Sponsored by ISUP

Renal Biopsy for Tumour Histopathology Reporting Guide

ICCR

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

OPERATIVE PROCEDURE (Note 1)

- ◯ Needle biopsy
- ◯ Incisional biopsy, wedge
- ◯ Other, *specify*

SPECIMEN LATERALITY (Note 2)

- ◯ Not specified
- ◯ Left
- ◯ Right
- ◯ Other (e.g., horseshoe kidney), *specify*

TUMOUR SITE (select all that apply) (Note 3)

- ☐ Upper pole
- ☐ Mid kidney
- ☐ Lower pole
- ☐ Cortex
- ☐ Medulla
- ☐ Other, *specify*

BLOCK IDENTIFICATION KEY (Note 4)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE[a] (select all that apply) (Note 5)

(Value list based on the World Health Organization Classification of Urinary and Male Genital Tumours (2022))

- ☐ Clear cell renal cell carcinoma
- ☐ Multilocular cystic renal neoplasm of low malignant potential
- ☐ Papillary renal cell carcinoma
- ☐ Chromophobe cell renal carcinoma
- ☐ Other oncocytic tumours of the kidney
- ☐ Collecting duct carcinoma
- ☐ Clear cell papillary renal cell tumour
- ☐ 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
- ☐ *TFE3*-rearranged renal cell carcinoma
- ☐ *TFEB*-altered renal cell carcinoma
- ☐ *ELOC* (formerly TCEB1)-mutated renal cell carcinoma
- ☐ Fumarate hydratase–deficient renal cell carcinoma
  - ◯ Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome–associated renal cell carcinoma
- ☐ Succinate dehydrogenase–deficient renal cell carcinoma
- ☐ *ALK*-rearranged renal cell carcinoma
- ☐ SMARCB1-deficient renal medullary carcinoma
- ☐ Other,[b] *specify*

Comments

[a] *Occasionally more than one histologic type of carcinoma occurs within the same kidney specimen. Each tumour type should be separately recorded.*

[b] *This would apply to cases that are pending additional studies to identify molecularly defined subtypes.*

DRAFT Version 2.0 Published XXXX ISBN: XXXX

PROVISIONAL HISTOLOGICAL TUMOUR GRADE (Note 6)

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Grade 1 - Nucleoli absent or inconspicuous and basophilic at 400x magnification
- ◯ Grade 2 - Nucleoli conspicuous and eosinophilic at 400x magnification, visible but not prominent at 100x magnification
- ◯ Grade 3 - Nucleoli conspicuous and eosinophilic at 100x magnification
- ◯ Grade 4 - Extreme nuclear pleomorphism and/or multi nuclear giant cells and/or rhabdoid and/or sarcomatoid differentiation

SARCOMATOID FEATURES (Note 7)

- ◯ Not identified
- ◯ Present

RHABDOID FEATURES (Note 8)

- ◯ Not identified
- ◯ Present

NECROSIS[c] (Note 9)

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present

[c] *Core element for clear cell renal cell carcinoma and chromophobe renal cell carcinoma only; in all other cases it is non-core.*

COEXISTING NON-NEOPLASTIC KIDNEY (Note 10)

- ◯ Not identified
- ◯ Present, *specify*

ANCILLARY STUDIES (Note 11)

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ Immunohistochemistry, *specify test(s) and result(s)*
  - ☐ Molecular findings, *specify test(s) and result(s)*
  - ☐ Other, *record test(s), methodology and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC).

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

⬆ Back

Scope

The dataset has been developed for biopsy specimens for neoplasms of renal tubular origin. Excision specimens are not included – a separate ICCR dataset is available and should be used for these cases.[2]

Urothelial carcinoma arising from the upper renal tract, Wilms tumours and other nephroblastic and mesenchymal tumours are not included. Metastatic tumours are excluded from this dataset. This dataset is not to be used for clearly benign tumours, such as papillary adenoma and oncocytoma. However other neoplasms of uncertain behaviour (e.g., clear cell papillary tumours, other oncocytic tumours) may be reported using this dataset.

This dataset is designed for the reporting of a single laterality of specimen i.e., left or right. If both lateralities are submitted then separate datasets should be completed.

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours, Urinary and Male Genital Tumours, 5th edition, 2022.[3] The ICCR dataset includes 5th edition Corrigenda, July 2024.[4]

Back

Note 1 – Operative procedure (Non-core)

Renal mass biopsies are most commonly obtained via core needle approach under imaging guidance in current practice. Less commonly, wedge biopsy may be performed, such as when an incidental lesion is found during kidney collection for possible organ transplantation.

Back

Note 2 – Specimen laterality (Core)

Specimen laterality information is important for correlation with clinical and imaging findings, as well as quality assurance and patient safety purposes.

