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Clinicopathologic features associated with survival after cytoreductive nephrectomy for nonclear cell renal cell carcinoma

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Abstract

Objectives: To report the overall survival (OS) outcomes of patients with nonclear cell renal cell carcinoma (nccRCC) treated at our institution with a cytoreductive nephrectomy (CN) and better understand the clinical and pathological characteristics of the patients that respond best.

Material and methods: We queried our prospectively maintained database for patients who underwent CN for nccRCC between 1989 and 2018. Histology was reviewed by an expert genitourinary pathologist, and nccRCC tumors were subdivided into papillary, unclassified, chromophobe, and other histology. Baseline clinicopathology, treatments, and survival outcomes were recorded. Preoperative hematological parameters including the neutrophil-to-lymphocyte ratio (NLR) were analyzed. Significant univariate predictors of OS were tested in a multivariate model.

Results: There were 100 nccRCC patients treated with CN. Median age was 61 years (IQR: 48−69) and 65% were male. There were 79 patient deaths with a median OS of 13.7 months (10.8−27.2). Estimated 2- and 5-year survival was 40.1% and 12.2%, respectively. Median follow-up of survivors was 13 months (IQR: 3−30). On multivariate analysis, increasing NLR (hazard ratio [HR] 1.27; 95% confidence interval [CI] 1.14−1.40, $P < 0.001$) and sarcomatoid features (HR 2.18; 95% CI 1.19−3.97, $P = 0.014$) conferred worse OS and the presence of papillary features were a favorable prognostic feature (HR 0.37; 95% CI 0.21−0.65, $P < 0.001$).

Conclusions: OS outcomes in patients with nccRCC who underwent a CN are consistently modest throughout the study period. Patients with papillary features and a lower preoperative NLR may be better candidates for a CN.

Keywords: Cytoreductive nephrectomy; Kidney; Renal cell carcinoma; Nonclear cell histology; Prognosis

1. Introduction

In 2019, there will be an estimated 73,820 Americans diagnosed with kidney cancer, predominantly renal cell carcinoma (RCC), and 14,770 deaths from kidney cancer [1]. RCC encompasses a collection of different morphological

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subtypes, with approximately 70% classified as clear cell RCC (ccRCC), and the remaining histologies often grouped into the category of non-ccRCC (nccRCC) [2]. Biologically, nccRCC behaves differently from ccRCC by metastasizing less frequently, but when metastases occur, nccRCC confers a worse prognosis than ccRCC [3]. Level 1 evidence from the United States and Europe demonstrated a significant survival advantage in ccRCC of approximately 5 months for cytoreductive nephrectomy (CN) compared with Interferon alone [4–6]. A survival benefit was presumed in patients with nccRCC, but no level 1 evidence evaluating the therapeutic effect of CN in this population of kidney cancer patients exists. More recent clinical trials have questioned the benefit of CN for ccRCC compared with Sunitinib [7,8]. While surgeons and oncologists initially applied the same approach to patients with nccRCC histology, it became evident that nccRCC is less responsive to conventional cytokine and targeted therapies used in ccRCC [9,10]. Therefore, we sought to determine the impact of a CN on overall survival (OS) in patients with nccRCC and identify any prognostic factors that predict improved patient outcomes.

The diagnosis and management of patients with nccRCC has evolved over time. The last 15 years has seen systemic therapy options for patients with metastatic RCC expanding, with the introduction of tyrosine kinase and checkpoint blockade inhibitors. Furthermore, the classification of RCC subtypes has changed over time [11]. Few studies and case series have published the outcomes from CN in patients with nccRCC, with 2-year survival reported at 25% to 50% [12–16]. Most retrospective studies comparing CN with systemic therapy alone report that CN improves survival for ccRCC and nccRCC, yet these studies are limited by selection biases [17]. Due to the low volume of cytoreductive nephrectomies for nccRCC, recent studies have come from population databases, however, these studies are limited by similar selection biases as single center case series and by a lack of a centralized pathology review, likely making it difficult to draw concrete conclusions about nccRCC histologic subtypes that are challenging to classify.

Therefore, we reviewed patients undergoing a CN for nccRCC at Memorial Sloan Kettering Cancer Center, using modern pathological tools to provide histological granularity and relevance to contemporary management. We aimed to report our experience with this operation, describe treatment outcomes, and identify clinical, pathological and hematological characteristics that are associated with prognosis after CN.

