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Long-term Outcomes With Ifosfamide-based Hypofractionated Preoperative Chemoradiotherapy for Extremity Soft Tissue Sarcomas

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Objectives: The objective of this study was to analyze outcomes for patients with soft tissue sarcoma of the extremities using neoadjuvant ifosfamide-based chemotherapy and hypofractionated reduced dose radiotherapy, followed by limb-sparing surgery.

Materials and Methods: An Institutional Review Board (IRB)-approved retrospective review of patients treated at a single institution between 1990 and 2013 was performed. In total, 116 patients were identified who received neoadjuvant ifosfamide-based chemotherapy and 28 Gy in 8 fractions of preoperative radiation (equivalent dose in 2 Gray fractions, 31.5 Gy [α/β 10] 36.4 Gy [α/β 3]) followed by limb-sparing surgery. Local recurrence (LR), distant failure (DF), and overall survival (OS) were calculated. Univariate and multivariate analysis for LR, DF, and OS were performed using Cox analysis. Statistical significance was set at a $P < 0.05$.

Results: Median follow-up was 5.9 years (range, 0.3 to 24 y). Actuarial LR at 3/6 years was 11%/17%, DF at 3/6 years was 25%/35%, and OS at 3/6 years was 82%/67%. On multivariate analysis, only a positive surgical margin was significantly correlated with worse local control ($P = 0.005$; hazard ratio [HR], 18.33; 95% confidence interval [CI], 2.41-139.34). Age over 60 years ($P = 0.03$; HR, 2.34; 95% CI, 1.10-4.98) and tumor size over 10 cm compared with tumor size ≤ 5 cm ($P = 0.03$; HR, 3.32; 95% CI, 1.15-9.61) were associated with worse OS.

Conclusions: Soft tissue extremity sarcoma patients treated using reduced dose hypofractionated preoperative radiotherapy in combination with ifosfamide-based chemotherapy shows acceptable local control and warrants further investigation.

Key Words: extremity sarcoma, hypofractionated radiotherapy, neoadjuvant chemotherapy, limb-sparing surgery, pathologic necrosis score (*Am J Clin Oncol* 2018;00:000-000)

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Soft tissue sarcoma (STS) of the extremities is a rare malignancy which makes determining ideal treatment recommendations challenging. According to the National Comprehensive Cancer Institute (NCCN) 2018 sarcoma guidelines, for example, patients with stage II/III resectable disease can be managed preoperatively with radiation (category 1), preoperative chemoradiation (category 2B), preoperative chemotherapy (category 2B), or proceed with surgery and consider adjuvant radiation alone (category 1) or radiation and chemotherapy (category 2B). Given the increased risks of local and distant recurrence in this patient population there is a strong rationale for a combined preoperative chemotherapy and radiation approach. A neoadjuvant approach offers several advantages including potential cytoreduction facilitating a less morbid resection, immediate treatment of micrometastatic disease, and the ability to evaluate treatment response through the pathologic necrosis score. The ideal way to combine chemotherapy and radiation is not clear, and it is unknown whether this approach improves outcomes. At our institution we have utilized a hypofractionated preoperative regimen in combination with chemotherapy for over 40 years. Hypofractionation offers advantages including reduced total treatment time, patient convenience, and potentially an improved therapeutic ratio for tumors with low α/β ratios (which may be true for at least some sarcomas). After our institutional experience with various dose-fractionation schedules, including 35 Gy given in 3.5 Gy fractions, and 17.5 Gy given in 3.5 Gy fractions, an 8 fraction regimen of 3.5 Gy per fraction resulted in the most promising balance between local control (LC) and toxicity and has become our standard institutional regimen.¹ This report provides an update of our experience of this shortened preoperative radiation regimen as the adoption of more modern ifosfamide-based and doxorubicin-based chemotherapy.

MATERIALS AND METHODS

Study Cohort

After approval from the Institutional Review Board, the surgical oncology database at our institution was searched for patients with extremity STS treated between 1990 and 2013 with ifosfamide-based/doxorubicin-based neoadjuvant chemoradiation followed by surgical resection with limb-sparing intent. Of the 288 patients who received ifosfamide/doxorubicin-based chemotherapy and radiation, 166 were excluded for conventionally fractionated radiation therapy (RT)

(ie, 50 Gy delivered in 2 Gy fractions), outside radiation records that did not contain sufficient technical detail for analysis, known metastatic disease at presentation, recurrent disease at presentation after previous definitive treatment, and 6 patients who required amputation after receiving preoperative chemotherapy and radiation, leaving 116 patients who represent the study population.

