Survival Analyses of Patients With Metastatic Renal Cancer Treated With Targeted Therapy With or Without Cytoreductive Nephrectomy: A National Cancer Data Base Study

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ABSTRACT

Purpose

The role of cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC) has become unclear since the introduction of targeted therapies (TT). We sought to evaluate contemporary utilization rates of CN and to examine the survival benefit of CN compared with non-CN patients treated with TT.

Methods

We used the National Cancer Data Base to identify patients with clinical mRCC treated with TT between 2006 and 2013. The intervention of interest was CN. Multivariable logistic regression predicting receipt of CN was performed. Overall survival (OS) was examined using Cox regression models and incremental survival analyses were performed. Sensitivity analyses using propensity scores were conducted.

Results

Of 15,390 patients treated with TT, 5,374 (35%) underwent CN between 2006 and 2013. Patients who were younger, privately insured, treated at an academic center, and had lower tumor stage and cN0 disease were more likely to undergo CN. The median OS of CN versus non-CN patients was 17.1 (95% CI, 16.3 to 18.0 months) versus 7.7 months (95% CI, 7.4 to 7.9 months; $P < .001$). In sensitivity analyses using propensity scores adjustment in addition to other available covariates, CN patients had a lower risk of any death (hazard ratio, 0.45; 95% CI, 0.40 to 0.50; $P < .001$). The survival benefit of CN was +0.7 and +3.6 months in patients who survived ≤ 6 and ≤ 24 months, respectively, versus no CN.

Conclusion

CN is performed in three of 10 patients with mRCC who are receiving TT. Several patient and sociodemographic characteristics were associated with receipt of CN. When feasible, CN may offer an OS benefit when combined with TT.

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INTRODUCTION

Kidney cancer is among the 10 most common cancers in the United States, with 61,560 cases diagnosed in 2015.¹ Despite a significant migration toward lower-stage disease as a result of the evolution of more sophisticated imaging, three of 10 patients present with primary metastatic renal cell carcinoma (mRCC).² Historically, management of patients with mRCC included cytoreductive nephrectomy (CN) in selected patients in combination with immunotherapy, given the results of two randomized trials demonstrating an overall survival (OS) advantage of 5.8 months in a combined analysis study.³

Thereafter, a better understanding of molecular pathways for RCC led to the development, testing, and approval by the US Food and Drug Administration of several targeted therapies (TT) at the end of 2005.⁴ The significant advent of TT has blurred the role of CN in contemporary patients diagnosed with mRCC. Recent reports indicate declining utilization rates of CN in the TT era.⁵⁻⁷ This decreasing use of CN may be a result of the lack of randomized trials testing the efficacy of CN in combination with TT, the availability of systemic options, and their significant benefit. Regardless, the most up-to-date guidelines support the role of CN with TT in the appropriate clinical setting.⁸

Given the paucity of data on this topic, we sought to examine the utilization rates of CN in combination with TT in patients with primary mRCC compared with TT alone. We also sought to identify patient and sociodemographic characteristics associated with the use of CN in combination with TT. As a secondary end point, we examined OS rates of patients treated with TT and CN versus TT alone. For this purpose, we relied on the National Cancer Data Base (NCDB), which serves as a robust quality improvement mechanism for cancer programs participating in the American College of Surgeons Commission on Cancer (CoC) approvals program.⁹ Our hypothesis stated that CN use has declined over time and that those patients who receive both CN and TT have more favorable OS than patients who receive TT alone.

METHODS

Data Source

A joint initiative of the American College of Surgeons CoC and the American Cancer Society, the NCDB is a national cancer registry that was established in 1989 and serves as a comprehensive clinical surveillance resource for cancer care in the United States. The NCDB compiles data from > 1,500 commission-accredited cancer programs in the United States and Puerto Rico; it captures nearly 70% of all newly diagnosed cancers.¹⁰

Study Cohort

All patients with primary mRCC at diagnosis, who were treated with at least one TT at any time between 2006 and 2013, were identified (International Classification of Diseases for Oncology, 3rd Edition: C649, 8000-8980) and American Joint Committee on Cancer Stage Manual, 7th edition.¹⁰ Receipt of TT was recorded as single- or multiagent chemotherapy in the NCDB, as previously reported.¹¹

CN patients were identified using the surgery of primary site codes (40, 50, and 70) based on the Facility Oncology Registry Standards, which records all primary surgical treatment provided in any NCDB-affiliated institution. Conversely, patients with surgery of primary site code 0 were

grouped as non-CN patients. We selected 2006 as the starting point, after the US Food and Drug Administration's approval of sorafenib and sunitinib.⁴ Overall, 15,390 patients with mRCC treated with TT were identified (Fig 1).

