Journal of Cancer Treatment and Research
2023; 11(1): 1-8
http://www.sciencepublishinggroup.com/j/jctr
doi: 10.11648/j.jctr.20231101.11
ISSN: 2376-7782 (Print); ISSN: 2376-7790 (Online)

Sunitinib Versus Pazopanib as Initial Therapy for Metastatic Renal Cell Carcinoma of Intermediate and Poor-Risk Characteristics: Real-World, a Single-Center

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To cite this article:

Hayriye Sahinli, Esra Zeynelgil, Ozlem Dogan, Dogan Yazilitas. Sunitinib Versus Pazopanib as Initial Therapy for Metastatic Renal Cell Carcinoma of Intermediate and Poor-Risk Characteristics: Real-World, a Single-Center. *Journal of Cancer Treatment and Research*. Vol. 11, No. 1, 2023, pp. 1-8. doi: 10.11648/j.jctr.20231101.11

Received: February 25, 2023; **Accepted**: March 15, 2023; **Published**: March 31, 2023

Abstract: *Background*: Sunitinib and pazopanib are tyrosine kinase inhibitors (TKIs) used as first-line therapy for metastatic renal cell carcinoma (mRCC). In this study, our objective was to evaluate the effectiveness of sunitinib or pazopanib in patients with intermediate or poor risk metastatic renal cell carcinoma. *Methods*: A total of 60 patients with metastatic renal cell carcinoma were retrospectively evaluated between January 2014 and December 2020. Survival analyzes were performed with the Kaplan-Meier and log-rank tests. *Results*: Forty-six (76.7%) patients were male. Of the patients who received sunitinib, 22 patients (57.9%) were in the intermediate risk group, while 16 patients (42.1%) were in the poor risk group. Among patients receiving pazopanib, 14 patients (63.6%) were in the intermediate-risk group, while 8 patients (36.4%) were in the poor-risk group. There were no significant difference in the intermediate risk group of patients in terms of median progression-free survival between sunitinib and pazopanib (p=0.742). No significant differences were found in terms of progression-free survival in the high-risk group of patients (p=0.254). There were no significant differences in overall survival in the intermediate-risk group of patients receiving sunitinib or pazopanib (p = 0.377). There were no significant differences in terms of overall survival in the high-risk patient group receiving sunitinib or pazopanib (p = 0.3777). *Conclusions:* There were no significant difference in terms of progression-free survival and overall survival between the intermediate and poor-risk patient groups receiving pazopanib or sunitinib.

Keywords: Renal Cell Cancer, Tyrosine Kinase Inhibitor, Pazopanib, Sunitinib, First-Line Treatment

1. Introduction

Renal cell carcinoma (RCC) is the most common solid lesion of the kidney [1]. It ranks fifth in men and tenth in women among all cancers worldwide. Renal tumors constitute 3% of all new cancer cases in women and 5% in men, and the median age of diagnosis is 64 [2]. Renal cell carcinoma accounts for approximately 85% of kidney tumors. About 25% of the patients present with either in the metastatic or locally advanced stage disease, and the 5-year survival rate of these patients is 8-12% [3]. About third of patients with early-stage disease relapse after effective treatment [4].

The prognosis of patients with RCC is commonly determined by the Memorial Sloan Kettering Cancer Center (MSKCC) criteria based on five risk factors. These risk factors are time interval less than 12 months between diagnosis and treatment, presence of anemia, high serum calcium concentration, high serum lactate dehydrogenase concentration, and Karnofsky performance status below 80%. These factors predict survival and are used to classify patients into three different risk groups which are favorable risk (no risk factors), moderate risk (1-2 risk factors) and poor risk (<3 risks) [5]. The 5-year survival rate was found to be less than 20% in metastatic RCC, and the median overall survival was found to be between 5 and 10.9 months in patients with poor risk factors [6, 7]. These criteria indicate that patients with poor risk factors have poor prognosis.

Metastatic RCC responds very poorly to classical chemotherapy. Although interferon-alpha or interleukin-2-based cytokine therapy was accepted as the standard treatment in metastatic disease until 2006, the response rate was only between 15-30% and had serious side effects [8].

