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Title

Patterns of care of superficial soft tissue sarcomas: It's not always just a lump

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Running Title

Superficial soft tissue sarcomas

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Abstract

Aim:

Superficial soft tissue sarcomas (S-STS) are generally considered low-risk tumours and have an excellent prognosis when treated with appropriate surgery and adjuvant therapy. However, they are often misdiagnosed then mistreated, leading to significant morbidity. This study aims to examine the patterns of care and outcomes of patients with S-STS, comparing those initially managed through sarcoma units versus elsewhere.

Methods:

Patients with S-STS from Prince of Wales Hospital in NSW (1995-2013) and Peter MacCallum Cancer Centre in Victoria (2009-2013) were identified from a national sarcoma database. Baseline variables, treatment and disease outcomes were recorded. Statistical tests performed included univariate and multivariate analyses, chi-square tests, as well as the Kaplan-Meier method for 5-year local recurrence and survival rates.

Results:

89 patients were identified, with 35% initially managed at a sarcoma unit and 65% elsewhere. Patients initially managed at sarcoma units had larger tumours (>5cm 39% vs 17%; p=0.036) with a trend to higher grade (61% vs 48%; p=0.39). Patients that were initially managed outside a sarcoma unit more often underwent open surgical biopsies (p<0.0005), had multiple operations (p<0.0005), and had higher rates of local recurrences (24% vs 6.5%, p=0.038).

They also had lower 5-year local recurrence-free survival ratios (p=0.022), but had higher metastasis-free survival (p=0.014). On multivariate analysis, only larger STS size and male gender predicted for poorer metastasis-free survival (p=0.042 and p=0.018 respectively).

Conclusion:

Patients with S-STS initially managed outside specialised sarcoma units undergo more operations, with risk of greater morbidity, and have greater risk of local recurrence.

Key words

Soft Tissue Neoplasms; Sarcoma; Patterns of Care Study; Radiotherapy, Surgery

Introduction

Soft tissue sarcomas (STS) are a rare group of neoplasms that make up less than 1% of all solid malignancies.[1] Superficial soft tissue sarcomas (S-STS) constitute an estimated one-third of all extremity and truncal STS, the vast majority of which lie within subcutaneous rather than cutaneous tissues.[2] It has been generally accepted that S-STS have a better overall prognosis compared to their deep counterparts, mainly characterized by their lower propensity to metastasise.[3-7]

However, the rarity and seemingly innocuous presentation of these superficial malignant tumours commonly lead to the mistaken pre-operative diagnosis of a benign soft tissue tumour, predominantly due to the overwhelmingly higher proportion of benign tumours among superficial soft tissue lesions.[8] This results in a large proportion of S-STS being mistakenly treated initially as benign soft tissue tumours, without an initial needle biopsy and then with only marginal instead of wide resections by practitioners at non-specialised centres, most of whom are often inexperienced in dealing with sarcomas.

Although the clinical differentiation of a S-STS from a benign soft tissue tumour remains notoriously challenging, the consensus established is that all superficial soft tissue tumours larger than 5 cm, deep tumours irrespective of size, or a lump that is increasing in size or hard in consistency, should be referred to a specialised sarcoma unit or at least discussed with an expert in managing soft tissue tumours.[9]

The quality of the initial surgery, specifically having wide, microscopically-negative margins, has been documented in numerous studies to be an important determinant of local control for STS in general.[7, 10-13] However, the effect of margins on metastasis and survival still remains debatable.[7, 11, 14] A series conducted in Sweden and a large cohort study by the Scandinavian Sarcoma Group have shown that unplanned excisions, mostly carried out at non-specialised centres, led to a greater proportion of resections with positive margins, repeated resections[15-17] and poorer local control and morbidity.[16, 18]

To date, few studies have compared the outcomes of patients with good prognosis superficial subcutaneous STS initially managed through specialised sarcoma units with those initially managed elsewhere.[15-17, 19] Only one study specifically compared oncologic outcomes of

patients with S-STS previously treated elsewhere to those referred directly to sarcoma centres.[18] There has never been a study in the Asia-Pacific setting documenting the patterns of care and outcomes of S-STS.

