Protocol for the Examination of Biopsy Specimens from Patients with Renal Cell Carcinoma

Version: 4.3.0.0

Protocol Posting Date: June 2026

The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

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

Procedure	Description
Biopsy	Includes specimens designated core needle biopsy, endoscopic biopsy, and others
Tumor Type	**Description**
Renal cell carcinomas	Includes all renal cell carcinoma subtypes

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

Procedure
Resection (use Kidney Resection protocol)
Tumor Type
Urothelial tumors (use Ureter, Renal Pelvis protocol)
Nephroblastic (Wilm's) tumors (use Wilm's Tumor Biopsy protocol)
Hematopoietic neoplasms (use the Precursor and Mature Lymphoid neoplasm, Myeloid and Mixed / Ambiguous Lineage Neoplasms or Plasma Cell Malignancies and Immunoglobulin Deposition Related Disorders protocol)
Sarcoma (use the Soft Tissue protocol)

Version Contributors

Author(s): Paari Murugan, MD, FCAP*, Robert W. Allan, MD, FCAP*, Gladell P. Paner, MD, FCAP*, Mahul B. Amin, MD, FCAP*, Jason R. Pettus, MD, FCAP*

Other Expert Contributors: John R. Srigley, MD, Sean Williamson, MD, Ying-Bei Chen, MD, PhD, Kiril Trpkov, MD, Michelle Hirsch, MD, PhD, Steven Smith, MD, PhD, Holger Moch, MD, Peter A. Humphrey, MD, PhD, Maria Carlo, MD, Viraj Master, MD, PhD, Lara R. Harik, MD, FCAP

** Denotes primary author.*

For any questions or comments, contact: cancerprotocols@cap.org.

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.

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Summary of Changes

v 4.3.0.0

- Removed the Histologic Features question to make Rhabdoid Features and Sarcomatoid Features two separate questions
- G4 Histologic Grade is now a list item, previously a list item response and GX, cannot be determined now a list item response (previously a list item)

Reporting Template

Protocol Posting Date: June 2026

Select a single response unless otherwise indicated.

CASE SUMMARY: (KIDNEY: Biopsy)

Standard(s):

This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

SPECIMEN

Procedure

___ Needle biopsy
___ Incisional biopsy
___ Other (specify): _____
___ Not specified

Specimen Laterality

___ Right
___ Left
___ Other (specify): _____
___ Not specified

TUMOR

+Tumor Site (select all that apply)

___ Upper pole
___ Middle
___ Lower pole
___ Other (specify): _____
___ Not known

Histologic Type (Note A)

Clear cell tumors
___ Clear cell renal cell carcinoma
___ Multilocular cystic renal neoplasm of low malignant potential
Papillary renal tumors
___ Papillary renal cell carcinoma
Oncocytic and chromophobe renal tumors
___ Chromophobe renal cell carcinoma
___ Other oncocytic tumors of the kidney (specify): _____
Collecting duct tumors
___ Collecting duct carcinoma
Other renal tumors
___ Clear cell papillary renal cell tumor
___ Mucinous tubular and spindle renal cell carcinoma
___ Tubulocystic renal cell carcinoma
___ Acquired cystic disease-associated renal cell carcinoma

___ Eosinophilic solid and cystic renal cell carcinoma
___ Renal cell carcinoma, NOS (unclassified)
Molecularly defined renal carcinomas
___ TFE3-rearranged renal cell carcinoma
___ TFEB-altered renal cell carcinoma
___ ELOC (formerly TCEB1)-mutated renal cell carcinoma
___ Fumarate hydratase-deficient renal cell carcinoma
___ Succinate dehydrogenase-deficient (SDH) renal cell carcinoma
___ ALK-rearranged renal cell carcinoma
___ SMARCB1-deficient renal medullary carcinoma
Other
___ Renal cell carcinoma, subtype pending additional studies
___ Other histologic type not listed (specify): _____
+Histologic Type Comment: _____

