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Soft tissue sarcoma of the extremity: Characterizing symptom duration and outcomes

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ABSTRACT

Background: We sought to investigate how the interval between symptom onset and diagnosis of soft tissue sarcoma (STS) of the extremity was associated with survival.
Methods: Patients treated for extremity STS years 2006–2015 were stratified by symptom duration: at least two, six or twelve months between symptom onset and diagnosis. Chi-square tests compared patient and tumor-related characteristics based on symptom duration. Survival analysis included Cox regression and Kaplan-Meier estimates.
Results: Of 113 patients included, mean age was 56.7 years, 52.2% were male, and 75.2% were white. Median tumor size was 75 mm, 48.7% were grade 3, and 38.1% were stage I. With symptom duration of either at least 6 or 12 months, a greater proportion of patients who experienced the specified symptom duration had lower grade tumors ($p < 0.01$ and $p = 0.01$, respectively) and lower stage disease ($p < 0.01$ and $p = 0.02$, respectively) than those who did not. Among all patients, survival estimates were similar between those who experienced a symptom duration of 2 ($p = 0.12$), 6 ($p = 0.18$) or 12 ($p = 0.61$) months and those who did not.
Conclusion: Patients with extremity STS who tolerated a longer symptom duration had less advanced disease. Reasons for prolonged symptom duration and methods to address these factors warrant further investigation.

1. Introduction

The American Cancer Society estimated that approximately 13,040 new cases of soft tissue sarcoma (STS) would be diagnosed in the United States in 2018 [1]. STS can occur in various locations of the body including the retroperitoneum, trunk and extremity [2]. The most common location is the extremity, with the lower extremity comprising 28% and the upper extremity comprising 12% of all STS [2]. Prior studies have investigated the prolonged symptom duration that might occur with STS [3–5]. The reported median symptom duration ranges from 1 to 6 months [3,4]. In addition, symptom duration has been categorized as patient-related, such as when a patient ignores the tumor because it is painless, and physician-related, such as when misdiagnosis occurs [3–5]. However, the definition of symptom duration used in previous studies has been variable and inconsistent. It is difficult to determine the time interval between symptom onset and diagnosis that might negatively affect patient outcomes. Therefore, the aim of this study was to determine if an association existed between symptom duration and survival among patients with STS of the extremity using specific time intervals for symptom duration.

2. Methods

After obtaining Institutional Review Board approval, we used our tumor registry to identify patients treated for extremity STS between 2006 and 2015. Demographic and clinical information was obtained from the tumor registry and medical record. We reviewed information regarding symptom presentation and duration, diagnosis, and reasons for prolonged symptom duration, if present. Methods of diagnosis included biopsy and imaging, with 80.5% being diagnosed via biopsy. Patients with an unknown time interval between symptom onset and diagnosis were excluded (n = 63). This left a sample size of 113

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patients for analysis.

Patients were stratified based on symptom duration: at least two months (short duration), six months (intermediate duration) or twelve months (long duration) between symptom onset and diagnosis. Thus, with short symptom duration (defined as 2 months), patients with a symptom onset to diagnosis interval < 2 months were compared to patients with a symptom onset to diagnosis interval ≥ 2 months. Similarly, with intermediate symptom duration (defined as six months), patients with a symptom onset to diagnosis interval < 6 months were compared to patients with a symptom onset to diagnosis interval ≥ 6 months. Finally, with long symptom duration (defined as 12 months), patients with a symptom onset to diagnosis interval < 12 months were compared to patients with a symptom onset to diagnosis interval ≥ 12 months.

