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Real-life experience of patients with sarcomatoid renal cell carcinoma: a multicenter retrospective study

Elvina ALMURADOVA[1,#], Tugba BASOGLU[2,#,*], Erdinc NAYIR[3], Ertugrul BAYRAM[4], Semra PAYDAS[4], Ivo GOKMEN[5], Serdar KARAKAYA[6], Berna OKSUZOGLU[6], Dilek ERDEM[7], Abdullah SAKIN[8], Mustafa ATCI[8], Burcu Belen GULBAGCI[9], Ilhan HACIBEKIROGLU[9], Arif Hakan ONDER[10], Serap KARAARSLAN[11], Melek Karakurt ERYILMAZ[12], Mustafa KORKMAZ[12], Ozan YAZICI1[3], Osman SUTCUOGLU[13], Baran AKAGUNDUZ[14], Hacı ARAK[15], Teoman SAKALAR[16], Dincer AYDIN[17], Yakup IRIAGAC[18], Ozkan ALAN[19], Murat MIDIK[1], Denis CETIN[1], Asli Dilara KIP[1], Serdar TURHAL[20], Turgut KACAN[21], Tolga KOSECI[4]

[1]Division of Medical Oncology, Ege University School of Medicine, Izmir, Turkey; [2]Division of Medical Oncology, Niğde Ömer Omer Halisdemir University Training and Research Hospital, Nigde, Turkey; [3]Division of Medical Oncology, Medikal Park Hospital, Mersin, Turkey; [4]Division of Medical Oncology, Cukurova University School of Medicine, Adana, Turkey; [5]Division of Medical Oncology, Trakya University School of Medicine, Edirne, Turkey; [6]Division of Medical Oncology, Abdurrahman Yurtaslan Hospital, Ankara, Turkey; [7]Division of Medical Oncology, VM Samsun Medikal Park Hospital, Samsun, Turkey; [8]Division of Medical Oncology, Okmeydani Training and Research Hospital, Istanbul, Turkey; [9]Division of Medical Oncology, Sakarya University School of Medicine, Sakarya, Turkey; [10]Division of Medical Oncology, Antalya Research and Training Hospital, Antalya, Turkey; [11]Department of Pathology, Izmir Tinaztepe University Faculty of Medicine, Izmir, Turkey; [12]Division of Medical Oncology, Necmettin Erbakan University School of Medicine, Konya, Turkey; [13]Division of Medical Oncology, Gazi University School of Medicine, Ankara, Turkey; [14]Division of Medical Oncology, Binali Yildirim University Mengücek Gazi Research and Training Hospital, Erzincan, Turkey; [15]Division of Medical Oncology, Gaziantep University School of Medicine, Gaziantep, Turkey; [16]Division of Medical Oncology, Necip Fazil City Hospital, Kahramanmaraş, Turkey; [17]Division of Medical Oncology, Derince Research and Training Hospital, Kocaeli, Turkey; [18]Division of Medical Oncology, Namik Kemal University School of Medicine, Tekirdağ, Turkey; [19]Division of Medical Oncology, Tekirdag City Hospital, Tekirdağ, Turkey; [20]Division of Medical Oncology, Anadolu Health Group, Istanbul, Turkey; [21]Bursa High Specialized Research and Training Hospital, Bursa, Turkey