Histologic Grade (WHO / ISUP) (Note B)
See table for renal carcinoma subtype grading requirements
___ G1, nucleoli absent or inconspicuous at 400x magnification
___ G2, nucleoli conspicuous and visible at 400x magnification, not prominent at 100x magnification
___ G3, nucleoli conspicuous at 100x magnification
___ G4, extreme nuclear pleomorphism and / or multinucleated giant cells and / or rhabdoid and / or sarcomatoid differentiation
___ GX, cannot be assessed: _____
___ Not applicable: _____
+Histologic Grade Comment: _____

Rhabdoid Features (Note C)
___ Not identified
___ Present
+Specify Percentage of Rhabdoid Component: _____ %
___ Cannot be determined (explain): _____

Sarcomatoid Features (Note C)
___ Not identified
___ Present
+Specify Percentage of Sarcomatoid Component: _____ %
___ Cannot be determined (explain): _____

+Necrosis (Note D)
___ Not identified
___ Present

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

+Tumor Comment: _____

ADDITIONAL FINDINGS

+Additional Findings
___ None identified
___ Other pathology present (specify): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Histologic Type

This protocol was updated to incorporate the changes made in the 5th edition WHO Urinary and Male Genital Tumors Classification.[1]

The updated entities that should be reported using the kidney cancer protocol are listed below:

Clear cell renal tumors
- Clear cell renal cell carcinoma
- Multilocular cystic renal neoplasm of low malignant potential

Papillary renal tumors
- Papillary renal cell carcinoma

Oncocytic and chromophobe renal cell tumors
- Chromophobe renal cell carcinoma
- Other oncocytic tumors of the kidney

Collecting duct tumors
- Collecting duct carcinoma

Other renal tumors
- Clear cell papillary renal cell tumor
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic renal cell carcinoma
- Acquired cystic disease-associated renal cell carcinoma
- Eosinophilic solid and cystic renal cell carcinoma
- Renal cell carcinoma, NOS

Molecularly defined renal carcinoma
- *TFE3*-rearranged renal cell carcinomas
- *TFEB*-altered renal cell carcinomas
- *ELOC* (formerly *TCEB1*)-mutated renal cell carcinoma
- Fumarate hydratase-deficient renal cell carcinoma
- Succinate dehydrogenase-deficient renal cell carcinoma
- *ALK*-rearranged renal cell carcinomas
- *SMARCB1*-deficient renal medullary carcinoma

The changes made in the 5th WHO edition are summarized below, and the reader is encouraged to reference the updated manuscript.

Papillary renal cell carcinoma: Subclassification into type 1 and type 2 is no longer recommended. This reflects the recognition that many tumors characterized as type 2 papillary renal cell carcinoma now represent other distinct entities (e.g., Fumarate hydratase-deficient renal cell carcinoma).

Other oncocytic tumors of the kidney: This is a heterogeneous group of renal tumors with eosinophilic/ oncocytic cells with oncocytoma-like and/or chromophobe renal cell carcinoma-like features. This includes hybrid oncocytic tumors (HOCT) that may occur sporadically or associated with Birt-Hogg-Dube syndrome; the emerging entities of eosinophilic vacuolated tumor (EVT), low-grade oncocytic tumor (LOT), and other eosinophilic/oncocytic tumors with intermediate (borderline) features.

Clear cell papillary renal cell tumor (CCPRCT): Renamed from carcinoma to tumor to reflect its indolent behavior.

Eosinophilic solid and cystic renal cell carcinoma: This was recognized as a separate entity characterized by solid and cystic architecture with voluminous eosinophilic cytoplasm, frequent (but not required) keratin 20 reactivity, and typically negative keratin 7 expression. The clinical behavior is indolent in the great majority of cases, and these tumors may occur in association with tuberous sclerosis complex or sporadically. In both settings, there are alterations in the *TSC1/2* genes.

