# Tumor Size is a Determinant of the Rate of Stage T1 Renal Cell Cancer Synchronous Metastasis

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**Purpose:** A recent multi-institutional analysis of 995 patients treated for renal cell cancer questioned the relationship between tumor size and the synchronous metastasis rate. We revisited the hypothesis that metastatic potential is unrelated to tumor size.

**Materials and Methods:** We tested the relationship between tumor size and synchronous metastasis in 22,204 patients with T1a and T1b renal cell cancer diagnosed and/or treated with nephrectomy for clear cell, papillary or chromophobe histological subtypes in 1 of 9 Surveillance, Epidemiology and End Results registries between 1988 and 2004.

**Results:** In the study population the synchronous metastasis rate was 9.6%, including 5.6% vs 14.2% for T1a vs T1b. Stratification by 1 cm tumor size intervals revealed that the rate increased with increasing tumor size, that is 4.8% at 1.0 cm or less, 4.2% at 1.1 to 2.0 cm, 4.9% at 2.1 to 3.0 cm, 7.1% at 3.1 to 4.0 cm, 12.1% at 4.1 to 5.0 cm, 13.3% at 5.1 to 6.0 cm and 18.4% 6.1 to 7.0 cm (chi-square trend $p < 0.001$). Cubic spline analysis showed that tumor size was virtually linearly related to the synchronous metastasis rate. Stratification by histological subtype in patients treated with nephrectomy revealed that clear cell renal cell cancer was most frequently associated with synchronous metastasis. Finally, tumor size was an independent predictor of synchronous metastasis in multivariate regression models adjusted for age, gender, histological subtype and year of diagnosis quartiles.

**Conclusions:** Our study confirms that tumor size is an important determinant of the likelihood of synchronous metastasis in patients with T1a and T1b renal cell cancer. The synchronous metastasis rate directly increases with increasing tumor size. Even patients with small renal masses are at risk for synchronous metastasis and patients with clear cell renal cell cancer are at highest risk.

**Key Words:** kidney; carcinoma, renal cell; neoplasm metastasis; neoplasm staging; nephrectomy

**Abbreviations and Acronyms**

HS = histological subtype

RCC = renal cell carcinoma

SEER = Surveillance, Epidemiology and End Results

SM = synchronous metastasis

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THE natural history of small renal masses was generally believed to be closely related to tumor size.[1–4] However, recently Klatte et al examined a multi-institutional database of 995 patients treated with nephrectomy for all RCC stages and reported that tumor size is unrelated to the SM rate.[5]

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We revisited the hypothesis that metastatic potential is unrelated to tumor size. We relied on the SEER database, which represents a large population based tumor registry. Fewer selection biases are operational in the SEER database than in multiinstitutional databases from large-scale tertiary centers, as in the report by Klatte et al.[5] Moreover, the SEER database includes not only patients treated with nephrectomy, but also data on patients unexposed to surgery, obviating the surgical selection bias, which may favor nonmetastatic cases.

## MATERIALS AND METHODS

### Patient Population

Patients diagnosed with RCC between 1988 and 2004 were identified in 9 SEER cancer registries, including the Atlanta, Detroit, San Francisco-Oakland and Seattle-Puget Sound metropolitan areas, and Connecticut, Hawaii, Iowa, New Mexico and Utah.[6] Two kidney cancer diagnostic codes (ICD-Oncology-2 code C64.9 and ICD-Oncology-9 code 189.0) served as study inclusion criteria. The presence of the 2 diagnostic codes resulted in the identification of patients with RCC and the exclusion of those with upper tract transitional carcinoma or noncortical renal tumors, ie melanoma, sarcoma, nephroblastoma and lymphoma. Surgically and nonsurgically managed stage T1a and T1b RCC cases were included in our analysis. Due to differences in the natural history of unclassified, sarcomatoid and collecting duct RCC those HSs were excluded from analysis. Only clear cell, chromophobe and papillary RCC were included. Histological subtyping was only applied to surgically managed cases. Since HS was not analyzed in nonsurgically managed cases, we performed all analyses in the entire population. Subsequently all analyses were repeated in patients who underwent nephrectomy. In those analyses HS served as a covariate. SM at RCC diagnosis was defined according to SEER stage.