**Correspondence: basoglutugba@gmail.com*
[#]Contributed equally to this work.

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Sarcomatoid renal cell carcinoma (sRCC) is a rare variant of renal cell carcinoma (RCC) and is associated with a poor prognosis. We reviewed the outcomes of patients from oncology centers in Turkey. Our aim is to share our real-life experience and to contribute to the literature. The demographic and clinical features, treatment, and survival outcomes of 148 patients with sRCC were analyzed. The median age at the time of diagnosis was 58 years (range: 19–83 years). Most patients (62.8%) had clear-cell histology. Most patients were in the intermediate Memorial Sloan-Kettering Cancer Center (MSKCC) risk group (67.6%) and were stage 4 at the time of diagnosis (63.5%). The most common sites of metastasis were the lung (60.1%), lymph nodes (47.3%), and bone (35.8%). The patients received a median of two lines (range: 0–6) of treatment. The most common side effects were fatigue, hematological side effects, hypertension, and hypothyroidism. The median follow-up was 20.9 months (range: 1–162 months). The median overall survival (OS) was 30.8 months (95% confidence interval: 24.9–36.7 months). In multivariate analysis, high MSKCC scores, sarcomatoid differentiation rates >50%, having stage 4 disease, and having lung metastasis at the time of diagnosis were independent factors for poor prognosis affecting OS. No difference was observed between patients who received tyrosine kinase inhibitor (TKI) as the first or second-line treatments. Similarly, no difference between TKI and immunotherapy as the second-line treatment. In conclusion, sRCC is a rare variant of RCC with a poor prognosis and response to treatment. Larger-scale prospective studies are needed to define an optimal treatment approach for longer survival in this aggressive variant.

Key words: renal cell carcinoma; sarcomatoid; metastatic; targeted therapy

Renal cell carcinoma (RCC) originates from the renal cortex and is responsible for up to 85% of all primary renal neoplasms [1]. RCC affects more than 400,000 individuals in the world every year and is more common in males [2]. However, RCC itself consists of several tumor subtypes. RCCs are classified according to cell type and growth pattern. In the current classification, 6 subtypes of RCC are defined: clear cell, papillary, chromophobe, oncocytic, collecting

duct, and molecularly defined renal cell carcinomas [3]. The prognosis of this disease has greatly improved with the development of targeted therapies specific to the vascular endothelial growth factor (VEGF) pathway [4] and immune checkpoint inhibitors (CPIs) [5, 6]. A transformation called sarcomatoid differentiation can be seen in many histological subtypes of renal cell carcinoma. In 2012, the International Society of Urological Pathology (ISUP) Consensus Conference acknowledged that a subtype of RCC containing atypical spindle cells and resembling "any form of sarcoma" can be considered sarcomatoid differentiated, and there is no minimum amount or percent required to establish the diagnosis of sarcomatoid differentiation [7]. In 2016 WHO (World Health Organization) endorsed these recommendations [8]. Tumor subtypes in which such sarcomatoid differentiation occurs are commonly referred to as sarcomatoid RCCs (sRCCs) [9].

sRCC was first described in 1968; however, the mechanisms driving this histology remain poorly understood [9]. The natural history and prognosis of sRCCs are very poor, most patients present with advanced-stage disease, and the median survival is approximately 6–12 months [10]. The treatment response of sRCC is also markedly different from that of clear-cell RCC. Conventional agents have not been successful in treating this disease [11, 12]. In sRCC, opinions on cytoreductive surgery are contradictory, as in clear-cell RCC [13, 14]. Although immunotherapies have recently shown the best survival in treating this type of kidney cancer, even these results have been extrapolated from other studies [5, 15].

