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Soft tissue sarcoma of the hand: Is unplanned excision a problem?

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ABSTRACT

Background: Soft tissue sarcoma (STS) of the hand are prone to unplanned excisions, altering oncologic outcomes. The aim of this study is to compare STS of the hand with initial treatment at an oncology center versus those initially treated at a non-oncology center. Additionally, we evaluated what factors were associated with oncologic outcomes.

Methods: We retrospectively identified patients with a STS of the hand using ICD-9 codes along with an institutional oncologic database. We included all adult patients with a non-metastatic STS of the hand ($n = 64$) with a median follow up of 4.0 years (IQR: 1.7–10.0).

Results: Eight-three percent ($n = 53$) of tumors had an unplanned excision, of which one was treated at the oncology center. Patients treated primarily at an oncology center were older (57.6 vs. 43.6 years), had fewer operations and tended to have a larger tumors (median 4.7 cm vs. 3.0 cm) compared to those initially treated at a non-oncology center. The 5-year survival for patients treated at an oncology center was 60% compared to 89% in those initially treated at a non-oncology center. Worse disease-free survival was associated with positive final margins and subfascial tumors.

Conclusion: Tumors with primary treatment at an oncology center were larger and presented in older patients, having worse overall survival compared to those initially treated at a non-oncology center. Initial treatment at a non-oncology center did not influence the oncologic outcomes, but lead to more re-excisions and amputations. Final tumor margins and tumor depth determined oncologic outcomes.

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Introduction

Soft tissue sarcomas (STS) occur in 2.2 per 1,000,000 persons per year [1], 2–9% [2,3] of which occur in the hand. There are current clinical recommendations stating that STS should be treated in a multidisciplinary fashion in a cancer center; however, because problems of recognition due to their low prevalence and incidence, hand sarcomas may be excised without oncologic workup, and frequently these surgeries are an “unplanned excision” (UE) [4–10].

Unplanned excisions at a non-specialized oncology centers

(non-oncology center) have been reported in up to 18–75% (average: 43%) of soft tissue sarcomas [2,5,11–26]. Following an UE with positive or ambiguous margins, a re-excision to achieve negative margins is advised. However, re-excision can be challenging in the hand because of the effect of larger resections on hand function [5,11–13,16,21,23–27]. Various studies have documented better [23], worse [19,20,24,28] and similar [2,5,14,16] oncologic outcomes in the setting of an unplanned excision versus a planned excision. It is unclear whether soft tissue sarcomas of the hand are different than STS in other anatomic locations [3,29–31]. Due to these potential differences in tumor biology, it is unclear whether principles of STS management apply to the hand.

The primary aim of this study was to compare patients with a soft tissue sarcoma of the hand with initial treatment at an oncology center to those initially treated at a non-oncology center and subsequently referred to our center. Additional aims were to

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evaluate the factors associated with tumor recurrence, metastasis, disease-free survival and overall survival in these patients.

Materials and methods

After Institutional Board approval, we used International Classification of Diseases 9th Revision codes for tumors of the upper extremity: “170.4”, “170.5”, “170.9”, “239.2”, “198.5”, “239.9”, “203.0”, “202.8”, “171.2”, “171.8”, “171.9”, “176.1”, “176.8” and “176.9” to identify patients with an upper extremity tumor ($n = 15,278$) from 1992 to 2015. To identify patients with a hand tumor, we performed a text search in the pathology reports matching “hand” and “finger” along with common misspellings and synonyms using STATA 13.0 (StataCorp LP, College Station, Texas, USA) ($n = 3267$). Additionally, we identified patients using an orthopaedic oncology registry that predates the institutional database, to identify patients treated from 1971 to 1992 [32]. We included all adult patients (18 years of age and older) with a non-metastatic soft tissue sarcoma (STS) of the hand that was histologically confirmed ($n = 95$) (Supplement 1). We excluded patients that were only seen for consultation ($n = 20$), had initial adequate oncologic treatment at an outside hospital ($n = 4$) or rejected standard surgical treatment ($n = 1$). Six patients were excluded because of insufficient data in the charts. At total of 64 patients with a STS of the hand were included in the analyses.

To collect information on patient characteristics, tumor characteristics, tumor treatment and oncologic outcomes we performed a manual chart review. Tumor size was retrieved from the medical charts, pathology reports or radiology reports and was retrievable in 39 of the tumors (61%). Definite histologic diagnosis and tumor grade was determined by musculoskeletal pathologists, tumor grade was reported for 59 of the 64 (92%). Radiologic imaging or operative reports were used to identify the tumor depth, either subcutaneous (suprafascial) or subfascial, and was retrievable in 57 of the 64 tumors (89%). Final histological margins were described in 61 of 64 patients (95%). Data was only missing for tumors treated initially at a non-oncology center.