This study had two aims: to describe the overall patterns of care of those S-STS cases that were eventually managed at the sarcoma units at Prince of Wales Hospital, New South Wales (NSW), Australia; and Peter MacCallum Cancer Centre, Victoria (VIC), Australia; and to compare the presentation, management and outcomes of S-STS patients initially managed through these specialised sarcoma units to those initially managed elsewhere.

Methods

We retrospectively identified a total of 89 consecutive patients diagnosed with S-STS. 64 of these patients were referred to the Prince of Wales Hospital (POWH) Sarcoma unit in NSW between 1995 and 2013, and the remaining 25 patients were referred to Peter MacCallum Cancer Center (PMCC) in VIC between 2009 and 2013. All patients were enrolled prospectively into a sarcoma database, approved by the relevant ethics committees, from the time of presentation to the sarcoma unit, and were closely monitored by the multidisciplinary teams from respective centres until the time of death or latest follow-up. Prospective database accuracy was cross-checked with retrospective review of hospital, surgeon and cancer center files and to obtain additional datapoints and to update most recent disease status. To ensure homogeneity of data, patients with concurrent metastatic disease at diagnosis or at referral to

a Sarcoma Unit, patients below the age of 16, as well as patients with S-STS of the breast were excluded from our analysis.

The site of disease was categorised into four groups: head/neck, trunk (including axilla and groin), distal extremity (forearm, hand, leg and feet), and proximal extremity. All diagnoses of S-STS were confirmed histologically.

Biopsies were classified as surgical biopsy (including excisional and incisional biopsy), and non-surgical (core, fine-needle aspiration, or punch/shave) biopsy. Most excisional biopsies performed in this study were conducted with intent to treat, and were therefore considered to be surgical treatment by either a marginal or wide resection, depending on the procedure. Although all incisional biopsies performed in the sarcoma units were performed with a diagnostic intent rather than treatment, these biopsies were all performed after a prior inconclusive needle biopsy. All margins were assessed microscopically, with positive margins being resections with tumour cells extending to at least one inked margin whether that margin represented a fascial margin or not. Use of adjuvant radiotherapy was recorded, and usually not used for patients with small lesions, less than 5cm in diameter, with a wide or fascial margin on final resection.

Outcomes measured included local recurrence (LR), distant metastasis (DM), and disease-specific survival (DSS), with estimated rates determined by the Kaplan-Meier method, while comparisons between those that presented directly to sarcoma units for management and those that were initially managed elsewhere were made using the log-rank test. Local recurrence and metastasis-free survival (MFS) intervals were calculated from the date of initial diagnosis to the date of diagnosis of local recurrence, distant metastasis or the date of

last follow-up. Disease-specific survival (DSS) was computed from the date of initial diagnosis to the date of death or date of last follow-up, with causes of death due to sarcoma treated as an "event", and other causes of death "censored" in the Kaplan-Meier method. All statistical analyses were performed using SPSS software, and p-values below 0.05 were considered to be statistically significant.

Results

Baseline characteristics are shown in Table 1. Of the 89 patients, 54% were male, and 46% female. Mean age at diagnosis was 56 years (range 19-88 years). The most common histological subtype of S-STS was pleomorphic malignant fibrous histiocytoma (MFH) (30%), followed by leiomyosarcoma (16%), myxofibrosarcoma (7%), angiosarcoma of soft tissue (6%), atypical lipomatous tumour/well differentiated liposarcoma (6%), myxoid liposarcoma (5%), epithelioid sarcoma (3%), myxoinflammatory fibroblastic sarcoma (3%), in descending order. Other morphologic types include dermatofibrosarcoma protuberans (2%), pleomorphic liposarcoma (2%), synovial sarcoma (2%), solitary fibrous tumour (2%), giant cell MFH (1%), adult fibrosarcoma (1%), inflammatory MFH (1%), embryonal rhabdomyosarcoma (1%), soft tissue tumour without further specification (1%), and dedifferentiated liposarcoma (1%). Additionally, 8 patients were classified as "other" subtypes (9%). 25% of tumours were >5cm and 53% were high-grade (grade 3).

