Response rates of pazopanib therapy in metastatic soft tissue sarcoma using real-world data

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Abstract. The present study was a retrospective single-center study. A total of 81 patients diagnosed with metastatic soft tissue sarcoma were included who received pazopanib therapy. Clinical data, including age at diagnosis, histological subtype, treatments received before pazopanib, number of metastatic sites at the time of initiation of treatment, progression-free survival and overall survival time under pazopanib treatment, side effects and response evaluation in follow-up imaging after initiation of pazopanib therapy, were recorded. The 81 patients had 11 different histological subtypes. The synovial sarcoma, leiomyosarcoma and pleomorphic sarcoma groups included 51 patients in total. The median overall survival time in the entire study cohort was 46 months, and the median progression-free survival time was 5 months. The clinical response rate was 46.3%. Patients with hemangioendothelioma and alveolar soft part sarcoma exhibited an improved response to treatment compared with that of patients with other subtypes. Line of therapy and tumor grade were not significantly associated with progression-free survival or clinical response. It was concluded that, regardless of subtype, patients with a low tumor grade and a small number of metastatic sites exhibited an improved response; although the difference in response for patients with a low tumor grade was not significant. In addition, administering the treatment as a second- or third-line therapy appeared to be more appropriate compared with administering it as a later-line therapy; however, this difference was not found to be statistically significant. Therefore, pazopanib should be evaluated as an option for a selected group of patients in whom these factors present together. A further advantage of pazopanib demonstrated was that treatment tolerance was generally good.

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Introduction

Sarcomas are a rare and heterogeneous group of malignant tumors of mesenchymal origin, which account for <1% of all adult cancers and ~21% of all pediatric cancers worldwide (1). There are >100 histological subtypes of sarcoma, most of which can occur at any age and are not limited to any specific part of the body. Soft tissue sarcomas often form in the muscles, nerves, fat, deep skin tissues and blood vessels (1), and the most common metastatic site is the lungs via the vasculature (1). The most common subtypes are liposarcoma, leiomyosarcoma, chondrosarcoma, osteosarcoma, pleomorphic and synovial sarcoma (2).

Similar to most other types of cancer, surgery is the primary treatment for patients with sarcoma (3). In metastatic disease, long-term disease-free survival and cure can be achieved by performing metastasectomy in selected patient groups, particularly those who have isolated lung metastasis (2). However, for most patients with metastatic soft tissue sarcoma, the goal of systemic therapy is to reduce the tumor burden, relieve symptoms, improve the quality of life and prolong survival (4). Targeted therapies have become increasingly important in recent years due to the limited response obtained with classical cytotoxic agents. Tyrosine kinase inhibitors, such as pazopanib and regorafenib, trabectidin and anti PDL-1 agents have been used to treat soft tissue sarcoma (4).

Pazopanib was the first tyrosine kinase inhibitor used to treat metastatic soft tissue sarcoma (5). It is generally preferred as salvage therapy for patients who progress after standard cytotoxic therapy (4). Considering that most patients eventually succumb to the disease, the main purpose of pazopanib treatment is to prolong their life expectancy (6). Therefore, progression-free survival and clinical response were considered to be the most important criteria of treatment success in the present study. The parameters predicted to affect these data were histological subtype, number of metastatic sites, line of pazopanib therapy and tumor grade. The aim of the present study was to evaluate the progression-free survival time and clinical response of patients with metastatic soft tissue sarcoma receiving pazopanib therapy, and to determine factors that may affect these data, such as histological subtype, number of metastatic sites, line of drug used, age, sex and tolerance to treatment side effects.

Materials and methods

Study design. The present study was a retrospective, single-center study conducted at Ege University (Bornova, Turkey). A total of 81 patients diagnosed with metastatic soft tissue sarcoma who received pazopanib therapy were evaluated between January 2012 and October 2020. All of the patients were followed up at Ege University. Notably, there were no exclusion criteria, patients who had metastatic disease and received pazopanib therapy were included.

Progression-free survival was defined as the time between the start of therapy and the date of progression or death, and overall survival was defined as the time between the date of diagnosis of metastatic disease and the date of death.

Statistical analysis. Continuous variables are presented as the median and range, and categorical variables are presented as number and percentage. Survival data were evaluated using the Kaplan-Meier method and were compared between groups using the log-rank test. The Stata program (version 14.2; Stata Corp LP) was used for all statistical analysis. The χ^2 test and Fisher's exact test were used to compare categorical variables. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Demographic characteristics and histological subtypes.

Characteristic	Patients
Total cohort, n (%)	81 (100)
Mean age, years (±SD)	44.75 (±14.9)
Sex, n (%)	
Female	51 (63)
Male	30 (37)
Histological subtypes, n (%)	
Synovial sarcoma	12 (14.8)
Plemorphic sarcoma	13 (16)
Leiomyosarcoma	26 (32.1)
Alveolar soft part sarcoma	4 (4.9)
Malignant peripheral nerve sheath tumor	4 (4.9)
Fibrosarcoma	6 (7.4)
Angiosarcoma	5 (6.2)
Chondrosarcoma	4 (4.9)
Ewing sarcoma	3 (3.7)
Epitheloid sarcoma	2 (2.5)
Hemangioendhotelioma	2 (2.5)

Results

Demographic data. Of the 81 patients included in the present study, 30 were male and 51 were female. The patients were diagnosed between 2012 and 2020. General patient characteristics are shown in Table I.

