Analysis of the factors influencing the survival time of patients with sarcomatoid renal cell carcinoma

YU-SHENG WANG, WEI-BING SHUANG, KE-QIANG YIN, XU-NAN TONG, MAN-CHENG XIA and HAO-SEN YANG

Department of Urology, The First Hospital of Shanxi Medical University, Yingze, Shanxi 030001, P.R. China

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Abstract. The aim of the present study was to identify the factors influencing the survival time of patients with sarcomatoid renal cell carcinoma (SRCC). Between January 2000 and September 2017, a total of 21 patients were enrolled, all of whom were diagnosed with SRCC. In total, eight prognostic factors were analyzed using the Kaplan-Meier estimator, a log-rank test and Cox's proportional hazards model. The log-rank test results revealed that there was a significant association between the proportion of sarcoma elements and survival time of patients with SRCC (P<0.05). In addition, there was a significant association between post-operative drug treatment and SRCC survival time (P<0.05). The results of the Kaplan-Meier estimate demonstrated that the survival curve of post-operative drug treatment was significantly greater compared with the survival curve of patients who did not undergo drug treatment (P<0.05). The survival curve of patients with a proportion of sarcoma elements <50% was significantly greater compared with the survival curve of patients with a proportion of sarcoma elements ≥50% (P<0.05). Furthermore, the Cox's proportional hazards model revealed that the mortality risk in post-operative patients without drug treatment was 5.822 times greater compared with that of patients with drug treatment (P<0.05). Mortality risk in patients with a proportion of sarcoma elements ≥50% was 4.682 times higher compared with that of patients with sarcoma elements <50% (P<0.05). Finally, post-operative drug therapy was revealed to be a protective factor which significantly affected the survival time of patients with SRCC [risk ratio (RR)=0.172], in addition to the proportion of sarcoma elements ≥50% (RR=4.682). In conclusion, drug therapy should be promoted upon patient diagnosis with SRCC and attention should be given to the proportion of sarcomatoid components.

Correspondence to: Dr Wei-Bing Shuang, Department of Urology, The First Hospital of Shanxi Medical University, 85 Jiefang Road, Yingze, Shanxi 030001, P.R. China
E-mail: shuangweibing@126.com

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Introduction

Renal cell carcinoma (RCC) is a common tumor, accounting for 21.82% of urinary tumors, second only to bladder and prostate cancer (1). In China, the incidence of renal cancer increases every year (2). There are several pathological types of renal cell carcinoma which include: Clear cell carcinoma, papillary renal cell carcinoma, chromophobe cell carcinoma, collecting ductal carcinoma and medullary carcinoma (2). Approximately 30% of patients with renal cell carcinoma exhibit distant metastasis at the time of initial diagnosis, and ~50% of patients with localized renal cell carcinoma exhibit distant metastasis following surgery (3). Sarcomatoid renal cell carcinoma (SRCC) is a rare type of renal cell carcinoma, with a high malignancy and a poor prognosis (4). SRCC accounts for ~5-7% of all RCC cases (5,6). The incidence of SRCC is increased in males compared with females, particularly in the unilateral and right kidney (4). The median survival time of patients is 6-12 months amongst those aged 31-81 (median age, 60 years) (4). Histologically, SRCC is composed of epithelial (cancerous) and mesenchymal (sarcomatoid) components, which is in difference to renal sarcoma (7,8). SRCC is a more aggressive and advanced form of kidney cancer, which has a shorter overall survival (9). It has therefore been the subject of many studies.

At present, SRCC treatment includes surgery, chemotherapy and radiotherapy, in addition to targeted biological and cytokine therapies (4). Surgery alone is often an inadequate measure to cure patients (10-12). Furthermore, SRCC does not respond well to cytotoxic chemotherapy, cytokines and targeted therapies (9,13). A higher percentage of sarcomatoid features are also associated with a poorer survival (14,15).

Considering the multitude of factors that influence the survival time of patients with SRCC, in the present study a multivariate Cox's proportional hazards regression model was used to analyze the factors affecting the survival time of patients with SRCC.

Materials and methods

Patients. The present study was ethically approved by the ethical review board of The First Hosptial of Shanxi Medical

University (approval no. 2018-K006). A retrospective review was performed to identify patients with SRCC whose diagnoses were confirmed using pathology between January 2000 and September 2017 at The First Hospital of Shanxi Medical University. In total, 21 patients were included (13 males; 8 females; mean age, 57 years; age range, 30-77 years). Four cases were treated at The First Hosptial of Shanxi Medical University; the other 17 cases were retrieved from a reference search. Clinical data were collected, including sex, age, maximum tumor size, the proportion of sarcoma elements, lymph node metastasis, distant metastasis, surgery and drug therapy. The proportion of sarcoma elements was defined as the proportion of sarcoma elements to the whole tumor observed under a microscope.