In addition to better understanding of the molecular biology of RCC in recent years, many molecular pathways that are to be targeted for treatment have been determined. Angiogenesis-related growth factors, in which the von Hippel-Lindau (VHL) gene also plays a role in its regulation, are the most important targets. Vascular endothelial growth factor (VEGF) is a cytokine that plays a critical role in tumor angiogenesis. The angiogenetic activity of RCC, which is a clinically vascularized tumor, is directly proportional to the expression of VEGF [9].

Sunitinib is a selective, multitargeted oral tyrosine kinase inhibitor (TKI) that inhibits receptor tyrosine kinases such as VEGFR-2, PDGFR-β, KIT and FLT3. In the pivotal phase 3 study, patients who received sunitinib as first-line treatment were found to have longer progression-free survival and higher objective response rates compared to those who received interferon alpha. Based on the results of this study, the use of sunitinib as first-line treatment in patients with advanced RRC was approved by the Food and Drug Administration (FDA) in February 2007 [10].

Pazopanib is a multitargeted tyrosine kinase inhibitor that inhibits tumor angiogenesis and cell proliferation. In the pivotal phase 3 study of pazopanib, the PFS was found to be longer and tumor response better compared to placebo [11]. Pazopanib was found to be noninferior to sunitinib in a comparative study conducted in 2013. These two agents have been approved by the FDA for first and second-line treatment of metastatic RCC.

In this study, the effectiveness of sunitinib and pazopanib was evaluated in the first-line treatment of patients with intermediate or high risk according to the MSKCC score.

2. Methods

This was a retrospective study that included 60 patients with metastatic RCC who received sunitinib and pazopanib between January 2014 and December 2020. Patients diagnosed with RCC were included in this study either by previous nephrectomy material or biopsy. Patients received sunitinib or pazopanib until progression. Patients whose treatment was discontinued due to intolerance were not included in the study. Patients who received interferon as first-line treatment and discontinued within one month due to intolerance were included in the study. Patients who received interferon for more than one month or until progression were excluded from the study. The risk classification was determined according to the criteria of the Memorial Sloan Kettering Cancer Center.

Pazopanib was administered orally 800 mg once a day. Sunitinib was administered orally at 50 mg once daily for 4 weeks, followed by 2 weeks off schedule. In case of recurrent toxicity, the sunitinib dose was reduced to 37.5 mg and pazopanib to 600 mg.

The response to treatment status, such as stable disease, partial response, complete response, and progressive disease, were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Overall survival (OS) was accepted for survivors as the time from the start of TKI therapy to the last visit date. Progression-free survival was determined as the time from the start of TKI treatment to the development of progression and to the last visit date in patients without disease progression.

Survival analyzes were performed according to treatment options, risk factors and patient factors, including age, gender, performance status, and de novo metastasis.

The study have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid in the Declaration of Helsinki.

3. Statistics

Statistical analyzes were performed with SPSS version 22 (IBM Corporation, New York, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine if the data were normally distributed. Categorical variables were analyzed with the exact Chi-square and Fisher tests. Kaplan-Meier and log rank tests were used for survival analysis. A value of P less than 0.05 was considered statistically significant.

4. Results

Characteristics of the patients are summarized in Table 1. A total of 60 patients were included in the study. During follow-up, 46 patients (76.7%) died and disease progression occurred in 54 patients (90%). Forty-six (76.7%) of the patients were men and 14 (23.3%) were women. The median age of the patients was 60 years (min-max: 39-86 years). The ECOG score of 19 (31.7%) patients was 0, while the remaining 41 (68.3%) patients had ECOG score 1 or 2. Forty-eight (80%) patients had history of nephrectomy. While 36 patients (60%) were in the intermediate risk group, 24 patients (40%) were in the high risk group.

