Use of Intraoperative Radiotherapy for Upper-extremity Soft-tissue Sarcomas

Analysis of Disease Outcomes and Toxicity

Jason A. Call, MD, Scott L. Stafford, MD, Ivy A. Petersen, MD, and Michael G. Haddock, MD

Objectives: To review outcomes for patients who received intraoperative radiotherapy (IORT) for upper-extremity sarcoma.

Methods: We identified patients with upper-extremity tumors who were treated with external beam radiotherapy, surgery, and IORT, with or without chemotherapy. Kaplan-Meier estimates for overall survival (OS), central control (CC), local control (LC), and distant control (DC) were obtained.

Results: Sixty-one patients were identified. Median age was 50 years (range, 13 to 95 y). Median follow-up was 5.9 years. Eleven patients had gross (R2; n = 1) or microscopic (R1; n = 10) disease at the time of IORT. IORT doses ranged from 7.50 to 20.00 Gy. External beam radiotherapy doses ranged from 19.80 to 54.00 Gy. OS at 5 and 10 years was 72% and 58%, respectively. LC at 5 and 10 years was 91% and 88%, respectively. DC at 5 and 10 years was 80% and 77%, respectively. Patients treated for recurrent disease had inferior 5-year OS compared with patients with first diagnoses (63% vs. 74%; $P = 0.02$) and lower 5-year LC (67% vs. 94%; $P < 0.01$). For patients with R1 or R2 resections, LC at 5 and 10 years was 100% and 86%, respectively; for patients with R0 resections, LC was 89% at both 5 and 10 years ($P = 0.98$). Severe toxicity attributable to treatment was noted for 4 patients (7%).

Conclusions: For upper-extremity sarcoma, treatment including IORT was associated with excellent LC, limb preservation, and survival. LC rates were excellent for patients with positive margins after resection. Patients with recurrent disease had worse outcomes, but limb preservation was achievable for most patients.

Key Words: extremity, intraoperative radiation, radiotherapy, sarcoma

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Radiotherapy has an important role in the local management of soft-tissue sarcomas in the extremities. A National Cancer Institute randomized trial showed that patients who underwent limb-sparing surgery with postoperative radiotherapy had similar disease-free survival and overall survival (OS) rates compared with patients with high-grade, soft-tissue sarcomas of the extremity who underwent amputation and received postoperative chemotherapy.[1] A second randomized trial showed that postoperative external beam radiotherapy (EBRT) improved local control (LC) for low-grade and high-grade soft-tissue tumors of the extremity after limb-conservation surgery.[2] Another randomized trial showed that brachytherapy improved the LC rate for high-grade sarcomas after en bloc resection.[3] Several factors affect LC after surgery, including tumor size, margin status, type of resection, deep versus superficial location, treatment for recurrent disease, patient age, and tumor grade.[3–24] Intraoperative radiotherapy (IORT) is one method of delivering high-dose radiation as a boost to areas of high risk. In this study, we reviewed our institutional experience with IORT, examining its efficacy and toxicity in patients with tumors of the upper extremity.

From the Department of Radiation Oncology, Mayo Clinic, Rochester, MN.
The authors declare no conflicts of interest.
Reprints: Michael G. Haddock, MD, Department of Radiation Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905.
E-mail: haddock.michael@mayo.edu.

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MATERIALS AND METHODS

Data were gathered from a prospectively maintained database after obtaining approval from the Mayo Clinic Institutional Review Board. Patients with upper-extremity tumors, whose treatment included IORT, were identified. Patients were treated at Mayo Clinic (Rochester, MN) from January 1, 1990, through December 31, 2009. IORT generally was used either for close or positive margins. Negative margins indicated that no tumor was identified at the inked edge of the resection. Retrieved data included patient age, tumor type and grade (low vs. high), treatment type (for recurrence vs. initial diagnosis), use of chemotherapy, use of EBRT, extent of resection, details of IORT, and patterns of relapse. Surgery was classified as R0 (negative margins), R1 (microscopic disease at the margin), or R2 (gross disease). We noted any severe toxic events associated with radiotherapy, as graded by the physician. Patients generally received follow-up at 4-month to 6-month intervals. The pattern of relapse was judged by the treating physician on the basis of the operative note and his or her knowledge of the procedure. Relapse patterns were scored at the time of relapse. Central relapse indicated relapse within the IORT field.

