

The Natural History and Prognosticative Factors of Adult Extremity Soft Tissue Sarcomas: An Asian Perspective

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Abstract

Introduction: We describe the natural history of Asian adult soft tissue sarcomas (STSs) in the extremities and predict prognosticative factors for local recurrence, metastasis and tumour-related death. **Materials and Methods:** Between January 1999 and May 2009, 67 adult patients with first presentation STSs of extremity sites underwent surgical treatment at a single institution. The associations between patient demographics and pathological features with local recurrence, metastasis and mortality were studied using univariate and multivariate analysis. **Results:** The mean age of our patients was 52.4 years with most presentations occurring in the thigh. Majority of Asian STSs were high grade (61.3%) and large tumours with 81.0% being >5 cm. Stages Ia, Ib, IIa, IIb, IIc, III and IV accounted for 6.6%, 6.6%, 26.2%, 11.5%, 3.3%, 42.6% and 3.3% of presentations, respectively. Patients were followed-up for a mean period of 45.9 months. On univariate analysis, high tumour grade and advanced stage (IIc to IV) were predictive of local recurrence and metastasis. Deep lesions were more likely to recur but not metastasise or cause death. Age, sex, size, and margin positivity were not predictive for all end-points. On multivariate testing, only pathological high grade was associated adversely with local recurrence [odds ratio (OR) = 10.0, 95% CI, 1.2 to 84.9, $P = 0.035$], metastasis (OR = 12.7, 95% CI, 2.46 to 65.2, $P = 0.002$) and mortality (OR = 16.2, 95% CI, 1.95 to 135.0, $P = 0.010$). **Conclusions:** Asian adult extremity soft tissue sarcomas present late and are most commonly found in the thigh. High pathological grade is a consistent independent predictor for local failure, distant spread and tumour-related death. Our results reaffirm the current thinking that tumour biology is of primary importance in determining patient outcomes.

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Introduction

Soft tissue sarcomas (STSs) are extremely rare tumours, making up about 1% of all malignancies.¹ In Singapore, they accounted for 0.7% of all cancers in males and 0.5% of all cancers in females with 217 case presentations in the period between 1998 and 2002.²

These tumours are mesenchymal tumours arising from connective tissue elements and are markedly heterogeneous. STSs can arise in virtually any anatomical site with extremity site presentation accounting for half of all tumours.³ Given the rarity of presentation at other anatomical sites, much of the basis of treatment of non-extremity sarcomas has been extrapolated from clinical trial evidence of patients

with extremity sarcomas.⁴ This study aims to provide much needed information on adult extremity STSs in an Asian population which is scarce in the current literature. Patient demographics, pathological data and predictive risk factors for local recurrence, metastasis and tumour-related death are analysed and described.

Materials and Methods

Between January 1999 and May 2009, 102 patients with STSs of extremity sites underwent inpatient treatment at a single institution. These patients were retrospectively reviewed and followed up with data collected in a computerised database.

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Patients were excluded from the study if they presented with recurrent local disease or if they did not undergo resection because of comorbid conditions, unresectable disease, patient choice for non-operative management or operative management at a different center. The eventual study group comprised 67 patients.

Clinical and pathological treatment data were reviewed and analysed. The age of the patient was determined at the date of diagnosis of the primary tumour. Extremity site was defined to include upper limb lesions at or distal to the shoulder/axilla, and lower limb lesions at or distal to the gluteal/groin. The size of the primary tumour was divided into 2 comparison groups: ≤ 5 cm vs > 5 cm and ≤ 10 cm vs > 10 cm. Depth was categorised as either superficial or deep to the investing fascia. Histological grade was classified using a binary system (low vs high) and histological diagnosis was assigned in accordance with the published criteria of the World Health Organization Classification of Tumours of Soft Tissue and Bone.⁵ Microscopic margin status was determined as part of the histopathologic assessment and lastly, patients were staged according to the 6th edition of the American Joint Committee on Cancer for Soft Tissue Sarcoma Staging System.