Covariates

Patient covariates included age, sex, race, residence location, insurance status, annual income, and percentage of individuals without a high school diploma in patient's area of residency. Comorbidity status was determined using the Charlson-Deyo classification.¹² Metastasectomy status was extracted using "Surgical Procedure of Other Sites," which included surgery to regional and distant lymph nodes, as well as distant sites. In patients who underwent CN, the timing of CN with regard to TT, when available, was also captured and categorized as CN before TT versus CN after TT.

Provider covariates included facility type, calculated according to the number of patients diagnosed with RCC within 1 year, and comprised community center (100 to 500 cases), comprehensive community cancer center (> 500 cases), and academic (> 500 cases with available graduate medical training). Facility location was reported as New England, Atlantic, East Central, West Central, or West Pacific. Tumor characteristics included histology subtype based on International Classification of Diseases for Oncology, 3rd edition codes and categorized as clear cell (8000, 8005, 8310, 8312-8316, 8359), papillary (8260), chromophobe (8270, 8290, 8317), collecting duct (8319), and sarcomatoid (8032, 8318, 8963). Fuhrman grade was determined from a composite variable using the NCDB's tumor grade variable for cases diagnosed before 2010 and the Collaborative Stage Data Collection System Site-Specific Factor 6 for cases diagnosed in 2010 or later (Fuhrman grades 1, 2, 3, 4). Clinical tumor was classified as cT1, cT2, cT3, or cT4 and nodal stages as cN0 or cN1. Death from any cause following mRCC diagnosis was abstracted. Follow-up duration was recorded from the time of diagnosis until death or lost to follow-up.

Statistical Analyses

Baseline patient, provider, and tumor disease characteristics were compared according to CN status (CN v non-CN). The *t* test or χ^2 test were used to assess any statistical significance between the two treatment groups for continuous and categorical variables, respectively. The proportion of

Fig 1. CONSORT diagram of patient selection within the National Cancer Data Base (NCDB), 2006 to 2013. CN, cytoreductive nephrectomy; ICD, International Classification of Diseases; mRCC, metastatic renal cell carcinoma; PUF, participant user file.

Table 1. Baseline Characteristics of 15,390 Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy According to Receipt of Cytoreductive Nephrectomy Between 2006 and 2013, As Listed in the National Cancer Data Base

Factor	Overall (N = 15,390)*	No CN (n = 10,016)*	CN (n = 5,374)*	P
Age at diagnosis in years, median (IQR)	63 (55.0 to 71.0)	64.0 (56.0 to 73.0)	60.0 (53.0 to 67.0)	< .001†
Sex				.089‡
Male	10,557 (68.6)	6,824 (68.1)	3,733 (69.5)	
Female	4,833 (31.4)	3,192 (31.9)	1,641 (30.5)	
Race				< .001‡
White	12,334 (80.1)	7,916 (79.0)	4,418 (82.2)	
Black	1,521 (9.9)	1,117 (11.2)	404 (7.5)	
Hispanic	986 (6.4)	645 (6.4)	341 (6.4)	
Other	549 (3.6)	338 (3.4)	211 (3.9)	
CCI				< .001‡
0	11,232 (73.0)	7,208 (72.0)	4,024 (74.9)	
1	3,106 (20.2)	2,038 (20.3)	1,068 (19.9)	
2	1,052 (6.8)	770 (7.7)	282 (5.2)	
Insurance status				< .001‡
Government	7,750 (50.4)	5,525 (55.2)	2,225 (41.4)	
Private	6,595 (42.9)	3,760 (37.5)	2,835 (52.8)	
No insurance	786 (5.1)	540 (5.4)	246 (4.6)	
Unknown	259 (1.7)	191 (1.9)	68 (1.3)	
Facility location				.007‡
Atlantic	5,085 (33.0)	3,377 (33.7)	1,708 (31.8)	
New England	697 (4.5)	479 (4.8)	218 (4.1)	
East Central	4,079 (26.5)	2,630 (26.3)	1,449 (27.0)	
West Central	2,765 (18.0)	1,767 (17.6)	998 (18.6)	
West	2,350 (15.3)	1,516 (15.1)	834 (15.5)	
Unknown	414 (2.7)	247 (2.5)	167 (3.1)	
Facility type				< .001‡
Academic	5,598 (36.4)	3,355 (33.5)	2,243 (41.7)	
Community	1,571 (10.2)	1,115 (11.1)	456 (8.5)	
Comprehensive community	6,791 (44.1)	4,632 (46.3)	2,159 (40.2)	
Unknown	1,430 (9.3)	914 (9.1)	516 (9.6)	
Patient location				.10‡
Metro county	11,992 (77.9)	7,840 (78.3)	4,152 (77.3)	
Urban county	2,454 (15.9)	1,565 (15.6)	889 (16.5)	
Rural county	341 (2.2)	207 (2.1)	134 (2.5)	
Unknown	603 (3.9)	404 (4.0)	199 (3.7)	
Population without high school degree, %				< .001‡
> 21	2,723 (17.7)	1,843 (18.4)	880 (16.4)	
13-20.9	4,061 (26.4)	2,706 (27.0)	1,355 (25.2)	
7-12.9	5,000 (32.5)	3,187 (31.8)	1,813 (33.7)	
< 7	3,256 (21.2)	2,042 (20.4)	1,214 (22.6)	
Unknown	350 (2.3)	238 (2.4)	112 (2.1)	
Median income quartiles, \$				< .001‡
< 38,000	2,698 (17.5)	1,839 (18.4)	859 (16.0)	
38,000-47,999	3,894 (25.3)	2,557 (25.5)	1,337 (24.9)	
48,000-62,999	4,189 (27.2)	2,722 (27.2)	1,467 (27.3)	
≥ 63,000	4,252 (27.6)	2,657 (26.5)	1,595 (29.7)	
Unknown	357 (2.3)	241 (2.4)	116 (2.2)	
AJCC clinical T stage				< .001‡
T1	3,120 (20.3)	1,533 (15.3)	1,587 (29.5)	
T2	1,936 (12.6)	1,298 (13.0)	638 (11.9)	
T3	3,294 (21.4)	2,408 (24.0)	886 (16.5)	
T4	1,607 (10.4)	893 (8.9)	714 (13.3)	
Unknown	5,433 (35.3)	3,884 (38.8)	1,549 (28.8)	
AJCC clinical N stage				< .001‡
N0	6,731 (43.7)	3,832 (38.3)	2,899 (53.9)	
N1	5,111 (33.2)	3,605 (36.0)	1,506 (28.0)	
Unknown	3,548 (23.1)	2,579 (25.7)	969 (18.0)	
Histology				< .001‡
Clear cell	12,177 (79.1)	8,074 (80.6)	4,103 (76.3)	
Papillary	608 (4.0)	361 (3.6)	247 (4.6)	
Chromophobe	94 (0.6)	50 (0.5)	44 (0.8)	
Collecting duct	112 (0.7)	46 (0.5)	66 (1.2)	
Sarcomatoid	809 (5.3)	373 (3.7)	436 (8.1)	
Other	1,590 (10.3)	1,112 (11.1)	478 (8.9)	

