



Standards and datasets for reporting cancers

Dataset for histopathological reporting of adult renal parenchyma neoplasms

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NICE has accredited the process used by The Royal College of Pathologists to produce its cancer datasets. Accreditation is valid for 5 years from 25 July 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

For full details on our accreditation visit: www.nice.org.uk/accreditation.

Foreword

The cancer datasets published by The Royal College of Pathologists (RCPATH) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 90% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The stakeholders consulted for this document were:

- British Association of Urological Surgeons (BAUS)/BAUS Section of Oncology
- British Uro-oncology Group
- British Association of Urological Pathologists (BAUP).

Supporting evidence and recommendations in this dataset are based on:

- PubMed literature searches (up to December 2016)
- World Health Organisation (WHO) classification, 2016¹
- NICE *Improving Outcomes Guidance*, 2002²
- International Collaboration on Cancer Reporting (ICCR) Renal Cancer datasets^{3,4}
- *TNM classification of malignant tumours* (7th and 8th editions)^{5,6} from the Union for International Cancer Control (UICC).

Evidence was sought by review of the previous dataset, Cumulative Index to Nursing and Allied Health (CINAHL) and PubMed searches reviewing recent articles on risk factors associated with renal cancer. Recent review articles on renal cancer were also reviewed. Strength of the data was assessed by the modified Scottish Intercollegiate Guidelines (SIGN) – see Appendix J.

Most of the supporting evidence is level C or D at least or meets the good practice point (GPP) criteria (see explanation of levels of evidence in Appendix J). No major conflicts in the evidence have been identified and any minor discrepancies between evidence have been resolved by expert consensus.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset.

A formal revision cycle for all cancer datasets takes place on a 3-yearly basis. However, each

year, the College will ask the author of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Clinical Effectiveness Department, Working Group on Cancer Services and Lay Governance Group and placed on the College website for consultation with the membership from 12 October to 9 November 2017. All comments received from the Working Group and membership will be addressed by the author to the satisfaction of the Chair of the Working Group and the Director of Publishing and Engagement.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness Department and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

Although kidney cancer is less common than other urological tumours, such as bladder or prostate cancer, it has a higher mortality rate. It is the seventh most common cancer in the UK and is more common in men than in women (3:2). In 2014, there were 12,523 new diagnoses and 4,421 deaths, accounting for 3% of all UK cancer deaths.⁷ The incidence rate has continued to rise, possibly through incidental detection in radiological investigations for other diseases. Up to 30% of patients present with metastatic disease,⁸ with less than 5% having a solitary metastasis. The recurrence rate is approximately 30% for disease that is localised at the time of nephrectomy.⁹ Around 60% of patients will have a major surgical resection as part of their treatment, with radical nephrectomy being the standard curative treatment for localised tumours that are not amenable to nephron-sparing surgery (partial nephrectomy).¹⁰ Effective treatment of metastatic disease is still a challenge, having a 5-year survival rate of less than 10%. The most common sites for metastases are lymph nodes, liver, brain, bone, the adrenal glands and lungs. Metastases may also occur at unusual sites many years after the initial diagnosis. The use of cytokine-based immunotherapy for advanced disease (interleukin-2 or interferon-alpha) has been limited by cytotoxicity. Targeted therapies against molecular signalling pathways active in clear cell renal cell carcinoma (RCC), such as the vascular endothelial growth factor and mammalian target of rapamycin pathways have shown some efficacy through clinical trials and newer immunotherapy approaches using immune checkpoint inhibitors (e.g. targeted programme death-1 pathway – PD1/PDL1) show promise.^{11–13} For papillary RCCs, treatment with MET inhibitors is the subject of clinical trials.

The management of renal tumours is the responsibility of the local multidisciplinary team (MDT). Patients referred centrally for surgery, according to the NICE guidance, *Improving Outcomes in Urological Cancers* (www.nice.org.uk), should include those with tumours involving the vena cava or heart, limited metastatic disease that might be amenable to resection, bilateral disease, hereditary disease (e.g. von Hippel-Lindau disease), those with tumours suitable for nephron-sparing surgery (partial nephrectomy), those for entry into clinical trials (including adjuvant therapy) and for patients requiring dialysis. Alternatives to surgery, such as surveillance or radiofrequency ablation, may also be considered for small

tumours in patients for whom nephrectomy/partial nephrectomy are not the preferred options and for those considered unfit to undergo surgical procedures. In such cases a biopsy should ideally be performed to ascertain the diagnosis and inform the management decision.

The NICE guidance further recommends that members of urological cancer teams should have specialised skills appropriate for their roles at each level of the service and that there should be a nominated lead pathologist for urological pathology. It is expected that the pathologists in a uropathology reporting team will participate in the national Uropathology External Quality Assessment (EQA) Scheme (www.histopathologyeqa.org). For difficult cases, referral pathways should also be established within each cancer network.

The tumour stage is the most important prognostic factor for determining patient outcome from RCC.^{14,15} Algorithms or nomograms, which incorporate this and multiple other pathological and clinical features, have been developed to stratify patients according to risk and to provide more accurate prognostic information than stage or grade alone.^{16–22} There is an increasing trend to tailor follow-up regimens according to the level of risk of recurrence and progression, as defined by these algorithms, benefiting patients at low risk by reducing the frequency of imaging and therefore radiation exposure. These algorithms also aim to identify patients at increased risk of developing metastatic disease, and who may therefore benefit from adjuvant treatment in the context of clinical trials. Increased accrual of patients into trials is part of the national NHS strategy to improve outcomes in cancer. Identification of patients eligible for trial entry is an important component of the MDT meeting, and part of the national cancer standards. Pathologists play a key role in the MDT and thorough standardised macroscopic and microscopic assessment of surgical specimens is therefore essential for appropriate clinical management.

This dataset applies to the pathological assessment of adult renal parenchymal tumours. It is the third edition of the dataset, following publication of the second edition in 2006.²³ It excludes those tumours arising in the renal pelvis, as these are included in the RCPATH *Dataset for tumours of the urinary collecting system*.²⁴ These pathology guidelines are based upon current factors used in clinical management. Some of these factors, such as the TNM staging system, were derived historically from consensus rather than an unbiased evidence base, but have subsequently received a degree of external validation. Therefore this dataset, though not based on a full evidence review, reflects current best clinical practice.

In 2012, the International Society of Urological Pathology (ISUP) held a consensus conference in Vancouver, Canada, on the classification and grading of renal tumours and handling and reporting of nephrectomy specimens.^{25–30} Consensus agreement on the topics discussed was defined as 65% or more agreement by the participants. In 2016, the WHO published an updated classification of urological tumours.¹ The ICCR recently published datasets for reporting of renal tumours in nephrectomy and biopsy specimens.^{3,4} These publications, previously published dissection protocols and guidance,^{15,31–33} and the previous edition of this dataset²³ form the basis of the best-practice recommendations contained within this third edition of the dataset. The 7th edition of the UICC TNM staging system (TNM 7) is recommended for use at the time of publication.⁵ The 8th editions of the American Joint Committee on Cancer (AJCC) and UICC staging systems published in early 2017 differ on a number of aspects of pathological staging criteria for some cancer sites.^{6,34} Following publication of errata that has resolved the main differences between the two regarding renal tumours, the RCPATH Working Group on Cancer Services has recommended that from 1 January 2018 the UICC TNM 8th edition (TNM 8) should be used. Details of both are given in Appendix A. Where there are differences between the two editions, these are highlighted in the relevant sections of text that follow. Where the two versions are the same, the term 'TNM' is used without specification of the edition.

1.1 Target users and health benefits of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons and oncologists, cancer registries and the National Cancer Intelligence Network. Standardised cancer reporting and MDT working reduce the risk of histological misdiagnosis and help to ensure that clinicians have all of the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer specific data also provides information for healthcare providers and epidemiologists, and facilitates international benchmarking and research.

The health benefits of conformity to the guidelines and reasons for adoption include:

- subtyping, grading and staging of renal tumours to determine subsequent optimal clinical management and follow-up
- consistent reporting of pathological risk factors, which vary depending on the tumour subtype and clinical context, to allow patients to make informed decisions about their care
- adoption of a consistent approach to classification and risk assessment of renal cancers, which is essential for audit and epidemiological studies.

2 Clinical information required on the specimen request form

Specification of the specimen laterality and the type of surgical procedure (biopsy, partial nephrectomy, simple or radical nephrectomy) are required. Information on whether the specimen has been obtained via an open, robotic or laparoscopic surgical approach may also be useful for audits of margin status. Indicating whether or not the ipsilateral adrenal gland is included with a radical nephrectomy is required information for the pathologist. If tissue has been removed prior to submission to the laboratory, this should be stated on the request form.

Pre-operative drug treatment (e.g. with tyrosine kinase inhibitors or immunotherapy) or tumour ablation (e.g. cryoablation, radio frequency ablation or external beam radiotherapy) may affect macroscopic and histological interpretation, therefore details of such therapy should be provided by the submitting clinician. In particular, information on prior tumour embolisation should be stated, as this negates any prognostic significance of observed tumour necrosis.

Providing clinical information on whether or not the patient has disease confined to the kidney, known metastatic disease or any known family history of renal cancer is recommended.

For separately submitted venous thrombus or lymph node specimens, the specimen site should be stated. Stating the level of inferior vena cava (IVC) involvement is required for correct TNM staging (pT3b or pT3c).

3 Preparation of specimens before dissection

Specimen types covered by this dataset include the following:

- biopsy of renal mass (needle or wedge)
- partial nephrectomy
- total (simple or radical) nephrectomy

- associated lymph node dissections.

3.1 Specimen receipt

In order to avoid delays in the booking-in process, specimen pots and forms must be clearly labelled by the submitting clinician with appropriate patient demographics and specimen details, in accordance with the laboratory procedure for acceptance of such specimens. A unique laboratory specimen number should be assigned upon receipt. A bar-coded numbering system is preferable, as this enables electronic tracking of samples at all stages of laboratory processing and facilitates audit of turnaround times.

3.2 Biopsy of renal mass

Biopsies are normally placed into formalin prior to receipt and do not require special handling before tissue processing. If biopsies are required for molecular genetic analysis, these are usually taken in addition to the routine biopsies and may be snap frozen in liquid nitrogen. See section 8 for further details on the handling and reporting of small biopsy specimens.

3.3 Radical nephrectomy

A radical nephrectomy includes the kidney and perinephric fat with surrounding Gerota's fascia, a length of ureter, and may or may not also include the adrenal gland. Adequate fixation is important for renal tumours, as good morphological preservation is essential for accurate classification, and because the assessment and sampling of key areas, such as the interface of the tumour with the renal sinus, is difficult if fixation is poor. Subsequent immunohistochemistry may also be affected by suboptimal fixation. Incision is therefore recommended on specimen receipt.

Prior inking of the full perinephric fat surgical margin is optional. It is recommended, however, that as a minimum any potential areas of margin involvement (e.g. where the tumour creates a bulge on the external aspect or is obviously visible on the surface) are inked before any incisions are made. Retraction of incised perinephric fat during fixation may otherwise make it difficult to identify a non-inked true surgical margin on later dissection. Similarly, if the hilar soft tissue margin is suspected to be involved, this should also be inked.