The treatment strategy has been described previously.¹ Medically operable patients with high-grade extremity STS were offered treatment after providing informed consent. Diagnostic needle or incisional biopsies were obtained in all patients without previous diagnosis. Some patients received excisional biopsies, with or without positive margins, before referral. These patients were treated with chemoradiation, followed by reexcision of the tumor bed to negative margins.

In total, 44 patients received 1 to 2 cycles of neoadjuvant ifosfamide and doxorubicin consisting of IV doxorubicin 25 mg/m²/day×3 days (total cumulative doxorubicin dose, 75 mg/m²) with ifosfamide 2000 mg/m²/day×5 days given with mesna. A total of 33 patients received ifosfamide alone, 30 patients received ifosfamide, doxorubicin, and cisplatin, 3 received some other chemotherapy regimen, and for 5 patients the exact type of chemotherapy could not be determined. The number of chemotherapy cycles varied according to the treating medical oncologist. Resection was planned for 2 to 3 weeks after completion of radiotherapy.

All patients on this retrospective study received a total dose of 3.5 Gy×8 treatments given daily. Assuming an α/β ratio of 4 for sarcomas^{2,3} this results in an equivalent dose in 2 Gray fractions (EQD2) of 35 Gy. This is lower than the standard preoperative dose of 50 Gy. The standard dose of 50 Gy was not determined through dose finding studies, and the total dose needed to achieve optimum LC may not necessarily be 50 Gy.² The dose delivered was determined nonrandomly based on our institutional experience.¹ Starting in 1975 a consecutive series of 83 patients with skeletal sarcomas and 100 with STSs was treated with preoperative intra-arterial adriamycin and 3.5 Gy×10 fractions of radiation. Surgery was performed 1 to 2 weeks following preoperative therapy. Local recurrences (LR) occurred in 3% of patients and 24 patients (13%) developed complications. The most common complications noted were: wound slough in 13, fracture of adjacent bone in 5, and lymphedema in 4 patients.⁴ There was a particularly high rate of complications seen in the skeletal sarcoma patients who had allografts placed with 56% of the 23 patients getting allografts requiring subsequent operative revision. As this regimen was developed for both skeletal and STSs the high rate of complications in the skeletal sarcoma patients coupled with the high LC rates led the group to do a subsequent study that continued to include chemotherapy but reduced the dose of radiation to 17.5 Gy in 3.5 Gy fractions. The local failure rate at 4 years with this reduced dose of radiation was 12%.^{5,6} This subsequently led the group to settle on a dose in between the previous 2 of 3.5 Gy×8 fractions.¹ Radiotherapy was delivered sequentially when ifosfamide and doxorubicin were given but when ifosfamide was given alone the radiation was typically given concurrently. All patients were computed tomography planned and treated with 3D conformal RT. Standard preoperative sarcoma margins for the time were used, typically a 4 to 5 cm longitudinal margin.

All resections were intended to be limb-sparing with negative margins (R0 resection). Biopsy sites were resected en bloc with the surgical specimen. Patients with positive surgical margins were reresected if possible. If sparing the limb was infeasible following preoperative chemoradiation or positive-margin

resection, amputation was performed. Patients were considered for postoperative chemotherapy or additional radiation based on multidisciplinary tumor board discussion. In total, 44 patients (36%) received additional adjuvant chemotherapy and 14 patients (12%) received a postoperative radiation boost.

Patients were seen in follow-up in surgical oncology, medical oncology, and/or radiation oncology. Patients were typically seen every 1 to 3 months for the first year, every 3 to 4 months for the second year, every 6 months through the fifth year, and annually thereafter. Chest imaging with computed tomography or x-ray was obtained every 6 months for the first 5 years and annually thereafter. Magnetic resonance imaging of the primary resection site was obtained every 6 months for the first 5 years and then annually thereafter.

Data Collection and Analysis

Patient records were identified using the surgical oncology database. Data abstracted from these charts included date of birth, date of diagnosis, upper or lower extremity site, preoperative tumor size, tumor histology, whether the first operation was intended as a cancer operation, pathologic necrosis score, acute and long-term wound complications, date of local failure, date of distant failure (DF), site of DF, date of last follow-up, and date of death. All non-LRs were scored as distant. In 5 cases the pathologist documented the pathologic necrosis score as a range; the lower bound of the range was used for analysis. Fifty patients in this analysis (43%) were also included in our previous analysis.

