Recurrence and Mortality after Surgical Treatment of Soft Tissue Sarcomas

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Abstract

Background: The recurrence rate after soft tissue sarcoma (STS) treatment ranges between 20-25 % ,and usually occurs within 2-3 years after primary surgery. In Africa, many of the patients present late, access to adjuvant therapy is not guaranteed either. The basis of this study was to establish patterns and factors affecting recurrence and mortality after surgical treatment at a national referral medical facility.

Methods: A five and a half years retrospective study between January 2003 and June 2007 and a six months prospective follow-up arm between July 2008 and March 2009.

Data reviewed from all eligible surgically treated patients were demographic variables, duration of symptoms, anatomical distribution, investigations, adjuvant therapy, tumour type, size, grade and stage and surgical margins status. The outcome variables were tumour recurrence and death.

Results: Mean age was 32.52±18.17 years. The male/female sex ratio was 0.97:1. The mean duration of symptoms was 10.87±18.75 months. The extremities had the most number of cases (62%). Fibrosarcoma was the most common histological type (36.0%) and the mean tumour size was 13.0 ±7.36 cm. Most (44.7%) patients presented with high grade tumours and 78.0 % of the patients presented with a recurrence. Most of the recurrences (71.7%) occurred within the first year of treatment.

Failure to get adjuvant therapy ($p<0.001$), tumour size >5cm ($p=0.02$), advanced stage (III and IV) ($p<0.001$), and positive microscopic margins ($p<0.001$) were adverse prognostic factors for recurrence. Presentation with a recurrent tumour ($p<0.027$), failure to receive adjuvant therapy ($p<0.001$), advanced stages (III and IV) ($p<0.001$), positive microscopic margins ($p<0.001$), and high grade tumours ($p<0.001$), were predictors for death.

Conclusions

Advanced stages of STS, higher histological grades, positive microscopic surgical margins, and failure to receive adjuvant treatment influenced both recurrence and mortality after surgical treatment. Better outcome results from surgical treatment of soft tissue sarcomas may be achieved if efforts to treat them earlier were to be a reality.

Introduction

Soft tissues sarcomas (STS) are an uncommon biologically and histologically heterogeneous group of malignant tumours of mesenchymal origin(1,2). They comprise about 1-3 % and 12-15 % of all malignant tumours in adults and children respectively (3,4). More than 50 different histological subtypes of soft tissue sarcoma have been identified (1).

The commonest areas of distribution in the body are the extremities (upper and lower limbs) and the intra-abdominal and retroperitoneal regions. The head and neck is the least involved region (5,6).

Most soft tissue sarcomas that are adequately treated will result in a cure (7-9). However, treated patients may end up with recurrences, necessitating re-treatment. Most large series report recurrence rates of between 20 and 25 %. This usually occurs 2-3 years after the primary treatment with two thirds of recurrences developing within 2 years of primary treatment (10). In Africa, patients with soft tissue sarcomas generally present late and have to travel long distances to treatment centers. Many do not benefit from radiotherapy and chemotherapy after the surgical procedure due to inadequate resources. As such recurrence rates may be much higher than those reported elsewhere (11).

In the few African series of soft tissue sarcomas , no outcome measures were evaluated (6,11). We studied the pattern and determinants of tumour recurrence at the Kenyatta National Hospital in Nairobi (KNH).

Methods

This study was conducted at the Kenyatta National Hospital (KNH), a referral and teaching hospital in Kenya.

Between 2002 and 2007, 436 cases of STS were recorded in the KNH pathology department. Of these, all patients who underwent resection with curative intent at various units were included. All age groups were included in this study. Patients excluded were those, (i) with tumours of bone origin (ii) whose records were not available or those whose records were incomplete (iii) with gross involvement of the resection margins (iv) who had other primary treatment modalities other than surgery.

