Clinical implications of tumor laterality in renal cell carcinoma

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Introduction: *It is unclear whether laterality has prognostic implications for patients with renal cell carcinoma (RCC). Some suggest that left sided tumors may have worse survival outcomes. The purpose of this study is to associate tumor characteristics and clinical outcomes with laterality in patients with RCC.*

Materials and methods: *Patients with RCC were identified in the National Cancer Database between 2004-2020. Patients were categorized as having either localized, regional or metastatic disease. Time-series charts were generated to demonstrate laterality differences and variance over time. Multivariable Cox proportional hazards regression was utilized to associate laterality with overall survival, stratified by clinical stage. Kaplan-Meier estimates were utilized to visualize survival functions.*

Results: *A total of 306,196 patients were included, 156,450 (51.1%) had right sided tumors and 283,282 (92.5%) had localized RCC. Localized tumors were more likely to be right sided (0.51 [95% CI 0.50-0.52], p < 0.001). Metastatic and regional tumors (cN+M0) were more likely to be left sided (0.48 [0.47-0.49], p < 0.001; and 0.43 [0.41-0.45], p < 0.001; respectively). For localized disease, smaller tumors were more likely to be right sided (< 2 cm: 0.52 [0.51-0.52], p < 0.001), while tumors > 7cm showed no significant site association (0.49 [0.49-0.50], p = 0.07). When stratified by staging, there were no significant associations between laterality and OS (localized RCC: HR 1.01 [0.99-1.02], p = 0.50; metastatic RCC: 1.03 [1.00-1.07], p = 0.7; cN+M0 RCC: 0.96 [0.86-1.07], p = 0.50).*

Conclusions: *Left-sided RCC tumors are associated with larger tumor size and a higher propensity for regional nodal involvement and distant metastases. However, they do not demonstrate more aggressive behavior leading to meaningful survival differences.*

Key Words: renal cell carcinoma, tumor laterality

Introduction

There are several well-known anatomic differences between the left and right kidney.[1] Grossly, the right kidney is located more caudally in the retroperitoneum, has a shorter and less complex renal vein, and a longer renal artery.[2] Lymphatic channels from the right kidney primarily drain into the paracaval and inter-aortocaval nodal regions, while those of the left primarily drain into the paraaortic region and may have a higher concentration of lymphovenous communications.[3] In renal cell carcinoma (RCC), this anatomic asymmetry is most clinically evident in cases of inferior vena cava (IVC) tumor thrombus, which are associated with right-sided laterality due to shorter renal vein length.

Biologic and physiologic differences between the left and right kidney are seldom described and largely assumed to be similar. In RCC, the T- and B-cells in left

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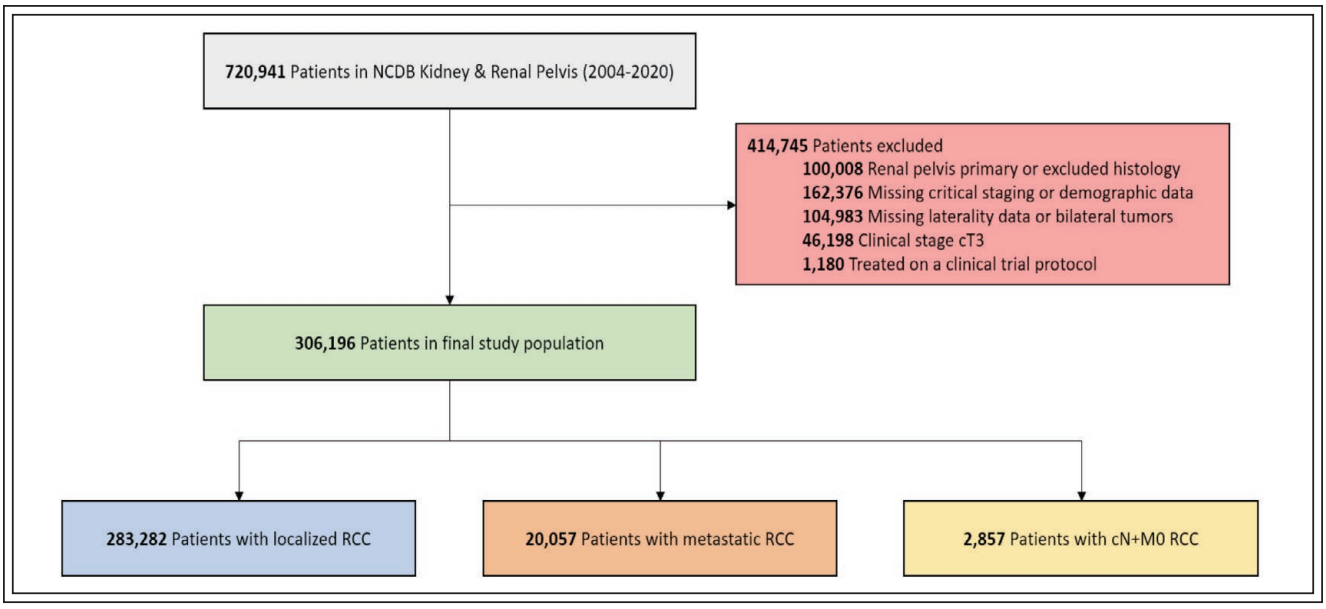

Figure 1. Flow diagram detailing selection of the final study population.