### Statistical Analysis

Statistical analysis was done with the chi-square and Student t test to compare proportions and means, respectively. Cubic spline analysis was used to graphically show the relationship between tumor size and SM rate. The advantage of cubic spline analysis is the lack of a predetermined relationship between tumor size and SM rate. For example, a linear or exponential relationship is not assumed. Instead, the relationship between tumor size and SM is entirely data driven. Finally, we used multivariate logistic regression models to test the relationship between the metastatic RCC rate and tumor size. Covariates were gender, age, race, histological subtypes and year of diagnosis quartiles. All statistical tests were performed with S-PLUS® Professional, version 1 or SPSS®, version 15.0 using 2-sided tests with significance considered at 0.05.

## RESULTS

Selection criteria identified 22,204 patients diagnosed with RCC between 1988 and 2004, of whom 19,735 (88.9%) were treated with nephrectomy and 2,469 (11.1%) were treated nonsurgically. Overall 61.7% of patients were male and 83.7% were white. Mean age at diagnosis was 63.3 years (median 65.0, range 18 to 100). Mean tumor size was 4.1 cm (median 4.0, range 0.1 to 7.0). Of all cases 53.3% were T1a and 46.7% were T1b, and 92.3% harbored clear cell HS. Of the patients 32.8% were diagnosed with RCC between 2001 and 2004.

Of the patients 2,136 (9.6%) and 20,068 (90.4%) did and did not have SM, respectively. The RCC metastatic rate was 5.6% in T1a cases and 14.1% in T1b cases ($p < 0.0001$, table 1). After tabulation by 1 cm tumor size intervals the SM rate was 4.8% at 1.0 cm or less, 4.2% at 1.1 to 2.0 cm, 4.9% at 2.1 to 3.0 cm, 7.1% at 3.1 to 4.0 cm, 12.1% at 4.1 to 5.0 cm, 13.3% at 5.1 to 6.0 cm and 18.4% 6.1 to 7.0 cm (chi-square trend $p < 0.001$, fig. 1, *A*). When patients were stratified by SM presence vs absence, statistically significant differences were recorded in age (mean 67.1 years, median 68.0, range 23 to 100 vs mean 62.9, median 64.0, range 18 to 100) and tumor size (mean 4.9 cm, median 5.0 vs mean and median 4.0 cm, Student's t test each $p < 0.001$). Males had a higher SM rate than females (10.2% vs 8.7%, chi-square test $p < 0.001$). SM stratification by HS revealed a rate of 4.5% for clear cell RCC vs 2.1% for papillary RCC vs 0.6% for chromophobe RCC ($p < 0.001$). The highest proportion of patients with SM (11.1%) was observed in the most historical year quartile (1988 to 1992) (chi-square test $p < 0.001$). Moreover, when data were stratified by surgical or nonsurgical management, important differences in the SM rate were recorded. In surgically managed cases the rate by 1 cm tumor intervals was 2.2% to 9.1% (chi-square trend $p < 0.001$, fig. 1, *B*). Conversely in nonsurgically managed cases the rate was 12.3% to 74.7% (chi-square test $p < 0.001$, fig. 1, *C*). In patients treated surgically vs nonsurgically mean age was 62.3 (median 64.0, range 18 to 97) vs 71.3 years (median 73.0, range 23 to 100) and mean tumor size was 4.1 cm (median 4.0) vs 4.3 (median 4.3, Student's t test each $p = 0.001$).

Figure 2, *A* shows cubic spline analysis of the tumor size-SM rate relationship in the overall population. The curve of this relationship approximated a linear relationship. Tumor size was virtually directly proportional to the SM rate. The slope of the cubic spline was least pronounced for 0.1 to 2 cm lesions and became steeper for 2.1 to 7 cm lesions. When data were stratified by surgical or nonsurgical treatment, the cubic spline pattern remained virtually unchanged (fig. 2, *B* and *C*). In patients treated with nephrectomy the cubic spline could be super-

**Table 1.** *Descriptive characteristics of entire study population of 22,204 patients diagnosed with RCC and those with vs without SM*

