Scope of the Guidelines

The reporting of renal cell carcinoma is facilitated by the provision of a checklist to ensure that pathologists provide all of the essential information to enable clinicians to optimize patient care. Classification of renal tumors is complicated by the wide range of morphologic types of renal cell carcinoma, some of which have recognized subtypes. Cytogenetic data have clarified the morphologic features of some of these tumors, but such data are not routinely available to assist most practicing pathologists attempting to classify individual tumors. Nevertheless, consideration should be given to cytogenetic evaluation for renal cortical tumors in young patients or tumors of unusual morphologic appearance regardless of the age of the patient. It is also important to note that although the biologic aggressiveness differs for the different types of renal cell carcinoma, staging and grading of renal cell carcinoma are driven by the behavior of clear cell carcinoma, the overwhelmingly most common subtype.

Several aspects of renal cell carcinoma classification remain problematic. Despite the large and growing number of renal cell carcinoma subtypes, classification of well-differentiated, low-grade tumors is relatively routine. However, with increasing tumor grade, the features by which renal cell carcinomas are classified may be lost or are at least obscured. Subclassifications of papillary renal cell carcinoma have been proposed but do not clearly have prognostic relevance independent of nuclear grade. The grading scheme proposed by Fuhrman et al and modifications thereof are used to grade clear cell renal carcinomas, but this scheme was developed before many renal cell carcinoma subtypes were recognized and may not be applicable to other subtypes. Difficulties also arise with respect to the stage of a renal carcinoma. In particular, it is difficult to assess the point at which a carcinoma has extended beyond the kidney. Based on the most current data, this guideline attempts to address these problematic points and suggest reasonable means of providing the information called for in the accompanying checklist.

Features the Association Recommends for Inclusion in the Final Report

These features are selected on the basis that they are generally accepted as being of prognostic importance, required for therapy, and/or traditionally expected. The guidelines adhere to the recommendations of the 2002 American Joint Committee on Cancer (AJCC) Cancer Staging Manual, the prognostic relevance of which has been validated. However, it is important to note that the recommendations are dynamic and are intended to change according to the state of current knowledge to optimize the prognostic usefulness of the TNM system. Particular attention is given to stage groupings of the TNM system that new data suggest contain subsets of disease with significantly different outcome. For example, patients with perinephric fat invasion and patients with direct ipsilateral adrenal involvement have pT3a disease, but several recent studies suggest that adrenal involvement confers a significantly worse prognosis. This information may encourage a pathologist to thoroughly sample the adrenal even in a patient with clear evidence of perinephric fat invasion.
I. Gross description

A. How the specimen was received: eg, fresh, in formalin, intact, fragmented, morcellated
B. How the specimen was identified: labeled (name, medical record number) and designated (eg, right radical nephrectomy).
C. If the specimen is a radical nephrectomy specimen, inspect the external aspect of the specimen (Gerota fascia) for evidence of tumor. Locate the ureteral and vascular margins in the renal hilus. These may be sampled before inking the specimen when they are most easily identified. A hemostatic forceps should be placed on the ureter so that it remains clear during and after inking. Ink the entire surface of the specimen. Cannulate the ureter using a small metal probe. Open the ureter longitudinally up to the level of the pelvis. Place the probe into a superolateral calyx, and push through the renal parenchyma and perinephric soft tissue. Place a second probe in an inferolateral calyx, and push through the renal parenchyma and perinephric soft tissue such that the 2 probes are now perpendicular to each other. Use a long, sharp knife to bivalve the kidney starting at its convex surface along the line of the metal probes. In this way, the kidney is opened along the collecting system. The renal veins should be subsequently opened to identify intravenous extension of tumor. Make additional cuts parallel or perpendicular to the first cut as necessary to cut the neoplasm along its greatest dimensions. In addition, cuts should be made to permit optimal viewing of the interface between the neoplasm and the perinephric fat because this is critical for assessing whether the neoplasm invades the perinephric fat and whether it approaches the margin of resection.

