

Family/Last name Date of birth Given name(s) Patient identifiers Date of request Accession/Laboratory number Elements in **black text** are **CORE**. Elements in **grey text** are **NON-CORE**.

SCOPE OF THIS DATASET

 indicates multi-select values     indicates single select values**PRE-OPERATIVE TREATMENT** (select all that apply) (Note 1)

- Tumour embolisation
- Cryoablation
- Radio frequency ablation
- External-beam radiation therapy (EBRT)
- Neoadjuvant systemic therapy
- Other, *specify*

**OPERATIVE PROCEDURE** (Note 2)

- Not specified
- Radical nephrectomy
- Total (simple) nephrectomy
- Partial nephrectomy
- Other, *specify*

**SPECIMEN LATERALITY** (Note 3)

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

**ACCOMPANYING/ATTACHED STRUCTURES** (select all that apply) (Note 4)

- Not submitted
- Adrenal gland
- Lymph nodes, *specify*

 Other organs, *specify***TISSUE REMOVED FROM SPECIMEN PRIOR TO SUBMISSION** (Note 5)

- No
- Yes, *specify*

**TUMOUR SITE** (select all that apply) (Note 6)

- Upper pole
- Mid zone
- Lower pole
- Cortex
- Medulla
- Other, *specify*

**TUMOUR FOCALITY** (Note 7)

- Cannot be assessed
- Unifocal
- Multifocal

Specify number of tumours **MAXIMUM TUMOUR DIMENSION** (Note 8)*(If multiple tumours the maximum dimension of up to the largest five should be recorded)*

- 
- Cannot be assessed

Tumour 1  mm    Tumour 4  mmTumour 2  mm    Tumour 5  mmTumour 3  mm**BLOCK IDENTIFICATION KEY** (Note 9)*(List overleaf or separately with an indication of the nature and origin of all tissue blocks)***HISTOLOGICAL TUMOUR TYPE<sup>a</sup>** (select all that apply) (Note 10)*(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

**HISTOLOGICAL TUMOUR TYPE<sup>a</sup> (Note 10) continued**

- 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,<sup>b</sup> *specify*

Comments

<sup>a</sup> Occasionally more than one histologic type of carcinoma occurs within the same kidney specimen. Each tumour type should be separately recorded.

<sup>b</sup> This would apply to cases that are pending additional studies to identify molecularly defined subtypes.

**HISTOLOGICAL TUMOUR GRADE (WHO/ISUP) (Note 11)**

- 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 12)**

- Not identified
- Present



**Extent of sarcomatoid component (Note 13)**

%

**RHABDOID FEATURES (Note 14)**

- Not identified
- Present

**NECROSIS<sup>c</sup> (Note 15)**

- Indeterminate
- Not identified
- Present



**Extent of necrosis**

(Applicable to clear cell renal cell carcinoma only)

%

<sup>c</sup> Core element for clear cell renal cell carcinoma and chromophobe renal cell carcinoma only; in all other cases it is non-core.

**EXTENT OF INVASION (Note 16)**

- Tumour limited to the kidney**

**Tumour in perinephric fat**

- Cannot be assessed
- Not identified
- Present

**Tumour in renal sinus**

- Cannot be assessed
- Not identified
- Present in fat and/or vascular spaces in the renal sinus

**Tumour extends beyond Gerota's fascia**

- Cannot be assessed
- Not identified
- Present

**Tumour in major veins (renal vein or its segmental branches, inferior vena cava)**

- Cannot be assessed
- Not identified
- Present

**Tumour in renal vein wall**

- Not identified
- Present

**Tumour in pelvicalyceal system**

- Cannot be assessed
- Not identified
- Present

**Tumour in adrenal gland**

- Cannot be assessed
- Adrenal gland not present
- Not identified
- Present
  - Direct extension
  - Metastasis

