

Survival and Complication Rates of Metastasectomy in Patients With Metastatic Renal Cell Carcinoma Treated Exclusively With Targeted Therapy: A Combined Population-based Analysis

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Abstract. Aim: This study analyzed the effect of metastasectomy on overall mortality (OM) and perioperative outcomes in patients with metastatic renal cell carcinoma (mRCC) treated exclusively with targeted therapy. Materials and Methods: Using the Surveillance, Epidemiology, and End Results (SEER) database (2006-2015), Kaplan–Meier analyses and multivariable Cox regression models tested for OM. Using the National Inpatient Sample (NIS) database (2006-2015), complication rates and in-hospital mortality were evaluated. Results: Within the SEER database, 437

(12.2%) out of 3,654 patients underwent metastasectomy. Metastasectomy was associated with lower OM risk (median survival 11 vs. 9 months, hazard ratio=0.83; $p=0.002$). Within the NIS database, 351 such patients were identified. Complications and in-hospital mortality were 55.0% and 4.6%, respectively. Conclusion: Metastasectomy in patients with mRCC treated exclusively with targeted therapy is associated with lower OM risk, however, based on short duration of expected survival. Complications and in-hospital mortality rates are not negligible.

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Both European and North-American guidelines (1, 2) consider metastasectomy a treatment option in metastatic renal cell carcinoma (mRCC). However, data supporting the role of metastasectomy in the targeted therapy era in patients with mRCC treated with cytoreductive nephrectomy are scarce (3, 4).

To the best of our knowledge, no previous studies have examined the role of metastasectomy in a controlled fashion, using a formal control group that was not treated with metastasectomy, in mRCC treated exclusively with targeted therapy. Therefore, we assessed the effect of metastasectomy

Table I. Descriptive characteristics of 3,654 patients with metastatic renal cell carcinoma (RCC) treated exclusively with targeted therapy, according to additional metastasectomy status, identified within the Surveillance, Epidemiology, and End Results (SEER) database (2006-2015).

Variable		Metastasectomy (n=437, 12.0%)	No metastasectomy (n=3,217, 88.0%)	p-Value
Age at diagnosis, years	Median (IQR)	62 (54-69)	64 (56-72)	<0.001
Ethnicity, n (%)	Caucasian	363 (83.1)	2645 (82.2)	0.5
	African American	38 (8.7)	335 (10.4)	
	Other	36 (8.2)	237 (7.4)	
Gender, n (%)	Male	308 (70.5)	2250 (69.9)	0.8
	Female	129 (29.5)	967 (30.1)	
Marital status, n (%)	Married	272 (62.2)	1940 (60.3)	0.9
	Never married	66 (15.1)	509 (15.8)	
	Previously married	86 (19.7)	664 (20.6)	
	Unknown	13 (3.0)	104 (3.2)	
Year of diagnosis, n (%)	2006-2010	183 (41.9)	1258 (39.1)	0.3
	2011-2015	254 (58.1)	1959 (60.9)	
Socioeconomic status, n (%) [#]	Quartile 1	112 (25.6)	826 (25.7)	0.9
	Quartile 2-4	325 (74.4)	2391 (74.3)	
Population density, n (%)	Urban	378 (86.5)	2785 (86.6)	0.9
	Rural	58 (13.3)	424 (13.2)	
	Unknown	1 (0.2)	8 (0.2)	
SEER region, n (%)	West	224 (51.3)	1627 (50.6)	0.7
	Midwest	57 (13.0)	367 (11.4)	
	North-East	52 (11.9)	407 (12.7)	
	South	104 (23.8)	816 (25.4)	
T-Stage, n (%) [*]	T1	103 (23.6)	607 (18.9)	0.001
	T2	84 (19.2)	600 (18.7)	
	T3	61 (14.0)	659 (20.5)	
	T4	52 (11.9)	487 (15.1)	
	Tx/0	137 (31.4)	864 (26.9)	
	N0/NX	312 (71.4)	2068 (64.3)	
N-Stage, n (%) [*]	N1	125 (28.6)	1149 (35.7)	0.004
	ccRCC	205 (46.9)	1258 (39.1)	
Histology, n (%)	Non-ccRCC	44 (10.1)	342 (10.6)	0.006
	NOSRCC	188 (43.0)	1617 (50.3)	
	G1/G2	11 (2.5)	322 (10.0)	
Fuhrman grade, n (%)	G3/G4	36 (8.2)	470 (14.6)	<0.001
	Unknown	390 (89.2)	2425 (75.4)	

