Impact of facility type and volume on survival in patients with metastatic renal cell carcinoma

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Introduction: *To investigate the impact of facility type and volume on survival in patients with metastatic renal cell carcinoma (mRCC).*

Materials and methods: *We investigated the National Cancer Database for patients with mRCC. Patients were stratified according to treatment facility type (academic vs. non-academic) and facility volume (high, intermediate, and low). Kaplan-Meier survival estimates and Cox proportional hazard models were fitted to evaluate overall survival (OS) as a function of facility type, volume, and different treatment modalities.*

Results: *A total of 27,598 patients were identified, of which 10,938 (40%) were treated at academic centers (AC) and 16,131 (60%) at non-academic centers (non-AC). Overall, 19,904 patients (72%) were treated in high-volume hospitals (HVH). Among patients treated at AC, 94% were treated at HVHs. Patients treated at AC were more likely to receive immunotherapy, undergo cytoreductive nephrectomy (CN) and metastasectomy. The 2 and 5 year OS rates for patients treated in AC were 29.7% (CI 28.8%-30.6%) and 13% (CI 12%-14%) vs. 21.7% (CI 21%-22.4%) and 8.4% (CI %7.91-%8.99) in the Non-AC, respectively ($p < 0.001$). Multivariate Cox regression analysis identified treatment at AC as an independent predictor of survival (HR 0.85, 95% CI 0.81-0.91, $p < 0.001$). Undergoing CN and receipt of immunotherapy was also associated with a survival benefit (HR 0.41, CI 0.40-0.43 and HR 0.63, CI 0.59-0.68 respectively, $p < 0.001$).*

Conclusions: *Treatment at ACs and HVHs was associated with a survival benefit in patients with mRCC. Patients treated at AC were more likely to receive immunotherapy, undergo CN and metastasectomy.*

Key Words: academic center, cytoreductive nephrectomy, high volume, immunotherapy, metastasectomy

Introduction

Kidney cancer is the 6th most common malignancy among men and 8th among women, accounting for an estimated 73,750 new cases and approximately 15,000 mortalities in 2020 in the United States.[1] Of all new cases, nearly 25% present with metastatic disease. Additionally, 20%-50% of renal cell carcinoma (RCC) patients with localized disease at diagnosis will eventually develop metastasis.[2,3]

Optimal management of patients with metastatic renal cell carcinoma (mRCC) continues to evolve. With the introduction of targeted therapies followed by immune checkpoint inhibitors and their subsequent combinations, the management of patients with mRCC is undergoing continuous re-evaluation. In addition

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to systemic therapy, surgical resection of the primary tumor and metastasectomy are important treatment options in select patients.[4] Additionally, conventional and stereotactic radiotherapy (RT) has been used in adjuvant settings following nephrectomy to prevent local recurrence and treat oligometastatic disease.[5,6]

Contemporary management of mRCC requires interdisciplinary and multi-disciplinary approaches and resources to provide the best curative or palliative care. Different facility settings provide care to mRCC patients with heterogeneous access to the resources, expertise, and clinical trial platforms. The facility type and volume-related outcome for various cancer therapies have been previously reported, demonstrating that facility type and higher volume is associated with better overall survival.[7-10] For localized RCC, several studies showed improved facility surgical volume outcomes, namely, decreased postoperative complication rates and decreased length of stay. However, limited data is available regarding the volume-outcome relationship in patients with mRCC.[11,12]

Patients treated at high volume hospitals (HVH) and academic centers (AC) may have more access to treatment options, clinical trials, and management expertise, improving survival outcomes. Therefore, we evaluated a large contemporary national registry to evaluate the association between facility volume or facility type and overall survival in patients with mRCC.

Materials and methods

Data source

The NCDB is a joint project between the Commission on Cancer (CoC) of the American Cancer Society and American College of Surgeons. It is a nationwide, hospital-based, database that currently captures around 70% of all newly diagnosed malignancies in the United States, from more than 1,500 participating CoC accredited hospitals. Collected data include patient demographics, tumor, facility and treatment-related variables.[13]

Study population

We queried the NCDB for patients with a primary diagnosis of renal cell carcinoma (Site code C64.9) between 2004 to 2015. We further selected patients with clinical stage $cT_{1-4}N_{1-3}M_1$ according to American Joint Committee on Cancer (AJCC) staging system. mRCC was defined as, the involvement of distant lymph nodes as well as bone or viscera. We excluded patients without histologically confirmed diseases, if the treatment modality for the primary site or for the metastasis is unknown and if they had another cancer diagnosis in their lifetime, Figure 1.

