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C-Reactive Protein Levels and Survival Following Cytoreductive Nephrectomy in 118 Patients with Metastatic Renal Cell Carcinoma Treated with Sunitinib: A Retrospective Study

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Background: This study aimed to evaluate the factors associated with a survival benefit for patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib, with and without cytoreductive nephrectomy (CN).

Material/Methods: This retrospective clinical study included 118 patients with mRCC who were treated with CN and sunitinib (CN-sunitinib) (N=70) and with sunitinib-alone (N=48). Categorical clinicopathological variables were compared with hypothesis tests using contingency tables and a chi-squared test. Independent indicators for progression-free survival (PFS) and overall survival (OS) were analyzed with univariate and multivariate Cox regression models. The Kaplan-Meier method and log-rank test were used to evaluate patient survival.

Results: The median PFS and OS for the 118 patients were 8.38 and 15.48 months, respectively. There were no significant differences between the CN-sunitinib group and the sunitinib-alone group for either PFS (7.2 months *vs.* 11.6 months; P=0.525) or OS (16.7 months *vs.* 15.2 months; P=0.839). Stratification of patients based on clinicopathological characteristics showed that CN was significantly associated with reduced PFS and OS for patients with lymph node metastasis (PFS, P<0.001; OS, P<0.001) and high International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk scores (PFS, P=0.003; OS, P=0.011). However, CN was associated with a significant survival benefit for patients with low levels of serum C-reactive protein (CRP<10 mg/L) (PFS, P=0.026; OS, P=0.007).

Conclusions: Sunitinib-alone without CN improved the survival of patients with mRCC who had high IMDC risk scores or lymph node metastasis. CN and sunitinib resulted in significantly improved survival in patients with low serum CRP.

MeSH Keywords: C-Reactive Protein • Carcinoma, Renal Cell • Nephrectomy • Prognosis

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Background

Worldwide, renal cell carcinoma (RCC) is the third most common malignancy of the genitourinary system and accounts for approximately 3% of all malignant tumors and 2% of all cancer deaths in adults [1]. Approximately 25–30% of patients have metastases at initial diagnosis of RCC diagnosis, and cytoreductive nephrectomy (CN) combined with systemic therapy has shown some efficacy for patients who have metastatic RCC (mRCC) [2]. The results from two randomized clinical trials conducted in the 1990s showed that CN significantly increased the survival of patients with mRCC compared with cytokine therapy alone, resulting in CN being recommended as the standard first-line treatment for mRCC [3,4]. However, there is currently insufficient clinical data available to determine whether CN confers a significant survival benefit for patients with mRCC in the current era of molecular targeted therapy [5–7].

Advances in the understanding of the molecular biology of RCC have led to the development of targeted therapy [8], including vascular endothelial cell growth factor (VEGF) antagonists, tyrosine kinase inhibitors (TKIs), and mTOR inhibitors [9,10]. Targeted therapy has provided new first-line and second-line treatment options for mRCC. However, there are no guidelines for the use of combination CN and targeted therapy in patients with mRCC, and the optimal sequence or combination of individual therapies for patients with mRCC remains to be identified [11].

Sunitinib is an oral receptor tyrosine kinase inhibitor (RTKI) that is approved for the treatment of RCC. In 2018, the results were published from the prospective phase III Clinical Trial to Assess the Importance of Nephrectomy (CARMENA), which compared outcome following treatment with sunitinib alone with nephrectomy plus sunitinib [12]. The findings from this trial showed no significant survival benefit for patients with mRCC treated with combined CN and sunitinib compared with sunitinib alone [12]. However, a retrospective study based on the US National Cancer Database (NCD) showed a survival benefit for CN combined with targeted therapy compared with sunitinib alone [13]. The findings from a retrospective study that included analysis of a cancer database showed than in patients with mRCC and favorable prognostic characteristics determined by Memorial Sloan Kettering Cancer Center (MSKCC) and Eastern Cooperative Oncology Group (ECOG) performance status, CN improved overall survival (OS) [14]. However, this trend was not observed in another study of patients with mRCC with poor MSKCC or ECOG performance status [15]. It remains unclear which subgroups of patients with mRCC obtain a survival benefit from treatment with combined CN and sunitinib compared with sunitinib alone [16].

Therefore, this retrospective study aimed to evaluate the factors associated with a survival benefit, in terms of progression-free survival (PFS) and overall survival (OS), in 118 patients with mRCC treated with sunitinib, with and without CN.

