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Cytoreductive nephrectomy in patients with metastatic renal cell carcinoma and venous thrombus—Trends and effect on overall survival

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Abstract

Purpose: Patients with metastatic renal cell carcinoma (mRCC) commonly present with tumor thrombi in the renal vein and inferior vena cava (IVC). The **benefit** of cytoreductive nephrectomy (CN) in this population is **unclear** and the effect on overall survival (OS) has been incompletely evaluated.

Materials and Methods: We queried the National Cancer Database from 2010 to 2013 for patients diagnosed with mRCC and tumor thrombi, which was defined as renal vein, infradiaphragmatic IVC, or supradiaphragmatic IVC. Descriptive statistics were performed and associations between clinicopathologic variables and utilization of CN were analyzed. Patients were matched on the receipt of CN and Kaplan-Meier analyses and multivariable Cox proportional hazards models were used to estimate survival.

Results: In total, 8,629 patients were found to have mRCC during the study period. Approximately 27% ($n = 2{,}376$) had tumor thrombus. Tumor thrombus was associated with increased rates of CN utilization, however rates decreased as thrombus level increased. In a matched Kaplan-Meier analysis, CN was associated with improved OS in patients without thrombus, **and with** renal vein **or** infradiaphragmatic thrombus (all $P < 0.01$). Patients with supradiaphragmatic thrombus did not benefit from CN ($P = 0.46$). This effect was confirmed in a Cox proportional hazards model.

Conclusions: Tumor thrombus is common in patients with mRCC. OS is poor, and patient and tumor specific factors influence the use of CN. Despite discrepancies in utilization, CN is associated with improved OS, although this effect appears to be limited to those with mRCC and tumor thrombus limited to the renal vein and infradiaphragmatic IVC.

Keywords: Renal cell carcinoma; Tumor thrombus; Cytoreduction surgical procedures; Outcomes; Survival analysis

1. Introduction

Cytoreductive nephrectomy (CN) is an important treatment option for patients presenting with metastatic renal cell carcinoma (mRCC), though recent studies have suggested that patient selection is critical, as those with poor risk disease are less likely to benefit from surgery [1–3]. Patients with mRCC have a high prevalence (29%–55%) of concurrent tumor thrombus with extension into the renal vein or inferior vena cava [4–6]. While the role of nephrectomy with tumor thrombectomy in patients with nonmetastatic disease has been well established, few contemporary studies have been conducted examining the benefit of CN in patients

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with mRCC and tumor thrombus. Additionally, use of CN has decreased in the era of targeted therapy, though because targeted therapy generally has little effect on tumor thrombi, CN likely will remain an important treatment modality for this subset of patients with mRCC [7].

Several small, contemporary studies have examined oncologic outcomes of CN in mRCC patients with tumor thrombus, but with conflicting results [6,8–12]. These series have mainly evaluated feasibility, survival with respect to the level of tumor thrombus, and complications. Importantly, there have been no recent studies that have compared survival between those who did or did not receive CN in this population. Ultimately, tumor thrombectomy at the time of CN adds complexity and risk with significant morbidity compared to nephrectomy alone, with increased operative time, blood loss, hospital stays, and resultant cardiac, renal, and respiratory complications [11]. These risks may delay or prevent patients from receiving systemic therapy or may alone attenuate the benefit of CN.

Thus, we sought to characterize the current usage of CN as well as compare outcomes of CN vs. no CN in a large, contemporary hospital-based registry of patients with mRCC and tumor thrombus.

2. Materials and methods

2.1. Data source

The National Cancer Database (NCDB) is a hospital registry-based database compiled from more than 1,500 Commission on Cancer accredited centers, and is sponsored jointly by the American College of Surgeons and the American Cancer Society. The NCDB captures more than 70% of newly diagnosed cancers in the United States and represents more than 34 million historical records [13].

2.2. Study population

Patients with a primary diagnosis of RCC were identified in the NCDB database (site code C649). Patients with metastases were identified as having clinical and/or pathologic M1 disease. Level of tumor thrombus was identified by the code for extension and was defined as renal vein (codes 600, 601), IVC below the diaphragm (code 610), and IVC above the diaphragm (code 620, 645). Histology was limited to clear cell (codes 8000, 8005, 8310, 8312, 8313, 8314, 8315, 8316, 8959), papillary (codes 8050, 8260), chromophobe (codes 8270, 8290, 8317), sarcomatoid (codes 8032, 8318, 8963), collecting duct (code 8319), and other variant histology (codes 8041, 8240, 8255, 8320, 8323). Cytoreductive surgery was limited to radical nephrectomy (codes 40, 50, 70, and 80). The study period selected was 2010 to 2013 as the code for tumor extension began in 2010 and we limited our analysis to 2013 to allow for at least 1 year of follow-up (Fig. 1).

