Risk Factors for Significant Wound Complications Following Wide Resection of Extremity Soft Tissue Sarcomas

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Abstract

Background Wound complications following resection of a localized soft tissue sarcoma have been associated with lower extremity location, large tumor volume, and use of preoperative radiation. Some of these wounds, however, show the potential for healing with local wound care and nonsurgical techniques. We are unaware of any published data establishing factors associated with nonhealing wounds that ultimately are treated with local or free vascularized tissue transfer.

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Questions/purposes The purpose of this study was to determine the variables associated with development of a significant wound complication defined as one that underwent a secondary procedure using local or free tissue transfer after resection of a localized soft tissue sarcoma. **Methods** Using our institution's cancer center database, we identified 140 patients who underwent resection of a localized extremity soft tissue sarcoma at our institution between 1997 and 2010. Thirty-two patients were excluded who underwent immediate planned vascularized tissue transfer, along with 26 patients who did not receive radiation, and an additional three patients were excluded who were followed for less than 1 month. This left 79 patients, including 18 treated with postoperative external beam radiotherapy and 61 with preoperative external beam radiotherapy. Of patients receiving radiation treatment before surgery, 13 received no additional radiation treatment, 33 underwent intraoperative radiation with electrons (IOERT) to sites considered at high risk for local recurrence, and an additional 15 had perioperative brachytherapy. Univariate and multiple regression analyses were performed using frequency of local or free tissue transfer at 3 weeks or greater postoperatively owing to wound-related complications as a dependent variable.

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Results Lower extremity location and vascular involvement were associated with use of delayed vascularized tissue coverage for wound-healing problems. Patients in this series who underwent preoperative external beam radiotherapy coupled with dose-escalated IOERT or chemotherapy had a similar rate of flap use compared with patients treated with postoperative radiation.

Conclusions Patients with tumors of the lower extremity involving major neurovascular structures and for whom radiation therapy is planned should be counseled specifically because they appear to be at increased risk for use of delayed local or free vascularized tissue transfer for a nonhealing wound following resection of a localized extremity soft tissue sarcoma.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

Approximately 10,000 patients per year in the United States are diagnosed with a soft tissue sarcoma, representing approximately 1% of all adult malignancies [12]. In the past, amputation routinely was recommended because of unacceptably high local recurrence rates associated with local excision. The combined effects of adjuvant multimodal therapy, improved imaging, and better surgical techniques have made limb salvage the standard treatment for the majority of localized soft tissue sarcomas.

Debate exists regarding the optimal timing, dose, and delivery method of radiation therapy in the treatment of localized sarcoma [7, 15]. External beam radiotherapy (EBRT) can be given preoperatively, postoperatively, or in combination. Interstitial brachytherapy has been used as a primary adjuvant therapy or in combination with preoperative or postoperative EBRT. Intraoperative radiation therapy (IORT) is an alternative method to achieve targeted dose escalation while at the same time minimizing toxicity to normal tissue [2, 10, 13]. This technique, when combined with preoperative or postoperative EBRT, may improve local control and overall survival in many disease sites [17].

Preoperative EBRT has several potential advantages over postoperative EBRT for patients with extremity soft tissue sarcoma. This includes a decrease in the volume of irradiation fields and EBRT dose, improved tissue oxygenation, and alteration in the implantability of cells that may be spread at the time of marginal resection. However, preoperative therapy may increase the risk of postoperative wound complications. Several well-designed retrospective and prospective studies document the increased incidence of

wound breakdown and need for repeat surgery attributed to preoperative EBRT [4, 14–16]. Despite the concern over wound complications, our practice has strongly favored a preoperative approach. A recent analysis of our experience [5] confirmed an increased risk of wound complications after neoadjuvant therapy, including a possible contribution from the addition of concurrent chemoradiotherapy, the use of which is controversial for localized sarcomas [5]. Therefore, given the limited data available, we sought to better determine factors that may be identified preoperatively that predispose patients to significant wound-healing complications, with attention to those that ultimately require vascularized tissue transfer. In particular, we asked whether radiation timing, dose escalation, or the use of chemotherapy increase the risk of wound healing complications ultimately treated with vascularized local or free tissue transfer.