We then stratified the study cohort according to the treatment facility type and annual facility volume. The NCDB assigns each treating facility into one of four categories; community cancer programs (CCP), comprehensive community cancer programs (CCCPs), academic centers (AC), and integrated network cancer programs (INCPs). We compared academic versus non-academic centers and divided the facilities by case volume according to the median number of patients treated over the study period. Our team grouped facilities into tertiles with high volume hospitals (HVH), defined as hospitals within the upper tertile, treating > 20 cases, medium volume hospitals (MVH) treating 10-20 cases and low volume hospitals (LVH) in the lowest tertile, treating less than 10 cases. We then stratified patients according to treatment modalities into 4 groups Group1: All patients with mRCC. Group 2: Subgroup of patients who had received any type of treatment. Group 3: Subgroup of patients who

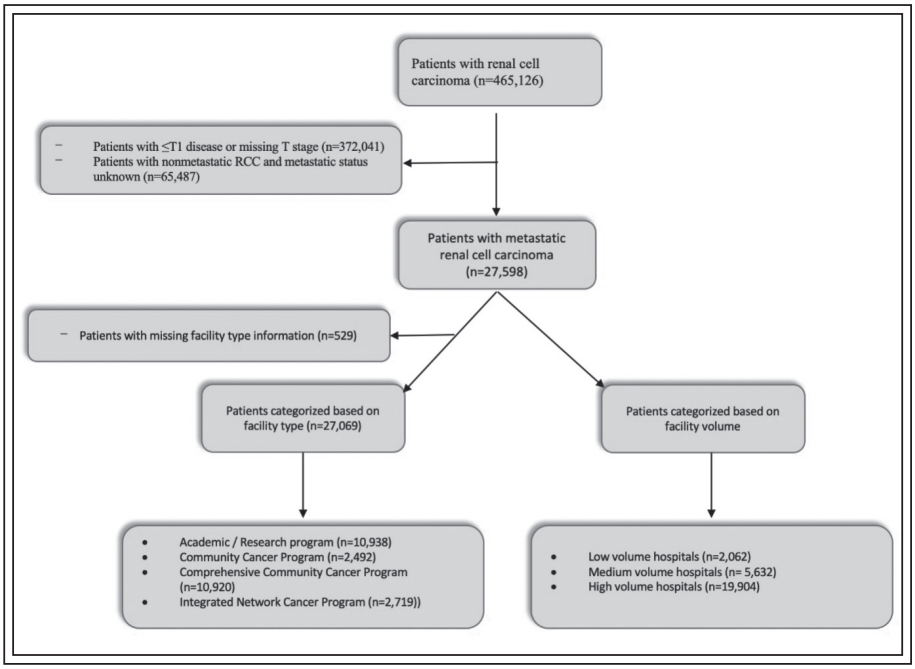

Figure 1. Flowchart that describes the patient selection criteria and reasons for exclusion in the NCDB.

had received only medical treatment (systemic or immune therapy) and Group 4: Subgroup of patients who had received nephrectomy with or without metastasectomy.

Covariates

We abstracted data on patient sociodemographics, including age at diagnosis, sex, race, residence (urban metropolitan or rural), Charlson comorbidity index, insurance status, household income, and education levels. Tumor-related variables included histology and TNM stage. Treatment-related variables included receipt of systemic therapy, radiation therapy, cytoreductive nephrectomy (CN), or metastasectomy.

Statistical analysis

We performed all statistical analysis using STATA statistical software version 15 (StataCorp. College Station, TX, USA). We used Analysis of variance (ANOVA) to evaluate univariate relationships between patient sociodemographics, clinical, and treatment pattern variables across different facility types and volumes. We fit multivariate logistic regression models to identify predictors for different treatment modalities (immunotherapy, CN, and metastasectomy). Overall survival (OS) was estimated using Kaplan-Meier survival curves. Univariate survival analysis was performed using the log-rank test to evaluate OS across different facility types and volumes. OS was further evaluated among different treatment groups by facility volume. Multivariable Cox regression analysis models with the stratified log-rank test were then fitted to identify independent predictors of OS. All tests were 2-sided, and the level of significance was set at 0.05. The study is exempt from IRB approval in accordance with institutional regulations when working with de-identified data.

Results

Patient and treatment characteristics

A total of 27,598 patients diagnosed with mRCC between 2004 to 2015 were identified. Of those, 10,938 (40.4%) were treated at AC and 16,131 (59.6%) treated at non-academic centers (non-AC). Overall, 19,904 patients (73.5%) were treated in HVHs. Among patients treated at AC, 10,339 (94.5%) were treated at HVHs. The sociodemographic, tumor and treatment characteristics of the patients stratified by facility volume (low, medium, high) and type (AC, non-AC) are depicted in Tables 1 and 2.

Patients treated at non-AC were older compared to AC, with patients over 70 years representing 35.9% vs. 28.3%, respectively. More African Americans and Hispanics were treated at AC compared to non-AC (10.8% vs. 8.3% and 8.7% vs. 6.9%, respectively). Regarding hospital volume, CN was adopted in 43.9% of patients treated at HVH vs. 35.1% and 31.2% of patients treated at LVH and MVH, respectively. Metastasectomy was performed in 9.3% of the patients in HVH, vs. 4.2% and 6% in patients treated at LVH and MVH. Six percent of the patients treated in HVH had immunotherapy, while 2.9% and 3.1% of patients had IO in LVH and MVH, respectively. Similarly, when comparing AC and non-AC; CN, metastasectomy, and receipt of immunotherapy were more frequently adopted in AC (47% vs. 36%, 11.4% vs. 5.9%, and 7.2% vs. 3.8, $p < 0.001$, respectively).

