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Clinical Investigation: Sarcoma

Prognostic Value of External Beam Radiation Therapy in Patients Treated With Surgical Resection and Intraoperative Electron Beam Radiation Therapy for Locally Recurrent Soft Tissue Sarcoma: A Multicentric Long-Term Outcome Analysis

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Summary

Recognition of the high risk of local recurrence and death from locally recurrent soft tissue sarcomas has led to interest in the use of radical intent surgical resection, external beam radiation

Background: A joint analysis of data from centers involved in the Spanish Cooperative Initiative for Intraoperative Electron Radiotherapy was performed to investigate long-term outcomes of locally recurrent soft tissue sarcoma (LR-STS) patients treated with a multidisciplinary approach.

Methods and Materials: Patients with a histologic diagnosis of LR-STS (extremity, 43%; trunk wall, 24%; retroperitoneum, 33%) and no distant metastases who underwent radical surgery and intraoperative electron radiation therapy (IOERT; median dose, 12.5 Gy) were considered eligible for participation in this study. In addition, 62% received external beam radiation therapy (EBRT; median dose, 50 Gy).

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therapy, and intraoperative electron radiation therapy (IOERT). These mature data add further evidence that an intensified radiation and surgical treatment promotes loco-regional control, compensating for some adverse disease features in the context of an advanced multimodality rescue strategy.

Results: From 1986 to 2012, a total of 103 patients from 3 Spanish expert IOERT institutions were analyzed. With a median follow-up of 57 months (range, 2-311 months), 5-year local control (LC) was 60%. The 5-year IORT in-field control, disease-free survival (DFS), and overall survival were 73%, 43%, and 52%, respectively. In the multivariate analysis, no EBRT to treat the LR-STS ($P=.02$) and microscopically involved margin resection status ($P=.04$) retained significance in relation to LC. With regard to IORT in-field control, only not delivering EBRT to the LR-STS retained significance in the multivariate analysis ($P=.03$).

Conclusion: This joint analysis revealed that surgical margin and EBRT affect LC but that, given the high risk of distant metastases, DFS remains modest. Intensified local treatment needs to be further tested in the context of more efficient concurrent, neoadjuvant, and adjuvant systemic therapy. © 2014 Elsevier Inc.

Introduction

Soft tissue sarcomas (STS) are uncommon tumors with heterogenous biological properties and histologic findings (1). Complete resection is the primary therapy for most STS in adults, but patients with locally recurrent STS (LR-STS) have poor local control and survival (2). Clinical practice has shifted from nonintervention or palliative treatment to more intensive multimodal approaches, with radical rescue surgery providing local control in approximately half of all patients (3, 4). The success of rescue treatment is highly dependent on the extent of local extension, invasion, fixation, and radicality of resection (2-4). A completely negative resection margin is often difficult to achieve owing to close proximity to or proven invasion of adjacent postresection tumor bed areas, or unresectable structures. Therefore, multimodal approaches including additional local therapies should be implemented to further improve patient outcomes and to optimize local control and survival (5). Few studies have specifically analyzed the prognosis of patients with LR-STS involving the extremities, trunk wall, and retroperitoneum (6-13). We performed a joint study of data from the Spanish Cooperative Initiative for Intraoperative Electron Radiotherapy to analyze long-term outcomes and novel risk factors for a group of patients with LR-STS treated with radical surgery and intraoperative electron beam radiation therapy (IOERT) in high-risk areas (postresection and prereconstruction), with and without external-beam radiation therapy (EBRT).