Sunitinib was administered to 38 (63.3%) of 60 patients and pazopanib to 22 (36.7%) patients as first-line treatment. The median age of patients receiving sunitinib was 59 years (min-max: 41-78 years), while the median age of the pazopanib group was 63 years (min-max: 39-86 years). The sunitinib receiving group consisted of 32 male patients (84.2%) and 6 (15.8%) females. There were 14 male (63.6%) and 8 female patients (36.4%) in the pazopanib group (p=0.069). In the sunitinib and pazopanib groups, the number of patients with an ECOG score of 0 was 12 (31.6%), 7 (31.8%), respectively; the number of patients with ECOG scores of 1 and 2 were 26 (68.4%) and 15 (68.2%), respectively (p = 0.999). In the sunitinib and pazopanib groups, the number of patients with de novo metastases was 26 (68.4) and 16 (72.7%), respectively, while the number of patients without de novo metastases was 12 (31.6%) and 6 (27.3%), respectively (p=0.726). Among

patients receiving sunitinib, 33 (86.8%) patients underwent nephrectomy and 5 (13.2%) did not. Of the patients receiving pazopanib, 15 (68.2%) patients underwent nephrectomy, while 7 patients (31.8%) did not (p=0.082). The sunitinib receiving group consisted of 22 (57.9%) patients with intermediate risk and 16 (42.1%) patients with high risk. The pazopanib group was composed of 14 (63.6%) patients with intermediate risk and 8 (36.4%) patients with high risk (p = 0.662).

The radiological response of the sunitinib group during treatment revealed a stable disease in 19 patients (50%), a partial response in 4 patients (10.5%) and progression in 15 patients (39.5%). In patients receiving pazopanib, stable disease was detected in 10 patients (45.5%), partial response in 7 patients (31.8%), and progression in 5 patients (22.7%).

4.1. Progression-Free-Survival Analysis

Median PFS was determined to be 7 months in sunitinib patients and 4 months in pazopanib patients (p = 0.716). There were no significant difference in progression-free survival between the groups (Figure 1). Median survival in patients both under and over 65 years of age was found to be 7 months (p=0.248). No differences were found in terms of PFS in patients under and over 65 years of age. Median PFS was found to be 7 and 3 months in male and female patients, respectively (p=0.035).