IQR: Interquartile range; ccRCC: clear-cell renal cell carcinoma; NOS: not otherwise specified. ^{*}7th TNM (7). [#]Defined according to census tract-level socioeconomic status (SES) index provided by the SEER database.

on overall mortality (OM) in a large cohort identified within the Surveillance, Epidemiology, and End Results (SEER) database (2006-2015). Moreover, we also relied on the National Inpatient Sample (NIS) database to examine complication rates and in-hospital mortality following metastasectomy.

Materials and Methods

Within the SEER database (2006-2015) (5), our study focused on patients aged 18 years or older with primary diagnosis of mRCC [International Classification of Disease for Oncology (ICD-O) site codes C64.9] (6). Patients treated exclusively with targeted therapy and those with known information on metastasectomy status were included. Autopsy and death certificate cases were excluded.

Covariates included age, gender, ethnicity, marital status, socioeconomic status, residence area, SEER-registry region, 2017 TNM classification (7), Fuhrman grade and histological subtypes. Descriptive statistics compared metastasectomy with no metastasectomy. Subsequently, estimated annual percentage change (EAPC) tested for annual metastasectomy rate. Multivariable logistic regression models predicting metastasectomy were also fitted. Adjustment variables consisted of all available covariates. Kaplan-Meier analyses and multivariable Cox regression (MCR) models tested for OM according to metastasectomy or not. Adjustment variables consisted of all available covariates. Finally, survival analyses were repeated after 1: 4 propensity score matching (PSM). The two groups were balanced according to all available covariates.

Within the NIS database (2006-2015) (8), we focused on patients aged 18 years or older with primary diagnosis of mRCC (ICD-9 codes 189.0, 197.x, 198.x). Patients treated with metastasectomy were

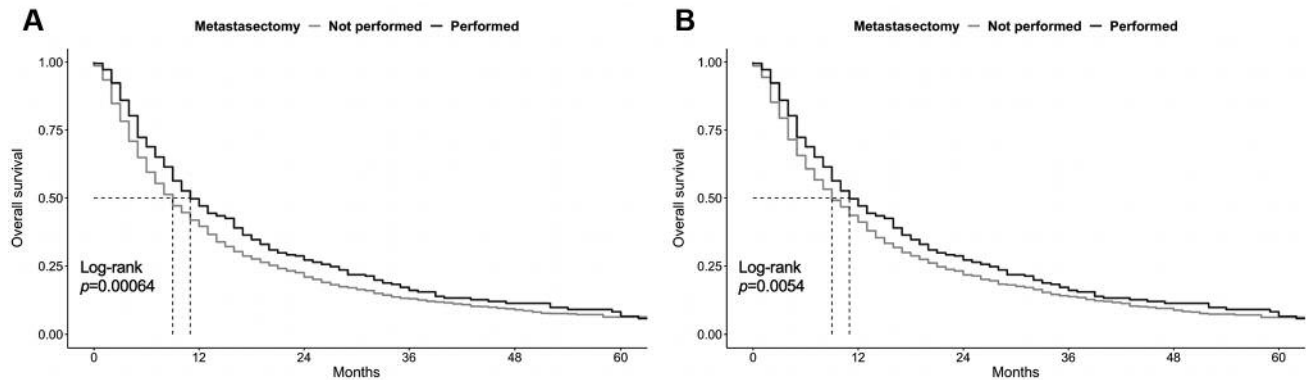


Figure 1. Kaplan-Meier curves for patients with metastatic renal cell carcinoma treated exclusively with targeted therapy identified within the Surveillance, Epidemiology and End Results database between 2006 and 2015, before (A) and after (B) 1:4 propensity score-matching, depicting overall survival rates stratified according to metastasectomy (performed, $n=3,217$; not performed= 437).

identified using concomitant codes of the site of metastases, as well as the code for the procedure corresponding to organ-specific resection, as previously described (9). Patients treated with both metastasectomy and nephrectomy (ICD-9 codes 55.4, 55.51, 55.52, 55.54) were excluded. Descriptive statistics focused on metastasectomy rates, as well as complication rates and in-hospital mortality. Subsequently, separate univariable logistic regression models assessed the association between covariates and overall complications. All results were weighted to reflect national estimates.