2. Material and methods

Following Institutional Review Board approval, we queried our prospectively collated nephrectomy database for all metastatic RCC patients treated at Memorial Sloan Kettering Cancer Center from July 1989 to May 2018 ($n = 986$). We included all patients with nccRCC histology that had metastatic disease at the time of nephrectomy ($n = 80$) and patients diagnosed as metastatic within 90 days of nephrectomy ($n = 24$).

All patient records were individually reviewed to ensure data accuracy. All available pathology specimens were rereviewed by a dedicated genitourinary pathologist (YBC), blinded to patient outcomes, of which 8 diagnoses were subsequently reclassified: 2 as ccRCC, 4 as a different nccRCC subtype, and 2 as not RCC. The remaining 100 nccRCC histological subtypes were grouped as papillary RCC (pRCC) ($n = 24$), chromophobe RCC (chRCC) ($n = 15$), unclassified RCC (uRCC) ($n = 36$), and other nccRCC ($n = 25$). Patients with uRCC and MiT family translocation RCC (tRCC) were further assessed by pathologists for the presence of papillary features, defined as a large component of multinodular and/or intracytic papillary growth [18]. Given the heterogeneous architectural patterns of uRCC and tRCC, a positive finding of papillary features was recorded when this component constituted >25% of the assessable tumor areas.

Preoperative clinicopathological factors and postoperative management were explored. Hematological parameters prior to surgery were recorded where available, including the neutrophil-to-lymphocyte ratio (NLR) and published biomarkers predictive for patient outcomes: hemoglobin, platelet, neutrophil, lactate dehydrogenase and calcium [19,20]. All laboratory values were treated as continuous variables, described with the median and interquartile range (IQR). Lactate dehydrogenase values were measured preoperatively in 55% of patients, limiting the ability to explore the use of risk stratification tools designed for metastatic ccRCC.

The main study outcome was OS. Estimated OS was first evaluated univariately via a Cox proportional hazards model. Time from the procedure to death from kidney cancer or last follow-up was recorded. Death from kidney cancer was considered as the event, and patients were censored at the date of last follow-up. Significant univariate predictors for OS were added into a multivariate model, and stepwise regression was employed until all variables were independently significant. For each significant variable, a Kaplan-Meier curve was used to illustrate the estimated effect on OS, with survivors censored at their last follow-up date. Continuous variables were stratified by their median value, and the log-rank test was used to compare the estimated survival. All statistical analyses were 2 sided and a Pvalue of <0.05 was considered significant. All statistical analyses were conducted using R version 3.5.1 (R Core Development Team, Vienna, Austria).

3. Results

Among 100 nccRCC patients, 65% of the cohort were male and the median age was 61 years (IQR: 48–69). Patients predominantly had a good performance status, with 90% having a Karnofsky Performance Status ≥80. Table 1

Table 1
Baseline cohort characteristics.

Variable	$n = 100$
Gender	
Female	35 (35%)
Male	65 (65%)
Age	61 (48, 69)
Race	
Asian	5 (5.0%)
Black	12 (12%)
White	75 (75%)
Unknown	8 (8.0%)
BMI	27.4 (22.9, 30.3)
Unknown	1
KPS	
<80	9 (10%)
≥80	81 (90%)
Unknown	10
Smoking history	
Current	3 (3.0%)
Former	42 (42%)
Never	54 (55%)
Unknown	1
Diabetes	
Yes	11 (11%)
No	85 (89%)
Unknown	4
Hypertension	
Yes	41 (43%)
No	55 (57%)
Unknown	4
Hypercholesterolemia	
Yes	19 (20%)
No	77 (80%)
Unknown	4
Prior cancer	
Yes	13 (13%)
No	86 (87%)
Unknown	1
Family history of cancer	
Yes	66 (67%)
No	33 (33%)
Unknown	1
Therapeutic era	
Post-2005	77 (77%)
Pre-2005	23 (23%)
Tumor side	
Left	60 (60%)
Right	40 (40%)
Tumor size	8.4 (6.0, 13.2)
Pathological tumor stage	
≤T2	26 (26%)
≥T3	74 (74%)
Nodal stage	
N0/NX	40 (40%)
N+	60 (60%)
Histology	
Chromophobe (chRCC)	15 (15%)
Other RCC	25 (25%)
Papillary (pRCC)	24 (24%)
Unclassified (uRCC)	36 (36%)
Papillary features	
Present	39 (39%)
Absent	61 (61%)
Sarcomatoid dedifferentiation	
Present	25 (26%)
Absent	72 (74%)
Unknown	3
Necrosis	
Present	30 (31%)
Absent	67 (69%)
Unknown	3
Neutrophil	5.65 (4.20, 7.12)
Unknown	20
Lymphocyte	1.40 (1.05, 1.80)
Unknown	21
Neutrophil to lymphocyte ratio	4.00 (2.80, 5.66)
Unknown	21
Hemoglobin	12.20 (10.80, 13.70)
Unknown	11
Platelets	303 (226, 384)
Unknown	11
Calcium	9.30 (8.90, 9.60)
Unknown	16
Lactate dehydrogenase	191 (160, 264)
Unknown	45

