Intraoperative radiotherapy electron boost followed by moderate doses of external beam radiotherapy in resected soft-tissue sarcoma of the extremities

Ignacio Azinovic[a], Rafael Martinez Monge[a]*, Jose Javier Aristu[a], Esteban Salgado[a], Elena Villafranca[a], Oscar Fernandez Hidalgo[a], Santiago Amillo[b], Miguel San Julian[b], Carlos Villas[b], Jose Manuel Aramendía[a], Felipe A. Calvo[b,c]

[a] Department of Oncology, Radiation Oncology Division, Clínica Universitaria, School of Medicine, University of Navarre, Av. Pio XII, 36, 31008 Pamplona, Spain
[b] Department of Orthopedics, Clínica Universitaria, School of Medicine, University of Navarre, Pamplona, Spain
[c] Department of Oncology, Hospital General Gregorio Marañón, Madrid, Spain
* Corresponding author

ABSTRACT

Purpose: To analyze the patterns offailure and the toxicity profile of intraoperative electron beam radiotherapy (IOERT) after resection of soft tissue sarcomas of the extremities (STS).
Patients and methods: Forty-five patients with extremity STS were treated with IOERT and moderate-dose postoperative radiotherapy (45–50 Gy). Twenty-six patients were treated for primary disease (PD) and 19 patients for an isolated recurrence (ILR). Tumor size was > 5 cm (maximum diameter) in 36 patients (80%), and high-grade histology in PD patients was present in 14 patients (54%). In nine patients, IOERT was used alone, due to previous irradiation or patient refusal. Chemotherapy (neoadjuvant and/or adjuvant) was mainly given to high-grade tumors.
Results: Nine patients relapsed in the extremity (20%), and 12 patients in distant sites (28%). Actuarial local control at 5 years was 88% for patients with negative/close margins and 57% for patients presenting positive margins (P = 0.04). Five patients (11%) developed neuropathy associated with the treatment. Extremity preservation was achieved in 40 patients (88%). With a median follow-up of 93 months (range: 27–143 months) for the patients at risk, 25 patients remain alive (a 7-year actuarial survival rate of 75% for PD and 47% for ILR; P = 0.01).
Conclusions: IOERT combined with moderate doses of external beam irradiation yields high local control and extremity preservation rates in resected extremity STS. Peripheral nerves in the IOERT field are dose-limiting structures requiring a dose compromise in the IOERT component to avoid severe neurological damage.

KEYWORDS
Soft tissue sarcoma; Intraoperative radiotherapy; External beam radiotherapy

1. INTRODUCTION

Intraoperative electron beam radiation therapy (IOERT) is an innovative boosting technique used to deliver single high-doses of irradiation (range of 10–20 Gy) in selected anatomic areas identified during the surgical procedure as high risk and/or residual disease sites, while avoiding surrounding dose-limiting structures. Studies of IOERT in multiple anatomical sites have produced valuable and reproducible results in terms of locoregional control and toxicity [6]. The potential advantage of using IOERT in retroperitoneal sarcomas has been explored and reported by institutions experienced in its use [19,22]. The NCI trial on retroperitoneal sarcomas reported improved local control rates and decreased incidence of enteritis, understood to be related to a lower external beam radiotherapy (EBRT) dose in the IOERT arm (35–40 Gy compared with 50–55 Gy in the EBRT-only arm) [19]. One of the advantages of IOERT was that the intra-abdominal organs could be protected from receiving full doses of irradiation, with a subsequent decrease in the incidence of severe enteritis and an increase in the local control rates [22].

The of use of a radiation boost in the extremities has been explored with the use of low-dose rate brachytherapy [8], but published results using electrons are limited. IOERT as part of a multidisciplinary approach to treating soft tissue sarcomas (STS) of the extremities has several theoretical advantages:

1. The delivery of the boost dose to the tumor bed after resection shortens the overall radiation treatment time.
2. The external beam irradiation (EBRT) dose component delivered to normal tissues can be decreased.
3. The IOERT dose component is selectively and exclusively given to a highly controlled thickness of tissue in the tumor bed area.

The present analysis describes a study with long-term follow-up in an institution with prospective treatment policy of IOERT boost plus modest EBRT doses postoperatively.

2. PATIENTS AND METHODS

2.1. Inclusion criteria

Between December 1986 and September 1994, 45 patients with extremity STS were treated with IOERT as a component of their radiation treatment. Only patients with resected extremity STS were included (patients with tumors arising in the gluteal or shoulder regions were excluded). All patients gave informed consent before study entry. The endpoint of the study was to evaluate patterns of failure, long-term side effects and secondarily the survival of a group of patients treated with IOERT as a boost in STS of the extremities.