Renal cell carcinoma, NOS: This category should be reserved for carcinomas that cannot be placed into one of the morphologically and molecularly defined categories. These are usually high-grade. Low-grade oncocytic tumors that are difficult to classify should be placed in the “Other oncocytic tumors of the kidney” group.

Molecularly defined renal cell carcinoma

The category of molecularly defined renal carcinoma was added to the 5th edition WHO to include carcinomas that demonstrate characteristic molecular alterations that define these tumor types.

TFE3-rearranged renal cell carcinomas: This was formerly called Xp11 translocation renal cell carcinoma. These tumors morphologically often show mixed papillary and solid architecture, with mixed clear and eosinophilic cytoplasm, sometimes with scattered psammoma bodies. These tumors are characterized by *TFE3* rearrangements, revealed by nuclear expression of *TFE3* protein or, preferably, demonstration of *TFE3* rearrangement by break-apart FISH or sequencing methods. Other immunohistochemical markers that may be positive include variable melanocytic markers, cathepsin K, and GPNMB.

TFEB-altered renal cell carcinoma: This category encompasses renal carcinoma that possess either a *TFEB* rearrangement or *TFEB*/6p21 amplification. *TFEB* rearranged carcinomas frequently display a biphasic pattern with smaller cells clustering around basement membrane-like material surrounded by larger epithelioid cells. However, other patterns can also be present that may overlap with clear cell renal cell carcinoma, *TFE3* rearranged renal cell carcinoma, and tumors with oncocytic features. *TFEB* amplified carcinoma is less characteristic and may appear poorly differentiated and infiltrative with papillary and oncocytic features. Useful markers for detection of *TFEB* rearranged carcinomas include the melanocytic markers melan-A and HMB45, cathepsin K, or nuclear reactivity for TFEB protein. *TFEB* amplified carcinomas may also have melanocytic marker and cathepsin K positivity, and some are positive for keratin 20, overlapping with the immunohistochemical pattern of eosinophilic solid and cystic renal cell carcinoma. If a break-apart FISH method is used, *TFEB* amplified carcinomas show numerous copies of the *TFEB* region, usually without rearrangement. Other genes at 6p21, such as *VEGFA*, are typically included in the amplicon. Whereas *TFE3/TFEB* rearranged carcinomas have a tendency to occur in younger patients (although not always), *TFEB* amplified carcinomas appear to occur in older patients and have a worse prognosis.[2,3]

ELOC mutated renal cell carcinoma: The *ELOC* gene was formerly known as *TCEB1*, therefore, this tumor was formerly known as *TCEB1* mutated renal cell carcinoma. These tumors tend to be small and of low stage, with prominent fibromuscular bands, overlapping with renal cell carcinoma with leiomyomatous or fibromyomatous stroma. Keratin 7 appears to be consistently expressed, and the tumor is characterized by bi-allelic inactivation of *ELOC*. Data are limited; however, behavior appears mostly favorable.

Fumarate hydratase (FH) deficient renal cell carcinoma: This entity was previously known as hereditary leiomyomatosis and renal cell carcinoma syndrome-associated renal cell carcinoma. This is typically an aggressive tumor with variable architecture patterns (papillary, solid, tubulocystic, cribriform) with high-grade appearing cells with prominent bright red macronucleoli and perinucleolar clearing. The morphological spectrum was recently expanded to include cases with low-grade oncocytic morphology. These tumors have mutations in the fumarate hydratase (*FH*) gene which can be demonstrated by lack of FH protein expression ("loss") and 2-succinocysteine (2SC) reactivity by immunohistochemistry. Rarely, mutated tumors may show focal or patchy FH staining, presumably due to a dysfunctional protein that remains recognizable by the antibody. Most patients are thought to have germline *FH* alterations and thus the hereditary leiomyomatosis and renal cell carcinoma syndrome, accompanied also by skin and uterine leiomyomas (in females); however, a subset of tumors appear to occur due to somatic *FH* mutations in the absence of the syndrome.