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Table 1. Baseline Characteristics of 15,390 Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy According to Receipt of Cytoreductive Nephrectomy Between 2006 and 2013, As Listed in the National Cancer Data Base (continued)

Factor	Overall (N = 15,390)*	No CN (n = 10,016)*	CN (n = 5,374)*	P
Fuhrman grade				< .001†
1/2	1,783 (11.6)	872 (8.7)	911 (17.0)	
3/4	5,808 (37.7)	1,761 (17.6)	4,047 (75.3)	
Unknown	7,799 (50.7)	7,383 (73.7)	416 (7.7)	
Metastasectomy	1,886 (12.3)	878 (8.8)	1,008 (18.8)	< .001‡

Abbreviations: AJCC, American Joint Committee on Cancer; CN, cytoreductive nephrectomy; CCI, Charlson comorbidity index; IQR, interquartile range.

*All values are expressed as number of patients (%).

†t test.

‡ χ^2 test.

patients undergoing CN was reported for each study year, and temporal trend analysis was evaluated using the estimated annual percentage change mixed linear regression methodology.¹³

First, multivariable logistic regression models for prediction of CN were performed (n = 15,390). This was done to identify patient, socio-demographic, and preoperative clinical characteristics associated with receipt of CN. Second, we compared OS rates between CN versus non-CN patients. Because follow-up and vital status information was only available in patients diagnosed between 2006 and 2012, survival analyses were limited to 12,995 patients (instead of 15,390). Kaplan-Meier curves were used to depict OS rates between the two groups. Multivariable Cox regression models were performed for prediction of all-cause mortality between CN versus non-CN patients after adjusting for all of the aforementioned variables. Furthermore, generalized estimating equations were used to account for clustering of outcomes within facility, assuming an independent correlation structure. As a result of inherent treatment selection biases associated with the CN group, sensitivity analyses were conducted by performing a weighted propensity score analysis.

Finally, in exploratory analyses, incremental survival benefits were compared between patients who received a CN versus those who did not in patients who survived ≤ 6 , 12, 18, and 24 months, as previously described.¹⁴ All statistical analyses were performed using Stata 13.1, with a two-sided significance level set at $P < .05$. An institutional review board waiver was obtained before conducting this study, in accordance with institutional regulation when working with de-identified administrative data.

RESULTS

Baseline Characteristics

Between 2006 and 2013, 15,390 patients were treated with at least one TT (Table 1). Overall, 5,374 (35%) underwent CN. CN and non-CN patients differed with respect to age, baseline comorbidities, insurance status, and median household income, as well as facility type, tumor stage distribution, nodal stage distribution, and histologic variants (all $P < .001$). The utilization rate of CN remained stable between 2006 and 2013 (range, 32% to 34%; estimated annual percentage change, +1.01%; 95% CI, -1.64% to 3.73%; $P = .39$).

