A Population Study to Identify Candidates for Cytoreductive Nephrectomy in Patients with Metastatic Sarcomatoid Renal Cell Carcinoma from the Surveillance, Epidemiology, and End Results (SEER) Database

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Background: This population study aimed to identify suitable candidates for cytoreductive nephrectomy in patients with metastatic sarcomatoid renal cell carcinoma (RCC) from the US Surveillance, Epidemiology, and End Results (SEER) database.

Material/Methods: Demographic and clinical data from 1,229 patients with metastatic sarcomatoid RCC were retrieved from the SEER database. Patients were divided into the cytoreductive nephrectomy group (n=937) and the no surgery group (n=292). Multivariate Cox regression analysis identified factors associated with overall survival (OS) and propensity score matching identified factors that significantly impacted the OS. Survival of propensity score-matched subgroups of patients with metastatic sarcomatoid RCC treated by cytoreductive nephrectomy or no surgery was determined by the Kaplan–Meier method and compared by the log-rank test.

Results: Of the 1,229 patients with metastatic sarcomatoid RCC retrieved from the SEER database, age, tumor size, T stage, and N stage were independent risk factors for patient survival. There were no significant differences in age, N stage, and tumor size between the cytoreductive nephrectomy-treated and non-surgically treated T stage cases following propensity score matching. OS benefits were found in cases with stage T1 (12 months increase), T2 (7.5 months increase), T3a (2 months increase), and T4 (3 months increase), but not in the T3b or T3c subgroups treated by cytoreductive nephrectomy, compared with patients with no surgical treatment.

Conclusions: Data from the SEER database showed that cytoreductive nephrectomy improved OS in patients with T1 and T2 metastatic sarcomatoid RCC with a significant long-term survival benefit of >6 months.

MeSH Keywords: Carcinoma, Renal Cell • Nephrectomy • SEER Program

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Background

Renal cell carcinoma (RCC) accounts for 2–3% of all adult malignancies, and approximately one-third of patients present with metastatic disease [1]. Although several advances have been made, metastatic RCC remains incurable. Cytoreductive nephrectomy has been established as a therapeutic consideration for metastatic RCC, especially from 1992 to 2004, during which time, immunotherapy with agents that targeted interleukin-2 and interferon-α represented the mainstay of therapy. Since several targeted kinase inhibitors (TKIs) against metastatic RCC have been approved since 2005, both the role of first-line cytoreductive nephrectomy and the timing of cytoreductive nephrectomy have been questioned. A randomized controlled trial, CARMENA, despite apparent limitations, suggested treatment with TKIs alone was not inferior to upfront cytoreductive nephrectomy combined with TKI in certain metastatic RCC patients [2]. However, stratifying patients with metastatic RCC who may benefit from cytoreductive nephrectomy is important. Current guidelines recommend that cytoreductive nephrectomy should be conducted in patients with metastatic RCC with the International Metastatic RCC Database Consortium (IMDC) favorable and intermediate-risk levels [3].

However, the histological subtypes have not been included in the IMDC risk analysis. Some histologic subtypes, such as sarcomatoid RCC have clinicopathological features that are associated with prognosis. Sarcomatoid RCC is a rare variant of RCC that represents approximately 5% of cases and is a poorly differentiated variant [4]. Previous studies have shown that sarcomatoid RCC is associated with advanced clinicopathological features and poor clinical outcome [5]. The role of cytoreductive nephrectomy in the management of patients with metastatic sarcomatoid RCC remains to be assessed. Therefore, the aim of this population study was to identify suitable candidates for cytoreductive nephrectomy in patients with metastatic sarcomatoid renal cell carcinoma (RCC) from the US Surveillance, Epidemiology, and End Results (SEER) database by evaluating cancer-specific survival (CSS) and overall survival (OS) at three months and six months.

