

IN FOCUS: RENAL CELL CARCINOMA

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The Paradigm Shift in Renal Mass Biopsy

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H&O Could you give a historical sketch of renal mass biopsy?

SC Historically, renal mass biopsy was not often used, and there was a fairly strong recommendation against its use, for small renal masses. The reason for this was that some early studies suggested a high false-negative rate, of approximately 18%, which was passed on in the literature. The biopsies would be considered negative but the patient would actually have a cancerous tumor of the kidney. This degree of unreliability was unacceptable. Additionally, until the last 5–10 years, the main treatment strategy available was surgical management, and it was felt that due to the high false-negative rate, surgery was indicated even if a biopsy were found to be negative. There was a strong message sent to the community that renal mass biopsy should not be performed in a routine manner for small renal masses. Furthermore, historically, it was believed that most small renal masses had substantial malignant potential, and it was thought that they required aggressive treatment (ie, radical or partial nephrectomy, which was the only therapy available). It was felt that renal mass biopsy, except in very specific circumstances, would not greatly modify the management. Given that there is always some risk associated with any medical procedure, renal mass biopsy was not recommended for most patients.

H&O How does the presence of benign renal masses affect the use of renal mass biopsy?

SC There are benign kidney tumors, the most common of which is oncocytoma, that are difficult to distinguish from malignant kidney tumors using the limited pathologic

specimen provided by renal mass biopsy. Microscopically, oncocytoma is an eosinophilic tumor, like many subtypes of kidney cancer. For example, there are eosinophilic variants of clear-cell (ie, granular kidney cancer), chromophobe, and papillary kidney cancer. Using the very limited pathologic material that is obtained via biopsy, most pathologists historically felt uncomfortable making the distinction between a benign oncocytoma and an eosinophilic variant of kidney cancer. The difficulty of making such a distinction is another explanation for the historical recommendation against the use of renal mass biopsy.

H&O What led to the so-called “renaissance” in renal mass biopsy?

SC Several important changes have recently emerged in the field. First, there was a tremendous increase in the number of small renal masses that were being diagnosed because of the greater prevalence of ultrasound and computed tomography for the evaluation of various abdominal discomforts and nonspecific complaints. A number of articles showed that approximately 20% of these small renal masses were benign, and for those that were malignant, approximately 75% were considered likely indolent. Thus, when considering all renal masses taken together, only approximately 20% carry an aggressive malignant potential. As a result, rather than presuming that all renal masses were malignant and potentially aggressive, researchers began to notice that many were benign or indolent.

A second major change was that several less aggressive management options were developed in the past 10–15 years. Not only was surgical excision possible, but thermal ablation with cryosurgery and radiofrequency ablation were introduced. These methods allowed fairly effective proactive treatment of small renal masses, without the risks associated with surgical excision. These options became very appealing approaches for treating small renal masses,

particularly in elderly patients or patients with substantial comorbidities. In addition, in the last 5–10 years, several articles have been published on active surveillance (observation) of renal masses in elderly patients with limited life expectancy, and a meta-analysis of approximately 10 such series showed that most of these small renal tumors have a relatively slow growth rate (mean = 0.28 cm/year), and a low risk of metastasis during a 2–3 year period (approximately 1–2%). This finding is consistent with the previously mentioned finding that many of the small renal masses discovered in the current era are benign or relatively indolent. In summary, clinicians now have available to them a number of different treatment options, which range from fairly aggressive surgical excision to observation, in recognition of the heterogeneity of these masses.

A third important development has been the introduction of molecular markers, such as CAIX, HMB-45, and cytokeratin, which can be used on a biopsy to distinguish benign from malignant tumors, and, if malignant, potentially aggressive from likely indolent. This development, along with the others already mentioned, began to make renal mass biopsy a more attractive endeavor than previously thought.

H&O How did you assess whether renal mass biopsy was in fact more useful than previously thought?

SC We examined all the articles in the field, using a full literature search, and divided articles into those published before 2001 and those published since 2001, when molecular factors could be considered as part of the diagnostic assessment. We found that some of the dogma concerning renal mass biopsy simply was untrue. For example, one of the most interesting findings was that the 18% false-negative rate that I described as part of the historical understanding of renal mass biopsy was inaccurate. In reality, our review showed that prior to 2001, the false-negative rate was approximately 4%, not 18%. Roughly 8% of biopsies were considered technical failure, wherein a radiologist was unable to obtain adequate information because the needle was not able to enter the mass or for other reasons, but technical failure is not synonymous with false-negative. Approximately 6% were considered indeterminate, wherein a biopsy was obtained but it was inadequate for a pathologist to distinguish between cancerous cells and noncancerous cells. The real false-negative rate was 4%. Finally, 1.3% of biopsies yielded a false-positive finding, meaning that cancer was judged to be present by the pathologist when in fact the mass was benign. When all categories of inadequate biopsies were combined, the sum was 18%, but only a minority of these were false-negatives, which is what we really worry about

from a clinical standpoint. Collectively, we found that even prior to 2001, a successful biopsy was yielded in an accurate manner in 82% of cases. This finding indicated that the database was much better than had been previously appreciated.