The majority (65%) of cases had initial resections in a non-specialised unit (Table 1) before subsequent referral, with no difference between POWH and PMCC (67% vs 60%, p=0.52). Tumours initially managed at sarcoma units, compared to initial management elsewhere, were larger (39% vs 17% >5cm, p=0.036), with a trend toward being higher grade (61% vs

48% grade 3, p=0.39). There were no significant baseline differences between tumours initially managed at PMCC and POWH except that 80% of tumours >5cm were managed directly at the sarcoma unit in PMCC, compared to 47% of those in POWH (p=0.036).

Treatment and subsequent incidence of local recurrence is summarized in Table 2. Overall, 64 (72%) patients had initial surgical biopsy, 53 (60%) patients had more than 1 operation, clear final margins were achieved in 67 (75%) patients, and radiotherapy was used for 25 patients (28%). There were no significant differences between the sarcoma units for patients that were directly treated at POWH or PMCC.

Patients managed initially at non-sarcoma units were more likely to have surgical (rather than non-surgical) biopsy (98% vs 23%; p <0.0005), more commonly had initial positive margins (85% vs 35%, p<0.0005), and more frequently required more than one operation (78% vs 26%; p<0.0005). There were no significant differences between both groups in attaining final clear margins (77% vs 74%, p=0.62). Radiotherapy was more often used if initially managed in a sarcoma unit (61% vs 10%; p<0.0005), even when only patients with high risk pathological features (>5cm, high grade, positive final margins) were analysed (60% vs 24%; p<0.003).

Follow-up data was available for 87 patients (98%) at a median follow-up of 28 months (2.3 years). Five-year LRFS was 82%, MFS 80% and DSS 87%. 16 of 89 (18%) patients developed LR. Of these, six subsequently developed distant metastases and five died of disease. Another 12 patients developed distant metastases without LR and 10 of these died from disease. All sarcoma related deaths occurred in patients with distant metastases. Of the 58 patients initially managed elsewhere, 8 were referred after LR, and 3 of these 8 (38%)

subsequently had further LR; 50 were referred after initial surgery elsewhere and had further management in a STS unit, 6 (12%) of these developed LR. Two of the 31 (6.5%) patients initially managed in a sarcoma unit developed LR (Fig 1). LR developed more commonly in patients initially managed elsewhere than in sarcoma units (24% versus 6.5%, p=0.038), even when only small and low-grade tumours were analysed (27% vs 0%, p=0.16). Surgical biopsy was also associated with local recurrence (p=0.006). Neither remained predictive on multivariate analysis. Patients managed initially at specialised centres had more distant metastases (39% vs 11% at 5-years, p=0.014), but this difference was no longer significant when other factors were taken into account (multivariate p=0.23), with male gender (p=0.018) and large tumour size (p=0.042) remaining significant. For DSS, there was no significant difference between patients initially managed at sarcoma units versus elsewhere (p=0.20), although male gender (p=0.032) and positive margins at first surgery (p=0.037) were significant on multivariate analysis (Table 3, Fig 2).

Discussion

One aim of our study was to describe the patterns of care and outcomes of patients with S-STS that were eventually managed at specialised sarcoma units in NSW and VIC. Like the referral patterns highlighted by the Indianapolis group, our study revealed that the surgical management of S-STS at non-specialised centres prior to referral was common.[18] These were largely attributed to the mistaken pre-operative diagnosis of a benign tumour. Recently completed guidelines developed by the Australasian Sarcoma Study Group recommend that "any mass lesion greater than 5cm in size, and lesions deep to or attached to deep fascia, should be considered a sarcoma until proven otherwise" and "Immediate referral to a

specialist sarcoma unit to be sought when a tumour of bone or soft tissue (other than simple lipoma) is suspected" [9].

