Clin Transl Oncol
DOI 10.1007/s12094-014-1157-y

RESEARCH ARTICLE

Intraoperative radiotherapy-containing multidisciplinary management of trunk-wall soft-tissue sarcomas

C. V. Sole · F. A. Calvo · M. Cambeiro · A. Polo · A. Montero · R. Hernanz · C. Gonzalez · M. Cuervo · D. Perez · M. S. Julian · R. Martinez-Monge

Received: 30 August 2013 / Accepted: 10 January 2014

Abstract
Purpose A joint analysis of data from centers within the intraoperative radiotherapy (IORT)-Spanish cooperative initiative was performed to investigate the main contributions of IORT to the multidisciplinary treatment of trunk-wall soft-tissue sarcoma (TW-STS).
Materials and methods Patients with a histologic diagnosis of TW-STS (primary tumor 53 %; locally recurrent 47 %) with absence of distant metastases, undergoing surgery with radical intent and IORT (median dose 12.5 Gy) were considered eligible for participation in this study. In addition, all primary tumors received external-beam radiotherapy (median dose 50 Gy).
Results From 1986 to 2012, a total of 68 patients were analyzed in the study from three Spanish institutions. With a median follow-up time of 53 months (range 4–316), 5-year local control (LC) was 58 %. Five-year IORT in-field control, disease-free survival (DFS) and overall survival were 70, 45 and 51 %, respectively. On multivariate analysis, only microscopically involved margin ($R1$) resection status retained significance in relation to LC (HR 3.97, $p < 0.001$). In regard to IORT in field control, incomplete resection (HR 3.23, $p = 0.008$) and recurrent disease status (HR 2.52, $p = 0.04$) retained a significant association in multivariate analysis.
Conclusion From this joint analysis emerges the fact that margin and disease status influences local and central control, but DFS remains modest, given the high risk of distant metastases. Intensified local treatment needs to be tested in the context of more efficient concurrent, neo-, and adjuvant systemic therapy.

Keywords Intraoperative radiotherapy · Trunk soft-tissue sarcoma · Local recurrence · Long-term outcomes

C. V. Sole (✉) · F. A. Calvo
Department of Oncology, Hospital General Universitario Gregorio Marañón, C/Doctor Esquerdo, 46, 28007 Madrid, Spain
e-mail: cvsole@uc.cl

C. V. Sole · F. A. Calvo
School of Medicine, Complutense University, Madrid, Spain

C. V. Sole
Service of Radiation Oncology, Instituto de Radiomedicina, Santiago, Chile

M. Cambeiro · R. Martinez-Monge
Service of Radiation Oncology, Clínica Universidad de Navarra, Pamplona, Spain

A. Polo · A. Montero · R. Hernanz
Service of Radiation Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain

C. Gonzalez
Service of Radiation Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

M. Cuervo
Service of Orthopedics and Traumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

D. Perez
Service of Orthopedics and Traumatology, Hospital Universitario Ramón y Cajal, Madrid, Spain

M. S. Julian
Service of Orthopedics and Traumatology, Clínica Universidad de Navarra, Pamplona, Spain

Published online: 31 January 2014

Introduction

Soft-tissue sarcomas (STS) are uncommon tumors arising from mesenchymal tissues throughout the body, with heterogenous biologies and histologies [1]. Trunk-wall STS (TW-STS) represent 20 % of all STS and include tumors of the chest wall and flank, spinal and paraspinal regions and tumors of the pelvic wall [2]. Although it has been reported that tumors in different anatomic locations exhibit different clinical behaviors, TW-STS are usually studied together with primary extremity tumors or with retroperitoneal or internal trunk tumors [3–5]. It has been reported that tumor site of involvement (extremity, head and neck, trunk wall and internal trunk or retroperitoneal) is relevant for overall survival (OS) with significantly different survival results [6, 7]. For extremity sarcomas a higher median survival (34 months) has been reported as compared to truncal [trunk wall and internal trunk (20 months)] or retroperitoneal (21 months) lesions [8]. Moreover, tumor site has also been associated with the advent of local recurrences [2]. Few studies have addressed specifically the prognosis for patients with TW-STS [9–13], and none has analyzed specifically a group of TW-STS patients treated with intraoperative radiotherapy (IORT). A joint analysis of data from the IORT-Spanish cooperative initiative for TW-STS patients approached using an IORT component with electron beams (IOERT) in high-risk areas (post-resection and pre-reconstruction) and surgical resection was planned. Reduced-dose external-beam radiotherapy (EBRT) was added for primary tumors. In this study, a joint analysis of multi-institutional data was gathered to investigate, on a mature cohort of patients, evidence of the contribution of a IOERT-containing multimodality approach in promoting LC and its impact in long-term tolerance.

