Tumor Size is Associated With Malignant Potential in Renal Cell Carcinoma Cases

R. Houston Thompson, Jordan M. Kurta, Matthew Kaag, Satish K. Tickoo, Shilajit Kundu, Darren Katz, Lucas Nogueira, Victor E. Reuter and Paul Russo*

From the Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York

Purpose: We evaluated our experience with renal cortical tumors to determine whether tumor size is associated with malignant histology and/or nuclear grade.
Materials and Methods: We identified 2,675 patients treated surgically at our institution for renal cell carcinoma or a benign tumor between 1989 and 2007. Histological subtype and tumor size were obtained from our kidney cancer database and logistic regression analysis was performed.
Results: Of the 2,675 tumors 311 (12%) were benign and 2,364 (88%) were renal cell carcinoma. The OR for the association of malignancy with tumor size was 1.16 (95% CI 1.11–1.22, p <0.001), indicating that each 1 cm increase in tumor size was associated with a 16% increase in the odds of malignancy. The incidence of benign tumors decreased from 38% for tumors less than 1 cm to 7% for tumors 7 cm or greater. In patients with clear cell renal cell carcinoma each 1 cm increase in tumor size increased the odds of high grade disease (Fuhrman grade 3–4) compared with low grade disease (Fuhrman grade 1–2) by 25% (OR 1.25, 95% CI 1.21–1.30, p <0.001). In this subset the incidence of high grade lesions increased from 0% for tumors less than 1 cm to 59% for tumors greater than 7 cm.
Conclusions: Our results confirm previous observations suggesting that the risks of malignancy and high grade tumors increase with tumor size. Patients with small renal masses are at low risk for harboring a high grade clear cell malignancy, which may be useful during initial consultation.

Key Words: kidney; carcinoma, renal cell; risk; neoplasm staging; histology

Abbreviations and Acronyms
RCC = renal cell carcinoma

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* Correspondence: Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, New York 10021 (e-mail: Russop@mskcc.org).

HISTORICALLY patients with a renal tumor have undergone radical nephrectomy in most situations. However, with recent concerns about chronic kidney disease[1] coupled with improvements in technology in patients with a renal mass minimally invasive and nephron sparing surgery are increasingly used.[2,3] In addition, active surveillance for small renal tumors in patients with significant comorbidities has recently been recognized as a reasonable alternative.[4] The decision to perform nephron sparing surgery or observe a small renal tumor is often recommended only after tumor size is evaluated. Thus, tumor size is of paramount importance when counseling patients with a newly diagnosed renal mass.

Previous observations suggest that there is a correlation between renal tumor size and the odds of harboring a malignant lesion. In a retrospective analysis of 2,770 patients Frank et al reported a positive correlation between tumor size and the probability of malignancy as well as a direct relationship between tumor size and the risk of harboring a high grade tu-

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mor.[5] External validation is important to determine whether causal relationships can be generalized to different but plausibly related populations.[6] To our knowledge the findings of Frank et al have not been validated outside of their single institution experience. We evaluated our experience with the relationship between renal tumor size and malignant potential.

MATERIALS AND METHODS

After receiving institutional review board approval we identified 2,675 adult patients treated surgically for a benign renal mass or RCC of any histological subtype between 1989 and 2007. Histological subtype was obtained from our prospectively maintained kidney cancer database. Tumors were categorized as clear cell, papillary, chromophobe, collecting duct, RCC unclassified, oncocytoma, angiomyolipoma, metanephric adenoma or benign other. Low grade was defined as Fuhrman nuclear grades 1 and 2, while high grade was defined as Fuhrman nuclear grades 3 and 4. Since application of the Fuhrman grading system for papillary and chromophobe RCC remains contentious and these subtypes are not routinely assigned such a nuclear grade at our institution, only the nuclear grade for clear cell RCC was used for analysis.

The frequency and percent of benign vs malignant tumors, clear cell vs papillary vs chromophobe vs RCC unclassified and low vs high grade clear cell RCC were summarized according to 1 cm intervals, including less than 1 cm, 1 to less than 2, 2 to less than 3, 3 to less than 4, 4 to less than 5, 5 to less than 6, 6 to less than 7 and 7 or greater. The comparison of low vs high grade RCC is only reported for clear cell RCC because, as mentioned, nuclear grade is not routinely recorded for nonclear cell RCC at our institution. The relationships of tumor size with pathological diagnosis and nuclear grade were evaluated using logistic regression models. The OR and 95% CI are reported for regression models. Statistical analysis was performed using Stata® 8.2 with $p < 0.05$ considered statistically significant.

