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

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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"

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): _____

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. Werntz 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).

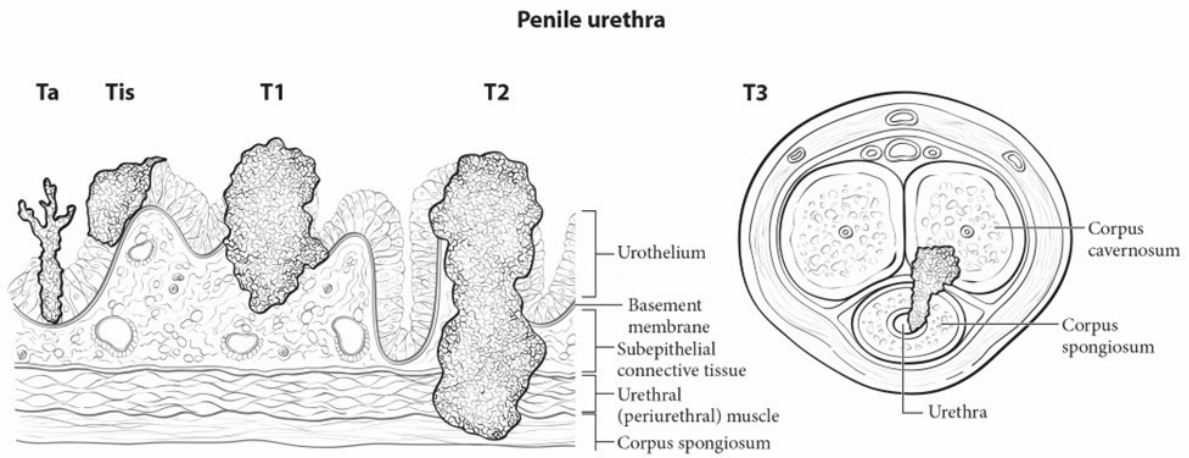

Figure 1. Definition of primary tumor (T) in penile urethra. From: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017. Reproduced with permission.

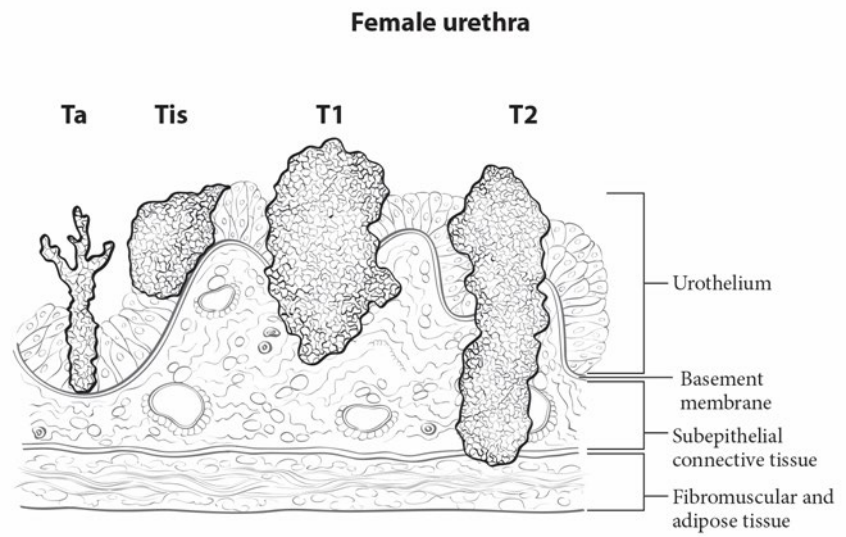

Figure 2. Definition of primary tumor (T) in female urethra. From: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017. Reproduced with permission.
By AJCC/UICC convention, the designation "T" refers to a primary tumor that has not been previously 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