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Research Article

Impact of the unplanned excision on the oncological outcomes of patients with soft tissue sarcomas: a single-center retrospective review of 490 patients

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ABSTRACT

Objective: This study aimed to (1) compare the oncological results of patients who underwent re-excision after unplanned excision with those who underwent planned excision and (2) analyze the impact of local recurrences on oncological outcomes.

Methods: Patients with soft tissue sarcoma who had been treated in our center between 2000 and 2018 were retrospectively reviewed. Patients were divided into two groups: Group PE (Planned excision; n = 345) and group UE (Unplanned excision; n = 145). Two groups were compared in terms of local recurrence-free survival (LRFS), metastasis-free survival (MFS), and overall survival (OS). Local recurrences effects over MFS and OS were also analyzed.

Results: There were 26 (17.9%) local recurrences in the UE group and 30 (8.7%) local recurrences in the PE group ($P = 0.005$). There was no difference in MFS and OS between study groups ($P = 0.278$ and $P = 0.848$, respectively). Five years MFS rates of UE and PE groups were 76.4% and 73.6%, and five-year OS rates of UE and PE groups were 70.3% and 73.9%, respectively ($P = 0.417$, $P = 0.656$). Patients with local recurrence had a 1.96 times higher risk of metastasis than patients without local recurrence ($P = 0.008$). Patients with local recurrence had 1.65 times higher risk of mortality than patients without local recurrence ($P = 0.047$).

Conclusion: Although local recurrence is much more common in the UE group, this outcome does not seem to affect MFS or OS. These results indicate that similar outcomes can be achieved if UE patients are referred and appropriately treated with wide re-resections.

Level of Evidence: Level III, Therapeutic Study

Introduction

Treatment of soft tissue sarcomas (STS) requires the collaboration of different medical fields during both diagnostic and treatment processes. Imaging studies, biopsy planning, neo-adjuvant therapy decisions, surgical excision with wide margins, adjuvant therapy decisions, and follow-up protocols are the main treatment steps in the management of soft tissue masses.[1,2] Because of the complexity, patients should be evaluated in multidisciplinary meetings in the presence of radiologists, oncologists, radiation oncologists, pathologists, and surgeons who are experienced in musculoskeletal tumors. Optimal oncological outcomes can be achieved only with a multidisciplinary approach.[1]

Marginal or intralesional unplanned excisions (UEs) of soft tissue sarcomas without appropriate preoperative imaging, biopsy, and multidisciplinary planning, performed by orthopedic surgeons whose primary field of experience is not orthopedic oncology, or by other surgeons who do not receive regular orthopedic oncology education as a part of their training curriculum, are serious medical problems seen all over the world. These kinds of operations, performed without adequate preoperative planning, are called "Whoops Surgery."[2,3] After these inappropriate operations, patients are generally referred to sarcoma centers, and re-excision is usually performed.[4,5] Some centers prefer to follow-up with adjuvant therapies.[6] The outcomes of these UEs have been reported, with different conclusions.[4,7-10] It is also reported that UEs are usually performed on more superficial and smaller tumors when compared with planned excisions (PEs).[8-11] As reported in the literature, one of the main limitations in such studies is that tumor characteristics (tumor depth and size), which may create possible selection biases, are generally in favor of the UE group. We hypothesized that UEs of soft tissue sarcomas may increase local recurrence rates and that local recurrence may negatively affect the oncological outcome. The aim of this study was to compare the oncological outcomes of planned versus UEs in terms of overall survival (OS), metastasis, and local recurrence and to analyze the effects of local recurrences over metastasis-free survival (MFS) and OS.