Although patients may have more than one tumour, it is uncommon for multiple tumours to be biopsied at once. Often biopsy would target the largest or more clinically worrisome tumour. A rare scenario in which multiple tumours may be sampled is in presumed von Hippel Lindau syndrome patients. If, for example, more than one tumour is being monitored for growth rate, both may be sampled as part of the same procedure.

Back

Note 3 – Tumour site (Non-core)

If provided by the submitting physician, the tumour site within the kidney should be noted. However, this information is not always given.

Back

Note 4 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. In the biopsy setting, the tissue is typically small, such that it can be submitted entirely in one or two tissue blocks without any dissection.

Back

Note 5 – Histological tumour type (Core and Non-core)

Histologic diagnosis of renal epithelial neoplasms is based on the 2022 WHO Classification of Urinary and Male Genital Tumours, 5th edition (Table 1).[3] The ICCR dataset includes 5th edition Corrigenda, July 2024.[4] Occasionally more than one histologic type of carcinoma occurs within the same kidney specimen. Each tumour type should be separately recorded.

Histologic tumour type has several important clinical implications, including for prognosis, treatment, likelihood of tumour multifocality, and implications of hereditary syndromes. Clear cell RCC is the most common subtype and generally considered to have a higher risk of metastasis than the other common subtypes, such as papillary and chromophobe RCC.[5] Much of the treatment guidelines for metastatic renal cancer are centred around clear cell RCC, with most other renal cancers being considered as 'non-clear cell' for treatment purposes.[6] Clear cell papillary renal cell tumour, formerly known as clear cell papillary RCC,[7] is an example of a tumour type that closely resembles clear cell renal cell carcinoma, yet is associated with highly favourable behaviour, such that it has been relabelled as a neoplasm rather than carcinoma in the latest WHO Classification.[3] Although these tumours may mimic clear cell RCC, almost no aggressive behaviour has been described. However, they have a relatively high rate of multifocality in both end-stage and non-end-stage kidneys.[8] Similarly, papillary RCC is more prone to multifocality than clear cell RCC. Other tumour histologies on the basis of their diagnosis have a strong implication for hereditary syndromes, such as FH-deficient RCC and SDH-deficient RCC,[9-13] implying a need for close surveillance of the patient and family members for development of subsequent tumours. Additionally, some tumour types are particularly aggressive, such as FH-deficient RCC, SMARCB1-deficient renal medullary carcinoma, RCC with *TFEB* amplification, and others,[9-11] which might necessitate different therapy in the metastatic setting than clear cell and other non-clear cell RCCs.

A group of emerging types of oncocytic renal tumours has recently been recognised, including eosinophilic solid and cystic RCC, low grade oncocytic tumour, and eosinophilic vacuolated tumour.[11] These appear to have recognisable differences in histology and immunohistochemistry, although they share similarities in molecular alterations involving the *TSC1/TSC2/MTOR* genes. Like the paradigm of clear cell RCC, these appear to have hereditary forms (associated with tuberous sclerosis complex) and sporadic forms (with mutations of the same genes). It remains to be determined whether these necessitate different clinical management, particularly in the case of low grade oncocytic tumour and eosinophilic vacuolated tumour, from the closest histologic mimic, chromophobe RCC. Eosinophilic solid and cystic RCC has been included as a distinct entity in the WHO Classification,[14] whereas the others in this group would currently fall under the category of 'other oncocytic tumours of the kidney'.[15] In some instances, oncocytic tumours cannot be reliably diagnosed on a biopsy because of tumour heterogeneity. In this situation, comment should be made on the report. For tumours that are judged to be of renal cell origin but which cannot be definitively placed into a specific category, due to either unusual morphology, mixed morphology of more than one entity, pure sarcomatoid pattern without a recognisable originating tumour histology, or other reasons, the category of RCC, NOS (not otherwise specified) can be used. Given that there are an increasing number of molecularly defined renal carcinomas and many laboratories may not have rapid access to the necessary immunohistochemical or molecular techniques to verify these diagnoses, it is reasonable to use the category 'other' and specify RCC, pending additional studies for subtype.

