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Local control results in extremity soft tissue sarcomas

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ABSTRACT

Aim: The aim of this study is to investigate local control results and effective predictive factors in local control of extremity soft tissue sarcomas, retrospectively.

Material and Method: 51 patients underwent postoperative adjuvant radiotherapy (RT) in Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between October 2008-January 2022. Patients who underwent post-operative adjuvant RT were treated with 60-68 Gy in 2 phases from 2 Gy /day using conformal radiotherapy technique. IMA chemotherapy protocol was applied to 31.4% of the patients after radiotherapy.

Results: The median follow up time was 46 months range (1-135). Recurrence was detected in 5 of the patients and the mean time of recurrence was 11.6 months (min: 3-max: 27). 10 patients developed metastasis at follow-up, the mean time until metastasis was 27 months (min: 18- max: 46). The mean overall survival (OS) was 103 (min:4-max:139) months and the OS of 2, 5 and 10 years were 93%, 65% and 60%, respectively. Disease-free survival (DFS) was 97 (min:4-max:139) months; 2, 5 and 10 years of DFS were 77%, 65% and 60%, respectively. The OS in patients aged ≥65 years old was significantly lower than in patients <65 years old (p=0.02). Overall and disease-free survival was significantly lower in patients undergoing chemotherapy (p=0.037 for overall survival, p=0.013 for disease-free survival). The occurrence of recurrence, metastasis or death within 3 years after the operation was significantly higher than after 3 years (p<0.001). Local failure was significantly higher in grade 3 tumors (p=0.05). All patients who recurred had grade 3 tumors. Metastasis and excitus were significantly higher in the follow-up of patients who underwent chemotherapy at one point during their treatment (p=0.027 for metastasis, p=0.042).

Conclusion: While favorable local control results are obtained with adjuvant high dose-conformal radiotherapy in extremity sarcomas, close follow up is important for distant metastasis and local recurrence, especially in the first 3 years.

Keyword: Extremity, sarcoma, survival, age, grade, radiotherapy

INTRODUCTION

Soft tissue sarcomas are tumors of mesenchymal origin and originate from the extremities in 43% of cases (1). The main treatment of these tumors is surgery and radiotherapy (RT) can be applied preoperatively or postoperatively. With the addition of radiotherapy to limb-sparing surgery, local control results are equivalent to amputation in soft tissue sarcomas (2). Surgical margin safety is the most important predictive factor in local recurrence in surgical treatment (3-6).

The standard surgical approach in extremity soft tissue sarcomas is wide local excision with a negative surgical margin (R0). In marginal excision, the tumor tissue is removed together with the reactive zone called pseudo-capsule. While in R1 resection, microscopic tumor tissue remains; in R2 resection macroscopic residual tumor remains. According to the NCCN (National Comprehensive Cancer Network) guidelines, 10 mm is considered a safe surgical margin (1).

In soft tissue sarcomas, reexcision is recommended in microscopic and macroscopic residual disease, and if re-excision is not possible in R2 resection, preoperative radiotherapy can also be applied to shrink the tumor. In the presence of a positive surgical margin in re-excision after preoperative RT, postoperative radiotherapy is applied to complete the total dose to 66-68 Gy. In the treatment of extremity soft tissue sarcomas, the use of arc IMRT (intensity modulated radiotherapy) or conformal RT techniques has reduced the rate of side effects secondary to radiotherapy such as edema and fibrosis.

The aim of this study is to investigate the local control results and effective predictive factors in local control of extremity soft tissue sarcomas retrospectively, that were treated with adjuvant radiotherapy.