Progression-free and overall survival data. A total of 81 patients were included in the study, and 18 of them were reported to be alive at the time of writing. The median overall survival time of the entire study cohort was 46 months (95% CI, 36.7-55.25).

Clinical progression had not yet developed in 3 patients whose follow-up continues. These patients were diagnosed with alveolar soft part sarcoma, pleomorphic sarcoma and hemangioendothelioma. In 1 patient diagnosed with synovial sarcoma, treatment was stopped due to the development of severe intolerance shortly after starting treatment, and progression-free survival could not be evaluated. The median progression-free survival time in the entire study cohort was 5 months (95% CI, 3.98-6.01; Table II).

Response to pazopanib therapy. In terms of the clinical response, the disease status at the first control imaging after starting pazopanib treatment was compared with that before treatment. Responses were grouped as complete response, partial response, stable disease and progressive disease.

Of the 81 patients included in the study, 80 were evaluated for clinical response. None of the patients showed a complete response. A total of 15 (18.75%) patients had a partial response, 22 (27.5%) patients had stable disease and 43 (53.75%) patients exhibited progressive disease.

The detection of a partial response or stable disease on initial follow-up imaging under pazopanib therapy was considered clinically significant, and both conditions were considered as a clinical response. The clinical response rate (partial response + stable disease) was 46.3% during the study period (Table III).

Factors affecting the response to pazopanib therapy

Histological subtypes. The present study included 12 patients with synovial sarcoma, 13 patients with pleomorphic sarcoma, 26 patients with leiomyosarcoma, 4 patients with alveolar soft part sarcoma, 4 patients with malignant peripheral nerve sheath tumors, 6 patients with fibrosarcoma, 5 patients with angiosarcoma, 4 patients with chondrosarcoma, 3 patients with Ewing sarcoma, 2 patients with epithelioid sarcoma and 2 patients with hemangioendothelioma (Table I).

The median progression-free survival time was 5 months (95% CI, 2.9-7.1) in patients with synovial sarcoma, 4 months (95% CI, 2.5-5.4) in patients with pleomorphic sarcoma, 4 months (95% CI, 2.3-5.6) in patients with leiomyosarcoma, 15 months (95% CI, 6.0-23.9) in patients with alveolar soft part sarcoma, 1.5 months (95% CI, 0-3.5) in patients with malignant peripheral nerve sheath tumors, 2 months (95% CI, 0.4-3.6) in patients with fibrosarcoma, 5 months (95% CI, 0.7-9.3) in patients with angiosarcoma, 8 months (95% CI, 3.1-12.9) in patients with chondrosarcoma, 7.5 months (95% CI, 0-17.9) in patients with Ewing sarcoma, 5 months (95% CI, 4.7-5.7) in patients with epithelioid sarcoma and 23 months (95% CI, 18.1-52.8) in patients with hemangioendothelioma (Table II). It was determined that different histological subtypes had no effect on the median progression-free survival (log-rank test, P=0.09; Table II; Fig. 1).

In the χ^2 analysis performed to compare groups of patients based on histological subtypes, the hemangioendothelioma group had a significantly longer median progression-free survival time compared with the leiomyosarcoma (P=0.02), malignant peripheral nerve sheath tumor (P=0.049), fibrosarcoma (P=0.032), angiosarcoma (P=0.037) and chondrosarcoma (P=0.049) groups. In addition, the alveolar soft part sarcoma group had a significantly

Table II. Progression-free survival according to histological subtypes.

Histological subtype	Patients, n (%)	Median progression-free survival, months	P-value
Synovial sarcoma	11 (13.75)	5 (2.9-7.1)	
Pleomorphic sarcoma	13 (16.25)	4 (2.5-5.4)	
Leiomyosarcoma	26 (32.5)	4 (2.3-5.6)	
Alveolar soft part sarcoma	4 (5)	15 (6-23.9)	
Malignant peripheral nerve sheath tumor	4 (5)	1.5 (0-3.5)	
Fibrosarcoma	6 (7.5)	2 (0.4-3.6)	
Angiosarcoma	5 (6.25)	5 (0.7-9.3)	
Chondrosarcoma	4 (5)	8 (3.1-12.9)	
Ewing sarcoma	3 (3.75)	7.5 (0-17.9)	
Epitheloid sarcoma	2 (2.5)	5 (4.7-5.7)	
Hemangioendhotelioma	2 (2.5)	23 (18.1-52.8)	
Total	80 (100)	5 (3.98-6.01)	0.09

Table III. Clinical response rates according to histological subtypes.