Data analysis. All patient data were analyzed using the Kaplan-Meier estimate and log-rank test for univariate analysis. In addition, survival curves between the two groups were compared using the log-rank method. A Cox's proportional hazard model was used for multivariate analysis. Data were assigned numbers, which are presented in Table I. SPSS version 20 (IBM Corp, Armonk, NY, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical data. In total, 14 patients had a proportion of sarcoma elements >50% in their tumor samples, and seven patients with <50%. Nine patients received drug treatment, whereas 12 patients did not. Full characteristics of the patient population are presented in Table II (16-26).

Univariate analysis. There was a significant negative association between the proportion of sarcoma elements and survival time (P<0.02). In addition, there was a significant positive association between drug treatment and survival time (P<0.02; Table III). The Kaplan-Meier curves revealed that the post-operative non-drug treatment group had a significantly shorter survival time compared with the drug treatment group (P<0.05; Fig. 1A). Patients with a proportion of sarcoma components ≥50% exhibited a significantly shorter survival time compared with the <50% group (P<0.05; Fig. 1B).

Multivariate analyses. The multivariate Cox's proportional hazard model revealed that drug treatment [risk ratio (RR), 0.171; 95% confidence interval (CI), 0.049-0.591; P=0.005] was a significant protective factor in survival time. Mortality risk in the post-operative non-drug therapy patients following surgery was 5.822 times greater compared with that of the post-operative drug therapy group. It also revealed that a ≥50% proportion of sarcoma elements (RR, 4.682; 95% CI, 1.345-16.299; P=0.015) was a significant risk factor for survival time. Mortality risk in the ≥50% group was 4.682 times higher compared with those in the <50% group (Table IV).

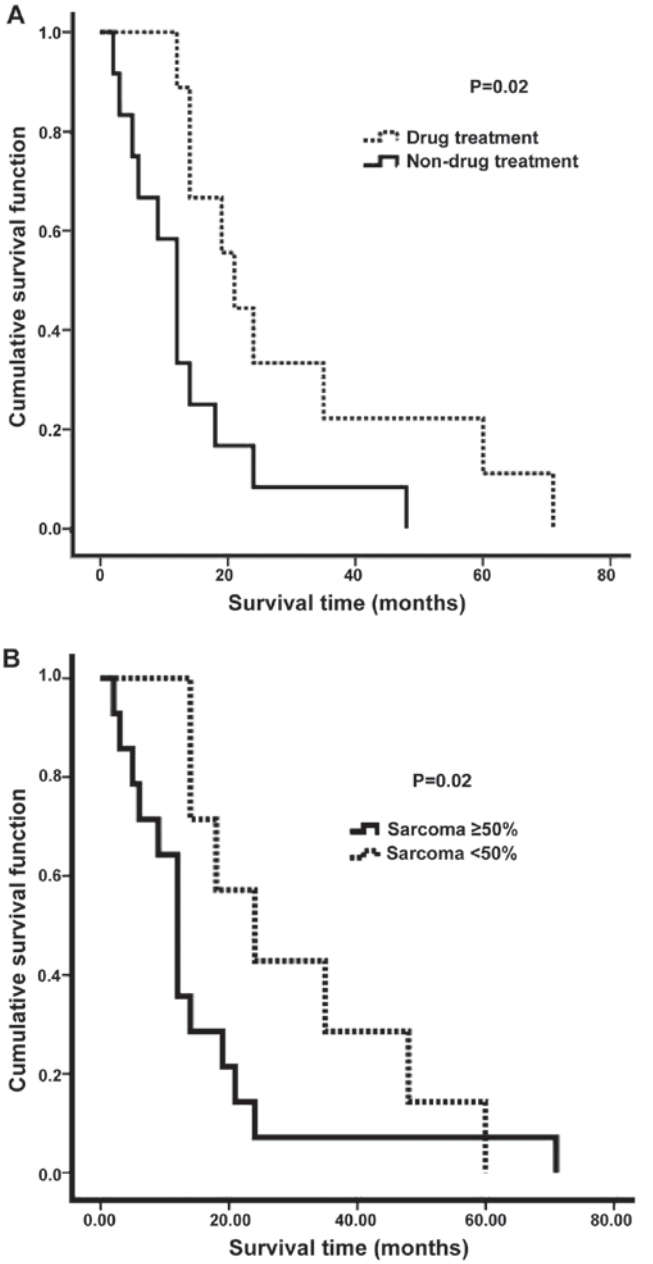

Figure 1. Survival curves of patients with sarcomatoid renal cell carcinoma. (A) Survival time in patients who had undergone drug treatment compared with those who had not. (B) Survival time in patients with a proportion of sarcoma elements ≥50% compared with those with a proportion of sarcoma elements <50%.