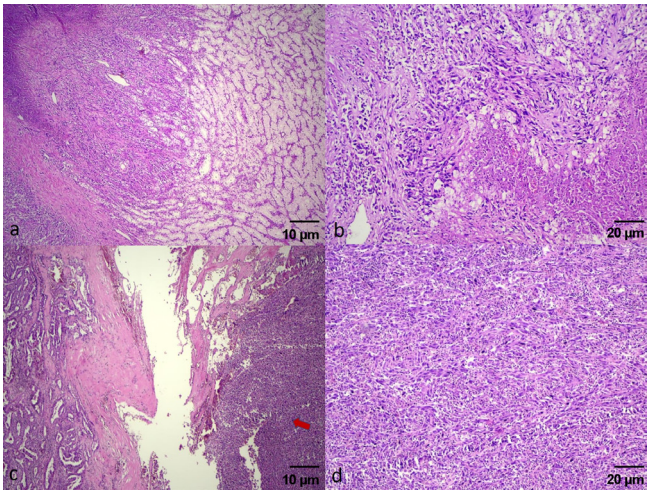

Figure 1. A) While there are clear-cell RCC areas on the right side of the picture, sarcomatoid RCC areas consisting of spindle cells (H&E ×10) on the left side. B) Intense necrosis at high magnification is observed in the sarcomatoid RCC areas adjacent to the clear-cell RCC (H&E ×20). C) Papillary RCC areas are observed in the region marked with a blue arrow and sarcomatoid RCC areas with a red arrow adjacent to it (H&E ×10). D) Papillary RCC adjacent sarcomatoid RCC areas with pleomorphic, spindle cells at greater magnification (H&E ×20).

There are no prospective studies of sRCC have been conducted. Retrospective studies available in the literature include small groups of patients. Sharing as much data as possible is essential for the optimal management of such rare tumors. To contribute to the literature, we analyzed the real-life data of patients diagnosed with sRCC in our country. To the best of our knowledge, this is the largest multicenter real-life retrospective study in the literature, in this regard.

Patients and methods

The study included 148 patients from 20 oncology centers in Turkey, who were older than 18 years and diagnosed with RCC with sarcomatoid differentiation. Data from the patients were collected between 2010 and 2020. Patients who did not have sufficient data in terms of histopathological evaluation and medical records, and without any percent of sarcomatoid differentiation were excluded from this study. Urologic pathologists reviewed the microscopic slides from all tumor specimens in all centers for the presence of a sarcomatoid component, defined as RCC with any malignant spindle cell component. Sarcomatoid features in renal cell carcinomas are primarily noticed on macroscopic evaluation. These areas tend to be firmer, gray in color, unlike the macroscopic features of typical renal cell carcinomas (yellow-orange areas in clear cell RCCs). In microscopic evaluation, in addition to areas with typical RCC features, areas consisting of cells with spindled and pleomorphic features are sufficient for the diagnosis of sarcomatoid RCC according to the features specified in the WHO 2016 directive (Figure 1).

The demographic characteristics of the patients, clinicopathologic features, efficacy and side effect data of different treatment preferences, and survival data were recorded from their files and analyzed. Progression-free survival (PFS) was defined as the time interval between the initiation of systemic treatment and progression. Overall survival (OS) was defined as the time interval between histological diagnosis and the time of death or last follow-up. Ethics committee approval for this study was obtained from the Ege University Faculty of Medicine Medical Research Ethics Committee (Decision number 19-6.1T/20, date 26.06.2019), and this study was conducted according to the principles of the Declaration of Helsinki.

Statistical analysis. All categorical variables are presented as frequencies and percentages; ranges were used for parameters with a median value. The chi-square test was used to compare categorical variables. Univariate and multivariate cox regression models were developed to assess factors that predict survival. OS and PFS were estimated using the Kaplan-Meier method and log-rank test. Then, 95% confidence intervals (CI) were calculated, and two-sided p-values of less than 0.05 were used to denote statistical significance. All statistical analyses were performed using Statistical Package for the Social Sciences, version 25.0 (IBM Corp., Armonk, NY, USA).

Table 1. Patients' characteristics.