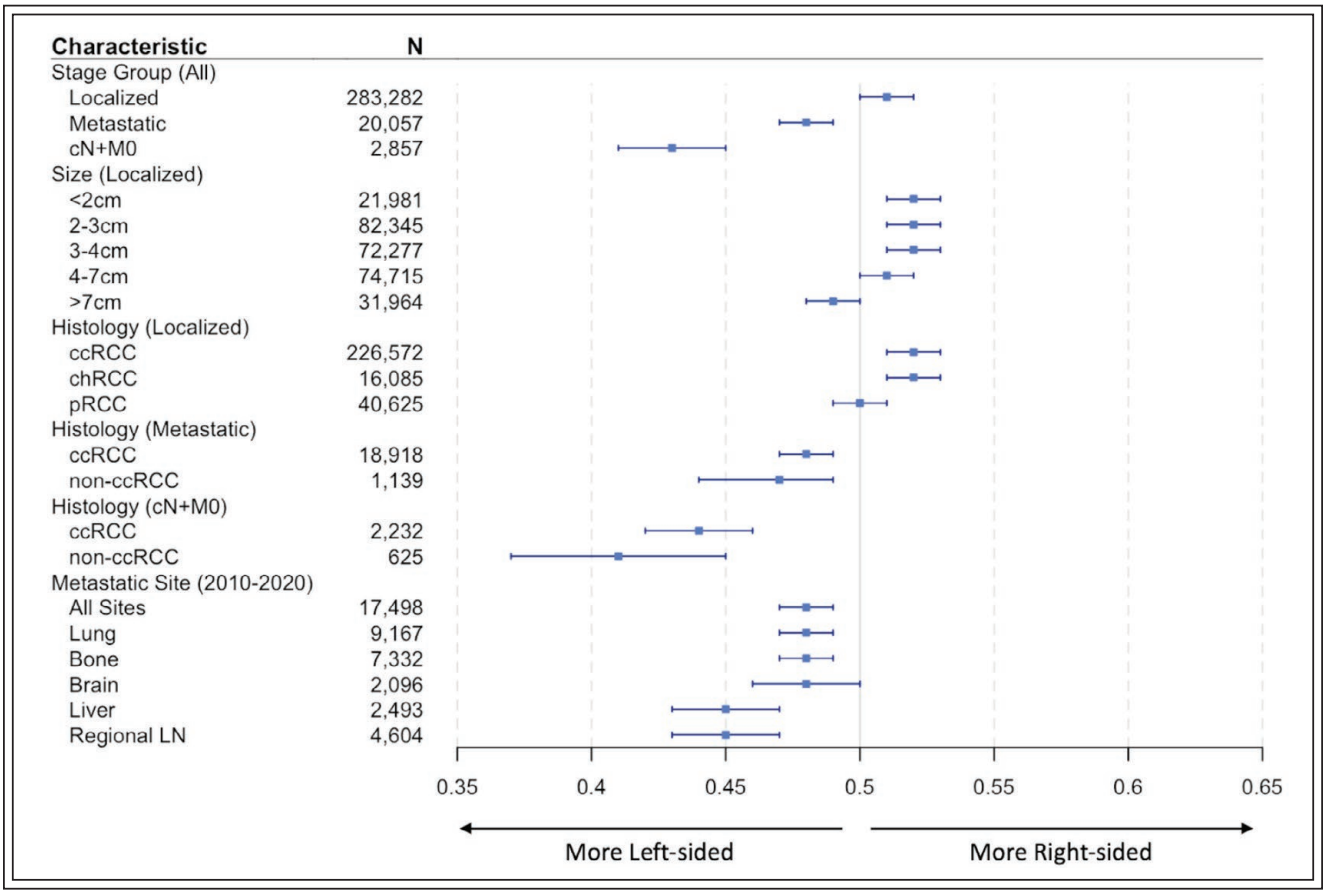

Figure 2. Forest plot demonstrating the proportion of patients with right sided tumors, across renal cell carcinoma subgroups.

sided tumors have been found to have higher diversity of antigen receptor CDR3 sequences, which was also associated with tumors of larger size, higher grade, and sarcomatoid status.[4]

To investigate RCC laterality further, two highly similar analyses were conducted using the SEER database – both reporting that left sided tumors have larger diameter, higher propensity for nodal involvement, and worse cancer-specific survival.[5,6] Both studies globally analyzed a heterogeneous cohort, including both localized and metastatic patients, substantially limiting clinical applicability and relying primarily on statistical adjustments to determine survival associations.

We hypothesize that these perceived laterality-associated survival differences result from left sided tumors presenting at a more advanced stage, and not from having inherently more aggressive behavior beyond the point of diagnosis. The primary objective of this study is to determine associations between tumor laterality and clinical presentation of patients with RCC, and to assess associations between laterality and overall survival within clinical stage groups.

Materials and methods

Data source and study population

RCC cases were identified in the National Cancer Database (NCDB) between 2004 and 2020. The NCDB includes more than 70% of incident cancer cases diagnosed in the United States, which are reported by member facilities of the Commission on Cancer. These facilities are not limited to academic centers, with more than 50% of participating facilities representing community cancer programs or comprehensive community cancer programs.[7] Trained

TABLE 1. **Right sided tumor characteristics**

Characteristic (stage group)	N	Right-sided	Proportion (95% CI)	p value
Stage group (all)				
Localized	283,282	145,615	0.51 (0.50-0.52)	< 0.001
Metastatic	20,057	9,600	0.48 (0.47-0.49)	< 0.001
cN+M0	2,857	1,235	0.43 (0.41-0.45)	< 0.001
Size (localized)				
< 2 cm	21,981	11,461	0.52 (0.51-0.53)	< 0.001
2-3 cm	82,345	42,870	0.52 (0.51-0.53)	< 0.001
3-4 cm	72,277	37,319	0.52 (0.51-0.53)	< 0.001
4-7 cm	74,715	38,147	0.51 (0.50-0.52)	< 0.001
> 7 cm	31,964	15,818	0.49 (0.48-0.50)	0.07
Histology (localized)				
ccRCC	226,572	116,881	0.52 (0.50-0.52)	< 0.001
pRCC	40,625	20,449	0.50 (0.49-0.51)	0.18
chRCC	16,085	8,285	0.52 (0.51-0.53)	< 0.001
Histology (metastatic)				
ccRCC	18,918	9,062	0.48 (0.47-0.49)	< 0.001
non-ccRCC	1,139	538	0.47 (0.44-0.49)	0.05
Histology (cN+M0)				
ccRCC	2,232	977	0.44 (0.42-0.46)	< 0.001
non-ccRCC	625	258	0.41 (0.37-0.45)	< 0.001
Nodal status (metastatic)				
cN0M+	14,881	7,263	0.49 (0.48-0.50)	0.08
cN+M+	5,176	2,337	0.45 (0.43-0.47)	< 0.001

Numeric proportions of right-sided tumors, stratified by stage group, tumor size, RCC histology, and nodal status. For the metastatic and cN+M0 subgroups, chRCC and pRCC were combined into a non-ccRCC group due to low sample size of patients with chRCC. Hypothesis testing compared the observed proportion to an expected proportion of 0.50 using one sample proportions testing with continuity correction.

