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TUMOR SIZE IS ASSOCIATED WITH MALIGNANT POTENTIAL IN RENAL CELL CARCINOMA

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Abstract

Objective—We evaluated our experience with renal cortical tumors to determine if tumor size is associated with malignant histology and/or nuclear grade.

Materials and Methods—We identified 2,675 patients treated surgically at Memorial Sloan-Kettering for renal cell carcinoma (RCC) or a benign tumor between 1989 and 2007. Histologic subtype and tumor size were obtained from our kidney cancer database and logistic regression analyses were performed.

Results—Among the 2,675 tumors, 311 (12%) were benign while 2,364 (88%) were RCC. The odds ratio for 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 percentage of benign tumors decreased from 38% for those less than 1 cm to 7% for tumors 7 cm or greater. For patients with clear cell RCC, each 1 cm increase in tumor size increased the odds of a high grade (Fuhrman grade 3–4) compared with a low grade (Fuhrman grade 1–2) tumor by 25% (odds ratio 1.25, 95% CI 1.21–1.30; $p < 0.001$). For this subset, the percentage of high grade tumors increased from 0% for tumors < 1 cm to 59% for tumors > 7 cm.

Conclusions—Our results confirm previous observations suggesting that the risk of malignancy and risk of high grade tumors increases with tumor size. Patients with small renal masses have a low risk for harboring a high-grade clear cell malignancy which may be useful during initial consultation.

Keywords

Carcinoma, renal cell; Kidney neoplasms; Neoplasm staging; Histology

Introduction

Historically, patients with a renal tumor underwent radical nephrectomy in most situations. However, with recent concerns for chronic kidney disease¹ coupled with improvements in technology for renal mass patients, minimally invasive and nephron sparing surgery are increasingly utilized.^{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 tumor.⁵ External validation is important to demonstrate whether causal relationships can be generalized to different but plausibly related populations.⁶ The findings of Frank et al. have not been validated outside of their single-institution experience. Herein, we evaluate our experience with the relationship between renal tumor size and malignant potential.

Materials and Methods

Following institutional review board approval, we identified 2,675 adult patients treated surgically for a benign renal mass or renal cell carcinoma (RCC) of any histologic 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 the application of the Fuhrman grading system for papillary and chromophobe RCC's remains contentious, and as 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.

Statistical Analysis

The frequency and percentage of benign vs. malignant tumors, clear cell vs. papillary vs. chromophobe vs RCC-unclassified, and low grade vs high grade clear cell RCC are summarized according to 1 cm intervals; <1cm, 1 - <2cm, 2 - <3cm, 4 - <5cm, 5 - <6cm, 6 - <7cm, and 7cm or greater. The comparison of low grade vs high grade RCC is only reported for clear cell RCC due to the fact, as mentioned above, that nuclear grade is not routinely recorded for non-clear cell RCC at our institution. The relationships of tumor size with pathologic diagnosis and nuclear grade were evaluated using logistic regression models. Odds ratios along with the 95% confidence intervals (CI) are reported for the regression models. Statistical analyses were performed using Stata 8.2 (Stata Corp., College Station, TX) with $p < 0.05$ considered statistically significant.

Results

Among the 2,675 patients included in this study, 311 (11.6%) were benign tumors and 2,364 (88.4%) were RCC. A summary of the histological subtypes for benign and malignant tumors are demonstrated in table 1. The most common histology was clear cell RCC, which occurred in 63% of all patients, followed by papillary RCC, chromophobe RCC, and oncocytoma.

The mean tumor size for 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 RCC tumors. Table 2 depicts the proportion of benign versus malignant tumors according to tumor size. There was a significant increase in the odds of having a malignant compared with a benign tumor as tumor size increased ($p < 0.001$). The odds ratio 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 percentage of benign tumors decreased from 37.5% for those less than 1 cm to 7.1% for tumors 7 cm or greater. Table 3 demonstrates the histologic subtype for patients with RCC according to tumor size in 1 cm intervals. The proportion of patients with clear cell, papillary, chromophobe, and RCC-unclassified occurred in 67–80%, 9–20%, 8–12%, and 0–6% of tumors in each 1 cm interval, respectively.