2.3. Study variables

Our independent variables of interest were the presence and level of tumor thrombus (none, renal vein, infradiaphragmatic, and supradiaphragmatic thrombus) and the use of CN in patients with mRCC. Other covariates included patient specific demographics, such as age, gender, race, Charlson-Deyo comorbidity classification (CDCC), insurance status, treatment facility type (community, academic, or integrated network), income (high, low, and unknown), percent without high school diploma, US region (East, Central, West, and unknown), and urban/metropolitan/rural residence status. Pathologic characteristics included tumor size (categorized as <4 cm, 4–7 cm, and >7 cm), histologic subtype (clear cell, papillary, chromophobe, collecting duct, sarcomatoid, other variants, and unknown), and location of metastasis (lung only vs. all other). Metastasectomy (surgical treatment to nonprimary kidney site) and the receipt of any systemic therapy (defined as chemotherapy, which captures targeted therapy, or immunotherapy) were also tabulated. For patients who received systemic therapy and underwent surgery, the sequence of each was recorded (before surgery, after surgery, before and after surgery). Our dependent variable and primary outcome was overall survival (OS).

2.4. Statistical analysis

We first performed descriptive statistics on patients mRCC stratified by the extent of tumor thrombus. We then focused on CN in mRCC patients with and without tumor thrombus. To balance preoperative confounding variables in this population, we calculated propensity scores predicting receipt of CN and performed one-to-one nearest neighbor matching between those who underwent CN and those who did not undergo CN. Covariates associated with the treatment (receipt of CN) and the outcome (OS) was included in the matching algorithm [14]. We attempted to balance the burden of metastatic disease by matching patients with lung metastasis only vs. all other metastases. We used the percent standardized differences to assess covariate balance in baseline characteristics between groups. A standardized difference ≤10% indicates a negligible imbalance in covariates between groups [15]. To account for guarantee-time bias, we constructed 90-day conditional landmark survival curves on the matched cohorts stratified by thrombus level using the Kaplan-Meier method [16]. Next, a Cox multivariable regression model for each level of thrombus was constructed to evaluate OS between treatments in the matched cohorts. The unique Facility ID was used to account for random effects. Study approval was obtained by the institutional review board (IRB# 042503). All statistical analyses were performed with Stata statistical software version 14 (StataCorp, College Station, TX).

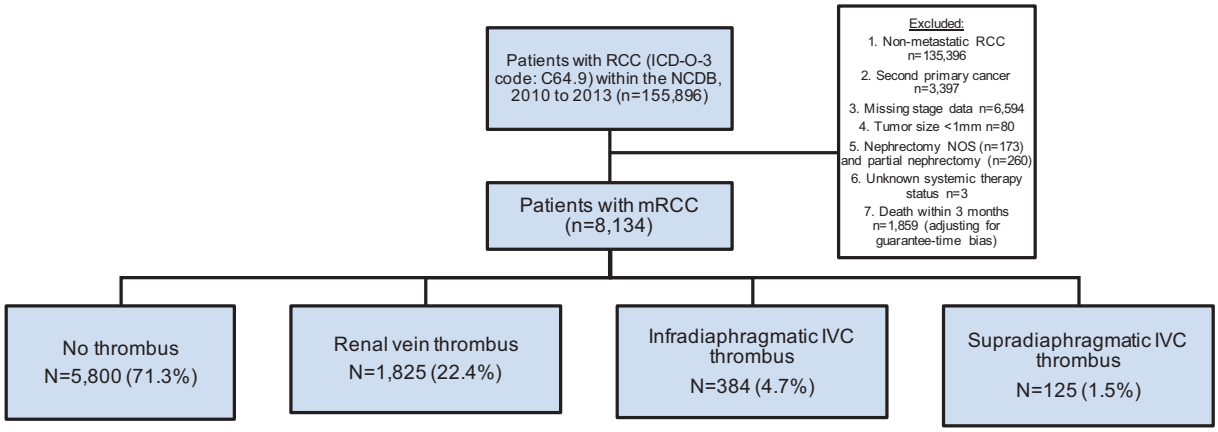

Fig. 1. Patient cohort.

