Published in final edited form as:

Eur Urol Oncol. 2020 February ; 3(1): 47–56. doi:10.1016/j.euo.2019.10.002.

The Association Between Small Primary Tumor Size and Prognosis in Metastatic Renal Cell Carcinoma: Insights from Two Independent Cohorts of Patients Who Underwent Cytoreductive Nephrectomy

Renzo G. DiNatale^{a,b,c}, Wanling Xie^d, Maria F. Becerra^{a,e}, Andrew W. Silagy^{a,f}, Kyrollis Attalla^a, Alejandro Sanchez^a, Roy Mano^a, Julian Marcon^{a,g}, Kyle A. Blum^{a,b}, Nicole E. Benfante^a, Martin H. Voss^h, Robert J. Motzer^h, Jonathan Coleman^a, Toni K. Choueiriⁱ, Ed Reznik^{c,j}, Paul Russo^a, Daniel Y.C. Heng^k, A. Ari Hakimi^{a,b,*}

^aUrology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

^bImmunogenomics and Precision Oncology Platform, Memorial Sloan Kettering Cancer Center, New York, NY, USA

^cComputational Oncology Service, Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

^dDepartment of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA

^eDepartment of Urology, University of Miami, Miller School of Medicine, Miami, FL, USA

^fDepartment of Surgery, University of Melbourne, Austin Hospital, Melbourne, Australia

^gDepartment of Urology, University Hospital of Munich, Munich, Germany

^hGenitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

ⁱDepartment of Medicine, Dana-Farber Cancer Institute, Boston, MA, USA

*Corresponding author. 353 E 68th Street, Office 525, New York, NY 10065, USA. Tel. +1 (646) 422-4497. hakimia@mskcc.org (A. Ari Hakimi).

Author contributions: A. Ari Hakimi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: DiNatale, Hakimi, Heng.

Acquisition of data: Becerra, Attalla, Benfante.

Analysis and interpretation of data: DiNatale, Reznik.

Drafting of the manuscript: Silagy, DiNatale.

Critical revision of the manuscript for important intellectual content: Mano, Sanchez, Marcon, Choueiri, Voss.

Statistical analysis: DiNatale, Xie, Reznik.

Obtaining funding: Hakimi, Voss.

Administrative, technical, or material support: Benfante, Blum.

Supervision: Russo, Coleman, Motzer, Heng.

Other: None.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

^jCenter for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

^kDepartment of Medicine, Tom Baker Cancer Center, Calgary, AB, Canada

Abstract

Background: One of the main challenges in the management of renal cell carcinoma (RCC) is risk-stratifying patients who present with metastatic disease. Tumor size is an important predictor of survival in the localized setting; however, this feature has not been explored fully in patients presenting with M1 RCC.

Objective: To assess the impact of tumor size on survival in patients with metastatic RCC who underwent cytoreductive nephrectomy (CN).

Design, setting, and participants: We queried the Memorial Sloan Kettering (MSK) nephrectomy database for patients who presented with M1 disease and underwent CN between 1989 and 2016 ($n = 304$). Primary tumor size was obtained from pathology reports. Data from the International Metastatic Database Consortium (IMDC) were used for validation purposes ($n = 778$).

Outcome measurements and statistical analysis: Overall survival (OS) estimates were computed using the Kaplan-Meier method. Cox regressions were used to test the association between tumor size and OS in univariate and multivariable analyses. Tumors ≤ 4 cm were compared with larger masses. Secondary analyses were performed to assess the robustness of these findings.

Results and limitations: Clear cell tumors ≤ 4 cm were significantly associated with improved OS in both the MSK (hazard ratio [HR]: 0.35, 0.17–0.72, $p = 0.004$) and IMDC (HR 0.54, 0.36–0.83, $p = 0.004$) cohorts. The association was observed even after adjusting for known prognostic factors (HR 0.40, 0.14–1.14, $p = 0.09$ and HR: 0.54, 0.33–0.90, $p = 0.02$ in the MSK and IMDC cohorts, respectively). Limitations of this study include the absence of patients who were considered poor surgical candidates as well as potential selection bias.

Conclusions: The primary tumor size ≤ 4 cm was independently associated with improved OS in patients with metastatic clear cell RCC who underwent CN. Additionally, the association between primary size and survival was found to be nonlinear. These findings suggest that there is a group of small metastatic RCCs that can convey a better overall prognosis. The potential role of primary tumor size when risk stratifying patients with M1 RCC should be explored further to determine its utility during clinical decision making.