Twenty-six patients had primary soft tissue sarcoma (PD) without distant metastasis at IORT, and 19 patients had an isolated local recurrence (ILR) after surgery. Patients with prior postoperative adjuvant treatments such as radiotherapy and/or chemotherapy were allowed to enter the study. Work-up to rule out metastatic disease included complete blood count, biochemical profile, chest X-ray, and/or thoracic and abdominal computed tomography.

Patient characteristics are shown in Table 1. The anatomical treatment sites included the upper extremity in eight patients and the lower extremity in 37 patients. Tumor characteristics are described in Tables 2 and 3. Malignant fibrous histiocytoma was the predominant histologic type in 13 patients; liposarcoma was found in 12 patients. Three patients had recurrent aggressive fibromatosis. The predominant tumor stage was IIIb (29%). Eighty percent of the lesions were larger than 5 cm in maximum dimension. Fourteen patients with PD (54%) had grade III tumors.

Thirteen patients underwent re-resection after presumed initial incomplete surgery. In nine of these, residual tumor was found. The other 32 patients underwent de novo surgery for primary or recurrent disease. The final surgical procedure at the time of IORT was considered as wide removal in 28 cases, marginal resection in 13 cases and compartmental resection in three cases. In one patient, radical surgery was not feasible. Close resection margins (< 5 mm) were found in eight patients and involved margins in seven patients (Table 4).

2.2. IOERT characteristics

The IOERT methodology has been described in detail elsewhere [3]. Applicator size was selected to encompass the entire surgical bed. If the surgical bed was extremely large, i.e. exceeding the available applicator size, either abutting fields were used or only the high-risk areas (the surgical tumor bed closer to the resection margin) defined by the surgeon were boosted. Electron beam energies were selected depending upon the amount of residual tumor. Usually, 6–9 MeV beams were used for high-risk areas or microscopic residual disease and 12–15 MeV for suspected macroscopic residue. The dose depended upon the amount of residual disease present; an IOERT boost dose of 10–15 Gy was delivered in areas with negative or close margins, and greater than 15 Gy was given in areas of macroscopic residual disease.

Since 1992, our treatment regimen has included displacing the peripheral nerves, i.e. moving them out of the IOERT field. If the nerves could not be physically displaced or if there was a risk of devitalizing the structure, then the IOERT nerve dose was limited to 10 Gy, and the nerves were protected with pliable lead sheets for the remaining component of the IOERT dose.

Fifty-six IOERT fields were treated in 45 patients. Ten patients were treated with multiple abutting fields, taking special care to avoid overlap (median number of fields was 2, range: 2–4). The main objective when using multiple IOERT fields was to avoid overlapping. The percentage of tissue overlapped never was over a few millimeters. The median applicator diameter, energy, and dose used were 9 cm, 9 MeV, and 15 Gy, respectively (Table 5). In 16 patients, the main neurovascular bundle was irradiated with IOERT. In all these 16 patients, nerve displacement and/or direct tumor contact was documented in the preoperative staging imaging studies, indicating the need for supplemental radiation due to the absence of wide tumor-free surgical margins.

2.3. External beam irradiation

Patients were scheduled for external irradiation 3–5 weeks after surgery. Field arrangement was designed to encompass the entire surgical scar and the surgical tumor bed. Standard fractionation of 1.8–2 Gy, 5 days per week to a total EBRT dose of 40–60 Gy was used. Mixed photons and electron beams were occasionally used to optimize dosimetry within the target volume. In patients with prior irradiation, IOERT was used as the only radiation treatment component. Preoperative irradiation was used in one patient with a multicentric recurrent liposarcoma of the lower limb. In nine patients, the EBRT treatment was not administered, due to prior full-dose adjuvant EBRT (Table 5).

2.4. Chemotherapy

Patients with high-grade tumors or recurrent histologies were given adjuvant chemotherapy either preoperatively (10 patients) and/or postoperatively (23 patients). Sixteen patients with PD and seven patients with ILR received adjuvant chemotherapy. Neoadjuvant chemotherapy consisted of three courses of intra-arterial cisplatinum 50 mg/m^2 and Doxorubicin 40 mg/m^2 i.v. every 28 days. Adjuvant chemotherapy consisted of 6–12 monthly cycles of Ifosfamide (1.5 g/m^2 days 1–3), Doxorubicin (50 mg/m^2 day 1), and Dacarbazine (400 mg/m^2 i.v. days 1–3).