The date of recurrent disease was determined by the date when the biopsy was conducted or the date when metastatic lesions were detected radiologically. The follow-up period was defined as the period from the date of diagnosis to the date of patient death or the date of the patient's last visit. The computation of the duration of freedom from local recurrence and metastasis was determined from the date of resection.

The associations between patient demographics and pathological features with local recurrence, metastasis and mortality were univariately analysed using the Statistical Package for the Social Sciences for Windows Version 17.0 (SPSS Inc., Chicago, IL, USA). Correlation univariate analysis using chi-squared testing was used for categorical data. Multivariate analysis using a logistic regression model with a stepwise variable selection method was applied to the same study factors. Statistical significance was defined as a *P* value of < 0.05 .

Results

Demographics

The mean age of our adult patients was 52.4 ± 16.2 (range, 22 to 84) years with a majority of patients (34.3%) being in the 40 to 49 year old age group. Chinese patients comprised 89.6% of the study group with Malay and Indian patients making up 7.5% and 3%, respectively. Male patients made up 59.7% of the study group.

Site Distribution

The most common extremity site presentation of STSs was found to occur in the thigh (64.2%, $n = 43$). Other sites include the gluteal (7.5%, $n = 5$), knee (7.5%, $n = 5$), forearm (4.5%, $n = 3$), calf (4.5%, $n = 3$), ankle (3%, $n = 2$), shoulder (3%, $n = 2$), wrist (3%, $n = 2$), arm (1.5%, $n = 1$) and foot (1.5%, $n = 1$) regions.

Among the STSs which presented in the thigh, 55.8% ($n = 24$) occurred in the posterior compartment, 23.2% ($n = 10$) presented in the medial compartment, 9.3% ($n = 4$) presented in the anterior compartment solely. These tumours also present multi-compartmentally with 9.3% ($n = 4$) occurring in the posterior medial compartment of the thigh and 2.3% ($n = 1$) in the anterior medial compartment (Table 1).

Table 1. Site Presentations of Asian Soft Tissue Sarcomas

Site	n	%
Gluteal	5	7.5
Thigh	43	64.2
-Posterior compartment	24	55.8
-Medial compartment	10	23.2
-Anterior compartment	4	9.3
-Posterior medial compartment	4	9.3
-Anterior medial compartment	1	2.3
Knee	5	7.5
Calf	3	4.5
Forearm	3	4.5
Shoulder	2	3.0
Ankle	2	3.0
Wrist	2	3.0
Arm	1	1.5
Foot	1	1.5
Total	67	100

Histology

Adipocytic (liposarcomas), myofibroblastic, smooth muscle, skeletal muscle, chondro-osseous, vascular tumours and tumours of uncertain differentiation accounted for 37.3%, 11.9%, 6.0%, 3.0%, 3.0%, 1.5%, 37.3% of tumours, respectively (Table 2).

Among adipocytic tumours, dedifferentiated liposarcomas, pleomorphic liposarcomas, myxoid liposarcomas and liposarcomas (not specified) accounted for 3.0%, 1.5%, 11.9%, and 20.9% of the total tumours. Myofibroblastic tumours include myxofibrosarcomas, fibromyxoid sarcomas, epithelioid and fibrosarcomas and they account for 7.5%, 1.5%, 1.5%, and 1.5% of all the tumours. The study group also comprised 6.0% of leiomyosarcomas (smooth muscle tumours), 3.0% each for rhabdomyosarcomas (skeletal muscle tumours) and soft tissue osteosarcomas (chondro-

Table 2. Histological Types, Subtypes and Pathological Grade of Patients with Soft Tissue Sarcomas