Data were analyzed for associations between outcomes and the percentage of pathologic necrosis, whether the first operation was intended as a cancer operation, tumor histology, and preoperative tumor size. LC was calculated from the date of biopsy to the date of first local disease recurrence. DF was calculated from the date of biopsy to the first evidence of DF, even if findings were thought to be indeterminate or ambiguous at the time. Date of death was obtained from the Social Security Death Index, the medical record, contacting surviving relatives, or published obituaries. Patients were censored at the date of last follow-up or the date of death.

The Kaplan-Meier method was used to evaluate the probability of overall survival (OS), LC, and DF.⁷ All time intervals were calculated from the date of biopsy. Univariate and multivariate Cox proportional hazards models were used to assess variables that may be associated with an increased risk of OS, LC, and DF.⁸ The variables included in the multivariate analysis included margin status, age, grade, pathologic necrosis score, histology, and tumor size. All analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC), and $P < 0.05$ for 2-sided tests were considered statistically significant.

RESULTS

Patient and Tumor Characteristics

Demographic and treatment-related details are shown in Table 1. Mean patient age at diagnosis was 47 years (SD, 16). In total, 22 patients (21%) had upper extremity tumors, whereas 92 patients (79%) had lower extremity tumors. Tumors ≤ 5 cm were present in 20 patients (17%), > 5 cm up to 10 cm in 40 patients (35%), and > 10 cm in 55 patients (47%). The most common histology was undifferentiated pleomorphic sarcoma, which was previously known as malignant fibrous histiocytoma.⁹ Pathologic necrosis score was available for 103 patients. Ten patients who were treated after excisional biopsy had no tumor seen after resection. For 2 patients, necrosis score was described only qualitatively in the pathology report and data were missing for 1

TABLE 1. Baseline Patient Clinical Characteristics (n = 116)

	n (%)
Median age at diagnosis (y)	46 (range, 13-83)
≤ 60	90 (78)
> 60	26 (22)
Sex	
Male	70 (60)
Female	46 (40)
Primary site	
Lower extremity	92 (79)
Upper extremity	24 (21)
First operation had oncologic intent	
No	21 (18)
Yes	95 (82)
Tumor size (cm)	
≤ 5	20 (17)
> 5, ≤ 10	40 (35)
> 10	55 (47)
Preoperative size unknown	1 (0.9)
Histology	
MFH/pleomorphic sarcoma NOS	36 (31)
Synovial sarcoma	31 (27)
Liposarcoma	19 (16)
Other	30 (26)
Grade	
3	92 (79)
2	15 (13)
1	1 (0.9)
Unknown	8 (7)
Surgical margin status	
Negative (R0)	108 (93)
Positive (R1)	7 (6)
Unknown	1 (0.9)
Pathologic necrosis score	
Tumor removed at biopsy	10 (9)
Unknown	3 (3)
< 95%	81 (70)
≥ 95%	22 (19)
Postoperative radiation boost	
No	102 (88)
Yes	14 (12)

MFH indicates malignant fibrous histiocytoma; NOS, not otherwise specified.

patient. The pathologic necrosis score was ≥ 95% in 22 of 103 patients (19%).

The mean follow-up for all 116 patients was 7.7 years, with a median of 5.9 years (range, 0.3 to 24 y).

LR

The actuarial overall LR rate for the 116 patients who underwent limb-sparing surgery was 11% at 3 years and 17% at 6 years. The median time to local failure was 1.8 years (range, 0.3 to 8.3 y). A total of 16 local failures were recorded (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/AJCO/A195>).

On univariate analysis, positive surgical margin ($P < 0.001$; hazard ratio [HR], 7.99; 95% confidence interval [CI], 2.70-23.63) and age over 60 years ($P = 0.004$; HR, 4.26; 95% CI, 1.58-11.47) were associated with risk of LR (Table 2). On multivariate analysis, only surgical margin status ($P = 0.005$; HR, 18.33; 95% CI, 2.41-139.34) was associated with an increased risk of LR (Fig. 1A).

DF

The actuarial overall DF rate at 3/6 years was 25%/35%. The median time to DF was 1.5 years (range, 0 to 8.0 y). The patient scored as having DF at 0 months was not thought to be metastatic on presentation at the time of treatment. Lung metastases first detected on subsequent chest imaging were noted in retrospect to be visible on initial staging workup and thus the patient was scored as having distant metastases at presentation, but included in analysis as that information was not known at the time of initial treatment.