Material and Methods

Patients

This retrospective study included 118 patients with metastatic renal cell carcinoma (mRCC) who were treated between May 2009 and June 2018 at the Department of Urology, Fudan University Shanghai Cancer Center (FUSCC) Shanghai, China. Patients were included in the study who had metastases on initial diagnosis and who were treated by urologists according to the standard treatment at our institution. Only patients eligible for combination cytoreductive nephrectomy (CN) and sunitinib therapy were included. All patients underwent baseline computed tomography (CT) or magnetic resonance imaging (MRI) and showed at least one measurable metastatic lesion that was ≥10 mm in greatest diameter at initial diagnosis. Follow-up CT or MRI was performed every two months during treatment.

Clinicopathological parameters were recorded and analyzed for all study participants and included gender, age, body mass index (BMI), Karnofsky performance status (KPS), C-reactive protein (CRP) levels [17], the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model score, the tumor-node-metastasis (TNM) stage, lymph node status, Fuhrman grade of the RCC, primary tumor size, necrosis, microvascular invasion, and number and location of metastases. Imaging findings were independently reviewed by senior radiologists, and the histopathology of the RCCs were independently confirmed by senior pathologists, all of whom were blinded to the patient treatment regimen.

Ethics approval for the study was obtained from the Ethics Committee of Fudan University Shanghai Cancer Center (FUSCC). Patients provided informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki II.

Treatment

Of the 188 patients with mRCC included in the study, 70 patients were treated with CN and sunitinib (the CN-sunitinib group), and 48 patients received only sunitinib (the sunitinib-alone group). Sunitinib was administered at 50 mg per day on a schedule of four weeks on and two weeks off. The CN-sunitinib group were treated with the same sunitinib regimen commencing between 3–6 weeks after CN.

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Statistical analysis

The primary endpoint was progression-free survival (PFS), which was defined as the time between the date of surgery (CN-sunitinib group) or the initiation of sunitinib therapy (sunitinib-alone group) to the date of tumor progression, second-line therapy, or death, whichever occurred first. Overall survival (OS) was the secondary endpoint and was defined as the date of surgery or initiation of sunitinib therapy to the date of death or last follow-up. The follow-up duration was determined using the Kaplan-Meier method with 95% confidence intervals (CIs) and assessed using a log-rank test. Categorical clinicopathological data were compared using a contingency table and the chi-squared (χ^2) test. Univariate analysis and multivariate Cox regression analysis were performed to identify independent predictors of outcome. For subgroup analysis, patients were stratified according to statistically significant indicators. All statistical analysis was performed with STATA version 12.0 software. Tests were two-sided, and a P-value <0.05 was considered significant. Target lesion response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Results

Prognosis in the two study groups with metastatic renal cell carcinoma (mRCC)

The prognosis in patients with mRCC who underwent cytoreductive nephrectomy (CN) was compared with the prognosis in patients treated with sunitinib-alone. Stratified analysis showed that patients with lymph node metastasis or with a high International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score showed more survival benefit from sunitinib-alone therapy, while significant survival benefits were found in the CN group for patients with low levels of serum C-reactive protein (CRP).

Clinicopathological characteristics of the two study groups

In this study, 59.3% (n=70) of patients with mRCC were enrolled in the CN-sunitinib group, and 40.7% (n=48) received sunitinib alone. Patients commonly switched to sorafenib, everolimus, axitinib, or clinical trials as second-line treatment in the CN-sunitinib group and the sunitinib-alone group in 34.3% and 39.6%, respectively. In patients with mRCC, until the last day of follow-up (8th July 2018), the median progression-free survival (PFS) was 8.4 months, and overall survival (OS) was 15.5 months, and included 109 patient deaths. As shown in Table 1, patients who underwent CN were younger (<60 years), had a higher Karnofsky performance score (KPS), lower CRP, and fewer metastases. The pathological characteristics showed that more patients presented clinical stage T3 and T4 primary tumors and tumor necrosis in the CN-sunitinib group. The most common sites for metastases included the lymph nodes, lung, bone, liver, vena cava, and retroperitoneal space.

Cox regression analysis and survival outcomes of the two study groups

In univariate Cox regression analysis (Figure 1), forest plots showed that significant predictors of poor PFS included gender, age, body mass index (BMI), KPS, IMDC, CRP, lymph node stage, Fuhrman grade, primary tumor size, histological subtype, the presence of necrosis, microvascular invasion, and number of organs with metastases. Univariate predictors for poor OS were similar to those for poor PFS. However, in multivariate analysis (Table 2), independent parameters for poor PFS included serum CRP<10 mg/L, (P<0.001), IMDC score for intermediate-risk disease (P<0.001), lymph node stage N0 (P=0.011), and absent microvascular invasion (P=0.007). In multivariate analysis of OS, CRP<10 mg/L (P=0.004), IMDC score for intermediate-risk disease (P<0.001), lymph node stage N0 (P=0.015), and absent microvascular invasion (P<0.001) were significantly correlated with poor OS.