Materials and methods

Patient characteristics and staging evaluation

From June 1986 to April 2012, patients with pathologically confirmed non-metastatic TW-STS, macroscopic resection (non-*R*2), performance status lower than 2 and aged $\geq$18 years were eligible for multimodal treatment. Patients with primary and locally recurrent tumors with a tumor size $\geq$5 cm, histologic grade $\geq$2 and curative resections with either close (<1 cm) or positive margins underwent surgical resection and IOERT. In addition, all patients with primary tumor status were treated with dose-reduced EBRT.

Pre-treatment evaluation consisted of a complete history and physical examination, complete blood count, renal and liver function tests, chest X-ray, and computerized tomography or magnetic resonance imaging (MRI) of the tumor site, chest, and abdomen. Data were prospectively collected and retrospectively analyzed at the time of scheduled follow-up. Patients were reclassified according to the 7th AJCC/UICC staging system for the analysis. Patient and treatment characteristics are listed in Table 1: there were no significant differences in baseline variables between the patients treated for primary and locally recurrent trunk STS.

Treatment characteristics

Details of EBRT technique, IOERT and adjuvant chemotherapy (CT) followed standards previously described [14]. External-beam radiation therapy was applied postoperatively (75 %) or preoperatively (25 %) and delivered with megavoltage equipment (6–15 MV) using 3D-conformal field technique (all primary tumors and none of the locally recurrent received EBRT for the present analysis). A total median dose of 50 Gy (range 40–54 Gy; 1.8–2.0 Gy/5 days/week) was prescribed according to the International Commission on Radiation Units and Measurements Report No. 50. EBRT was planned according to preoperative computed tomography or MRI scans. We defined PTV as gross target volume (GTV) for preoperative EBRT and surgical tumor bed [clinical target volume (CTV)] for postoperative EBRT patients, with a safety margin of 5 cm in the craniocaudal direction and 2–3 cm in the lateral direction. The surgical scar on the surface was included in the irradiation field whenever possible. Surgical approach (4–6 weeks before postoperative or after preoperative treatment) consisted of wide ($n = 46$, 68 %) or marginal resection ($n = 22$, 32 %). The IOERT program was performed in a non-dedicated linear accelerator with outpatient radiotherapy activity by the three institutions. After sarcoma resection and before reconstruction, 10–20 Gy (median 12.5 Gy) was delivered in a single fraction to a one- ($n = 54$, 79 %) or two-field ($n = 14$, 21 %) PTV, using a median energy of 9 MeV (range 4–20 MeV) (Table 2). Dose was prescribed to the 90 % isodose line, covering the surgical bed and/or directed to the area of concern for a narrow or positive margin of resection. 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, allowing dosimetric adaptation and uniform dose distribution. Computed tomography-guided treatment has been available since 2008 [15]. Patients with higher histologic grade (3–4) and tumor size ($\geq$5 cm) were offered adjuvant CT (most commonly CT consisted of 4 or 5 cycles of doxorubicin 75 mg/m^2 and ifosfamide 5 g/m^2, every 3 weeks).

