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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Epirubicin and Ifosfamide with Preoperative Radiation for High-Risk Soft Tissue Sarcomas

Eric Lu, MD[1], Kelly S. Perlewitz, MD[2], James B. Hayden, MD, PhD[3], Arthur Y. Hung, MD[4], Yee-Cheen Doung, MD[3], Lara E. Davis, MD[5], Atiya Mansoor, MD[6], John T. Vetto, MD[7], Kevin G. Billingsley, MD[7], Andy Kaempf, MS[8], Byung Park, PhD[8], and Christopher W. Ryan, MD[5]

[1]Department of Medicine, Oregon Health and Science University, Portland, OR; [2]Providence Cancer Institute, Newberg, OR; [3]Department of Orthopedics, Oregon Health and Science University, Portland, OR; [4]Department of Radiation Medicine, Knight Cancer Institute, Oregon Health and Science University, Portland, OR; [5]Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR; [6]Department of Anatomical Pathology, Oregon Health and Science University, Portland, OR; [7]Department of Surgery, Division of Surgical Oncology, Oregon Health and Science University, Portland, OR; [8]Biostatistics, Knight Cancer Institute, Oregon Health and Science University, Portland, OR

ABSTRACT

Background. The optimal treatment of high-risk soft tissue sarcomas (STS) of the extremities remains controversial. We report follow-up from a phase II study of dose-intense chemotherapy with preoperative hypofractionated radiation in this population supplemented with subsequent data from an extensive institutional experience using this regimen.

Methods. Patients with localized, intermediate- or high-grade STS of the extremity or body wall measuring > 5 cm were treated with epirubicin 30 mg/m^2/day and ifosfamide 2.5 g/m^2/day on days 1–4 every 21 days for 3 preoperative and 3 postoperative cycles. During cycle 2 of preoperative therapy, epirubicin was omitted, and a total of 28 Gy of radiation (8 fractions) was delivered. Twenty-five patients were treated on the phase II study (2002–2005). Fifty-one additional patients were identified from a retrospective chart review (2005–2014).

Results. The 5-year rates for overall survival, distant disease-free survival, and freedom from local regional failure were 70.4% (95% CI 59.2–83.7%), 55.9% (95% CI 44.5–70.2%), and 87.2% (95% CI 77.9–96.5%) respectively. Thirty-eight percent of tumors (29/76) demonstrated $\geq 90\%$ pathologic response. Wound complications occurred in 32% (24/76) of patients.

Discussion. Treatment with preoperative radiation and pre- and post-operative epirubicin and ifosfamide was associated with favorable clinical outcomes. Survival and recurrence rates were comparable to those reported with other preoperative chemotherapy regimens in high-risk extremity sarcomas. Use of trimodality therapy should be considered for appropriate high-risk STS patients.

High-risk soft tissue sarcomas (STS) of the extremity include those that are large (> 5 cm) and of intermediate- or high-grade.[1] The mainstay of treatment consists of surgery with wide excision and radiation therapy.[2–4] Despite good rates of local control with this approach, approximately half of patients with high-risk STS of the extremity will die from metastatic disease.[5] Historical rates of 5-year overall survival (OS) and freedom from local regional failure (LRF) for stage III STS are 50–60% and $\sim$ 85%, respectively.[1,6] Various chemotherapy regimens have been studied as an adjunct to surgery in an attempt to improve outcomes for high-risk disease, but the use of chemotherapy in this setting remains controversial.[7,8]

One strategy for the treatment of high-risk extremity STS is the use of combination preoperative chemotherapy and radiation.[9] Neoadjuvant chemotherapy may potentially

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C. W. Ryan, MD
e-mail: ryanc@ohsu.edu

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treat micro-metastatic disease, act as a radiation-sensitizing agent, decrease the chance of local recurrence, and help downsize the tumor. Initial trials of neoadjuvant chemoradiotherapy involved the use of local intra-arterial doxorubicin followed by radiation therapy prior to surgical resections.[10–12] This approach was supplanted by intravenous chemotherapy, and various radiation strategies have been developed to integrate radiation with chemotherapy, including concurrent and interdigitated.[11,13–17]

In 2008, we published the results of a phase II study using an intensified chemotherapy regimen consisting of epirubicin and ifosfamide combined with preoperative hypofractionated radiation in patients with large, intermediate- or high-grade STS of the extremities or body wall.[18] We now report longer-term follow-up of these subjects supplemented with data from subsequent patients treated off-study at our institution.