Figure 2 shows that the survival curves of the two study groups, the CN-sunitinib group and the sunitinib-alone group, did not show a significant difference (PFS: 7.2 months, P=0.525; OS: 11.6 months, P=0.839). Stratified survival analysis showed that CN treatment was significantly associated with poor PFS and OS in patients with lymph node metastasis (PFS: P<0.001; OS: P<0.001) (Figure 3A, 3B) and in patients with high-risk IMDC score subgroups (PFS: P=0.003; OS: P=0.011) (Figure 3C, 3D). However, in patients with mRCC with a lower CRP (<10 mg/L), significant survival benefits were found in the CN-sunitinib group compared with the sunitinib-alone group (PFS: P=0.026; OS: P=0.007) (Figure 3E, 3F).

Tumor response outcomes were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The proportion of patients with a partial response (PR), stable disease (SD), and progressive disease (PD) was 15.7%, 60.0%, and 24.3% in the CN-sunitinib group, and 14.6%, 70.8%, and 14.6% in the sunitinib-alone group, respectively. No significant differences were found between the objective response rate (ORR) (24.3% in the CN-sunitinib group *vs.* 27.1% in the sunitinib-alone group) and the disease control rate (DCR) (75.7% in the CN-sunitinib group *vs.* 85.4% in the sunitinib-alone group) between the two treatment groups.

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Table 1. Baseline clinicopathological characteristics of the 118 patients with metastatic renal cell carcinoma (mRCC) treated with cytoreductive nephrectomy (CN) and sunitinib, or sunitinib-alone.

Characteristics	CN-Sunitinib (N=70)	Sunitinib-alone (N=48)	*P*-value
Gender, no. (%)			0.113
Male	46 (65.7)	38 (79.2)	
Female	14 (34.3)	10 (20.8)	
Age, no. (%)			**<0.001**
≥60 years	27 (38.6)	33 (68.8)	
<60 years	43 (61.4)	15 (31.2)	
BMI, no. (%)			0.612
≥23 kg/m^2	31 (44.3)	19 (39.6)	
<23 kg/m^2	39 (55.7)	29 (60.4)	
Karnofsky performance status score, no. (%)*			**0.003**
90–100	25 (35.7)	6 (12.5)	
80–90	35 (50.0)	28 (58.3)	
70–80	10 (14.3)	14 (29.2)	
CRP, no. (%)			**0.008**
≥10 mg/L	49 (70.0)	22 (45.8)	
<10 mg/L	21 (30.0)	26 (54.2)	
IMDC risk category, no. (%)##			0.297
Intermediate-risk	36 (51.4)	20 (41.7)	
High-risk	34 (48.6)	27 (58.3)	
Tumor stage, no./total no.(%)#			
T1	0/70	2/48 (4.2)	**0.003**
T2	6/70 (8.6)	9/48 (18.8)	
T3	35/70 (50.0)	27/48 (56.2)	
T4	29/70 (41.4)	10/48 (20.8)	
Lymph node stage, no./total no. (%)#			0.261
N0	38 (54.3)	21 (43.8)	
N1	32 (45.7)	27 (56.3)	
Fuhrman grade of renal cell carcinoma, no. (%)**			0.204
1–2	58 (82.9)	37 (77.1)	
3–4	12 (17.1)	11 (22.9)	
Primary tumor size, no. (%)			**0.024**
≥7 cm	45 (64.3)	40 (83.3)	
<7 cm	25 (35.7)	8 (16.7)	

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Table 1 continued. Baseline clinicopathological characteristics of the 118 patients with metastatic renal cell carcinoma (mRCC) treated with cytoreductive nephrectomy (CN) and sunitinib, or sunitinib-alone.

