Diagnosis of Renal Cell Carcinoma
A Clinician's Perspective

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KEYWORDS

• Renal cell carcinoma • Clear cell • Biopsy • Prognosis • Biomarker

ABSTRACT

Renal cell carcinoma (RCC) is a heterogeneous disease. A rigorous diagnostic assessment by a pathologist with close communication with the clinician provides more accurate prognostication and informed treatment decisions. In the localized setting, an accurate prognostic assessment directs patients to potential adjuvant clinical trials. For patients with advanced disease, the pathologic assessment may have a direct impact on the systemic therapy algorithm. Additionally, it provides the basis for continuous efforts in biomarker development. In rare histologic subtypes, the interaction between clinicians and pathologists provides an opportunity to offer patients specific clinical trials. Molecular characterization platforms may identify targets for therapeutic intervention.

OVERVIEW

Renal cell carcinoma (RCC) is a relatively common cancer. In 2014, the incidence of RCC in the United States was estimated to be 63,920 cases (kidney and renal pelvic cancers), potentially resulting in 13,860 deaths.[1] Pathologic assessment[2] (see also Hirsch et al, Adult Renal Cell Carcinoma: A Review of Established Entities Form Morphology to Molecular Genetics, Surgical Pathology Clinics, 2015, Volume 8, Issue 4 and Mehra et al, Emerging Entities in Renal Neoplasia, Surgical Pathology Clinics, 2015, Volume 8, Issue 4) plays a crucial role in both localized and metastatic settings where the findings therein define the appropriate management of patients with kidney cancer.

In the localized setting, the pathologist's analysis of the tumor biopsy triggers distinct strategies in the management of small unilateral or bilateral renal masses. After partial or radical nephrectomy, the pathology assessment of the tumor defines the risk of recurrence and aids in determining the monitoring and follow-up plans. In the metastatic setting, the pathologic findings can direct the systemic treatment approach. Non–clear cell RCC (non-ccRCC) deserves special attention given the limited therapeutic agents for this heterogeneous category of disease entities. Over the past decade, new RCC subtypes have been identified for which the clinical outcome may not be fully established.[3] In addition, some specific pathologic features, such as the presence of sarcomatoid differentiation, add major prognostic information that clinicians are likely to use both to refine the overall prognosis estimation and to select treatment options.

This article aims to summarize the clinician's perspective on the pathologic diagnosis of RCC, with a focus on clinicians' expectations of the pathologist to optimize the use of pathologic

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features, including not only histologic assessment but also immunohistochemistry and cytogenetic and molecular strategies, in the management of kidney cancer.

RENAL MASS BIOPSY: EXPECTATIONS FROM THE CLINICIANS

SMALL RENAL MASSES AND LOCALIZED RENAL CELL CARCINOMA

The increasing incidence of small renal masses (SRMs), defined as less than 4 cm,[4] has led to the development of more conservative management strategies to include ablative techniques or active surveillance in select cases. To choose the best strategy, clinicians rely on the biopsy diagnosis provided by pathologists to distinguish from 3 chief groups of lesions: benign tumor, indolent cancer, and aggressive cancer.

Percutaneous biopsy for diagnostic assessment of SRMs has the potential to avoid unnecessary surgeries and support treatment decisions, especially in patients at increased surgical risk.[5] It has been demonstrated that SRM biopsies have both acceptable sensitivity, ranging from 86% to 100%, and specificity for the diagnosis of malignancy.[6] The overall positive predictive value for the diagnosis of malignancy in a report encompassing 2474 renal tumor biopsies was 97.5%, with an overall sensitivity of 92.1% and a specificity of 89.7%.[7] Although these results may be illustrative of high-volume centers, such accuracy is now expected of routine renal mass biopsies, with the understanding that the rate of nondiagnostic biopsy, commonly due to insufficient material, is approximately 22%, according to a large report of 1000 biopsies from a single institution.[8] In addition to differentiating malignant tumors (see also Hirsch et al, Adult Renal Cell Carcinoma: A Review of Established Entities Form Morphology to Molecular Genetics, Surgical Pathology Clinics, 2015, Volume 8, Issue 4 and Mehra et al, Emerging Entities in Renal Neoplasia, Surgical Pathology Clinics, 2015, Volume 8, Issue 4) from benign lesions (see also Arias-Stella and Williamson, Updates in Benign Lesions of the Genitourinary Tract, Surgical Pathology Clinics, 2015, Volume 8, Issue 4) histologic subtype and Fuhrman grade can be assessed on a core biopsy with success rates of 86% to 100%[6] and 64% to 93%, respectively.[9,10]

Molecular analysis performed on renal biopsy specimens may also serve as a diagnostic tool and be part of the decision-making process. Recently, a study attempted to characterize the genetic alterations associated with metanephric adenoma (MA), a rare indolent kidney tumor that may be difficult to differentiate from a small malignant kidney cancer. Because this is a benign tumor, surveillance may be appropriate in most situations, sparing the loss of nephrons. This study identified the v-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600E mutation in 26 of 29 MA cases (approximately 90%). Given that BRAF V600E mutations are present in approximately 90% of all MA cases[11] and BRAF immunohistochemistry is sensitive and specific,[12] this could serve as a potential valuable diagnostic tool in the differential diagnosis of SRMs undergoing a kidney biopsy.

METASTATIC RENAL CELL CARCINOMA

The use of renal mass biopsy in patients presenting with radiological findings suggestive of metastatic disease is usually more limited. It is commonly restricted to patients not eligible for primary nephrectomy due to comorbidities or to other poor prognostic criteria,[13] which usually drive physicians to offer patients upfront systemic therapy.[14,15] In this specific setting, the role of biopsy is not only to confirm the RCC diagnosis but also to specify the histologic subtype of the tumor, especially if it is of the clear cell subtype where therapeutic options may be available. Conversely, despite the lack of specific systemic therapies for non-ccRCC, identification of such specific histologic tumor subtypes is critical for communicating information about prognosis and potential therapeutic options for patients with metastatic disease, including the potential for clinical trials.

NEPHRECTOMY SPECIMEN: EXPECTATIONS FROM THE CLINICIANS

Unlike other tumor types where histology can drive distinct therapeutic approaches, RCC is still managed with the same algorithm irrespective of histologic subtype. In patients with localized or locally advanced disease who underwent partial or radical nephrectomy with a curative intent, the pathologist's report encompasses the distinct parameters that define the risk of recurrence.[16] Among these, tumor stage and grade are important features for the prediction of RCC recurrence after nephrectomy. The primary tumor stage, as determined by the latest version of the TNM staging system, is a powerful predictor of cancer-specific survival (CSS).[17,18] According to the 2009 TNM staging system, the 5-year CSS ranges from 94.9% in pT1a to 27.1% in pT4 cancers. In addition, one of the most commonly