2.5. Toxicity

The toxicities noted include only those potentially related to local effects from local treatments. Toxicity related to chemotherapy is not included. Patients with suspected neuropathy underwent close follow-up with periodic neurological evaluation. Toxicity was recorded following the Common Toxicity Criteria, version 2.0.

2.6. Statistical analysis

Survival analysis was performed using the Kaplan–Meier method [10]. Differences in survival and local control rates were assessed by the log-rank test in univariate analysis [13].

3. RESULTS

3.1. Patterns of failure

For the entire group, Isolated local recurrence was detected in six patients (13%), combined local failure and distant metastasis in three patients (7%), and distant metastasis alone in 11 patients (24%). Three local failures (12%) were observed in the PD group, compared to six (31%) in the ILR group (P = not significant (n.s.)). The rates of distant metastasis were similar among groups (23% in PD and 37% in ILR, P = n.s.). Two of the nine local failures were found in the subcutaneous tissue (outside the IOERT boost). Five of nine local failures were observed in recurrent tumors, and seven of nine

occurred in tumors initially larger than 5 cm. Of the nine local failures diagnosed, four had a successful local salvage treatment: in two patients, the limb was amputated; one patient received chemotherapy and local re-irradiation; and one received surgery and re-irradiation. Most patients presenting distant failure had lung metastases (11 patients). Other metastatic sites were the liver, bone, and kidney. One patient developed a second primary, a pancreatic tumor. The median time interval to local recurrence after IOERT was 20 months (range: 3–125 months); for distant metastasis, this was 18 months (range: 4–138 months).

Five-year actuarial local control was strongly related to the status of the surgical margins. Eighty-eight percent of the patients with negative/close margins and 57% with positive margins were controlled (P = 0.04) (Fig. 1). The initial disease status showed a trend for improved local control. Patients with PD had an 88% 5-year actuarial local control, compared to 60% for the ILR group (P = 0.05) (Fig. 2). Furthermore, patients receiving adjuvant EBRT had a slightly superior local control rate (85%) than those patients in whom EBRT was omitted (74%) (P = 0.09).

Patients with high-grade primary tumors showed a trend for improved control rate (93%) than patients with low-grade primaries (83%) or recurrent tumors (75%), (P = 0.1).

The initial size of the tumor, histological grade, location (upper vs. lower extremity), and sex were not associated with significant differences in local failure.

3.2. Survival analysis

At the time of this analysis, 29 patients remain alive. With a median follow-up of 93 months for the surviving patients (limits: 27–143 months), 7-year actuarial survival for PD is 75% and 47% for the ILR subset (P = 0.01). (Fig. 3). In univariate analysis, only histological grade and disease status showed a trend as a prognostic factor for long-term survival. Patients with low grade tumors had a 92% 7 year survival compared to 70% 7-year survival for patients with high grade tumors, and 47% 7-year survival for ILR patients (P = 0.05). Tumor size was not a predictor of long-term survival, probably because of the small sample size. Patients with T1 tumors had an 85% 5-year survival, compared to 63% for patients with T2 tumors (P = 0.2). Surgical margins did not significantly affect survival. The 5 year survival was 65% in those patients with negative or close margins and 71% in those patients with positive margins.

3.3. Toxicity and functional status of the extremity

EBRT-induced radiation dermatitis (grade II–III) occurred in nine patients. Four patients developed soft tissue necrosis requiring skin-graft for repair. Delayed wound healing occurred in four patients. EBRT was not delayed by postoperative complications. One patient with a seroma developed swelling of the irradiated area, fever, and impairment of the function in the extremity 40 months after surgery. No local recurrence was demonstrated and symptoms disappeared with antibiotics.

Late toxicity was evaluated in those patients at risk who survived more than one year after IOERT (31 patients evaluable). The two major complications observed were amputation and neuropathy. In three patients, severe toxicity required amputation. Two patients developed ischemia and symptomatic fibrosis, which was associated with neuropathy in one. Both patients presented with a large tumor mass at diagnosis (8 and 10 cm maximum diameter, respectively) and amputation of the extremity would otherwise have been the first treatment option using standard criteria. The third amputee developed an isolated local recurrence that was managed with reirradiation, which induced severe normal tissue toxicity that required amputation for symptomatic control (Table 6).

