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ORIGINAL ARTICLE

Intraoperative electron beam radiotherapy followed by moderate doses of external beam radiotherapy in the treatment of resected soft tissue sarcomas of the extremities

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Summary

Purpose: *Soft tissue sarcomas (STS) have a high incidence of local recurrence. In an effort to improve the local control rate and the survival in patients with STS, treatment strategies employing intraoperative electron beam radiotherapy (IOERT) in combination with external beam radiotherapy (EBRT) and extensive surgical resection have been explored. This study assesses the rate of overall survival (OS), local control and toxicity of this multimodal approach for primary and recurrent STS of the extremities.*

Patients and methods: *From 1999 to 2004, 36 patients were treated at Agios Savvas Cancer Hospital for primary or recurrent extremity STS with IOERT as a component of their treatment. All patients underwent surgical resection, IOERT, and most of them received postoperative EBRT with a median dose of 45 Gy. Chemotherapy was given to patients with high grade tumors. Thirteen patients were treated for primary disease and 23 for isolated local recurrence.The locations of the tumors were as follows: upper limbs n=19, lower limbs n=17. Tumor size was >5 cm in 16 (44%) patients and high-grade histology (II-III) was present in 24 (67%) patients. Six (17%) patients had positive surgical margins.*

Results: *With a median follow up of 24 months (range 6-48) OS was 72% (84.5% for patients with low grade lesions compared to 65% for high grade lesions, p=0.127, and 90% for tumors <5 cm compared to 50% for tumors >5 cm, p=0.0136). Overall local tumor control rate was 89% (92% in primary disease group versus 87% in isolated local recurrence group, p=0.136, and 93% for patients with negative surgical margins versus 67% for those with positive margins, p=0.0013). Distant metastases occurred in 10 patients (1 of 13 (8%) with primary disease, and 9 of 23 (39%) with isolated local recurrence). All distant metastases were to the lungs. Twelve (33%) patients developed moderate neurotoxicity.*

Conclusion: *In selected patients, IOERT results in excellent local control and OS with acceptable toxicity.*

Key words: external beam radiotherapy, extremity, intraoperative electron beam radiotherapy, limbs, soft tissue sarcoma

Introduction

IOERT refers to the delivery of a single high-dose irradiation at the time of an operation to selected anatomical areas thought to be at high risk or to residual disease sites.

IOERT is been used as part of a multidisciplinary approach for the treatment of STS. The prognosis of STS is correlated with the degree of local or distant failure risk [1-3]. Local control is directly dependent on the complete or incomplete character of the surgical resection. However, surgery can be associated with significant morbidity and functional loss. With the addition of radiation, selected patients are able to undergo conservative surgery with less morbidity and

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superior therapeutic results [4]. In addition, several studies of either preoperative or postoperative radiation therapy indicate that there is a dose-dependent effect on tumor local control [5,6].

EBRT doses, however, are often compromised by the surrounding normal tissue tolerance. This problem is attempted to be solved with the use of IOERT, which possesses several practical and theoretical advantages. Firstly, the use of IOERT allows the radiation oncologist to minimize the radiation dose to the surrounding normal tissues, by shielding critical structures or excluding them from the radiation field during surgery. Furthermore, the use of electrons, with the characteristic fall-off in dose based on depth, results in the protection of normal tissues deep to the tumor bed. Another benefit is that the delivery of a boost dose to the tumor bed in a single fraction, during surgery, shortens the overall radiation treatment time, which might be correlated with better outcome by preventing the tumor cells repopulation. In addition, the radiation oncologist is allowed to directly visualize the tumor bed, making direct treatment planning and having greater control over the dose prescription and distribution. Finally, this approach offers the radiobiological advantage to give treatment before significant fibrosis can occur, therefore the field to be treated is not yet oxygen-deprived, and hence less radioresistant.

Patients and methods

Patients

Between February 1999 and April 2004, 36 patients with extremity STS were treated at "Agios Savvas" Cancer Hospital with IOERT as a component of their multimodal treatment. Endpoints of this study were the evaluation of the patterns of local and distant failure, side effects and survival rate in this group of patients. Thirteen patients had primary STS and 23 had an isolated local recurrence. Work-up to rule out distant metastasis included complete blood count, biochemical profile, chest X-ray, and thoracic and abdominal computed tomography. Patients were clinically examined every 3 months and submitted to a CT scan every 6 months after surgery.