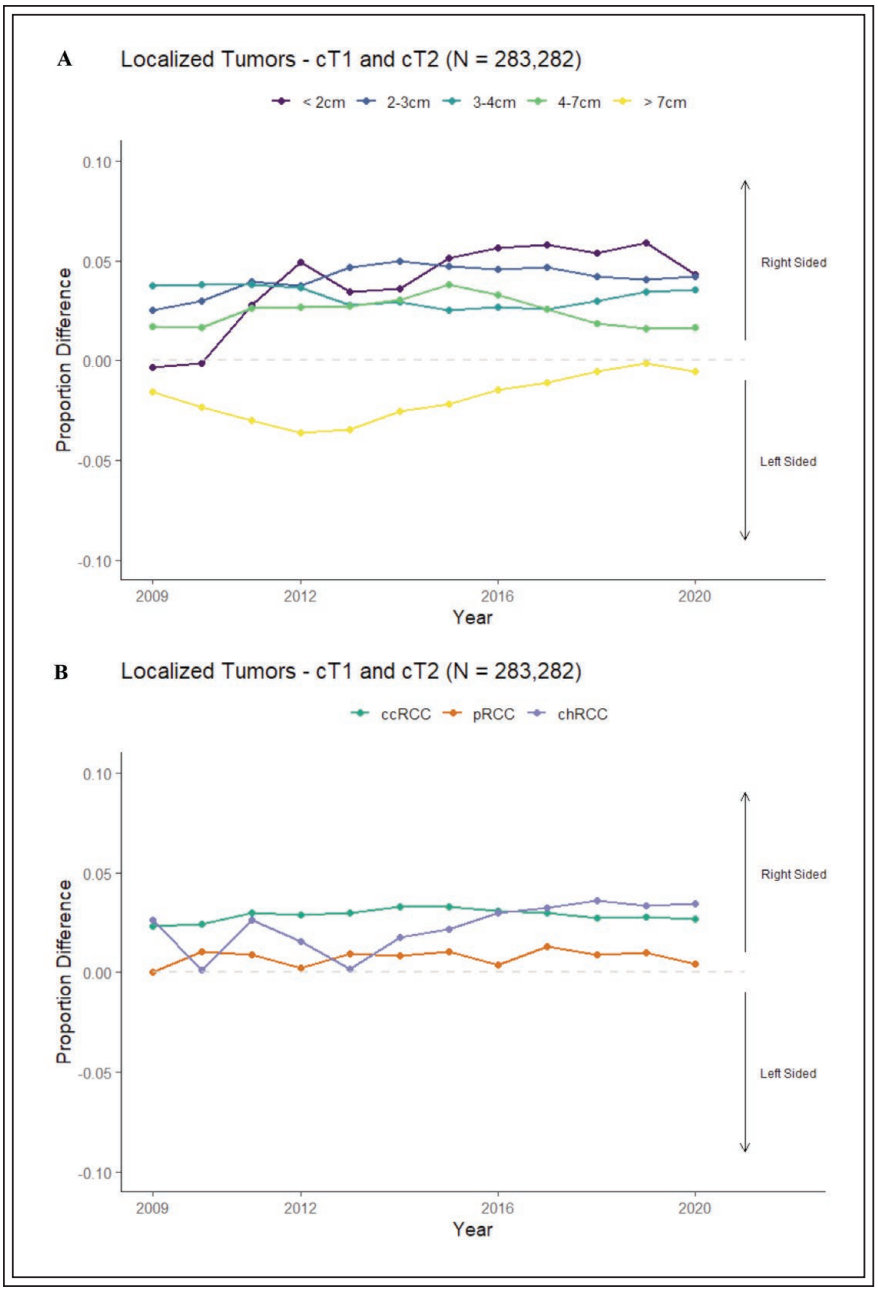

Figure 3. Among clinically localized cT1 and cT2 tumors, time series charts showing the difference in laterality proportion of renal masses over the year of diagnosis, presented as a 5-year average, stratified by **A:** the size of tumor, and **B:** tumor histology.

data abstractors collect and submit data to the NCDB using standardized coding definitions as specified in the most recent Commission on Cancer Facility Oncology Registry Data Standards guideline.[8] This study was conducted using deidentified data and was determined to be exempt from review by the Oregon Health & Science University institutional review board. This study was reported in a manner consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[9]

Patients included had tumors with the following histologies: clear cell (ccRCC), papillary (pRCC), or chromophobe (chRCC); excluding all other histologic subtypes. Patients with cT3 tumors were excluded, as these have a strong laterality bias due to asymmetric renal vein anatomy. Patients were excluded if they did not have complete staging and demographic data for the included variables, including laterality and tumor size. Patients with bilateral tumors were excluded. Patients were excluded if they received treatment on a clinical trial or experimental protocol. The years 2004-2020 were chosen as this was the full extent of the data set at the time the analysis was conducted (December 2023).