RESULTS

Of the 2,675 patients in this study 311 (11.6%) had benign tumors and 2,364 (88.4%) had RCC. Table 1 lists the histological subtypes of benign and malignant tumors. The most common histology was clear cell RCC, which occurred in 63% of all patients, followed by papillary RCC, chromophobe RCC and oncocytoma.

Mean size of the 311 benign tumors was 4.0 cm (median 3.0, range 0.5 to 16.5) compared to 5.4 cm (median 4.3, range 0.5 to 23.0) for the 2,364 RCCs. Table 2 shows the proportion of benign vs malignant tumors according to tumor size. There was a significant increase in the odds of a malignant vs a benign tumor as tumor size increased ($p < 0.001$). The OR for the association of malignancy with tumor size was 1.16 (95% CI 1.11–1.22), indicating that each 1 cm increase in tumor size was associated with a 16% increase in the odds of malignancy. The percent of benign tumors decreased from 37.5% for those less than 1 cm to 7.1% for tumors 7 cm or greater. Table 3 lists histological subtypes in patients with RCC according to tumor size in 1 cm intervals. The proportion of patients with clear cell RCC, papillary RCC, chromophobe RCC and RCC unclassified was 67% to 80%, 9% to 20%, 8% to 12% and 0% to 6% for tumors in each 1 cm interval, respectively.

Table 4 lists the proportion of low and high grade lesions by tumor size in the 1,523 patients with clear cell RCC who also had tumor grade recorded. Each 1 cm increase in tumor size increased the odds of a high grade vs a low grade clear cell tumor by 25% (OR 1.25, 95% CI 1.21–1.30, $p < 0.001$). In 1,523 patients with clear cell carcinoma only 16% of tumors less than 3 cm were high grade compared to 59% of those 7 cm or greater.

Table 1. *Histological subtype in 2,675 patients treated surgically for renal mass*

Tumors	No. Tumors (%)
Benign:	
Oncocytoma	232 (74.5)
Angiomyolipoma	35 (11.2)
Metanephric adenoma	8 (2.6)
Other	36 (11.6)
Malignant:	
Conventional clear cell	1,679 (71.0)
Papillary	341 (14.4)
Chromophobe	239 (10.1)
Collecting duct	7 (0.3)
RCC unclassified	98 (4.1)

DISCUSSION

An increased detection rate of small incidental renal tumors has led to difficult decision making for clinicians.[7] With observations that these smaller tumors tend to be more indolent[5] various treatment options may be offered to this patient population. In the past radical nephrectomy was the standard of care in all patients with a renal mass. Recently there has been much success in treating small renal tumors with partial nephrectomy and other investigative ablative techniques.[1,3,8–11] A role for active surveillance has also been proposed in elderly and comorbidly ill patients.[4] Determining the likelihood of malignancy of a renal mass is important when deciding on a management strategy. In this study we externally validated the findings of Frank et al,[5] confirming that the risk of malignancy is directly associated with the size of the renal mass. Furthermore, we

Table 2. *Benign tumors vs RCC according to size in patients treated surgically for renal mass*

Size (cm)	No. Benign (%)	No. RCC (%)
Less than 1	6 (37.5)	10 (62.5)
1–Less than 2	56 (19.2)	236 (80.8)
2–Less than 3	77 (16.5)	391 (83.5)
3–Less than 4	58 (13.0)	390 (87.0)
4–Less than 5	30 (8.7)	315 (91.3)
5–Less than 6	23 (10.0)	206 (90.0)
6–Less than 7	13 (6.6)	183 (93.4)
7 or Greater	48 (7.1)	633 (92.9)

Table 4. *Low vs high grade tumors in 1,523 patients treated surgically for clear cell RCC*

	No. Grade (%)	
Size (cm)	Low	High
Less than 1	6 (100)	0
1–Less than 2	138 (84)	26 (16)
2–Less than 3	206 (83)	43 (17)
3–Less than 4	177 (73)	65 (27)
4–Less than 5	131 (67)	64 (33)
5–Less than 6	83 (58)	59 (42)
6–Less than 7	81 (62)	49 (38)
7 or Greater	163 (41)	232 (59)

also present evidence that larger tumors are more likely to harbor high grade tumors, specifically for the clear cell RCC subtype.