Type	n (%)	Subtype	n	%	% of High grade tumours within type/subtype
Adipocytic	25 (37.3)	Liposarcoma dedifferentiated	2	3.0	29.2
		Liposarcoma pleomorphic	1	1.5	29.2
		Liposarcoma Myxoid	8	11.9	29.2
		Liposarcoma not specified	14	20.9	29.2
Myofibroblastic	8 (11.9)	Myxofibrosarcoma	5	7.5	60
		Fibromyxoidsarcoma	1	1.5	0
		Epitheloid	1	1.5	100
		Fibrosarcoma	1	1.5	100
Smooth muscle	4 (6.0)	Leiomyosarcoma	4	6.0	100
Skeletal muscle	2 (3.0)	Rhabdomyosarcoma	2	3.0	100
Chondro-osseous	2 (3.0)	Soft Tissue Osteosarcoma	2	3.0	100
Vascular	1 (1.5)	Haemangiopericytoma	1	1.5	0
Uncertain Differentiation	25 (37.3)	Synovial Sarcoma	7	10.4	83.3
		Alveolar soft part	1	1.5	*
		Malignant Fibrous Histiocytoma (MFH)	10	14.9	88.9
		Spindle cell	2	3.0	
		Uncertain	5	7.5	75
67 (100)		67	100		

*Grade not known

osseous tumours) and finally 1.5% of haemangiopericytomas (vascular tumours). STSs of uncertain differentiation include malignant fibrous histiocytomas (MFH)/ spindle cell tumours (17.9%), synovial sarcomas (10.4%) and alveolar soft part tumours (1.5%). Of all STSs, 7.5% could not be subtyped.

Size and Grade of Local Tumours

The sizes of resected tumour specimens were measured in 3 dimensions (Table 3). Measured cephalo-caudally, the tumours had a mean of 120.3 ± 68.8 mm (range, 10 to 300 mm). A mean of 84.0 ± 43.1 mm (range, 15 to 205 mm) was found measured transversely and when measured superficially to deep, a mean of 62.7 ± 39.2 mm (range, 5 to 150 mm) was calculated. The median size of these tumours measured cephalo-caudally, transversely and superficially to deep was 129 mm, 90 mm and 60 mm, respectively. Majority of the STSs were high grade tumours (61.3%) and large tumours, with 81.0% and 57.1% of patients presenting with tumours >5 cm and >10 cm, respectively.

Stage

Our patients generally presented with advanced stage tumours. Stages Ia, Ib, IIa, IIb, IIc, III and IV accounted for 6.6%, 6.6%, 26.2%, 11.5%, 3.3%, 42.6% and 3.3%, respectively, in our study group.

Surgical Resection and Margins

Most patients (67.1%) underwent wide resections, 26.9% underwent radical resections and 6.0% underwent amputations. Overall, margin positivity rate was 32.3%. Of all stage I tumours, a 100% clear margin rate was achieved. Stage 3 tumours (large >5 cm, deep and high grade) had a 83.3% clear margin rate.

End Points and Predictors of Local Recurrence, Metastasis and Mortality

Our patients were followed up for a mean of 45.9 ± 29.9 months (range, 0.5 to 112.0 months). We found an overall post operative wound infection rate

Table 3. Dimensions of Asian Soft Tissue Sarcomas

Dimensions (mm)	Mean	Median	Range	SD
Cephalo-caudal	120.3	129.0	10-300	68.8
Transverse	84.0	90.0	15-205	43.1
Superficial-deep	62.7	60.0	5-150	39.2

of 9.8%, local recurrence rate of 21.2%, 33.3% metastatic rate and 23.9% mortality rate.

Risk factors analysed for events of local recurrence, metastasis and death included the age at presentation (<40 vs $\geq$ 40 years), sex, grade of tumours (high vs low), size ($\leq$ 5cm vs >5cm, $\leq$ 10cm vs >10cm), depth of tumour (superficial vs deep), margin positivity, and stage (I-IIb vs IIc-IV). On univariate analysis, we found that deep lesions, high tumour grade and advanced stage IIc to IV lesions were predictive of local recurrence with a *P* value of 0.03, 0.008, and 0.002, respectively. High tumour grade and advanced stage lesions were also adverse prognostic factors for metastasis with *P* values of 0.001 and <0.001, respectively. High grade lesions, advanced stage IIc to IV lesions, local recurrence and presence of metastasis were predictive of mortality (*P* = 0.002, <0.001, 0.01, <0.001, respectively).

Age, sex, size, and margin positivity were not predictive of local recurrence, metastasis or mortality. In addition, deep lesions did not predict for metastasis or mortality (Table 4).