Characteristics	CN-Sunitinib (N=70)	Sunitinib-alone (N=48)	*P*-value
Histology subtype, no. (%)			**0.848**
Clear cell	55 (78.6)	37 (77.1)	
Non-clear cell	15 (21.4)	11 (22.9)	
Necrosis, no. (%)			**0.008**
Yes	48 (68.6)	43 (89.6)	
No	22 (31.4)	5 (10.4)	
Microvascular invasion, no. (%)			0.335
Yes	38 (54.3)	32 (66.7)	
No	32 (45.7)	16 (33.3)	
Number of metastatic organs, no. (%)			**0.012**
1	34 (50.0)	17 (35.4)	
2	28 (40.0)	17 (35.4)	
3	6 (8.6)	11 (22.9)	
4	1 (1.4)	3 (6.3)	
Location of metastases, no./total no. (%)			
Lung	39/70 (55.7)	28/48 (58.3)	0.778
Bone	26/70 (37.1)	14/48 (29.2)	0.369
Liver	8/70 (11.4)	8/48 (16.7)	0.414
Brain	1/70 (1.4)	2/48 (4.2)	0.353
Pleural	3/70 (4.3)	2/48 (4.2)	0.975
Vena cava	2/70 (2.9)	8/48 (16.7)	**0.008**
Retroperitoneal	2/70 (2.9)	7/48 (14.6)	**0.018**
Other	12/70 (17.1)	10/48 (20.8)	0.613

* The Eastern Cooperative Oncology Group (ECOG) performance status scores ranged from 0–5; a higher score indicated increased disability, and a score of 5 indicated death; ** The Fuhrman grade for renal cell carcinoma (RCC) was assessed on a scale of 1–4, with grade 1 indicating the lowest grade (well-differentiated), and grade 4 the highest grade (poorly-differentiated); # The tumor node metastasis (TNM) stage according to the Union for International Cancer Control (UICC) classification for malignant tumors; ## The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model was based on five factors: time from diagnosis to systemic treatment <1 year; hemoglobin level < the lower limit of the normal range; lactate dehydrogenase (LDH) level 1.5×the upper limit of the normal range; corrected serum calcium >2.5 mmol per liter; and the Karnofsky performance status (KPS) score <8. Patients with one or two factors were classified as intermediate-risk; those with three or more factors were classified high-risk.

Drug-related adverse events

Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Table 3 shows the adverse events that occurred in the patients during this study. The most common adverse events associated with sunitinib therapy were hematotoxicity, gastrointestinal toxicity, and hand-foot skin and mucosal toxicity. Hand-foot syndrome was the most common adverse event, which occurred in 64.3% of patients in the CN-sunitinib group and 52.1% in the sunitinib-alone group (P=0.049). Anemia was the second most common adverse event, which occurred in 34.4% of patients in the

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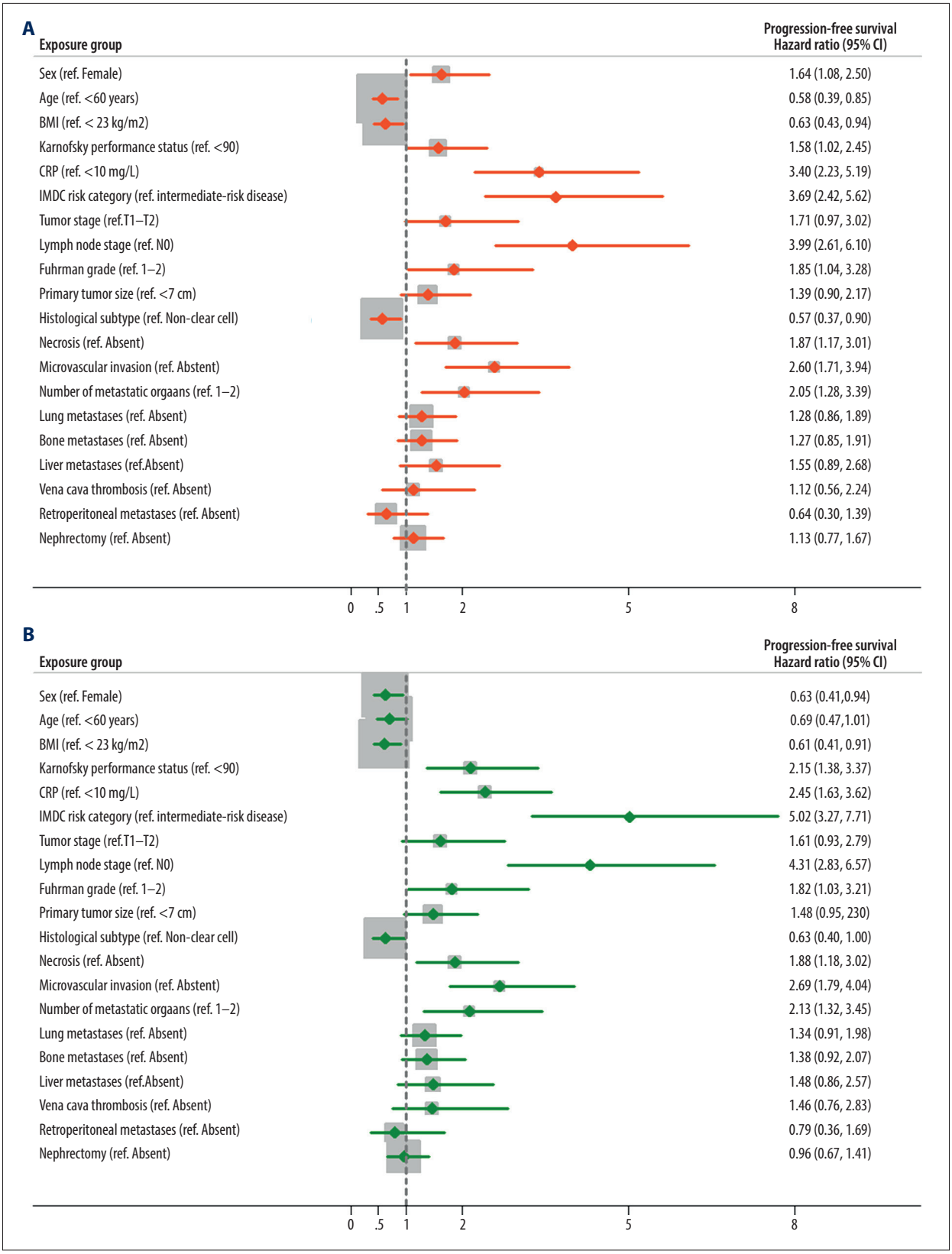