Patient characteristics are shown in Table 1. In 19 cases, the patients suffered from sarcomas of the upper extremities and in 17 cases from sarcomas of the lower extremities. Tumor histology and characteristics are described in Table 2.

The surgical resection was incomplete in 6 cases and complete with a zone of histologically healthy surgical margin (>5 mm) in 30 cases.

IOERT characteristics

The IOERT methodology has been described in detail elsewhere [7]. At "Agios Savvas" Cancer Hospital we use a mobile electron beam linear accelerator (Novac 7 - Hytesis) that is placed inside the operation room and can be moved around the room and adjust to accommodate the patient's position on the operating table. Applicator size was selected to encompass the entire surgical bed. Patients were irradiated with electron energies of 5 MeV, 7 MeV or 9 MeV and a radiation dose between 10-15 Gy was delivered depend-

Table 1. Patients characteristics (n=36)

	n	*%*
Age, years		
median	48	
range	24-74	
Gender		
male	22	61
female	14	39
Performance status		
0-1	36	100

Table 2. Histological types of STS and tumor characteristics

Histology	*n*	*%*
liposarcoma	12	33
MFH	9	25
fibrosarcoma	4	11
leiomyosarcoma	3	8
rhabdomyosarcoma	2	6
alveolar sarcoma	1	3
not identified	5	14
Grade		
I	12	33
II-III	24	67
Size (cm)		
T1 (≤5)	20	56
T2 (>5)	16	44
AJCC stage*		
I	12	33
II	17	47
III	7	20

MFH: malignant fibrous histiocytoma
* The same staging system is used for both primary and recurrent tumors

ing on the tumor size, histological grade and location. For an 8-cm applicator size, the depth of the 80% isodose curve was 24 mm for 9 MeV energy (Figures 1 and 2). Applicator diameters, energies and doses of radiation are shown in Table 3.

EBRT characteristics

Patients where scheduled for EBRT 3-4 weeks after surgery. Fields were designed to encompass the surgical scar and the surgical bed. Standard fractionation of 1.8 Gy, 5 days per week to a mean total EBRT dose of 45 Gy was used. In 10 patients with isolated local recurrence EBRT was not administered, due to prior full dose adjuvant EBRT (Table 3).

Chemotherapy

Twenty patients with high grade lesions were treated with postoperative chemotherapy. Adjuvant chemotherapy consisted of 6-12 cycles of doxorubicin (50 mg/m² i.v., day 1), dacarbazine (400 mg/m²/day i.v., days 1-3) and ifosfamide (1.5 g/m²/day i.v., days 1-3) with mesna uroprotection [8,9].

Table 3. IOERT and EBRT characteristics

Characteristic	*n*	*%*
IOERT		
No. of fields		
single	36	100
Applicator diameter (cm)		
4	10	28
6	8	22
8	12	33
10	4	11
12	2	6
Energy (MeV)		
5	2	5
7	15	42
9	19	53
Dose (Gy)		
10-12	13	36
15	23	64
EBRT		
Dose (Gy)		
35-40	5	14
41-45	19	53
46-50	2	5
No EBRT	10	28

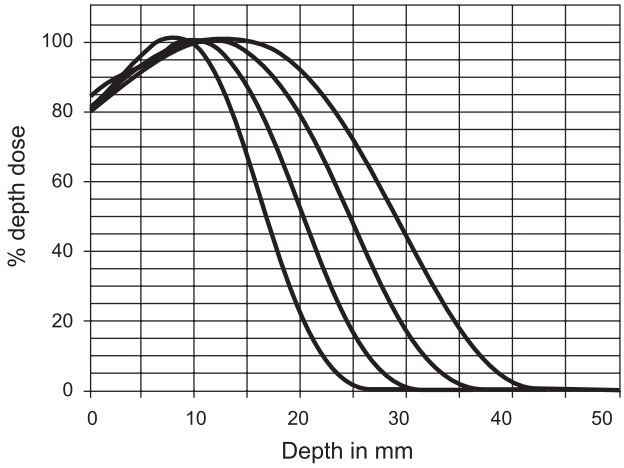

Figure 1. Depth dose curves in water for Novac 7.