Based on a combination of histologic grade and histologic diagnosis, we grouped tumors into low grade (7 acral myxoinflammatory fibroblastic sarcoma; 2 low grade fibrosarcoma; 1 angiomatoid fibrous histiocytoma; 1 dermatofibrosarcoma protuberans; 1 low grade epithelioid malignant schwannoma; 1 granular cell sarcoma; 1 low grade malignant solitary fibrous tumor; 1 low grade malignant peripheral nerve sheath tumor; 1 low grade spindle cell sarcoma) and high grade (13 epithelioid sarcoma; 10 synovial sarcoma; 6 clear cell carcinoma; 6 undifferentiated pleomorphic sarcoma; 4 high grade fibrosarcoma; 3 leiomyosarcoma; 1 high grade myxoinflammatory sarcoma; 1 high grade malignant peripheral nerve sheath tumor; 1 malignant tenosynovial giant cell tumor).

An unplanned excision was defined as surgery that was performed without following oncologic principles of treatment. Disease-free survival was the time from treatment at the oncology center to the time of local tumor recurrence or distant metastasis. We considered patients to be deceased by the underlying tumor if patients had been reported deceased in the presence of a metastasis at final follow up or if no other cause of death was reported. Overall survival was determined as the time from treatment at the oncology center to time of death due to the tumor or last available follow-up.

Statistical analysis

Continuous variables were presented as median and interquartile range (IQR) and categorical variables were presented as

count and proportion. To compare the differences in patient age, tumor location, tumor size, tumor depth, tumor grade, unplanned excision, final margin status, number of operations, radiotherapy, recurrence, soft tissue reconstruction and level of amputation of tumors treated at a non-oncology hospital or an oncology center, we used the Mann-Whitney *U* test or Fisher's Exact test. A correlation between age and tumor size was determined using a Spearman's rank correlation coefficient.

To evaluate the factors associated with local recurrence, metastasis, disease free survival and overall survival, we used a Cox's proportional hazards model. To address the missing data on tumor size, tumor grade, tumor depth and final histologic margin in patients initially treated at a non-oncology center we performed a multiple imputation using chained equations, assuming the data were missing at random [33,34]. We imputed 100 values per missing data-point and used predictive mean matching to impute tumor size; logistic regression to impute tumor depth and final histologic margin and ordered logistic regression to impute values for tumor grade. We used multiple imputation estimates to calculate hazard ratios, 95% confidence intervals, standard errors and *p*-values for these explanatory variables by simulating the models 1000 times.

To mitigate confounding effect all variables with a $p < 0.10$ in bivariate analysis along with final margin status, tumor depth, tumor size and histologic grade were entered in a multivariable Cox survival regression model. All statistics tests were performed using STATA 13.0 (StataCorp LP, College Station, Texas, USA).

Results

Study population

We included 64 patients with a STS of the hand with a median age of 46.1 years (IQR: 33.4–60.6) and a median follow up of 4.0 years (IQR: 1.7–10.0) (Table 1). Tumors were located at the level of the metacarpals in 41 of the patients (64%), followed by the phalanges in 18 (28%) and carpal extension in five (7.8%). Pain or tenderness was reported by 13 patients (33%), five patients (13%) reported paresthesias or dysesthesias and only one patient (2.5%) had night pain. The median tumor size was 3.0 cm (IQR: 1.6–5.0) and they were mostly subcutaneous (suprafascial) ($n = 41$, 73%). The most common tumors were epithelioid sarcoma ($n = 13$, 20%), synovial sarcoma ($n = 10$, 16%), undifferentiated pleomorphic sarcoma ($n = 8$, 13%), myxoinflammatory sarcoma ($n = 8$, 13%) and fibrosarcoma ($n = 7$, 11%).

Treatment location

Of the hand STS, 81% ($n = 52$) were primarily treated at a non-oncology center of which all were unplanned excisions. One patient with a low grade fibrosarcoma had an unplanned excision at the oncology center that was followed by tumor bed excision and brachytherapy. One patient had an amputation at the level of the PIP joint at a non-oncology center and a subsequent metacarpal amputation at the oncology center. The remainder of the patients underwent non-oncological excisions ($n = 44$), or other non-oncologic treatments including: incision ($n = 3$), synovectomy ($n = 2$), exploration ($n = 1$) or shave biopsy ($n = 1$). Six patients had aspiration of the tumor prior to excision because a ganglion cyst was suspected. The median time to referral was 3.2 months (range: 0.6–13.5).

Of the patients with an unplanned excision at a non-oncology center, initial margins were positive in 40 of the 41 (98%) patients where this information was available. Six patients that had an UE had a positive final margin after final treatment at the oncology

Table 1
Patient demographics.

Age, median (IQR)	46.1 (33.4–60.6)
Location, n(%)	
Phalangeal	18 (28)
Metacarpal	41 (64)
Carpal extension	5 (7.8)
Symptoms, n(%)*	
Tenderness/pain	13 (33)
Increasing mass	10 (25)
No pain or constitutional symptoms	6 (15)
Paresthesia/dysesthesia	5 (13)
Ulceration	3 (7.5)
Other	2 (5.0)
Night pain	1 (2.5)
Histologic grade, n(%)**	
1	16 (27)
2	20 (34)
3	23 (39)
Size, cm, median (IQR)***	3.0 (1.6–5.0)
Tumor histology, n(%)	
Epithelioid sarcoma	13 (20)
Synovial sarcoma	10 (16)
Undifferentiated pleomorphic sarcoma	8 (13)
Myxoinflammatory sarcoma	8 (13)
Fibrosarcoma	7 (11)
Clear cell sarcoma	6 (9.4)
Leiomyosarcoma	3 (4.7)
MPNST	2 (3.1)
Dermatofibrosarcoma protuberans	1 (1.6)
Angiomatoid fibrous histiocytoma	1 (1.6)
Epithelioid malignant schwannoma	1 (1.6)
Granular cell sarcoma	1 (1.6)
Liposarcoma	1 (1.6)
Malignant solitary fibrous tumor	1 (1.6)
Malignant synovial GCT	1 (1.6)
Spindle cell sarcoma	1 (1.6)

* missing in 24 patients.