**Tumour in other organs/structures**

- Not identified
- Present, *specify site(s)*

**LYMPHOVASCULAR INVASION IN ADJACENT KIDNEY (Note 17)**

- Not identified
- Present

**MARGIN STATUS (Note 18)**

- Cannot be assessed
- Not involved
- Involved (select all that apply)
  - Renal parenchymal margin (partial nephrectomy only)
  - Renal capsular margin (partial nephrectomy only)
  - Perinephric fat margin (partial nephrectomy only)
  - Gerota's fascial margin
  - Renal vein margin
  - Ureteral margin
  - Other, *specify*

**LYMPH NODE STATUS** (Note 19) No nodes submitted or found

Number of lymph nodes examined

 Not involved Involved

Number of positive lymph nodes

 Number cannot be determined

Size of largest focus

 mm**Extranodal extension<sup>d</sup>** Not identified Present<sup>d</sup> Extranodal extension is synonymous with extracapsular extension/spread.**COEXISTING PATHOLOGY IN NON-NEOPLASTIC KIDNEY** (select all that apply) (Note 20) Not identified Insufficient tissue for evaluation (<5 mm tissue adjacent to the tumour) Tubular (papillary) adenoma(s) Glomerular disease, *specify type* Tubulointerstitial disease, *specify type* Vascular disease, *specify type* Cyst(s), *specify type* Other, *specify***ANCILLARY STUDIES** (Note 21) 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***PATHOLOGICAL STAGING (UICC TNM 8<sup>th</sup> edition)<sup>e</sup>** (Note 22)**TNM Descriptors** (only if applicable) (select all that apply) m - multiple primary tumours at a single site r - recurrent tumours after a disease free period y - classification is performed during or following multimodality treatment**Primary tumour (pT)** TX<sup>f</sup> Primary tumour cannot be assessed T0 No evidence of primary tumour T1 Tumour 7 cm or less in greatest dimension, limited to kidney T1a Tumour 4 cm or less T1b Tumour more than 4 cm but not more than 7 cm T2 Tumour more than 7 cm in greatest dimension, limited to kidney T2a Tumour more than 7 cm but not more than 10 cm T2b Tumour more than 10 cm, limited to the kidney T3 Tumour extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia T3a Tumour extends into the renal vein or its segmental branches, or invades pelvicalyceal system, or tumour invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia T3b Tumour extends into the vena cava below the diaphragm T3c Tumour extends into the vena cava above the diaphragm or invades the wall of the vena cava T4 Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)**Regional lymph nodes (pN)** NX<sup>f</sup> Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Metastasis in regional lymph node(s)**Distant metastasis (pM)** Not applicable M1 Distant metastasis<sup>e</sup> Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8<sup>th</sup> Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 12<sup>th</sup> July 2024).<sup>f</sup> TX and NX should be used only if absolutely necessary.

## 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<sup>1</sup>). 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). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

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.

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## Scope

This dataset has been developed for excision specimens of the kidney. 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.

Biopsy specimens are not included – a separate ICCR dataset is available and should be used for these cases.<sup>2</sup>

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, 5<sup>th</sup> edition, 2022.<sup>3</sup> The ICCR dataset includes 5<sup>th</sup> edition Corrigenda, July 2024.<sup>4</sup>

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## **Note 1 – Pre-operative treatment (Non-core)**

Preoperative treatments may alter the gross and microscopic appearance of the tumour. Tumour embolization may result in patchy or extensive necrosis, and embolization material may be observable in blood vessels. Immediately following tumour ablation, cells have been reported to be eosinophilic with loss of cell borders.<sup>5</sup> However, there are scant data on histologic appearances long after ablation. In some settings, nephrectomy after immune checkpoint inhibitor therapy may be increasingly seen. Although there are also limited data on tumour morphology post-immunotherapy, some reports have found that the tumour cells may be overrun by inflammatory cells to the point that neoplastic cells are almost obscured.<sup>6,7</sup>

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## **Note 2 – Operative procedure (Core)**

Partial nephrectomy specimens consist of only part of the kidney, ranging from enucleation with minimal to no adjacent normal tissue to larger resections that include part of the renal sinus fat or renal pelvis. Perinephric fat may be attached or detached, depending on whether the surgeon has removed it for visualisation.

