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RISK OF METASTATIC RENAL CELL CARCINOMA ACCORDING TO TUMOR SIZE

R. Houston Thompson, MD, Jennifer Hill, MD, Yuriy Babayev, MD, Angel Cronin, MS, Matt Kaag, MD, Shilajit Kundu, MD, Melanie Bernstein, Jonathan Coleman, MD, Guido Dalbagni, MD, Karim Touijer, MD, and Paul Russo, MD

From the Department of Surgery- Urology Service, Memorial Sloan-Kettering Cancer Center, New York, NY 10065

Abstract

Purpose—Recent evidence suggests significantly discordant findings regarding tumor size and the risk of metastases in renal cell carcinoma (RCC). Herein, we present our experience with RCC and evaluate the association between tumor size and risk of metastases in a large cohort of patients.

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

Results—Among the 2,691 patients, 162 presented with metastatic RCC. Only 1 of 781 patients with a tumor <3cm had M1 RCC at presentation and tumor size was significantly associated with metastases at presentation (odds ratio 1.25 for each 1cm increase, $p<0.001$). Among the 2,367 patients who did not present with metastases, 171 developed metastatic disease during a median follow-up of 2.8 years. In this group, only 1 of the 720 patients with RCC <3cm developed a de novo metastases during follow-up. Metastases-free survival was significantly associated with tumor size (hazard ratio 1.24 for each 1cm increase, $p<0.001$).

Conclusion—In our experience, tumor size is significantly associated with synchronous metastases and asynchronous metastases following nephrectomy. Our results suggest that risk of metastatic disease for patients with tumors <3cm is negligible.

Keywords

Kidney neoplasms; Nephrectomy; Carcinoma; renal cell; Survival; Treatment outcome

INTRODUCTION

During the last half century, renal tumor size has been reported by multiple institutions to be significantly associated with risk of metastases- both synchronous and asynchronous.^{1–3} Additionally, autopsy data of renal cell carcinoma (RCC) suggests that risk of metastases is significantly associated with size of the primary tumor, albeit with a higher prevalence of metastases across all tumor sizes.⁴ This is also supported in the von Hippel Lindau literature where risk of metastases in patients with tumors less than 3cm was reported to be negligible.

⁵ More recently, Kunkle et al reported their experience with 110 biopsy-proven metastatic RCC patients suggesting that tumor size is significantly associated with synchronous metastases and that no patient with a tumor <2cm had a synchronous metastases.⁶

Within the past year, an important multi-institutional observation disputed the above findings.⁷ Klatte et al combined data from 5 institutions including France, Germany, Italy, and California identifying 1,208 patients with tumors 4cm or less who were treated with nephrectomy, including 72 patients who presented with metastatic RCC. In their analysis, tumor size was not associated with metastatic disease and the presence of M1 RCC was reported in 7%, 6%, 5%, and 8% of patients with tumors ≤1cm, 1.1 – 2cm, 2.1 – 3cm, and 3.1 – 4cm, respectively.⁷ These results have significant implications since the frequency of patients diagnosed with small renal masses is increasing and non-operative surveillance protocols are currently being employed for patients with small renal tumors.⁸ Therefore, we reviewed our experience with 2,691 renal mass patients, among whom 162 presented with synchronous metastatic disease and an additional 171 developed de novo asynchronous metastases during follow-up to address the current discordant literature with respect to primary tumor size.

MATERIALS AND METHODS

Patient Selection

Upon approval from the Institutional Review Board, we reviewed the Memorial Sloan-Kettering nephrectomy database and identified 2,691 patients treated with radical or partial nephrectomy between 1989 and 2008. Patients were selected based on the presence of a sporadic, unilateral, enhancing renal cortical tumor with either benign histology or any renal cell carcinoma histologic subtype. Patients who had a prior nephrectomy for a renal cortical tumor at an outside institution were excluded.

Variables collected from the database included age, gender, histology, tumor size, TNM stage, date of metastatic recurrence following surgery, and follow-up duration. A patient was considered to have metastatic disease if it was biopsy proven or if 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 metastases”, the patient chart was reviewed by a urologic oncology fellow and the senior author for a consensus before statistical analyses were performed. Among the 2,691 patients, 114 (4%) had “possible metastases” at time of presentation. After review of these charts including follow-up information, 80 patients were determined to be M0 and 34 patients were determined to be M1 prior to statistical analysis.