This was a five and a half years retrospective descriptive study between January 2003 and June 2008. A six month prospective arm was added to the study and sixteen consecutive patients were recruited between July 2008 and September 2008 and followed up for 6 months.

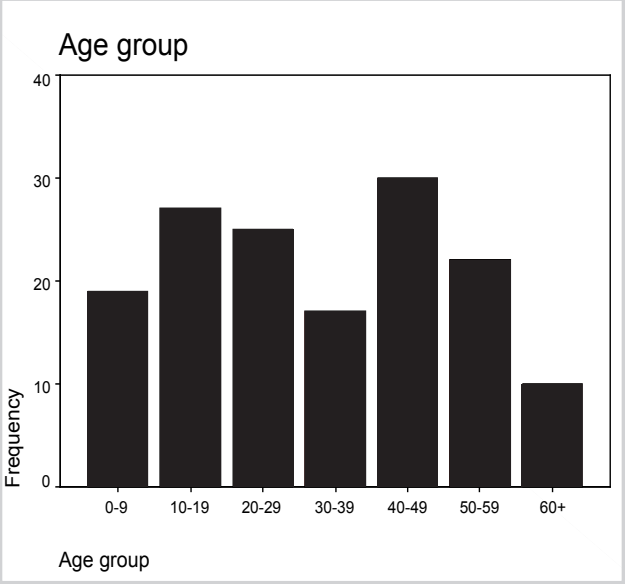
The patient files were obtained from the records department and details transferred into a study questionnaire. Demographic data included age and gender of the patient. Clinical data included the duration of disease symptoms, the body region involved, radiological diagnostic tests done, the nature of surgical treatment offered, and the use of adjuvant therapies. Pathological data included the histological type, tumour size, grade, stage, and the microscopic margin status. Follow-up information included the site of recurrence, follow-up period and status (alive, dead, and lost to follow-up) at last follow-up.

Data were analyzed using the SPSS version 11.1, and results presented in tables and graphs. Univariate analyses were used to obtain relationships between various patient and tumour variables and recurrence. The Chi square test was used to compare the proportions of different variables for outcomes. The independent t-test was used to determine the relationship between means of various continuous variables and outcomes. The level of statistical significance was set at $p < 0.05$. Approval for the study was granted by the KNH Ethics and Research Committee.

Results

The mean age was 32.52 $\pm$18.17 years and the median age was 32.0 years. The age range was from 0.5 to 75 years. All age groups were affected (Fig. 1).There were 74 males (49.3%), and 76 females (50.7%).

Fig. 1: Bar chart of age group distribution



The duration of symptoms prior to surgery ranged from 0.5 to 144 months. The mean duration was 10.87$\pm$18.75 months (median 6.0 months). In one patient, the tumour was discovered incidentally when a routine obstetric ultrasound was done during pregnancy.

Most of the STS were distributed in the extremities (62.2%) and the abdominal/retroperitoneal regions (15.3%) (Table 1).

Table 1: Body Region Distribution of the Soft Tissue Sarcomas at KNH

Body Region	Frequency	Percentage
Head and Neck	11	7.3
Thoracic Region	9	6.0
Abdominal Trunk	14	9.3
Intra-abdominal or retroperitoneal	23	15.3
Upper limbs	28	18.7
Lower limbs	65	43.3
Total	**150**	**100**

The Common histological types included fibrosarcoma (36%), rhabdomyosarcoma (26%), liposarcoma and leiomyosarcoma (Table 2). Rare tumours (labeled as 'Others') included neurofibrosarcoma, alveolar soft tissue sarcoma, myxofibrosarcoma, haemangiosarcoma, haemangiopericytoma, pleomorphic sarcoma, primitive neuro-ectodermal tumour (PNET) and malignant peripheral nerve sheath tumour. About one third of patients evaluated were younger than 20 years of age (Table 2).