Radical nephrectomy is removal of the entire kidney for tumour or presumptive tumour, typically extending to the Gerota fascia, containing the kidney, perinephric fat, renal sinus tissue, renal artery, renal vein, and a length of ureter. The adrenal gland may or may not be included. Regional lymphadenectomy is not generally performed, even with a radical nephrectomy. A few lymph nodes may occasionally be present in the renal hilum around major vessels. Other regional lymph nodes (e.g., paracaval, para-aortic, and retroperitoneal) may be submitted separately if there is clinical suspicion of involvement.

A total (also known as simple) nephrectomy also constitutes removal of the entire kidney. However, the operative indication is usually presumptively benign disease. With a total (simple) nephrectomy, the resection may not necessarily extend to the Gerota fascia.

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## **Note 3 – Specimen laterality (Core)**

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

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## Note 4 – Accompanying/attached structures (Core)

The most common attached structures with a radical nephrectomy specimen are the ipsilateral adrenal gland and lymph nodes in the hilar area. In the past, radical nephrectomy routinely included the adrenal gland; however, in current practice, removal of the adrenal gland is not routine.<sup>8,9</sup> The European Association of Urology guidelines indicate that ipsilateral adrenalectomy should not be performed if there is no clinical evidence of invasion.<sup>10</sup> Rarely, adrenal-renal fusion causes the adrenal gland to be adherent to, or intermingled with, the renal parenchyma. Specific anatomic regions of lymph nodes are also not necessarily resected unless they appear abnormal by clinical or imaging findings. If additional lymph node sites are not specifically dissected, the search of the hilar region only identifies lymph nodes in a minority of specimens (20% in one study).<sup>9,11,12</sup> Other adjacent structures are rarely removed with the kidney but may be resected if the tumour is adherent or invading them, such as the liver or spleen.

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## Note 5 – Tissue removed from specimen prior to submission (Non-core)

The pathologist should be made aware of any tissue removed from the specimen prior to examination, the manner in which it has been removed (biopsy, for example), and both what has been removed and the site from which it has been removed. This should be stated on the specimen request form. Preferably, removal of samples for tissue banking and similar functions should be performed with the assistance of the pathologist, so that diagnosis, staging, and margin assessment are not compromised.

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## Note 6 – Tumour site (Non-core)

The site of the tumour within the kidney should be stated in the macroscopic description for a nephrectomy specimen. This facilitates correlation with the radiology and may provide relevant information for support of a particular diagnosis, for example medullary location of a tumour could support diagnosis of SMARCB1-deficient deficient renal medullary carcinoma or collecting duct carcinoma.<sup>3</sup>

For partial, total and radical nephrectomy specimens, information regarding the location of the tumour in relation surgical margins should be documented. Tumour location in relation to the renal sinus, collecting system, renal capsule is important for staging purposes.

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## Note 7 – Tumour focality (Core and Non-core)

Multifocality of tumours within a specimen should be specified (core). Multifocality of tumours is a feature of some of the genetic tumour syndromes that can be associated with renal cell carcinoma (RCC) and can be a clue to their diagnosis, for example von Hippel-Lindau syndrome, Birt Hogg Dube syndrome, hereditary papillary RCC, *BAP1* tumour predisposition syndrome.<sup>3</sup> Other genetic tumour syndromes are more characteristically (although not exclusively) associated with unifocal RCCs (SDH-deficient RCC, FH-deficient RCC in the context of hereditary leiomyomatosis and RCC syndrome). Multiple tumours can also be seen in the setting of tuberous sclerosis and acquired cystic kidney disease, and may be of discordant subtype. Less

commonly multifocal RCCs can be encountered in a sporadic setting (4.3-25%).<sup>13</sup> There may be an increased risk of recurrent disease following nephron-sparing surgery in patients with multifocal and bilateral RCC.<sup>13</sup>

The number of tumours should be specified (non-core). The ISUP consensus meeting recommendation is for the documentation of the tumour dimensions for the largest 5 tumours,<sup>13</sup> and for the provision of the diagnostic and prognostic parameters associated with the most significant tumours. Papillary adenomas should not be counted in the 'number of tumours' but the presence and number may be mentioned separately.