On univariate analysis, tumor size > 10 cm was associated with a higher risk of DF ($P = 0.03$; HR, 3.36; 95% CI, 1.17-9.69). On multivariate analysis, tumor size > 10 cm remained significant for an increased risk of DF ($P = 0.03$; HR, 3.84; 95% CI, 1.16-12.76) (Table 3).

OS

The actuarial OS rate at 3/6 years was 82%/67%. The median time from biopsy to death was 4.2 years (0.4 to 21.4 y).

On univariate analysis, age over 60 years ($P < 0.001$; HR, 3.07; 95% CI, 1.72-5.48), tumor size > 10 cm ($P = 0.003$; HR, 4.42; 95% CI, 1.67-11.75) compared with tumor size ≤ 5 cm correlated with worse OS, whereas synovial sarcoma histology correlated with improved OS compared with patients with malignant fibrous histiocytoma histology ($P = 0.02$; HR, 0.38; 95% CI, 0.17-0.86) (Table 4). On multivariate analysis, age over 60 years ($P = 0.03$; HR, 2.34; 95% CI, 1.10-4.98) and tumor size over 10 cm compared with tumor size ≤ 5 cm ($P = 0.03$; HR, 3.32; 95% CI, 1.15-9.61) remained significantly associated with worse OS, whereas synovial histology was not significantly associated (Table 4, Figs. 1B, C).

TABLE 2. Univariate and Multivariate Analysis (Cox model) for Local Failure

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
Margin (R0 vs. R1)	7.99	2.70-23.63	< 0.001	18.33	2.41-139.34	0.005
Age (≤ 60 vs. > 60 y)	4.26	1.58-11.47	0.004	1.82	0.46-7.19	0.39
Grade (1 or 2 vs. 3)	1.37	0.31-6.02	0.68	1.56	0.31-7.93	0.59
Necrosis (≥ 95% vs. < 95%)	1.55	0.49-4.87	0.46	2.29	0.61-8.62	0.22
Extremity (upper vs. lower)	0.92	0.26-3.21	0.89	—	—	—
Postoperative boost (none vs. boost)	1.59	0.45-5.61	0.47	—	—	—
Histology (MFH vs. synovial)	0.27	0.06-1.33	0.12	1.04	0.15-7.30	0.97
Histology (MFH vs. liposarcoma)	0.46	0.09-2.20	0.32	0.56	0.10-3.30	0.53
Histology (MFH vs. other)	0.85	0.27-2.70	0.33	2.15	0.49-9.43	0.31
Tumor size (≤ 5 vs. 5 to 10 cm)	3.83	0.46-31.9	0.21	3.43	0.36-32.86	0.29
Tumor size (≤ 5 vs. > 10 cm)	4.15	0.52-33.4	0.18	7.02	0.74-66.57	0.09

Bold values are statistically significant.

CI indicates confidence interval; HR, hazard ratio; MFH, malignant fibrous histiocytoma (here this category includes entities later called pleomorphic sarcoma).

FIGURE 1. Clinical outcomes including local control for patients after limb-sparing surgery according to surgical margin status (microscopically negative vs. positive margins) $P < 0.001$ (A) and overall survival according to (B). Age at diagnosis (60 y and above vs. below 60 y; $P < 0.001$) and tumor size (≤ 5 vs. 5 to 10 vs. > 10 cm) (C). For ≤ 5 vs. 5 to 10 cm; $P = 1.0$. For 5 to 10 vs. > 10 cm; $P = 0.0318$. For ≤ 5 vs. > 10 cm; $P = 0.0013$. Bonferroni corrected P -values for (C).

Toxicity

Acute and long-term toxicities were recorded for 17 patients (15%). This includes 12 patients (10%) with acute and perioperative complications (6 seromas/hematomas, 5 surgical-site infections, and 1 slow wound healing requiring rotational

flap closure). Three patients had late femur fractures in the radiation field, 1 patient suffered a hardware failure, and 1 patient suffered contractures in multiple fingers which resolved completely to full range of motion following a revision operation.