The plane of the initial incision depends upon personal preference and tumour location, as there is no single agreed method for doing this.³⁰ Whichever method is chosen should maximise the visualisation of the tumour/renal sinus interface, which is a key area for macroscopic assessment. The typical initial incision, and that which reached consensus (93.2% agreement) on the pre-meeting survey of the ISUP Vancouver consensus conference,³⁰ is a midline longitudinal incision along the long axis of the kidney, from the lateral or medial aspect, dividing the kidney into broadly symmetrical anterior and posterior halves. Further incisions may be necessary to expose adequately tumours that are predominantly anteriorly or posteriorly located, and very large tumours will not fix properly unless additional incisions are made. While cuts parallel to the initial longitudinal incision will achieve further tumour exposure, a perpendicular incision is preferable when using the evidence-based method of post-fixation assessment of the tumour preferred by the dataset authors (see section 4.1.1).³¹ Alternative methods for the initial incision include inserting a probe into the collecting system, and opening along this plane, or probing and opening along the hilar vein vasculature. The latter method is discouraged, however, owing to the risk of disrupting intravascular tumour thrombi. Large tumours will generally require at least 24 hours of fixation before further detailed dissection and sampling can be easily undertaken.

Renal tumours have a propensity to spread via invasion into the renal vein and gross evidence of invasion into this vein or its 'segmental (muscle containing) branches' (i.e. tributaries) is part of TNM 7 staging. Gross venous involvement is not required for TNM 8, nor is involvement limited to muscle containing branches of the vein. Nonetheless, the renal

vein should be carefully examined macroscopically. This may be done on the fresh specimen, if preferred. If so, the renal vein margin is removed first (in transverse section) before opening the initial part of the vein to inspect for visible thrombi. When opening the vein with scissors, care needs to be taken not to disrupt the renal sinus area, as this may lead to later difficulty in interpretation.

Fresh or snap-frozen samples of tumour may be required for research purposes, genetic studies or clinical trials, but this must not compromise later assessment of the specimen for diagnostic purposes. If fresh tumour (and background kidney) sampling is required, specimens should be refrigerated if there is likely to be a time delay in harvesting the tissue. Cooling of the specimens is effective in aiding tissue preservation for many molecular studies, but some research techniques (e.g. tissue culture) require minimal time delay and will therefore need careful liaison between the pathologist, surgeon and the laboratory/tissue bank in order to provide optimum sample quality.

In centres where there is likely to be a delay in transportation to the laboratory, it is helpful to agree a method of specimen opening by the surgeons, to facilitate fixation, before transporting in formalin. Biomedical scientists may also be trained to open specimens on receipt.

3.4 Simple nephrectomy

Simple nephrectomy specimens consist of a kidney with a variable amount of attached perinephric fat and a length of ureter. They may be removed laparoscopically, robotically or by open nephrectomy. They should be incised, as above, to ensure adequate tumour fixation.

3.5 Partial nephrectomy

A partial nephrectomy specimen consists of the tumour that has been enucleated, or is excised with a variable amount of surrounding renal tissue, with or without attached perinephric fat. Part of the pelvicalyceal system may also be included. If the specimen is sufficiently large to require slicing prior to fixation, the parenchymal (intra-renal) surgical margin should be inked first, and optionally the external surface. Slicing perpendicular to the plane of the parenchymal margin enables optimal assessment of the distance of the tumour from this margin.

3.6 Lymph node dissections

These do not require special processing, and are generally fixed *en bloc* in formalin, but large lymph node masses may require incision to facilitate fixation.

4 Specimen handling and block selection

4.1 Gross examination

4.1.1 Nephrectomy specimens

Careful examination of nephrectomy specimens is essential, as the TNM staging system includes features noted on macroscopic assessment. Handling of nephrectomy specimens is similar for simple and radical nephrectomies.

The specimen should first be orientated. This is aided by the position of the ureter, the hilar structures and also the adrenal gland, if present. The ureter extends inferiorly from the hilum along the medial border. At the hilum, the renal vein normally lies anterior to the renal artery (although there are frequent anatomical variations) and the renal pelvis is posterior to both. If the adrenal gland is present, this is usually situated within the suprarenal fat.

Any potential areas of surgical margin involvement should be inked, as noted for handling of fresh specimens (see section 3.3). Gerota's fascia is the plane of surgical dissection and is the connective tissue layer enclosing the perirenal fat, kidney and adrenal gland. Microscopically it is not distinct, but for practical purposes, tumour contacting the soft tissue margins is regarded as involvement of Gerota's fascia (pT4).

The intact specimen may be weighed and measured in three dimensions, although these measurements are primarily a simple record of what has been received, rather than being of particular clinical significance, as they will be affected by the variance in the amount of attached perinephric fat. The kidney and tumour measurement, excluding the attached fat, is usually recorded. The fat should not be stripped off in order to do this, as this would hamper subsequent assessment of perinephric fat invasion.

External structures are examined first, before detailed examination of the tumour.

The length of the ureter included and its appearance, whether of normal calibre or not, is normally recorded. Careful opening of the ureter (after transverse removal of the surgical margin) enables detection of incidental focal lesions.

The renal artery should be identified and the margin sampled transversely.

The renal vein should be carefully inspected, as previously noted in section 3.3, for the presence of tumour thrombi. After transverse sampling of the renal vein margin, opening and inspection of the initial part of the vein is possible, taking care to avoid disruption of the renal sinus. Gross invasion of the vein or its 'segmental (muscle containing) branches' (i.e. the tributaries of the renal vein) is part of TNM 7 staging (pT3a). Gross identification of vascular involvement is not required for stage pT3a in TNM 8, nor is there a requirement for involved vessels to have muscular walls. Rounded tumour nodules in the renal sinus fat may represent vascular involvement.

Large thrombi in the renal vein may protrude beyond the surgical margin of the vein, and the true margin may shrink back further on fixation. For the assessment of margin involvement, it is important to observe whether the tumour thrombus is adherent to the vein wall at the margin or not (and to confirm this microscopically). A loose thrombus within the lumen or simply protruding from the vein does not constitute a positive margin.³⁰

If the IVC is involved, part of this vein wall may be included with the nephrectomy specimen, and this becomes the main venous vascular surgical margin. Alternatively, an IVC thrombus may be submitted separately. Separate IVC thrombi are inspected for the presence of any adherent vein wall, which should be sampled.

The hilar fat is examined for the presence of lymph nodes, which should be counted and inspected for the presence of gross metastases, measuring the size of the largest metastasis. Lymph nodes are found in the hilar region in less than 10% of nephrectomy specimens.³³ One study of 871 nephrectomy specimens showed that grossly palpable lymph nodes were positive in 80% of cases, but all of the lymph nodes identified microscopically (detected in less than 25% of cases) were benign.³⁵ Detection of lymph nodes by palpation is considered sufficient.

The size of the adrenal gland is recorded and its appearance noted. It is particularly important to observe whether the gland is directly invaded by the renal tumour or contains any discrete nodules, which may be tumour metastases or adrenal neoplastic or hyperplastic lesions. Direct invasion into the adrenal gland and metastatic involvement are distinguished in TNM staging (pT4 and pM1, respectively).

Post-fixation assessment of the renal tumour is facilitated by slicing the entire kidney in the horizontal (transverse) plane, perpendicular to the initial longitudinal incision, and then laying out the slices in sequence for closer inspection.³¹ The location of the tumour is noted (upper, lower, interpolar) and whether or not it is primarily arising within the medulla or cortex.

The maximum dimension of the tumour should be recorded, in millimetres, as this is part of TNM staging (pT1 or pT2). This measurement includes tumour extension into perinephric fat, but not the length of any tumour thrombus within the renal vein. Care should be taken around the measurements that represent cut-off points for staging categories i.e. 40 mm, 70 mm and 100 mm (TNM pT1a, pT1b and pT2a, respectively). One study reported that there is up to 10% difference in the radiological and pathological measurements of tumour size, therefore careful gross measurement is of importance.³⁶

When there are multiple tumours, the maximum dimension of the largest five should be recorded³⁰ and, additionally, that of any smaller tumours if they differ in gross appearance from the larger tumours, or appear to be of higher stage.

Macroscopic assessment of tumour spread into the perinephric or renal sinus tissue is important for staging purposes. If there is visible or suspected perinephric fat invasion, the minimum distance of the tumour from the closest perinephric fat margin/Gerota's fascia should be assessed and, if less than 10 mm, it is recommended that it is measured.

The renal sinus is the cavity on the medial aspect of the kidney that consists of fat and connective tissue containing the renal pelvis, the branches of the renal artery, the tributaries of the renal vein and lymphatics and nerves. There is no renal capsule separating the parenchyma from the renal sinus fat. Multiple studies have demonstrated the significance of renal sinus invasion, which is considered to be one of the most important prognostic parameters, as it represents the main route of extra-renal tumour spread. In view of this, thorough inspection and adequate sampling of the renal sinus is an essential part of specimen dissection.³⁷⁻³⁹

Tumour spread into the pelvicalyceal system should be recorded. Although it is not part of TNM 7 staging, it is included in TNM 8 (pT3a).

A digital photograph of the gross specimen provides a visual record of the tumour location, appearance and extent and is particularly useful for annotating the sites from where blocks have been taken.

4.1.2 Partial nephrectomy

Partial nephrectomy specimens should be measured in three dimensions, noting the kidney tissue size. There may be attached perinephric fat. The parenchymal (intra-renal) surgical margin should be inked. Optionally, the external surface may also be inked. The latter will require inking if there is suspected external margin involvement. The specimen should be sliced perpendicular to the parenchymal surgical margin. This will enable the maximum size of the tumour to be measured. The presence of any visible or suspected invasion into the perinephric fat or possible involvement of the external margin (i.e. the fat or capsular margin) should be noted. It is recommended that the minimum distance of the tumour from the parenchymal margin is measured.

4.1.3 Lymphadenectomy specimens

Specimens are usually measured in three dimensions, or weighed. Lymph nodes are identified by palpation and the number recorded. They are described as either macroscopically normal or involved by tumour. If there is a visible nodal metastasis, the size should be recorded as this may be relevant for further treatment decisions.

