

Prognostic Factors in Soft Tissue Sarcoma Patients Treated with Pre- or Postoperative Radiotherapy

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ABSTRACT

Objective: Soft tissue sarcoma (STS) is a very rare, heterogeneous, solid tumor of mesenchymal origin that accounts for about 1% of adult malignancies and 15% of pediatric malignancies. The aim of this study was to analyze the data of STS patients who were treated with surgery and preoperative radiotherapy, postoperative radiotherapy, or chemotherapy between 2010 and 2017 for prognostic factors.

Methods: The study included 22 patients with a diagnosis of any type of STS who were treated at a training and research hospital between 2010 and 2017. Data regarding patient age and sex, histological type of the tumor, tumor size, tumor localization, tumor grade, time of radiotherapy (preoperative or postoperative), prescribed radiation dose, chemotherapy treatment regime, length of follow-up, survival, and recurrence of the tumor were analyzed.

Results: A total of 22 patients with a mean age of 60.5 ± 16.2 years (range: 34–86 years) were included in the study. In all, 54.5% of the group had a high-grade sarcoma. The mean follow-up for all 22 patients was 34.1 ± 22.4 months (range: 5–98 months), with a median of 28.0 months. The mean overall survival (OS) was 82.3 ± 8.3 months (range: 66.0–98.6). The 3-year OS rate was 78.4%. The mean recurrence-free survival (RFS) was 72.5 ± 8.8 months (range: 55.0–89.5 months) and the 3-year RFS rate was 69.3%.

Conclusion: The OS was lower in the group that received chemotherapy and in cases of larger tumors. Preoperative or postoperative administration of radiotherapy did not have any significant effect on OS or RFS. Studies with larger samples are needed to further define the effects of radiotherapy and chemotherapy on OS and complications.

INTRODUCTION

Soft tissue sarcoma (STS) is a rare, nonhomogeneous solid tumor of mesenchymal origin that accounts about 1% of adult tumors and 15% of pediatric tumors.^[1–3] The incidence of STS has been increasing in recent years, most probably as a result of the increase in Kaposi's sarcoma as well as enhanced diagnosis capacity.^[4]

This nonhomogeneous group of mesenchymal tumors may originate from soft tissue or several organs, and the classification includes adipocytic tumors, vascular tumors, endothelial tumors, and fibroblastic tumors, as well as those of smooth muscle and skeletal muscle.^[2] STS occurs predominantly in elderly patients, with the highest incidence at 50 to 60 years of age.^[2,5] However, incidence varies widely when considered histological type in relation to sex

and age.^[2,5] For instance, embryonal rhabdomyosarcoma is always a disease of the young, while malignant fibrous histiocytoma is a disease of the older age group.^[2,5]

Environmental and hereditary factors both impact the pathogeny of STS. The identified causes include physical and chemical factors, viruses, ionizing radiation, and hereditary or acquired immunological defects.^[2,5,6] Some sarcomas are more likely to develop with genetic syndromes that have been associated with the pathogeny of STS, such as retinoblastoma syndrome, Li-Fraumeni syndrome, and familial adenomatous polyposis.^[2,3,5,6]

Recent studies have indicated that grade, tumor size, surgical margins, histology, location, radiotherapy, age, and sex are important prognostic factors for STS.^[5,7,8,9]

Surgery accompanied by adjuvant radiotherapy as needed is the gold standard for achieving local control of STS.^[3,5,7,9–12] The role of chemotherapy in the cure of STS is underrecognized, but it is currently improving.^[5,13] The aim of surgery and radiotherapy is local control of the STS, whereas the aim of chemotherapy is systemic control as curative, supportive, or palliative therapy.^[5,7] Treatment is best planned by a multidisciplinary group with the aim of reducing local recurrence, discussing reconstructive strategies, planning for rehabilitation, and improving survival.^[3,5,7]

The purpose of this study was to analyze the data of STS patients who were treated with surgery and preoperative radiotherapy, postoperative radiotherapy, or chemotherapy between 2010 and 2017 to assess prognostic factors.