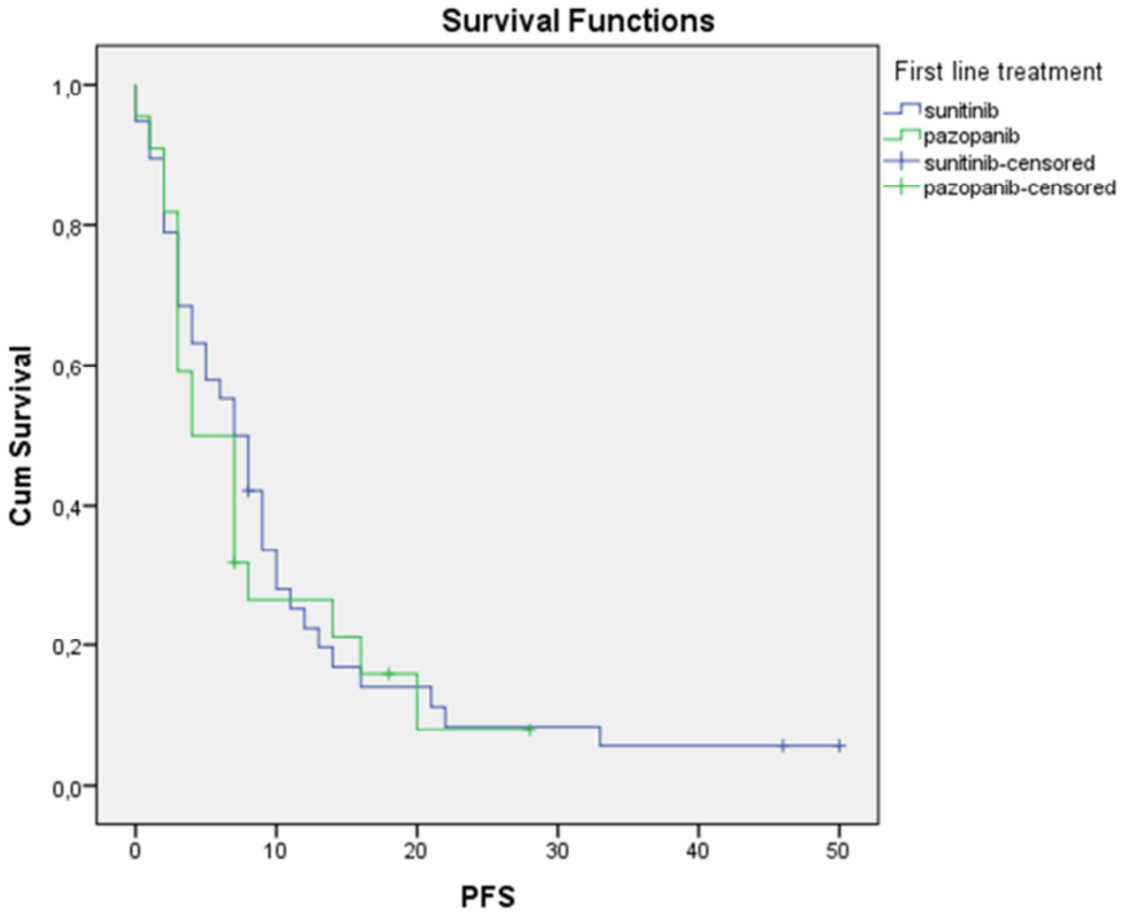

Figure 1. *Progression-free survival curve in patients receiving sunitinib or pazopanib.*

The median PFS was found to be 9 months in patients with an ECOG score of 0, and 5 months in patients with an ECOG score of 1 and 2 (p=0.008). The median PFS was 4 months in patients with de novo metastatic disease and 9 months in those without de novo metastasis (p=0.210). The median PFS was 7 months in patients who underwent nephrectomy and 6 months in patients who did not (p=0.733). The median PFS was 9 months in patients in the intermediate risk group according to the MSKCC score and 4 months in patients in the high risk group (p=0.000). The median PFS of the sunitinib group was found to be 4 months in high-risk patients, while it was found to be 10 months in intermediate-risk patients (p=0.002). The median PFS of the patients who received pazopanib was found to be 7 months in the intermediate risk group and 3 months in the high risk group (p=0.027). There were no significant difference in the median PFS of the patients in the intermediate-risk group who received sunitinib or pazopanib (p=0.742). No significant differences were found in terms of median PFS between sunitinib and pazopanib groups in high-risk patients (p=0.254). The median PFS was 6 months in patients with a right kidney tumor and 7 months in patients with a left kidney tumor (p=0.604) (Table 2).

4.2. Overall Survival Analysis

The median overall survival (OS) of patients receiving

sunitinib was found to be 15 months, while it was 17 months in patients receiving pazopanib (p=0.531). There were no significant difference in median OS between the pazopanib and sunitinib groups (Figure 2). The median survival of patients under and over 65 years of age was found to be 19 and 9 months, respectively (p = 0.103). The median OS was 8 months in female patients and 19 months in male patients (p=0.008). The median survival of patients with an ECOG score of 0 was 26 months, and 10 months in patients with an ECOG score of 1 to 2 (p=0.014). Median survival was 21 months in patients with de novo metastatic disease and 11 months in those without de novo metastasis (p=0.167). The median survival in patients with and without nephrectomy was 19 and 8 months, respectively (p=0.172). The median OS was 13 months in patients with right kidney tumor and 15 months in patients with left kidney tumor (p=0.743). The median OS was 23 months in patients with intermediate risk according to the MSKCC score, while it was 9 months in patients with high risk (p = 0.001). The median survival of patients who received sunitinib was 26 months in the intermediate risk group and 9 months in the high risk group (p=0.009). The median survival of the patients who received pazopanib was 19 months in the intermediate risk group and 8 months in the high risk group (p=0.027). There were no significant difference between the survival rate of patients in the intermediate risk group receiving sunitinib or pazopanib (p=0.397) (Figure 3). Similarly, there were no significant difference between median survival of patients in the high-risk group receiving sunitinib or pazopanib (p=0.377) (Figure 4). No significant differences were found between sunitinib and pazopanib treatments in terms of overall survival of patients in the intermediate and high risk groups (Table 3).

