Protocol for the Examination of Cystectomy Specimens From Patients With Carcinoma of the Urinary Bladder

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
Cystectomy	Includes specimens designated partial, total, or radical cystectomy, radical cystoprostatectomy (for bladder cancer), and anterior pelvic exenterations
Tumor Type	**Description**
Carcinomas	Includes invasive carcinomas of the urinary bladder, 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, transurethral resection of the bladder tumor[#] (TURBT), or enucleations (consider Urinary Bladder Biopsy/TURBT protocol)
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens

[#] Transurethral resection of a bladder tumor is NOT considered to be the definitive resection specimen, even though the entire cancer may be removed.

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

Tumor Type
Urachal Carcinoma
Lymphoma (consider the Lymphoid Neoplasm protocols)
Sarcoma (consider the Soft Tissue protocol)

Authors
Lara R. Harik, MD, FCAP*; Gladell P. Paner, MD, FCAP*; Hikmat A. Al-Ahmadie, MD; Robert W. Allan, MD; Mahul B. Amin, MD; Mehmet Asim Bilen, MD; Bernard H. Bochner, MD; Charles C. Guo, MD; Antonio Lopez-Beltran, MD, PhD; Jesse K. McKenney, MD; Ankur R. Sangoi, MD; S. Joseph Sirintrapun, MD; Roxanne Wadia, MD; Sara E. Wobker, MD; Ming Zhou, MD, PhD.
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 ie, 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 to content and Explanatory Note
- 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: (URINARY BLADDER: Cystectomy, Anterior Exenteration)
Standard(s): AJCC-UICC 8
This protocol is recommended for reporting noninvasive urothelial tumors (papillary and flat), but it is not required for accreditation purposes.

SPECIMEN (Note A)

Procedure
___ Partial cystectomy
___ Radical cystectomy (total cystectomy)
___ Radical cystoprostatectomy
___ Anterior pelvic exenteration
___ Other (specify): _____
___ Not specified

TUMOR

Tumor Site (select all that apply)
___ Trigone
___ Right lateral wall
___ Left lateral wall
___ Anterior wall
___ Posterior wall
___ Dome
___ Other (specify): _____
___ Cannot be determined: _____

Histologic Type (Note B) (select all that apply)
Urothelial
___ Papillary urothelial carcinoma, noninvasive
___ 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)
Glandular
___ Adenocarcinoma, NOS
___ Adenocarcinoma, enteric
___ Adenocarcinoma, mucinous
___ Adenocarcinoma, mixed
___ 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 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 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
___ 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 D) (select all that apply)
___ Noninvasive papillary carcinoma
___ Urothelial carcinoma in situ
___ Invades lamina propria (subepithelial connective tissue)
___ Invades superficial muscularis propria (inner half)
___ Invades deep muscularis propria (outer half)
___ Invades perivesical soft tissue microscopically
___ Invades perivesical soft tissue macroscopically (extravesical mass)
 # Use the Urethral checklist for tumors that involve the urethral mucosa without invasion, tumors that involve the urethral mucosa with invasion of subepithelial connective tissue / prostate stroma, or tumors that involve prostatic ducts and acini with or without stromal invasion.
___ Invades adjacent structure(s)#
  ___ Prostatic stroma (transmural invasion from the bladder tumor) (Note D)
  ___ Seminal vesicles
  ___ Uterus
  ___ Vagina
  ___ Adnexa
  ___ Pelvic wall
  ___ Abdominal wall
  ___ Rectum
  ___ Other (specify): _____
___ Cannot be determined: _____
___ No evidence of primary tumor

Lymphatic and / or Vascular Invasion (Note E)
___ Not identified
___ Present
___ Cannot be determined: _____

+Tumor Configuration (select all that apply)
___ Papillary
___ Solid / nodule
___ Flat
___ Ulcerated
___ Other (specify): _____
___ Cannot be determined: _____

+Treatment Effect Post Neoadjuvant Chemotherapy (BCG not included)
___ No known presurgical neoadjuvant therapy

___ Complete response: the absence of histologically identifiable residual cancer cells and extensive fibrosis of the tumor bed after presurgical neoadjuvant therapy (TRG1)
___ Strong response: predominant fibrosis of the tumor bed with residual cancer cells occupying less than 50% of this area (TRG2)
___ Weak and no response: residual cancer cells occupying greater than or equal to 50% of the tumor bed or absence of regressive changes (TRG3)
___ Other (specify): _____

+Tumor Comment: _____

MARGINS (Note F)