MATERIAL AND METHODS

In all, 22 patients with any diagnosis of STS who were treated at a training and research hospital between 2010 and 2017 were identified from a retrospectively maintained institutional database and included in the study. The data were collected retrospectively after receiving the approval of the ethical board (2018/514/12) and the permission of hospital management. Patients with insufficient clinical information in the records were excluded.

Data collection

The data collected from the patient record system were details of patient age and sex, histological type of the tumor, tumor size, tumor localization, tumor grade, prescribed radiation dose, chemotherapy treatment regime, length of follow-up, survival, and recurrence of the tumor.

Descriptive histological subtypes were defined according to the latest World Health Organization classification of soft tissue tumors. Tumor aggressiveness was assessed as high, low, or intermediate grade, as defined by the National Federation of Centers for Combating Cancer. Tumor size was classified into 4 groups, and resection margins were

categorized as R0 (microscopic negative margins) or R1 (microscopic positive margins). Radiotherapy was administered either preoperatively or postoperatively. Data about disease status (recurrence, local, or distant) and the patient's vital status (survival/death) were determined from follow-up records.

Radiation techniques

The clinical target volume (CTV) was created with a longitudinal margin of 4 cm and a radial margin of 1.5 cm and the gross tumor volume, or the location from which the original tumor was removed if there was adequate area. The CTV was assessed on an individual basis based on the preoperative radiological history, surgical report, pathological parameters, and the size of the scar. The surgical drain and incision were included in the first therapy volume. In appropriate patients, postoperative boost radiation was delivered using a shrinking field technique after 46–50 Gy.

Preoperative radiotherapy at a dose of 46–50 Gy in 23–25 fractions over 4.5 weeks was administered to 5 patients, and 17 patients received a postoperative dose of 60–66 Gy in 30–33 fractions implemented over 6–6.5 weeks.

Statistical analysis

All statistical analyses were performed using PASW Statistics for Windows, Version 18.0. (SPSS, Inc., Chicago, IL, USA). Patient characteristics were defined with descriptive statistics. Overall survival (OS) and recurrence-free survival (RFS) were statistically assessed. The Kaplan-Meier method was used for survival analysis. Differences between subgroups were analyzed for their significance using the log-rank test.

RESULTS

A total of 22 patients with a mean age of 60.5 ± 16.2 years (range: 34–86 years) were included in the study. Of the group, 59.1% was older than 60 years of age and 68.2% were male. Characteristics of the soft tissue tumors are presented in Table 1.

Only 7 patients were treated with 3-dimensional conformal radiotherapy. The remainder was treated with intensity-modulated radiotherapy. Distant recurrence was determined in 3 of the patients. Chemotherapy was administered to a total of 6 patients due to tumor recurrence. Treatment characteristics are provided in Table 2.

Wound healing complications were seen in only one patient, who was treated with preoperative radiotherapy and surgery. Amputation was performed for a patient who had undergone excision with positive margins (R1) and postoperative radiotherapy because early local recurrence was identified. The total recurrence rate was 27.3%. Recurrence was determined in 4 patients with undifferentiated/

Table 1. Characteristics of soft tissue tumors

	n	%
Histological type		
Fibroblastic and myofibroblastic tumors	6	27.3
Adipocytic tumors	4	18.2
Smooth muscle tumors	3	13.6
Undifferentiated/unclassified sarcomas	6	27.3
Vascular tumors	2	9.1
Tumors of uncertain differentiation	1	4.5
Tumor size (cm)		
<5	3	13.6
5–10	12	54.6
11–15	4	18.2
>15	3	13.6
Location of the tumor		
Upper limbs	1	4.5
Lower limbs	12	54.6
Trunk	9	40.9
Grade		
High grade	12	54.5
Low grade	7	31.9
Intermediate	3	13.6

unclassified sarcoma, one with a fibroblastic and myofibroblastic tumor, and one with an adipocytic tumor. The median RFS was 11 months.