Table 1 Patient, tumor and treatment characteristics

Parameter	Variable	$n = 68$ (%)	Primary $n = 36$ (53 %)	Recurrent $n = 32$ (47 %)	p value
Patient variables					
Age	Median age (years)	54 (31–74)	56 (31–74)	52 (35–70)	0.63
Gender	Male	37 (54)	22 (61)	15 (47)	0.24
	Female	31 (46)	14 (39)	17 (53)	
Karnofsky performance status	<90	14 (21)	6 (17)	8 (25)	0.72
	≥90	54 (79)	30 (83)	24 (75)	
Pre-surgical variables					
Tumor size	Median tumor size (cm)	9 (2–20)	9 (3–20)	8 (2–18)	0.33
Tumor localization	Thoracic wall	42 (62)	24 (67)	18 (56)	0.41
	Abdominal wall	18 (26)	8 (22)	10 (31)	
	Pelvis	8 (12)	4 (11)	4 (13)	
Tumor depth	Deep	42 (62)	23 (64)	19 (60)	0.78
	Superficial	26 (38)	13 (36)	13 (40)	
Microscopic surgical specimen					
Histologic subtype	Liposarcoma	11 (16)	5 (14)	6 (19)	0.73
	Sarcoma NOS	9 (13)	3 (8)	6 (19)	
	Malignant fibrous	13 (19)	9 (25)	4 (12)	
	histiocytoma	9 (13)	5 (14)	4 (12)	
	Leiomyosarcoma	8 (12)	4 (11)	4 (12)	
	Synovial sarcoma	18 (27)	10 (28)	8 (23)	
	Other				
Mitosis count	Low–medium	56 (82)	30 (83)	26 (81)	0.82
	High	12 (18)	6 (17)	6 (19)	
Necrosis	Yes	30 (40)	17 (47)	13 (41)	0.60
	No	38 (60)	19 (53)	19 (59)	
Histologic grade	I–II	39 (57)	20 (56)	19 (59)	0.82
	III–IV	29 (43)	16 (44)	13 (41)	
Surgery					
Surgical procedure	Wide excision	46 (68)	26 (72)	20 (63)	0.23
	Simple local excision	22 (32)	10 (28)	12 (37)	
Margin status	*R*0	47 (69)	27 (75)	20 (63)	0.27
	*R*1	21 (31)	9 (25)	12 (38)	
IOERT technical parameters					
IOERT dose (cGy)	Median IOERT dose (cGy)	1,250 (1,000–2,000)	1,250 (1,000–2,000)	1,500 (1,000–2,000)	0.16
IOERT energy (MeV)	Median IOERT energy (MeV)	9 (4–20)	9 (4–20)	10 (4–18)	0.46
IOERT applicator size (cm)	Median IOERT applicator size (cm)	9 (5–15)	9 (5–15)	8 (5–15)	0.22
EBRT-CT treatment					
Adjuvant CT	Yes	22 (32)	12 (33)	10 (31)	0.83
	No	46 (68)	24 (67)	22 (69)	
EBRT	Yes	36 (53)	36 (100 %)	0 (0)	<0.001
	No	32 (47)	0 (0)	32 (100)	

IOERT intraoperative electron-beam radiotherapy, *EBRT* external-beam radiotherapy, *CT* chemotherapy, *NOS* not otherwise specified

Follow-up and toxicity evaluation

All patients were required to be followed according to a common protocol every 3 months after treatment completion for the initial 3 years and every 6 months for 3 additional 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

Table 2 Correlations between macroscopic/microscopic pathology characteristics and IOERT technical parameters

Pathology/IOERT treatment	Applicator size Median/range	IOERT dose (Gy) Median/range	IORT energy (MeV) Median/range
T_{max} size (cm)			
2.0–3.0	7/6–10	12.5/10–20	8/4–12
3.1–6.0	9/6–15	12.5/12.5–20	8/4–20
6.1–10.0	8/5–15	12.5/12.5–20	9/6–20
10.1–15.0	9/5–15	12.5/10–15	8/4–18
15.1–20.0	9/9–15	12.5/10–15	9/6–20
Margin resection status			
*R*0	9/5–15	12.5/10–20	8/4–18
*R*1	9/5–15	12.5/10–20	9/6–20

Multiple field technique procedures in 15 (26 %) patients

T_{max} tumor maximal dimension

toxicities were evaluated according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer score [16].

Statistical analysis

Data collected was analyzed using SPSS (version 19.0) statistical software. Baseline characteristics as well as clinical and pathological factors were described using frequency (percentage) and median values, and were compared using a Chi square or Mann–Whitney test. The primary endpoint of the analysis was LC. Secondary endpoints were IOERT in-field control, disease-free survival (DFS) and OS. For survival outcomes potential associations were assessed in univariate and multivariate analysis using the Cox proportional hazards model. Based on, first, p values ≤ 0.10 in univariate analyses, and second, on clinical relevance, multivariate analysis was performed using a stepwise regression model to identify variables that have an effect (two-sided p test ≤ 0.05) on survival outcomes.

Results

Median follow-up time for all patients was 53 months (range 4–316). Twenty-nine patients remained alive at the time of analysis. Median follow-up for surviving patients was 56 months (range 4–311). Of the 40 deceased patients, 38 (95 %) died from sarcoma progression, and 2 (5 %) died from causes unrelated to their tumors or treatment. Crude local relapse (LR) rate was 44 % ($n = 30$), and 35 % ($n = 24$) developed distant metastases [most commonly pulmonary ($n = 20$, 83 %)]. Of the 30 patients who had local progression, 12 (40 %) were rescued with a second surgical rescue. The other 18 patients (14 had synchronic distant metastases) with local relapse received chemotherapy alone ($n = 13$), or received no further therapy ($n = 5$).