Histological subtype	Patients, n (%)	Partial response, n (%)	Stable disease, n (%)	Progressive disease, n (%)	P-value
Synovial sarcoma	11 (13.75)	2 (2.5)	3 (3.7)	6 (7.5)	
Pleomorphic sarcoma	13 (16.25)	2 (2.5)	3 (3.7)	8 (10.0)	
Leiomyosarcoma	26 (32.5)	5 (6.25)	6 (7.5)	15 (18.7)	
Alveolar soft part sarcoma	4 (5)	2 (2.5)	2 (2.5)	0 (0)	
Malign peripheral nerve sheath tumor	4 (5)	0 (0)	0 (0)	4 (5.0)	
Fibrosarcoma	6 (7.5)	0 (0)	1 (1.2)	5 (6.25)	
Angiosarcoma	5 (6.25)	0 (0)	3 (3.7)	2 (2.5)	
Chondrosarcoma	4 (5)	0 (0)	2 (2.5)	2 (2.5)	
Ewing sarcoma	3 (3.75)	1 (1.2)	1 (1.2)	1 (1.2)	
Epitheloid sarcoma	2 (2.5)	1 (1.2)	1 (1.2)	0 (0)	
Hemangioendhotelioma	2 (2.5)	2 (2.5)	0 (0)	0 (0)	
Total	80 (100)	15 (18.8)	22 (27.5)	43 (53.7)	0.093

longer median progression-free survival time compared with the malignant peripheral nerve sheath tumor (P=0.007), fibrosarcoma (P=0.008) and epithelioid sarcoma (P=0.018) groups. When comparing all subtypes between each other, no effect of the histological subtype on the clinical response was detected in the analysis (Pearson's χ^2 test, P=0.093; Table III).

Tumor grade. The tumor grade was evaluated in 33 patients. Among them, 1 patient had a grade 1-2 tumor, 4 patients had grade 2 tumors, 3 patients had grade 2-3 tumors and 25 patients had grade 3 tumors (Table SI).

The progression-free survival time was 10 months in the 1 patient with tumor grade 1-2, the median progression-free survival time was 21 months (min-max, 5-36 months) in the 4 patients with tumor grade 2, 3 months (min-max, 3-10 months) in the 3 patients with tumor grade 2-3 and 5 months (min-max, 1-17 months) in the 25 patients with tumor grade 3 (Table SI).

Due to the small number of patients, when the 8 patients with a tumor grade <3 were evaluated as a single group, the median progression-free survival time was calculated as 10 months (min-max, 3-36 months). No statistically significant difference was found in the comparison of these patients with the remaining 25 patients with grade 3 tumors (log-rank test, P=0.103; Table SI).

A clinical response was obtained in 1 patient with tumor grade 1-2 (100%) and in 4 patients with tumor grade 2 (100%). A clinical response was obtained in 1 of 3 patients with tumor grade 2-3 (33.3%) and 9 of 25 patients with tumor grade 3 (36%). No statistically significant association was found between tumor grade and clinical response (Pearson's χ^2 test, P=0.069; Table SII).

Line of pazopanib treatment. A total of 3 patients received pazopanib as first-line treatment, 26 patients received pazopanib as second-line treatment, 35 patients received pazopanib as third-line treatment, 13 patients received pazopanib as fourth-line treatment and 3 patients received pazopanib as fifth-line treatment.

