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Extremity Soft Tissue Sarcoma Resections

How Wide Do You Need to Be?

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Abstract

Background Sarcomas require a wide margin of resection including a cuff of normal tissue to minimize the risk of local recurrence. The amount of tissue that constitutes a wide margin is unclear in the literature.

Questions/purposes We therefore determined whether a close resection margin for soft tissue sarcoma resulted in an increased incidence of locally recurrent disease and whether additional factors, including radiation therapy, outside biopsies, and tumor biology, affected the risk of local recurrence.

Methods We retrospectively reviewed 117 patients with soft tissue sarcomas resected with negative margins from 2001 to 2007. Gross specimens were inked and the closest macroscopic margins were sent for microscopic examination. Resection margins were categorized as less than 1 mm, 1–5 mm, or greater than 5 mm. We evaluated additional factors that might influence local recurrence, including radiation therapy, outside biopsies, sarcoma type, grade, and stage at presentation, and development of metastatic disease.

Results Four of 117 patients (3.4%) developed local recurrence. The incidence of local recurrence was similar in patients with less than 1-mm margins and greater than 1-mm margins: two of 45 patients (4.4%) and two of 64 patients (3.1%), respectively. Due to the low number of local recurrences, quantitative margin extent and the other factors evaluated did not affect local recurrence.

Conclusions The extent of a margin necessary to prevent local recurrence of soft tissue sarcoma remains unclear as the power of our study was limited by the low number of local recurrences. Relatively low local recurrence rates can be achieved even with close margins.

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

Introduction

Soft tissue sarcomas of the extremities are a heterogeneous group of neoplasms that arise from mesenchymal tissue and represent approximately 1% of all cancers [7, 13, 19]. Soft tissue sarcomas require a wide surgical resection margin consisting of the pseudocapsule and a cuff of normal tissue around the tumor to minimize the risk for local recurrence [19, 22, 24, 26]. Positive resection margins reportedly increase the risk of local recurrence [4, 19, 22–26]. Controversy exists as to the amount of the surrounding normal tissue that constitutes an adequate negative margin [2, 3, 10, 11, 13–17] to prevent local recurrence. The issue of what constitutes an adequate margin is complicated by the question of the relative importance of qualitative versus quantitative margin. Investigators have attempted to assign

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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quantitative values to various qualitative tissue planes in an effort to determine the appropriate clinical resection guidelines [10–12]. Few authors have looked specifically at the relationship between close but negative margins and local recurrence [2, 8, 14, 16, 18, 19, 21]. Evaluation of the literature is complicated by varying inclusion and exclusion criteria and numerous confounders. Guidelines regarding the quantitative amount of tissue required for an adequate surgical margin is lacking in the literature. The primary surgeon and multidisciplinary team are left to determine the benefits of limb salvage with functional preservation and a potentially close margin versus a wider ablative margin.

Our primary purpose was to determine whether a narrow quantitative margin places patients at increased risk for local recurrence. A secondary aim was to determine whether additional factors, including radiation therapy, outside biopsies, sarcoma type, grade, and stage at presentation, and development of metastatic disease, affected the risk of local recurrence in this patient population.

Patients and Methods

A retrospective review of our prospective database identified 177 patients operated on with intent of a wide resection for soft tissue sarcoma from 2001 to 2007. We included (1) patients with soft tissue sarcoma of any stage and grade, (2) patients without and with radiation therapy or chemotherapy, and (3) patients who were biopsied or had incomplete excisions at an outside hospital and underwent wide reexcision at our institution. We excluded 16 patients younger than 18 years of age, two patients with intraabdominal extension of tumor, two patients who underwent amputation, seven patients with well-differentiated liposarcomas, five patients who were operated on for metastatic lesions to the extremity, and 11 patients who were operated on for a local recurrence after a remote tumor resection at an outside facility; we excluded 11 patients with positive resection margins as the literature suggests local recurrence risk for this patient population is increased [10, 19, 24–26]; and we excluded six patients with negative margins described in the pathology report as "completely excised" since the quantitative margin extent was unknown. These 60 exclusions left 117 patients for the study population. Followup ranged from 1 to 118 months (median, 44 months; mean, 45 months). Fourteen patients (12%) were lost to followup at a median time of 40 months (mean, 32 months; range, 1–96 months). Thirty-four patients (29%) died, of which 27 died of disease (23%). No patients were recalled specifically for this study; all data were obtained from medical records and radiographs. IRB approval was obtained from the institution before initiation of the investigation.