Figure 1. (**A, B**) Forest plots of the univariate regression Cox analysis of progression-free survival (PFS) and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC).

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Table 2. Multivariate Cox regression analyses of progression-free survival (PFS) and overall survival (OS) of the 118 patients with metastatic renal cell carcinoma (mRCC).

Covariates	Multivariate analysis of PFS		Multivariate analysis of OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender (Ref. F)	1.200 (0.744–1.937)	0.454	1.199 (0.772–1.860)	0.419
Age (Ref. <60 years)	0.703 (0.436–1.134)	0.149	–	–
BMI (Ref. <23 kg/m^2)	0.654 (0.424–1.008)	0.055	0.793 (0.524–1.202)	0.274
Karnofsky performance status (Ref. <90)	0.926 (0.545–1.574)	0.777	1.322 (0.783–2.234)	0.297
CRP (Ref. <10 mg/L)	2.609 (1.600–4.254)	**<0.001**	2.039 (1.263–3.292)	**0.004**
IMDC risk category (Ref. intermediate-risk)	3.208 (1.791–5.748)	**<0.001**	4.970 (2.772–8.913)	**<0.001**
Lymph node stage (Ref. N0)	2.119 (1.191–3.771)	**0.011**	1.958 (1.142–3.358)	**0.015**
Fuhrman grade (Ref. 1–2)	1.556 (0.817–2.960)	0.178	1.371 (0.727–2.585)	0.330
Histological subtype (Ref. non-clear cell)	0.695 (0.415–1.164)	0.167	0.857 (0.511–1.437)	0.559
Necrosis (Ref. absent)	1.308 (0.745–2.298)	0.350	1.209 (0.688–2.124)	0.510
Microvascular invasion (Ref. absent)	1.986 (1.207–3.267)	**0.007**	3.090 (1.873–5.096)	**<0.001**
Number of metastatic organs (Ref. 1–2)	1.215 (0.698–2.114)	0.491	1.215 (0.680–2.173)	0.511

CRP – C-reactive protein; BMI – body mass index; IMDC – International Metastatic Renal Cell Carcinoma Database Consortium; HR – Hazard ratio; CI – confidence interval.