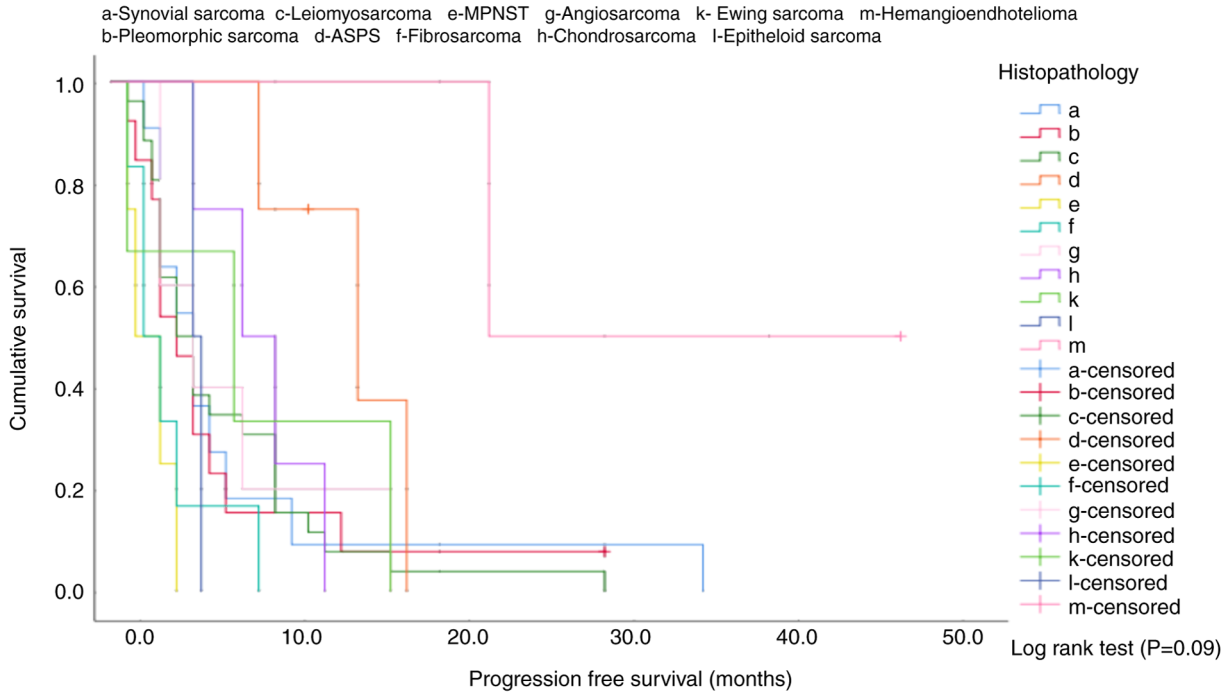

Figure 1. Kaplan-Meier curve of progression-free survival time of patients with different histological subtypes. ASPS, alveolar soft part sarcoma; MPNST, malignant peripheral nerve sheath tumor.

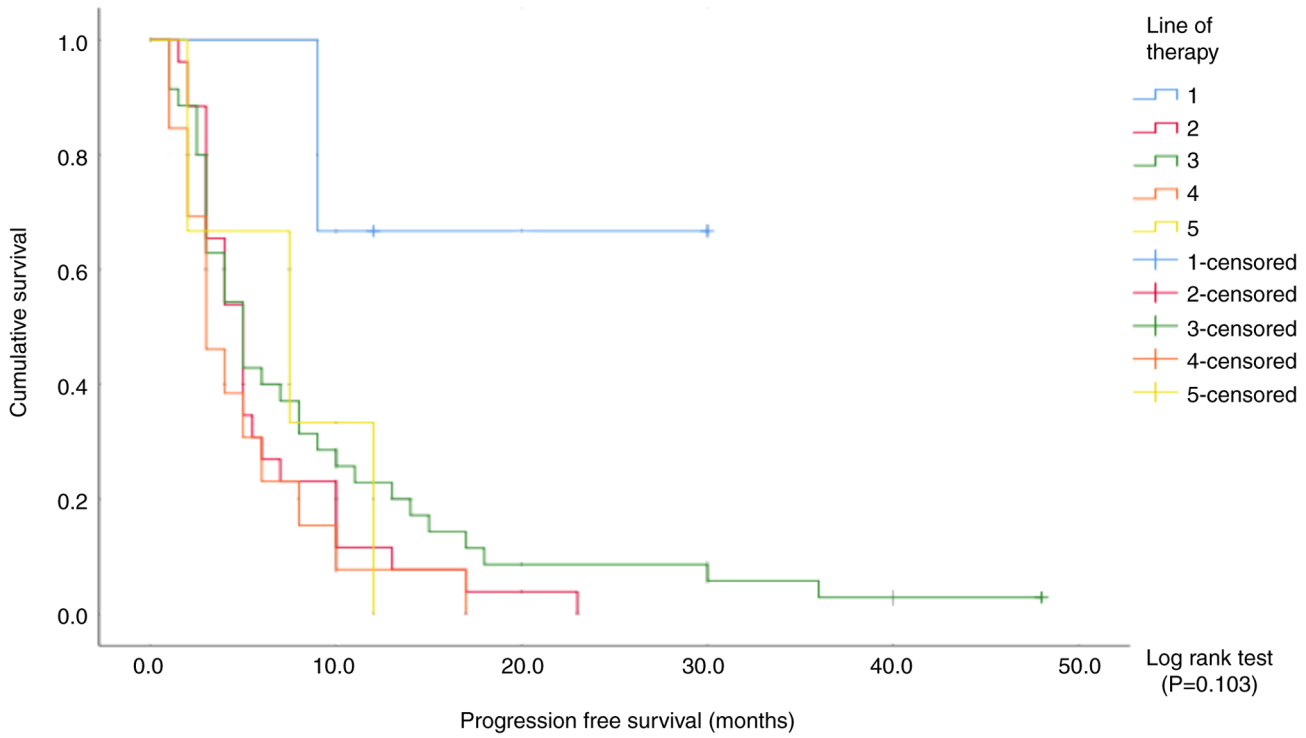

Figure 2. Kaplan-Meier curve of progression-free survival time of patients divided into groups based on the line of pazopanib therapy.

A total of 40 of the 81 patients received ifosfamide-adriamycin as first-line treatment. The most commonly prescribed second-line treatment regimens were gemcitabine-docetaxel and pazopanib.

