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Combining limb-sparing surgery with radiation therapy in high-grade soft tissue sarcoma of extremities – Is it effective?

D.A. Müller [a,*], G. Beltrami [b], G. Scoccianti [b], F. Frenos [b], R. Capanna [b]

[a] Department of Orthopedic Surgery, University Hospital Balgrist, Forchstrasse 340, 8008 Zürich, Switzerland
[b] Department of Orthopedic Oncology, Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 3, 50134 Firenze, Italy

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Abstract

Background: Limb-sparing surgery in combination with radiation therapy is a well-established treatment for high-grade soft tissue sarcomas of the extremities. But selection of cases and optimal sequence of irradiation and surgery still remain controversial.
Methods: 769 patients with a high-grade soft tissue sarcoma of the extremities, who underwent a limb-sparing surgery, were retrospectively reviewed. Group 1 (N = 89) was treated with neo-adjuvant radiation therapy, group 2 (N = 315) with adjuvant irradiation and group 3 (N = 365) with surgery alone.
Results: After a mean follow up of 45 months 95 local recurrences occurred resulting in a local recurrence-free survival of 83.2% after 5 years and 75.9% after 10 years. Contaminated surgical margins (Odds ratio: 2.42) and previous inadequate surgeries (Odds ratio: 1.89) were identified as risk factors for failed local control. Neo-adjuvant radiation therapy provides the best local recurrence-free rate for 5 years (90.0%), whereas after 10 years (78.3%) adjuvant irradiation showed better local control. The metastatic-free rate was independent from achieved surgical margins (p = 0.179). Group 1 showed the highest rate of revision surgery (9.0%), followed by group 3 (5.5%) and group 2 (4.4%) (p = 0.085). However, the rate of irradiation-correlated side effects was higher in group 2 (15.2%) than in group 1 (11.2%) (p = 0.221).
Conclusion: Surgery has to be effective for successful local control and remains the mainstay of the treatment in combination with neo-adjuvant as well as adjuvant irradiation. In really wide or even radical resections the benefit of radiation therapy can be discussed as the irradiation induced side effects are not negligible.

Keywords: High-grade; Soft tissue sarcoma; Radiation therapy; Limb-sparing surgery; Local recurrence; Distant metastasis

Introduction

Soft tissue sarcomas are a heterogeneous group of relatively rare malignant neoplasms that arise in mesenchymal tissue. Although soft tissue sarcomas can arise in virtually any anatomic site, patients with extremity sarcomas represent more than half of all patients.[1] Historically, successful local control has been obtained with radical resections through amputation.[2] Although amputation provides local control in vast majority of patients, functional and psychological consequences are significant. Contemporary approaches to surgical management of soft tissue sarcomas have focused on resections with wide negative margins preserving the function of the affected limb. Adjuvant radiation therapy, administered either preoperatively or postoperatively, has been shown to improve the probability of local control in these instances and result in cure rates

* Corresponding author. Universitätsklinik Balgrist, Forchstrasse 340, CH-8008 Zürich, Switzerland. Tel.: +41 44 386 11 11; fax: +41 44 386 11 09.
E-mail addresses: daniel.mueller@balgrist.ch (D.A. Müller), giovannibeltrami@virgilio.it (G. Beltrami), guido.scoccianti@alice.it (G. Scoccianti), frenosfilippo@gmail.com (F. Frenos), capannar@aou-careggi.toscana.it (R. Capanna).

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that are comparable to those achieved with more extensive resections.[3,4] The European Society for Medical Oncology (ESMO) highly recommends the use of radiation therapy as an adjuvant to surgery in intermediate and high-grade, deep tumours with a diameter over 5 cm.[5] The optimal timing of the radiation therapy still remains controversial and often depends on the clinical situation. The advantages of preoperative radiotherapy include equivalent treatment effect with delivery of a smaller total dose and exposure of a smaller volume of normal tissue to irradiation. This is particularly important when considering that these two factors have been shown to have an effect on joint stiffness and radiation fibrosis, impacting functional outcome.[6,7] The disadvantage of preoperative radiation therapy is the higher risk of wound complications.[8–12] The main problems of postoperative administered radiotherapy are that prolonged wound healing may delay the onset of irradiation, a higher dose is necessary, the irradiated volume tends to be larger and the incidence of late complications may be higher.[6,11]

The aim of this study was therefore to compare local control, oncological outcome and complications for surgical excisions of high-grade soft tissue sarcomas localized in extremities, combined with preoperative radiation therapy, postoperative radiation therapy or no irradiation at all.

