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Primary Tumor Necrosis Predicts Distant Control in Locally Advanced Soft Tissue Sarcomas Following Preoperative Concurrent Chemoradiotherapy

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Abstract

Purpose—Various neoadjuvant approaches have been evaluated for the treatment of locally advanced soft tissue sarcomas. This retrospective study describes a uniquely modified version of the Eilber regimen developed at University of Chicago.

Methods and Materials—Thirty-four patients (28 stage III and 6 stage IV) patients with locally advanced soft tissue sarcomas of an extremity were treated between 1995 and 2008. All patients received preoperative therapy including ifosfamide (2.5 g/m²/day × 5 days) with concurrent radiation (28 Gy in 3.5 Gy daily fractions), sandwiched between various chemotherapy regimens. Postoperatively, 47% received further adjuvant chemotherapy.

Results—Most tumors (94%) were grade 3 and all were T2b, with a median size of 10.3 cm. Wide excision was performed in 29 patients (85%), and 5 required amputation. Of the resected tumor specimens, 50% exhibited high (≥90%) treatment-induced necrosis and 11.8% had a complete pathologic response. Surgical margins were negative in all patients. The 5-year survival was 42.3% for all patients and 45.2% for stage III patients. For limb-preservation patients, the 5-year local control was 89.0% and reoperation was required for wound complications in 17.2%.

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The 5-year freedom from distant metastasis (FFDM) was 53.4% (stage IV patients excluded), and FFDM was superior if treatment-induced tumor necrosis was $\geq 90\%$ (84.6% vs. 19.9%, $p=0.02$).

Conclusion—This well-tolerated concurrent chemoradiotherapy approach yields excellent rates of limb preservation and local control. The resulting treatment-induced necrosis rates are predictive of subsequent metastatic risk, and this information may provide an opportunity to guide postoperative systemic therapies.

Keywords

sarcoma; radiation therapy; chemotherapy; surgery; necrosis

Introduction

Soft tissue sarcomas represent a heterogeneous group of tumors which account for approximately 1% of adult cancers(1). Most patients present with deep and large (>5 cm) tumors, both of which are unfavorable prognostic factors for disease control and survival(2).

Prior to the era of adjuvant therapy, locally-advanced extremity sarcomas were generally managed with radical compartmental surgeries or amputations, often resulting in significant functional deficits(3,4). The randomized study by Rosenberg and co-workers demonstrated in 1982 that limb-sparing surgery combined with adjuvant radiotherapy (RT) represents a well-tolerated alternative to amputation(5). Several subsequent randomized trials(6,7) and retrospective series(4,8,9) have since validated this limb-sparing approach and have confirmed that adjuvant RT is an important component of therapy, at least for most high-grade tumors. The local control rate with this approach generally exceeds 85%, and many of the local recurrences that do occur can be surgically salvaged(4).

More recently, preoperative RT regimens have substituted for postoperative RT, particularly in marginally resectable tumors. Advocates of preoperative RT suggest several potential advantages over postoperative therapy, including 1) tumor shrinkage that may enable less radical resection, and 2) lower morbidity of RT because treatment volumes and doses can be safely reduced in the preoperative setting. A multi-center randomized trial in Canada directly compared preoperative and postoperative RT approaches, showing no significant differences in local control, metastasis, or survival rates at 5 years. There were somewhat more frequent wound complications in the preoperative RT arm; however, long-term toxicities (including fibrosis and joint stiffness) occurred more frequently in the postoperative group(10,11).

In recent decades, chemotherapy(12,13) and combined chemoradiotherapy (chemo/RT)(14–22) regimens have been explored for preoperative management of locally advanced tumors. The theoretical advantages of preoperative chemo/RT over RT alone include the possibility of better local tumor responses and earlier treatment of potential micro-metastases. However, combined chemo/RT may also carry greater risks for toxicity, at least in the acute setting. Several such chemo/RT regimens have been developed, but none is presently considered superior. Doxorubicin has been the principle chemotherapy drug used in these trials, based on its known activity in the postoperative adjuvant setting (23). Ifosfamide is an additional drug with single-agent activity against sarcomas(24), and it too is commonly integrated into preoperative regimens.