Table 1: World Health Organization classification of renal epithelial neoplasms.[3]

Descriptor	ICD-O codes[a]
Clear cell renal tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1
Papillary renal tumours	
Papillary adenoma	8260/0
Papillary renal cell carcinoma†	8260/3
Oncocytic and chromophobe renal tumours	
Oncocytoma	8290/0
Chromophobe cell renal carcinoma	8317/3
Other oncocytic tumours of the kidney	
Collecting duct tumours	
Collecting duct carcinoma	8319/3
Other renal tumours	
Clear cell papillary renal cell tumour†	8323/1
Mucinous tubular and spindle cell carcinoma	8480/3
Tubulocystic renal cell carcinoma	8316/3
Acquired cystic disease–associated renal cell carcinoma	8316/3
Eosinophilic solid and cystic renal cell carcinoma	8311/3
Renal cell carcinoma, NOS	8312/3
Molecularly defined renal carcinomas	
TFE3-rearranged renal cell carcinoma	8311/3
TFEB-altered renal cell carcinoma	8311/3
ELOC (formerly TCEB1)-mutated renal cell carcinoma	8311/3
Fumarate hydratase–deficient renal cell carcinoma	8311/3
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome–associated renal cell carcinoma	8311/3
Succinate dehydrogenase–deficient renal cell carcinoma	8311/3
ALK-rearranged renal cell carcinoma	
SMARCB1-deficient renal medullary carcinoma	8510/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third Edition, second revision (ICD-O-3.2).[16] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries. Subtype labels are indented. Incorporates all relevant changes from the 5th edition Corrigenda, July 2024.[4]

† Labels marked with a dagger constitute a change in terminology of a previous code.

Back

Note 6 – Provisional histological tumour grade (Core)

In the biopsy setting, histologic grading is not final, but provisional because it can change in the nephrectomy specimen due to frequent heterogeneity in renal cancer. Histologic grade of renal cancer is best validated in clear cell RCC and papillary RCC.[17,18] The currently accepted WHO/International Society of Urological Pathology (ISUP) grading system[19,20] utilises nucleolar prominence, rather than the multiple nuclear parameters of the prior Fuhrman grading system.[19,20] Nucleoli visible/prominent at 10x objective magnification define grade 3, whereas nucleoli that are prominent only at higher magnification warrant grade 2. If nucleoli are inconspicuous/absent even at high magnification (40x), this warrants nuclear grade 1. Grade 4 includes sarcomatoid or rhabdoid features, as well as bizarre multilobate nuclei. There is no consensus on the area of higher-grade tumour required to assign said grade. Some studies have used an entire high-magnification field as the threshold.[21]

The WHO/ISUP grading system[19,20] is relevant to clear cell and papillary RCC; however, less data exist for other tumour types.[22] For chromophobe RCC, some alternative grading systems have been proposed, considering that these tumours typically have variable nuclei, yet they are classically favourable. However, no validated grading system for chromophobe carcinoma is currently available, and it is typically appropriate to indicate that grade is 'not applicable' for this tumour type, unless an alternate grade is required by institutional protocols or clinical trials. The 2022 WHO Classification notes that grade may not be useful for *TFE3* rearranged RCC, and may be misleading for tumours such as tubulocystic RCC, acquired cystic kidney disease-associated RCC, eosinophilic solid and cystic RCC, and eosinophilic vacuolated tumour, which have prominent nucleoli despite usually favourable behaviour.[23] In these scenarios, there is no universal agreement as to whether a descriptive grade should be provided, despite the lack of prognostic value, or if 'not applicable' should be used.

Tumours such as collecting duct carcinoma, SMARCB1-deficient renal medullary carcinoma, and FH-deficient RCC are typically considered inherently aggressive, and thus should be considered aggressive independent of grade.[23] In other histologic subtypes of RCC, it is reasonable to provide a grade, with the caveat that grading has not been validated in tumour subtypes other than clear cell and papillary RCC. Indicating that grade 'cannot be determined' should be rarely chosen, as it is unlikely that a tumour can be diagnosed as RCC but grade cannot be assessed. One scenario might be if there is no viable tumour post-treatment, but the tumour was thought to be, or proven to be, a RCC pre-treatment.[24]

Back

Note 7 – Sarcomatoid features (Core)

The term sarcomatoid features is synonymous with sarcomatoid changes, morphology and (de) differentiation. Sarcomatoid features should be noted in the pathology report if identified. This change can be present with any RCC subtype,[10,25] and is thought to be not a unique subtype but a form of de-differentiation in a high grade disease.[10,25,26] The presence of sarcomatoid features warrants a WHO/ISUP grade 4 diagnosis in the clear cell RCC and papillary RCC (the types that generally conform to conventional WHO/ISUP grading).[10,25] If the underlying RCC subtype is identified in the lower grade areas, then it should be labelled as the specific RCC subtype with sarcomatoid differentiation. If the tumour is composed entirely of sarcomatoid morphology and the workup confirms a tumour of renal epithelial origin then it can be diagnosed as a RCC, NOS with sarcomatoid features. Sarcomatoid change constitutes a very aggressive RCC disease with most tumours being stage IV disease upon diagnosis,[25,27] and these tumours are associated with a significantly increased risk of death.[28] Recent evidence has shown thar RCCs with sarcomatoid change often benefit significantly from immune checkpoint therapy.[10,25,29-31] These dedifferentiated tumours also commonly overexpress PD-L1, and have increased immune infiltrates in the tumour microenvironment.[29,31]