3. Results

A total of 8,134 patients met our inclusion criteria. Clinical covariates stratified by receipt of CN are presented in Table 1. Tumor thrombus was present in 28.7% (2,334 of 8,134) of patients. Of these cases, tumor thrombus was present in the renal vein, infradiaphragmatic IVC, and supradiaphragmatic IVC in 78.2% (1,825 of 2,334), 16.5% (384 of 2,334), and

Table 1
Baseline demographics and standardized differences following matching of cohort on propensity for receipt of CN in patients with mRCC

	Unmatched ohort				Standardized difference	
Variable	Overall	No CN	CN	*P* value	Unmatched	Matched
No. patients	8,134 (100)	2,839 (34.9)	5,295 (65.1)	–	–	–
Age, years						
<65	4,901 (60.3)	1,451 (51.1)	3,450 (65.2)	<0.01	−35.5	1.6
65–79	2,700 (33.2)	1,050 (37.0)	1,650 (31.2)			
≥80	533 (6.6)	338 (11.9)	195 (3.7)			
Mean age, year (SD)	61.7 (11.5)	64.4 (12.2)	60.3 (10.8)	<0.01	–	–
Gender						
Male	5,576 (68.6)	1,878 (66.2)	3,698 (69.8)	<0.01	−7.9	2.2
Female	2,558 (31.4)	961 (33.8)	1,597 (30.2)			
Race						
White	6,273 (77.1)	2,097 (73.9)	4,176 (78.9)	<0.01	−6.7	−0.4
Black	658 (8.1)	306 (10.8)	352 (6.6)			
Hispanic/other	890 (10.9)	332 (11.7)	558 (10.5)			
Unknown	313 (3.8)	104 (3.7)	209 (3.9)			
CDCC						
0	5,866 (72.1)	1,980 (69.7)	3,886 (73.4)	<0.01	−10.7	−0.2
1	1,735 (21.3)	621 (21.9)	1,114 (21.0)			
≥2	533 (6.6)	238 (8.4)	295 (5.6)			
Insurance						
Medicare	3,023 (37.2)	1,273 (44.8)	1,750 (33.1)	<0.01	6.0	0.6
Private	3,750 (46.1)	1,022 (36.0)	2,728 (51.5)			
Medicaid/other	791 (9.7)	301 (10.6)	490 (9.3)			
None	445 (5.5)	197 (6.9)	248 (4.7)			
Unknown	125 (1.5)	46 (1.6)	79 (1.5)			
Income						
High	4,705 (57.8)	1,567 (55.2)	3,138 (59.3)	<0.01	−8.9	−2.8
Low	3,323 (40.9)	1,224 (43.1)	2,099 (39.6)			
Unknown	106 (1.3)	48 (1.7)	58 (1.1)			
Percent with no high school degree						
≥29%	1,410 (17.3)	545 (19.2)	865 (16.3)	<0.01	10.9	−0.1
20%–28.9%	1,834 (22.5)	673 (23.7)	1,161 (21.9)			
14%–19.9%	1,928 (23.7)	692 (24.4)	1,236 (23.3)			
<14%	2,613 (32.1)	801 (28.2)	1,812 (34.2)			
Unknown	348 (4.3)	128 (4.5)	221 (4.2)			

(*continued*)

Table 1 (***Continued***)