Five patients developed neurotoxicity. The median time to the onset of neurotoxicity was 13 months (range: 8 – 21 months). It was grade 1 (paresthesia not interfering with daily life) in one patient and grade 3–4 (objective weakness and/or sensory loss or paresthesia interfering with daily life) in the remaining four. No patient had paralysis (sensory grade 4). In three cases, the nerve had been included in the IOERT field. The chance of developing neuropathy was present in three out of 12 patients (25%) if the peripheral nerve had been included in the IOERT field and in two out of 18 patients (11%) if the nerve had not been irradiated. In four of five patients with nerve damage, the tumor size and the IOERT dose selected were greater than 12 cm and > 15 Gy, respectively. Three of the five patients showed symptomatic recovery 12 months after the onset of neuropathy (two partial, one total) (Table 7).

Of the 31 evaluable patients, 24 (77%) have a functional extremity without limitations for daily activities. Four patients walk with crutches, and five have a functionally impaired extremity due to toxicity after treatment: three amputations and two non-reversible neuropathies. Two patients with initial severe neuropathy have improved over time and lead a normal daily life. The final extremity preservation rate was 88% (40 out of 45 patients) (Table 8).

4. DISCUSSION

Initial positive experiences with both the feasibility of and tolerance to IOERT in the treatment of tumors arising in several anatomical sites prompted the investigation of IOERT in extremity STS [2,3]. Technical considerations, such as the optimal access of the IOERT applicators into the surgical bed and the highly controllable dosimetry of electrons in flat surfaces, led to inclusion of this modality as an intraoperative radiation component. Another possible advantage of IOERT is that it can be administered as an up-front radiation boost, simultaneously with surgical resection, which might allow total EBRT dose to be decreased without jeopardizing local control or survival.

IOERT clinical trials have been mainly conducted on patients with locally advanced malignancies in the abdomen and pelvis [6,14]. IOERT improves the therapeutic ratio by decreasing the toxicity in dose-limiting normal tissues that can be displaced or protected during IOERT. IOERT might indirectly improve the quality of therapy, as a secondary endpoint, by decreasing the overall treatment time [19]. This increase in the therapeutic ratio may also translate into survival benefit, especially in cancer sites with high risk of isolated loco-regional relapse [1]. The contribution of local control to

survival in patients with extremity STS is controversial [17,20]. However, quality of life is an important endpoint in these patients and is particularly dependent on strategies providing high local control rates, which translates into extremity preservation.

Scarce data exist regarding local control, tissue tolerance, effectiveness, feasibility, and functional status after treatment with IOERT in extremity STS [21]. The present report describes long-term follow-up results obtained in a cohort of patients treated with IOERT. The 20% local failure rate obtained is similar to the 15–20% reported in contemporary reports of EBRT-only series [7]. Furthermore, the observed 12% rate in primary tumors is among the best results described in published series using conventional multimodal treatment. The experience with IOERT in soft tissue sarcomas of the extremities is limited. In a recent update of the Mayo Clinic experience, Petersen et al. reported a 4% local failure rate for primary tumors and 17% for recurrent tumors using a comparable methodological approach [15]. Eble et al. reported an 8% local failure for stage IIB–IIIB tumors [15] and Dubois et al. reported no local recurrences in a smaller series of 18 STS patients treated with an IOERT component [4].

The present data are derived from a low number of patients in each disease category, which does make difficult the assessment of real prognostic information. In this particular group of patients, surgical margins have been closely related to local failure, a factor that has been previously reported [9,16]. However, the optimal radiation dose required to control macroscopic residual disease is still unknown. IOERT trials have not yet been able to determine whether a dose-control relationship in resected STS is related to the amount of residual disease. This uncertainty applies to both to the IOERT and EBRT radiation components.

The addition of chemotherapy in the treatment of highgrade sarcomas may have contributed to improved local control rates. Combined treatment modalities increase the effect of radiation significantly, achieving significant improvement in local control and survival in other human tumors [11]. In the present study, 55% of the patients received concurrent chemotherapy and irradiation. A recent published meta-analysis suggested that adjuvant chemotherapy significantly reduced the metastasis rate and contributed to decrease the incidence of local failure [18]. This metaanalysis estimation showed a 27% reduction in the risk of local recurrence, which corresponded to an estimated absolute survival benefit of 6% at 10 years.