A partial nephrectomy may be performed for clinical stage T1a tumors. For such specimens, ink the renal parenchymal resection margin and “bread loaf” the tumor perpendicular to the inked surface. Vascular and ureteral structures generally do not accompany partial nephrectomy specimens. The perinephric soft tissue will also usually not be included, although sinus fat may be and must be carefully examined if it is present (see E, “Tumor description,” No. 4). The important clinical information for partial nephrectomies is usually only tumor type, size, and renal parenchymal margin status, but some urologists will submit a separate specimen consisting of overlying perinephric fat for evaluation of tumor involvement.

D. Length of ureter, other structures included (eg, adrenal)

E. Tumor description

1. Site within the kidney: State whether the tumor is located at the superior or inferior pole or in the mid portion of the kidney. If possible, determine whether the tumor is centered on the medulla or cortex. This information is important for some tumor types (eg, collecting duct carcinoma) in which the site of origin may support the diagnosis.

2. Size in 3 dimensions

3. Gross characteristics: Describe the color and consistency of the tissue and the degree of heterogeneity. State whether the tissue is friable and whether there are areas of necrosis and hemorrhage. Note and sample any areas with a homogeneous, tan, bulging surface (so-called fish-flesh quality), which may represent sarcomatoid dedifferentiation.

4. The relationship to the perinephric soft tissue. Determine whether the tumor protrudes into the perinephric soft tissue. Many renal cell carcinomas are large enough to distort the renal capsule and create a fungiform protrusion into the perinephric soft tissue, which alone is not sufficient to qualify as perinephric soft tissue invasion. Determine whether the interface between tumor and soft tissue is smooth and contoured with a pushing border (features that argue against soft tissue invasion) or irregular (a feature that suggests soft tissue invasion). The identification of separate tumor nodules in the perinephric fat by gross examination is diagnostic of pT3 disease. Under the 2002 AJCC system, extension into the renal sinus fat is also regarded as extrarenal extension (pT3a). In 1 study that specifically addressed extension into the sinus fat, this was a vastly more common route of perinephric soft tissue extension. In that study, no tumor penetrated the capsule that had not also invaded the sinus. In addition, the earliest evidence of macroscopic venous invasion (pT3b) is seen in the sinus fat. In fact, it has been suggested that sinus fat involvement begins as venous invasion, at least in clear cell carcinoma. In comparison with patients with only perinephric fat invasion by clear cell renal cell carcinoma, patients with sinus fat invasion seem to have a worse prognosis.

5. Renal vein invasion: Macroscopic invasion of veins in the renal sinus and beyond indicates a pT3b tumor. Whether the venous tumor is present only as a thrombus or invades the venous wall should also be noted because the latter is associated with a
worse prognosis. While the only assessment required by the AJCC is whether the thrombus extends to the diaphragm, some studies have suggested that the prognosis is adversely affected by increasing distal extension of the tumor thrombus.13,14 These studies have correlated the degree of extension with the relationship to anatomic structures such as the hepatic veins. Although such correlations require clinical and/or radiologic information, it is recommended that a measurement be given from the tip of the thrombus to the renal sinus.

F. Additional pathology (eg, hydronephrosis, pyelonephritis, arteriolonephrosclerosis): It is recommended that an additional stain be ordered up-front on the nonneoplastic renal parenchyma. This stain may be a periodic acid–Schiff or a silver stain such as Jones methenamine silver. These stains enhance the review of the glomerular architecture and also serve as a prompt to address the condition of the nonneoplastic kidney. This is important because diseases such as diabetic nephropathy and hypertensive nephrosclerosis are common in the renal cell carcinoma age group.15

G. Adrenal involvement: Involvement of the adrenal by renal cell carcinoma can be reliably determined by computed tomography scan.16–18 As a result, adrenalectomy may not be performed as a component of a radical nephrectomy. In the current TNM classification, direct involvement of the adrenal is indicative of a pT3a tumor, whereas if the adrenal is involved by metastatic renal cell carcinoma, the finding requires a designation of M1 and does not affect the pT classification. Several studies have suggested that adrenal involvement, even by direct extension, is an ominous finding and should warrant a designation of pT4.5,7