Material and Methods

Data source and study population

Patients with metastatic sarcomatoid renal cell carcinoma (RCC) and patients with conventional RCC who were diagnosed from 2004 to 2015 were identified from the US Surveillance, Epidemiology, and End Results (SEER) database. SEER incorporates high-quality data derived from 18 cancer registries and covers approximately 27.8% of the U.S. population (based on the 2010 census) [6]. Sarcomatoid RCC was identified using the histologic type codes ICD-O-3 8318 (RCC, sarcomatoid) and conventional RCC was identified using the kidney parenchyma site-specific CS factor 4 code 010, and the histologic type codes ICD-O-3 8310 (clear cell adenocarcinoma, not otherwise specified [NOS]), 8312 (RCC), 8260 (papillary adenocarcinoma, NOS), 8317 (RCC, chromophobe type), and 8255 (adenocarcinoma with mixed subtypes). Only patients with microscopically confirmed RCC were included in this study. Cases without follow-up or without adequate clinical details were excluded. Cases with kidney parenchyma CS tumor size code 000 (no mass/tumor found) were also excluded.

Variables

For each identified patient in the SEER database, data were obtained on age, race, gender, laterality, marital status at diagnosis, histological type ICD-O-3, grade, the stage according to the sixth edition of the American Joint Committee on Cancer (AJCC) (2004+), T stage (2004+), N stage (2004+), M stage (2004+), RX Summ–Surg Prim Site (1998+), CS tumor size (2004+), CS site-specific factor 4 (2004+), SEER cause-specific death classification, survival in months, and vital status recode (study cutoff used).

Propensity score matching

Statistical analysis included three main steps. First, continuous variables such as age at diagnosis and tumor size were transformed into categorical variables using X-Tile version 3.6.1 software (Yale University) [7], to identify the best cut-off point based on the lowest P-values and the maximum chi-square of log-rank tests. Second, multivariable Cox regression analysis was used to identify variables that could significantly impact the OS or CSS of patients with metastatic sarcomatoid RCC. Third, in the comparison of OS or CSS of metastatic sarcomatoid RCC treated by cytoreductive nephrectomy (derived using RX Summ-Surg Prim Site code 40, 50, and 80) versus NS (derived using RX Summ-Surg Prim Site code 0), propensity score matching was conducted using the MatchIt property in R version 3.6.0 [8], to reduce potential confounding effects and treatment selection bias. Propensity matching was performed with factors that could significantly impact cancer survival from the Cox analysis results. A 1: 1 nearest-neighbor matching with a caliper distance of 0.2 was used.

Statistical analysis

The clinical and pathological characteristics of the propensity score-matched subgroups of patients with metastatic sarcomatoid RCC treated by cytoreductive nephrectomy or without surgery were compared. The values of unordered categorical variables were compared using the chi-square test. The ordered categorical variables were compared using Goodman and

Kruskal's gamma. Fisher's exact test and Bonferroni's correction was used for multiple comparisons. Continuous variables were compared with the Student's t-test. The Mann-Whitney U test was used to compare variables that did not have a normal distribution. Cumulative survival was estimated by the Kaplan-Meier method and compared by log-rank tests. Statistical analysis was performed with SPSS version 25.0 for Windows (IBM Corp., Armonk, NY, USA). All tests were two-sided. A p-value <0.05 was considered significant.

Results

Clinical data

Totals of 1,894 cases of sarcomatoid RCC with ICD-O-3 code 8318 and 1,776 cases of conventional RCC with Kidney Parenchyma CS Site-Specific Factor 4 code 010 were identified from the SEER database. After removing 10 cases with CS tumor size code 0 and 5 cases without known survival months, 3,655 cases of sarcomatoid RCC were retrieved. A total of 1,507 cases of metastatic sarcomatoid RCC were retrieved from the 3,655 cases of sarcomatoid RCC, excluding 117 cases with CS tumor size code 999 (unknown tumor size), six cases with extremely abnormal tumor size (two cases with tumor size code 1 measuring only 1 mm, four cases with tumor size larger than 70 cm, including one case of CS tumor size code 700, two cases of CS tumor size code 989, and one case of CS tumor size code 980), 47 cases of Tx (primary tumor not assessed), and 108 cases of Nx (regional lymph nodes not assessed). A total of 937 cases that underwent cytoreductive nephrectomy and 292 cases that received no surgery were retrieved.