TABLE 3. Univariate and Multivariate Analysis (Cox model) for Distant Failure

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
Margin (R0 vs. R1)	1.23	0.38-4.00	0.73	3.93	0.67-23.06	0.13
Age (≤ 60 vs. > 60 y)	1.71	0.87-3.36	0.12	1.24	0.50-3.06	0.64
Grade (1 or 2 vs. 3)	3.82	0.92-15.86	0.07	4.15	0.94-18.37	0.06
Necrosis ($\geq 95\%$ vs. $< 95\%$)	1.73	0.83-3.59	0.14	1.34	0.58-3.11	0.49
Extremity (upper vs. lower)	0.99	0.46-2.15	0.98	—	—	—
Postoperative boost (none vs. boost)	0.56	0.17-1.82	0.34	—	—	—
Histology (MFH vs. synovial)	0.70	0.29-1.66	0.42	1.46	0.50-4.28	0.49
Histology (MFH vs. liposarcoma)	0.81	0.30-2.16	0.67	1.25	0.39-4.01	0.70
Histology (MFH vs. other)	1.18	0.54-2.58	0.68	1.79	0.69-4.65	0.23
Tumor size (≤ 5 vs. 5 to 10 cm)	1.25	0.39-4.07	0.71	1.04	0.30-3.67	0.95
Tumor size (≤ 5 vs. > 10 cm)	3.36	1.17-9.69	0.03	3.84	1.16-12.76	0.03

Bold values are statistically significant.

CI indicates confidence interval; HR, hazard ratio; MFH, malignant fibrous histiocytoma (here this category includes entities later called pleomorphic sarcoma).

TABLE 4. Univariate and Multivariate Analysis (Cox model) for Overall Survival

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
Margin (R0 vs. R1)	1.89	0.67-5.33	0.23	2.92	0.62-13.83	0.18
Age (≤ 60 vs. > 60 y)	3.07	1.72-5.48	< 0.001	2.34	1.10-4.98	0.03
Grade (1 or 2 vs. 3)	1.54	0.65-3.64	0.32	1.50	0.60-3.75	0.39
Necrosis ($\geq 95\%$ vs. $<95\%$)	1.57	0.82-3.00	0.17	1.35	0.65-2.83	0.42
Extremity (upper vs. lower)	0.98	0.49-1.95	0.95	—	—	—
Postoperative boost (none vs. boost)	0.71	0.26-1.99	0.52	—	—	—
Histology (MFH vs. synovial)	0.38	0.17-0.86	0.02	0.96	0.36-2.57	0.94
Histology (MFH vs. liposarcoma)	0.50	0.20-1.25	0.14	0.73	0.25-2.09	0.55
Histology (MFH vs. other)	0.82	0.42-1.59	0.55	1.16	0.53-2.53	0.71
Tumor size (≤ 5 vs. 5 to 10 cm)	2.33	0.82-6.67	0.11	1.44	0.47-4.42	0.52
Tumor size (≤ 5 vs. > 10 cm)	4.42	1.67-11.75	0.003	3.32	1.15-9.61	0.03

Bold values are statistically significant.

CI indicates confidence interval; HR, hazard ratio; MFH, malignant fibrous histiocytoma (here this category includes entities later called pleomorphic sarcoma).

DISCUSSION

There has been longstanding interest in improving outcomes for extremity sarcoma patients. Although LC rates following limb-sparing surgery with adjuvant radiation are relatively high in the 80% to 95% range,¹⁰⁻¹⁸ the risk of distant metastasis is relatively high and creates an obvious motivation to incorporate chemotherapy. Various strategies have been tested including a 44 Gy split course radiotherapy regimen with mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) pioneered by the group at Massachusetts General Hospital (MGH).¹⁹ An update of this regimen for 66 patients with a median follow-up of 46 months showed a 5-year locoregional, distant recurrence-free survival, and OS of 91%, 64%, and 86%.²⁰ This original pilot work at MGH led to the Radiation Therapy Oncology Group doing a multi-institutional phase II study (RTOG 9514) of chemoradiation in ≥ 8 cm intermediate or high-grade extremity and truncal STSs.¹³ With a median follow-up of 7.7 years the 5-year locoregional failure was 22% and distant metastasis was 22%.¹⁴ Unfortunately this study showed a high rate of toxicity, including 3 treatment-related deaths. It is felt this was related to the fact that the dose of ifosfamide was 25% higher than in the MGH experience and large radiation fields were utilized.

At our own institution we have taken a different approach with respect to the total radiation dose utilized in the preoperative setting when given in combination with chemotherapy.