Margin Status for Invasive Tumor
___ All margins negative for invasive tumor
+Closest Margin(s) to Invasive tumor (select all that apply)
___ Right ureteral: _____
___ Left ureteral: _____
___ Urethral: _____
___ Soft tissue: _____
 # For partial cystectomies, if the specimen is received unoriented precluding identification of specific margins, it should be denoted here.
___ Other margin(s) (specify)#: _____
+Distance from Invasive Tumor to Closest Margin
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Other (specify): _____
___ Cannot be determined: _____
___ Invasive tumor present at margin
+Margin(s) Involved by Invasive Tumor (select all that apply)
___ Right ureteral: _____
___ Left ureteral: _____
___ Urethral: _____
___ Soft tissue: _____
 # For partial cystectomies, if the specimen is received unoriented precluding identification of specific margins, it should be denoted here.
___ Other margin(s) (specify)#: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

Margin Status for Carcinoma in Situ / Noninvasive Papillary Urothelial Carcinoma
Non-invasive tumors include flat urothelial carcinoma in situ and non-invasive papillary urothelial carcinoma
___ All margins negative for carcinoma in situ / noninvasive papillary urothelial carcinoma
___ Carcinoma in situ / noninvasive papillary urothelial carcinoma present at margin
+Margin(s) Involved by Carcinoma in Situ / Noninvasive Papillary Urothelial Carcinoma (select all that apply)
___ Right ureteral: _____
___ Left ureteral: _____
___ Urethral: _____
___ 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: _____
+Specify Location of Involved Lymph Nodes: _____
___ 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# (select all that apply)
___ Not applicable
___ Non-regional lymph node(s): _____
___ Other site(s), excluding non-regional lymph nodes (specify): _____
___ 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
___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
___ pTa: Non-invasive papillary carcinoma
___ pTis: Urothelial carcinoma *in situ*: "flat tumor"
___ pT1: Tumor invades lamina propria (subepithelial connective tissue)
pT2: Tumor invades muscularis propria
___ pT2a: Tumor invades superficial muscularis propria (inner half)
___ pT2b: Tumor invades deep muscularis propria (outer half)
___ pT2 (subcategory cannot be determined)
pT3: Tumor invades perivesical soft tissue
___ pT3a: Tumor invades perivesical soft tissue microscopically
___ pT3b: Tumor invades perivesical soft tissue macroscopically (extravesicular mass)
___ pT3 (subcategory cannot be determined)
pT4: Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
___ pT4a: Extravesical tumor invades directly into prostatic stroma, uterus, or vagina
___ pT4b: Extravesical tumor invades pelvic wall, abdominal wall
___ pT4 (subcategory cannot be determined)

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 lymph node metastasis
___ pN1: Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
___ pN2: Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
___ pN3: Lymph node metastasis to the common iliac lymph nodes

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
pM1: Distant metastasis
___ pM1a: Distant metastasis limited to lymph nodes beyond the common iliacs
___ pM1b: Non-lymph-node distant metastases
___ pM1 (subcategory cannot be determined)

ADDITIONAL FINDINGS

+Associated Epithelial Lesions (Note C) (select all that apply)
___ None identified
___ 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)
___ Adenocarcinoma of prostate (use separate synoptic report for carcinoma of prostate)
___ Inflammation / regenerative changes
___ Therapy-related changes (specify): _____
___ Cystitis cystica et glandularis
___ Keratinizing squamous metaplasia
___ Intestinal metaplasia
___ Other (specify): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Sections for Microscopic Evaluation

Bladder

Sections of bladder for microscopic evaluation for cystectomy specimens, several representative sections of the tumor, including the macroscopically deepest penetration, should be sampled. Submit several sections of the mucosa remote from the carcinoma, especially if abnormal, including the lateral wall(s), dome, and trigone. Submit one section of ureteral margin, unless submitted separately as frozen section specimens, and 1 section of urethral margin. If a long segment of the ureter(s) is present, then additional sections from the mid-portion may be necessary, as urothelial cancer often is multifocal. If no tumor is identified in the initial histologic sections, additional sampling should be done or submit the entire bladder lesion if feasible. In the post-neoadjuvant chemotherapy setting with no grossly identifiable lesion, all bladder sites should be sampled and correlation with the prior transurethral resection site(s) for sampling is encouraged.

