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Postoperative Adjuvant Sorafenib or Sunitinib for Nonmetastatic Renal Cell Carcinoma with Venous Tumor Thrombus: a Prospective Cohort Study

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Abstract

PURPOSE: To evaluate the efficacy and safety of antiangiogenic agents (sorafenib and sunitinib) as postoperative adjuvant therapy in patients with nonmetastatic renal cell carcinoma (RCC) and venous tumor thrombus (VTT). *MATERIAL AND METHODS:* From March 2006 to January 2016, 147 patients who met the inclusion criteria were enrolled; 27 patients received sorafenib, and 17 patients received sunitinib. After radical nephrectomy and thrombectomy, the duration of maintenance targeted medication treatment was approximately 1 year. The primary objective was to compare disease-free survival (DFS) between each experimental group and control. Secondary end points included overall survival (OS) and toxic effects. *RESULTS:* The three groups were well balanced in terms of age, body mass index, gender, performance status, medical history, American Society of Anesthesiologists score, surgical approach, and tumor side and size. However, more patients receiving adjuvant therapy had inferior vena cava tumor thrombus. DFS and OS did not differ significantly between groups ($P = .459$ and .871, respectively). After adjusting for potential confounding factors, results of multivariate analysis proved that postoperative adjuvant therapy was not an independent factor for predicting DFS and OS ($P > .05$ for both). The subgroup analyses for inferior vena cava tumor thrombus found similar results. The common adverse events were hand-foot syndrome, diarrhea, fatigue, and neutropenia. The adverse effects were mild in both groups, and the incidence was not significantly different between sorafenib and sunitinib. *CONCLUSIONS:* Adjuvant treatment postoperatively with sorafenib or sunitinib showed no survival benefit relative to control for patients with nonmetastatic RCC and VTT in a prospective cohort study.

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Introduction

Cancer of the renal pelvis and kidney is the second most common type of genitourinary malignancy in China, with an approximated 66,800 new cases and 23,400 mortality that occurred in 2015 [1]. For adults, renal cell carcinoma (RCC) accounts for a large proportion of kidney cancers. During the past few decades, the extensive use of cross-sectional imaging has resulted in the increasing number of patients presenting with low-stage disease. For most localized RCCs, surgery is the most reliable treatment modality, which can achieve satisfactory oncologic control [2]. However, RCC has a natural tendency of enlarging from the kidney along its route of venous drainage, which was identified in 4% to 10% of RCC patients [3]. These patients were classified as T3 according to TNM system of the 2010 American Joint Committee on Cancer [4]. Radical nephrectomy combining thrombectomy is currently the only potential cure for cases that have nonmetastatic RCC involving venous tumor thrombus (VTT) [5]. For these patients, although full surgical

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resection is performed, the risk of tumor recurrence can be nearly 50% in 3 years [6]. Therefore, surgery alone may not be sufficient for patients with nonmetastatic RCC and VTT.

Previous trials of postoperative adjuvant interleukin-2/interferon, chemotherapy, or hormonal therapy in patients with resected RCC at high risk for recurrence have all proven to be negative [7]. Small molecule agents targeting vascular endothelial growth factor pathway (sorafenib and sunitinib) can prolong the time to progression for patients with advanced RCC [8,9]. Based on these facts, it seems to be meaningful to apply antiangiogenic agents for high-risk kidney cancer in the postoperative adjuvant setting. In two published randomized controlled studies, sunitinib was given for 1 year and compared to placebo in localized RCC cases at high risk for tumor recurrence after nephrectomy. Although one study demonstrated that 1 year of sunitinib therapy resulted in a 1.2-year longer time before the disease recurred, the other study did not show a survival benefit [10,11]. This study is the first prospective cohort study to examine the role of postoperative adjuvant therapy (sorafenib or sunitinib) in nonmetastatic RCC patients with VTT.

