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Original Article

Prognostic significance of sarcomatoid features in metastatic renal cell carcinoma treated with cytoreductive nephrectomy and targeted therapy

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Abstract: Introduction: The presence of sarcomatoid features in localized renal cell carcinoma (RCC) is associated with worse outcomes. We sought to use a national database to evaluate the outcomes and prognosis of metastatic RCC (mRCC) with sarcomatoid features treated with cytoreductive nephrectomy (CN) and targeted therapy (TT). Methods: The National Cancer Database (2010-2013) was used to identify patients with mRCC at diagnosis. Only patients who underwent CN followed by TT were included. Kaplan-Meier curves, log-rank test, and multivariate Cox regression analysis were used to compare overall survival (OS) between mRCC with and without sarcomatoid features. Subgroup analysis in patients with clear cell RCC (ccRCC) was performed. Results: A total of 1,427 patients with mRCC treated with CN followed by TT were included of which 364 (26%) had mRCC with sarcomatoid features. mRCC with sarcomatoid features were more likely to have Fuhrman grade 4 cancer. mRCC with sarcomatoid features had worse OS than mRCC without sarcomatoid features (24.6 vs 12.0 months, P < 0.001). For the clear cell cohort, mRCC with sarcomatoid features had worse OS than mRCC without sarcomatoid features (26.2 vs 14.0 months, P < 0.001). Multivariate Cox regression showed sarcomatoid features was significantly associated with worse OS in the overall cohort (hazard ratio [HR] =1.63, 95% confidence interval [CI] =1.38-1.91, P < 0.001) and the ccRCC subcohort (HR=1.53, 95% CI=1.23-1.90, P < 0.001). Discussion/Conclusion: mRCC with sarcomatoid features treated with CN and TT has a very poor and drastically different prognosis compared with mRCC without sarcomatoid features. With the expansion of systemic RCC therapies, investigation is needed to optimize treatment in this high-risk cohort.

Keywords: Carcinoma, renal cell, cytoreduction surgical procedures, prognosis, nephrectomy, molecular targeted therapy

Introduction

There has been an increase in the national incidence of kidney cancer [1], with the recent data from 2020 predicting approximately 73,000 incident cases along with roughly 15,000 deaths [2]. As our understanding of the molecular biology underlying renal cell carcinoma (RCC) continues to evolve, it is becoming apparent that the variant biology of RCC subtypes can lead to vastly different clinical outcomes and thus require tailored management strategies [3].

There are numerous histological classes and subclasses of RCC. Across all these histological classes overlies the finding of 'sarcomatoid differentiation' as a modifier of these classes. According to two recent studies, sarcomatoid renal cell carcinoma (sRCC) is not a unique histological subtype of RCC but rather a reflection of cells undergoing de-differentiation via an epithelial to mesenchymal transition such that their cellular features resemble mesenchymal tissue. It is imperative that the sarcomatoid component lacks any epithelial characteristics. Characteristic features of the sarcomatoid com-

ponent include heterogenous or uniform regions of spindle cells with high cellularity and cellular atypia [4, 5]. Unfortunately, the majority (~75%) of patients with this finding typically present with metastatic disease and have a historical median survival of 4-12 months [6].

In select patients, cytoreductive nephrectomy (CN) to remove the primary tumor may be of benefit. Historically the data regarding the utility of CN were performed in the cytokine treatment era and did show a survival benefit [7-9]. More recently trials such as CARMENA [10] and SURTIME [11] have questioned the utility of CN with targeted therapy (TT). Indeed, there has been a subsequent controversy surrounding variant RCC histology and the efficacy of CN.

Furthermore, a new age of TT has dawned where tyrosine kinase inhibitors (TKI) and vascular endothelial growth factor inhibitors (VEGF-I) are used in a variety of RCC clinical settings. Typically, these agents have been studied in the broader RCC population without a focus on the at-risk patient with sarcomatoid features on their final pathology.