| | No. Pts | No. No SM (%) | No. SM (%) | p Value (chi-square test) | No. Surgery (%) | No. No Surgery (%) | p Value (chi-square test) |
|---|---|---|---|---|---|---|---|
| Gender: | | | | <0.001 | | | 0.3 |
| M | 13,704 | 12,309 (89.8) | 1,395 (10.2) | | 12,202 (89.0) | 1,502 (11.0) | |
| F | 8,500 | 7,759 (91.3) | 741 (8.7) | | 7,533 (88.9) | 967 (11.1) | |
| Race: | | | | 0.13 | | | <0.001 |
| White | 18,604 | 16,790 (90.2) | 1,814 (9.8) | | 16,601 (89.2) | 2,003 (10.8) | |
| Other | 3,600 | 3,278 (91.1) | 322 (8.9) | | 3,134 (87.1) | 466 (12.9) | |
| Tumor size intervals (cm): | | | | <0.001 | | | <0.001 |
| 0.1–1.0 | 483 | 460 (95.2) | 23 (4.8) | | 362 (74.9) | 121 (25.1) | |
| 1.1–2.0 | 2,272 | 2,176 (95.8) | 96 (4.2) | | 2,035 (89.6) | 237 (10.4) | |
| 2.1–3.0 | 4,422 | 4,206 (95.1) | 216 (4.9) | | 4,035 (91.2) | 387 (8.8) | |
| 3.1–4.0 | 4,663 | 4,334 (92.9) | 329 (7.1) | | 4,230 (90.7) | 433 (9.3) | |
| 4.1–5.0 | 4,115 | 3,618 (87.9) | 497 (12.1) | | 3,608 (87.7) | 507 (12.3) | |
| 5.1–6.0 | 3,430 | 2,973 (86.7) | 457 (13.3) | | 3,046 (88.8) | 384 (11.2) | |
| 6.1–7.0 | 2,819 | 2,301 (81.6) | 518 (18.4) | | 2,419 (85.8) | 400 (14.2) | |
| HS:* | | | | <0.001 | | | Not applicable |
| Clear cell | 18,222 | 17,405 (95.5) | 817 (4.5) | | 18,222 | — | |
| Papillary | 1,195 | 1,170 (97.9) | 25 (2.1) | | 1,195 | — | |
| Chromophobe | 318 | 316 (99.4) | 2 (0.6) | | 316 | — | |
| T stage: | | | | <0.001 | | | <0.001 |
| T1a | 11,840 | 11,176 (94.4) | 664 (5.6) | | 10,062 (90.1) | 1,178 (9.9) | |
| T1b | 10,364 | 8,892 (85.8) | 1,472 (14.2) | | 9,073 (87.5) | 1,291 (12.5) | |
| Treatment: | | | | <0.001 | | | Not applicable |
| Surgery | 19,735 | 18,891 (95.7) | 844 (4.3) | | — | — | |
| No surgery | 2,469 | 844 (47.7) | 1,292 (52.3) | | — | — | |
| Diagnosis yr (quartile): | | | | <0.001 | | | 0.03 |
| 1988–1992 | 4,757 | 4,230 (88.9) | 527 (11.1) | | 4,215 (88.6) | 542 (11.4) | |
| 1993–1996 | 4,617 | 4,178 (90.5) | 439 (9.5) | | 4,071 (88.2) | 546 (11.8) | |
| 1997–2000 | 5,551 | 4,999 (90.1) | 552 (9.9) | | 4,916 (88.6) | 635 (11.4) | |
| 2001–2004 | 7,279 | 6,740 (92.6) | 539 (7.4) | | 6,533 (89.8) | 746 (10.2) | |

* In 19,735 patients treated with nephrectomy.

imposed on that of the overall population. In nonsurgically managed cases the initial part of the curve was steeper than in surgically managed cases, indicating a more increased SM rate. Moreover, in nonsurgically treated patients with 0 to 2 cm lesions the curve shifted upward, reflecting the overall higher SM rate in this subgroup. The y axis scale shifted upward in patients treated nonsurgically since the rate of SM was higher in this subgroup (fig. 2, *C*).

Stratification of the SM rate according to HS in 19,735 surgically treated patients revealed that clear cell RCC HS was most frequently associated with SM for the T1a and T1b subtypes (table 2). For example, the rate was 2.3% vs 1.3% vs 1.0% in patients with T1a clear cell vs papillary vs chromophobe RCC ($p < 0.001$). Similar findings were recorded for T1b lesions, that is 6.8% vs 3.6% vs 0% for clear cell vs papillary vs chromophobe RCC.

Finally, multivariate logistic regression models were used to test the effect of tumor size, age, gender, race, histological subtype and year of diagnosis quartiles on the SM rate (table 3). Two separate multivariate analyses were performed. One analysis focused on all patients and excluded HS from covariates, and the other focused on surgically treated patients and included HS among covariates (table 3). On each analysis tumor size was modeled as a categorically coded variable or as a cubic spline. In all 4 models tumor size was an independent predictor of SM (each $p < 0.001$). Also, age ($p \leq 0.05$), gender ($p < 0.001$) and year of diagnosis quartiles ($p < 0.05$) achieved independent predictor status in all 4 models. HS achieved independent predictor status in surgically treated patients ($p = 0.002$). Papillary and chromophobe RCC had a protective effect on the SM rate relative to clear cell RCC.