Statistical Analysis

The Kaplan-Meier method was used to calculate and estimate OS, LC, distant control (DC), and central control (CC). DC was estimated after excluding patients with known metastatic disease at the time of IORT. Biologically effective dose (BED) was calculated using the linear-quadratic model. The log-rank test was used to compare results of OS, LC, and DC by tumor and treatment characteristics (eg, size, grade, recurrent vs. primary diagnosis, IORT dose, BED, and margin status). Cox regression analysis was used to investigate the correlation between IORT dose and LC. P values <0.05 were considered statistically significant. All statistical analyses were performed using JMP software (version 8.0; SAS Institute Inc., Cary, NC).

RESULTS

Patient and Tumor Characteristics

We reviewed data from 61 patients with upper-extremity tumors. Patient characteristics are presented in Table 1. Most were treated with IORT using electrons (6 to 15 MeV) prescribed to the 90% isodose line, directed at the area of concern for a narrow margin of resection. The IORT dose was chosen according to the EBRT dose, margins, and volumes. The median cone width was 7 cm (range, 4.0 to 9.5 cm) for patients with this information available. The median length was 12 cm (range, 6 to 15 cm) for patients with this information available. All patients had a single field except for 1 patient who had 2 fields. One patient received intraoperative high-dose rate brachytherapy (dose, 10.00 Gy; depth, 5 mm). Another patient was treated on a protocol that administered etanidazole concurrently with IORT.

TABLE 1. Patient Characteristics (N = 61)

Characteristics	Value
Age (y), median (range)	50 (13-95)
Duration of follow-up (y), median (range)	5.9 (0.3-17.3)
Tumor size, N (%)	
< 5 cm	21 (34)
≥ 5 cm	38 (62)
Unknown	2 (3)
Tumor grade, N (%)	
High	50 (82)
Low	10 (16)
Unknown	1 (2)
Tumor spread, N (%)	
Regional nodal spread	3 (5)
Distant metastasis	4 (7)
History, N (%)	
Primary diagnosis	53 (9)
Recurrent disease	8 (13)
Prior radiotherapy	4 (7)
Surgery outcome, N (%)*	
R0	50 (82)
R1	10 (16)
R2	1 (2)
Systemic therapy, N (%)	
Concurrent chemotherapy with EBRT	6 (10)
Concurrent etanidazole with IORT	1 (2)
Chemotherapy sequential with EBRT	4 (7)
Chemotherapy concurrent and sequential to EBRT	10 (16)
None	40 (66)
Timing of EBRT, N (%)	
Before IORT	48 (79)
After IORT	13 (21)
EBRT dose (Gy), median (range)	
All patients	50.40 (19.80-54.00)
Prior radiotherapy	40.20 (19.80-51.20)
No prior radiotherapy	50.40 (30.60-54.00)
IORT dose (Gy), median (range)*	
R0	10.00 (7.50-20.00)
R1	12.50 (10.00-20.00)
R2 (n = 1)	10.00

*Surgery was classified as R0 (negative margins), R1 (microscopic disease at the margin), or R2 (gross disease).

EBRT indicates external beam radiotherapy; IORT, intraoperative radiotherapy.

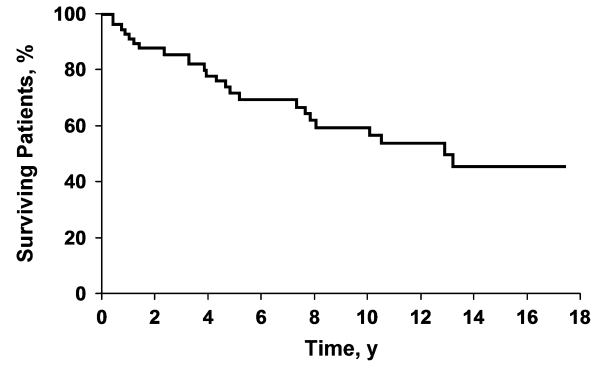

FIGURE 1. Overall survival. Survival rates at 5 and 10 years were 72% and 58%, respectively.

Survival and Tumor Control

The OS curve is shown in Figure 1. OS at 5 and 10 years was 72% and 58%, respectively. CC after 5 and 10 years was 93% and 90%, respectively, and LC for all patients at 5 and 10 years was 91% and 88%, respectively (Fig. 2). IORT dose had no apparent effect on LC by Cox regression analysis ($P = 0.23$) or when comparing patients treated with doses >10 Gy versus ≤10 Gy (log-rank test, $P = 0.99$). Similarly, there was no significant association between BED and LC (Cox regression analysis, $P = 0.14$) or when comparing the patients receiving >80.5 Gy10 to those receiving ≤80.5 Gy10 (log-rank test, $P = 0.35$). Compared with LC, the rates of DC were somewhat lower—at 5 and 10 years, they were 80% and 77%, respectively (Fig. 2).