Descriptive statistics regarding initial patient presentation, physician-related factors in symptom duration (i.e. misdiagnosis, extended duration of workup), and patient-related factors in symptom duration (i.e. ignoring symptoms, attributing symptoms to other cause) were calculated. Chi-square tests were used to compare categorical variables such as gender and initial treatment type between patients who experienced the specified symptom duration and those who did not. The two-sample *t*-test was used to compare mean age at diagnosis. The Wilcoxon rank-sum test was used to compare median tumor size. Cox regression was used to estimate the risk of cause-specific death associated with symptom duration. Both crude and adjusted Cox regression analyses were performed. The adjusted model included the variables age, sex, race, grade, stage, tumor size, histology and initial treatment type as covariates in order to account for their effect on survival. Kaplan-Meier cause-specific survival estimates were calculated, and the log-rank test compared the equality of survival functions.

Cancer staging was based on the American Joint Committee on Cancer Staging Manual, 7th edition [6]. A p-value less than 0.05 was used to determine statistical significance for all tests. Analyses were performed using Stata version 14.0 (StataCorp LP, College Station, TX, USA).

3. Results

The study sample included 113 patients with STS of the extremity. The sample was 52.2% male, 75.2% white, and mean age was 56.7 years. Median tumor size was 75 mm, 75.2% were located in the lower extremity, and 23.0% were liposarcoma (Table 1). The most common initial presentation was a mass in 89 patients (78.8%), and pain in 20 patients (17.7%) (Table 1). The median (range) time between symptom onset and diagnosis for the entire study sample was 3 (0–168) months. A total of 68 patients (60.2%) experienced physician or patient-related factors that lengthened their symptom duration, with a median (range) symptom duration of 6 (1–168) months. One patient presented to his physician immediately after noticing a mass in his extremity. However, the mass was misdiagnosed as a lipoma, and thus, the patient's symptom duration was lengthened to one month until the correct diagnosis was obtained. Physician-related factors lengthened symptom duration for 18 patients (15.9%) and included error in initial clinical diagnosis for 15 patients (13.3%). Patient-related factors lengthened symptom duration for 50 patients (44.3%) and included 35 patients (31.0%) who ignored their symptoms (Table 1).

With symptom duration of ≥ 6 months between symptom onset and diagnosis (intermediate symptom duration), patients who experienced an intermediate symptom duration had grade 1 tumors (43.5% versus 16.4%; $p < 0.01$) and stage I disease (60.9% versus 22.4%; $p < 0.01$) more often than patients who did not experience an intermediate symptom duration (Table 2). Similarly, with symptom duration of ≥ 12 months (long symptom duration), patients who experienced a long symptom duration had grade 1 tumors (47.8% versus 22.2%; $p = 0.01$) and stage I disease (60.9% versus 32.2%; $p = 0.02$) more often than patients who did not experience a long symptom duration (Table 2).

Table 1
Disease presentation and tumor characteristics.

Characteristic	n (%)
Initial Presentation	
Mass	89 (78.8)
Pain	20 (17.7)
Pathologic fracture	1 (0.9)
Asymptomatic/Incidentally Discovered	1 (0.9)
Unknown	2 (1.8)
Physician-Related Factors in Symptom Duration	18 (15.9)
Misdiagnosis	15 (13.3)
Delay in workup	3 (2.7)
Median Symptom Duration Associated with Physician-Related Factors in Symptom Duration in Months (Range)	6 (1–36)
Patient-related Factors in Symptom Duration	50 (44.3)
Attributed symptoms to other cause	8 (7.1)
Ignored symptoms	35 (31.0)
Other	7 (6.2)
Median Symptom Duration Associated with Patient-Related Factors in Symptom Duration in Months (Range)	7 (1–168)
Median Symptom Duration in Months (Range)	3 (0–168)
Median Symptom Duration Associated with Physician or Patient-Related Factors Lengthening Symptom Duration in Months (Range)	6 (1–168)
Location	
Upper extremity	27 (23.9)
Lower extremity	85 (75.2)
Unknown	1 (0.9)
Laterality	
Left	50 (44.3)
Right	61 (54.0)
Unknown	2 (1.8)
Median Tumor Size in Millimeters (Range)	75 (2–300)
Grade	
1	31 (27.4)
2	9 (8.0)
3	55 (48.7)
Unknown	18 (15.9)
Stage	
I	43 (38.1)
II	17 (15.0)
III	34 (30.1)
IV	8 (7.1)
Unknown	11 (9.7)
Histology	
Liposarcoma	26 (23.0)
Synovial Sarcoma	12 (10.6)
Fibromyxosarcoma	16 (14.2)
Leiomyosarcoma	17 (15.0)
Other	42 (37.2)