Succinate dehydrogenase-deficient renal cell carcinoma: This rare renal cell carcinoma typically has bland, bubbly eosinophilic cells, overlapping with oncocytic tumors such as oncocytoma and chromophobe renal cell carcinoma. The most diagnostic finding is immunohistochemistry for *SDHB* showing abnormal absence of staining in the tumor cells ("loss") serving as a surrogate marker for SDH gene complex alterations. Contrasting to most other oncocytic tumors, these neoplasms are typically negative for KIT and entirely negative for keratin 7. Most patients have germline *SDHB* alterations and thus the hereditary SDH-deficient tumor syndrome.

ALK-rearranged renal cell carcinoma: *ALK*-rearranged renal cell carcinoma is newly included in the 5th edition WHO Classification. These tumors show variable morphology, including solid, papillary, and cribriform patterns. Mucin production is a common feature. Tumors are characterized by rearrangements of *ALK* demonstrated by positive immunohistochemistry or abnormal FISH. Although very rare, this tumor type may be particularly relevant for treatment, as *ALK* inhibitors appear to have benefit.

SMARCB1-deficient renal medullary carcinoma: *SMARCB1*-deficient renal medullary carcinoma was previously designated renal medullary carcinoma but has been brought under the umbrella of molecularly defined renal cell carcinoma. This tumor type retains the classical association with renal medullary location and strong association with sickle cell trait or rarely other hemoglobinopathies. The name was updated to include the characteristic loss of *SMARCB1* (also known as *INI1, BAF47*) demonstrable by immunohistochemistry that serves as a surrogate for *SMARCB1* inactivation on 22q11.23. An important point to emphasize is that this category should be reserved for those tumors with medullary location/phenotype that are very frequently, but not always associated with sickle cell trait. Other renal cell carcinoma subtypes, for example clear cell with sarcomatoid transformation or FH deficient renal cell carcinoma, may show secondary *SMARCB1* loss and should be categorized according to the underlying morphologic/genetic feature.

The category of "Other histologic type not listed (specify)" can be used to diagnose entities that are emerging provisional entities such as, biphasic hyalinizing psammomatous renal cell carcinoma, or thyroid-like follicular renal cell carcinoma.

In recognition of the increasing number of molecularly defined renal cell carcinomas, a category of "Renal cell carcinoma, subtype pending additional studies" has been added to the protocol. Since many pathologists will not have immediate access to the immunohistochemistry (IHC) and molecular studies required to define these rare tumors, this category facilitates preliminary sign-out while awaiting reference lab results. An addendum report should be issued on completion of the additional studies.

References

1. WHO Classification of Tumours Editorial Board. *Urinary and male genital tumours*. Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours series, 5th ed.; vol. 8). https://publications.iarc.fr/610.
2. Kammerer-Jacquet SF, Gandon C, Dugay F, et al. Comprehensive study of nine novel cases of TFEB-amplified renal cell carcinoma: an aggressive tumour with frequent PDL1 expression. *Histopathology.* 2022 Aug;81(2):228-238.
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B. Histologic Grade

Accurate grading requires an adequate sample of tissue, which is not always available from needle biopsy specimens. Tumor grade in a biopsy sample may underestimate the grade found in resection specimens, as grade is determined by the worst area encountered. This is especially true for larger tumors where heterogeneity is commonly present. However, due to the increased consideration of active surveillance, RCC tumor grading on biopsy specimens is encouraged, with the understanding that low-grade in a biopsy sample does not rule out the presence of higher-grade areas in the tumor.

The WHO/ISUP grading system has supplanted the Fuhrman system as the grading standard.[1,2] Grade should be assigned based on the highest-grade cells present in a single high-power field rather than the most predominant pattern. Grade is based upon the degree of nucleolar predominance (grades 1-3) and presence of nuclear pleomorphism including giant cells, sarcomatoid, or rhabdoid features (grade 4). This grading system has been validated for both clear cell and papillary renal cell carcinoma; however, it has not been validated for other RCC subtypes.[3,4] Nevertheless, the WHO/ISUP grade should be included for descriptive purposes. The following table[5,6] outlines the utility of grading in the different subtypes of renal carcinoma.