## DISCUSSION

Our hypothesis stated that tumor size is unrelated to the rate of SM and it originated from the report by Klatte et al.[5] They examined the SM rate in a population of 995 patients with small RCC treated with nephrectomy at 1 of 5 tertiary care centers in Europe or the United States and found no association between tumor size and SM rate.

We revisited this relationship in a population of 22,204 patients with RCC diagnosed and treated in 1 of 9 SEER registries between 1988 and 2004. Our findings reject the hypothesis that tumor size is unrelated to SM rate. Instead, tumor size was virtually linearly related to SM rate. Linear relationship CIs were relatively wide, especially for small tumors. Moreover, the clear cell RCC HS was associated with the highest SM rate compared

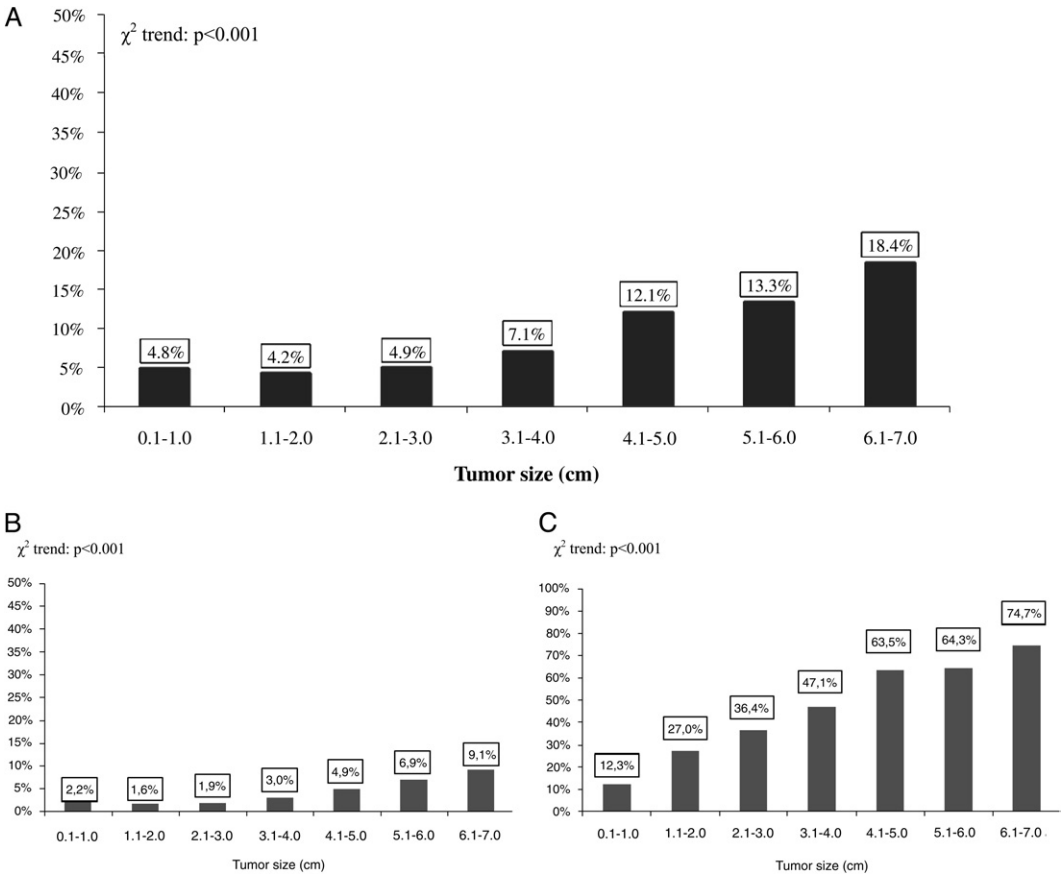


**Figure 1.** Synchronous metastasis rates by 1 cm tumor size intervals in overall population of 22,204 patients (*A*), and subsets of 19,735 treated with nephrectomy (*B*) and 2,469 treated nonsurgically (*C*). *χ2*, chi-square.

