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Original Article

Retrospective Analysis of Clinicopathologic and Management Aspects of Soft Tissue Sarcoma

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ABSTRACT

Background: Soft tissue sarcomas (STS) are a group of rare aggressive tumors of mesenchymal origin, separated into over 50 different subtypes by histological and molecular classifications. In this analysis we evaluated the clinicopathologic and management aspects of STS. We analyzed the prognostic and predictive factors affecting both OS &PFS.

Patients and methods: Medical records of 92patients with STS were reviewed retrospectively. Overall survival (OS) and progression free survival (PFS) were estimated and factors potentially influencing these outcomes were analyzed.

Results: The mean age of patients was 45.30 ± 15.95 years (range 16–84 years). Median OS was 35.6±5.2 months and median PFS was 10.2 months. Age was assessed as a predictive factor for OS and patients < 50 years had higher median OS (42.3 months) compared to patients > 50 years' old who had median OS (13.2 months) with no statistically significance (P = 0.069). Also patients ≤ 50 years had median PFS (12.1 months' vs 10.1 months) in patients ≥ 50 years with no statistically significance on PFS. Type of pathology was also highly significantly correlated to overall survival (P = 0.000), liposarcoma had improved OS (42.3 months)) compared to other histopathological subtypes. However, it showed no statistically significance to PFS (P= 0.036) with higher median PFS in liposarcoma (22.3 months) compared to other histopathological subtypes.

Conclusion: Mean age was found to be 45.9 ±15 years old, with type of pathology. Histopathological subtypes and disease status were assessed as predictive and prognostic factors and were found to be highly correlated to OS. Effect of RTH on OS and PFS is well noted

Keywords
Clinicopathologic,
Soft Tissue Sarcoma,
Prognostic Factors

Introduction

Soft tissue sarcomas (STS) are a group of rare aggressive tumors of mesenchymal origin, separated into over 50 different subtypes by histological and molecular classifications [1]. Treatment planning involving surgeons, radiation oncologists, and medical oncologists with experience in treating sarcoma patients should be the standard of care

Chemotherapy is the mainstay of treatment for patients with unresectable metastatic disease, and is usually administered with palliative intent. Although postoperative radiation therapy is not proven to improve the survival, a recent analysis of the Surveillance, Epidemiology and End Result (SEER) noticed survival outcome improvement in patients with high-grade tumors, treated with this combined modality [2].

Patients and methods

Medical records of all patients with histologically confirmed soft tissue sarcoma at clinical oncology department of Ain Shams University between 2011 and 2017 were retrospectively reviewed, Ninety-Two patients were retained in this analysis.
Histological subtypes were pooled for analysis into liposarcoma, leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma (UPS) or 'other' subgroups. Gender, age, tumor grade, histological subgroup, primary tumor site involvement and site of metastases (liver, lung, bone and 'other') were assessed as predictive & prognostic factors for OS & PFS.
The end points of this study were Overall survival(OS) which was defined as the time interval between the date of diagnosis either by biopsy or wide local excision and death due to any cause or last follow up, and Progression free survival (PFS) which was defined as the time interval between the date of definitive surgery and the date of first relapse or metastasis.

Results

Patients Characteristics

As regard age of patients 39 patients were found to be ≤ 50 years old, 51 patients were ≥ 50 years old, with range of age between 16–84 years.

49 patients (53.2%) was found to have Extremity STS, 8 patients (8.6%) with head and neck,17 patients with trunk (18.4%), 8 patients with retroperitoneal STS (8.6%), 8 patients with chest STS (8.6%), 2 patients with visceral STS (2.1%). Tumor grade was 10.8 % for GI, 31.5% GII and 57.6% for GIII.

In this series 24 patients had liposarcoma (26.1%), 12 patients with leiomyosarcoma (13%), 11 patients with spindle cell sarcoma NOS (12%), 8 patients with Dermatofibrosarcoma protuberance (8.7%), 5 patients with synovial sarcoma (5.4%), and 32 patients with other histological subtypes (34.7%).