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

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 a variety of treatment options may be offered to this population of patients. In the past, radical nephrectomy was the standard of care for 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 for 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 report we externally validate 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 also present evidence that larger tumors are more likely to harbor high-grade tumors specifically in the clear cell RCC subtype.

To date, pre-operative imaging modalities are unable to reliably predict histology for renal mass patients. However, immuno-PET imaging holds promise for future imaging endeavours.¹² Additionally, preoperative biopsy of renal masses was initially found to have a high rate of false negatives and a non diagnostic rate of 31%.¹³ However, in more recent studies preoperative renal biopsy has been shown to have a high diagnostic accuracy especially for predicting malignancy.¹⁴ While we have recently observed a close correlation between CT size and pathologic size of renal tumors,¹⁵ preoperative diagnosis of histology remains problematic. Thus, a presumptive diagnosis and subsequent management of most renal tumors is currently limited to tumor size based on radiographic imaging.

There are many factors which may lead a clinician to undertake a particular interventional or observational approach. One such factor is renal tumor size. Our data suggests 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% increase risk of malignancy. This data supports the findings from the Mayo Clinic⁵ and it is remarkable that we observed nearly identical odds ratios for the association of malignancy with tumor size; odds ratios of 1.17 and 1.16 for the Mayo Clinic and our data, respectively. From a clinical standpoint, the tables presented herein can be used when counselling 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 in size, our data (table 1) suggests that there is a 13% chance of a benign lesion while there is an 87% chance that the mass is RCC. Since 68% of RCC tumors 3–4 cm have clear cell histology, the example patient could be further informed (Table 2) that there is a 59% chance that the renal mass has clear cell histology. Furthermore, since 27% of patients with clear cell RCC 3–4 cm have high grade lesions (Table 4), the example patient could also be informed that there is a 16% chance that their renal mass is a high grade clear cell RCC. Thus, these tables can be useful during initial consultation and when deciding upon a management approach.

There are several limitations to this study that merit discussion. Our data represent a retrospective review of findings at a single center and 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 managed surgically. While standard of care at our institution during the study time

frame was to manage renal mass patients 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 associated with different grading parameters. However, the diagnoses and grading at our institution were determined by pathologists accustomed to assessing neoplastic diseases. Additionally, our results are remarkably similar to surgical series where a single pathologist was utilized.⁵

Conclusions

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

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Table 1

Histological subtypes for 2,675 patients treated surgically for a renal mass

Benign Tumors	No. Tumors (%)
Oncocytoma	232 (74)
Angiomyolipoma	35 (11)
Metanephric adenoma	8 (3)
Benign other	36 (12)
Malignant Tumors	
Conventional clear cell	1679 (71)
Papillary	341 (14)
Chromophobe	239 (10)
Collecting duct	7 (0.3)
RCC Unclassified	98 (4)

Table 2

Proportion of benign versus RCC tumors according to tumor size in patients treated surgically for a renal mass

Size in cm	No. Benign (%)	No. RCC (%)
<1	6 (37.5)	10 (62.5)
1-<2	56 (19)	236 (81)
2-<3	77 (17)	391 (83)
3-<4	58 (13)	390 (87)
4-<5	30 (9)	315 (91)
5-<6	23 (10)	206 (90)
6-<7	13 (7)	183 (93)
7 or greater	48 (7)	633 (93)

Table 3

Proportion of clear cell, papillary, chromophobe and RCC-unclassified by tumor size in 2,365 patients treated surgically for RCC

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

Table 4

Proportion of low grade versus high grade tumors for 1,523 patients with patients treated surgically for clear cell RCC

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