To date preoperative imaging modalities have been unable to reliably predict histology in patients with a renal mass. However, immuno-positron emission tomography holds promise for future imaging endeavors.[12] Additionally, preoperative biopsy of renal masses was initially found to have a high rate of false-negative results and a 31% nondiagnostic rate.[13] However, in more recent studies preoperative renal biopsy has been shown to have high diagnostic accuracy, especially for predicting malignancy.[14] While we recently observed a close correlation between size on computerized tomography and the pathological size of renal tumors,[15] the preoperative diagnosis of histology remains problematic. Thus, a presumptive diagnosis of and subsequent management for most renal tumors is currently limited to tumor size based on radiographic imaging.

Many factors may lead a clinician to perform a particular interventional or observational approach. One such factor is renal tumor size. Our data suggest that an increase in renal tumor size is significantly associated with an increased likelihood of malignancy. Specifically we observed that each 1 cm increase in tumor size is associated with a 16% increased risk of malignancy. These data support findings from the Mayo Clinic.[5] It is remarkable that we observed almost identical ORs for the association of malignancy with tumor size, that is an OR of 1.17 and 1.16 for Mayo Clinic and our data, respectively. From a clinical standpoint the tables presented can be used when counseling a patient with an enhancing renal mass about the risks of malignancy. For example, if a patient presents with a renal tumor that is between 3 and 4 cm, our data suggest that there is a 13% chance of a benign lesion, while there is an 87% chance that the mass is RCC (table 2). Since 68% of 3 to 4 cm RCCs have a clear cell histology, the sample patient could be further informed that there is a 59% chance that the renal mass has a clear cell histology (table 3). Furthermore, since 27% of patients with 3 to 4 cm clear cell RCC have high grade lesions (table 4), the sample patient could also be informed that there is a 16% chance that the renal mass is high grade clear cell RCC. Thus, these tables may be useful during the initial consultation and when deciding upon a management approach.

Several limitations of this study merit discussion. Our data represent a retrospective review of findings at a single center. As such, our findings are subject to the inherent biases of this type of analysis. More importantly our data represent a group of patients who were treated surgically. While the standard of care at our institution during the study period was to manage a renal mass surgically, patients who were not treated surgically, perhaps due to widespread metastases or inoperable tumors, were not captured in our surgical database. Furthermore, histological diagnosis and grading was not obtained from a single pathologist, which may be

Table 3. *RCC histology by tumor size in 2,365 patients treated surgically*

Size (cm)	No. Clear Cell (%)	No. Papillary (%)	No. Chromophobe (%)	No. RCC Unclassified (%)
Less than 1	8 (80.0)	1 (10.0)	1 (10.0)	0
1–Less than 2	168 (71.0)	36 (15.0)	19 (8.0)	13 (6.0)
2–Less than 3	266 (68.0)	73 (18.7)	33 (8.4)	19 (4.9)
3–Less than 4	265 (68.0)	75 (19.5)	39 (10.0)	10 (2.5)
4–Less than 5	213 (67.6)	51 (16.3)	38 (12.0)	13 (4.1)
5–Less than 6	152 (74.5)	29 (14.2)	19 (9.3)	4 (2.0)
6–Less than 7	142 (77.6)	19 (10.4)	17 (9.3)	5 (2.7)
7 or Greater	465 (73.9)	57 (9.1)	73 (11.6)	34 (5.4)

associated with different grading parameters. However, diagnoses and grading at our institution were determined by pathologists accustomed to assessing neoplastic disease. Additionally, our results are remarkably similar to those in surgical series in which a single pathologist was used.[5]

CONCLUSIONS

Our results confirm previous observations suggesting that the risks of malignancy and higher grade tumors increase as renal tumor size increases. The tables presented can be useful during the initial consultation with patients with a renal mass.

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