Localized disease was found in 64 patients (69.6%), 28 patients were metastatic (30.4%) with the lung being the most common site of metastasis (21 patients), 23 patients had locally recurrent disease

Treatment Characteristics

Most patients had wide local excision (77.1%) with 27% had adequate margin, 15 patients had no surgery only biopsied, 5 patients had amputation and only one patient had palliative surgery.

EBRT was delivered to 49 patients (53.2 %) received with dose ranging from 50 to 66 Gy. Two patients (4 %) received preoperative RTH, 34 (69.3%) patients had post-operative RTH,13 patients (26.7%) received palliative RTH either to bone or brain. Most of the patients received 3DCRT, few people received 2D. Energy was missed from patients' files.

CTH was delivered to 29 patients (31.5%). All of 29 patients received 1st line regimen, 17 patients (58.6%) received second line and 9 patients (31%) received third line

Table 1. Patients Characteristics

Age	**92**	
≤ 50	39	
≥ 50	51	
Range	16 – 84	
Gender	**92**	
Female	41	44.5
Male	51	55.5
Comorbidities	**92**	
Yes	21	22.8
No	71	77.2
FH	**92**	
First degree	2	2.2
Second degree	3	3.3
NO FH	85	92.3
Tumor Site	**92**	
Extremities	49	53.2
Head & Neck	8	8.6
Trunk	17	18.4
Retroperitoneal	8	8.6
Chest	8	8.6
Visceral	2	2.1
Histological Subtype	**92**	
Liposarcoma	24	26.1
Leiomyosarcoma	12	13.0
Spindle Cell Sarcoma NOS	11	12.0
Dermatofibrosarcoma protuberance	8	8.7
Synovial Sarcoma	5	5.4
Others	32	34.7
Grade	**92**	
I	10	10.8
II	29	31.5
III	53	57.6
Stage	**92**	
I	13	14.1
II	22	23.9
III	25	27.2
IV	28	30.4
NA	4	4.3
Histological Subtype	**92**	
Liposarcoma	24	26.1
Leiomyosarcoma	12	13.0
Spindle Cell Sarcoma NOS	11	12.0
Dermatofibrosarcoma protuberance	8	8.7
Synovial Sarcoma	5	5.4
Others	32	34.7
Classification	**92**	
Localized	**64**	69.6
Metastatic	**28**	30.4
Synchronous	14	50
Lung	10	71.4
Bone	3	21.4
Brain	5	35.7
Liver	8	57.1
Other	6	42.8
Metachronous	14	46.4
Lung	11	78.5
Bone	3	21.4
Brain	2	14.2
Liver	4	28.5
Other	3	21.4
Locally recurrent	23	25

SD= Standard Deviation, FH = Family History, NOS= Not Otherwise Specified

Table 2. Summarize lines of treatment used

Line of treatment	No of patients	(%)
Surgery	**92**	
NO	15	16.3
WLE	71	77.1
Amputation	5	5.4
Palliative	1	1.2
RTH	**49**	53.2
Pre-op	2	4
Post-Op	34	69.3
Palliative	13	26.7
CTH	**29**	31.5
1st Line	29	100.0
2nd line	17	58.6
3rd line	9	31.0
Type of CTH		
UK	1	3.40
Single	11	37.90
Combination	23	79.30
Targeted	3	10.30

WLE= Wide local excision, RTH= Radiotherapy, Pre-op= preoperative, Post-op= postoperative, CTH= Chemotherapy, UK= Unknown