Treatment predictors

The results of the multivariable logistic regression model for predictors of treatment patterns are summarized in Table 3. Patients treated at high volume and academic centers when compared to their counterparts were more likely to receive CN (OR: 1.36 [95% CI 1.21 to 1.51]; $p < 0.001$ and OR: 1.42 [95% CI 1.34 to 1.51]; $p < 0.001$, respectively), metastasectomy (OR: 1.52 [95% CI 1.19 to 1.93]; $p = 0.001$ and OR: 1.74 [95% CI 1.57 to 1.93]; $p < 0.001$, respectively) and immunotherapy (OR: 1.43 [95% CI 1.08 to 1.9]; $p = 0.001$ and OR: 1.51 [95% CI 1.34 to 1.71]; $p < 0.001$, respectively).

Several clinical and sociodemographic variables were also associated with received treatment modalities. Notably, patients who were younger than 60 years old, had private insurance and had lower CCI score were more likely to receive immunotherapy, undergo CN and metastasectomy.

Patients with clinical node-positive disease were more likely to receive immunotherapy and less likely to receive CN or metastasectomy. Hispanics and African Americans were less likely to receive immunotherapy or undergo metastasectomy, Table 3.

Survival analysis

The mean follow up time was 15.6 months +/- 20.4. Figure 2a displays Kaplan-Meier survival curves for mRCC patients separated by facility type. The 2 and 5 year OS rates for patients treated at AC were 29.7% (CI 28.8%-30.6%) and 13% (CI 12%-14%) vs. 21.7% (CI 21%-22.4%) and 8.4% (CI %7.91-%8.99) in the non-AC ($p < 0.001$). Figure 2b shows survival curves based on facility volumes. The 2 and 5 year OS rates for patients treated in high, medium and low volume centers were 26.5% (CI 25.8%-27.1%) and 11.5% (CI 10.9%-12%) vs.

TABLE 1. **Patient clinical and demographic characteristics based on facility volume**

Demographics	Low	Intermediate	High	Total	p value
Number of patients	2,062	5,632	19,904	27,598	
Gender					< 0.001
Female	717 (34.77%)	2062 (36.61%)	6582 (33.07%)	9361 (33.92%)	
Male	1345 (65.23%)	3570 (63.39%)	13322 (66.93%)	18237 (66.08%)	
Age					< 0.001
< 60	631 (30.6%)	1801 (31.98%)	7451 (37.43%)	9883 (35.81%)	
60-69	604 (29.29%)	1702 (30.22%)	6335 (31.83%)	8641 (31.31%)	
70-79	501 (24.3%)	1316 (23.37%)	4065 (20.42%)	5882 (21.31%)	
≥ 80	326 (15.81%)	813 (14.44%)	2053 (10.31%)	3192 (11.57%)	
Race					0.002
White	1834 (88.94%)	4893 (86.88%)	17103 (85.93%)	23830 (86.35%)	
African American	160 (7.76%)	500 (8.88%)	1909 (9.59%)	2569 (9.31%)	
Asian	38 (1.84%)	138 (2.45%)	451 (2.27%)	627 (2.27%)	
Other	30 (1.45%)	101 (1.79%)	441 (2.22%)	572 (2.07%)	
Ethnicity					< 0.001
Non-Hispanic	1814 (93.65%)	5009 (93.91%)	17320 (91.72%)	24143 (92.31%)	
Hispanic	123 (6.35%)	325 (6.09%)	1563 (8.28%)	2011 (7.69%)	
Insurance type					< 0.001
Medicare	1037 (50.29%)	2778 (49.33%)	8324 (41.82%)	12139 (43.99%)	
Medicaid	162 (7.86%)	428 (7.6%)	1621 (8.14%)	2211 (8.01%)	
Other government	26 (1.26%)	55 (0.98%)	294 (1.48%)	375 (1.36%)	
Private	693 (33.61%)	2008 (35.65%)	8143 (40.91%)	10844 (39.29%)	
Unknown	35 (1.7%)	96 (1.7%)	456 (2.29%)	587 (2.13%)	
Facility type					< 0.001
AC	69 (3.35%)	530 (9.41%)	10339 (51.94%)	10938 (39.63%)	
CCP	1164 (56.45%)	1142 (20.28%)	186 (0.93%)	2492 (9.03%)	
CCCP	473 (22.94%)	3306 (58.7%)	7141 (35.88%)	10920 (39.57%)	
INCP	323 (15.66%)	571 (10.14%)	1825 (9.17%)	2719 (9.85%)	
No facility reported	33 (1.6%)	83 (1.47%)	413 (2.07%)	529 (1.92%)	
Charlson Deyo comorbidity index					0.482
CCI = 0	1505 (72.99%)	4118 (73.12%)	14688 (73.79%)	20311 (73.6%)	
CCI ≥ 1	557 (27.01%)	1514 (26.88%)	5216 (26.21%)	7287 (26.4%)	
T stage					0.002
T2	801 (39.5%)	2080 (37.81%)	7122 (36.64%)	10003 (37.09%)	
T3	802 (39.55%)	2254 (40.97%)	8399 (43.21%)	11455 (42.48%)	
T4	425 (20.96%)	1167 (21.21%)	3918 (20.16%)	5510 (20.43%)	
Nephrectomy					< 0.001
Radical	629 (31.22%)	1946 (35.06%)	8403 (42.85%)	10978 (40.4%)	
Partial	25 (1.24%)	64 (1.15%)	271 (1.38%)	360 (1.32%)	
None	1361 (67.54%)	3541 (63.79%)	10936 (55.77%)	15838 (58.28%)	
Radiation therapy					< 0.001
No	1595 (78.26%)	4124 (73.72%)	14837 (74.92%)	20556 (74.92%)	
Yes	443 (21.74%)	1470 (26.28%)	4968 (25.08%)	6881 (25.08%)	
Chemotherapy					< 0.001
No	1123 (54.46%)	3025 (53.71%)	10058 (50.53%)	14206 (51.47%)	
Yes	939 (45.54%)	2607 (46.29%)	9846 (49.47%)	13392 (48.53%)	