4.2 Block selection

4.2.1 Nephrectomy

Blocks are selected to enable accurate tumour typing, staging and the assessment of margin status. These should include:

- renal vein surgical margin. The margin is only regarded as positive if the tumour is adherent to the vein wall at the margin. Direct invasion of the vein wall at the margin raises the possibility of local tumour recurrence.
- renal vein with tumour thrombus, if present, to confirm gross observation
- surgical margins of other hilar (arterial) vessels
- tumour blocks, to represent:
 - all areas with different macroscopic appearances (solid areas of differing appearance e.g. yellow, white or cystic areas) to enable tumour typing and grading and to detect any sarcomatoid areas. Generous sampling is required, with a minimum one block per centimetre, owing to the heterogeneity of these tumours.³⁰
 - necrosis with adjacent tumour. The presence of tumour necrosis is included in algorithms used for clinical management. High-grade areas are often present adjacent to areas of necrosis.
 - interface with the perinephric fat, to include areas suspicious of invasion. Where the tumour bulges into perinephric fat it may be difficult to be certain of true fat invasion, therefore any areas of suspected fat invasion should be generously sampled.
 - minimum distance to the (inked) perinephric surgical margin or the hilar soft tissue margin (if less than 10 mm)
 - interface with the renal sinus tissue. This should be generously sampled. Ideally the entire interface should be blocked,³¹ but with extensive tumours this may generate a large number of blocks. The ISUP Consensus conference recommended,³⁰ as a minimum, three blocks of the interface (but with only one confirmatory block required if the tumour overtly invades the fat). If the interface has not been entirely sampled, further blocks are recommended if large tumours (>70 mm) still appear kidney-confined following microscopic assessment of the initial sections.
 - any direct contiguous extension into the adrenal gland
 - interface with normal parenchyma (aids interpretation of immunohistochemistry, if required, by providing an internal control)
 - adjacent renal pelvis. Sampling of the renal pelvis is of particular importance in tumours where the differential diagnosis is between a collecting duct carcinoma and a urothelial carcinoma, as identification of the origin of the latter from the pelvicalyceal urothelium will aid correct diagnosis.
 - in the case of multiple tumours, the largest five should be sampled, and any smaller lesions with a differing gross appearance or ones that appear to be of higher stage.³⁰ In the setting of acquired cystic renal disease, all solid tumours should be sampled, as this condition may be associated with different morphological tumour types.⁴⁰

Additional blocks to include:

- uninvolved renal parenchyma (to detect any underlying renal pathology). This should be sampled as distant as possible from the tumour, to minimise histological changes due to mass effect.
- any other incidental or satellite lesions
- adrenal gland (for metastases or incidental adrenal pathology)

- ureteric surgical margin and any focal ureteric lesions
- all hilar lymph nodes. If obvious nodal metastases are present, they may be sampled to confirm this macroscopic observation, rather than processing the entire lymph node. Areas of suspected extranodal spread should be sampled.

4.2.2 Partial nephrectomy

Blocks to include:

- tumour, generously sampled, as above, for typing and grading
- tumour with areas of suspected perinephric fat invasion, and (if included) renal sinus invasion
- tumour and the closest parenchymal margin
- tumour and the closest perinephric fat/capsular margin (if less than 10 mm)
- uninvolved parenchyma, as distant as possible from the tumour (ideally more than 5 mm).

4.2.3 Lymph node dissections

Blocks to include:

- all palpable lymph nodes
- grossly involved lymph nodes do not require processing in their entirety, but should be sampled to confirm metastatic deposits. If extranodal tumour extension is suspected grossly, such areas should also be selected for blocking.

5 Core data items

This is an evidence-based list of items that are essential for prognosis or management. These are included in the reporting proforma at Appendix F.

5.1 Clinical

Items include:

- surgical procedure (partial, simple or radical nephrectomy)
- specimen laterality (e.g. left, right, horseshoe kidney)
- site of other included specimens (IVC thrombus, lymph nodes)
- any pre-operative treatment.

Details of the above are essential items of clinical information to be provided by the submitting clinician.

[Details of specimen type and site are required – level of evidence GPP.]

5.2 Pathological

5.2.1 Macroscopic

Tumour focality (unifocal, multifocal)

The majority of RCCs are solitary. Sporadic multifocal tumours are uncommon, reported in large series studies as up to 5%.³⁰ Multiple tumours may be seen in hereditary carcinoma syndromes, such as von Hippel-Lindau, Birt-Hogg-Dubé, hereditary leiomyomatosis and

RCC (HLRCC) syndrome, tuberous sclerosis and hereditary papillary carcinoma.¹ They also occur with renal oncocytosis and in acquired cystic kidney disease. It is therefore important to record tumour multifocality. The ISUP consensus conference recommended that the largest five tumours should be described and assessed as a minimum.³⁰ This should include those of the highest stage.

[Tumour focality is of diagnostic importance – level of evidence C.]

Tumour size

The maximum dimension of the tumour (or the largest five tumours, if multiple) should be recorded in millimetres.

Tumour size is part of the TNM staging system, with cut-off points for prognostic significance applied at 40, 70 and 100 mm for stages T1a, T1b and T2a, respectively.^{5,6} Any extension of tumour into perinephric fat or renal sinus fat is included in the tumour size, but a tumour thrombus in the renal vein should be excluded from the measurement.³⁰ Tumour size correlates with clinical outcome for localised clear cell RCC, with the probability of death having been shown to increase with tumour size, as a continuous variable.⁴¹ Tumour size predicts infiltration into the renal sinus, with the majority of tumours >70 mm (97%) showing renal sinus fat or vein invasion and therefore unlikely to be kidney confined.⁴²

[Tumour size is of prognostic importance – level of evidence C.]

5.2.2 Microscopic

Histological tumour type

The 2016 WHO classification should be used for renal tumours.¹ This classification is primarily based upon morphological findings but also incorporates molecular and genetic information. Tumour typing is required as the clinical behaviour and prognosis differs for some tumour types. Many large-scale and multicentre studies have demonstrated that differing morphology affects prognosis.^{14,27,43–46} A large multicentre study of 5,339 patients showed tumour type to predict cancer-specific mortality in univariate and multivariate analysis,⁴⁷ and a large single-centre study of 3,062 patients showed on multivariate analysis that the clear cell versus non-clear cell tumour subtype had predictive value in terms of metastasis-free survival.⁴⁸ Tumour subtype may also influence the choice of adjuvant therapy.⁴⁹

The commonest renal tumour in adults is RCC, accounting for over 90%. RCCs are classified into several types, the most common being clear cell (70–80%), papillary (10–15%) and chromophobe (3–5%) RCCs. Benign oncocytomas account for approximately 5% of all renal neoplasms.

Clear cell carcinoma has a worse prognosis than papillary or chromophobe RCC when equivalent pT1 or pT2 tumours are compared.^{50,51}

The rare collecting duct carcinoma (1–2%) shows very aggressive clinical behaviour.¹

Papillary RCC can be divided into two main types histologically – types 1 and 2.^{28,52} On immunohistochemistry, type 1 tumours more often show CK7 positivity than type 2 tumours. In molecular studies, type 1 tumours have been shown to have alterations in the MET pathway, differing from the type 2 tumours that show NRF2-ARE pathway activation and also exhibit several molecular subtypes.⁵³ Subtyping of papillary RCC is of importance, since type 1 tumours have been shown to have a better prognosis than type 2 tumours, with type 1 tumours generally smaller, of lower nuclear grade and lower stage at presentation.⁵⁴ An oncocytic type of papillary RCC has also been described, but is included under the general category of papillary RCC.¹

The remainder of the renal tumour types are uncommon and are detailed in the 2016 WHO classification.¹ In this edition of the classification, there are a number of changes from the previous 2004 version,⁵⁵ which was included in the second edition of this dataset. The main changes are summarised below.

Entities renamed or modified:

- multilocular cystic RCC – renamed multilocular cystic renal neoplasm of low malignant potential
- carcinoma of the collecting ducts of Bellini – renamed collecting duct carcinoma
- Xp11 translocation carcinoma – renamed MiT family translocation RCC, a category that includes TFE3 and TFEB translocation tumours
- carcinoid – renamed well-differentiated neuroendocrine tumour
- neuroendocrine carcinoma – subdivided into small cell and large cell types
- papillary adenoma – the maximum diameter allowable for this diagnosis has been changed from 5 mm to 15 mm
- cystic nephroma has been divided into paediatric and adult types. The former have DICER mutations.

Several rarer entities that were only provisionally recognised at the ISUP Vancouver consensus conference²⁸ have been included in the 2016 WHO classification, as their morphological features are distinctive and their immunoprofiles and molecular characteristics are now better defined. New entities added under the renal cell tumour category are:

- clear cell papillary RCC
- succinate dehydrogenase (SDH)-deficient RCC – these possess inherited germline mutations in the SDH gene (usually SDHB). There is an association with paragangliomas and pheochromocytomas. A family history may be evident.
- tubulocystic RCC
- acquired cystic disease-associated RCC
- HLRCC-associated RCC. The patients have an inherited germline mutation in the FH gene, coding for fumarate hydratase. Cutaneous and uterine leiomyomas are associated with these RCCs.

A number of other described entities are not yet included in the WHO classification, as there is still limited experience with such tumours and few series publications to date. These include thyroid-like follicular RCCs, RCCs with anaplastic lymphoma kinase (ALK) gene rearrangements, RCC with angioleiomyomatous stroma, RCC with monosomy 8 and TCEB1 mutation, and the oncocyctic RCC occurring post-neuroblastoma. These are regarded as emerging entities²⁸ and should be included under 'other' in the reporting proforma.

If multiple tumours are present, either of the same or differing types, their pathological findings should be recorded separately. If there are many present of the same type, the largest five only need be described, provided that this includes those of the highest stage.

Most tumours (>95%) are sporadic, but familial cancer syndromes occur, including:¹

- von Hippel-Lindau syndrome
- hereditary papillary RCC
- HLRCC

- Birt-Hogg-Dubé syndrome
- tuberous sclerosis
- succinate dehydrogenase-deficient RCC.

If multiple tumours are encountered, the possibility of a genetic disease should be considered and discussed with the clinician and/or in an MDT meeting. Tumours showing unusual morphology, occurring in younger patients (less than 30 years of age), or occurring where there is a strong family history, may be indicative of an underlying genetic cause and case referral to an expert for a second opinion is advised.

For tumours that prove difficult to type, it may be helpful to take extra blocks in order to find low-grade areas with more typical morphology, and/or immunohistochemistry may be required. The category of unclassified RCC is used for those tumours that after thorough gross, microscopic and immunohistochemical investigation do not fit clearly into any of the defined categories. These include both low- and high-grade tumours and this aspect of their morphology needs to be clear in the histological description.

Tumours with a mixed morphology of recognisable subtypes are placed in the 'other' category, with an added description of the different subtypes present. Multiple tumours that have different morphology, but are clearly separate tumours, are not regarded as mixed and should be classified and assessed separately.

[Tumour type has prognostic significance – level of evidence C.]

Tumour grade

The Fuhrman grading system has been widely used in clinical practice for prediction of the clinical behaviour of clear cell and papillary RCCs. This system involves assignment of grades 1–4, based on the simultaneous assessment of three parameters: nuclear size, nuclear contour and nucleolar prominence.⁵⁶ Owing to difficulties in consistently applying Fuhrman grading (in particular for grade 3), with resultant problems in intra- and inter-observer reproducibility,^{57–60} it was proposed at the ISUP Vancouver consensus conference that a new nucleolar grading system be adopted.²⁷ The WHO/ISUP tumour grading system has since been recommended in the 2016 WHO classification and should be used instead of the Fuhrman system.¹

The WHO/ISUP tumour grade (1–4) is assigned according to the highest grade that occupies a high power field area and is summarised in Appendix C. It is a four-tiered system, with grades 1–3 assessed upon the degree of nucleolar prominence and grade 4 assigned to tumours with highly pleomorphic tumour cells and those with sarcomatoid and/or rhabdoid morphology. In clear cell RCCs, the higher grade areas are often those with a predominance of cells with eosinophilic cytoplasm. This grading system is applicable to clear cell and papillary RCCs^{57,60} but has not been validated as a prognostic indicator for use with other tumour types. Although other grading systems have been proposed for chromophobe RCCs,^{61,62} as yet there is no internationally accepted grading system for use in clinical practice for these particular tumours. They should not be graded.¹ Grading is also not applicable to collecting duct carcinomas, which by definition are high-grade malignancies. The WHO/ISUP grades may be used descriptively for other tumour types in histology reports, but a statement should be added to emphasise that this grading system has only been validated for use as a prognostic parameter in clear cell and papillary RCCs.