Note: Hemoglobin has been gender adjusted by adding 0.5 to all females.

summarizes the clinicopathological characteristics of the study cohort.

Of the 4 histological groups, 15 patients had chRCC, 24 patients had pRCC, 36 patients had uRCC, and 25 patients were classified as other nccRCC. Other nccRCC included collecting duct ($n = 6$), renal medullary carcinoma ($n = 4$), and tRCC ($n = 2$). Pathologists identified papillary features in 39 tumors: pRCC ($n = 24$), uRCC ($n = 13$), and tRCC ($n = 2$). The chRCC tumors were larger ($P = 0.023$) and had a higher proportion that exhibited sarcomatoid features ($P = 0.020$). Other nccRCC tumors occurred in younger patients ($P < 0.001$). (Supplementary Table 1)

Median follow-up of survivors was 13.3 months (3–30.4). Preoperatively, 7 patients received systemic therapy. Two patients had a significant therapeutic response, 4 experienced mixed responses with toxicity (hematuria ($n = 3$), gastrointestinal ($n = 1$)), and 1 did not respond and had a nephrectomy performed between systemic treatments. Postoperatively, 64 patients received systemic therapy, 34 patients did not, and 2 were unknown. Most cytoreductive nephrectomies were performed after the introduction of targeted therapies (2006–2018) and the majority of patients received targeted therapy as their first-line treatment (Table 1). Ultimately, all patients' deaths were cancer-related, with 79 patients dying and a median OS of 13.7 months (10.8–27.2). Estimated 2- and 5-year OS were 40.1% and 12.2%, respectively.

On univariate analysis, pathological tumor stage ≥T3, node positive disease, presence of sarcomatoid features, increasing neutrophil count, decreasing lymphocyte count, increasing NLR, increasing hemoglobin, and increasing

Table 2
Overall survival: univariate analysis.

Variable	Number	HR	95% CI	*P* value
Gender	100			0.5
Female		Ref.		
Male		1.16	0.73−1.85	
Age	100	0.99	0.97−1.00	0.10
Race	100			0.8
Asian		Ref.		
Black		1.31	0.35−4.89	
White		1.55	0.43−7.52	
Unknown		1. 79	0.48−4.96	
BMI	99	1.00	0.97−1.04	0.8
KPS	90			0.2
<80		Ref.		
≥80		0.57	0.28−1.17	
Smoking history	99			0.7
Current		Ref.		
Former		1.58	0.48−5.20	
Never		1.38	0.42−4.49	
Diabetes	96			0.13
No		Ref.		
Yes		1.70	0.89−3.23	
Hypertension	96			0.5
No		Ref.		
Yes		0.86	0.54−1.36	
Hypercholesterolemia	96			>0.9
No		Ref.		
Yes		1.00	0.58−1.73	
Prior cancer	99			0.7
No		Ref.		
Yes		1.12	0.57−2.20	
Family history of cancer	99			0.7
No		Ref.		
Yes		1.08	0.67−1.76	
Therapeutic era	100			0.5
Cytokine era		Ref.		
Targeted era		1.21	0.72−2.03	
Tumor side	100			0.6
Left		Ref.		
Right		1.12	0.71−1.78	
Tumor size	99	1.02	0.97−1.06	0.5
Pathological tumor stage	100			0.009
≤T2		Ref.		
≥T3		1.97	1.15−3.35	
Nodal stage	100			0.005
N0/NX		Ref.		
N+		1.94	1.21−3.12	
Histology	100			0.2
Chromophobe (chRCC)		Ref.		
Other RCC		1.61	0.78−3.30	
Papillary (pRCC)		0.79	0.40−1.56	
Unclassified (uRCC)		1.08	0.56−2.09	
Sarcomatoid dedifferentiation	97			0.002
Absent		Ref.		
Present		2.27	1.38−3.73	
Necrosis	97			0.4
Absent		Ref.		
Present		1.22	0.75−1.97	
Papillary features	100			0.025
Absent		Ref.		
Present		0.60	0.38−0.95	
Neutrophil	80	1.34	1.17−1.54	<0.001
Lymphocyte	79	0.54	0.29−1.02	0.025
Neutrophil to lymphocyte ratio	79	1.27	1.16−1.40	<0.001
Hemoglobin	89	0.84	0.75−0.94	0.004
Platelets	89	1.00	1.00−1.01	<0.001
Calcium	84	0.99	0.58−1.68	>0.9
Lactate dehydrogenase	55	1.00	1.00−1.00	0.2