X-tile and Cox regression analysis

Using X-Tile, we identified the best cutoff points for age at diagnosis and tumor size as 75-years-old (maximum chi-square 33.4, Miller-Seigmund P<0.0001) and 15 cm (maximum chi-square 15, Miller-Seigmund P=0.0149), respectively. Among variants of age, race, sex, laterality, marital status at diagnosis, tumor size, T stage, and N stage, multivariate Cox analyses demonstrated that age (P=0), T stage (P=0.004), and N stage (P=0) were independent risk factors for OS in metastatic sarcomatoid RCC, while T stage (P=0.01), N stage, (P=0), and tumor size (P=0.004) were independent risk factors for CSS in metastatic sarcomatoid RCC. Then, propensity score matching was performed to balance age, tumor size, T stage, and N stage in the cytoreductive nephrectomy-treated or non-surgically-treated patients with metastatic sarcomatoid RCC.

Subgroup analysis

The OS and CSS of T1 (90 cases without surgical treatment; 56 cases of cytoreductive nephrectomy), T2 (63 cases without surgical treatment; 89 cases of cytoreductive nephrectomy), T3a (20 cases of without surgical treatment; 297 cases of cytoreductive nephrectomy), T3b (40 cases of NS, 335 cases of cytoreductive nephrectomy), and T4 (65 cases of NS, 134 cases of cytoreductive nephrectomy) patients with metastatic sarcomatoid RCC treated by cytoreductive nephrectomy or non-surgically were compared, followed by propensity score matching to reduce potential confounding effects and treatment selection bias. There were no significant differences in age, N stage, and tumor size in the cytoreductive nephrectomy-treated and non-surgically-treated cases following propensity score matching (Table 1). Survival benefits were found in the T1, T2, T3a, and T4 subgroups of metastatic sarcomatoid RCC, but not in T3b patients treated by cytoreductive nephrectomy compared with non-surgically treated patients (Figures 1, 2).

As shown in Figure 3, there were 12 and 7.5 months of OS benefit in T1 and T2 metastatic sarcomatoid RCC patients treated by cytoreductive nephrectomy, respectively, compared with non-surgically treated patients. In T3a and T4 patients, there was a statistically significant benefit in OS with cytoreductive nephrectomy treatment; however, the OS benefit was relatively small (2 months and 3 months, respectively). Only 26 cases of T3c metastatic sarcomatoid RCC were retrieved, 10 of whom received non-surgical treatment while the other 16 received cytoreductive nephrectomy. Following propensity score matching, no survival benefit was found in patients treated by cytoreductive nephrectomy (data not shown).

We compared the OS and CSS of the non-surgically treated and cytoreductive nephrectomy-treated metastatic sarcomatoid RCC patients in the N0 and N1 subgroups, in the >75 years or <75 years subgroups, and tumor size >15 cm or <15 cm groups, after excluding other variables that affected survival. A survival benefit was found in patients treated by cytoreductive nephrectomy in all these subgroups (data not shown).

Discussion

As the median overall survival (OS) was only 7 months in the 60 cases of metastatic sarcomatoid renal cell carcinoma (RCC) reported by Mian et al. undergoing cytoreductive nephrectomy, these authors questioned if cytoreductive nephrectomy was beneficial in this population [9]. Shuch et al. compared the results of cytoreductive nephrectomy treatment in metastatic RCC patients with or without sarcomatoid features and found that patients with metastatic sarcomatoid RCC undergoing cytoreductive nephrectomy had a poor prognosis with a median OS

Table 1. Clinical and pathological characteristics of propensity score-matched patients with metastatic sarcomatoid renal cell carcinoma treated by cytoreductive nephrectomy or no surgery.

Variables			CN		NS		Significant	
			No.	%	No	%	P	Method
T1	N	0	29	78.4	29	78.4	1	chi-square
		1	8	21.6	8	21.6		
			Mean	SD	Mean	SD	P	Method
	Age (years)		63.2	11.9	63.3	11.3	0.968	t-test
	Tumor size (cm)		5.0	1.69	5.02	1.46	0.883	t-test
T2	N	0	33	60	33	60	1	chi-square
		1	22	40	22	40		
			Mean	SD	Mean	SD	P	Method
	Age (years)		60.5	11.6	60.7	10.4	0.924	t-test
	Tumor size (cm)		10.8	2.91	10.8	2.76	0.957	t-test
T3a	N	0	12	60	9	45	0.337	chi-square
		1	8	40	11	55		
			Mean	SD	Mean	SD	P	Method
	Age (years)		61.8	11.6	61.9	8.6	0.988	t-test
	Tumor size (cm)		7.33	4.1	7.13	3.8	0.871	t-test
T3b	N	0	15	37.5	15	37.5	1	chi-square
		1	25	62.5	25	62.5		
			Mean	SD	Mean	SD	P	Method
	Age (years)		58.7	9.6	61.9	8.6	0.212	t-test
	Tumor size (cm)		9.93	3.95	10.0	4.87	0.934	t-test
T4	N	0	29	51.8	26	46.4	0.57	chi-square
		1	27	48.2	30	53.6		
			Mean	SD	Mean	SD	P	Method
	Age (years)		61.7	10.4	61.4	10.8	0.901	t-test
	Tumor size (cm)		12.4	5.71	10.8	4.18	0.085	t-test