Table 2 shows 5-year LC, DC, and OS after stratifying by disease and treatment variables. Large tumors (> 5 cm) had a lower OS ($P = 0.02$) and seemed to have worse DC, although the latter difference was not significant ($P = 0.08$). Patients with recurrent disease had a worse survival at 5 years compared with those with initial disease ($P = 0.02$). In addition, the LC rate was lower for patients with recurrence ($P < 0.01$). Low-grade tumors had worse LC after 5 years ($P < 0.01$), but DC and OS rates were similar. Recurrent disease status at the time of IORT was more common in patients with low-grade tumors (3 of 10) compared with patients with high-grade

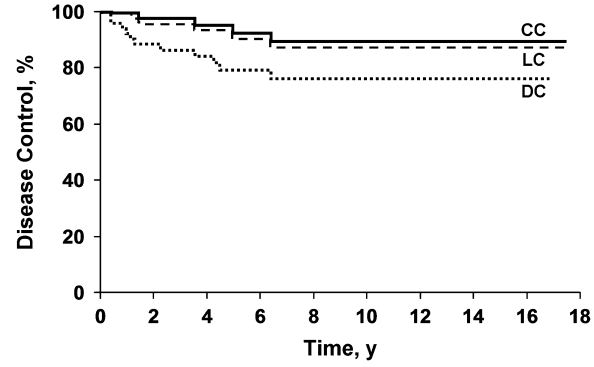

FIGURE 2. Disease control. Local control (LC) rates at 5 and 10 years were 91% and 88%, respectively. Central control (CC) rates at 5 and 10 years were 93% and 90%, respectively. Distant control (DC) rates at 5 and 10 years were 80% and 77%, respectively.

TABLE 2. Local Control, Distant Control, and Overall Survival After 5 Years

	Size			Tumor Grade			Diagnosis			Margins		
Outcome	≥ 5 cm (%)	< 5 cm (%)	*P*	High (%)	Low (%)	*P*	Recurrent (%)	First (%)	*P*	R1 or R2 (%)	R0 (%)	*P*
Local control	91	89	0.40	96	65	< 0.01	67	94	< 0.01	100	89	0.98
Distant control	69	94	0.08	80	79	0.99	70	82	0.19	79	80	0.40
Overall survival	62	89	0.02	71	77	0.21	63	74	0.02	73	71	0.20

tumors (5 of 50). For patients with R1 or R2 resection, LC at 5 and 10 years was 100% and 86%, respectively. This was similar to the level of control seen in patients with R0 resection (89% at both 5 and 10 y; Fig. 3).

Five patients had local treatment failure. One patient had an above-elbow amputation, and another had a midforearm amputation. The crude rate of amputation for local recurrence was 3%. The other 3 patients with local failure who did not have amputation at recurrence underwent wide excision (n = 1), received chemotherapy alone (n = 1), or received no therapy (n = 1).

Toxic Events

Four patients had severe toxic events that likely were caused by radiotherapy. None of these patients had chemotherapy as a component of treatment. Two patients had wound complications after surgery and IORT. One patient had avascular necrosis of the humerus. This patient received 50.4 Gy of EBRT in 28 fractions, followed by IORT to a dose of 12.5 Gy using 9 MeV electrons. Another patient had severe peripheral neuropathy after preoperative EBRT (45.00 Gy in 25 fractions), followed by resection and IORT (12.50 Gy, using 12 MeV electrons). The affected nerve was in the IORT field.

DISCUSSION

To our knowledge, this is the first report that focuses solely on the outcomes of patients with upper-extremity, soft-tissue sarcomas whose treatment regimens included IORT. Overall, our results show that this treatment is effective in terms of LC and toxicity. Several groups have successfully implemented IORT for patients with extremity sarcomas. Haddock et al[25] described 91 patients with limb and girdle sarcomas who received IORT (electrons only) as a component of therapy. OS correlated with the grade and size of the tumor, and LC at 3 years was excellent (92%). In that series, disease status (primary vs. recurrent) seemed to have an effect on LC ($P = .01$). However, tumor size and grade had no effect on LC.