to papillary and chromophobe HS rates. Important stage migration occurred during the study period. To address this effect we tabulated the SM rate by year of diagnosis quartiles and noted that the rate decreased from 11.1% to 7.4%. Moreover, we added the year of diagnosis variable in multivariate models predicting the odds of SM after adjustment for all other covariables. In these multivariate models the coefficients indicating the odds of SM did not change absolute or relative value in meaningful fashion. Old age predisposed to a higher SM rate, most likely due to diagnostic and investigational conservatism in elderly patients. The protective effect of female gender on stage distribution is consistent with the results of Woldrich et al, who noted that females had a higher localized stage RCC rate.[7]

Our findings corroborate the generally established notion that tumor size predicts RCC metastatic potential. The association between tumor size and the SM rate was previously examined by Karakiewicz et al in a multi-institutional database from 5 European tertiary centers[8] and by Hutterer et al in a multi-institutional database from 11 European and North American centers of excellence.[9] In this report the investigators also found a virtually linear relationship between tumor size and the SM rate. Unlike in the current series, their analysis focused on all RCC stages. Although no other investigators confirmed the relationship between tumor size and the SM rate for T1a or T1b stage RCC, several other groups examined the effect of tumor size on the recurrence[10,11] or mortality[12,13] rate. In those reports tumor size was directly related to RCC recurrence or RCC specific mortality. For example, the UCLA group recently confirmed the prognostic impact of tumor size on RCC specific survival in T2 RCC cases.[14] That group also reported that tumor size predicts RCC specific survival in T3 RCC cases.[15]

The reason for the lack of agreement between our findings and those of the UCLA group[5] regarding the effect of tumor size on the SM rate of T1a tumors may be at least 2-fold. 1) Sample size in the UCLA analysis (995 patients) was relatively small, especially when stratification was performed according to 1 cm tumor size intervals and the population was divided into 4 subgroups. 2) The tertiary care center nature of participating institutions may have introduced a referral bias. Under this premise patients with large primary but nonmetastatic tumors might have been overrepresented, which may have artificially lowered the SM