TABLE 1 (Cont'd). **Patient clinical and demographic characteristics based on facility volume**

Demographics	Low	Intermediate	High	Total	p value
Immunotherapy					< 0.001
No	1969 (96.9%)	5389 (97.15%)	18450 (93.99%)	25808 (94.85%)	
Yes	63 (3.1%)	158 (2.85%)	1180 (6.01%)	1401 (5.15%)	
More than one treatment					< 0.001
No	1173 (56.89%)	3347 (59.43%)	11360 (57.07%)	15880 (57.54%)	
Yes	889 (43.11%)	2285 (40.57%)	8544 (42.93%)	11718 (42.46%)	
Diagnosed before 2012					< 0.001
No	698 (33.85%)	1905 (33.82%)	7358 (36.97%)	9961 (36.09%)	
Yes	1364 (66.15%)	3727 (66.18%)	12546 (63.03%)	17637 (63.91%)	
Metastasectomy					< 0.001
No	1891 (91.71%)	5097 (90.5%)	17010 (85.46%)	23998 (86.96%)	
Yes	97 (4.7%)	358 (6.36%)	1996 (10.03%)	2451 (8.88%)	
Unknown	74 (3.59%)	177 (3.14%)	898 (4.51%)	1149 (4.16%)	

AC = academic centers; CCP = community cancer programs; CCCP = comprehensive community cancer programs; INCP = integrated network cancer programs

20.6% (CI 19.5%-21.7%) and 7.9% (CI 7.1%-8.8%) vs. 20.8% (CI 18.9%-22.8%) 7.1% (CI 5.8%-8.7%) respectively ($p < 0.001$). Notably, patients diagnosed and managed after 2012 (concomitant with the introduction of immunotherapy trials) had a significantly lower overall risk of mortality than those diagnosed before 2012 (HR: 0.83 [95% CI 0.81 to 0.86]; $p < 0.001$), Figure 3.

Table 4 results of univariate and multivariate-adjusted Cox regression models evaluating predictors of OS. Patients treated at AC had a lower overall risk of mortality (HR: 0.88 [95% CI 0.85 to 0.91]; $p < 0.001$). Moreover, patients who underwent CN (HR: 0.41 [95% CI 0.40 to 0.43]; $p < 0.001$) or immunotherapy (HR: 0.65 [95% CI 0.60 to 0.69]; $p < 0.001$) had improved survival. Other factors associated with an increased risk of overall mortality were increasing age, higher CCI, and higher T stage. As tabulated in Table 5, higher facility volume was associated with improved survival for the subgroups of patients who received any treatment (Group 2), who had received systemic chemotherapy or immunotherapy (Group 3), and who underwent nephrectomy with or without metastasectomy (Group 4) (HR: 0.87 [95% CI 0.84 to 0.91]; $p < 0.001$, HR: 0.89 [95% CI 0.85 to 0.93]; $p < 0.001$, and HR: 0.89 [95% CI 0.84 to 0.94]; $p < 0.001$, respectively).

Discussion

Using a national cancer dataset, we demonstrated that patients with primary mRCC undergoing treatment at ACs or high-volume facilities were likely to have better overall survival than those receiving care at non-ACs or low and medium volume facilities. Median survival time after diagnosis was significantly higher in patients treated at ACs when compared to those treated at non-ACs. Furthermore, we demonstrated that facility type and volume is an important independent predictor for receiving immunotherapy, undergoing CN or metastasectomy which may have contributed to the improved survival outcomes for mRCC patients treated at ACs and HVHs.