MATERIALS AND METHODS

Patients

Eligibility criteria for the phase II study have been previously described.[18] Briefly, patients aged $\geq$ 18 years with histologically confirmed intermediate- or high-grade STS of the extremities or body wall measuring $>$ 5 cm were eligible. Both superficial and deep tumors were allowed. Subjects must have had no contraindications to limb-sparing surgery. Those with metastatic disease were excluded.

Patients in the phase II study initiated therapy between December 2002 and May 2005 and were enrolled at the following institutions: Oregon Health and Science University; Medical College of Wisconsin; Lutheran General Hospital; University of Chicago; and the University of Illinois at Chicago.

Subsequently, pharmacy administration and Radiation Oncology records at Oregon Health and Science University were used to identify patients with non-metastatic, $>$ 5 cm, intermediate- or high-grade STS of the extremities or body wall who initiated treatment with the same regimen from May 2005 until October 2014. An IRB-approved, retrospective chart review was conducted to extract data from the medical records on these patients including demographics, pathology, and radiographic information. Surgical outcome data collected included: surgical procedure performed (limb-sparing, amputation, or body wall resection), margin status, and occurrence of wound complications defined as those requiring a second surgical intervention up to 6 months following the original resection.

Treatment

Chemotherapy consisted of 3 cycles of preoperative and 3 cycles of postoperative therapy on a 21-day cycle. Epirubicin 30 mg/m^2/day and ifosfamide 2.5 g/m^2/day were given on days 1–4. During cycle 2, epirubicin was omitted (Fig. 1). Patients received intravenous hydration, mesna, and antiemetics per institutional guidelines. Growth factor support with pegfilgrastim or filgrastim was administered after each chemotherapy cycle.

External beam radiotherapy was initiated concomitantly at the start of cycle 2 of chemotherapy (with epirubicin omitted). This consisted of 28 Gy administered as 8 fractions of 3.5 Gy each. Patients were planned with 3-D conformal techniques based on contrast-enhanced CT simulation. Intensity Modulated Radiation Therapy (IMRT) was not used. Surgical resection of the tumor was performed after 3 cycles of chemotherapy. Limb-sparing technique was performed whenever possible with the intent of obtaining negative margins. A postoperative radiation boost to the surgical bed (2 Gy $\times$ 6 fractions) was administered to patients with positive surgical margins.

Pathology review of the resected tumor was performed by pathologists with expertise in sarcoma. Pathologic response was quantified predominantly by estimation of the percent of tumor necrosis present in the resected specimen as well as any additional treatment-related changes such as hyalinization and fibrosis.

Follow-up Visits and Study Procedures

After completion of treatment, subjects were followed for local recurrence, metastatic disease, and survival by medical history, physical examination, and imaging at the discretion of the treating physician. Typical follow-up included a CT scan of the chest and MRI of the primary tumor site every 4 months for the first 2 years, every 6 months for the third year, and yearly for the fourth and fifth years. Radiographic findings suspicious for local recurrence or metastatic disease were used to determine recurrence. Biopsy of suspected lesions was left to the discretion of the treating physician.

Study Endpoints and Statistical Analysis

Primary outcomes included OS, distant disease-free survival (DDFS, time to distant metastasis or death), and freedom from LRF (time to local recurrence, excluding patients who underwent limb amputations and considering death as a competing risk). Starting from the date of tumor resection, the Kaplan–Meier method provided OS and DDFS estimates while one minus the cumulative incidence function yielded freedom from LRF estimates.