There were no significant differences in median tumor size. But with symptom duration of ≥ 2 months, a greater proportion of patients who experienced the specified symptom duration had tumors greater than 50 mm in size compared to those who did not (60.0% versus 51.2%; $p = 0.02$). In contrast, with symptom duration of ≥ 12 months, a smaller proportion of patients who experienced the specified symptom duration had tumors greater than 50 mm in size compared to those who did not (52.2% versus 57.8%; $p = 0.01$, respectively) (Table 2). There were no differences in tumor histology based on any specified symptom duration (Table 2).

With symptom duration of ≥ 6 months (intermediate symptom duration), patients who experienced an intermediate symptom duration underwent surgery as their initial treatment more often than patients who did not (80.4% versus 53.7%; $p = 0.04$) (Table 3). However, this finding was not significant when symptom duration was specified as ≥ 2 or 12 months. There were no significant differences in the use of chemotherapy (Table 3). But with intermediate symptom duration (at least 6 months) a greater proportion of patients who experienced the specified symptom duration did not receive radiotherapy compared to those who did not experience an intermediate symptom duration (58.7% versus 37.3%; $p = 0.03$) (Table 3).

Table 2
Patient and tumor characteristics based on specific symptom durations.

Characteristic	Symptom Duration ≥2 Months			Symptom Duration ≥6 Months			Symptom Duration ≥12 Months		
	No, n (%)	Yes, n (%)	p-value	No, n (%)	Yes, n (%)	p-value	No, n (%)	Yes, n (%)	p-value
Total (n = 113)	43 (38.1)	70 (62.0)		67 (59.3)	46 (40.7)		90 (79.7)	23 (20.4)	
Mean Age in Years (SD)	59.3 (19.3)	55.1 (17.8)	0.24	60.7 (18.2)	51.0 (17.3)	0.01*	57.3 (18.8)	54.4 (16.9)	0.51
Sex			0.55			0.25			0.96
Female	19 (44.2)	35 (50.0)		29 (43.3)	25 (54.4)		43 (47.8)	11 (47.8)	
Male	24 (55.8)	35 (50.0)		38 (56.7)	21 (45.7)		47 (52.2)	12 (52.2)	
Race			0.17			0.13			0.61
White	34 (79.1)	51 (72.9)		51 (76.1)	34 (73.9)		66 (73.3)	19 (82.6)	
Black	8 (18.6)	9 (12.9)		11 (16.4)	6 (13.0)		14 (15.6)	3 (13.0)	
Asian	0	6 (8.6)		1 (1.5)	5 (10.9)		6 (6.7)	0	
Other	1 (2.3)	4 (5.7)		4 (6.0)	1 (2.2)		4 (4.4)	1 (4.4)	
Median Tumor Size in Millimeters (Range)	100 (12–245)	73 (2–300)	0.68	90 (2–245)	71 (10–300)	1.00	78 (2–300)	67 (10–300)	0.91
Tumor Size in Millimeters			0.02*			0.13			0.01*
≤ 50	9 (20.9)	22 (31.4)		15 (22.4)	16 (34.8)		20 (22.2)	11 (47.8)	
> 50	22 (51.2)	42 (60.0)		38 (56.7)	26 (56.5)		52 (57.8)	12 (52.2)	
Unknown	12 (27.9)	6 (8.6)		14 (20.9)	4 (8.7)		18 (20.0)	0	
Grade			0.46			< 0.01*			0.01*
1	10 (23.3)	21 (30.0)		11 (16.4)	20 (43.5)		20 (22.2)	11 (47.8)	
2	3 (7.0)	6 (8.6)		4 (6.0)	5 (10.9)		6 (6.7)	3 (13.0)	
3	25 (58.1)	30 (42.9)		44 (65.7)	11 (23.9)		51 (56.7)	4 (17.4)	
Unknown	5 (11.6)	13 (18.6)		8 (11.9)	10 (21.7)		13 (14.4)	5 (21.7)	
Stage			0.43			< 0.01*			0.02*
I	12 (27.9)	31 (44.3)		15 (22.4)	28 (60.9)		29 (32.2)	14 (60.9)	
II	7 (16.3)	10 (14.3)		11 (16.4)	6 (13.0)		12 (13.3)	5 (21.7)	
III	14 (32.6)	20 (28.6)		26 (38.8)	8 (17.4)		32 (35.6)	2 (8.7)	
IV	4 (9.3)	4 (5.7)		8 (11.9)	0		8 (8.9)	0	
Unknown	6 (14.0)	5 (7.1)		7 (10.5)	4 (8.7)		9 (10.0)	2 (8.7)	
Histology			0.34			0.16			0.74
Liposarcoma	10 (23.3)	16 (22.9)		14 (20.9)	12 (26.1)		19 (21.1)	7 (30.4)	
Synovial Sarcoma	2 (4.7)	10 (14.3)		5 (7.5)	7 (15.2)		9 (10.0)	3 (13.0)	
Fibromyxosarcoma	6 (14.0)	10 (14.3)		9 (13.4)	7 (15.2)		13 (14.4)	3 (13.0)	
Leiomyosarcoma	5 (11.6)	12 (17.1)		8 (11.9)	9 (19.6)		13 (14.4)	4 (17.4)	
Other	20 (46.5)	22 (31.4)		31 (46.3)	11 (23.9)		36 (40.0)	6 (26.1)	