The mean length of follow-up for all 22 patients was 34.1 ± 22.4 months (range: 5–98 months), with a median of 28.0 months. The mean OS was 82.3 ± 8.3 months (range: 66.0–98.6 months). The 3-year OS rate was 78.4%. The mean RFS was 72.5 ± 8.8 months (range: 55.0–89.5 months) and the 3-year RFS rate was 69.3%

Independent prognostic factors associated with OS and RFS are presented in Table 3.

Univariate analysis demonstrated that those who did not undergo chemotherapy and whose tumor size was ≤ 10 cm had a better OS rate.

DISCUSSION

STS is a rare type of cancer with more than 50 histological subtypes and life-threatening neoplasms, though it represents less than 1% of all human cancers.^[5]

Despite the small sample size, the characteristics of the patients and STS in this study were found to be similar to previous study results. Although there were only a few of each subtype, the study findings add valuable details of

Table 2. Treatment characteristics

	n	%
Time of radiotherapy		
Preoperative	5	22.7
Postoperative	17	77.3
Radiotherapy modality		
Intensity-modulated radiation therapy	15	68.2
3-dimensional conformal radiotherapy	7	31.8
Total dose (Gy)		
≤ 50	5	22.7
≥ 60	17	77.3
Time interval between operation and radiotherapy (days)		
≤ 30	10	45.5
> 30	12	54.5
Resection margins classification		
R0	16	72.7
R1	6	27.3
Recurrence of the tumor		
None	16	72.7
Local	1	4.5
Distant	3	13.7
Locoregional	2	9.1
Chemotherapy		
Yes	6	27.3
No	16	72.7

outcomes when patients with STS are properly treated in general clinical practice.

The median age of our patients was 62 years (range: 34–86 years) which was higher than that of similar studies in literature.^[5,8,14,15]

There was a slight male predominance. In accordance with the literature, the tumor locations observed were; upper and lower limbs (59.1%) and trunk (40.9%).^[16,17] In our study, half of the patients had a high-grade STS, which is consistent with the range of 30% to 67% reported in other studies.^[8,18,19]

There are various factors that affect local recurrence and distant metastasis. Adverse factors for local recurrence include positive margins, age over 50 years, and a deep location, whereas adverse factors for distant metastasis are a high grade, larger size, deep location, and a high Ki-67 protein marker level.^[20] Previous research has examined variables of age, sex, stage, grade, size, surgical margins, and distant metastasis and reported them to be prognostic factors for overall survival in STS.^[8,19,21] In our study,

Table 3. Independent prognostic factors associated with overall and recurrence-free survival

	Overall survival				Recurrence-free survival			
	Mean/ Median (months)	95% CI	Log Rank	p	Mean/ Median (months)	95% CI	Log Rank	p
Age (years)								
≤65	89.8	74.6–104.0	0.923	.329	82.1	62.3–102.0	1.510	.219
>65	55.5	32.0–79.0			34.0	21.3–46.6		
Gender								
Male	78.4	54.1–102.6	.018	.894	78.2	58.5–98.0	.608	.435
Female	66.5	49.5–83.5			34.4	22.6–46.3		
Time of radiotherapy								
Preoperative	36.2	19.4–52.6	1.326	.249	26.0	7.8–44.2	1.982	.159
Postoperative	85.1	68.3–101.9			77.3	59.6–95.0		
Total dose (Gy)								
<50	73.3	33.9–112.8	0.358	.549	56.5	15.7–97.3	.716	.398
≥60	66.1	53.3–78.9			47.1	37.0–57.3		
Radiotherapy modality								
Intensity-modulated radiation therapy	35.7	29.5–41.8	.385	.535	31.9	24.3–39.5	.121	.728
3-dimensional conformal radiotherapy	87.4	68.2–106.6			76.0	50.2–101.8		
Resection margins								
R0	66.8	55.2–78.5	.005	.945	46.3	35.8–56.8	.120	.729
R1	75.3	39.1–111.6			67.7	33.3–102.0		
Tumor size (cm)								
≤10	89.5	73.9–105.1	6.073	.014	80.4	62.5–98.2	2.852	.091
>10	26.1	20.0–32.3			22.6	14.6–30.6		
Chemotherapy								
Yes	28.500	24.9–32.1	4.196	.041	17.0	9.2–24.9	7.348	.007
No	92.357	81.7–103.0			85.8	70.2–101.4		
Location of the tumor								
Upper or lower limbs	90.1	75.4–104.8	0.661	0.416	74.2	51.0–97.4	0.075	.784
Trunk	41.5	30.7–52.3			38.6	26.9–50.2		

only tumor size and the need for additional chemotherapy were found to be prognostic factors.