Materials and Methods

Patient

Eligible patients were older than 18 years and had histologically and clinically confirmed non–clear cell or clear cell RCC with VTT within 12 weeks of surgical resection of the primary mass and tumor thrombus. Other eligibility criteria included absence of macroscopic residual or metastatic disease after surgery, no previous systemic treatment, a good Eastern Cooperative Oncology Group performance status (0 or 1), and sufficient liver and bone marrow function. A creatinine clearance ≥40 ml/min for renal function was required. Exclusion criteria included bilateral RCC, hereditary or familial RCC, known HIV infection, uncontrolled hypertension, a major cardiovascular event or disease within 12 months before study entry, or preexisting thyroid disorder. Patients with carcinoma of the collecting ducts and renal medullary carcinoma were also excluded.

From March 2006 to January 2016, 147 patients undergoing radical nephrectomy and thrombectomy at our center who met the inclusion criteria were enrolled. All patients had the status of distant metastasis confirmed using imaging examinations and were staged in the light of the TNM system of the 2010 American Joint Committee on Cancer [4]. Thrombus level was classified according to the Mayo classification [12]. The present study was approved by Medical Ethics Committee of our hospital, and informed consent was acquired from each patient.

Study Design

The trial was a single-institution, nonrandomized, prospective cohort study. Patients were classified to three groups according to postoperative treatment. The decision to receive sunitinib or sorafenib therapy was made mainly by the patients. Systemic treatment was initiated only if the patients recovered from the surgery with no complication. The treatment regimen was approximately 1 year of either sorafenib taken orally at 400 mg twice per day during a 4-week cycle or sunitinib taken orally at 50 mg per day for a 6-week cycle (4 weeks on treatment, 2 weeks off). The National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 was applied to evaluate the severity of treatment-related adverse events. Dose reductions were allowed for patients with grade 3 or higher drug-related toxic effects. Patients who experienced side effects that alleviated to below grade 2 within 4 weeks were escalated to full doses. Patients were removed from therapy if the dose reduction occurred more than twice for either agent. Therapy continued until disease recurrence, unacceptable toxicities, or patient withdrawal.

Assessment and Outcomes

Evaluation for toxic effects was performed every 6 weeks. Imaging (CT or MR) of the chest, abdomen, pelvis, and other applicable sites was performed every two cycles (interval of 2-3 months) during treatment for the initial year and every 6 months thereafter until disease recurrence. Diagnosis of recurrence was based on confirmed imaging or histologic findings. The patients who received systemic therapy after surgery were followed up for at least 12 months. All patients in the control group were imaged every 2 to 3 months for the initial year and then every 6 months thereafter.

The primary endpoint was disease-free survival (DFS), which was defined as the interval between inclusion and tumor recurrence, occurrence of a second tumor, or all-cause mortality. Patients who were alive without tumor recurrence were censored at the last follow-up. Secondary end points included overall survival (OS) and adverse effects.

Statistical Analysis

All continuous data were shown as mean and standard deviation (SD) with a normal distribution, or as the median and interquartile range (IQR) when not normally distributed. For continuous data, the one-way analysis of variance or Kruskal-Wallis tests were applied to analyze the comparisons. For categorical variables, comparisons were performed by using the Pearson chi-square or Fisher exact test. We compared the three groups' survival using the Kaplan-Meier method with log-rank test. Univariable and multivariable Cox proportional hazards analyses were also applied. Variables achieving P value < .05 in the univariate analysis and therapy subgroup were incorporated in the multivariable model to determine independent predictive factors. All statistical analyses were performed with R software (version 3.3.1). Two-tailed tests were applied for all comparisons, and a P value < .05 was deemed to be statistically significant.

Results

The present study included 147 patients between March 2006 and January 2016; 27 patients received sorafenib, 17 patients received sunitinib, and 103 patients received no adjuvant therapy postoperatively. Baseline demographic and clinical features are presented in Table 1. In line with the disease features of RCC, most patients included in the present study were male and had a good body condition. The three groups were well balanced in terms of age, body mass index (BMI), gender, performance status, medical history, American Society of Anesthesiologists (ASA) score, surgical approach, and tumor side and size. There were significant differences for level and length tumor thrombus, and pathological stage among the three groups (P < .05 for all). More patients receiving adjuvant therapy had inferior vena cava tumor thrombus. After surgery, most patients were confirmed to have clear cell RCC. Positive lymph node was identified in five patients, four patients, and nine patients for sorafenib, sunitinib, and control. No significant differences were observed among the three groups with regard to histology, Fuhrman grade, tumor necrosis, sarcomatoid feature, perirenal fat invasion, sinus fat invasion, or collecting system invasion.