Local control for the study population at 5 and 10 years was 58 and 47 % (Fig. 1a). Univariate Cox proportional hazard analyses showed that patients with locally recurrent status ($p = 0.04$) and incomplete resection [*R*1 ($p = 0.001$)] were associated with a higher probability of LR (Table 3). After adjustment for other covariates only *R*1 resection ($p < 0.001$) remained significantly associated with LR (Table 4). IOERT in-field control at 5 and 10 years was 67 and 56 % (Fig. 1b). Univariate analyses showed that locally recurrent patients ($p = 0.03$), high mitotic count ($p = 0.04$) and *R*1 resection ($p = 0.004$) were associated with a higher probability of IOERT in-field relapse (Table 3). In multivariate analysis an incomplete resection ($p = 0.008$) and locally recurrent status ($p = 0.04$) retained a significant association in regard to IOERT in-field relapse (Table 4). DFS at 5 and 10 years was 45 and 36 % (Fig. 1c). Univariate Cox proportional hazard analyses showed that recurrent tumor status ($p = 0.04$) and incomplete margin status ($p = 0.002$) were associated with a higher probability of overall metastases (Table 3). No tumor necrosis ($p = 0.04$) was associated with a decreased likelihood of metastases. After adjustment for other covariates recurrent status ($p = 0.01$), tumor necrosis ($p = 0.02$) and incomplete margin status ($p = 0.01$) retained a significant association with DFS (Table 4). OS at 5 and 10 years was 51 and 36 % (Fig. 1d). On univariate analysis, age ≥ 50 years old ($p = 0.02$) and *R*1 margin status ($p = 0.01$) were at a significantly higher risk of overall death (Table 3). No tumor necrosis ($p = 0.05$) was associated with a decreased chance of death. We found on multivariate analysis that age ≥ 50 years old ($p = 0.03$), recurrent tumor status ($p = 0.04$), *R*1 margin ($p = 0.003$) and tumor necrosis ($p = 0.04$) were significantly associated with OS (Table 4).

Overall 10 patients (15 %) had grade ≥ 3 acute toxicity [severe skin reactions ($n = 5$, grade 3) and wound-healing disturbances ($n = 4$, grade 3; $n = 1$, grade 4)]. Eight patients (12 %) developed chronic toxicity ≥ 3 [neuropathy ($n = 3$, grade 3), necrosis/fistula/ulcer ($n = 2$, grade 3) and severe chronic lymphedema ($n = 3$, grade 3)]. No perioperative or long-term death from treatment occurred.

Discussion

STS can be classified according to their location as extremities, head and neck, trunk wall and internal trunk (retroperitoneal space, intra-abdominal area, pelvis and