Variable	Unmatched ohort			*P* value	Standardized difference	
	Overall	No CN	CN		Unmatched	Matched
Region						
East	3,133 (38.5)	1,175 (41.4)	1,958 (37.0)	<0.01	9.1	−2.0
Central	3,553 (43.7)	1,195 (42.1)	2,358 (44.5)			
West	1,229 (15.1)	406 (14.3)	823 (15.5)			
Unknown	219 (2.7)	63 (2.2)	156 (2.9)			
Urban/rural						
Rural	2,15 (2.6)	77 (2.7)	138 (2.6)	<0.01	−0.0	−1.2
Metropolitan	6,242 (76.7)	2197 (77.4)	4,045 (76.4)			
Urban	1,387 (17.1)	441 (15.5)	946 (17.9)			
Unknown	290 (3.6)	124 (4.4)	166 (3.1)			
Facility type						
Community	3,546 (43.6)	1,347 (47.4)	2,199 (41.5)	<0.01	10.6	2.8
Academic	3,603 (44.3)	1,171 (41.2)	2,432 (45.9)			
Integrated network	766 (9.4)	258 (9.1)	508 (9.6)			
Unknown	219 (2.7)	63 (2.2)	156 (2.9)			
Histology						
Clear cell	6,528 (80.3)	2,352 (82.8)	4,176 (78.9)	<0.01	2.9	−0.6
Papillary	358 (4.4)	112 (3.9)	246 (4.6)			
Chromophobe	75 (0.9)	11 (0.4)	64 (1.2)			
Collecting duct	53 (0.7)	11 (0.4)	42 (0.8)			
Sarcomatoid	456 (5.6)	101 (3.6)	355 (6.7)			
Other	302 (3.7)	22 (0.8)	280 (5.3)			
Unknown	362 (4.5)	230 (8.1)	132 (2.5)			
Size, cm (SD)	9.2 (5.1)	8.2 (4.3)	9.6 (5.4)	<0.01	–	–
Size category						
<4 cm	3,648 (44.8)	1144 (40.3)	2,504 (47.3)	<0.01	−19.6	−0.4
4−7 cm	1,945 (23.9)	750 (26.4)	1,195 (22.6)			
>7 cm	2,188 (26.9)	664 (23.4)	1,524 (28.8)			
Unknown	353 (4.3)	281 (9.9)	72 (1.4)			
Laterality						
Left	4,103 (50.4)	1364 (48.1)	2,739 (51.7)	<0.01	−14.7	−1.5
Right	3,920 (48.2)	1382 (48.7)	2,538 (47.9)			
Bilateral	42 (0.5)	35 (1.2)	7 (0.1)			
Unknown	69 (0.9)	58 (2.0)	11 (0.2)			
Lung metastasis only						
Yes	2,200 (27.1)	548 (19.3)	1,652 (31.2)	<0.01	−27.6	0.0
No	5,934 (72.9)	2,291 (80.7)	3,643 (68.8)			
Tumor thrombus						
None	5,800 (71.3)	2,339 (82.4)	3,461 (65.4)	<0.01	–	–
Renal vein	1,825 (22.4)	365 (12.9)	1,460 (27.6)			
Infradiaphragmatic IVC	384 (4.7)	97 (3.4)	287 (5.4)			
Supradiaphragmatic IVC	125 (1.5)	38 (1.3)	87 (1.6)			
Metastasectomy						
No	6,677 (82.1)	2,551 (89.9)	4,126 (77.9)	<0.01	32.9	2.3
Yes	1,457 (17.9)	288 (10.1)	1,169 (22.1)			
Systemic therapy						
No	3,079 (37.9)	968 (34.1)	2,111 (39.9)	<0.01	−12.0	1.3
Yes	5,055 (62.1)	1,871 (65.9)	3184 (60.1)			
Before surgery	–	–	*207 (6.5)*			
After surgery	–	–	*2,851 (89.5)*			
Before and after surgery	–	–	*122 (3.8)*			
Unknown	–	–	*4 (0.1)*			
Year						
2010	1,935 (23.8)	654 (23.0)	1,281 (24.2)	0.05	−2.2	0.5
2011	1,971 (24.2)	716 (25.2)	1,255 (23.7)			
2012	1,972 (24.2)	650 (22.9)	1,322 (25.0)			
2013	2,256 (27.7)	819 (28.8)	1,437 (27.1)			

5.4% (125 of 2,334), respectively. Patients with a tumor thrombus were more likely to undergo a CN compared with patients without a tumor thrombus ($P < 0.01$); however, as the level of thrombus increased, the rate of CN decreased from 80.0% to 69.6% (Fig. 2). The rate of utilization of CN in all patients remained stable over time ($P = 0.05$), however