All patients on this retrospective study received a total dose of 3.5 Gy $\times$ 8 treatments. Assuming an α/β ratio of 4 for sarcoma^{2,3} this results in an EQD2 of 35 Gy. This dose was determined through clinical experience where a dose of 35 Gy in 10 fractions (EQD2 44 Gy, α/β ratio 4) was too high and a dose of 17.5 Gy in 5 daily fractions (EQD2 22 Gy, α/β ratio 4) was too low. It is important to note that at the time these doses were evaluated older radiation techniques and chemotherapy that is no longer utilized (ie, intra-arterial adriamycin) today were used.

This update of patients treated with ifosfamide-based chemotherapy continues to provide evidence of acceptable tumor control with a local failure rate of 17% at 6 years. On multivariate analysis margin status was a significant predictor of increased LR, consistent with previous reports.^{21,22} Other published experiences with hypofractionated preoperative radiotherapy have reported LC rates of 80% to 95%, which are comparable with LC rates reported in series of conventionally fractionated treatment (Table 5). The dose of radiation delivered in our study is most similar to a Polish experience of 5 Gy $\times$ 5 given preoperatively with no chemotherapy.²⁹ With a median follow-up of about 3 years the LR rate in that study was 19%. Depending on the true α/β for sarcomas a dose of 5 Gy $\times$ 5 might have EQD2 range including 31.25 Gy ($\alpha/\beta = 10$) to 37.5 Gy ($\alpha/\beta = 4$). In this Polish experience and our experience the LC rate is somewhat lower than that reported in series using the standard 50 Gy preoperative dose where LC rates are being

TABLE 5. Selected Series of Patients Treated With Hypofractionated Radiotherapy for Soft Tissue Sarcoma

Series	No. Patients	Dose	Chemotherapy	LC
Eilber et al ¹	496	3.5 Gy $\times$ 8	Yes	89% at 5 y
Mack et al ²³	75 (67 R0, 8 R1)	3.0 Gy $\times$ 10	Yes	R0: 97% at 5 y R1: 50% at 5 y
Temple et al ²⁴	53 upper limb only	3.0 Gy $\times$ 10	Yes	96% at 5 y
Ryan et al ²⁵	25	3.5 Gy $\times$ 8	Yes, dose-intense epirubicin and ifosfamide	88% at 2 y
Jacinto et al ²⁶	49	Median 2.5 Gy $\times$ 12	76% received chemotherapy	81% at 5 y
MacDermid et al ²⁷	34	3.5 Gy $\times$ 8	Yes	89.0% at 5 y
Soyfer et al ²⁸	21 elderly patients	3.0 Gy $\times$ 13-16	No	86% at 26 mo
Kosela-Paterczyk et al ²⁹	272 (167 with primary tumors)	5 Gy $\times$ 5	Yes in 81%, for "more chemosensitive subtypes (eg, synovial sarcoma)"	81% at 3 y
Kubicek et al ³⁰	13 patients, 14 tumors	SBRT: 7 Gy $\times$ 5 for 12 patients; 8 Gy $\times$ 5 for 2 deeper tumors	3 patients had chemo before SBRT	1 local failure at 488 d. Median follow-up, 279 d

LC indicates local control; SBRT, stereotactic body radiation therapy.

reported closer to about 90%. It is difficult to compare our results directly to more modern series but does raise the question whether future studies should consider a higher preoperative dose than what we delivered. In the setting of utilizing intensity modulated RT and smaller margins, which there is now data to support,¹⁷ it is possible that a higher dose of radiation would be well tolerated compared with the older techniques that we had utilized at the time at our institution when we began to use 3.5 Gy×8 fractions. This is also potentially true in light of using different chemotherapy than used previously. Higher doses may potentially improve the LC rate as we saw when we previously used 3.5 Gy×10. Modern radiation planning and treatment delivery techniques could likely allow this higher dose to be delivered with reduced toxicities compared with our previous experience.