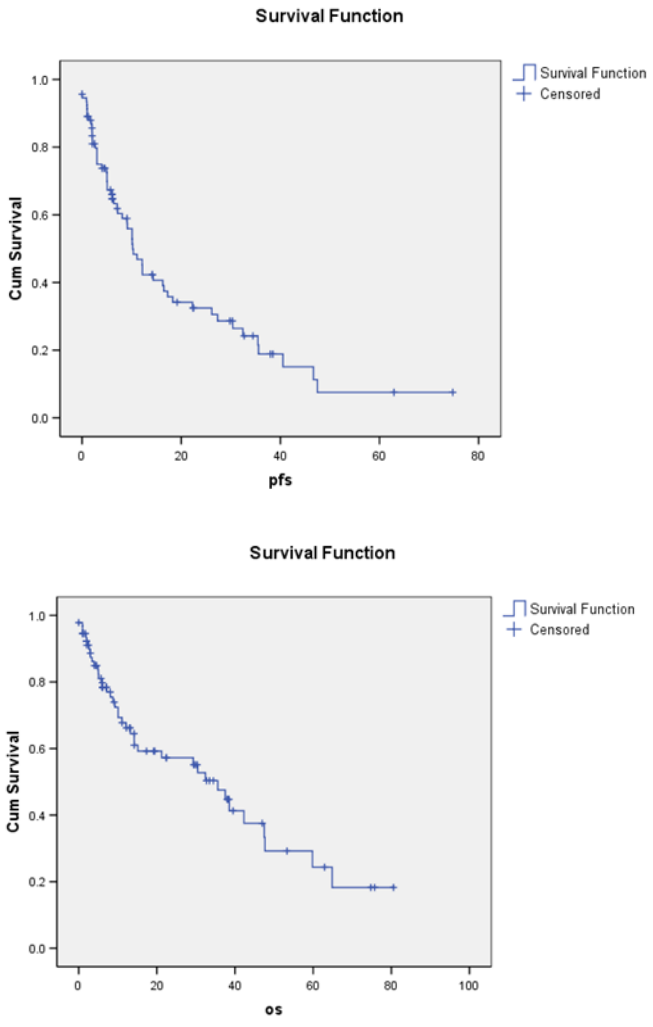

Figure 1. Kaplan Meier Plot of OS & PFS in months.

Disease outcome and patient survival

In our series OS and PFS were calculated to 92 patients, the median OS was 35.6±5.2 months. Median PFS was 10.2 months.

Prognostic & Predictive Factors

Many factors were tested to find out if they can potentially influence OS and PFS.

Discussion

In our series, a total of 92 patients with STS were included in, clinico-pathological data were investigated and reported in our results, many variables were evaluated as prognostic and predictive factors and correlated with overall survival and progression free survival.

In our analysis, the mean age was (45.3 ± 15.9) with range (16-84 years). Median OS was 35.6±5.2 months and median PFS was 10.2 months.

Age was assessed as a predictive factor for OS and patients < 50 years had higher median OS (42.3 months) compared to patients > 50 years' old who had median OS (13.2 months) with no statistically significance (P = 0.069) this is due to limited number of patients. Also patients ≤ 50 years had median PFS (12.1 months' vs 10.1 months) in patients ≥ 50 years with no statistically significance on PFS.

Type of pathology was also highly significantly correlated to overall survival (P = 0.000), liposarcoma had improved OS (42.3 months)) compared to other histopathological subtypes. However, it showed no statistically significance to PFS (P= 0.036) with higher median PFS in liposarcoma (22.3 months) compared to other histopathological subtypes.

In EORTC series of 2,185 patients with follow-up data, the median survival time was 51 weeks. A univariate analysis demonstrated a highly significant favorable prognostic value of young age, good performance status, absence of liver and bone metastases, low histopathologic grade. Patients with liposarcoma and those with synovial sarcoma had a significantly better survival time (Van Glabbeke *et al*, 1999).

Although tumor grade is well known as a determinant factor of PFS. In our series tumor grade was evaluated in relation to OS & PFS and was found to be non-significant (P= 0.716& 0.547). (Coindre JM, *et al* 2001), This could be attributed to most of patients in our analysis had high-grade tumors**.**

In our analysis, type of surgery was correlated to OS and those patients who had WLE had better overall survival (38.5months) compared to those who didn't do surgery (7.1 months) with non -significant (P = 0.089) this is probably due to higher number of patients underwent WLE in contrast to no surgery and this emphasis the effect of limb sparing surgery on OS.