As expected, we found a better OS in patients under 65 years of age, but as our sample size was small, we didn't find a significant relationship between age and OS.

STS of the extremities, head, and neck are generally smaller and recognized earlier, whereas STS of the thigh or retroperitoneum, for example, may get very large due to late presentation.^[5] Patients with STS localized on the trunk demonstrate better survival rates than those with extremity sarcomas.^[22,23] In our study, we didn't find any significant difference between trunk and extremity STS.

The standard treatment for STS is surgery, usually followed by radiotherapy with or without chemotherapy if the tumor is not at an early stage.^[20] The National Comprehensive Cancer Network guidelines suggest radiation therapy for extremity sarcomas, for high-grade lesions, and for low-grade lesions that are larger than 5 cm or have a close or positive margin.^[24]

Typically, treatment is planned by a multidisciplinary team with the aim of decreasing the likelihood of local recurrence, improving function, and increasing OS.^[5] An appropriate surgical resection of the STS is the most critical step, but this is not always possible depending on the location

and size of the tumor. In such cases, radiotherapy can be administered for local control and to preserve function.^[5] Most patients need radiation therapy with extensive resection.^[20] In our study, surgery and radiotherapy were used with all of the patients. A larger proportion of patients were treated with postoperative radiotherapy (77.3%) than with preoperative radiotherapy. A standard dose of preoperative radiation treatment is 50 Gy delivered over a 5-week period, whereas postoperative radiation doses are higher, generally about 60 Gy (if the surgical margins are positive, the dose increases to 66 Gy), and it is delivered over 6–7 weeks.^[5,20] In general, it is necessary to wait 3–6 weeks after surgery to start treatment to make sure that the surgical wound has healed.^[5] In our study, radiotherapy treatment was initiated for 45.5% of the patients in the first 30 days after surgery and for 55.5% after 30 days.

In a study of 190 patients with extremity STS treated with randomized preoperative radiotherapy (50 Gy) or postoperative radiotherapy (66 Gy), no difference was found in LC (93%), DM (25%), and PFS (65%).^[27] Initially, better OS results were reported with preoperative radiotherapy due to deaths other than sarcoma. But after 6 years of follow-up, no difference in OS was observed. Similarly, in our study, we found no difference in OS or RFS between the preoperative and postoperative radiotherapy groups.

In this study, a wound healing complication was seen in only one patient, who was treated with combined preoperative radiotherapy and surgery. Preoperative radiotherapy increases early wound complications.^[20] It has been reported that although more wound healing problems occurred with preoperative radiotherapy (35%) than with postoperative radiotherapy (15%), late fibrosis was more common with postoperative radiotherapy (48%) than preoperative radiotherapy (31%).^[20]

There are no definitive data about the efficacy and safety of chemotherapy in STS treatment.^[24,25] The effect of adjuvant chemotherapy for a high-grade STS is controversial due to the lack of consistent effects on survival.^[24,25] Since STS is a rare disease, most studies consist of a small number of patients with tumors of different histological subtypes, initial sites of the disease, and patient characteristics.^[3] In some studies, a lower risk for local recurrence was observed among patients treated with adjuvant chemotherapy, but without any significant effect on OS. In addition, inconsistent results in clinical studies comparing single versus combination chemotherapy have indicated that there is no clear OS benefit to combination chemotherapy.^[20]

Chemotherapy is not usually used in cases of low-grade sarcoma, superficial lesion, high-grade tumor <5 cm in size, or intermediate-grade tumor 5–10 cm in size that have been totally resected.^[20] However, in one recent study, the authors found that standard neoadjuvant chemotherapy provided a benefit in patients with high-risk STS.^[26] This

study reported a statistically significant and clinically relevant difference in RFS and OS at 3 years averaging 20%.