Methods and Materials

Patient characteristics and staging evaluation

This study was approved by our institutional review board and performed in compliance with local ethical and clinical practice guidelines. The study population comprised adult patients (>18 years) with pathologically confirmed nonmetastatic LR-STS and curative resections with either close (<1 cm) or positive margins. The tumor board recommended a multimodal approach after taking into account initial treatment characteristics, location, resectability, and clinical status. All patients (n=103) were invited to participate in a developmental protocol that consisted of rescue surgery, EBRT, and IOERT delivered to the area of the tumor bed that was at risk for residual disease EBRT plus IOERT program, but 40 patients (39%) elected not to consent the EBRT component (patients who did not consent EBRT had greater concerns related to retreatment toxicity or issues related to treatment efficacy). Two treatment strategies were operational along the period: 63 patients (61%) were treated according to a research protocol that consisted of EBRT, surgery, and IOERT with or without adjuvant chemotherapy (EBRT group). The remaining 40 patients were treated with surgery plus IOERT, but without EBRT (non-EBRT group) and served as the control cohort. The surgical approach and adjuvant chemotherapy were discussed on an individual basis. Prospectively collected hospital records of 103 patients registered in the IOERT program and treated for LR-STS between June 1986 and April 2012 were retrospectively reviewed at the time of scheduled follow-up. Pretreatment evaluation consisted of a complete history and physical examination, complete blood count, renal and liver function tests, chest x-ray, and computed tomography (CT) or magnetic resonance imaging (MRI) of the tumor site, chest, and abdomen. Patients were reclassified according to the seventh American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system. Patient and treatment characteristics are listed in Table 1. No significant differences in baseline variables were detected between patients treated with or without EBRT.

Treatment characteristics

EBRT and concomitant and adjuvant chemotherapy were administered following standards described elsewhere (5). Conformal 3-dimensional postoperative EBRT (n=63, 62%) was delivered with megavoltage equipment (6-15 MV). Fields were arranged taking into account doses delivered to normal tissues during radiation therapy for the primary tumor. However, no specific dose−volume constraints were indicated in the treatment protocol. Non-irradiated patients (n=46) received a total median dose of 50 Gy (range, 45-50.4 Gy [1.8-2.0 Gy/5 days/wk]) and re-irradiated patients (n=17) received 30.6 Gy (range, 21.6-30.6 Gy [1.8 Gy/5 days/wk]), both of which were prescribed to the isodose line that covered the planning target volume (PTV) to obtain a homogeneity of ±5% of the prescribed dose according to the International Commission on Radiation Units and Measurements Report No. 50. The technique for the EBRT component consisted of conventional (2D-RT) EBRT for patients treated between 1986 and 1992 (n=12, 20%), and conformal (3D-CRT) EBRT for patients treated after 1992 (n=49, 80%). PTV for 2D-RT was defined as tumor bed plus 3 cm in the radial directions in all cases, and for the longitudinal directions a 5-cm margin was applied for extremity LR-STS and a 3-cm margin was added for trunk wall and retroperitoneal LR-STS (the field could be shortened to include

Table 1 Patient, tumor, and treatment characteristics

Parameter	Variable	All patients n = 103 (%)	EBRT group n = 63 (61%)	No-EBRT group n = 40 (39%)	*P* value
Patient variables					
Age	Median age (y)	53 (23-78)	54 (31-78)	52 (33-76)	.89
Sex	Male	40 (39)	26 (41)	14 (35)	.71
	Female	63 (61)	37 (59)	16 (65)	
Karnofsky perfomance status	<90	27 (26)	15 (24)	12 (30)	.55
	≥90	76 (74)	48 (76)	28 (70)	
Time interval from primary to LR (mo)	≥24	54 (53)	32 (51)	22 (55)	.68
	<24	49 (47)	31 (49)	20 (45)	
Presurgical variables					
Tumor size	Median tumor size (cm)	9 (2-24)	9 (3-24)	10 (3-20)	.78
Tumor localization	Extremity	44 (43)	32 (51)	12 (30)	.19
	Retroperitoneum	34 (33)	18 (28)	16 (40)	
	Trunk wall	25 (24)	13 (21)	12 (30)	
Tumor depth	Deep	79 (77)	46 (73)	33 (83)	.46
	Superficial	24 (23)	17 (27)	7 (17)	
Microscopic surgical specimen					
Histologyc subtype	Liposarcoma	38 (37)	21 (33)	17 (43)	.53
	Malignant fibrous histiocytoma	19 (18)	14 (22)	5 (13)	
	Leiomyosarcoma	11 (11)	5 (8)	6 (10)	
	Sarcoma NOS	8 (8)	6 (10)	2 (3)	
	Synovial sarcoma	8 (8)	7 (11)	1 (2)	
	Other	19 (18)	10 (16)	9 (14)	
Mitosis count	Low-medium	83 (81)	49 (78)	34 (85)	.44
	High	20 (19)	14 (22)	6 (15)	
Necrosis	Yes	44 (43)	24 (39)	20 (50)	.60
	No	59 (57)	39 (61)	20 (50)	
Histologic grade	1-2	73 (71)	46 (63)	27 (68)	.82
	3	30 (29)	17 (37)	13 (32)	
Surgery					
Surgical procedure	Wide excision	64 (62)	40 (63)	24 (60)	.78
	Simple local excision	39 (38)	23 (37)	16 (40)	
Margin status	R0	62 (60)	37 (59)	25 (63)	.68
	R1	41 (40)	26 (41)	15 (37)	
IOERT technical parameters					
IOERT dose (cGy)	Median IOERT dose (cGy)	1250 (1000-2000)	1200 (1000-2000)	1250 (1000-2000)	.89
IOERT energy (MeV)	Median IOERT energy (MeV)	9 (4-20)	8 (4-20)	9 (4-18)	.54
IOERT applicator size (cm)	Median IOERT applicator size (cm)	9 (5-15)	9 (5-15)	10 (5-15)	.65
EBRT-CT treatment					
Adjuvant CT	Yes	36 (35)	19 (30)	17 (41)	.28
	No	67 (65)	44 (70)	23 (58)	
EBRT to the primary tumor	Yes	31 (30)	17 (27)	14 (35)	.21
	No	72 (70)	46 (73)	26 (65)	