Discussion

Identifying the factors that impact the biological behavior of SRCC is essential for understanding the natural course of the disease in patients. Drug treatment induces adverse effects in almost every patient (27). Therefore, it is necessary to avoid treating patients who will not ultimately benefit from drug therapy. It is evident that the clinical behavior of SRCC results from complex interactions between multiple prognostic factors (27). The reported effects of chemotherapy and immunotherapy on SRCC differentiation are contradictory (27). Therefore, determining the prognostic factors of survival may be helpful in selecting patients for drug treatment.

It was hypothesized that drug treatment would have a beneficial effect on survival time. There are certain rationales for administering drug treatment for SRCC. Firstly, improved survival time was revealed in patients receiving high-dose interleukin-2 (IL-2) therapy, compared with patients treated

Table I. Factors and assignments of sarcomatoid renal cell carcinoma.

Factors	Variable name	Assignments
Age	X1	(year)
Sex	X2	Female, 0; male, 1
Sarcoma elements	X3	<50%, 0; ≥50%, 1
Lymph node metastasis	X4	No, 0; Yes, 1
Distant metastasis	X5	No, 0; Yes, 1
Maximum diameter of the tumor	X6	(cm)
Treatment method	X7	Conservative, 0; surgery, 1
Drug treatment	X8	No, 0; Yes, 1
Survival time	t	(months)
Survival outcome	Y	Censored, 0; death, 1

Table II. Characteristics of the patient population.

Patient	Sex	Age (years)	Maximum tumor size	Sarcoma ≥50%	Lymph node metastasis	Distant metastasis	Surgery	Drug treatment	Survival time (months)
1	Male	65	9	Yes	No	Yes	Yes	No	2
2	Male	53	5.3	Yes	Yes	Yes	Yes	No	3
3	Male	56	6	No	Yes	No	Yes	No	48
4	Male	61	8	No	Yes	Yes	Yes	No	14
5	Male	44	4.2	Yes	No	Yes	Yes	Yes	21
6	Female	30	8.2	Yes	Yes	Yes	No	No	6
7	Female	47	5	No	No	No	Yes	No	24
8	Male	70	6.5	Yes	No	Yes	Yes	No	5
9	Male	35	19	Yes	Yes	Yes	Yes	Yes	14
10	Male	43	6	Yes	No	No	Yes	No	12
11	Male	40	10	Yes	No	No	Yes	No	12
12	Female	62	13	Yes	Yes	Yes	Yes	Yes	71
13	Male	47	6	Yes	No	No	Yes	No	12
14	Male	55	9	No	No	Yes	Yes	Yes	35
15	Male	59	2.5	Yes	No	Yes	Yes	Yes	19
16	Female	77	7	Yes	Yes	No	Yes	Yes	24
17	Female	66	7	Yes	No	No	Yes	No	9
18	Female	68	8	No	Yes	Yes	Yes	Yes	60
19	Male	30	12	No	No	No	No	Yes	14
20	Female	77	7	Yes	Yes	Yes	Yes	Yes	12
21	Female	64	5.8	No	No	No	Yes	No	18

with surgery alone or any other form of immunotherapy. The relative risk of mortality is 10.4 times higher in patients not receiving high-dose IL-2 therapy (28). Furthermore, surgical resection and high-dose IL-2-based immunotherapy may serve a function in the successful treatment of SRCC (28). Another report suggested that treatment with interferon-α, compared with vinblastine or medroxyprogesterone, achieves a small improvement in survival time (29). Secondly, a recent study has revealed that the use of multiple targeted tyrosine kinase inhibitors, including sorafenib and sulinitinib, have produced a positive effect on patient survival time (30). Thirdly, chemotherapy with doxorubicin and gemcitabine may reverse clinical deterioration in certain patients, and cause the stabilization or regression of metastases (31). In addition, the combination of doxorubicin and gemcitabine has antitumor activity in patients with SRCC (11). However, in the present study, a significant beneficial effect of drug treatment on survival time was observed compared with the non-drug treatment group ($P<0.05$). The survival time of patients with postoperative drug treatment was 21 months, which was significantly higher compared with 12 months in the postoperative non-drug treatment group (Table III; $P<0.05$). Drug treatment was much more commonly administered in Japan compared with China, consequently resulting in a longer survival time in Japan (26).