Patients and Methods

After obtaining approval from our institutional review board, we identified 140 patients who underwent resection of a biopsy-proven localized extremity soft tissue sarcoma at our institution between 1997 and 2010 (Table 1). Patients were followed postoperatively for an average of 44 months (range, 1–149 months). Thirty-two patients were excluded who underwent immediate planned vascularized tissue transfer owing to the surgeon's preoperative anticipation of a significant soft tissue defect that would make primary closure difficult or impossible. An additional 26 patients who did not receive radiation were excluded, along with three patients who were followed for less than 1 month. This left 79 patients available for study. Twenty-five patients (32%) had surgery or unplanned tumor excision before initial presentation at our institution. Seven of these patients underwent reresection followed by adjuvant radiation, while the remaining patients were treated with a neoadjuvant radiation dose before definitive resection.

Eighteen patients underwent wide resection followed by postoperative EBRT. The remaining 61 patients received EBRT before the definitive oncologic resection. Of patients receiving radiation treatment before surgery, 13 received no additional radiation treatment, 33 underwent IORT with electrons (IOERT) to sites considered at high risk for local recurrence, and an additional 15 had catheters inserted after resection for subsequent perioperative brachytherapy. IOERT was administered using a Mobetron linear accelerator (IntraOp Medical Corp, Sunnyvale, CA, USA) in varying doses (median, 12.5 Gy; range, 10–15 Gy) using 6- to 9-MeV electrons. Patients who underwent IOERT and brachytherapy were those thought to be at high risk for local recurrence owing to the proximity to major neurovascular structures.

Table 1. Patient demographics

Variable	Value (mean)
Age	
Mean	58.4
Range	17–88
Sex	
Male	31
Female	48
Diagnosis (n = 140)	
Fibromyxosarcoma	14
Malignant fibrous histiocytoma	11
High-grade sarcoma NOS	8
Myxoid liposarcoma	7
Synovial sarcoma	7
Leiomyosarcoma	6
Pleomorphic liposarcoma	6
Well-differentiated liposarcoma	4
Round cell liposarcoma	4
Epithelioid sarcoma	2
Extraskeletal myxoid chondrosarcoma	2
Malignant peripheral nerve sheath tumor	2
Epithelioid leiomyosarcoma	1
Desmoid	1
Clear cell sarcoma	1
Extraskeletal osteosarcoma	1
Giant cell rich osteosarcoma	1
Fibrosarcoma	1
Tumor size (cm ³)	
Mean	1371.9
Range	5.4– 6240.0
Tumor location	
Lower extremity	67
Neurovascular involvement	16
Radiation type	
Preoperative only	13
Preoperative and intraoperative	33
Preoperative and brachytherapy	15
Postoperative only	18

NOS = not otherwise specified.

Charts were reviewed retrospectively and no patients were recalled specifically for the purposes of this study. Data collected included patient age, sex, pathologic diagnosis, resected specimen size, timing and type of radiation, tumor location (upper or lower extremity), involvement of major neurovascular structures, and history of prior unplanned surgery. Tumor volume was determined by measurements provided in the pathology report regarding the resected specimen size. Vascular involvement was considered significant if the preoperative MR images

Fig. 1A–D (A) A photograph shows a localized high-grade sarcoma of the left groin after neoadjuvant radiation. (B) Preoperative MRI reveals a large centrally necrotic soft tissue mass protruding through the skin, and abutting the left femoral artery. (C) An intraoperative photograph after wide resection with intraoperative radiation (IOERT) is shown. (D) Immediate reconstruction using a vertical rectus fasciocutaneous flap was performed.

showed a major neurovascular bundle encased by or closely associated with the tumor (Fig. 1).

Univariate and multiple regression analyses were performed using frequency of local or free tissue transfer at 3 weeks or greater postoperatively owing to wound-related complications as dependent variables. Local or free vascularized tissue transfer was recommended if the wound showed no healing potential at 3 weeks postoperatively despite local surgical or nonsurgical wound care. Fifteen patients were treated with a local rotational flap, and three patients with a vascularized free flap. All flaps were viable and wounds successfully healed at the most recent followup.

Descriptive statistics were used to summarize the demographic and clinical characteristics. The outcome of interest was wound complication that underwent delayed flap coverage, and was a dichotomous outcome. To assess the factors associated with the outcome, a two-step model selection procedure was performed. First, the univariate analysis was applied. If a variable with a p value less than 0.30 was found, it was considered in the multivariate model selection step. The final model with the best set of factors associated with the outcome was determined by the backward elimination

procedure and the variable remained in the model if the *p* value was less than 0.30. The unadjusted odds ratio (OR) from the univariate model and the adjusted OR for the multivariate model, 95% CI, and the *p* values were reported. Using a two-sided test, a *p* value less than 0.05 was considered statistically significant. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Eighteen patients (22.8%) ultimately underwent delayed vascularized flap coverage after the index resection following

multiple attempts at surgical or nonsurgical local wound care. All delayed flaps were performed for tumors involving the lower extremity (Table 2), thus we were not able to perform univariate logistic regression analysis for this variable.

