Survival of Patients Undergoing Cytoreductive Surgery for Metastatic Renal Cell Carcinoma in the Targeted-Therapy Era

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Abstract. *Background/Aim: In the cytokine era, cytoreductive nephrectomy (CN) improves survival for patients with metastatic renal cell carcinoma (mRCC). We analyzed the effect of CN on the survival of patients diagnosed with mRCC in the era of tyrosine kinase inhibitors (2005-present). Patients and Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify adult patients diagnosed with mRCC between 2005 and 2009. The primary outcome was overall survival, analyzed with multivariable Cox models. Results: Out of 7,143 incident mRCC cases reported to SEER between 2005-2009, 2,629 (37%) underwent CN. Patients undergoing CN were younger, and more likely to be white, male, and married. Patients with stage T3 tumors were most likely to undergo CN (64%). Patients that underwent CN had improved one-year survival (61% vs. 22%). On multivariable analysis, CN was associated with improved overall survival(hazard ratio[HR]=0.40 95% confidence interval [CI]=0.37-0.43). Conclusion: In the targeted-therapy era, patients with mRCC undergoing CN have improved survival after adjusting for tumor stage and demographic characteristics.*

The incidence of renal cell carcinoma (RCC) is rising in the United States at the rate of approximately 3% per year, however, mortality from the disease is declining less than 1% per year (1). The rising incidence is driven by tumors localized to the kidney, often detected incidentally on cross-sectional imaging, while the incidence of RCC cases that are metastatic at the time of diagnosis (mRCC), has not declined (2). As only 11% of patients with mRCC are expected to survive five years (2), mRCC remains a significant cause of cancer death in the US and therefore much research effort has been directed towards more effective therapy.

Cytoreductive surgery, whereby the primary tumor is removed in the setting of metastatic disease, has been the mainstay of the management of mRCC since nephrectomy and interferon-alpha was shown to increase survival over interferon-alone in a randomized clinical trial (3). However, since 2005, six new drugs targeting the mammalian target of rapamycin (mTOR) or vascular endothelial growth factor (VEGF) pathways have been approved by the US Food and Drug Administration for use in mRCC (4). These targeted agents have extended the progression-free survival of patients with mRCC over the previous standards-of-care, thereby becoming first-line therapy (5, 6). It has been questioned whether cytoreductive nephrectomy is still beneficial in this era of more effective systemic therapy for mRCC. We, therefore, performed an analysis of population-level data from the targeted therapy era (2005 and later) to determine the differences in cancer-specific and overall survival in patients that did or did not receive cytoreductive surgery for mRCC.

Patients and Methods

After this study was deemed exempt by the Institutional Review Board, data were obtained from the Surveillance, Epidemiology, and End Results (SEER) dataset (7), a publicly available national tumor database. Included cases were RCC that were metastatic at the time of diagnosis, as defined by the American Joint Committee on Cancer (AJCC) TNM classification, sixth edition (8), between 2005 and 2009. RCC cases were selected using ICD-0-3 codes for each subtype of RCC, as well as RCC 'not otherwise specified' (NOS). Cases with an unknown surgical history, and those diagnosed in patients under 18 years of age were excluded.

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Patients were classified as undergoing cytoreductive surgery if they had a partial, simple, or radical nephrectomy, with or without resection of adjacent organs. Patients that underwent thermal ablation (n=22) were considered non-surgically managed. Local tumor and nodal staging were classified using the AJCC TNM classification, with T staging consolidated into T0,T1,T2,T3,T4, or Tx for the purposes of analysis. Race was categorized as: white, black, or other. Age was considered at the time of diagnosis and analyzed as a continuous variable. RCC histotypes were considered individually for multivariate analyses, but dichotomized as clear cell or non-clear cell for the purposes of subgroup analyses.