A total of 2 of the 3 patients who were treated with pazopanib as first-line treatment did not develop clinical progression until follow-up, and the progression-free survival time was 23 months in a single patient that developed progression. The median progression-free survival time was 5 months (95% CI, 3.8-6.1) in patients who received pazopanib as second-line treatment, 5 months (95% CI, 3.4-6.6) in patients who received pazopanib as third-line treatment, 3 months (95% CI, 1.2-4.76)

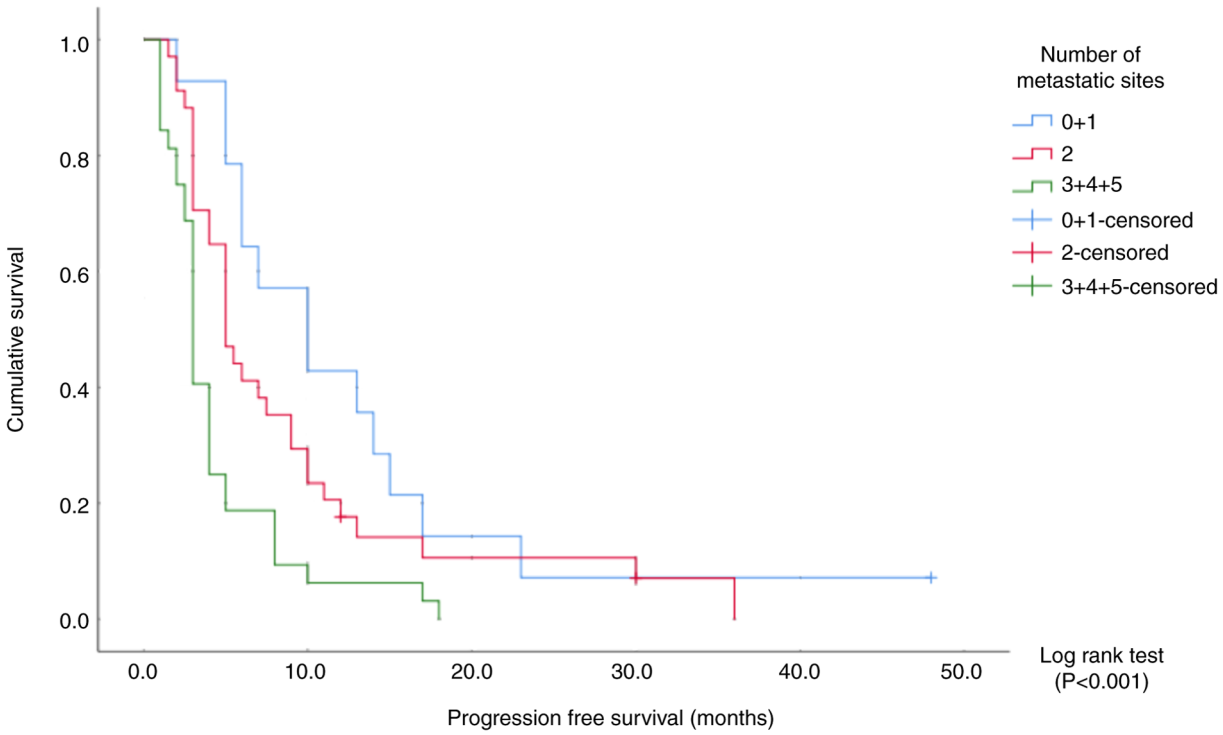

Figure 3. Kaplan-Meier curve of progression-free survival time of patients with different numbers of metastatic sites (analysis 1).