Table 1. *Clinicopathological characteristics of patients according to treatment options.*

Variables	Sunitinib N (%)	Pazopanib N (%)	P value
Gender			
Female	6 (15.8)	8 (36.4)	0.069
Male	32 (84.2)	14 (63.6)	
Age			
<65	26 (68.4)	11 (50)	0.157
≥65	12 (31.6)	11 (50)	
Localization of tumor			
Right kidney	20 (52.6)	8 (36.4)	0.224
Left kidney	18 (47.4)	14 (63.6)	
ECOG performance score			
0	12 (31.6)	7 (31.8)	0.985
1 -2	26 (68.4)	15 (68.2)	
De novo metastasis			
No	12 (31.6)	6 (27.3)	0.726
Yes	26 (68.4)	16 (72.7)	
Nephrectomy			
No	5 (13.2)	7 (31.8)	0.082
Yes	33 (86.8)	15 (68.2)	
MSKCC score			
İntermediate risk	22 (57.9)	14 (63.6)	0.662
High risk	16 (42.1)	8 (36.4)	

Table 2. *Effect of clinicopathological variables on progression-free survival.*

Variables	PFS (95% Cl)	P value
Age		
<65	7 (3.1-10.8)	0.248
≥65	7 (4.7-9.2)	
Gender		
Female	3 (2.1-3.9)	0.035
Male	7 (5.1-8.8)	
ECOG performance score		
0	9 (5.1-12.8)	0.08
1-2	5 (1.2-2.4)	
De novo metastasis		
No	9 (7.2-10.7)	0.210
Yes	4 (1.4-6.5)	
Nephrectomy		
Yes	7 (4.0-9.9)	0.733
No	6 (1.4-10.5)	
MSKCC score		
İntermediate risk	9 (5.7-12.2)	0.000
High-risk	4 (2.4-5.5)	
Localization of tumor		
Right kidney	6 (0.0-12.4)	0.604
Left kidney	7 (4.8-9.1)	
First line treatment		
Sunitinib	7 (4.5-9.4)	0.716
Pazopanib	4 (0.9-7.1)	

Table 3. *Effect of clinicopathological variables on overall survival.*

Variables	OS (95% Cl)	P value
Age		
<65	19 (11.1-26.9)	0.103
≥65	9 (6.2-11.7)	
Gender		
Female	8 (2.9-13.1)	0.008
Male	19 (9.4-28.5)	
ECOG performance score		
0	26 (15.7-36.3)	0.014
1-2	10 (6.9-13.0)	
De novo metastasis		
No	21 (6.7-35.2)	0.167
Yes	11 (4.1-17.8)	
Nephrectomy		
Yes	19 (13.1-24.8)	0.172
No	8 (3.4-12.5)	
MSKCC score		
İntermediate risk	23 (14.3-31.6)	0.001
High-risk	9 (6.2-11.7)	
Localization of tumor		
Right kidney	13 (0.7-25.2)	0.743
Left kidney	15 (5.8-24.1)	
First line treatment		
Sunitinib	15 (5.8-24.1)	0.531
Pazopanib	17 (7.1-26.8)	