Extent of surgical margins was evaluated as predictive factor on OS, patients with inadequate margins had OS (47.6 months' vs 30.4 months) in patients with adequate margins but with statistically not significant (P= 0.473). Also this is due lower number

Table 3. Predictive Factors Analysis for OS

	Total No.	OS (months)	95% Confidence Interval		Log rank test		
		Median	Lower Bound	Upper Bound	X^2	P-value	Sig.
Age (yrs)							
< 50 yrs	52	42.300	27.408	57.192	3.315	0.069	NS
> 50 yrs	40	13.200	.000	37.436			
Gender							
Female	41	38.530	30.815	46.245	2.097	0.148	NS
Male	51	15.130	2.734	27.526			
Comorbidities							
No	71	37.500	28.466	46.534	1.164	.281	NS
Yes	21	14.200	.000	39.191			
Site							
Extremities	49	37.500	23.616	51.384	2.735	0.741	NS
Head & Neck	7	47.470	-	-			
Trunk	17	30.470	15.905	45.035			
Retroperitoneal	3	4.000	.000	14.353			
Visceral	3	14.200	-	-			
Chest	8	9.270	4.279	14.261			
Margin							
Adequate	24	30.470	1.784	59.156	0.516	0.473	NS
Inadequate	11	47.670	25.967	69.373			
NA	57	-	-				
LNs							
No	81	35.600	25.972	45.228	0.355	0.551	NS
Yes	11	38.530	3.764	73.296			
Grade							
I	11	47.470	29.324	65.616	0.667	0.716	NS
II	29	Not reached	-	-			
III	52	30.470	4.189	56.751			
Pathology							
Liposarcoma	24	42.300	21.460	63.140	22.832	0.000	HS
Spindle Cell Sarcoma NOS	11	8.100	5.836	10.364			
Leiomyosarcoma	12	9.270	0.000	18.768			
DFSP	8	21.230	0.000	45.744			
Synovial Sarcoma	5	Not reached	-	-			
Others	32	38.530	24.254	52.806			

S= Significant, NS= Non-Significant, HS= Highly Significant

of patients and lack of documentation of surgical margins details **Atean et *al.*** reported that the extent of free resection margin

Table 3. Predictive Factors Analysis for OS continued

	Total No.	OS (months)	95% Confidence Interval		Log rank test		
		Median	Lower Bound	Upper Bound	X^2	P-value	Sig.
Classification							
Metastatic	28	32.430	.000	65.996	0.443	0.506	NS
Localized	64	35.600	20.660	50.540			
Metastatic							
Synchronous	14	7.170	4.717	9.623	11.321	0.001	S
Metachronous	14	47.670	34.741	60.599			
Surgery							
Biopsy only	16	7.170	3.042	11.298			
WLE	71	38.530	27.629	49.431	4.837	.089	NS
Amputation	5	13.200	2.250	24.150			
RTH							
No	43	10.100	4.432	15.768	17.781	0.000	HS
Yes	49	47.470	24.566	70.374			
CTH							
No	63	30.470	9.562	51.378	1.236	0.266	NS
Yes	29	38.530	26.810	50.250			

S= Significant, NS= Non-Significant, HS= Highly Significant

is related to the outcome (DSS and DFS). The impact of resection margin status on local control was demonstrated by other investigators. However, the effect of positive margin and local recurrence as independent prognostic factors for metastasis-free survival and OS is still a matter of debate **(Pisters PW, *et al* 1996).**

In contrast, recent reports argued that surgical excision with negative margins not only improves local control but also enhances OS **(Dickinson I.C, *et al* 2006**).