A fairly common preoperative chemo/RT regimen was popularized by Eilber and co-workers at the University California at Los Angeles(14–16). One of their early regimens included intra-arterial doxorubicin and sequentially delivered hypo-fractionated RT (35 Gy in 3.5 Gy fractions), followed by limb-sparing surgery(15). Despite the advanced

presentations of tumors, all patients in this study avoided amputation and only 3% recurred locally. However, complications of this regimen were frequent with 23% requiring re-operation, prompting modifications of RT dose. A subsequent trial with 17.5 Gy in 3.5 Gy fractions resulted in a higher rate of local failure, so the investigators ultimately settled on 28 Gy in 3.5 Gy daily fractions(14). The protocol was also modified to include intravenous administration of doxorubicin in place of intra-arterial, based on a randomized comparison that showed equivalent efficacy(16). More recently, ifosfamide was added to the regimen, resulting in higher tumor necrosis rates and better overall survival rates. The 5-year survival was 77% with a regimen containing ifosfamide, compared to 64% without(14).

Another modern chemo/RT regimen employs MAID (mesna, doxorubicin, ifosfamide and dacarbazine) sandwiched sequentially around split-course standard-fractionation RT. A pilot study with this regimen yielded favorable outcomes and was reported by DeLaney and co-workers from Massachusetts General Hospital(18). This regimen was subsequently transitioned into a multi-institutional cooperative trial (RTOG 9514) which demonstrated high rates of limb-sparing (92%) and favorable rates of overall survival and local control(19).

The multidisciplinary sarcoma group at University of Chicago has developed several uniquely modified versions of the Eilber regimen that involve hypo-fractionated RT given with sequential and concurrent chemotherapy. An earlier such regimen was evaluated in a phase II multi-institutional trial involving 25 patients(20). A subsequent version of this regimen has since been our standard practice in patients who are marginal candidates for limb-preserving surgery. This regimen yields high rates of treatment-induced necrosis, limb preservation, and local control. Additionally, we find that the treatment-induced tumor necrosis rate is significantly prognostic in terms of freedom from subsequent distant metastasis.

Methods and Materials

A retrospective review was performed on adult patients with a diagnosis of soft tissue sarcoma treated at the University of Chicago Hospitals between 1995 and 2008. A protocol detailing this analysis was approved by the University of Chicago Institutional Review Board (IRB) and the Cancer Clinical Trials Review Committee of the University of Chicago Cancer Center. Individual consent was waived by our IRB because of the retrospective nature of this study. For inclusion, subjects were required to have locally advanced soft tissue sarcomas deep to the fascia of an extremity or limb, treated with preoperative chemo/RT. Patients with limited metastases were also eligible for chemo/RT, consistent with published practices of other institutions (15,17,21). Pathologic diagnosis and grading was reviewed by a single pathologist (AGM). The staging workup included MRI of the primary tumor, chest CT, cell blood count and metabolic serum profile in all patients.

All patients received preoperative hypofractionated external beam RT to a dose of 28 Gy in 3.5 Gy daily fractions, delivered with concurrent ifosfamide ($2.5 \text{ g/m}^2/\text{day} \times 5 \text{ days}$). RT was delivered with a megavoltage linear accelerator with conventional beam arrangements, using custom immobilization and 3-dimensional treatment planning. Most treatment plans consisted of two parallel-opposed or tangential beams. IMRT was not used. RT dose was prescribed to an isodose line that encompassed the entire tumor plus margin. This RT margin was typically 5 cm (proximal and distal) but varied between patients and was tailored to the specific patient/tumor anatomy, in order to maximize coverage of potential microscopic disease while minimizing toxicity. Patients also received two cycles of preoperative chemotherapy, one cycle 21 days before and one 21 days after day #1 of concurrent chemo/RT. These two cycles consisted of various regimens including ifosfamide

+ doxorubicin (2.5 g/m²/day and 20 mg/m²/day × 3 days), ifosfamide alone (2.8 g/m²/day × 5 days), doxorubicin + cisplatin (30 mg/m²/day × 2 days and 120 mg/m²/day × 1 day), or epirubicin + ifosfamide (30 mg/m²/day and 2.5 g/m²/day × 4 days). In one patient with angiosarcoma this consisted of weekly paclitaxel (80 mg/m²). All chemotherapy was delivered intravenously via a central line.