Acute toxicity was minor in the present study, and postoperative complications caused no delays in the initiation of the EBRT. Late effects described in this series may be difficult to analyzed as severe normal tissue complications are understood as multifactorial in origin and cannot be attributed to a single treatment modality. Severe late effects led to amputation in three patients. It can be speculated that an amputation would have been the best treatment option due to the initial tumor extent, which made them poor candidates for extremity preservation. One patient presented with a second recurrence of a desmoid tumor in which free surgical margins were not obtained. Furthermore, four IOERT fields were used, and vascular damage with immediate repair was reported during surgery. Amputation was done below the zone treated with external irradiation. In a second case, amputation was performed after obtaining a poor functional outcome. This patient, who had positive resection margins, presented recurrent disease after one previous course of irradiation. Therefore, other causes

besides IOERT may also have contributed to the toxicity that led to amputation in these cases.

Neuropathy is a dose-limiting toxicity in IOERT for extremity STS and other anatomic sites treated with this modality. Animal studies have shown that the tolerance of nerve structures to IOERT may be lower than 15 Gy [12]. In these studies, 30% of the animals developed neuropathy with IOERT doses of 15 Gy. In the present series, doses of IOERT greater than 10 Gy combined with external irradiation of 40–50 Gy were considered to be potentially harmful to nerve tissues. Sixteen percent of the patients developed symptoms associated with peripheral neuropathy. In three of these patients, substantial improvement was observed over time, with successful recovery after prolonged follow-up. Our current policy mandates, as the first technical option, displacing any nerve included in the target. If this cannot be done or if the nerve structure might be damaged by traction or perineural dissection, then a 5 Gy dose is delivered without shielding, followed by 10 Gy with shielding (individualized lead layers). Conversely, if the nerve is considered to be in a low risk area, it is shielded for the entire procedure. The data reported in this study are previous to the activation of the nerve protection policies.

A possible advantage of using IOERT as a boosting technique is the reduction in the overall treatment time. Only two patients in the entire series received an EBRT component total dose higher than 50 Gy, which is an EBRT value lower than recommended in the radical management of STS [5]. IOERT boost does shorten the overall treatment time, with the additional potential advantage of facilitating the integration of chemo-radiation segments in the initial part of the multidisciplinary treatment.

In conclusion, the present data demonstrate that IOERT as a boosting technique in the radical management of extremity STS is feasible and showing local control rates comparable to those reported in the treatment of other tumor sites approached with IOERT. The toxicity described in the present series is acceptable; however, careful attention should be paid to peripheral nerves as specific IOERT doselimiting structures.

REFERENCES

1. Abe M, Takahashi M, Ono K, Tobe T, Inamoto T. Japan gastric trials in intraoperative radiation therapy. Int J Radiat Oncol Biol Phys 1988; 15:1431–3.
2. Calvo FA, Azinovic I, Martinez Monge R. Intraoperative radiotherapy for the treatment of soft tissue sarcomas of central anatomical sites. Radiat Oncol Invest 1995;3:90–6.
3. Calvo FA, Santos M, Brady LW. Intraoperative radiotherapy. Clinical experiences and results. Heidelberg: Springer; 1991.
4. Dubois JB, Debrigode C, Hay M, et al. Intra-operative radiotherapy in soft tissue sarcomas. Radiother Oncol 1995;34:160–3.
5. Fein DA, Lee RW, Lanciano R, et al. Management of extremity soft tissue sarcomas with limb-sparing surgery and postoperative irradiation: do total dose, overall treatment time, and the surgeryradiotherapy interval impact on local control? Int J Radiat Oncol Biol Phys 1995;32:969–76.