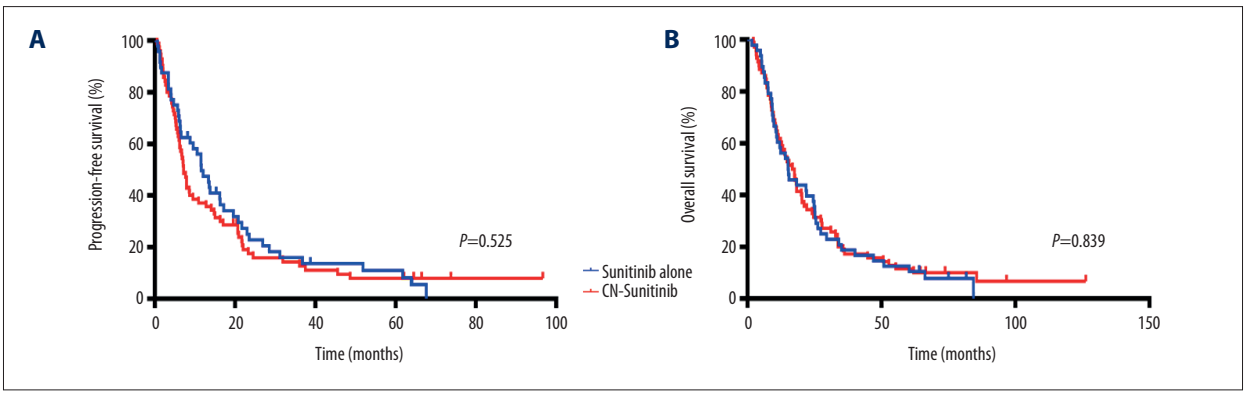

Figure 2. Kaplan-Meier survival analysis of progression-free survival (PFS) and overall survival (OS) shows no significant difference between the sunitinib-alone group and the cytoreductive nephrectomy (CN)-sunitinib group. (**A**) The median PFS was 7.2 and 11.6 months in the CN-sunitinib group and the sunitinib-alone group, respectively (log-rank χ^2=0.404, P=0.525). (**B**) The median OS was 16.8 and 15.2 months in the CN-sunitinib group and the sunitinib-alone group, respectively (log-rank χ^2=0.041, P=0.839).

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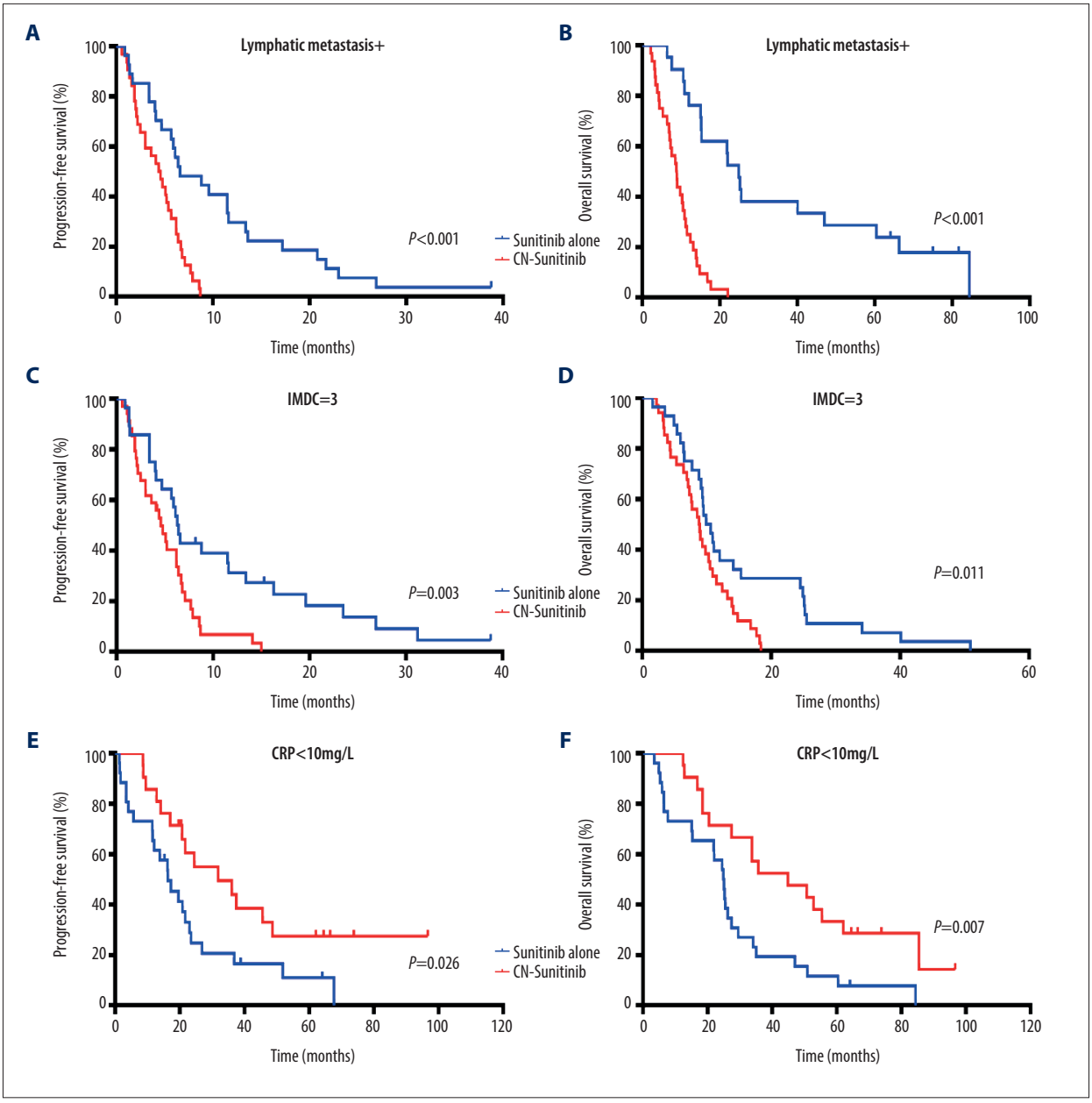