Toxicity

Only IOERT toxicities were registered. Toxicities related to chemotherapy or EBRT are not reported. Adverse events were recorded following the NCI Common Toxicity Criteria, version 2.0.

Statistical analysis

OS time was calculated from the initiation of treatment for this malignancy (for patients who presented with recurrence, OS was measured from the initiation of treatment for recurrent disease) to the date of the most recent follow-up or the time of death. Survival analysis was performed using the Kaplan-Meier method. Differences in survival and local control rates were assessed by the log-rank test in univariate analysis.

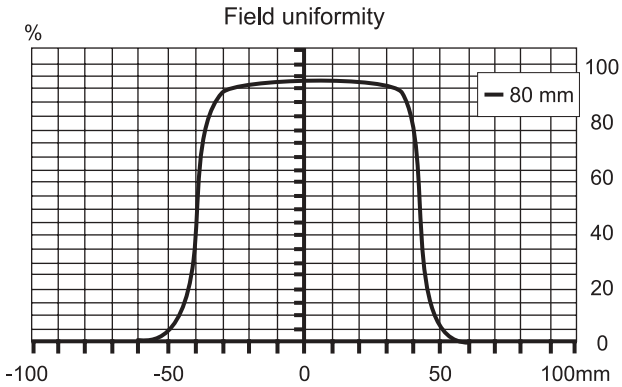

Figure 2. Profile at the depth of maximum dose of an electron beam with nominal energy 9 MeV and applicator size 80 mm.

Results

Patterns of local and distant failure

With a median follow-up of 24 months (range 6-48) isolated local recurrence was detected in 3 (8.5%) patients, combined local and distant failure in one (3%) patient, and distant metastasis alone in 9 (25%) patients. One (8%) local recurrence was observed in the primary disease group, compared to 3 (13%) in the isolated local recurrence group (p=0.83). Distant metastasis was observed in one (8%) patient with primary disease and in 9 (39%) patients with isolated local recurrence. In all patients distant failure was to the lungs.

Overall local tumor control rate was 89%. No statistically significant difference in local control rate was found between patients with primary disease and those with isolated local recurrence (92% *versus* 87%, respectively, p=0.136). Local tumor control was related to the status of the surgical margins. Ninety-three percent of the patients with negative margins did not recur compared with 67% of those with positive surgical margins (p=0.0013).

One patient developed isolated local recurrence that was managed with ambutation. The extremity preservation rate was 97% (35 out of 36 patients).

Survival analysis

Ten out of 36 (28%) patients died, 8 (80%) of them with distant metastatic disease and 2 (20%) with local recurrence. With a median follow-up of 24 months (range 6-48), OS was 72% (Figure 3). In univariate analysis, surgical margins and tumor size were significant prognostic factors. Patients with negative surgical margins had 80% OS compared to 33% of patients with positive margins (p=0.0013, Figure 4). Patients with T1 (≤5 cm) tumors had 90% OS compared to 50% for patients with T2 (>5 cm) tumors (p=0.0136, Figure 5). The OS according to grade was 84.5% for patients with low grade lesions and 65% for those with high grade lesions (p=0.127, Figure 6). Patients with primary disease had 84.5% OS rate compared to 65% for those with isolated local recurrence (p=0.13, Figure 7).

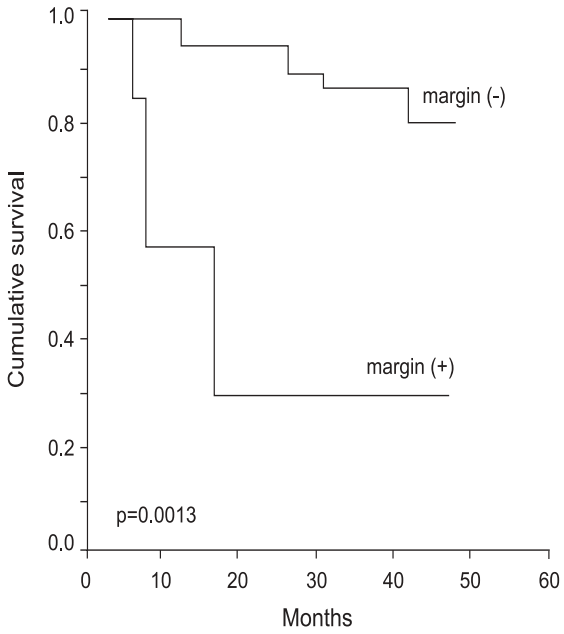

Figure 4. Overall survival according to surgical margins.