Patient summary: We evaluated the impact of small tumor size on prognosis in patients with metastatic kidney cancer who undergo removal of the primary tumor. Very small masses (≤ 4 cm) were associated with better prognosis in patients with clear cell tumors.

Keywords

Cytoreductive surgical procedures; Metastasis; Nephrectomy; Renal cell carcinoma

1. Introduction

Approximately 30% of patients diagnosed with renal cell carcinoma (RCC) will present with metastatic disease [1]. Management options in this setting include observation, debulking surgery, and systemic therapies [2]. Cytoreductive nephrectomy (CN) has been shown to improve prognosis, ameliorate symptoms, and facilitate pathologic diagnosis [3–5]. However, a recent trial has sparked renewed debate about the survival benefit provided by this procedure, emphasizing the importance of patient selection and risk stratification in this setting [6,7].

In order to guide management in patients presenting with M1 disease, risk scores that consider performance status and laboratory values (ie, Memorial Sloan Kettering Cancer Center [MSKCC] and International Metastatic Database Consortium [IMDC] scores) have been proposed as useful selection tools [5,8]. These scores, however, were developed to predict outcomes in patients undergoing therapy regardless of any surgical management [9,10]. They also fail to include all the factors that go into the decision-making process when selecting patients for CN [11]; for example, measures of metastatic burden and operative difficulty, which have been shown to have an influence on prognosis, are not included [12–15].

Despite being a significant predictor of outcomes in patients with localized disease, the role of primary tumor size in the prognosis of metastatic RCC has not been explored fully [16], and previous studies have reported conflicting results [13,14,17–19]. Given the role of small primary tumor size as a favorable prognostic factor in localized RCC, we hypothesized that this association also held true for patients presenting with metastatic disease. Therefore, we aimed to evaluate the association between small primary tumor size (≤ 4 cm) and survival in two independent surgical cohorts of patients with M1 RCC at presentation.

2. Patients and methods

2.1. Patients

Following institutional review board approval, we queried our prospectively maintained database to identify patients undergoing nephrectomy between August 1989 and February 2016. CN was defined as any nephrectomy performed in patients with a diagnosis of metastatic RCC. Distant metastases were diagnosed by pathologic confirmation or evidence of metastatic progression on sequential imaging. The Memorial Sloan Kettering (MSK) cohort consisted of 304 individuals who presented with M1 disease and underwent CN (Supplementary Fig. 1A). To validate the findings, a collaboration with the IMDC was established. As previously described [10], the IMDC cohort consisted of 5221 patients who received targeted therapy between 2004 and 2016 at multiple institutions. Of these patients, 778 underwent CN (Supplementary Fig. 1B).

2.2. Definitions

Baseline demographic and clinical characteristics were obtained from medical records. The location and number of metastatic sites were retrieved from clinical and radiographic reports; unifocal disease was defined as a single distant disease site (excluding regional

nodes). Primary specimens were reviewed by specialized genitourinary pathologists, and tumor size was defined as the maximum diameter of the primary tumor (in cm) on pathologic review. Based on current staging definitions, a 4 cm cutoff was used for the primary tumor analysis, categorizing patients as having small (≤ 4 cm) or large tumors [2]. Primary tumors with sarcomatoid dedifferentiation were automatically considered grade 4 in the analysis.

IMDC risk scores were calculated for patients in the MSK cohort who received targeted therapy (55.3%). Individuals treated before 2000 did not have risk score data available. The laboratory values used to calculate the scores were obtained at the time of metastatic diagnosis and based on a single blood draw. Any patient missing at least one of the parameters needed to compute the IMDC score was categorized as “unknown.” To account for the improvement in RCC management over time, we included the year in which CN was performed in our analyses.

2.3. Statistical analysis

Fisher’s exact tests were used to compare differences in categorical variables at baseline. For continuous variables, Mann-Whitney U and Spearman rank correlation tests were used to avoid normality assumptions. The primary outcome of the study was overall survival (OS), evaluated from the time of nephrectomy to the time of death or last follow-up. The Kaplan-Meier method was used to compute survival estimates. Univariate and multivariable (adjusted) Cox models were then used to evaluate the association between OS and size ≤ 4 cm. We fitted a separate univariate Cox regression with size as a continuous variable and a quadratic term for size.