Univariable comparisons stratified by undergoing cytoreductive surgery were performed using either Chi-squared or Fisher's exact tests for categorical variables, and Kruskal–Wallis signed-rank tests for continuous variables. Survival analyses were performed using the product limit estimation and presented using Kaplan–Meier plots. Multivariable analyses were performed using Cox proportional hazards models adjusted for race, sex, year of diagnosis, age at diagnosis, marital status, T stage, N stage, SEER region, and histotype, with all-cause death as the primary outcome. All survival models are presented as hazard ratios (HR) with 95% confidence intervals (CI). Descriptive data are presented as the median (interquartile range) or number (percent). All tests were two-tailed and *p*-values of less than 0.05 were considered statistically significant. Data extraction, coding, and statistical analyses were performed independently by two investigators (MRA and ES), with differences resolved by consensus. The final analyses were performed using R version 2.14.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 7,143 mRCC cases were reported to SEER between 2005 and 2009, out of which 2,629 (37%) underwent cytoreductive surgery. Patients undergoing cytoreductive surgery were younger, and more likely to be white, male, and married as compared to patients not undergoing surgery (Table I). While there were T and N staging differences between the groups, the patterns are difficult to determine due to the lack of complete staging data in approximately one-third of the non-surgical patients (Table II). Similarly, there were a large proportion of cases with histology coded as RCC NOS in the non-surgical cohort as their diagnoses relied on biopsy. As shown in Figure 1, patients with T3 tumors had the highest probability (64%) of undergoing cytoreductive surgery. In contrast, only 31% of patients with T1 tumors and 41% of patients with T2 tumors underwent cytoreductive surgery.

After a median follow-up of 13 (4-28) months, 45% of patients undergoing cytoreductive surgery were alive compared to 17% in the non-surgical group. The 1-and 2-year survival rates were 61% and 42%, respectively, in the cytoreductive-surgery group and 22% and 10% in the non-surgical group. Cytoreductive surgery was associated with improved overall survival (HR=0.33, 95% CI=0.31-0.36). Survival analyses stratified by stage and histology are shown in Figure 2. In each sub-group tested, cytoreductive surgery was associated with improved overall survival (all $p<0.001$).

The results of multivariable Cox models adjusting for available demographic and tumor characteristics for the overall cohort, as well as each of the aforementioned subgroups, are shown in Table III. In all models, advanced age was found to be associated with decreased survival (data not shown). In all tested cohorts, cytoreductive surgery remained an independent predictor of overall survival (all $p<0.001$).

Table I. *Demographic and geographic characteristics of patients included in this study.*

Variable	Cytoreductive surgery				*p*-Value
	Yes (N=2629)		No (N=4514)		
Age, median (Q1, Q3), years	61 (53, 68)		68 (59, 78)		<0.001
Gender					<0.001
Male	1858	71%	2935	65%	
Female	771	29%	1579	35%	
Race					<0.001
White	2269	86%	3698	82%	
Black	191	7%	530	12%	
Other	169	6%	286	6%	
Marital Status					<0.001
Married	1770	67%	2373	53%	
Not married	859	33%	2141	47%	
Year of diagnosis					0.81
2005	498	19%	821	18%	
2006	522	20%	887	20%	
2007	540	21%	920	20%	
2008	548	21%	940	21%	
2009	521	20%	946	21%	
SEER Registry					0.01
Alaska	1	0%	11	0%	
Atlanta	84	3%	148	3%	
California excluding SF/SJM/LA	629	24%	1046	23%	
Connecticut	99	4%	205	5%	
Detroit	108	4%	248	5%	
Greater Georgia	176	7%	315	7%	
Hawaii	42	2%	64	1%	
Iowa	157	6%	218	5%	
Kentucky	171	7%	266	6%	
Los Angeles	271	10%	411	9%	
Louisiana	163	6%	326	7%	
New Jersey	260	10%	449	10%	
New Mexico	59	2%	139	3%	
Rural Georgia	6	0%	8	0%	
San Francisco-Oakland	124	5%	228	5%	
San Jose-Monterey	62	2%	99	2%	
Seattle (Puget Sound)	163	6%	267	6%	
Utah	54	2%	66	1%	

Table II. Tumor characteristics.

Variable	Cytoreductive surgery				*p*-Value
	Yes (N=2629)		No (N=4514)		
T Stage					<0.001
T0	0	0%	32	1%	
T1	389	15%	879	19%	
T2	401	15%	568	13%	
T3	1521	58%	861	19%	
T4	255	10%	577	13%	
TX	63	2%	1597	35%	
N Stage					<0.001
N0	1718	65%	1959	43%	
N1	413	16%	787	17%	
N2	290	11%	423	9%	
NX	208	8%	1345	30%	
Histological type					<0.001
RCC, NOS (8312)	513	20%	3029	67%	
Clear cell (8310)	1619	62%	1147	25%	
Sarcomatoid (8318)	249	9%	163	4%	
Other	248	9%	175	4%	
Laterality					<0.001
Left	1358	52%	2121	47%	
Right	1259	48%	1985	44%	
Bilateral	6	0%	67	1%	
Unknown	6	0%	341	8%	

NOS: Not otherwise specified, RCC: renal cell carcinoma.