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MATERIAL AND METHOD

The study was carried out with the permission of University of Health Science Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.06.2022, Decision No: 2022/06-124). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

Between October 2008 and January 2022, 57 patients underwent radiotherapy with the diagnosis of extremity soft tissue sarcoma in Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Radiation Oncology Clinic. 6 of the patients with metastases at the time of diagnosis and patients undergoing preoperative RT dismissed from study. All patients underwent postoperative adjuvant radiotherapy. Histopathological examination results were consistent with liposarcoma in 14 (27.5%) patients, synovial sarcoma in 9 (17.7%) patients, pleomorphic sarcoma in 7 (13.8%) patients, leiomyosarcoma in 5 (9.8%) patients, and fibrosarcoma in 4 (7.8%) patients. The histopathological subtype was not clear in 12 (23.6%) patients. In this study, the treatment outcomes of 51 patients with extremity soft tissue sarcoma who underwent postoperative adjuvant RT and the prognostic factors affecting local control and overall survival were retrospectively analyzed. The records of all patients were examined from the hospital computer system. The prognostic factors such as age, grade, tumor diameter, time between surgery and RT, surgical margin and the latest status of the patients were recorded.

Treatment Details

Wide local exicion was applied to 25 patients, marginal exicion was applied to 23 patients. Surgery type was unclear in 3 patients. Patients with tumor continuity in the surgical margin and patients with a surgical margin of less than 1 mm were considered as positive surgical margins. Patients who underwent post-operative adjuvant RT were treated with 60-68 Gy radiotherapy in 2 phases from 2 Gy /day using conformal radiotherapy technique. IMA (Ifosfamid, mesna, adriamycin) chemotherapy protocol was applied to 31.4% of the patients after radiotherapy. After the completion of the adjuvant treatments, the patients were called for control with MRI every 3 months for 2 years, every 6 months after two years, and once a year after 5 years

Statistical Analysis

SPSS version 22 was used for statistical analysis. Kaplan Meier method was used in the overall and disease-free survival analysis of the patients. Patient, tumor, and treatment-related variables were evaluated by log rank test. $P<0.05$ was considered statistically significant.

RESULTS

The follow-up period was median 46 months (range 1-135). The median age of the patients was 55 years (min: 18-max: 87). 35 (68.6%) of the patients were male and 16 (31.4%) of the patients were female. Tumor localization was in the lower extremities in 80.4%. Histopathological examination revealed grade 3 tumors for 37.3%. The tumor diameter was between 5.1-10 cm with a rate of 41.2%. The surgical margin was negative in 78.4% of cases. The median radiotherapy dose was 66 Gy (min: 50-max: 70). **Table 1** shows the general characteristics of the patients and treatment modalities.

Tablo 1. Characteristics features of the patients and treatment modalities

	n (%)
Gender	
Female	16 (31.4)
Male	35 (68.4)
Age	
18-35	5 (9.8)
36-65	35 (68.6)
>65	11 (21.6)
Pathology	
Liposarcoma	14 (27.5)
Synovial sarcoma	9 (17.7)
Pleomorphic sarcoma	7 (13.8)
Leiomyosarcoma	5 (9.8)
Fibrosarcoma	4 (7.8)
Others	12 (23.6)
Grade	
1	12 (23.6)
2	6 (11.8)
3	19 (37.3)
Unknown	14 (27.5)
Tumor Size	
≤5 cm	14 (27.5)
5.1.-10 cm	21 (41.2)
10.1-15 cm	16 (31.3)
Tumor Localization	
Upper extremity	10 (19.6)
Lower extremity	41 (80.4)
Radiotherapy Doses(Gy)	
≤60	11 (21.6)
>60	40 (78.4)
Margin Status	
Negative	40 (78.4)
Positive	11 (21.6)
Chemotherapy	
+	16 (31.4)
-	32 (62.7)
Unknown	3 (5.9)

Recurrence was detected in 5 of the patients and the mean time of recurrence was 11.6 months (min: 3-max: 27). In 10 patients developed metastasis at follow-up, the mean time until metastasis was 27 months (min: 18- max: 46). The most common organs with metastases were lung (8), bone (5), brain (1), liver (1) and adrenal (1), respectively.

The mean overall survival (OS) was 103 (min:4-max:139) months (**Figure 1**). The OS of 2, 5 and 10 years were 93%, 65% and 60%, respectively. Disease-free survival (DFS) was 97 (min:4-max:139) months (**Figure 2**). 2, 5 and 10 years of DFS were 77%, 65% and 60%, respectively.