*p-value significant at the < 0.05 level.

Overall cause-specific survival was 83.5% at five years and 81.1% at ten years (Fig. 1). Symptom duration did not negatively impact survival based on any specified symptom duration. There was no significant change in the risk of death per one-month increase in the interval between symptom onset and diagnosis (HR = 1.003; 95% CI: 0.959–1.049) (Table 4). Nor were there significant differences in cause-specific survival when symptom duration was specified as 2 months (HR = 0.762; 95% CI: 0.231–2.509), 6 months (HR = 1.512; 95% CI:

Table 3
Treatment patterns based on specific symptom durations.

Characteristic	Symptom Duration ≥2 Months			Symptom Duration ≥6 Months			Symptom Duration ≥12 Months		
	No, n (%)	Yes, n (%)	p-value	No, n (%)	Yes, n (%)	p-value	No, n (%)	Yes, n (%)	p-value
Initial Treatment			0.74			0.04			0.30
None	2 (4.7)	1 (1.4)		3 (4.5)	0		3 (3.3)	0	
Chemotherapy	7 (16.3)	9 (12.9)		13 (19.4)	3 (6.5)		15 (16.7)	1 (4.4)	
Radiation	8 (18.6)	11 (15.7)		14 (20.9)	5 (10.9)		16 (17.8)	3 (13.0)	
Surgery	25 (58.1)	48 (68.6)		36 (53.7)	37 (80.4)		55 (61.1)	18 (78.3)	
Unknown	1 (2.3)	1 (1.4)		1 (1.5)	1 (2.2)		1 (1.1)	1 (4.4)	
Surgery Type			0.19			0.03*			0.38
None	7 (64.3)	9 (12.9)		14 (20.9)	2 (4.4)		14 (15.6)	2 (8.7)	
Excisional Biopsy	12 (27.9)	34 (48.6)		21 (31.3)	25 (54.4)		33 (36.7)	13 (56.5)	
Limb-sparing Resection	21 (48.8)	24 (34.3)		28 (41.8)	17 (37.0)		38 (42.2)	7 (30.4)	