The interval between the completion of concurrent chemo/RT and surgery was 4–8 weeks for most patients (median 5.8 weeks, range 2.3–11.6). Wide surgical excision was then performed if possible; otherwise, amputation was performed. A single pathologist (AGM) examined the marginal distance and the percentage of necrosis in each tumor specimen. Postoperatively, 47 % patients received additional chemotherapy. For all patients except one, this consisted of 3–6 cycles of ifosfamide + doxorubicin (2.5 g/m²/day and 20 mg/m²/day × 3 days) repeated every 21 days. In one patient with an epithelioid leiomyosarcoma, this consisted of four cycles of doxorubicin and dacarbazine. The decision whether to administer postoperative chemotherapy was at the discretion of the medical oncologist and patient.

The details of treatment, disease control, and toxicity were extracted from clinic charts and hospital electronic medical records. Overall survival data were supplemented by death records in the Social Security Death Index (SSDI). Hematologic toxicity was scored based on the NIH grading system. Median follow-up interval (which includes SSDI-based survival data) was 33.5 months (range, 3–127) and median follow-up based on actual clinic visits was 27 months (range, 3–119).

Data were analyzed with JMP statistical software (SAS, Cary, NC). Actuarial outcomes were calculated using the method of Kaplan and Meier(25) and compared with the log rank test(26). Freedom from distant metastases (FFDM) was based on the appearance of any distant recurrence in living patients (deaths without recurrence were censored at the date of death). Patients with distant metastases at diagnosis were excluded from analysis of FFDM. Patients requiring amputation were excluded from local control analyses, since stump recurrences were defined as distant failures. All intervals were defined as the time between the completion of RT and the event. Prognostic factors were evaluated using the log-rank test for univariate analysis, and factors found to be significant were subsequently re-tested for independent prognostic significance via Cox regression modeling for multivariate analysis.

Results

Thirty-four patients met the inclusion criteria and were entered into this analysis. Patient and tumor characteristics are detailed in Table 1. The majority of the primary tumors were located in the lower extremity. There was a wide range of histologic sarcoma subtypes, however the most common was malignant fibrous histiocytoma. Median tumor size at presentation based on maximum radiographic dimension was 10.5 cm (range 5.5–20 cm.), and most tumors were grade 3. Six patients had metastases at the time of diagnosis. Four of the six had lung metastases, one of whom had additional mediastinal metastases. Two patients had metastatic disease based only on involvement of regional lymph nodes.

Treatment and post-therapy pathologic findings are detailed in Table 2. Most patients were considered marginal candidates for limb salvage surgery at time of diagnosis. Ultimately, 29 patients (85.3%) were able to undergo wide local excision of the tumor after chemo/RT; the other 5 were deemed unresectable and required amputation. Upon pathologic examination, all of the specimens showed negative surgical margins; however 14 showed tumor within ≤5 mm of the margin. 17 specimens (50%) showed treatment-induced tumor necrosis of ≥90%, and 4 (11.8%) of these showed a complete absence of viable-appearing tumor cells. Necrosis

rates did not differ significantly based on the types of preoperative chemotherapy drugs that were used (in addition to the concomitant ifosfamide/RT that all patients received). Also, the frequency of high treatment-induced necrosis ($\geq 90\%$) was similar in the 4 patients with distant metastases at diagnosis, compared with the patients with localized disease at diagnosis.

During preoperative chemo/RT, all patients experienced some degree of hematologic toxicity (8.8% grade 2, 38.2% grade 3, 52.9% grade 4), and most had mild to moderate transient RT-related dermatitis. Of the patient who underwent local excision, five patients (17.2%) experienced local complication that required reoperation. Two of these procedures involved wound debridement with flap revision, and two involved hematoma drainage (one infected) with flap revision. All reoperations occurred within six weeks of tumor resection, except for one which occurred 4.5 months after the primary surgery to release contracture of quadriceps muscles. Four patients (13.8%) experienced symptomatic fibrosis, and five (17.2%) experienced lymphedema. One patient who had received RT to the right hip experienced an 'in-field' femoral neck fracture 10 months after RT.

