A systematic review and meta-analysis of lymphovascular invasion in patients treated with radical cystectomy for bladder cancer. *Urol Oncol* 2018;36:293-305.

E. Sections for Microscopic Evaluation

Urethra

In urethrectomy specimens, submit 1 section per centimeter of tumor, including the macroscopically deepest penetration. Documentation of tumor in relation to surrounding anatomic structures (such as corpus spongiosum, corpus cavernosum, prostate, periurethral muscle, vagina, and bladder) is critical to proper staging. The distal and proximal urethral margins should be submitted (or distal urethra and bilateral ureteral margins if bladder is included), if not evaluated intraoperatively by frozen section. These margins are typically submitted en face in order to see the entire urothelial lining; however, if the tumor is grossly in close proximity to the margin, a perpendicular section showing relationship to ink may be more appropriate. The surrounding radial soft tissue margins should also be submitted, guided by the closest approximation of the tumor to ink by gross evaluation.

Lymph Nodes

Submit 1 section from each grossly positive lymph node. The size of grossly positive lymph nodes should be carefully recorded, especially if only representative sections are submitted that do not account for the largest dimension. All other lymph nodes should be entirely submitted, as presence of nodal disease may be used as an indication for adjuvant therapy.

Other Tissues

Submit 1 or more sections of other organs included in the resection. If the tumor grossly appears to invade the prostate, uterus, bladder, or vagina, sections should be targeted, such that the relationship of the infiltrating tumor in the urethra and the adjacent viscus is clearly demonstrable. Submit several sections of the urinary bladder mucosa remote from the carcinoma, especially if abnormal, including the lateral wall(s), dome, and trigone, because urothelial neoplasia is frequently multifocal. One section from each ureteral margin should be submitted if not evaluated by frozen section. Representative sections of the peripheral zone, central zone, and seminal vesicles should be included because concomitant prostatic adenocarcinoma is not uncommon. The gross examination may help target sampling of selective abnormal-appearing areas.

F. Margins

Resection margins, including those mentioned in Note E, should be carefully specified. Whether the margin is submitted en face or perpendicular to the inked surface should be clearly stated in the block summary.

G. Pathologic Stage Classification

The TNM Staging System for carcinomas of the urethra of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.¹

Staging of primary tumor is based on the extent of invasion into male and female urethral and surrounding structures (Figures 1 and 2).

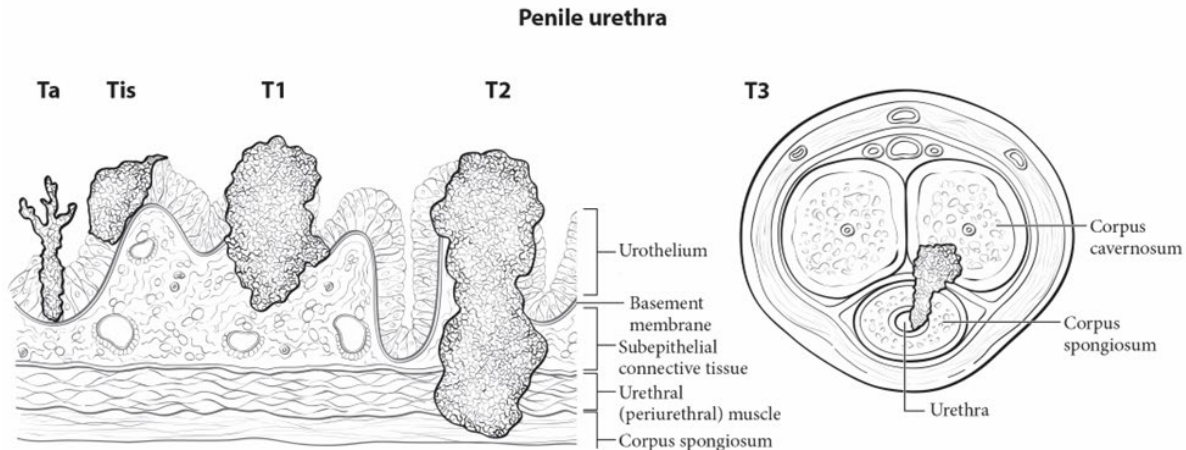


Figure 1. Definition of primary tumor (T) in penile urethra. From: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017. Reproduced with permission.

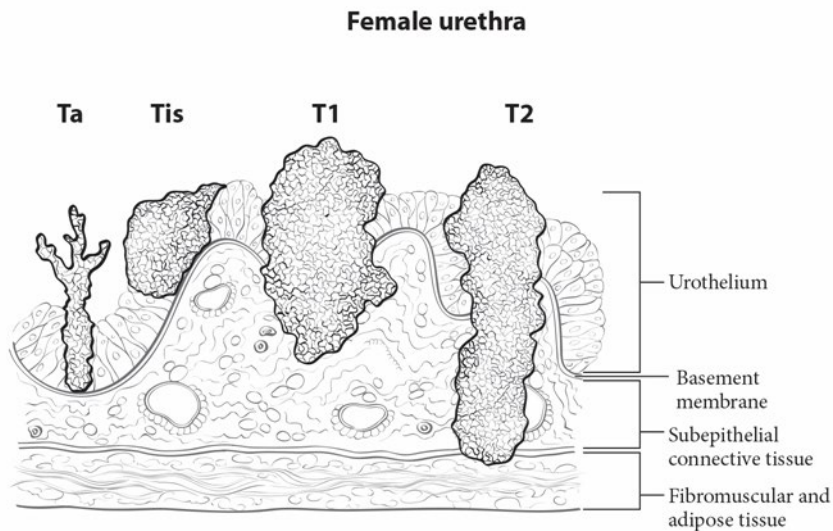


Figure 2. Definition of primary tumor (T) in female urethra. From: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017. Reproduced with permission. By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (e.g., when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

Primary Tumor (T)

The suffix “m” should be added to the appropriate T category to indicate multiple tumors. The suffix “is” may be added to any T to indicate the presence of associated carcinoma in situ.

Involvement of non-regional lymph nodes (beyond inguinal and true pelvis) constitutes metastatic disease.

TNM Descriptors**TNM Stage Classifications**

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

TNM**Suffixes**

For identification of special cases of TNM or pTNM classifications, the “(m)” T suffix and “(sn)” and “(f)” N suffixes are used. Although they do not affect the stage grouping, they indicate cases needing special analysis.

The “(m)” T suffix indicates the presence of multiple primary synchronous tumors in a single site and is recorded in parentheses: e.g., pT1(m).

References

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