Histologic Diagnosis of Renal Mass Biopsy

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- Context.—Core biopsy has been increasingly used for clinical decision-making in the management of patients with renal masses. The sensitivity and specificity of histologic diagnoses of renal mass biopsies depend on many factors such as adequate sampling and tissue processing, diagnostic skill and experience, and appropriate use of ancillary techniques.

Objective.—To review the indications, emphasize the importance of obtaining adequate diagnostic material, and introduce a general diagnostic approach, in conjunction with immunohistochemistry, in diagnosis of renal mass biopsies.

Data Sources.—Literature review and personal experiences in daily practice and consultation diagnosis of renal masses in a large tertiary medical center.

The incidence of small renal masses has steadily increased during the last few decades in the United States and globally. One of the main reasons is the widespread use of abdominal imaging for nonspecific symptoms or diseases and follow-up of patients with a cancer diagnosis. In the past several years, significant advances in the treatment of renal tumors, such as increased nephron-sparing partial nephrectomy rather than radical nephrectomy, have been noted. Also, a few emerging treatment modalities, such as active surveillance and ablative therapies, have become routinely available. Recently, a number of effective molecular targeted therapies for specific types of renal cell carcinoma (RCC) were established for patients with advanced or metastatic disease. In addition, owing to the advances in biopsy techniques, complications from biopsies are extremely rare and morbidity is very low. As a result, pathologists are increasingly called upon to make diagnoses based on core needle biopsies of renal masses.

INDICATIONS AND OBJECTIVES

The indications for renal mass biopsy continue to expand, they include but are not limited to the following: (1) ruling out metastasis in patients versus a second primary renal tumor in patients who have renal and other primary tumors; (2) ruling out recurrence in patients who have a history of renal tumor; (3) confirming that patients have multiple synchronous tumors; (4) ruling out the possibilities of infection/abscess or lymphoma; (5) evaluating whether the patients are candidates for active surveillance or ablative therapy; and (6) establishing a histologic diagnosis for targeted therapies or enrollment in clinical trials for patients presenting with disseminated metastasis or unresectable tumors.

The overall objective of renal mass biopsy is to establish the histologic diagnosis by following sequential steps: (1) determine whether a renal mass is a neoplasm or not; (2) in the case of a neoplasm, determine if it is benign or malignant; (3) establish the final histologic diagnosis, and to a lesser extent, provide a grade if the tumor is malignant; and (4) report any additional adverse prognostic features.

ADEQUACY, SENSITIVITY, AND SPECIFICITY

To make core biopsy diagnosis of a renal mass, it is critical to obtain adequate diagnostic material and establish a standard laboratory procedure in working with small biopsy specimens. The key for the diagnosis is to be familiar with different tumor entities with characteristic morphology and to understand the wide spectrum of tumor heterogeneity. By developing a systematic approach, one can categorize the tumor and create a sensible differential diagnosis based on the growth pattern and cellular morphology. Immunohistochemistry is particularly helpful for renal mass biopsy diagnosis in selected situations.

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There are many challenges in accurate histologic diagnosis of renal masses with high accuracy. The data reported in the literature indicate excellent sensitivity and specificity on histologic diagnosis of renal mass biopsies. Generally, pathologists can distinguish very accurately between benign (including nonneoplastic) and malignant neoplasms with nearly 100% specificity. Also, pathologists can accurately determine the histologic subtypes of tumors.

However, assignment of tumor grade has not been very accurate owing to small sampling size and frequent intratumoral heterogeneity in renal tumors.

### DIAGONSTIC APPROACHES OF RENAL MASS BIOPSY

There are many challenges in accurate histologic diagnosis of renal masses by core biopsy. First, the limited core biopsy material may not represent all the diagnostic features that are required for a specific histologic diagnosis. Second, classification of renal neoplasms is becoming increasingly more complex; the current 2016 World Health Organization classification recognizes 16 distinct types of renal neoplasms (Table 1). Third, there are no morphologic features that are diagnostic of a certain histologic type of tumor, that is, one type of tumor can have many histologic growth patterns and/or cytologic features, and conversely, one growth pattern or cytologic feature can be seen in a variety of tumor types.