Thus, there is a gap in our understanding of outcomes for metastatic RCC (mRCC) patients with sarcomatoid differentiation who have been managed with CN and contemporary TT management strategies. The objective of this study was to evaluate the outcomes and prognosis of patients treated with CN and TT utilizing a national database. We hypothesized that, in contrast to other RCC patients, those mRCC patients who had sarcomatoid features on final pathology treated with CN and TT would fare worse than those without this histologic finding.

Methods

Data source

We designed this study using the National Cancer Database (NCDB) as a retrospective cohort study. This validated dataset is released jointly from the American Cancer Society and the American College of Surgeons' Commission on Cancer (CoC). The dataset is de-identified. It contains information regarding patient characteristics, facility information, cancer staging, types of treatment, and follow up [12]. This study was deemed exempt from review by our Institutional Review Board.

Cohort design

We sought to identify a cohort of patients with metastatic renal cell carcinoma who initially underwent cytoreductive nephrectomy followed by adjuvant targeted therapy. These patients were then stratified by the presence of sarcomatoid features on their pathology. We utilized NCDB years 2010-2013 to attempt to best capture a timeframe when targeted therapy was in robust use. From all patients in NCDB from 2010-2013 we excluded patients whose presentation was not their first or only cancer diagnosis to identify patients with a *de novo* presentation. We then included those who had metastatic cancer as their initial presentation. Within these patients with initially presenting metastatic cancer, we included patients who had cytoreductive surgery +/- metastatectomy. Surgical approach was only available starting from 2010. From this surgical cohort, we then included those who received systemic therapy. We then removed patients whose systemic therapy preceded surgery. Patients who received external beam radiation as adjunctive therapy were included but any other kind of radiation therapy led to exclusion from our study cohort. Additionally, those who had received any hormonal or immunotherapy as initial therapy or those who had radiation therapy that was not external beam were excluded from this cohort of patients. This gave us a cohort of patients who had metastatic disease on initial presentation who underwent cytoreductive surgery +/- metastatectomy followed by TT. Kidney cancer cases within this cohort were identified by including patients who had International Classification of Diseases for Oncology, third edition (ICD-O-3) topography code C64.9 and histology codes 8000 to 8980, which includes all major RCC histologies. We then limited the organ to kidney, giving us organ specific cases with known RCC histologies. This provided us the cohort of mRCC patients who underwent CN followed by TT. Within this surgical and systemic therapy cohort we tabulated which cases had sarcomatoid features on final pathology. We also stratified by Furhman nucleolar grade. Only patients with complete survival data were included in the final analysis. Lastly, we sequentially excluded cases with missing or unknown data on key variables. We designed a subcohort of clear cell RCC patients from this main mRCC group for further analysis.

Table 1. Demographic description of mRCC cohort with or without sarcomatoid features

	Sarcomatoid Features (n=364)	Without Sarcomatoid Features (n=1,063)	*P* value
Age Median (IQR)	59 (53-66)	61 (54-67)	0.002
Sex			0.121
F	95 (26.1%)	323 (30.4%)	
M	269 (73.9%)	740 (69.6%)	
Race			0.382
White	318 (87.4%)	955 (89.8%)	
Black	26 (7.1%)	65 (6.1%)	
Other/unknown	20 (5.5%)	43 (4.1%)	
Charlson/Deyo Score			0.109
0	271 (74.5%)	733 (69.0)	
1	75 (20.6%)	254 (23.9)	
≥ 2	18 (5.0%)	76 (7.2)	

Measured covariates and outcomes

The following covariates were included in our analysis: age, gender, race, Charlson-Deyo comorbidity score, insurance status, median household income, educational attainment of the residency area, urban/rural status, facility type and location, year of diagnosis, approach of surgery (open, lap, robotic), systemic therapy administration, external beam radiation administration, metastatectomy, final histology, TNM staging, sarcomatoid differentiation status, and Furhman grade. Our outcome of interest was overall survival (OS) of the entire cohort and of the ccRCC sub cohort, stratified by sarcomatoid status.