Variables and definitions:

Clinically localized disease was defined as cT1,2N0M0, regional as cT1,2,4N+M0, and metastatic disease was defined as cT1,2,4NanyM+. Consistent with previously reported NCDB studies, cytoreductive nephrectomy was defined as the receipt of radical, total, or partial nephrectomy as the initial therapy after diagnosis of metastatic ccRCC.[10-12] Delayed nephrectomy was defined as the receipt of radical, total, or partial nephrectomy after initiation of systemic therapy as the initial therapy after diagnosis of metastatic ccRCC. Targeted therapy was defined as the receipt of single or multi-agent systemic chemotherapy, immunotherapy was defined as the receipt of systemic immunotherapy, and combination therapy was defined as meeting criteria for both targeted and immunotherapy simultaneously as

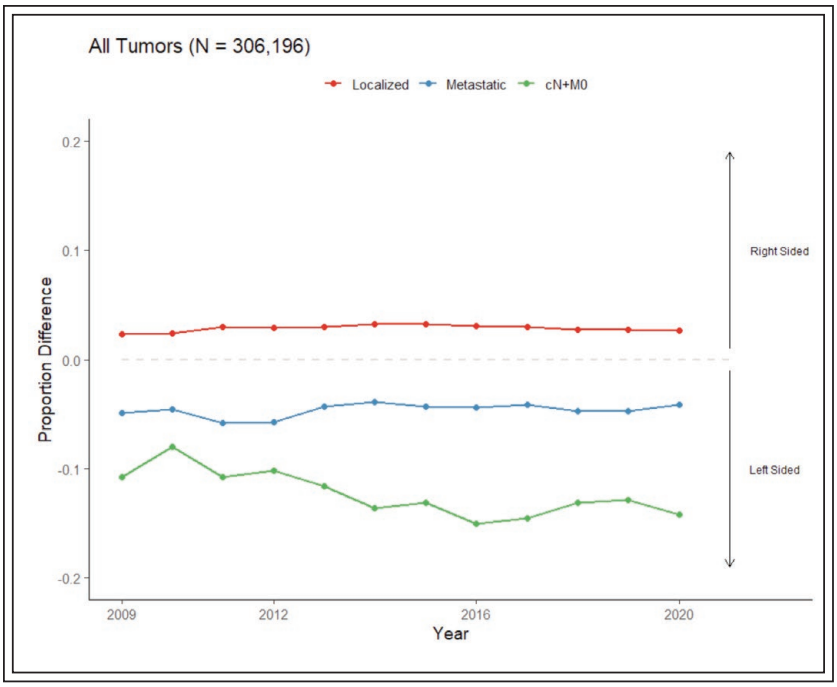

Figure 4. Differences in laterality proportion of renal masses over the year of diagnosis, stratified by clinical stage, presented as a 5-year average. Y-axis proportion difference is right minus left, such that values greater than zero are more right sided.

first-line therapy.[13-16] Systemic therapies are classified using the SEER*Rx Interactive Drug Database and coded into the NCDB without identifying specific drug names.[17]

Age was defined as age at initial diagnosis. Tumor size was stratified by clinically relevant cutoffs adapted from clinical staging and commonly utilized active surveillance criteria.[18,19] Comorbidities were measured according to the Charlson-Deyo method and scored as discrete count categories (0, 1, 2, or ≥ 3) per NCDB reporting standards.[20,21]

Statistical analysis:

Patients were stratified by tumor laterality and univariate comparisons were conducted using Wilcoxon rank sum and Pearson's Chi-square testing, when appropriate. Based on these results, in addition to variables thought to be clinically relevant, several subgroups were assessed for differential laterality, by testing against an expected value of 0.50 using one sample proportions testing with continuity correction. Multivariable logistic regression analysis based on tumor laterality was then conducted using available clinically relevant variables. Several time-series charts were generated to visually demonstrate laterality differences and their variance over time, presented as a 5-year moving average of laterality difference to facilitate data visualization.

Survival analysis was conducted using multivariable Cox proportional hazards modeling for the outcome of overall survival. Multiple analyses were done to assess whether laterality is associated with overall survival within staging groups. Kaplan-Meier estimates were utilized to visualize survival functions associated with these analyses.

Statistical significance was defined as a 2-tailed alpha risk ≤ 0.05. Statistical analyses and data visualization were performed using R version 4.2.1 (R Project for Statistical Computing, Vienna, Austria). Tabular data summary and visualization was facilitated by the gtsummary R package. Survival analysis was performed using the survival and survminer packages.

Results

Study population

After applying the inclusion and exclusion criteria, the final study population included 306,196 patients, Figure 1. Right-sided tumor laterality was present in 156,450 (51.1%) cases. At initial diagnosis, 283,282 (92.5%) patients had localized RCC, 20,057 (6.6%) metastatic RCC, and 2,857 (0.9%) cN+M0 RCC. Median follow up period for patients alive at last contact was 43.0 months [IQR 18.8-77.6].

Tumor laterality

Laterality proportions for selected subgroups are visualized in Figure 2 and are numerically described in Table 1. Clinically localized tumors were more likely to be right sided (right-proportion [95CI]: 0.51 [0.50-0.52], $p < 0.001$), while clinically metastatic and cN+M0 tumors were more likely to be left sided (0.48 [0.47-0.49], $p < 0.001$; and 0.43 [0.41-0.45], $p < 0.001$; respectively). For clinically localized tumors, smaller tumor sizes were more likely to be right sided (< 2 cm: 0.52 [0.51-0.53], $p < 0.001$), while tumors > 7cm did not have a statistically significant laterality association (0.49 [0.48-0.50], $p = 0.07$). For clinically localized tumors, ccRCC