The pathologic diagnosis of renal mass biopsy should start by evaluating the adequacy of diagnostic material on each core(s) and levels of multiple sections. During this step, the pathologist assesses the presence of clonal neoplastic cells and their relationship with adjacent normal renal parenchyma (if present); this step quickly rules out the possibility of a nonneoplastic process. Then the pathologist should attempt to classify the tumor in the following broad categories: tumors with clear cells, tumors with papillary growth pattern, tumors with oncocytic cells, tumors with predominantly cystic component, tumors with spindle cells, and high-grade carcinomas lacking classic morphologic features of known types of RCCs. At the same time, the pathologist should also look for additional features that are characteristic for specific types of tumors, as we will discuss below. Along with the initial diagnostic category, the pathologist should take into consideration the patient’s age and sex, tumor size, location, and imaging characteristics of the tumor, as well as the frequency of renal cortical tumors. Apart from the 2 most common benign tumors—oncocytoma and angiomylolipoma—the first group includes the 5 most common types of RCC: clear cell, papillary, chromophobe, clear cell papillary, and unclassified RCCs. The second group comprises the less common types: collecting duct carcinoma, multilocular cystic renal neoplasm of low malignant potential, mucinous tubular spindle cell carcinoma, acquired cystic disease-associated RCC, and tubulocystic RCC. The third group comprises pediatric and young-adult tumors, including microphthalmia transcription factor–family translocation–associated RCC and medullary carcinoma. The fourth group comprises tumors associated with familial syndromes, such as von Hippel-Lindau–associated clear cell RCC; hereditary leiomyomatosis and renal cell carcinoma syndrome–associated RCC; and succinate dehydrogenase–deficient RCC.

### CATEGORIZATION AND DIAGNOSIS OF RENAL TUMORS

The most common neoplasms that are routinely encountered are clear cell, papillary, chromophobe RCCs, and oncocytoma, which together account for nearly 90% of all renal cortical tumors.

One newer entity is clear cell papillary RCC, which has been established as one of the common types of RCC, and accounts for 3% to 4% of these tumors. All the others are rare tumors.

Tumors with clear cells obviously are the most common type of renal masses that pathologists encounter. In addition to clear cell RCC, the differential diagnosis should include several other types of RCCs in which the tumor may be primarily composed of clear cells, such as chromophobe, clear cell papillary, and Xp11 translocation and papillary RCCs. Clear cells can also be predominant in renal urothelial carcinoma. Rarely, angiomylolipoma, particularly the epithelioid form, may contain pale eosinophilic to clear cytoplasm.

Among tumors with clear cells, clear cell (conventional) RCC is by far the most common type. It is often recognized by its characteristic thin sinusoidal vascular or alveolar pattern in addition to having clear cytoplasm. One feature that we have found particularly helpful is the heterogeneity

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**Table 1. World Health Organization (2016) Classification of Renal Cell Tumors**

| Clear cell renal cell carcinoma |
| Multilocular cystic renal neoplasm of low malignant potential |
| Papillary renal cell carcinoma |
| HLRCC-associated renal cell carcinoma |
| Chromophobe renal cell carcinoma |
| Collecting duct carcinoma |
| Renal medullary carcinoma |
| MiT-family translocation-associated renal cell carcinoma |
| Succinate dehydrogenase–deficient renal cell carcinoma |
| Mucinous tubular and spindle cell carcinoma |
| Tubulocystic renal cell carcinoma |
| ACD-associated renal cell carcinoma |
| Clear cell papillary renal cell carcinoma |
| Renal cell carcinoma, unclassified |
| Papillary adenoma |
| Oncocytoma |

Abbreviations: ACD, acquired cystic disease; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; MiT, microphthalmia transcription factor.