Statistical methodology

Demographic, patient level, tumor stage and grade, treatment(s), and OS are reported. For continuous variables we report medians with interquartile ranges (IQR). Frequencies and percentages were used for categorical variables. Comparisons of continuous variables were conducted using Wilcoxon rank-sum tests, and for categorical variables we used chi-squared analysis. Survival was depicted using Kaplan-Meier curves and compared using the Log-Rank test. Multivariable Cox regression analysis was used to investigate the effect of sarcomatoid features on OS. We repeated the regression model in the subgroups of patients in the ccRCC cohort. A significance level of 0.05 was used for all statistical tests. All data analysis was performed using STATA 15 (StataCorp LP, College Station, TX).

Results

Cohort & demographics

We included a total of 1,427 patients with mRCC who underwent CN followed by TT, 364 (26%) of which had sarcomatoid features. **Table 1** presents a demographic description of this cohort of patients who underwent CN, stratified by the presence of sarcomatoid features on primary pathology. The patients who harbored tumors with sarcomatoid features tended to be younger, with a median age of 59 years (vs 61 years, P= 0.002). There were no other statistically significant demographic differences between the groups. Roughly one third of the entire cohort was female. The cohort was mostly caucasian (87.4% of the sarcomatoid cohort, 89.8% without sarcomatoid features) and of good performance status (74.5% of the sarcomatoid cohort, 69% without sarcomatoid features).

Pathology & treatment

As expected, the sarcomatoid group had statistically significant differences from the non-sarcomatoid group on final histopathology. **Table 2** illustrates significantly more Furhman grade 4 tumors, pT4 disease, and node positive disease within the sarcomatoid cohort. There was no difference in surgical approach between the two groups with most patients having open surgery. Roughly a quarter of each group had radiation. Interestingly, 21.3% of the non-sarcomatoid feature cohort underwent metastatectomy. There is a statistically significant difference when compared to the 15.9% metastatectomy rate for those patients with sarcomatoid features.

Comparison of survival

The median OS of the entire cohort of patients who underwent CN followed by TT for mRCC was 19.6 months. In the overall cohort, those patients who had sarcomatoid features on final pathology had worse OS than those without

Table 2. Pathologic and surgical description of mRCC cohort with or without sarcomatoid features

	Sarcomatoid Features (n=364)	Without Sarcomatoid Features (n=1,063)	*P* value
Fuhrman grade			< 0.001
1-2	18 (5.0%)	232 (21.8%)	
3	62 (17.0%)	497 (46.8%)	
4	284 (78.0%)	334 (31.4%)	
Pathologic T stage			< 0.001
T1	15 (4.1%)	109 (10.3%)	
T2	45 (12.4%)	187 (17.6%)	
T3	247 (67.9%)	689 (64.8%)	
T4	57 (15.7%)	78 (7.3%)	
Pathologic N stage			< 0.001
N0	125 (34.3%)	412 (38.8%)	
N+	107 (29.4%)	203 (19.1%)	
Nx	132 (36.3%)	448 (42.1%)	
Surgical approach			0.817
Robotic	30 (8.2%)	91 (8.6%)	
Laparoscopic	81 (22.3%)	252 (23.7%)	
Open	253 (69.5%)	720 (67.7%)	
Radiation	93 (25.6%)	302 (28.4%)	0.292
Metastasectomy	58 (15.9%)	226 (21.3%)	0.028

such features (24.6 months vs 12.0 months, P < 0.001) (**Figure 1**). In the clear cell sub-cohort, median OS was 23.7 months for all patients. In comparing those with and without sarcomatoid pathology it is notable that OS was worse for those who had sarcomatoid features (26.2 months vs 14.0 months, P < 0.001) (**Figure 1**).