Factors Associated With CN

In multivariable logistic regression models for prediction of CN (N = 15,390), patients 60 to 69, 70 to 79, and 80 years or older (odds ratio [OR] = 0.68, 0.45, and 0.18; all $P < .001$) and patients with a Charlson comorbidity index (CCI) ≥ 2 (OR = 0.74; $P < .001$) were less likely to undergo CN than their younger (< 50 years) and

CCI 0 counterparts, respectively (Table 2). Black patients were significantly less likely to undergo CN (OR = 0.64) compared with white patients ($P < .001$). To examine if the effect of race was driven by other covariates, interaction terms between race and CCI, insurance type, facility type, and cT stage were performed, in separate models. No examined interactions were statistically significant (all $P \geq .05$). Furthermore, patients without insurance (OR = 0.76), as well as those treated at community (OR = 0.61), comprehensive community (OR = 0.72), or integrated network programs (OR = 0.79; all $P \leq .025$), were less likely to be treated with CN than Medicare/Medicaid-insured patients and those treated at academic centers. Finally, higher cT stage and patients with clinically node-positive disease were also less likely to undergo CN (Table 2).

Survival Analyses

Overall, 10,882 deaths were recorded (n = 12,995 included in survival analyses). The mean time to any death was 32.5 months (median, 17.1 months; 95% CI, 16.3 to 18.0 months) for CN versus 14.9 months (median, 7.7 months; 95% CI, 7.4 to 7.9 months) for non-CN. The 1-, 2-, and 3-year OS rates were 62.7% (95% CI, 61.3% to 64.1%), 39.1% (95% CI, 37.7% to 40.6%), and 27.7% (95% CI, 26.3% to 29.1%) versus 34.7% (95% CI, 33.7% to 35.8%), 17.1% (95% CI, 16.2% to 17.9%), and 9.8% (95% CI, 9.1% to 10.5%) for CN and non-CN patients, respectively (log-rank $P < .001$; Fig 2). In multivariable Cox regression analyses, CN patients had a lower risk of any death, after adjusting for all available covariates (hazard ratio [HR], 0.49; 95% CI, 0.46 to 0.52; $P < .001$; Table 3). To minimize treatment selection biases, propensity scores were adjusted in sensitivity analyses. The findings remained virtually unchanged (Appendix Tables A1, A2, and A3, online only).

In a subgroup analysis focusing on individuals treated exclusively with CN who had available data on timing of CN and survival (n = 4,223), 88.4% and 11.6% received CN before and after TT, respectively. The 1-, 2-, and 3-year OS rates were 61.2%, 37.8%, and 26.6% for patients who underwent CN before TT versus 73.3%, 48.1%, and 35.3% for patients who underwent CN after TT, respectively (log-rank $P < .001$; Fig 3).

Incremental Benefit Analysis

An OS benefit from CN was observed in all examined survival times (Table 4). The longer an individual survived, the greater the

Table 2. Multivariable Logistic Regression Predicting Receipt of Cytoreductive Nephrectomy Adjusting for Clustering Within Hospital and Multiple Patient and Hospital Characteristics in Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy Between 2006 and 2013, As Listed in the National Cancer Data Base (N = 15,390)

Factor	Odds Ratio	95% CI	P
Race			
White	1.0 (Ref)	0.56 to 0.74	< .001
Black	0.64	0.79 to 1.09	.364
Hispanic	0.93	0.86 to 1.25	.709
Other	1.04		
Age at diagnosis, years			
< 50	1.0 (Ref)		
50-59	0.88	0.77 to 1.00	.050
60-69	0.68	0.60 to 0.77	< .001
70-79	0.45	0.39 to 0.52	< .001
≥ 80	0.18	0.14 to 0.22	< .001
Sex			
Male	1.0 (Ref)		
Female	1.01	0.94 to 1.09	.776
CCI			
0	1.0 (Ref)		
1	1.00	0.91 to 1.10	.990
≥ 2	0.74	0.64 to 0.86	< .001
Insurance status			
Medicare/Medicaid	1.0 (Ref)		
Private	1.27	1.17 to 1.38	< .001
No insurance	0.76	0.63 to 0.92	.004
Unknown	0.72	0.49 to 1.06	.097
Facility location			
Atlantic	1.0 (Ref)		
New England	0.88	0.72 to 1.09	.245
East Central	1.13	0.99 to 1.29	.079
West Central	1.08	0.93 to 1.25	.303
West	1.09	0.93 to 1.27	.276
Unknown	0.73	0.55 to 0.97	.031
Facility type			
Academic	1.0 (Ref)		
Community	0.61	0.52 to 0.72	< .001
Comprehensive community	0.72	0.64 to 0.80	< .001
Integrated network program	0.79	0.64 to 0.97	.025
Unknown	1.30	1.13 to 1.49	< .001
Patient location			
Metro county	1.0 (Ref)		
Urban county	1.10	0.99 to 1.23	.086
Rural county	1.38	1.07 to 1.80	.015
Unknown	0.99	0.76 to 1.29	.913
Median income quartiles, \$			
< 38,000	1.0 (Ref)		
38,000-47,999	1.07	0.95 to 1.21	.282
48,000-62,999	1.04	0.91 to 1.19	.595
≥ 63,000	1.12	0.95 to 1.32	.188
Unknown	1.57	0.39 to 6.39	.528
Population without high school degree in patient's area of residence, %			
≥ 21	1.0 (Ref)		
13-20.9	1.01	0.89 to 1.14	.928
7-12.9	1.13	0.99 to 1.30	.074
< 7	1.15	0.97 to 1.37	.100
Unknown	0.68	0.15 to 3.04	.613
AJCC clinical T stage			
T1	1.0 (Ref)		
T2	0.46	0.40 to 0.52	< .001
T3	0.35	0.31 to 0.40	< .001
T4	0.70	0.60 to 0.82	< .001
Unknown	0.40	0.35 to 0.45	< .001

