Metastatic Renal Cell Carcinoma Risk According to Tumor Size

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Purpose: Recent evidence suggests significantly discordant findings regarding tumor size and the metastasis risk in renal cell carcinoma cases. We present our experience with renal cell carcinoma. We evaluated the association between tumor size and the metastasis risk in a large patient cohort.

Materials and Methods: Using our prospectively maintained nephrectomy database we identified 2,691 patients who were treated surgically for a sporadic renal cortical tumor between 1989 and 2008. Associations between tumor size and synchronous metastasis at presentation (M1 renal cell carcinoma) were evaluated with logistic regression models. Metastasis-free survival after surgery was estimated using the Kaplan-Meier method in 2,367 patients who did not present with M1 renal cell carcinoma and were followed postoperatively.

Results: Of the 2,691 patients 162 presented with metastatic renal cell carcinoma. Only 1 of 781 patients with a tumor less than 3 cm had M1 renal cell carcinoma at presentation and tumor size was significantly associated with metastasis at presentation (for each 1 cm increase OR 1.25, $p < 0.001$). Of the 2,367 patients who did not present with metastasis metastatic disease developed in 171 during a median 2.8-year followup. In this group only 1 of the 720 patients with renal cell carcinoma less than 3 cm showed de novo metastasis during followup. Metastasis-free survival was significantly associated with tumor size (for each 1 cm increase HR 1.24, $p < 0.001$).

Conclusions: In our experience tumor size is significantly associated with synchronous and asynchronous metastases after nephrectomy. Our results suggest that the risk of metastatic disease is negligible in patients with tumors less than 3 cm.

Key Words: kidney neoplasms; nephrectomy; carcinoma, renal cell; mortality; treatment outcome

Abbreviations and Acronyms

RCC = renal cell carcinoma

Submitted for publication November 19, 2008.

Study received institutional review board approval.

Supported by the Stephen Hanson Family Fellowship and NIH T32 CA82088.

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During the last half century renal tumor size has been reported by groups from multiple institutions to be significantly associated with the risk of synchronous and asynchronous metastasis.[1–3] Additionally, RCC autopsy data suggest that the metastasis risk is significantly associated with primary tumor size, although with a higher prevalence of metastasis across all tumor sizes.[4] This is also supported by the von Hippel-Lindau literature, in which the risk of metastasis in patients with tumors less than 3 cm was negligible.[5] More recently Kunkle et al reported their experience with 110 patients with biopsy proven metastatic RCC, suggesting that tumor size is significantly associated with synchronous metastasis and no patient with a tumor less than 2 cm had synchronous metastasis.[6]

0022-5347/09/1821-0041/0
THE JOURNAL OF UROLOGY®

Vol. 182, 41-45, July 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2009.02.128

In the last year an important multi-institutional observation disputed those findings.[7] Klatte et al combined data from 5 institutions, including those in France, Germany, Italy and California, and identified 1,208 patients with tumors 4 cm or less treated with nephrectomy, including 72 who presented with metastatic RCC.[7] Tumor size was not associated with metastatic disease and M1 RCC was reported in 7%, 6%, 5% and 8% of patients with tumors 1 or less, 1.1 to 2, 2.1 to 3 and 3.1 to 4 cm, respectively. These results have significant implications since the rate of patients diagnosed with small renal masses is increasing and nonoperative surveillance protocols are currently being used in patients with small renal tumors.[8] Therefore, we reviewed our experience with 2,691 patients with a renal mass, of whom 162 presented with synchronous metastatic disease and an additional 171 showed de novo asynchronous metastasis during followup, to address the current discordant literature on primary tumor size.

MATERIALS AND METHODS

Patient Selection

Upon receiving institutional review board approval we reviewed the nephrectomy database at our institution and identified 2,691 patients treated with radical or partial nephrectomy between 1989 and 2008. Patients were selected based on a sporadic, unilateral, enhancing renal cortical tumor with benign histology or any renal cell carcinoma histological subtype. Patients who underwent prior nephrectomy elsewhere for a renal cortical tumor were excluded from analysis.

Variables collected from the database included age, gender, histology, tumor size, TNM stage, metastatic recurrence date after surgery and followup. A patient was considered to have metastatic disease if it was biopsy proven or there was clear radiographic evidence of disseminated disease. Indeterminate lesions, such as a small pulmonary nodule, were not considered metastatic disease. In cases of possible metastasis the patient chart was reviewed by a urological oncology fellow and the senior author to reach a consensus before statistical analysis was performed. Of the 2,691 patients 114 (4%) had possible metastasis at presentation. After a review of these charts including followup information 80 cases were determined to be M0 and 34 were determined to be M1 before statistical analysis.