In our study, we also found a 6-year actuarial rate of DF of 35%. Our distant metastasis rate is similar to the 5-year distant metastasis free rate of 64% reported by the MGH group and comparable with the 5-year 22% distant metastasis rate reported on RTOG 9514. No factors on multivariate analysis were significant predictors of distant metastasis. This is in contrast to a recent pooled analysis showing tumor size, grade, and histology as significant predictors of developing distant metastasis.³¹

OS at 6 years was 67%. This is lower than the 5-year OS of 86% reported by the MGH group but similar to the 5-year rate of 71% reported by RTOG 9514. On multivariate analysis age over 60 years and tumors > 10 cm were significantly correlated with decreased OS. These factors are similar to those reported in the previously mentioned pooled analysis where age, tumor size, grade, and histology were significant predictors of OS.³¹ When comparing the OS of patients on this study treated with chemotherapy compared with other studies that treated with radiation without chemotherapy, such as the National Cancer Institute of Canada (NCIC) randomized study (5 y OS, 70%), the rates are similar.¹⁵ Although there are clearly differences in the patient populations of this study and that of the NCIC study (only about 35% on NCIC study with tumors > 10 cm) this shows that our efforts of intensifying systemic therapy have not resulted in major OS gains. One perspective on this is that the chemotherapy might not change OS and that LC is acceptable so future treatments should move forward with radiation only. Another perspective is to recognize that the distant metastasis rate is still high in this group of patients and that efforts should be directed at possibly modifying the systemic therapy we are using to see if we can make progress in reducing the risk of distant metastasis. It seems of lesser importance to include chemotherapy as a modality to improve LC.

Since the initial development of our preoperative regimen, more information has become available regarding the efficacy of chemotherapy for STSs. Chemotherapy remains controversial in the setting of STSs, and practice patterns vary by institution. With significant numbers of STS patients developing metastatic disease, efforts are needed to improve the clinical efficacy of systemic therapies in the definitive setting. We expect that in the future patients will increasingly be stratified by and selected for chemotherapy and other systemic therapy based on molecular analysis and other technologies including advanced imaging.^{32,33} The Cancer Genome Atlas recently published novel insights into the genomic classification of 6 major types of sarcomas.³⁴ This type of information will assist in the rational testing and integration of targeted agents in systemic therapy, which will play an increasing role.^{35–38} Caution will be needed when combining new drugs with radiation as some have caused unacceptable toxicity, for example, with sunitinib³⁹ or thalidomide.⁴⁰ As such, there is rationale for trials exploring the further optimization of preoperative

radiation and chemotherapy. We also believe that as the role of targeted therapies increases, shortening the time a patient needs to receive radiation will help its integration into future treatment paradigms.

Developing predictive and prognostic biomarkers in sarcomas would clearly be helpful to optimally identify patients most likely to benefit from intensified therapy. To that end, we previously investigated whether treatment-induced pathologic necrosis score was prognostic of LC and OS.¹ We found pathologic necrosis score of ≥ 95% was correlated with improved LC and OS. However, in the current series we were unable to demonstrate a prognostic significance for pathologic necrosis. It is possible that in our previous series that pathologic necrosis score was covariate with ifosfamide-based chemotherapy and that in this more modern chemotherapy cohort this effect was lost.⁴¹

Others have examined the prognostic significance of pathologic necrosis score as well. Some of these investigations have showed favorable prognosis associated with high pathologic necrosis after preoperative chemotherapy,^{42–45} radiation,^{46,47} or both.^{27,48} However, others have found that pathologic necrosis is not prognostic for clinical outcomes.^{20,41,49–51} Most recently, Schaefer and colleagues reviewed 100 patients treated with neoadjuvant chemotherapy or RT and concluded the percent of residual viable cells, as evaluated by the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) score, is not prognostic. They suggest that hyalinization/fibrosis is associated with favorable outcomes.⁵² Given the heterogenous nature of STS and the number of conflicting studies, the prognostic significance of treatment-induced pathologic necrosis score is likely to remain controversial.⁵³ The COG—NRG ARST1321 trial (ClinicalTrials.gov Identifier: NCT02180867), which is currently accruing patients, has designated treatment-induced pathologic necrosis as the primary endpoint. This trial should provide prospective guidance on any potential correlation between prognosis and pathologic necrosis score.

This was a retrospective study and so it comes with the inherent limitations of such a study. One of the main limitations in this regard concerns toxicity. Many patient records did not routinely document grade 1 and or 2 changes and so these are likely underestimated in our study. From the information that we were able to gather the acute wound complication rate of 11% is comparable with that expected with standard fractionated RT. The full details of chemotherapy were also not available for all patients and so this is also a limitation. A further limitation is that patients treated to 50 Gy preoperatively were not reviewed for comparison.

This hypofractionated preoperative radiation approach in combination with chemotherapy is effective and provides a promising platform on which to test novel chemoradiation combinations to make a larger impact on OS for sarcoma patients.

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