Amputation	3 (7.0)	3 (4.3)		4 (6.0)	2 (4.4)		5 (5.6)	1 (4.4)	
Chemotherapy			0.47			0.36			0.54
None	25 (58.1)	47 (67.1)		38 (56.7)	34 (73.9)		54 (60.0)	18 (78.3)	
Neoadjuvant	3 (7.0)	9 (12.9)		8 (11.9)	4 (8.7)		11 (12.2)	1 (4.4)	
Adjuvant	4 (9.3)	4 (5.7)		6 (9.0)	2 (4.4)		7 (7.8)	1 (4.4)	
Other	10 (23.3)	9 (12.9)		13 (19.4)	6 (13.0)		16 (17.8)	3 (13.0)	
Unknown	1 (2.3)	1 (1.4)		2 (3.0)	0		2 (2.2)	0	
Radiotherapy			0.16			0.03*			0.08
None	17 (39.5)	35 (50.0)		25 (37.3)	27 (58.7)		41 (45.6)	11 (47.8)	
Neoadjuvant	9 (20.9)	15 (21.4)		18 (26.9)	6 (13.0)		20 (22.2)	4 (17.4)	
Adjuvant	11 (25.6)	16 (22.9)		17 (25.4)	10 (21.7)		22 (24.4)	5 (21.7)	
Other	6 (14.0)	2 (2.9)		7 (10.5)	1 (2.2)		7 (7.8)	1 (4.4)	
Unknown	0	2 (2.9)		0	2 (4.4)		0	2 (8.7)	

*p-value significant at the < 0.05 level.

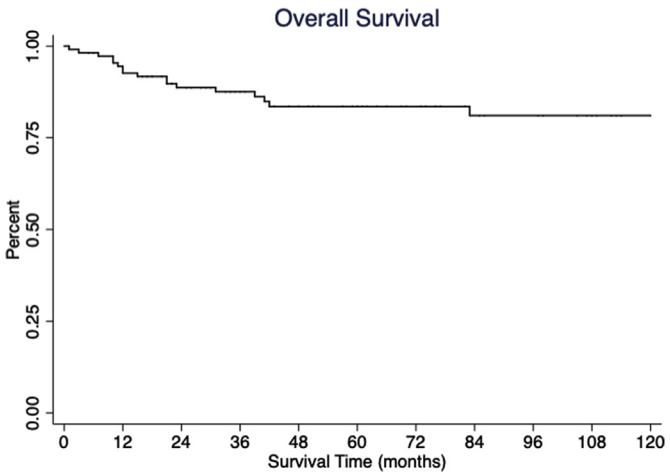

Fig. 1. Overall survival.

Table 4
Hazard ratios for risk of death based on specific symptom durations.

Symptom Duration	Crude Hazard Ratio	95% CI	Adjusted Hazard Ratio[a]	95% CI
Per month	0.958	0.895–1.026	1.003	0.959–1.049
< 2 months	Reference		Reference	
≥2 months	0.468	0.180–1.215	0.762	0.231–2.509
< 6 months	Reference		Reference	
≥6 months	0.494	0.174–1.406	1.512	0.364–6.287
< 12 months	Reference		Reference	
≥12 months	0.720	0.207–2.507	3.387	0.712–16.103

[a] Adjusted for age, sex, race, grade, stage, tumor size, histology, and initial treatment type.