Treatment protocols for S-STS at the sarcoma units in our study typically entail core needle biopsy then wide resection, or a wide repeat excision in the case of re-excisions. In some instances where anatomical constraints made it difficult to perform a wide resection without significant morbidity, marginal excisions were utilized. Excisional biopsy is rarely performed and only for small tumours (< 3cm) and when subsequent formal oncological excision will not be compromised. Sarcoma Unit policy for neoadjuvant or adjuvant radiotherapy is for those with high risk features, including >5cm, high grade, and/or positive final margins. The use of (neo)adjuvant chemotherapy remains controversial in localized STS and it may be offered on a case by case basis for patients with high risk features such as large, deep, high grade tumours[9].

Our study highlighted the relatively good prognosis of S-STS, having rates that are similar to most other studies focusing on S-STS, although somewhat lower than in the Indianapolis study (LRFS 90% and MFS 85% respectively).[5, 18, 20-23] An explanation for this would be the disproportionate representation of larger and higher-grade tumours compared to the Indianapolis study. These rates were comparatively better than those in studies including deep tumours, although some of these have shown that when controlled for size and grade, outcomes for S-STS do not differ greatly from deep STS.[5, 7, 17, 20, 21, 24, 25]

Patients initially managed elsewhere rather than at a sarcoma unit were more likely to undergo surgical biopsy (rather than non-surgical, generally core needle biopsy) - 98% vs 23%, and were therefore by definition less likely to have a pre-operative diagnosis and more likely to undergo an "oops" operation. They had higher rates of initial positive margins (85% vs 35%), and were more likely to undergo multiple operations to attain final adequate margins (>1 surgery: 78% vs 26%). These findings were also reiterated by the Swedish sarcoma series, and although their studies included deep tumours, we can extrapolate these trends specifically to S-STS, especially when they are more frequently mistaken as benign lesions and are managed as such.[15, 16] Hence, it is fair to suggest that these patterns of care are likely to be predominant in the setting of a non-specialised unit. Given these greater rates of surgical biopsies and need for multiple operations, it is likely that patients initially managed elsewhere will have greater surgical morbidity and potentially worse long term functional outcomes.

Our study, mirroring findings from the Swedish and Indianapolis group, showed that patients that were managed directly at sarcoma units had significantly higher LRFS rates than the patients that were initially managed at a non-specialised unit.[15, 16, 18] The reasons behind this stark difference are likely to be multifactorial, and may be related to surgical technique and experience, tumour spillage at inadvertent surgery, and reduced use of (neo)adjuvant radiotherapy (61% vs 10%; $p<0.0005$). Patients initially managed in non-sarcoma units are likely to be located in non-metropolitan settings, remote from radiotherapy units. This has been shown to be a predictor for lower radiotherapy utilisation for other tumour sites and may be part of the explanation for lower radiotherapy use in this setting.[26] Additionally, when small and low-grade tumours were examined, only patients initially managed at non-sarcoma centres developed LR, suggesting the contribution of unplanned excisions to the development

of LR even for low-risk tumours. Small, low grade superficial sarcomas, when adequately excised in a sarcoma unit rarely require adjuvant radiotherapy. Even though final margin status was similar for patients treated in either setting was the same, patients having initial resections in non-sarcoma units may benefit from more liberal use of radiotherapy to decrease the risk of local recurrence. Although our study did not show a prognostic significance of surgical margins for LRFS, numerous other larger studies have indicated otherwise, and we find it reasonable to attribute this difference partly to the relatively smaller numbers in this study.[7, 10-13]

We also noted higher proportions of tumours >5 cm and high-grade tumours being managed directly at sarcoma units, probably because practitioners were more likely to refer up-front larger lesions. Not surprisingly therefore, we found better MFS and DSS rates in patients that were initially managed at non-specialised units than their counterparts managed at sarcoma units, and this reflected similar findings by Lewis and colleagues.[19] It is likely that the poorer MFS rates in patients managed initially at sarcoma units reflects the higher proportion of these patients having high-grade and large tumours, noting that MFS was worse on univariate but not multivariate analysis.