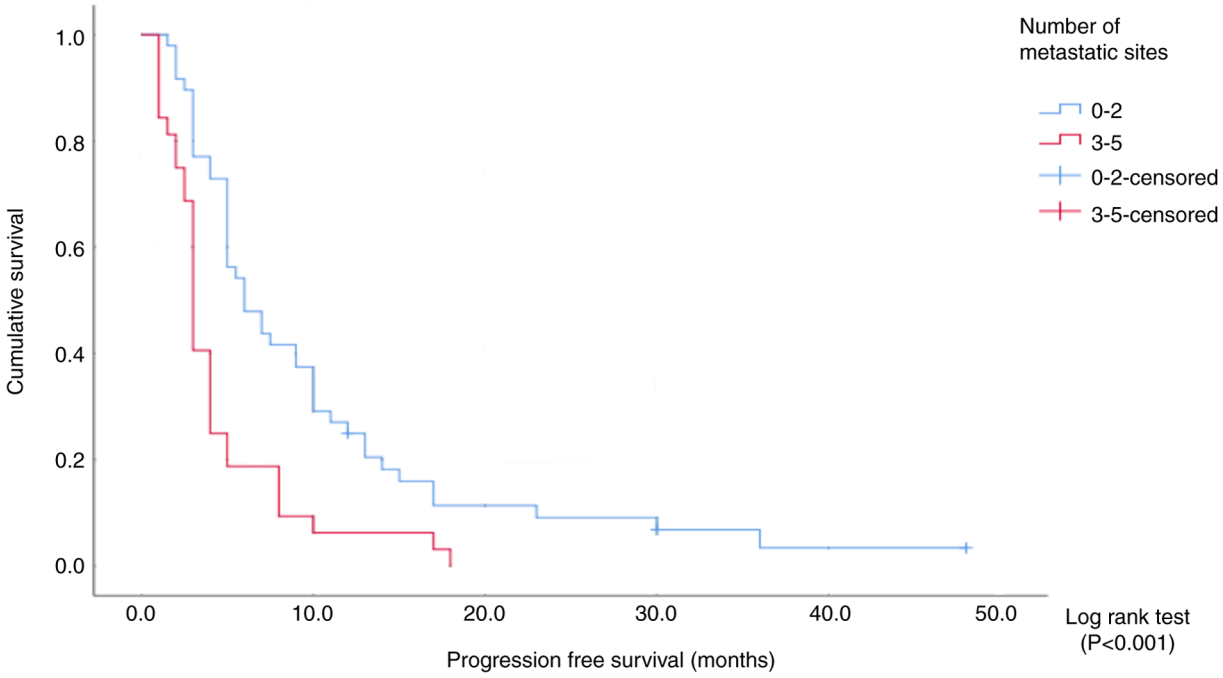

Figure 4. Kaplan-Meier curve of progression-free survival time of patients with different numbers of metastatic sites (analysis 2).

in patients who received pazopanib as fourth-line treatment and 7.5 months (95% CI, 0-16.3) in patients who received pazopanib as fifth-line treatment (Table SIII). No significant association between progression-free survival and the line of pazopanib therapy was observed (log-rank P=0.103; Fig. 2).

The clinical response rate was 100% in patients who received pazopanib therapy as first-line treatment, 46.2% in those who received pazopanib therapy as second-line treatment, 48.6% in those who received pazopanib therapy as third-line treatment, 15.4% in those who received pazopanib therapy as fourth-line treatment and 66.7% in those who received pazopanib therapy as fifth-line treatment.

The patients were first evaluated separately and then divided into three groups: i) First- and second-line therapy; ii) third-line therapy; and iii) fourth- and fifth-line therapy. In both evaluations of the groups, no effect of the line of therapy

Table IV. Progression-free survival according to the number of metastatic sites (analysis 1).

No. of metastatic sites	Patients, n (%)	Median progression-free survival, months (95% CI)	P-value
0-1	14 (17.5)	10 (4.5-15.4)	
2	34 (42.5)	5 (3.8-6.2)	
≥3	32 (40)	3 (2.6-3.3)	
Overall	80 (100)		<0.001

Table V. Progression-free survival according to the number of metastatic sites (analysis 2).

No. of metastatic sites	Patients, n (%)	Median progression-free survival, months (95% CI)	P-value
0-2	48 (60)	6 (3.7-8.2)	
≥3	32 (40)	3 (2.6-3.3)	
Overall	80 (100)		<0.001

Table VI. Clinical response rates according to the number of metastatic sites (analysis 1).

No. of metastatic sites	Patients, n (%)	Partial response, n (%)	Stable disease, n (%)	Progressive disease, n (%)	P-value
0-1	14 (17.5)	5 (6.3)	6 (7.5)	3 (3.7)	
2	34 (42.5)	7 (8.8)	12 (15.0)	15 (18.7)	
≥3	32 (40.0)	3 (3.7)	4 (5.0)	25 (31.3)	
Overall	80 (100)	15 (18.8)	22 (27.5)	43 (53.7)	<0.001

on the clinical response was observed (Pearson's χ^2 test, P=0.053; Table SIV).

Number of metastatic sites. Overall, 64 patients had lung metastases (80%); 12 of them had only lung metastases (15%) and 52 of them had lung and other metastases. Only 1 patient who received pazopanib did not have a metastatic disease. Of the remaining 80 patients, 14 had 1 metastatic site, 34 had 2 metastatic sites, 22 had 3 metastatic sites, 9 had 4 metastatic sites and 1 had 5 metastatic sites.

The median progression-free survival time was 10 months (95% CI, 4.5-15.4) in patients with ≤1 metastatic site, 5 months (95% CI, 3.8-6.2) in those with 2 metastatic sites, and 3 months (95% CI, 2.6-3.3) in those with ≥3 metastatic sites (Fig. 3 and Table IV). Patients were also divided into groups of patients with 0-2 and ≥3 sites. The median progression-free survival time was 6 months (95% CI, 3.7-8.2) in the first group and 3 months (95% CI, 2.6-3.3) in the second group (Fig. 4 and Table V). In both cases, the number of metastatic sites had an effect on the progression-free survival (log-rank P<0.001; Tables IV and V). By contrast, there was no significant difference in progression-free survival between patients with 0-1 sites and those with 2 sites (Pearson χ^2 analysis, P=0.150).