Data derived from Moch et al.27
of clear cell RCCs, which means that different growth patterns, cell morphologies, and variable composition of stromal tissue can be found in the same tumor. For example, a clear cell RCC can have areas of solid (Figure 1, A), alveolar (Figure 1, A), or tubular growth patterns, or feature clear cells embedded in edematous to hyalinized stroma with hemorrhage and hemosiderin pigments (Figure 1, B). Cytologic heterogeneity can span tumor cells with different nuclear grades (Figure 1, C) and cytoplasmic variability ranging from clear, pale, to dense eosinophilic (Figure 1, D). The tumors may have bland spindle cells (Figure 1, E), epithelioid/rhabdoid cells (Figure 1, F), or exhibit sarcomatoid appearance. This heterogeneity is usually not found in other common types of RCC. In addition, infiltration of tumor with lymphocytes or plasma cells is more commonly seen in clear cell RCC. Sarcoid-like granulomas so far have been seen only in clear cell RCC according to one study.31 We have commonly encountered misclassification of chromophobe, clear cell papillary, and translocation RCCs, and even angiomylipomas, as clear cell RCC.

Tumors with a papillary growth pattern are the second most common category encountered in renal mass biopsy. Even though the prototype tumor with papillary pattern is papillary RCC (Figure 2, A and B), a variety of renal neoplasms can have papillary architectures; these include clear cell (Figure 2, C), clear cell papillary (Figure 2, D), and rarely chromophobe (Figure 2, E), and mucinous tubular spindle cell RCCs, collecting duct carcinoma (Figure 2, F), as well as metanephric adenoma or metastatic carcinoma.32 Papillary RCC is the second most common type of RCC, accounting for 10% to 15% of all RCCs, and likely a higher percentage of small renal masses.27 It is widely accepted that papillary RCCs can be subclassified in types 1 and 2, primarily on the basis of their cytologic features. In addition to the defining characteristic of papillary growth, other helpful features are thick encapsulation; tubular, tubulopapillary, and glomeruloid growth; and presence of mucinous material, foamy macrophages, and psammoma bodies in the fibrovascular core. Papillary RCCs, primarily exhibiting solid or tubular growth patterns or clear cells, can be problematic. The most common tumors that may be misclassified as papillary RCCs are the following: metanephric adenoma, epithelial-predominant nephroblastoma,33 clear cell RCC with prominent papillary growth pattern, clear cell papillary RCC, and translocation RCC.

The third major category of renal tumors comprises oncocytic neoplasms. This category frequently is diagnostically challenging, not only on core biopsy but also for nephrectomy specimens.34-37 Differential diagnoses of an oncocytc renal tumor include a wide range of entities. The common oncocytc tumors are oncocytoma, chromophobe RCC, hybrid oncocytic tumor, clear cell RCC with granular cells, as well as type 2 and oncocytc-type papillary RCCs. In addition, the acquired cystic renal disease-associated RCC,
succinate dehydrogenase–deficient RCC, and the recently described eosinophilic solid and cystic RCC have prominent eosinophilic cytoplasm. Furthermore, nonrenal tumors such as epithelioid angiomylipoma, adrenal cortical tumors, and renal carcinoid tumors may also appear oncocytic.

A prognostic approach can be pursued for this group of tumors, involving assessment of whether tumor is low or high grade. Low-grade oncocytic renal neoplasms include oncocytoma, eosinophilic variant of chromophobe RCC, or hybrid oncocytic tumors associated with Birt–Hogg–Dube syndrome and oncocytic papillary RCCs. High-grade oncocytic renal neoplasms usually include clear cell RCCs with granular cells, type 2 papillary RCCs, or unclassified RCCs. Immunohistochemical staining with a panel of markers is usually necessary to make a more specific diagnosis.

The next category comprises cystic renal tumors, which are relatively common, and account for approximately 20% of these tumors, and can be either intrinsically cystic or tumors with secondary cystic changes. Core biopsy of cystic renal tumors can be particularly problematic for the radiologist, especially cystic tumors that are considered Bosniak type 2 or 3 cystic masses. Both clear cell and papillary RCCs can undergo significant cystic degeneration or necrosis. The key to diagnosing this group of tumor is to identify whether there is any solid tumor component. It is advisable that the diagnosis be conservative and that possible differential diagnoses be provided. It is expected that most of the unsatisfactory diagnoses will be from this group.