platelets were associated with poor survival outcomes. (Table 2) Survival did not vary significantly between 4 histological subtypes. However, the presence of papillary features among pRCC, uRCC, and tRCC tumors, was associated with a survival benefit on univariate and multivariate analysis (hazard ratio [HR] 0.37; 95% confidence interval [CI] 0.21−0.65, $P < 0.001$). (Fig. 1) The presence of sarcomatoid features in the primary tumor specimen was a predictor of worse OS on univariate and multivariate analysis (HR 2.18; 95% CI 1.19−3.97, $P = 0.014$). (Fig. 2) (Table 3)

There were 79 patients with NLR data available. Median preoperative NLR value was 4.00 (IQR: 2.80−5.66). No significant difference was found in the NLR scores between the histological subtypes ($P = 0.8$). When NLR was dichotomized by the median value, patients with a low NLR had better OS ($P = 0.004$) (Fig. 3). On multivariate Cox-regression analysis, an increasing preoperative NLR was a significant independent predictor of all-cause mortality (HR 1.27; 95% CI 1.14−1.40, $P< 0.001$).

4. Discussion

Nonclear cell variants of metastatic RCC are aggressive, difficult to treat, and less studied to date. This study sought to characterize patient outcomes following CN for nccRCC. The review, spanning 29 years, represents the largest reported cohort of nccRCC CN from a single institution, and included a centralized histology review using current diagnostic criteria and ancillary tools. Patients had a 2- and 5-year OS of 40.1% and 12.2%, respectively. Increased NLR and sarcomatoid features conferred worse OS and the presence of papillary features were associated with improved survival.

CN for nccRCC is uncommon, therefore most studies to date have relied on pooled-institutional and population databases. A meta-analysis of patients with either ccRCC or nccRCC demonstrated an improved survival for patients treated with a CN compared with systemic therapy only, although the outcomes are modest [17]. Heng et al. reported

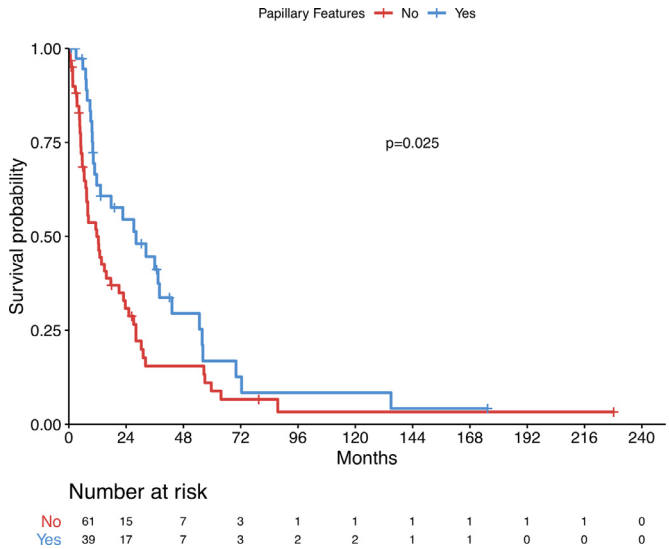

Fig. 1. Kaplan-Meier overall survival estimate stratified by papillary features.

the results of CN for nccRCC across 30 different institutions, showing a median survival of 15.3 months [13]. Additionally, in 2 separate SEER-based studies, Airzer et al. between 2004 and 2009 and Marchioni et al. between 2010 and 2014 reported a 2-year cancer-specific mortality rate of 59.2% and 52.6% after CN for patients with nccRCC, respectively [12,15]. These outcomes are similar to our experience, highlighting the shorter survival after CN for nccRCC compared with ccRCC [21]. However, multi-institutional and population based studies are limited by no centralized pathological review and often have restrictions on reportable outcomes.