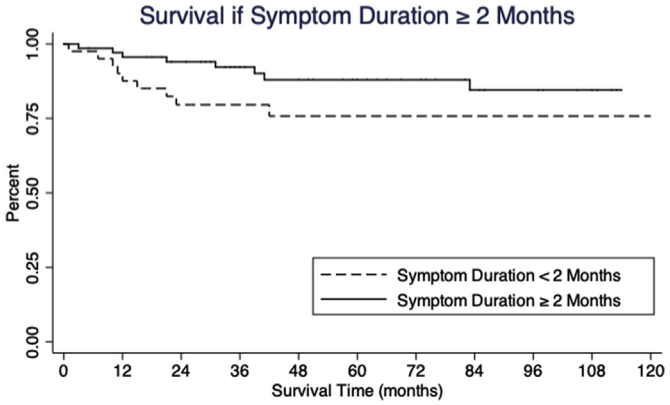

Fig. 2. Survival if symptom duration ≥2 months.

0.364–6.287), or 12 months (HR = 3.387; 95% CI: 0.712–16.103) (Table 4). Kaplan-Meier analysis yielded similar results. There was no significant difference in 5- or 10-year cause-specific survival rates between those who experienced the specified symptom duration and those who did not when symptom duration was 2 months (p = 0.12, Fig. 2, Table 5), 6 months (p = 0.18, Fig. 3, Table 5) or 12 months (p = 0.61, Fig. 4, Table 5).

4. Discussion

This study analyzed characteristics of patients treated for STS of the extremity at a National Cancer Institute designated comprehensive cancer center. The median time between symptom onset and diagnosis was 3 months. This was less than other reports, in which the median duration of symptoms before diagnosis was 5–7 months [7,8]. The

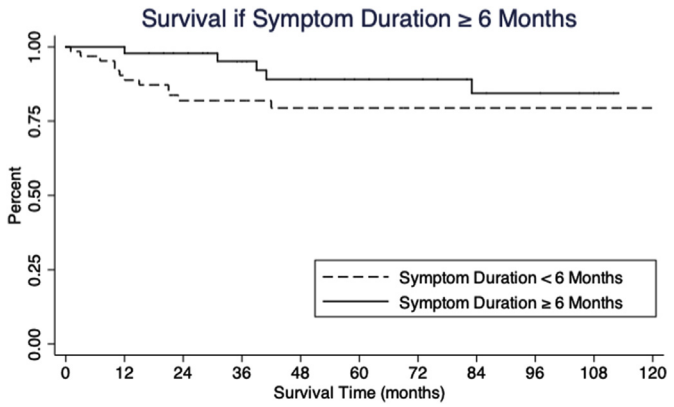

Fig. 3. Survival if symptom duration ≥6 months.

Table 5
Kaplan-Meier survival estimates based on specific symptom durations.

Symptom Duration	5-year Survival Rate	10-year Survival Rate	p-value
Overall	83.5%	81.1%	
< 2 months	76.0%	76.0%	0.12
≥2 Months	88.0%	84.6%	
< 6 months	79.6%	79.6%	0.18
≥6 Months	89.0%	84.4%	
< 12 months	81.5%	81.5%	0.61
≥12 Months	90.6%	80.6%	

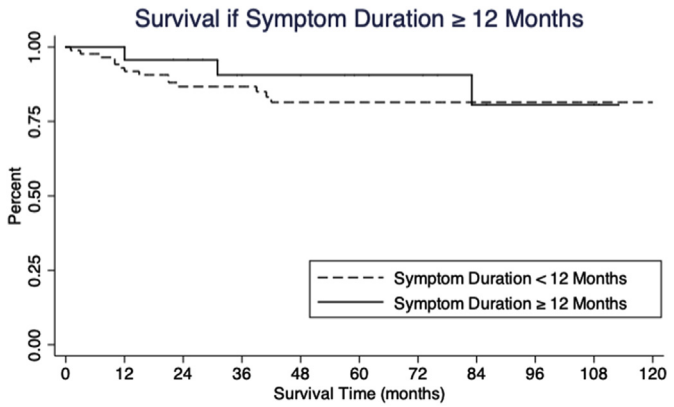

Fig. 4. Survival if symptom duration ≥12 months.