Table 2: Histological Types for Patients with Soft Tissue Sarcomas

Histological Type	Age less than 20		Age ≥ 20	
	Frequency	%	Frequency	%
Fibrosarcoma	**10**	**19.6**	**44**	**44.4**
Rhabdomyosarcoma	**29**	**56.9**	**10**	**10.1**
MFH	**5**	**9.8**	**5**	**5.1**
Liposarcoma	**0**	**0.0**	**11**	**11.1**
Leiomyosarcoma	**0**	**0.0**	**10**	**10.1**
DFSP	**1**	**2.0**	**7**	**7.1**
Synovial Sarcoma	**1**	**2.0**	**6**	**6.1**
Other	**5**	**9.8**	**6**	**6.1**
Total	**51**	**100.0**	**99**	**100.0**

Patients presented with tumour sizes ranging from 2 to 46 centimeters (cm). The mean STS size was 13.0±7.36 cm. Most of the patients, presented with poorly differentiated (44.7%) and moderately differentiated (34%) STS. There were 32 patients (21.3%) with well differentiated STS at presentation. Most tumours were stage II and III according to the American Joint Committee on Cancer (AJCC) / International Union against Cancer Staging (Table 3).

Table 3: Distribution of Patients according to AJCC Stage

AJCC Stage	Frequency	%
I	5	3.3
II	70	46.7
III	71	47.3
IV	4	2.7
Total	**150**	**100.0**

X-rays, ultrasounds, CT scans and MRI scans were ordered in 94, 24, 25 and six patients respectively. Table 4 depicts the surgical procedures carried out for the 150 lesions.

Table 4: Surgeries carried out

Type of surgery	Frequency	%
Intralesional/Marginal excision	4	2.7
Wide /radical excision	111	74.0
Amputation/disarticulation	35	23.3
Total	**150**	**100.0**

After surgical extirpation of the tumours, 66 (44.0%) patients had negative histological surgical margins whereas 84 patients (56.0%) had positive histological margins. The average tumour size for the negative margins groups was 11.6 cm and that in the positive margin group 14.1 cm indicating that larger tumors were more likely to have positive margins($p = 0.037$). Eighty seven (68%) patient received adjuvant therapy (27 radiotherapy, 43 chemotherapy, and 17 given both chemo and radiotherapy).

One hundred and seventeen patients (78.0 %) developed recurrences. The recurrence rate was determined by dividing the number of patients who presented with recurrences by the total number of patients treated surgically during the study period. Out of the 134 retrospective cases, 113 (84.3 %) patients developed recurrence after a mean follow-up of 1.6 years. In the prospective arm, 4 patients (26.7%) developed recurrences during the six month follow-up period. Most recurrences were local (51.3%, n = 77). Recurrences in the chest were recorded in 26 patients. Other sites in 14 patients included regional lymph nodes basins, central nervous system and other regions.

At univariate analysis, recurrence of tumour was influenced by tumour size ($p= 0.02$), grade ($p= 0.002$), AJCC stage ($p < 0.001$), positive histological margin ($p < 0.001$) and receipt of adjuvant treatment ($p < 0.001$). Recurrence was not influenced by age, gender, anatomical region, histological type and type of resection (Table 5, 6).

Table 5: Influence of demographic and pathological variables on recurrence and mortality

Variable	OUTCOME					
	Recurrence			Death		
	Yes	No	P value	Alive	Dead	P value
Age 0-20 yrs	40	11	0.927	20	28	0.109
Age >20 yrs	77	21		55	41	
Age<50 years	95	28	0.723	62	56	0.844
Age >50 years	22	5		13	13	
Male	60	14	0.369	38	34	0.868
Female	57	19		37	35	
Head & Neck	9	2	0.782	3	7	0.147
Other Regions	91	31		72	62	
Head, Neck & Abdomen	26	8	0.807	11	19	0.057
Other Regions	91	25		64	50	
Fibrosarcoma Histology	41	13	0.56	33	20	0.062
Other Histologies	76	20		42	49	
Primary Local Tumour	99	30	0.57	60	64	0.027***
Recurrent Tumour	18	3		15	5	
Tumour <5cm	10	7	0.02***	9	7	0.723
Tumour>5cm	107	26		66	62	