H. Lymph nodes: Involvement of regional lymph nodes is an adverse prognostic indicator.19–21 This appears to be true even in patients who already have distant metastases.19,22,23 The regional nodes may be designated renal hilar, paracaval, aortic (para-aortic, peri-aortic, or lateral aortic), or retroperitoneal, not otherwise specified.3 At least 80% of the time, lymph nodes are not identified in a radical nephrectomy specimen.24 Based on the last 1,000 radical nephrectomy specimens at Stanford Hospital, Stanford, CA, renal hilar lymph nodes were identified at gross dissection in surgical pathology in only 5% of cases. Enlarged nodes from the renal hilus are often separately submitted by the urologist. According to the AJCC, if a lymph node dissection is performed, it should ordinarily include at least 8 nodes.3

I. Tissue submitted for special investigation. In patients younger than 20 years, tissue should, if possible, be submitted for cytogenetics. Although it must be acknowledged that translocation carcinomas occur across the entire age spectrum, they represent a much higher fraction of pediatric carcinomas.25 If a frozen section of the tumor reveals unusual morphologic features in an adult, cytogenetics should be considered and frozen tissue should be procured. Although karyotypic information may be helpful in the classification of common types of renal cell carcinoma, its greatest value is clearly in the diagnosis of translocation carcinomas.

II. Diagnostic information

A. Laterality of tumor and type of resection
B. Histologic type: the World Health Organization 2004 classification of renal cell carcinoma is recommended.26

1. Clear cell carcinoma
2. Multilocular cystic carcinoma
3. Papillary carcinoma
4. Chromophobe carcinoma
5. Mucinous tubular and spindle carcinoma
6. Collecting duct carcinoma
7. Medullary carcinoma
8. Translocation carcinomas (include Xp11 and 6:11)
9. Tubulocystic carcinoma
10. Acquired cystic disease–associated carcinoma
11. Renal cell carcinoma, unclassified
12. Other (specify)

Outcome for renal cell carcinoma has been strongly correlated with histologic tumor type,1,27,28 and accurate classification of renal cell carcinomas is essential. The different types of tumor and the features necessary for diagnosis are very well demonstrated in the 2004 World Health Organization monograph.29 Readers are referred to that resource for most questions of classification. Only selected topics in classification are addressed herein.

Two types of papillary renal cell carcinoma have been recognized.30–32 Type 1 carcinomas are composed of basophilic cells with scant cytoplasm arranged in a single layer, whereas type 2 carcinomas have more abundant, often eosinophilic cytoplasm and pseudostratified nuclei. Some groups have found a better prognosis for type 1 tumors.33,34 Although the 2 types have been demonstrated to correlate with nuclear grade,1,35 some authors recommend that an attempt be made to separate papillary tumors into the 2 proposed types.

A difficulty also exists with tumors that show papillary architecture but clear cell cytologic features. Some such tumors have been found to have cytogenetic changes typical of clear cell carcinoma.36,37 This would support a practice of classifying these tumors as clear cell carcinoma;
Assessment for perinephric fat invasion is often not straightforward. Most renal cell carcinomas bulge into the perinephric soft tissue in a circumscribed manner with pushing borders as noted in the gross description section. Histologically, one should identify carcinoma cells admixed with adipocytes without intervening fibrous tissue before diagnosing extrarenal spread of carcinoma. We suspect that perinephric fat invasion is often overdiagnosed in general practice and suggest that when doubt exists, one should adhere to the requirement of carcinoma infiltrating adipocytes.

E. Presence of necrosis: Coagulative tumor cell necrosis has been found to be of prognostic significance for clear cell and chromophobe carcinomas\textsuperscript{7,34,43,44} and should therefore be reported.