Abbreviations: CT = chemotherapy; EBRT = external beam radiation therapy; IOERT = intraoperative electron beam radiation therapy; NOS = not otherwise specified.

the end of the compartment). Clinical target volume (CTV) for the 3D-CRT technique included the surgical tumor bed plus a 2-cm margin in the radial directions. A 3-cm margin in the longitudinal (proximal and distal) directions was used in the case of extremity locations, and for trunk wall and retroperitoneal LR-STS, a 2-cm margin was used. PTV was defined as CTV plus a 1 cm margin in longitudinal and radial directions. The surgical approach (4-6 weeks before EBRT treatment) consisted of wide resection (62%) or marginal resection (38%). Patients with a higher histologic grade (grade 3) and tumor size (≥5 cm) were offered adjuvant chemotherapy (most commonly 4 or 5 cycles of doxorubicin 75 mg/m^2 and ifosfamide 5 g/m^2 every 3 weeks). The IOERT program was performed in a nondedicated linear accelerator under an outpatient regimen. After resection and before reconstruction, 10 to 20 Gy (median, 12.5 Gy) were delivered in a single fraction to 1-field PTVs (n = 75, 73%) or 2-field PTVs (n = 28, 27%) using a median energy of 9 MeV (range, 4-20 MeV) (Table 2). The dose was delivered to the 90% isodose line covering the surgical bed. The IOERT dose was chosen according to the EBRT dose, margins (intraoperative margin status was assessed using frozen pathologic sections) and surgical bed volumes. Beveled (15°-45°) Lucite circular applicators (size range, 5-15 cm) were adjusted to collimate the target surface air gap, thus allowing dosimetric adaptation and uniform dose distribution. IOERT CT-guided treatment has been available since 2008 (14).

Table 2 Correlations between macroscopic/microscopic pathology characteristics and intraoperative electron beam radiation therapy (IOERT) technical parameters

	Applicator size	IOERT dose (Gy)	IORT energy (MeV)
Pathology/IOERT treatment	Median/ range	Median/ range	Median/ range
Tmax size (cm)			
2.0-3.0	6/5-8	12.5/10-20	8/4-20
3.1-6.0	9/5-9	12.5/12.5-20	8/4-20
6.1-10.0	9/6-10	12.5/10-15	9/6-20
10.1-15.0	9/7-15	12.5/12.5-15	9/4-20
15.1-24.0	9/9-15	12.5/10-15	9/6-20
Margin resection status			
R0	9/5-15	12.5/10-20	9/4-20
R1	9/5-15	12.5/12.5-20	9/6-20

Abbreviation: Tmax = tumor maximal dimension.
Multiple field technique procedures in 28 (27%) patients.

Follow-up and toxicity evaluation

All patients were followed up according to a common protocol every 3 months after completion of treatment for the first 3 years and every 6 months for an additional 3 years thereafter. Patients were restaged 4 weeks after EBRT and routinely every 6 months with chest x-ray and CT or MRI of the initial tumor site.

Acute and late toxicities were evaluated according to the criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (15).