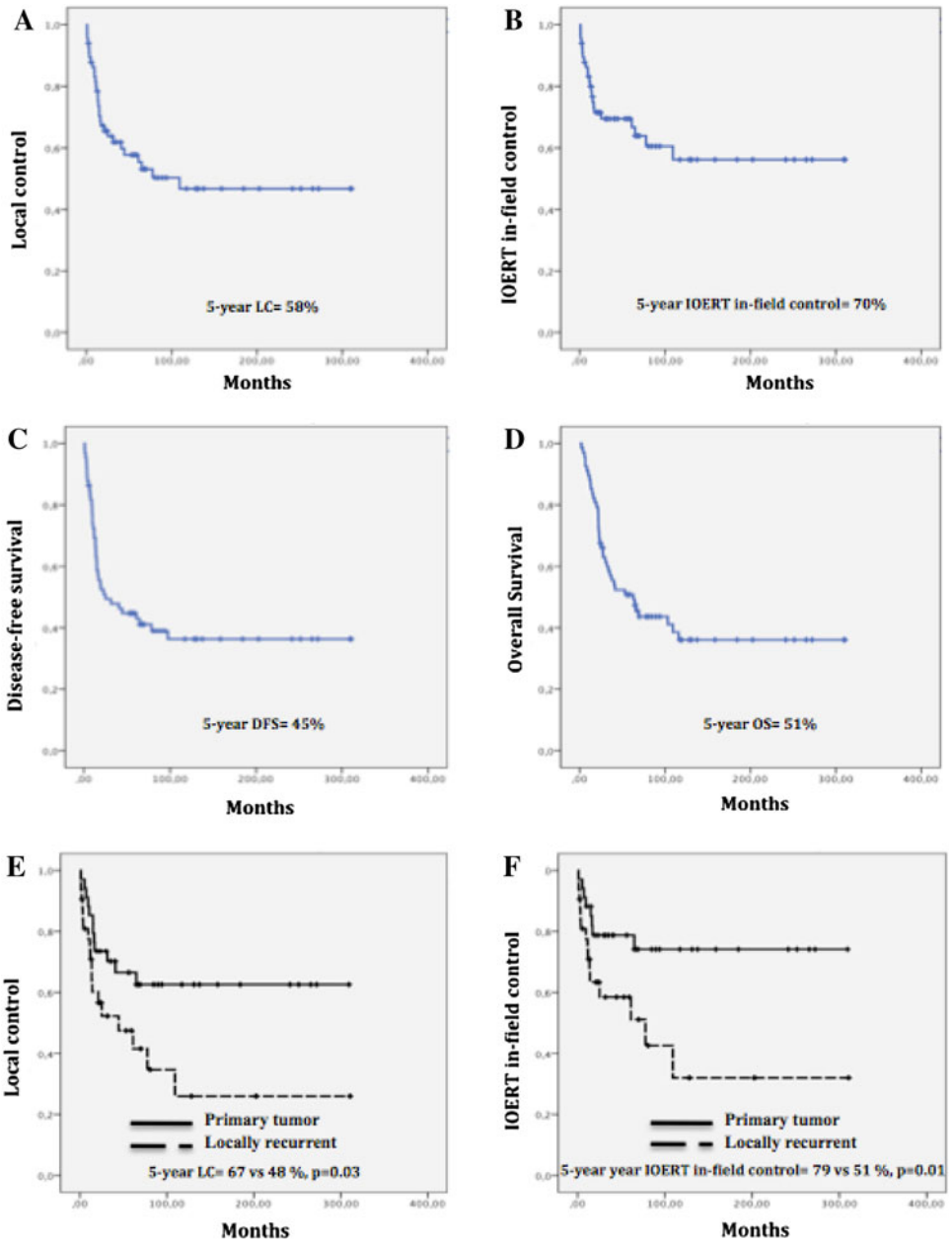

Fig. 1 Kaplan–Meier curves for all 68 patients for local control (**a**), IOERT in field control (**b**), disease-free survival (**c**), overall survival (**d**) and local control (**e**) and IOERT in field control (**f**) according to disease status

intrathoracic) [2]. TW-STS are usually analyzed together with STS of other primary sites [13]. Some authors included visceral and retroperitoneal tumors, while others studied only STS of the chest wall [9–11] indicating that this location is a determinant of prognosis. In our study location [thoracic wall was the most frequent tumor site (62 %)] was not a significant predictor of poor survival. It is likely that surgical procedures and therapeutic strategies in most teams remain similar, regardless of the location of TW-STS.

To our knowledge, this is the first reported study that focuses on long-term outcomes of patients with TW-STS treated with IOERT. Discrimination between STS localization is important because it has been consistently reported that patients treated for TW-STS have worse overall outcomes when compared with those with extremity STS [3, 5].

Our relevant findings can be summarized as follows. First, in a group of high-risk patients (high-grade tumors, incomplete/close margin resections), the 5-year LC and OS rates of 58 and 51 % compare well with more favorable cohorts of patients treated with surgery with and without EBRT (Table 5) [3, 4]. Second, we found that recurrent tumor, *R*1 resection status and no tumor necrosis were associated with adverse overall outcomes. Third, we identified long-term control and survival for patients within

Table 3 Univariate analyses of associations between the patient, tumor and treatment with local control, IOERT in-field control, disease-free survival and overall survival