Materials and Methods

Soft tissue sarcoma patients who had been treated between 2000 and 2018 at Ege University Orthopedics and Traumatology Department were retrospectively reviewed. The study was approved by Ege University, School of Medicine Medical Researches Ethics

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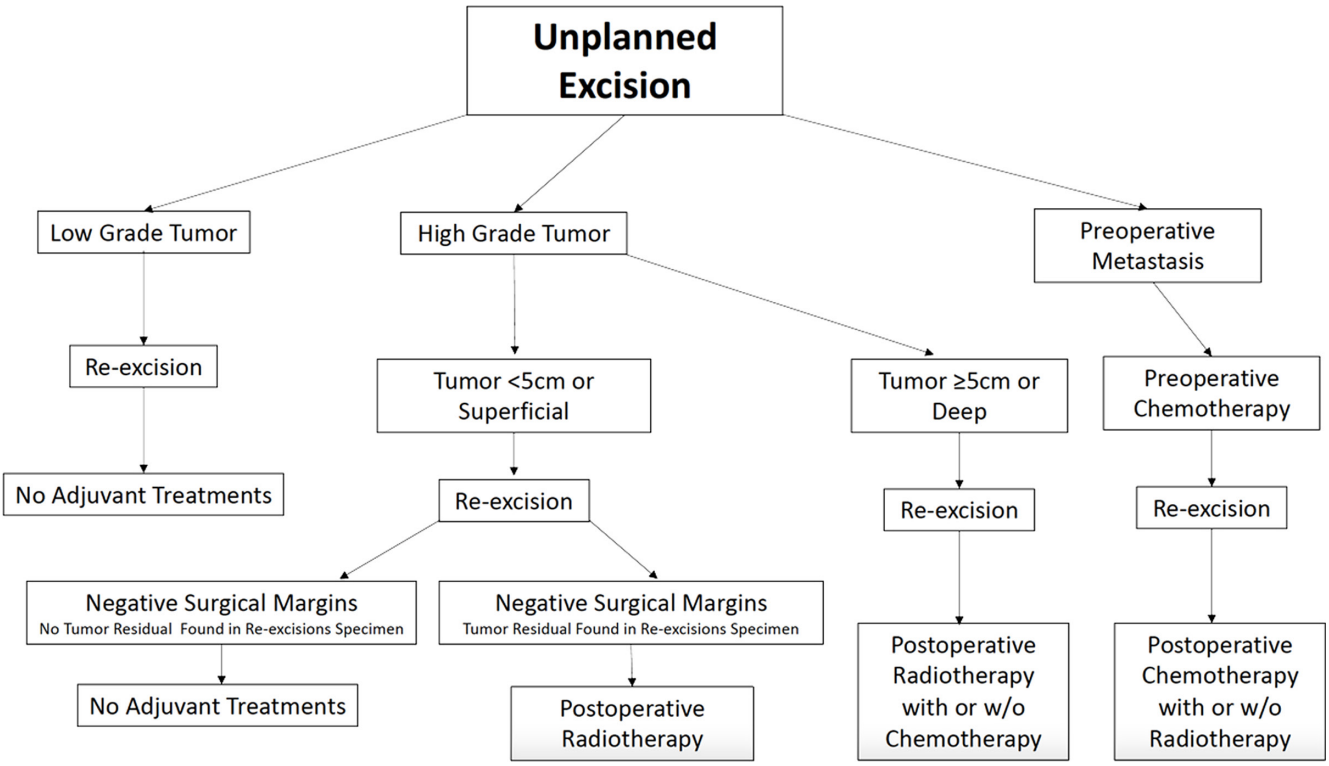

Figure 1. Treatment algorithm of patients with soft tissue sarcomas who underwent unplanned excisions.

Committee (approval number: 99169796-050.06.04) and was conducted according to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective design of the study.

Patients with a minimum of 12 months of follow-up were included in the study. All cases in this study were treated with a multidisciplinary approach, based on the decision of the Bone and Soft Tissue Tumors Council of Ege University, School of Medicine Hospital. Patients with incomplete medical archive data and who were lost to follow-up were excluded from the study. Definitive surgery (re-excisions or PEs) dates were taken as follow-up starting points for both study groups.

Patients were divided into 2 study groups. Group 1 is the PE group, in which the first operations were performed in Ege University, School of Medicine Orthopedic Surgery and Traumatology Department with preoperative multidisciplinary planning. On the other hand, group 2 is the UE group, in which the first operations were performed in some other hospitals without any preoperative multidisciplinary planning but the patients were then referred to Ege University School of Medicine Orthopedic Surgery and Traumatology Department either right after the UEs or after recurrences. Local recurrence-free survival (LRFS), MFS, and OS were analyzed in both groups. The effect of local recurrences on MFS and OS was also analyzed.

Group 2 patients who were referred to Ege University School of Medicine Orthopedic Surgery and Traumatology Department after UEs were evaluated with dynamic contrast-enhanced magnetic resonance imaging (MRI). Staging was evaluated usually with lung computed tomography (CT) or positron emission tomography (PET)–CT in selected cases. With the outcomes of these MRI evaluations and staging procedures, the patients in group 2 were discussed in multidisciplinary meetings for further treatments. In the UE group, as most of the patients did not have preoperative MRI, the size of the tumors reported in pathology reports was taken into consideration. Re-excisions were performed without neoadjuvant or adjuvant treatments for patients who had low-grade tumors or superficial high-grade tumors smaller than 5 cm in diameter. Patients who had tumors greater than 5 cm received neoadjuvant or adjuvant treatments (chemotherapy, radiotherapy, or both).[12] Patients who had preoperative metastasis received neoadjuvant or adjuvant (or both) chemotherapy (Figure 1).

Follow-up protocols included physical examination, MRI of the surgical site, and CT scan of the thorax every 3 months in the first year, every 4 months in second and third years, every 6 months after the fourth and fifth years, and once every year thereafter. After 3 years, lung examination was performed by lung CT or plain radiographs, interchangeably. In recent years, PET-CT has been used in selected cases.

Statistical analysis

Stata Statistical Software version 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, Tex, USA: StataCorp

HIGHLIGHTS

- Marginal or intralesional unplanned excisions (UEs) of soft tissue sarcomas without appropriate preoperative diagnostic measures and surgical planning are serious global medical problems which usually result in additional morbidity for the patients. The aim of this study was to compare the oncological outcomes of planned versus UEs in terms of overall survival (OS), metastasis, and local recurrence and to analyze the effects of local recurrences over metastasis-free survival (MFS) and OS.
- The results showed 17.9% local recurrences in the UE group and 8.7% local recurrences in the PE group ($P=0.005$). Patients with local recurrence had a 1.96 times higher risk of metastasis than patients without local recurrence (P=0.008). Patients with local recurrence had 1.65 times higher risk of mortality than patients without local recurrence ($P=0.047$).
- This results indicate that although local recurrence is more common in the UE group, after UE group is provided with appropriate treatment in a specialized center, similar outcomes in terms of MFS and OS can be achieved. Treatment of these patients should be provided in centers that can offer a multidisciplinary approach.

LP.) and SPSS Statistics Software version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA: IBM Corp.) were used to analyze the data. The significance level was set at $P < .05$.

Overall survival was calculated from definitive surgery dates until the death date, regardless of cause, or until the date of the last follow-up. Metastasis-free survival was calculated from definitive surgery dates until the date of metastasis, the date of death regardless of cause, or the date of the last follow-up. Local recurrence-free survival was calculated from definitive surgery dates until the date of local recurrence, the date of death regardless of cause, or the date of the last follow-up. Kaplan–Meier and competing risk methods were used in survival analyses. The Cox proportional hazards model is used in order to obtain hazard ratios and its confidence interval while performing Kaplan–Meier survival analyses. Sub distribution hazard ratios were obtained from the Fine-Gray model while performing competing risk analyses.

Prognostic factors (age, tumor size, preoperative lung metastasis, tumor grade) were analyzed using the log-rank test for categorical parameters and the Cox model for continuous parameters.

Results

A total of 515 patients were identified from Ege University Bone and Soft Tissue Tumors multidisciplinary meeting archives. Twenty-five patients were excluded due to insufficient data and loss of follow-up. The study cohort included 156 patients with 12-23 months of follow-up, 153 patients with 24-59 months of follow-up, and 181 patients with 60 months or more of follow-up. Finally, 490 patients were divided into 2 groups.

Group 1 (PE) consisted of 345 patients whose first operations were performed in Ege University Orthopedics Surgery Department with preoperative multidisciplinary planning.

Group 2 (UE) consisted of 145 patients whose first operations were performed outside sarcoma centers without preoperative multidisciplinary planning. Further treatments of these patients were performed at Ege University Orthopedics Surgery Department. Due to the fact that the lesions in this group were mostly not evaluated using MRI before unplanned surgery and that there is a lack of information in the first post-operative center pathology reports, data about the depth of the tumors and excision type (whole or piecemeal) were mostly unavailable. Eighty-five patients in the UE group were referred to Ege University, School of Medicine Orthopedic Surgery Department soon after UEs. The surgical resection sites of these patients were evaluated using MRI and discussed in multidisciplinary meetings, and none of these patients' surgical resection sites had radiologically detectable residual tumors. The mean time interval between UE and re-excision among these patients was 4 months (range, 1-30 months).

Sixty patients in the UE group were referred with radiologically evident tumors (recurrence or residual tumor). Most of the patients in this residual tumor group received neoadjuvant radiation therapy and chemotherapy in selected cases. The mean time interval between UE and re-excision among these patients was 11.9 months (range, 1-24 months).

This study included patients who had been treated from 2000 to 2018. During this period of time, different chemotherapy protocols were administered as neoadjuvant or adjuvant therapies. Adjuvant therapy protocols included 50.4 Gy (1.8-2 Gy daily doses) external beam radiation therapy, a combination of mitomycin–cisplatin–doxorubicin as chemotherapy protocol between 1994 and 2007, and a combination of cisplatin–doxorubicin as chemotherapy protocol between 2007 and 2018. Discussing the efficacy of these different protocols in detail is beyond the scope of this study and will be the subject of another study.

Patient characteristics, tumor localization, and tumor types of the study groups are presented in Table 1.

FNCLCC Grade 1 tumors were categorized as low-grade tumors, and grade 2 and 3 tumors were categorized as high-grade tumors. The PE group consisted of 38 (11%) low-grade, 300 (86.9%) high-grade, and 7 (2.1%) undetermined tumors. The UE group consisted of 16 (11%) low-grade, 128 (88.2%) high-grade, and 1 (0.8%) undetermined tumors. There was no statistically significant difference between the study groups in terms of tumor grades ($P = .966$). Patients with high-grade tumors had a 2.8 times higher risk of mortality than patients with low-grade tumors (log-rank test, $P = .002$; Cox regression, $P = .003$; HR = 2.805; 95% CI = 1.403/5.503).

The study groups were compared in terms of pre-definitive surgery lung metastasis. Thirty-one (9%) patients in the PE group had preoperative lung metastasis, while 19 (13.1%) patients in the UE group had preoperative lung metastasis. There was no statistically significant difference between the groups in terms of pre-definitive surgery lung metastasis ($P = .191$). Patients with pre-definitive surgery lung metastasis had a 5.1 times higher risk of mortality than patients without pre-definitive surgery lung metastasis (log rank test, $P < .001$; Cox regression, $P < .001$; HR = 5.114, 95% CI = 3.511/7.448).

The relationships between tumor size (diameter) and LRFS, MFS, and OS were analyzed. There was no statistically significant relationship

Table 1. Patient characteristics, tumor locations, and tumor types of study groups

		Study groups		
		Planned excision (n = 345)	**Unplanned excision (n = 145)**	***P***
Mean age		50.1	47.3	0.131
Mean follow-up		57.1 months	55.8 months	
Tumor size (cm)		10.2 cm	6.2 cm	<0.001
Tumor grade	Low	38 (11)	16 (11)	0.966
	High	300 (86.9)	128 (88.3)	
Preoperative lung metastasis	Positive	31 (9)	19 (13.1)	0.191
	Negative	314 (81)	126 (86.9)	
Location	Upper Ext.	65 (18.8)	35 (24.1)	0.002
	Thorax	10 (2.9)	17 (11.8)	
	Pelvis	6 (1.7)	2 (1.4)	
	Gluteal	8 (2.4)	4 (2.8)	
	Thigh	197 (57.1)	60 (41.4)	
	Cruris	46 (13.3)	18 (12.4)	
	Foot	13 (3.8)	9 (6.2)	
Tumor types	DFSP	8 (2.3)	11 (7.6)	0.004
	FS	21 (6.1)	17 (11.7)	
	LMS	15 (4.3)	10 (6.9)	
	LS	93 (27)	21 (14.5)	
	MPNST	18 (5.2)	5 (3.4)	
	PCS	112 (32.5)	46 (31.7)	
	SS	36 (10.4)	18 (12.4)	
	Others	42 (12.2)	17 (11.7)	

DFSP, dermatofibrosarcoma protuberans; FS, fibrosarcoma; LMS, leiomyosarcoma; LS, liposarcoma; MPNST, malignant peripheral nerve sheath tumor; PCS, pleomorphic cell sarcoma; SS, synovial sarcoma.

between tumor size and LRFS (P=.176). The risk of developing metastasis increased by 1.068 times with each 1 cm increase in tumor diameter (P < .001, HR=1.068, 95% CI=1.042/1.096). The risk of mortality increased by 1.066 times with each 1 cm increase in tumor diameter (P < .001, HR=1.066, 95% CI=1.043/1.089).

Thirty (8.7%) patients in the PE group had local recurrences, while 26 (17.9%) patients in the UE group had local recurrences after definitive surgery performed in our department. Patients in the UE group had a 2.13 times higher risk of local recurrence than patients in the PE group (P=0.005, HR=2.129928, 95% CI=1.262/3.593). Five-year LRFS rates of the UE and PE groups were 84.1% and 91.9%, respectively (P=.014).

The effects of local recurrence on MFS and OS were also analyzed. While performing this analysis, in order to make an appropriate comparison and to eliminate possible selection biases, only patients with high-grade tumors larger than 5 cm and who had no lung metastases prior to definitive surgery were selected. In univariate analysis, patients with local recurrence (n=31) were found to have a 2.1 times higher risk of metastasis than patients without local recurrence (n=218) (n=249; log rank test, P=.002; Cox regression, P=.003; HR=2.152; 95% CI=1.287/3.596, Figure 2A). Patients with local recurrence had 1.7 times higher risk of mortality than patients without local recurrence (n=257; log rank test, P=.032; Cox regression, P=.035; HR=1.736, 95% CI=1.041/2.894, Figure 2B).

Multivariate analysis revealed that local recurrence increased the risk of metastasis by 2.3 times and increased the risk of mortality by 1.7 times (Tables 2A and B).

After excluding patients who had lung metastasis (n=50) before definitive surgery, non-metastatic patients were evaluated and it was found that 86 (27.8%) non-metastatic patients in the PE group and 30 (24%) non-metastatic patients in the UE group progressed into the metastatic stage during the follow-up period. According to the time to event survival analysis, there was no difference in terms of MFS between the study groups (log-rank test, P=.278, Figure 3A). Likewise, there was no difference in terms of OS between the study groups (log-rank test, P=.848, Figure 3B). The 5-year MFS rates for the UE and PE groups were 76.4% and 73.6%, respectively (P=.417), and the 5-year OS rates for the UE and PE groups were 70.3% and 73.9%, respectively (P=.656).

In 85 patients in the UE group, MRI examination was found to be negative for residual tumor. However, in this group of patients, pathological examination revealed tumor residuals in 57 (67%) patients. The sensitivity of MRI in detecting residual tumors in the UE group was 51.3%, the specificity was 100%, the positive predictive value was 100%, the negative predictive value was 33%, and the accuracy was 60.7%.

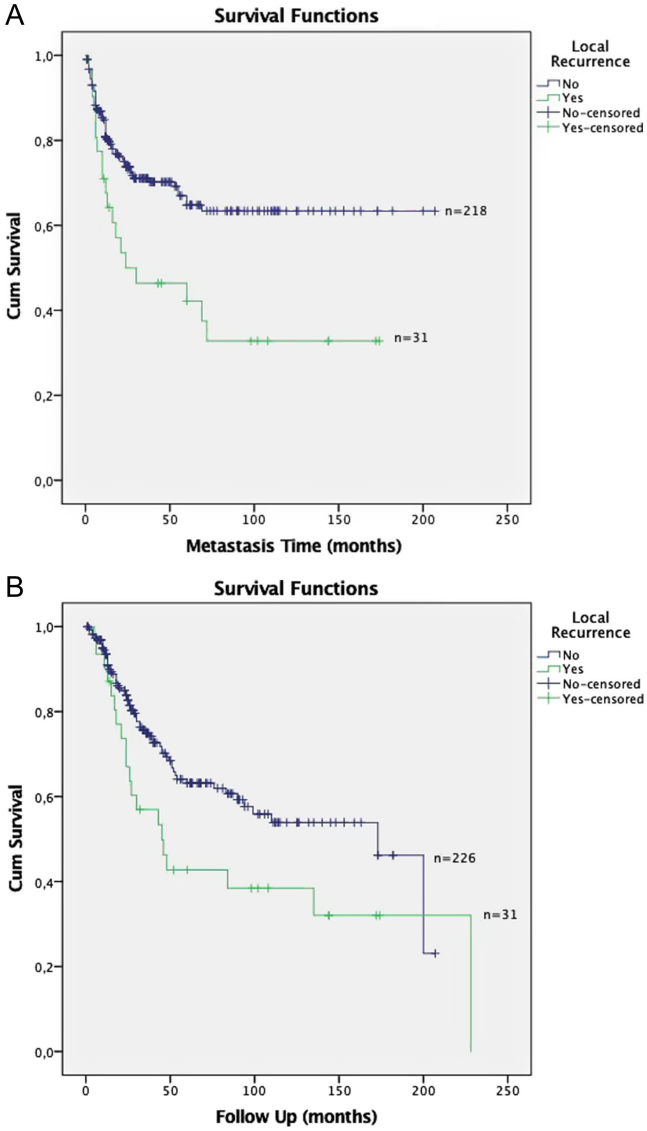

Figure 2. A, B. (A). Kaplan–Meier metastasis-free survival analysis of patients (no preoperative metastasis, tumor > 5 cm, high grade) with and without local recurrence (log rank test, P=.002) (Cox regression, P=.003; HR=2.152, 95% CI=1.287/3.596). (B). Kaplan–Meier overall survival analysis of patients (no preoperative metastasis, tumor > 5 cm, high grade) with and without local recurrence (log rank test, P=.032) (Cox regression, P=.035; HR=1.736 95% CI=1.041/2.894).

Discussion

The effect of UEs on LRFS and MFS is controversial. Some studies have reported that UEs of soft tissue sarcomas negatively affect

Table 2. A, B. Multivariate analysis of (A) metastasis-free survival and (B) overall survival (patients with preoperative lung metastasis are excluded).

A. Multivariate analysis of metastasis-free survival				
Variables	**Patients (n=408)**	***P***	**Exp (B)**	**95% CI for Exp (B)**
Tumor size	≤5 cm (128), >5 cm (280)	0.001	2.296	1.401/3.176
Tumor grade	Low (55), high (353)	0.014	3.119	1.264/7.696
UE versus PE	UE (106), PE (302)	1.000	1.000	0.634/1.576
Local recurrence	No (360), yes (48)	0.000	2.301	1.469/3.604
B. Multivariate analysis of overall survival				
Variables	**Patients (n=418)**	***P***	**Exp (B)**	**95% CI for Exp (B)**
Tumor size	≤5 cm (129), >5 cm (289)	0.000	3.253	1.924/5.498
Tumor grade	Low (56), High (362)	0.067	1.976	0.954/4.093
UE versus PE	UE (109), PE (309)	0.310	1.258	0.808/1.958
Local recurrence	No (369), yes (49)	0.015	1.761	1.116/2.779

UE, unplanned excision; PE, planned excision.

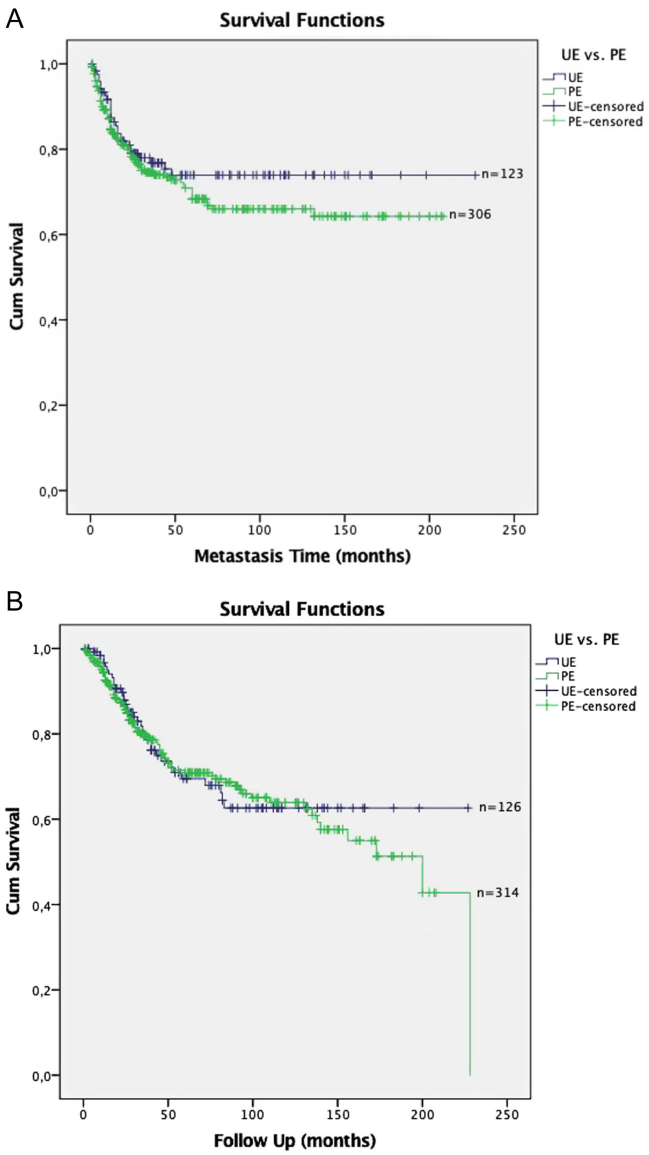

Figure 3. A, B. (A). Kaplan–Meier metastasis-free survival curves of planned excision (group 1) and unplanned excision (group 2) study groups (log rank test, $P=.278$). (B). Kaplan–Meier overall survival curves of planned excision (group 1) and unplanned excision (group 2) study groups (log rank test, $P=.848$)

LRFS and MFS, despite appropriate further oncological treatments.[13-15] On the other hand, other studies showed that oncological outcomes similar to patients with planned surgeries can be achieved in patients who had undergone UEs; if appropriate, further oncological treatments such as wide re-resections, bed resections, and adjuvant radiotherapy and/or chemotherapy are utilized.[4,7-11,16] In our study, the UE group was found to have a 2.13 times higher risk of local recurrence than the PE group ($P=.005$, HR=2.129928, 95% CI=1.262/3.593).

In a recent meta-analysis, Sacchetti et al[17] reported that patients who had local recurrence had a 1.5 times higher risk of distant metastasis and 2.3 times higher risk of mortality. The effects of local recurrences on MFS and OS were also analyzed in our study. Patients with local recurrence had a 1.965 times higher risk of metastasis ($P=0.008$, HR=1.965, 95% CI=1.194/3.233) and 1.656 times higher risk of mortality than patients without local recurrence ($P=.047$, HR=1.656, 95% CI=1.006/2.726).

Thirty-one (9%) patients in the PE group had preoperative lung metastasis, while 19 (13.1%) patients in the UE group had preoperative lung metastasis. There was no statistically significant difference between groups in terms of pre-definitive surgery lung metastasis ($P=0.191$). Although there was no statistically significant difference, the rate of lung metastasis before pre-definitive surgery was found to be higher in patients in the UE group. Rehders et al[14] reported that patients who had tumor residue in re-excision specimens had a higher risk of metastasis than patients who did not have tumoral residue in re-excision specimens (53% vs. 24%, $P=.001$). In our series, 13 (22.8%) out of 57 patients who had residual tumor tissue in re-excision specimens had distant metastasis, while 2 (7.1%) out of 28 patients who did not have residual tumor tissue in re-excision specimens had distant metastasis (log-rank test, $P=.099$). Although there was no statistically significant difference, the MFS rate was found to be lower in patients with residual tumors during the follow-up. These two results may be due to the loss of time between the two excisions in the UE group and may indicate the importance of having re-excisions performed soon after UEs.

Several studies have reported that tumor size is one of the most important prognostic factors in MFS and OS.[18-22] Shemesh et al[23] compared UE and PE patients and reported a significant difference in size between the two groups (4.9 cm vs. 9.4 cm). Likewise, one of the major differences between the study groups of our study was tumor size. The mean tumor size was 10.2 cm in the PE group and 6.2 cm in the UE group. Although there was a 4 cm difference in mean tumor size between the study groups, there was no statistically significant difference in MFS and OS (log-rank tests, $P=.278$ and $P=.848$). In a recent propensity score matching study, Nakamura et al[16] reported no differences between UE and PE groups in terms of disease-specific survival. Likewise, Arai et al[7] compared 168 PE patients with 63 UE patients and reported similar LRFS, MFS, and OS rates in the study groups, even though the UE group had smaller and more superficial tumors than the PE group. These results may indicate the importance of having initial definitive treatment in tumor centers, as unplanned group patients, who had smaller tumors than planned group patients and who would have had better results if they had been treated in sarcoma centers initially, had similar outcomes with planned group patients.

Chui et al[24] reported that 47.8% of patients' re-excision specimens contained tumoral residue, and Hanasilo et al[25] reported that 91.3% of patients' re-excision specimens contained tumoral residue. Koulaxouzidis et al[5] reported that 53.13% of tumoral residual cells were found after re-excisions, with 46.9% of the first pathological reports being misleading. In addition, the LRFS rates of UE patients were lower, and the mean local recurrence time was also shorter. In our study, 57 out of 85 patients (67.1%) in the UE group who did not have any clinically or radiologically detectable recurrent disease had a residual tumor in re-excision specimens. Moreover, with today's imaging technology, detecting the existence of microscopic tumor residual cells in patients with marginal or intralesional excisions is not always possible.[26,27] Therefore, these results may indicate the importance of re-excisions, which are performed soon after UEs.

There were several limitations in this study. First, most of the patients in the UE group did not have appropriate imaging studies before the initial excision. Therefore, the tumor depth (over/under fascia) of the study groups could not be compared. Additionally, due

to the lack of preoperative MRI studies, the mean tumor sizes of the UE group have mostly been assessed from pathological reports, while the mean tumor sizes for the PE group have been assessed from both MRI reports and pathological examination reports. Morbidity and the need for soft tissue reconstruction of UEs could not be analyzed due to a lack of data. How neoadjuvant and adjuvant therapies affect MFS and OS is the subject of future research; hence, this issue was not included in this study and can be considered as one of the limitations of our study.

Despite the fact that local recurrence is much more common in the UE group, this outcome does not seem to affect MFS or OS. These results indicate that similar outcomes can be achieved if UE patients are referred and treated properly with wide re-resections with/without adjuvant therapies in orthopedic oncology centers.

Local recurrence continues to be a major problem because patients with local recurrence face higher risks of metastasis and mortality than patients without local recurrence. Preoperative planning, aiming for wide surgical margins, and a multidisciplinary approach are essential in order to avoid local recurrence and to reach an optimal oncologic outcome in soft tissue sarcoma treatment.

Ethics Committee Approval: Ethical committee approval was received from the Medical Researches Ethics Committee of Ege University, School of Medicine (approval no: 99169796-050.06.04).

Informed Consent: The requirement for informed consent was waived because of the retrospective design of the study.

Author Contributions: Design – D.S.; Supervision – D.S.; Data Collection and/or Processing – A.C.A., B.Y., İ.T.; Analysis and/or Interpretation – F.S.; Literature Review – H.K.; Writing – A.C.A.

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