Patient and Tumor Characteristics can Predict Nondiagnostic Renal Mass Biopsy Findings

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Purpose: Identification of patient and tumor characteristics associated with nondiagnostic biopsies is necessary to improve prebiopsy counseling and patient selection.

Materials and Methods: We reviewed the clinical records and prebiopsy imaging of all patients treated with percutaneous biopsy for a renal mass 7 cm or less. Univariate and multivariate logistic regression models were constructed to examine the association between biopsy outcome and clinical/radiographic features.

Results: A total of 565 biopsies of renal tumors 7 cm or less in 525 patients were included in the study. There was no significant difference in age, body mass index, Charlson comorbidity score or gender between the patient cohorts with diagnostic and nondiagnostic biopsy. In 83 of 565 patients (14.7%) overall and in 72 of the 413 (17.4%) with a mass of 4 cm or less the biopsy findings were nondiagnostic. Overall 14.7% of masses were cystic and 85.3% were solid with a median tumor size of 2.75 cm (IQR 2.05−4.25). Independent predictors of nondiagnostic biopsy included cystic features, enhancement less than 20 HU, left tumor, tumor diameter and skin-to-tumor distance. The nondiagnostic rate of repeat biopsies was 20.8%, which did not statistically differ from the nondiagnostic rate at the initial renal mass biopsy attempt. Radiologist or pathologist experience was not associated with the biopsy nondiagnostic rate. In 7 of 565 patients (1.2%) hospital admission was required for adverse events after biopsy.

Conclusions: Nondiagnostic renal mass biopsies are more common in cystic, nonenhancing, small masses when patients have a skin-to-tumor distance of 13 cm or greater. Excluding patients with these criteria decreased the nondiagnostic rate from 14.7% to 8.7%.

Key Words: kidney; carcinoma, renal cell; biopsy; diagnosis; pathology

**Abbreviations
and Acronyms**

BMI = body mass index

ccRCC = clear cell RCC

CT = computerized tomography

FNA = fine needle aspiration

RCC = renal cell carcinoma

RMB = renal mass biopsy

SRM = small renal mass

US = ultrasound

THE incidence and detection of RCC has increased significantly in the last 50 years.[1] Increased use of cross-sectional imaging techniques have enabled the detection of SRMs when they are asymptomatic, causing stage migration in RCC[2] with masses 4 cm or less representing 48% to 66% of new diagnoses.[3]

Recently concern has been raised about overtreatment of SRM because as many as 33% of SRMs are found to

0022-5347/15/1936-1899/0
THE JOURNAL OF UROLOGY®
© 2015 by AMERICAN UROLOGICAL ASSOCIATION EDUCATION AND RESEARCH, INC.

http://dx.doi.org/10.1016/j.juro.2014.12.021
Vol. 193, 1899-1904, June 2015
Printed in U.S.A.

www.jurology.com | **1899**

be benign tumors[4] and many tumors have minimal metastatic potential.[5] However, it is difficult to evaluate the risk associated with SRMs using imaging alone and many urologists perform RMB to provide a better assessment of the cancer risk in specific patients.[6] Improved biopsy techniques allow for a safer and more accurate diagnosis in many patients[7] and may decrease the total costs of treatment by identifying those with benign renal masses.[8] However, the optimal use of RMB continues to be debated and biopsy is performed in the minority of patients who are treated for RCC.[9]

The ideal use of RMB remains a topic of debate, although algorithms have been developed to help guide treatment decisions based on pathological findings.[10] A consistent limitation of RMB is an approximately 15% to 22% rate of nondiagnostic or indeterminate findings.[6,11−13] Many factors may contribute to nondiagnostic biopsy findings, including sampling of tissue outside the target lesion (miss), failure to adequately sample the mass or obtaining tissue that is inadequate to pathologically diagnose a renal neoplasm.

Identification of patient and tumor characteristics associated with nondiagnostic biopsy is necessary to improve prebiopsy counseling and patient selection but few groups have evaluated predictors of nondiagnostic RMB findings. Therefore, we evaluated patient characteristics and tumor features that are predictive of nondiagnostic findings after percutaneous RMB.