To evaluate the robustness of the 4-cm threshold, we calculated the hazard ratios (HRs) for stratifying tumors into small and large groups across a range of size cutoffs (range 3–14 cm); for easier interpretation, a local polynomial smoothing approach was used (span = 2). Additionally, the subpopulation treatment effect pattern plot (STEPP) method, a nonparametric approach, was used to estimate the 2- and 5-yr survival probabilities across the size range ($r^2 = 60$, $r_1 = 20$). Significance was defined as $p < 0.05$, all tests were two sided, and correction for multiple testing was performed using the Benjamini-Hochberg approach. All analyses were performed in the R platform v3.5.0.

3. Results

3.1. Baseline characteristics

A total of 304 patients from the MSK cohort were included in the analysis; median tumor size was 8.5 cm (interquartile range [IQR] 6.3–11.0). Baseline characteristics of patients with small renal masses (≤ 4 cm, $n = 21$ [6.9%]) were compared with those with larger tumors. Patients in the small size group were less likely to present with high-grade tumors (G3–4, 57.1% vs 80.9%, $p = 0.005$) and locally advanced disease (stage pT3 or higher, 42.9% vs 74.9%, $p = 0.003$). These patients were also more likely to undergo partial nephrectomy (38.1% vs 12.4%, $p < 0.001$). Additionally, the rate of multifocal disease and number of metastatic sites differed between the size groups (42.9% vs 65.4%, $p = 0.06$, and

1 vs 2, $p = 0.01$, respectively). Similarly, in the IMDC cohort ($n = 778$; Supplementary Table 1), median size was 8.8 cm (IQR 6.5–11.0). Patients with small tumors were less likely to present with pT3 stage or higher (44.7% vs 73.3%, $p < 0.001$) and had a lower rate of multifocal disease (57.4% vs 73.1%, $p = 0.03$).

In general, patients with smaller tumors tended to have fewer metastatic sites (Spearman rank correlation, $\rho = 0.15$, $p = 0.009$; Fig. 1). Regarding the specific disease locations, patients with small masses showed a lower rate of lung/pleura (33.3% vs 63.6%, $p = 0.009$) and regional node involvement (14.3% vs 37.1%, $p = 0.04$). In addition, a substantial proportion of patients in the MSK cohort ($n = 105$, 34.6%) had surgery in the pretargeted therapy era, and only 168 (55.3%) received systemic therapy at any point during their management. Of these, only 20/168 (11.9%) received targeted therapy before surgery (Table 1).

3.2. Survival analysis

The median follow-up time in the MSK cohort was 44.2 mo (IQR 23.7, 74.4). The 2- and 5-yr OS estimates were 65.8% and 31.2%, respectively. In the IMDC cohort, the median follow-up time was 28.7 mo (IQR 12.0, 47.9), and the 2- and 5-yr OS estimates were 65.3% and 28.3%, respectively. We observed a significant difference in OS when using a 4 cm size cutoff to distinguish small versus large masses (HR 0.35, 0.17–0.72, $p = 0.004$ and HR 0.54, 0.36–0.83, $p = 0.004$, in the MSK and IMDC cohorts, respectively). A subgroup analysis, stratifying patients into clear cell RCC (ccRCC) and non-clear cell RCC histology, showed that tumor size was a significant prognostic factor only in patients diagnosed with ccRCC (Fig. 2). The association between common sites of metastasis and survival was assessed only in the MSK cohort, and results were corrected for multiple testing (Fig. 3). Only metastatic spread to the central nervous system (HR 1.70, $p < 0.001$, $q = 0.002$, which included the brain and the spinal cord) were significantly associated with worse prognosis. A multivariable analysis was then performed (in the clear cell subgroup) accounting for baseline imbalances, metastatic sites with prognostic significance, and other potential confounders (Fig. 4A). These results seem to suggest that tumor size ≥ 4 cm is independently associated with better prognosis (HR 0.40, 0.14–1.14, $p = 0.086$). Similar results were seen in the IMDC cohort (HR 0.54, 0.33–0.90, $p = 0.018$; Fig. 4B). The concordance indices of multivariable regression models, in the MSK cohort, with and without primary tumor size were 0.70 and 0.69, respectively.