Variables	All patients, n (%)	Sarcomatoid component		p-value
		<50%	≥50%	
Gender				
Female	42 (28.4)	16	26	0.55
Male	106 (71.6)	40	66	
Diagnostic age				
<60 years	80 (54.1)	30	50	0.53
≥60 years	68 (45.9)	26	42	
MSKCC group				
Low + intermediate	112 (75.7)	48	64	0.02
High	36 (24.3)	8	28	
Histopathological subtype				
Clear cell	93 (62.8)	8	26	0.03
Others	55 (37.2)	48	66	
Stage groups				
Stage <4	54 (36.5)	32	22	<0.001
Stage	94 (63.5)	24	70	
Nephrectomy status				
Yes	123 (83.1)	49	74	0.18
No	25 (16.9)	7	18	
Grade groups				
Grade <3	18 (12.2)	12	6	0.02
Grade ≥3	104 (70.3)	36	68	
Unknown	26 (17.5)			
Histopathological lymph node involvement				
Yes	35 (23.6)	8	27	0.005
No	87 (58.8)	42	45	
Unknown	26 (17.6)			
Necrosis				
Yes	80 (54.1)	31	49	0.85
No	64 (43.2)	24	40	
Unknown	4 (2.7)			
Renal vein invasion				
Yes	43 (29.1)	11	32	0.03
No	105 (70.9)	45	60	
Ureteral invasion				
Yes	25 (16.9)	4	21	0.01
No	123 (23.1)	52	71	
Lymphovascular invasion				
Yes	35 (23.6)	13	22	0.92
No	99 (66.9)	37	62	
Unknown	14 (9.5)			

Abbreviation: MSKCC-Memorial Sloan Kettering Cancer Center

Table 2. Treatment characteristics.

Treatment	Frequency (%)
First-line treatment	
Sunitinib/Pazopanib	96 (64.8)
Interferon	40 (27)
Everolimus	2 (1.4)
Axitinib + Pembrolizumab	1 (0.7)
Chemotherapy	4 (2.7)
None	5 (3.4)
Second-line treatment	
Sunitinib/Pazopanib/Axitinib	70 (47.2)
Nivolumab	26 (17.6)
Everolimus	7 (4.7)
Chemotherapy	2 (1.4)
Sorafenib	1 (0.7)
Third-line treatment	
Sunitinib/Pazopanib/Axitinib	17 (11.5)
Nivolumab	15 (10.1)
Everolimus	13 (8.8)
IFN	1 (0.7)
Chemotherapy	1 (0.7)

Results

In this study, 148 patients were included, with a male predominance (71.6%). The median age at the time of diagnosis was 58 (range, 19–83). All patients had different rates of sarcomatoid differentiation with different histology. Most patients had clear-cell histology (62.8%), were in the intermediate Memorial Sloan-Kettering Cancer Center (MSKCC) risk group (67.6%), and were stage 4 at the time of diagnosis (63.5%). The descriptive characteristics of the patients are presented in Table 1. In patients with metastasis at the time of diagnosis, the most common sites of metastasis were the lung (n=89, 60.1%), lymph nodes (n=70, 47.3%), and bones (n=53, 35.8%). Eight patients had brain metastases at the time of diagnosis (5.4%). Brain metastases occurred in 22 patients during the follow-up period. Moreover, 108 patients underwent primary surgery at baseline or after metastasis had developed. Six patients underwent metastasectomy during the follow-up. The patients received a median of two lines (range: 0–6) of treatment. Five patients with metastatic disease did not receive any treatment for different reasons (i.e., age, poor performance, and wound-healing problems). As shown in Table 2, tyrosine kinase inhibitors (TKIs) were mostly preferred as the first and second lines of treatment. Gemcitabine-based regimens were administered to all patients for whom chemotherapy was preferred. The combination of adriamycin, capecitabine, and carboplatin was the most preferred. Moreover, 112 patients experienced drug-related adverse events with varying degrees during any step of treatment. Eighteen patients experienced at least one grade 3–4 adverse event during the treatment course. Furthermore, 50 patients required dose modifications (29 patients) or the discontinuation of treatment (21 patients) due to side effects during the treatment period. The three most common side effects were fatigue, hematological side effects (i.e., anemia, thrombocytopenia, and neutropenia), hypertension, and hypothyroidism (in descending order: rash, diarrhea, liver dysfunction, stomatitis, and renal dysfunction). Treatment was discontinued due to grade 4 pneumonitis in one patient receiving nivolumab as a second-line treatment and in one patient receiving everolimus as the third-line treatment. The median follow-up period was 20.9 months (range: 1–162 months), and the number of patients decreased to 85 at the end of the analysis. The median OS was 30.8 months (95% CI: 24.9–36.7 months). No statistically significant difference in survival was observed between patients who received TKI as the first-line treatment and those who received TKI or