[Tumour grade has prognostic significance – level of evidence C.]

Tumour necrosis

In multiple studies tumour necrosis has been shown to be of prognostic importance, independent of tumour stage and grade, for both clear cell and chromophobe RCCs,

although it is less commonly seen in the latter.^{27,50,63–65} Its presence in papillary RCCs is of uncertain significance, however, as these tumours frequently show areas of necrosis and associated haemorrhage with cholesterol clefts. This necrosis is possibly due to a different mechanism.²⁷

Macroscopic (confluent) necrosis may be difficult to identify with certainty, therefore it is recommended that it is confirmed microscopically. Coagulative necrosis noted microscopically should be distinguished from areas of haemorrhage and fibrin deposition or areas of fibrosis, by the presence of dead ‘ghost’ tumour cells and/or cellular debris. Areas of coagulative necrosis often show abrupt transition from viable areas of tumour. Any amount of necrosis should be reported for prognostic algorithms.¹⁸ Whether necrosis is identified macroscopically or on microscopy should also be specified, as the causal mechanism is possibly different (i.e. the former probably tumour thrombus related infarction) and only the latter has known prognostic significance.

If there has been prior tumour embolisation, tumour necrosis cannot be used for prognostic purposes. On the proforma at Appendix F, this is recorded as ‘cannot be assessed’.

Although at the ISUP Vancouver consensus conference agreement was reached (69%) for assessing the amount of necrosis present in clear cell RCCs, this is regarded as a recommended but non-core item (see section 6.3) as there is no agreed method for its estimation.²⁷

It has been proposed that the presence of necrosis should be incorporated into tumour grading, as studies have shown that within a single grade the presence or absence of necrosis affects prognosis.^{66,67} This has not been agreed internationally, but recording of the presence of tumour necrosis will also allow this parameter to be incorporated retrospectively into any subsequent modified grading system.

[Tumour necrosis has prognostic significance – level of evidence C.]

Sarcomatoid morphology

This refers to the presence of a malignant component resembling a sarcoma, and is usually of spindle cell type. This morphology is present in approximately 5% of RCCs and may be seen with any of the main histological tumour subtypes. It should not be confused with areas of ‘streaming’ or elongation of tumour cells, which may represent compressed tubular structures, where the tumour cells still appear epithelial in nature and bland rather than being truly sarcomatoid. Sarcomatoid morphology is assigned grade 4 in the WHO/ISUP grading system.¹ Associated heterologous elements are rare. Multiple studies have shown that the presence of this morphology is associated with poor prognosis, with distant metastases in 45–77% at presentation and a 5-year survival of around 15–22%.^{27,68–71} The poor prognosis has, however, been shown to be stage dependant.⁷²

The proportion of sarcomatoid morphology may have prognostic significance, but recording this is not considered to be a core item (see section 6.4). At the ISUP Vancouver consensus conference, there was consensus agreement that any amount of sarcomatoid morphology should be reported, with no minimum amount required (71% agreement) and that the underlying tumour type should be described.²⁷ Rarely, tumours may be purely sarcomatoid. This is reported in one study to be 4% of those tumours that show some degree of sarcomatoid morphology.⁶⁸ Purely sarcomatoid tumours should be reported as WHO/ISUP grade 4 and placed in the unclassified RCC category.^{1,27}

[Sarcomatoid morphology is associated with poor prognosis – level of evidence C.]

Rhabdoid morphology

Rhabdoid morphology refers to the presence of epithelioid cells with abundant dense eosinophilic cytoplasm and a large eccentric nucleus, which often has a prominent nucleolus.

These cells are desmin negative and cytokeratin positive on immunohistochemistry and the intracytoplasmic inclusions are vimentin positive. Rhabdoid morphology is assigned grade 4 in the WHO/ISUP grading system,¹ and multiple studies have shown its presence to be associated with aggressive behaviour and a poor prognosis,^{73,74} independent of stage and grade,⁷⁵ and it is reported to be more common in clear cell RCC.⁷⁶ Approximately 25% of tumours with this morphology also contain sarcomatoid areas.¹ At the ISUP Vancouver consensus conference, there was consensus agreement (73%) that the presence or absence of rhabdoid morphology should be reported. Reporting the extent of rhabdoid morphology (see section 6.5), however, did not reach consensus and is regarded as a non-core item.²⁷

[Rhabdoid morphology is associated with poor prognosis – level of evidence C.]

Perinephric fat invasion

Perinephric fat invasion is part of TNM staging (pT3a). It is defined as either (a) direct contact between the tumour and the fat, or (b) extension of irregular tongues of tumour into perinephric tissue, with or without stromal desmoplasia.³⁰ A pushing margin alone is not diagnostic of perinephric fat invasion, even if the tumour extends significantly beyond the contour of the kidney. Histological assessment can be difficult, as the presence of a pseudocapsule may be hard to distinguish from a markedly attenuated true renal capsule. The nature of the boundary between the tumour and the fat has previously been shown to be prognostically important, with direct invasion of the fat having a worse outcome when compared with tumours with a pushing margin, with or without a pseudocapsule (27% 3-year survival versus 75%, respectively).⁷⁷ Perinephric fat invasion is compatible with a diagnosis of benign oncocytoma but there is no associated stromal reaction when this occurs.⁷⁸

Vascular invasion identified within this fat is also regarded as evidence of perinephric fat involvement/extra-renal spread (pT3a).

Involvement of Gerota's fascia, taken as the surgical margin of the perinephric fat attached to a radical nephrectomy specimen, is categorised as TNM stage pT4.

[Perinephric fat invasion has prognostic significance – level of evidence C.]

Renal sinus invasion

This is defined as direct contact between the tumour and (a) the renal sinus fat or (b) loose connective tissue of the sinus that is clearly beyond the renal parenchyma or (c) the involvement of any endothelial-lined spaces of any size within the sinus.³⁰ If renal sinus involvement is seen, histology reports should indicate whether this is due to direct invasion, vascular invasion or both. The lack of a capsule at the parenchyma/fat interface facilitates tumour access to the rich vascular network in the sinus. Largely through the extensive work of Bonsib, the renal sinus is recognised as the principal route for extra-renal spread of RCCs and careful and thorough sampling of the renal sinus is therefore imperative for accurate staging of otherwise kidney-confined tumours.³⁷⁻³⁹ Renal sinus invasion has been shown to rise sharply when tumours exceed 40 mm in size and those over 70 mm in size are rarely kidney-confined (3%).⁴²

Renal sinus invasion has also been noted to predict more aggressive behaviour than perinephric fat invasion.⁷⁹

Renal sinus fat invasion is part of TNM staging (pT3a).

[Renal sinus invasion has prognostic significance – level of evidence C.]

Renal vein involvement

In the current TNM 7 staging, only gross invasion of the renal vein, or its 'segmental muscle-containing branches', is considered to be pT3a.⁵ The gross impression should be confirmed microscopically. Visible rounded nodules in the renal sinus often represent vascular

involvement and should also be assessed on microscopy.³⁹ Vascular invasion that is only discovered on microscopy, but in which the tumour thrombi are considered large enough to have been visible macroscopically, should also be regarded as gross vein involvement for TNM 7. For TNM 8 stage pT3a,⁶ vascular invasion does not have to be visible grossly, and involved branches (tributaries) of the renal vein do not need to be muscle-containing.

The renal vein margin is considered positive only if tumour is adherent to the vein margin on microscopic examination. Histological confirmation is therefore necessary to determine margin status. The presence of invasion of the vein wall at the margin is a risk for local tumour recurrence and should be included in histology reports.⁸⁰

Involvement of the IVC is part of TNM staging. IVC margin involvement requires tumour adherence to the vein wall. The level of IVC involvement (pT3b or pT3c) depends upon clinical information provided on the extent of the intravascular tumour thrombus. Gross IVC involvement is required for TNM 7 stages pT3b and pT3c, but not for TNM 8. However, any evidence of IVC wall invasion microscopically, at any level, is pT3c.

[Renal vein/IVC involvement is part of TNM staging – level of evidence C.]

Lymphovascular invasion

Lymphovascular invasion identified within the kidney or tumour is not currently part of TNM staging,^{5,6} although its presence in the renal sinus or perinephric tissues is interpreted as extra-renal spread (pT3a). At the ISUP Vancouver consensus conference, 59% of participants thought that it should be reported if seen, but this did not reach consensus agreement.²⁷ Its value as a prognostic parameter has shown conflicting results in the literature,²⁷ but it has been reported in some studies to have prognostic significance in low-stage RCCs, independent of tumour grade,⁸¹ and to correlate with survival, independent of tumour size, tumour type and grade.^{82–84} Lymphatic spread to the hilar lymph nodes is more common in papillary RCC and collecting duct carcinoma than in clear cell RCC.⁸⁵ The inclusion of lymphovascular invasion in histology reports is recommended in the ICCR dataset³ and it is included here as a core item for reporting.

[Lymphovascular invasion has prognostic significance – Level of evidence C.]

Invasion of the pelvicalyceal system

Invasion of the pelvicalyceal system is not part of the current TNM 7 staging,⁵ but it is included in stage pT3a in TNM 8.⁶ It has been shown, in some studies, to be associated with poor survival in patients with clear cell RCC.^{86–88} A meta-analysis study,⁸⁹ which included 17 studies and over 9,000 patients, showed that its presence has a negative impact on the overall survival and recurrence-free survival. Documenting its presence is included as a core item.

[Pelvicalyceal system invasion has prognostic significance – level of evidence C.]

Adrenal involvement

The incidence of ipsilateral adrenal gland invasion is reported as 1–5% and adrenal metastases, at the time of nephrectomy, as 2%.⁹⁰ Large size, upper pole location and venous invasion are all risk factors for adrenal involvement. Adrenal invasion was included in the pT3a category in earlier editions of TNM staging, but owing to its poor outcome,^{64,91} it is now categorised as either pT4, when there is contiguous invasion of the ipsilateral adrenal gland, or as pM1, when there are adrenal metastases.^{5,6}

[Adrenal gland involvement has prognostic significance – level of evidence C.]