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## **Note 8 – Maximum tumour dimension (Core and Non-core)**

Accurate reporting of renal mass size is imperative for staging and prognostication of RCC. Accordingly, the maximum dimension of a tumour is the sole defining feature for the pT1 and pT2 categories for the TNM staging classification.<sup>14-17</sup> For RCC, tumour size has been found to correlate with outcome as a continuous variable.<sup>16,18</sup> Most importantly, there is clear evidence that as tumours increase in size, especially beyond 70 millimetres (mm), there is high risk for extension into hilar and/or perinephric soft tissue.<sup>16,17,19-21</sup> Measurement of tumour size should be undertaken following detailed dissection of the gross specimen (longitudinally and horizontally) and the greatest dimension should be recorded.

It is recommended that dimensions be recorded for up to the largest five tumours. However, only the largest dimension is required (core) for staging purposes.<sup>13,20</sup> A well circumscribed mass with multinodularity should be considered as unifocal. (It is prudent to consider the possibility that the secondary nodules represent large nodules within veins/vein branches.) However, discrete masses of similar subtype in separate poles of the kidney (multifocal) should be measured separately and a range of sizes can be included.<sup>13,20</sup> It is relevant to provide separate individual greatest tumour dimensions for each mass if they are of varying subtype, or if the highest grade or highest stage tumour is not the largest. Tumour extending into extracapsular tissue and/or the renal sinus, in continuity with the primary tumour is conventionally included in the measurement. However, tumour within the renal vein is typically not included in this measurement, since some tumours may have a polypoid so-called 'tumour thrombus' that extends to the vena cava or rarely, the heart.

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## **Note 9 – Block identification key (Non-core)**

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise, in which case a subsequent reviewer would not have seen the gross specimen and would need to know the anatomic sites from which samples were taken for staging purposes. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.

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## Note 10 – 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, 5<sup>th</sup> edition (Table 1).<sup>3</sup> The ICCR dataset includes 5<sup>th</sup> edition Corrigenda, July 2024.<sup>4</sup> 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.<sup>22</sup> 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.<sup>23</sup> Clear cell papillary renal cell tumour, formerly known as clear cell papillary RCC,<sup>24</sup> 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. 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.<sup>25</sup> 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,<sup>26-30</sup> 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,<sup>26-28</sup> 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.<sup>28</sup> 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,<sup>31</sup> whereas the others in this group would currently fall under the category of ‘other oncocytic tumours of the kidney’.<sup>32</sup> 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.<sup>3</sup>**

Descriptor	ICD-O codes <sup>a</sup>
<i>Clear cell renal tumours</i>	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1
<i>Papillary renal tumours</i>	
Papillary adenoma	8260/0
Papillary renal cell carcinoma†	8260/3
<i>Oncocytic and chromophobe renal tumours</i>	
Oncocytoma	8290/0
Chromophobe cell renal carcinoma	8317/3
Other oncocytic tumours of the kidney	
<i>Collecting duct tumours</i>	
Collecting duct carcinoma	8319/3
<i>Other renal tumours</i>	
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
<i>Molecularly defined renal carcinomas</i>	
<i>TFE3</i> -rearranged renal cell carcinoma	8311/3
<i>TFEB</i> -altered renal cell carcinoma	8311/3
<i>ELOC</i> (formerly <i>TCEB1</i> )-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
<i>ALK</i> -rearranged renal cell carcinoma	
<i>SMARCB1</i> -deficient renal medullary carcinoma	8510/3

<sup>a</sup> These morphology codes are from the International Classification of Diseases for Oncology, third Edition, second revision (ICD-O-3.2).<sup>33</sup> 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 5<sup>th</sup> edition Corrigenda, July 2024.<sup>4</sup>

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

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## Note 11 – Histological tumour grade (WHO/ISUP)(Core)