Back

Note 8 – Rhabdoid features (Core)

The term rhabdoid features, similar to sarcomatoid features, is synonymous with rhabdoid change(s), morphology, and (de)differentiation. Rhabdoid features, similar to sarcomatoid change is regarded as a sign of de-differentiation of high grade tumours and is associated with poor disease outcome.[29,32] Rhabdoid and sarcomatoid morphologies are often present in the same tumours.[32] Rhabdoid differentiation can also be associated with any RCC subtype, but it is more commonly associated with clear cell RCC.[32] It also constitutes a WHO/ISUP grade 4.[10] Rhabdoid morphology is defined by non-cohesive polygonal/round cells with eccentric high grade nuclei and eosinophilic cytoplasmic inclusions.[32] Generally, rhabdoid differentiation is less studied than its sarcomatoid counterpart but is regarded empirically by many to be synonymous with the sarcomatoid differentiation.[29] Studies have often lumped the sarcomatoid and rhabdoid RCC as one category.[29] There is also some evidence that rhabdoid RCC might respond to immune checkpoint therapy.[29]

Back

Note 9 – Necrosis (Core)

The presence of histological tumour necrosis has been shown to be a prognostic indicator for clear cell RCC and chromophobe renal cell carcinoma independent of tumour stage.[20,33-39] Papillary renal cell carcinoma often contains foci of necrosis; however, the prognostic significance of this is debated.[33,40,41] The presence of microscopic tumour-type (granular) necrosis, defined as the existence of granular nuclear and cytoplasmic debris,[36,37,42,43] should be recorded for clear cell carcinoma and chromophobe renal cell carcinoma if present (core). At present, it is non-core for the remainder of histological tumour types due to limited data, but it is recommended that the presence of necrosis be recorded. For patients who have undergone pre-surgical renal embolization, the degree of tumour-associated necrosis cannot be assessed, because thromboembolic infarction results in coagulative necrosis, which is difficult to distinguish from tumour-associated necrosis.[44] Likewise, the presence of and extent of necrosis in tumours that have been treated with neoadjuvant therapies (immune checkpoint inhibitors, targeted therapies, ablative therapies, etc.) likely loses its relevance, as it is usually not possible to discern tumour necrosis from treatment response. In the biopsy setting, necrosis cannot be comprehensively evaluated due to sampling; however, if necrosis is present, it should be noted.

Back

Note 10 – Coexisting non-neoplastic kidney (Non-core)

If a biopsy performed for mass/neoplasm shows unequivocal histologic feature of a medical renal disease like amyloidosis or diabetic nephropathy, it is appropriate to report these findings.[45-49] However, changes such as glomerular sclerosis and interstitial fibrosis should be interpreted with caution due to the possibility of distortion by mass effect.

Back

Note 11 – Ancillary studies (Non-core)

While there are no established predictive markers for treatment response, ancillary tests for diagnostic/ prognostic purposes should be performed in selected cases, especially to identify molecularly defined renal carcinoma subtypes. It may be reasonable to defer advanced molecular studies for tumour resection in the biopsy setting.

Ancillary studies, particularly immunohistochemistry, fluorescence in situ hybridisation (FISH), cytogenetics/ copy number assessment, and next-generation sequencing (NGS), are of help in the diagnosis of selected tumour types. However, in many cases, diagnosis can be achieved without the need for any of these methodologies, especially in the most common types, including clear cell, papillary, and chromophobe RCC.[9]

Some helpful immunohistochemical markers include PAX8 (or PAX2) for confirmation that a tumour is of renal cell origin, with caveat that some upper tract urothelial carcinomas are also positive for this marker.[50] Carbonic anhydrase 9 (CA9) is a helpful marker to support that a tumour is clear cell RCC. However, this should be utilised with caution when 1) renal cell origin is not certain (it can be positive in non-renal carcinomas); and 2) positivity can be present in tumours or tissues with ischemia/necrosis, due to the role of this protein in the hypoxia pathway.[9] Clear cell RCC usually shows diffuse circumferential membrane positivity, so focal staining for this marker may be interpreted as equivocal or negative, especially when only present adjacent to areas of necrosis or in the tips of papillary structures.