Lymph node involvement

Lymph node status, with the total number of nodes, the number involved and the presence or absence of extracapsular spread, should be recorded.⁹² Regional lymph node dissection at

nephrectomy is uncommon, owing to a combination of the lack of proven clinical benefit in low-risk patients,⁹³ the increased use of laparoscopic nephrectomy (which makes lymphadenectomy more difficult) and the low frequency of positive ipsilateral hilar lymph nodes. Palpable hilar lymph nodes are present in nephrectomy specimens in less than 10% of cases.⁹⁴ A literature review by Capitanio and Leibovich⁹⁵ suggests that regional lymph node dissection should still be considered in those with large or locally advanced tumours and those with lymphadenopathy or with suspected adverse pathology, as these patients may have better cancer control as a result. Survival is adversely affected by the number of lymph nodes involved (i.e. more than four positive nodes),⁹⁶ although the TNM staging only requires specification of the presence (pN1) or absence (pN0) of nodal metastases. Regional lymph nodes include the hilar, abdominal aortic (preaortic, paraaortic and retroaortic) and caval (precaval, paracaval and retrocaval) lymph nodes. Involvement of lymph nodes at more distant sites is regarded as metastatic spread in TNM staging (pM1).^{5,6}

[Lymph node status has prognostic significance – level of evidence C.]

TNM staging

Staging is the single most important prognostic factor.³⁰ The TNM staging system recommended for use in 2017 by the RCPATH Working Group on Cancer Services is UICC TNM 7.⁵ This has been validated in multiple studies.^{47,97} From 1 January 2018, UICC TNM 8 should be used.⁶ Details of both are in Appendix A. The version used should be clearly stated in histology reports.

[The TNM stage has prognostic significance – level of evidence C.]

Margin status

In nephrectomy specimens, the surgical margins of the ureter, hilar vessels, perinephric fat/Gerota's fascia and the renal sinus soft tissue margin should be assessed and the findings documented in the histology report. Residual tumour puts the patient at risk of local recurrence and poorer overall survival.⁹⁸ Incidental urothelial lesions may have implications for other parts of the urinary tract.

Direct invasion of the vein wall identified at the renal vein or IVC surgical margin should be reported, as this is a risk factor for tumour recurrence.⁹⁹

For partial nephrectomy specimens, the parenchymal (intra-renal) surgical margin and the perinephric fat margin (or the renal capsular margin, if no fat is present) should be assessed and their status documented. One study involving a literature review of 3,803 cases showed that a positive margin in partial nephrectomy specimens seldom correlates with tumour recurrence and that a negative margin does not exclude the risk of recurrence.¹⁰⁰ Nonetheless, reporting margin status is considered an essential part of histology reports and is the subject of the British Association of Urological Surgeons (BAUS) audits on operative results.

[Assessment of margin status – level of evidence GPP.]

Non-neoplastic kidney

Surgical treatment for renal tumours, particularly total nephrectomy, results in general nephron loss and a reduction of overall renal function. It is therefore important to detect any existing disorder that might further compromise the function of the remaining kidney tissue. Several studies have shown the clinical significance of recognising these changes.^{101–103}

The most common disorders reported in nephrectomy specimens are arterionephrosclerosis/hypertensive nephropathy (30%) and diabetic nephropathy (20%). Other medical renal disorders reported incidentally include thrombotic microangiopathy, focal sclerosing glomerulonephritis, amyloidosis and IgA nephropathy.¹⁰⁴

Advanced diabetic nephropathy or over 20% global glomerulosclerosis are associated with significantly compromised renal function six months post radical nephrectomy.¹⁰⁵

The appearance of the background kidney tissue should therefore be carefully assessed in blocks taken as distant from the tumour as possible. Kidney tissue immediately adjacent to the tumour will show a variable degree of changes simply due to mass pressure effect from the tumour (e.g. chronic inflammation, fibrosis, glomerulosclerosis) and is therefore unreliable for assessment.

For those pathologists who do not normally report medical kidney disorders, it is advisable to have a low threshold for requesting special stains (e.g. periodic acid-Schiff and Jones methenamine silver) and seeking a second opinion from a medical renal pathologist if there is any suspicion of underlying pathology that may be of clinical significance.

[Status of the background kidney is of clinical significance – level of evidence C.]

6 Non-core data items

6.1 Removal of tissue prior to receipt

It is important for the pathologist to be aware if any tissue has been removed prior to receipt, as this may compromise pathological assessment.

6.2 Tumour site (upper, middle, lower pole, cortex, medulla)

Correlating the site of the tumour with imaging findings is helpful in cases where specimen orientation is difficult. The relationship of the tumour to the renal capsule and renal sinus is important in assessment of stage. Noting the location of the tumour in the medulla is useful in cases where a collecting duct carcinoma (or medullary carcinoma) is in the differential diagnosis.¹

6.3 Extent of tumour necrosis

The extent of tumour necrosis is currently of uncertain prognostic significance. It has been reported in one study that 20% (by area) of necrosis is of significance for kidney-confined tumours (TNM stages 1 and 2), conferring a worse outcome,⁹¹ and other studies have also reported that the quantity of necrosis, rather than simply its presence, is significant.^{106,107}

Although it is recommended that the percentage of necrosis is estimated and recorded,^{3,27} this has not been included in the core items, as it is recognised that this is subject to wide variance according to whether it is clearly identified macroscopically or not, and also by the extent of tumour sampling.

6.4 Extent of sarcomatoid morphology

One study has demonstrated a lower survival rate for those with over 50% sarcomatoid morphology,⁷¹ and others have shown correlation between the percentage of sarcomatoid morphology and cancer-specific mortality or overall survival.^{108,109} Currently, there is no internationally agreed method of reliably calculating the amount of sarcomatoid morphology present, and assessment of extent is affected by tumour sampling. Therefore, it is regarded as a non-core item. However, in line with the ICCR dataset, it is recommended that an estimate of extent is included in histology reports.³

6.5 Extent of rhabdoid morphology

There is no strong evidence of the prognostic significance of the extent of rhabdoid morphology, therefore it is not a core item. However, providing an estimate of the proportion of the tumour with this appearance is nonetheless recommended for inclusion in histology reports, as it is in the ICCR dataset,³ since it may provide useful information for future research studies.

6.6 Risk assessment scores

A number of risk assessment scores have been proposed for use for patient risk stratification post nephrectomy, in order to guide follow-up regimes and suitability for adjuvant therapy in clinical trials. These include the University of California Integrated Staging System (UISS) score, the Mayo Clinic SSIGN score, the Kattan nomogram (Memorial Sloane Kettering) and the Leibovich Score (LS).^{17–19,110} The latter (LS), also known as the Mayo score, is used to predict metastasis-free survival in patients with clear cell RCC who are without metastases at the time of surgery. It is the most commonly used in the UK and has been shown to be slightly better for predicting survival outcomes.^{20,111} It incorporates solely pathological parameters of tumour stage, grade, size, regional lymph node status and the presence or absence of histological necrosis to give a numerical score. The LS score may therefore be readily incorporated into histology reports, if required, for MDT patient management discussions. This is detailed in Appendix E.

6.7 Representative block

It is good practice to record in the report, or on the laboratory computer system, the number of a block that is representative of the tumour. This enables rapid selection of a block for clinical trials or genetic studies at a later date, without having to retrieve and review the entire case.

7 Diagnostic coding and staging

7.1 Diagnostic coding

Coding is recommended and is useful for data retrieval, workload measurement and audit. SNOMED coding should be applied (see Appendix B).

A comparison of SNOMED systems is given in Table 2 in Appendix B.

7.2 Staging

The 7th edition of UICC TNM is currently recommended for tumour staging. The 8th edition of UICC TNM should be implemented from 1 January 2018 (see Appendix A).^{5,6}

8 Reporting of small biopsy specimens

The frequency of renal biopsy specimens is increasing for a variety of reasons. Where radiological surveillance of small renal masses, ablation therapy or palliative treatment are potential options, a definitive histological diagnosis aids clinical management decisions.¹¹² Biopsies may also be useful if a benign renal tumour or an inflammatory process is suspected, thus avoiding unnecessary invasive surgery, or if a kidney potentially harbours a metastasis from another site and alternative non-surgical definitive treatment is more appropriate. Metastatic lesions suspected to be RCC secondaries may also be amenable to biopsy for confirmatory histological diagnosis. The number of biopsies is expected to continue to rise with the advent of molecular targeted therapies.

A systematic review of the literature showed renal mass biopsies to be highly sensitive and specific (97.5% and 96.2%, respectively) when a diagnostic result was obtained, with low complication rates.¹¹³ Biopsies have been shown to be most often non-diagnostic for small renal masses (40 mm or less) and cystic lesions, but repeat biopsy may enable accurate diagnosis.¹¹⁴ Pathological assessment may be challenging on these limited samples.^{115,116}

Many of the core data items required for nephrectomy specimen reporting, as above, are also relevant to reporting biopsy specimens. A reporting proforma is included at Appendix G as an aide-mémoire. This proforma also applies to small wedge biopsy specimens, although these are much less commonly performed.

For core biopsies, the laterality of the specimen should be stated by the submitting clinician, for identification and safety purposes. It is helpful to be provided with information on the tumour location, particularly if located in the medulla, where a collecting duct carcinoma and urothelial carcinoma may be part of the differential diagnosis.

Macroscopically, the number and length of the biopsy cores is recorded to provide documentation of what was received. Ideally, it is advisable to place individual cores into separate cassettes and to serially section these limited samples, retaining multiple spare sections for immunohistochemistry. However, this will depend upon laboratory capacity.

On microscopy, if the biopsy is non-diagnostic this should be stated and the reason noted. The tissue should be examined at multiple levels through the block before reporting as inadequate for diagnosis.

If a tumour is present, the tumour type should be recorded where possible. Diagnosis of some tumours, such as clear cell, chromophobe, or papillary RCCs or benign entities, such as angiomyolipoma or metanephric adenoma, with classical histological features, may be straightforward on biopsy samples. More difficult lesions will require further assessment with immunohistochemistry.²⁹

Oncocytic tumours are particularly challenging in biopsies, in particular the differential diagnosis between a benign oncocytoma and a chromophobe carcinoma. A biopsy may show features of a benign oncocytoma. However, the difficulty of confidently excluding a chromophobe RCC (particularly the eosinophilic variant) owing to potential overlapping features in the two tumours, or excluding a rare 'hybrid' tumour (i.e. hybrid oncocytoma-chromophobe tumour, with or without associated oncocytosis or known Birt-Hogg-Dubé syndrome), mean caution is advised in diagnosis as biopsy samples might not be representative of the entire lesion. In this scenario, although the morphology and immunoprofile of the tumour may be consistent with an oncocytoma, it is recommended that the term 'oncocytic renal neoplasm, with features favouring an oncocytoma' or similar wording is used as the final diagnosis on such specimens, to emphasise the limitations of making a diagnosis on a small biopsy sample. This cautious approach is supported by the results of a survey of expert uropathologists with a special interest in renal tumour pathology, of whom only 64% stated that they would report an oncocytoma definitively on a renal biopsy.¹¹⁷ Despite extensive biomarker studies, the distinction between different oncocytic lesions remains problematic.¹¹⁸ However, active surveillance may still be appropriate, even with the uncertainty in diagnosis, owing to the generally slow growth of these oncocytic lesions.¹¹⁹

Owing to the heterogeneity seen in clear cell RCCs, tumour grading on biopsy specimens is of limited value. However, the grade should be recorded, as it will at least indicate the minimum grade that is present. It should be clear from the report, however, that this may underestimate the true tumour grade.¹¹³

The presence of sarcomatoid or rhabdoid morphology, tumour necrosis or lymphovascular invasion should be recorded, if seen. If part of the pelvicalyceal system is included, a

comment should be made on the appearance of the included urothelium, and of involvement by tumour, if identified.