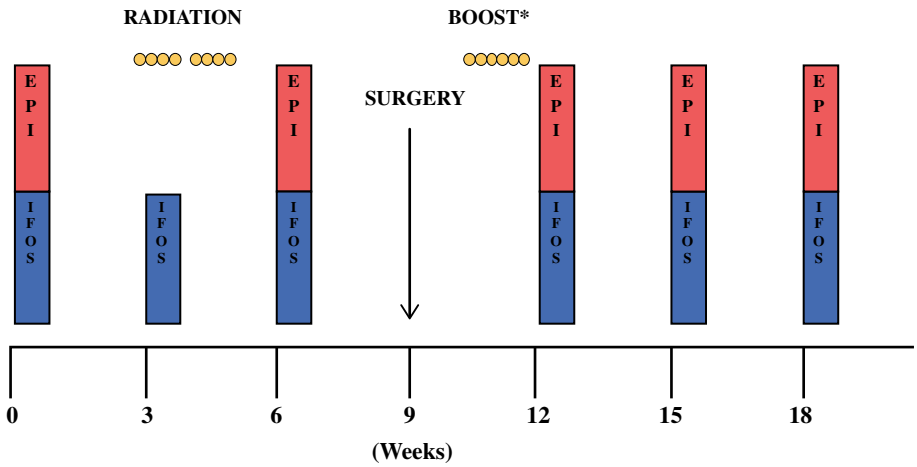

FIG. 1 Treatment Schema. Diagram of therapeutic regimen, including chemotherapy, radiation therapy, and surgical resection. EPI indicates epirubicin; IFOS, ifosfamide; *boost was given to patients with positive margins only

Our secondary objective was to explore potential predictors of clinical outcome. Univariate survival analysis using the log-rank test (for OS and DDFS) or Gray's test (for LRF) was performed to evaluate associations between variables of interest and each of the three primary clinical outcomes. Nine variables were examined: percent pathologic response (≥ 95 and $\geq 90\%$ cutoffs), histology (pleomorphic/NOS, myxoid liposarcoma, all liposarcomas, synovial), grade, location, margin status, age, tumor size, tumor depth, and number of chemotherapy cycles completed.

RESULTS

Patient Demographics

A total of 76 patients were included in the analysis: 25 from the initial phase II protocol and an additional 51 identified from retrospective chart review. Baseline characteristics of trial versus non-trial patients are shown in Table 1. Most tumors were located in the lower extremity (71%), median size was 10 cm, and the predominant histology was pleomorphic/NOS (47%).

Outcomes and Pathologic Response

Ninety-five percent (72/76) of patients completed all 3 preoperative chemotherapy cycles and 64% (49/76) completed all 6 pre- and post-operative cycles.

Surgical outcomes and pathology findings are summarized in Table 2. Negative margins were achieved in 89% (68/76) of patients. Of the patients with extremity tumors, 93% (65/70) underwent a limb-sparing surgical resection. Of the 5 patients who underwent amputation: 3 were borderline limb-salvage candidates who ultimately decided on amputation; 1 was converted to amputation during attempted limb-sparing surgery given proximity to vital structures; 1 suffered arterial graft failure after limb-sparing attempt and required amputation. Overall, wound complications occurred in 32% (24/76) of patients. Following limb-sparing procedures for extremity tumors, the wound complication rate was 32% (21/65), with a 39% rate (20/51) for lower extremity tumors and 7% rate (1/14) for upper extremity tumors. A total of 38 wound complications requiring surgical intervention occurred among 24 subjects.

Pathologic response was assessed in all 76 resected tumors. Thirty-two percent (24/76) of assessable specimens demonstrated $\geq 95\%$ pathologic response and 38% (29/76) demonstrated $\geq 90\%$ pathologic response.

Time-to-event estimates were generated by the Kaplan–Meier (for OS and DDFS) or cumulative incidence (for LRF) method (Fig. 2). Median follow-up time was 3.6 years (2 months to 12 years) among all patients and 4.3 years (5 months to 12 years) among survivors. The 5-year rates for OS, DDFS, and freedom from LRF were 70.4% (95% CI 59.2–83.7%), 55.9% (95% CI 44.5–70.2%), and 87.2% (95% CI 77.9–96.5%), respectively. There was no significant difference in outcomes between trial and non-trial patients (5-year OS (63.9% vs. 75.6%, $p = 0.686$), DDFS (64.7% vs. 48.7%, $p = 0.510$), freedom from LRF (86.1% vs. 86.0%, $p = 0.748$)). Of note, two late deaths occurred due to suspected therapy-related myelodysplasia/acute myeloid leukemia, seven years following therapy in both cases.