Several studies have reported more favorable survival outcomes for various cancer types and better outcomes for surgical procedures in patients treated at ACs and HVHs.[9,10,14-16] More specifically, volume-outcome relation was studied for localized and locally advanced RCC; authors reported undergoing nephrectomy or nephrectomy with inferior vena cava thrombectomy HVHs is associated with better postoperative outcomes and longer overall survival.[17-19] But little is known about the impact of facility type and volume on mRCC outcomes. Recently, higher facility volumes were found associated with a survival advantage for mRCC.[20,21] However, correlation with facility type and evaluation of predictors for contemporary treatment options like the receipt of immunotherapy, CN, and metastasectomy has not been previously studied.

With a better understanding of the genetic and molecular mechanism of RCC, novel systemic therapies providing survival advantages in advanced diseases have emerged.[2,22] With these new treatment options, the management of mRCC became more complex. The appropriate use of systemic therapies, sequencing of treatment options, and selecting surgical

TABLE 2. **Patient clinical and demographic characteristics based on facility type**

Demographics	**Non-academic**	**Academic**	**Total**	**p value**
Number of patients	16,131	10,938	27,069	
Gender				< 0.001
Male	10817 (64.93%)	7420 (67.84%)	18237 (66.08%)	
Female	5843 (35.07%)	3518 (32.16%)	9361 (33.92%)	
Age				< 0.001
< 60	5586 (33.53%)	4297 (39.29%)	9883 (35.81%)	
60-69	5097 (30.59%)	3544 (32.4%)	8641 (31.31%)	
70-79	3759 (22.56%)	2123 (19.41%)	5882 (21.31%)	
≥ 80	2218 (13.31%)	974 (8.9%)	3192 (11.57%)	
Race				< 0.001
White	14672 (88.07%)	9158 (83.73%)	23830 (86.35%)	
African American	1387 (8.33%)	1182 (10.81%)	2569 (9.31%)	
Asian	341 (2.05%)	286 (2.61%)	627 (2.27%)	
Other	260 (1.56%)	312 (2.85%)	572 (2.07%)	
Ethnicity				< 0.001
Hispanic	1091 (6.96%)	920 (8.77%)	2011 (7.69%)	
Non-Hispanic	14576 (93.04%)	9567 (91.23%)	24143 (92.31%)	
Insurance				< 0.001
Medicare	7919 (47.53%)	4220 (38.58%)	12139 (43.99%)	
Medicaid	1199 (7.2%)	1012 (9.25%)	2211 (8.01%)	
Other government	212 (1.27%)	163 (1.49%)	375 (1.36%)	
Private	6239 (37.45%)	4605 (42.1%)	10844 (39.29%)	
Unknown	254 (1.52%)	333 (3.04%)	587 (2.13%)	
Charlson Deyo comorbidity index				< 0.001
CCI = 0	12069 (72.44%)	8242 (75.35%)	20311 (73.6%)	
CCI ≥ 1	4591 (27.56%)	2696 (24.65%)	7287 (26.4%)	
T stage				< 0.001
T2	6329 (38.79%)	3674 (34.49%)	10003 (37.09%)	
T3	6597 (40.44%)	4858 (45.6%)	11455 (42.48%)	
T4	3389 (20.77%)	2121 (19.91%)	5510 (20.43%)	
Nephrectomy				< 0.001
Radical	5910 (36.04%)	5068 (47.03%)	10978 (40.4%)	
Partial	187 (1.14%)	173 (1.61%)	360 (1.32%)	
None	10303 (62.82%)	5535 (51.36%)	15838 (58.28%)	
Radiation therapy				0.033
No	12318 (74.42%)	8238 (75.68%)	20556 (74.92%)	
Yes	4233 (25.58%)	2648 (24.32%)	6881 (25.08%)	
Chemotherapy				0.902
No	8545 (51.29%)	5661 (51.76%)	14206 (51.47%)	
Yes	8115 (48.71%)	5277 (48.24%)	13392 (48.53%)	
Immunotherapy				< 0.001
No	15807 (96.19%)	10001 (92.81%)	25808 (94.85%)	
Yes	626 (3.81%)	775 (7.19%)	1401 (5.15%)	
Metastasectomy				< 0.001
No	14542 (90.15%)	9025 (82.51%)	23567 (87.06%)	
Yes	1054 (6.53%)	1330 (12.16%)	2384(8.81%)	
Unknown	535 (3.32%)	583 (5.33%)	1118 (4.13%)	

TABLE 3. **Multivariable logistic regressions analysis for predictors of different treatment modalities**