Category and Tumor Type	**Notes**
RCC subtypes validated for WHO/ISUP grading	
Clear cell RCC	
Papillary RCC	
RCC subtypes where WHO/ISUP grading is clearly not applicable	
Chromophobe RCC	WHO/ISUP grading is not applicable; alternative schemes have been proposed, such as chromophobe tumor grade and grading by necrosis and sarcomatoid change
TFE3-rearranged RCC	Studies show that WHO/ISUP grade may not be useful

RCC subtypes where WHO/ISUP grading is potentially useful	
SDH-deficient RCC	Low and high-grade features using Fuhrman or WHO/ISUP grading seem to be associated with outcome, suggesting the potential value of nuclear grading
Mucinous tubular and spindle cell carcinoma	
ELOC-mutated RCC[a]	
TFEB-altered RCC	WHO/ISUP grade may help separate aggressive *TFEB*-amplified RCC from *TFEB*-rearranged RCC
RCC, NOS	Includes tumors with heterogeneous morphology; providing information on nuclear grade[b] would be helpful to communicate potential prognosis to clinicians
FH-deficient RCC including HLRCC-RCC	The vast majority of tumors have high-grade[b] nuclei, in keeping with their aggressive behavior, but rare low-grade potentially indolent tumors have been reported; therefore, specifying the low-grade tumors (to distinguish from the more common high-grade tumors) may be helpful
Inherently aggressive RCC subtypes irrespective of WHO/ISUP grading	
Collecting duct carcinoma	Inherent high-grade nuclei and almost uniform aggressive clinical course in these tumor types obviates use of nuclear grading
SMARCB1-deficient renal medullary carcinoma	
RCC subtypes where WHO/ISUP grading is potentially misleading	
Tubulocystic carcinoma	Nuclear grading[b] may be problematic because of pure or predominantly high-grade–appearing nuclei despite the overall indolent behavior of tumor types
Acquired cystic disease-associated RCC	
Eosinophilic solid and cystic RCC and eosinophilic vacuolated tumor	
Renal epithelial neoplasms where low WHO/ISUP grade features are essential for accurate histological classification	
Papillary adenoma	
Multilocular cystic renal neoplasm of low malignant potential	
Clear cell papillary renal cell tumor	
Renal epithelial neoplasm with no or limited data on grading or behavior	
ALK-rearranged RCC	
Other oncocytic tumors	
Other oncocytic tumors	Other oncocytic tumors in the 5th edition WHO classification are low or high-grade tumors even though their histological features are not predictive of clinical behavior

a

FH, fumarate hydratase; HLRCC-RCC, hereditary leiomyomatosis, and renal cell carcinoma syndrome–associated renal cell carcinoma; RCC, renal cell carcinoma; SDH, succinate dehydrogenase.

[a]Formerly *TCEB1*-mutated RCC. [b]Nuclear grade: used here when a grading system is not specified in the literature, or when the data span the Fuhrman and WHO/ISUP grading systems or when they mention nuclear grade without specific criteria. WHO/ISUP grading may be generally inferred from nuclear features, with G1 and G2 tumors being low-grade and G3 and G4 tumors being high-grade.

References

1. Moch H, Humphrey PA, Ulbright TM, Reuter VE, eds. World Health Organization (WHO) Classification of Tumours: *Pathology and Genetics of the Urinary System and Male Genital Organs*. Geneva, Switzerland: WHO Press; 2016.
2. Delahunt B, Cheville JC, Martignoni G, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol.* 2013; 37:1490-1504.