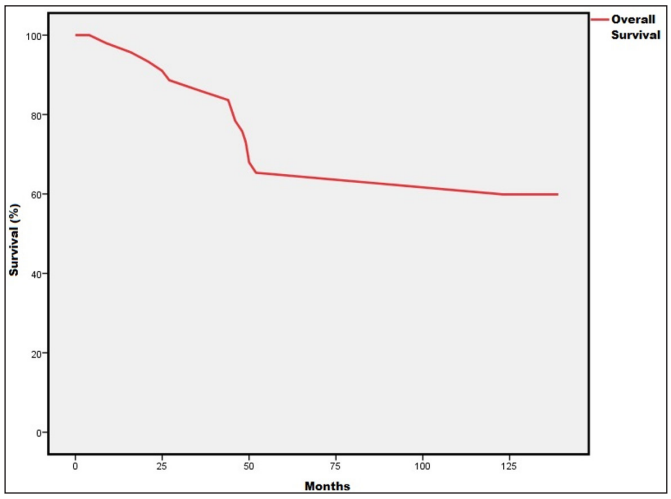

Figure 1. Overall survival

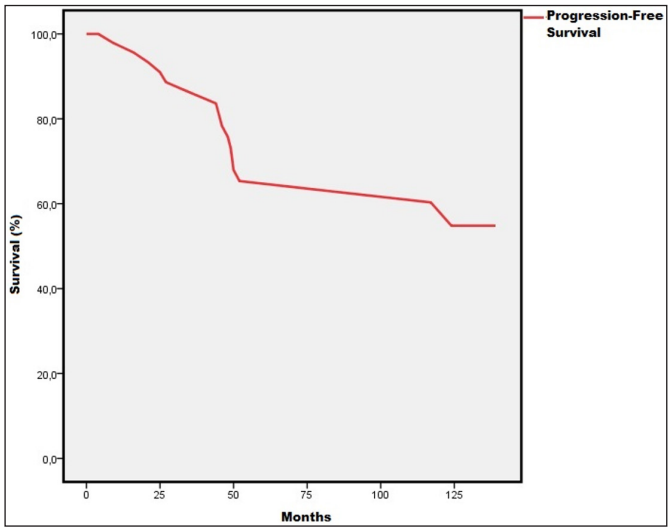

Figure 2. Event-free survival (Event: recurrence, metastasis or death)

The OS in patients ≥ 65 years old was significantly lower than in patients <65 years old (Log rank, p=0.02) (**Figure 3**). OS and DFS was significantly lower in patients undergoing chemotherapy (Log rank, p=0.037 for OS, p=0.013 for DFS). The effect of variables such as gender (p=0.77 for OS, p=0.81 for DFS), tumor T stage (AJCC version 8) (p=0.68 for OS, p=0.74 for DFS), tumor grade (p=0.40 for OS, p=0.21 for DFS), time between operation and radiotherapy (p=0.39 for OS, p=0.38 for DFS), surgical margin positivity or proximity (p=0.18 for OS, p=0.13 for DFS) on overall and disease-free survival could not be shown in our study because the limited number of patients was not sufficient to show the difference. The occurrence of recurrence, metastasis or death within 3 years after the operation is significantly higher than after 3 years (chi-square, p<0.001).