**missing in 5 patients.

***missing in 25 patients.

center. Of these six patients, two underwent amputation (one in combination with radiotherapy), two patients received adjuvant radiotherapy (one in combination with chemotherapy), one patient rejected any further treatment and for one patient it was unknown. Three (25%) of the patients treated at the oncology center had positive margins, two after an excision and one after amputation. The two tumors that were excised received adjuvant radiotherapy and the other patient received adjuvant chemotherapy after amputation.

After referral to the oncology center, 31 patients (60%) underwent re-excision, 20 patients underwent subsequent amputation (39%) and one patient with a low-grade liposarcoma was monitored without further treatment. Of the patients that underwent re-excision, residual tumor was histologically confirmed in 26 patients (51%).

Patients treated at an oncology center were older than those initially treated at a non-oncology center, 57.6 years (IQR: 46.6–72.5) versus 43.6 years (32.9–57.2), $p = 0.044$ (Table 2). Additionally, larger tumors appeared to be treated initially at the oncology center compared to those primarily treated at a non-oncology center without statistical significance; 4.7 cm (IQR: 1.9–5.5) versus 3.0 cm (1.5–4.0) ($p = 0.069$). There was a positive correlation between patient age and tumor size ($\rho = 0.43$, $p = 0.0061$). Tumors that were referred to the oncology center had a larger number of surgeries in comparison to those treated initially at an oncology center ($p = 0.001$). It was observed that there were more phalangeal and single ray amputations in patients that had initial treatment at a non-oncology center without statistical significance, when excluding tumors with carpal

extension (Fig. 1). There was no difference in radiotherapeutic or chemotherapeutic treatment in either group of patients.

Oncologic outcome

Recurrence

The overall recurrence rate was 13% ($n = 8$) and occurred in epithelioid sarcoma ($n = 2$), fibrosarcoma ($n = 2$), clear soft tissue part cell sarcoma ($n = 2$), synovial sarcoma ($n = 1$) and undifferentiated pleomorphic sarcoma ($n = 1$) at a median of 1.1 years (IQR: 0.32–2.4).

Metastasis

Metastasis were confirmed in 15 patients at a median of 1.4 years (IQR: 0.45–3.0) and were seen in synovial sarcoma ($n = 4$), epithelioid sarcoma ($n = 2$), clear cell sarcoma of soft tissue ($n = 2$), undifferentiated pleomorphic sarcoma ($n = 2$), spindle cell sarcoma ($n = 1$), malignant solitary fibrous tumor ($n = 1$), high grade fibrosarcoma ($n = 1$), malignant peripheral nerve sheath tumor ($n = 1$) and leiomyosarcoma ($n = 1$). Metastasis occurred to the lungs ($n = 8$), the axillary lymph nodes ($n = 4$), the forearm and chest ($n = 1$), the epitrochlear lymph nodes ($n = 1$), and the upper arm ($n = 1$). Positive final margin was independently associated with the development of metastasis (HR: 5.4, 95% CI: 1.3–22.5, $p = 0.022$) (Table 3, Supplement 2 & Fig. 2).

Disease-free survival

Overall 19 patients had recurrence of disease either locally or as a metastasis. The 1-year, 5-year and 10-year disease-free survival was 85%, 69% and 66% respectively. In multivariable Cox's regression, a positive margin (HR: 3.9, 95% CI: 1.0–14.8, $p = 0.048$) was independently associated with worse disease-free survival (Fig. 2).

Overall survival

During the time-frame of this study eight patients had deceased due to the STS. These patients had a synovial sarcoma ($n = 2$), fibrosarcoma ($n = 1$), undifferentiated pleomorphic sarcoma ($n = 1$), malignant peripheral nerve sheath tumor ($n = 1$), spindle cell sarcoma ($n = 1$) or malignant solitary fibrous tumor ($n = 1$). The 1-year survival was 100% and the 5- and 10-year survival were both 83%.

Patients treated initially at an oncology center had worse overall survival, 60% 5-years survival, compared to patients treated initially at non-oncology center, 89% 5-year survival ($p = 0.021$) (Table 4 & Fig. 2). However, there was no association when multivariable Cox regression was performed with corrections for tumor size (HR: 1.5, 95% CI: 0.96–2.4, $p = 0.078$).

Discussion

Sixty-four soft tissue sarcomas of the hand that were treated at our institution were retrospectively identified. Of these tumors 81% underwent initial surgery, mostly unplanned excisions, at a non-oncology center. When comparing tumors that were initially treated at an oncology center to those initially treated at a non-oncology center we noted that (1) patients were older in the oncology center group (2) tumors tended to be larger in the oncology center group and (3) patients had worse survival if treated initially at an oncology center. Other oncologic outcomes were similar amongst both groups; however, this was at the cost of more operations and phalangeal amputations in patients that were

Table 2
Comparison of tumors treated at different centers.