3. Sika-Paotonu D, Bethwaite PB, McCredie MRE, Jordan TW, Delahunt B. Nucleolar grade but not Fuhrman grade is applicable to papillary renal cell carcinoma. *Am J Surg Pathol.* 2006; 30:1091-1096.
4. Delahunt B, Sika-Paotonu D, Bethwaite PB, et al. Grading of clear cell renal cell carcinoma should be based on nucleolar prominence. *Am J Surg Pathol.* 2011; 135:1134-1139
5. Raspollini MR, Moch H, Tan PH, et al. *Tumours of the kidney.* In: WHO Classification of Tumours Editorial Board, eds. Urinary and Male Genital Tumours. WHO Classification of Tumours. Geneva, Switzerland: WHO Press; 2022.
6. Paner GP, Chumbalkar V, Montironi R, et al. Updates in Grading of Renal Cell Carcinomas Beyond Clear Cell Renal Cell Carcinoma and Papillary Renal Cell Carcinoma. *Adv Anat Pathol.* 2022 May 1;29(3):117-130.

C. Sarcomatoid and Rhabdoid Features

Sarcomatoid and Rhabdoid features may be observed on biopsy samples of renal masses. Sarcomatoid carcinoma is not a specific morphologic or genetic subtype of renal cell carcinoma but is considered a pattern of dedifferentiation of different renal carcinoma subtypes.[1,2,3,4] Sarcomatoid change in a renal cell carcinoma is associated with an adverse outcome.[1,4] Sarcomatoid morphology may be found in any histologic subtypes of renal cell carcinomas, including clear cell, papillary, chromophobe, collecting duct, and other rare and unclassified subtypes.[1,2,3,4] When the background carcinoma subtype is recognized, it should be specified under histologic type (see Note A). Pure sarcomatoid carcinoma or sarcomatoid carcinoma associated with epithelial elements that do not conform to usual renal carcinoma cell types should be considered as renal cell carcinoma, NOS. Sarcomatoid morphology is also incorporated into the WHO/ISUP grading system as grade 4.

Rhabdoid features, like sarcomatoid features, are a characteristic of high-grade disease. Rhabdoid cells have abundant eosinophilic cytoplasm with an eccentric nucleus and often a prominent nucleolus. These cells mimic rhabdomyoblasts but do not show true skeletal muscle differentiation.[4,5,6,7] Rhabdoid features are associated with adverse outcomes, and about 25% concurrently show sarcomatoid features. Rhabdoid morphology is also by definition WHO/ISUP grade 4.[4]

References

1. WHO Classification of Tumours Editorial Board. *Urinary and male genital tumours*. Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours series, 5th ed.; vol. 8). https://publications.iarc.fr/610.
2. de Peralta-Venturina M, Moch H, Amin M, et al. Sarcomatoid differentiation in renal cell carcinoma: a study of 101 cases. *Am J Surg Pathol.* 2001; 25:275-278.
3. Cheville JC, Lohse CM, Zincke H, et al. Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome. *Am J Surg Pathol.* 2004; 28:435-441.
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5. Kuroiwa K, Kinoshita Y, Shiratsuchi H, et al. Renal cell carcinoma with rhabdoid features: an aggressive neoplasm. *Histopathology.* 2002; 41:538-548.
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D. Necrosis

Tumor necrosis is an important prognostic factor in renal cell carcinoma.[1,2,3] Necrosis on biopsy may be subject to significant sampling error; the reporting is an optional element. The prognostic significance of necrosis independent of tumor stage has been identified in clear cell and chromophobe renal cell carcinoma.[2,4] In addition, tumor-associated necrosis has been shown to be an important prognostic factor for clear cell RCC, independently of WHO/ISUP grade. The prognostic significance of necrosis in papillary renal cell carcinoma is controversial. Large papillary carcinomas commonly display cystic necrosis and yet do not exhibit extrarenal spread.[5] Tumor necrosis cannot be assessed as a prognostic factor when patients have undergone presurgical arterial embolization, as tumor-type necrosis cannot be definitively distinguished from treatment effect.

References

1. Delahunt B, Cheville JC, Martignoni G, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol.* 2013; 37:1490-1504.
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