Statistical Methods

Metastases at presentation were grouped according to tumor size at 1 cm intervals. They are presented descriptively using the incidence and percent. Median tumor size in patients with and without M1 RCC was compared using the Wilcoxon rank sum test. Associations between tumor size and M1 RCC were also evaluated with logistic regression models, entering tumor size as continuous, from which we plotted the risk of M1 RCC by tumor size. For the development of asynchronous de novo metastasis after nephrectomy metastasis-free survival was estimated using the Kaplan-Meier method. The probability of metastasis according to tumor size at 1 cm intervals is shown descriptively, while Cox proportional hazards regression was used to evaluate associations when considering tumor size as continuous. Only patients who did not present with metastasis and had postoperative followup available were included in survival analysis. Statistical analysis was performed using Stata™ 8.2 with $p < 0.05$ considered statistically significant.

RESULTS

Of the 2,691 patients studied 2,367 (88%) had RCC and 324 (12%) had a benign tumor. At surgery 162 patients had documented metastatic disease and were considered to have M1 RCC. Table 1 lists baseline demographics in patients with and without M1 RCC. Median tumor size was significantly greater in patients who did vs did not present with metastasis (8.5 vs 4.0 cm, $p < 0.001$). Figure 1 shows the percent of patients who presented with metastasis according to 1 cm tumor size intervals. Only 1 of the 781 patients (0.1%) with a primary tumor less than 3 cm had metastatic RCC at presentation and that tumor was 2.9 cm. After the primary tumor size was 3 cm or greater the risk of M1 RCC gradually increased from 1.8% to 17.0% in patients with a tumor 3 to 3.9 and 7 cm or greater, respectively. In a logistic regression model tumor size was significantly associated with metastasis at presentation (for each 1 cm increase OR 1.25, 95% CI 1.21–1.30, $p < 0.001$). Figure 2 shows the predicted probability of M1 RCC based on primary tumor size.

Of the 2,529 patients who did not present with metastasis 162 were not followed after surgery, leaving 2,367 available for analysis. Median followup in patients without metastasis was 2.8 years (mean 4.0, range 0.1 to 18.9), during which 171 showed de novo asynchronous metastatic RCC. Figure 3 shows metastasis-free survival.

Table 1. *Baseline demographics in patients with and without metastasis at presentation*

	M0 RCC		M1 RCC	
Median age (range)	62	(19–95)	62	(32–85)
No. gender (%):				
M	1,576	(62)	113	(70)
F	953	(38)	49	(30)
Median cm tumor size (range)	4.0	(0.5–23)	8.5	(2.9–20)
No. nephrectomy (%):				
Partial	1,109	(44)	9	(6)
Radical	1,420	(56)	153	(94)
No. histology (%):				
Clear cell	1,536	(61)	146	(90)
Papillary	334	(13)	5	(3)
Chromophobe	240	(9)	3	(2)
Collecting duct	5	(0.2)	1	(0.6)
RCC unclassified	90	(4)	7	(4)
Benign	324	(13)	0	