Table 1. Baseline Characteristics

	Sorafenib	Sunitinib	Control	*P* Value
No. of patients	27	17	103	
Mean (SD) age, years	56.2 (12.8)	50.0 (7.2)	57.3 (12.6)	.077
Mean (SD) BMI	25.1 (4.2)	25.1 (3.0)	24.5 (3.4)	.643
Male, *n* (%)	20 (74.1)	15 (88.2)	81 (78.6)	.529
ECOG performance status, *n* (%)				.948
0	20 (74.1)	13 (76.5)	75 (72.8)	
1	7 (25.9)	4 (23.5)	28 (27.2)	
Presenting symptoms, *n* (%)	19 (70.4)	11 (64.7)	68 (66.0)	.898
Diabetes mellitus, *n* (%)	10 (37.0)	3 (17.6)	19 (18.4)	.104
Hypertension, *n* (%)	9 (33.3)	4 (23.5)	33 (32.0)	.757
ASA score, *n* (%)				.283
1 + 2	22 (81.5)	16 (94.1)	80 (77.7)	
3 + 4	5 (18.5)	1 (5.9)	23 (22.3)	
Tumor laterality, *n* (%)				.562
Left	14 (51.9)	6 (35.3)	47 (45.6)	
Right	13 (48.1)	11 (64.7)	56 (54.3)	
Surgical approach, *n* (%)				.821
Open	15 (55.6)	8 (47.1)	51 (49.5)	
Minimally invasive	12 (44.4)	9 (52.9)	52 (50.5)	
Thrombus level, *n* (%)				.002
Level 0	13 (48.1)	3 (17.6)	68 (66.0)	
Level I	4 (14.8)	6 (35.3)	12 (11.7)	
Level II	10 (37.0)	8 (47.1)	17 (16.5)	
Level III	0 (0.0)	0 (0.0)	3 (2.9)	
Level IV	0 (0.0)	0 (0.0)	3 (2.9)	
Median (IQR) thrombus length, cm	3.5 (1.5-5.0)	4.0 (3.0-6.0)	2.0 (1.0-4.0)	.002
Median (IQR) maximum tumor width, cm	9.0 (6.0-10.0)	8.0 (4.8-10.0)	6.8 (5.0-9.0)	.124
Pathological stage, *n* (%)				.001
T3a	13 (48.1)	3 (17.6)	68 (66.0)	
T3b	14 (51.9)	14 (82.3)	32 (31.0)	
T3c	0 (0.0)	0 (0.0)	3 (2.9)	
Histological subtype, *n* (%)				.959
Clear cell	24 (88.9)	15 (88.2)	87 (84.5)	
Papillary	1 (3.7)	0 (0.0)	6 (5.8)	
Unclassified	2 (7.4)	2 (11.8)	10 (9.7)	
Fuhrman grade, *n* (%)				.849
1 + 2	11 (40.7)	7 (41.2)	52 (50.5)	
3 + 4	12 (44.4)	8 (47.1)	41 (39.8)	
Not determined	4 (14.8)	2 (11.8)	10 (9.7)	
Tumor necrosis, *n* (%)	15 (55.6)	10 (58.8)	43 (41.7)	.239
Sarcomatoid feature, *n* (%)	2 (7.4)	1 (5.9)	1 (1.0)	.080
Perirenal fat invasion, *n* (%)	5 (18.5)	1 (5.9)	12 (11.7)	.439
Sinus fat invasion, *n* (%)	0 (0.0)	2 (11.8)	7 (6.8)	.230
Collecting system invasion, *n* (%)	10 (37.0)	8 (47.1)	34 (33.0)	.522
Positive lymph node, *n* (%)	5 (18.5)	4 (23.5)	9 (8.7)	.107

ECOG, Eastern Cooperative Oncology Group.