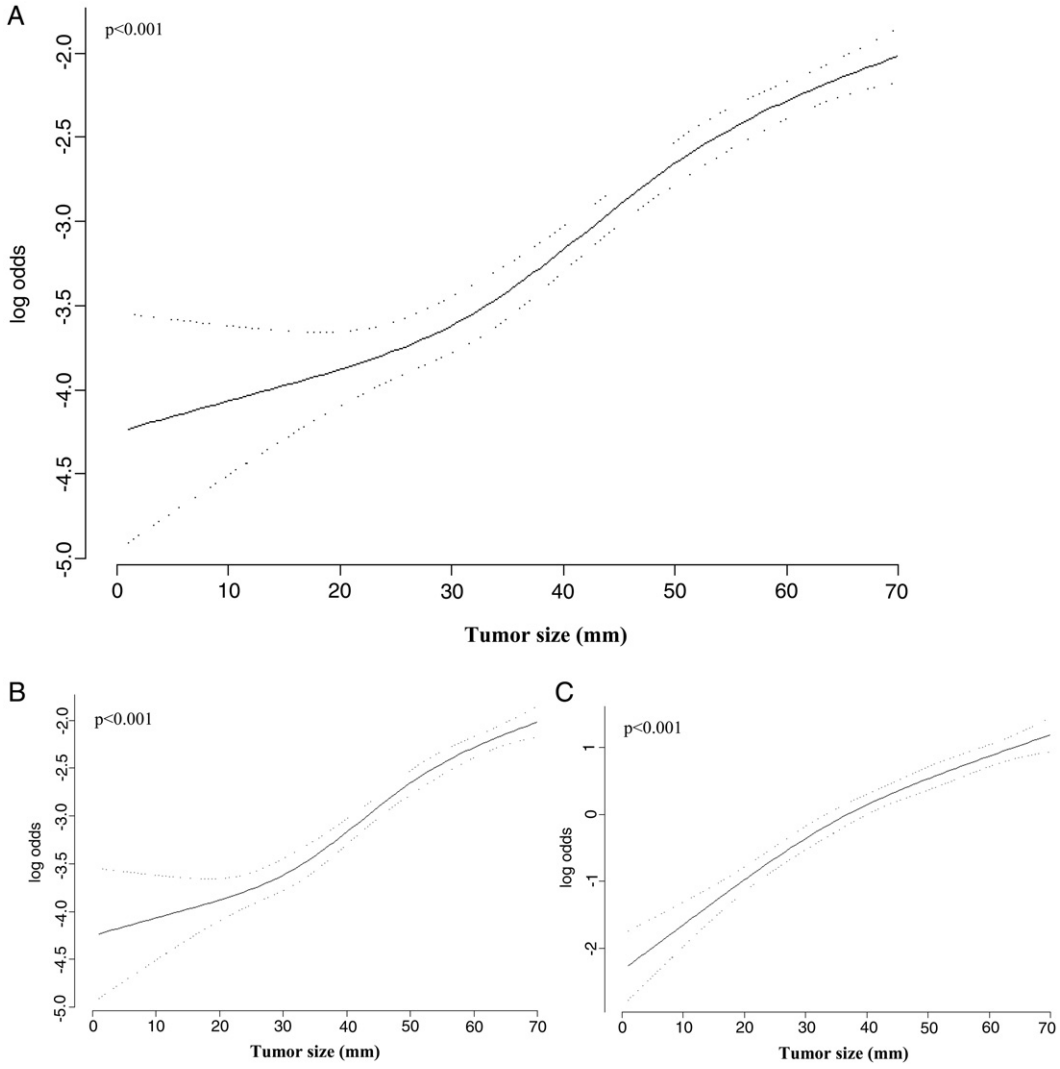


**Figure 2.** Cubic spline analysis shows relationship of tumor size and SM rate in overall population of 22,204 patients (*A*), and in subsets of 19,735 treated with nephrectomy (*B*) and 2,469 treated nonsurgically (*C*). Bold curve represents logistic regression line. Dotted lines represent 95% CI.

rate in patients with large T1a lesions. It is common to refer cases of large nonmetastatic primary tumors for surgery to tertiary care centers. The population based nature of our sample and the inclusion of nonsurgically managed cases eliminated the potential effect of surgical referral bias.

Our study has limitations. 1) The extent of the diagnostic evaluation may have differed among patients. Some may have undergone more detailed radiographic and/or scintigraphic assessments than others. For example, some cases may have been staged with chest x-ray alone vs others with computerized tomography of the chest. The SM rate may be substantially higher using the latter modality. Similarly some patients with bone pain may have been assessed with bone scans vs others with skeletal surveys and computerized tomography. It is known that osteolytic metastases may be under diagnosed by bone scan. It is also possible that the cohort of Klatte et al was not assessed in fully standardized fashion.[5] 2) Our patient population was restricted to individuals with histologically confirmed RCC. In everyday clinical practice the association between tumor size and SM may be predominantly applied to patients without a histologically confirmed RCC diagnosis. However, as many as 25% of small renal masses consist of angiomyolipoma, onco-

**Table 2.** *SM by HS and T stage in 19,735 patients with nephrectomy*

| | No./Total No. (%)* | | |
|---|---|---|---|
| T Stage | Clear Cell | Papillary | Chromophobe |
| T1a | 227/9,630 (2.3) | 11/813 (1.3) | 2/219 (0.9) |
| T1b | 590/8,592 (6.8) | 14/382 (3.6) | 0/99 |
| Overall | 817/18,222 (4.5) | 25/1,195 (2.1) | 2/318 (0.6) |

* Chi-square test p <0.001.

**Table 3.** *Multivariate logistic regression models of effect of tumor size and other covariables on SM rates*

| Variable | Tumor Size Odds Ratio (p value) As Cubic Spline | Tumor Size Odds Ratio (p value) Categorically |
|---|---|---|
| *Overall 22,204 pts** | | |
| Tumor size (cm): | 1.04 (<0.001) | — |
| | — | (<0.001) |
| 0.1–1.0 vs 6.1–7.0 | | 0.21 (<0.001) |
| 1.1–2.0 vs 6.1–7.0 | | 0.21 (<0.001) |
| 2.1–3.0 vs 6.1–7.0 | | 0.23 (<0.001) |
| 3.1–4.0 vs 6.1–7.0 | | 0.35 (<0.001) |
| 4.1–5.0 vs 6.1–7.0 | | 0.60 (<0.001) |
| 5.1–6.0 vs 6.1–7.0 | | 0.69 (<0.001) |
| Gender (female vs male) | 0.80 (<0.001) | 0.80 (<0.001) |
| Race (other vs white) | 1.00 (0.9) | 0.99 (0.9) |
| Diagnosis yr (quartiles): | (<0.001) | (<0.001) |
| 1993–1996 vs 1989–1992 | 0.94 (0.09) | 0.88 (0.07) |
| 1997–2000 vs 1989–1992 | 0.99 (0.9) | 0.97 (0.6) |
| 2001–2004 vs 1989–1992 | 0.77 (<0.001) | 0.74 (<0.001) |
| *19,735 Pts with nephrectomy†* | | |
| Tumor size (cm): | 1.04 (<0.001) | — |
| | — | (<0.001) |
| 0.1–1.0 vs 6.1–7.0 | | 0.22 (<0.001) |
| 1.1–2.0 vs 6.1–7.0 | | 0.17 (<0.001) |
| 2.1–3.0 vs 6.1–7.0 | | 0.20 (<0.001) |
| 3.1–4.0 vs 6.1–7.0 | | 0.33 (<0.001) |
| 4.1–5.0 vs 6.1–7.0 | | 0.52 (<0.001) |
| 5.1–6.0 vs 6.1–7.0 | | 0.76 (0.008) |
| Gender (female vs male) | 0.63 (<0.001) | 0.62 (<0.001) |
| Race (other vs white) | 0.88 (0.43) | 0.88 (0.2) |
| HS: | (0.002) | (0.002) |
| Papillary vs clear cell | 0.52 (0.003) | 0.51 (0.002) |
| Chromophobe vs clear cell | 0.09 (0.02) | 0.09 (0.02) |
| Diagnosis yr (quartiles): | (0.02) | (0.009) |
| 1993–1996 vs 1989–1992 | 0.71 (0.001) | 0.70 (0.001) |
| 1997–2000 vs 1989–1992 | 0.87 (0.2) | 0.85 (0.11) |
| 2001–2004 vs 1989–1992 | 0.83 (0.07) | 0.81 (0.03) |