Two of 29 patients who underwent wide local excision experienced a local recurrence, for an actuarial 5-year local control rate of 89.0% (Table 3). One of these two patients had presented with a 12-cm high-grade thigh leiomyosarcoma that recurred along the sciatic nerve 30 months after her initial resection. The second patient had a 20-cm high-grade node-positive liposarcoma of the thigh that first recurred below the knee (outside the irradiated volume) and then subsequently failed within the original irradiated tumor bed 12 months after her initial resection. An analysis of potential prognostic factors within this limb-sparing surgery subgroup found no significant associations between local control and the following variables: surgical margin distance (≤ 5 vs. > 5 mm), tumor size ($>$ vs. ≤ 12 cm), interval between RT and surgery ($<$ vs. ≥ 5.8 weeks), and percent treatment-induced necrosis ($<$ vs. $\geq 90\%$). There were, however, interesting trends observed: no patient with $\geq 90\%$ necrosis experienced a local failure and no patient with tumor size < 12 cm experienced a local failure.

The actuarial survival rate for all patients in this study was 42.3% at 5 years. Figure 1 shows the survival and freedom from distant metastasis (FFDM) for patients with stage III disease at diagnosis; actuarial 5-year survival and FFDM for this subgroup were 45.2% and 53.4%, respectively (Table 3). An analysis of potential prognostic factors within this subgroup found a significant association between FFDM and treatment-induced necrosis; FFDM was better in those with $\geq 90\%$ treatment-induced tumor necrosis (84.6% vs. 19.9%, $p=0.02$), compared to those with less necrosis (Figure 2A). Two factors were significantly associated with better survival in this subgroup: surgical margins > 5 mm after limb sparing surgery (61.9% vs. 0%, $p = 0.02$) and short (< 5.8 week) interval between RT and surgery (80.0% vs. 28.8%, $p = 0.02$); of these two significant factors, only the interval between chemo/RT and surgery maintained significance on multivariate analysis (RR 5.34, $p=0.013$). Additionally, patients with $\geq 90\%$ treatment-induced tumor necrosis showed a trend toward improved survival (67.3% vs. 26.9%, $p = 0.09$), compared to those with less necrosis (Figure 2B).

Local control, DFDM, and survival rates did not differ significantly based on the types of preoperative chemotherapy drugs that were used (in addition to the concomitant ifosfamide/RT that all patients received). In terms of postoperative adjuvant chemotherapy, its administration or lack thereof led to no detectable differences in terms of any of the outcome endpoints.

Discussion

Our results demonstrate that this regimen of concurrent chemotherapy and rapidly-delivered radiation prior to surgery for locally advanced soft tissue sarcomas is well-tolerated and allows a high rate of limb-preservation (85.3% in this series). Local control after limb-sparing surgery was excellent. Despite this, the prognosis of this patient group remains poor overall, with 5-year survival rates of only 42.3% for all patients and 45.2% for patients presenting with localized disease. This was due largely to development of disseminated disease; only 53.4% of patients presenting with localized disease remained free of distant metastases at 5 years.

The superiority of chemo/RT over RT in the preoperative setting has not yet been demonstrated in a randomized fashion. The few published trials that report on histological response following standard RT suggest relatively low rates of treatment-induced necrosis. For example, Choong and co-workers observed >80% necrosis in only 15 of 38 (39%) tumors after 50.4 Gy in 1.8 Gy daily fractions (27). DeLaney and coworker performed a comparison of pre-operative chemo/RT patients (MAID-based regimen) against historical patients treated with RT, with or without sequential adjuvant chemotherapy (18). They noted substantially better outcomes in the chemo/RT group in terms of survival (87% vs. 58%), disease-free survival (70% vs. 42%) and metastasis-free survival (75% vs. 44%) at 5 years. This study suggests an advantage to chemo/RT but is limited by the potential biases inherent to retrospective analyses.