We assessed the robustness of the 4 cm cutoff by fitting multiple Cox models using sequential increments (of 0.1 cm) on the size cutoff to stratify patients into small and large groups. Univariate results on the discovery cohort were false discovery rate corrected and reported at 0.5 cm intervals. The association was found to be significant for any cutoff between 3.5 and 8.5 cm, and the concordance indices ranged from 0.51 to 0.56 (Supplementary Table 2); the same approach was followed while adjusting for potential confounders (Fig. 5). To estimate the impact of size on survival without using any pre-established cutoff, we fit a univariate Cox model including size (in cm) as a continuous covariate with a quadratic term for size. In this case, a 1-cm difference in tumor size (for ccRCC tumors only) translated into a 31% higher risk of death in the MSK cohort (HR 1.31,

1.10–1.60, $p = 0.01$) and a 10% higher risk in the IMDC cohort (HR 1.10, 1.00–1.20, $p = 0.04$). Similarly, the STEPP approach showed greater tumor size (up to around 6 cm) to be associated with lower 2- and 5-yr survival probability, in both cohorts (Supplementary Fig. 2).

4. Discussion

In this study, we showed that for patients with metastatic ccRCC undergoing CN, a smaller primary tumor size results in a lower risk of death. Results were consistent even after accounting for other known prognostic factors.

Previous studies have shown a survival benefit in patients treated with interferon who undergo CN [3,4]. Similarly, retrospective analyses evaluating the role of CN in the targeted therapy era have shown a survival benefit in patients who undergo this procedure [20]. On the contrary, the recently published CARMENA trial failed to show improved survival in the CN arm [6], and experts have argued that poor case selection may have influenced these results, emphasizing the importance of risk stratifying patients prior to making any management decisions in this setting [7,21].

Both patient and disease factors require balanced consideration when managing patients with metastatic RCC. The assessment of patient fitness and hematologic parameters play an important role when choosing the right approach [8,13]. In fact, commonly used criteria such as the MSKCC/IMDC risk scores have been proposed as useful tools to help select patients for CN [5,12]. However, these scores were not developed for this purpose and fail to include tumor-related factors that are central to preoperative assessment [9,10]. Surgical decisions include the operative approach, potential need for adjuvant procedures, and best timing for surgery (eg, therapy first vs surgery first). Additionally, the total extent of metastatic burden is factored into the decision-making process (patients with widely disseminated disease are seldom considered surgical candidates). All these criteria have been shown to independently affect survival after a CN [5,12,14,22].

The size of the primary tumor, although important in localized disease, has not been explored fully in the metastatic setting, and different studies have reported conflicting results [23–25]. The risk of death from metastatic RCC was thought to be dependent on the underlying tumor biology rather than on the dimensions of the primary tumor. However, recent translational studies have shown that these features are closely inter-related; small primary tumors, for example, tend to be more homogeneous and exhibit lower genomic instability, which are related to a less aggressive disease course [26]. Patients who undergo CN represent a unique opportunity to study the impact of primary tumor size in prognosis, as removal of the primary tumor allows precise measurement of tumor dimensions.

The importance of primary tumor size in the presence of disseminated disease is supported by our results. We found that a 1-cm difference in primary tumor size can lead to a 10–31% relative difference in the risk of death, which could have important implications when risk stratifying individuals with metastatic RCC. To note, we believe that the association between primary tumor size and survival is nonlinear, and that the survival advantage observed is

likely restricted to the smallest of primary tumors (which potentially exhibit biologic features that render them less aggressive). This would explain the plateauing observed in the sliding approach presented in Figure 5 and the results from the STEPP approach (Supplementary Fig. 2), where the effect of size seems to become irrelevant at around 6–7 cm. We did not observe the same results in patients with non–clear cell tumors. However, the number of individuals in this subgroup was rather small, preventing us from reaching any significant conclusions. We believe that our study presents unique insights into the role of primary tumor size in the metastatic RCC setting. Previously reported series have been notably smaller and have explored the role of primary tumor size mostly as secondary analyses, without adequate assessment of extreme groups or nonlinear relationships with survival [13,14,17–19].

Our study also suggests an important relationship between small primary tumor size and metastatic disease extent; primary tumor size was associated with fewer disease sites. Even though both measures of metastatic extent used (ie, number of metastatic sites and multifocality rate) differed significantly between the size groups, multivariable analysis showed primary tumor size to be an independent predictor of survival after accounting for this difference. We must acknowledge, however, that the total burden of disease could not be accurately ascertained with the data at hand, and potential residual confounding cannot be ruled out. Mixed results have been reported regarding the association of metastatic extent and prognosis in the CN setting; patients whose primary tumors represent a higher percentage of the total volume of disease seem to benefit the most from surgical intervention. However, a few small retrospective studies have also shown that total disease volume does not influence survival [27–29]. We think that both features (primary tumor size and metastatic burden) are a reflection of the underlying tumor biology, which is (potentially) the real driver of disease aggressiveness in this setting. In order to overcome some of these limitations, future studies aiming to further elucidate these associations should include precise measurements of total disease burden.