At the last follow-up (February 2017), 33 patients have finished postoperative systemic therapy for at least 12 months, that is, roughly 9 cycles of sunitinib and 13 cycles of sorafenib. No patient was removed from the trial due to adverse events. Mean follow-up time for patients in the sorafenib, sunitinib, and control group was 39.4 ± 21.0, 36.6 ± 19.4, and 44.4 ± 28.7 months, respectively. Mean DFS was 24.1 months for sorafenib, 26.8 months for sunitinib, and 34.4 months for control. No significant difference was found for DFS among the three groups (P = .459; Figure 1*A*). Events were recorded for 16 patients in sorafenib group, 10 patients in sunitinib group, and 54 patients in control group. Mean OS was 35.5 months for sorafenib, 34.6 months for sunitinib, and 39.5 months for control. No significant difference was found for OS among the three groups (P = .871; Figure 1*B*). Events were recorded for 11 patients in sorafenib group, 5 patients in sunitinib group, and 40 patients in control group. After adjusting for potential confounding factors, results of multivariate analysis proved that postoperative adjuvant therapy was not an independent factor for predicting DFS and OS (P > .05 for both; Table 2).

For patients with RCC and inferior vena cava tumor thrombus, mean DFS was 17.6 months for sorafenib, 21.9 months for sunitinib, and 32.0 months for control. No significant difference was found for DFS among the three groups (P = .380; Figure 2*A*). Events were recorded for 9 patients in sorafenib group, 8 patients in sunitinib group, and 18 patients in control group. Mean OS was 28.6 months for sorafenib, 30.9 months for sunitinib, and 38.6 months for control. No significant difference was found for OS among the three groups (P = .525; Figure 2*B*). Events were recorded for 7 patients in sorafenib group, 4 patients in sunitinib group, and 15 patients in control group. After adjusting for potential confounding factors, results of multivariate analysis proved that postoperative adjuvant therapy was not an independent factor for predicting DFS and OS (P > .05 for both; Table 3).

Sunitinib and sorafenib both were well tolerated, and most toxic effects were comparable [13]. The patient distribution with respect to toxicity is outlined in Table 4. In the present study, the most common adverse events were hand-foot syndrome, diarrhea, fatigue, and neutropenia. Most of them were mild (grade 1 or 2) and can be easily managed. The

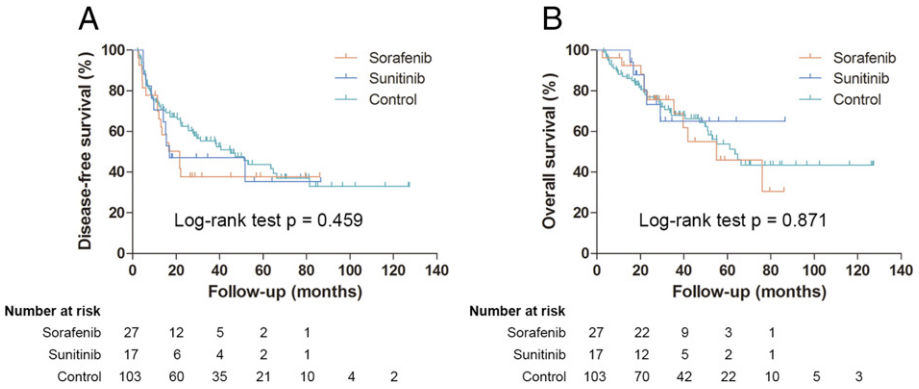

Figure 1. DFS (A) and OS (B) for patients with nonmetastatic RCC and tumor thrombus.

frequency of adverse events did not differ significantly between sorafenib and sunitinib ($P > .05$ for both). Adverse events that led to dose reductions included grade 3 diarrhea for four patients (two on sorafenib and two on sunitinib) and grade 3 neutropenia for three patients (two on sorafenib and one on sunitinib).

Discussion

Approximately 4% to 10% of RCC patients have lesions extending into the venous drainage system, generating VTT [14]. Most patients with no preoperative distant metastasis can be well managed with full surgical resection; however, the risk of tumor recurrence can be nearly 50% in 3 years [15]. Therefore, postoperative adjuvant therapy may be needed for these patients. Hence, this prospective cohort study was performed to compare survival time with adjuvant sunitinib or sorafenib versus control and ascertain the postoperative role of antiangiogenic agents in patients with nonmetastatic RCC and VTT.