Table 6: Influence of pathological and treatment variables on recurrence and mortality

Variable	OUTCOME					
	Recurrence			Death		
	Yes	No	P value	Alive	Dead	P value
Grade I & II	57	26		60	17	<0.001***
Grade III	60	7	0.002***	15	52	
Stages I & II	48	27		59	14	
Stages III & IV	69	6	<0.001***	16	55	<0.001***
Positive Margins	78	6		29	50	
Negative Margins	39	29	<0.001***	46	19	<0.001***
Wide/Radical Excision	87	24	0.614	60	45	
Amputation/Disarticulation	26	9		15	20	0.142
Intralesional/Marginal Excision	4	0	0.576	0	4	0.05***
Wide/Radical Excision/Amputation	113	33		75	65	
Adjuvant Therapy	56	31		61	23	<0.001***
No Adjuvant Therapy	61	2	<0.001***	14	46	
Adjuvant Radiotherapy Only	14	13	0.085	24	3	
Adjuvant Chemotherapy Only	31	12		22	18	0.003***
Recurrence at Primary Site				41	31	
Lung/Chest Recurrence				0	26	<0.001***

***-Result Statistically Significant

At the last follow up, 75 (50.0 %) patients were alive, 69 (46.0 %) were dead and 6 (4.0%) patients had been lost to follow up. The mean duration between treatment and death (the disease specific survival) was 0.93±0.84 years while the median was 0.80 years. The range was 0.1 to 3.5 years. Predictors of mortality included recurrence ($p < 0.001$), grade of tumour ($p < 0.001$), AJCC stage ($p < 0.001$), margin status ($p < 0.001$) and adjuvant treatment ($p < 0.001$). Age, gender, anatomical site and histological type did not influence mortality after surgical treatment (Table 5, 6).

Discussion

The results of this study show that all age groups were affected and a significant proportion of patients were younger than 20 years of age. This younger population is in contrast with other published reports. In the study by Lahat et al, the age at diagnosis is more than two decades older with 10.4 % of the patients younger than 20 years (12). Our results also show a bimodal distribution of STS with peak frequency in the second and fifth decades. Although the typology of STS was different for the peaks, neither age nor tumour type influenced recurrence or mortality. Pisters et al (1996) analysed prognostic factors in 1,041 patients, and found age over 50 years to significantly influence recurrence (13). The divergent result in our study is probably due to late disease across all age groups diluting the prognostic impact of age.

There was a wide range in the duration of symptoms before patients presented to hospital (0.5-144 months). We suggest the reasons for these are, inappropriate health seeking behaviours of patients, challenges with access to surgical services, inefficient referral services and centralized oncology services in the big cities. The delays thus occasioned probably explain the large tumours and high rates of positive margins, recurrences and death.

The anatomical distribution of the tumours was also similar to other published series. In their review, Clark MA et al found distribution to the lower limb, upper limbs, retroperitoneal/intraperitoneal, trunk and head/neck in 40%, 20%, 20%, 10% and 10% of cases respectively (15).

Most patients usually have either a CT or MRI scan to help in planning for surgery. In this study only 31% of patients underwent CT or MRI scanning before surgery, and for those who had them done, it was more often than not a secondary imaging modality, usually after an initial X-ray film or an ultrasound scan. Despite the availability of a CT scan at the KNH during the entire study period, and an MRI scan later, it was possible their high costs made it difficult for patients to access the tests. There is need to uncover the reasons for minimal use of CT and MRI scans in order to match our practice to global ones and limit adverse outcomes.