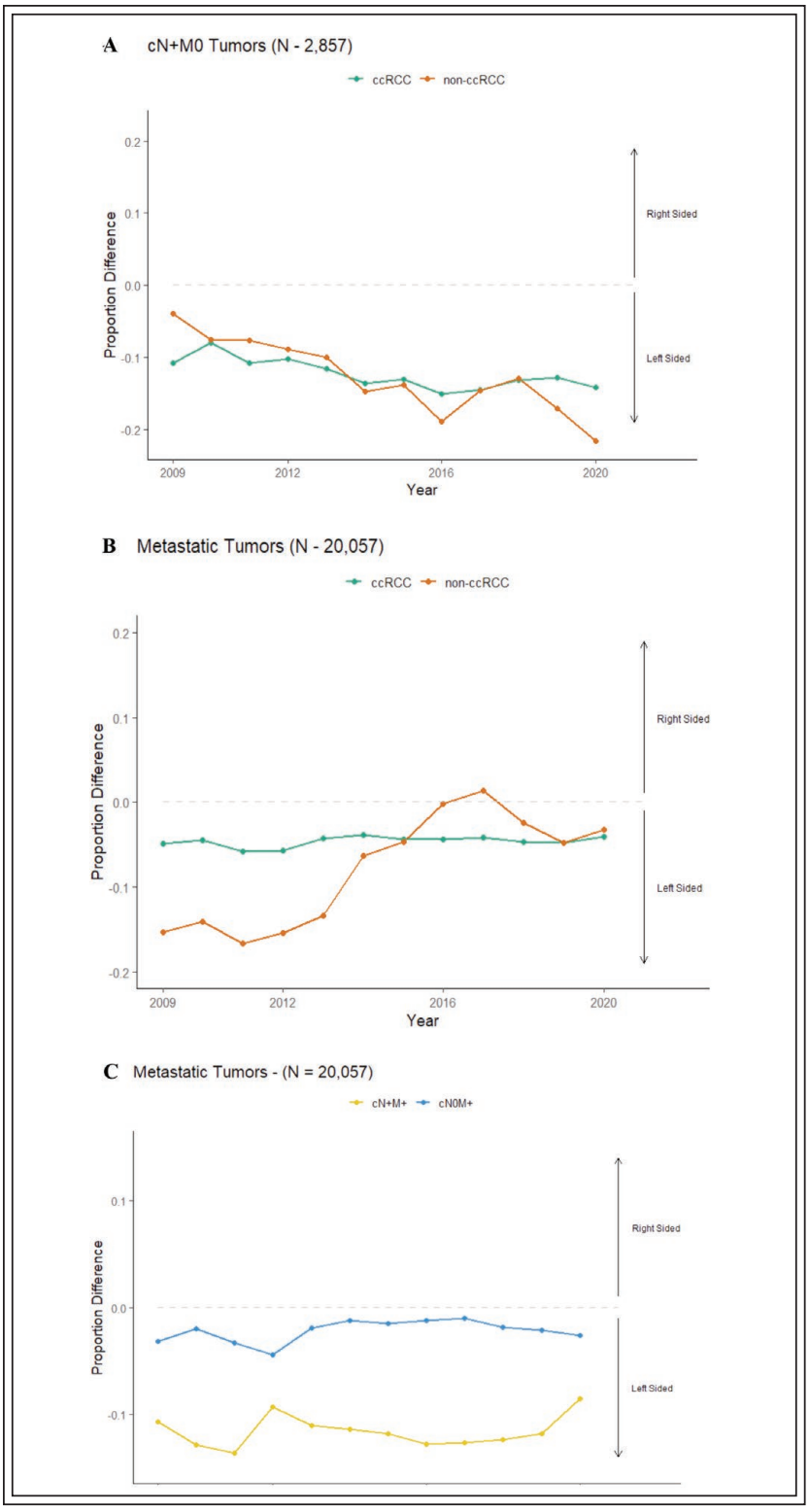

Figure 5. Difference in laterality proportion of renal masses over the year of diagnosis, presented as a 5-year average, stratified by ccRCC versus non-ccRCC histology, among **A:** cN+M0 staging, **B:** clinically metastatic RCC, **C** node positivity among patients with clinically metastatic RCC.

and chRCC tumors were associated with right sided laterality (0.52 [0.51-0.53], p < 0.001; and 0.52 [0.51-0.53], p < 0.001; respectively), while pRCC tumors did not have a statistically significant laterality association (0.50 [0.49-0.51], p = 0.18). The above findings were charted as a time series, and the described laterality proportions were found to be stable over the time period studied. Figure 3 and Figure 4.

Both ccRCC and non-ccRCC tumors exhibited associations with left sided laterality in patients with metastatic and cN+M0 RCC (metastatic: ccRCC 0.48 [0.47-0.49], p < 0.001; non-ccRCC 0.47 [0.44-0.49], p = 0.05; cN+M0: ccRCC 0.44 [0.42-0.46], p < 0.001; non-ccRCC 0.41 [0.37-0.45], p < 0.001), Figure 5a and 5b. Among patients with metastatic RCC, patients with clinical nodal positivity exhibited an association with left sided laterality, while those with clinically negative lymph nodes did not demonstrate a statically significant laterality association (0.45 [0.43-0.47], p < 0.001; and 0.49 [0.48-0.50], p = 0.08; respectively), Figure 5c. Patients with metastatic RCC and liver metastases were significantly more likely to have left sided primary tumor laterality (0.45 [0.43-0.47], p < 0.001), while patients with other distant metastatic sites had similar laterality proportions to the overall metastatic subgroup, Figure 2 and Table 1.

Univariable comparisons of demographics between patients with right and left sided tumors laterality are available Table 2. Multivariable comparisons between patients with right and left sided tumor laterality revealed that patients with right sided tumors were less likely to be female (HR [95CI]; 0.99 [0.99-0.99], p < 0.001), have pRCC histology (HR [95CI]; 0.99 [0.98-0.99], p < 0.001), larger tumor size (HR [95CI] for size > 7cm; 0.97 [0.96-0.98], p < 0.001), cN+ (HR [95CI]; 0.95 [0.94-0.96], p < 0.001), and cM+ (HR [95CI]; 0.99 [0.98-1.0], p = 0.001), Table 3.