All statistical tests were two-sided with a level of significance set at $p < 0.05$ and performed using the R software environment for statistical computing and graphics (version 3.4.1; <http://www.r-project.org/>).

Results

Within the SEER database (2006-2015), 3,654 patients with mRCC were identified, of whom 437 (12.2%) underwent metastasectomy (Table I). Metastasectomy patients were significantly younger (62 vs. 64 years, $p < 0.001$), more frequently harbored lower T-stage tumors ($p = 0.001$), N0/NX stage ($p = 0.004$) and clear-cell histology ($p = 0.006$). Metastasectomy utilization rate was not significantly different over the study period (from 16.3 to 13.0%, EAPC=-2.3%, $p = 0.2$).

In multivariable logistic regression models, independent predictors of lower metastasectomy rate were older age [odds ratio (OR)=0.9, 95% confidence interval (CI)=0.8-0.9, $p < 0.001$], T3 (OR 0.5, 95% CI=1.4-5.8, $p < 0.001$) and T4 stages (OR=0.6, 95% CI=0.4-0.9, $p = 0.01$) and N1 stage (OR=0.7, 95% CI=0.6-0.9, $p = 0.02$).

Before 1:4 PSM, median overall survival for those who underwent metastasectomy *versus* those who did not was 11 (95% CI=10-13) compared with 9 (95% CI=8-9) months ($p = 0.0008$), respectively (Figure 1A). In MCR models predicting OM, metastasectomy was associated with lower OM [hazard ratio (HR)=0.83, 95% CI=0.73-0.94, $p = 0.002$].

After 1:4 PSM, all covariates were balanced between metastasectomy ($n=347$) and no-metastasectomy ($n=1,713$) patients. Median overall survival with PSM was 11 (95% CI=10-13) *versus* 9 (95% CI=9-10) months ($p = 0.0005$), respectively (Figure 1B). In MCR models predicting OM, metastasectomy was still significantly associated with lower OM (HR=0.80, 95% CI=0.71-0.91, $p = 0.001$).

Within the NIS database (2006-2015), 351 patients treated with metastasectomy were identified. Only 31 patients were treated with stereotactic radiosurgery metastasectomy (Table II). Metastasectomy patients had a median age of 64 years [interquartile range (IQR)=56-71], were mainly treated at teaching hospitals (62.4%) and in either medium- (62.4%) or high-volume centers (37.6%). The median length of stay was 7 days (IQR=4-11 days). Overall, complications occurred in 193 (55.5%) of the patients. The most frequent complication types were pulmonary (21.9%) and transfusions (15.7%). The in-hospital mortality rate was 4.6% (16 patients).

The most common site of metastasis was the lung (82.3%), followed by bone (24.5%), liver (15.9%), the brain (14.2%), lymph nodes (13.9%) and the adrenal glands (8.8%). Metastasectomy was predominantly performed for lung (79.2%), followed by bone (3.7%), liver (3.4%), lymph nodes (2.0%), adrenal (1.7%) and brain (1.1%) metastases. At univariable logistic regression analyses predicting overall complications, none of the examined variables reached statistical significance (all $p > 0.05$).

Discussion

Previous retrospective data suggested that select patients with favorable or intermediate risk (10) may benefit from metastasectomy after cytoreductive nephrectomy and may achieve better survival outcomes (3, 4, 11). However, to the best of our knowledge, no previous studies specifically

Table II. Descriptive characteristics of 351 patients treated with metastasectomy for metastatic renal cell carcinoma, identified within the National In-patient Sample (2006-2015).