The degree of treatment-induced necrosis was a major prognostic factor after induction therapy with our chemo/RT regimen. Eilber and coworkers similarly demonstrated improved outcomes associated with near-complete necrosis rates; 5-year survival rates were 80% vs. 62%, $p=0.001$ (14). We hypothesize that a high rate of primary tumor necrosis is indicative of treatment-responsive tumor biology, and thereby predicts the likelihood that systemic treatment can eradicate sub-clinical micrometastases. This is supported by our finding of superior 5-year FFDM in patients with a high rate ($\geq 90\%$) of necrosis (84.6% vs. 19.9%, $p=0.02$). This reveals an additional potential advantage of neoadjuvant chemo/RT over RT alone: local pathologic response may identify patients with treatment-sensitive tumor biology, and thus might allow for better tailoring of adjuvant systemic therapies in the postoperative period.

A potential disadvantage of induction chemo/RT compared to RT is the greater risk of toxicity. In the DeLaney matched cohort study, wound complications requiring intervention occurred relatively frequently (29%) after MAID-based chemo/RT (18). Interestingly, however, when the MAID regimen was used in a multi-institutional cooperative trial, the reported wound complication rate was only 11% (19). We also report a reasonably low rate of wound complications after limb-preserving surgery with our regimen (17.2%). These rates seem to be acceptable, given that wound complication rates of 25–35% have been reported following treatment with pre-op RT alone (8,28).

There are several notable differences between our induction regimen and the MAID-based regimen used in RTOG 9514. The MAID-based regimen uses sequential administration of chemotherapy and RT, while ours employs concurrent and sequential. Furthermore, the RT in the MAID-based regimen is a split-course schedule with standard sized 2 Gy fractions, whereas ours uses a continuous course of hypofractionated therapy (3.5 Gy/day) delivered over a very short time period. Based on these differences, one might predict a greater tumoricidal effect with our regimen based on basic radiobiological principles (29). It is, however, difficult to compare results across studies given the differences in patient populations (Table 3). For example, 94% of our patients had grade 3 tumors, while only

80% of tumors on RTOG 9514 were grade 3. Despite these differences, our patients presenting with localized disease experienced 3-year rates of local recurrence and death (11% and 29%) that are comparable to those from RTOG9514 (10%, and 25%)(19). Another potential advantage of our regimen relates to toxicity. The MAID-based regimen is fairly intensive, with 83% of patients experiencing grade 4 hematological toxicity and an additional 5% suffering treatment-related mortality in RTOG9514 (19). When thalidomide was added to this MAID-based regimen, toxicity additionally included a 40% risk of thromboembolic events (30). In our series, we did observe some expected toxicities related to the irradiated extremity, however only 53% of our patients experienced grade 4 hematologic toxicity and we encountered no treatment-related deaths.

A regimen similar to ours was reported by investigators at University of Calgary(21). It involved a somewhat hypofractionated RT schedule (30 Gy in 3 Gy fractions), in which RT sequentially follows doxorubicin (30 mg/day for 3 days). Again, it is difficult to directly compare their results with our own because of differences in patient populations; only 48% of the tumors in that study were grade 3 and about a third of them measured <5 cm. This regimen yielded a high rate of limb-salvage (95%) in this favorable population, however 4 of the 71 patients (5.6%) who underwent limb-preserving surgery had positive surgical margins and three of them subsequently failed locally. Overall, we believe that these results support the use of Eilber-like RT schedules that utilize relatively large fraction sizes. It remains unclear, however, whether the Calgary regimen might have benefited from the addition of concomitant chemotherapy, thereby better exploiting radiosensitization and maximizing local tumor responses.

There are some limitations of this study that should be mentioned. First, locally advanced soft tissue sarcomas are rare, and this is reflected in our relatively small sample size. Second, the nature of this analysis carries the common limitations inherent to retrospective studies including the potential for selection bias.