Parameter	Variable	Local control			IOERT in-field control			Disease-free survival			Overall survival		
		HR	95 % CI	*p* value	HR	95 % CI	*p* value	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Patient variables													
Gender	Male	1.0	0.67–2.82	0.39	1.0	0.65–3.34	0.36	1.0	0.57–2.50	0.65	1.0	0.83–3.53	0.15
	Female	1.37			1.47			1.19			1.67		
Age (years)	<50	1.0	0.51–2.77	0.69	1.0	0.54–3.47	0.51	1.0	0.87–3.04	0.13	1.0	1.15–4.15	*0.02*
	≥50	1.19			1.37			1.63			2.19		
Karnofsky performance status	<90	1.0	0.22–1.59	0.32	1.0	0.31–2.74	0.85	1.0	0.31–2.30	0.72	1.0	0.22–2.56	0.80
	≥90	0.64			0.91			0.81			0.78		
Pre-surgical variables													
Tumor status	Primary	1.0	1.05–4.56	*0.04*	1.0	1.12–6.28	*0.03*	1.0	1.04–3.60	*0.04*	1.0	0.91–3.10	0.09
	Recurrent	2.19			2.65			1.92			1.64		
Tumor size (cm)	≤10	1.0	0.75–3.18	0.24	1.0	0.55–2.94	0.58	1.0	0.83–2.92	0.17	1.0	0.86–3.06	0.14
	>10	1.54			1.27			1.55			1.62		
Tumor localization	Thoracic wall	1.0	0.71–3.24	0.28	1.0	0.58–3.34	0.47	1.0	0.65–2.46	0.49	1.0	0.68–2.58	0.40
	Abdominal wall	1.52	0.31–3.85	0.89	1.39	0.38–5.01	0.63	1.26	0.51–3.68	0.52	1.33	0.52–3.79	0.51
	Pelvis	1.09			1.37			1.37			1.40		
Tumor depth	Deep	1.0	0.70–6.12	0.19	1.0	0.57–17.75	0.28	1.0	0.51–4.12	0.51	1.0	0.33–3.24	0.96
	Superficial	2.12			4.87			1.33			1.03		
Microscopic surgical specimen													
Histologic subtype	Liposarcoma	1.0	0.41–2.78	0.91	1.0	0.27–1.98	0.54	1.0	0.62–4.04	0.34	1.0	0.56–3.64	0.46
	Others	1.06			0.73			1.58			1.42		
Mitosis count	Low–medium	1.0	0.81–4.89	0.14	1.0	1.04–6.68	*0.04*	1.0	0.94–4.49	0.07	1.0	0.82–4.31	0.14
	High	1.99			2.61			2.06			1.88		
Necrosis	Yes	1.0	0.29–1.46	0.25	1.0	0.47–2.51	0.86	1.0	0.31–1.08	0.11	1.0	0.28–1.09	0.09
	No	0.65			1.08			0.59			0.55		
Histologic grade	I–II	1.0	0.74–3.14	0.30	1.0	0.41–2.59	0.96	1.0	1.04–3.96	*0.04*	1.0	1.0.–3.45	*0.05*
	III–IV	1.53			1.02			2.04			1.82		
Surgery													
Resection	Wide resection	1.0	0.64–3.89	0.32	1.0	0.65–6.24	0.23	1.0	0.41–2.32	0.77	1.0	0.61–2.39	0.48
	Local resection	1.58			2.01			1.17			1.22		
Margin status	*R*0	1.0	1.90–8.30	*<0.001*	1.0	1.53–8.21	*0.003*	1.0	1.48–5.31	*0.002*	1.0	1.65–5.98	*<0.001*
	*R*1	3.97			3.54			2.80			3.15		
IOERT technical parameters													
IOERT dose (Gy)	<1,250	1.0	0.40–1.73	0.63	1.0	0.35–1.87	0.62	1.0	0.51–1.79	0.82	1.0	0.36–1.30	0.25
	≥1,250	0.83			0.81			0.93			0.68		

Table 3 continued

Parameter	Variable	Local control			IOERT in-field control			Disease-free survival			Overall survival		
		HR	95 % CI	*p* value	HR	95 % CI	*p* value	HR	95 % CI	*p* value	HR	95 % CI	*p* value
IOERT energy (MeV)	<6	1.0	0.36–1.50	0.39	1.0	0.28–2.37	0.91	1.0	0.45–1.58	0.59	1.0	0.50–1.79	0.87
	≥6	0.73			0.93			0.84			0.95		
IOERT applicator size (cm)	<9	1.0	0.48–1.99	0.94	1.0	0.39–2.02	0.78	1.0	0.50–1.73	0.82	1.0	0.51–1.80	0.89
	≥9	0.97			0.89			0.93			0.96		
CT treatment													
Adjuvant chemotherapy	Yes	1.0	0.68–3.71	0.28	1.0	0.65–4.73	0.27	1.0	0.51–2.98	0.64	1.0	0.46–2.68	0.81
	No	1.59			1.75			1.24			1.11		

EBRT was not analyzed as a prognostic factor because of complete overlap with disease status data

Values in italic indicate $p < 0.05$

IOERT intraoperative electron-beam radiotherapy

the worse categories of adverse outcome features. Finally, it must be stated that the real value of IOERT in these patients must be analyzed in a randomized study (although this is very difficult due to the low incidence of this disease).

Salas et al. [13] analyzed 343 primary TW-STS (thoracic wall, 82.5 %; abdominal wall, 12.3 % and pelvic wall, 5.2 %) patients of the French Sarcoma Group database. With a median follow-up of 91 months, the 5-year OS, DFS and LC rates were 60.4, 68.9 and 58.4 %, respectively. In multivariate analysis previous history of radiotherapy (PHR) and grade predicted LC; PHR, size and grade were prognostic factors for MFS. Factors influencing OS were age, size, PHR, depth, grade and surgical margins. The predictive factors of incomplete response were PHR, size and T3.