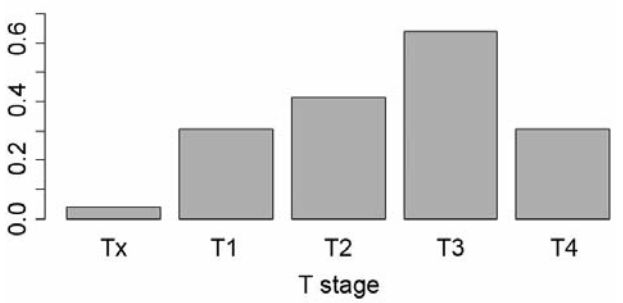

Figure 1. *Proportion of patients undergoing cytoreductive surgery by primary tumor stage.*

Discussion

More effective targeted-agents have revolutionized the management of mRCC. While level I evidence supporting the use of cytoreductive surgery exists from the cytokine era, there have been few data examining its efficacy in the targeted-therapy era. A retrospective analysis of 78 patients compared progression-free and overall survival in those undergoing cytoreductive surgery and subsequent targeted-therapy *versus* targeted-therapy alone (9). While the HR for not undergoing surgery was 1.9 for overall survival, this did not reach statistical significance, suggesting a lack of power. Our group and others have questioned whether cytoreductive surgery is still relevant, given that it may delay or preclude the administration of systemic therapy (10). Indeed, the utilization of cytoreductive nephrectomy in the US increased between 2001 and 2005, but has declined steadily since (11). This is unlikely to be accounted for by a lack of eligibility for surgery as there has been a migration away from patients with poor risk toward favorable-risk mRCC overall (12). Instead, there has likely been a change in practice patterns away from surgical management due to the availability of new systemic agents. However, whether this strategy is superior to multi-modal management is unclear. A recent analysis of SEER demonstrated a survival benefit of cytoreductive nephrectomy in patients with non-clear cell histology in the targeted therapy era (13). This is not surprising because targeted agents have inferior response rates for these histotypes compared to clear cell tumors (14). We, therefore, sought to perform a broader comparison of survival in patients with mRCC managed with cytoreductive surgery to those who were not using a national tumor registry. Specifically, we stratified the analyses by histotype and primary tumor stage in an attempt to identify particular patient subsets for whom cytoreductive nephrectomy is associated with improved survival.

We chose overall survival as an outcome due to the high rate of death from mRCC (87% in this analysis), as well as to eliminate potential errors in coding the cause of death in the registry. We found that surgery was associated with improved overall survival. After adjusting the analysis for available sociodemographic and tumor factors, cytoreductive surgery remained independently associated with better survival. In fact, other than medullary histology, not undergoing surgery was the strongest predictor of death in the multivariable analyses. The magnitude of the survival benefit of cytoreductive surgery in these data is similar to that seen in a population-based analysis performed during the cytokine era (15).

Undoubtedly primary tumor stage may have an impact on resectability, which will in turn affect eligibility for cytoreductive surgery. In an attempt to exclude this scenario, we performed sub-group analyses stratified by primary tumor stage. Surprisingly, fewer than half of all patients with T1 or T2 tumors underwent cytoreductive surgery. While these locally-confined tumors are generally resectable, it is possible that a very high burden of metastatic disease contributed to the election of non-surgical management. However, we found that the protective effect of cytoreductive surgery was greatest at lower tumor stages (with HRs of 0.32, 0.32, 0.38, and 0.54 for T1, T2, T3, and T4, respectively). It has been shown that complete resection of