Owing to the fact that only about half of the MSK cohort received targeted therapy, IMDC risk scores could not be calculated reliably for many patients (ie, time from diagnosis to treatment not available). Therefore, in order to adjust our estimates for potential differences in the baseline risk of individuals, we accounted for low performance status (Karnofsky performance status) and laboratory abnormalities (as per the IMDC criteria) in multivariable survival analysis. Motzer/MSKCC criteria were not used since even fewer patients had serum lactate dehydrogenase data available, and all patients who had not undergone nephrectomy at presentation (ie, all individuals included) would be considered at least at intermediate risk, providing a potentially misleading view of the actual baseline risk [9]. Additionally, since RCC prognosis has improved significantly over recent years, we adjusted our results for the year in which nephrectomies were performed [30]. Even after accounting for these factors, small primary tumor size seemed to be associated with better prognosis, demonstrating its independent effect on survival.

The retrospective nature of the study predisposes us to potential selection biases. Factors such as widely disseminated disease or significant comorbidities (with poor performance status) would preclude surgical intervention; therefore, patients with these features are likely

under-represented in these surgical cohorts. Comorbidity data were not available for analysis, and we think that this could potentially reduce the precision of our estimates. However, given that performance status was indeed accounted for in the analysis and that this is arguably a more important determinant of prognosis (in itself related to the presence of clinically significant comorbidities), we believe it to be very unlikely that the absence of these data would change the direction of the association between size and survival. Another potential limitation is that the two cohorts differ significantly with regard to their management. The IMDC set represents a much more contemporary cohort (accrued since 2004), consisting exclusively of patients treated with targeted therapy. In contrast, about a third of the individuals in the MSK cohort were managed before the advent of these treatments. One could argue, however, that since a wide variety of patients, treated at different times with several strategies, were included in the analysis, results are more likely to be generalizable at the population level. To address this potential comparability issue, we have provided subgroup analyses for the MSK cohort stratifying patients by the year in which the nephrectomy was performed (before/after 2004, as per the IMDC accrual date) as well as by the administration of systemic therapy (Supplementary Table 3).

5. Conclusions

Our data support the role of tumor size as an independent prognostic factor in patients with metastatic ccRCC undergoing CN. This association was restricted to the smallest of primary tumors, which seem to represent an extreme group of more indolent tumors. Additionally, a significant relationship was observed between primary tumor size and metastatic extent. These findings should be considered when conducting research in this setting. However, the role of primary tumor size when risk stratifying patients with metastatic RCC should be explored further to determine its utility during clinical decision making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding/Support and role of the sponsor:

This work was supported by the Sidney Kimmel Center for Prostate and Urologic Cancers and in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

Financial disclosures: A. Ari Hakimi certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

References

- [1]. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7–30. [PubMed: 29313949]
- [2]. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney cancer, version 2.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2017;15:804–34. [PubMed: 28596261]
- [3]. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001;345:1655–9. [PubMed: 11759643]