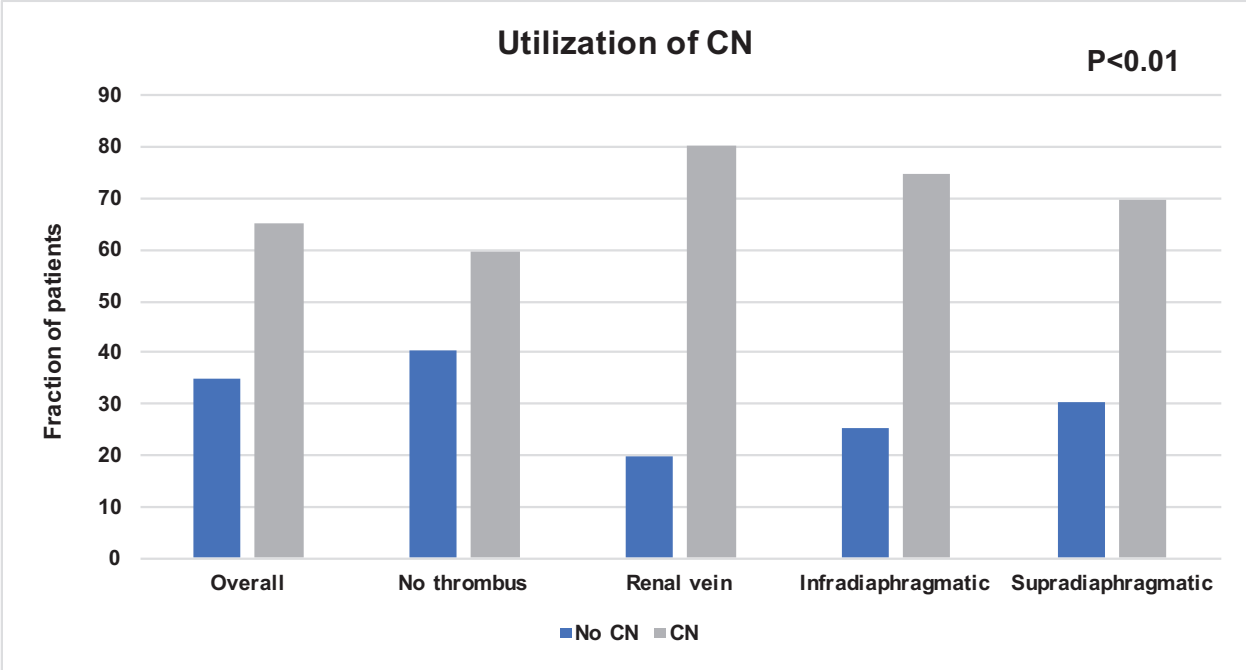

Fig. 2. Utilization of CN in patients with mRCC stratified by the presence and level of tumor thrombus.

the rate of CN in patients with thrombus only increased from 76.9% to 79.9% ($P = 0.03$).

Next, we evaluated predictors of receipt of CN in our target population of patients with mRCC and tumor thrombus (Table 2). Older age (≥65 years), Black race, Medicaid or no insurance, unknown tumor size, and thrombus involving the supradiaphragmatic IVC were all associated with significantly less likelihood of CN. On the other hand, treatment at an academic facility or a facility with unknown academic status and later year of treatment was associated with increased likelihood of CN.

To evaluate the effect of CN on OS, patients were matched based on receipt of CN as described in the Methods section (Supplemental Figure 1). Median follow-up in the unmatched cohort was 8.9 (4.9–18.2) months for patients who did not undergo CN and 18.9 (9.0–31.8) months for patients who did undergo CN. In the matched cohort, median follow-up time was 8.9 (4.8–18.8) for no CN and 18.9 (9.0–31.8) months for CN. Kaplan-Meier curves were constructed using the matched cohort stratified by the level of tumor thrombus and the receipt of CN (Fig. 3). Median survival in the matched cohort of patients who did not undergo CN was 10.7 (95% confidence interval [CI] 9.9–11.5), 9.2 (95% CI 7.8–11.2), 11.5 (95% CI 7.9–15.5), and 10.3 (95% CI 4.1–21.9) months in those with no thrombus, renal vein, infradiaphragmatic, and supradiaphragmatic IVC thrombus, respectively. Median survival in patients who did undergo CN was 24.2 (95% CI 22.8–25.5), 24.0 (95% CI 22.4–26.3), 22.3 (95% CI 19.2–30.2), and 13.1 (95% CI 10.2–17.4) months in those with no thrombus, renal vein, infradiaphragmatic, and supradiaphragmatic IVC thrombus, respectively. Significant improvement in OS in patients who underwent CN was demonstrated in patients with no thrombus (log rank test $P < 0.01$), renal vein ($P < 0.01$), infradiaphragmatic ($P < 0.01$) thrombus. However, no improvement in OS was seen in those with supradiaphragmatic thrombus ($P = 0.60$). Finally, we constructed 4 independent multivariable Cox proportional hazards models stratified by level of thrombus in the **propensity score** matched cohort (Table 3). Patients who underwent CN had improved OS in the cohort with no thrombus (hazard ratio [HR] 0.52, CI 0.48–0.56, $P < 0.01$), renal vein (HR 0.43, CI 0.36–0.52, $P < 0.01$), and infradiaphragmatic (HR 0.68, CI 0.47–0.97, $P = 0.03$). No OS benefit was demonstrated in patients with supradiaphragmatic IVC thrombus who underwent a CN (HR 0.58, CI 0.20–1.72, $P = 0.33$).