(continued in next column)

Table 2. Multivariable Logistic Regression Predicting Receipt of Cytoreductive Nephrectomy Adjusting for Clustering Within Hospital and Multiple Patient and Hospital Characteristics in Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy Between 2006 and 2013, As Listed in the National Cancer Data Base (N = 15,390) (continued)

Factor	Odds Ratio	95% CI	P
AJCC clinical N stage			
N0	1.0 (Ref)		
N1	0.51	0.47 to 0.56	< .001
Unknown	0.56	0.50 to 0.63	< .001
Year of diagnosis			
2006	1.0 (Ref)		
2007	0.93	0.78 to 1.10	.401
2008	1.23	1.03 to 1.47	.019
2009	1.08	0.90 to 1.29	.391
2010	1.18	0.98 to 1.43	.079
2011	1.08	0.90 to 1.31	.391
2012	1.13	0.94 to 1.36	.182
2013	1.06	0.88 to 1.26	.552

Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson comorbidity index; Ref, reference.

OS benefit of CN (+0.7 months in patients who survived ≤ 6 months versus +3.6 months in patients who survived ≤ 24 months). Even after adjusting for all other covariates, CN remained statistically significantly associated with better OS outcomes than non-CN. Moreover, the beneficial effect of CN on mortality increased with increasing incremental OS time: HR from 0.71 (95% CI, 0.65 to 0.78) in ≤ 6 months OS to 0.62 (95% CI, 0.59 to 0.66) in ≤ 24 months OS; all $P < .001$.

DISCUSSION

According to national guidelines, CN before systemic therapy is recommended in patients with potentially surgically resectable primary cancer.⁸ These recommendations are based on the Southwest Oncology Group and European Organisation for Research and Treatment of Cancer randomized trials in patients with metastatic disease who underwent nephrectomy followed by interferon therapy versus interferon alone.^{15,16} Although there is an ongoing clinical trial assessing the role of CN with TT (Clinical Trial to Assess the Importance of Nephrectomy [CARMENA]), existing data for CN in this context have thus far been infrequently examined. After the immunotherapy era, the question persists of whether CN should remain an integral part of the treatment management of patients with mRCC. The objective of the current study was to examine contemporary utilization rates of CN in combination with TT within a large and robust sample cohort. Secondary and exploratory analyses include survival and incremental survival benefit.

Several findings were noteworthy. First, we found that CN use was stable between 2006 and 2012; performance of CN was relatively seldom in approximately three of 10 patients with mRCC treated with TT. Second, several of the examined patient and sociodemographic characteristics, unrelated to the patient's disease, were also shown to be associated with receipt of CN. For example, black patients and Medicare/Medicaid/uninsured patients were less likely to undergo CN. Third, our results revealed

Fig 2. Kaplan-Meier survival analyses of patients with metastatic renal cell carcinoma treated with targeted therapy stratified according to cytoreductive nephrectomy (CN) status (yes or no), National Cancer Data Base, 2006 to 2012. Data were restricted to 12,995 patients with no missing information on vital status or follow-up time.

a significant OS advantage for patients receiving both CN and TT compared with TT alone (median OS, 17.1 months; 95% CI, 16.3 to 18.0 months *v* 7.7 months; 95% CI, 7.4 to 7.9 months). Finally, the survival advantage of patients who underwent surgical resection was not only maintained compared with non-CN patients but significantly augmented with increasing lengths of survival even after adjusting for all other covariates (HR from 0.71 to 0.62; all $P < .001$).