Statistical analysis

Data were analyzed using SPSS (version 19.0). The primary endpoint of the analysis was local control (freedom from EBRT in-field progression). Secondary endpoints were IOERT in-field control (freedom from IOERT in-field progression), disease-free survival (DFS), and overall survival (OS). Potential associations for survival outcomes were assessed in the univariate and multivariate analyses using the Cox proportional hazards model. Based on P values $\leq$.10 in the univariate analysis and clinical relevance, multivariate analysis was performed using a stepwise regression model to identify variables that have an effect on survival outcomes ($P \leq .05$, 2-sided).

Results

Median follow-up time for all patients was 57 months (range, 2-311 months). A total of 41 patients remained alive at the time of the analysis. The median follow-up for surviving patients was 80 months (range, 4-311 months). Of the 62 deceased patients, 55 (89%) died of progression of sarcoma, and 7 (11%) died of causes unrelated to their sarcomas or treatment. The crude local relapse rate was 34% (n = 35); 36% of the patients (n = 37) developed distant metastases (most commonly pulmonary [n = 18, 49%]). Of the 35 patients who had local progression, 18 (51%, crude rate) underwent a new surgical procedure for rescue [median time to surgical rescue 23.3 months (range, 6.7-61.4 months)], with long-term local sarcoma control in 11 patients (61%, crude rate). The remaining 17 patients had synchronous distant metastases with local relapse and received chemotherapy alone (n = 82%) or no further therapy (n = 18%).

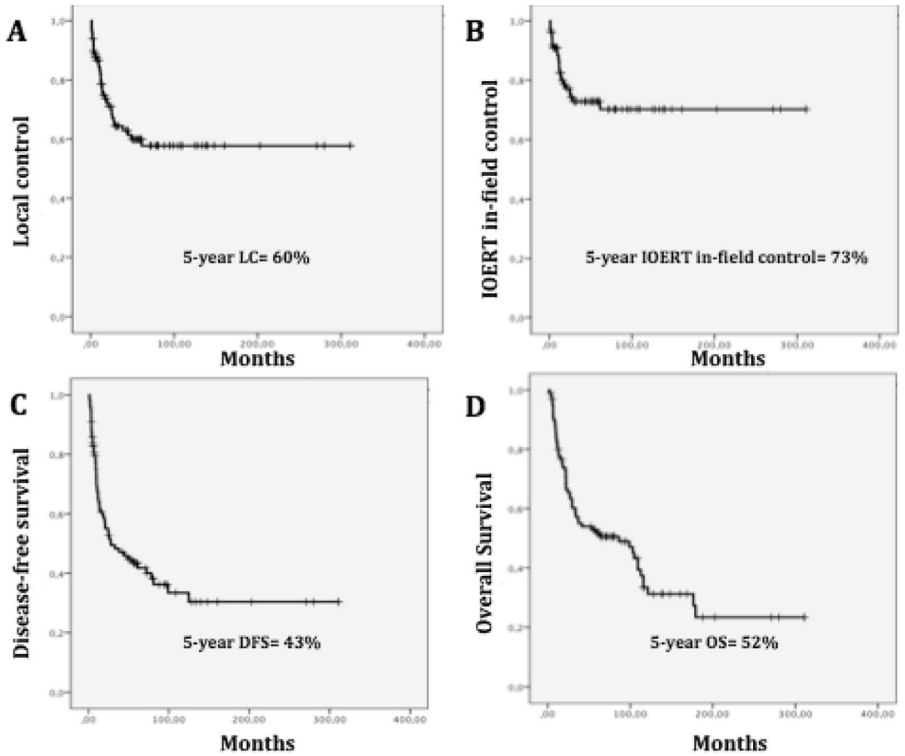

Fig. 1. Kaplan-Meier curves for all 68 patients: local control (A), IOERT in-field control (B), disease-free survival (C), and overall survival (D).