On multivariate analysis and controlling for the same risk factors, only pathological high grade was associated adversely with local recurrence (OR = 10.0, 95% CI, 1.2 to 84.9, *P* = 0.035), metastasis (OR = 12.7, 95% CI, 2.46 to 65.2, *P* = 0.002) and also mortality (OR = 16.2, 95% CI, 1.95 to 135.0, *P* = 0.010). When the event of local failure and metastatic spread was added to risk factors in the multivariate analysis of mortality, only metastatic spread was an independent risk factor (OR = 78.0, 95% CI, 8.28 to 735.2, *P* = 0.000)

Discussion

Soft tissue sarcomas are rare but deadly entities. Changes in treatment philosophies and improved knowledge have

Table 4. Univariate Association of Asian Patient Demographic Profiles, Pathological Features with Local Recurrence, Metastasis and Tumour-related Death after Surgery

Factor	Proportion of patients (%) with local recurrence†	<i>P</i> value*	Proportion of patients (%) with metastasis†	<i>P</i> value*	Proportion of patients (%) with tumour related death†	<i>P</i> value*
Age		N.S.		N.S.		N.S.
<40 years	36.4		33.3		16.7	
$\geq$ 41 years	18.2		33.3		25.5	
Sex		N.S.		N.S.		N.S.
Male	17.5		25.7		20.0	
Female	26.9		45.5		29.6	
Pathological Grade		0.008		0.001		0.002
High	33.3		53.1		39.5	
Low	0		9.5		0.04	
Pathological Size						N.S.
<5 cm	9.1	N.S.	12.5	N.S.	16.7	
$\geq$ 5 cm	21.6		37.0		25.5	
<10 cm	11.5	N.S.	20.0	N.S.	27.8	
$\geq$ 10 cm	25.0		41.2		18.5	
Tumour Depth		0.029		N.S.		N.S.
Superficial	0		9.1		6.7	
Deep	26.9		39.1		28.8	
Margins		N.S.		N.S.		N.S.
Positive	17.6		14.3		25.0	
No	20.5		42.5		22.2	
Stage		0.002		<0.001		<0.001
I-IIb	6.3		11.1		6.5	
IIc-IV	39.3		60.0		46.7	
Local Recurrence	-	-	-	-		0.011
Metastasis	-	-	-	-		<0.001

**P* values are derived from chi-square test.

†Univariate analysis was applied to a denominator of 67 patients.

not seen marked improvements in survival of patients over time.⁶ As STSs grow in a centrifugal fashion, pain, oedema and swelling rarely occur secondary to compression of surrounding normal tissue. They often present to the unsuspecting surgeon as a painless deep mass with no adverse effect on patient function or health. Unplanned and inadequate resections lead to unnecessary morbidity and increased recurrence rates.⁷ It is vital for physicians to be vigilant of the presentation characteristics of these tumours as expeditious referrals to a multispecialty tertiary care centre improve outcomes.⁸

Advanced disease presentation commonly featured in our Asian patients. A vast majority (81%) presented with large tumours of size >5 cm and slightly more than half (57.1%) of patients had tumours of size >10 cm. Deep lesions accounted for 77.6% of presentations. Both measures of central tendency of local tumours were more than 5 cm in all 3 dimensions. Almost half (45.9%) of patients also had stage III to IV disease. A paucity of Asian literature on this disease and a corresponding lack of patient or physician understanding of the presentation of these malignant tumours may be responsible in accounting for the late detection and therefore advanced presentation of the disease. This trend may reflect the inherent cultural mentality of the Asian population in not seeking medical attention for what appears to be asymptomatic benign diseases. In this regard, patient and physician education may contribute to improving detection rates. Western studies have found presentations of soft tissue sarcomas across a spectrum with Mankin et al⁹ reporting stage III presentations of only 11.4% while Weitz⁶ reported majority of 1261 tumours to be more than 5 cm (61%), deep (78%), and high grade (63%). Grimers et al¹⁰ also reported advanced cases with the average size of tumours being 10 cm in 1460 patients.