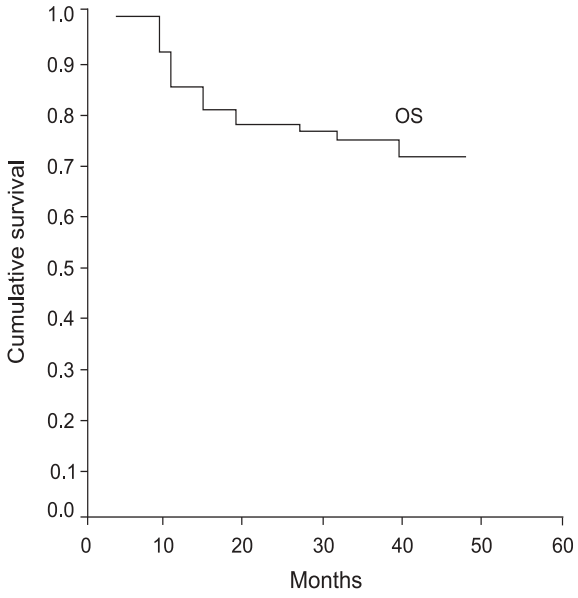

Figure 3. Overall survival = 72% (median follow-up 24 months)

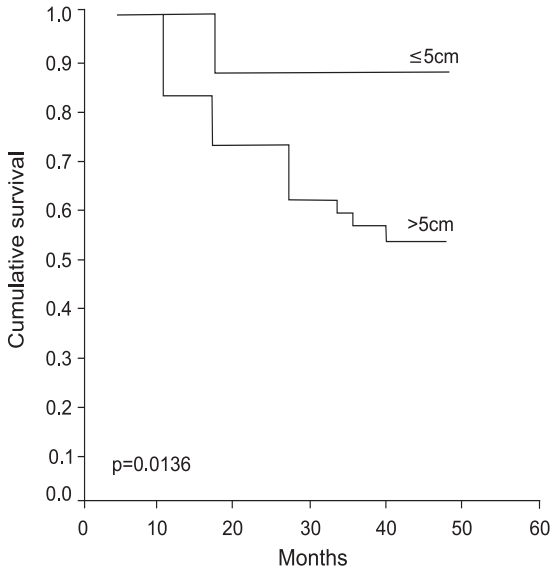

Figure 5. Overall survival according to tumor size.

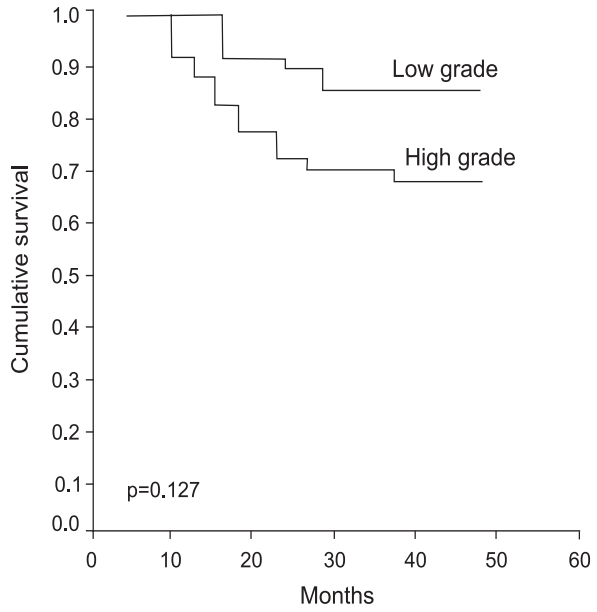

Figure 6. Overall survival according to grade.