	Initial treatment		P-value
	Oncology center (n = 12)	Referring center (n = 52)	
Age, median (IQR)	57.6 (46.6–72.5)	43.6 (32.9–57.2)	0.044*
Location, n (%)			0.21**
Phalangeal	1 (8.3)	17 (33)	
Metacarpal	10 (83)	31 (60)	
Carpal extension	1 (8.3)	4 (7.7)	
Tumor Size, cm, median (IQR)^a	4.7 (1.9–5.5)	3 (1.5–4.0)	0.069***
Depth, n(%)^b			0.46**
Subcutaneous	7 (64)	34 (76)	
Subfascial	4 (36)	11 (24)	
Histologic grade, n(%)^c			0.85**
1	3 (25)	13 (28)	
2	5 (42)	15 (32)	
3	4 (33)	19 (40)	
Tumor grade, n(%)			>0.99**
Low-grade	3 (25)	13 (27)	
High-grade	9 (75)	36 (74)	
Unplanned excision, n(%)	1 (8.3)	52 (100)	<0.001**
Final margin, n(%)^d			
Positive	3 (25)	6 (12)	0.36**
Negative	9 (75)	43 (88)	
Number of operations, n (%)			<0.001**
1	9 (75)	2 (3.9)	
2	3 (25)	42 (81)	
3	0	8 (15)	
Soft tissue reconstruction, n(%)	4 (33)	15 (29)	0.74**
Radiotherapy, n(%)	8 (67)	30 (58)	0.75**
Chemotherapy, n(%)	1 (8.3)	3 (5.8)	0.57**

* Using Mann-Whitney U test.
 ** Using Fisher's Exact test.
 *** Using Student's t-test.
 Significant values (p<0.05) printed in bold.
^a Missing in 25 patients.
^b Missing in 7 patients.
^c Missing in 5 patients.
^d Missing in 3 patients.

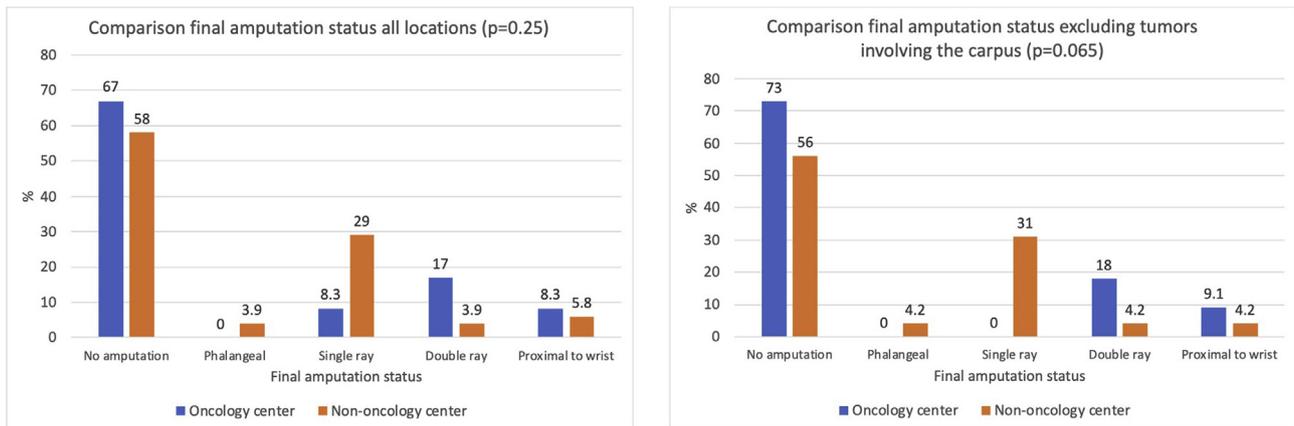


Fig. 1. Final amputation status in patients treated initially at a non-oncology center or oncology center (A) all locations (B) excluding tumors extending to the carpalia.

Table 3
Multivariable Cox regression using multiple imputation estimation.

	Recurrence			Metastasis			Disease free survival			Overall survival		
	HR (SE)	95% CI	p-value	HR (SE)	95% CI	p-value	HR (SE)	95% CI	p-value	HR (SE)	95% CI	p-value
Age	*	*	*	*	*	*	1.0 (0.015)	[0.99, 1.0]	0.29	1.0 (0.023)	[0.98, 1.1]	0.35
Tumor size	1.1 (0.23)	[0.72, 1.6]	0.70	1.3 (0.22)	[0.90, 1.8]	0.17	1.2 (0.19)	[0.86, 1.6]	0.30	1.5 (0.44)	[0.85, 2.7]	0.16
Final margins: positive	5.5 (5.8)	[0.68, 43.7]	0.11	5.4 (3.9)	[1.3, 22.5]	0.022	3.9 (2.6)	[1.0, 14.8]	0.048	0.77 (0.92)	[0.075, 8.0]	0.83
Depth: subfascial	2.3 (1.9)	[0.43, 11.9]	0.34	2.7 (1.6)	[0.84, 8.5]	0.096	2.6 (1.4)	[0.92, 7.3]	0.073	2.1 (1.7)	[0.44, 10.3]	0.34
Histologic grade: high grade	3.2 (2.3)	[0.81, 12.9]	0.095	1.7 (0.81)	[0.69, 4.3]	0.24	2.0 (0.82)	[0.86, 4.5]	0.11	0.58 (0.34)	[0.18, 1.8]	0.35

* Age p > 0.10.
 Significant values (p<0.05) printed in bold.