Included non-neoplastic renal parenchyma should be assessed for incidental co-existing medical conditions, taking into account that mass effect by a tumour commonly results in some degree of adjacent inflammation, tubular atrophy, glomerulosclerosis and scarring.

9 Reporting of frozen specimens

Intraoperative frozen sections are uncommon in renal tumour pathology, as a total nephrectomy is the usual procedure for excision of malignant or large renal tumours.¹²⁰ When nephron-sparing surgery is the intent, as with partial nephrectomy, a frozen section of the parenchymal (intra-renal) margin may be requested, in order to confirm completeness of excision of the tumour. In such instances it is important that the true surgical margin is indicated by the surgeon, and marked with a suture if necessary, to assist correct orientation of the specimen. It is not practical to assess a large area of the intra-renal margin by frozen section.

Routine frozen section for assessment of hilar/para-aortic lymph nodes at nephrectomy is not recommended owing to potential sampling error and should be restricted to those that appear grossly to contain metastatic tumour deposits, and only if this will alter the surgical procedure being undertaken.

10 Immunohistochemistry/molecular tests

10.1 Immunohistochemistry

Immunohistochemistry may be required in the differential diagnosis of metastatic tumours and for classification of renal tumours, particularly on small biopsy specimens. It is generally not necessary for RCCs that have typical morphology of clear cell, papillary or chromophobe RCCs. In cases where the morphology is complex, or the tumour has overlapping features of different tumour types (e.g. oncocytic tumours) or is of high grade, a low threshold for requesting immunohistochemistry is advisable and a panel of antibodies is recommended.

Extensive coverage of immunohistochemistry panels is beyond the scope of this dataset, as these will require updating and modification as new antibodies become available. Best-practice recommendations were published by ISUP in 2014^{121,122} and these provide a helpful approach to the judicious use of immunohistochemistry in clinical practice, with various suggested panels for use, depending upon the morphological differential diagnosis.

In the metastatic setting, the PAX-8 (nuclear stain) is regarded as the most useful antibody for confirming renal origin, because it is expressed in the different types of RCC.¹²³ PAX-8 is, however, also positive in thyroid tumours and those of Mullerian origin. Expression of CD10 is not specific enough to determine renal origin, but a negative result favours a non-renal primary malignancy and RCC is normally reliably negative for TTF1, CDX2, oestrogen receptor and PSA.¹²¹

For subtyping of renal tumours, CAIX is helpful, being positive in clear cell RCC even when high grade or sarcomatoid, and it shows a particular 'cup-like' staining pattern in the indolent clear cell papillary RCCs. It is negative in most other RCC tumour types. Caution is advised in interpretation of CAIX staining, however, as hypoxic tissue adjacent to necrotic zones in other tumour types may show CAIX expression.

CK7 is strongly positive in papillary RCC, in conjunction with AMACR (although type 2 papillary RCCs have a more variable staining pattern). Clear cell papillary RCCs are usually CK7 positive, but are AMACR negative. CK7 is also the most useful stain in aiding distinction between a chromophobe RCC (strong diffuse staining) and an oncocytoma (focal staining only permitted). The Hale's colloidal iron special stain is also positive in the former and negative in the latter, but is not available in all laboratories as it may be technically challenging to achieve reliable results. Attention to morphological features is particularly important in making this differential diagnosis. Features that do not exclude the diagnosis of an oncocytoma are focal atypia (degenerative type), perinephric fat infiltration (without a stromal reaction) and, although rare, vascular involvement.^{78,124} The presence of multiple mitoses, atypical mitoses or significant necrosis, however, is regarded as unacceptable for the diagnosis of an oncocytoma. Many other RCC tumour types may have eosinophilic cells and immunohistochemistry may be required to avoid misdiagnosis of tumours with similar morphology.¹²⁵

For tumours with high-grade epithelioid morphology, it is prudent to have a low threshold for excluding an epithelioid angiomyolipoma, using a combination of HMB45 and Melan-A (usually positive) and cytokeratin stains (usually negative), as these tumours may mimic grade 4 clear cell RCCs morphologically, especially if fat-poor.

The rare MiT family of RCCs typically show poor staining for cytokeratins and may be positive for melanoma markers (HMB45 and Melan-A), AMACR and cathepsin K.

Urothelial carcinoma may be difficult to distinguish from collecting duct carcinoma. Their immunoprofiles overlap, but PAX-8, p63 and GATA-3 are most useful in this scenario. PAX-8 is only positive in approximately 20% of urothelial carcinomas and the latter two antibodies should be positive in urothelial carcinoma, but not usually in collecting duct carcinoma.

A summary table of typical immunoprofiles of some renal tumours using the more commonly available antibodies is given at Appendix D. This is not an exhaustive list and, as with all immunohistochemistry, interpretation should be based on well-fixed areas and always correlated with the morphological findings.

10.2 Molecular studies and biomarkers

Fluorescence in situ hybridisation (FISH), conventional karyotyping or molecular cytogenetics may be required to determine the tumour type for the rarer tumour groups or for those with unusual morphology, and will be beyond the scope of many laboratories. FISH is particularly helpful for confirming the diagnosis of the MiT family translocation RCCs, with more reliable results than immunohistochemistry for TFE3/TFEB, although the latter may be helpful for selecting cases requiring assessment by FISH. Multiprobe FISH has also been reported to be useful in distinguishing between an oncocytoma and chromophobe RCC,¹ the latter typically showing multiple chromosome losses.

It is therefore recommended that expert referral for molecular studies is undertaken when tumours are encountered in (a) a younger age group of less than 30 years (and may be considered for patients between 30 and 40 years of age), (b) if there is a strong family history of renal tumours, (c) if there are multiple tumours (in the absence of a known genetic syndrome), (d) the tumour is believed to be a rare type with genetic associations (succinate dehydrogenase-deficient RCC, HLRCC-associated RCC) or (e) if the morphology is unusual.

Research into establishing reliable diagnostic, prognostic and predictive biomarkers and therapeutic molecular targets for RCC has revealed commonly mutated genes, such as VHL, BAP1, PBRM1, SETD2 and KDM5C.^{126–128} The potential prognostic use of proliferation markers, such as Ki-67, p53 and PTEN, has also been studied.¹²⁹ However, tumour heterogeneity poses a problem in the development of reliable biomarkers for routine clinical use, particularly on small biopsy specimens.^{130,131} Although BAP1 mutations have been

reported to be associated with aggressive disease and poor survival,^{128,132,133} there are currently no validated biomarkers with proven clinical utility over and above assessment of tumour grade and stage.^{29,121,134}

11 Criteria for audit

The following standards are suggested as criteria that might be used to audit aspects of the dataset:

- availability of pathology reports and data at MDT meetings (National Cancer Standards):
 - standard: 90% of cases discussed at MDT meetings where biopsies or resections have been taken should have pathology reports/core data available for discussion at the time of the meeting
 - standard: 90% of cases where pathology has been reviewed for the MDT meeting should have the process of review recorded.

Recommended by the RCPATH as key performance indicators

(<https://www.rcpath.org/profession/clinical-effectiveness/key-performance-indicators-kpi.html>):

- cancer resections must be reported using a template or proforma, including items listed in the English COSD, which are by definition core data items in RCPATH cancer datasets. English Trusts are required to implement the structured recording of core pathology data in the COSD by January 2016.
 - standard: 95% of cancers reported as structured data reflecting the cancer dataset.
- histopathology specimen report turnaround times:
 - standard: 80% within seven calendar days, 90% within 10 calendar days (a preliminary report may be issued in cases requiring referral or genetic analysis).

The following criteria may be assessed in periodic reviews of histological reports on renal tumour specimens:

- correlation between renal tumour biopsy reports and subsequent surgical resections
- surgical margin status of partial nephrectomy specimens.

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Appendix A TNM staging (UICC 7th and 8th editions)

UICC 7th edition (for use until 31st December 2017)

pT – Primary tumour

pTX Primary tumour cannot be assessed

pT0 No evidence of primary tumour

pT1 Tumour 7 cm or less in greatest dimension, limited to kidney

pT1a Tumour 4 cm or less

pT1b Tumour more than 4 cm but not more than 7 cm

pT2 Tumour more than 7 cm in greatest dimension, limited to the kidney

pT2a Tumour more than 7 cm but not more than 10 cm

pT2b Tumour more than 10 cm, limited to the kidney

pT3 Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia

pT3a Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia

pT3b Tumour grossly extends into the vena cava below the diaphragm

pT3c Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava

pT4 Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

pN – Regional lymph nodes

pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastasis

pN1 Regional lymph node metastasis

pM – Distant metastasis

pM1 Distant metastasis

Optional additional descriptors for T stage:

m = multiple primary tumours at a single site e.g. pT1b(m) – stating highest-stage tumour

y = for classification during/after multimodal therapy e.g. ypT2a

r = for recurrent tumours after a disease free period – use prefix r

Stage grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1–2	N1	M0
	T3	Any N	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

UICC 8th edition (for use from 1st January 2018)

pT – Primary tumour

- pTx Primary tumour cannot be assessed
pT0 No evidence of primary tumour
pT1 Tumour 7 cm or less in greatest dimension, limited to kidney
 pT1a Tumour 4 cm or less
 pT1b Tumour more than 4 cm but not more than 7 cm
pT2 Tumour more than 7cm in greatest dimension, limited to the kidney
 pT2a Tumour more than 7 cm but not more than 10 cm
 pT2b Tumour more than 10 cm, limited to the kidney
pT3 Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
 pT3a Tumour extends into the renal vein or its segmental branches, or tumour invades the pelvicalyceal system or tumour invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia
 pT3b Tumour extends into the vena cava below the diaphragm
 pT3c Tumour extends into the vena cava above the diaphragm or invades the wall of the vena cava
pT4 Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

pN – Regional lymph nodes

- pNx Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in regional lymph node(s)

pM – Distant metastasis

- pM1 Distant metastasis

Optional additional descriptors for T stage:

- m = multiple primary tumours at a single site e.g. pT1b(m) – stating highest-stage tumour
y = for classification during/after multimodal therapy e.g. ypT2a
r = for recurrent tumours after a disease free period – use prefix r

Stage grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1–2	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Appendix B SNOMED coding

Topographical codes are used in SNOMED to indicate the organ/site of lesions and morphological codes (M) are used to indicate the morphological diagnosis.