Fibrosarcoma was the most common STS followed by rhabdomyosarcoma and liposarcoma. This result is similar with most previous accounts for fibrosarcoma but different with regards to the other types. Studying 951 patients with extremity sarcoma Koea et al found fibrosarcoma, MFH, and liposarcoma to be most common (16). In Nigeria, fibrosarcoma and MFH were most common (11). At the Florida Cancer Data System, between 1981 and 2004, tumour histologies were leiomyosarcoma and gastrointestinal stromal tumour (LMS/GIST) (43.5%), malignant fibrous histiocytoma (MFH) (31.5%), liposarcoma (19.0%), and fibrosarcoma (6.0%) (17). The differences in the patterns reinforce the need to describe local disease patterns for diverse geographical regions to unearth peculiarities.

Tumour size was predictive of recurrence in this study. The Italian study by Fiore M et al found that size >10 cm was an independent predictor of death (18). Stojadinovic A et al analysed 2,123 patients with completely resected localized primary STS treated from 1982 to 1999 in New York and found that a tumour size bigger than 5 cm ($p<0.001$) was a negative prognostic factor for tumour related mortality for retroperitoneal, head and neck, thoracic and visceral STS (10). Strategies to diagnose the lesions when early and small should be emphasized to avoid the adverse outcomes. Large tumours are locally aggressive and therefore difficult to completely resect at surgery.

Thirty five patients (23.3%) underwent an amputation or disarticulation for local control of extremity tumours. The most frequent type of surgery was wide or radical excision which was carried out in 111 patients (74%). This amputation rate is much higher than amputation rates in Western studies of between 5 and 10 % (15,19). It is plausible that the large and advanced extremity lesions occasioned the frequent amputations.

In this study, patients who received adjuvant treatment as radiotherapy, chemotherapy or both, were less likely to get a recurrence and die. In the trial by Khatri et al patients in a group who received chemotherapy had a significantly lower recurrence rate while Clark et al and Hueman et al have reported

the beneficial effects of radiotherapy (4, 15, 20). According to Dickey et al, local recurrences may occur in up to 60% of patients in fibrosarcoma and reduced to about 25% with adjuvant therapy (21).

Despite many studies documenting the benefit provided by adjuvant radiotherapy, only 44 (29.3%) patients received radiotherapy in our study. In the West, reasons for not receiving adjuvant therapy include wound complications, old age and complicating additional disease (5). The reasons locally are more logistical and tied to resources. Many travel long distances to come to the KNH for chemotherapy and radiotherapy and find this not tenable.

A number of other factors were associated with recurrence and death after surgery. The rate of negative microscopic margin of 44% in this study is much lower than 78% in a Memorial Sloan-Kettering study(22). In the latter study, positive margins nearly doubled the risk of local recurrence and increased the risk of distant recurrence and disease-related death.

High tumour grade confers an inherent aggressive biological behaviour which increases the risk for both local and distant recurrence and death(23).In this study, primary presentation with a recurrent tumour was an adverse prognostic factor for death but did not influence local recurrence (p=0.570). The occurrence of local relapse per se might favour the systemic spread of disease and, therefore, directly affect survival, or it might simply be a marker of biological tumour aggressiveness (5).

This study had limitations. Not all the records of the patients were readily available during the study period. Some patients were not available for follow up; whereas patients who had been recently treated had not been followed up for a significant duration of time, and therefore their outcomes had not been observed. Some of the patients were referrals, having been treated in other institutions. Their initial treatment records were not available. The various patients were managed by surgeons or surgical teams with varying expertise and experience and this may have impacted on the outcome. Moreover the expertise or experience of the surgeon was not a variable in this study. The sample in this study may have had a bias since it only included patients who were chosen to undergo surgery. This may have contributed to some of the differences observed between results of this study and studies done in other centers.

Conclusion

Patients present late with STS at this referral facility contributing to high proportion of patients with positive margins, recurrence and death in this study. Surgical microscopic margins, tumour size, grade of tumours, AJCC stages, and receipt of adjuvant therapy are prognostic factors for recurrence and death.