Among all patients (*n* = 79), vascular involvement was the single statistically significant risk factor for a patient being treated with delayed vascularized tissue coverage (OR, 3.6; 95% CI, 1.1–12.4) (Table 3). Compared with postoperative radiation, brachytherapy showed the largest OR of wound complication (OR, 5.06; 95% CI, 0.8–31.7). Preoperative radiation therapy alone had an OR of 1.37 (95% CI, 0.2–11.7), while preoperative radiation therapy coupled with IOERT had an OR of 2.07 (95% CI, 0.4–11.5).

Table 2. Descriptive statistics for wound complications requiring a delayed flap

Variable	No (N = 61)	Yes (N = 18)	Total (N = 79)	<i>p</i> value
Prior resection				0.8609*
No	42 (68.9%)	12 (66.7%)	54 (68.4%)	
Yes	19 (31.1%)	6 (33.3%)	25 (31.6%)	
Lower extremity				0.0410*
No	12 (19.7%)	0 (0.0%)	12 (15.2%)	
Yes	49 (80.3%)	18 (100.0%)	67 (84.8%)	
Vascular involvement				0.0252*
No	52 (85.2%)	11 (61.1%)	63 (79.7%)	
Yes	9 (14.8%)	7 (38.9%)	16 (20.3%)	
Tumor size (cm ³)				0.1030 [†]
Number	61	18	79	
Mean (SD)	1237.1 (1495.4)	1828.7 (1908.6)	1371.9 (1605.2)	
Median	393.8	1180.0	686.4	
Q1, Q3	180.0, 1900.0	607.5, 2028.0	185.6, 2028.0	
Range	(5.4–5292.0)	(50.2–6240.0)	(5.4–6240.0)	
Radiation				0.2246*
Preoperative	11 (18.0%)	2 (11.1%)	13 (16.5%)	
Preoperative + IOERT	25 (41.0%)	8 (44.4%)	33 (41.8%)	
Preoperative + brachytherapy	9 (14.8%)	6 (33.3%)	15 (19.0%)	
Postoperative	16 (26.2%)	2 (11.1%)	18 (22.8%)	
Chemotherapy				0.4384*
No	40 (65.6%)	10 (55.6%)	50 (63.3%)	
Yes	21 (34.4%)	8 (44.4%)	29 (36.7%)	
Age at diagnosis				0.4542 [†]
Number	61	18	79	
Mean (SD)	57.5 (18.8)	61.3 (16.8)	58.4 (18.3)	
Median	57.0	66.5	63.0	
Q1, Q3	43.0, 73.0	50.0, 72.0	43.0, 73.0	
Range	(17.0–88.0)	(23.0–82.0)	(17.0–88.0)	
Male				0.5592*
Female	36 (59.0%)	12 (66.7%)	48 (60.8%)	
Male	25 (41.0%)	6 (33.3%)	31 (39.2%)	

IOERT = intraoperative radiation therapy with electrons; Q1 = first quartile; Q3 = third quartile; * chi-square; [†]Wilcoxon rank sum.

Table 3. Logistic regression model

Variable	Unit/comparison	Univariate analysis				Multivariate analysis			
		Unadjusted OR	95% CI		p value	Adjusted OR	95% CI		p value
Prior resection	Yes versus no	1.11	0.36	3.39	0.8609				
Vascular involvement	Yes versus no	3.68	1.13	12.00	0.0309	3.60	1.05	12.40	0.0424
Radiation type and timing	Preoperative/brachytherapy versus postoperative alone;	5.33	0.89	32.15	0.0578	5.06	0.81	31.71	0.0835
	Preoperative alone versus postoperative alone;	1.46	0.18	11.94	0.5535	1.37	0.16	11.71	0.7744
	Preoperative/IOERT versus postoperative alone	2.56	0.48	13.62	0.6515	2.07	0.37	11.51	0.4081
Chemotherapy	Yes versus no	1.52	0.52	4.44	0.4400				
Age at diagnosis	Per 10 years older	1.13	0.83	1.52	0.4420				
Gender	Female versus male	1.39	0.46	4.19	0.5601				
Tumor size (cm ³)	Per 1000 cm ³ increase	1.24	0.91	1.68	0.1749				

OR = odds ratio; IOERT = intraoperative radiation therapy with electrons; * the estimate for lower extremity does not exist owing to small sample size.