Asian STS site presentations, like the western counterparts, were largely in the lower extremities, with the thigh being a predominant site. Large, deep seated lesions in the thigh should therefore be viewed with a high index of malignancy suspicion and a low threshold for tissue biopsy. In this study, the most common types of STSs found in our Asian patients were liposarcomas (37.3%), MFH (14.9%) and synovial sarcomas (10.4%). These are similar to histopathology cited in Western studies which have consistently found the most common types to be malignant fibrous histiocytoma (MFH), liposarcoma, fibrosarcoma, synovial sarcoma and leiomyosarcoma.^{9,11}

Although STSs have traditionally been treated using wide excisional surgery and amputation, developments of new surgical paradigms, superior radiotherapy delivery, and novel adjuvant agents for STSs have facilitated a shift towards limb-conservation. This trend is borne out in this study where our patients mostly underwent function and

limb-preserving surgery in the form of wide or radical resections. Amputations were performed in only 6.0% of cases and were performed below the knee for STSs involving the foot (n = 1), ankle (n = 2) and calf (n = 1). Wide excisional surgery requiring nerve sacrifice was performed in 6% of patients. Over a mean follow-up period of 45.9 months, an overall postoperative wound infection rate of 9.8%, local recurrence rate of 21.2%, 33.3% metastatic rate and 76.1% survival rate were found. This is consistent with the results reported from other specialised centres.^{8,9}

Several studies have looked at risk factors predicting local failure. Weitz et al⁶ found that age >50 years, presentation with locally recurrent tumour, tumour size >5 cm, histologic subtype fibrosarcoma, limb-sparing resection, and positive microscopic margin were independent adverse prognostic factors for local recurrence of disease. Pisters et al⁸ in a study of 1041 patients, found significant independent adverse prognostic factors for local recurrence to be greater than 50 years of age, recurrent disease at presentation, microscopically positive surgical margins, and the histologic subtypes fibrosarcoma and malignant peripheral-nerve tumour. Lachenmayer et al,¹² in a study of superficial STSs with 108 patients, found tumour size >5 cm to be the only prognostic risk factor for local recurrence on multivariate analysis. Cahlon et al¹³ studied local recurrence rates after a pathologically negative re-resection and without radiotherapy and found that on multivariate analysis only age >50 and stage III disease are significant predictors for local recurrence.

Factors predicting for distant spread of disease and mortality have also been described. Saddegh et al¹⁴ reported that multivariate analysis identified large tumour size and high histological grade as significant risk factors for metastatic disease and tumour-related death. Pisters⁸ also found that for distant recurrence, large tumour size, high histologic grade, deep location, recurrent disease at presentation, leiomyosarcoma, and nonliposarcoma histology were independent adverse prognostic factors. As for disease-specific survival, large tumour size, high grade, deep location, recurrent disease at presentation, the histologic subtypes leiomyosarcoma and malignant peripheral-nerve tumour, microscopically positive surgical margins, and lower extremity site were adverse factors. Lachenmayer et al¹² further reported that age >60 and high grade tumours were the corresponding adverse factors for metastasis. Survival analysis detected age, the presence of positive regional lymph nodes, resection quality, distant metastases, tumour size, and tumour grading as significant risk factors of tumour related death. Kaytan et al¹⁵ reported that significant adverse prognostic factors for survival were high grade tumours, presence of local recurrence, and development of metastases in univariate analyses.

Development of metastases and old age were the only adverse prognostic factors by multivariate analysis.

A recent French study¹⁶ with 367 superficial STSs retained histological type and wide resection as factors predicting local recurrence, histological type and grade as prognostic factors of distant spread while age, histological type, grade and wide resection are factors influencing survival.