The utilization trends of CN reported in the current study contrast with those from previous reports that showed a declining use of CN in the TT era. For example, Conti et al,⁶ using the SEER database of patients with mRCC diagnosed between 1993 and 2010, found that starting in 2005, the utilization rate of CN decreased by 0.6% per year (annual percentage change, -1.8%). Although our overall rates of CN are similar, a few reasons can explain the difference found in trends. First, our cohort was composed of only patients who received systemic therapy; hence, trends in systemic therapy use could have influenced our results. Additionally, we provide a more contemporary evaluation of CN rates, and we rely on a larger sample size of CNs per year.

Although our report suggests an overall stabilization of CN use with TT in recent years, the overall rate of CN observed in the current study (approximately 30%) was lower than the overall rate of CN observed in data originating from centers of excellence (approximately 58% to 85%).^{14,17,18} This may be even more worrisome, considering that the NCDB is a sample of patients treated by cancer-accredited programs with a minimum threshold of 100 cases per year. The obvious contrast in utilization rates of CN with TT in the population-based versus academic setting is disconcerting, because it may suggest underuse of CN in the general population. This becomes even more problematic when considering that certain patient and sociodemographic characteristics (eg, race, insurance) unrelated to clinical factors were found to be associated with receipt of CN in the current cohort.

Regarding survival analyses, the current study corroborates the survival benefit of CN with TT compared with TT alone, as previously reported. Using multi-institutional data from the International Metastatic Database Consortium, Choueiri et al¹⁹

showed that CN patients had improved OS compared with non-CN patients treated with vascular endothelial growth factor therapy (19.8 *v* 9.4 months; HR, 0.44; $P < .01$). Similarly, an updated report from Heng et al¹⁴ showed that the median OS of patients with mRCC treated with TT with CN versus without CN was 20.6 versus 9.5 months, respectively ($P < .001$). Other reports relying on population-based cohorts have also suggested improved OS in CN patients without providing actual information on the use of TT.²⁰⁻²² Therefore, the purported survival benefit of CN compared with non-CN patients in those reports merely assumes that patients received TT. In addition, those reports did not contain information on comorbidities, performance status, and other clinical variables, which may render comparative effectiveness of the two groups substantially unfair, because patients with poor health are unlikely to be considered for CN.

It is noteworthy that patients who underwent CN after TT had better OS compared with those who underwent CN before TT. That being said, caution is warranted when interpreting such results because of the limited sample size and significant treatment selection bias of how clinicians opted to administer TT, that is, before or after CN. Ultimately, the results of the EORTC-30073-GUCG trial (NCT01099423) will be better at elucidating the question of timing of CN with respect to TT.

To our knowledge, this study is the largest sample size to date showing that CN has an OS benefit in patients treated with TT, while adjusting for other factors. However, careful patient selection remains critical in determining if patients will benefit from CN. The surgery, although safe, is associated with non-negligible complications and perioperative mortality rates.²³⁻²⁵ Patients with poor survival outcomes or those with a rapidly progressing disease are less likely to benefit from CN. For example, Choueiri et al¹⁹ found that patients with poor risk features (as defined according to the International Metastatic Database Consortium criteria) and patients with poor performance status²⁶ did not benefit from CN. The National Comprehensive Cancer Network guidelines endorse the preoperative risk factors identified by Culp et al²⁷ that are associated with the likelihood of CN benefit, in particular for patients with lung-only metastases, good prognostic features, and good performance status. However, this model awaits external validation. Unfortunately, we could not assess the presence of the identified risk factors in previous studies, which prevented us from validating the selection criteria developed by Culp et al.²⁷ Nonetheless, the current study may be used to remind clinicians to adopt a rigorous selection criteria in individuals for whom systemic therapy is planned. Finally, it is important to reiterate that the current findings are applicable only to patients with a potentially surgically resectable primary tumor mass who are planning to undergo systemic therapy. The current findings do not suggest CN for all-comers.

The current study is not without limitations. First, the analyses are retrospective in nature; this comes with an unavoidable selection bias that is prevalent in all nonprospective, non-randomized studies. Specific to this point, it is essential to recognize that the NCDB only includes CoC-accredited hospitals. It may be plausible that some patients with mRCC diagnosed at a CoC hospital then receive treatment at a non-CoC hospital, which would be considered as non-CN according to our analyses. Furthermore, patients diagnosed at a CoC hospital who then

Table 3. Multivariable Cox Regression Model Adjusted For All Covariates Estimating Overall Mortality in Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy Between 2006 and 2012, As Listed in the National Cancer Data Base (n = 12,995)