Histologic grade of renal cancer is best validated in clear cell RCC and papillary RCC.<sup>34,35</sup> The currently accepted WHO/International Society of Urological Pathology (ISUP) grading system<sup>19,20</sup> utilises nucleolar prominence, rather than the multiple nuclear parameters of the prior Fuhrman grading system.<sup>19,20</sup> 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.<sup>36</sup>

The WHO/ISUP grading system<sup>37,38</sup> is relevant to clear cell and papillary RCC; however, less data exist for other tumour types.<sup>39</sup> 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.<sup>37</sup> 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.<sup>37</sup> 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.<sup>7</sup>

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## Note 12 – 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,<sup>27,40</sup> and is thought to be not a unique subtype but a form of de-differentiation in a high grade disease.<sup>27,40,41</sup> 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).<sup>27,40</sup> 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,<sup>40,42</sup> and these tumours are associated with a significantly increased risk of death.<sup>43</sup> Recent evidence has shown that RCCs with sarcomatoid change often benefit significantly from immune checkpoint therapy.<sup>27,40,44-46</sup> These dedifferentiated tumours also commonly overexpress PD-L1, and have increased immune infiltrates in the tumour microenvironment.<sup>44,46</sup>

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## Note 13 – Extent of sarcomatoid component (Non-core)

The percentage of sarcomatoid differentiation should be reported if possible. Some studies have shown that the percentage of sarcomatoid component is associated with worse prognosis in univariate and multivariate survival analysis.<sup>43,47,48</sup> A cutoff as low as 10% has been shown to be significantly associated with worse overall survival.<sup>47</sup> One study found that each increase of 10% of the sarcomatoid component increases the risk of death by 6%.<sup>43</sup>

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## Note 14 – 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.<sup>29,32</sup> Rhabdoid and sarcomatoid morphologies are often present in the same tumours.<sup>49</sup> Rhabdoid differentiation can also be associated with any RCC subtype, but it is more commonly associated with clear cell RCC.<sup>49</sup> It also constitutes a WHO/ISUP grade 4.<sup>27</sup> Rhabdoid morphology is defined by non-cohesive polygonal/round cells with eccentric high grade nuclei and eosinophilic cytoplasmic inclusions.<sup>49</sup> Generally, rhabdoid differentiation is less studied than its sarcomatoid counterpart but is regarded empirically by many to be synonymous with the sarcomatoid differentiation.<sup>44</sup> Studies have often lumped the sarcomatoid and rhabdoid RCC as one category.<sup>44</sup> There is also some evidence that rhabdoid RCC might respond to immune checkpoint therapy.<sup>44</sup>

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## Note 15 – Necrosis (Core and Non-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.<sup>38,50-56</sup> Papillary renal cell carcinoma often contains foci of necrosis; however, the prognostic significance of this is debated.<sup>50,57,58</sup> The presence of microscopic tumour-type (granular) necrosis, defined as the existence of granular nuclear and cytoplasmic debris,<sup>53,54,59,60</sup> 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.<sup>61</sup> 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.

It has been shown that tumour necrosis >10% is associated with a less favourable outcome, whereas for TNM stage 1 and 2 tumours a cutpoint of 20% of the area of the tumour showing necrosis has been suggested to have prognostic significance.<sup>62</sup> Extensive necrosis in low grade RCC has been suggested to be associated with a more favourable prognosis, although most of the tumours in this study were of non-clear cell type.<sup>61</sup> At present, the prognostic significance of the amount of necrosis within a tumour is uncertain. Despite this, it has been recommended that this be recorded as a percentage, if possible (non-core).<sup>38,56</sup>

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## Note 16 – Extent of invasion (Core and Non-core)

Extrarenal invasion includes invasion of perirenal fat, renal sinus including renal sinus fat and/or lymphovascular invasion (LVI), and renal vein or its large branches (core). Extent of invasion in renal cancer has prognostic significance and is one of the main contributors to tumour staging, in addition to tumour size. A main pathway of extrarenal extension, especially for clear cell renal cancer, is involvement of the renal sinus (the hilar fat that surrounds the collecting system and blood supply), which may manifest as involvement of blood vessels (vein branches and/or LVI) within the sinus soft tissue, or as direct infiltration of fat.<sup>21,63,64</sup>