median time between symptom onset and diagnosis among patients who experienced a prolonged symptom duration was 6 months, with a median of 6 months for physician-related factors and 7 months for patient-related factors. Literature regarding the timeliness of diagnosis of bone and soft tissue sarcomas report a median symptom duration associated with physician-related factors of 3–6 months and a median symptom duration associated with patient-related factors of 1–4 months [3–5,9]. However, these studies used various definitions of symptom duration, which may be the reason for the discrepancy in median symptom duration. For instance, George and Grimer defined patient-related symptom duration as the period between symptom onset and presentation to a physician, and physician-related symptom duration as the period between patient presentation and diagnosis at a specialist center [3]. Nakamura et al. used a symptom onset to diagnosis interval of 6 months to investigate if a prolonged symptom duration affected the survival of patients with STS [9].

Reasons for prolonged symptom duration include patient-related factors, as well as hospital and physician-related factors [3–5,10,11]. Brouns et al. investigated prolonged symptom duration of STS and found that the median patient-related symptom duration was four

months and was most often because the mass did not cause pain and was thus ignored [4]. The median physician-related symptom duration was six months and was most often due to of misdiagnosis [4]. Similarly, Clark and Thomas investigated prolonged symptom duration in referral to a specialized sarcoma unit and found that a common cause for prolonged symptom duration was the general practitioner and misdiagnosis [10]. Furthermore, George and Grimer reported that the depth and rate of growth of the mass might also affect the timeliness of diagnosis [3]. The median patient-related symptom duration was greater in patients with a mass increasing in size versus a mass stable in size (45.5 days versus 14.0 days, respectively; $p = 0.002$), while the median physician-related symptom duration was greater with superficial masses versus deep masses (132.9 days versus 70.0 days, respectively; $p = 0.038$) [3]. Perhaps physicians in that study were less likely to associate superficial masses with soft tissue sarcoma, and thus symptom duration was prolonged due to physician-related factors.

Not only have the reasons for prolonged symptom duration been investigated, but the effect that prolonged symptom duration has on patient outcomes has also been examined [5,7,9,12]. The results have been conflicting. Goedhart et al. studied prolonged symptom duration of osteosarcoma and found that prolonged symptom duration (at least four months) did not affect survival [5]. Similarly, Rougraff et al. analyzed patients with high-grade STS of the flank or extremity and found that the duration of symptoms before diagnosis did not significantly affect survival [7]. Likewise, the current study found that symptom duration did not negatively impact survival. In contrast, some research has shown that prolonged symptom duration negatively affects survival. For instance, Nakamura et al. found that patients with STS treated within six months of symptom onset had better survival than those with a symptom to treatment time greater than six months (5-year overall survival rate of 77.0% versus 59.7%, respectively; $p = 0.04$) [9]. The authors noted that 18 of 100 patients in the study presented with metastatic disease, and those 18 patients were excluded from overall survival analysis [9]. However, it is important to note that patients with well-differentiated liposarcomas and dermatofibrosarcoma protuberance were excluded from their study because of the good prognosis associated with those histologic types [9]. Thus the results of their study may not be entirely comparable to studies, such as our study, that included all histologic types in the analysis. Finally, other authors have reported that prolonged symptom duration may be associated with improved survival [13]. For example, Saintha et al. analyzed patients with STS and found that a longer duration of symptoms had a positive effect on survival (HR = 0.998; 95% CI: 0.997–0.999) [13]. Although patients with epithelioid and synovial sarcoma had a longer duration of symptoms compared to patients with other histologic types of sarcoma, the authors did not specifically assess the association between symptom duration and survival while accounting for histologic type of sarcoma [13]. Further research into this topic is warranted.