The clinical response rate was 78% in patients with 0 or 1 metastatic sites, 55% in those with 2 sites, 27% in those with 3 sites, and 10% in those with 4 or 5 sites. The patients were first divided into three groups: i) 0 or 1 sites; ii) 2 sites; and iii) ≥3 sites. In the analysis, the number of metastatic sites was significantly associated with clinical response (Pearson's χ^2 test, P=0.001; Table VI). When the patients were divided into two groups: i) 0, 1 or 2 sites; and ii) ≥3 sites), the number of metastatic sites was also significantly associated with the clinical response (Fisher's exact test two-sided test, P=0.001; Tables VI and VII).

Safety. A total of 65 patients were evaluated for tolerance to treatment (data not shown). In 4 patients, the treatment was continued with dose reduction. Pazopanib treatment could not be continued as planned in 1 patient because of grade 4 fatigue and was stopped before the first cycle was completed.

The adverse effects were evaluated in 65 patients. No side effects were observed in 29 patients. A total of 16 patients had grade 1-2 side effects, 19 patients had grade 3-4 side effects and 2 patients had both grade 1-2 and grade 3-4 side effects.

The most common side effects were hypothyroidism (29.7%), elevated liver enzymes (18.9%), hypertension (16.2%), fatigue (16.2%), emesis (10.8%), graying of hair (10.8%), diarrhea (10.8%), pneumothorax (8.1%), cardiac side effects (8.1%), hand-foot syndrome (5.4%) and neutropenia (5.4%). The side effects that led to treatment discontinuation or interruption were fatigue, arrhythmia, pnomotorax, hand-foot syndrome and dyspnea.

Table VII. Clinical response rates according to the number of metastatic sites (analysis 2).

No. of metastatic sites	Patients, n (%)	Partial response, n (%)	Stable disease, n (%)	Progressive disease, n (%)	P-value
0-2	48 (60.0)	12 (15.0)	18 (22.5)	18 (22.5)	
≥3	32 (40.0)	3 (3.7)	4 (5.0)	25 (31.3)	
Overall	80 (100)	15 (18.8)	22 (27.5)	43 (53.7)	<0.001

Discussion

In the present study, the median overall survival time was 46 months. The overall survival time was the time from detection of metastasis to death. A previous prospective study had a period of 24 months for overall survival in 212 patients diagnosed with soft tissue sarcoma at the University of Mannheim (Germany) (7). The overall survival time may have been markedly longer in the present study compared with this previous study because most patients that received pazopanib therapy were in the later stages of disease; therefore, patients who died in the earlier stages without receiving this therapy were not included in the present study.

The median progression-free survival time in the entire study cohort was 5 months, which is consistent with the literature. In the sub-analysis of two clinical studies organized by the European Organization for Research and Treatment of Cancer (EORCT), median progression-free survival time was found to be 4.4 months in the patients with metastatic soft tissue sarcoma that received pazopanib therapy (8).

No statistical significance was found in the analysis based on histological subtypes for progression-free survival. This is considered to be due to the large differences in the number of patients between the groups. The synovial sarcoma, leiomyosarcoma and pleomorphic sarcoma groups included a total of 51 patients, the median progression-free survival times were found to be 5, 4 and 4 months, respectively, and the clinical response rates were close to each other. The histological subtype did not affect the success of treatment in these three groups, in which pazopanib treatment was administered most frequently.

The median progression-free survival time was 1.5 months in patients with malignant peripheral nerve sheath tumors and 2 months in patients with fibrosarcoma. Notably, only 1 of the 10 patients achieved a clinical response in these groups. The median progression-free survival time of the placebo group was calculated as 1.5 months in the PALETTE study organized by the EORCT, which led to United States Food and Drug Administration approval of pazopanib (4).

In the χ^2 analysis performed to compare groups of patients with different histological subtypes, a notably longer progression-free survival was observed in patients with hemangioendothelioma (23 months) and alveolar soft part sarcoma (15 months) compared with that of patients with other subtypes; There were 2 patients in the hemangioendothelioma group and 1 patient did not progress during the 48-month follow-up period. Pazopanib therapy appears to be an ideal option for hemangioendothelioma. In addition, pazopanib therapy has been used as a first-line treatment for alveolar soft part sarcoma (9). The data from the present study therefore supports administering pazopanib as a first-line treatment in metastatic alveolar soft part sarcoma.

It has been demonstrated that low and moderate grade tumors have longer progression free and overall survival under pazopanib therapy (8). However, in the present study, no statistically significant effect of tumor grade on progression-free survival and clinical response was observed. This may have been due to the small number of patients that were evaluated.

Pazopanib is generally not recommended for first-line use in the treatment of soft tissue sarcomas. In the present study, only 3 patients received pazopanib as the first-line treatment. Among them, 2 had alveolar soft part sarcoma and 1 had low-grade leiomyosarcoma. In the analysis, the line of treatment had no effect on progression-free survival or clinical response rates. The fact that these parameters were lower in patients given pazopanib as fourth- or fifth-line treatment was considered to be due to increase in the tumor burden as a result of the increase in the number of failed lines and the worsening of the performance status of the patients. In subtypes in which pazopanib was most often used, such as synovial sarcoma, leiomyosarcoma, pleomorphic sarcoma and angiosarcoma, it still seems to be the most appropriate option after regimens containing anthracyclines and ifosfamide. Furthermore, 3 patients with Ewing sarcoma in the study received this treatment as fourth- or later-line treatment, and 2 had a clinical response (both had isolated lung metastases). There were four different metastatic sites in 1 patient who showed disease progression. It was suggested that pazopanib could also be considered as an option for later-line treatment for patients with Ewing sarcoma whose disease is still under control.