Predictor Variables

The following variables were examined: pathologic response, histology, grade, location, margin status, age, tumor size, tumor depth, and number of chemotherapy cycles completed. No significant associations were found between these variables and OS, DDFS, or freedom from LRF (Supplementary Table 1). Of note, negative margins were associated with a trend towards improved local

TABLE 1 Patient characteristics

Characteristic	Trial $n = 25$	Non-trial $n = 51$	Total $n = 76$
Age, years			
Median	53	49	52
Range	26–76	23–75	23–76
Sex			
Male	16 (64%)	36 (71%)	52 (68%)
Female	9 (36%)	15 (29%)	24 (32%)
Largest tumor dimension, cm			
Median	10.0	11.0	10.0
Range	5.2–35.0	5.3–24.0	5.2–35.0
Grade			
Intermediate	3 (12%)	16 (31%)	19 (25%)
High	22 (88%)	35 (69%)	57 (75%)
Anatomic site			
Lower extremity	17 (68%)	37 (73%)	54 (71%)
Upper extremity	5 (20%)	11 (22%)	16 (21%)
Body wall	3 (12%)	3 (6%)	6 (8%)
Tumor histology			
Pleomorphic/NOS	14 (56%)	22 (43%)	36 (47%)
Synovial	3 (12%)	10 (20%)	13 (17%)
Myxofibrosarcoma	0 (0%)	8 (16%)	8 (11%)
Liposarcoma	4 (16%)	3 (6%)	7 (9%)
Myxoid	3 (12%)	3 (6%)	6 (8%)
Dedifferentiated	1 (4%)	0 (0%)	1 (1%)
Leiomyosarcoma	2 (8%)	3 (6%)	5 (7%)
MPNST	1 (4%)	3 (6%)	4 (5%)
ESMC	1 (4%)	0 (0%)	1 (1%)
Extraosseous osteosarcoma	0 (0%)	1 (2%)	1 (1%)
Angiosarcoma	0 (0%)	1 (2%)	1 (1%)

NOS not otherwise specified, *MPNST* malignant peripheral nerve sheath tumors, *ESMC* extraskeletal myxoid chondrosarcoma

control rates, with 5-years rates of 89.4% for negative margins and 75.0% for positive margins ($p = 0.170$). Pathologic response was associated with a trend towards improvement, with $\geq$ 90% pathologic response associated with a favorable 5-year OS (82.9% vs. 62.9%, $p = 0.210$) and 5-year DDFS (68.6% vs. 48.7%, $p = 0.253$).

DISCUSSION

Sarcoma centers vary in the use of chemotherapy for treatment of high-risk STS, including the timing of chemotherapy, regimen employed, or whether to use chemotherapy at all. The question of whether chemotherapy improves outcomes in high-risk patients has not been adequately answered. Most randomized trials conducted in this setting have been flawed by relatively small sample sizes and heterogeneity of histological subtypes, anatomical locations, and regimens employed. Taking these shortcomings into consideration, the results of meta-analyses of adjuvant studies conducted to date nonetheless suggest a small benefit of adjuvant chemotherapy in improving local control, distant metastatic, and OS rates.[7,8]

Herein, we have reported our results using pre- and post-operative chemotherapy with epirubicin and ifosfamide combined with preoperative radiation for high-risk extremity and body wall sarcomas. As outlined in Table 3, our 5-year OS and local control rates of 70.4 and 87.2%, respectively, are similar to other studies employing neoadjuvant chemoradiation therapy, acknowledging that there are some differences in truncal sarcoma inclusion, starting points for time-to-event outcomes, and statistical methods used to estimate local control rate across studies. Our outcomes compare favorably with historical controls for patients not receiving chemotherapy in randomized