In clear cell renal cancer, as the tumour size increases above 50 millimetres (mm), there is a marked increase in the incidence of sinus invasion, such that >90% of tumours over 70 mm invade the sinus.<sup>21</sup> Therefore, it is judicious to consider more extensive sampling of the renal sinus interface for larger clear cell tumours. Although this invasion may be subtle, evidence suggests that it is prognostically significant. One study found a higher frequency of underdiagnosed sinus invasion in patients with small tumours who died of metastatic RCC, compared to a control group of patients who did not die of metastatic RCC.<sup>65</sup> Another study suggested that recurrence-free and cancer-specific survival decrease with increasing extent of vein branch invasion from the segmental branches to the main renal vein.<sup>66</sup> In non-clear cell tumours, it is more tenable for tumours to be large without involving the sinus, such as chromophobe and papillary subtypes.<sup>67</sup>

A pattern of invasion in renal cancer that differs from that of many other cancer types is the finger-like protrusion of large tumour nodules into vein branches, including the main renal vein and vena cava, rarely even up to the level of the atrium of the heart. This pattern of invasion, although often macroscopically obvious, may be microscopically deceptive, as intravenous tumour nodules in the sinus but not main renal vein may be so large that they are misinterpreted as multinodular or multifocal tumour rather than intravascular spread.<sup>20,67,68</sup> Involvement of blood vessels (vein branches and/or LVI) within the sinus soft tissue is regarded as pT3. Sinus invasion, vein branch invasion, perinephric invasion, and main renal vein invasion all constitute pT3a (see **NOTE 22 – PATHOLOGICAL STAGING**). In view of the complex vascularity in the renal sinus, including the intrarenal portion, any amount of LVI is considered pT3a.

Invasion of the renal vein lumen and all other parameters of Extent of invasion are core, whereas invasion of the renal vein wall is non-core. Invasion of the vena cava wall affects stage categories pT3b and pT3c, which are driven by level of vena cava involvement (extension above the diaphragm or not) and muscular wall invasion. Involvement of the renal pelvis/collecting system was not addressed in prior TNM staging systems. However, in the most recent TNM staging, it has been included as another form of pT3a.<sup>14,15</sup> Specific definitions of what constitutes renal pelvis invasion have not yet been described. However, tumour in the renal pelvis lumen should typically be considered pT3a. Tumour involving the adrenal gland is subdivided into direct invasion (pT4) and discontinuous involvement/metastasis (pM1).

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## Note 17 – Lymphovascular invasion in adjacent kidney (Non-core)

Lymphovascular invasion (LVI) in this note is defined as involvement of intrarenal or perirenal small vessels without mural smooth muscle (lymphatic or vascular). Intratumoral small vessel involvement is difficult to reliably determine in highly vascular neoplasms and is not included here. Small vessel LVI should be separated from invasion of large veins (renal vein and/or main branches) and vessel involvement in the renal sinus, both of which constitute criteria for category pT3a disease.<sup>20</sup>

A few studies attempting to assess small vessel invasion as a separate parameter found it was significantly associated with an increased risk of metastasis and adverse disease-free and cancer-specific survival rates on univariate analyses. Limitations include variable definitions of LVI and inclusion of intratumoral vessel involvement in some studies.<sup>69-72</sup> Tumours with LVI were also associated with more aggressive features such as high grade and stage disease and sarcomatoid features.<sup>71,72</sup> LVI was also an indicator of worse outcome on multivariate analyses in pT1 and pT2 tumours.<sup>70,71</sup> Although studies are limited, reporting of LVI as separate parameter is recommended (non-core).