- [4]. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R, European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001;358:966–70. [PubMed: 11583750]
- [5]. Heng DY, Wells JC, Rini BI, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol* 2014;66:704–10. [PubMed: 24931622]
- [6]. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med* 2018;379:417–27. [PubMed: 29860937]
- [7]. Larcher A, Wallis CJD, Bex A, et al. Individualised indications for cytoreductive nephrectomy: which criteria define the optimal candidates? *Eur Urol Oncol* 2019;2:365–78. [PubMed: 31109902]
- [8]. Ito H, Shioi K, Murakami T, et al. C-reactive protein in patients with advanced metastatic renal cell carcinoma: usefulness in identifying patients most likely to benefit from initial nephrectomy. *BMC Cancer* 2012;12:337. [PubMed: 22857740]
- [9]. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999;17:2530. [PubMed: 10561319]
- [10]. Ko JJ, Xie W, Kroeger N, et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. *Lancet Oncol* 2015;16:293–300. [PubMed: 25681967]
- [11]. Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? *Cancer* 2010;116:3378–88. [PubMed: 20564061]
- [12]. Manley BJ, Tennenbaum DM, Vertosick EA, et al. The difficulty in selecting patients for cytoreductive nephrectomy: an evaluation of previously described predictive models. *Urol Oncol* 2017;35:35.e1–5.
- [13]. Shuch B, La Rochelle JC, Wu J, et al. Performance status and cytoreductive nephrectomy: redefining management in patients with poor performance. *Cancer* 2008;113:1324–31. [PubMed: 18661529]
- [14]. Capitanio U, Abdollah F, Matloob R, et al. Effect of number and location of distant metastases on renal cell carcinoma mortality in candidates for cytoreductive nephrectomy: implications for multimodal therapy. *Int J Urol* 2013;20:572–9. [PubMed: 23163758]
- [15]. Tilki D, Hu B, Nguyen HG, et al. Impact of synchronous metastasis distribution on cancer specific survival in renal cell carcinoma after radical nephrectomy with tumor thrombectomy. *J Urol* 2015;193:436–42. [PubMed: 25063493]
- [16]. Bhindi B, Abel EJ, Albiges L, et al. Systematic review of the role of cytoreductive nephrectomy in the targeted therapy era and beyond: an individualized approach to metastatic renal cell carcinoma. *Eur Urol* 2019;75:111–28. [PubMed: 30467042]
- [17]. You D, Jeong IG, Song C, et al. Analysis of pre-operative variables for identifying patients who might benefit from upfront cytoreductive nephrectomy for metastatic renal cell carcinoma in the targeted therapy era. *Jpn J Clin Oncol* 2015;45:96–102. [PubMed: 25341544]
- [18]. Gu L, Li H, Wang H, et al. Presence of sarcomatoid differentiation as a prognostic indicator for survival in surgically treated metastatic renal cell carcinoma. *J Cancer Res Clin Oncol* 2017;143:499–508. [PubMed: 27844145]
- [19]. Sharma P, Zargar-Shoshtari K, Caracciolo JT, et al. Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. *Urol Oncol* 2015;33:339.e17–23.
- [20]. Choueiri TK, Xie W, Kollmannsberger C, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. *J Urol* 2011;185:60–6. [PubMed: 21074201]
- [21]. Motzer RJ, Russo P. Cytoreductive nephrectomy—patient selection is key. *N Engl J Med* 2018;379:481–2. [PubMed: 29860908]

- [22]. Lyon TD, Gershman B, Shah PH, et al. Risk prediction models for cancer-specific survival following cytoreductive nephrectomy in the contemporary era. *Urol Oncol* 2018;36:499.e1–7.
- [23]. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the Ssign score. *J Urol* 2002;168:2395–400. [PubMed: 12441925]
- [24]. Thompson RH, Houston Thompson R, Hill JR, et al. Metastatic renal cell carcinoma risk according to tumor size. *J Urol* 2009;182:41–5. [PubMed: 19450840]
- [25]. Bhindi B, Thompson RH, Lohse CM, et al. The probability of aggressive versus indolent histology based on renal tumor size: implications for surveillance and treatment. *Eur Urol* 2018;74:489–97. [PubMed: 30017400]
- [26]. Turajlic S, Xu H, Litchfield K, et al. Deterministic evolutionary trajectories influence primary tumor growth: TRACERx Renal. *Cell* 2018;173:595–610.e11. [PubMed: 29656894]
- [27]. Pierorazio PM, McKiernan JM, McCann TR, Mohile S, Petrylak D, Benson MC. Outcome after cytoreductive nephrectomy for metastatic renal cell carcinoma is predicted by fractional percentage of tumour volume removed. *BJU Int* 2007;100:755–9. [PubMed: 17822456]
- [28]. Blute ML, Ziemlewicz TJ, Lang JM, et al. Metastatic tumor burden does not predict overall survival following cytoreductive nephrectomy for renal cell carcinoma: a novel 3-dimensional volumetric analysis. *Urology* 2017;100:139–44. [PubMed: 27667156]
- [29]. Barbastefano J, Garcia JA, Elson P, et al. Association of percentage of tumour burden removed with debulking nephrectomy and progression-free survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *BJU Int* 2010;106:1266–9. [PubMed: 20346042]
- [30]. Beisland C, Johannesen T, Klepp O, et al. Overall survival in renal cell carcinoma after introduction of targeted therapies: a Norwegian population-based study. *OncoTargets Ther* 2017;10:371–85.

*Spearman rank correlation estimates differ between clear cell ($\rho = 0.19$, $p = 0.001$) and non clear-cell ($\rho = -0.28$, $p = 0.17$) histologies.

Fig. 1 –.

Association between primary tumor size and number of metastatic sites. Scatterplot showing the positive correlation between primary tumor size (cm) and the number of metastatic sites. The marginal plots show the distribution of each variable. Smaller tumors were found to have fewer metastatic sites affected; the finding was specific to clear cell renal cell carcinoma.

