Identification of tumor size as the only factor associated with non-diagnostic biopsies in patients with small renal masses

Charlie J. Gillis[1]; Ricardo Rendon[2]; Landan P. MacDonald[3]; Michael A.S. Jewett[4]; Christopher French[5]; Henry Ajzenberg[6]; Ashraf Almatar[7]; Mohammed Abdolell[8]; Michael Organ[5]
[1]Facultyof Medicine, Memorial University, St. John's NL, Canada; [2]Department of Urology, Dalhousie University, Halifax, NS, Canada; [3]School of Medicine, Dalhousie University, Saint John, NB, Canada; [4]Departments of Surgery (Urology) and Surgical Oncology, Princess Margaret Cancer Centre, University Health Network and University of Toronto, Toronto, ON, Canada; [5]Department of Urology, Memorial University, St. John's NL, Canada; [6]School of Medicine, Queen's University, Kingston ON, Canada; [7]Department of Urology, King Fahad Specialist Hospital-Dammam, Dammam, Saudi Arabia; [8]Department of Diagnostic Radiology, Dalhousie University, Halifax, NS, Canada

Cite as: *Can Urol Assoc J* 2019 November 29; Epub ahead of print.
http://dx.doi.org/10.5489/cuaj.6103

Published online November 29, 2019

***

Abstract

Introduction: As greater numbers of small renal masses (SRMs) are discovered incidentally, renal tumor biopsy (RTB) is an increasingly recognized step for the management of these lesions, ideally for the prevention of surgical overtreatment for benign disease. While the diagnosis can often be obtained preoperatively by RTB, indeterminate results create greater difficulty for patients and clinicians. This study examines a series of RTBs, identifying the portion of these that were able to yield a diagnosis, and correlates patient factors, including RENAL and PADUA scoring, with the outcome of a non-diagnostic result.
Methods: Patients were identified as having undergone RTB at the Princess Margaret Cancer Centre in Ontario, Canada, between January 2000 and December 2009. Data was compiled from these 423 patients and analyzed using CART methodology to determine the level of association between various patient and tumor factors and the outcome of a non-diagnostic biopsy. Tumor size was further used to develop a classification tree to describe the prediction of a non-diagnostic biopsy.
Results: Of these 423 patients undergoing RTB, 66 (16%) resulted in a non-diagnostic biopsy. The only patient or tumor factor that was found to be associated with a non-diagnostic outcome was mass size, where small masses (<1.28 cm diameter) were found to have a 38% chance of

being non-diagnostic, compared with a 13% chance in those tumors >1.28 cm diameter (86% accuracy, 95% confidence interval [CI] 0.82–0.89).
Conclusions: When evaluating SRMs for diagnostic workup, mass size is the only tumor or patient characteristic associated with a non-diagnostic RTB.

Introduction

Incidence of renal cell carcinoma has been increasing in the last several decades, mostly attributed to increased detection of small renal masses (SRMs) ≤4 cm by cross-sectional imaging[1]. Over 50% of RCC are now found incidentally[2]. SRMs confer a lower risk of malignancy compared to other renal masses[3], yet surgical management of SRMs is frequently performed without a pre-treatment histological diagnosis[4]. SRM size is inversely associated with malignant potential, with benign pathology findings in 40% of masses <1 cm and 20% between 1 and 4 cm[5]. The resection of benign lesions has increased by 82% from 2000-2009[5], reflecting extirpative management of higher numbers of SRMs. Pre-treatment options for these masses are limited, given their presentation often in the absence of additional clinical or radiological findings[6]. Despite increasing surgical excision of greater numbers of SRMs, the mortality rate of RCC has remained stable, suggesting an overtreatment of benign disease[1,5].

As the ideal management of SRMs involves treatment of potential malignant disease with preservation of renal function and the avoidance of overtreatment, renal tumor biopsy (RTB) can provide accurate histological classification to help guide treatment decisions[7]. A large meta-analysis of 5228 patients[8] undergoing RTB found an overall median diagnostic rate of 92%, with a sensitivity and specificity of 99.7 and 93.2%. Despite these high reported rates, this can represent a diagnostic challenge when an indeterminate RTB is obtained, and little is known about the patient or tumor characteristics that may result in a failed RTB. This study attempts to determine demographic factors, including RENAL and PADUA scoring, that may be related to a non-diagnostic biopsy, as well as developing a classification tree for the prediction of a non-diagnostic biopsy.