CN – cytoreductive nephrectomy; NS – no surgery, CI – confidence interval.

of only 4.9 months [10]. Shuch et al. concluded that patients with metastatic sarcomatoid RCC if identified preoperatively, should undergo first-line systemic therapy rather than cytoreductive nephrectomy [10]. These two studies did not compare the impact of cytoreductive nephrectomy compared with the non-surgical treatment in patients with metastatic sarcomatoid RCC or the impact of cytoreductive nephrectomy on different subgroups of metastatic sarcomatoid RCC. In the present study, we compared survival between different subgroups of patients with metastatic sarcomatoid RCC treated with cytoreductive nephrectomy or non-surgical treatment, after balancing other variables impacting survival. We found a relative long-term (longer than 6 months) OS benefit in patients with T1 and T2 metastatic sarcomatoid RCC treated by cytoreductive nephrectomy compared with non-surgically treated patients. Therefore, cytoreductive nephrectomy may be considered in these patients. In patients with T3a and T4 metastatic sarcomatoid RCC, there was a statistically significant benefit in OS with cytoreductive nephrectomy treatment. However, the OS benefit was relatively short (less than 3 months). Therefore,
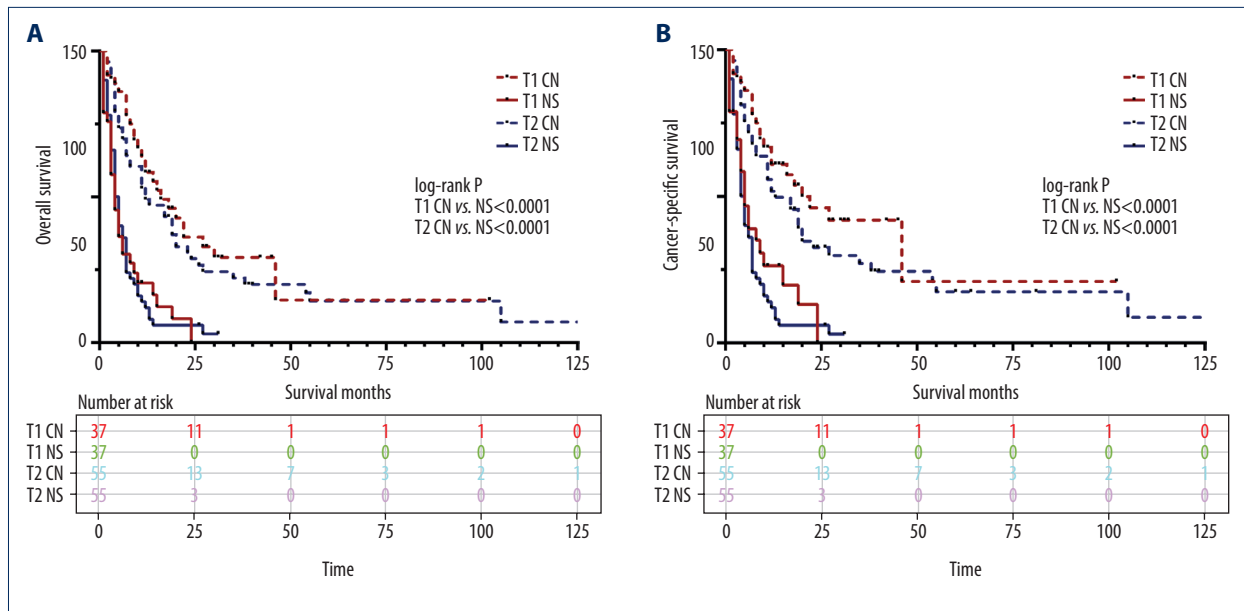
Figure 1. Overall survival (OS) and cancer-specific survival (CSS) in patients with stage T1 and T2 metastatic sarcomatoid renal cell carcinoma treated with cytoreductive nephrectomy or no surgery. Kaplan-Meier overall survival (OS) curves (**A**) and cancer-specific survival (CSS) (**B**) for patients with propensity score-matched stage T1 and T2 metastatic sarcomatoid renal cell carcinoma treated by cytoreductive nephrectomy or no surgery. CN – cytoreductive nephrectomy; NS – no surgery.
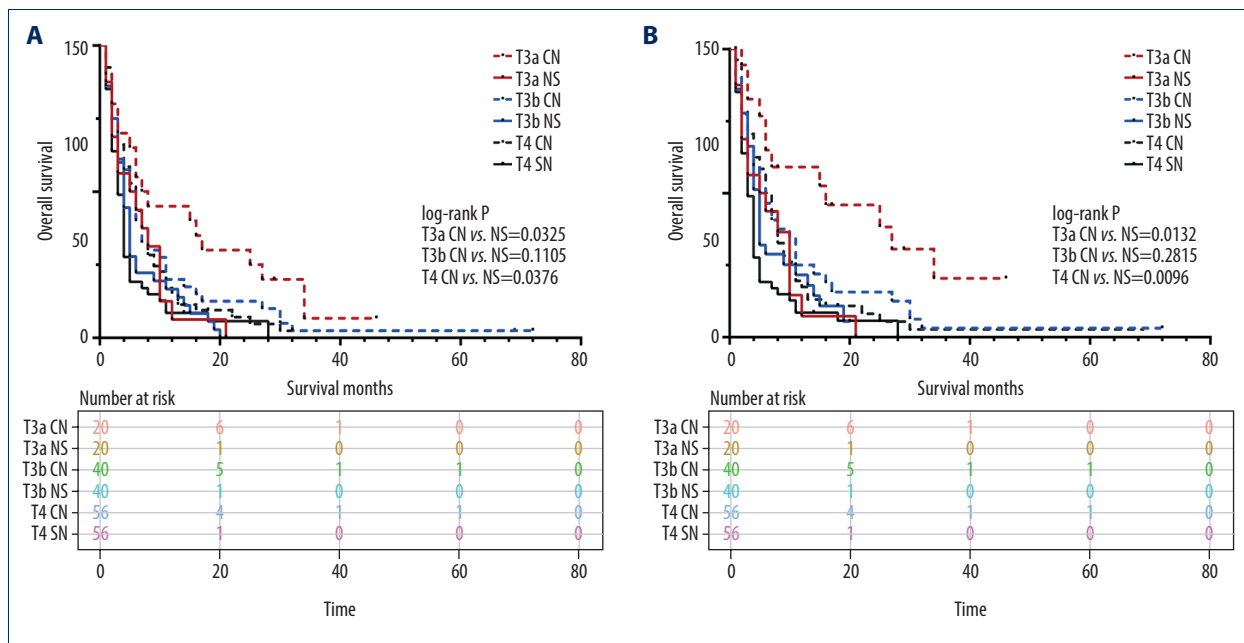