TABLE 2. **Patient and tumor demographic information**

Characteristic	Right, n = 156,450	Left, n = 149,746	p value
Age	64 (54, 72)	64 (55, 72)	0.008
Sex			< 0.001
Male	98,518 (63%)	93,054 (62%)	
Female	57,932 (37%)	56,692 (38%)	
Race			0.4
White	129,981 (83%)	124,180 (83%)	
Black	19,041 (12%)	18,448 (12%)	
Other	7,428 (4.7%)	7,118 (4.8%)	
Charlson			0.9
0	104,072 (67%)	99,444 (66%)	
1	31,427 (20%)	30,119 (20%)	
2	11,725 (7.5%)	11,294 (7.5%)	
3+	9,226 (5.9%)	8,889 (5.9%)	
Facility type			0.6
Academic	59,479 (38%)	56,792 (38%)	
Non-Academic	96,971 (62%)	92,954 (62%)	
Histology			< 0.001
ccRCC	126,920 (81%)	120,802 (81%)	
pRCC	21,105 (13%)	20,949 (14%)	
chRCC	8,425 (5.4%)	7,995 (5.3%)	
Size			< 0.001
< 2 cm	11,694 (7.5%)	10,785 (7.2%)	
2-3 cm	43,669 (28%)	40,323 (27%)	
3-4 cm	38,552 (25%)	36,250 (24%)	
4-7 cm	41,152 (26%)	39,808 (27%)	
> 7 cm	21,383 (14%)	22,580 (15%)	
cN			< 0.001
cN0	152,878 (98%)	145,285 (97%)	
cN+	3,572 (2.3%)	4,461 (3.0%)	
cM			< 0.001
cM0	146,850 (94%)	139,289 (93%)	
cM+	9,600 (6.1%)	10,457 (7.0%)	

Patient and tumor demographics among the entire study population, stratified by tumor laterality. Median (IQR) and N (%) reported. Wilcoxon rank sum and Pearson's Chi-squared testing utilized for comparisons.

Survival analysis:

Multivariable Cox proportional hazards regression analysis not accounting for clinical stage demonstrated worse overall survival associated with left sided tumor laterality (HR [95% CI]; 1.05 [1.03-1.06], p < 0.001). However, multivariable Cox regressions within each clinical stage group did not demonstrate clinically significant associations between left sided laterality and overall survival (localized RCC: HR [95CI] 1.01 [0.99-1.02], p = 0.50; metastatic RCC: 1.03 [1.00-1.07], p = 0.7; cN+M0 RCC: 0.96 [0.86-1.07], p = 0.50), Table 4,5,6,7. Kaplan-Meier estimates for OS are available to visually demonstrate survival functions, Figure 6,7,8,9.

Discussion

Primarily, this analysis demonstrates that RCC tumors presenting with large size, regional nodal involvement, or distant metastases, particularly liver metastases,

TABLE 3. **Right-sided tumor analysis**

Characteristic	OR	95% CI	p value
Age	1.00	1.00, 1.00	0.065
Sex			
Male	—	—	
Female	0.99	0.99, 0.99	< 0.001
Race			
White	—	—	
Black	1.00	0.99, 1.00	0.8
Other	1.00	0.99, 1.01	0.7
Charlson			
0	—	—	
1	1.00	1.0, 1.00	0.7
2	1.00	0.99, 1.01	0.7
3+	1.00	0.99, 1.01	0.8
Facility type			
Academic	—	—	
Non-Academic	1.00	1.00, 1.00	0.7
Histology			
ccRCC	—	—	
pRCC	0.99	0.98, 0.99	< 0.001
chRCC	1.00	0.99, 1.01	0.8
Size			
< 2 cm	—	—	
2-3 cm	1.00	0.99, 1.01	0.8
3-4 cm	1.00	0.99, 1.00	0.2
4-7 cm	0.99	0.98, 1.00	0.003
> 7 cm	0.97	0.96, 0.98	< 0.001
cN			
cN0	—	—	
cN+	0.95	0.94, 0.96	< 0.001
cM			
cM0	—	—	
cM+	0.99	0.98, 1.0	0.001

Multivariable logistic regression analysis for the outcome of right-sided tumor. Higher ORs indicate higher association with right sided laterality as compared to the reference.

TABLE 4. **Entire population survival analysis**

Characteristic	HR	95% CI	p value
Age	1.04	1.04, 1.04	< 0.001
Sex			
Male	—	—	
Female	0.83	0.81, 0.84	< 0.001
Race			
White	—	—	
Black	1.16	1.13, 1.18	< 0.001
Other	0.89	0.85, 0.92	< 0.001
Charlson			
0	—	—	
1	1.21	1.19, 1.23	< 0.001
2	1.51	1.48, 1.54	< 0.001
3+	1.87	1.82, 1.91	< 0.001
Facility type			
Academic	—	—	
Non-Academic	1.1	1.08, 1.11	< 0.001
Histology			
ccRCC	—	—	
pRCC	0.72	0.70, 0.73	< 0.001
chRCC	0.55	0.52, 0.57	< 0.001
Nephrectomy			
No	—	—	
Yes	0.37	0.37, 0.38	< 0.001
Laterality			
Right	—	—	
Left	1.05	1.03, 1.06	< 0.001

Multivariable Cox proportional hazards regression for the outcome of overall survival, among the entire study population, without accounting for tumor stage.

are more likely to be left sided. However, patients with left sided RCC did not have worsened overall survival when compared with patients in their same stage group. Overall, left sided RCC tumors seem to present with more advanced clinical stage, but do not have a worse prognosis beyond the point of diagnosis.

Previous cancer registry studies have associated left sided RCC laterality with worse prognosis. Using the SEER and ZfKD databases, Strauss et al found that patients with left sided tumors were more likely to present with higher T stages, regional nodal involvement, and distant metastasis, and to have worsened cancer-specific survival.[6] A similar SEER analysis by Guo et al identified similar results, with left sided RCC associated with later clinical stage and worse CSS.[5] Among a single-institution cohort of patients with metastatic RCC, Choueiri et al noted that left sided tumors were associated with worse overall survivals.[22]

The NCDB is uniquely suited to address the clinical implications of RCC tumor laterality, as it is the largest and most representative data source in the United States, capturing approximately 70% of all cancer cases in the country.[23] The highly representative nature of the data limits bias due to referral patterns associated with academic tertiary care centers. Additionally,