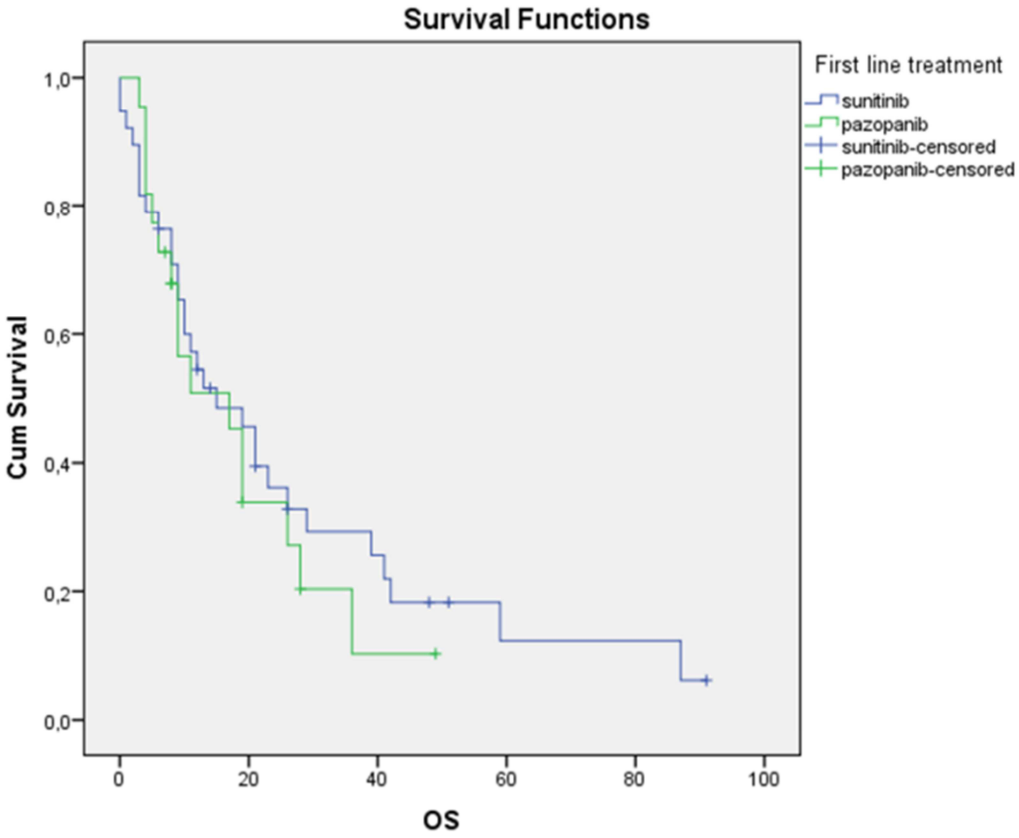

Figure 2. *Overall survival curve in patients receiving sunitinib or pazopanib.*

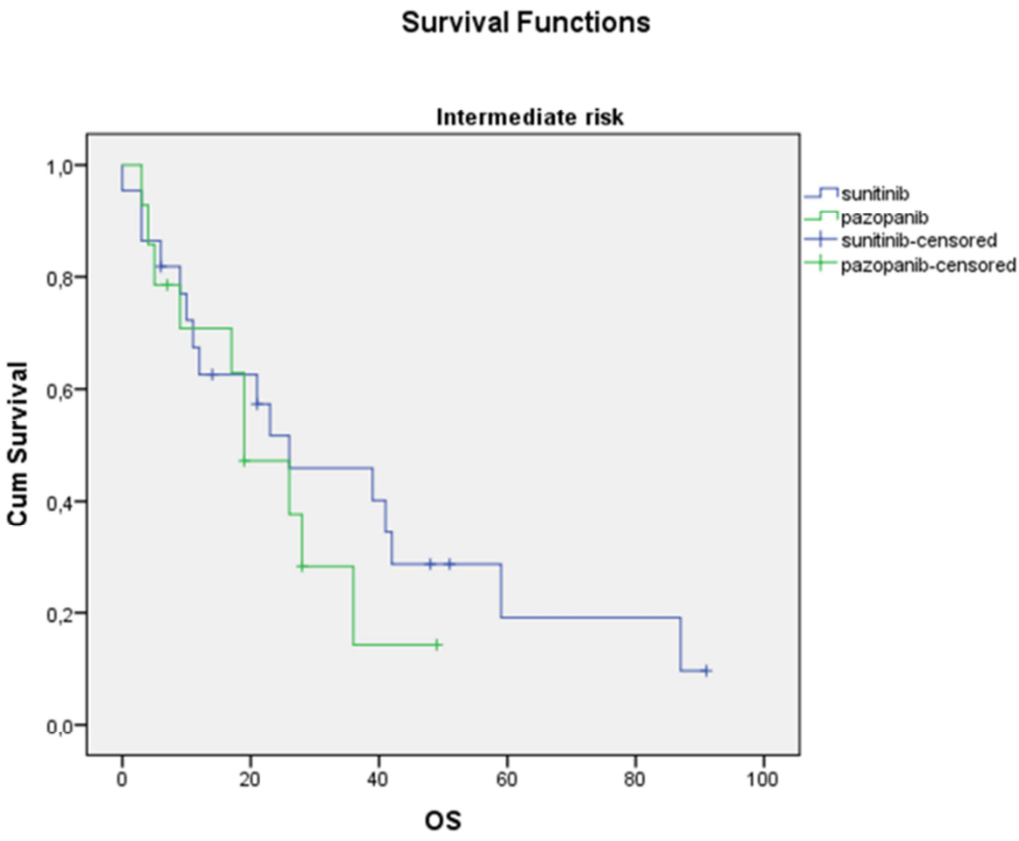

Figure 3. *Overall survival curve of sunitinib and pazopanib in patients with intermediate risk.*