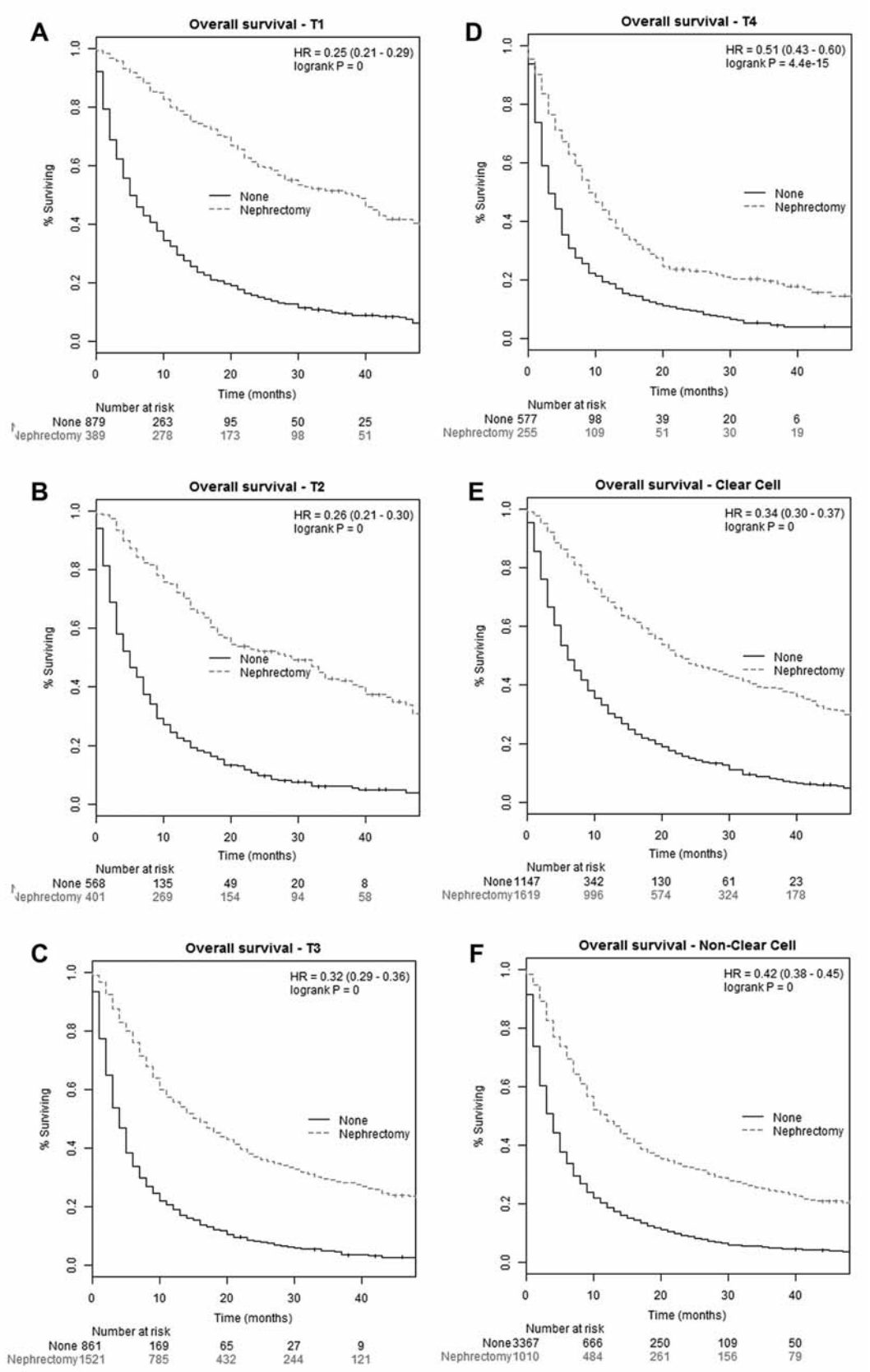

Figure 2. *Overall survival stratified by cytoreductive surgery and primary tumor stage. A: T1, B: T2, C: T3, D: T4, E: clear cell, F: non-clear cell.*

Table III. *Impact of cytoreductive surgery on all-cause mortality from metastatic renal cell cancer.*

Cohort	N	Events	Unadjusted				Adjusted[a]			
			Hazard ratio	95% Confidence limits		*p*-Value	Hazard ratio	95% Confidence limits		*p*-Value
Overall[b]	7143	5182	0.33	0.31	0.36	<0.0001	0.40	0.37	0.43	<0.0001
Clear cell[c]	2766	1662	0.34	0.30	0.37	<0.0001	0.36	0.32	0.40	<0.0001
Non-clear cell[c]	4377	3520	0.42	0.38	0.45	<0.0001	0.45	0.40	0.49	<0.0001
T1[d]	1268	831	0.25	0.21	0.29	<0.0001	0.32	0.26	0.40	<0.0001
T2[d]	969	663	0.26	0.21	0.30	<0.0001	0.32	0.26	0.40	<0.0001
T3[d]	2382	1599	0.32	0.29	0.36	<0.0001	0.38	0.33	0.43	<0.0001
T4[d]	832	667	0.51	0.43	0.60	<0.0001	0.54	0.44	0.66	<0.0001