Effect of sarcomatoid features on overall survival

Multivariate Cox regression revealed that sarcomatoid features were significantly associated with worse OS in the overall cohort (hazard ratio [HR] 1.63, 95% confidence interval [CI] 1.38-1.91, P < 0.001) and the clear cell subcohort (HR 1.53, 95% CI 1.23-1.90, P < 0.001) [**Table 3**]. The model adjusted for age, sex, race, comorbidity, insurance, education, income, residence location, facility type, facility location, Fuhrman grade, pathologic T stage, pathologic N stage, surgical approach, radiation, and metastasectomy.

Discussion

In the TT era, there is a lack of data regarding outcomes for mRCC patients with sarcomatoid differentiation who have been managed with CN and novel TT agents. Our study was designed to use national data to determine contemporary outcomes and prognosis of such patients treated with CN and TT. We found that patients with sarcomatoid mRCC tended to be younger and have more advanced disease pathologically. In the entire cohort and ccRCC subcohort, OS was roughly half for those with sarcomatoid features on final histopathology (overall cohort: 24.6 months vs 12.0 months, P < 0.001; ccRCC cohort: 26.2 months vs 14.0 months, P < 0.001). On multivariate analysis controlling for multiple covariates, we found that sarcomatoid features were significantly associated with worse overall survival (overall cohort HR 1.63, 95% CI 1.38-1.91, P < 0.001; ccRCC subcohort HR 1.53, 95% CI 1.23-1.90, P < 0.001). These results suggest that sarcomatoid differentiation is a marker of aggressive disease and portend poor prognosis even in the setting of cytoreductive nephrectomy and treatment with targeted therapy agents.

It is believed that a sarcomatoid cellular differentiation finding reflects an epithelial to mesenchymal transition and thus microscopically, one will find both epithelial and mesenchymal (or sarcomatoid) cellular features, such as dense cellularity, atypia, or spindle cells [4]. Recent molecular subtyping of sarcomatoid RCC samples has shown that these tumors retain some of the alterations of the parent histology but have distinct mutational and transcriptional profile [13]. Future research looking at which mutational and transcriptional profiles correlate with response to CN and TT treatments may offer personalized medicine and improved prognoses to patients. Epidemiologically, sarcomatoid features are thought to account for ~5% of all RCC [14]. They are found in 5-8% of ccRCC, 2-3% of papillary RCC, and 8-9% of chromophobe tumors [15-17]. While sarcomatoid features are present in only a small number of tumors, the implications of this finding for prognosis and outcomes are dramatic; they present with large primary tumors and usually with metastatic disease.