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## **Note 18 – Margin status (Core)**

The most relevant margins in renal cancer specimens are the renal parenchymal margin for partial nephrectomy specimens and the renal vein margin for radical nephrectomy specimens. Although it is also prudent to examine other margins, such as the ureter, renal artery, and perinephric fat surfaces, it is much rarer for these to be involved by tumour. Extensive inking of all perinephric fat in large nephrectomy specimens is probably unnecessary, except in areas of suspected tumour adherence. However, in partial nephrectomy specimens the parenchymal margins should be inked. Ink on the fibrous pseudo capsule does not represent a positive margin. The latter requires tumour cells in direct contact with ink. Even though this situation does not necessarily imply that there is residual tumour left in the patient. In partial nephrectomy, the perinephric fat is often dissected away from the renal capsule to allow visualisation of the renal contour for tumour localisation during surgery. The surgeon or pathologist would likely encounter substantial difficulty in separating this fat from the renal capsule in the event of true soft tissue infiltration, so unexpected positive soft tissue margin in the perinephric soft tissue (including Gerota fascia) is rare.

In some specimens, the renal capsule may be disrupted due to laparoscopic extraction or other specimen handling. However, usually it is reasonable to regard the margin as negative if the perinephric fat, whether attached or detached, shows no infiltration. When tumour abuts the parenchymal margin in partial nephrectomy specimens, it is appropriate to regard this as a positive margin. However, it is rare for there to be residual tumour in the remaining kidney after grossly complete surgical resection, so surveillance is usually undertaken rather than completion nephrectomy for microscopic positive margin. In some patients, this may reflect that the tumour protrudes into a space, such as a vascular lumen or the renal pelvis. As such, there would be no additional tissue adherent to the tumour for the surgeon to remove. However, the tumour would be abutting the inked margin, causing interpretation as a positive margin.

In radical nephrectomy, tumour that involves the main renal vein may protrude from the vein margin after removal of the surgical staples or clips, due to retraction of the vein wall and polypoid growth of tumour into the lumen. Convention is that this protrusion beyond the vein edge does not constitute a positive margin unless tumour cells are microscopically adherent to or invading the vein wall at the margin.<sup>68,73</sup> So, it is reasonable to sample the vein margin either by amputating the vein edge in cross section with the tumour thrombus in the lumen, then microscopically examining for adherence/invasion of the tumour into the wall, or alternatively, to cut the freely mobile vein edge in a strip without the luminal tumour and examine microscopically for any tumour cells adherent to the wall.

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## Note 19 – Lymph node status (Core and Non-core)

At autopsy, regional lymph node metastasis is observed in about 20% of patients with metastatic RCC, which is less frequent than metastasis to the lung (75%), liver and bone (40%) and soft tissue (35%).<sup>74</sup> According to the current TNM staging system, only patients with (N1) and without (N0) affected lymph nodes are distinguished. Up to 10% of RCC patients with nephrectomy are nodal positive.<sup>75</sup>

In general, patients with exclusive lymph node involvement show a significantly worse prognosis compared with patients without metastatic disease.<sup>76,77</sup> Patients with T1 and T2 primary carcinomas with lymph node metastases have worse outcome than those with T3 RCC without metastases.<sup>78,79</sup> Probability of metastasis of small organ-confined RCC to regional lymph nodes (renal hilar, preaortic, para-aortic, retroaortic, interaortocaval, precaval, paracaval, and retrocaval) is deemed small.<sup>80,81</sup> Therefore, regional lymph node resection is infrequently performed at most institutions, because its therapeutic benefit is unclear. In a prospective randomised phase 3 trial managed by the European Organization for Research and Treatment of Cancer (EORTC),<sup>82</sup> radical nephrectomy with complete lymphadenectomy was compared with radical nephrectomy alone. No survival advantage of complete lymph node dissection in conjunction with radical nephrectomy could be demonstrated. Moreover, performing a lymphadenectomy routinely after proper preoperative staging would result in unnecessary overtreatment of 96% of patients.<sup>9</sup>

Lymph node status (number of lymph nodes present and number positive) is a core element, since there is clear prognostic value for lymph node-positive patients. However, size of largest metastatic focus and extra nodal extension has not been fully validated to provide additional prognostic information, so these elements are non-core.