Obtaining complete removal after surgery is crucial for definitive control of STS. Predictive factors for the achievement of complete removal have been defined in several locations [17]. Although margin status is a common listed risk factor for local recurrence, what constitutes adequate surgical margins is still not appropriately defined. In the current analysis positive microscopic resection margins were the only factor that remained significantly associated with LC in multivariate analysis. Margin resection status may have a different prognostic impact in different settings [17]. Call et al. [17] analyzed 61 patients (treated with EBRT plus IORT) with upper extremity STS by margin status. The patients with positive margins had similar prognoses to patients with negative margins (5- and 10-year LC rates 100 and 86 vs. 89 % at both; $p = 0.98$).

Histological grade is an independent predictive factor for metastasis development in most adult STS [14]. Unsurprisingly therefore, grade was again the most important independent prognostic factor for DFS in the present series of TW-STS.

Distant metastases remain the dominant pattern of progression for high-risk STS [2]. Although the effect of adjuvant CT on survival for resected soft-tissue sarcoma remains to be recognized [18], intensified local treatment needs to be tested in the context of more efficient concurrent, neo-, and adjuvant systemic therapy.

Tumor location may not only be prognostic of outcome but may also play a role in treatment morbidity [19]. Rimner et al. demonstrated the wound reoperation and edema problems. In regard to treatment-related toxicity, a treatment regimen that included IOERT for trunk-wall sarcomas was tolerable for our 68 patients. The low rate of severe toxic events suggests that a multimodality approach with EBRT and an IOERT-boost component for primary tumors and IOERT only for recurrent with PHR is feasible with acceptable risks and without prohibitive long-term side effects [20]. The high-risk location should be carefully

Table 4 Factors associated with local control, IOERT in-field control, disease-free survival and overall survival in multivariate analyses

Parameter	Variable	Local control			IOERT in-field control			Disease-free survival			Overall survival		
		HR	95 % CI	*p* value	HR	95 % CI	*p* value	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Patients													
Age (years)	≤50	–	–	–	–	–	–	–	–	–	1.0	1.13–6.38	*0.03*
	>50										2.68		
Pre–surgical variables													
Tumor status	Primary	–	–	–	1.0	1.05–6.27	*0.04*	1.0	1.21–5.33	*0.01*	1.0	1.08–3.26	*0.04*
	Recurrent				2.52			2.54			1.75		
Microscopic surgical specimen													
Histologic grade	I–II	–	–	–	–	–	–	1.0	1.15–4.76	*0.02*	1.0	1.03–4.76	*0.04*
	III–IV							2.38			2.12		
Surgery													
Margin status	*R*0	1.0	1.90–8.30	*<0.001*	1.0	1.36–7.67	*0.008*	1.0	1.15–4.88	*0.01*	1.0	1.43–5.88	*0.003*
	*R*1	3.97			3.23			2.48			2.90		

Values in italic indicate $p < 0.05$

IOERT intraoperative electron-beam radiotherapy

Table 5 Truncal versus extremity STS local recurrence risk

	N	Median follow-up (months)	Disease status		(Neo)adjuvant EBRT (%)	Neo (adjuvant) CT (%)	5-year local control		*p* value
			Primary (%)	Recurrent (%)			Extremity (%)	Trunk (%)	
Le Vay et al. [3]	389	80	90	10	64	25	84	71	<0.0001
DeLaney et al. [4]	154	75	87	13	100	15	82	42	0.001
Zagars et al. [5]	1,225	114	84	16	100	33	87	84	ns
Sole et al.	68	53	53	47	53	32	–	58	–

considered during IORT administration, minimizing the volume irradiated. Organs at risk definition, dose-volume histograms availability and 3D dose-distribution estimations are decisive contributions to IOERT optimization [15]. Detailed planning on the part of the surgeon and radiation oncologist with detailed input from the radiologist prior to surgery and from the pathologist at the time of resection is required for dose-escalation strategies within the tumor bed region (field-within-field technique). Future clinical research needs to focus on functional outcome and quality of life.

In conclusion, we found that patients with TW-STS that received IOERT could be treated safely and had high LC rates. A level of adverse prognostic features (non-radical resections) might be compensated by multimodal local treatment. Our results suggest that patients with with close or positive margins could benefit from further intensified local treatment strategies.

Acknowledgments Authors express their gratitude to all the health care professionals involved in the IOERT programs along the time period analyzed and in particular to the pioneer senior surgeons involved: Prof. Jose Cañadell (University Clinic of Navarra) and Prof. Miguel Ferrer (Hospital General Universitario Gregorio Marañon). Supported in part by a grant from the Health Institute of Research Carlos III, Spanish Ministry of Science and Innovation (project code PI11-02908).