MATERIALS AND METHODS

After receiving institutional review board approval we reviewed the clinical and radiological records of 613 percutaneous RMBs 7 cm or less performed from January 2000 to April 2014 at our institution. Excluded from study were 24 biopsies without available prebiopsy imaging within 3 months before RMB and 24 repeat biopsies in patients already in the study. Prebiopsy and intrabiopsy imaging were analyzed with our institutional PACS (picture archiving and communication system) (McKesson, San Francisco, California). Nondiagnostic biopsy was defined as normal renal parenchyma or fibrotic/necrotic material insufficient for pathological diagnosis. A select group of abdominal radiologists perform RMB and designated pathologists review genitourinary specimens at our institution using immunohistochemistry to facilitate diagnosis when indicated.

RMB is generally performed under ultrasound guidance to obtain core samples using an 18 gauge BioPince® biopsy device. FNA is occasionally done for smaller cystic lesions and CT guidance is used primarily for exophytic medial and superior pole masses at radiologist discretion. The biopsy indication was at treating physician discretion. RMB is performed before all ablation procedures and discussed with patients considering surgery or surveillance. Final treatments in this cohort included surgery in 173 patients (30%), ablation in 196 (35%) and ablation plus surveillance in 196 (35%). During the study period 22.5% of patients with a renal mass 7 cm or less treated with surgery underwent biopsy preoperatively.

Putative prognostic factors for nondiagnostic biopsy included the imaging modality used before biopsy (magnetic resonance imaging vs US vs CT), laterality (left vs right), biopsy guidance imaging modality (CT vs US), biopsy type (FNA vs core vs FNA plus core), exophytic vs endophytic appearance on imaging (exophytic defined as greater than 50% tumor extending beyond the renal capsule), any cystic feature, proximity to liver or spleen, proximity to other organs, renal mass enhancement (20 HU or less vs greater than 20), any fat (present vs absent), any calcification (present vs absent), necrosis/hemorrhage (present vs absent), mass anterior or posterior position, mass polarity (inferior pole vs interpolar vs superior pole), mass mean axial diameter, patient BMI, skin-to-tumor distance, radiologist/pathologist experience and number of biopsy cores obtained.

We assessed differences in patient and tumor characteristics in the diagnostic and nondiagnostic groups using the 2-sided t-test with unequal variances, or the chi-square or Fisher exact test for each characteristic as appropriate. Univariate and multivariate logistic regression models were constructed to examine the association of biopsy outcome with clinical and radiographic features. All analysis was done with SAS®, version 9.2 with 2-sided $p \leq 0.05$ considered significant.

RESULTS

A total of 565 biopsies from 525 patients were included in study. Supplementary table 1 (http://jurology.com/) lists patient characteristics. There was no significant difference in age, BMI, Charlson comorbidity score or gender between the diagnostic and nondiagnostic biopsy patient cohorts. Biopsy findings were nondiagnostic in 83 of 565 patients (14.7%) overall and in 72 of 413 (17.4%) with a mass 4 cm or less. Overall 14.7% of the masses were cystic and 85.3% were solid with a median size of 2.75 cm (IQR 2.05−4.25). Enhancement (greater than 20 HU) after intravenous contrast administration was seen in 84.8% of renal masses while 4.4% were pseudo-enhancing (10 to 20 HU), 2.3% were nonenhancing and 8.5% could not be evaluated due to unavailable precontrast CT. The skin-to-tumor distance was 13 cm or greater in 9.2% of masses.

In 482 RMBs (85.3%) pathological evaluation of tissue resulted in diagnosis of a neoplasm. The diagnosis was RCC in 346 cases (71.8%), including clear cell in 75.1%, papillary in 13.9%, chromophobe in 1.4% and RCC unspecified in 9.5%. Oncocytoma was diagnosed in 77 (16.0%), angiomyolipoma in 11 (2.3%) and another malignant neoplasm in 47 (9.8%), including urothelial cancer, collecting duct

carcinomas, lymphoma or leukemia. In 83 biopsies with initial nondiagnostic findings the final pathological diagnosis on RMB was benign renal parenchyma in 43 (51.8%) and necrotic, fibrotic or sclerotic tissue in 28 (33.7%) while in 12 (14.4%) the biopsy tissue sample was inadequate.