immunotherapy as the second-line treatment. OS was 38.8 months for patients who received TKI (p=0.07) and 31.04 months for those who received immunotherapy (p=0.85). The Kaplan-Meier curves are shown in Figure 2. In the multivariate analysis, high MSKCC scores, sarcomatoid differentiation rates of >50%, the presence of stage 4 disease, and the presence of lung metastasis at the time of diagnosis were determined as independent factors for poor prognosis affecting OS. The survival of patients with high MSKCC scores was statistically significantly lower than those with low and intermediate MSKCC scores (Figure 3). The results of the univariate and multivariate analyses of factors that affect survival are presented in Table 3.

Discussion

sRCC is a rare subtype of RCC associated with a poor prognosis [16]. In the literature, data on sRCC, which has aggressive biology, are insufficient. To the best of our knowledge, this is the largest retrospective real-life study in this regard.

Patients with sRCC often present between 54 and 63 years of age, and the male-to-female ratio ranges from 1.3:1 to 2:1 [9]. The demographic characteristics of patients in this study were consistent with those presented in the literature. Unlike pure ccRCC, sarcomatoid RCC contains pleomorphic and high-grade sarcoma-like cells along with the epithelial component. This type of RCC tumors is categorized as grade IV by convention [9–11]. In various retrospective studies, sarcomatoid differentiation was most frequently seen in clear-cell RCC [17]. Reports from the one of most valuable research related to this tumor type, where Bakouny and colleagues evaluated the integrated molecular characterization of sRCC, confirmed that clear-cell histology was the main background histological type (over 70%) [18]. Likewise, in our study, the most common histological type with sarcomatoid differentiation was clear-cell histology (62.8%) [17, 19]. Patients diagnosed with RCC often present in the local stage (82%), and only 16% of patients present in the metastatic stage [20]. However, this cannot be said considering sRCC as in this study, approximately ≥ 50% of the patients with sRCC presented with unresectable or metastatic disease [21]. In population-based studies conducted so far, the most common site of metastasis of sRCC was the lungs similar to that reported in clear-cell RCC (34.6–71.0%) [10]. This metastatic site is followed by the bone (13.0–44.0%), lymph nodes (25%), liver (12.6–23.0%), and brain (5.1–16.0%) [9]. This sequence was similar to that presented in this study. Historically, various therapeutic agents have been attempted for treating metastatic sRCC. Because of the sarcoma-like histology of sRCC and due to its success in treating sarcoma-type tumors, doxorubicin-based treatments have been used in many studies [11, 12, 22, 23]. However, the results were very contradictory. Although a very good response was observed in retrospective studies, no objective response was obtained in a phase 2 study [11]. Then, for this purpose, the combination of gemcitabine and doxorubicin was attempted [23]. In this study, the treatment regimen applied to patients receiving chemotherapy was gemcitabine-based; however,

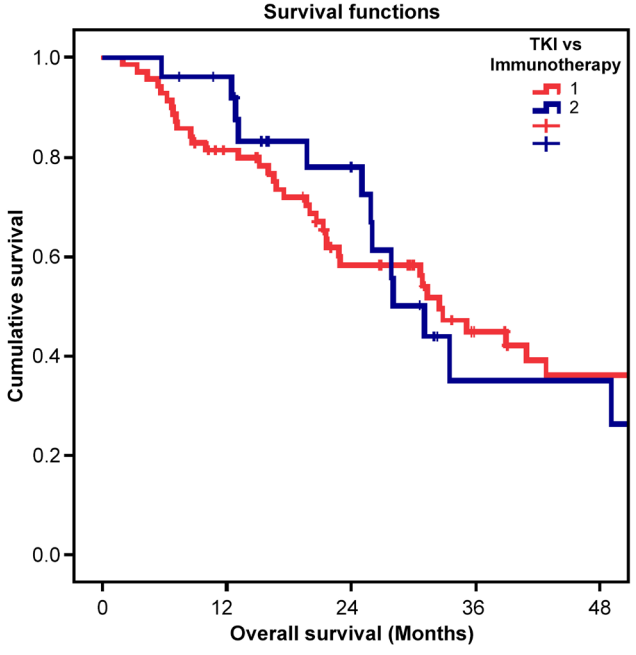

Figure 2. Survival curve of patients treated with immunotherapy and patients receiving TKI as the second-line treatment.