6. Gunderson LL. Rationale and results of intraoperative radiation therapy. Cancer 1994;74:537–41.
7. Gwin Jr JL. Optimizing local control in soft tissue sarcoma of the extremity. Oncology 1994;8:25–31.
8. Harrison LB, Franzese F, Gaynor JJ, Brennan MF. Long term results of a prospective randomized trial of adjuvant brachytherapy in the management completely resected soft tissue sarcoma of the extremity and superficial trunk. Int J Radiat Oncol Biol Phys 1993;27:259–65.
9. Herbert SH, Corn BW, Solin LJ, et al. Limb-preserving treatment for soft tissue sarcomas of the extremities. The significance of surgical margins. Cancer 1993;72:1230–8.
10. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
11. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high risk-rectal carcinoma. N Engl J Med 1991; 324:709–15.
12. LeCouteur RA, Gillette EL, Powers BE, Child G, McChesney SL, Ingram JT. Peripheral neuropathies following experimental intraoperative radiation therapy (IORT). Int J Radiat Oncol Biol Phys 1989; 17:583–90.
13. Mantel N. Evaluation of survival data and two new rank order statistics arising in its considerations. Cancer Chemother Rep 1966; 50:163–70.
14. Martinez Monge R, Jurado M, Azinovic I, et al. Intraoperative radiotherapy in recurrent gynecological cancer. Radiother Oncol 1993;28:127–33.
15. Petersen IA, Calvo FA, Gunderson LL, et al. Extremity and trunk soft tissue sarcomas. In: Gunderson LL, Willett CG, Harrison LB, Calvo FA, et al., editors. Intraoperative radiation. Totowa, NJ: Humana Press; 1999. p. 359–78.
16. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14:1679–89.
17. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of softtissue sarcomas of the extremities. Prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 1982;196:305–15.
18. Sarcoma-Meta-Analysis-Collaboration, Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults. Lancet 1997;350: 1647–54.
19. Sindelar WF, Kinsella TJ, Chen PW, et al. Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial. Arch Surg 1993;128:402–10.
20. Stotter A, A'hern RP, Fisher C, Mott AF, Fallowfield ME, Westbury G. The influence of local recurrence of extremity soft tissue sarcoma on metastasis and survival. Cancer 1990;65:1119–29.
21. Wijffels RTM, Mehta DM, Spauwen PHM, Hoekstra HJ. Limbsparing treatment with surgery and intraoperative radiotherapy (IORT) for a second local recurrence of myxoid liposarcoma in the popliteal region, after previous surgery and high dose radiation. J Surg Oncol 1993;53:64–7.
22. Willett CG, Suit HD, Tepper JE, Mankin HJ, Convery K, Rosenberg AL. Intraoperative electron beam radiation therapy for retroperitoneal soft tissue sarcoma. Cancer 1991;68:278–83.

Table 1. Patient characteristics and site of the intraoperative electron beam radiotherapy (IOERT) boost		
	n	**%**
Number	45	
Age (years)		
Median	42	
Range	11–78	
Sex		
Male	26	58
Female	19	42
KPS > 70%	45	100
Location		
Upper limb	8	18
Lower limb	37	82
KPS, Karnofsky performance status.		

Table 2. Histology in primary sarcoma and isolated local recurrences treated with IOERT			
Histology	**Primary**	**ILR**	**Total**
Liposarcoma	6	6	12
MFH	7	6	13
Synovial sarcoma	3	1	4
Rhabdomyosarcoma	3	-	3
Fibrosarcoma	3	1	4
Hemangiopericytoma	3	-	3
Alveolar sarcoma	1	-	1
Leiomyosarcoma	-	2	2
Aggressive fibromatosis	-	3	3
MFH, malignant fibrous histiocytoma ILR, isolated local recurrence			

Table 3. Tumor characteristics		
Tumor type	**n**	**%**
Primary	26	58
AJCC stage		
IA	2	4
IB	8	18
IIB	2	4
IIIA	1	2
IIIB	13	29
ILR	19	22
Size		
T1	8	18
T2	36	80
N/A	1	2
Grade (primary tumors)		
I–II	12	46
III	14	54

Table 4. Type of surgery during the IOERT procedure		
	n	**%**
Type of surgery		
Wide	28	62
Marginal	13	28
Compartmental	3	6
Not specified	1	2
Surgical margins		
Negative	30	67
Close (<5 mm)	8	20
Positive	7	13

Table 5. IOERT and external beam radiotherapy (EBRT) characteristics		
IOERT	**n**	**%**
No. of IOERT fields	56	
Single	35	78
Multiple	10	22
Applicator diameter (cm)		
5–7	14	25
8–9	4	7
10–15	38	68
Energy (MeV)		
6–9	40	71
10–15	14	25
20	2	4
Dose (Gy)		
10–12	24	43
15	24	43
20	8	14
External beam radiotherapy (Gy)		
30	1	2
40–45	8	18
46–50	25	56
> 50	2	4
No EBRT	9	20

Table 6. Toxicity related to local treatment		
	n	**(%)**
Acute		
Infection	4	9
Dermatitis	2	4
Soft tissue necrosis	4	9
Delayed wound healing	4	9
Late		
Neuropathy	5	11
Symptomatic fibrosis	2	4
Amputation	3	7
Bone fracture	2	4
Edema	2	4
Toxicity related to chemotherapy is not shown.		