Statistical Methods

Metastases at presentation were grouped according to tumor size at 1cm intervals and presented descriptively using frequencies and percentages. Median tumor size for 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 development of asynchronous de novo metastases following nephrectomy, metastases-free survival was estimated using the Kaplan-Meier method. The probability of metastasis according to tumor size at 1cm intervals is presented descriptively, while Cox proportional hazards regression was used to evaluate associations when considering tumor size as continuous. For the survival analyses, only patients who did not present with metastases and who had postoperative follow-up were included. Statistical analyses were performed using the Stata software package 8.2 (Stata Corp., College Station, TX) and p-values <0.05 were considered statistically significant.

RESULTS

Among the 2,691 patients studied, 2,367 (88%) had RCC while 324 (12%) had a benign tumor. At time of surgery, 162 patients had documented metastatic disease and were considered to have M1 RCC. Baseline demographics for patients with and without M1 RCC are presented in Table 1. Median tumor size was significantly higher for patients who presented with metastases compared with patients who did not present with metastases (8.5cm vs 4.0cm, $p<0.001$, respectively). Figure 1 demonstrates the percentage of patients who presented with metastases according to 1cm tumor size intervals. Among the 781 patients with a primary tumor less than 3cm, only one (0.1%) patient had metastatic RCC at presentation and that single patient's tumor was 2.9cm. Once the primary tumor size reached 3cm or greater, the risk of M1 RCC gradually increased from 1.8% to 17.0% for patients with a tumor 3–3.9cm and ≥ 7 cm, respectively. In a logistic regression model, tumor size was significantly associated with metastases at presentation (odds ratio 1.25 for each 1cm increase; 95% CI 1.21–1.30, $p<0.001$) and the predicted probability of M1 RCC based on primary tumor size is demonstrated in Figure 2.

Among the 2,529 patients who did not present with metastases, 162 were not followed after surgery leaving 2,367 patients available for analysis. Median follow-up for patients without metastasis was 2.8 years (mean 4.0, range 0.1 to 18.9) during which 171 patients developed de novo asynchronous metastatic RCC. Metastases-free survival is demonstrated in Figure 3. Table 2 demonstrates the 3-year probability of developing metastatic disease during follow-up according to 1cm tumor size intervals. Among the 720 patients with a primary tumor less than 3cm, only one patient developed asynchronous metastatic RCC following surgery and that single patient's tumor was 2.5cm. Metastases-free survival was significantly associated with tumor size (hazard ratio 1.24 for each 1cm increase, 95% CI 1.20–1.27; $p<0.001$).

DISCUSSION

For many decades, tumor size has been an important clinical and pathologic feature for patients with RCC.^{1, 3, 4, 6} The AJCC primary tumor classification for RCC separates the pT1a, pT1b, and pT2 categories entirely based on tumor size⁹ 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 patients in clinic, the decision to perform nephron sparing surgery or undergo a period of watchful waiting is heavily dependant on tumor size.^{8, 11, 12} Tumor size has also been reported to be an independent predictor of progression-free survival and cancer-specific survival after surgery,^{13, 14} although observations with smaller cohorts of patients do not validate the independent predictability of tumor size and outcome.^{15–17} With regards to tumor size and risk of synchronous metastatic disease, most observations support that tumor size represents a significant predictor of synchronous and asynchronous metastases.^{1–6} However, this was challenged by a recent multi-institutional observation suggesting that 5–7% of 1,208 surgically managed patients with renal tumors <3 cm harbor synchronous metastases.⁷ Our anecdotal experience did not support such a high rate of metastases in patients with small renal masses leading us to perform a retrospective review of 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 case of metastatic disease, either at time of presentation or during follow-up, for approximately 300 patients with tumors <2 cm, a notable finding also observed by Kunkle et al.⁶ Furthermore, we only observed one case of synchronous metastases and a second case of asynchronous metastases following surgery in nearly 500 patients with tumors 2–3cm. Additionally, our regression models suggest that tumor size is significantly associated with risk of synchronous metastases and with

metastases-free survival following surgery- with nearly identical odds and hazard ratios (1.25 and 1.24, respectively). If validated by others, these results have important implications. For example, the number of patients being diagnosed with small and incidental renal masses is increasing and as the population ages we anticipate an increasing number of patients with significant comorbidities who are found to have small renal masses during work up of non-related symptoms. Some of these patients are being offered a period of expectant management with serial imaging given that recent data suggests an indolent and slow pattern of growth for many of these masses.^{18, 19} Our data support that patients with small renal masses are at low risk of metastatic disease and those with comorbidities could be safely followed with serial imaging, especially until the tumor demonstrates growth or reaches a size >2.5cm.