Conflict of interest The authors declare no potential and real commercial conflicts of interest.

References

1. Borden EC, Baker LH, Bell RS, Bramwell V, Demetri GD, Eisenberg BL, et al. Soft tissue sarcomas of adults: state of the translational science. Clin Cancer Res. 2003;9:1941–56.
2. Coindre JM, Terrier P, Bui NB, Bonichon F, Collin F, Le Doussal V, et al. Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol. 1996;14:869–77.
3. LeVay J, O'Sullivan B, Catton C, Bell R, Fornasier V, Cummings B, et al. Outcome and prognostic factors in soft tissue sarcoma in the adult. Int J Radiat Oncol Biol Phys. 1993;27:1091–9.
4. Delaney TF, Kepka L, Goldberg SI, Hornicek FJ, Gebhardt MC, Yoon SS, et al. Radiation therapy for control of soft-tissue sarcomas resected with positive margins. Int J Radiat Oncol Biol Phys. 2007;67:1460–9.
5. Zagars GK, Ballo MT, Pisters PW, Pollock RE, Patel SR, Benjamin RS, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. Cancer. 2003;97:2530–43.
6. Singer S, Corson JM, Demetri GD, Healey EA, Marcus K, Eberlein TJ. Prognostic factors predictive of survival for truncal and retroperitoneal soft-tissue sarcoma. Ann Surg. 1995;221:185–95.

7. Mattavelli D, Miceli R, Radaelli S, Mattavelli F, Cantù G, Barisella M, et al. Head and neck soft tissue sarcomas: prognostic factors and outcome in a series of patients treated at a single institution. Ann Oncol. 2013;24:2181–9.
8. Gutierrez JC, Perez EA, Franceschi D, Moffat FL Jr, Livingstone AS, Koniaris LG. Outcomes for soft-tissue sarcoma in 8,249 cases from a large state cancer registry. J Surg Res. 2007;141:105–14.
9. Greager JA, Patel MK, Briele HA, Walker MJ, Wood DK, Gupta TK. Soft tissue sarcomas of the adult thoracic wall. Cancer. 1987;59:370–3.
10. Gordon MS, Hajdu SI, Bains MS, Burt ME. Soft tissue sarcomas of the chest wall. Results of surgical resection. J Thorac Cardiovasc Surg. 1991;101:843–54.
11. Gross JL, Younes RN, Haddad FJ, Deheinzelin D, Pinto CA, Costa ML. Soft-tissue sarcomas of the chest wall: prognostic factors. Chest. 2005;127:902–8.
12. Duranti L, Gronchi A, Stacchiotti S, Fiore M, Casali PG, Collini P, et al. Localised thoracic sarcomas: outcome improvement over time at a single institution. Eur J Cancer. 2013;49:2689–97.
13. Salas S, Bui B, Stoeckle E, Terrier P, Ranchere-Vince D, Collin F, et al. Soft tissue sarcomas of the trunk wall (STS-TW): a study of 343 patients from the French Sarcoma Group (FSG) database. Ann Oncol. 2009;20:1127–35.
14. Petersen IA, Krempien R, Beauchamp C. Extremity and trunk soft-tissue sarcomas. In: Gunderson LL, Willet CG, Calvo FA, Harrison LB, eds. Intraoperative irradiation techniques and results. Current clinical oncology, 2nd ed. New York, Heidelberg: Humana Press, Springer; 2011. p. 387–405.
15. Pascau J, Santos Miranda JA, Calvo FA, Bouché A, Morillo V, González-San Segundo C, et al. An innovative tool for intraoperative electron beam radiotherapy simulation and planning: description and initial evaluation by radiation oncologists. Int J Radiat Oncol Biol Phys. 2012;83:287–95.
16. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31:1341–6.
17. Call JA, Stafford SL, Petersen IA, Haddock MG. Use of intraoperative radiotherapy for upper-extremity soft-tissue sarcomas: analysis of disease outcomes and toxicity. Am J Clin Oncol. 2012;37:81–5.
18. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer. 2008;113:573–81.
19. Rimner A, Brennan MF, Zhang Z, Singer S, Alektiar KM. Influence of compartmental involvement on the patterns of morbidity in soft tissue sarcoma of the thigh. Cancer. 2009;115:149–57.
20. Calvo FA, Sole CV, Cambeiro M, Montero A, Polo A, Gonzalez C, et al. Prognostic value of external beam radiation therapy for locally recurrent soft tissue sarcoma: a multicentric long-term outcome analysis. Int J Radiat Oncol Biol Phys. 2014;88:143–50.