Table 3 Univariate analyses of associations between the patient, tumor, and treatment with local control, intraoperative electron beam radiation therapy (IOERT) in-field control, disease-free survival, and overall survival

		Local control			IOERT in-field control			Disease-free survival			Overall survival		
Parameter	Variable	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Patient variables													
Sex	Male	1.0			1.0			1.0			1.0		
	Female	0.98	0.50-1.91	.95	0.80	0.39-1.64	.54	0.80	0.47-1.36	.41	0.87	0.33-1.53	.45
Age (y)	<50	1.0			1.0			1.0			1.0		
	≥50	1.09	0.54-2.20	.81	0.82	0.34-1.97	.65	1.33	0.76-2.33	.32	1.59	1.02-2.32	.05
Karnofsky perfomance status	<90	1.0			1.0			1.0			1.0		
	≥90	0.61	0.28-1.51	.34	0.78	0.34-2.04	.45	0.84	0.35-2.10	.67	0.88	0.20-2.16	.71
Time interval from primary to LR (mo)	≥24	1.0			1.0			1.0			1.0		
	<24	2.47	1.03-5.19	.04	2.95	0.73-7.61	.17	3.65	1.21-7.23	.01	3.18	1.25-6.88	.01
Presurgical variables													
Tumor size (cm)	≤10	1.0			1.0		.67	1.0			1.0		
	>10	1.64	0.91-2.94	.10	1.17	0.58-2.32		1.14	0.869-1.88	.60	1.22	0.74-2.23	.31
Tumor localization	Extremity	1.0			1.0			1.0			1.0		
	Retroperitoneal	2.26	0.85-4.64	.14	2.33	0.78-6.09	.27	1.75	0.83-3.49	.19	1.35	0.74-2.50	.33
	Trunk wall	1.59	0.71-3.10	.31	1.33	0.55-3.18	.53	1.61	0.79-3.08	.23	1.30	0.73-2.33	.38
Tumor depth	Superficial	1.0			1.0			1.0			1.0		
	Deep	1.91	0.74-4.11	.22	2.98	0.37-8.75	.35	1.21	0.43-3.82	.41	1.24	0.37-3.91	.86
Microscopic surgical specimen													
Histologic subtype	Liposarcoma	1.0			1.0		.88	1.0			1.0		
	Others	1.24	0.68-2.56	.49	1.05	0.53-2.08		1.53	0.90-2.55	.13	1.31	0.77-2.23	.32
Mitosis count	Low-medium	1.0			1.0		.16	1.0			1.0		
	High	2.14	0.95-4.81	.07	1.95	0.78-4.94		1.60	0.91-2.68	.13	1.39	0.66-2.89	.39
Necrosis	Yes	1.0			1.0		.88	1.0			1.0		
	No	0.75	0.26-2.41	.35	1.12	0.54-2.61		0.51	0.21-1.25	.23	0.65	0.31-1.19	.17
Histologic grade	1-2	1.0			1.0		.23	1.0			1.0		
	3	1.86	1.02-3.43	.05	1.55	0.76-3.18		2.26	1.17-4.36	.02	1.64	0.96-2.79	.07
Surgery													
Resection	Wide resecrion	1.0			1.0	0.62-5.77	.29	1.0	0.43-2.19	.74	1.0	0.51-2.87	.46
	Local resection	1.22	0.61-3.19	.30	1.91			1.21			1.29		
Margin status	R0	1.0			1.0	1.03-3.28	.05	1.0			1.0		
	R1	1.96	1.28-2.95	.02	1.68			1.58	1.08-2.54	.04	2.10	1.10-3.80	.04
IOERT technical parameters													
IOERT dose (Gy)	<1250	1.0			1.0		.78	1.0			1.0		
	≥1250	0.93	0.51-1.72	.83	0.90	0.45-1.82		1.08	0.65-1.78	.77	0.93	0.55-1.57	.79
IOERT energy (MeV)	<6	1.0			1.0		.71	1.0			1.0		
	≥6	0.87	0.39-1.65	.42	0.82	0.23-2.12		1.10	0.68-1.78	.71	1.42	0.81-2.17	.20
IOERT applicator size (cm)	<9	1.0			1.0		.38	1.0			1.0		
	≥9	0.92	0.39-1.89	.84	0.74	0.38-1.44		0.90	0.46-1.62	.75	0.78	0.47-1.29	.33
Adjuvant treatment													
EBRT treatment to primary tumor	Yes	1.0			1.0	0.31-1.20	.16	1.0	0.44-1.19	.20	1.0	0.31-1.25	.32
	No	0.68	0.38-1.23	.21	0.61			0.72			0.67		
EBRT treatment to LR-STS	Yes	1.0			1.0	1.0-3.61	.05	1.0	0.76-2.16	.36	1.0	0.81-2.45	.31
	No	1.80	1.05-3.17	.04	1.94			1.28			1.49		
EBRT re-irradiation	Yes	1.0			1.0			1.0			1.0		
	No	0.75	0.42-2.01	.55	0.85	0.54-1.74	.73	0.68	0.25-2.09	.71	0.92	0.33-2.32	.88
Adjuvant chemotherapy	Yes	1.0			1.0		.82	1.0			1.0		
	No	1.18	0.50-2.80	.70	1.12	0.43-2.89		1.33	0.71-2.48	.38	1.18	0.41-2.73	.77