Figure 2. Overall survival (OS) and cancer-specific survival (CSS) in patients with stage T3a, T3b, and T4 metastatic sarcomatoid renal cell carcinoma treated with cytoreductive nephrectomy or no surgery. Kaplan-Meier overall survival (OS) curves (**A**) and cancer-specific survival (CSS) (**B**) for patients with propensity score-matched stage T3a, T3b, and T4 metastatic sarcomatoid renal cell carcinoma treated by cytoreductive nephrectomy or no surgery. CN – cytoreductive nephrectomy; NS – no surgery.
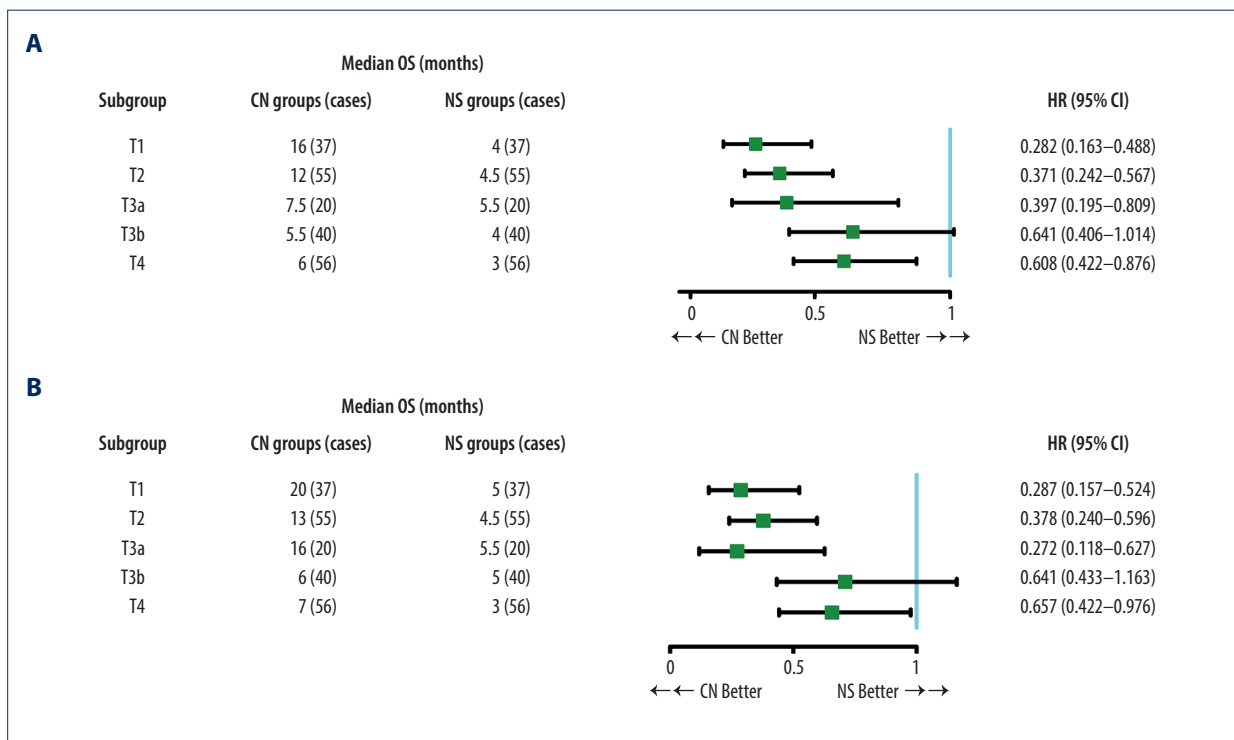
Figure 3. Median overall survival (OS) and cancer-specific survival (CSS) in patients with different T stage metastatic sarcomatoid renal cell carcinoma treated with cytoreductive nephrectomy or no surgery. Comparison of the median overall survival (OS) (**A**) and cancer-specific survival (CSS) (**B**) of propensity score-matched different T stages of metastatic sarcomatoid renal cell carcinoma patients treated with cytoreductive nephrectomy or no surgery. CN – cytoreductive nephrectomy; NS – no surgery; OS – overall survival; CSS – cancer-specific survival; CI – confidence interval; HR – hazard ratio.