Supplementary table 2 (http://jurology.com/) and table 1 show associations of nondiagnostic findings with common patient and tumor characteristics. Independent predictors of nondiagnostic biopsy overall included laterality, cystic features, radiological enhancement less than 20 HU, tumor diameter and skin-to-tumor distance. Similarly when considering only SRMs 4 cm or less, cystic features, radiological enhancement less than 20 HU, tumor diameter and skin-to-tumor distance were independent predictors of nondiagnostic RMB.

Cystic Masses

A total of 83 masses were classified as cystic, including 4, 1, 10 and 18 that were Bosniak category 2, 2f, 3 and 4, respectively.[14] The biopsy method was core sampling in 88% of RMBs, FNA in 3% and a combination of core sampling and FNA in 9%. The nondiagnostic rate of RMB for cystic masses was 39.8%. Of the 50 cystic masses in which a diagnosis was obtained from biopsy 45 (90%) were malignant, including 35 ccRCCs, 2 papillary RCCs, 5 unspecified RCCs, 1 squamous cell carcinoma and 1 oncocytic neoplasm. Five cystic masses (10%) were oncocytoma.

Table 1. *Multivariable logistic regression analysis of 565 renal masses 7 cm or less and 413 masses 4 cm or less*

	OR (95% CI)	p Value
7 cm or Less		
Side:		0.04
Lt	1.75 (1.02–2.98)	
Rt	Referent	
Features:		<0.0001
Cystic	4.42 (2.38–8.21)	
Solid	Referent	
Renal mass enhancement (HU):		0.01
20 or Less	2.84 (1.26–6.41)	
Greater than 20	Referent	
Mean axial diameter (cm):		0.01
4 or Less	2.66 (1.27–5.55)	
Greater than 4	Referent	
Skin-tumor distance (cm):		0.02
13 or Greater	2.40 (1.15–5.01)	
Less than 13	Referent	
4 cm or Less		
Features:		<0.0001
Cystic	4.85 (2.42–9.72)	
Solid	Referent	
Renal mass enhancement (HU):		0.004
20 or Less	3.57 (1.49–8.52)	
Greater than 20	Referent	
Mean axial diameter (cm)	0.59 (0.39–0.90)	0.01
Skin-tumor distance (cm):		0.02
13 or Greater	2.62 (1.17–5.85)	
Less than 13	Referent	

Radiographic Enhancement

Of 38 tumors with 20 HU or less enhancement 25 (65.8%) were pseudo-enhancing and 13 (34.2%) were nonenhancing. Overall nondiagnostic findings were noted in 16 of these lesions (42.1%), including 9 pseudo-enhancing and 7 nonenhancing masses. Of the 22 tumors with diagnostic RMB 17 (77.3%) were malignant and 5 (22.7%) were benign, including 9 ccRCCs, 5 papillary RCCs, 2 unspecified RCCs, 1 collecting duct carcinoma, 1 oncocytoma, 1 metanephric adenoma, 1 fibrotic specimen, 1 unspecified neoplasm and 1 unspecified benign neoplasm.

Skin-to-Tumor Distance

Median skin-to-tumor distance was 10 cm (IQR 8.5–11). When skin-to-tumor distance was analyzed as a continuous variable, each cm of distance was associated with an increased risk of nondiagnostic biopsy (OR 1.20, 95% CI 1.08–1.34, p = 0.001). A total of 14 biopsies (26.9%) of 52 tumors with a skin-to-tumor distance of 13 cm or greater were nondiagnostic.

Patients with Initial Nondiagnostic Biopsy

Of 83 biopsies that were initially nondiagnostic repeat RMB was done in 24 cases (28.9%), 7 (8.4%) were treated with surgery, 10 (12.1%) were treated with thermal ablation and 42 (50.6%) were followed with surveillance imaging. In 5 of the 24 patients (20.8%) nondiagnostic findings were present in the second biopsy. This nondiagnostic rate did not statistically differ from the 14.7% rate at the initial RMB attempt (p = 0.38). In 16 of 24 patients (66.7%) malignancy was identified after initially nondiagnostic biopsy, including ccRCC in 12, unspecified carcinoma in 2 and papillary RCC in 2. A benign tumor was eventually diagnosed in 3 patients (12.5%), including oncocytoma in 1 and angiomyolipoma in 2.