Our results also showed that patients who received RTH had better overall survival (47.4 months' vs 10.1 months) in those who didn't receive (P = 0.000), also the effect of RTH on PFS was addressed and patients who received RTH had better PFS than those who didn't (14.3 months vs 5 months) with statistically significant P= 0.002).

In 2010 SEER analysis was conducted to determine the effect of radiation therapy on overall survival among patients with primary soft tissue sarcomas, of this cohort 47 % of patients received RTH the 3-year overall survival was 73% in patients who received radiation therapy vs. 63% for those who did not receive radiation therapy (p < 0.001) **(Koshy M, *et al* 2010).**

As regard CTH either single or combination, our analysis showed that patients who received CTH showed median survival (38.5 months vs 30.4 months) in those who didn't receive CTH with no statistically significance (P= 0.266)). Also CTH didn't show any statistically significance when correlated to PFS (median PFS 7.1 months vs 12.1 months in patients who didn't receive; P= 0.088) this can be justified by the lack of details on response after each CTH line and the each progression happened after.

In a randomized control phase III trial assessing whether dose intensification of doxorubicin with ifosfamide improves survival of patients with advanced soft-tissue sarcoma compared with doxorubicin alone **(Judson I, *et al* 2014).**

There was no significant difference in overall survival between groups (median overall survival 12·8 months in the doxorubicin group vs 14·3 months in the doxorubicin and ifosfamide group; p=0·076). Median PFS was significantly higher (7·4 months for the doxorubicin an ifosfamide group vs 4.6 months for the doxorubicin group; p=0·003). More patients in the doxorubicin and ifosfamide group than in the doxorubicin group had an overall response rate (26% vs 14%; p<0·0006) **(Judson I, *et al* 2014).**

Table 4. Prognostic Factors Analysis for PFS

	Total No.	OS (months)	95% Confidence Interval		Log rank test		
		Median	Lower Bound	Upper Bound	X^2	P-value	Sig.
Age (yrs)							
< 50 yrs	52	12.170	3.992	20.348	1.429	0.232	NS
> 50 yrs	40	10.100	6.818	13.382			
Gender							
Female	41	17.270	6.366	28.174	1.614	0.204	NS
Male	51	10.100	7.805	12.395			
Comorbidities							
No	71	10.330	7.434	13.226	0.012	0.914	NS
Yes	21	9.130	0.000	24.680			
Site							
Extremities	49	11.100	2.952	19.248	5.983	0.308	NS
Head & Neck	7	7.100	1.634	12.566			
Trunk	17	14.330	7.044	21.616			
Retroperitoneal	8	4.000	0.000	14.353			
Visceral	3	5.070	-	-			
Chest	8	6.000	1.572	10.428			
Margin							
Adequate	24	12.130	0.664	23.596	0.236	0.627	NS
Inadequate	11	35.470	.000	81.942			
NA	57	-	-	-			
LNs							
No	81	12.130	7.360	16.900	5.762	0.016	NS
Yes	11	6.100	3.867	8.333			
Grade							
I	11	17.270	3.279	31.261	1.207	0.547	NS
II	29	11.100	4.120	18.080			
III	52	10.100	6.301	13.899			
Pathology							
Liposarcoma	24	22.300	.000	46.571	11.908	0.036	NS
Spindle Cell Sarcoma NOS	11	6.100	1.089	11.111			
Leiomyosarcoma	12	5.070	0.000	11.809			
DFSP	8	9.100	2.873	15.327			
Synovial Sarcoma	5	6.400	1.837	10.963			
Others	32	16.270	10.967	21.573			