Methods

Patient data was obtained from a prospectively maintained database at the Princess Margaret Cancer Centre, with eligible patients having undergone a percutaneous RTB during the period of January 2000 to December 2009. This study included 423 patients with SRMs (Table 1) who received a biopsy for the purposes of determining a management plan, prior to ablation therapy, or for monitoring post-ablation. Prediction of a non-diagnostic biopsy was attempted using CART (computation and regression tree) methodology assessing patient and tumor

characteristics as well as RENAL and PADUA scoring (Table 2). This study cohort was previously investigated by Organ et al in developing a classification tree for the prediction of malignancy[9].

Classification trees are easily interpreted clinical tools that partition a set of variables to predict an associated target outcome. This type of analysis inherently analyzes association of variables, while also developing a useful decision model when facing an unclear clinical situation. A classification tree was generated for the prediction of a non-diagnostic biopsy using mass size as the associated variable. The classification tree model was developed using the *rpart* package in the R language for statistical computing[10]. Tumor volume was calculated based on imaging for three dimensions using the geometrical equation for the volume of an ellipsoid ($\frac{4}{3}\pi xyz$). The associated tumor volume calculated with the CART analysis was converted for an approximation of tumor diameter, a more clinically useful distinction.

Results

Prediction of non-diagnostic biopsy was attempted using CART methodology for patient and tumor variables as well as RENAL and PADUA. In this cohort of 423 patients undergoing RTB for SRMs, 66 (16%) of the biopsies were non-diagnostic. Of the patients undergoing biopsy, 66% were male with a median age of 65. Most of these masses (68%) were found incidentally. Biopsy results were found to be malignant in 79% of masses, mostly represented by clear cell RCC (47%). Papillary RCC, chromophobe RCC and other malignant variations comprised the remainder of malignant masses, with 13%, 4%, and 15% respectively. For benign histological diagnoses, oncocytomas comprised 13%of overall masses, angiolipomas represented 5%, and rare findings included 1 case each of a benign cystic mass and metanephric adenoma. Other benign lesions were found in 3% of masses. For staging of disease, 355 masses were found as T1a stage lesions, 58 masses were discovered to be T1b, 17 masses were T2a and 13 T2b. No masses were found to be T3a or higher on biopsy results. For the masses which did not yield a diagnostic biopsy, all tissue results showed normal renal parenchyma and therefore were assumed to be missed biopsies.

When assessing RENAL scores for tumor imaging, the mean radius score of masses was found to be 1.3. The endophytic component had a mean score of 1.6. Nearness to sinus or collecting system was found to have a mean score of 2.0. by RENAL score, 136 of masses were anteriorly located, with 100 posterior and 121 found to be neither. Location to polar lines was found to have a mean score of 1.8.

For PADUA scoring, tumor size and exophytic/endophytic scores were the same. Proximity to collecting system was found to have a mean score of 1.3. By PADUA scores, 212 masses were determined to be anterior, with 147 found to be posterior. Longitudinal scores for

this mass series resulted in a mean of 1.8. For renal rim, mean score was 1.4, and renal sinus was found to have a mean score of 1.5.

The only patient or tumor characteristic that was predictive of non-diagnostic biopsies was tumor volume. Very small masses <1.09 cm^3 had a 38% chance of being non-diagnostic vs. 13% in tumors that were larger with an accuracy 86% (95% CI 0.8212, 0.89) (Figure 1). Assuming an approximately spherical mass, performing a biopsy in a mass smaller than 1.28 cm diameter is associated with a three-fold risk of obtaining a non-diagnostic biopsy. Overall, total RENAL and PADUA scores were unable to predict non-diagnostic biopsies. A classification tree was developed to identify associated variables and classify those variables to clinically stratify patients who may result in a non-diagnostic biopsy. However, as tumor volume was the only variable found to be associated, this classification tree is not clinically useful in predicting non-diagnostic biopsy.

Discussion

The use of biopsy in the pre-operative diagnosis of SRMs has increased substantially. Despite this change in practice at high volume centers, RTB still has limitations with instances of technical failure and indeterminate or inaccurate pathological diagnosis. Furthermore, the results from large high volume centers are not generalizable to less experienced institutions. Biopsy is being increasingly recommended in management guidelines in the setting where the clinical treatment decision is affected by the results of the biopsy[11,12].

This study looked at patient and tumor characteristics along with RENAL and PADUA scoring to predict non-diagnostic biopsies. Age, sex, tumor location, and endophytic component were not associated with diagnostic rates. Tumor size (volume) was associated with a positive biopsy rate, with very small masses <1.28 cm diameter having a lower diagnostic yield.