In the present study, the mean time to tumor recurrence or mortality was similar between subjects who received postoperative sunitinib or sorafenib and those who did not receive any adjuvant therapy. It should be noted that there may be inherent selection bias and uncontrolled confounding factors because of the nonrandomized design. In the comparison of baseline demographic and clinical features, there were significant differences for level and length tumor thrombus, and pathological stage among the three groups. More patients receiving adjuvant therapy had inferior vena cava tumor thrombus. Hence, the further multivariate Cox analyses were performed. After adjusting for other variables, postoperative adjuvant therapy was not associated with DFS and OS. The subgroup analyses of RCC patients with inferior vena

Table 2. Cox Proportional Hazards Regression for DFS and OS in Patients with RCC and Venous Tumor Thrombus

Characteristic	DFS			OS		
	Univariate	Multivariate		Univariate	Multivariate	
	P Value	HR (95% CI)	*P* Value	*P* Value	HR (95% CI)	*P* Value
Age	.159			.282		
BMI	.127			.036	0.92 (0.83-1.02)	.126
Sex (female vs male)	.585			.990		
Presenting symptoms	.255			.062		
Diabetes	.403			.997		
Hypertension	.886			.394		
ASA score (3 + 4 vs 1 + 2)	.060			.335		
Tumor laterality (right vs left)	.137			.345		
Surgical approach (MI vs open)	.945			.121		
Thrombus height						
Renal vein only	Ref.			Ref.		
IVC below diaphragm	.389			.312		
IVC above diaphragm	.389			.168		
Thrombus length	.234			.032	1.09 (0.92-1.30)	.316
Tumor width	.002	1.08 (1.00-1.17)	.059	<.001	1.21 (1.08-1.36)	.001
Histological subtype (ccRCC vs non-ccRCC)	.181			.005	0.43 (0.14-1.32)	.139
Fuhrman grade (high vs low)	.010	1.63 (1.00-2.66)	.049	.015	1.42 (0.75-2.71)	.281
Tumor necrosis	.187			.292		
Sarcomatoid feature	.294			.381		
Perirenal fat invasion	.874			.936		
Sinus fat invasion	.951			.564		
Collecting system invasion	.005	1.83 (1.11-3.02)	.018	.012	1.95 (0.95-4.00)	.071
Lymph node status (positive vs negative)	.916			.607		
Therapy subgroup						
Control	Ref.		Ref.	Ref.		Ref.
Sorafenib	.246	1.05 (0.57-1.96)	.875	.777	0.88 (0.41-1.88)	.736
Sunitinib	.506	0.84 (0.39-1.79)	.645	.695	0.40 (0.10-1.46)	.163

MI, minimally invasive; *IVC*, inferior vena cava; *ccRCC*, clear cell renal cell carcinoma.

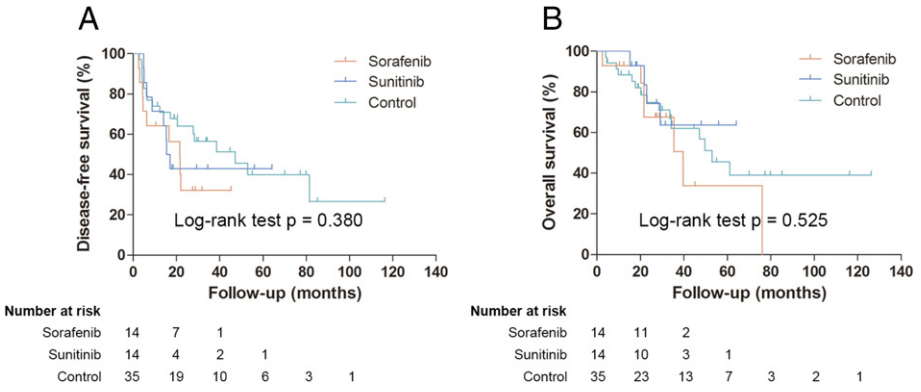

Figure 2. DFS (A) and OS (B) for patients with nonmetastatic RCC and inferior vena cava tumor thrombus.

cava tumor thrombus were also performed. The results indicated that there was also no survival advantage for either drug. In spite of the positive role of VEGF-targeted therapy in cases with distant metastasis, our findings failed to identify any benefit from the two agents, sorafenib or sunitinib, versus control when taken in the postoperative adjuvant setting.