F. Extent of local tumor spread: This extent is based on the T component of the TNM classification.

1. Primary tumor cannot be assessed (TX)
2. No evidence of primary tumor (T0)
3. Tumor measures 7 cm or less and is confined to the kidney (T1)
4. Tumor measures less than 4 cm and is confined to the kidney (T1a)
5. Tumor measures more than 4 cm but less than 7 cm and is confined to the kidney (T1b)
6. Tumor measures more than 7 cm but is confined to the kidney (T2)
7. Tumor extends into major veins or directly invades adrenal gland or perinephric fat but not beyond Gerota fascia (T3)
8. Tumor directly invades adrenal gland or perinephric fat but is not beyond Gerota fascia (T3a)*
9. Tumor extends into renal vein(s) segmental (muscle containing) branches or vena cava or its wall below the diaaphragm (T3b)
10. Tumor extends into vena cava above the diaaphragm of the wall of the vena cava (T3c)
11. Tumor extends beyond Gerota fascia (T4)

*Assessment for perinephric fat invasion is often not straightforward. Most renal cell carcinomas bulge into the perinephric soft tissue in a circumscribed manner with pushing borders as noted in the gross description section. Histologically, one should identify carcinoma cells admixed with adipocytes without intervening fibrous tissue before diagnosing extrarenal spread of carcinoma. We suspect that perinephric fat invasion is often overdiagnosed in general practice and suggest that when doubt exists, one should adhere to the requirement of carcinoma infiltrating adipocytes.

G. Microscopic evidence of angiolymphatic invasion should be assessed and documented.

H. Margins of resection

1. No tumor identified at margins
2. Tumor present at renal parenchymal margin of resection (partial nephrectomy)
3. Tumor present at soft tissue margin of resection
4. Intravascular tumor present at venous margin of resection
5. Tumor is present at ureter margin
6. Other

I. Lymph node metastases: Not surprisingly, the presence of lymph node metastases adversely affects
### Special Article / Renal Cell Carcinoma Guideline

**Association of Directors of Anatomic and Surgical Pathology**  
**Final Anatomic Diagnosis Checklist**  
**Renal Cell Carcinoma**  
*(Excluding Pediatric Renal Tumors and Tumors of the Renal Pelvis)*

<table>
<thead>
<tr>
<th>Accession No.</th>
<th>Part No.</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Name:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Organ
- Kidney
- Kidney and adrenal
- Other ________________________________

#### Site
- Right
- Left
- Other ________________________________

#### Operation
- Radical nephrectomy
- Radical nephrectomy and adrenalectomy
- Partial nephrectomy
- Other ________________________________

#### Specimen Weight (Required) ________________

#### Tumor Size (Required) _______ × ______ × ______ cm

#### Other Gross Features (Required)
Describe appearance of tumor, location within the renal lobe with respect to cortex vs medulla, if possible, presence of necrosis, extension into the perinephric fat or the fat of the renal sinus, macroscopic invasion of veins

#### Tumor Type (World Health Organization 2004) (Required)
- Clear cell carcinoma
- Multilocular cystic carcinoma
- Papillary carcinoma (optional: specify type 1 vs type 2)
- Chromophobe cell carcinoma
- Mucinous tubular and spindle carcinoma
- Collecting duct carcinoma
- Medullary carcinoma
- Translocation carcinomas (includes Xp11 and 6:11)*
- Tubulocystic carcinoma*
- Acquired cystic disease–associated carcinoma (specify subtype)*
- Renal cell carcinoma, unclassified
- Other ________________________________

* These tumors, although not listed in the 2004 World Health Organization classification, are now well recognized and will likely be included in future editions. Any subtype of renal cell carcinoma might be seen in the setting of acquired cystic kidney disease, but papillary and clear cell types are most common and should be reported as such. The tumor described as “acquired cystic disease–associated renal cell carcinoma” by Tickoo et al1 appears to be a distinct subtype.

