# *Pathological characteristics of the large renal mass: potential implication for clinical role of renal biopsy*

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***Introduction:*** *To assess whether patients with a large renal mass, treated by radical nephrectomy (RN), could have benefited from preoperative renal mass biopsy (RMB). The decision to perform partial nephrectomy (PN) for an organ-confined > 4 cm renal mass can be complex. Albeit often feasible, oncologic safety of PN in this cohort is debated. Yet, a significant portion of large renal masses that undergo RN prove benign or indolent, indicating a potential role for RMB to guide nephron preservation.*

***Materials and methods:*** *We queried prospectively maintained databases from three institutions to identify patients who underwent RN for localized > 4 cm renal mass. We excluded patients with nodal or distant metastases. Multivariable analysis assessed how clinicopathologic variables, mass anatomic complexity, and patient comorbidities related to the likelihood of harboring an indolent neoplasm.*

***Results:*** *A total of 702 patients underwent RN for localized > 4 cm renal mass (median tumor size 7.0 cm (IQR 5.5-9.2); 12.8% (n = 90) of patients were diagnosed with oncocytoma/oncocytic neoplasm (n = 27, 3.8%) or chromophobe RCC (n = 63, 9.0%). When stratified by tumor size, indolent tumors comprised 10.1% of 4-7 cm masses, 15.6% of ≥ 7-10 cm masses, and 17.3% of ≥ 10 cm tumors. Upon multivariate analysis, younger age was associated with indolent tumors (p = 0.04, OR 0.97, 95% CI 0.94-0.99).*

***Conclusions:*** *Approximately 1 in 8 patients with a renal mass > 4 cm harbored benign or low risk indolent potential lesions and were associated with younger age. As such, patients with large renal masses for whom risk trade-offs between PN and RN are unclear, present a unique opportunity for greater utilization of RMB.*

**Key Words:** renal mass biopsy, partial nephrectomy, radical nephrectomy, kidney cancer, renal cell carcinoma

## Introduction

In 2021, approximately 76,080 patients will be diagnosed with cancer of the kidney and renal pelvis, leading to 13,780 deaths in the United States.[1] Due in part to the increased utilization of cross-sectional imaging, there has been a rise in the diagnosis of incidental localized renal mass.[2] While the majority of these lesions are found to harbor renal cell carcinoma (RCC), a significant proportion will prove benign with recent assessments of claims data suggesting that > 30% of resected masses did not show malignancy upon resection.[3,4] Currently, the standard of care for the treatment of patients with localized RCC is surgical extirpation,[5] either with partial nephrectomy (PN) or radical nephrectomy (RN) with the former approach preferred in patients with masses < 4 cm and the latter for those with higher oncologic risk.

Clinicians seeking to calibrate the intensity of treatment may find it difficult to balance risks of

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undertreatment or overtreatment. As such, over the past decade, there has been an ongoing debate surrounding how renal mass biopsy (RMB) can be optimally utilized for renal mass risk stratification.[6] Accordingly, some experts have argued for routine RMB in the evaluation of all renal masses[7] while others urge caution.[8,9] Key opinion leaders and guideline panels suggest that RMB be utilized judiciously in select patients where it can provide clinically "actionable" information.[5,6]

Patients with a large renal mass (LRM) often undergo RN as enthusiasm to perform PN is dampened by not only perioperative risks, but also by oncologic concerns. While concerns about the oncologic safety of PN in larger masses (> 4 cm) has historically limited its application, recent cohorts have demonstrated equivalent oncologic outcomes between PN and RN in preselected patient cohorts.[10,11] Additionally, a portion of large renal masses that undergo resection, prove benign or indolent,[12] suggesting that there is a preoperative opportunity for better patient risk stratification. Using histology data from Surveillance, Epidemiology and End Results (SEER) in pT1 and pT2 RCC's, Rothman et al showed that while the probability of high-grade tumors increase with rising tumor size, the odds of chromophobe RCC also increase at a rate of 8% per 1 cm increase in size.[13] Indeed, RMB is an extremely accurate tool for assessing for presence of benign and/or indolent renal masses such oncocytoma and chromophobe renal cell carcinoma. Thus, while often technically feasible, the decision to perform PN in patients with LRMs is nuanced and may be better calibrated employing preoperative RMB to match disease biology with appropriate treatment intensity. Here, we examined a multi-institutional cohort of patients who underwent RN at tertiary referral centers to assess rate of benign and indolent disease and evaluate whether renal biopsy could have potentially impacted critical clinical decision-making.