The results are comparable to those of preoperative molecular targeted therapies in patients undergoing radical nephrectomy and thrombectomy in which the effect of downsizing tumor of VEGF-targeted therapy in metastatic and localized RCC is not seen. For example, presurgical sunitinib was administered in 72 potential candidates for partial nephrectomy. Downsizing was observed in 65 (83%) masses, with partial responses in 15 (19%) patients. Most of them can be subsequently managed with partial nephrectomy with accompanying acceptable surgical morbidity and functional outcomes [16]. However, targeted molecular therapies had a limited clinical effect on RCC tumor thrombi and primitive tumor [17,18]. After targeted molecular therapies, most patients had stable or upstaged thrombi. Regarding primary tumor, most patients had a stabilization or an increase in tumor size.

In the postoperative adjuvant setting, the concern has been proposed with regard to whether the micrometastases that probably lead to recurrent disease are of a blood supply that is as susceptible to the effect of VEGF-targeted therapy as is the case in macrometastases. Given the absent benefit from VEGF-targeted therapy, it may be rational to draw the conclusion that antiangiogenic therapy does not exert persistent antitumor effects in micrometastases. In particular, studies with experimental mouse renal tumor xenograft models found an incomprehensible result that targeted molecular agents improve metastatic neoplasm growth and reduce OS [19]. Results from several studies may explain this finding. Ebos et al. [20] investigated molecular plasma changes induced by sunitinib, including those both indirectly and directly targeted by agent. They found that many

Table 3. Cox Proportional Hazards Regression for DFS and OS in Patients with RCC and Inferior Vena Cava Tumor Thrombus

Characteristic	DFS			OS		
	Univariate	Multivariate		Univariate	Multivariate	
	P Value	HR (95% CI)	*P* Value	*P* Value	HR (95% CI)	*P* Value
Age	.602			.647		
BMI	.766			.481		
Sex (female vs male)	.578			.516		
Presenting symptoms	.820			.680		
Diabetes	.115			.261		
Hypertension	.077			.190		
ASA score (3 + 4 vs 1 + 2)	.104			.121		
Tumor laterality (right vs left)	.032	0.59 (0.27-1.30)	.189	.030	0.64 (0.25-1.67)	.360
Surgical approach (MI vs open)	.476			.085		
Thrombus height						
IVC below diaphragm	Ref.			Ref.		
IVC above diaphragm	.588			.348		
Thrombus length	.374			.164		
Tumor width	<.001	1.18 (1.05-1.32)	.007	<.001	1.25 (1.08-1.44)	.002
Histological subtype (ccRCC vs non-ccRCC)	.453			.019	0.25 (0.08-0.74)	.012
Fuhrman grade (high vs low)	.675			.427		
Tumor necrosis	.854			.905		
Sarcomatoid feature	.464			.649		
Perirenal fat invasion	.566			.897		
Sinus fat invasion	.794			.289		
Collecting system invasion	.029	1.42 (0.66-3.04)	.366	.104		
Lymph node status (positive vs negative)	.471			.686		
Therapy subgroup						
Control	Ref.		Ref.	Ref.		Ref.
Sorafenib	.176	2.03 (0.87-4.73)	.103	.361	1.31 (0.51-3.33)	.578
Sunitinib	.485	1.20 (0.49-2.94)	.689	.706	0.70 (0.22-2.21)	.545

Table 4. Adverse Event in Sorafenib and Sunitinib Groups

	Sorafenib	Sunitinib	*P* Value
Hand-foot syndrome, *n* (%)	17 (63.0)	10 (58.8)	.784
Diarrhea, *n* (%)	15 (55.6)	10 (58.8)	.831
Fatigue, *n* (%)	14 (51.9)	9 (52.9)	.944
Hypertension, *n* (%)	9 (33.3)	7 (41.2)	.598
Rash, *n* (%)	10 (37.0)	5 (29.4)	.603
Mucositis, *n* (%)	8 (29.6)	7 (41.2)	.431
Pruritus, *n* (%)	6 (22.2)	3 (17.6)	.714
Nausea, *n* (%)	6 (22.2)	6 (35.3)	.343
Anorexia, *n* (%)	4 (14.8)	4 (23.5)	.690
Hypothyroidism, *n* (%)	4 (14.8)	6 (35.3)	.114
Alopecia, *n* (%)	10 (37.0)	6 (35.3)	.907
Vomiting, *n* (%)	4 (14.8)	3 (17.4)	1.000
Neutropenia, *n* (%)	9 (33.3)	8 (47.1)	.363