Figure 3. (**A–F**) Kaplan-Meier subgroup survival analysis for the progression-free survival (PFS) and overall survival (OS). Lymph node metastasis, International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model risk category, and C-reactive protein (CRP) showed a significant difference between the cytoreductive nephrectomy (CN)-sunitinib and sunitinib-alone groups.

CN-sunitinib group compared with 20.8% in the sunitinib-alone group (P=0.009). Diarrhea occurred in 38.1% of patients in the CN-sunitinib group compared with 25.0% of patients in the sunitinib-alone group (P=0.002). Alopecia occurred in 25.7% of patients in the CN-sunitinib group compared with 16.7% of patients in the sunitinib-alone group (P=0.017).

Discussion

In 2011, the International Consultation on Urological Diseases and European Association of Urology consultation on Minimally Invasive Surgery in Urology (ICUD-EAU) recommended that targeted therapy, including sunitinib, pazopanib, and bevacizumab, in combination with interferon-α (IFN-α) should be first-line treatment options in certain patients with metastatic or unresectable renal cell carcinoma (RCC) who had favorable

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Table 3. Adverse events on hematotoxicity, digestive toxicity, hand-foot skin, mucosal toxicity and other symptomatic toxicity of the 118 patients with metastatic renal cell carcinoma (mRCC).

Event	CN-Sunitinib (N=70)		Sunitinib alone (N=48)	
	No. of patients (%)			
Anemia*	22	(34.4)	10	(20.8)
Thrombocytopenia	21	(30.0)	14	(29.2)
Leukocytopenia	14	(20.0)	13	(27.1)
Diarrhea#	27	(38.2)	12	(25.0)
liver dysfunction	11	(15.7)	9	(18.7)
Hand-foot syndrome**	45	(64.3)	25	(52.1)
Rash	15	(21.4)	12	(25.0)
Alopecia##	18	(25.7)	8	(16.7)
Asthenia	16	(22.9)	10	(20.8)
Oral mucositis	10	(14.3)	9	(18.7)
Hypertension	12	(17.1)	8	(16.7)
Hypothyroidism	9	(12.9)	5	(10.4)
Fever and allergy	4	(5.7)	1	(2.1)
Angina	0		1	(2.1)

* P=0.009; ** P=0.049; # P=0.002; ## P=0.017.

or intermediate prognosis according to the Memorial Sloan Kettering Cancer Center (MSKCC) score [15]. Although combination therapy with cytoreductive nephrectomy (CN) and targeted therapy is currently used in clinical practice, the therapeutic role of CN remains to be determined [18,19]. This study evaluated the factors associated with a survival benefit for patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib, with and without CN. The findings from the present study showed that treatment with sunitinib-alone without CN improved the survival of patients with mRCC who had high International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk scores or lymph node metastasis. However, treatment with CN and sunitinib resulted in significantly improved survival for patients with low serum CRP levels <10 mg/L.

The findings in the present study are supported by the findings from two previously published observational studies. Wood and Margulis [20] and Stroup et al. [21] found that survival endpoints were not significantly different between patients with mRCC treated with CN plus sunitinib compared with sunitinib-alone. In the current study, we performed an additional subgroup analysis of patients with mRCC stratified into two groups based on several clinicopathological factors. CN treatment was significantly associated with poor progression-free survival (PFS) and overall survival (OS) in patients with lymph node metastasis and high IMDC risk scores. However, CN offered significant survival benefits compared with sunitinib-alone treatment for patients with mRCC with low serum CRP concentrations. Therefore, some of the conflicting findings from previous clinical studies that identified benefit from CN might have been influenced by independent parameters, including lymph node metastasis, IMDC risk score, and serum CRP level.