Our results demonstrate that this well-tolerated preoperative approach yields excellent rates of limb-preservation and local control for patients with locally advanced soft tissue sarcomas. Despite the excellent local responses, however, distant failure continues to be a major challenge with high-grade disease. Using this regimen, we find that the rate of treatment-induced tumor necrosis is a strong predictor for future distant metastatic risk. This may present an important opportunity for tailoring subsequent systemic interventions. Further research is still needed to determine which regimen is optimal in promoting limb preservation, minimizing complications, and preventing dissemination of soft tissue sarcomas.

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Figure 1.
Actuarial survival and freedom from distant metastasis in patients with localized disease at time of diagnosis.

Figure 2.
Actuarial survival (**A**) and freedom from distant metastasis (**B**) based on treatment-induced necrosis rates.

Table 1

Patient and Tumor Characteristics		Number (percent)
Age	median 56.5 (range 22–76)	
Gender	Female	20 (58.8)
	Male	14 (41.1)
Histology	Malignant fibrous histiocytoma	10 (29.4)
	Synovial cell sarcoma	4 (11.8)
	Pleomorphic (NOS)	3 (8.8)
	Fibrosarcoma	3 (8.8)
	Malig. peripheral nerve sheath	3 (8.8)
	Spindle cell	3 (8.8)
	Extraskeletal chondrosarcoma	3 (8.8)
	Leiomyosarcoma	2 (5.9)
	Liposarcoma	1 (2.9)
	Clear cell sarcoma	1 (2.9)
	Angiosarcoma	1 (2.9)
Stage	III	28 (82.4)
	IV	6 (17.6)
Grade	High	32 (94.1)
	Intermediate	2 (5.9)
	Low	0 (0)
Depth	Superficial	0 (0)
	Deep	34 (100)
Size (greatest dim)	<120 mm	22 (64.7)
	≥120 mm	12 (32.3)
Primary Location	Lower extremity:	
	Thigh	24 (70.1)
	Distal lower extremity	3 (8.8)
	Knee	1 (2.9)
	Lower extremity girdle	1 (2.9)
	Upper extremity:	
	Proximal arm	2 (5.9)
	Elbow	2 (5.9)
	Upper extremity girdle	1 (2.9)

Table 2

Treatment and pathologic response		Number (percent)
Pre-op therapy:		
Concurrent chemo/RT	Ifos/28 Gy	34 (100)
Sequential chemo regimen	Dox/Ifos	19 (55.9)
	Ifos	3 (8.8)
	Dox/CDDP	8 (23.5)
	Epi/Ifos	3 (8.8)
	Paclitaxel	1 (2.9)
Post-op chemo administered	yes	16 (47)
	no	18 (52.9)
Resection type	Local excision	29 (85.3)
	Amputation	5 (14.7)
Interval between completion of RT and resection	< 5.8 weeks	20 (58.8)
	≥5.8 weeks	14 (41.2)
Surgical margin distance	Positive	0 (0)
	≤5 mm	14 (41.2)
	>5 mm	20 (58.8)
Treatment-induced necrosis	<50%	9 (26.5)
	50–89%	8 (23.5)
	≥90%	17 (50)

Dox=doxorubicin, Ifos=ifosfamide, CDDP=cisplatin, Epi=epirubicin

Table 3

Study	% with Grade 3	% with high necrosis in pathology (definition of high)	Amputations	Local recurrence rate (time point)	Survival (time point)
Eilber <i>et. al.</i> (14)	80	52 ($\geq 95\%$)	excluded	11% (5-yr)	71% (5-yr)
Delaney <i>et. al.</i> (18)	48	30 ($\geq 99\%$)	6%	8% (5 yr)	87% (5-yr)
Mack <i>et. al.</i> (21)	48	not stated	5%	10% (5-yr)	63% (5-yr)
Kraybill <i>et. al.</i> (19)	80	65 ($\geq 75\%$)	8%	10% (3-yr)	75% (3-yr)
Ryan <i>et. al.</i> (20)	88	40 ($\geq 95\%$)	12%	12% (2-yr)	84% (2-yr)
Current study	94	50 ($\geq 90\%$)	15%	4% (2-yr) 8% (3-yr) 11% (5-yr)	83% (2-yr) [*] 71% (3-yr) [*] 45% (5-yr) [*]

* excluding patients with metastatic disease at diagnosis