## Materials and methods

We queried prospectively maintained kidney cancer databases from three tertiary academic referral centers: Fox Chase Cancer Center, University of Chicago, and Penn State University. The design of this study and the data share agreement were approved by the respective Institutional Review Boards. We identified patients with a localized renal mass > 4 cm who underwent RN. Patients with nodal or distant metastases were excluded. Clinicopathologic variables, mass anatomic complexity, patient comorbidities, and surgical approach techniques were indexed. Histopathology and staging data were gathered based on the pathology report from each institution. Where available, date and histopathologic findings of RMB were gathered. Our cohort was then divided into indolent and non-indolent groups based on tumor histology. The indolent histology group included oncocytoma, "oncocytic neoplasm", chromophobe RCC, and other benign tumors such as angiomyolipoma (AML); while the non-indolent group included all other malignant histology.

Descriptives of demographic and clinical factors were assessed via median (IQR) and proportions (percentage) for continuous and categorical variables respectively. The association between demographic and clinical variables and the likelihood of harboring benign/indolent pathology at resection was examined using multiple logistic regression. All analyses were done using SAS 9.4.

## Results

A total of 702 patients underwent RN for a renal mass > 4 cm at the three institutions who met inclusion and exclusion criteria. A summary of clinicopathologic data is listed in Table 1. The median patient age was 62 years (IQR 52-71), with men accounting for 64.1% of the cohort. Median Charlson Comorbidity Index (CCI) was 1 (IQR 0-3) and preoperative serum creatinine (SCr) and eGFR were 0.97 mg/dL (IQR 0.8-1.2) and 76 mL/min per 1.73 $m^2$ (IQR 62.0-90.6),

TABLE 1. **Clinicopathologic variables**

| **Variable** | **Median (IQR) n%** |
|---|---|
| Age | 62 (52-71) |
| Sex (male) | 450 (64.1%) |
| Laterality | |
| Right | 343 (48.9%) |
| Left | 352 (50.1%) |
| Bilateral | 2 (0.3%) |
| Race | |
| White | 558 (83.2%) |
| Black | 82 (12.2%) |
| Hispanic | 13 (1.9%) |
| Other | 18 (2.7%) |
| Tumor size (cm) | 7.0 (5.5-9.2) |
| Nephrometry score | 10 (9-11) |
| Preoperative eGFR | 76.0 (62-90.6) |
| Postoperative eGFR | 55.9 (46.3-66.2) |
| Length of stay | 3 (2-5) |

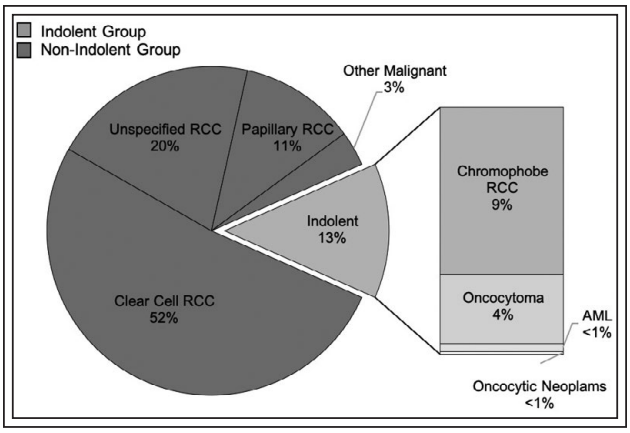


**Figure 1.** Final surgical pathology (n = 702) for patients with localized tumors > 4 cm who underwent radical nephrectomy at the Fox Chase Cancer Center, Penn State Health Hershey Medical Center, and University of Chicago.

respectively. Median tumor size was 7 cm (IQR 5.5-9.2) with a median RENAL nephrometry score[14] of 10 (IQR 9-11). Final pathology reports identified 90 (12.8%) patients harboring tumors meeting criteria for the indolent group, and 3 (0.4%) patients who had an angiomyolipoma (AML). Figure 1 summarizes distribution of tumor histopathology in the cohort with clear cell RCC accounting for 51.6% of tumors. When stratified by tumor size, indolent tumors comprised 10.1% of 4-7 cm masses, 15.6% of ≥ 7-10 cm masses, and 17.3% of ≥ 10 cm tumors. Table 2 shows on multivariable analysis (MVA), only younger age (p = 0.04, OR 0.97, 95% CI 0.94-0.99) was found to be significantly associated with likelihood of indolent pathology.