Other markers with major diagnostic roles include staining for FH and 2SC, which support diagnosis of FH-deficient RCC (abnormal negative and positive nuclear, respectively), and SDHB, which supports a diagnosis of SDH-deficient RCC (abnormal negative).[9] Abnormal negative staining for SMARCB1 (INI1) would support a diagnosis of SMARCB1-renal medullary carcinoma (in a patient with hemoglobinopathy) or RCC, NOS with medullary phenotype (in the absence of hemoglobinopathy).[51,52] Cathepsin K, TFE3, and TFEB proteins may be used to support the diagnosis of*TFE3*-rearranged RCC and *TFEB*-altered RCC.[9,53] However, cathepsin K is only positive in a subset of translocation tumours and TFE3/TFEB proteins have some technical challenges in staining.[9,53] In general, a positive FISH result for *TFE3* or *TFEB* is highly supportive of the diagnosis of *TFE3*-rearranged RCC and *TFEB*-altered RCC.

A subset of *TFE3* gene fusions may be subtle or negative using FISH due to intrachromosomal inversion within the X chromosome, such as gene partners *NONO, RBM10, RBMX*, and *GRIPAP1*.[9,54] As such, NGS methods such as anchored multiplex fusion testing may be superior for recognising tumours with such cryptic fusions/rearrangements. Although confirmation of these diagnoses is desirable, it is probably reasonable in low resource settings to regard a tumour with suspicious features and negative CA9 as non-clear cell RCCs or suspicious for translocation carcinomas. It is also reasonable to report a tumour with these studies pending using the 'other' category and 'renal cell carcinoma, pending additional studies for subtype'.

A group of emerging oncocytic renal tumours has been found to have recurrent gene alterations in *TSC1*, *TSC2,* and *MTOR*.[11] Similarly, in the setting of a metastatic renal cancer, where confirmation of clear cell RCC is desired prior to therapy initiation or enrolment in a clinical trial, molecular testing with recognition of *VHL* or related gene alterations may be helpful.[9] Usage of conventional cytogenetics or copy number testing can also help to recognise the common chromosomal alterations of RCC types, such as 3p loss in clear cell RCC, multiple chromosomal losses in chromophobe RCC, or trisomy 7/17 in papillary RCC.

⬆ Back

References

1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.

2 International Collaboration on Cancer Reporting (2024). *Renal epithelial neoplasms Histopathology Reporting Guide. 2nd edition*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/renal-tubular/ (Accessed TBC 2024).

3 WHO Classification of Tumours Editorial Board (2022). *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8*, IARC Publications, Lyon.

4 WHO Classification of Tumours Editorial Board (2022). *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8 - Corrigenda July 2024. Available from:* file:///C:/Users/fleurw/Downloads/Uro5%20Corrigenda%20doc_2024-07-08%20(1).pdf (Accessed 2nd August 2024).

5 Amin MB, Amin MB, Tamboli P, Javidan J, Stricker H, de-Peralta Venturina M, Deshpande A and Menon M (2002). Prognostic impact of histologic subtyping of adult renal epithelial neoplasms: an experience of 405 cases. *Am J Surg Pathol* 26(3):281-291.

6 National Comprehensive Cancer Network (NCCN) (2021). *NCCN Clinical Practice Guidelines in Oncology - Kidney Cancer*. Version 2.2024. Available from: https://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf (Accessed 8th July 2024).

7 Williamson SR (2021). Clear cell papillary renal cell carcinoma: an update after 15 years. *Pathology* 53(1):109-119.

8 Cheville J, Helenon O, Hes O and Kapur P (2022). *Clear cell papillary renal tumour*. In: *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8*, WHO Classification of Tumours Editorial Board (ed), IARC Publications, Lyon.

9 Williamson SR, Gill AJ, Argani P, Chen YB, Egevad L, Kristiansen G, Grignon DJ and Hes O (2020). Report From the International Society of Urological Pathology (ISUP) Consultation Conference on Molecular Pathology of Urogenital Cancers: III: Molecular Pathology of Kidney Cancer. *Am J Surg Pathol* 44(7):e47-e65.

10 Trpkov K, Hes O, Williamson SR, Adeniran AJ, Agaimy A, Alaghehbandan R, Amin MB, Argani P, Chen YB, Cheng L, Epstein JI, Cheville JC, Comperat E, da Cunha IW, Gordetsky JB, Gupta S, He H, Hirsch MS, Humphrey PA, Kapur P, Kojima F, Lopez JI, Maclean F, Magi-Galluzzi C, McKenney JK, Mehra R, Menon S, Netto GJ, Przybycin CG, Rao P, Rao Q, Reuter VE, Saleeb RM, Shah RB, Smith SC, Tickoo S, Tretiakova MS, True L, Verkarre V, Wobker SE, Zhou M and Gill AJ (2021). New developments in existing WHO entities and evolving molecular concepts: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. *Mod Pathol* 34(7):1392-1424.