4. Discussion

The role of CN in the treatment of patients with mRCC in the targeted therapy era is complex as recently reported data further obscures any true benefit of CN and as newer immunotherapeutic agents move into the first-line treatment for metastatic disease [3,17]. Nevertheless, CN will likely remain an important part of the multidisciplinary management of these complex patients. The question of whether CN is beneficial in patients with tumor thrombus, particularly thrombus above the diaphragm, remains incompletely evaluated as the landmark SWOG 8949 trial did not include all levels of tumor thrombus [18]. Therefore, results from our study have the potential to inform the current literature. Our study has 4 key findings. First, we demonstrate that tumor thrombi are present in more than one quarter of patients with metastatic disease and that utilization of CN increases when a thrombus is present but decreases as the

Table 2
Logistic regression predicting the receipt of CN in patients with mRCC and tumor thrombus

Variable	OR	95% Confidence Interval	*P* value
Age, years (Referent = <65)			
65–79	0.55	0.39–0.78	<0.01
≥80	0.16	0.09–0.28	<0.01
Gender (Referent = Male)			
Female	0.89	0.69–1.15	0.36
Race (Referent = White)			
Black	0.44	0.27–0.70	<0.01
Hispanic/other	0.69	0.46–1.03	0.07
Unknown	1.16	0.57–2.34	0.68
CDCC (Referent = 0)			
1	1.00	0.75–1.33	0.97
≥2	0.76	0.48–1.21	0.25
Insurance (Referent = Medicare)			
Private	0.90	0.63–1.30	0.58
Medicaid/other	0.53	0.33–0.87	0.01
None	0.32	0.18–0.59	<0.01
Unknown	0.55	0.21–1.45	0.23
Income (Referent = High)			
Low	0.90	0.66–1.23	0.53
Unknown	0.64	0.18–2.21	0.48
Percent with no high school degree (Referent = ≥29%)			
20%–28.9%	1.07	0.72–1.59	0.72
14%–19.9%	0.97	0.64–1.46	0.88
<14%	1.27	0.81–1.98	0.30
Unknown	1.58	0.68–3.71	0.29
Region (Referent = East)			
Central	1.27	0.92–1.75	0.15
West	1.15	0.76–1.74	0.50
Unknown	–	–	–
Urban/Rural (Referent = Rural)			
Metropolitan	1.19	0.59–2.40	0.63
Urban	1.59	0.76–3.30	0.22
Unknown	0.71	0.26–1.93	0.51
Facility type (Referent = Community)			
Academic	1.51	1.11–2.07	<0.01
Integrated network	1.29	0.76–2.19	0.36
Unknown	3.26	1.16–9.17	0.03
Size category (Referent = <4 cm)			
4–7cm	0.93	0.67–1.29	0.68
>7 cm	0.90	0.68–1.19	0.47
Unknown	0.06	0.03–0.11	<0.01
Thrombus location (Referent = Renal vein)			
Infradiaphragmatic IVC	0.74	0.54–1.01	0.06
Supradiaphragmatic IVC	0.51	0.32–0.83	<0.01
Year (per year increase)	1.12	1.00–1.24	0.04

level of thrombus rises. Second, we identify several associations between clinicodemographic variables, such as age, treatment facility type, and tumor thrombus level, and the receipt of CN in patients with mRCC and tumor thrombus. Third, we show that in the metastatic setting, the presence of renal vein and even infradiaphragmatic IVC thrombus does not significantly adversely affect OS, while supradiaphragmatic IVC thrombus is associated with worse OS. Finally, we illustrate that CN retains a significant OS benefit in patients with mRCC and tumor thrombus, however this benefit is attenuated at higher levels of thrombus above the diaphragm.

The biologic predisposition to involve and invade the venous system is a hallmark of RCC and is present in 5%–10% of all kidney tumors, with nearly one third of these patients presenting with metastatic disease [19]. Other series have reported ranges from 29% to 55% of patients presenting with concomitant metastatic disease and tumor thrombus [4–6]. However, no study has evaluated a large population-based or registry database to determine the incidence of tumor thrombi in patients with mRCC. Consistent with prior reports, we found that up to 28% of patients with metastatic disease have some level of tumor thrombus. Three quarters of these patients undergo CN. It is interesting that patients with thrombus are more likely to undergo CN compared with patients who do not have a thrombus. It is possible that those with thrombus are more likely to be symptomatic and require a palliative nephrectomy. The risk of progression and embolus may also increase the utilization of CN in these patients.