TABLE 5. **Localized renal cell carcinoma survival analysis**

Characteristic	HR	95% CI	p value
Age	1.05	1.05, 1.06	< 0.001
Sex			
Male	—	—	
Female	0.85	0.84, 0.87	< 0.001
Race			
White	—	—	
Black	1.25	1.22, 1.28	< 0.001
Other	0.84	0.80, 0.88	< 0.001
Charlson			
0	—	—	
1	1.35	1.32, 1.38	< 0.001
2	1.82	1.77, 1.87	< 0.001
3+	2.46	2.38, 2.53	< 0.001
Facility type			
Academic	—	—	
Non-Academic	1.1	1.08, 1.12	< 0.001
Histology			
ccRCC	—	—	
pRCC	0.85	0.83, 0.87	< 0.001
chRCC	0.61	0.58, 0.64	< 0.001
Size			
< 2 cm	—	—	
2-3 cm	1	0.96, 1.05	0.9
3-4 cm	1.2	1.15, 1.26	< 0.001
4-7 cm	1.49	1.42, 1.56	< 0.001
> 7cm	2.29	2.19, 2.41	< 0.001
Nephrectomy			
No	—	—	
Yes	0.44	0.43, 0.45	< 0.001
Laterality			
Right	—	—	
Left	1.01	0.99, 1.02	0.5

Multivariable Cox proportional hazards regression for the outcome of overall survival, among patients with clinically localized RCC.

TABLE 6. **Metastatic renal cell carcinoma survival analysis**

Characteristic	HR	95% CI	p value
Age	1	1.00, 1.00	0.01
Sex			
Male	—	—	
Female	1.02	0.98, 1.06	0.3
Race			
White	—	—	
Black	1.1	1.03, 1.17	0.007
Other	0.94	0.85, 1.03	0.2
Charlson			
0	—	—	
1	1.07	1.02, 1.12	0.006
2	1.1	1.02, 1.19	0.015
3+	1.15	1.04, 1.26	0.004
Facility type			
Academic	—	—	
Non-Academic	1.18	1.13, 1.23	< 0.001
Histology			
ccRCC	—	—	
pRCC	1.12	1.03, 1.22	0.009
chRCC	1.1	0.89, 1.36	0.4
Nephrectomy			
No nephrectomy	—	—	
Up-front nephrectomy	0.49	0.47, 0.51	< 0.001
Delayed nephrectomy	0.38	0.34, 0.42	< 0.001
Therapy			
Targeted Therapy	—	—	
Immunotherapy	0.69	0.66, 0.73	< 0.001
Combination TT/IT	0.66	0.61, 0.72	< 0.001
Laterality			
Right	—	—	
Left	1.03	1.00, 1.07	0.072

Multivariable Cox proportional hazards regression for the outcome of overall survival, among patients with clinically metastatic RCC.

the large patient population afforded by the NCDB allowed the survival analysis to be conducted within clinical stage groups, confirming that left-sidedness is not a harbinger of poor prognosis when compared to right sided tumors of similar stage.

Analysis of site specific metastatic spread revealed that left sided tumors were more likely to metastasize to regional lymph nodes and the liver, when compared to other common metastatic sites such as bone, brain and lung. There are few published articles discussing variations in metastatic spread with regards to disease laterality in RCC. Nini et al found that while patients with bilateral RCC were more likely to have lymph node involvement and nodal progression, disease laterality was not an independent predictor for either.[24] Raffoul and colleagues suggested that left sided disease may have a tendency to spread to the pancreas due to a shared lymphovascular track traversing Gerota's

TABLE 7. **Node positive renal cell carcinoma survival analysis**

Characteristic	HR	95% CI	p value
Age	1.02	1.02, 1.03	< 0.001
Sex			
Male	—	—	
Female	0.94	0.84, 1.06	0.3
Race			
White	—	—	
Black	1.09	0.93, 1.27	0.3
Other	0.99	0.72, 1.35	> 0.9
Charlson			
0	—	—	
1	1.24	1.08, 1.42	0.002
2	1.45	1.19, 1.76	< 0.001
3+	1.34	1.07, 1.68	0.011
Facility type			
Academic	—	—	
Non-Academic	1.16	1.03, 1.30	0.013
Histology			
ccRCC	—	—	
pRCC	1.16	1.00, 1.34	0.05
chRCC	0.56	0.40, 0.79	< 0.001
Size			
< 2 cm	—	—	
2-3 cm	0.96	0.58, 1.60	0.9
3-4 cm	1.07	0.65, 1.76	0.8
4-7 cm	1.33	0.82, 2.18	0.2
> 7 cm	1.84	1.13, 2.98	0.014
Nephrectomy			
No	—	—	
Yes	0.32	0.28, 0.36	< 0.001
Laterality			
Right	—	—	
Left	0.96	0.86, 1.07	0.5

Multivariable Cox proportional hazards regression for the outcome of overall survival, among patients with cN+M0 RCC.

fascia.[25] Unfortunately, we were unable to assess pancreatic involvement, as it is not specifically tracked as a metastatic site in the NCDB.

It is well-established that RCC is increasingly being detected at earlier stages, due to the increased availability and utilization of CT scans and ultrasound, resulting in incidental identification of asymptomatic small renal masses.[26] Assuming the true incidence of RCCs is equal across laterality, we hypothesize that right sided tumors may be detected earlier due to the asymmetry of ultrasound practices with regard to laterality. Right upper quadrant ultrasound is often obtained as an early step in the workup of nausea or abdominal pain, capturing the right kidney but not the left.[27] Additionally, retroperitoneal ultrasound can have better resolution on the right than the left due to a broad acoustic window afforded by the liver.[28] Though these hypotheses are conceivable, our data is not adequate to directly support them.