Few single center series have evaluated the role of CN in patients with nccRCC [14,16]. In the largest previously published single institution analysis investigating CN between 1991 and 2006, Kassouf et al. reported 92 nccRCC cytoreductive cases with a 2-year OS of 24%. Moreover, they described an increased proportion of patients with nodal disease, however, surprisingly, this was reported to be a favorable feature in their cohort [14]. Carrasco et al. reviewed the Mayo Clinic's experience of 505 cytoreductive nephrectomies between 1970 and 2008, including 40 with nccRCC [16]. This cohort consisted of 57.5% of patients with papillary RCC, reporting 3-year cancer-specific survival of 22% for nccRCC patients, similar to the 25.7% (17.7%–37.1%) 3-year survival in our cohort.

The role and timing of CN as part of the multimodal management of ccRCC is evolving, especially with new effective systemic therapies being introduced. The rationale for cytoreduction in ccRCC and nccRCC is to debulk a potentially immunosuppressive disease, avoid the seeding

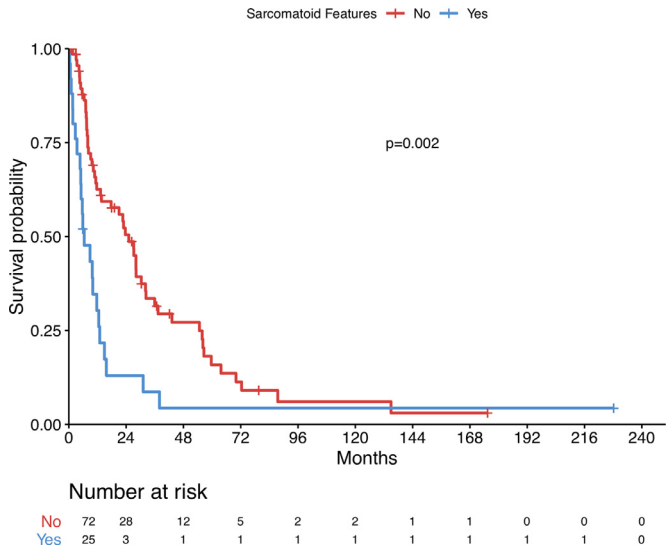

Fig. 2. Kaplan-Meier overall survival estimate stratified by sarcomatoid features.

Table 3
Overall survival: multivariate analysis.

N = 79	HR	95% CI	*P*value
Pathological tumor stage			0.052
≤T2	Ref.		
≥T3	1.91	0.97–3.74	
Sarcomatoid differentiation			0.014
Absent	Ref.		
Present	2.18	1.19–3.97	
Papillary features			<0.001
Absent	Ref.		
Present	0.37	0.21–0.65	
NLR	1.27	1.14–1.40	<0.001

of new metastases, and to manage local symptoms and systemic paraneoplastic symptoms. The CARMENA trial evaluated the effect of CN in ccRCC on OS [7], however, given that treatment outcomes in nccRCC are different, it is important to test the impact of CN over time in this population. Therefore, we evaluated the outcomes of patients treated across the cytokine and targeted therapy eras, to explore the impact of newer treatments. In our cohort, we did not find a significant difference in OS across these eras and, given that baseline patient characteristics did not differ significantly over time, this highlights the inefficacy of newer therapies in this population. This is further supported by the comparable survival outcomes that were described in earlier single center studies and more recent population studies. The 7 patients that received systemic therapy prior to a delayed nephrectomy did not have improved OS. Finally, a third of the cohort did not receive systemic therapy after CN; they included patients with stable metastases observed and untreated to last follow-up, and patients with rapidly progressive metastases unfit for systemic therapy. However, with the advent of newer immunotherapy, renewed investigation will be required to reevaluate the role of CN in this therapeutic era [14].

With diagnoses covering multiple decades, it was important to undertake in-house specimen review to ensure that the diagnoses were consistent with contemporary RCC classification. The uRCC tumors contributed the largest proportion of the cytoreductive cases. These tumors could be subdivided into those with and without papillary features. All 4 groups of nccRCC were aggressive, despite the relatively indolent courses that may be ascribed in localized presentations.

