Protocol for the Examination of Resection Specimens From Patients With Carcinoma of the Ureter and Renal Pelvis

Version: 2.3.0.0
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
Ureterectomy	Includes specimens designated ureterectomy and nephroureterectomy
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 (consider the Ureter and Renal Pelvis Biopsy protocol)
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens

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

Tumor Type
Lymphoma (consider the Lymphoid Neoplasm protocols)
Sarcoma (consider the Soft Tissue protocol)
Renal cortical and medullary tumors (consider the separate Kidney protocol)

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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 (i.e., 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 2.3.0.0

- 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: (URETER, RENAL PELVIS: Resection)
Standard(s): AJCC-UICC 8

SPECIMEN (Note A)

Procedure
___ Nephroureterectomy
___ Ureterectomy
___ Other (specify): _____
___ Not specified

Specimen Laterality
___ Right
___ Left
___ Not specified

TUMOR

Tumor Site (select all that apply)
___ Ureter: _____
___ Renal pelvis: _____
___ Kidney: _____
___ Cannot be determined: _____

+Tumor Size
___ Greatest dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _____

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 carcinoma
___ 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 Extent (Note D)
___ Noninvasive papillary carcinoma
___ Carcinoma in situ
___ Invades subepithelial connective tissue
___ Invades muscularis
___ Invades beyond muscularis into periureteral fat or peripelvic fat or renal parenchyma (for renal pelvis only)
___ Invades beyond muscularis into the periureteric fat (for ureters only)
___ Invades adjacent organs or through the kidney into perinephric fat: _____
___ 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: _____

+Tumor Comment: _____

MARGINS (Note F)

Margin Status for Invasive Carcinoma
___ All margins negative for invasive carcinoma
+Closest Margin(s) to Invasive Carcinoma (select all that apply)
___ Proximal ureteral: _____
___ Distal ureteral: _____
___ Bladder cuff: _____
___ Deep soft tissue: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
+Distance from Invasive Carcinoma to Closest Margin
Specify in Millimeters (mm)
___ Exact distance: _____ mm

___ Other (specify): _____
___ Cannot be determined
___ Invasive carcinoma present at margin
Margin(s) Involved by Invasive Carcinoma (select all that apply)
___ Proximal ureteral: _____
___ Distal ureteral: _____
___ Bladder cuff: _____
___ Deep soft tissue: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

Margin Status for Carcinoma in Situ / Noninvasive Papillary Urothelial Carcinoma
___ All margins negative for carcinoma in situ / noninvasive papillary urothelial carcinoma
___ Noninvasive low-grade papillary urothelial carcinoma present at margin
Margin(s) Involved by Low-grade Papillary Urothelial Carcinoma (select all that apply)
___ Proximal ureteral: _____
___ Distal ureteral: _____
___ Bladder cuff: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Carcinoma in situ / noninvasive high-grade papillary urothelial carcinoma present at margin
Margin(s) Involved by Carcinoma in Situ / Noninvasive Papillary Urothelial Carcinoma (select all that apply)
___ Proximal ureteral: _____
___ Distal ureteral: _____
___ Bladder cuff: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES (Note G)

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 H)
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: Papillary noninvasive carcinoma
___ pTis: Carcinoma in situ
___ pT1: Tumor invades subepithelial connective tissue
___ pT2: Tumor invades the muscularis
___ pT3: For renal pelvis only-Tumor invades beyond muscularis into peripelvic fat or into the renal parenchyma or For ureter only-Tumor invades beyond muscularis into periureteric fat
___ pT4: Tumor invades adjacent organs, or through the kidney into the perinephric fat

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: Metastasis less than or equal to 2 cm in greatest dimension, in a single lymph node
___ pN2: Metastasis greater than 2 cm, in a single lymph node; or multiple lymph nodes

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 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)
___ Inflammation / regenerative changes
___ Therapy-related changes (specify): _____
___ Cautery artifact
___ Ureteritis cystica et glandularis
___ Non-keratinizing squamous metaplasia
___ Keratinizing squamous metaplasia
___ Intestinal metaplasia
___ Other (specify): _____

Pathologic Findings in Ipsilateral Nonneoplastic Renal Tissue (Note I) (select all that apply)
___ No or insufficient renal parenchyma
___ None identified
___ Glomerular disease (specify type): _____
___ Tubulointerstitial disease (specify type): _____