#### Histologic Grade (Required)
1. (small nuclei resemble those of mature lymphocytes)
2. (larger nuclei with more open chromatin and small nucleoli)
3. (nucleoli readily visible on examination with ×10 objective)
4. (marked nuclear pleomorphism, multiple macronucleoli)

#### Not applicable (applies to chromophobe carcinoma)

#### Sarcomatoid Dedifferentiation
- Sarcomatoid dedifferentiation is not identified
- Areas of sarcomatoid dedifferentiation are identified
- Specify percentage of total tumor: ________________________________

#### Depth of Tumor Invasion (Required)
- Primary tumor cannot be assessed (TX)
- No evidence of primary tumor (T0)
- Tumor measures 7 cm or less and is confined to the kidney (T1)
- Tumor measures less than 4 cm and is confined to the kidney (T1a)
- Tumor measures more than 4 cm but less than 7 cm and is confined to the kidney (T1b)
- Tumor measures more than 7 cm but is confined to the kidney (T2)
- Tumor extends into major veins or directly invades adrenal gland or perinephric fat but not beyond Gerota fascia (T3)
- Tumor directly invades adrenal gland or perinephric fat but not beyond Gerota fascia (T3a)
- Tumor extends into renal vein(s) or vena cava or its segmental (muscle-containing) branches or vena cava below the diaphragm (specify presence/absence of wall invasion) (T3b)
- Tumor extends into vena cava above the diaphragm or the wall of the vena cava (T3c)
- Tumor extends beyond Gerota fascia (T4)
Microscopic Angiolymphatic Invasion (Required)
Identified
Not identified

Margins of Resection (Required)
No tumor identified at margins
Tumor present at renal parenchymal margin of resection (partial nephrectomy)
Tumor present at soft tissue margin of resection
Intravascular tumor present at venous margin of resection (specific presence or absence of wall invasion)*
Tumor is present at ureter margin
Other __________________________________________________________________________
* Retraction of vein over fully resected tumor must be excluded.

Lymph Nodes, Regional* (Required)
Number examined ______________________________________________________________________
Number positive _______________________________________________________________________
Comments ____________________________________________________________________________
* Regional lymph nodes include renal hilar, paracaval, para-aortic, periaortic, lateral aortic, and retroperitoneal, not otherwise specified.

Additional Findings (Required)
Acquired cystic renal disease, diabetic nephropathy, arterioknephrosclerosis, pyelonephritis, papillary adenoma,
tubulopapillary hyperplasia, cysts
Specify ______________________________________________________________________________

Adrenal Gland (Optional)
No histopathologic changes present
Tumor directly invades the adrenal gland (T3a)
Adrenal involved by metastasis (M1)
Nodular/diffuse cortical hyperplasia present
Cortical adenoma is present (specify size)
Other ______________________________________________________________________________

Ancillary Studies (Optional)

pTN Stage* (Required)
A. Primary tumor
pTX Primary tumor cannot be assessed
pT0 No evidence of primary tumor
pT1a Tumor 4 cm or less, confined to kidney
pT1b Tumor 7 cm or less, confined to kidney
pT2 Tumor more than 7 cm, confined to kidney
pT3a Tumor directly invades adrenal gland or perinephric tissues but not beyond Gerota fascia
pT3b Tumor grossly extends into renal vein(s) or segmental (muscle-containing) branches or vena cava or below diaphragm
pT3c Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava
pT4a Tumor invades other organs or structures
pT4b Tumor perforates visceral peritoneum
B. Regional lymph nodes
pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in a single regional lymph node
pN2 Metastasis in more than 1 regional lymph node
C. Distant metastasis
pMX Cannot be assessed
pM0 No distant metastasis
pM1 Distant metastasis

References
the outcome of patients with renal cell carcinoma. The number of nodes sampled and the number positive should be reported. Although the prognosis may not be adversely affected by an increasing number of positive nodes (pN1 vs pN2) or the size of the largest metastatic focus, these should be reported. The prognosis seems to be significantly adversely affected by extranodal extension of the metastatic focus and, therefore, it is recommended that this be assessed and reported as well.  

References


* Committee members are John P. Higgins, MD (chair), Jesse K. McKenney, MD, James D. Brooks, MD, Pedram Argani, MD, and Jonathan I. Epstein, MD, from the Departments of Pathology and Urology, Stanford University, Stanford, CA; and Pathology, Johns Hopkins Medical Institutions, Baltimore, MD.

Address reprint requests to Dr Higgins: Dept of Pathology, Room L235, Stanford University, 300 Pasteur Dr, Stanford, CA 94305.