On multivariate analysis, we found that sarcomatoid features, increased NLR, and papillary features were predictive for patient outcomes. Sarcomatoid differentiation was present in 26% of the cohort, with previous studies also finding the presence of sarcomatoid features to be associated with a poor prognosis following CN in both ccRCC and nccRCC [22,23]. While not statistically significant on multivariate analysis (P= 0.052), pathological tumor stage ≥T3 had an increased hazard (1.91) for OS following cytoreduction, consistent with other studies of CN in ccRCC [24].

Papillary features among patients with nccRCC is an interesting favorable pathological feature. We have previously reported this finding in a clinical trial of advanced nccRCC treated with Everolimus plus Bevacizumab [18]. The heterogeneous nature of our cohort suggests that papillary features may confer a more indolent disease course in the metastatic setting in general. As this cohort was diagnosed from the primary tumor specimen, future research efforts may help determine whether this is a finding that can be reliably detected through a preoperative biopsy to assist in patient selection for CN.

While hemoglobin, platelets, lymphocyte, and neutrophil values were all predictive of OS on univariate analysis, the NLR was the only hematological parameter that was significant on multivariate regression analysis. Interestingly, this

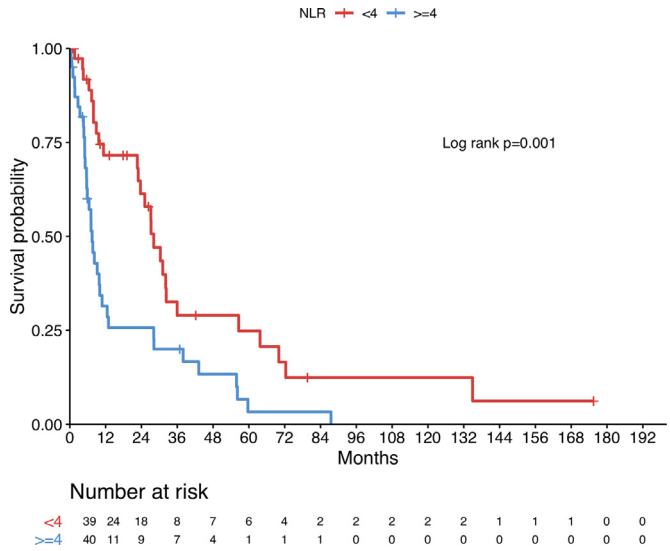

Fig. 3. Kaplan-Meier overall survival estimate stratified by NLR.

parameter is not present in established ccRCC risk scores. Although the preoperative NLR is a nonspecific snapshot, which may vary with nononcological events including stress, trauma, and infections, it has previously been demonstrated to predict poor oncological outcomes for genitourinary cancers [25,26]. Furthermore, an elevated NLR has also been associated with reduced survival following CN in patients with ccRCC, where tumors have a well described immune system interaction [27–30]. However, the impact of changes in the NLR has not been studied in CN for patients with nccRCC. Further research into the associations between the NLR and events within the tumor microenvironment may help to better characterize the role of this prognostic marker.

Limitations to this study exist in the cohort design and its retrospective nature, thereby allowing intrinsic biases that may affect the results. Patients with nccRCC are a heterogeneous group, from which we have a relatively small sample size and a diverse range of histologies. Conversely, the strength of limiting the analysis to this institution was that we were able to undertake a pathological rereview utilizing our centralized tumor repository. Our findings, particularly those relying on pathological inferences, will require external validation. Additionally, although prognostic stratification has been designed for patients with metastatic ccRCC initiating systemic therapy [19,20], these prognostic models have not been used for survival following CN in patients with nccRCC, so it is unclear whether they would have utility for this population. Finally, this study does not account for the volume and location of metastatic disease. While difficult to quantify uniformly retrospectively, this could represent an avenue for future research into the management of metastatic nccRCC.

5. Conclusion

Our study has identified predictors of OS outcomes following CN for nccRCC. Sarcomatoid differentiation and an increased preoperative NLR were associated with adverse OS, while tumors exhibiting papillary features had a more indolent OS. These variables identified may help in selecting suitable candidates for CN in metastatic nccRCC. Future studies using a preoperative biopsy to identify papillary and sarcomatoid features are needed to validate this information.

Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.07.011.

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