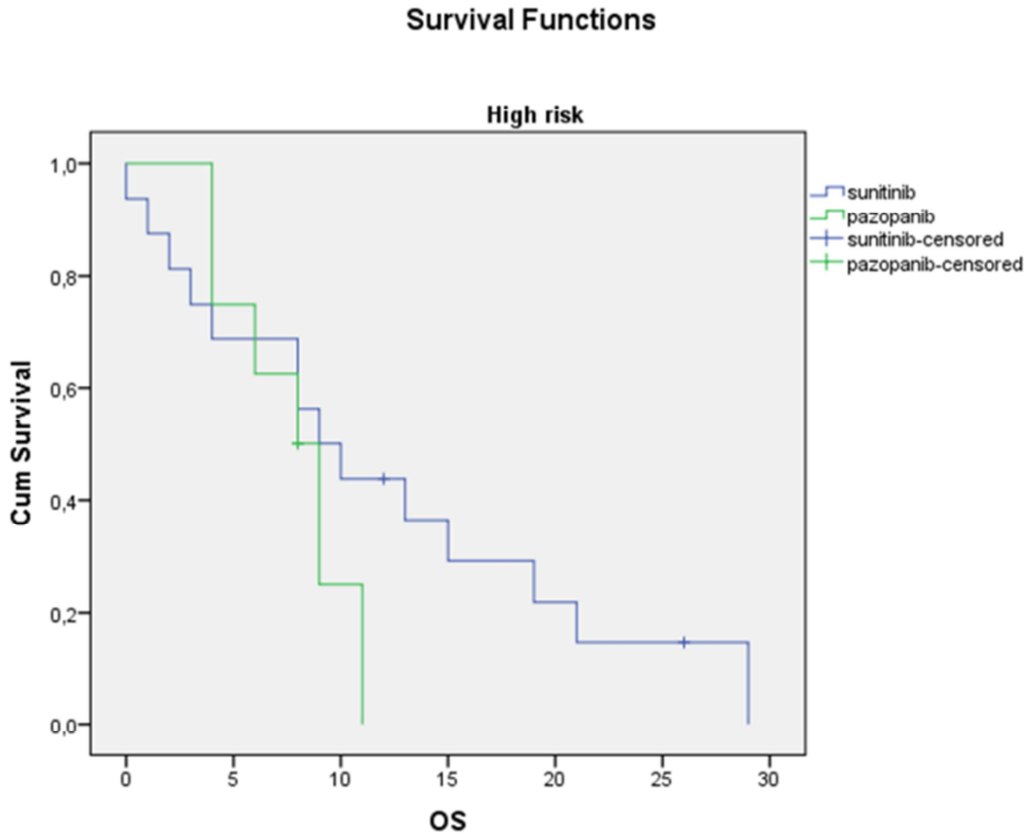

Figure 4. *Overall survival curve of sunitinib and pazopanib in poor-risk group of patients.*

5. Discussion

In this single-center study, the efficacy of sunitinib and pazopanib was evaluated in patients in intermediate and high-risk groups according to the MSKCC score. In our study, there were no significant difference in PFS or OS between sunitinib and pazopanib treatments in patients in both risk groups.

In our study, median PFS and OS of patients in the intermediate-risk group receiving sunitinib were found to be 9 and 26 months, while the median PFS and OS of patients in the high-risk group were found to be 4 and 9 months, respectively. In the pivotal study of sunitinib conducted by Motzer et al., PFS and OS of patients in the intermediate and poor risk groups were found to be 10 and 20.7 months, and 4 and 9 months, respectively [12]. In this study, the number of patients in intermediate and poor risk groups was 56% vs. 6%, respectively. In our study, the percentage of patients in the intermediate and poor risk groups receiving sunitinib was 57.9% and 42.1%, respectively. In our study, the median overall survival of the patients in the poor risk group was more favorable compared to the study by Motzer et al. However, this difference was considered to be due to the low number of patients in the poor risk group in the study by Motzer et al.