11 Trpkov K, Williamson SR, Gill AJ, Adeniran AJ, Agaimy A, Alaghehbandan R, Amin MB, Argani P, Chen YB, Cheng L, Epstein JI, Cheville JC, Comperat E, da Cunha IW, Gordetsky JB, Gupta S, He H, Hirsch MS, Humphrey PA, Kapur P, Kojima F, Lopez JI, Maclean F, Magi-Galluzzi C, McKenney JK, Mehra R, Menon S, Netto GJ, Przybycin CG, Rao P, Rao Q, Reuter VE, Saleeb RM, Shah RB, Smith SC, Tickoo S, Tretiakova MS, True L, Verkarre V, Wobker SE, Zhou M and Hes O (2021). Novel, emerging and provisional renal entities: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. *Mod Pathol* 34(6):1167-1184.

12 Gill AJ (2018). Succinate dehydrogenase (SDH)-deficient neoplasia. *Histopathology* 72(1):106-116.

13 Carlo MI, Hakimi AA, Stewart GD, Bratslavsky G, Brugarolas J, Chen YB, Linehan WM, Maher ER, Merino MJ, Offit K, Reuter VE, Shuch B and Coleman JA (2019). Familial Kidney Cancer: Implications of New Syndromes and Molecular Insights. *Eur Urol*.

14 Argani P, McKenney JK, Hartmann A, Hes O, Magi-Galluzzi C and Trpkov K (2022). *Eosinophilic solid and cystic renal cell carcinoma*. In: *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8*, WHO Classification of Tumours Editorial Board (ed), IARC Publications, Lyon.

15 Hartmann A, Gill AJ, He H, Kryvenko ON, Ohashi R and Tretiakova M (2022). *Other oncocytic tumours of the kidney*. In: *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8*, WHO Classification of Tumours Editorial Board (ed), IARC Publications, Lyon.

16 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM and Whelan S (eds) (2020). *International Classification of Diseases for Oncology, Third edition, Second revision ICD-O-3.2*. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577 (Accessed 16th August 2024).

17 Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, Egevad L, Algaba F, Moch H, Grignon DJ, Montironi R, Srigley JR and Members of the IRTP (2013). The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol* 37(10):1490-1504.

18 Delahunt B, Eble JN, Egevad L and Samaratunga H (2019). Grading of renal cell carcinoma. *Histopathology* 74(1):4-17.

19 Raspollini MR, Moch H, Tan PH, Amin MB and Turajlic S. *Renal cell tumours: Introduction*. In: *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8*, WHO Classification of Tumours Editorial Board (ed), IARC Publications, Lyon.

20 Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, Egevad L, Algaba F, Moch H, Grignon DJ, Montironi R, Srigley JR and the members of the ISUP Renal Tumor Panel (2013). The International Society of Urological Pathology (ISUP) Grading System for Renal Cell Carcinoma and Other Prognostic Parameters. *Am J Surg Pathol.* 37:1490-1504.

21 Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL and Zincke H (2002). An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. *J Urol* 168(6):2395-2400.

22 Paner GP, Chumbalkar V, Montironi R, Moch H and Amin MB (2022). Updates in Grading of Renal Cell Carcinomas Beyond Clear Cell Renal Cell Carcinoma and Papillary Renal Cell Carcinoma. *Adv Anat Pathol* 29(3):117-130.

23 REPEAT OF 19 TO BE REMOVED Raspollini MR, Moch H, Tan PH, Amin MB and Turajlic S. *Renal cell tumours: Introduction*. In: *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8*, WHO Classification of Tumours Editorial Board (ed), IARC Publications, Lyon.

24 Hwang MJ, Brennan PM, Monge BM, Alkamachi B, Rohra P, Peshoff MM, Sharma P, Sircar K, Tamboli P and Rao P (2024). Best practices and recommendations for grossing and reporting of post-immunotherapy nephrectomy specimens: a single-institution experience of 70 cases. *Diagnostic Histopathology* 30(5):275-281.

25 Blum KA, Gupta S, Tickoo SK, Chan TA, Russo P, Motzer RJ, Karam JA and Hakimi AA (2020). Sarcomatoid renal cell carcinoma: biology, natural history and management. *Nat Rev Urol* 17(12):659-678.

26 Manley BJ and Hsieh JJ (2016). Sarcomatoid renal cell carcinoma: genomic insights from sequencing of matched sarcomatous and carcinomatous components. *Transl Cancer Res* 5(Suppl 2):S160-s165.

27 Wang Z, Kim TB, Peng B, Karam J, Creighton C, Joon A, Kawakami F, Trevisan P, Jonasch E, Chow CW, Canales JR, Tamboli P, Tannir N, Wood C, Monzon F, Baggerly K, Varella-Garcia M, Czerniak B, Wistuba I, Mills G, Shaw K, Chen K and Sircar K (2017). Sarcomatoid Renal Cell Carcinoma Has a Distinct Molecular Pathogenesis, Driver Mutation Profile, and Transcriptional Landscape. *Clin Cancer Res* 23(21):6686-6696.