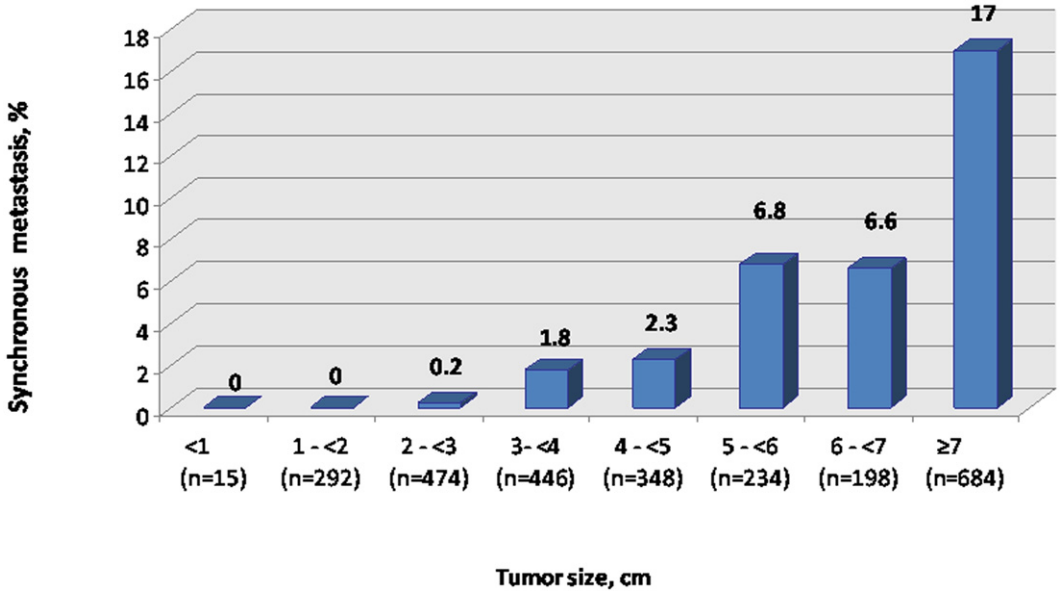

Figure 1. Percent of patients presenting with metastatic RCC according to 1 cm intervals

Table 2 lists the 3-year probability of metastatic disease during followup according to 1 cm tumor size intervals. Only 1 of the 720 patients with a primary tumor less than 3 cm showed asynchronous metastatic RCC after surgery and that tumor was 2.5 cm. Metastasis-free survival was significantly associated with tumor size (for each 1 cm increase HR 1.24, 95% CI 1.20–1.27, p <0.001).

DISCUSSION

For many decades tumor size has been an important clinical and pathological feature in patients with RCC.[1,3,4,6] The American Joint Committee on Cancer primary RCC classification separates the pT1a, pT1b and pT2 categories entirely based on tumor size[9] and significant differences in cancer specific survival are observed in these staging categories (97%, 87% and 71% 5-year cancer specific survival, respectively).[10] When evaluating renal mass cases at the clinic, the decision to perform nephron sparing surgery or undergo a period of watchful waiting heavily depends on tumor size.[8,11,12] Tumor size is also an independent predictor of progression-free and cancer specific survival after surgery,[13,14] although observations in smaller patient cohorts did not validate the independent predictability of tumor size and outcome.[15–17] With regard to tumor size and the risk of synchronous metastatic disease most observa-

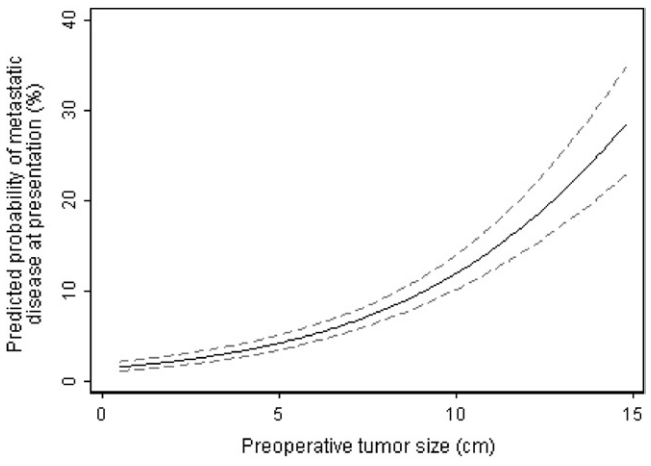

Figure 2. Predicted probability of metastasis at presentation based on primary tumor size. Dashed lines represent 95% CI.

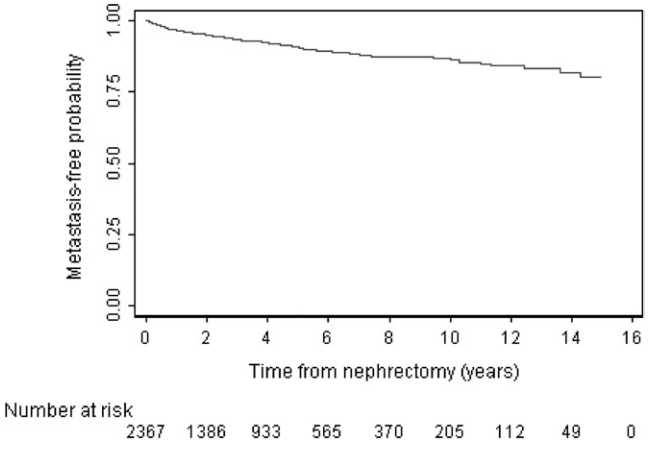

Figure 3. Metastasis-free survival in 2,367 patients with renal mass treated surgically who did not have metastasis at presentation.