In a recent study by Richard *et al.*, 10% of the biopsies were non-diagnostic after the first attempt, with an 8.5% complication rate[13]. This study also found an association between non-diagnostic biopsies and exophytic component of mass, in contrast to our findings, but also found an association with tumor volume. A subsequent biopsy series again by Richard *et al.* from the same center was not able to reproduce the association between the exophytic component and indeterminate biopsy result[4], but the association with tumor volume was retained.

There have been multiple suggested causes of an indeterminate biopsy for patients with an SRM, with conflicting evidence found for these variables. A failed biopsy may include technical variables, such as biopsy learning curve, user technique, tumor heterogeneity, and respiratory movement during the procedure[14]. Multiple studies have found associations between tumor size and an indeterminate yield, while other series have found no association[4,13,15–18]. Leveridge *et al*. found tumor size was associated with non-diagnostic biopsy[16], as well as the type of tumor -- whether cystic or solid, a finding also described by two other series[18,19].

More recently, Seager et al[20] investigated a cohort of 95 SRMs, with a high predominance of masses ≤2 cm, biopsied with either US or CT guidance. Anteriorly located masses were highly associated with an outcome of non-diagnostic biopsy with an odds ratio (OR) of 13.8. Upper pole masses were also found to have an OR of 4.35 for an indeterminate yield, but this series did not find an association between either the tumor volume nor RENAL or PADUA scoring. This cohort comments on a more anatomically challenging biopsy for a mass in an upper pole location, given the proximity of vital adjacent structures, but this finding is not replicated in multiple other biopsy series[4,13,16].

This study was performed at a single institution, limiting the validity of the results to other centres with varied patient populations or settings. In addition, having been performed at a high-volume centre, this study may represent a higher biopsy accuracy rate than those observed at lower-volume centres. In terms of patient factors, this study only looked at age, gender, and symptoms for association factors with non-diagnostic biopsies. However, there may be other patient factors not analyzed in this series that have an association with a failed biopsy, including patient BMI, comorbid conditions, comorbid medications (ex. Anticoagulants), and skin-to-tumor distance. These metrics were previously investigated by Prince et al[19], who did not demonstrate an association with BMI or comorbidity, but found predictive factors for yielding non-diagnostic biopsy to be cystic features, enhancement <20 HU, left tumor, tumor diameter, and skin-to-tumor distance.

The findings from this study help inform the management of SRMs by reaffirming that a biopsy should be performed only in the setting where histological diagnosis affects treatment, particularly in the setting of active surveillance. Furthermore, small masses in younger patients need to be further elucidated or surgically removed. For those with a very small tumor identified on imaging and considering biopsy, there is a higher likelihood of both indeterminate results and complications with subsequent biopsies. In addition to the consideration of size, it should be noted as well that the results from this study suggest that a biopsy can be considered in those masses in close proximity to the collecting duct and regardless of location within the kidney structure itself. Location and exophytic component should not preclude a renal tumor biopsy when considering a non-diagnostic outcome.

In a patient-informed decision-making discussion, the limitations of biopsy should be carefully conveyed to patients about to undergo a RTB. A non-diagnostic yield is not indicative of a benign mass, as a histological diagnosis of malignancy may be found in 73% of repeat biopsies[16]. Repeat biopsy may be a viable option in patients who initially face a non-diagnostic result, as a diagnosis is obtained in 80% of these patients[21]. Seeding of the biopsy tract has been a theoretical concern for uptake of renal tumor biopsy; however, this outcome has not been reported in any modern renal mass biopsy series[21].

There is increasing recognition of renal tumor biopsy to obtain a histological diagnosis prior to treatment, especially considering the risk of overtreatment with surgical management of benign disease. Non-diagnostic yield remains a challenge for clinicians. In this study, the only patient or tumor variable that was associated with a non-diagnostic RTB was tumor size, with a threefold risk in masses <1.28 cm diameter compared to larger masses >1.28 cm diameter. The limitations of biopsy should be discussed with patients, and a repeat biopsy frequently yields a histological diagnosis.