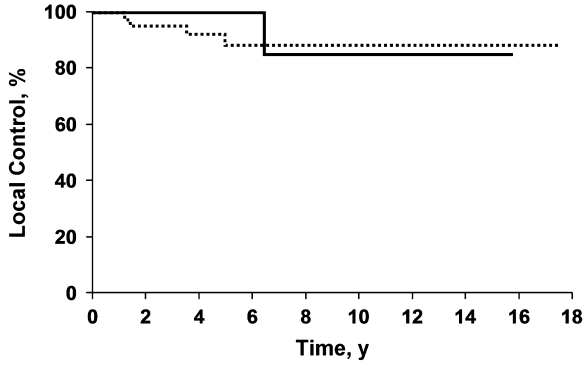

FIGURE 3. Local control, stratified by resection margin status. No significant difference ($P = 0.98$) was observed between patients with positive margins (dashed line) or negative margins (solid line).

Azinovic et al[26] described IORT (using electrons) and moderate-dose postoperative EBRT (45 to 50 Gy) in 45 patients with extremity sarcomas. LC at 5 years was 88% for patients with negative or close margins (< 5 mm), and 57% for patients with positive margins ($P = 0.04$). LC was better in the setting of treatment for primary disease compared with recurrent disease, but the difference was not significant ($P = 0.05$). Tumor grade was predictive of OS but not of local failure. The authors also noted that out of 31 patients evaluable after 1 year, 5 patients ultimately had peripheral neuropathy develop (1 patient with grade 1 disease; 4 patients with grade 3 or 4 disease). Doses of IORT administered were 10 Gy (n = 1), 15 Gy (n = 3), and 20 Gy (n = 1).

Eble et al[27] treated extremity sarcomas of 25 patients by using IORT (using electrons) and postoperative EBRT. At a median follow-up of 26.8 months, 2 patients had a local recurrence. Margin status was not predictive of LC for this group. In a separate study by Dubois et al,[28] 18 of 31 patients treated with surgery, IORT (using photons or electrons), and EBRT (45 to 50 Gy delivered postoperatively) had tumors localized in the extremities or trunk. None of the 18 had a local failure.

In clinical studies, soft-tissue sarcomas of the upper extremities often have been grouped together with the more common lower-extremity sarcomas. Many of the reports have small numbers of patients, making it difficult to draw meaningful conclusions about the importance of tumor location. Herbert et al[24] had a subset of 16 patients with upper-extremity tumors who had 100% LC, DC, and OS, although this outcome was not significantly different from the lower numbers reported for lower-extremity tumors. Marcus et al[22] described 87 patients with low-grade, soft-tissue sarcomas. They reported no difference in LC between tumors of the upper extremity compared with other nonretroperitoneal sites, but they had only 18 patients with upper-extremity tumors. Although a report from Tanabe et al[14] showed that LC was worse for patients with upper-extremity sarcomas compared with lower-extremity tumors (66% vs. 86% at 5 years), the difference was not statistically significant ($P = 0.11$), nor was there a difference in OS. Pisters et al[23] described a review of 1041 patients with extremity sarcomas. In their study, multivariate analysis showed that a proximal, lower-extremity site was a predictor of poor disease-specific survival. However, LC did not differ significantly by tumor location.

IORT is an attractive method of dose escalation for extremity tumors with close or positive margins. Higher radiation doses may improve outcome in select patients with soft-tissue sarcomas. In a prior report from our institution, Sawyer

TABLE 3. Summary of Local Control of Extremity Sarcomas, Stratified by Margin Status

	Positive Margins			Negative Margins		
References	N	5-Year LC Rate	Treatment	N	5-Year LC Rate	Treatment
Pisters et al[23]	242	59%	Surgery ± RT ± CT	777	80%	Surgery ± RT ± CT
Alekhteyar et al[32]	17	59% (at 2 y)	Surgery + BT	—	—	—
Alekhteyar et al[32]	10	90% (at 2 y)	Surgery + BT + EBRT	—	—	—
Heslin et al[19]*	42	63%	Surgery ± RT ± CT	126	89%	Surgery ± RT ± CT
Tanabe et al[14]	24	62%	Surgery + EBRT	71	91%	Surgery + EBRT
Bell et al[11]	48	50% (crude)	Surgery + EBRT ± CT	52	92% (crude)	Surgery + EBRT ± CT
Herbert et al[24]	19†	55%	Surgery + EBRT ± BT ± CT	37	100%	Surgery + EBRT ± BT ± CT
Azinovic et al[26]	7	57%	Surgery + IORT ± EBRT ± CT	38‡	88%	Surgery + IORT ± EBRT ± CT
Sadoski et al[31]	28	82%	Surgery + EBRT ± boost (IOERT, EBRT, or BT)	104	97%	Surgery + EBRT ± boost (IOERT, EBRT, or BT)
Current series	11	100%	Surgery + EBRT + IORT ± CT	50	89%	Surgery + EBRT + IORT ± CT