Factor	HR	95% CI	P
Cytoreductive nephrectomy			
No	Ref		
Yes	0.49	0.46 to 0.52	< .001
Age, years			
< 50	Ref		
50-59	0.98	0.91 to 1.05	.584
60-69	0.92	0.85 to 0.98	.014
70-79	0.98	0.91 to 1.07	.713
≥ 80	1.06	0.95 to 1.17	.287
Sex			
Male	Ref		
Female	0.99	0.95 to 1.03	.713
Race			
White	Ref		
Black	1.04	0.96 to 1.12	.350
Hispanic	0.82	0.75 to 0.89	< .001
Other	0.91	0.81 to 1.03	.141
CCI			
0	Ref		
1	1.11	1.06 to 1.17	< .001
≥ 2	1.17	1.08 to 1.26	< .001
Population without high school degree in patient's area of residence, %			
≥ 21	Ref		
13-20.9	0.93	0.87 to 0.99	.027
7-12.9	0.95	0.89 to 1.03	.207
< 7	0.94	0.86 to 1.03	.171
Unknown	0.38	0.25 to 0.57	< .001
Median income quartiles, \$			
< 38,000	Ref		
38,000-47,999	1.04	0.97 to 1.12	.225
48,000-62,999	1.04	0.97 to 1.12	.256
≥ 63,000	1.00	0.91 to 1.09	.919
Unknown	3.19	2.17 to 4.68	< .001
Insurance status			
Medicare/Medicaid	Ref		
Private	0.92	0.88 to 0.97	.001
No insurance	0.92	0.84 to 1.15	.111
Unknown	0.98	0.84 to 1.15	.822
Facility location			
Atlantic	Ref		
New England	1.03	0.92 to 1.15	.595
East Central	1.10	1.04 to 1.17	.001
West Central	1.05	0.99 to 1.12	.126
West	1.03	0.97 to 1.11	.327
Unknown	0.87	0.75 to 1.01	.071
Facility type			
Academic	Ref		
Community	1.10	1.02 to 1.18	.013
Comprehensive community	1.12	1.07 to 1.18	< .001
Integrated network program	1.09	0.97 to 1.22	.134
Unknown	1.25	1.17 to 1.33	< .001
Patient location			
Metro county	Ref		
Urban county	1.02	0.96 to 1.09	.508
Rural county	0.98	0.84 to 1.13	.752
Unknown	1.12	0.98 to 1.29	.104
AJCC clinical T stage			
T1	Ref		
T2	1.02	0.95 to 1.08	.632
T3	1.03	0.97 to 1.09	.399
T4	1.02	0.95 to 1.10	.551
Unknown	0.99	0.93 to 1.05	.668

(continued in next column)

Table 3. Multivariable Cox Regression Model Adjusted For All Covariates Estimating Overall Mortality in Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy Between 2006 and 2012, As Listed in the National Cancer Data Base (n = 12,995) (continued)

Factor	HR	95% CI	P
AJCC clinical N stage			
N0	Ref		
N1	1.42	1.36 to 1.50	< .001
Unknown	1.21	1.14 to 1.27	< .001
Year of diagnosis			
2006	Ref		
2007	1.07	0.98 to 1.17	.143
2008	1.07	0.98 to 1.17	.112
2009	1.09	1.00 to 1.19	.043
2010	1.05	0.97 to 1.15	.236
2011	0.92	0.87 to 1.04	.275
2012	0.97	0.88 to 1.06	.470
Histology			
Clear cell	Ref		
Papillary	1.03	0.93 to 1.15	.550
Chromophobe	0.90	0.70 to 1.18	.451
Collecting duct	1.72	1.44 to 2.05	< .001
Sarcomatoid	1.75	1.59 to 1.93	< .001
Other	1.31	1.23 to 1.40	< .001
Fuhrman grade			
1/2	Ref		
3/4	1.41	1.32 to 1.50	< .001
Unknown	1.21	1.14 to 1.29	< .001
Metastasectomy			
No	Ref		
Yes	0.87	0.82 to 0.92	< .001
Unknown	1.12	0.88 to 1.43	.351

Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson comorbidity index; HR, hazard ratio; Ref, reference.

underwent systemic therapy at a non-CoC hospital would also be completely missed in our database. That said, the current results do not strongly diverge from previously published data.

We attempted to address the inherent selection bias by performing propensity analyses that adjust for treatment-related selection bias. However, we recognize the limitations of propensity adjustment. Ultimately, the results of the randomized trial (Clinical

Fig 3. Kaplan-Meier survival analyses of patients with metastatic renal cell carcinoma treated with cytoreductive nephrectomy and targeted therapy (TT) stratified according to timing of surgery (before or after systemic therapy), National Cancer Data Base, 2006 to 2012. Data were restricted to 4,223 patients with available information on timing of surgery and targeted therapy.

Table 4. Incremental Survival Analysis With Cytoreductive Nephrectomy Stratified by Survival Time in Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy Between 2006 and 2012, As Listed in the National Cancer Data Base (n = 12,995)

OS (months)	Median OS (m)		Incremental Benefit (months)	P (log-rank)	HR (95% CI)*
	No CN	CN			
≤ 6	3.32 n = 3,456	4.04 n = 727	+0.72	< .001	0.71 (0.65 to 0.78) P < .001
≤ 12	4.67 n = 5,394	6.51 n = 1,677	+1.84	< .001	0.66 (0.62 to 0.71) P < .001
≤ 18	5.45 n = 6,307	8.25 n = 2,294	+2.80	< .001	0.65 (0.61 to 0.69) P < .001
≤ 24	5.85 n = 6,737	9.46 n = 2,678	+3.61	< .001	0.62 (0.59 to 0.66) P < .001

Abbreviations: CN, cytoreductive nephrectomy; HR, hazard ratio; OS, overall survival.