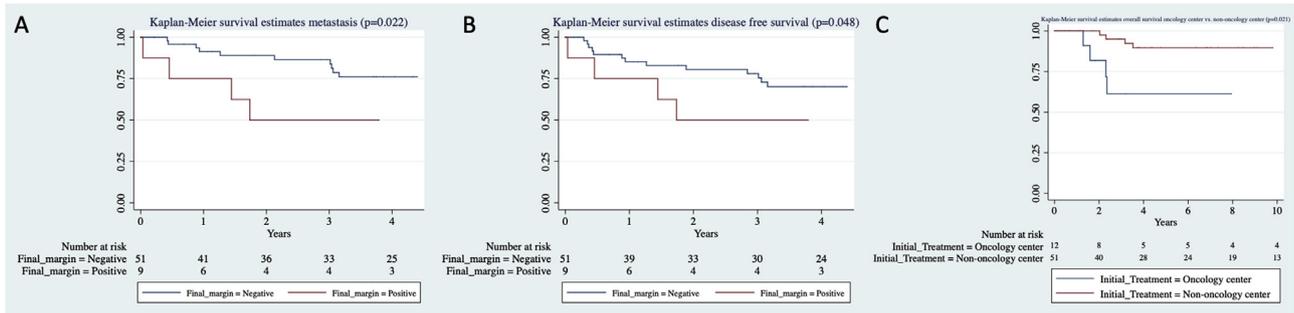


Fig. 2. Kaplan-Meier survival estimate for (A) metastasis depending on final margin status. (B) disease-free survival depending on final margin status (C) overall survival.

Table 4
Cox regression for oncologic outcomes oncology center vs. non-oncology center.

	HR (SE)	95% CI	p-value
Recurrence	0.62 (0.51)	[0.12, 3.1]	0.56
Metastasis	0.43 (0.24)	[0.15, 1.3]	0.13
Disease free survival	0.44 (0.22)	[0.17, 1.2]	0.10
Overall survival	0.20 (0.14)	[0.05, 0.78]	0.021

Multivariable Cox regression for overall survival			
	HR (SE)	95% CI	p-value
Overall survival			
Treatment non-oncology center	0.50 (0.42)	[0.096, 2.6]	0.40
Tumor size	1.5 (0.35)	[0.96, 2.4]	0.078

Significant values (p<0.05) printed in bold.

treated initially at a non-oncology center. Positive margins showed an association, and subfascial tumors presented a higher risk for metastasis.

The results of this study need to be interpreted in the lights of its strengths and limitations. First, the retrospective nature and the time-span over which patients were identified increases loss to follow-up. Nonetheless, due to the nature of our institution patients with a musculoskeletal malignancy rarely seek treatment elsewhere. In addition, to attain significant numbers in this type of rare conditions, a long study period is necessary. Second, there may be referral bias, which can be seen in the difference in tumor size and age of the patients treated initially at both centers. This referral pattern has also been reported in other high-volume centers [5,23,35]. Third, no standardized treatment protocol was used in patients, besides that all patients with an unplanned excision were advised to undergo re-excision, in all but one: a low grade liposarcoma that was monitored. Additionally, there was substantial missing data of the tumor sizes due to many unplanned excisions at non-oncology centers, but we aimed to address this by using multiple imputation by chained equations. This allows values to be imputed based on the missing variables distribution. Lastly, the tumor histology varied in the patients treated initially at an oncology center and non-oncology center. To account for this, we grouped the tumors into high and low grade and found this to be comparable in both groups.

Most of the STS in the hand (81%) had an unplanned excision prior to presenting at our oncology center. Referral to a specialized oncology center has been recommended for soft tissue masses that are >5 cm (or >3 cm in the hand as some have suggested), subfascial, cause pain, or are rapidly growing [36–39]. The high rate of UEs is probably due a lower suspicion for a malignancy because 72% of the tumors were smaller than 5 cm. This is similar to the 75% reported by Puhaindran et al. in their series of 53 hand sarcoma [18]. As previously reported, we found that tumors treated at a non-oncology center were smaller and patients were younger than those treated at an oncology center [5,11,12,14,16,22,23,26]. It has

been accepted that treatment at a non-specialized oncology center leads to wider resections, altered treatments due to inadequate biopsies along with more histologic misdiagnosis, emphasizing the importance of multidisciplinary oncologic treatment at a specialized center [6].