sunitinib-induced circulating proangiogenic factors rely on tumor and are associated with antitumor potency. Griffioen et al. [21] firstly described the angiostatic response in RCC at the tissue level upon treatment with VEGF-targeted therapy. Their results indicated that discontinuation of treatment with tyrosine kinase inhibitors leads to accelerated endothelial cell proliferation. Based on the histologic examination in a xenograft study, Hammers et al. [22] suggested that invertible epithelial to mesenchymal transition might be correlated with acquired tumor resistance to tyrosine kinase inhibitors in patients with clear cell RCC. Despite their unavoidable shortages, those mouse tumor xenograft models likely recognized a process that is related to the present human trial. Those possibly effective models may provide insight into the pathophysiology of VEGF-targeted therapy of RCC to guide prospective studies.

A number of trials have looked into whether adjuvant antiangiogenic agents can improve outcomes of high-risk RCC after nephrectomy. To date, results have been reported for two studies [10,11]. The ASSURE trial was the first randomized phase 3 study. The recruited 1943 patients were randomized 1:1:1 to sorafenib, sunitinib, or placebo. No survival advantage was found for either drug, with not even a trend towards benefit in the treatment arm [10]. The second was a double-blind, placebo-controlled, randomized phase 3 trial (S-TRAC) involving 615 patients. Patients were randomized 1:1 to sunitinib or placebo. The DFS results for sunitinib were as follows: hazard ratio 0.76; 95% confidence interval (CI) 0.85-1.23; $P = .03$, which contradict ASSURE. On the basis of conflicting results from the two available studies, the European Association of Urology RCC guidelines panel does not recommend adjuvant therapy with sunitinib for patients with high-risk RCC after nephrectomy [23].

Several limitations of this study need to be acknowledged. First, the study was a single-center analysis with nonrandomized design. There may be inherent selection bias and uncontrolled confounding factors. Hence, the multivariable analyses were performed. Second, though we tried to follow up all patients until February 2017, the length of follow-up was still relative insufficient, especially for patients receiving targeted therapy. Third, this study had a small sample size of 147 patients, and the number of subjects in the adjuvant therapy groups was smaller than that of the control group.

Conclusion

Despite these limitations, the present study initially investigates the use of sorafenib or sunitinib as postoperative adjuvant therapy in nonmetastatic RCC patients with VTT. Based on our results, these drugs should not be recommended for nonmetastatic RCC patients with VTT in the postoperative adjuvant setting.

Conflict of Interest

The authors have no conflicts of interest to declare.

References

[1] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, and He J (2016). Cancer statistics in China, 2015. *CA Cancer J Clin* **66**, 115–132.

[2] Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, and Merseburger AS, et al (2015). EAU Guidelines on Renal Cell Carcinoma: 2014 Update. *Eur Urol* **67**, 913–924.

[3] Gu L, Wang Z, Chen L, Ma X, Li H, Nie W, Peng C, Li X, Gao Y, and Zhang X (2017). A proposal of post-operative nomogram for overall survival in patients with renal cell carcinoma and venous tumor thrombus. *J Surg Oncol* **115**, 905–912.

[4] Edge SB and Compton CC (2010). The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* **17**, 1471–1474.

[5] Wang B, Li H, Ma X, Zhang X, Gu L, Li X, Fan Y, Gao Y, Liu K, and Zhu J (2015). Robot-assisted laparoscopic inferior vena cava thrombectomy: different sides require different techniques. *Eur Urol* **69**, 1112–1119.

[6] Kirkali Z and Van Poppel H (2007). A critical analysis of surgery for kidney cancer with vena cava invasion. *Eur Urol* **52**, 658–662.

[7] Pal SK and Haas NB (2014). Adjuvant therapy for renal cell carcinoma: past, present, and future. *Oncologist* **19**, 851–859.