Materials and methods

A consecutive case series of 1229 patients treated in one institution for a soft tissue sarcoma of the extremities between 1994 and 2013 was retrospectively reviewed. Tumours were initially classified into low- or high-grade according to the classification of Broders et al.[13] (Grades 1 and 2 as low-grade, 3 and 4 as high-grade) and in recent years according to the French Federation classification (FNCLCC)[14] (grade 1 as low and grades 2 and 3 as high-grade). 345 patients (28%) diagnosed for a low-grade soft tissue sarcoma, 84 (6.8%) patients treated by primary amputation and 31 patients (2.5%) with known metastatic disease at the time of diagnosis were excluded. 769 patients (62.6%) matched the criteria of a limb salvage procedure for a high-grade, non-metastatic soft tissue sarcoma. The work has been approved by the local ethical committee and all the subjects gave informed consent to the study.

According to the treatment regimen for local control the patients were divided in 3 different groups for further analysis. In Group 1 (89 cases; 11.6%) a neo-adjuvant external radiation therapy was applied, followed by a complete surgical excision of the tumour. In Group 2 (315 cases; 41.0%) the soft tissue sarcoma was first treated by surgery and afterwards by adjuvant radiation therapy in the postoperative course. All the patients in Group 3 (365 cases; 47.4%) underwent only a surgical procedure without any radiation therapy.

The specific characteristics of the patients for the 3 different groups were indicated in Table 1. The enrolment of the patients in the groups was not randomized. A multidisciplinary team consisting of orthopaedics, radio-oncologists and oncologists decided the treatment modality and sequence. The decision to add radiation therapy was influenced by size and location of the tumour, as well as severity of the surgical resection. Additionally, there was an evolution of practice, as there was a shift from adjuvant to neo-adjuvant radiation therapy during the observed study period. 74% of patients in Group 1 were treated in the last 5 years, compared to 56% in Group 2 ($p = 0.004$).

In 286 cases (37.2%) an inadequate surgical treatment was performed in another hospital prior the referral to our institution. 171 patients (22.2%) needed a radicalization of the surgical margins due to a previous intralesional non-planned excision and 115 patients (14.9%) showed a macroscopic local recurrence necessitating a surgical excision.

An additional rotational or free flap was necessary in 157 patients (20.4%) to provide sufficient soft tissue coverage after the resection.

Table 1
Patient characteristics.

Variables	Group 1: Adjuvant surgery (N = 89)	Group 2: Neo-adjuvant surgery (N = 315)	Group 3: Surgery alone (N = 364)
Age			
Mean	48.5 years	53.7 years	55.8 years
Age groups			
<18 years	2 (2.2%)	10 (3.2%)	22 (6.0%)
18–30 years	15 (16.9%)	33 (10.5%)	25 (6.8%)
31–50 years	29 (32.6%)	87 (27.6%)	82 (22.5%)
51–70 years	35 (39.3%)	119 (37.8%)	136 (37.3%)
>70 years	8 (9.0%)	66 (20.9%)	100 (27.4%)
Sex			
Male	33 (37.1%)	159 (50.5%)	183 (50.1%)
Female	56 (62.9%)	156 (49.5%)	182 (49.1%)
Localisation			
Proximal upper limb	10 (11.2%)	44 (14.0%)	44 (12.0%)
Distal upper limb	3 (3.4%)	44 (14.0%)	50 (13.7%)
Proximal lower limb	60 (67.4%)	149 (47.3%)	174 (47.7%)
Distal lower limb	16 (18.0%)	78 (24.7%)	97 (26.6%)
Tumour size			
<5 cm	15 (16.8%)	103 (32.7%)	170 (46.6%)
5–10 cm	37 (42.6%)	155 (49.2%)	100 (27.4%)
>10 cm	37 (42.6%)	57 (18.1%)	95 (26.0%)
Diagnosis			
Liposarcoma	27 (30.4%)	63 (20.0%)	36 (9.9%)
Undifferentiated pleomorphic sarcoma	18 (20.2%)	56 (17.8%)	63 (17.3%)
Leiomyosarcoma	3 (3.4%)	56 (17.8%)	59 (16.2%)
Synovial sarcoma	19 (21.3%)	27 (8.6%)	59 (16.2%)
Fibrosarcoma	6 (6.7%)	25 (8.0%)	46 (12.6%)
Fibromyxoid sarcoma	4 (4.5%)	25 (8.0%)	44 (12.1%)
Others	12 (13.5%)	62 (19.8%)	57 (15.7%)
Chemotherapy			
Preoperative	41 (46.1%)	5 (1.6%)	13 (3.6%)
Postoperative	4 (4.5%)	93 (29.5%)	19 (5.2%)
Pre- and post-operative	26 (29.2%)	17 (5.4%)	13 (3.6%)
None	18 (20.2%)	200 (63.5%)	320 (87.6%)