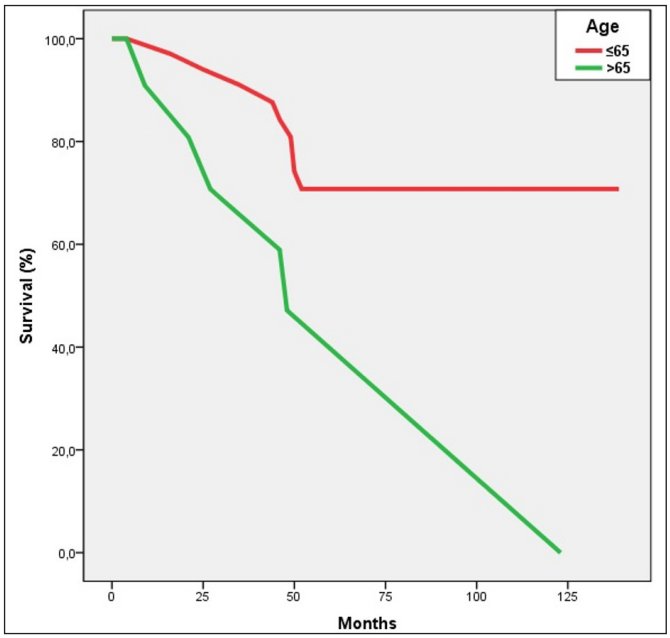

Figure 3. Overall survival by age

When the relationship between the tumor grade and recurrence was examined, the probability of recurrence of grade 3 tumors was close to significant compared to grade 1 or 2 (chi-square, p= 0.059) (**Figure 4**). All patients who recurred had grade 3 tumors and had a surgical margin ≤ 2mm. Metastasis and excitus were significantly higher in the follow-up of patients who underwent chemotherapy at one point during their treatment, while 8 of 24 patients who received chemotherapy died, 6 of 32 patients who did not receive chemotherapy died during follow-up. (chi-square, p=0.027 for metastasis, p=0.042 for excitus).

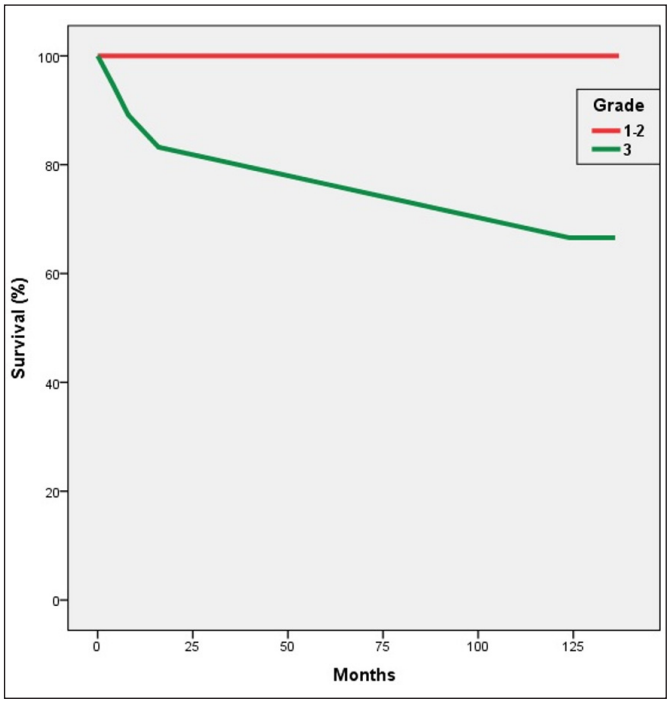

Figure 4. Recurrence-free survival by tumor grade

DISCUSSION

Undifferentiated pleomorphic sarcoma, liposarcoma and leiomyosarcoma are the most common cases in adult soft tissue sarcomas (7). In our study, liposarcoma (27.5%) was the most common histopathological subtype followed by synovial sarcoma (17.7%) and pleomorphic sarcoma (13.8%).

Surgical resection is the primary treatment in soft tissue sarcomas and radiotherapy is applied in the preoperative or postoperative period. The standard surgical treatment is wide excision with a negative surgical margin (R0). However, marginal excision can also be performed in tumors close to neurovascular structures because there is difficulty to provide a negative surgical margin. Sometimes, preoperative radiotherapy is applied to the patients to shrink the tumor before surgery. In our study, all patients underwent postoperative adjuvant-conformal radiotherapy after limb-sparing surgery.