		Predictors for immunotherapy			Predictors for cytoreductive nephrectomy			Predictors for metastasectomy		
		Odds ratio	**95% CI**	**p value**	**Odds ratio**	**95% CI**	**p value**	**Odds ratio**	**95% CI**	**p value**
Facility volume	Low		reference			reference			reference	
	Medium	0.88	(0.64, 1.2)	0.43	1.22	(1.08, 1.37)	< 0.001	1.28	(0.99, 1.66)	0.059
	High	1.43	(1.08, 1.9)	0.01	1.36	(1.21, 1.51)	< 0.001	1.52	(1.19, 1.93)	0.001
Facility type										
	Non-academic		reference			reference			reference	
	Academic	1.51	(1.34, 1.71)	< 0.001	1.42	(1.34, 1.51)	< 0.001	1.74	(1.57, 1.93)	< 0.001
Race	White		reference			reference			reference	
	African American	0.59	(0.47, 0.75)	< 0.001	0.88	(0.74, 1.06)	0.17	0.75	(0.62, 0.9)	0.002
	Asian	1.27	(0.91, 1.77)	0.15	0.97	(0.78, 1.21)	0.78	0.93	(0.69, 1.27)	0.668
	Other	0.98	(0.63, 1.55)	0.95	0.72	(0.65, 0.8)	< 0.001	1.75	(1.28, 2.4)	0.001
Ethnicity	Non-Hispanic		reference			reference			reference	
	Hispanic	0.62	(0.48, 0.79)	< 0.001	0.54	(0.49, 0.6)	< 0.001	0.81	(0.67, 0.97)	0.023
Insurance	Private		reference			reference			reference	
	Medicare	0.81	(0.69, 0.96)	0.01	0.78	(0.73, 0.84)	< 0.001	0.87	(0.76, 0.99)	0.029
	Medicaid	0.68	(0.54, 0.85)	< 0.001	0.62	(0.56, 0.68)	< 0.001	0.91	(0.77, 1.08)	0.284
	Other government	0.52	(0.29, 0.93)	0.03	0.76	(0.61, 0.96)	0.02	0.63	(0.41, 0.98)	0.039
Charlson Deyo comorbidity index										
	CCI = 0		reference			reference			reference	
	CCI ≥ 1	0.86	(0.75, 0.99)	0.03	0.89	(0.84, 0.95)	< 0.001	1.14	(1.02, 1.26)	0.018
T stage	T2		reference			reference			reference	
	T3	0.90	(0.8, 1.02)	0.11	1.44	(1.36, 1.53)	< 0.001	0.79	(0.71, 0.87)	< 0.001
	T4	0.78	(0.66, 0.93)	0.01	0.51	(0.47, 0.55)	< 0.001	0.79	(0.69, 0.92)	0.002
Radiation therapy										
	No		reference			reference			reference	
	Yes	0.89	(0.78, 1.01)	0.08	0.63	(0.59, 0.67)	< 0.001	2.33	(2.12, 2.57)	< 0.001
Immunotherapy										
	No					reference			reference	
	Yes	N/A	1.99	(1.77, 2.25)		< 0.001	0.78	(0.64, 0.95)		0.015
Surgery	No		reference			reference				
	Yes	1.98	(1.75, 2.23)	< 0.001	N/A	2.21	(2, 2.44)	< 0.001		
Gender	Female		reference			reference			reference	
	Male	1.17	(1.03, 1.32)	0.01	1.08	(1.02, 1.14)	0.01	1.03	(0.93, 1.14)	0.548
Age	< 60		reference			reference			reference	
	60-69	0.64	(0.56, 0.74)	< 0.001	0.76	(0.71, 0.81)	< 0.001	0.87	(0.78, 0.98)	0.021
	70-79	0.80	(0.66, 0.97)	0.02	0.74	(0.68, 0.8)	< 0.001	0.84	(0.72, 0.97)	0.019
	≥ 80	0.22	(0.14, 0.34)	< 0.001	0.29	(0.26, 0.34)	< 0.001	0.5	(0.38, 0.65)	< 0.001
N stage	N0&Nx		reference			reference			reference	
	N1	0.89	(0.78, 1.01)	0.07	0.57	(0.53, 0.6)	< 0.001	0.64	(0.57, 0.71)	< 0.001
	N2&N3	1.24	(1.02, 1.5)	0.03	0.47	(0.43, 0.52)	< 0.001	0.6	(0.49, 0.73)	< 0.001

TABLE 4. **Multivariable Cox regression analysis for predictors of overall survival**