TABLE 2 Surgical and pathologic outcomes

Outcome	Number (%)
Surgical procedure*	
Limb-sparing	65/70 (93%)
Amputation	5/70 (7%)
Microscopic margins	
R0 (negative)	68/76 (89%)
R1 (positive)	8/76 (11%)
Pathologic response	
≥ 95%	22/76 (29%)
≥ 90%	29/76 (38%)
Wound complications**	
Yes	24/76 (32%)
No	52/76 (68%)
Type of wound complication***	
Wound infection	17 (45%)
Planned secondary closure	6 (16%)
Seroma/hematoma	6 (16%)
Wound dehiscence	5 (13%)
Wound necrosis	2 (5%)
Arterial thrombosis	1 (3%)
Arterial laceration	1 (3%)

*Excluded 6 patients with body wall resections

**Defined as complications requiring a second surgical intervention up to 6 months following the original resection

*** n=38 wound complications among 24 patients

trials, with published 5-year OS rates ranging from 47 to 68% in recent trials.[6,19–21] While the control arm of EORTC 62931 reported a similar 5-year OS rate of 68%, this study was notable for inclusion of a significant number of tumors < 5 cm and only 48% were high-grade.[21]

Our dose-intense regimen of epirubicin and ifosfamide was originally adapted to the neoadjuvant setting from a positive adjuvant report from the Italian Sarcoma Group.[6] The incorporation of ifosfamide into adjuvant regimens as well as dose-intensification made possible by colony-stimulating factors have been cited as possible reasons for better outcomes noted in later studies.[8] Our regimen is among the highest anthracycline and ifosfamide doses studied in the neoadjuvant and adjuvant settings.[6, 22,23] Recent studies have suggested that shorter courses of chemotherapy may be as efficacious as longer courses employed in older studies, illustrating that the optimal regimen remains to be defined.[22,23]

While there has been a recent trend towards the use of histology-specific chemotherapy for metastatic disease, anthracycline plus ifosfamide regimens such as ours remain the most active for the neoadjuvant or adjuvant setting and will continue to serve as a reference for future studies.[8] This is supported by a recent trial, which found neoadjuvant anthracycline plus ifosfamide therapy to be superior to a histology-tailored approach.[23] The investigation of newer molecular-targeted and immunotherapy agents in the treatment of advanced sarcoma is an area of intense interest, and studying these newer therapies in the high-risk localized setting is the logical next step. Our group has published on the addition of the VEGF-R tyrosine kinase inhibitor sorafenib to our chemoradiotherapy regimen, and we continue to study this approach in ongoing trials (NCT02050919).[24] A current Children's Oncology Group trial is adding pazopanib to doxorubicin, ifosfamide, and radiation (NCT02180867).

Compared to most other neoadjuvant trials, a unique feature of our regimen is the use of a short-course, high-dose-per-fraction radiation scheme modeled after the one described by Eilber et al.[25] We observed a 5-year local control rate of 87.2% (95% CI 77.9–96.5%), similar to what has been reported with more standard fractionation strategies.[4,26,27] The convenience of this regimen (only 8 fractions of 3.5 Gy each) and favorable rate of local control should encourage more widespread use of such a fractionation scheme.

One recognized downside of preoperative radiotherapy is an increased incidence of acute wound complications.[26] In our experience, wound complications occurred in 32% of patients who underwent limb-sparing procedures and were nearly entirely a phenomenon of lower extremity tumors. We defined wound complications as those requiring a second surgical intervention, and thus our results may not be directly comparable to studies that used broader definitions encompassing complications such as prolonged deep packing, seroma aspiration, or requirement for IV antibiotics.[26] Furthermore, our relatively high-rate of surgical intervention for wound complications may represent an institutional preference for early operative management over nonoperative methods for wound infections.