Table 7. Treatment parameters involved in neuropathy development in evaluable patients followed more than 12 months with extremity preserved			
Parameter	**Total**	**Neuropathy**	**%**
IOERT field	31	5	16
Nerve included	12	3	25
Nerve excluded	18	2	11
Unknown	1	–	–
IOERT applicator size (cm)			
6–10		1	
12		3	
12		1	
Dose (Gy)			
10		1	
15		3	
20		1	

Table 8. Extremity outcome data: functionality and amputation evaluation						
Functional outcome	**Primary**		**ILR**		**Total**	**%**
	n	**%**	**n**	**%**		
Impairment						
None	13	29	7	16	20	45
Minor	4	9	-	-	4	9
Major	4	9	3	7	7	16
Not evaluable	5	11	9	20	14	31
	n	**Total**	**%**	**Comments**		
Limb preservation	40	45	88			
Amputation due to toxicity	3	45	7	Four IOERT fields, one reirradiation		
Amputation due local failure	2	45	4			

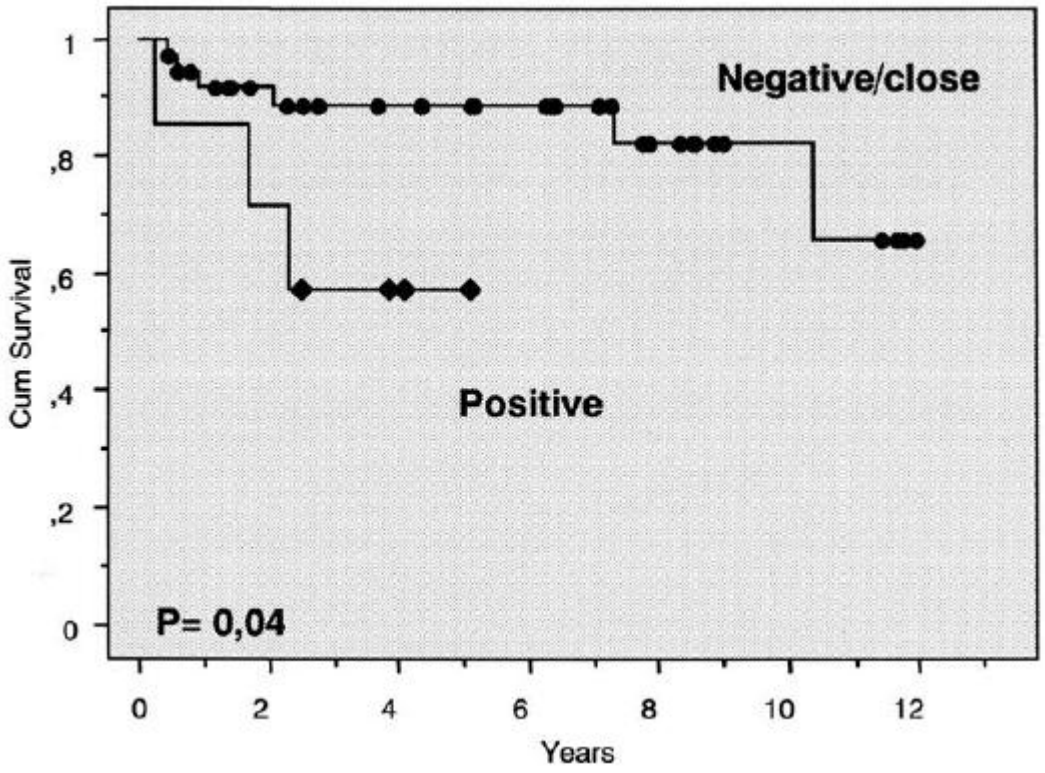

Figure 1. Actuarial local control according to surgical margins.