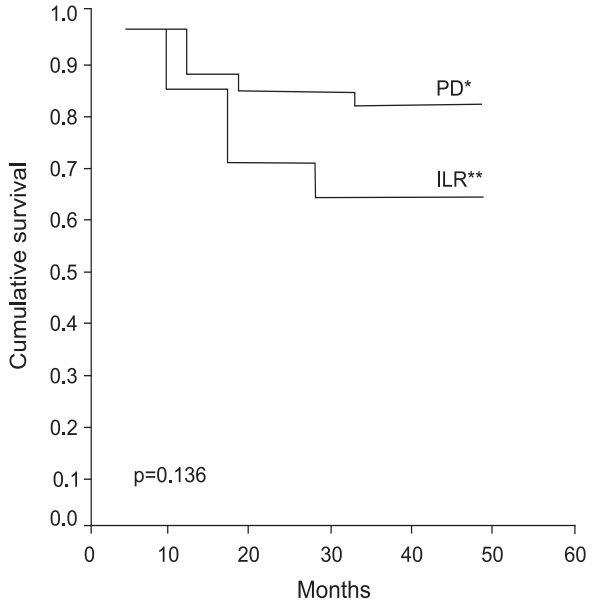

Figure 7. Overall survival according to disease status (*primary vs **isolated local recurrence).

Toxicity

There were no IOERT-induced acute toxicities. Delayed wound healing occurred in 2 patients. EBRT was not delayed by postoperative complications.

Late toxicity was evaluated in those patients who survived more than one year after IOERT (26 patients). The major complication observed was peripheral neuropathy: grade 2 motor neuropathy in one patient (mild objective weakness of the lower limbs, not interfering with daily activities) and grade 2 sensory neuropathy in 2 patients (paresthesia, not interfering with daily activities). Grade 1 peripheral neuropathy was observed in 10 patients (Figure 8). The median time to the onset of neurotoxicity was 11 months.

Of the 26 evaluable patients, 25 had a functional extremity without limitations for daily activities one year postoperatively.

Discussion

The experience with IOERT in STS of the extremities is limited. In a recent update of the Mayo Clinic experience, Haddock et al. [10] reported a 92% local control rate (n=91) at 3 years with a median follow-up of 2.9 years (95% local control in primary lesions *versus* 81% in recurrent tumors), and a 3-year OS 76% (87% in patients with low grade lesions compared to 70% in those with high grade lesions). Calvo et al. [11], in the Pamplona IOERT series, reported an 88% local control rate (n=33) and 76% OS rate (77% in the primary disease group *versus* 54% in the isolated local recurrence group) with a median follow-up of 36 months. Dubois et al. [12] reported no local recurrences in a small series of 18 STS patients. Azinovich et al. [13] reported an 88% actuarial local control rate for patients with negative surgical margins *versus* 57% for patients with positive margins (n=45), and a 7-year actuarial survival of 75% in patients with primary disease *versus* 47% in patients with isolated local recurrence. Finally, in the Heidelberg IOERT series, after a mean follow-up of 27 months, 92% local control rate and 77% OS were achieved (Table 4).

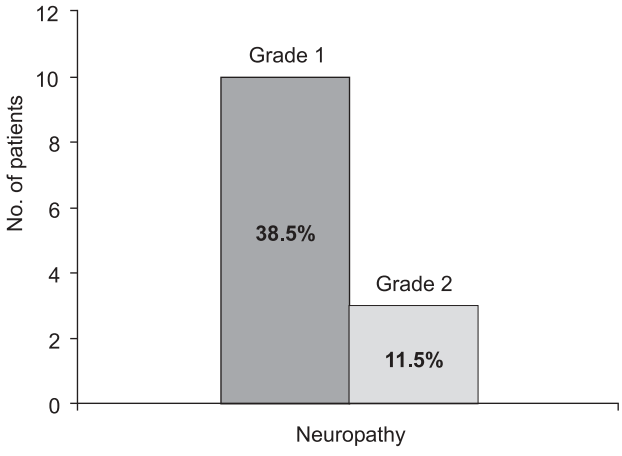

Figure 8. Incidence of peripheral neuropathy.

Table 4. Series with resection and IOERT complementary to EBRT in extremity STS

Series	*No. of patients*	*Local recurrence at 3 yrs (%)*	*Distant metastasis at 3 yrs (%)*	*3-yr overall survival (%)*
Mayo Clinic	91	7	–	76
Pamplona	33	12	21	76
Heidelberg	25	8	–	77