28 Zhang BY, Thompson RH, Lohse CM, Leibovich BC, Boorjian SA, Cheville JC and Costello BA (2015). A novel prognostic model for patients with sarcomatoid renal cell carcinoma. *BJU Int* 115(3):405-411.

29 Hahn AW, Lebenthal J, Genovese G, Sircar K, Tannir NM and Msaouel P (2022). The significance of sarcomatoid and rhabdoid dedifferentiation in renal cell carcinoma. *Cancer Treat Res Commun* 33:100640.

30 Tannir NM, Signoretti S, Choueiri TK, McDermott DF, Motzer RJ, Flaifel A, Pignon JC, Ficial M, Frontera OA, George S, Powles T, Donskov F, Harrison MR, Barthélémy P, Tykodi SS, Kocsis J, Ravaud A, Rodriguez-Cid JR, Pal SK, Murad AM, Ishii Y, Saggi SS, McHenry MB and Rini BI (2021). Efficacy and Safety of Nivolumab Plus Ipilimumab versus Sunitinib in First-line Treatment of Patients with Advanced Sarcomatoid Renal Cell Carcinoma. *Clin Cancer Res* 27(1):78-86.

31 Motzer RJ, Banchereau R, Hamidi H, Powles T, McDermott D, Atkins MB, Escudier B, Liu LF, Leng N, Abbas AR, Fan J, Koeppen H, Lin J, Carroll S, Hashimoto K, Mariathasan S, Green M, Tayama D, Hegde PS, Schiff C, Huseni MA and Rini B (2020). Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade. *Cancer Cell* 38(6):803-817.e804.

32 Kuroda N, Karashima T, Inoue K, Kasajima A, Ohe C, Kawakami F, Mikami S, Matsuura K, Moriyama M, Nagashima Y, Petersson F, Lopez JI, Cohen RJ, Michal M and Hes O (2015). Review of renal cell carcinoma with rhabdoid features with focus on clinical and pathobiological aspects. *Pol J Pathol* 66(1):3-8.

33 Cheville JC, Lohse CM, Zincke H, Weaver AL and Blute ML (2003). Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. *Am J Surg Pathol* 27(5):612-624.

34 Amin MB, Paner GP, Alvarado-Cabrero I, Young AN, Stricker HJ, Lyles RH and Moch H (2008). Chromophobe renal cell carcinoma: histomorphologic characteristics and evaluation of conventional pathologic prognostic parameters in 145 cases. *Am J Surg Pathol* 32(12):1822-1834.

35 Delahunt B, McKenney JK, Lohse CM, Leibovich BC, Thompson RH, Boorjian SA and Cheville JC. (2013). A novel grading system for clear cell renal cell carcinoma incorporating tumor necrosis. *Am J Surg Pathol* 37: 311-322.

36 Dagher J, Delahunt B, Rioux-Leclercq N, Egevad L, Coughlin G, Dunglison N, Gianduzzo T, Kua B, Malone G, Martin B, Preston J, Pokorny M, Wood S and Samaratunga H (2019). Assessment of tumour-associated necrosis provides prognostic information additional to World Health Organization/International Society of Urological Pathology grading for clear cell renal cell carcinoma. *Histopathology* 74(2):284-290.

37 Ohashi R, Martignoni G, Hartmann A, Caliò A, Segala D, Stöhr C, Wach S, Erlmeier F, Weichert W, Autenrieth M, Schraml P, Rupp NJ, Ohe C, Otsuki Y, Kawasaki T, Kobayashi H, Kobayashi K, Miyazaki T, Shibuya H, Usuda H, Umezu H, Fujishima F, Furusato B, Osakabe M, Sugai T, Kuroda N, Tsuzuki T, Nagashima Y, Ajioka Y and Moch H (2020). Multi-institutional re-evaluation of prognostic factors in chromophobe renal cell carcinoma: proposal of a novel two-tiered grading scheme. *Virchows Arch* 476(3):409-418.

38 Klatte T, Said JW, de Martino M, Larochelle J, Shuch B, Rao JY, Thomas GV, Kabbinavar FF, Belldegrun AS and Pantuck AJ (2009). Presence of tumour necrosis is not a significant predictor of survival in clear cell renal cell carcinoma: higher prognostic accuracy of extent based rather than presence/absence classification. *J Urol* 181:1558-1564.

39 Delahunt B, Srigley JR, Egevad L and Montironi R (2014). International Society of Urological Pathology grading and other prognostic factors for renal neoplasia. *Eur Urol* 66(5):795-798.

40 Yang C, Shuch B, Kluger H, Humphrey PA and Adeniran AJ (2020). High WHO/ISUP Grade and Unfavorable Architecture, Rather Than Typing of Papillary Renal Cell Carcinoma, May Be Associated With Worse Prognosis. *Am J Surg Pathol* 44(5):582-593.