References

1. Hollingsworth JM, Miller DC, Daignault S, et al. Rising Incidence of Small Renal Masses: A Need to Reassess Treatment Effect. *JNCI: Journal of the National Cancer Institute* 2006;98:1331–4.
2. Luciani LG, Cestari R, Tallarigo C. Incidental renal cell carcinoma—age and stage characterization and clinical implications: study of 1092 patients (1982–1997). *Urology* 2000;56:58–62.
3. Frank I, Blute ML, Cheville JC, et al. Solid renal tumors: an analysis of pathological features related to tumor size. *J Urol* 2003;170:2217–20.
4. Richard PO, Jewett MAS, Tanguay S, et al. Safety, reliability and accuracy of small renal tumor biopsies: results from a multi-institution registry. *BJU International* 2017;119:543–9.
5. Johnson DC, Vukina J, Smith AB, et al. Preoperatively Misclassified, Surgically Removed Benign Renal Masses: A Systematic Review of Surgical Series and United States Population Level Burden Estimate. *Journal of Urology* 2015;193:30–5.
6. Beland MD, Mayo-Smith WW, Dupuy DE, et al. Diagnostic Yield of 58 Consecutive Imaging-Guided Biopsies of Solid Renal Masses: Should We Biopsy All That Are Indeterminate? *American Journal of Roentgenology* 2007;188:792–7.
7. Chenam A, Lau C. Management of Small Renal Masses. In: Daneshmand S, Chan KG, eds. *Genitourinary Cancers*.Vol 175. Cham: Springer International Publishing; 2018:105–26.
8. Marconi L, Dabestani S, Lam TB, et al. Systematic Review and Meta-analysis of Diagnostic Accuracy of Percutaneous Renal Tumor Biopsy. *European Urology* 2016;69:660–73.
9. Organ M, MacDonald LP, Jewett MAS, et al. Classification tree for the prediction of malignant disease and the prediction of non-diagnostic biopsies in patients with small renal masses. *Canadian Urological Association Journal* 2018;13.
10. Abdolell M, LeBlanc M, Stephens D, et al. Binary partitioning for continuous longitudinal data: categorizing a prognostic variable. *Statistics in Medicine* 2002;21:3395–409.
11. Jewett MAS, Rendon R, Lacombe L, et al. Canadian guidelines for the management of the small renal mass (SRM). *Canadian Urological Association Journal* 2015;9:160.
12. Sanchez A, Feldman AS, Hakimi AA. Current Management of Small Renal Masses, Including Patient Selection, Renal Tumor Biopsy, Active Surveillance, and Thermal Ablation. *JCO* 2018;36:3591–600.
13. Richard PO, Jewett MAS, Bhatt JR, et al. Renal Tumor Biopsy for Small Renal Masses: A Single-center 13-year Experience. *European Urology* 2015;68:1007–13.
14. Seager MJ, Patel U, Anderson CJ, et al. Image-guided biopsy of small (≤4 cm) renal masses: the effect of size and anatomical location on biopsy success rate and complications. *BJR* 2018;91:20170666.
15. Salem S, Ponsky LE, Abouassaly R, et al. Image-guided biopsy of small renal masses in the era of ablative therapies. *International Journal of Urology* 2013;20:580–4.

16. Leveridge MJ, Finelli A, Kachura JR, et al. Outcomes of Small Renal Mass Needle Core Biopsy, Nondiagnostic Percutaneous Biopsy, and the Role of Repeat Biopsy. *European Urology* 2011;60:578–84.
17. Menogue SR, O'Brien BA, Brown AL, et al. Percutaneous core biopsy of small renal mass lesions: a diagnostic tool to better stratify patients for surgical intervention. *BJU International* 2013;111:E146–51.
18. Jeon HG, Seo SI, Jeong BC, et al. Percutaneous Kidney Biopsy for a Small Renal Mass: A Critical Appraisal of Results. *The Journal of Urology* 2016;195:568–73.
19. Prince J, Bultman E, Hinshaw L, et al. Patient and Tumor Characteristics can Predict Nondiagnostic Renal Mass Biopsy Findings. *The Journal of Urology* 2015;193:1899–904.
20. Seager M, Patel U, Anderson C, et al. Image-guided biopsy of small (≤ 4cm) renal masses: the effect of size and anatomical location on biopsy success rate and complications. *The British Journal of Radiology* https://doi.org/10.1259/bjr.20170666.
21. Patel HD, Johnson MH, Pierorazio PM, et al. Diagnostic Accuracy and Risks of Biopsy in the Diagnosis of a Renal Mass Suspicious for Localized Renal Cell Carcinoma: Systematic Review of the Literature. *Journal of Urology* 2016;195:1340–7.