In this study, we identified that overall survival was worse in patients that were treated initially at the oncology center. These findings are likely a reflection of a larger tumor size in that population, which has been shown to decrease survival [2,5,19]. Lewis et al. described similar findings in 1092 STS of all locations [23]. They attributed this to two things (1) lower threshold to refer larger and aggressive tumors and (2) that re-excisions are often more radical, potentially excising tumor cells extending outside of the pseudocapsule. Specifically for sarcoma of the hand, Pradhan et al. did not identify that previous treatment influenced overall survival in 63 sarcoma of the hand [2]. These findings are supported by two large studies on STS of all anatomic locations [5,16]. On the other hand, other studies have reported worse oncologic outcomes after unplanned excision, especially in high-grade or larger tumors [14,19,22,25]. This may be explained by incomplete excision of residual disease after unplanned excisions. The absence of this finding in the hand may be because re-excision in the form of an amputation substantially increases radicality. In a larger study, it is possible that subfascial tumors (HR: 2.6, 95% CI: 0.92–7.3, p=0.073) and high-grade tumors (HR: 2.0, 95% CI: 0.86–4.5, p=0.11) may have an association with disease-free survival. The same may be true for higher histologic grade and recurrence (HR: 3.2, 95% CI: 0.81–12.9, p=0.095) and the development of metastasis in subfascial tumors (HR: 2.7, 95% CI: 0.84–8.5, p=0.096).

Residual disease was present in 51% of the patients after unplanned excision. To ascertain the absence of residual disease re-excision is recommended within 12 weeks [5,24]. However, due to lacking diagnostic work-up, sub-optimal surgical approaches, distant contamination and unclear resection margins, planning of the re-excision is challenging [14,25]. Additionally, intra-operative scar tissue and the absence of anatomic boundaries make it difficult to identify adequate resection margins for negative margins [7,14,19]. This is especially troublesome in the hand because of the close vicinity of vital structures. It is also notable that there was a higher rate of phalangeal amputations after treatment at a non-oncology center. Limb sparing surgery is uncommon in hand sarcoma treatment because of the need for early rehabilitation to restore hand function, and multiple surgeries increase problems with stiffness and loss of hand function.

As was also seen in this study, unplanned excisions lead to more surgeries to achieve same oncologic outcomes. The delayed referral at a median of 3.2 months, may also have a negative impact on outcomes. It is unclear whether delayed presentations have a relationship to triage or referral center capacity. It is possible that in non-oncology center treatment, an unplanned excision was

curative in some cases, and late re-excision improved survival of patients with residual disease. Unplanned excision increases the need for post-operative radiotherapy, which has been shown to decrease hand function [5,18,20]. Additionally, due to the extent of re-excisions, soft tissue coverage is often necessary, this was not the case in our series [5,11,20,24,26]. Lastly, healthcare costs increase due to additional surgeries, especially because re-excisions are often more expensive than primary excision [40].

The recurrence rate of hand sarcoma is 6–32% [2,17,18,41] and is associated with positive surgical margin [2] and limb sparing/salvage surgery [42]. In this series, recurrences appeared more often in tumors of higher grade, which has been described for sarcoma of other parts [15,24,43]. Twenty-three percent of the patients developed metastasis and this was associated with positive margins and was more common in high grade tumors, similar to earlier reports [2,41]. Our findings suggest that surgical radicality and tumor biology are the main drivers of oncologic outcomes, and that re-excisions can ameliorate the negative effect of an unplanned excision. Nonetheless, it may well be that oncologic outcomes of STS treated initially at a non-oncology center could have been superior if initial treatment was at an oncology center.

Conclusions

Due to the referral bias of larger and more aggressive tumors to an oncology center these patients had worse overall survival. Initial treatment at a non-oncology center had similar oncologic outcomes as those treated at an oncology center at the cost of more surgeries, especially amputations highlighting the challenge of disease control after unplanned excision. Oncologic outcomes are determined by the nature of the surgical margin (appropriate oncologic treatment), tumor grade, and tumor depth in STS of the hand. The question regarding “When to refer a mass of the hand to an oncology center?” remains unanswered but our recommendation would be when the tumor is larger than 3 cm, or the comprehensive care is not available at the treating institution. At least patients should be given the option to decide or opt for a tertiary care center.

Declaration of interest

None

Conflict of interest statement

The authors certify that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejso.2019.03.024>.