The efficacy of sunitinib in patients with poor risk has been evaluated only in retrospective studies. In one of these studies, the effectiveness of sunitinib and sorafenib was compared in patients in the poor risk group, and the median PFS and OS of sunitinib were found to be 5 months and 9.3 months, respectively [13]. In our study, similar findings were obtained with that study (4 vs. 9 months).

In our study, the median PFS and OS of patients in the intermediate-risk group receiving pazopanib were found to be 7 and 19 months, while the median PFS and OS of patients in the high-risk group were found to be 3 and 7 months, respectively. In a Flipper study, after pazopanib was administered to 40 patients in intermediate and poor risk groups, 30 patients were evaluated at the end of the study, and the median PFS and OS were found at 4.5 and 9 months, respectively. In the Flipper study, 67.7% of the patients were in the poor risk group [14]. In our study, the percentage of patients who received pazopanib in the poor risk group was 36.6%.

In a study by Kim et al., in which the effectiveness of sunitinib and pazopanib was compared in patients with poor risk factors, the median PFS of patients receiving pazopanib and sunitinib was found to be 9.8 and 4.3 months, respectively ($p=0.030$). Median OS was found to be 14.4 months and 8.9 months in patients receiving pazopanib and sunitinib, respectively ($p=0.04$). As a result of that study, it was determined that pazopanib was more favorable compared to sunitinib in patients in the poor risk group [15]. However, in our study, no significant differences were found between sunitinib and pazopanib in terms of median PFS ($p=0.254$) and median OS ($p=0.377$) in patients with poor risk factors.

In the COMPARZ study, no significant differences were

found between sunitinib and pazopanib in terms of PFS and OS [16]. However, pazopanib was found to be safer compared to sunitinib. Patients in the poor risk group were not included in the COMPARZ study. In our study, no significant differences were found between sunitinib and pazopanib in terms of both PFS and OS. Patients in the poor-risk group were included in our study. In a retrospective study by Lalani et al. from Canada, which included 670 patients, it was found that survival was longer in patients receiving sunitinib, especially in the intermediate risk group, compared to patients receiving pazopanib. However, in that study, the number of patients who received sunitinib was higher compared to the number of patients who received pazopanib (577 vs. 93), and, in addition, pazopanib was preferred in more fragile patients with multiple comorbidities [17]. For those reasons, the survival of patients receiving pazopanib could have been found to be shorter than that of patients receiving sunitinib.

In the RECORD-1 study conducted by Motzer et al., short survival was found in patients with high performance scores [18]. Similarly, in our study the survival of patients with high performance scores was found to be shorter. In our study, the median PFS and OS of patients with a performance score of 0 were found to be 9 and 26 months, while the median PFS and OS of patients with performance scores 1 and 2 were found to be 5 and 10 months, respectively. As a result, survival was found to be worse in patients with high performance scores.

Renal cell carcinoma is more common in men than in women. It is about two times more prevalent in men than in women [19]. In our study, 76.7% of the patients were male, consistent with the literature. The difference in PFS and OS between female and male patients was not evaluated in the COMPARZ study. However, in our study, both PFS and OS were found to be worse in women. It was considered that this difference might be due to the small number of patients.

The most important limitation of our study was that it was a single-center study with a small sample size.

6. Conclusions

When pazopanib and sunitinib were compared in the first-line treatment of advanced and metastatic RCC no significant differences were found in terms of PFS and OS in patients in intermediate and poor risk groups. However, multicenter studies (pazopanib versus nivolumab in combination with pazopanib, and sunitinib versus nivolumab in combination with sunitinib) are required to standardize the first line treatment in intermediate and poor risk mRCC.

Ethics Committee Approval

The ethics committee approved the study of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital.

Conflict of Interest

The authors declare that they have no conflict of interest.

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