[8] Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, and Desai AA, et al (2007). Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* **356**, 125–134.

[9] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, and Kim ST, et al (2007). Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* **356**, 115–124.

[10] Haas NB, Manola J, Uzzo RG, Flaherty KT, Wood CG, Kane C, Jewett M, Dutcher JP, Atkins MB, and Pins M, et al (2008–2016). Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet* **387**, 2016.

[11] Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, Chang YH, Escudier B, Donskov F, and Magheli A, et al (2016). Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med* **375**, 2246–2254.

[12] Blute ML, Leibovich BC, Lohse CM, Cheville JC, and Zincke H (2004). The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. *BJU Int* **94**, 33–41.

[13] Zhao J, Zhu Y, Zhang C, Wang X, He H, Wang H, Wu Y, Zhou W, and Shen Z (2013). Sorafenib or sunitinib as postoperative adjuvant therapy for Chinese patients with locally advanced clear cell renal cell carcinoma at high risk for disease recurrence. *Urol Oncol* **31**, 1800–1805.

[14] Abbasi A, Johnson TV, Ying K, Baumgarten D, Millner R, and Master VA (2012). Duplicated vena cava with tumor thrombus from renal cancer: use of venogram for safer operative planning. *Urology* **79**, e57–e58.

[15] Abel EJ, Margulis V, Bauman TM, Karam JA, Christensen WP, Krabbe LM, Haddad A, Golla V, and Wood CG (2016). Risk factors for recurrence after surgery in non-metastatic RCC with thrombus: a contemporary multicentre analysis. *BJU Int* **117**, E87-94.

[16] Lane BR, Derweesh IH, Kim HL, O'Malley R, Klink J, Ercole CE, Palazzi KL, Thomas AA, Rini BI, and Campbell SC (2015). Presurgical sunitinib reduces tumor size and may facilitate partial nephrectomy in patients with renal cell carcinoma. *Urol Oncol* **33**, 112 e15–21.

[17] Cost NG, Delacroix Jr SE, Sleeper JP, Smith PJ, Youssef RF, Chapin BF, Karam JA, Culp S, Abel EJ, and Brugarolas J, et al (2011). The impact of targeted molecular therapies on the level of renal cell carcinoma vena caval tumor thrombus. *Eur Urol* **59**, 912–918.

[18] Bigot P, Fardoun T, Bernhard JC, Xylinas E, Berger J, Roupret M, Beauval JB, Lagabrielle S, Lebdai S, and Ammi M, et al (2014). Neoadjuvant targeted molecular therapies in patients undergoing nephrectomy and inferior vena cava thrombectomy: is it useful? *World J Urol* **32**, 109–114.

[19] Ebos JM, Lee CR, Cruz-Munoz W, Bjarnason GA, Christensen JG, and Kerbel RS (2009). Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. *Cancer Cell* **15**, 232–239.

[20] Ebos JM, Lee CR, Christensen JG, Mutsaers AJ, and Kerbel RS (2007). Multiple circulating proangiogenic factors induced by sunitinib malate are tumor-independent and correlate with antitumor efficacy. *Proc Natl Acad Sci U S A* **104**, 17069–17074.

[21] Griffioen AW, Mans LA, de Graaf AM, Nowak-Sliwinska P, de Hoog CL, de Jong TA, Vyth-Dreese FA, van Beijnum JR, Bex A, and Jonasch E (2012). Rapid angiogenesis onset after discontinuation of sunitinib treatment of renal cell carcinoma patients. *Clin Cancer Res* **18**, 3961–3971.

[22] Hammers HJ, Verheul HM, Salumbides B, Sharma R, Rudek M, Jaspers J, Shah P, Ellis L, Shen L, and Paesante S, et al (2010). Reversible epithelial to mesenchymal transition and acquired resistance to sunitinib in patients with renal cell carcinoma: evidence from a xenograft study. *Mol Cancer Ther* **9**, 1525–1535.

[23] Bex A, Albiges L, Ljungberg B, Bensalah K, Dabestani S, Giles RH, Hofmann F, Hora M, Kuczyk MA, and Lam TB, et al (2017). Updated European Association of Urology guidelines regarding adjuvant therapy for renal cell carcinoma. *Eur Urol* **71**, 719–722.