While several studies have looked at single or multi-institutional series of CN with tumor thrombectomy, the current study is the first to evaluate this population in a registry-based cohort and is therefore able to evaluate clinicodemographic factors associated with the receipt of CN. We found that older patients were less likely to undergo CN with tumor thrombectomy, representing expected preoperative selection inherent in this high-risk surgery. Interestingly, CDCC did not significantly influence likelihood of receipt of CN in our cohort, suggesting that surgeons may weigh chronological age more heavily than physiologic status, which may warrant reconsideration. Furthermore, racial disparities may exist as Black patients and those with poorer insurance coverage were less likely to undergo CN. On the other hand, we found that academic treatment centers were more likely to perform a CN, likely reflecting the referral patterns of operative candidates to tertiary centers. The association between more recent treatment year and receipt of CN may represent improved imaging associated with better preoperative diagnosis or merely improved coding of the database.

Our major finding is that CN retains an OS benefit in patients with mRCC and tumor thrombus, although the benefit is restricted to patients with thrombus below the diaphragm. After accounting for guarantee-time bias, there was no significant difference in 30- or 90-day mortality in cohorts stratified by thrombus level. Several studies have evaluated the prognostic value of tumor thrombi level in patients with nonmetastatic and metastatic RCC. In a large multicenter European study of patients with nonmetastatic RCC who underwent nephrectomy with thrombectomy, Wagner et al. found improved OS for patients with renal vein involvement compared with IVC involvement [20]. However, in their study, the level of IVC involvement did not impact OS. One possible