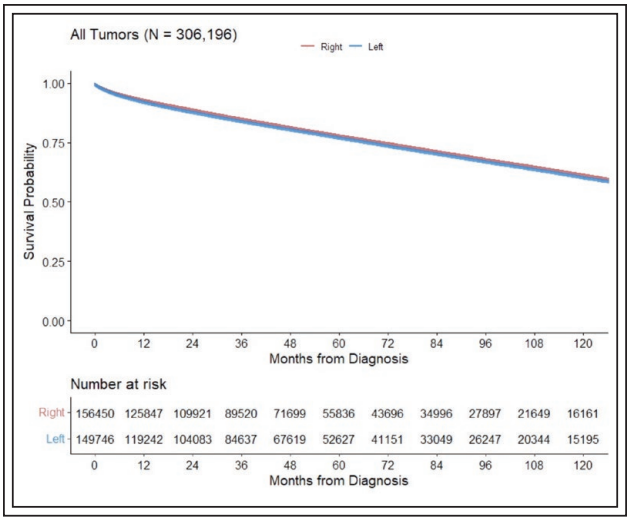

Figure 6. Kaplan-Meier estimates for overall survival, stratified by tumor laterality, for the entire patient population.

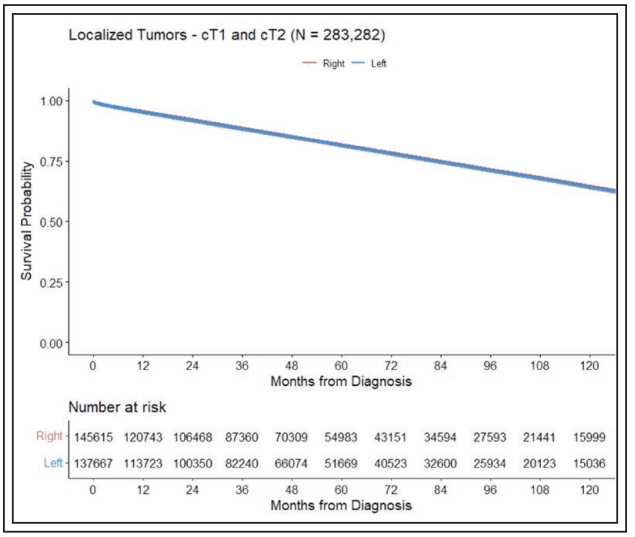

Figure 7. Kaplan-Meier estimates for overall survival, stratified by tumor laterality, among patients with clinically localized tumors.

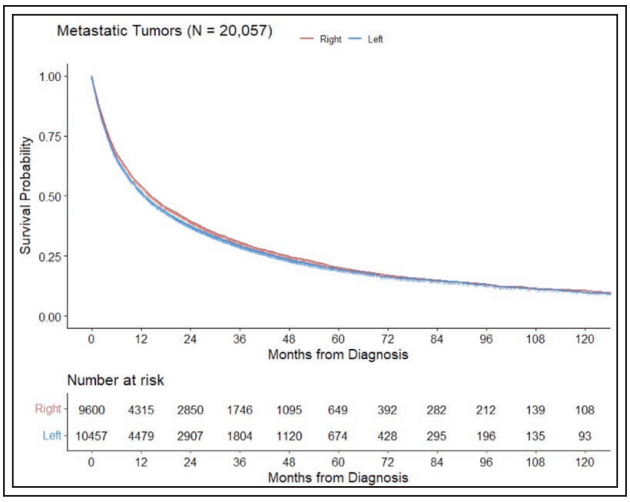

Figure 8. Kaplan-Meier estimates for overall survival, stratified by tumor laterality, among patients with clinically metastatic tumors.

Alternatively, it is possible that left-sided RCC is truly associated with greater propensity for advanced disease beyond what can be explained by incidental detection differences alone. This discrepancy could plausibly stem from known biologic, anatomic, and pathophysiologic differences between the left and right kidney. Most notably, laterality differences in vascular supply, lymphatic drainage, and tumor-immune microenvironment can all be contributing to these findings.[1,2] However, the idea that left-sided tumors are inherently more biologically aggressive is disputed by our finding that overall survival was not associated with laterality when analyzed within clinical stage groups.

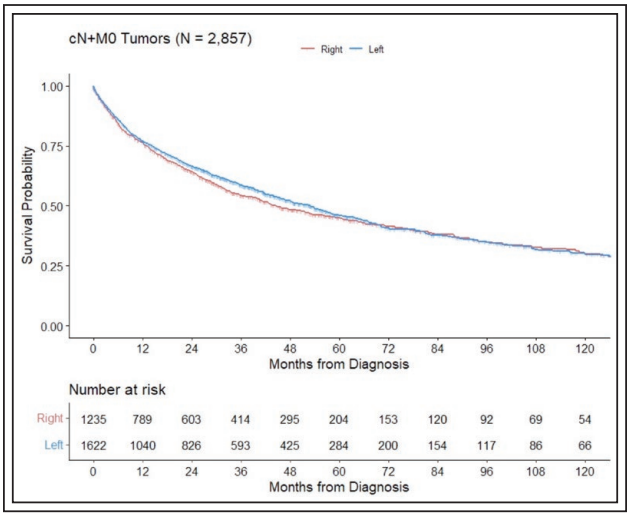

Figure 9. Kaplan-Meier estimates for overall survival, stratified by tumor laterality, among patients with cN+M0 tumors.

Limitations

There are several limitations to this analysis. Importantly, the NCDB has a large and representative patient population, but highly limited data granularity, precluding the inclusion of: imaging modality of initial tumor detection, body mass index, renal function, MSKCC or IMDC risk status, metastatic volume, tumor mutational burden, and PD-L1 status, all of which would have contributed substantially if able to be included in the analysis. Additionally, there is an inherent risk of selection bias due to unmeasured confounding variables in observational studies. Finally, the NCDB does not track pancreatic, thyroid, or adrenal sites of distant metastasis, which are clinically relevant sites of RCC metastasis that would have contributed positively if available.

Conclusion

Left-sided tumor laterality was associated with larger tumor size, propensity for regional nodal involvement, and distant metastases, particularly liver metastases. However, tumor laterality was not associated with overall survival when analyzed within clinical stage groups. Overall, left-sided RCC tumors seem to present with more advanced clinical stage but do not demonstrate more aggressive behavior beyond the point of diagnosis. □

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