S= Significant, NS= Non-Significant, HS= Highly Significant

Table 4. Prognostic Factors Analysis for PFS continued

	Total No.	OS (months)	95% Confidence Interval		Log rank test		
		Median	Lower Bound	Upper Bound	X^2	P-value	Sig.
Classification							
Metastatic	28	6.100	3.844	8.356	10.072	0.002	S
Localized	64	16.270	8.593	23.947			
Metastatic							
Metachronous	14	10.200	1.193	2.807	3.367	0.067	NS
Synchronous	14	2.000	7.707	12.693			
Surgery							
Biopsy only	16	5.030	0.038	10.022	17.068	0.000	HS
WLE	71	14.330	6.984	21.676			
Amputation	5	8.100	.000	21.047			
RTH							
No	43	5.030	0.000	11.747	9.972	0.002	S
Yes	49	14.330	9.174	19.486			
CTH							
No	63	12.170	4.192	20.148	2.909	0.088	NS
Yes	29	7.170	4.662	9.678			

S= Significant, NS= Non-Significant, HS= Highly Significant

In 2017 a subgroup analysis a subgroup analysis of the EORTC 62012 study, a Phase III trial of doxorubicin versus doxorubicin –ifosfamide chemotherapy in 455 patients with advanced soft tissue sarcoma (STS). Analysis of the main study showed that combination chemotherapy improved tumor response and progression-free survival, but differences in overall survival (OS) were not statistically significant. The study analyzed factors prognostic for tumor response and OS, and assessed histological subgroup and tumor grade as predictive factors to identify patients more likely to benefit from combination chemotherapy **(RJ Young, *et al* 2017).**

Conclusion

Soft tissue sarcoma is a heterogeneous group of rare tumors, a total of 92 patients were analyzed between 2011 to 2017. Median age was found to be 45.9 ±15 years old, with median OS was 35.6±5.2 months and median PFS was 10.2 months.

Histopathological subtypes and type of metastasis were assessed as prognostic factors and were found to be highly correlated to OS. Tumor grade is a strong predictor for PFS but our series showed no significance, possibly due to more number of high grade tumors.

Effect of RTH on OS and PFS is well noted. Extent of surgical margin could be a predictive factor for OS and also Prognostic factor of PFS.

References

1. Fletcher CDM, Bridge JA, Hogendoorn PCW, et al. WHO classification of tumours of soft tissue and bone. 4th ed. Lyon: IARC; 2013.
2. Koshy M, Rich SE, Mohiuddin MM. Improved survival with radiation therapy in high-grade soft tissue sarcomas of the extremities: a SEER analysis. Int J Radiat Oncol Biol

Phys 2010; 77: 203–9.
3. Van Glabbeke M1, van Oosterom AT, Oosterhuis JW, Mouridsen H, Crowther D, Somers R, Verweij J, Santoro A, Buesa J, Tursz T. Prognostic Factors for the Outcome of Chemotherapy in Advanced Soft Tissue Sarcoma: An Analysis of 2,185 Patients Treated With Anthracycline-Containing First-Line Regimens—A European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol. 1999; 17(1):150-7.
4. Coindre JM, Terrier P, Guillou L, Le Doussal V, Collin F, Ranchère D, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 2001; 91:1914–26.
5. Pisters P, Leung D, Woodruff J, Shi W, Brennan M. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996; 14: 1679–89.
6. Dickinson IC, Whitwell DJ, Battistuta D, Thompson B, Strobel N, Duggal A, et al. Surgical margin and its influence on survival in soft tissue sarcoma. ANZ J Surg 2006; 76:104 –9.
7. Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, Kerst JM, Sufliarsky J, Whelan J, Hohenberger P, Krarup-Hansen A, Alcindor T, Marreaud S, Litière S, Hermans C, Fisher C, Hogendoorn PC, dei Tos AP, van der Graaf WT. European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first -line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014; 15(4):415-23.
8. Robin J. Young, Saskia Litière, Michela Lia, Pancras C.W. Hogendoorn, Cyril Fisher, Gunhild Mechtersheimer, Søren Daugaard, Raf Sciot, Françoise Collin, Christina Messiou, Viktor Grünwald, Alessandro Gronchi, Winette van der Graaf, Eva Wardelmann & Ian Judson (2017) Predictive and prognostic factors associated with soft tissue sarcoma response to chemotherapy: a subgroup analysis of the European Organisation for Research and Treatment of Cancer