	Univariate			Multivariate		
	Hazard ratio	**95% CI**	**p value**	**Hazard ratio**	**95% CI**	**p value**
Facility volume						
Low & medium		reference			reference	
High	0.82	(0.8, 0.85)	< 0.001	0.98	(0.94, 1.01)	0.306
Facility type						
Non-academic		reference			reference	
Academic	0.79	(0.76, 0.81)	< 0.001	0.88	(0.85, 0.91)	< 0.001
Race						
White		reference			reference	
African American	1.18	(1.13, 1.24)	< 0.001	1.01	(0.96, 1.06)	0.756
Asian	0.98	(0.89, 1.07)	0.622	0.97	(0.88, 1.07)	0.511
Other	0.95	(0.86, 1.05)	0.33	1.08	(0.95, 1.23)	0.228
Ethnicity						
Non-Hispanic		reference			reference	
Hispanic	0.82	(0.78, 0.87)	< 0.001	1.07	(1.03, 1.12)	0.001
Insurance						
Private		reference			reference	
Medicare	1.43	(1.39, 1.47)	< 0.001	1.07	(1.03, 1.12)	0.001
Medicaid	1.21	(1.15, 1.28)	< 0.001	1.04	(0.99, 1.11)	0.138
Other government	1.27	(1.13, 1.44)	< 0.001	1.04	(0.92, 1.19)	0.51
Unknown	1.13	(1.03, 1.25)	0.012	1.04	(0.93, 1.15)	0.52
Charlson comorbidity index						
CCI = 0		reference			reference	
CCI ≥ 1	1.15	(1.11, 1.18)	< 0.001	1.11	(1.07, 1.14)	< 0.001
T stage						
T2		reference			reference	
T3	1.04	(1.01, 1.07)	0.01	1.12	(1.08, 1.16)	< 0.001
T4	1.56	(1.5, 1.61)	< 0.001	1.33	(1.27, 1.38)	< 0.001
Nephrectomy						
None		reference			reference	
Partial	0.44	(0.39, 0.5)	< 0.001	0.44	(0.38, 0.5)	< 0.001
Radical	0.39	(0.38, 0.4)	< 0.001	0.41	(0.4, 0.43)	< 0.001
Radiation therapy						
No		reference			reference	
Yes	1.14	(1.1, 1.17)	< 0.001	1.09	(1.06, 1.13)	< 0.001
Chemotherapy						
No		reference			reference	
Yes	0.74	(0.72, 0.76)	< 0.001	0.66	(0.64, 0.68)	< 0.001
Immunotherapy						
No		reference			reference	
Yes	0.57	(0.54, 0.61)	< 0.001	0.63	(0.59, 0.68)	< 0.001
Gender						
Female		reference			reference	
Male	0.89	(0.86, 0.91)	< 0.001	0.96	(0.93, 0.99)	0.006
Age						
< 60		reference			reference	
60-69	1.09	(1.06, 1.13)	< 0.001	0.98	(0.94, 1.02)	0.279
70-79	1.25	(1.2, 1.3)	< 0.001	1.1	(1.05, 1.15)	< 0.001
≥ 80	1.65	(1.56, 1.75)	< 0.001	1.16	(1.09, 1.24)	< 0.001

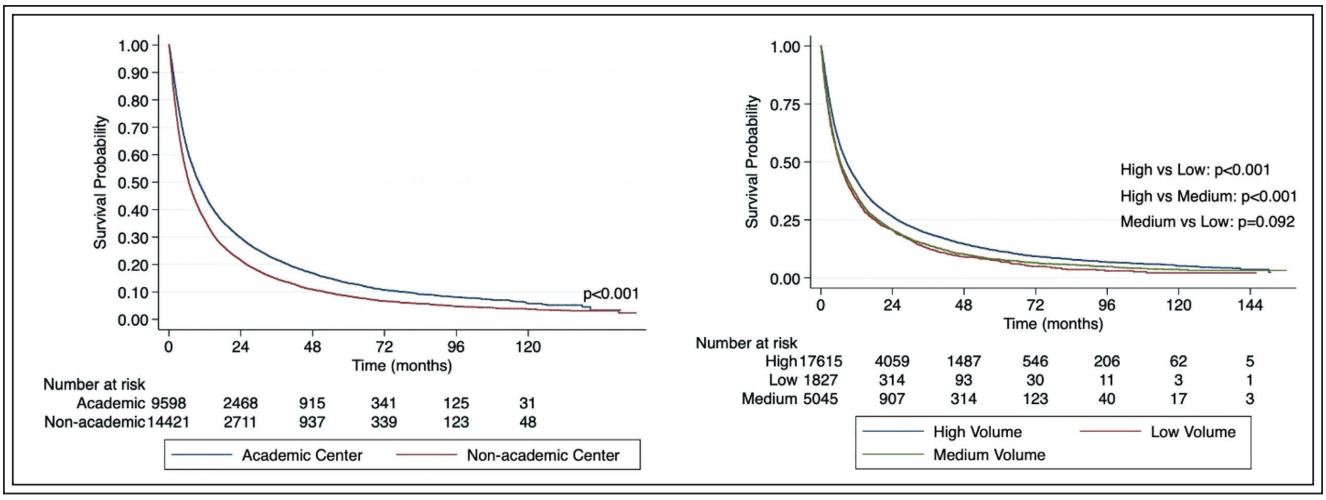

Figure 2a, b. Kaplan-Meier survival curves comparing overall survival among different facility types and volumes.

candidates play an important role. The management of this challenging disease requires clinical experience and a multi-disciplinary team approach.

