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

Running title: RT in "Oops" surgery for soft tissue sarcoma

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abstract

BACKGROUND: 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 "Oops" operations is inconclusive. We report on the effect of RT after an unplanned surgery before the re-resection. **METHODS**: Sixty-five 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 (75.4%) cases, 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 (14.3%) patients who received RT first and in 9 out of 16 (56.25%) who underwent reoperation before RT (P= .001). Disease-free progression was higher in cases of low-grade malignancy (P = .049). The clinical diagnosis of lipoma was associated with better outcome than non-lipoma (P = .034). The presence of residual tumor at reoperation did not impact disease control. Patient age, time between symptom onset and diagnosis, hospital level of initial diagnosis (tertiary versus non-tertiary), anatomic site, tumor size, and margin status at the initial excisional biopsy were not significantly correlated with outcome. **CONCLUSION**: Initiating treatment with RT followed by unplanned "oops" resection of soft tissue sarcoma before the re-resection improves disease free survival as opposed to vice –versa.

KEYWORDS: sarcoma, irradiation, unplanned, resection

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 [2]. Unplanned surgery of an STS results in inferior outcomes [3]. The negative effect of the violation of oncological principles in the resection of STS is well known [4], but patient management is not always straightforward when the pathological evaluation reveals a diagnosis of sarcoma. In a recently published executive summary of an ASTRO Clinical Practice Guideline in the treatment of soft tissue sarcoma, the oncological surgery is recommended after an unplanned resection of STS. The addition of radiation therapy in this case shows a strong recommendation level [5]. Saeed et al showed in single institution study that preoperative RT might improve local control and disease-free survival in “Oops” operations of STS. [6]

The published data on the role of adjuvant radiation therapy (RT) in this clinical scenario is non-conclusive [7]. The treatment algorithm is well established for classic STS presentation and corroborating pathological diagnosis and staging, and it is accepted that small superficial tumors can be followed without additional treatment [8][9]. The addition of RT in stage 3 STS is recognized as significantly improving local control [10][11]. 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 [12]. 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, sex, and surgical margins are important for determining prognosis [13]. The management of patients who had undergone unplanned resection of STS, however, is still

not clear [14]. It has been shown that the addition of radiation therapy may improve the local control it case of an unplanned surgery. It is usually recommended after the re-resection considering the risk of the wound complications [15]. We developed a protocol of intermittent RT after the primary unplanned resection of an STS before the re-resection. The primary goal of this observational longitudinal cohort study was to compare the long-term results between the patients who had undergone a primary unplanned STS resection and were subsequently treated with RT before the reoperation with those who received irradiation after the 2nd re-wide resection.

MATERIALS AND METHODS

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

Patient Population

Four hundred and eighty-eight patients diagnosed with STS were detected through a review of electronic medical records (Chameleon system) at our Medical Center in years 2013 and 2020. There were 65 cases included into our study in which the diagnosis of STS was done after unplanned surgery. Upon the adoption of the preoperative radiation therapy as a standard of treatment of properly diagnosed and staged soft tissue sarcoma of extremities in early 2000s, our institution applied the similar approach to the “oops” operations. It was decided that re-operation with neo-adjuvant irradiation is recommended in any case of unplanned resection, irrespective of the local stage due to the violation of general principals of the surgery, which are common on “oops” operations. There were patients at the same period who received radiation therapy after

the re- resection performed in other centers. There was also one 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 re- resection included the simulation with a wire placed on a scar. In most cases the CTV formed based on clinical examination, recognition of the former tumor location by patient, description of any available imaging (mostly, ultrasound), postoperative scar hematoma and the pathology results. It included 1.5-2 cm in transversal dimension and usually 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 (PTV) included an additional 1 cm margin around the CTV. There was no principal difference in the CTV volume in the pre or post re-resection irradiation. The treatment was provided by photons or electrons depend on the physician's decision. The dose- fractionation scheme included 56 Gy in 28 fractions in the preoperative setting, prescribed to PTV in the preoperative setting and 60 Gy in the post 2nd surgery. We choose dose of 56 Gy in the post "oops" irradiation (higher than a standard 50 Gy in regular fractionation in the usually diagnosed STS), assuming the worse scenario of the tumor bed violation. If the radiation therapy provided after the second surgery the provided dose was more than 60 Gy, 2 Gy per fraction as it globally accepted. The re- resection was usually done 4 to 6 months after the completion of radiotherapy or in case of the 2nd surgery first, at a time of the wound healing. All patients were followed clinically every 2-3 months for the first 2 years and every 4-6 months thereafter.