Abbreviations: CI = confidence interval; CT = chemotherapy; EBRT = external beam radiation therapy; HR = hazard ratio; LR = local recurrence.

Local control for the study population at 5 and 10 years was 60% and 58% (Fig. 1A). Univariate Cox proportional hazard analyses showed that patients with a time interval from primary tumor diagnosis to local relapse <24 months ($P=.04$), incomplete resection ($P=.02$), high histologic grade ($P=.05$), and no EBRT administered to treat the LR-STS ($P=.04$) were associated with a higher probability of local relapse (Table 3). After adjustment for other covariates, the variables that remained significantly associated with local relapse were no EBRT to the LR-STS ($P=.02$) and R1 margin status ($P=.04$) (Table 4). IOERT in-field control at 5 and 10 years was 73% and 70% (Fig. 1B). Univariate analysis showed that patients with R1 resection ($P=.05$) and no EBRT to treat the LR-STS ($P=.05$) had a higher probability of IOERT in-field relapse (Table 3). In the multivariate analysis, only no EBRT to treat the LR-STS ($P=.03$) retained a significant association with regard to IOERT in-field relapse (Table 4). DFS at 5 and 10 years was 43% and 33% (Fig. 1C). Univariate Cox proportional hazard analysis showed that time interval from primary tumor diagnosis to local relapse <24 months ($P=.01$), high histologic grade ($P=.02$),

Table 4 Factors associated with local control, intraoperative electron beam radiation therapy (IOERT) in-field control, disease-free survival, and overall survival in multivariate analyses

		Local control			IOERT in-field control			Disease-free survival			Overall survival		
Parameter	Variable	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Patient variables													
Time interval from primary to LR (mo)	≥24	-	-	-	-	-	-	1.0			1.0		
	<24							3.87	1.36-7.88	.006	3.44	1.29-7.08	.008
Microscopic surgical specimen													
Histologic grade	1-2	-	-	-	-	-	-	1.0			-	-	-
	3							2.41	1.06-4.92	.04			
Surgery													
Margin status	R0	1.0	1.06-3.34	.04	-	-	-	1.0			1.0		
	R1	1.73						1.72	1.11-2.83	.03	2.41	1.21-4.21	.02
IOERT technical parameters													
CT treatment EBRT treatment to LR-STS	Yes	1.0			1.0			-	-	-	-	-	-
	No	2.12	1.18-3.23	.02	2.08	1.10-3.64	.03						

Abbreviations: CI = confidence interval; CT = chemotherapy; EBRT = external beam radiation therapy; HR = hazard ratio.

and R1 resection status ($P=.04$) were associated with a higher probability of metastasis (Table 3). After adjustment for other covariates, primary tumor diagnosis to local relapse <24 months ($P=.006$), high histologic grade ($P=.04$), and incomplete margin status ($P=.03$) retained a significant association with DFS (Table 4). Overall survival at 5 and 10 years was 52% and 33% (Fig. 1D). In the univariate analysis, patients with age ≥50 years ($P=.05$), a time interval from primary tumor diagnosis to local relapse <24 months ($P=.01$), and an R1 margin status ($P=.04$) were at a significantly higher risk of death (Table 3). Multivariate analysis showed that only R1 margin status ($P=.02$) and primary tumor diagnosis to local relapse <24 months ($P=.006$) were significantly associated with OS (Table 4).