Another general category of renal tumors in core biopsy can be described by spindle cell pattern. The tumors range from low-grade tumor that is composed of relatively bland cells with minimal cytologic atypia to high-grade tumor with marked nuclear atypia, frequent mitoses, and necrosis resembling that of high-grade sarcoma. This category includes all types of RCCs with sarcomatoid component, mucinous tubular spindle cell carcinoma, papillary RCC with low-grade spindle cell foci, mixed epithelial and stromal tumor of the kidney, fat-poor angiomylipoma, renal leiomyoma or leiomyosarcoma, and other primary renal sarcomas. Immunohistochemical staining with markers such as Pax8, pan-cytokeratin, SMA, and HMB-45 is helpful in diagnosing these tumors.

The last general category includes high-grade carcinomas. This group of tumors is characterized by sheets, nests, or cords of tumor cells; these tumors exhibit a growth pattern that differs from any of the recognizable RCCs. The tumor cells are usually epithelioid with marked cytologic atypia and are frequently associated with prominent stromal desmoplasia. This group includes all high-grade RCCs, collecting duct carcinoma, medullary carcinoma, urothelial carcinoma, and metastatic carcinomas. It is helpful to stain the tumors with an initial panel of markers, including Pax8,
transcription factor; Pax8, paired box 8 transcription factor; RCC, renal cell carcinoma; RCCm, renal cell carcinoma marker; SMA, smooth muscle cadherin, kidney-specific cadherin; MiT, microphthalmia transcription factor; OCT4, octamer-binding transcription factor 4; Pax2, paired box 2 GATA-binding protein 3; HMB-45, human melanoma black 45; HMWCK, high-molecular-weight cytokeratin; INI-1, integrase interactor 1; Ksp-cadherin, kidney-specific cadherin; MiT, microphthalmia transcription factor; OCT4, octamer-binding transcription factor 4; Pax2, paired box 2 transcription factor; Pax8, paired box 8 transcription factor; RCC, renal cell carcinoma; RCCm, renal cell carcinoma marker; SMA, smooth muscle actin; TFE3, transcription factor EB; TFE3, transcription factor for immunoglobulin heavy-chain enhancer 3; Vim, vimentin; WT1, Wilms tumor 1.

GATA3, p63, cytokeratin (CK) 7/CK20, and TTF1. Correlation with radiologic findings and clinical history is paramount for final diagnosis.

The aforementioned general categorization provides framework for a differential diagnosis in renal mass core biopsy. However, tumors that have mixed features of variable growth patterns and cytologic features (clear, oncocytic, or spindle) are frequently encountered.41 In a small biopsy specimen, it is also very helpful to assess other minor features that are more commonly associated with a particular type of tumor. For example, if the biopsy tissue contains interface of tumor with normal kidney parenchyma, a thick capsule is often seen in papillary RCC; an infiltrative margin is more frequently seen in high-grade RCC such as clear cell RCC, collecting duct carcinoma, or medullary carcinoma; and a pushing margin is often seen in oncocytoma or chromophobe RCC. Mucinous material is more often seen in papillary RCC and mucinous tubular spindle cell RCC. Clusters of foamy macrophages are often seen in papillary RCC, metanephric adenoma, and mucinous and tubular spindle cell RCC; and psammoma body calcifications can be seen in type 1 papillary, chromophobe, and translocation RCCs, and metanephric adenoma.

Finally, IHC staining is particularly useful and perhaps indispensable in many situations in resolving differential diagnoses or confirming the morphologic diagnosis. Several comprehensive review articles on this topic and a practice guideline with recommendations were published by the International Society of Urological Pathology (ISUP) in 2014. Table 2 summarizes the common positive and negative markers for the most common renal neoplasms. For histologic subtyping of renal tumors, ISUP recommends that the use and choice of IHC should be based on careful morphologic evaluation and differential diagnosis based on constellation of growth pattern and cytologic features. The ISUP did not make specific recommendations regarding the use of IHC for histologic diagnosis on biopsy. It is our opinion that histologic diagnosis can be made reliably on examination of hematoxylin-eosin–stained sections alone for many tumors with classic morphology. The most common situations that may need IHC are those tumors that have overlapping or mixed morphologic features, unusual growth patterns or cell types, or cases where metastasis is possible.