TABLE 2. **Clinicopathologic variables**

| Variable | OR | 95% Confidence limits | | p value |
|---|---|---|---|---|
| Age | 0.97 | 0.943 | 0.999 | 0.04 |
| Sex | 0.556 | 0.274 | 1.127 | 0.10 |
| Tumor size (cm) | 1.096 | 0.98 | 1.226 | 0.11 |
| Preoperative eGFR | 1.017 | 1.0 | 1.034 | 0.06 |
| Nephrometry score | 1.333 | 0.977 | 1.818 | 0.07 |

## Discussion

Large renal masses are primarily managed by tumor resection. Historically, patients underwent RN for renal masses of any size. With advances in surgical technique, nephron sparing surgery (NSS) in the form of PN was introduced in select patients.[15] This group included those with an imperative indication for PN, including solitary kidney, bilateral renal masses, or those with chronic kidney disease (CKD) so to reduce associated adverse effects of poor renal function or forgo imminent need for renal dialysis.[15,16] As this surgical skillset propagated, the criteria for patients also expanded to include those with normal renal function and normal contralateral kidney.[17]

As PN became widely adopted in clinical practice, multiple institutional studies,[18,19] metanalyses,[20] and eventually a randomized clinical trial (EORTC 30904) found that patients undergoing PN for smaller masses (≤ 5 cm) had a lower risk of CKD while preserving oncologic safety comparted to those undergoing RN.[21,22] As such, PN is the preferred clinical approach in patients with T1a masses whose tumors are amenable to PN.[5,11]

The decision between PN versus RN in patients with LRMs harbors an added level of complexity and must carefully integrate patient factors such as comorbidities, renal function, tumor factors, and both surgical and oncologic risks.[11,23] In particular, oncologic safety of PN has only been assessed in preselected retrospective cohorts.[24] The sole prospective randomized trial of PN versus RN, only enrolled patients with masses < 5 cm.[22] Thus, even when PN is technically possible and perioperative risks are acceptable, clinicians and patients may be deterred from nephron preservation by potential oncologic concerns.[11] Yet, our multi-institutional data demonstrate that nearly 13% of patients with > 4 cm masses harbor either benign or indolent renal tumors that theoretically could be diagnosed with preoperative RMB. In fact, in our cohort of pre-selected patients who underwent RN, as tumor size increased, likelihood of benign histology rose. This is consistent with previous reports that document a complex relationship between tumor size and likelihood of benign pathology.[13,25] Such preoperative knowledge of tumor biology can spare some patients from surgery or influence critical decision making regarding moving forward with nephron preservation.

Historical concerns of RMB diagnostic accuracy and potential for needle tract seeding have been explored in recent literature. A meta-analysis by Marconi et al found that the overall sensitivity and specificity

for RMB accurately diagnosing a malignant lesion was 99.7% and 98.2%, respectively, with a histologic concordance rate of 96%. However, the concordance rate for histologic grade dropped to 66.7%, only to increase to 86.5% using a simplified 2-tier (high versus low grade) system.[6,26] Although the accuracy of RMB in determination of tumor grade may be fair, it is excellent at identifying oncocytic tumors. Another cited concern for RMB is needle tract seeding leading to tumor upstaging or recurrence. While some groups have reported on seeding of tumor along the needle tract,[27] one must be refrain from labeling RMB unsafe.[28] In much larger cohorts and meta-analysis, seeding has been a rare event with Macroni et al reporting only 1 out of 3900 patients.[26,29]

Prediction of benign and indolent histology in the preoperative setting without the use of renal biopsy is notoriously challenging.[30] Upon multivariable analysis, Table 2, only younger age was found to be significantly associated with indolent tumor pathology (p = 0.04, OR 0.97, CI 0.943-0.999). In this cohort, each year of life was associated with a 3% reduction in likelihood that a benign mass will be found upon extirpation. In this analysis, nephrometry score approached significance as a predictor of indolent pathology. As such, these data suggest large tumors with high anatomic complexity present a particular opportunity for improved preoperative risk stratification and personalized tailoring of treatment strategies via RMB.

As any retrospective assessments, the current study suffers from inherent limitations. All three institutions are tertiary referral centers, which may result in a bias case mix in complexity. Although multi-institutional collaboration affords analysis of larger datasets and, thus, is more likely to be generalizable, granularity of datasets tends to be heterogeneous. Thus, missing data was noted in several analyzed variables. Although the total RENAL score was available for most patients in our cohort, data regarding each component of RENAL score was not indexed for all patients. Data regarding whether RMB was performed was also not always available. While the vast majority of patients are likely to have gone onto surgery without RMB, incomplete data prevented meaningful analysis of RMB's role in our cohort. Additionally, by design, our cohort only included patients treated with RN. It is important to note that this is a pre-selected group that excludes patients with large renal mass who underwent PN. Yet, by examining RN patients only, we believe this study underscores the potential deliverable of RMB in patient with large renal mass in shifting management towards nephron preservation.

## Conclusions

Nearly 1 out of 8 patients in our cohort of patients who underwent RN harbored benign or low risk oncocytic lesions. Importantly, in this cohort, younger age was associated with a higher chance of benign or indolent pathology. As such, RMB may be particularly helpful in appropriately calibrating the complex choice of PN versus RN in patients with large renal mass who stand to benefit the most from nephron preservation. □

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