Interoperator Variability

To evaluate whether experience with RMB contributed to indeterminate findings we evaluated the individual nondiagnostic rates of radiologists who performed biopsy (part *A* of figure). Of the 11 attending radiologists who performed at least 20 RMBs each there was no association between experience and the nondiagnostic rate (p = 0.76). In the 462 procedures in which a trainee (resident or fellow) was involved there was no difference in the nondiagnostic rate compared to procedures without a trainee (14.7% vs 15.7%, p = 0.80). In addition, there was no association between the experience of the pathologist who evaluated RMB specimens and the nondiagnostic rate (p = 0.67, part *B* of figure).
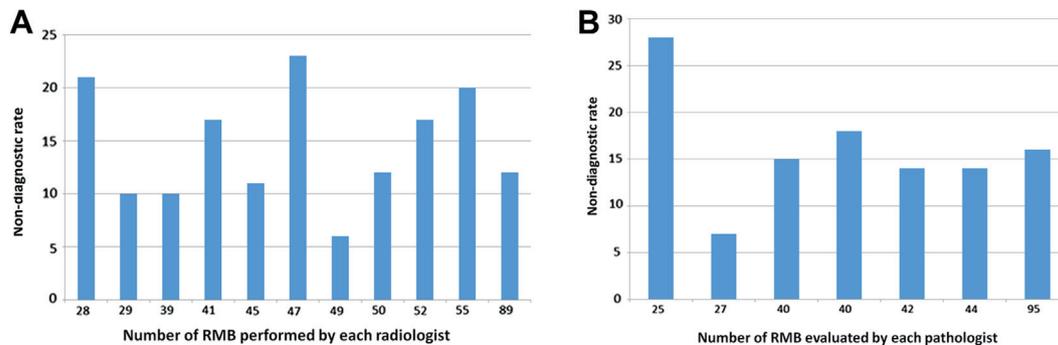
A, among 11 attending radiologists who performed at least 20 RMBs there was no association between number of RMBs and nondiagnostic rate (p = 0.76). B, among 7 attending pathologists who evaluated at least 20 RMBs there was no association between experience and nondiagnostic rate (p = 0.67).

Biopsy Complications

In 7 of 565 patients (1.2%) hospital admission was required after RMB. In 4 patients no additional intervention was required including 2 with symptomatic perinephric hematoma, 1 with dehydration/hematuria, which resolved, and 1 with hypotension thought to be medication related. Intervention was required in 3 patients (transfusion due to bleeding). A major complication (Clavien-Dindo classification grade 3a[15]) developed in a patient who required selective renal arterial embolization to manage postoperative hemorrhage and hemodynamic instability.

DISCUSSION

Although the usefulness of RMB in certain patients remains a topic of debate, RMB use increased significantly in recent years.[9] Despite improved biopsy techniques and imaging guidance a significant percent of patients who undergo RMB have nondiagnostic pathological findings. In this study approximately 15% of patients had nondiagnostic RMB, consistent with prior large series.[6,11] Four patient or tumor characteristics were identified as independently predictive of a nondiagnostic result of RMB for small masses, including tumor size, cystic features, an increased skin-to-tumor distance and absent radiological enhancement.

The decision to treat incidental SRMs is often not straightforward. Individual factors must be considered in each patient and biopsy can provide meaningful information to help guide treatment in some patients. Typically pathological information is used to estimate the risk of cancer mortality compared to the risk of mortality from competing comorbidities[16] or guide decision making when deciding among surveillance, surgery or ablation for a SRM.[17]

While a low rate of biopsy related morbidity was observed in this and other studies,[6] a persistent criticism of RMB is that some patients do not benefit because RMB is nondiagnostic. Similar or higher nondiagnostic biopsy rates were reported in other large RMB series depending on the definition of nondiagnostic findings.[3,7,11] In more than half of the nondiagnostic biopsies normal renal parenchyma was identified, indicating a miss during percutaneous sampling. Another potential technical cause of nondiagnostic biopsy is the inability to accurately target the lesion in obese patients. Tumor characteristics that likely impact biopsy outcomes include cystic morphology (tumors may contain only small islands of malignant cells, leading to targeting challenges), lack of radiological enhancement, tumor size and skin-to-tumor distance.