Cytoreductive nephrectomy has been associated with improved survival in select patients.[23] A European registry-based study evaluating 736 patients with mRCC showed that the CN caseload correlates with lower high-grade morbidity.[24] Also, another study evaluating the effect of metastasectomy in RCC reported that patients treated in academic centers had higher odds of undergoing metastasectomy.[25] Similarly, we found a greater likelihood of receiving undergoing CN and metastasectomy at ACs and HVHs, a potential explanation of the survival benefit.

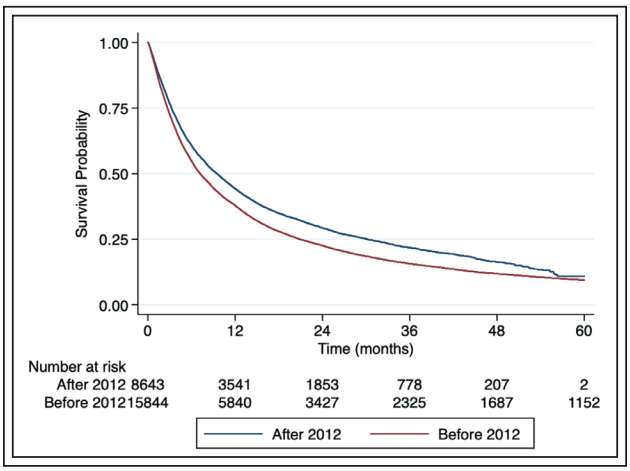

Figure 3. Kaplan-Meier survival curves comparing patients diagnosed and treated before and after 2012.

The introduction of novel immunotherapy agents improved the outcomes for advanced RCC patients.[26,27] We observe, better survival rates in patients with mRCC, better survival rates in patients with mRCC diagnosed after the year 2012, which correlates with the start of immunotherapy trials in kidney cancer with the CheckMate 025 trial. (HR: 0.83 [95% CI 0.81 to 0.86]; $p < 0.001$). However, the utilization of these agents by physicians in different hospital-level settings is not well evaluated. In academic and high-volume settings, with greater access to clinical trials, support staff, and more familiarity with these newer agents, the utilization of IO in the treatment of mRCC may be greater than the non-academic and low volume settings. In our study, the probability of receiving immunotherapy for mRCC patients was significantly higher at ACs and HVHs (OR: 1.51 [95% CI 1.31 to 1.71]; $p < 0.001$ and OR: 1.43 [95% CI 1.08 to 1.9]; $p = 0.01$).

One of the most important aspects of health care delivery for cancer patients involves the need for high-quality centers with centralized care. On the other hand, health policy makers should consider that regionalization of care may introduce barriers to access and aggravate racial and socioeconomic disparities in health care. Such disparities are already existent in our study; the likelihood of having IO or undergoing CN is 32% and 38% less for Medicaid patients when compared with private insurance holders and African Americans were less likely to receive immunotherapy or undergo metastasectomy (OR: 0.59 [95% CI 0.47 to 0.75]; $p < 0.001$ and OR: 0.75 [95% CI 0.62 to 0.9]; $p = 0.002$).

There are several important limitations to this study. Due to the study's retrospective nature from a national database system, there is an inherent

TABLE 5. **Multivariate Cox regression model for predictors of overall survival in patient subgroups managed with different treatment approaches**

	Facility volume	Hazard ratio with 5% confidence intervals	p value
Group 1*	Low & Medium	reference	
	High	0.92(0.89, 0.95)	< 0.001
Group 2	Low & Medium	reference	
	High	0.87 (0.84, 0.91)	< 0.001
Group 3	Low & Medium	reference	
	High	0.89 (0.85, 0.93)	< 0.001
Group 4	Low & Medium	reference	
	High	0.89 (0.84, 0.94)	< 0.001

*Group1: All patients who had metastatic disease
Group 2: Subgroup of Group 1, patients who had received any type of treatment.
Group 3: Subgroup of Group 2 patients who had received medical treatment (systemic or immune therapy)
Group 4: Subgroup of Group 2, patients who had received nephrectomy with or without metastasectomy.

possibility of treatment selection bias: either due to available resources, physician or patient preferences. Second, we only investigated the impact of facility volume on survival and did not evaluate the effect of individual provider volumes. The NCDB does not contain identifiers that would allow an appropriate calculation of provider volume. mRCCs are often treated by a multi-disciplinary team involving urologists, radiologists, and medical and radiation oncologists. Although systemic therapy remains the cornerstone of mRCC management, surgery and radiotherapy play a critical role in determining the overall survival and quality of life for most patients with mRCC. Therefore, overall facility volume rather than individual provider volume may be a better metric for determining the volume-outcome. Third, our findings can only be generalized to facilities participating in the NCDB. Fourth, there is no available data to measure cancer-specific survival, although most deaths in this high-risk population are likely attributable to mRCC. Finally, inherent to any NCDB analyses, the miscoding of variables cannot be excluded as a source of bias.

Conclusions

The available evidence suggests that treatment at ACs and HVHs is associated with improved OS in patients with mRCC. These results may reflect better access to resources and treatment options, including the use of immunotherapy and delivery of higher quality, guideline-based surgical treatment approaches. □

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