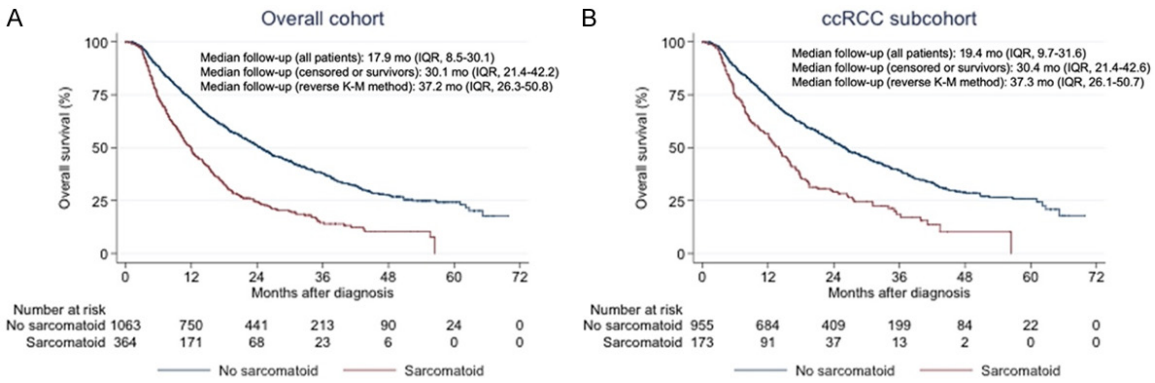

Figure 1. Kaplan-Meier curves of overall survival stratified by sarcomatoid features in the (A) overall cohort (n=1,427) and (B) clear cell RCC subcohort (n=1,128). *For (A), median follow-up (all patients): 17.9 months (IQR, 8.5-30.1); median follow-up (censored or survivors): 30.1 months (IQR, 21.4-42.2); median follow-up (reverse K-M method): 37.2 months (IQR, 26.3-50.8). For (B) median follow-up (all patients): 19.4 months (IQR, 9.7-31.6); median follow-up (censored or survivors): 30.4 months (IQR, 21.4-42.6); median follow-up (reverse K-M method): 37.3 months (IQR, 26.1-50.7).*

Table 3. Multivariate Cox regression investigating the effect of sarcomatoid features on overall survival

Contribution of Sarcomatoid Features to Overall Survival	HR (95% CI)	*P* value
Overall Cohort (n=1,427)		
No Sarcomatoid	Reference	
Sarcomatoid	1.63 (1.38-1.91)	< 0.001
ccRCC Subcohort (n=1,128)		
No Sarcomatoid	Reference	
Sarcomatoid	1.53 (1.23-1.90)	< 0.001

Some have argued that these patients have the worst survival among all RCC patients [13], and our study further strengthens this correlation of sarcomatoid features with poor prognosis.

More contemporary series that are focused on patients with sarcomatoid histology have described a grim picture. Data has shown that sarcomatoid patients have worse survival in the non-metastatic setting, that mRCC patients with sarcomatoid features have worse OS compared to ccRCC [18], and that non-ccRCC patients fare worse when they have sarcomatoid features compared to ccRCC patients with the same sarcomatoid differentiation [19]. Our data support these prior findings in that globally, having sarcomatoid features on pathology is a poor prognostic indicator, even when controlling for other cofounding factors as evidenced by our finding of OS decreasing by roughly half in those patients with sarcomatoid features.

Related to this is the question of how patients with sarcomatoid features fare with either surgical or systemic management. Institutional [20] and national [21] cohorts have described trends suggesting that patients with sarcomatoid features have worse outcomes compared to those with other subtypes of mRCC when treated surgically. Our finding of worse OS in the overall and ccRCC cohort support these findings. A natural extension is to question the efficacy of the novel TT agents to this patient cohort. Multiple retrospective reports have described how patients with sarcomatoid features have a limited response to TKI or VEGF-I agents [22, 23], but no prospective data exists. Given that all the patients in our cohort received TT one can then infer that the decrease in OS reflects how such agents lack efficacy against this particular histologic subtype. Future research focusing on prospective trials could offer novel insights into the optimal treatment regimens for sarcomatoid subtype mRCC. Our study augments this literature by reporting similar outcomes from a national, multicenter dataset.

This study has significant limitations. NCDB collects its data from CoC affiliated hospitals and while it does capture a large amount of oncologic surgical cases it is not fully generalizable to the community. We would surmise that sarcomatoid mRCC cases are of such high disea-

se burden and complexity that most patients would be managed at high-volume referral centers. One data point that is lacking in our study is the degree of sarcomatoid features on final pathology, as some studies have stratified by this parameter [23], which unfortunately is not captured in NCDB. Furthermore, we do not know the specifics of the TT that these patients receive which limits the applicability of our conclusions. However, our findings validate previous institutional reports utilizing a national, generalizable, dataset.

Conclusions

Patients with mRCC and sarcomatoid features treated with cytoreductive nephrectomy and targeted therapy have a very poor and drastically different prognosis compared with mRCC without sarcomatoid features. With the rapid expansion of systemic RCC therapies, further prospective investigation is needed to optimize management in this high-risk cohort.

Disclosure of conflict of interest

None.

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