Comparing the results from studies that used IOERT complementary to EBRT in the management of extremity STS (Table 4) with those that used EBRT alone (Table 5), a better trend of locoregional control in the series using IOERT is evident [14-16]. The National Cancer Institute (NCI) has published the definite results of a phase III randomized trial on retroperitoneal sarcomas, comparing a standard postoperative EBRT dose (50-55 Gy) to an IOERT dose of 20 Gy followed by EBRT of 35-40 Gy [17,18]. This trial did not show any significant difference in disease-free and OS between the two arms. However, a trend towards improvement in local control and a significant reduction in complication rates were observed in patients receiving IOERT, demonstrating the advantage of IOERT in sparing irradiation to healthy tissues and critical organs. Local control rate (89%) and OS rate (72%) in our study are comparable to the most relevant series in the literature. We didn't observe any statistically significant difference in OS between primary disease and isolated local recurrence patients or between low and high grade tumors subgroups, but this could possibly be attributed to the short follow-up period and the small number of patients.

The addition of chemotherapy in the treatment of high-grade sarcomas may have contributed to improved local control and OS. A recent study from Italian Cooperative Group (n=104), suggested a benefit in both disease-free and OS in the adjuvant chemotherapy arm [19]. In addition, the Southeastern Cancer Study Group reported a local control rate of 98.5% at a median follow-up of 7 years after treatment of STS with preoperative doxorubicin and irradiation [20]. A recently published meta-analysis by the Sarcoma Meta-analysis Collaboration Group provided evidence that adjuvant chemotherapy significantly reduced the metastasis rate and contributed to the decrease of the incidence of local failure [21]. In our study, 55% of the patients received adjuvant chemotherapy.

In several studies, a significant correlation is noted between histological grade of STS and the frequency of distant metastases. In their study, Gunderson et al. reported 13% distant metastases in grades I and II, and 42% in grades III and IV [22]. In our study, distant metastasis was observed in 2 out of 12 patients (17%) with low grade STS (grade I) and in 8 out of 24 patients (33%) with high grade lesions (grade II-III).

Peripheral neuropathy is the principal dose-limiting toxicity for IOERT in pelvic and extremity STS treatment. The high incidence of peripheral neuropathy might be explained by the difficulty to exclude nerves from the IOERT field and by their relatively low tolerance in large single fractions of irradiation. Animal studies from the NCI [23] and the Colorado State University [24] have shown that the tolerance of nerve structures to IOERT might be lower than 15 Gy (Table 6). In the present study, 36% of the patients developed peripheral neuropathy. Nevertheless, only 3 of them had moderate symptoms (grade 2) while the rest experienced only mild symptoms (paresthesia or weakness) not interfering with daily activities. Acute adverse events were minor and postoperative complications caused no delays in the initiation of EBRT.

Table 5. Series with resection and EBRT in extremity STS

Series	*No. of patients*	*Local recurrence (%)*	*Distant metastasis (%)*	*5-yr overall survival (%)*	*Follow-up (yrs)*
National Cancer Institute	271	9	31	–	1-8
M. D. Anderson	190	28	32	70	5-16
Massachusetts General Hospital	180	15	14	–	2-15

Table 6. IOERT tolerance for normal tissues in dogs

Tissue	*Dose (Gy)*	*Toxicity*
Esophagus, full-thickness	20	Ulcerations and strictures
Esophagus, partial-thickness	40	No sequelae at this dose
Duodenum, lateral wall	20	Ulcerations, fibrosis and stenosis
Bile duct	20	Fibrosis and stenosis
Lung	20	Fibrosis
Aorta	30	Fibrosis
Vena cava	30	Fibrosis
Heart, atrium	20	Moderate fibrosis
Bladder	20	Stenosis and obstruction
Ureter	30	Stenosis and obstruction
Kidney	30	Fibrosis
Peripheral nerve	15	Sensory-motor neuropathy
Spinal cord	20	Hemorrhage and myelopathy

In conclusion, IOERT appears to be a highly effective modality, increasing the radiation dose to the sites of highest risk, as determined intraoperatively, eliminating at the same time the possibility of geographic miss by the radiation beam. Experience shows that IOERT adds only a small amount of time to the surgical procedure and if it is used in moderately low doses keeps the complications rates very low. However, results that have been published with the use of IOERT in the treatment of extremity STS indicate that the outcomes of patients who have received this treatment are similar to other approaches. On the other hand, because of the small number of studies using IOERT as a boosting technique in extremity STS, more, well organized, randomized trials need to be done, in order to confirm any benefit of this modality in tumor local control and patients' outcome.

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