Figures and Tables

Fig. 1.

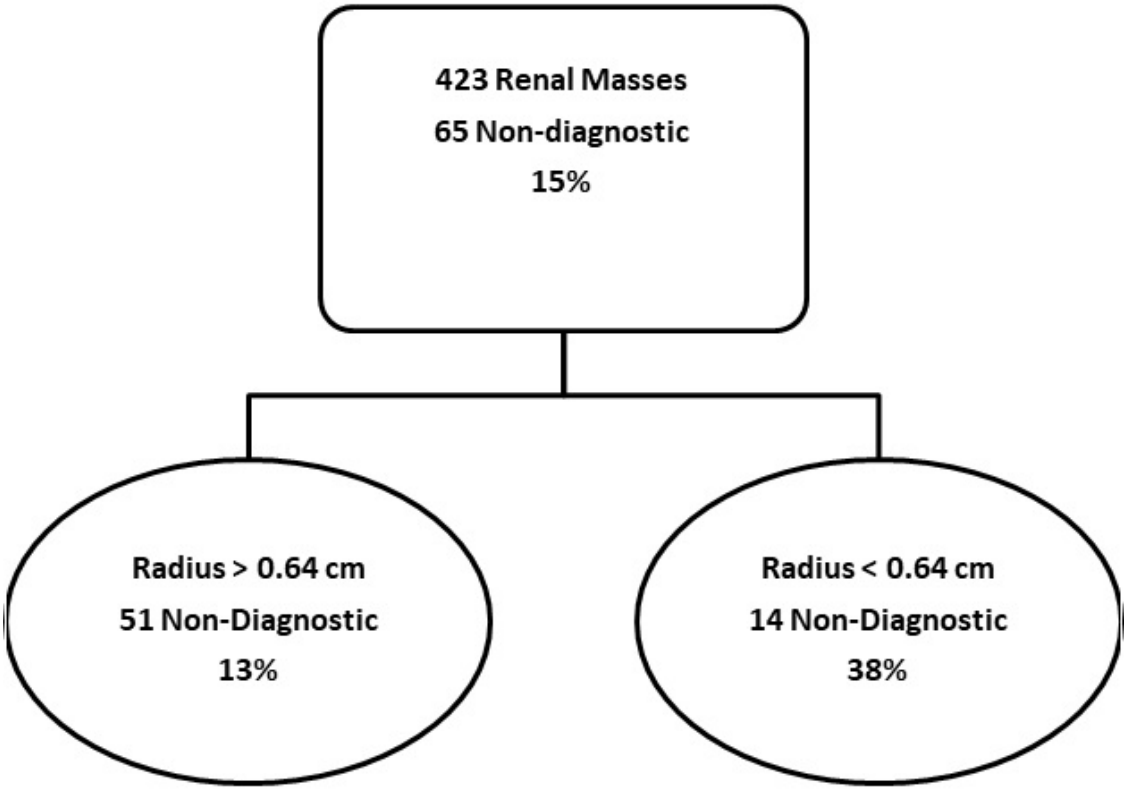

Table 1. Patient and tumor characteristics of patients with SRMs undergoing RTB	
Characteristic	**Patients**
Total patients	423
Diagnostic biopsies	357
Non-diagnostic, n (%)	66 (16)
Male, n (%)	278 (66)
Age at surgery or biopsy, median (range)	65 (32–91)
Incidental, n (%)	288 (68)
Symptomatic, n (%)	84 (20)
Symptoms not available, n (%)	51 (12)
Tumor characteristics	
Imaging tumor volume in cm^3, median (range)	8.7 (0–2252)
Endophytic %, median (range)	50 (5–100)
Tumor histology	
Malignant, n (%)	281 (79)
Clear-cell RCC, n(%)	167 (47)
Papillary RCC, n (%)	45 (13)
Chromophobe RCC, n (%)	14 (4)
Malignant other, n (%)	55 (15)
Benign, n (%)	76 (21)
Oncocytoma, n (%)	47 (13)
Angiomyolipoma, n (%)	16 (5)
Benign cystic, n (%)	1 (0)
Metanephric adenoma, n (%)	1 (0)
Leiomyoma, n (%)	0 (0)
Cystic nephroma, n (%)	0 (0)
Benign other, n (%)	11 (3)
TMN stage, n	
T1a	335
T1b	58
T2a	17
T2b	13
T3a	0

RCC: renal cell carcinoma; RTB: renal tumor biopsy; SRM: small renal mass.