cytoreductive nephrectomy needs to be reconsidered in this population. There was no statistically significant survival benefit in patients with T3b and T3c metastatic sarcomatoid RCC treated by cytoreductive nephrectomy compared with non-surgically treated patients, which suggested that cytoreductive nephrectomy might not be useful in these patients.

To avoid non-beneficial cytoreductive nephrectomy for subgroups of metastatic sarcomatoid RCC, we must consider preoperative identification methods. A renal biopsy might be an accessible strategy. However, it has been reported that only 9.2% of cases of metastatic sarcomatoid RCC cases could be identified from preoperative biopsy [11]. This finding could be because sampling a limit of tumor regions by a small gauge needle could not provide adequate tissue or preserve cellular architecture to determine sarcomatoid features reliably. Another possible strategy could be to resect or biopsy a distant site of metastasis. However, it has been reported that 38% of metastasis sites derived from sarcomatoid RCC contained only high-grade carcinoma elements without sarcomatoid features [12]. Accurate preoperative diagnosis by radiography is also difficult [13]. Although the 292 cases of patients with sarcomatoid RCC in the non-surgically treated group in the present study were microscopically confirmed, it should be

noted that many other patients with sarcomatoid RCC might not be diagnosed without operation. Further studies are needed to investigate how to identify sarcomatoid RCC preoperatively by biopsy, imaging, or by molecular biomarkers in serum or urine. Sarcomatoid RCC can be diagnosed preoperatively in the future, and the results in the present study may aid decision-making in a wider clinical practice.