Overall, 16 patients (16%) had grade ≥3 acute toxicity (severe skin reactions [n=7, grade 3] and wound-healing disorders [n=5, grade 3; n=4, grade 4]). Severe skin reactions and wound-healing disorders were more frequently observed in patients with extremity LR-STS (n=3, grade 3) and trunk wall LR-STS (n=2, grade 3; n=2, grade 4), respectively. Thirteen patients (13%) developed chronic toxicity ≥3 (neuropathy [n=6, grade 3], necrosis/fistula/ulcer [n=3, grade 3], and severe chronic lymphedema [n=7, grade 3]). Neuropathy, necrosis/fistula/ulcer and severe chronic lymphedema were more frequently observed in patients with retroperitoneal LR-STS (n=3, grade 3), trunk wall LR-STS (n=2, grade 3) and extremity LR-STS (n=7, grade 3), respectively. No significant differences were observed in acute or chronic toxicity between patients who received EBRT to treat the local relapse and those who did not. No perioperative deaths or deaths related to long-term treatment were recorded.

Discussion

To our knowledge, this is the first study to focus on long-term outcomes in patients with LR-STS treated with IOERT, surgical resection, and EBRT. Our most relevant findings can be summarized as follows. First, we observed that not combining EBRT with surgical resection and IOERT in patients with LR-STS was significantly associated with an increased probability of LR and IOERT in-field relapse. Second, we found that patients with a time interval <24 months between primary tumor diagnosis and local relapse had an increased probability of overall metastasis and death. Finally, patients with microscopically positive margins had worse overall outcomes.

Several expert IOERT institutions with broad inclusion criteria (primary advanced and locally recurrent) and mixed cohorts of extremity, trunk wall, and retroperitoneal sarcomas have reported results comparable to those in the present analysis (Table 5). The present retrospective single-center analysis included only patients with LR-STS. Selection was not based on primary site, volume of tumor recurrence, or modalities of initial treatment. All patients had close margins (<1 cm) or positive margins (R1), features related to difficult surgical resection and adverse prognosis (3).

Discrimination between primary advanced and LR-STS in IOERT-based studies is important, because worse overall outcomes are consistently described for LR-STS (5, 6). Several groups have successfully implemented and reported combined management (IORT and surgical resection) in mixed cohorts for patients with primary and LR-STS (5-year local control [60%-80%]) (11-13).

Although it is widely accepted that the quality of the surgical margin is of paramount importance for local control, what constitutes adequate surgical margins is not well established. Positive surgical margins have been consistently reported as an adverse prognostic factor for local control (12, 13). Oertel et al (12) reported high 5-year local control (78%) and OS (77%) in the largest single-institution experience reported to date (n=153), in which IOERT combined with moderate doses of EBRT for the management of extremity STS (32% recurrent). Local control was more favorable for patients with complete margin resection (5-year locoregional control 85% vs 60%, $P=.03$). Azinovic et al (13) analyzed 45 patients with extremity sarcomas (42% recurrent

Table 5 Series reporting long-term outcomes for patients with soft tissue sarcomas

	N	Median follow-up (mo)	IORT	Disease status		(Neo) Adjuvant EBRT	Neo (Adjuvant) CT	5-year local Kaplan-Meier estimate			
				Primary	Recurrent			IOERT in-field LC	LC	DFS	OS
Zagars et al*	1225	114#	<1%	84%	16%	100%	33%	NR	83%	60%	71%§
DeLaney et al*	154	75	10%	87%	13%	100%	15%	NR	76%	47%	65%
Alektiar et al†	32	33	100%	37%	63%	78%	13%	NR	62%	82%	55%§
Petersen et al†	87	42	100%	49%	51%	89%	12%	NR	59%	55%	29%§
Dziewieski et al†	46	20	100%	13%	87%	52%	4%	NR	51%	NR	NR
Krempien et al†	67	30	100%	39%	61%	67%	NR	72%	40%	50%‖	28%§
Tran et al*	50	59	100%	30%	70%	37%	32%	55%	26%	51%‖	25%§
Azinovic et al‡	45	93#	100%	74%	26%	80%	73%	NR	80%¶	56%¶	NR
Oertel et al‡	153	33	100%	62%	38%	62%	NR	NR	78%	48%‖	77%

Abbreviations: CT = chemotherapy; DFS = disease-free survival; EBRT = external beam radiation therapy; IORT = intraoperative radiation therapy; LC = local control; OS = overall survival.

* Mixed cohorts (retroperitoneum, pelvis, extremity, head-and-neck, and/or trunk wall).

† Retroperitoneal soft tissue sarcoma only.

‡ Extremity soft tissue sarcoma only.

§ Disease-specific survival.

‖ Distant metastasis-free survival.

¶ Crude rates.