### Table 2. Immunohistochemical Profile of Common Renal Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Positive Markers</th>
<th>Negative Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell RCC</td>
<td>Vim, CAIX, CK, EMA, CD10, RCCm, PAX8, PAX2</td>
<td>CK7, Ksp-cadherin, parvalbumin</td>
</tr>
<tr>
<td>Papillary RCC, mucinous tubular spindle cell RCC</td>
<td>CK, CK7, AMACR, RCCm</td>
<td>CD117, Ksp-cadherin, WT1</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>CK, CK7, E-cad, Ksp-cad, CD117</td>
<td>Vim, CAIX, AMACR</td>
</tr>
<tr>
<td>Collecting duct carcinoma</td>
<td>P63, HMWCK, PAX8, INI-1</td>
<td>CD10, RCCm, CK20, GATA3</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>P63, HMWCK, OCT4, PAX8</td>
<td>INI-1, RCCm, GATA3</td>
</tr>
<tr>
<td>Clear cell papillary RCC</td>
<td>PAX8, CK7, CD10, Vim, AMACR</td>
<td>AMACR, RCCm, CD10</td>
</tr>
<tr>
<td>Mit-family translocation RCC</td>
<td>Cathepsin-K, TFE3, TFEB, RCCm</td>
<td>EMA, CK (or weak)</td>
</tr>
<tr>
<td>RCC with sarcomatoid</td>
<td>PAX8, CK7, CD10, Vim, AMACR</td>
<td></td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td>HMB-45, Melan-A, SMA</td>
<td></td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>Ksp-cad, CD117, Parvalbumin, S100A1</td>
<td>CK, CD10, RCCm, PAX8</td>
</tr>
<tr>
<td>Metanephric adenoma</td>
<td>WT1, CD57, S100</td>
<td>CK7, MOC31, CD82</td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>CK, CK7, CK20, p63, GATA3, Uroplakin 2 and 3</td>
<td>AMACR, RCCm</td>
</tr>
</tbody>
</table>

Abbreviations: AMACR, a-methylacyl-CoA racemase; CAIX, carbonic anhydrase 9; CK, cytokeratin; EMA, epithelial membrane antigen; GATA3, GATA-binding protein 3; HMB-45, human melanoma black 45; HMWCK, high-molecular-weight cytokeratin; INI-1, integrase interactor 1; Ksp-cadherin, kidney-specific cadherin; MiT, microphthalmia transcription factor; OCT4, octamer-binding transcription factor 4; Pax2, paired box 2 transcription factor; Pax8, paired box 8 transcription factor; RCC, renal cell carcinoma; RCCm, renal cell carcinoma marker; SMA, smooth muscle actin; TFE3, transcription factor EB; TFE3, transcription factor for immunoglobulin heavy-chain enhancer 3; Vim, vimentin; WT1, Wilms tumor 1.

SUMMARY

To make a pathologic diagnosis from a renal mass biopsy, it is very important to acquire adequate material and take great care to successfully work with small amounts of tissue by establishing standard laboratory procedures. For pathologists, it is critical to be familiar with different tumor entities and understand renal tumor heterogeneity very well. By using a systematic approach, pathologists can categorize the tumors on the basis of dominant growth pattern and cell type, and subsequently make a sensible, differential diagnosis. Assessment of additional features that are more commonly seen in certain tumors can further narrow down the differential diagnosis. Immunohistochemistry is very helpful and occasionally indispensable in biopsy diagnosis of renal masses. Pathologists should be aware of the limitations and common pitfalls of biopsy diagnosis discussed in this article. Finally, biopsy findings should be correlated with clinical and radiologic features, and pathologists should clearly communicate the histologic diagnosis and possible uncertainty to the treating physician.

### References