History of prior resection, use of chemotherapy, age at diagnosis, and tumor volume did not show a statistically significant association with use of delayed vascularized tissue transfer.

Discussion

Radiation and chemotherapy are believed to inhibit wound healing presumably by prevention of collagen synthesis [6, 8]. Preoperative EBRT combined with IOERT increases the efficacy of radiation to the tumor bed, while ostensibly limiting morbidity to surrounding normal tissue, thus potentially minimizing the long-term adverse effects of radiation treatment [2, 10, 13]. Previous studies have focused largely on the timing of radiation as the main predictor of wound-healing problems after tumor resection [7, 15]. Preoperative radiation, particularly in the lower extremity, has been cited as a risk factor for significant wound complications [3–5, 15]. We sought to more specifically determine the factors associated with use of delayed vascularized tissue transfer for nonhealing wounds following resection of a localized extremity sarcoma.

There are numerous significant limitations of our study. The data presented may be underpowered to detect a significant association of one of the variables with use of delayed flap coverage, thus it is important to avoid drawing definitive conclusions from the limited sample size. However, soft tissue sarcomas are rare, and the ability to study the variables associated with complications related to their treatment is challenging. We have limited our conclusions to those that are statistically significant and point out trends to

the reader that are likely to be of clinical significance. No patients in our series underwent amputation as a primary treatment. Although there perhaps is a trend toward increased use of delayed flap coverage with IOERT and brachytherapy, these modalities typically are used for patients in whom amputation is likely a viable alternative, thus perhaps creating an inequitable comparison to patients who underwent preoperative or postoperative radiation alone. Again, the rarity of these cases makes it difficult to amass a large enough series to control for this difference. Longer-term followup and accumulation of more patients for study might clarify whether a difference exists among the various radiation types presented. An additional limitation is the potential for selection bias, particularly with respect to radiation type and timing, and for the indications for delayed flap coverage. As noted previously, patients who underwent intraoperative boost therapy were those who were thought to be at high risk for local recurrence, typically owing to the proximity to major neurovascular structures. We attempted to analyze neurovascular involvement as a separate variable from radiation type or timing to account for this potential confounder. We also excluded patients who were thought to need a flap at the initial resection owing to the surgeon's preoperative anticipation of significant soft tissue defects that would make primary closure difficult if not impossible. Eliminating this type of selection bias would be difficult even in a prospective study, as it would be unethical in some cases to randomize patients to treatment arms when the surgeon anticipates a complication that could be avoided. Finally, intraoperative radiation is a technology that requires significant investment of human resources and capital, thus the data presented here may not be generalizable to other centers

that treat patients with localized extremity sarcomas and do not have access to this technology.

O'Sullivan et al. [15] conducted one of the most frequently cited studies documenting the association between preoperative radiation and local wound complications. In a randomized study of 190 patients with a localized extremity sarcoma, they reported an 18% increase in wound complications among patients treated with preoperative radiation, although little information was provided in terms of morbidity associated with the particular wounds. Although overall wound complications (35% versus 17%) and reoperations (45% versus 31%) were more common in the preoperatively radiated group, a larger percentage of patients with wound complications in the postoperative radiation group required other invasive procedures (16% versus 25%) or deep wound packing (35% versus 44%). In a followup study from Davis et al. [7], patients in the postoperative radiation group were noted to have a higher incidence of radiation-induced fibrosis, joint stiffness, and lower functional scores.

More recently, some authors have focused attention to perioperative boost technique as a possible explanation for significant wound complications after tumor resection. Devisetty et al. [9] reviewed the results of 1765 patients with localized soft tissue sarcoma, treated at Massachusetts General Hospital, with low-dose (median, 20 Gy) neoadjuvant radiation. They found a strong correlation between brachytherapy and severe acute wound complications and a relatively smaller effect of either EBRT or IORT. Similarly, in a retrospective review of 27 patients, Kunos et al. [13] found that IORT after preoperative radiation did not confer a higher risk of immediate or delayed wound complications. Similar to previous studies, we found that use of delayed flap coverage was strongly associated with tumors involving major neurovascular structures, and that all of the nonhealing wounds were in tumors of the lower extremity [1, 11].

Patients with lower extremity sarcomas with vascular involvement and for whom radiation is planned should be considered for immediate simultaneous vascularized tissue transfer, regardless of radiation timing. Longer followup and accumulation of a larger data set would help to clarify whether this particular outcome is associated with radiation type or timing.

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