Topographical codes	SNOMED 2 or 3	SNOMED-CT terminology	SNOMED-CT code
Kidney	T71000	Kidney structure (body structure)	64033007

Morphological codes	SNOMED 2 or 3	SNOMED-CT terminology	SNOMED-CT code
Malignant neoplasm, NOS	M80003	Malignant neoplasm, primary (morphologic abnormality)	86049000
Clear cell renal cell carcinoma	M83103	Clear cell adenocarcinoma (morphologic abnormality)	30546008
Multilocular cystic renal cell neoplasm of low malignant potential	M83161	No code yet	No code yet
Papillary renal cell carcinoma	M82603	Papillary adenocarcinoma (morphologic abnormality)	4797003
Hereditary leiomyomatosis renal cell carcinoma-associated renal cell carcinoma	M83113	No code yet	No code yet
Chromophobe renal cell carcinoma	M83173	Renal cell carcinoma, chromophobe cell (morphologic abnormality)	128667008
Hybrid oncocytic chromophobe tumour	M83173	Renal cell carcinoma, chromophobe cell (morphologic abnormality)	128667008
Collecting duct carcinoma	M83193	Collecting duct carcinoma (morphologic abnormality)	128669006
Renal medullary carcinoma	M85103	Medullary carcinoma (morphologic abnormality)	32913002
MiT family associated translocation renal cell carcinomas	M83113	No code yet	No code yet
Succinate dehydrogenase-deficient renal cell carcinoma	M83113	No code yet	No code yet
Mucinous tubular and spindle cell carcinoma	M84803	Mucinous adenocarcinoma (morphologic abnormality)	72495009

Morphological codes	SNOMED 2 or 3	SNOMED-CT terminology	SNOMED-CT code
Tubulocystic renal cell carcinoma	M83163	Cyst-associated renal cell carcinoma (morphologic abnormality)	128666004
Acquired cystic disease-associated renal cell carcinoma	M83163	Cyst-associated renal cell carcinoma (morphologic abnormality)	128666004
Clear cell papillary renal cell carcinoma	M82551	No code yet	No code yet
Renal cell carcinoma, unclassified	M83123	Renal cell carcinoma (morphologic abnormality)	41607009

SNOMED-P (Procedure) codes

Local P codes should be recorded. At present, P codes vary according to the SNOMED system used in different institutions.

Appendix C WHO/ISUP grading system

Grade X	Grade cannot be assessed
G1	Nucleoli absent or inconspicuous and basophilic at 400x magnification
G2	Nucleoli conspicuous and eosinophilic at 400x magnification but inconspicuous at 100x magnification
G3	Nucleoli conspicuous and eosinophilic at 100x magnification
G4	Marked nuclear pleomorphism and/or multinucleate giant cells and/or rhabdoid and/or sarcomatoid differentiation

Reference images are available on the pathology imagebase at: <https://isupweb.org>

Appendix D Immunohistochemistry summary table

Tumour type	Positive	Negative
Clear cell RCC	CK, EMA, Vimentin, CD10, RCCm, CAIX , PAX8	CK7, CD117 , Cathepsin-K, HMB45, AMACR (or focal +)
Papillary RCC	CK, CK7, AMACR , RCCm, Vimentin	CD117, WT1, CD57, CAIX , Cathepsin K
Chromophobe RCC	CK, CK7 (diffuse) , CD117, E-Cadherin, EMA	Vimentin, CAIX, AMACR, Cathepsin-K, HMB45, RCCm
Oncocytoma	CD117, CK7 (focal + only)	Vimentin, HMB45, CAIX
Collecting duct RCC	CK7, HMWCK, PAX8, INI-1, EMA	CD10, RCCm, CK20, GATA3, CAIX, p63, OCT4
Medullary carcinoma	HMCK, OCT4, PAX8	INI-1, RCCm, GATA3, HMWCK, p63
Urothelial carcinoma	CK, CK7, CK20, p63, GATA3 , Vimentin, HMWCK	RCCm, CD10, PAX8 (20% +)
MiT family translocation RCCs	Cathepsin-K, TFE3/TFEB, RCCm HMB45-(t(6,11), Melan A-(t(6,11), AMACR, PAX8	CK (or weak +), EMA, CA-IX (or focal +)
Angiomyolipoma/epitheloid angiomyolipoma	HMB45, Melan-A, SMA , Cathepsin-K	CK, EMA, CK7, CA-IX, CD10, RCCm, PAX8, CD117
Clear cell papillary RCC	CK, CK7, CAIX (cup-like), HMWCK	AMACR , CD117, Cathepsin-K
Mucinous tubular and spindle cell carcinoma	CK7, AMACR, PAX8, EMA , E-cadherin, Vim (or neg), CrGA (occasional cases +)	CAIX, RCCm, CD10, p63, CK20, HMWCK
Metanephric adenoma	WT1, CD57, S100	AMACR, RCCm

CK = broad-spectrum cytokeratin

HMWCK = high-molecular-weight cytokeratin

RCC = renal cell carcinoma

Bold type denotes the most useful antibodies for inclusion in initial immunohistochemistry panels.

Appendix E Leibovich score

For clear cell renal cell carcinoma only, assess:

Primary tumour stage

pT1a	0
pT1b	2
pT2	3
pT3–4	4

Tumour size

<10cm	0
≥10cm	1

Regional lymph node status

pNx/pN0	0
pN1–pN2	2

Nuclear grade

1–2	0
3	1
4	3

Histologic (coagulative) tumour necrosis

No necrosis	0
Necrosis	1

Total above to give a score of 0–11

Low risk = 0–2

Intermediate risk = 3–5

High risk = 6 and above

Appendix F Reporting proforma for nephrectomy specimens

Surname: Forenames: Date of Birth: Sex:
Hospital: Hospital No: NHS No:
Date of Surgery: Date of Report Authorisation: Report No:
Date of Receipt: Pathologist: Clinician:

Previous treatment (neoadjuvant chemotherapy/radiotherapy) Yes No Not known

Nature of specimen/procedure and core macroscopic items

Specimen laterality

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

Operative procedure

Radical nephrectomy Simple nephrectomy Partial nephrectomy
Not specified Other

Adrenal gland Absent Present
Lymph nodes Absent Present Details:
IVC thrombus Absent Present
Other structures included (specify site):

Tumour focality

Unifocal Multifocal (Specify number of tumours) Cannot be assessed

Maximum tumour dimension (up to 5 tumours)mmmmmmmmmm

Tumour present (grossly) in major veins (renal vein, its segmental branches, inferior vena cava)

Not identified Uncertain Cannot be assessed
If present: Renal vein Renal vein and IVC

Core microscopic items

Histological tumour type:

Clear cell renal cell carcinoma
Multilocular cystic renal cell neoplasm of low malignant potential
Papillary renal cell carcinoma
Type 1 Type 2 Oncocytic NOS
Hereditary leiomyomatosis renal cell carcinoma-associated renal cell carcinoma
Chromophobe renal cell carcinoma
Hybrid oncocytic chromophobe tumour
Collecting duct carcinoma
Renal medullary carcinoma
MiT family associated translocation renal cell carcinomas
Xp11 t(6;11) Other (specify)
Succinate dehydrogenase (SDH)-deficient renal cell carcinoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Clear cell papillary renal cell carcinoma
Renal cell carcinoma, unclassified
Other (specify)

WHO/ISUP tumour grade

Not applicable GX – cannot be assessed G1 G2 G3 G4

Sarcomatoid morphology

Not identified Present

Rhabdoid morphology

Not identified Present

Tumour necrosis

Not identified Macroscopic (confluent) Microscopic (coagulative)
Cannot be assessed (e.g. post embolisation)

Microscopic extent of invasion

Perinephric fat invasion (tumour spread beyond renal capsule or within vessels in perinephric fat)

Not identified Present Cannot be assessed/Not applicable

Invasion beyond Gerota's fascia

Not identified Present Cannot be assessed/Not applicable

Renal sinus invasion

Not identified Cannot be assessed/Not applicable
Present in fat Present in vascular spaces Present in fat and vascular spaces

Tumour present in major veins microscopically (renal vein, its segmental branches, inferior vena cava)

Not identified Gross involvement confirmed microscopically
Microscopic involvement only Cannot be assessed/Not applicable

Lymphovascular invasion (Intrarenal or intratumoral)

Not identified Present

Tumour in the pelvic/lyceal system

Not identified Present Cannot be assessed/Not applicable

Tumour in adrenal gland (if present)

Not involved Cannot be assessed/Not applicable
Present, direct extension Present, metastasis

Tumour extending into other organs/structures (if present)

Not identified Cannot be assessed
Tumour present, specify sites

Regional lymph nodes status

Not applicable
Total number of lymph nodes examined
Number of positive lymph nodes..... Or Number cannot be determined
Size of largest focus mm
Extranodal extension Not identified Present Cannot be assessed

Resection margin status

Not involved Cannot be assessed
Involved
If involved, site: Renal vein IVC
Other (soft tissue/parenchymal etc) (specify)
If renal vein or IVC margin involved is there invasion of the vein wall? Yes No

Co-existing pathology in non-neoplastic kidney

Insufficient tissue for evaluation No background pathology identified
Present specify type:.....

Metastatic spread (if specimen submitted)

Not applicable Not identified
Present specify site:

Tumour stage (TNM edition UICC 7 UICC 8)

pT..... pN..... pM..... (M1 only, if applicable)

Signature:

Date:

SNOMED CODES:

Appendix G Reporting proforma for renal biopsy specimens

Surname: Forenames: Date of Birth: Sex:
Hospital: Hospital No: NHS No:
Date of Surgery: Date of Report Authorisation: Report No:
Date of Receipt: Pathologist: Clinician:

Nature of specimen/procedure and core macroscopic items

Core biopsy Wedge biopsy

Specimen laterality

Not specified
Left (Unifocal Multifocal
Right (Unifocal Multifocal
(Tick all appropriate options above, if bilateral)
Other (eg horseshoe): specify: (Unifocal Multifocal

Core microscopic items

Histological type:

Non-diagnostic (specify)
Clear cell renal cell carcinoma
Multilocular cystic renal cell neoplasm of low malignant potential
Papillary renal cell carcinoma
Type 1 Type 2 Oncocytic NOS
Hereditary leiomyomatosis renal cell carcinoma-associated renal cell carcinoma
Chromophobe renal cell carcinoma
Hybrid oncocytic chromophobe tumour
Collecting duct carcinoma
Renal medullary carcinoma
MiT family associated translocation renal cell carcinomas
Xp11 t(6;11) Other (specify)
Succinate dehydrogenase (SDH)-deficient renal cell carcinoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Clear cell papillary renal cell carcinoma
Renal cell carcinoma, unclassified
Other (specify)

WHO/ISUP tumour grade

Not applicable GX – cannot be assessed G1 G2 G3 G4

Sarcomatoid morphology

Not identified Present

Rhabdoid morphology

Not identified Present

Tumour necrosis

Not identified Present

Lymphovascular invasion

Not identified Present

Co-existing pathology in non-neoplastic kidney

Not applicable (e.g. insufficient tissue for evaluation)
No background pathology identified
Present specify type:

Signature:

Date:

SNOMED CODES:

Appendix H Reporting proforma for nephrectomy specimens in list format

Element name	Values	Implementation comments
Previous treatment (neoadjuvant chemotherapy/radiotherapy)	Single selection value list: <ul style="list-style-type: none"> • Yes • No • Not known 	
Specimen laterality	Single selection value list: <ul style="list-style-type: none"> • Right • Left • Not specified • Other 	
Specimen laterality, Other specify	Free text	Only applicable if 'Specimen laterality, Other' is selected.
Operative procedure	Single selection value list: <ul style="list-style-type: none"> • Radical nephrectomy • Simple nephrectomy • Partial nephrectomy • Not specified • Other 	
Adrenal gland	Single selection value list: <ul style="list-style-type: none"> • Absent • Present 	
Lymph nodes	Single selection value list: <ul style="list-style-type: none"> • Absent • Present 	
Lymph nodes, Details	Free text	Only applicable if 'Lymph nodes, Present' is selected.
IVC thrombus	Single selection value list: <ul style="list-style-type: none"> • Absent • Present 	
Other structures included	Free text	
Tumour focality	Single selection value list: <ul style="list-style-type: none"> • Unifocal • Multifocal 	