*All patients were considered to have high risk (high grade, deep ≥ 5 cm tumor).
†Did not include patients with close margins (≤ 5 mm; 1 of 10 had local failure) or grossly positive margins (1 of 2 had local failure).
‡Included 8 patients with close margins (≤ 5 mm).
BT indicates brachytherapy; CT, chemotherapy; IOERT, intraoperative electron beam radiotherapy; IORT, intraoperative radiotherapy; LC, local control; RT, radiotherapy.

et al[29] observed improved OS and LC rates for patients treated with a boost dose of radiation (either brachytherapy, EBRT, or intraoperative electron radiotherapy).

In our patient series, outcomes for patients with positive margins were encouraging in terms of LC, although the number of patients in this subgroup was small (n = 11). Positive surgical margins consistently have been reported as an adverse prognostic factor for LC.[11–17,19,20,23] For patients with extremity sarcomas who received preoperative radiotherapy, a boost with EBRT postoperatively did not confer an LC benefit, according to a recent report from Al Yami et al.[30] This approach has the disadvantage of a further delay before boost delivery, which may allow tumor repopulation. In addition, postoperative boost doses of radiation may not be as effective, given the potential for hypoxia in the tumor bed after surgery. Such factors are mitigated by using IORT as a boost. IORT may facilitate more precise delivery of radiation to a high-risk area, thereby substantially decreasing the boost treatment volume.

Positive margins in different settings may have a different LC prognosis.[20] Sadoski et al[31] analyzed results by margin status and by tumor site. Patients with lower-extremity tumors had similar 5-year LC rates compared with those with upper-extremity tumors (97% vs. 96%) if margins were negative. However, for patients with positive margins, upper-extremity tumors had 50% LC at 5 years and lower-extremity tumors had 94% LC ($P = 0.02$). Of the 28 patients with positive margins, 1 had an intraoperative electron boost, 8 had a brachytherapy boost, 16 had an EBRT boost, and 3 had no boost. In contrast, the 11 patients with positive margins in our study had 100% LC at 5 years with an IORT boost. The patients with positive margins had similar prognoses to patients in our study with negative margins. As shown in Table 3, outcomes for patients with positive margins in our series also compared favorably with those of previous studies.

A treatment regimen that included IORT for upper-extremity sarcomas was tolerable for our 61 patients. Only 4 patients had severe toxic events that were considered attributable to radiotherapy. Also, the rate of limb preservation was excellent, with only 2 patients ultimately requiring amputation.

In our study, the LC rate at 5 years was 91%, but the DC rate was somewhat lower (80%). CC was high in our patients (93% at 5 y). The 5-year DC rate was 94% for smaller tumors but only 69% for tumors meeting this size criterion ($P = 0.08$). In addition, larger tumor size was predictive of worse OS ($P = 0.02$). These results were consistent with previous findings (ie, that size predicts the rate of distant relapse). For example, tumors >5 cm were predictive of distant recurrence and lower disease-specific survival in the experience treating extremity sarcomas reported by Pisters et al.[23]

Interestingly, our results showed that LC was worse for patients with low-grade tumors ($P \leq 0.01$). Although some retrospective studies have observed the opposite finding, with higher local failure rates for higher-grade tumors,[10,14] the large review by Pisters et al[23] did not find any difference in LC when stratifying by tumor grade. For the group with low-grade tumors, a higher proportion of patients had recurrent disease status at the time of IORT. This finding of worse LC with low-grade tumors may be attributable to the limitations of our study (small and retrospective).

Patients in the current study who were treated for recurrence had poor LC and OS compared with patients receiving treatment for an initial diagnosis. This was consistent with other reports of patients treated for recurrent sarcomas. In the report by LeVay et al,[21] patients with recurrent disease had lower cause-specific survival at 5 years, although LC during the same period was similar. In the report by Pisters et al,[23] patients treated for recurrent disease had worse LC, distant recurrence, and disease-specific survival. However, our study showed that many patients with recurrent disease may maintain LC (67% at 5 years) by using a treatment approach that incorporates IORT.

CONCLUSIONS

Treatment that included IORT was safe and effective in our patient cohort. IORT and EBRT were associated with excellent LC, limb preservation, and survival. The use of IORT for upper-extremity tumors was associated with a low rate of

severe toxicity. The LC rate was high, even for patients with positive margins. Distant relapse was the main pattern of treatment failure. Patients treated for recurrent disease generally had worse outcomes, but LC and limb preservation were achievable for most patients.

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