It was predicted that increased tumor burden may adversely affect treatment success, because it is considered that it may be harder to maintain disease control (8). The present analyses demonstrated that the number of metastatic sites affected both progression-free survival and clinical response rates. It was not possible to clearly differentiate between patients with oligometastatic and multimetastatic disease. In the present study, no significant difference was found in the progression-free survival of patients with 0-1 sites and 2 sites. This suggested that patients with ≤2 different metastatic sites could be considered as to have oligometastatic disease.

An advantage of pazopanib over conventional cytotoxic therapies is its tolerance; this is especially true for elderly patients (8). In the present study, treatment tolerance was generally good. The most common adverse effects were hypothyroidism, elevated liver enzyme levels, hypertension, fatigue, diarrhea, hair graying and emesis. This is similar to the side effects reported in another study (10). None of the

patients developed grade 3-4 anemia or neutropenia. In 3 patients, pneumothorax and cardiac side effects (arrhythmia and heart failure) developed, and the clinical recommendation was close follow-up of these patients.

In summary, the success of pazopanib therapy and the factors affecting its success have been discussed. Pazopanib therapy was the most successful in patients with alveolar soft part sarcoma and hemangioendothelioma, whereas it was less successful in patients with malignant peripheral nerve sheath tumors and fibrosarcoma.

It was concluded that regardless of the subtype, the response rates of patients with a small number of metastatic sites were improved compared with those of higher number of metastatic sites. In addition, administering the treatment as a second- or third-line treatment appeared to be more successful than administering it as a later-line therapy. Therefore, pazopanib should be evaluated as an option for a selected group of patients in whom the aforementioned factors present together.

Studies to predict the success of pazopanib therapy for soft tissue sarcomas are ongoing. Although there is currently no definitive biomarker to identify patients with soft tissue sarcoma that may benefit from pazopanib therapy, the TP53 mutation status stands out in this regard. A retrospective analysis of 19 patients with advanced soft tissue sarcoma who received pazopanib therapy at the Ohio State James Comprehensive Cancer Center (Columbus, OH, USA) demonstrated a markedly longer median progression-free survival time in the group with TP53 mutations (6). In another retrospective study involving 67 patients at Yonsei Cancer Center (Seoul, South Korea) between 2013 and 2019, biopsy samples were re-examined for programmed death-ligand 1 (PD-L1) expression, and an inverse association was found between PD-L1 expression and the success of pazopanib treatment (11). As a result, a clinical study assessing the use of pazopanib in combination with immune checkpoint inhibitors has been initiated and early results are promising (12); the progression-free suvival was 7.7 months and it was found to be longer compared with that obtained in the EORCT trial and the present study, which were 4.4 and 5 months rescpectively (8,12). As studies on these issues become more comprehensive, clearer data will emerge. Notably, the use of next-generation sequencing technology has become increasingly widespread to provide additional genetic information in cancer treatment (13). In a previous report in which a patient achieved a complete response under pazopanib therapy, several somatic mutations and chromosome amplifications were identified by NGS. For example, somatic mutations, including platelet-derived growth factor receptor α p.T83S and platelet-derived growth factor receptor β exon 13 skipping were found. These findings are consistent with the mechanism of action of pazopanib. Pazopanib is a multiple kinase inhibitor that limits tumor growth by targeting angiogenesis via inhibition of enzymes including vascular endothelial growth factor receptor, platelet-derived growth factor receptor and c-KIT. Patients with these genetic alterations may be better responders to pazopanib therapy (13).

A major limitation of the present study was that it was a single-center, retrospective study. As the study covers patients over a long period, certain patient data could not be accessed, and factors such as tumor grade and treatment tolerance could not be fully evaluated. However, considering how rare sarcomas are and that pazopanib treatment is given only in metastatic disease and generally in later-line therapy, the number of patients increased the reliability and generalizability of the present study. In conclusion, the progression-free survival and response rates of patients with a small number of metastatic sites were better regardless of subtype.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CMS collected all the data, performed the statistical analysis and wrote the manuscript. PG contributed to analyzing the data, writing and drafting the manuscript, and organizing the tables and figures. UAS treated the patients, helped in collecting the data and designing the study. All authors have read and approved the final version of the manuscript. CMS and UAS confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Ege University Ethics committee (approval no. 21-6-1T/83; Bornova, Turkey). The patients provided written informed consent for their participation in the study.

Patient consent for publication

The patients provided written informed consent for the publication of any data and images.

Competing interests

The authors declare that they have no competing interests.

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