*Adjusted for age, sex, race, Charlson comorbidity index, education, income, insurance, type and location of facility, cT stage, cN stage, year of diagnosis, histology, Fuhrman grade, and metastasectomy status.

Trial to Assess the Importance of Nephrectomy [CARMENA], NCT00930033) evaluating the role of CN with sunitinib or sunitinib alone will represent the strongest level of evidence for CN in the TT era. However, the trial may be underpowered to detect a true OS benefit with the availability of many systemic therapies, a relatively small sample size of 576 patients, and an accrual period of 10 years.²⁸ Hence, by the time that results are available, systemic treatment of mRCC may have evolved.

Second, the NCDB does not contain information on important preoperative laboratory variables that have been shown to be independent prognostic factors (eg, albumin, lactate dehydrogenase) and performance status. Third, the database does not provide the exact TT used (eg, vascular endothelial growth factor or mammalian target of rapamycin inhibitors) nor does it provide information on lines of treatment. Fourth, we could not examine cancer control outcomes, such as cause-specific mortality or progression-free survival. However, OS remains a predominant end point for comparative effectiveness studies. Fifth, we extracted patients with metastatic disease at the time of database entry; it is possible that some patients had undergone CN at another center and hence represent metachronous metastatic disease.

To conclude, our findings suggest that on a population-based level, three of 10 patients with mRCC treated with TT undergo CN.

Several patient and sociodemographic factors were associated with receipt of CN. OS was more favorable in patients who underwent CN and TT compared with TT alone. Careful patient selection remains warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Survival Analyses of Patients With Metastatic Renal Cancer Treated With Targeted Therapy With or Without Cytoreductive Nephrectomy: A National Cancer Data Base Study

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Appendix

Sensitivity analyses of weighted propensity score methodologies.

Table A1. Standardized Mean Differences Before and After Cytoreductive Nephrectomy: Propensity Score Weighting in 15,390 Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy Between 2006 and 2013, As Listed in the National Cancer Data Base

Factor	Standardized Mean Difference Before Propensity Weighting (%)	Standardized Mean Difference After Propensity Weighting (%)
Age at diagnosis	−35.9	−3.3
Sex		
Male	−2.9	0.3
Female		
Race		
White	−2.9	0.1
Black		
Hispanic		
CCI		
0	−9.1	−0.2
1		
2		
Insurance status		
Government		
Private	−26.7	0.4
No insurance		
Unknown		
Facility location		
Atlantic		
New England		
East Central	5.7	0.9
West Central		
West		
Unknown		
Facility type		
Academic		
Community	−11.3	0.1
Comprehensive community		
Unknown		
Patient location		
Metro county		
Urban county	1.1	0.9
Rural county		
Unknown		
Population without high school degree, %	7.0	−0.7
≥ 21		
13-20.9		
7-12.9		
< 7		
Unknown		
Median income quartiles, \$		
< 38,000		
38,000-47,999	7.2	−0.4
48,000-62,999		
≥ 63,000		
Unknown		

(continued in next column)

Table A1. Standardized Mean Differences Before and After Cytoreductive Nephrectomy: Propensity Score Weighting in 15,390 Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy Between 2006 and 2013, As Listed in the National Cancer Data Base (continued)

Factor	Standardized Mean Difference Before Propensity Weighting (%)	Standardized Mean Difference After Propensity Weighting (%)
AJCC clinical T stage		
T1		
T2	−27.7	0.5
T3		
T4		
Unknown		
AJCC clinical N stage		
N0	−30.0	1.5
N1		
Unknown		

Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson comorbidity index.

Table A2. Survival Times According to Receipt of Cytoreductive Nephrectomy in Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy Between 2006 and 2012, As Listed in the National Cancer Data Base, After Inverse Probability Weighting With Propensity Score Adjustments

Survival Time (years)	CN % Surviving	No CN % Surviving	<i>P</i>
1	61.4	35.1	< .001
2	38.1	17.4	
3	26.8	10.1	

Abbreviation: CN, cytoreductive nephrectomy.

Table A3. Multivariable Adjusted Cox Regression Model Using Inverse Probability Weighting With Propensity Score Estimating Overall Mortality in Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy Between 2006 and 2012, As Listed in the National Cancer Data Base*

Cytoreductive Nephrectomy	HR	95% CI	<i>P</i>
No			
Yes	Ref 0.48	0.45 to 0.51	< .001

Abbreviations: HR, hazard ratio, Ref, reference.

*Adjusted for inverse probability weighting and histology, Fuhrman grade, and metastasectomy.