Fig. 2 –.

Survival estimates of individuals with small primary tumors (< 4 cm) compared with their larger counterparts. Kaplan-Meier curves showing the association between small primary tumor size (< 4 cm) and prolonged survival in both the (A–C) MSK and (D–E) IMDC cohorts. Results are shown separately for all individuals and broken down by primary histology (clear cell vs non-clear cell). The effect of size on survival seems to be exclusive to patients with clear cell renal cell carcinoma. HR = hazard ratio; IMDC = International Metastatic Database Consortium; MSK = Memorial Sloan Kettering; NR = not reported.

Fig. 3 –.
Most common sites of metastasis and their impact on survival. Summary of the most common sites of disease and their association with overall survival (right). Univariate Cox regressions were used to test the association between the presence of metastasis in these locations and survival. Only central nervous system (CNS) involvement was associated with worse prognosis after correction for multiple testing ($q < 0.05$). HR = hazard ratio.

A Memorial Sloan Kettering Cancer Center (MSKCC) clear cell cohort (n = 222)* **B International Metastatic Database Consortium (IMDC) clear cell cohort (n = 546)***

*Individuals with missing data were not included in the analysis (n=56 and n=137 in the MSK and IMDC cohorts, respectively).

Fig. 4 –.

Multivariable (adjusted) Cox regression estimates of the association between small primary tumor size (≤ 4 cm) and survival after accounting for other prognostic factors. Forest plot showing the results of multivariable Cox regressions in both (A) the MSK and (B) the IMDC cohorts. Small tumor size (≤ 4 cm) was independently associated with survival after accounting for other known prognostic factors. CI = confidence interval; CN = cytoreductive nephrectomy; CNS = central nervous system; IMDC = International Metastatic Database Consortium; KPS = Karnofsky performance status; MSK = Memorial Sloan Kettering.

Fig. 5 –.

Relative effect of primary tumor size on survival across the size spectrum accounting for other prognostic factors. Results of the univariate and multivariable Cox regression analyses using sequential size cutoffs (0.1 cm increments). The top panels represent the distribution of tumor size in the (A) MSK and (B) IMDC cohorts. (C and D) The bottom panels show the hazard ratios and 95% confidence intervals for a small tumor compared with a large one at each size cutoff. Smaller tumor size seems to be associated with better survival in both cohorts. CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Database Consortium; MSK = Memorial Sloan Kettering; MSKCC = Memorial Sloan Kettering Cancer Center.

Baseline characteristics and systemic therapies in the MSK cohort, comparing small versus large tumors based on a 4-cm cutoff in primary tumor size

Table 1 –

	Level	Overall	4 cm	>4 cm	p value
N		304	21	283	
Age at nephrectomy (yr), median (IQR)		61 (53, 69)	64 (59, 68)	61 (53, 69)	0.44
Sex, n (%)	Female	90 (29.6)	6 (28.6)	84 (29.7)	0.99
	Male	214 (70.4)	15 (71.4)	199 (70.3)	
BMI, n (%)	Nonobese (BMI 30 kg/m ²)	186 (61.2)	8 (38.1)	178 (62.9)	0.07
	Obese	94 (30.9)	10 (47.6)	84 (29.7)	
	NA	24 (7.9)	3 (14.3)	21 (7.4)	
Histology, n (%)	Clear cell	278 (91.4)	17 (81.0)	261 (92.2)	0.09
	Non-clear cell	26 (8.6)	4 (19.0)	22 (7.8)	
Pathologic T stage, n (%)	pT1/T2	80 (26.3)	12 (57.1)	68 (24.0)	0.003
	pT3/T4	221 (72.7)	9 (42.9)	212 (74.9)	
	NA	3 (1.0)	0 (0.0)	3 (1.1)	
Pathologic N stage, n (%)	pN0	139 (45.7)	3 (14.3)	136 (48.1)	0.37
	pN1/N2	59 (19.4)	3 (14.3)	56 (19.8)	
	NA	106 (34.9)	15 (71.4)	91 (32.2)	
Fuhrman nuclear grade, n (%)	High (G3/G4)	241 (79.3)	12 (57.1)	229 (80.9)	0.005
	Low (G1/G2)	43 (14.1)	8 (38.1)	35 (12.4)	
	NA	20 (6.6)	1 (4.8)	19 (6.7)	
Surgical approach, n (%)	Partial nephrectomy	27 (8.9)	8 (38.1)	19 (6.7)	<0.001
	Radical nephrectomy	277 (91.1)	13 (61.9)	264 (93.3)	
Symptoms at presentation, n (%)	No	192 (63.2)	16 (76.2)	176 (62.2)	0.246
	Yes	112 (36.8)	5 (23.8)	107 (37.8)	
Lab abnormalities or KPS <80, n (%)	No	90 (29.6)	10 (47.6)	80 (28.3)	0.08
	Yes	163 (53.6)	8 (38.1)	155 (54.8)	
	Unknown (before 2000)	51 (16.8)	3 (14.3)	48 (17.0)	
IMDC risk group, n (%)	Favorable	20 (6.6)	3 (14.3)	17 (6.0)	0.05
	Intermediate	93 (30.6)	6 (28.6)	87 (30.7)	