	<ul style="list-style-type: none"> • Cannot be assessed 	
Tumour focality, Multifocal, Specify number of tumours	Integer	Only applicable if 'Tumour focality, Multifocal' is selected.
Maximum tumour dimension 1	Integer	
Maximum tumour dimension 2	Integer	Only applicable if 'Tumour focality, Multifocal, Specify number of tumours' is >1.
Maximum tumour dimension 3	Integer	Only applicable if 'Tumour focality, Multifocal, Specify number of tumours' is >2.
Maximum tumour dimension 4	Integer	Only applicable if 'Tumour focality, Multifocal, Specify number of tumours' is >3.
Maximum tumour dimension 5	Integer	Only applicable if 'Tumour focality, Multifocal, Specify number of tumours' is >4.
Tumour present (grossly) in major veins	Single selection value list: <ul style="list-style-type: none"> • Present • Not identified • Uncertain • Cannot be assessed 	
Tumour present (grossly) in major veins, Present	Single selection value list: <ul style="list-style-type: none"> • Renal vein • Renal vein and IVC 	Only applicable if 'Tumour present (grossly) in major veins, Present' is selected.
Histological tumour type	Single selection value list: <ul style="list-style-type: none"> • Clear cell renal cell carcinoma • Multilocular cystic renal cell neoplasm of low malignant potential • Papillary renal cell carcinoma, type 1 • Papillary renal cell carcinoma, type 2 • Papillary renal cell carcinoma, oncocytic • Papillary renal cell carcinoma, NOS • Hereditary leiomyomatosis renal cell carcinoma-associated renal 	

	<p>cell carcinoma</p> <ul style="list-style-type: none"> • Chromophobe renal cell carcinoma • Hybrid oncocytic chromophobe tumour • Collecting duct carcinoma • Renal medullary carcinoma • MiT family associated translocation renal cell carcinomas, Xp11 • MiT family associated translocation renal cell carcinomas, t(6;11) • MiT family associated translocation renal cell carcinomas, Other • Succinate dehydrogenase (SDH)-deficient renal cell carcinoma • Mucinous tubular and spindle cell carcinoma • Tubulocystic renal cell carcinoma • Acquired cystic disease-associated renal cell carcinoma • Clear cell papillary renal cell carcinoma • Renal cell carcinoma, unclassified • Other 	
Histological tumour type, MiT family associated translocation renal cell carcinomas, Other, specify	Free text	Only applicable if 'Histological tumour type, MiT family associated translocation renal cell carcinomas, Other' is selected.
Histological tumour type, other specify	Free text	Only applicable if 'Histological tumour type, Other' is selected.
WHO/ISUP tumour grade	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Not applicable • GX • G1 • G2 	

	<ul style="list-style-type: none"> • G3 • G4 	
Sarcomatoid morphology	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Present • Not identified 	
Rhabdoid morphology	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Present • Not identified 	
Tumour necrosis	<p>Multiple selection value list:</p> <ul style="list-style-type: none"> • Macroscopic (confluent) • Microscopic (coagulative) • Not identified • Cannot be assessed 	
Perinephric fat invasion	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Present • Not identified • Cannot be assessed/Not applicable 	
Invasion beyond Gerota's fascia	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Present • Not identified • Cannot be assessed/Not applicable 	
Renal sinus invasion	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Present in fat • Present in vascular spaces • Present in fat and vascular spaces • Not identified • Cannot be assessed/Not applicable 	
Tumour present in major veins microscopically	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Gross involvement confirmed microscopically • Microscopic involvement only • Not identified • Cannot be assessed/Not applicable 	

Lymphovascular space invasion	Single selection value list: <ul style="list-style-type: none"> • Present • Not identified 	
Tumour in the pericalyceal system	Single selection value list: <ul style="list-style-type: none"> • Present • Not identified • Cannot be assessed/Not applicable 	
Tumour in adrenal gland	Single selection value list: <ul style="list-style-type: none"> • Present, direct extension • Present, metastasis • Not identified • Cannot be assessed/Not applicable 	
Tumour extending into other organ/structures	Single selection value list: <ul style="list-style-type: none"> • Tumour present • Not identified • Cannot be assessed 	
Tumour extending into other organ/structures, specify	Free text	Only applicable if 'Tumour extending into other organ/structures, Tumour present' is selected.
Regional lymph node status	Single selection value list: <ul style="list-style-type: none"> • Applicable • Not applicable 	
Total number of lymph nodes examined	Integer	
Number of positive lymph nodes	Integer	
Number of lymph nodes cannot be determined	Single selection value list: <ul style="list-style-type: none"> • True • False 	False if number of positive nodes >0
Size of largest focus	Size in mm	
Extranodal extension	Single selection value list: <ul style="list-style-type: none"> • Present • Not identified • Cannot be assessed 	

Resection margin status	Single selection value list: <ul style="list-style-type: none"> Involved Not involved Cannot be assessed 	
Resection margin status, Involved site	Single selection value list: <ul style="list-style-type: none"> Renal vein IVC Other 	Only applicable if 'Resection margin status, Involved' is selected.
Resection margin status, Involved site, Other	Free text	Only applicable if 'Resection margin status, Involved site, Other' is selected.
Resection margin status, Renal vein or IVC margin vein wall invasion	Single selection value list: <ul style="list-style-type: none"> Yes No 	Only applicable if 'Resection margin status, Involved site, Other' is selected.
Co-existing pathology in non-neoplastic kidney	Single selection value list: <ul style="list-style-type: none"> Insufficient tissue for evaluation No background pathology identified Present 	
Co-existing pathology in non-neoplastic kidney, specify	Free text	Only applicable if 'Co-existing pathology in non-neoplastic kidney, Present' is selected.
Metastatic spread	Single selection value list: <ul style="list-style-type: none"> Present Not identified Not applicable 	
Metastatic spread, specify	Free text	Only applicable if 'Metastatic spread, Present' is selected.
TNM edition	Single selection value list: <ul style="list-style-type: none"> UICC7 UICC8 	
pT category	Single selection value list: <ul style="list-style-type: none"> pTX pT0 pT1a pT1b 	

	<ul style="list-style-type: none"> • pT2a • pT2b • pT3a • pT3b • pT3c • pT4 • ypTX • ypT0 • ypT1a • ypT1b • ypT2a • ypT2b • ypT3a • ypT3b • ypT3c • ypT4 	
pN category	<p>Single selection value list:</p> <ul style="list-style-type: none"> • pNX • pN0 • pN1 • ypNX • ypN0 • ypN1 	
pM category	<p>Single selection value list:</p> <ul style="list-style-type: none"> • pM1 • ypM1 • Not applicable 	
SNOMED Topography code	<p>May have multiple codes. Look up from SNOMED tables.</p>	
SNOMED Morphology code	<p>May have multiple codes. Look up from SNOMED tables.</p>	

Appendix I Reporting proforma for renal biopsy specimens in list format

Element name	Values	Implementation comments
Nature of specimen	Single selection value list: <ul style="list-style-type: none"> • Core biopsy • Wedge biopsy 	
Specimen laterality	Multiple selection value list: <ul style="list-style-type: none"> • Right • Left • Other (e.g. horseshoe) 	
Left focality	Single selection value list: <ul style="list-style-type: none"> • Unifocal • Multifocal 	Only applicable if 'Specimen laterality, Left' is selected.
Right focality	Single selection value list: <ul style="list-style-type: none"> • Unifocal • Multifocal 	Only applicable if 'Specimen laterality, Left' is selected.
Specimen laterality, Other, specify	Free text	Only applicable if 'Specimen laterality, Other' is selected.
Other focality	Single selection value list: <ul style="list-style-type: none"> • Unifocal • Multifocal 	Only applicable if 'Specimen laterality, Other' is selected.
Histological tumour type	Single selection value list: <ul style="list-style-type: none"> • Clear cell renal cell carcinoma • Multilocular cystic renal cell neoplasm of low malignant potential • Papillary renal cell carcinoma, type 1 • Papillary renal cell carcinoma, type 2 • Papillary renal cell carcinoma, oncocytic • Papillary renal cell carcinoma, NOS • Hereditary leiomyomatosis renal cell carcinoma-associated renal cell carcinoma • Chromophobe renal cell carcinoma • Hybrid oncocytic chromophobe 	

	<p>tumour</p> <ul style="list-style-type: none"> • Collecting duct carcinoma • Renal medullary carcinoma • MiT family associated translocation renal cell carcinomas, Xp11 • MiT family associated translocation renal cell carcinomas, t(6;11) • MiT family associated translocation renal cell carcinomas, Other • Succinate dehydrogenase (SDH)-deficient renal cell carcinoma • Mucinous tubular and spindle cell carcinoma • Tubulocystic renal cell carcinoma • Acquired cystic disease-associated renal cell carcinoma • Clear cell papillary renal cell carcinoma • Renal cell carcinoma, unclassified • Other 	
Histological tumour type, MiT family associated translocation renal cell carcinomas, Other, specify	Free text	Only applicable if 'Histological tumour type, MiT family associated translocation renal cell carcinomas, Other' is selected.
Histological tumour type, Other, specify	Free text	Only applicable if 'Histological tumour type, Other' is selected.
WHO/ISUP tumour grade	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Not applicable • GX • G1 • G2 • G3 • G4 	
Sarcomatoid morphology	Single selection value list:	

	<ul style="list-style-type: none"> • Present • Not identified 	
Rhabdoid morphology	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Present • Not identified 	
Tumour necrosis	<p>Multiple selection value list:</p> <ul style="list-style-type: none"> • Present • Not identified 	
Lymphovascular space invasion	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Present • Not identified 	
Co-existing pathology in non-neoplastic kidney	<p>Single selection value list:</p> <ul style="list-style-type: none"> • Insufficient tissue for evaluation • No background pathology identified • Present 	
Co-existing pathology in non-neoplastic kidney, specify	Free text	Only applicable if 'Co-existing pathology in non-neoplastic kidney, Present' is selected.
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	<p>At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type</p> <p>or</p> <p>A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.</p>
Grade B	<p>A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type</p> <p>or</p> <p>Extrapolation evidence from studies described in A.</p>
Grade C	<p>A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type</p> <p>or</p> <p>Extrapolation evidence from studies described in B.</p>
Grade D	<p>Non-analytic studies such as case reports, case series or expert opinion</p> <p>or</p> <p>Extrapolation evidence from studies described in C.</p>
Good practice point (GPP)	<p>Recommended best practice based on the clinical experience of the authors of the writing group.</p>

Appendix K AGREE monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Foreword
2 The health question(s) covered by the guideline is (are) specifically described	1
3 The population (patients, public etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	1
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword, 1
12 There is an explicit link between the recommendations and the supporting evidence	3–10
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–10
16 The different options for management of the condition or health issue are clearly presented	3–10
17 Key recommendations are easily identifiable	5, 6
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–I
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	11
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword