Scientific Article

Radiation Therapy Before Repeat Wide Resection for Unplanned Surgery of Soft Tissue Sarcoma (“Oops” Operation) Results in Improved Disease-Free Survival

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Abstract

Purpose: The main goal of treatment of soft-tissue sarcomas is achieving wide negative margins to improve local control and prevent recurrence. The role of radiation therapy (RT) is well established in sarcomas of the extremities; however, its role in unplanned surgery of soft-tissue sarcoma (when a mass presumed to be benign is resected and the pathology comes back as sarcoma, usually referred to as an “oops” operation) is inconclusive. This article reports on the effect of RT after an unplanned surgery before the reresection.

Methods and Materials: A total of 65 patients who had undergone an unplanned resection of a postoperatively diagnosed soft-tissue sarcoma were treated with RT and/or surgery and retrospectively evaluated for disease progression. Treatment started with RT in 49 cases (75.4%), including 8 cases of no further surgery. A repeat wide resection was performed directly after the initial surgery in 16 patients, followed by RT in 15 of them.

Results: The disease recurred in 7 out of 49 patients (14.3%) who received RT first and in 9 out of 16 (56.2%) who underwent reoperation before RT ($P = .001$). Disease-free progression was higher in cases of low-grade malignancy ($P = .049$). A clinical diagnosis of lipoma was associated with a better outcome than a diagnosis of nonlipoma ($P = .034$). The presence of residual tumor at reoperation did not affect disease control. Patient age, time between symptom onset and diagnosis, hospital level of initial diagnosis (tertiary versus nontertiary), anatomic site, tumor size, and margin status at the initial excisional biopsy were not significantly correlated with the outcome.

Conclusion: Initiating treatment with RT followed by unplanned “oops” resection of soft-tissue sarcoma before the reresection improved disease-free survival as opposed to vice versa.

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Introduction

Soft-tissue sarcoma (STS) is a rare malignant tumor, with 13,460 new cases having been registered in the US during 2020.1 General practitioners or general surgeons...
are commonly first to diagnose soft-tissue tumors as benign and proceed directly to excision without appropriate imaging studies and staging procedures. Unplanned surgery of an STS results in inferior outcomes. The negative effect of the violation of oncological principles in the resection of STS is well known, but patient management is not always straightforward when the pathologic evaluation reveals a diagnosis of sarcoma. In a recently published executive summary of an American Society for Radiation Oncology Clinical Practice Guideline in the treatment of STS, the oncological surgery is recommended after an unplanned resection of STS. The addition of radiation therapy (RT) in this case shows a strong recommendation level. Saeed et al showed in single-institution study that preoperative RT might improve local control and disease-free survival in unplanned surgery of STS (when a mass presumed to be benign is resected and the pathology comes back as sarcoma, usually referred to as an "oops" operation).

The published data on the role of adjuvant RT in this clinical scenario is nonconclusive. The treatment algorithm is well established for classic STS presentation and corroborating pathologic diagnosis and staging, and it is accepted that small superficial tumors can be followed without additional treatment. The addition of RT in stage 3 STS has been recognized to significantly improve local control. It has also been proven that preoperative RT achieves local control similar to that of postoperative RT in stage 3 STS, and with better functional outcome. Kattan et al developed a postoperative nomogram for 12-year sarcoma-specific death according to which tumor size, grade, location in the body, and relation to the fascia, as well as the patient’s sex and the surgical margins, are important for determining prognosis. The management of patients who have undergone unplanned resection of STS, however, is still not clear. It has been shown that the addition of RT may improve local control in case of an unplanned surgery. RT is usually recommended after the reresection, considering the risk of the wound complications. We developed a protocol of intermittent RT after the primary unplanned resection of an STS before the reresection. The primary goal of this observational longitudinal cohort study was to compare the long-term results of patients who had undergone a primary unplanned STS resection and were subsequently treated with RT before the reoperation with those of patients who received irradiation after the second surgery, a wide resection.

### Materials and Methods

Approval of our institutional review board to conduct this study was obtained in February 2021. Informed consent was waived for this retrospective medical record review.

### Patient population

A total of 488 patients diagnosed with STS were detected through a review of electronic medical records (Chameleon system) at our medical center in the years 2013 to 2020. There were 65 cases included in our study in which the diagnosis of STS was done after unplanned surgery. Upon the adoption of the preoperative RT as a standard of treatment of properly diagnosed and staged soft-tissue sarcoma of the extremities in the early 2000s, our institution applied a similar approach to the "oops" operations. It was decided that reoperation with neo-adjuvant irradiation is recommended in any case of unplanned resection, irrespective of the local stage, owing to the violation of general principals of the surgery, which is common in "oops" operations. There were patients during the same period who received RT after the reresection performed in other centers. There was also 1 patient who did not receive irradiation at all.

No patients with benign tumors were treated with irradiation therapy or included in our study population.

### Treatment protocol and data acquisition

The protocol of the neo-adjuvant irradiation before the reresection included simulation with a wire placed on a scar. In most cases, the clinical target volume (CTV) was formed based on clinical examination, recognition of the former tumor location by the patient, description of any available imaging (mostly ultrasound), the postoperative scar hematoma, and the pathology results. It included a 1.5- to 2-cm transversal dimension and usually was 4 cm longitudinally around the hematoma or the virtually restored volume of the initial tumor. It also included the postoperative scar and drainage places. The planning treatment volume included an additional 1-cm margin around the CTV. There was no principal difference in the CTV in the irradiation before or after reresection. The treatment was provided by photons or electrons, depending on the physician’s decision. The dose-fractionation scheme included 56 Gy in 28 fractions in the preoperative setting, prescribed to the planning treatment volume, and 60 Gy in the setting after the second surgery. We chose a dose of 56 Gy after the "oops" irradiation (higher than the standard 50 Gy in regular fractionation in the usually diagnosed STS), assuming the worse scenario of tumor-bed violation. If the RT was provided after the second surgery, the dose was more than 60 Gy, 2 Gy per fraction, as is globally accepted. The reresection was usually done 4 to 6 months after the completion of RT, or in cases when the second surgery occurred first, at the time of the wound healing. All patients were followed clinically every 2 to 3 months for the first 2 years and every 4 to 6 months thereafter.
Clinical characteristics, including demographics, symptom duration, initial clinical and pathologic diagnoses, clinical staging, and the status of surgical margins after biopsy were evaluated for disease-free survival (DFS). We defined survival without recurrence until the last visit as a “good” outcome and others as “bad” outcomes.

**Statistical methods**

Fisher’s exact test was used for the analysis of different clinical variables and the choice of starting treatment with RT or with repeat surgery. After it emerged that the decision to start with RT was strongly correlated with tumor grade, we repeated the analysis for cases with tumor grades higher than 1. We also performed a survival analysis to test the effect of various variables on survival time. The time to outcome was defined starting from the date of the first surgery to the time of death, recurrence, or end of follow-up, between the years 2013 to 2020. In addition to Cox proportional regression, we used a parametric survival analysis for interval-censored data, because the time of recurrence could not be defined precisely. To maximize the width of the interval for outcomes other than death, we defined the date of absence of recurrence at the start of follow-up. We tested various parametric distributions (exponential, Weibull, Gompertz, lognormal, and logistic) to check the reliability of our results. All P values were 2-sided, and a P value < .05 was considered significant. The analysis was done using Stata, version 16 SE.

**Results**

We conducted a retrospective analysis of 65 patients treated in our department for unplanned surgery for superficial STS. They comprised 39 males and 26 females, and the median age of the cohort was 66 years (range, 18-97 years). The patient and tumor characteristics are listed in Table 1. Most of the patients (49 [75.4%]) received RT to the primary tumor bed or to residual disease at a median (SD) dose of 56 Gy (7.5 Gy) in standard fractionation of 1.8 to 2 Gy per fraction (5 times a week for 4-6 weeks) before definitive surgery; 16 patients (16.6%) proceeded directly to wide local resection, 15 of them after RT. Eight patients did not undergo the repeat wide resection. The results are presented in Table 2.

| Characteristic                                      | Patients, No. (%) |
|-----------------------------------------------------|------------------|
| **Tumor grade**                                     |                  |
| 1                                                   | 15 (23.1)        |
| 2                                                   | 3 (4.6)          |
| 3                                                   | 47 (72.3)        |
| **Histology**                                       |                  |
| Angiosarcoma                                        | 1 (1.54)         |
| Fibrosarcoma                                        | 10 (15.39)       |
| Leomyosarcoma                                       | 11 (16.92)       |
| Liposarcoma                                         | 5 (7.69)         |
| Malignant peripheral nerve sheath tumor             | 5 (7.69)         |
| Pleomorphic sarcoma                                 | 10 (15.39)       |
| Spindle sarcoma                                     | 7 (10.77)        |
| Synovial sarcoma                                    | 6 (9.23)         |
| Not otherwise specified                             | 10 (15.39)       |
| **Tumor size**                                      |                  |
| Median, cm                                          | 4.41             |
| <5 cm                                               | 36 (55.4)        |
| >5 cm                                               | 18 (27.7)        |
| No data                                             | 11 (16.9)        |
| **Level of diagnosing hospital**                    |                  |
| Tertiary                                            | 7 (10.8)         |
| Nontertiary                                         | 58 (89.2)        |

The rate of acute wound complications, including dehiscence and infection, in the group receiving RT before the second resection was 26.2% (11 out of 42), compared with 25% (4 out of 16) patients in the other group.

The STS recurred in 7 out of 49 patients (14.3%) who received RT as the first step of treatment (3 with both local and distal metastasis, 2 with local recurrence alone, and 2 with distal metastasis only). The disease recurred in 9 out of 16 patients (56.25%) who started with a repeat wide resection (6 with both local and distal metastasis, 1 with local recurrence alone, and 2 with only distal metastasis).
metastasis) \((P = .001)\). Distant metastasis occurred in 5 out of 49 (10.2%) and 8 out of 16 (50%) patients who had RT first or repeat wide resection first, respectively. The most important factor associated with improvement of DFS was following the protocol of RT before the repeat wide excision. The relative risk among those starting with surgery versus starting with RT was 4.29 (confidence interval [CI], 1.92-9.56). Disease progressed in 2 of 8 patients who did not undergo a repeat wide resection after RT. Tumors with high-grade malignancy were associated with a worse outcome. The STS recurred in 1 out of 15 patients with a grade 1 tumor, 2 out of 3 with a grade 2 tumor, and 12 out of 45 with a grade 3 tumor \((P = .049)\). The Kaplan-Meier survival estimates are given in Fig. 1.

An initial clinical diagnosis of lipoma versus nonlipoma before the first surgery was associated with a significantly better outcome. The disease recurred in only 1 of 17 patients (26.15%) suspected of having lipoma, whereas it recurred in 15 out of 47 patients (31.9%) with other diagnoses \((P = .034)\). The relative risk of recurrence among patients with nonlipoma versus lipoma was 5.31 (CI, 0.76-37.23).

### Table 2 Results

| Characteristic                              | Patients, No. (%) |
|--------------------------------------------|-------------------|
|                                            | No disease progression (n = 49 [75.4%]) | Disease progression, recurrence, or death (n = 16 [24.6%]) |
| Age, mean (SD), y                           | 57.49 (18.72)     | 59.9 (16.38)     |
| Treatment protocol                         |                   |                   |
| RT first                                   | 42 (85.7)         | 7 (43.75)         |
| Surgery first                              | 7 (14.3)          | 9 (56.25)         |
| Initial diagnosis                          |                   |                   |
| Lipoma                                     | 16 (32.7)         | 1 (6.25)          |
| Nonlipoma                                  | 33 (67.3)         | 15 (93.75)        |
| Grade                                      |                   |                   |
| 1                                          | 14 (28.6)         | 1 (6.25)          |
| 2                                          | 1 (2)             | 2 (12.5)          |
| 3                                          | 34 (69.4)         | 13 (81.25)        |
| Findings in repeat resection               |                   |                   |
| Residual tumor                             | 26 (53)           | 9 (56.25)         |
| No tumor found                             | 19 (38.8)         | 3 (18.75)         |
| No pathology (no second surgery)           | 4 (8.2)           | 4 (25)            |
| Level of diagnosing hospital               |                   |                   |
| Tertiary                                   | 5 (10.2)          | 2 (13.3)          |
| Nontertiary                                | 23 (46.9)         | 8 (53.3)          |
| Ambulatory                                 | 21 (42.9)         | 5 (33.3)          |
| Anatomic site                              |                   |                   |
| Upper limb                                 | 12 (24.5)         | 2 (12.5)          |
| Lower limb                                 | 28 (57.1)         | 8 (50)            |
| Trunk                                      | 9 (18.4)          | 6 (37.5)          |
| Margins after first surgery                |                   |                   |
| Positive                                   | 43 (87.8)         | 13 (81.25)        |
| Negative                                   | 2 (4.1)           | 0 (0)             |
| Unknown                                    | 4 (8.1)           | 3 (18.75)         |
| Tumor size                                 |                   |                   |
| <5 cm                                      | 31 (73.8)         | 8 (72.7)          |
| >5 cm                                      | 11 (26.2)         | 3 (27.3)          |
Patient age, time between symptom onset and date of diagnosis, the hospital level of initial diagnosis (tertiary vs nontertiary), the anatomic site of the tumor, the size of the tumor (larger or smaller than 5 cm), and the status of margins at the initial excisional biopsy were not statistically correlated with the outcome. The presence of residual disease at the second surgery (wide re-excision) also did not have an additive effect on the outcome. The full clinical characteristics were missing for most patients owing to the retrospective nature of the study. The applied statistics took into account the incomplete data.

Analysis of a subsample of 50 cases with higher-grade tumors (grades 2 and 3) yielded similar results. The only variables that were significantly related to the outcome were the starting treatment (RT or surgery) and the clinical diagnosis (lipoma or nonlipoma). Recurrence of STS occurred in 9 out of 15 patients who started with surgery and in only 6 out of 35 patients who started with irradiation (relative risk, 3.5; CI, 1.51-8.09; \( P = .006 \)). There were 14 recurrences among 36 nonlipoma cases and only 1 recurrence among 14 lipoma cases (relative risk, 5.44; CI, 90.79-37.6; \( P = .039 \)).

Starting treatment with RT was the only significant covariate in the univariate Cox regression, with a hazard ratio of 5.88 (95% CI, 2.16-15.95; \( P = .001 \)).

### Table 3  Characteristic of patients receiving radiation therapy first vs surgery first

| Characteristic                  | Patients, No. (%) |
|--------------------------------|-------------------|
|                                | RT first (n = 49 [75.4%]) | Surgery first (n = 16 [24.6%]) |
| Age, median, y                 | 64                | 67.5               |
| Initial diagnosis              |                   |                   |
| Lipoma                         | 15 (30.61)        | 2 (12.5)           |
| Nonlipoma                      | 34 (69.39)        | 14 (87.5)          |
| Grade                          |                   |                   |
| 1                              | 15 (30.61)        | 0 (0)              |
| 2                              | 2 (4.08)          | 1 (6.25)           |
| 3                              | 32 (65.31)        | 15 (93.75)         |
| Findings in repeat resection   |                   |                   |
| Residual tumor                 | 22 (44.9)         | 13 (81.25)         |
| No tumor found                 | 20 (40.82)        | 2 (12.5)           |
| No pathology                   | 7 (14.28)         | 1 (6.25)           |
| Margins after first surgery    |                   |                   |
| Positive                       | 42 (85.71)        | 15 (93.75)         |
| Negative                       | 2 (4.08)          | 0 (0)              |
| Unknown                        | 5 (10.2)          | 1 (6.25)           |
| Tumor size                     |                   |                   |
| Mean (SD), cm                  | 4.3 (2.39)        | 5.1 (2.47)         |
| <5 cm                          | 31 (63.27)        | 8 (50)             |
| >5 cm                          | 12 (24.49)        | 3 (18.75)          |
| Time from diagnosis to radiation therapy, median (SD), mo | 3 (10) | 9 (65) |
| Acute wound complications      |                   |                   |
| No complications               | 31 (73.8)         | 10 (62.5)          |
| Acute complication             | 11 (26.2)         | 4 (25)             |

**Figure 1**  Kaplan-Meier survival estimates.
diagnosis (hazard ratio, 6.07; \( P = .08 \)) was associated with grade 2 or 3 compared with grade 1 (hazard ratio, 6.7; \( P = .066 \)) but did not reach a level of significance. The interval-censored regression confirmed these results for all tested distributions.

In addition, there were relatively few deaths among the study participants during the study period (4 that were related to the main diagnosis of STS and 1 that was not related).

**Discussion**

The initial management of superficial tumors across the body is often performed by primary physicians or general surgeons. A situation when a mass presumed to be benign is resected and the pathology comes back as sarcoma is often referred to as an “oops” operation. The reported rate of unplanned resection of STS is high: 18% to 50%. In our tertiary hospital, 65 out of 488 operations (13%) performed for STS in the past 7 years were initially diagnosed as benign tumors after an unplanned resection. Rehders et al showed that the results of “oops operations” are inferior to those of planned surgery for STS. Radiation therapy was reported to significantly improve local control in stage 3 STS in the extremities. Neo-adjuvant RT has been shown to result in better functional outcomes with similar local control and noncompromising overall survival. Haas et al emphasized the value of RT in the treatment of patients with STS.

According to the predictive nomogram for treatment of STS, a small, superficial sarcoma, resected with adequate margins, does not need further RT owing to the good results of surgery alone. Smolle et al showed that RT significantly improves the results of treatment if sarcoma is revealed after the unplanned surgery. The authors stated, however that RT should be recommended in the adjuvant rather than the neo-adjuvant setting, considering the high risk of wound complications. The question of timing of RT before or after the reresection is still unresolved. It is also unknown whether the tumor or tumor bed remaining after the first surgery, soiled by inappropriate surgery, is associated with a higher than usual risk of local recurrence. Therefore, we regarded this situation differently as accepted today (adjuvant or neo-adjuvant RT). We studied the role of RT in a dose of 56 Gy in 28 fractions (larger than the usual dose of 50 Gy in preoperative RT) between the unplanned surgery and a definitive wide resection. The most important result of our analysis was significantly superior DFS in patients whose treatment regimen started with RT as opposed to those who proceeded directly to a repeat wide resection.

The common clinical characteristics for defining the prognosis and choice of treatment in classically staged STS (size, anatomic location, histopathology, and involved margins at surgery) were not correlated with the primary outcome in our study. As expected, a higher grade of tumor was correlated with a worse outcome. Although more patients with high-grade malignancy were found in the group receiving RT after the second surgery, after the subanalysis of this parameter, the outcome of DFS was better for the patients receiving RT before the second resection. Most of the clinical diagnoses of lipoma were associated with high-grade malignancy on pathologic examination. It was intriguing to observe that patients receiving surgery primarily for the clinical diagnosis of lipoma achieved better results compared with patients with other diagnoses. Notably, the higher rate of distal metastasis was observed in the group who received RT after the repeat wide resection.

Unexpectedly, the presence of residual tumor at the second surgery did not significantly affect DFS. The early introduction of RT in the first group may theoretically be of added value for the improved results. However, this statement needs further investigation. The important observation in our research was a similar rate of acute wound complications in both groups.

The relatively small number of patients in our cohort and the design of our study precluded an analysis of overall survival as well as that of any potentially harmful effect of RT in terms of secondary malignancies or other sequelae. We assume that RT has a minimal effect on survival in the setting of “oops” operations, based on the results of previous studies.

**Conclusion**

The results of the current analysis indicate that RT should be administered before the definitive operation in cases of unplanned surgery. Multicenter randomized studies are warranted to further validate this protocol.

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