The next step was to assess the risk of a biopsy. The dogma had stated that a substantial risk was associated with renal mass biopsy. Our review showed that although approximately 80% of patients experienced some bleeding around the kidney associated with the biopsy procedure, only 1–2% of patients required hospitalization for observation or transfusion. This level of risk was much lower than expected. The risk of pneumothorax was also assessed; chest radiographs after every renal mass biopsy showed that 15–20% of patients experienced a small pneumothorax. However, less than 1% of patients require treatment for pneumothorax after renal mass biopsy. Finally, the risk of needle track seeding was assessed. This condition occurs when tumor cells seed the track the needle leaves behind as it is removed. In the literature, we found only eight reported cases of this event occurring after renal mass biopsy and none since 1994. This phenomenon is very uncommon. It is believed that with an infiltrative, centrally located, aggressive-appearing renal mass, biopsy is not recommended because of high risk of needle track seeding. If radiologists are careful not to biopsy such high-risk tumors, the risk of needle track seeding is greatly diminished.

H&O How has the introduction of molecular factors changed the paradigm?

SC My colleagues and I reviewed the literature on renal mass biopsy since 2001, the era during which molecular factors became available. We found that in seven studies comprising 362 patients, only one complication was reported (0.3%). The false-negative rate was 0.6% and the false-positive rate was 0.0%. Some technical failures, in which the radiologist was unable to target the mass with the needle, did occur (5.2%). Furthermore, there were some cases in which the biopsy sample was inadequate for a pathologist to assess the status of the mass (3.8%). Overall, 90% of biopsies are accurate and the false-negative or -positive rates, wherein the biopsy is actually misleading, total less than 1% in the modern era. Beyond knowing whether a mass is malignant or benign, we are now interested to know whether it is high- or low-grade, whether it is aggressive or indolent, and what the correlation is between the grade and the histologic subtype. The accuracy of these assessments in the modern era is approximately 80% or higher. Finally, we found some studies that included molecular analyses by fluorescence

(Continued on page 258)

(In Focus: RCC, continued from page 254)

in situ hybridization or polymerase chain reaction (ex vivo and retrospectively), and this increased the accuracy of renal mass biopsy to nearly 95%. It is important to note that some of these studies were done with ex vivo biopsy, and will need to be repeated in vivo to establish clinical relevance.

H&O What is the viewpoint on renal mass biopsy at present?

SC We believe that renal mass biopsy is indicated in certain situations, including when there is a suspicion of lymphoma, an abscess, or a metastatic lesion that has spread into the kidney. In these circumstances, a biopsy should be performed because it could help guide a non-surgical treatment. These indications have been known for several years and remain applicable in the modern era. If the patient is young and healthy, or is uncomfortable with the small degree of uncertainty associated with renal mass biopsy, proactive surgical treatment should be used and biopsy can be avoided. Similarly, patients who are very old or have prohibitive comorbidities, who are not candidates for aggressive therapy, are not candidates for biopsy. If the elderly patient will be treated with observation and is not a candidate for proactive treatment, for example, biopsy would not change the management plan. In between these extremes are those patients who may want to consider several treatment options, such as surgery, thermal ablation, and observation; in these patients, in whom it is uncertain how aggressive the treatment should be, biopsy should be considered to stratify the risk of the tumor and help to guide the decision-making process. In this subgroup of patients, the risk of managing a patient while possessing suboptimal information about the patient's tumor may exceed the risk of the biopsy itself. Renal mass biopsy may help to prevent either overtreatment or undertreatment.

H&O What are the primary areas of research going forward?

SC One of the main conclusions of the research my colleagues and I conducted is that this is an important area for further investigation. Renal mass biopsy has a more solid database in its favor than was previously appreciated. Therefore, its use should be considered more often. However, there are still many important questions that have not been answered. Some of the recent studies employed molecular analyses on ex vivo biopsies, and it is unknown whether this practice correlates with the clinical setting. In vivo data using molecular analyses are needed. So far, some of the studies are relatively small, and larger prospective studies are needed. Furthermore, studies are needed that analyze how large the needle cores are and how that size affects the yield of information and the risk of complications. We need more data about heterogeneity of renal masses. For example, how many cores into the tumor are needed to accurately determine its biologic aggressive potential? We know that one core is probably insufficient for most renal tumors because of the potential that the needle enters necrotic tissue, which would be misleading. How many cores are needed to overcome issues of heterogeneity and sampling error within the tumor? These are some of the important issues that will require further investigation as this field evolves.

Suggested Readings

- Lane BR, Samplaski MK, Herts BR, Zhou M, Novick AC, Campbell SC. Renal mass biopsy: a renaissance? *J Urol.* 2008;179:20-27.
- Volpe A, Kachura JR, Geddie WR, et al. Techniques, safety and accuracy of sampling of renal tumors by fine needle aspiration and core biopsy. *J Urol.* 2007; 178:379-386.
- Stephenson AJ, Kuritzky L, Campbell SC. Screening for urologic malignancies in primary care: pros, cons, and recommendations. *Cleve Clin J Med.* 2007;74 suppl 3:S6-S14.