Margin positivity did not reach statistical significance when used as a prognostic factor for all end points. This is likely due to a small sample size as it is known that margin positivity affects local recurrence. The event of local recurrence and its influence on survival is still controversial. Authors such as Stojadinovic et al¹⁷ have found that positive margins not only doubles the risk of local recurrence but also that of distant recurrence and disease-related death in a report of 2084 cases of localised adult STSs. Eilber et al¹⁸ reported a threefold increase in mortality rate after local relapse in intermediate to high grade extremity tumours. Lewis et al¹⁹ also found that local recurrence was an independent predictor of distant metastases and tumour mortality. On the other hand, results from the National Cancer Institute (NCI) randomised trial and the Memorial Sloan-Kettering Cancer Center (MSKCC) adjuvant brachytherapy trial showed that improved local control did not translate into survival benefits.^{20,21} Even if local recurrence predicts for poorer survival, it is not known if it is causative of or simply a marker of inherent tumour aggressiveness. Both mechanisms can also coexist. We found local failure to be predictive of mortality on univariate analysis but not multivariate analysis. These findings are in agreement with the view that local failure is a marker of poorer survival but may not be causative.

Astute clinical judgment is needed during the planning of a surgery to achieve a balance of tissue and function preservation versus that of wide surgical clearance and low recurrence rates. Margin free status however, is not necessarily the only marker of surgical adequacy as not all anatomical sites are equal. The barrier of spread concept by Kawaguchi et al²² suggests that wide margins may not be necessary if a barrier to spread exists. A carefully considered positive margin adjacent to a critical structure to facilitate limb preservation results in very low rates of local recurrence (4%) when planned irradiation is carried out.²³ Two manifestations of recurrent disease have been proposed by Evans et al.²⁴ It is suggested that local failure post radical resection carries a grim prognosis whereas that following planned limited surgery for function preservation reflects “local persistence” and is largely benign.

We also found that deep seated tumours were more likely to recur in our patients. Interestingly, the proportions of large, deep tumours metastasising and having tumour-related

death are also higher than superficial lesions though these differences did not reach statistical significance.

It appears that some factors such as grade and tumour size are consistently prognostically relevant while other factors only occasionally so. Tumour biology is recognised as one of the most important determinants of patient outcome and is used in all staging systems for STSs. A subset of small high grade tumours have been found to have a prognosis that approaches that of high risk traditional STSs.²⁵ More than half of STSs in this study (61.3%) were high grade. The liposarcomas in this study were generally well differentiated lesions with only 29.3% of lesions being high grade. Malignant Fibrous Histiocytoma (MFH) and synovial sarcomas were most commonly high grade tumours (>80%) and can be expected to have a worse prognosis. Mankin et al⁹ found that patients with leiomyosarcomas, clear cell sarcomas, and malignant fibrous histiocytomas had a poorer survival rate, while those with fibrosarcomas, liposarcomas, and neurofibrosarcomas fared better. In our study, tumour grade is prognostically relevant on both uni- and multivariate analysis predicting for adverse outcomes of local and distant failure as well as tumour-related death. Stage IIc and above lesions are >5 cm in size and high grade tumours. We found that stage IIc and above lesions also predict for poorer outcomes on univariate analysis. Our data highlights the importance of grade as a predictor factor and reflects that large tumour size in the presence of high grade lesions is also a good cut off predictor of poor outcomes. Our findings are in agreement with consistently found risk factors and this implies that our data is valid. We also did not find older age and sex to be predictive of local recurrence, metastasis or mortality unlike other published studies.

Several limitations in this study have to be acknowledged. Firstly, the study was retrospectively conducted and with a small sample size which blunts statistical power and analysis. The effects of neo-adjuvant and adjuvant therapy on patient outcomes were also not taken into account. However, all patients included in this study were primarily treated with the exclusion of recurrent presentations which minimises referral bias. Histopathological slides were also reviewed by a single specialised pathologist. This allows consistent methodology of tumour grading and size measurements. None of our patients were also lost to follow-up. We therefore believe our data to be prognostically valid despite these shortcomings. It is also to our best knowledge, one of the few papers, if not the only study, which describes the natural history and predictors of local recurrence, metastasis and mortality of these rare tumours in an Asian population. On the whole, our patients presented with advanced disease and we found Asian presentations to be histopathologically similar to the findings in western studies. The individual

prognostic contributions of age, sex, size, margin positivity were little with a small sample size and deep tumours were only more likely to recur without impacting events of metastasis or death. The importance of tumour grade as an independent factor in predicting all adverse outcomes cannot be over emphasised.

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