* Age coded continuously OR 1.03 ($p < 0.001$).
† Age continuously coded OR 1.01 ($p = 0.05$).

cytoma and adenoma.[16] Under that premise the proportion of patients with benign histology may lower the overall SM rate. Similarly we focused only on clear cell, papillary and chromophobe HSs. A small proportion of solid masses may harbor unclassified[17] or collecting duct[18] RCC, or sarcomatoid[19] histology, which increase the SM rate. Klatte et al included 1 patient each with unclassified and collecting duct RCC, which may have increased the SM rate since each patient had metastatic disease.[5] Conversely Klatte et al also included 141 patients with benign histology, which clearly lowered the SM rate relative to that in our cohort. Nevertheless, the rate was substantially higher in the series by Klatte et al than in our study (T1a RCC rate 7% vs 5.6%). Besides sample size limitations, referral and selection biases, we have no other explanation for this discrepancy. 3) We assessed the overall rate of SM. Unfortunately the scope of our data did not allow us to examine the SM rate from a site specific perspective. Therefore, we cannot comment on the rate of liver vs lung vs bone vs brain metastasis according to tumor size. 4) The relationship between tumor size and SM was virtually linear and so our analysis cannot be used to dichotomize between patients at low vs high risk for metastatic RCC. Therefore, site and individual risks of metastasis must be interpreted by the clinician according to multiple other intervening variables such as patient age, performance status or disease symptoms. 5) HS might have been misclassified since no central pathology review was performed. Under this potential premise it is conceivable that the SM rate could be different from the reported value, especially for the chromophobe HS, which was the least common (1.4%) of the 3 variants. 6) Tumor size was determined in nonstandardized fashion since the SEER database does not guarantee standardized assessment of this variable. Generally pathological tumor size measurements were done in surgically treated cases but radiographic measurements were invariably used in nonsurgically managed cases.

## CONCLUSIONS

Our study confirms that tumor size is an important determinant of the likelihood of SM in patients with T1a and T1b RCC. The SM rate directly increases with increasing tumor size. Even patients with small renal masses are at risk for SM and patients with clear cell RCC are at highest risk.

## REFERENCES


1. Herrlinger A, Schott G, Schafhauser W et al: The significance of tumor diameter in renal cell carcinoma. Urologe A 1992; **31:** 70.
2. Eschwege P, Saussine C, Steichen G et al: Radical nephrectomy for renal cell carcinoma 30 mm. or less: long-term follow results. J Urol 1996; **155:** 1196.
3. Remzi M, Ozsoy M, Klingler HC et al: Are small renal tumors harmless? Analysis of histopathological features according to tumors 4 cm or less in diameter. J Urol 2006; **176:** 896.
4. Crispen PL, Boorjian SA, Lohse CM et al: Outcomes following partial nephrectomy by tumor size. J Urol 2008; **180:** 1912.
5. Klatte T, Patard JJ, de Martino M et al: Tumor size does not predict risk of metastatic disease or prognosis of small renal cell carcinomas. J Urol 2008; **179:** 1719.
6. Ries LAG, Melbert D, Krapcho M et al: SEER Cancer Statistics Review, 1975-2004, based on November 2006 SEER data submission. National Cancer Institute, Surveillance Epidemiology and End Results. Available at http://seer.cancer.gov/csr/1975_2004/. Accessed January 2007.
7. Woldrich JM, Mallin K, Ritchey J et al: Sex differences in renal cell cancer presentation and survival: an analysis of the National Cancer Database, 1993–2004. J Urol 2008; **179:** 1709.
8. Karakiewicz PI, Lewinshtein DJ, Chun FK et al: Tumor size improves the accuracy of TNM predictions in patients with renal cancer. Eur Urol 2006; **50:** 521.