The equivalent survival between those who experienced the specified symptom duration and those who did not might be because patients who experienced long symptom duration had lower grade tumors and lower stage disease than patients who did not experience long symptom duration. Evidence supporting the association between lower grade tumors and greater symptom duration has been published. Nandra et al. found that patients with high-grade STS had a lower median duration of symptoms prior to diagnosis compared to patients with low-grade tumors (20 weeks versus 44 weeks, respectively; $p < 0.05$) [14]. Similarly, Saithna et al. found that patients with high-grade STS had a significantly lower duration of symptoms compared to patients with low-grade soft tissue sarcoma (mean symptom duration of 45.8 weeks versus 107.2 weeks) [13]. The results of the current study and the aforementioned literature suggest that patients who tolerate prolonged symptom duration are able to do so because they have lower grade tumors and lower stage disease. This allows for equivalent survival compared to patients who did not experience prolonged symptom duration based upon the biology of the sarcoma.

Although grade and stage appeared to be associated with symptom duration, we found no differences in the histological type of tumor between patients who experienced the specified symptom durations and those who did not. Prior research has shown that certain histologic types of STS are associated with longer symptom duration [12,13]. Urakawa et al. found that patients with leiomyosarcoma and synovial sarcoma had the longest time intervals between symptom onset and visitation with a specialist (median time 30.8 and 36.0 months, respectively), while patients with Ewing sarcoma had the shortest time interval (median time 2.0 months) [12]. In addition, Saithna et al. found that patients with STS that was of the epithelioid or synovial type had a significantly greater symptom duration compared to patients with all other histologic types (mean duration 125.4 weeks versus 65.6 weeks) [13].

Finally, we found no difference in median tumor size between patients who experienced the specified symptom durations and those who did not. However, a greater proportion of patients who experienced a symptom duration ≥ 2 months had tumors greater than 50 mm compared to those who did not, while the converse was true when symptom duration was at least 12 months, wherein a greater proportion of patients who experienced a long symptom duration had tumors smaller than 50 mm compared to those who did not. Prior research has found no significant association between tumor size and symptom duration [12,14]. Nandra et al. found that the median duration of symptoms among patients with soft tissue and bone sarcomas was the same for patients with tumors smaller than the median tumor size and patients with tumors greater than the median (median duration of symptoms was 26 weeks for both groups) [14]. Similarly, Urakawa et al. found no difference in the median time from symptom onset to visitation with a specialist between patients with tumors less than 5 cm and those with tumors greater than 5 cm (median time 7.1 and 6.0 months, respectively; $p = 0.45$) [12].

This study had some limitations. It had a relatively small sample size and included tumors of multiple histologic types (liposarcoma, leiomyosarcoma, et cetera). This study might not have sufficient power to detect all differences that existed between patients who experienced the specified symptom duration and those who did not. A larger, perhaps multi-institutional study, might allow for such differences to be better evaluated. Also, this study was retrospective and data was obtained via medical record review. Thus some information was missing or unknown, which may impact the accuracy of the analyses performed. Furthermore, recall bias may have affected the results because the details of symptom onset and duration were largely obtained from self-report detailed in the medical record.

However, this study had several advantages. It used data collected from a comprehensive cancer center to clearly define how the duration of time between symptom onset and diagnosis of STS of the extremity impacted outcomes. This study provides evidence to support the notion that prolonged symptom duration, and thus a prolonged time period until treatment initiation, does not necessarily portend poorer survival for patients with low-grade and low-stage STS of the extremity. Further research to investigate the reasons for prolonged symptom duration, particularly in patients with high-grade and high-stage disease, while accounting for histologic type of tumor, is warranted. Addressing the reasons for prolonged symptom duration in such patients may lead to improvements in patient outcomes.

5. Conclusion

Patients who tolerated a prolonged symptom duration had less advanced disease, which appeared to permit equivalent outcomes. Reasons for prolonged symptom duration and the role that histologic type of tumor plays in the association between symptom duration and survival should be further investigated.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.05.016.

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