This study had several limitations. First, the SEER data may be limited by unrecorded variables, underreported and incomplete data, variations in data coding and reporting, and migration of patients in and out of the SEER registry area. Second, a limitation of the sarcomatoid RCC data in the SEER database lacks information about the percentage of the sarcomatoid tumor component in each patient. Previous studies have shown that a greater percentage of the sarcomatoid component is associated with a worse outcome [14]. As patients with sarcomatoid RCC in the non-surgically treated group were mainly diagnosed based on needle biopsy tissue, while in the cytoreductive nephrectomy group was mainly on surgically removed specimens, it is reasonable to assume that the percentage of sarcomatoid component in the non-surgically treated group might be higher than that in the cytoreductive nephrectomy group. Considering the potential bias of

the percentage of sarcomatoid component between the cytoreductive nephrectomy group and the non-surgically treated group, survival benefits in the cytoreductive nephrectomy-treated patients found in the present study might be more significant if we could eliminate the bias. Third, in this cohort of patients with metastatic sarcomatoid RCC, only stages according to the sixth edition of the American Joint Committee on Cancer (AJCC) were used, while several modifications in T and N stages have recently been made. We integrated the 6th edition of N1 and N2 stages into N1 according to the 8th edition of the AJCC TNM staging criteria. The T stage changes in different AJCC editions should be taken into consideration when applying the results of the present study. Fourth, there was no detailed information on systemic therapy, such as targeted therapy, chemotherapy, and immunotherapy for this cohort of patients with metastatic sarcomatoid RCC. As a result, we did not know whether systemic therapies between the cytoreductive nephrectomy group and the non-surgically treated group were balanced. Since we retrieved patients with metastatic sarcomatoid RCC diagnosed from 2004 to 2015 from the SEER database in the present study, it was presumed that most of these patients were treated with targeted therapy, based the American Urological Association (AUA) guideline recommendations.

Targeted therapy for metastatic sarcomatoid RCC, compared with RCC, has shown poor results [15]. A small retrospective study on response to checkpoint inhibitors in patients with metastatic sarcomatoid RCC showed promising outcomes, with a complete response (CR) in up to 15% and an objective response rate (ORR) of 62% [16]. Therefore, the findings from the present study should be validated by future studies with larger numbers of patients with metastatic sarcomatoid RCC treated with checkpoint inhibitors. Fifth, for some subgroups, such as T3a and T3c cases, the samples were small. Sixth, sarcomatoid RCC is often difficult to diagnose accurately without surgically excised specimens or biopsies and histology. Since only patients with histologically confirmed sarcomatoid RCC

were included in the present study, it is possible that some non-surgical patients had sarcomatoid RCC that was not diagnosed because of no available tissue or insufficient tissue was available for histology. Seventh, although we balanced survival-related variables between the cytoreductive nephrectomy group and the non-surgically treated group, the impacts of selection bias between these two groups could not be completely eliminated. Regardless of these study limitations, the study included the largest samples of patients with metastatic sarcomatoid RCC to date and focused on identifying optimal subgroups suitable for cytoreductive nephrectomy. The results of this study may aid in future clinical decision-making. Future efforts should be aimed at the preoperative diagnosis of sarcomatoid RCC, and if identified, randomized controlled trials comparing cytoreductive nephrectomy and non-surgical treatment should be conducted.

Conclusions

This population study aimed to identify suitable candidates for cytoreductive nephrectomy in patients with metastatic sarcomatoid renal cell carcinoma (RCC) from the US Surveillance, Epidemiology, and End Results (SEER) database. The findings showed that cytoreductive nephrectomy improved the overall survival (OS) in patients with T1 and T2 metastatic sarcomatoid RCC with a significant long-term survival benefit of more than six months. Although these findings support that cytoreductive nephrectomy may be considered in patients with T1N, M1, and T2N sarcomatoid RCC, caution should be taken, as the short-term survival benefit during less than three months was not demonstrated in patients with T3 and T4 metastatic sarcomatoid RCC.

Conflict of interest

None.

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