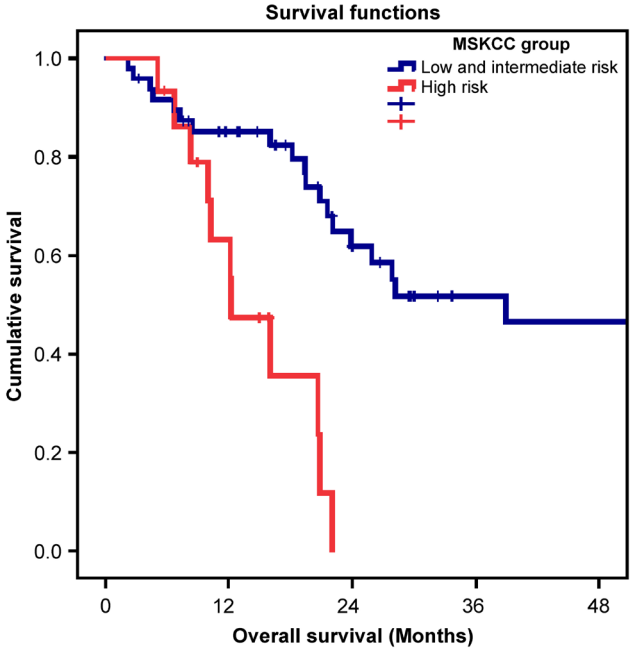

Figure 3. Survival curve of the MSKCC low, intermediate, and high-risk groups.

Table 3. Cox Regression analyses.

Parameters	Univariate analysis			Multivariate analysis		
	p-value	HR	95% CI	p-value	HR	95% CI
Female vs. Male	0.49	1.18	0.72–1.93			
Age at diagnosis ≥60 years vs. <60 years	0.78	1.06	0.68–1.63			
MSKCC High vs. Intermediate/low	0.005	2.02	1.24–3.30	0.05	1.59	0.92–2.61
Nephrectomy No vs. Yes	0.56	1.20	0.63–2.27			
Stage at diagnosis Stage IV vs. Other	0.001	2.33	1.44–3.77	0.49	1.33	0.58–3.06
Sarcomatoid differentiation rate ≥ 50% vs. < 50%	0.02	1.43	0.72–2.72	0.05	1.38	0.70–2.70
Histological grade Grade 3-4 vs. Grade 1-2	0.30	1.47	0.62–2.15			
Tumor diameter ≥ 9 cm vs. < 9 cm	0.36	1.29	0.53–1.74			
Positive lymph nodes Yes vs. No	0.01	1.84	0.61–2.19	0.86	1.05	0.56–1.97
Tumor necrosis Yes vs. No	0.18	1.35	1.18–12.8			
Lymphocyte infiltration Yes vs. No	0.36	1.28	0.95–3.94			
Renal vein invasion Yes vs. No	0.01	1.78	1.10–2.86	0.91	0.97	0.56–1.67
Ureter invasion Yes vs. No	0.03	1.82	1.04–3.17	0.91	1.04	0.50–2.14
Metastasis at diagnosis Yes vs. No	<0.001	2.59	1.61–4.16	<0.001	2.45	1.50–4.00
Cytoreductive surgery Yes vs. No	0.36	1.28	0.75–2.18			
Metastasectomy Yes vs. No	0.43	1.59	0.50–5.05			
Lung metastasis Yes vs. No	0.01	2.16	1.35–3.48	0.002	2.13	1.32–3.44
Hepatic metastasis Yes vs. No	0.68	1.13	0.62–2.04			
Brain metastasis Yes vs. No	0.10	1.86	0.87–3.95			
Treatment discontinuation due to side effects Yes vs. No	0.95	1.01	0.63–1.63			

