Protocol for the Examination of Biopsy Specimens from patients with Carcinoma of the Ureter and Renal Pelvis

Version: 2.4.0.0
Protocol Posting Date: March 2025
The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

This protocol may be used for the following procedures AND tumor types:

Procedure	Description
Biopsy	Includes specimens designated biopsy or endoscopic transurethral resection
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)

The following should NOT be reported using this protocol:

Procedure
Resection (consider the Ureter and Renal Pelvis Resection protocol)
Cytologic specimens

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

Tumor Type
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)
Sarcoma (consider the Soft Tissue protocol)
Renal cortical and medullary tumors (consider the separate Kidney protocol)

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Glossary:
Author: Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.
Expert Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements

The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Summary of Changes

v 2.4.0.0

- Content update including the addition of “Well-differentiated neuroendocrine tumor” to Histologic Type and updates to explanatory notes
- Lymphatic and / or Vascular Invasion changed from optional to core

Reporting Template
Protocol Posting Date: March 2025
Select a single response unless otherwise indicated.
CASE SUMMARY: (URETER, RENAL PELVIS: Biopsy)
This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

SPECIMEN

Specimen (Note A)
___ Renal pelvis
___ Ureter
___ Other (specify): _____
___ Not specified

Specimen Laterality
___ Right
___ Left
___ Not specified

TUMOR

Histologic Type (Note B) (select all that apply)
Urothelial
___ Papillary urothelial carcinoma, non-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)

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
___ 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)
___ Non-invasive papillary carcinoma
___ Carcinoma in situ
___ Invades subepithelial connective tissue
___ Invades muscularis
___ Invades beyond muscularis into peripelvic fat or renal parenchyma (for renal pelvis only)
___ Invades beyond muscularis into periureteric fat (for ureter only)
___ Invades adjacent organs or through the kidney into perinephric fat: _____
___ Cannot be determined: _____

Lymphatic and / or Vascular Invasion
___ Not identified
___ Present
___ Cannot be determined: _____

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

Muscularis (Note D)
___ Not identified
___ Present in specimen
___ Cannot be determined: _____

+Tumor Comment: _____

ADDITIONAL FINDINGS

+Associated Epithelial Lesions (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
___ Cautery artifact
___ Ureteritis cystica et glandularis
___ Non-keratinizing squamous metaplasia
___ Keratinizing squamous metaplasia
___ Intestinal metaplasia
___ Other (specify): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. History

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 II). 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.

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

<u>Urothelial tumors</u>

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. 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 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. 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.
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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.
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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.
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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.
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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 (T1), muscularis propria (T2). 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, 1) the lamina propria is absent beneath the urothelium lining the renal papillae in the pelvis and is thin along the minor calyces and 2) the muscularis mucosae is essentially absent in the ureter/renal pelvis and any muscle invasion is considered pT2.

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 T1, 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 (Ta) that must be distinguished from true invasion of subepithelial structures. 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 T3.

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.