Interestingly the experience of the physicians who performed RMB or evaluated RMB tissue pathology was not associated with nondiagnostic rates. This observation may reflect the practice of triaging more challenging cases to more experienced radiologists or pathologists, leading to selection bias.

Cystic masses have the highest rate of nondiagnostic RMB (40%). This is likely because cystic masses lack large areas of solid tumor, making adequate sampling less likely. Sampling the small soft tissue components is likely to be technically challenging while aspirating fluid for cytology is relatively insensitive. Given the 60% rate of diagnostic findings for cystic masses, physicians may defer biopsy of renal masses with cystic features. Similar to cystic features the absence of contrast enhancement in tumors is associated with a higher risk of nondiagnostic biopsy (42%). With the high rates of nondiagnostic biopsy for cystic and nonenhancing renal masses, the limitations of RMB should be discussed before biopsy and RMB should be used judiciously in these patients.

To our knowledge this study is the first to describe skin-to-tumor distance as an independent

Table 2. *Hypothetical improvement in nondiagnostic rate when excluding patients with specific features*

Masses	No. Nondiagnostic/Total No. (%)
Overall	83/565 (14.69)
Excluding:	
38 Enhancing 20 HU or less	67/527 (12.71)
52 Skin-tumor distance 13 cm or greater	69/513 (13.45)
83 Cystic	50/482 (10.40)
Any criterion	37/424　(8.72)

risk factor for nondiagnostic biopsy. In patients with tumors at a distance of 13 cm or greater from the body surface the rate of nondiagnostic biopsy was 27%, likely reflecting the increased technical difficulty of maneuvering the biopsy needle in deep tissue and the decreased visualization of the needle and tumor when using US guidance for these biopsies. However BMI was not predictive of nondiagnostic RMB. A possible explanation is that the distribution of adipose tissue is more critical than the amount of adipose tissue. Specifically superficial adipose tissue may impact tumor targeting and/or imaging less than perinephric adipose tissue. As a result, the skin-to-tumor distance is a more accurate predictor than BMI, which does not necessarily reflect fat distribution.

Small tumor size was likewise predictive of nondiagnostic findings on multivariate analysis. Patients with masses less than 4 cm were 2.7 times more likely to have a nondiagnostic biopsy compared to patients with masses greater than 4 cm, likely due to the technical difficulty of hitting a smaller target with the biopsy needle. In patients with masses less than 2 cm the risk of metastasis is low. Many of these patients may be candidates for active surveillance protocols in the setting of a nondiagnostic result.

Exclusion from study of patients with factors predictive of nondiagnostic findings may have improved the success rate (table 2). However, a small number of nondiagnostic biopsy results is likely unavoidable because RMB is often recommended for atypical renal lesions. Given the low morbidity, RMB may still be a preferred management option for some atypical masses even if the yield is comparatively lower. RMB may be cost-effective when done judiciously,[8] and improving patient selection may increase the diagnostic rate and decrease the costs associated with additional biopsies. As noted, patients with an initial nondiagnostic biopsy have a similar probability of nondiagnostic findings after a second RMB (20.8% vs 14.7%, p = 0.50). Notably 77.4% of patients with nondiagnostic biopsy who underwent repeat biopsy or surgery were diagnosed with malignancy, similar to the 68.1% malignancy rate in patients who underwent initial RMB (p = 0.33).

Patients selected for RMB at our tertiary care center may be more likely to have an atypical appearance since biopsy is not performed in all patients with renal masses. This may have negatively biased the rate of diagnostic biopsy because patients with findings highly suggestive of malignancy may have not undergone biopsy. However, this investigation is representative of contemporary practice at a tertiary care center and the nondiagnostic rates are similar to those in other large studies. Further, RMB use increased in the last few years, which may have skewed results as indications for RMB evolved. Interestingly nondiagnostic rates did not change significantly during the different periods analyzed. Finally, since this was not a randomized study, direct comparison of results based on biopsy technique was not possible. In conclusion, nondiagnostic findings are present in 15% of RMBs and more common in masses that are cystic, nonenhancing, small (less 4 cm) or have a skin-to-tumor distance of 13 cm or greater.

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