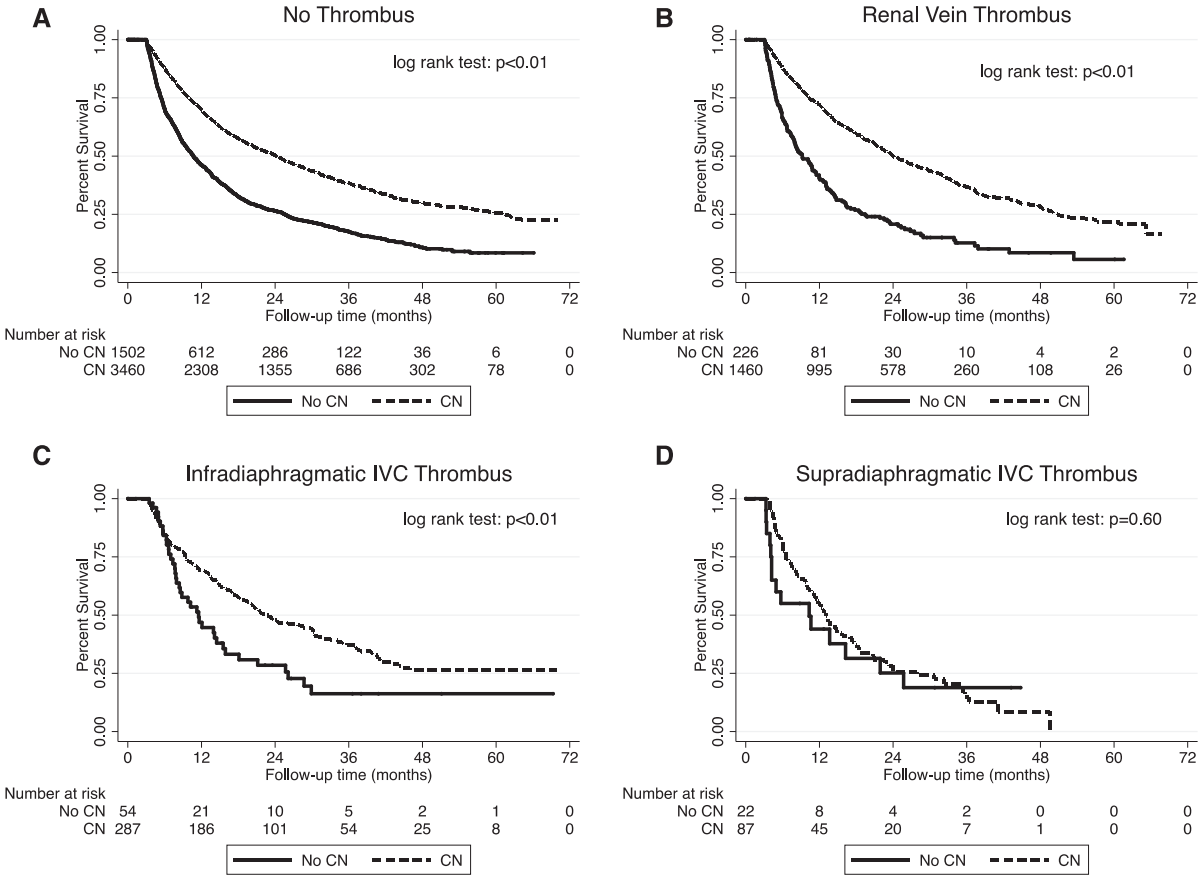

Fig. 3. Kaplan-Meier survival curves in the matched cohorts stratified by receipt of CN in patients with no thrombus (A), renal vein thrombus (B), infradiaphragmatic thrombus (C), and supradiaphragmatic thrombus (D).

explanation is that IVC invasion worsens the prognosis such that small differences based on the level of IVC invasion are negligible. In our study, however, the thrombus beyond the diaphragm was clearly associated with worse OS. In the largest multicenter study on CN with thrombectomy, Abel et al. also found that supradiaphragmatic thrombi had poorer OS compared with both renal vein and infradiaphragmatic thrombi [11]. Median OS stratified by tumor thrombus level was similar between our study and that by Abel et al. (24.0 vs. 21.7, 22.3 vs. 19.5, and 13.1 vs. 9.2 months for renal vein, infradiaphragmatic, and supradiaphragmatic IVC, respectively). Except for the highest levels of tumor thrombus (i.e., supradiaphragmatic) OS in patients undergoing CN with thrombectomy is similar compared with patients undergoing CN without tumor thrombectomy.

Table 3
Individual Cox proportional hazards model constructed on the propensity score matched cohorts for patients with mRCC stratified by level of thrombus. Additional variables controlled for in the model include age, gender, race, CDCC, insurance status, facility type, urban/rural status, US location, income level, education, histology, size, lung metastasis only, metastasectomy, laterality, systemic treatment, and year of treatment

Level of thrombus	HR	95% Confidence Interval	*P* value
No thrombus (Referent = No CN)			
CN	0.52	0.48–0.56	<0.01
Renal vein (Referent = No CN)			
CN	0.43	0.36–0.52	<0.01
Infradiaphragmatic (Referent = No CN)			
CN	0.68	0.47–0.97	0.03
Supradiaphragmatic (Referent = No CN)			
CN	0.58	0.20–1.72	0.33

Our study has several limitations in addition to those expected from large retrospective database studies, notably including selection bias with respect to those who underwent CN. First, we used the variables available to determine the level of tumor thrombus which may be too broad and represent large heterogeneous populations of patients. Second, the database lacks important operative details on extent of resection, grafting and reconstruction, and the need and type of bypass employed for higher levels of thrombus. Another consideration is that microscopic vein invasion, an important pathologic variable with biologic significance, is not documented and could not be included. In the current era, first-line immunotherapy with nivolumab and ipilimumab for patients with intermediate and poor risk mRCC may further alter the landscape of CN and may alter our results. Finally, we attempted to

account for burden of metastatic disease by controlling for metastasectomy (which would imply lower burden of disease) as well as matching patients with lung metastasis only; however, no statistical manipulation can fully account for differences between groups in terms of variables that are not tabulated in the database. Nevertheless, our study reveals several important findings regarding the presentation and management of mRCC patients with tumor thrombi, and should be considered, especially when treating older patients with higher CDCC scores with tumors above the diaphragm.

5. Conclusions

Tumor thrombus is present in more than 28% of patients with mRCC. The presence of tumor thrombus is associated with increased rates of CN although rates do decrease as the level of thrombus increases. In a multivariable model, thrombus above the diaphragm but not below the diaphragm portended a worse OS than renal vein thrombus. When stratified by level of thrombus in a matched cohort analysis, CN was associated with an OS benefit in patients with no tumor thrombus, renal vein thrombus, and infradiaphragmatic thrombus. Patients with supradiaphragmatic thrombus did not experience an OS benefit with CN.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.03.009.

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