___ Vascular disease (specify type): _____
___ Inflammation (specify type): _____
___ Other (specify): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Procedure

A relevant history is important for interpretation of all upper urinary tract (renal pelvis and ureter) specimens. A history of renal stones, recent urinary tract procedures, infections, or obstruction can influence the interpretation of random biopsies obtained from patients with hematuria. Any neoplasms previously diagnosed should be specified, including the histologic type, primary site, and histologic grade. Primary tumors may be associated with hereditary nonpolyposis colon cancer (HNPCC) syndrome (Lynch syndrome). Renal pelvic tumors are more often seen in analgesic abusers, who often have analgesic nephropathy, including papillary necrosis. If prior therapy has been given, it should be described (systemic or intravesical chemotherapy, immunotherapy, radiation, etc.). The method of collection and date also should be specified in urine cytology specimens. Cytologic specimens from the ureter or renal pelvis may be over-interpreted if their site of sampling is not stated.

Sections for Microscopic Evaluation

Segmental ureterectomy is performed for tumors of the proximal or mid ureter. The length and diameter of the intact ureter is recorded, with a search for a mass by palpation and visual inspection. Proximal and distal cross-section margins are taken, and the outer aspect of the ureter is inked. The ureter is then opened longitudinally and assessed for mucosal abnormalities. After fixation in 10% formalin, sections are taken to demonstrate the deepest invasion of any lesion(s). At least one section of the uninvolved ureter should be submitted.

Radical nephroureterectomy with bladder cuff

Gross examination and sampling should document the relationship of tumor to adjacent renal parenchyma, peripelvic fat, nearest soft tissue margin, and ureter. Sections of grossly unremarkable kidney, pelvis, and ureter should be obtained. The important urothelial margin is the urinary bladder cuff, which can be sampled as shave sections.

B. Histologic Type

Like the urinary bladder, the vast majority (more than 95%) of carcinomas of the renal pelvis and ureter are urothelial in origin.[1,2,3,4,5] The most recent 2022 World Health Organization (WHO) classification of tumors of the urinary tract, including for ureter and renal pelvis, is provided in this note. Benign tumors are included in this classification because, within the same patient, a spectrum of differentiation from benign to malignant tumors may be seen, either at the same time or over the clinical course of the disease. The full spectrum of invasive urothelial carcinoma and its subtypes (variants) as found in the urinary bladder may also be found in the upper tract. 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 is important. The 2022 WHO classification, requires 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.

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, predisposes patients to urological cancer, particularly upper tract urothelial carcinoma.[6,7,8] Upper tract urothelial carcinoma develops in up to 28% of patients with known Lynch syndrome. Therefore, pathologists should be aware of Lynch syndrome and their important role in identifying Lynch syndrome patients by considering appropriate tissue tests. Recently several guidelines have been published regarding when and what tissue testing is appropriate for screening patients with upper tract urothelial carcinoma.

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. Moch H, Humphrey PA, Ulbright TM, Reuter VE. W*HO 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 ureters and renal pelves. In: *Tumors of the Kidney, Bladder, and Related Urinary Structures*. *AFIP Atlas of Tumor Pathology*. Series 4. Washington, DC: American Registry of Pathology; 2004:375-379.
4. 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.
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;22:1435-1448.
6. Roupret M, Seisen T, Birtle AJ, et al. European Association of Urology Guidelines on Upper Tract Urothelial Carcinoma: 2023 Update. *Eur Urol.* 2023;84:49-64.
7. Mork M, Hubosky SG, Rouprêt M, et al. Lynch syndrome: a primer for urologists and panel recommendations. *J Urol*. 2015;194(1):21-29.
8. Lonati C, Necchi A, Rivas JG, et al. Upper tract urothelial carcinoma in the Lynch Syndrome tumour spectrum: a comprehensive overview from the European Association of Urology – Young Academic Urologists and the Global Society of Rare Genitourinary Tumors. *Eur Urol Oncol.* 2022;5:30-41.