Clinical characteristics, including demographics, symptom duration, initial clinical and pathological diagnoses, clinical staging, and status of surgical margins after biopsy were evaluated for disease-free survival (DFS). We defined a "good" outcome as survival without recurrence until the last visit and a "bad "outcome for the others.

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 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 of 2013 to 2020. In addition to Cox proportional regression, we used a parametric survival analysis for interval-censored data because the time of recurrence can 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, loglogistic) 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 by means of STATA 16 SE.

RESULTS

We conducted a retrospective analysis of 65 patients treated in our department for unplanned surgery for superficial STS. They were comprised of 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 (n = 49, 75.4%) received RT to the primary tumor bed or

to residual disease at a Median dose of 56 Gy (SD ±7.5) in standard fractionation of 1.8-2 Gy per fraction(5 times a week for 4 to 6 weeks) before definitive surgery and 16 patients (16.6%) proceeded directly to wide local resection, following RT in 15 of them. Eight patients did not undergo the repeat wide resection. The results are presented in Table 2.

The distribution of factors which could negatively impact the local control or survival among the groups of patients who started with RT in comparison to those who proceeded straight to re-resection was as the following: median age, in years- 64 vs 67.5, mean tumor size (SD), in cm – 4.3 (2.39) vs 5.1 (2.47), percentage of initial clinical diagnosis of lipoma was 30.61% and 12.5% respectively. The percentage of high-grade malignancy in the group who received RT first was 65.31% vs 93.75% in the group who started with surgery. The presence of the positive margins after the first surgery was 85.71% and 93.75% in the initial RT therapy or surgery, accordingly. The pathologies result after 2nd surgery showed negative margins in all cases. The median time before the 1st unplanned resection and the start of RT was 3 months (SD=10) in the pre 2nd surgery irradiation and 9 months (SD=65) in the post 2nd operation groups respectively, as presented in table 3.

The rate of acute wound complications in a group of pre 2nd resection, including dehiscence and infection was 26.2% (11 out of 42) and 25% (4 out of 16) patients in the other group.

The STS recurred in 7 out of 49 (14.3%) patients 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 (56.25%) who started with a repeat wide resection (P = .001) (6 with both local and distal metastasis, 1 with local recurrence alone and 2 with only distal metastasis). Distant metastasis occurred in 5 out of 49 (10.2%) and 8 out of 16 (50%) of patients who had RT first or re-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 of 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 worse outcome. The STS recurred in 1 out of 15 patients with grade 1 tumor, 2 out of 3 with grade 2 tumor, and 12 out of 45 with grade 3 tumor (P = .049). The Kaplan-Meier survival estimates are given in Figure 1.

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

Patient age, time between symptom onset and date of diagnosis, the hospital level of initial diagnosis (tertiary versus non-tertiary), the anatomic site, size of the tumor (greater or smaller than 5 cm), and the status of margins at the initial excisional biopsy were not statistically correlated with 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 due to the retrospective nature of the study. The applied statistics took in account the incomplete data.

Analysis of a subsample of 50 cases with higher-grade tumors (2 and 3) yielded similar results. The only variables that were significantly related to outcome were the starting treatment (RT or surgery) and the clinical diagnosis (lipoma or non-lipoma). STS recurrence occurred in 9 out of 15 cases who started with surgery and in only 6 cases out of 35 who started with

irradiation (*P* = .006) RR=3.5(CI = 1.51,8.09). There were 14 recurrences among 36 non-lipoma cases and only 1 recurrence among 14 lipoma cases (*P* = .039) RR=5.44 (CI=90.79,37.6). Starting treatment with RT was the only significant covariate in the univariate Cox regression with a Hazard ratio (HR) of 5.88 (95% CI=2.16,15.95, *P* = .001). Clinical diagnosis (HR=6.07, *P* = .08) was associated with grade 2 or 3 compared to grade 1 (HR=6.7, *P* = .066), but did not reach a level of significance. The interval censored regression confirmed these results for all tested distributions.

Finally, there were relatively few deaths among the study participants during the study period (4 cases related and 1 case not related to the main diagnosis of STS).