References

- [1] Alderman AK, Myra Kim H, Kotsis SV, Chung KC. Upper-extremity sarcomas in the United States: analysis of the surveillance, epidemiology, and end results database, 1973–1998. *J Hand Surg Am* 2003;28:511–8. <https://doi.org/10.1053/jhsu.2003.50076>.
- [2] Pradhan A, Cheung YC, Grimer RJ, Peake D, Al-Muderis OA, Thomas JM, et al. Soft-tissue sarcomas of the hand. *J Bone Joint Surg Br* 2008;90:209–14. <https://doi.org/10.1302/0301-620X.90B2.19601>.
- [3] Gustafson P, Arner M. Soft tissue sarcoma of the upper extremity: descriptive data and outcome in a population-based series of 108 adult patients. *J Hand Surg Am* 1999;24:668–74. <https://doi.org/10.1053/jhsu.1999.0668>.
- [4] Giuliano AE, Eilber FR. The rationale for planned reoperation after unplanned total excision of soft-tissue sarcomas. *J Clin Oncol* 1985;3:1344–8. <https://doi.org/10.1200/JCO.1985.3.10.1344>.
- [5] Smolle MA, Tunn PU, Goldenitsch E, Posch F, Szkandera J, Bergovec M, et al. The prognostic impact of unplanned excisions in a cohort of 728 soft tissue sarcoma patients: a multicentre study. *Ann Surg Oncol* 2017;24:1596–605. <https://doi.org/10.1245/s10434-017-5776-8>.
- [6] Mankin HJF, Mankin CJLST, Simon MA. The hazards of the biopsy, revisited for the members of the musculoskeletal tumor society. *J Bone Jt Surg* 1996;78:656–63. <https://doi.org/10.1097/01241398-199611000-00060>.
- [7] Noria S, Davis A, Kandel R, Levesque J, O’Sullivan B, Wunder J, et al. Residual disease following unplanned excision of soft-tissue sarcoma of an extremity. *J Bone Joint Surg Am* 1996;78:650–5.
- [8] Paszat L, O’Sullivan B, Bell R, Bramwell V, Groome P, Mackillop W, et al. Processes and outcomes of care for soft tissue sarcoma of the extremities. *Sarcoma* 2002;6:19–26. <https://doi.org/10.1080/1357714022012752>.
- [9] Ferguson PC. Surgical considerations for management of distal extremity soft tissue sarcomas. *Curr Opin Oncol* 2005;17:366–9. <https://doi.org/10.1097/01.cco.0000166651.38417.c8>.
- [10] Nystrom L, Reimer N, Reith J, Dang L, Zlotecki R, Scarborough M, et al. Management of soft tissue sarcoma. *Sci World J* 2013;2013:852462. <https://doi.org/10.1007/978-1-4614-5004-7>.
- [11] Morii T, Aoyagi T, Tajima T, Yoshiyama A, Ichimura S, Mochizuki K. Unplanned resection of a soft tissue sarcoma: clinical characteristics and impact on oncological and functional outcomes. *J Orthop Sci* 2015;20:373–9. <https://doi.org/10.1007/s00776-014-0689-x>.
- [12] Koulaxouzidis G, Schwarzkopf E, Bannasch H, Stark GB. Is revisional surgery mandatory when an unexpected sarcoma diagnosis is made following primary surgery? *World J Surg Oncol* 2015;13:1–10. <https://doi.org/10.1186/s12957-015-0719-y>.
- [13] Rehders A, Stoecklein NH, Poremba C, Alexander A, Knoefel WT, Peiper M. Reexcision of soft tissue sarcoma: sufficient local control but increased rate of metastasis. *World J Surg* 2009;33:2599–605. <https://doi.org/10.1007/s00268-009-0262-5>.
- [14] Bianchi G, Sambri A, Cammelli S, Galuppi A, Cortesi A, Righi A, et al. Impact of residual disease after “unplanned excision” of primary localized adult soft tissue sarcoma of the extremities: evaluation of 452 cases at a single institution. *Musculoskelet Surg* 2017;101:243–8. <https://doi.org/10.1007/s12306-017-0475-y>.
- [15] Chandrasekar CR, Wafa H, Grimer RJ, Carter SR, Tillman RM, Abudu A. The effect of an unplanned excision of a soft-tissue sarcoma on prognosis. *J Bone Jt Surg Br* 2008;90:203–8. <https://doi.org/10.1302/0301-620X.90B2.19760>.
- [16] Fiore M, Casali PG, Miceli R, Mariani L, Bertulli R, Lozza L, et al. Prognostic effect of re-excision in adult soft tissue sarcoma of the extremity. *Ann Surg Oncol* 2006;13:110–7. <https://doi.org/10.1245/ASO.2006.03.030>.
- [17] Bray PW, Bell RS, Bowen CVA, Davis A, Sullivan BO. Sarcoma and limb salvage. *J Hand Surg Am* 1997;495–503.
- [18] Puhaindran ME, Rohde RS, Chou J, Morris CD, Athanasian EA. Clinical outcomes for patients with soft tissue sarcoma of the hand. *Cancer* 2011;117:175–9. <https://doi.org/10.1002/cncr.25593>.
- [19] Rougraff BT, Davis K, Cudahy T. The impact of previous surgical manipulation of subcutaneous sarcoma on oncologic outcome. *Clin Orthop Relat Res* 2005;85–91. <https://doi.org/10.1097/00003086-200509000-00016>.
- [20] Thacker MM, Potter BK, Pitcher JD, Temple HT. Soft tissue sarcomas of the foot and ankle: impact of unplanned excision, limb salvage, and multimodality therapy. *Foot Ankle Int* 2008;29:690–8. <https://doi.org/10.3113/FAI.2008.0690>.
- [21] Lin PP, Guzel VB, Pisters PWT, Zagars GK, Weber KL, Feig BW, et al. Surgical management of soft tissue sarcomas of the hand and foot. *Cancer* 2002;95:852–61. <https://doi.org/10.1002/cncr.10750>.
- [22] Potter BK, Adams SC, Pitcher JD, Temple HT. Local recurrence of disease after unplanned excisions of high-grade soft tissue sarcomas. *Clin Orthop Relat Res* 2008;466:3093–100. <https://doi.org/10.1007/s11999-008-0529-4>.
- [23] Lewis JJ, Leung D, Espat J, Woodruff JM, Brennan MF. Effect of reexcision in extremity soft tissue sarcoma. *Ann Surg* 2000;231:655–63. <https://doi.org/10.1097/0000658-200005000-00005>.
- [24] Funovics PT, Vaselec S, Panotopoulos J, Kotz RI, Dominkus M. The impact of re-excision of inadequately resected soft tissue sarcomas on surgical therapy, results, and prognosis: a single institution experience with 682 patients. *J Surg Oncol* 2010;102:626–33. <https://doi.org/10.1002/jso.21639>.
- [25] Qureshi YA, Huddy JR, Miller JD, Strauss DC, Thomas JM, Hayes AJ. Unplanned excision of soft tissue sarcoma results in increased rates of local recurrence