Abbreviations: HR-hazard ratio; MSKCC-Memorial Sloan Kettering Cancer Center

the results of the survival analysis could not be properly interpreted because the number of patients was small. VEGF tyrosine kinase and mammalian target of rapamycin inhibitors have demonstrated limited efficacy in non-clear-cell RCC [24, 25]. In two small phase 2 trials (ASPEN and ESPN), sunitinib displayed a trend toward better outcomes than everolimus in patients with non-clear-cell RCC [26, 27]. The ASPEN trial showed a median PFS of 5.6 vs. 8.3 months and an objective response rate of 9% vs. 18%. The median PFS was 3.5–5.3 months, and the median OS was 8.2–11.7 months in other studies [24]. Simultaneously, some authors reported that improvement in survival was not durable and led to failure. In this study, 64.8% of the patients were treated with TKI as the first-line therapy. The median OS of these patients was 30.8 months (95% CI, 24.5–37.2 months). It was significantly superior to the data reported so far.

Since 1992, immunotherapy in the form of interleukin (IL)-2 has been used to treat RCC [28]. This effective but very toxic treatment agent has left its place in current immunotherapies. A post-hoc analysis of CheckMate 214 sRCCs who received the immune CPI combination regimen showed an overall response rate of 61% and a PFS of 26.5 months; however, the median OS was not reached [29]. Such successful results have also been observed in patients receiving anti-VEGF and immunotherapy combination regimens [30]. In this study, the patients could only receive immunotherapy in the second-line, and no statistically significant difference in

survival was observed between VEGF-treated and immunotherapy-treated patients (OS = 38.8 months for TKI vs. 31.04 months for immunotherapy (p=0.85)).

An average of 50% of patients receiving sunitinib therapy required dose reductions [31,32]. In this study, the patients who required treatment termination and dose adjustments also reached this percentage. The most common grade 3–4 side effects among patients receiving TKIs were similar to those in the original studies and were mainly fatigue and hematological toxicity [32]. de Peralta-Venturina and Shuch showed in their studies that patients with a higher percentage (>50%) of sarcomatoid dedifferentiation had a worse prognosis [33, 34]. As there is no accepted cut-off value for differentiation, we analyzed 50% of sarcomatoid features. Patients with >50% sarcomatoid differentiation had a poor prognosis. The presence of advanced disease and lung metastasis at the time of diagnosis, which was among the factors that adversely affected the prognosis, were similar to the results of other previous studies (p=0.002; 95% CI 1.32–3.44 for lung metastasis; p = 0.05; 95% CI, 0.70–2.70 for sarcomatoid). The reported median survival is approximately 6–13 months in patients with sRCC; however, in our study, the median OS was 30.8 months [10, 35]. It is higher than historical data. We could not explain the reason; however, most patients underwent nephrectomy during the course (83.1%); however, whether it could lead to longer survival is unknown. The main treatment for sarcoma is surgical resection [36]. Perhaps, the excision of the primary tumor is also important for sRCC, which includes sarcomatoid differentiation and most often metastasizes to the lung. Some small retrospective studies also support the positive effects of nephrectomy on survival [37]. Although this subgroup has not been evaluated in studies, such as CARMENA, where primary tumor resection is evaluated, it may be a subject of research in the future [38].

In conclusion, there are some inferences from the small patient series in the literature and the lack of randomized trials. Therefore, there is no standard treatment approach for sRCC, and there are many unknowns. If we can elucidate the tumor biology and genetic changes more clearly in sRCC, we can develop standard treatment approaches that will contribute more to enhancing survival in the future.

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