DISCUSSION

The initial management of superficial tumors across the body is often performed by primary physicians or general surgeons [2]. A situation when a mass presumed to be benign is resected, and a pathology comes back as sarcoma is usually referred as “oops” operation. The rate of unplanned resection of STS is reportedly high: 18-50 % [14]. ln our tertiary hospital, 65 out of 488 operations (13%) performed for STS in last 7 years initially diagnosed as benign tumors following an unplanned resection. Rehders et al showed that the results of “oops operations” are inferior to planned surgery for STS [4]. Radiation therapy was reported to significantly improve local control in stage 3 extremity STS [16][17]. The neo-adjuvant RT has been shown to result in better functional outcomes with similar local control and non-compromising overall survival [12]. Haas R.L et al emphasizes the value of RT in the treatment of STS patients [18].

According to the predictive nomogram for treatment of STS the small superficial sarcoma, resected with adequate margins does not need further RT due to the good results of

surgery alone [13]. Smolle M.A. et al showed that radiation therapy significantly improves the results of treatment if sarcoma revealed after the unplanned surgery [15]. The authors stated, however that radiation therapy should be recommended in the adjuvant rather than the neo-adjuvant setting, considering the high risk of wound complications. The question of timing of radiation therapy before or after the re-resection is still unresolved. It is also unknown whether the remained after the 1st surgery tumor or tumor bed, soiled by inappropriate surgery represents 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 dose of 56 Gy in 28 fractions (larger than usual 50 Gy in the 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 the defining the prognosis and choice of treatment in classically staging STS (size, anatomical place, 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. In spite that more patients with high grade malignancy were found in in the post 2nd surgery RT group, after the sub-analysis of this parameter, the results of DFS were better for the pre 2nd resection RT patients. Most of the clinical diagnoses of lipoma were associated with high-grade malignancy on pathological examination. It was intriguing to observe that patients operated primarily for the clinical diagnosis of lipoma achieved better results compared to those with other diagnoses. Notably, the higher rate of distal metastasis was observed in the group who received radiation therapy after the re-wide resection.

Unexpectedly, the presence of residual tumor at the second surgery did not significantly impact DFS. The early introduction of radiation therapy in the 1st group may theoretically be of added value for the improved results. This statement needs however further prove. 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 minimal impact on survival in the setting of "Oops" operations, based on the results of previous studies [19].

CONCULSION

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

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TABLES AND FIGURES

Table 1. Patient and Tumor Characteristics.

Characteristic	No. of patients
Sex	
Male	39 (60%)
Female	26 (40%)
Age y	
18-29	4 (6.1%)
30-39	8 (12.3%)
40-49	13 (20%)
50-59	6 (9.2%)
60-69	8 (12.3%)
70-79	21 (32.3%)
80-89	4 (6.1%)
90-99	1 (1.5%)
Median	66
Clinical diagnosis	
Lipoma	17 (26.2%)
Non-lipoma	48 (73.8%)
Anatomical site	
Upper extremity	15 (23.1%)
Lower extremity	36 (55.4%)
Body	14 (21.5%)
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%)
Lipoarcoma	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%)
Non-Otherwise Specified	10 (15.39%)
Tumor size	
<5 cm	36 (55.4%)
>5 cm	18 (27.7%)
No data	11 (16.9%)
Median	4.41 cm
Hospital level of diagnosis	
Tertiary	7 (10.8%)
Non-tertiary	58 (89.2%)

Table 2. Results.

		No Disease progression (n=49) [75.4%]	Disease progression \ recurrence \ 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)
	Non-Lipoma	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 path (no 2nd surgery)	4 (8.2)	4 (25)
Hospital level of diagnosis (%)			
	Tertiary	5 (10.2)	2 (13.3)

	Non-tertiary	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 1st surgery (%)			
	Positive	43 (87.8)	13 (81.25)
	Negative	2 (4.1)	0 (0)
	Unknown	4 (8.1)	3 (18.75)
Tumor size (%)			
	Smaller than 5 cm	31 (73.8)	8 (72.7)
	Greater than 5 cm	11 (26.2)	3 (27.3)

Table 3. Patient characteristic RT first vs Surgery first.

		RT first (n=49) [75.4%]	Surgery first (n=16) [24.6%]
Age (Median, years)			
		64	67.5
Initial diagnosis (%)			
	Lipoma	15 (30.61)	2 (12.5)
	Non-Lipoma	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 path	7 (14.28)	1 (6.25)
Margins after 1st 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)
	Smaller than 5 cm	31 (63.27)	8 (50)
	Greater than 5 cm	12 (24.49)	3 (18.75)
Time from Dx to RT			
	Median (SD), m	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.