References

1. NCCN Clinical Practice Guidelines in Oncology Soft Tissue Sarcoma V.3.2007 available at: www.nccn.org accessed 9th March 2013.
2. Borden EC, Baker LH, Bell RS, et al. Soft tissue sarcomas of adults: State of translational science. Clin Cancer Res. 2003; 9:1941-1956.
3. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. CA Cancer J Clin. 2004; 54:8-29.
4. Khatri VP, Goodnight Jr JE. Extremity soft tissue sarcoma: controversial management issues. Surg Oncol. 2005; 14:1-9.
5. Coumier JN, Pollock RE. Soft Tissue Sarcomas. CA Cancer J Clin. 2004; 54:94-109.
6. Buhari MO, Adigun IA, Rahman GA et al. Soft Tissue Sarcoma of the Head and Neck: Description of 27 cases and Review of the Literature. Res J Med Sci. 2009; 3:19-22.
7. Bowden L, Booher RJ. The principles and technique of resection of soft parts for sarcoma. Surgery. 1958; 44:963-76.
8. Gerrand CH, Wunder JS, Kandel RA, et al. Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. J Bone Joint Surg Br. 2001; 83:1149-55.
9. Schwartz DL, Einck J, Bellon J, et al. Fast neutron radiotherapy for soft tissue and cartilaginous sarcomas at high risk for local recurrence. Int J Radiat Oncol Biol Phys. 2001; 50:449-56.
10. Stojadinovic A, Leung DH, Allen P, et al. Primary adult soft tissue sarcoma: time-dependent influence of prognostic variables. J Clin Oncol. 2002; 20:4344-52.
11. Adigun IA, Rahman GA, Buhari MO, et al: Soft tissue sarcoma in black Africans: Pattern, distribution and management dilemma. J Nat Med Ass. 2007; 99:88-93.

12. Lahat G, Lazar A, Lev D. Etiology, Potential Environmental and Genetic Factors. Surg Clin N Am. 2008; 88:451-481.
13. Pisters PW, Leung DH, Woodruff J, et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol. 1996; 14:1679-89.
14. Gurney JG, Young Jr JL, Roffers SD et al. Soft Tissue Sarcomas. National Cancer Institute SEER Review 1973-2003 Pediatric Monograph. 111-123.
15. Clark MA, Fisher CI, Judson I et al. Soft tissue sarcomas in adults. N Engl J Med. 2005; 35:701-11.
16. Koea JB, Leung D, Lewis JL et al. Histopathological Type: An Independent Prognostic Factor in Primary Soft Tissue Sarcoma of the Extremity? Ann Surg Oncol. 2003; 10:437-440.
17. Gutierrez JC, Perez EA, Francescoli D, et al. Outcomes for Soft Tissue Sarcomas in 8,249 Cases from a Large State Cancer Registry. J Surg Res. 2007; 141:105-114.
18. Fiore M, Grosso F, Lo Vullo S, et al. Myxoid/ Round cell and Pleomorphic Liposarcomas: Prognostic Factors and Survival in a series of patients treated at a Single Institution. Cancer. 2007; 109:2522-31.
19. Clark MA, Thomas JM. Amputation for soft-tissue sarcoma. Lancet Oncol. 2003; 4:335-42.
20. Hueman MT, Thornton K, Herman JM et al. Management of extremity soft tissue sarcoma. Surg Clin N Am. 2008; 88:539-557.
21. Dickey ID, Floyd J. Fibrosarcoma. eMedicine Journal. 2007; 8:1-12. Accessed at www.emedicine.com on March 2, 2007.
22. Stojadinovic A, Leung DHY, Hoos A, et al. Analysis of the prognostic significance of microscopic margins in 2,084 localised primary adult soft tissue sarcomas. Ann Surg. 2002; 235:424-434.
23. Coindre JM, Terrier P, Cuillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcoma. Cancer. 2001; 91:1914-1926.