41 Chan E, Stohr BA, Butler RS, Cox RM, Myles JL, Nguyen JK, Przybycin CG, Reynolds JP, Williamson SR and McKenney JK (2022). Papillary Renal Cell Carcinoma With Microcystic Architecture Is Strongly Associated With Extrarenal Invasion and Metastatic Disease. *Am J Surg Pathol* 46(3):392-403.

42 Tan PH, Cheville JC, Williamson SR, et al. (2022). *Clear cell renal cell carcinoma*. In: *Urinary and Male Genital Tumours, WHO Classification of Tumours, 5th edition, Volume 8*, WHO Classification of Tumours Editorial Board (ed), IARC Publications, Lyon.

43 Samaratunga H, Delahunt B, Srigley JR, Berney DM, Cheng L, Evans A, Furusato B, Leite KRM, MacLennan GT, Martignoni G, Moch H, Pan CC, Paner G, Ro J, Thunders M, Tsuzuki T, Wheeler T, van der Kwast T, Varma M, Williamson SR, Yaxley JW and Egevad L (2020). Granular necrosis: a distinctive form of cell death in malignant tumours. *Pathology* 52(5):507-514.

44 Collins J and Epstein JI (2017). Prognostic significance of extensive necrosis in renal cell carcinoma. *Hum Pathol* 66:108-114.

45 Bijol V, Mendez GP, Hurwitz S, Rennke HG and Nosé V (2006). Evaluation of the nonneoplastic pathology in tumor nephrectomy specimens: predicting the risk of progressive renal failure. *Am J Surg Pathol* 30(5):575-584.

46 Bonsib SM and Pei Y (2010). The non-neoplastic kidney in tumor nephrectomy specimens: what can it show and what is important? *Adv Anat Pathol* 17(4):235-250.

47 Henriksen KJ, Meehan SM and Chang A (2007). Non-neoplastic renal diseases are often unrecognized in adult tumor nephrectomy specimens: a review of 246 cases. *Am J Surg Pathol* 31(11):1703-1708.

48 Sarsık B, Simşir A, Yılmaz M, Yörükoğlu K and Sen S (2013). Spectrum of nontumoral renal pathologies in tumor nephrectomies: nontumoral renal parenchyma changes. *Ann Diagn Pathol* 17(2):176-182.

49 Truong LD, Shen SS, Park MH and Krishnan B (2009). Diagnosing nonneoplastic lesions in nephrectomy specimens. *Arch Pathol Lab Med* 133(2):189-200.

50 Reuter VE, Argani P, Zhou M, Delahunt B and Members of the ISUP Immunohistochemistry in Diagnostic Urologic Pathology Group (2014). Best practices recommendations in the application of immunohistochemistry in the kidney tumors: report from the International Society of Urologic Pathology consensus conference. *Am J Surg Pathol* 38(8):e35-49.

51 Ohe C, Smith SC, Sirohi D, Divatia M, de Peralta-Venturina M, Paner GP, Agaimy A, Amin MB, Argani P, Chen YB, Cheng L, Colecchia M, Compérat E, Werneck da Cunha I, Epstein JI, Gill AJ, Hes O, Hirsch MS, Jochum W, Kunju LP, Maclean F, Magi-Galluzzi C, McKenney JK, Mehra R, Nesi G, Osunkoya AO, Picken MM, Rao P, Reuter VE, de Oliveira Salles PG, Schultz L, Tickoo SK, Tomlins SA, Trpkov K and Amin MB (2018). Reappraisal of Morphologic Differences Between Renal Medullary Carcinoma, Collecting Duct Carcinoma, and Fumarate Hydratase-deficient Renal Cell Carcinoma. *Am J Surg Pathol* 42(3):279-292.

52 Sirohi D, Smith SC, Ohe C, Colombo P, Divatia M, Dragoescu E, Rao P, Hirsch MS, Chen YB, Mehra R and Amin MB (2017). Renal cell carcinoma, unclassified with medullary phenotype: poorly differentiated adenocarcinomas overlapping with renal medullary carcinoma. *Hum Pathol* 67:134-145.

53 Martignoni G, Gobbo S, Camparo P, Brunelli M, Munari E, Segala D, Pea M, Bonetti F, Illei PB, Netto GJ, Ladanyi M, Chilosi M and Argani P (2011). Differential expression of cathepsin K in neoplasms harboring TFE3 gene fusions. *Mod Pathol* 24(10):1313-1319.

54 Gandhi JS, Malik F, Amin MB, Argani P and Bahrami A (2020). MiT family translocation renal cell carcinomas: A 15th anniversary update. *Histol Histopathol* 35(2):125-136.