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## Note 20 – Coexisting pathology in non-neoplastic kidney (Core)

In addition to renal cancer, there may be clinically significant findings in the non-tumour tissue of nephrectomy specimens. Some of the diagnoses that have been noted in tumour nephrectomy specimens include vascular sclerosis/hypertensive changes, diabetes, amyloidosis, atheroembolic disease, thrombotic microangiopathy, sickle cell nephropathy, focal segmental glomerulosclerosis (FSGS), IgA nephropathy, and collapsing glomerulopathy, among others.<sup>83-87</sup> Therefore, it is helpful during gross examination to select at least one area that appears most normal, away from the tumour for histologic evaluation of medical renal disease. In some patients, especially with benign or low risk tumour histologies, a diagnosis such as amyloidosis may be more clinically impactful than the renal neoplasm. However, in partial nephrectomy specimens with scant adjacent benign renal parenchyma, it is probably wise to be judicious in rendering definitive diagnoses, as the zone immediately surrounding the tumour is thought to have changes related to the tumour pseudocapsule and obstruction that may not reflect the kidney as a whole.<sup>84</sup> It has been proposed that less than 5 mm of adjacent renal parenchyma may be used as a cutoff as insufficient for evaluation of nonneoplastic disease.<sup>88</sup>

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## Note 21 – 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.

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.<sup>26</sup>

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.<sup>89</sup> 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.<sup>26</sup> 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).<sup>26</sup> 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).<sup>90,91</sup> Cathepsin K, TFE3, and TFEB proteins may be used to support the diagnosis of *TFE3*-rearranged RCC and *TFEB*-altered RCC.<sup>26,92</sup> However, cathepsin K is only positive in a subset of translocation tumours and TFE3/TFEB proteins have some technical challenges in staining.<sup>26,92</sup> 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*.<sup>26,93</sup> 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*.<sup>28</sup> 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.<sup>26</sup> 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.

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## Note 22 – Pathological staging (Core)

The pathological primary tumour (T), regional lymph node (N) and distant metastasis (M) categories are considered as generic required (core) elements for most ICCR cancer datasets. Staging data should be assessed according to the 8<sup>th</sup> edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) Cancer Staging Manual.<sup>13-17,19,20,94,95</sup>

Staging of kidney carcinomas are based on size (pT1 and pT2) and extent beyond the kidney (pT3 and pT4). Tumours that are limited to the kidney and measure up to 7 centimetres (cm) in greatest dimension are considered pT1, with substaging (pT1a and pT1b) based on size up to or more than 4 cm, respectfully. Similarly, pT2 tumours measure greater than 7 cm and are limited to the kidney; substaging pT2 tumours includes size greater than 7 cm and up to 10 cm (pT2a) and size greater than 10 cm (pT2b).

Extension of tumour beyond the kidney is characteristic of pT3 disease. This can occur in three ways: (i) tumour extends into the venous system (i.e., renal vein, renal vein branch, or the vena cava. This no longer is required to be grossly identified, as per the 8<sup>th</sup> edition of the UICC/AJCC Cancer Staging Manual;<sup>14,15</sup> (ii) tumour invades through the renal capsule into perinephric adipose tissue and/or it invades sinus ( hilar) adipose tissue and/or vessels; and/or (iii) tumour invades the pelvicalyceal system. It should be noted that multiple studies have shown that most, but not all kidney tumours greater than 7 cm extend beyond the confines of the kidney (i.e., pT3).<sup>19,21</sup> All of the latter are considered pT3a, except extension into the vena cava below and above the diaphragm which are considered pT3b and pT3c, respectively. Invasion of the vena cava wall also constitutes pT3c. Accordingly, careful examination and sampling of the renal hilum are paramount to accurate kidney tumour staging and prognostication. Tumour extension beyond the Gerota fascia or directly into the adrenal gland or other structures is considered pT4 disease, whereas hematogenous spread to the adrenal gland or to other sites is M1 disease.

Renal neoplasms of low or unknown malignant potential (e.g., clear cell papillary tumour, other oncocytic tumours) can be staged according to TNM.

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