We have previously reported the side effects associated with this chemoradiotherapy regimen, which are substantial but expected given the agents involved.[18] Long-term follow-up revealed two late deaths from suspected therapy-related myeloid neoplasms. Both epirubicin and ifosfamide have known associations with such neoplasms, with an estimated risk of 1% per year beginning 1–3 years after starting chemotherapy and lasting 5–7 years after its cessation.[28–30] Although the risk of developing a secondary myeloid neoplasm is low, it should be a factor when determining the risk/benefit ratio of adjunctive chemotherapy for individual patients. Increased understanding of cancer genetic susceptibility among sarcoma patients may further inform the risk of secondary malignancy moving forward.[31]

Pathologic necrosis after preoperative therapy is a well-established prognostic marker in osteosarcoma and

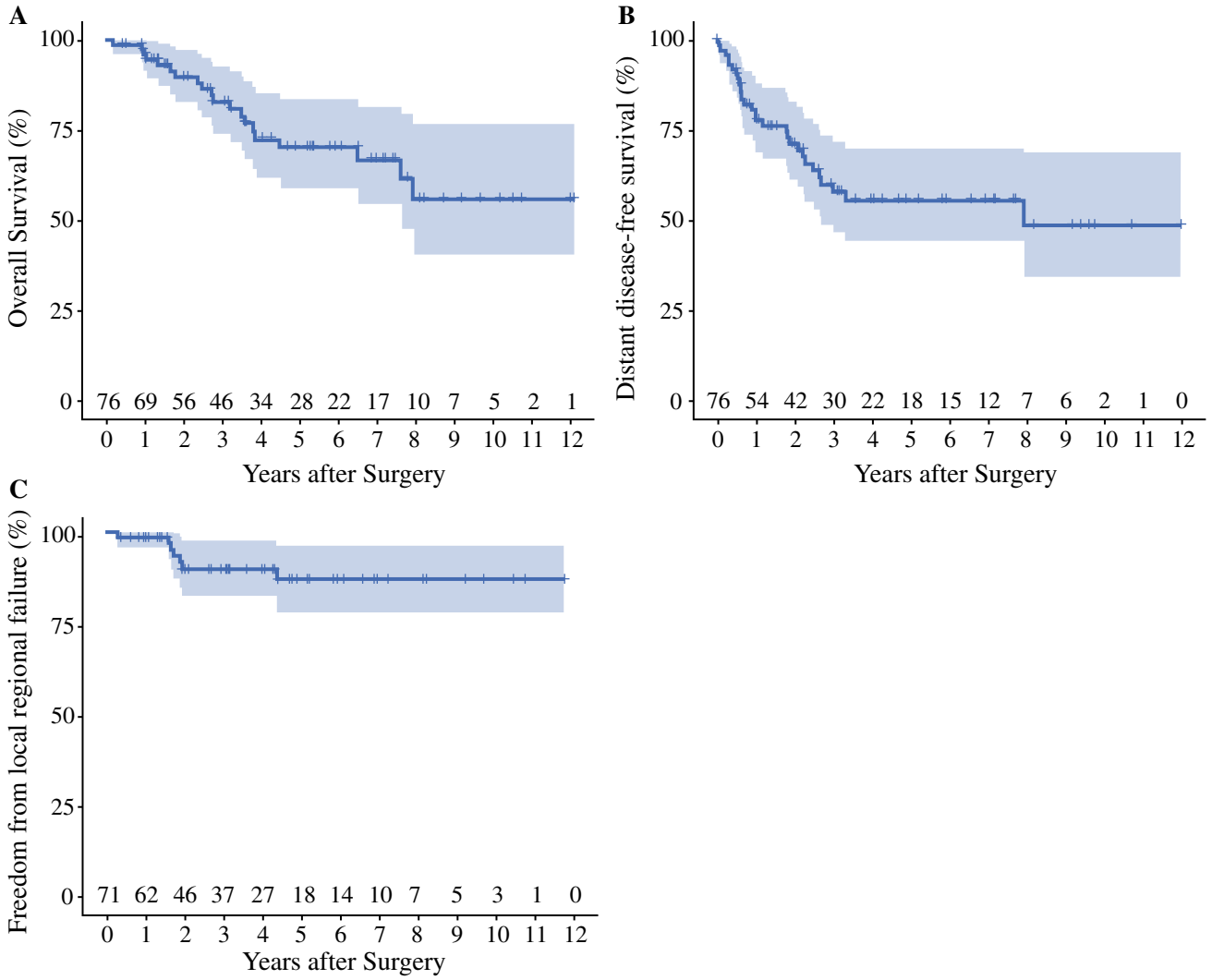

FIG. 2 Kaplan-Meier curves of **a** Overall Survival and **b** Distant Disease-Free Survival, and **c** a cumulative incidence-based curve depicting Freedom from Local Regional Failure (5 amputations excluded). Censored events are noted with crosses, with the number at risk detailed along the X-axis. 95% confidence intervals are shaded in blue