C. Histologic Grade

Flat intraepithelial lesions and papillary and invasive lesions are graded separately.[1,2,3,4,5,6] 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 vast majority of invasive urothelial carcinoma are high-grade with uncommon cases of invasive low-grade tumors reported. 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. 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. Delahunt B, Amin MB, Hofstader F, Hartmann A, Tyczynski JE. Tumours of the renal pelvis and ureter. 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; 2004:150-153.
4. Murphy WM, Grignon DJ, Perlman EJ. Tumors of the ureters and renal pelves. In: *Tumors of the Kidney, Bladder, and Related Urinary Structures*. *AFIP Atlas of Tumor Pathology*. Series 4. Washington, DC: American Registry of Pathology; 2004:375-379.
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;22:1435-1448.
6. Mostofi FK. *Histological typing of urinary bladder tumours. In: WHO Histological Classification of Tumours.* No. 10. Geneva, Switzerland: World Health Organization; 1973.

D. Extent of Invasion

Depth of invasion and pathologic stage are the most important prognostic indicators for patients with neoplasms of the upper urinary tract.[1,2,3] A critical role of the surgical pathologist is to diagnose the depth and extent of invasion into the subepithelial connective tissue/lamina propria (pT1), muscularis propria (pT2), or beyond (pT3 or pT4). The patterns of invasion are similar to the urinary bladder, except that for renal pelvis carcinoma, the type of tumor involvement of the kidney, when present, impacts stage. Also, it is important to note that the lamina propria is absent beneath the urothelium lining the renal papillae in the pelvis and is thin along the minor calyces.

As in the urinary bladder, in papillary tumors, invasion occurs most often at the base of the tumor and very infrequently in the stalk. Tumor infiltrating the lamina propria is pT1, and like the urinary bladder, there is no accepted approach for assessing depth of lamina propria invasion. Designation of a tumor if muscularis propria muscle-invasive or not is important. Upper tract papillary urothelial carcinoma may also have inverted non-invasive growth pushing into subepithelial structures (pTa) that must be distinguished from true invasion. For renal pelvic tumors, in situ extension of carcinoma into renal collecting ducts and renal tubules does not affect stage, while carcinoma invading into the renal parenchyma is pT3. Renal pelvic carcinoma that invades through the kidney into perinephric fat is pT4. Patients with upper tract urothelial carcinoma often present at higher stage compared to patients with urinary bladder carcinoma.

References

1. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
2. Roupret M, Seisen T, Birtle AJ, et al. European Association of Urology Guidelines on Upper Tract Urothelial Carcinoma: 2023 Update. *Eur Urol.* 2023;84:49-64.
3. Gupta R, Paner GP, Amin MB. Neoplasms of the upper urinary tract: a review with focus on urothelial carcinoma of the pelvicalyceal system and aspects related to its diagnosis and reporting. *Adv Anat Pathol.* 2008;15(3):127-139.

E. Lymphatic and/or Vascular Invasion

Urothelial carcinoma may invade blood vessels or lymphatic channels.[1,2] This is an important prognostic factor in upper urinary tract urothelial carcinoma. In suspicious cases, blood vessels can be highlighted by immunohistochemical staining for factor VIII-related antigen, CD31 or CD34. Staining can help resolve the problem of differentiating lymphatic versus artifactual space formation by tumor cells, a frequent

finding seen in urothelial tumors invading the lamina propria. Retraction artifact is also prominent in micropapillary urothelial carcinoma.

References
1. Hurei S, Roupret M, Ouzzane A, et al. Impact of lymphovascular invasion on oncological outcomes in patients with upper tract urothelial carcinoma after radical nephroureterectomy. *BJU Int.* 2013;111:1199-207.
2. Novara G, Matsumoto K, Kassouf W, et al. Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper tract: an international validation study. *Eur Urol.* 2010;57:1064-71.

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. In renal pelvis, ureter, and nephroureterectomy specimens, the margins may include radial hilar soft tissue margin, bladder cuff, and ureteral, renal parenchymal, and Gerota's fascia margins, depending on the type of surgical specimen.

G. Lymph Nodes

Regional lymph nodes are not always submitted or identified in cases of resection, but evaluation of these nodes is important.[1] 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. Limited data indicate that the presence of extranodal extension may be clinically significant.

The regional lymph nodes for the renal pelvis are renal hilar, paracaval, aortic, and retroperitoneal. The regional lymph nodes for the ureter are renal hilar, iliac (common, internal [hypogastric], external), paracaval, periuereteral, and pelvic.

Involvement of lymph nodes beyond the regional lymph nodes is considered distant metastasis (M1).