9. Hutterer GC, Patard JJ, Jeldres C et al: Patients with distant metastases from renal cell carcinoma can be accurately identified: external validation of a new nomogram. BJU Int 2008; **101:** 39.

10. Kattan MW, Reuter V, Motzer RJ et al: A postoperative prognostic nomogram for renal cell carcinoma. J Urol 2001; **166:** 63.

11. Sorbellini M, Kattan MW, Snyder ME et al: A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. J Urol 2005; **173:** 48.

12. Zisman A, Pantuck AJ, Wieder J et al: Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. J Clin Oncol 2002; **20:** 4559.

13. Karakiewicz PI, Briganti A, Chun FK et al: Multi-institutional validation of a new renal cancer-specific survival nomogram. J Clin Oncol 2007; **25:** 1316.

14. Klatte T, Patard JJ, Goel RH et al: Prognostic impact of tumor size on pT2 renal cell carcinoma: an international multicenter experience. J Urol 2007; **178:** 35.

15. Lam JS, Klatte T, Patard JJ et al: Prognostic relevance of tumour size in T3a renal cell carcinoma: a multicentre experience. Eur Urol 2007; **52:** 155.

16. Shannon BA, Cohen RJ, de Bruto H et al: The value of preoperative needle core biopsy for diagnosing benign lesions among small, incidentally detected renal masses. J Urol 2008; **180:** 1257.

17. Karakiewicz PI, Hutterer GC, Trinh QD et al: Unclassified renal cell carcinoma: an analysis of 85 cases. BJU Int 2007; **100:** 802.

18. Karakiewicz PI, Trinh QD, Rioux-Leclercq N et al: Collecting duct renal cell carcinoma: a matched analysis of 41 cases. Eur Urol 2007; **52:** 1140.

19. Kuroda N, Toi M, Hiroi M et al: Review of sarcomatoid renal cell carcinoma with focus on clinical and pathobiological aspects. Histol Histopathol 2003; **18:** 551.

## EDITORIAL COMMENT

This review using the SEER database reconfirms an observation made from autopsy data in the last century, that is that primary RCC size is proportional to the likelihood of metastasis. Although some recent studies questioned this finding, these authors reconfirm the original observation in a rather convincing manner.

There are clearly a number of limitations to this study and the authors address most of them. There is no central pathological evaluation, no standard metastatic assessment, a bias toward surgical cases and a lack of long-term followup, which would be helpful in supporting the initial findings. With that said, the take-home message is that size is proportional to metastasis and clear cell carcinoma has a higher SM incidence than papillary carcinoma. I would not be willing to make any assessment with reference to chromophobe renal carcinoma without a standardized pathological evaluation.

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## REPLY BY AUTHORS

We agree that the SEER database lacks some important information which would have strengthened our results. Despite its limitations, our study corroborates the findings from a large, tertiary care European cohort (5,376 patients), which showed similar results regarding the rate of synchronous metastasis (reference 9 in article). In that study a nomogram was developed and the presence of a 2.5 cm tumor (T1a) was associated with a predicted 3.0% risk of synchronous metastasis. Similarly, in patients with T1b RCC the presence of a 6.5 cm lesion was associated with a 5.8% risk of synchronous metastasis. These observations are similar to the 2.3% and 6.7% synchronous metastasis rates among surgically treated patients in the SEER database with T1a and T1b tumors, respectively. These findings at least partially confirm the validity of the nomogram predicting metastatic RCC that was developed and externally validated in a European cohort (reference 9 in article). Moreover, they also confirm that the metastatic potential of small renal masses is similar on both sides of the Atlantic. However, it is noteworthy that the synchronous metastasis rates in these 2 studies are significantly higher than those recently reported by Thompson et al in a single institution, tertiary care center study.[1]

## REFERENCE

1. Thompson RH, Hill JR, Babayev Y et al: Metastatic renal cell carcinoma risk according to tumor size. J Urol 2009; **182:** 41.