	Level	Overall	4 cm	>4 cm	p value
	Poor	50 (16.4)	0 (0.0)	50 (17.7)	
	Unknown	141 (46.4)	12 (57.1)	129 (45.6)	
Year of nephrectomy, <i>n</i> (%)	1989–1999	48 (15.8)	4 (19.0)	44 (15.5)	0.1
	2000–2004	57 (18.8)	6 (28.6)	51 (18.0)	
	2005–2009	78 (25.7)	2 (9.5)	76 (26.9)	
	2010–2014	96 (31.6)	5 (23.8)	91 (32.2)	
	2015 and after	25 (8.2)	4 (19.0)	21 (7.4)	
Metastasectomy, <i>n</i> (%)	No	151 (49.7)	7 (33.3)	144 (50.9)	0.17
	Yes	153 (50.3)	14 (66.7)	139 (49.1)	
Radiotherapy, <i>n</i> (%)	No	175 (57.6)	11 (52.4)	164 (58.0)	0.65
	Yes	129 (42.4)	10 (47.6)	119 (42.0)	
Targeted therapy administered, <i>n</i> (%)	No targeted therapy	136 (44.7)	11 (52.4)	125 (44.2)	0.87
	Targeted therapy before CN	20 (6.6)	1 (4.8)	19 (6.7)	
	Targeted therapy after CN	148 (48.7)	9 (42.9)	139 (49.1)	
Lines of therapy, <i>n</i> (%)	Untreated	136 (44.7)	11 (52.4)	125 (44.2)	0.77
	1 line	69 (22.7)	3 (14.3)	66 (23.3)	
	2 lines	38 (12.5)	2 (9.5)	36 (12.7)	
	3+ lines	61 (20.1)	5 (23.8)	56 (19.8)	
	Immune-checkpoint blockade (anti-PD1, anti-CTLA4)	35 (11.5)	2 (9.5)	33 (11.7)	0.99
Agents administered	Anti-VEGF treatment (TKI, bevacizumab)	152 (50.0)	9 (42.9)	143 (50.5)	0.65
	MTOR inhibitor (everolimus, temsirolimus)	77 (25.3)	4 (19.0)	73 (25.8)	0.61
Metastatic disease sites, median (IQR)		2 (1, 3)	1 (1, 2)	2 (1, 3)	0.01
Disease sites (cat), <i>n</i> (%)	Multifocal	194 (63.8)	9 (42.9)	185 (65.4)	0.06
	Unifocal	110 (36.2)	12 (57.1)	98 (34.6)	
Metastatic sites, <i>n</i> (%)	Lung or pleura (%)	187 (61.5)	7 (33.3)	180 (63.6)	0.009
	Bone (%)	124 (40.8)	11 (52.4)	113 (39.9)	0.36
	Regional nodes (on imaging) (%)	108 (35.5)	3 (14.3)	105 (37.1)	0.04
	CNS metastases (%)	102 (33.6)	8 (38.1)	94 (33.2)	0.64
	Liver (%)	55 (18.1)	2 (9.5)	53 (18.7)	0.39

Level	Overall	4 cm	>4 cm	p value
Distant nodes (on imaging) (%)	58 (19.1)	2 (9.5)	56 (19.8)	0.39
Adrenal (%)	47 (15.5)	2 (9.5)	45 (15.9)	0.75

BMI = body mass index; cat = category; CN = cytoreductive nephrectomy; CNS = central nervous system; IMDC = International Metastatic Database Consortium; KPS = Karnofsky performance status; MSK = Memorial Sloan Kettering; MTOR = mammalian target of rapamycin; NA = not available; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.