Variable	Value
Age, years	
Median (IQR)	64 (56-71)
Year of treatment, n (%)	
2006-2010	183 (52.1)
2011-2015	168 (47.9)
Gender, n (%)	
Male	222 (63.2)
Ethnicity, n (%)	
Caucasian	223 (63.5)
African American	28 (8.0)
Other/unknown	100 (28.5)
CCI, n (%)	
0	219 (62.4)
1	79 (22.5)
≥2	53 (15.1)
Insurance, n (%)	
Medicare	155 (44.2)
Medicaid	43 (12.3)
Private	128 (36.5)
Other	25 (7.1)
Region, n (%)	
Midwest	84 (23.9)
Northeast	61 (17.4)
South	137 (39.0)
West	69 (19.7)
Income quartile, n (%) [#]	
First	95 (27.1)
Second	90 (25.6)
Third	86 (24.5)
Fourth	70 (22.8)
Annual hospital volume, n (%) [*]	
Low	0 (0)
Medium	219 (62.4)
High	132 (37.6)
Teaching status, n (%)	
Teaching	219 (62.4)
Non-teaching	132 (37.6)
Complication, n (%)	
Yes	193 (55.0)
Transfusion, n (%)	
Yes	55 (15.7)
Length of stay, days	
Median (IQR)	7 (4-11)
In hospital mortality, n (%)	
Yes	16 (4.6)

IQR: Interquartile range; CCI: Charlson Comorbidity Index. [#]Defined according to ZIPINC variable provided by the NIS database. ^{*}Defined by calculating the total number of procedures in the sample for each unique hospital identifier per year.

investigated the potential survival benefit of metastasectomy in patients with mRCC treated exclusively with targeted therapy.

Firstly, the rate of metastasectomy for patients with mRCC treated exclusively with targeted therapy was 12.0%

(437 patients). This rate is slightly inferior to those previously reported for patients previously treated with cytoreductive nephrectomy (4, 11). Nonetheless, the lower rates reported in the current study are expected in a non-cytoreductive nephrectomy-treated cohort and are in agreement with recommendations for use of metastasectomy in highly select patients (1, 2).

Secondly, metastasectomy patients were younger and more frequently harbored tumor with lower TNM stage. Additionally, higher stage and nodal involvement represented independent predictors of lower metastasectomy use. These findings also suggest that metastasectomy in patients with mRCC treated exclusively with targeted therapy is generally reserved for those with more favorable tumor phenotype.

Thirdly, metastasectomy was associated with lower OM both before (HR=0.83, $p=0.002$) and after 1: 4 PSM (HR=0.80, $p=0.001$). However, these highly statistically significant relative benefit ratios for metastasectomy were based on a short absolute benefit of only 2 months (median overall survival 11 *versus* 9 months). These median overall survival values indicate that our cohort of patients with mRCC very closely approximated the poor-risk group (12). Therefore, metastasectomy use should be critically reviewed in a multidisciplinary context owing to the short absolute survival benefit that we identified.

Fourthly, only one study previously investigated metastasectomy within the NIS (13). Conversely from Meyer *et al.* (14), we only excluded patients simultaneously treated with cytoreductive nephrectomy. Even though the vast majority of patients were treated at teaching hospitals, the overall complication rate (55.0%) and in-hospital mortality (4.6%) after metastasectomy were non-negligible. These rates were higher than those previously reported from population-based database (14) and centers of excellence (13, 15).

Despite the strengths of this study, important limitations need to be acknowledged, such as the retrospective nature, as well as the lack of information about laboratory variables, performance status, exact tumor burden, dose and duration of targeted therapy and immunotherapy.

Conflicts of Interest

All the Authors declare they have no potential conflict of interest to disclose in regard to this study.

Authors' Contributions

Conception and design: Palumbo, Karakiewicz. Acquisition of data: Palumbo, Pecoraro, Knipper, Rosiello, Tian. Analysis and interpretation of data: Palumbo, Karakiewicz, Pecoraro, Knipper, Rosiello, Tian. Drafting of the article: Palumbo, Pecoraro, Karakiewicz. Statistical analysis: Palumbo, Tian. Critical revision of the article for important intellectual content: Shariat, Simeone, Briganti, Saad, Berruti, Antonelli. Supervision: Karakiewicz. Obtaining funding/administrative support: None.

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