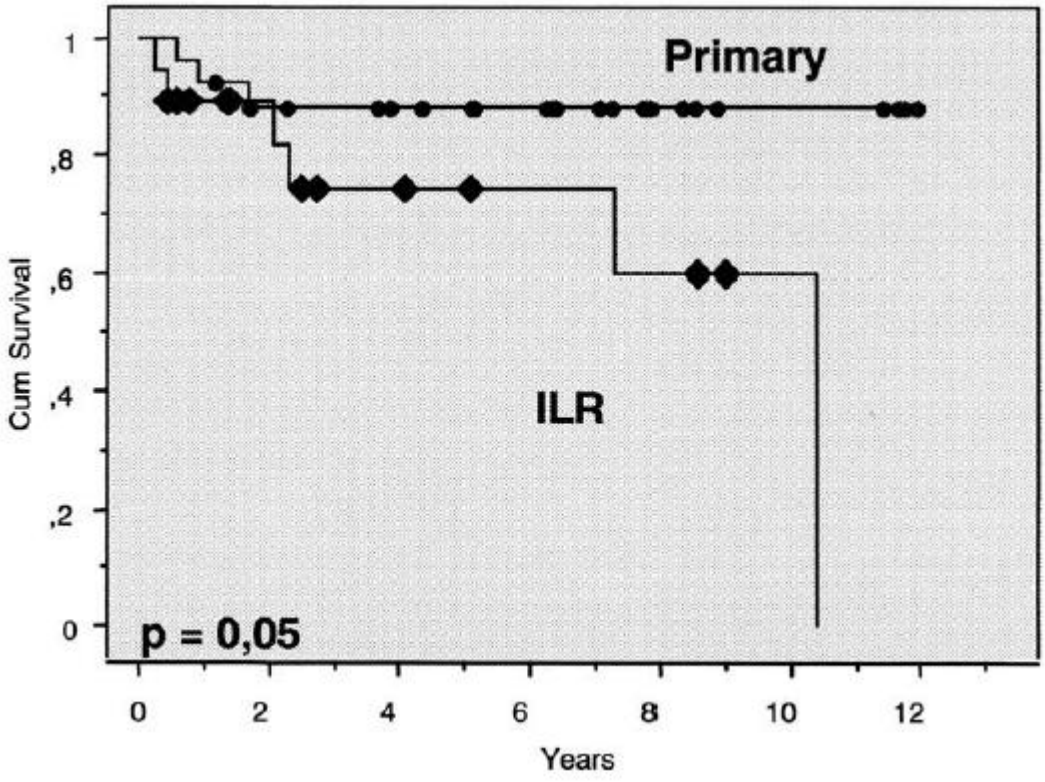

Figure 2. Actuarial local control according to sarcoma status (primary vs. isolated local recurrence (ILR)).

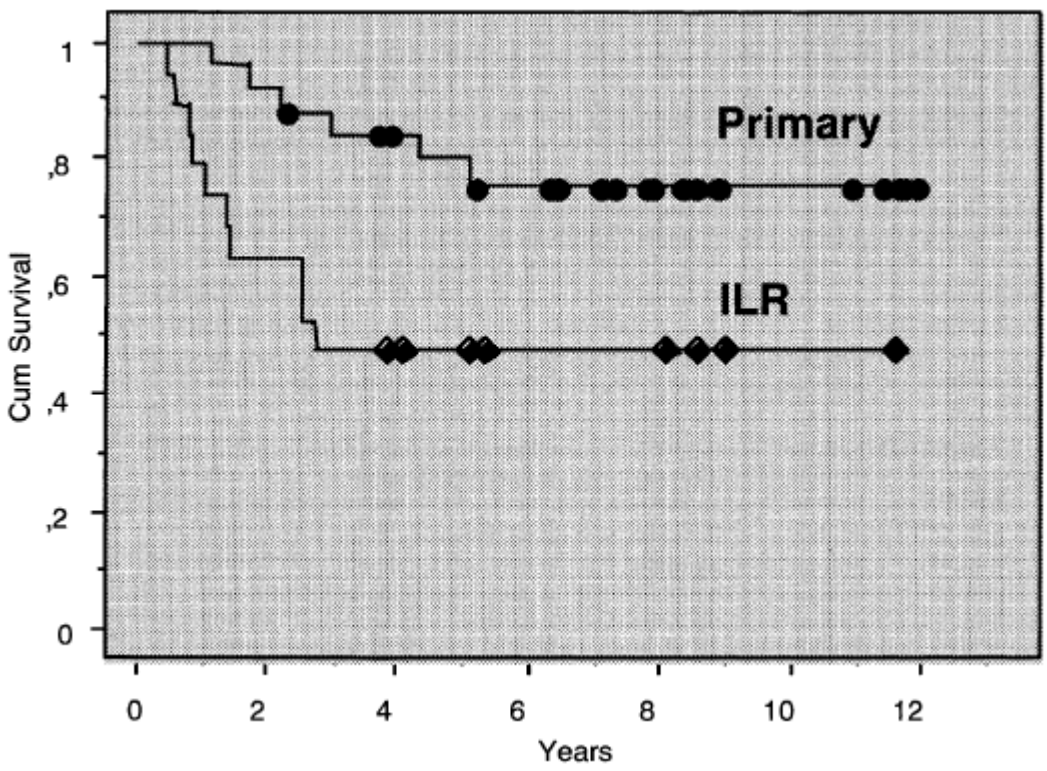

Figure 3. Actuarial survival in patients with primary soft tissue sarcoma and ILR, P = 0.01