One limitation of our study was its retrospective design. There may have been selection bias involved in our study: our study only included patients that were referred to two institutions representative of NSW and VIC, meaning that our current registry only included patients that have been referred to our centres. There are several other sarcoma units in Australia, and patients referred to these other units were not included in the current study, but there is no reason to believe that our results are not generalizable to these patients. Patients never referred to a sarcoma unit are not included. We have also recognised a discrepancy between

the timelines and the corresponding proportions of patients of the two centres enrolled into the study, and that has led to the observed shorter follow-up period for the Victorian group of patients (NSW median follow-up 2.5 years vs VIC median follow-up 1.0 years).

Conclusion

Patients who are initially managed outside a specialised sarcoma unit are more likely to undergo surgical biopsies and have more than one operation, potentially with greater morbidity. They are less likely to undergo radiotherapy and have poorer local control compared to those treated directly in a sarcoma unit. We recommend that initial treatment outside a sarcoma unit should be considered a risk factor for poor local control, and that subsequent treatment may need to be adjusted, including the addition of radiotherapy. Comprehensive assessment of all soft tissue lesions should be in accordance with recommended guidelines, and it is imperative for all patients with suspicious subcutaneous lumps, particularly those above five centimetres, firm or rapidly growing, to be referred early to a specialised sarcoma unit.

Meeting Presentations

This manuscript is based on data presented at the following Scientific Meeting:

Tam M, Thompson SR, Schipp D, Bae S, Crowe PJ. Patterns of care of superficial soft tissue sarcomas: It's not always just a lump. Poster presentation, *Australian Sarcoma*

Group/Australasian Sarcoma Study Group Annual Scientific Meeting, Brisbane, Australia. 2015.

Ethical Considerations

This research was reviewed by the appropriate hospital ethics committees and performed in accordance with the ethical standards laid down in the Declaration of Helsinki

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Table 1. Baseline factors, by location of first resection

Factors	Categories	Non-sarcoma unit n=58 (%)	Sarcoma unit n=31 (%)	Total n=89 (%)	p-value
Gender	Male	32 (55%)	16 (52%)	48 (54%)	0.75
	Female	26 (45%)	15 (48%)	41 (46%)	
Age (years)	<65	40 (69%)	17 (55%)	57 (64%)	0.19
	≥65	18 (31%)	14 (45%)	32 (36%)	
Size of tumour (cm)	≤ 5 cm	45 (78%)	19 (61%)	64 (72%)	0.036
	> 5 cm	10 (17%)	12 (39%)	22 (25%)	
	Unknown	3 (5%)	0 (0.0%)	3 (3.4%)	
Grade of tumour	1	21 (36%)	7 (23%)	28 (31%)	0.39
	2	8 (14%)	5 (16%)	13 (15%)	
	3	28 (48%)	19 (61%)	47 (53%)	
	Unknown	1 (1.7%)	0 (0.0%)	1 (1.1%)	
Site of tumour	Head/Neck	7 (12%)	3 (9.7%)	10 (11%)	0.79
	Trunk	13 (22%)	6 (19%)	19 (21%)	
	Distal extremity	25 (43%)	12 (39%)	37 (42%)	
	Proximal extremity	13 (22%)	10 (32%)	23 (26%)	