Adjusted for: [a]age, sex, year of diagnosis, race, marital status, SEER region, N stage. [b]also for histology, T stage; [c]also for T stage; [d]also for histology.

the primary tumor and metastatic sites is associated with superior survival (16), and these data would support that concept. It is unclear why patients with T3 tumors were most likely to receive surgery. It is possible that these patients had a large proportion of their total disease burden contained within the primary lesion, as the proportion of disease resected has been correlated with improved kidney cancer-specific survival (17). An alternate explanation may be the selection of patients with tumor thrombus for surgery due to inability of targeted agents to downstage a tumor thrombus in a clinically meaningful way (18).

An important issue to consider with these data is the diagnostic uncertainty with regard to histotype in the non-surgical cohort. For these patients, percutaneous biopsy of either the primary tumor or metastatic sites is typically used to make the diagnosis. While percutaneous biopsy has been reported to be 96% accurate with regard to clear cell histology, the accuracy declines significantly for non-clear cell histology (19). Therefore, we sub-analyzed the clear cell cases as the cleanest available dataset. Again, cytoreductive surgery was associated with improved overall survival on both univariable and multivariable analyses. The association between cytoreductive surgery was similar, albeit weaker, in patients with non-clear cell histology, although this represents a heterogeneous group.

There are several possible mechanisms by which cytoreductive surgery may improve survival. Resection of the primary tumor and complete metastasectomy likely represents the only chance for long-term cure, as the effect of targeted-therapy on the primary renal tumor entails a modest size reduction (20, 21). In addition, removal of tumor thrombus with the primary tumor may delay or prevent fatal vascular events. Finally, debulking may prevent adjacent organ invasion/obstruction and has been postulated to delay early progression (22).

There are several confounders that may contribute to the increased survival of patients undergoing cytoreductive surgery. Good performance status has been shown to be a strong predictor of survival in mRCC (23, 24), and it is possible that patients deemed surgical candidates may have better performance status than those that are not. In addition, the utilization of cytoreductive nephrectomy is higher in academic or teaching centers (11), which may affect access to specialists, technology, or other resources that may prolong survival.

A major limitation of these data is the lack of information regarding systemic therapy. There is a group of patients in both the surgical and non-surgical groups that will not be eligible for or receive systemic therapy. Indeed, it has been shown that almost 30% of patients undergoing cytoreductive nephrectomy will not be given systemic therapy for a variety of reasons, including rapid progression (25). In addition, it is possible that although targeted agents were available for mRCC during the time period studied, immunotherapy was utilized in some. Another limitation is the lack of ability to control for the location or number of metastatic sites, as these have been shown to be prognostic (16, 26). Other prognosticators, including serum hemoglobin, lactate dehydrogenase (LDH), calcium, and albumin were also unavailable for our dataset, and could vary between the surgical and non-surgical groups (23, 27).

Despite these limitations, these data provide an assessment of outcomes of patients that undergo cytoreductive surgery in the targeted therapy era, given that no prospective data currently exist. The CARMENA trial, which plans to randomize 576 patients to either cytoreductive surgery followed by sunitinib, or to sunitinib alone, is targeted to complete in 2015. Until then, these data suggest that cytoreductive surgery should continue to play a role in the multidisciplinary management of mRCC. Perhaps the more

prudent question is the optimal sequencing of systemic therapy with cytoreductive surgery. The SURTIME trial, which is randomizing patients to cytoreductive surgery and adjuvant sunitinib, or sunitinib before and after surgery, should help shed light on this issue.

Conclusion

Despite guidelines recommending cytoreductive nephrectomy for resectable renal tumors in patients with mRCC, fewer than half of the patients in this analysis with primary tumors localized to the kidney underwent surgery. In the targeted therapy era, patients undergoing cytoreductive surgery continue to have improved overall survival compared to those who do not. This is true across primary tumor stage, and for patients with both clear and non-clear cell histology. While level I data are forthcoming, it appears that cytoreductive surgery should continue to be part of the management of selected patients with mRCC in the targeted therapy era. The optimal sequencing of surgery and systemic therapy merits further study.

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