In 2018, the prospective phase III Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) evaluated the efficacy of sunitinib alone or following nephrectomy in 450 patients with mRCC [12]. The results showed noninferiority of sunitinib-alone compared with CN-sunitinib for OS (18.4 months *vs.* 13.9 months) and PFS [12]. The overall response rate (ORR) was similar for the two groups and was 29.1% for sunitinib-alone group compared with 27.4% for the CN-sunitinib group [12], which was comparable with the rates found in the present study of 27.1% for sunitinib-alone group and 24.3% for CN-sunitinib group. In the CARMENA study, the median OS was increased in the sunitinib-alone group compared with the CN-sunitinib group for Memorial Sloan Kettering Cancer Center (MSKCC) intermediate-risk patients (23.4 months *vs.* 19.0 months) and MSKCC low-risk patients (13.3 months *vs.* 10.2 months) [12]. In 2019, the findings from the SURTIME randomized clinical trial that included 458 patients with mRCC showed that CN did not improve PFR at 28-weeks and that pretreatment with sunitinib selected for patients who were resistant to systemic therapy before CN [22]. However, no further subgroup analysis was performed in the SURTIME study. In the present current study, CN-sunitinib prolonged the survival of patients with mRCC when compared with sunitinib-alone in patients with low serum CRP levels (<10 mg/L).

Advances the understanding of the molecular pathways involved in the development and metastasis of RCC has resulted in the development of single and combined targeted therapy for mRCC [23–25]. Primary tumors with invasive phenotypes tend to undergo metastasis, and CN may reduce initial tumor spread and reduce the risk of metastasis [26]. However, complications from previous CN may delay the time to initiation of systemic targeted therapy, which may reduce prognosis [27–29]. Although CRP is a regarded as a non-specific inflammatory marker, it is also associated with disease severity in cardiovascular diseases and urological malignancy [30]. Measurement of serum CRP levels, the neutrophil-to-lymphocyte ratio, and the platelet-to-lymphocyte ratio have previously been reported as prognostic indicators in patients with mRCC following treatment with tyrosine kinase inhibitors (TKIs) [31]. In 2017, a meta-analysis of nine studies that included 1,199 patients

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with mRCC showed that an increased CRP level correlated with poor prognosis in patients receiving TKI treatment [32]. The results from these previously published studies support the findings from the present retrospective clinical study.

In this study of CN-sunitinib compared with sunitinib-alone for mRCC, 38.1% of patients experienced side effects, including 32.8% in the CN-sunitinib group and 42.7% in the sunitinib-alone group. Common severe adverse events associated with sunitinib therapy included mucosal inflammation, neutropenia, thrombocytopenia, anemia, and hand-foot syndrome. Unavoidable complications of prior CN, such as pulmonary injury, thromboembolism, blood loss, metabolic and gastrointestinal disorders, infection, and disease progression might influence not only the adverse events associated with targeted therapy, but also delay the survival benefits of established therapies for mRCC [33,34]. The recently reported finding from the SURTIME randomized controlled clinical trial showed that patients with mRCC did not experience more surgical complications whether they received systemic therapy before or after CN [35].

The strengths of the present study included the use of a stratified analysis of prognostic indicators, which identified factors significantly associated with the survival benefit of CN in patients with mRCC. Also, a series of statistical methodologies, including the chi-squared test, and Cox regression analysis were performed to identify mixed prognostic factors. However, this study also had several limitations. This study was retrospective and did not include randomization of the patient treatment groups, and there may have been unknown differences between these groups. However, this study did identify the influence of clinicopathological variables on the outcome of treatment with CN-sunitinib compared with sunitinib-alone, despite the finding of no overall difference in survival between the two treatment arms. In this study, postoperative complications may have prevented patients from being given systemic therapy that may have caused adverse events. Finally, the study sample size was based on a Chinese population cohort that was relatively small. There remains a need to study combined treatment with CN for mRCC in larger controlled multicenter studies, and to evaluate further the potential prognostic role of CRP in patients with mRCC and in the response to sunitinib.

Conclusions

The aims of this retrospective clinical study were to evaluate the factors associated with a survival benefit for patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib, with and without cytoreductive nephrectomy (CN). The findings showed that sunitinib-alone without CN improved the survival of patients with mRCC who had high International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk scores or lymph node metastasis. Also, patients treated with CN and sunitinib who had lower C-reactive protein (CRP) levels showed significantly improved survival.

Conflict of interest

None.

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