Local control rates have been improved with limb-sparing surgery and adjuvant RT in soft tissue sarcomas in some studies (1,7-11). In two randomized studies, the contribution of adjuvant RT to local control in patients with soft tissue sarcoma who underwent limb-sparing surgery was mentioned (2,12). In a prospective-randomized study by Yang et al. (2), it was mentioned that adjuvant RT was effective in reducing local relapses without affecting overall survival rates. In the study of Gronchi et al. (13) it was stated that local control directly affects survival. In our study, high local control rates were obtained with adjuvant RT. The number of patients with local recurrence was 5 (9.9%) and the mean time of recurrence development was 11.6 months (min 3-max.27 months). We think that the use of conformal radiotherapy technique and high radiotherapy doses (66-68 Gy) were effective in our low local recurrence rate.

In our study, the mean overall survival was 103 (min:4-max:139) months and the overall survival of 2, 5 and 10 years were 93%, 65% and 60%, respectively. Disease-free survival was 97 (min:4-max:139) months. Disease-free survival of 2, 5 and 10 years were 77%, 65%, and 60%, respectively. Our results is consistent with the literature.

Tumor grade is very important in patients with soft tissue sarcoma in terms of both local recurrence and distant metastasis (3,6). In our study, grade 3 tumors were the majority (37.3%) of the patients. Local failure was significantly higher in grade 3 tumors (p=0.05). All the patients with local recurrence (5 patients) had grade 3 tumors.

Since the tumor diameter is large in soft tissue sarcomas and the risk of recurrence and distant metastasis is high in high-grade tumors, these tumors may benefit from chemotherapy (14). In addition, in some studies, the role of chemotherapy in the treatment of soft tissue sarcomas is still controversial. A meta-analysis by Pervaiz et al. (15) showed only a marginal efficacy with respect to local recurrence, distant recurrence and overall survival. In the study of Woll et al. (16) there was no difference in overall survival and recurrence-free survival with adjuvant external RT and doxorubucin-ifosfamide chemotherapy. In the randomized phase-2 study of Stone et al. (17) the efficacy of neoadjuvant chemotherapy in adult soft tissue sarcomas was investigated and no significant survival advantage was seen.

In our study, adjuvant chemotherapy was applied to 16 (31.4%) patients. In univariate analysis, overall (p=0.037) and disease-free survival (p=0.013) were statistically lower in patients undergoing adjuvant chemotherapy. This can be due to the fact that metastasis and mortality rates are higher in these patient group since chemotherapy was generally applied in higher risk patients.

In our study, the rate of patients ≥65 years old was 21.6% and overall survival in these patients was significantly lower compared to patients <65 years old in univariate analysis (p=0.02). This may be due to the high incidence of comorbid diseases in elderly patients, higher rate of non-cancer deaths and difficulties in treatment applications to older patients.

In soft tissue sarcomas, surgical margin is the most important risk factor for local recurrence (3-6). According to the NCCN guidelines, 10 mm surgical margin is considered safe (1). In our study, due to the low number of patients, the effects of surgical margin on disease-free and overall survival could not be statistically evaluated but all patients who recurred had surgical margin ≤ 2mm. Surgical margin is adjacent in 2 patients and <1mm in 1 patient .

In the study of Falk et al. (18,19) ablation therapies such as surgery, radiofrequency and radiotherapy had a significant survival advantage in metastatic sarcomas compared to patients who did not receive these treatments (p=0.0001). In the study of Lindsay et al. (20), it was shown that stereotactic body RT provided a survival advantage in lung metastases.

In our study, the rate of patients with metastases was 19.6% (10 patients) and lung metastasis was the most common. While metastasectomy was performed in 4 out of 8 patients who devoleped lung metastases, whole brain radiotherapy (30 gy) was applied to 1 patient with brain metastasis. Additionally recurrence, metastasis or death in the first 3 years after operation was significantly higher than after 3 years (p<0.001). These findings support the need for close follow-up of the patients, especially in the first 3 years.

CONCLUSION

While favorable local control results are obtained with adjuvant high dose-conformal radiotherapy in extremity sarcomas, close follow up is important for distant metastasis and local recurrence, especially in the first 3 years.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Science Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Researchs Ethics Committee (Date: 23.06.2022, Decision No: 2022/06-124).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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