Ewing's sarcoma,[32,33] with ≥ 90% necrosis being used as the cutoff for association with favorable outcome.[34] However, this prognostic significance of treatment-induced pathologic necrosis remains undefined in patients with STS, with one study finding better patient outcomes for tumors with ≥ 95% pathologic necrosis but other studies not finding such an association.[25,35] We did not find a statistically significant association between pathologic response and clinical outcomes, but did observe a trend towards improved OS and DDFS when ≥ 90% pathologic response was used as the cutoff; this lack of statistical significance may be a result of the small sample size. Thus, the potential association of pathologic response with clinical outcome and optimal approach for quantifying this measure should continue to be investigated in future studies.[36]

The primary limitation of this study is that most of the data were obtained via retrospective chart review and sampled from a single institution. Neither baseline characteristics nor outcomes between the prospective study and retrospectively-identified patients were significantly different, which suggests an institutional consistency in choosing patients for neoadjuvant treatment. Nonetheless, the generalizability of these results may be limited by nuances of patient population and institutional practice that cannot be measured. Chart review methodology also carries the inherent risk of sampling error, but we feel this was minimized by using two sources to identify patients and by the existence of a centralized sarcoma practice at our institution.

In conclusion, our institutional experience with a treatment regimen consisting of preoperative radiation with pre- and post-operative epirubicin and ifosfamide is notable for

TABLE 3 Studies using anthracycline and ifosfamide with preoperative radiation therapy

Author	Year	*N*	Tumor size (cm)	Chemotherapy agents	Radiation dose (Gy)	OS (time)	Local control (time)
Current study	2017	76	5.2–35.0 (median 10.0)	Epirubicin, ifosfamide	28	70.4% (5 year)	87.2% (5 year)*
Sauer	1999	23	–	Doxorubicin, ifosfamide	60-64	83% (3 year)	–
Eilber	2001	496	<5 (20%) 5–10 (50%) >10 (30%)	Variable**	28-35	71% (5 year)	89% (5 year)
Edmonson	2002	39	1.6–30 (median 10.0)	Doxorubicin, cisplatin, ifosfamide, mitomycin	45	80% (5 year)	90% (5 year)
Ruka	2004	100	–	Ifosfamide, doxorubicin, cisplatin	20	76% (5 year)	93% (n/a)
MacDermed	2010	34	5.5–20 (median 10.5)	Ifosfamide, various others	28	42% (5 year)	89% (5 year)
Kraybill	2010	64	8.2–55.0 (median 15)	Doxorubicin, ifosfamide, dacarbazine	44	71% (5 year)	78% (5 year)
Look Hong	2013	66	2.5–35.5 (median 10)	Doxorubicin, ifosfamide, dacarbazine	44	86% (5 year)	89% (5 year)
Mullen	2014	113	5–10 (34%) >10 (66%)	Doxorubicin, ifosfamide, dacarbazine	44	86% (5 year)	93% (5 year)

*For control rates, $n = 71$ (amputations excluded)

**Reflect the evolution of treatment at UCLA over 20 years (doxorubicin; doxorubicin plus cisplatin; or doxorubicin, cisplatin, ifosfamide)

favorable OS, DDFS, and freedom from LRF rates in patients with high-risk STS. The decision to employ this or other trimodality therapy regimens in the management of high-risk STS of the extremities and body wall should be made on a patient-by-patient basis, taking into consideration the risk of metastatic disease, the potential but uncertain improvements in outcome with these treatments, and the known risks of such therapy.

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