Chemotherapy is most often given to patients with recurrence or metastasis, so a lower survival rate is expected in these patients. As expected, we found that the patients who did not need chemotherapy treatment had a better OS and RFS.

The present study has some limitations, including its retrospective nature, which may have induced selection bias. Also, the sample size is quite small, the age range is very broad, and the multiple histological types were included. Even so, this study makes a contribution to the literature with a report evaluating the outcomes of the multidisciplinary approach used at our hospital for different types of STS.

CONCLUSION

In summary, this article contains demographic and survivorship data of 22 STS patients. The OS was lower in the group that received chemotherapy and those who had larger tumors. Preoperative or postoperative administration of radiotherapy did not have any significant effect on OS or RFS. Prospective studies are necessary to further define the effects of radiotherapy and chemotherapy on OS and complications.

Ethics Committee Approval

Approved by the local ethics committee.

Informed Consent

Retrospective study.

Peer-review

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Authorship Contributions

Concept: G.Y., R.D.; Design: G.Y., S.A.G.; Data collection &/or processing: H.B.Ç., S.A.G.; Analysis and/or interpretation: H.B.Ç., S.A.G.; Literature search: Ö.O.Ş., G.Y.; Writing: Ö.O.Ş., G.Y.; Critical review: R.D.

Conflict of Interest

None declared.

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Ameliyat Öncesi ve Sonrası Radyoterapi Uygulanmış Yumuşak Doku Sarkomlarında Tedavi Sonuçları ve Prognostik Faktörler

Amaç: Yetişkin malignitelerinin yaklaşık %1'ini ve pediatrik malignitelerin %15'ini oluşturan yumuşak doku sarkomları (YDS) oldukça nadir görülen, mezenkimal kaynaklı heterojen solid tümörlerdir. Bu çalışmada, 2000–2017 yılları arasında cerrahi, ameliyat öncesi ve sonrası radyoterapi ve kemoterapiyle tedavi edilen hastaların tedavi sonuçları ve bunu etkileyen etmenler değerlendirildi.

Gereç ve Yöntem: Bir eğitim ve araştırma hastanesinde 2000–2017 yılları arasında YDS tanısı ile tedavi edilen 22 hasta araştırmaya dahil edildi. Analizlerde kullanılan değişkenler: Yaş, cinsiyet, histolojik tip, tümör büyüklüğü, evresi, radyoterapinin uygulanma zamanı, radyasyon dozu, kemoterapi tedavi şeması, izlem sayıları, sağkalım ve nüks zamanlarıydı.

Bulgular: Yaş ortalaması 60.5±16.2 (34–86) olan 22 hastanın %54.5'inin ileri evre sarkoması vardı. Ortalama izlem süresi 34.1±22.4 ay (5–98) idi. Üç yıllık genel sağkalım hızı %78.4 ve ortalama sağkalım 82.3±8.3 ay (66.0–98.6) idi. Ortalama nüksüz sağkalım 72.5±8.8 (55.0–89.5 ay) ve üç yıllık nüksüz sağkalım hızı %69.3 bulundu. Kemoterapiye gerek duyulmayan ve tümör çağı küçük olan hastalarda sağkalım daha uzundu.

Sonuç: Genel sağkalım, kemoterapiye gerek duyan ve tümör çapı büyük olan hastalarda daha düşüktür. Radyoterapinin ameliyat öncesi ya da sonrası verilmesinin genel ve nüksüz sağkalım üzerinde istatistiksel olarak anlamlı etkisi saptanmamıştır. Radyoterapi ve kemoterapi uygulamalarının genel ve nüksüz sağkalımı üzerindeki etkilerini değerlendirmek için daha büyük örneklemli araştırmalar gerekmektedir.

Anahtar Sözcükler: Ameliyat öncesi/sonrası radyoterapi; sağkalım hızları; yumuşak doku sarkomları.