Table 2. Treatment factors and outcome, by location of first resection

Factors	Non-Sarcoma Unit n=58 (%)	Sarcoma Unit n=31 (%)	Total n=89 (%)	p-value
Surgical biopsy prior to resection	57 (98%)	7 (23%)	64 (27%)	<0.0005
More than one operation	45 (78%)	8 (26%)	53 (60%)	<0.0005
Clear final margins	43 (74%)	24 (77%)	67 (75%)	0.62
Use of radiotherapy	6 (10%)	19 (61%)	25 (28%)	<0.0005
Local recurrence	14 (24%)	2 (6.5%)	16 (18%)	0.038

Table 3: Analysis of Clinico-Pathologic and Treatment Variables. P-values<0.05 highlighted bold

Factors	Categories	Univariate p-value for local recurrence	Cox-model p-value for local recurrence	Univariate p-value for distant metastasis	Cox-model p-value for distant metastasis	Univariate p-value for disease-specific mortality	Cox-model p-value for disease-specific mortality
Gender	Male	0.45	0.809	**0.023**	**0.015**	0.28	**0.022**
	Female						
Age	<65	0.20	0.61	0.40	0.68	0.36	0.16
	≥65						
Size of tumour	≤ 5 cm	0.36	0.59	**0.013**	**0.046**	0.107	0.25
	> 5 cm						
	Unknown						
Grade of tumour	1	0.50	0.87	**0.016**	0.31	0.30	0.48
	2						
	3						
	Unknown						
Site of tumour	Head/Neck	0.091	0.72	0.27	0.35	0.204	0.48
	Trunk		0.96		0.97		0.99
	Distal extremity		0.84		0.96		0.18
	Proximal extremity		0.30		0.11		0.15

Type of biopsy prior to resection	Other	**0.006**	0.99	0.22	0.31	0.73	0.80
	Needle biopsy		0.91		0.97		1.0
	Surgical biopsy		0.94		0.12		0.50
Location of initial management	Non-specialised unit	**0.038**	0.87	**0.009**	0.25	0.76	0.17
	Sarcoma unit						
Margins of first surgery	Microscopically positive	0.23	0.18	0.13	0.15	0.53	**0.032**
	Microscopically negative						
Number of operations	1	0.16	0.12	0.14	1.0	0.99	0.34
	>1						
Use of radiotherapy	Yes	0.21	0.65	0.12	0.71	0.68	0.26
	No						

Fig 1: Patterns of Local Recurrence (LR, Local Recurrence)

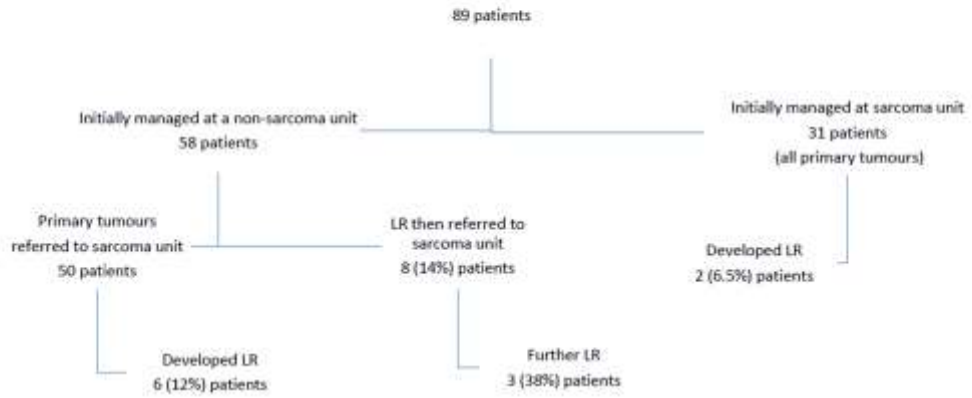

Fig 2: Kaplan-Meier Curve: Local Recurrence-Free Survival: Initial Management at Sarcoma Unit versus at Non-Sarcoma Unit, p=0.022