Prostate and Prostatic Urethra

Prostatic urethral involvement should be carefully investigated in cystectomy specimens. Sections should include the prostatic urethra, including at the margin and with the surrounding prostatic parenchyma. Representative sections of the peripheral zone, central zone, and seminal vesicles should be included. Close gross examination may help target sampling of selective abnormal-appearing areas.

Lymph Nodes

Submit one section from each grossly positive lymph node. All other lymph nodes should be entirely submitted, as presence of nodal disease may be used as an indication for adjuvant therapy. Lymph nodes may be grossly or microscopically detected in the perivesical fat.

Other Tissues

Submit one or more sections of uterus (as indicated) and one or more sections of vagina, seminal vesicles, and other organs (as indicated). If the tumor grossly appears to invade the prostate, uterus, or vagina, sections should be targeted, such that the relationship of the infiltrating tumor in the bladder wall and the adjacent viscus is clearly demonstrable.

B. Histologic Type

The vast majority (more than 95%) of carcinomas of the urinary bladder are urothelial cell in origin.[1,2,3,4,5,6,7,8] The most recent 2022 World Health Organization (WHO) classification of epithelial tumors of the urothelial tract is provided in this note. Benign epithelial tumors are included in this classification because, within the same patient, a spectrum of differentiation from benign to malignant tumors may be seen in the bladder, either at the same time or over the clinical course of the disease.

Several subtypes (formerly variants) and divergent differentiations of invasive urothelial carcinoma are now recognized, and their presence should be documented. Invasive urothelial carcinoma subtypes such as sarcomatoid, micropapillary and plasmacytoid are recognized to be more aggressive. In cases of mixed urothelial subtypes and/or divergent differentiations, each component should be reported, including admixed neuroendocrine carcinoma if present. The distinction between a urothelial carcinoma with divergent squamous, glandular, or Müllerian differentiation and a pure squamous cell carcinoma, adenocarcinoma or Müllerian carcinoma is important. The 2022 WHO classification, require a pure histology of squamous cell carcinoma, adenocarcinoma or Müllerian to designate a tumor as such, all others with concomitant 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

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. Comperat E, Amin MB, Epstein JI, et al. The Genitourinary Pathology Society Update on classification of variant histologies, T1 substaging, molecular taxonomy, and immunotherapy and PD-L1 testing. *Adv Anat Pathol.* 2021;28:196-208.
4. 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.
5. Murphy WM, Grignon DJ, Perlman EJ. Tumors of the urinary bladder. In: *Tumors of the Kidney, Bladder, and Related Urinary Structures. AFIP Atlas of Tumor Pathology*. Series 4. Washington, DC: American Registry of Pathology; 2004.
6. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Tumors of the urinary system. In: *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs.* Lyon, France: IARC Press; 2004.
7. Mostofi FK, Davis CJ, Sesterhenn IA. Histologic typing of urinary bladder tumors. In: *World Health Organization International Histologic Classification of Tumours.* 2nd ed. Heidelberg, Germany: Springer-Verlag, Berlin; 1999.
8. 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;22:1435-1448.

C. Histologic Grade

Flat intraepithelial lesions and papillary and invasive lesions are graded separately.[1,2,3,4,5,6,7,8,9] In the 1973 WHO classification, papillary lesions were classified as papillomas and transitional cell carcinomas, grades 1, 2 and 3. Due to the need for a universally acceptable system, the World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification was proposed in 1998. This system is adopted in the 2004 WHO classification and has been validated by many studies to be prognostically significant. The 2016 WHO and 2022 WHO systems used essentially the same classification with minor modifications. Other systems may still be used according to institutional preference. Tumor grade according to both the 2004 WHO system and the 1973 WHO system may be concurrently used. The 2022 WHO system includes descriptive reporting of papillary urothelial carcinoma with mixed grades (low-grade with <5% high-grade component).

2004 WHO/1998 ISUP Consensus Classification for Urothelial Lesions

Normal
    Normal
Hyperplasia
    Flat hyperplasia
    Papillary hyperplasia

Flat Lesions with Atypia
- Reactive (inflammatory) atypia
- Atypia of unknown significance
- Dysplasia (low-grade intraurothelial neoplasia)#
- Carcinoma in situ (high-grade intraurothelial neoplasia)##

Papillary Neoplasms
- Papilloma
- Inverted papilloma
- Papillary neoplasm of low malignant potential
- Papillary carcinoma, low-grade###
- Papillary carcinoma, high-grade###

Invasive Neoplasms
- Lamina propria invasion
- Muscularis propria (detrusor muscle) invasion

#May include cases formerly diagnosed as “mild dysplasia.”
##Includes cases with “severe dysplasia.”
###Option exists to provide descriptive diagnosis on low grade papillary urothelial carcinoma with focal high-grade component.