Median follow-up for surviving patients.

tumors) treated with moderate-dose postoperative EBRT (45-50 Gy) and IOERT. Five-year local control was 87%, and margin status (negative or close margins vs positive margins [$P = .04$]) significantly affected local control. In the current analysis, positive microscopic resection margins were significantly associated with poor overall outcomes in the multivariate analysis. Nonetheless, to compare results from different institutional experiences and to evaluate the effect of different treatment modalities on local control, a strict definition of the margin assessment procedure is required. Several routines for margin assessment have been described (16). Most studies report that the margin is assessed by the surgeon and validated by the pathologist or jointly assessed by both. The surgeon can measure the thickness of the closest margin of surrounding tissue on the fresh specimen, omitting areas of shortest distances where there is fascial involvement. The pathologist can measure the thickness of the tumor macroscopically on fresh or formalin-fixed specimen using several slices. In recent years, reports on the surgical margin have generally been accompanied by the microscopic tumor tissue location at the specimen perimeter (17). Finally, the shortest distance without fascial coverage can be measured microscopically as the distance from tumor tissue to an inked surface (16). Interpretation of these anatomical and histological features is even more uncertain in postresection and irradiated sarcoma specimens. In the present analysis, the pathologist defined a positive margin during surgery using frozen section analysis.

Histological grade is an independent predictive factor for development of metastasis in most cases of adult STS (4). Not surprisingly, therefore, grade was also an independent prognostic factor for DFS in the present analysis. Intensified local treatment needs to be tested in the context of more efficient concurrent, neoadjuvant, and adjuvant systemic therapy. Although the effect of adjuvant chemotherapy on survival for resected STS has yet to be established (18), distant metastases remain the dominant pattern of progression for high-risk extremity STS (3).

We acknowledge several limitations of our study. First, the treated population (103 patients treated over 26 years) was heterogeneous, receiving different treatment combinations, sequences, and doses. Radiation therapy technology and consensus on gross tumor volume and clinical target volume has also changed over time (19). Second, we included extremity, trunk, and retroperitoneal STS together, although it is currently recognized that there are very specific and unique anatomical challenges relating to the management of recurrence in each of these sites, and for the retroperitoneal site at least, there may be biologic differences in behavior and prognosis (3). The fact that anatomic site was not a significant predictor of overall outcomes is likely a reflection of a number limitation of our clinical data. Finally, it is very difficult to assess the specific contribution of the IOERT treatment component, because this analysis cannot compare local sarcoma control with or without intraoperative electron irradiation. Locally recurrent STS (oligorecurrence) is a broad disease category comprising several types of patients and tumors (20). Oligorecurrence involves a restricted locoregional tumor burden and has been proposed as a common criterion for treatment strategy optimization (20). Intraoperative radiation therapy is an attractive method of dose escalation for LR-STS with close or positive margins (5). IORT has several advantages over EBRT, such as more precise delivery of radiation to a surgically identified high-risk area, mobilization of dose-sensitive organs at risk, temporarily out of the radiation boost field, and shortening of overall treatment time (dose-dense radiation therapy). As reported by Azinovic et al (13), patients receiving adjuvant EBRT in the current analysis had a higher local control rate than patients in whom EBRT was omitted (85% vs 74%). Even more, we observed that not receiving EBRT for the local relapse was associated with an increased likelihood of IOERT in-field relapse. Although most LR-STS tumors recurred within the IOERT field (69%), in the present analysis a higher IOERT dose did not improve local control. Novel technologies could potentially make IOERT

considerations more influential, especially in an attempt to induce immune stimulation against sarcomas (21).

Treatment-related toxicity, including that induced by IOERT administered to treat LR-STS, was well tolerated by our 103 patients. The low rate of severe toxic events suggests that a multimodality approach with re-resection and IOERT is feasible without prohibitive long-term side effects. Location-associated risk should be carefully assessed during IOERT administration to minimize the irradiated volume. The definition of organs at risk, availability of dose−volume histograms, and estimations of 3D dose distribution play a key role in optimization of IOERT (14). Detailed planning on the part of the surgeon and radiation oncologist, along with detailed input from the radiologist before surgery and from the pathologist at the time of resection, is decisive for dose-escalation strategies within the tumor bed (field-within-field technique). Future clinical research should focus on functional outcome and quality of life.

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