Reasons for the recent discordant literature regarding tumor size and risk of metastases are not entirely clear. Klatte et al reported on 1,208 small renal mass patients (4cm or less) including 72 patients with metastases at presentation, noting that 6–7% of patients with tumors <2cm had metastatic disease.⁷ This is in stark contrast to our data, which includes 2,691 patients including 162 with metastatic disease at presentation and 1,227 patients with tumors <4cm, and the data reported by Kunkle et al,⁶ which includes 110 patients with metastatic disease at presentation matched with 250 controls, where not a single case of metastatic disease was observed in a patient with a tumor <2cm. It is plausible to conclude that the discordant results are in part related to unique referral patterns. While the report from Klatte et al included data from France, Italy, and Greece, the only center in the United States was UCLA which is a large referral center for metastatic RCC. We would suggest that the rare patient with metastatic disease and a very small renal tumor would be more likely to present to UCLA for an evaluation although the percentage of patients UCLA contributed to the combined database was not reported.⁷ Nevertheless, our data, where we used a relatively strict definition of metastases, supports the notion that as tumor size increases so does the risk of metastatic disease. This is supported by Kunkle et al where the definition of metastatic disease required biopsy confirmation.⁷ The results from Klatte et al, where M stage was assigned “according to 2002 definitions” although 56% had biopsy confirmation, remain intriguing and thus, further investigation is needed.

This study is not without limitations. Our analysis represents a retrospective, single institution experience and our results are subject 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 disease or those deemed unfit for surgery may be less likely to be referred to our urology department. Additionally, nearly half of the patients in this study were treated with partial nephrectomy, suggesting that patients with tumors that were 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 the observations from Kunkle et al where the odds ratio for risk of metastatic disease by tumor size were 1.25 and 1.22, respectively.

CONCLUSION

In our experience, tumor size is significantly associated with synchronous metastases and asynchronous metastases following nephrectomy. Our results suggest that risk of metastatic disease for patients with tumors <3cm is negligible.

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

Figure 2.
Predicted probability of metastases at presentation based on primary tumor size. Dashed lines represent 95% confidence intervals.

Figure 3. Metastases-free survival for 2,367 renal mass patients treated surgically who did not have metastases at presentation

Table 1

Age, gender, tumor size, treatment, and histology for patients with and without metastases at time of presentation

	M0 RCC	M1 RCC
No. pts	2,529	162
Median age (range)	62 (19–95)	62 (32–85)
Gender		
Male (%)	1,576 (62)	113 (70)
Female (%)	953 (38)	49 (30)
Median cm tumor size (range)	4.0 (0.5–23)	8.5 (2.9–20)
Surgery		
Partial Nephrectomy (%)	1,109 (44)	9 (6)
Radical Nephrectomy (%)	1,420 (56)	153 (94)
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

Table 2

Probability of developing de novo asynchronous metastatic RCC after nephrectomy according to 1cm intervals

Tumor Size	No. pts	No. developing metastasis during follow-up	3-year probability of metastasis, % (95% CI)	Median follow-up for survivors (IQ range)
<1cm	13	0	0	3.6 (0.5–6.4)
1 - <2	273	0	0	2.6 (1.0–5.3)
2 - <3	434	1	0	2.8 (1.0–5.9)
3 - <4	413	10	2 (1, 4)	2.5 (1.0–5.5)
4 - <5	323	5	2 (1, 5)	3.1 (1.2–6.6)
5 - <6	202	11	3 (1, 7)	3.1 (0.8–6.5)
6 - <7	172	23	12 (7, 19)	4.2 (1.1–6.7)
7+	537	122	20 (17, 25)	3.2 (1.1–6.7)