The vast majority of invasive urothelial carcinoma are high-grade with uncommon cases of invasive low-grade tumors are reported, that usually have limited involvement of the lamina propria. Invasive urothelial carcinoma subtypes are graded as high-grade tumors, although these tumors should not be considered as a homogenous group in terms of behavior. Pure squamous carcinomas and adenocarcinomas are graded based on tumor differentiation as well-differentiated, moderately differentiated, and poorly differentiated.

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. Downes MR, Hartmann A, Shen A, et al. International Society of Urological Pathology (ISUP) Consensus Conference on Current Issues in Bladder Cancer. Working Group 1: comparison of bladder grading system performance. *Am J Surg Pathol.* 2023; online ahead of print
3. 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.
4. Amin MB, Comperat E, Epstein JI, et al. The Genitourinary Pathology Society update on classification and grading of flat and papillary urothelial neoplasia with new reporting recommendations and approach to lesions with mixed and early patterns of neoplasia. *Adv Anat Pathol.* 2021;28:179-195.
5. 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.
6. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Tumors of the urinary system. In: *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs.* Lyon, France: IARC Press; 2004.
7. Murphy WM, Grignon DJ, Perlman EJ. Tumors of the urinary bladder. In: *Tumors of the Kidney, Bladder, and Related Urinary Structures*. *AFIP Atlas of Tumor Pathology*. Series 4. Washington, DC: American Registry of Pathology; 2004.

8. 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;22:1435-1448.
9. 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 and extent of invasion into the subepithelial connective tissue/lamina propria/submucosa (pT1), muscularis propria (pT2), or beyond (pT3 or pT4).[1,2,3] Depth of invasion is a critical prognostic determinant in invasive urothelial carcinoma. In cystectomy specimen, invasion into the muscularis propria should be subcategorized as pT2a and pT2b based on the depth of involvement. Note that pT2 is not applicable for cancers arising in diverticulum because of the lack of muscularis propria. Likewise, tumor extension into the perivesical tissue (pT3) should be subcategorized into pT3a and pT3b, the latter best assessed on gross examination by the identification of macroscopic involvement of the perivesical tissue.

Involvement of the prostate gland may occur in several different patterns. Tumors (carcinoma in situ, papillary or invasive carcinoma) can first spread along the prostatic urethral mucosa and prostate glands and subsequently invade prostatic stroma (transurethral mucosal route) (Figure 1). Tumors may also invade through the bladder wall and the base of the prostate directly into the prostate gland. Tumors can also invade into extravesical fat and then extend back into the prostate gland. The latter two routes are considered direct transmural invasion. The AJCC 8th edition staging manual defines direct extension of urinary bladder cancer into the prostate gland as pT4 disease and excludes transurethral mucosal prostatic stroma invasion from the pT4a staging status. However, there is limited data on the best methodology to stage urothelial carcinoma that concurrently involves the urinary bladder and the prostatic urethra. In patients who have a large urinary bladder carcinoma that has invaded through the full thickness of the bladder wall and thereby secondarily involves the prostatic stroma, a pT4 stage should be assigned per urinary bladder staging. In other circumstances in which involvement by urothelial carcinoma is seen in both sites, separate urinary bladder and prostatic urethral staging should be assigned. Transmucosal route into prostatic stroma from a bladder cancer without transmural prostatic stromal invasion is now categorized as pT2 per urethral cancer staging, and the concomitant bladder proper cancer is given a separate stage category according to the bladder cancer staging.