Table 2. *Probability of de novo asynchronous metastatic RCC after nephrectomy according to 1 cm intervals*

Tumor Size (cm)	No. Pts	No. Metastasis at Followup	% 3-Yr Metastasis Probability (95% CI)	Median Yrs Survivor Followup (IQR)
Less than 1	13	0	0	3.6 (0.5–6.4)
1–Less than 2	273	0	0	2.6 (1.0–5.3)
2–Less than 3	434	1	0	2.8 (1.0–5.9)
3–Less than 4	413	10	2 (1–4)	2.5 (1.0–5.5)
4–Less than 5	323	5	2 (1–5)	3.1 (1.2–6.6)
5–Less than 6	202	11	3 (1–7)	3.1 (0.8–6.5)
6–Less than 7	172	23	12 (7–19)	4.2 (1.1–6.7)
7+	537	121	20 (17–25)	3.2 (1.1–6.7)

tions support the notion that tumor size is a significant predictor of synchronous and asynchronous metastases.[1–6] However, this was challenged by a recent multi-institutional observation suggesting that 5% to 7% of 1,208 surgically treated patients with renal tumors less than 3 cm harbored synchronous metastasis.[7] Our anecdotal experience did not support such a high rate of metastasis in patients with small renal masses, leading us to retrospectively review our kidney cancer nephrectomy database.

Our results do not support a high or higher than previously thought risk of metastatic disease in patients with small renal masses. In fact, we did not observe a single patient with metastatic disease at presentation or during followup of the approximately 300 with tumors less than 2 cm, a notable finding also observed by Kunkle et al.[6] Furthermore, we only observed 1 case of synchronous metastasis and another of asynchronous metastasis after surgery in almost 500 cases of 2 to 3 cm tumors. Additionally, our regression models suggest that tumor size is significantly associated with the risk of synchronous metastasis and with metastasis-free survival after surgery with an almost identical OR and HR (1.25 and 1.24, respectively). If validated by others, these results have important implications. For example, the number of patients diagnosed with small, incidental renal masses is increasing. As the population ages, we anticipate an increasing number of patients with significant comorbidities who are found to have small renal masses during assessment for nonrelated symptoms. Some of these patients are being offered a period of expectant management with serial imaging, given that recent data suggest an indolent and slow pattern of growth for many of these masses.[18,19] Our data support the notion that patients with small renal masses are at low risk for metastatic disease and those with comorbidities could be safely followed with serial imaging, especially until the tumor demonstrates growth or becomes greater than 2.5 cm.

Reasons for the recent discordant literature on tumor size and metastasis risk are not entirely clear. Klatte et al reported on 1,208 patients with a renal mass 4 cm or less, including 72 with metastasis at presentation, and noted that 6% to 7% with tumors less than 2 cm had metastatic disease.[7] This is in contrast to our data, which included 2,691 patients, of whom 162 had metastatic disease at presentation and 1,227 had tumors less than 4 cm. Kunkle et al reported on 110 patients with metastatic disease at presentation matched with 250 controls and no metastatic disease was observed in a patient with a tumor less than 2 cm.[6] It is plausible to conclude that the discordant results are in part related to unique referral patterns. While the report by Klatte et al included data from France, Italy and Greece, the only center in the United States was UCLA,[7] which is a large referral center for metastatic RCC cases. We suggest that the rare patient with metastatic disease and a small renal tumor would be more likely to present to UCLA for evaluation, although the percent of patients contributed by UCLA to the combined database was not reported. Nevertheless, our data using a relatively strict definition of metastasis supports the notion that as tumor size increases, so does the risk of metastatic disease. This is supported by the study by Kunkle et al, in which the definition of metastatic disease required biopsy confirmation.[6] Results in the study by Klatte et al, in which M stage was assigned according to 2002 definitions although 56% of cases had biopsy confirmation,[7] remain intriguing and, thus, further investigation is needed.

Our study is not without limitations. Our analysis represents a retrospective, single institution experience and our results are subject to the inherent biases that surround these investigations. Additionally, our results are limited by a referral bias to our tertiary care facility. Patients who are surgical candidates or request surgical intervention may be more likely to be referred to our institution, whereas patients with metastatic dis-

ease or those deemed unfit candidates for surgery may be less likely to be referred to our urology department. Also, almost half of the patients were treated with partial nephrectomy, suggesting that those with tumors amenable to partial nephrectomy and possibly less likely to metastasize were more likely to be referred to our institution. However, our results are remarkably similar to those of Kunkle et al[6] with an OR of 1.25 and 1.22, respectively, for the risk of metastatic disease by tumor size.

CONCLUSIONS

In our experience tumor size is significantly associated with synchronous and asynchronous metastases after nephrectomy. Our results suggest that the risk of metastatic disease is negligible in patients with tumors less than 3 cm.

ACKNOWLEDGMENTS

Tom Manion assisted with data abstraction.

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