References
1. Seisen T, Shariat SF, Cussenot O, et al. Contemporary role of lymph node dissection at the time of radical nephroureterectomy for upper tract urothelial carcinoma. *World J Urol.* 2017;35:535-548.

H. Pathologic Stage Classification

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

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 1)
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.

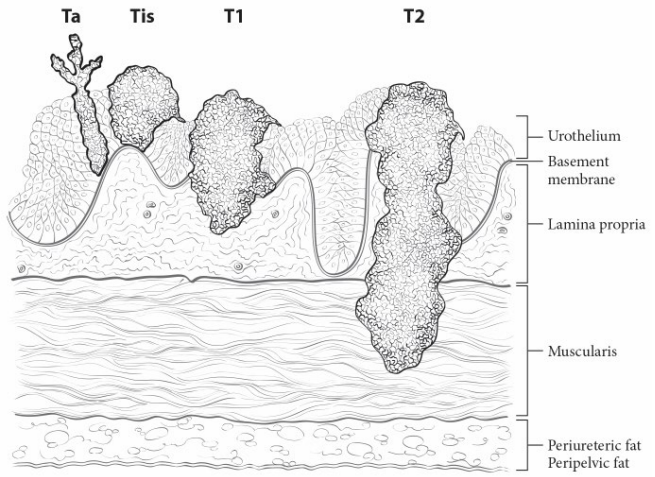

Figure 1. Depth of invasion of Ta to T2 tumors. From: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017. Reproduced with permission.

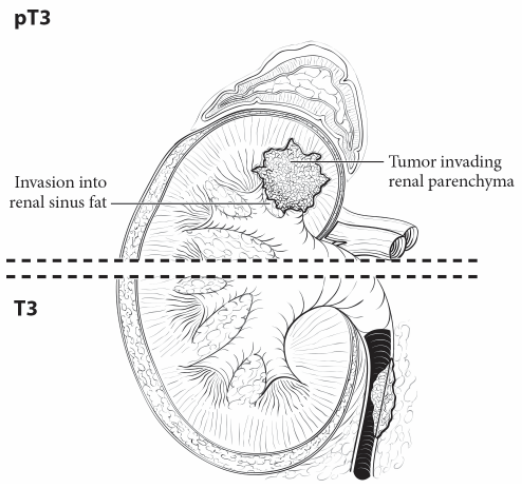

Figure 2. T3 for renal pelvis invades into renal parenchyma or peripelvic fat (above), whereas T3 for ureter invades into periureteric fat (below). From: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual. 8th ed.* New York, NY: Springer; 2017. Reproduced with permission.

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 (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.

References

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

I. Pathologic Findings in Nonneoplastic Kidney

It is important to recognize that medical kidney diseases may be present in nonneoplastic renal tissue in nephrectomy and nephroureterectomy specimens.[1,2] Arterionephrosclerosis (or hypertensive nephropathy) and diabetic nephropathy are seen in approximately 30% and 20% of cases, respectively. Other medical renal diseases that have been identified include thrombotic microangiopathy, focal segmental glomerulosclerosis, and IgA nephropathy. The findings of greater than 20% global glomerulosclerosis or advanced diffuse diabetic glomerulosclerosis are predictive of significant decline in renal function 6 months after radical nephrectomy.[2] Evaluation for medical renal disease should be performed in each case; PAS and/or Jones methenamine silver stains should applied if necessary. Consultation with a nephropathologist should be pursued as needed.

However, no studies have specifically measured peritumoral-related changes in the renal cortex. Some tumors have no peritumoral changes. Oncocytoma is the best example. While some large tumors often have a large zone of peritumoral changes compared with smaller tumors. The pseudocapsule may contain sclerotic glomeruli, tubular atrophy and show fibrointimal thickening of arteries, followed by a zone of several millimeters of acute tubular injury, none of which is representative of the cortex elsewhere.[3] A judgement whether the amount of nonneoplastic renal parenchyma is sufficient for evaluation of medical kidney diseases should be made on a case by case basis. Two studies have used 1 mm to 5 mm as the cut-off for insufficient renal parenchyma[4,5]; 5 mm of nonneoplastic renal parenchyma is a reasonable recommendation.

References

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2. Bijol V, Mendez GP, Hurwitz S, Rennke HG, Nose V. Evaluation of the nonneoplastic pathology in tumor nephrectomy specimens: predicting the risk of progressive failure. *Am J Surg Pathol.* 2006;30:575-584.
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