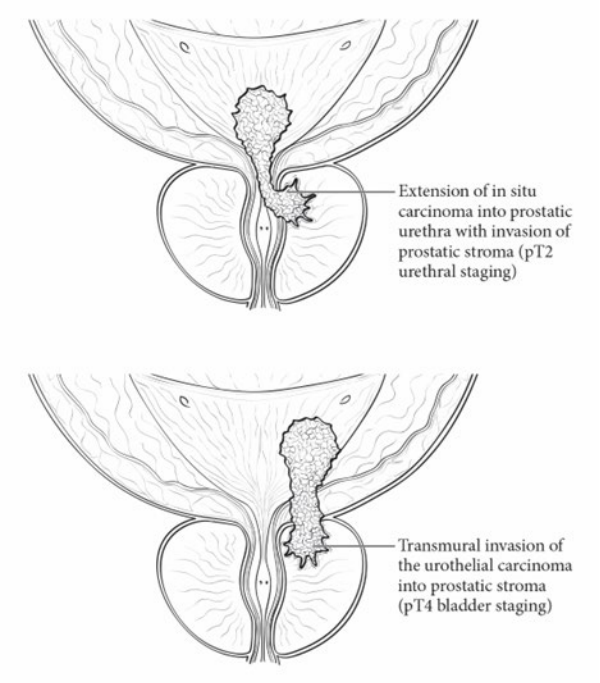

Figure 1. Prostatic invasion from urinary bladder cancer via direct transmural and extravesical route (pT4 bladder staging) and transurethral invasion (pT2 urethral staging). From: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017. Reproduced with permission.

References

1. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
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E. Lymphatic and/or Vascular Invasion

Urothelial carcinoma may invade blood vessels or lymphatic channels. Lymphatic and/or vascular invasion has been shown to be an independent predictor of recurrence and decreased overall survival.[1,2,3] Presence of lymph-vascular invasion in TURBT specimens is associated with higher nodal metastasis. In suspicious cases, blood vessels can be highlighted by immunohistochemical staining for factor VIII-related antigen, CD31 or CD34. Staining will not resolve the problem of differentiating lymphatic versus artifactual space entrapment by tumor cells, and as mentioned, this is frequently seen in urothelial tumors invading the lamina propria. Retraction artifact is also prominent in micropapillary urothelial carcinoma.

References

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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.
3. Lotan Y, Gupta A, Shariat SF, et al. Lymphovascular invasion is independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. *J Clin Oncol*. 2005;23:6533-6539.

F. Margins

Resection margins, including those mentioned in Note A, should be carefully specified. Statements about deep soft tissue margins should specify whether peritoneal surfaces are involved by tumor. Soft tissue margin location if identifiable should be documented. In cases of partial cystectomy, the bladder wall cut margin should be assessed. It is not an uncommon practice for surgeons to submit the distal ureters as separate margins.

G. TNM and Stage Groupings

The TNM Staging System for carcinomas of the urinary bladder of the AJCC is recommended.[1] A cystoprostatectomy specimen may contain three separate primaries: carcinoma of the urinary bladder, carcinoma of the prostate and carcinoma of the urethra. Depending on the pathology in a given case, the number of protocols to be used in a cystoprostatectomy specimen will vary.

By AJCC 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) (Figure 2)

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.

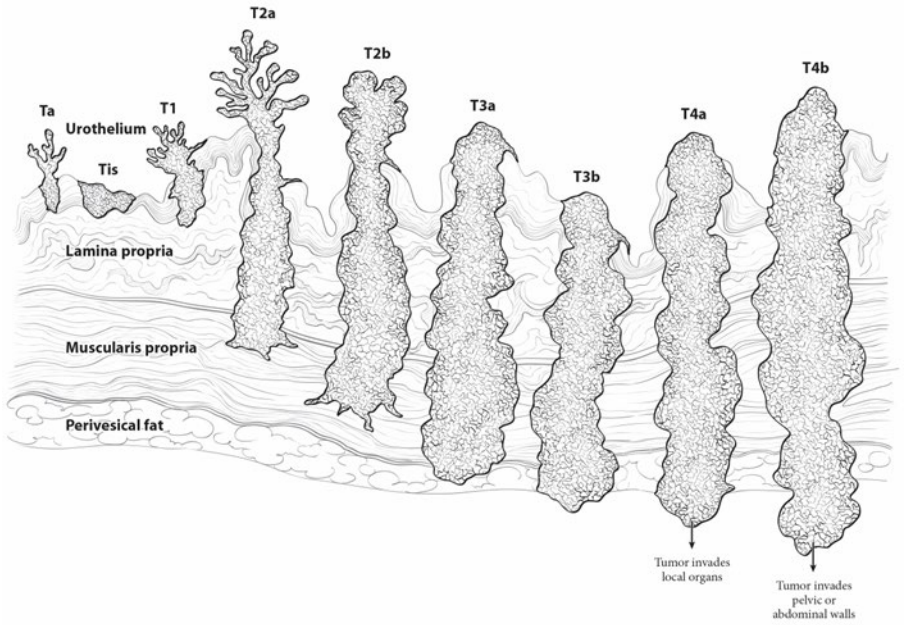

Figure 2. Extent of Tis, Ta, T1, and T3. From: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017. Reproduced with permission.

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y” and “r” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, 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.

References

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