Table III. Univariate analyses of factors affecting cancer-specific survival time.

Factors	Cases	Median survival (months)	1-year survival rate (%)	P-value
Age (years)				0.551
<60	12	14	83.3	
≥60	9	14	66.7	
Sex				0.148
Female	8	14	75	
Male	13	18	76.9	
Maximum tumor diameter (cm)				0.565
<7	9	18	77.8	
≥7	12	14	75	
Sarcoma components (%)				0.02[a]
<50	7	12	100	
≥50	14	24	64.2	
Surgery				0.25
Yes	19	14	78.9	
No	2	6	50	
Drug treatment				0.02[a]
Yes	9	21	66.7	
No	12	12	58.3	
Lymph node metastasis				0.12
Yes	9	14	77.8	
No	12	12	75	
Distant metastasis				0.61
Yes	11	14	72.7	
No	10	12	60	

[a]P<0.05.

Table IV. Analytical results by Cox's proportional hazard model.

Factors	bj	S_{bj}	Wald value	P-value	Exp (B)	95% confidence interval
Sarcoma components	1.544	0.636	5.885	0.015	4.682	(1.345, 16.299)
Chemotherapy/Biological drug therapy	-1.768	0.634	7.786	0.005	0.171	(0.049, 0.591)

It was confirmed the survival rate of patients with ≥50% sarcoma elements was worse compared with the <50% group. This is consistent with other reports demonstrating that sarcomatoid architecture predicts poor survival (32,33). The mean survival time of the patients in the ≥50% group was only 14 months, whereas those in the <50% group had an mean survival time of 27 months, in other words that the higher the proportion of the sarcoma elements, the worse the prognosis of the patients (34). Numerous studies have demonstrated that sarcomatoid differentiation is associated with a poor prognosis (30,35-38). Patients with sarcomatoid differentiation have more aggressive tumor characteristics compared with those without sarcomatoid differentiation. Furthermore, it has been reported that sarcomatoid differentiation is an independent prognostic predictor of overall survival time (26). Furthermore, the 2-year survival rate of patients in the ≥50% group was 7.1%, whereas the survival rate for the <50% group was 42%. In conclusion, the higher the proportion of sarcoma elements, the worse the prognosis and the shorter the survival time.

The present study has a number of limitations. The number of studied SRCC cases was relatively small, due to the limited cases allotted. It was not possible to further analyze the types of drug treatment, so univariate and multivariate analyses could only be performed from the perspective of whether drug treatment was or was not used.

Analyzing the prognostic factors of survival for patients with SRCC would be valuable in guiding treatment. In the present study, the multivariate analysis of SRCC survival revealed that drug treatment was a protective factor that

affected survival time (RR=0.172). Additionally, the proportion of sarcoma elements ≥50% was a risk factor that affected survival time (RR=4.682). Therefore, when a patient is diagnosed with SRCC, drug therapy may extend the patient's survival time to a certain extent. In addition, judging the proportion of sarcomatoid components may provide a reference to judge a patient's condition. However, SRCC is rare in clinical practice and the number of cases is limited. The present study has certain limitations and further cases will be collected for further analysis.

In the present study, the multivariate analysis of the survival time with SRCC revealed that postoperative drug treatment is a protective factor that affects survival time (RR=0.172). The proportion of sarcoma elements ≥50% is a risk factor that affects survival time (RR=4.682). Therefore, when a patient is diagnosed with SRCC, postoperative drug therapy may extend the patient's survival time to a certain extent. In addition, judging the proportion of sarcomatoid components on time may provide a certain reference to understanding the patient's condition.

Ultimately, the present study has identified that postoperative drug treatment and sarcoma elements were protective and risk factors for SRCC. However, due to the fact that SRCC is rare in clinical practice, the present research was not able to further analyze the effects of different drugs on the survival of patients with SRCC.

To the best of our knowledge, until now, there has not been any research analyzing the survival time of patients with SRCC.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YW collected clinical data and wrote the manuscript. WS designed and supervised the current study. KY, XT, MX and HY collected and interpreted clinical data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the ethical standards of the Institutional Review Board of the First Hospital of Shanxi Medical University (approval no. 2018-K006), in addition to the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional Review Board of the First Hospital of Shanxi Medical University waived the requirement for informed consent due to the retrospective design of this study.

Patient consent for publication

All patients provided their consent for publication.

Competing interests

The authors declare that they have no competing interests.

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