- despite full further oncological treatment. *Ann Surg Oncol* 2012;19:871–7. <https://doi.org/10.1245/s10434-011-1876-z>.
- [26] Arai E, Nishida Y, Tsukushi S, Wasa J, Ishiguro N. Clinical and treatment outcomes of planned and unplanned excisions of soft tissue sarcomas. *Clin Orthop Relat Res* 2010;468:3028–34. <https://doi.org/10.1007/s11999-010-1392-7>.
- [27] Han I, Kang HG, Kang SC, Choi JR, Kim HS. Does delayed reexcision affect outcome after unplanned excision for soft tissue sarcoma? *Clin Orthop Relat Res* 2011;469:877–83. <https://doi.org/10.1007/s11999-010-1642-8>.
- [28] Qureshi SS, Puri A, Agarwal M, Desai S, Jambhekar N. Recurrent giant cell tumor of bone with simultaneous regional lymph node and pulmonary metastases. *Skeletal Radiol* 2005;34:225–8. <https://doi.org/10.1007/s00256-004-0824-4>.
- [29] Brien LW, Terek RM, Geer RJ, Caldwell G, Brennan MF, Healey JH. Treatment of soft-tissue sarcomas of the hand. *J Bone Jt Surg - Ser A* 1995;77:564–71. <https://doi.org/10.2106/00004623-199504000-00009>.
- [30] Owens J, Shiu M, Smith R, Hajdu S. Soft tissue sarcomas of the hand and foot. *Cancer* 1985;55:2010–8.
- [31] Buecker PJ, Villafuerte JE, Hornicek FJ, Gebhardt MC, Mankin HJ. Improved survival for sarcomas of the wrist and hand. *J Hand Surg Am* 2006;31:452–5. <https://doi.org/10.1016/j.jhssa.2005.11.005>.
- [32] Mankin HJ. A computerized system for orthopaedic oncology. *Clin Orthop Relat Res* 2002;252–61.
- [33] Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res* 2011;20:40–9. <https://doi.org/10.1002/mpr.329>. Multiple.
- [34] Hayati Rezvan P, Lee KJ, Simpson JA. The rise of multiple imputation: a review of the reporting and implementation of the method in medical research Data collection, quality, and reporting. *BMC Med Res Methodol* 2015;15:1–14. <https://doi.org/10.1186/s12874-015-0022-1>.
- [35] Blay JY, Soibinet P, Penel N, Bompas E, Duffaud F, Stoeckle E, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. *Ann Oncol* 2017;28:2852–9. <https://doi.org/10.1093/annonc/mdx484>.
- [36] Rydholm A. Improving the management of soft tissue sarcoma. Diagnosis and treatment should be given in specialist centres. *BMJ* 1998;317:93–4.
- [37] Buvarp Dyrop H, Vedsted P, Raedkjaer M, Safwat A, Keller J. Routes to diagnosis for suspected sarcoma: the impact of symptoms and clinical findings on the diagnostic process. *Sarcoma* 2016. <https://doi.org/10.1155/2016/8639272>.
- [38] Johnson CJ, Pynsent PB, Grimer RJ. Clinical features of soft tissue sarcomas. *Ann R Coll Surg Engl* 2001;83:203–5.
- [39] MacGillis KJ, Heaberlin J, Mejia A. Clinical decision making for a soft tissue hand mass: when and how to biopsy. *J Hand Surg Am* 2018;1–7. <https://doi.org/10.1016/j.jhssa.2018.03.032>.
- [40] Alamanda VK, Delisca GO, Mathis SL, Archer KR, Ehrenfeld JM, Miller MW, et al. The Financial burden of reexcising incompletely excised soft tissue sarcomas: a cost analysis. *Ann Surg Oncol* 2013;20:2808–14. <https://doi.org/10.1245/s10434-013-2995-5>.
- [41] Talbert M, Zagars GK, Sherman N, Romsdahl MM. Conservative surgery and radiation therapy for soft tissue sarcoma of the wrist, hand, ankle and foot. *Cancer* 1990;66:2482–91.
- [42] McPhee M, McGrath BE, Zhang P, Driscoll D, Gibbs J, Peimer C. Soft tissue sarcoma of the hand. *J Hand Surg Am* 1999;24:1001–7. <https://doi.org/10.1053/jhsu.1999.1001>.
- [43] Zagars GK, Ballo MT, Pisters PWT, Pollock RE, Patel SR, Benjamin RS, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. *Cancer* 2003;97:2530–43. <https://doi.org/10.1002/cncr.11365>.