All patients were discussed at the multidisciplinary musculoskeletal oncology tumor board where a decision was made regarding chemotherapy, radiation, and surgery. Patients with greater than 5-cm, deep, high-grade tumors without major comorbidities were offered neoadjuvant chemotherapy and radiation therapy followed by wide surgical resection. Patients with less than 3-cm superficial sarcomas were generally resected without additional therapy, and all other patients were encouraged to have preoperative radiation therapy followed by wide surgical resection.

The institutional protocol for the handling of specimens was consistent throughout the study period. In the operating room, the tumor specimen was oriented with four different sutures before sending it fresh to the pathology department. In the pathology department, the specimen was handled according to the protocol created by the College of American Pathologists for soft tissue tumors [20]. The specimen was marked with ink. One-centimeter sections were taken throughout the specimen. Areas with the closest proximity of tumor to the ink macroscopically were submitted in cassettes for microscopic examination. The distance of the tumor from the inked margin was reported in centimeters for all margins less than 2 cm. For the purposes of the study, we reviewed pathology reports and documented the closest margin to the tumor. The specimens were not rereviewed by a pathologist. A margin was considered positive if ink was noted on the margin; we excluded 11 patients for this reason as noted above. Negative margins were categorized as less than 1-mm margins (45 patients), 1- to 5-mm margin (38 patients), and greater than 5-mm margin (26 patients). Eight patients had no residual tumor noted in the specimen after neoadjuvant therapy or wide reexcisions after outside incomplete excisions.

The surveillance protocol for soft tissue sarcoma at the institution consisted of a baseline MRI of the local tumor site 6 months after tumor resection in conjunction with a CT of the chest or chest/abdomen/pelvis. Patients with intermediate- and high-grade lesions then had CT and MRI performed every 4 months for 2 years, followed by every 6 months for 3 additional years. Patients greater than 5 years from their resection then had a choice of MRI or physical examination of the local site with posteroanterior/lateral chest radiograph once a year. Patients with low-grade sarcomas were followed with MRI of the local site and chest radiograph or CT of the chest/abdomen/pelvis every 6 months, depending on sarcoma type, for a total of 5 years. After 5 years, patients had a chest radiograph and physical examination or MRI at the patient's discretion.

The primary outcome measured was local recurrence (Table 1). Additional variables extracted from the records included whether the patient received radiation therapy, whether the biopsy was performed on the outside or at the treating institution, followup interval, tumor type

Table 1. Characteristics of patients with recurrent disease

Sarcoma type	Margin (mm)	Radiation therapy	Outside biopsy?	Time to recurrence (months)	Grade	AJCC stage	Metastatic disease?	Disease status
Epithelioid	1–5	Preoperative	Yes	25	3	III	Yes	DOD
Fibrosarcoma	< 1	Preoperative + postoperative	No	42	1	IIA	No	NED
Myxofibrosarcoma	< 1	Preoperative	No	20	3	III	Yes	DOD
Myxofibrosarcoma	> 5	Preoperative	No	17	3	IIB	No	NED

AJCC = American Joint Committee on Cancer; DOD = died of disease; NED = no evidence of disease.

Table 2. Sarcoma type and local recurrences

Sarcoma type	Number of patients	Number of local recurrences
Pleomorphic sarcoma NOS	31 (26.5%)	
Myxoid liposarcoma	16 (13.7%)	
Leiomyosarcoma	11 (9.4%)	
Synovial sarcoma	11 (9.4%)	
Myxofibrosarcoma	9 (7.7%)	2
MPNST	7 (6.0%)	
Liposarcoma-high grade	5 (4.3%)	
Extraskeletal myxoid chondrosarcoma	5 (4.3%)	
Fibromyxoid sarcoma	5 (4.3%)	
Rhabdomyosarcoma	4 (3.4%)	
Fibrosarcoma	4 (3.4%)	1
Epithelioid sarcoma	3 (2.6%)	1
Radiation-induced sarcoma	2 (1.7%)	
Kaposi sarcoma	1 (< 1%)	
Extraskeletal osteosarcoma	1 (< 1%)	
Low-grade sarcoma NOS	1 (< 1%)	
DFSP	1 (< 1%)	

NOS = not otherwise specified; MPNST = malignant peripheral nerve sheath tumors; DFSP = dermatofibrosarcoma protuberans.

(Table 2), grade, and stage at presentation, and whether the patient developed metastatic disease (Table 3). Date of death and cause of death were also noted.

Comparison of rates of local recurrence between quantitative margin groups was not performed due to a low number of local recurrences (Table 3). We explored the possibility of a Cox model for assessing whether radiation status, outside biopsy, tumor grade and stage at presentation, and development of metastatic disease increased the risk of local recurrence, but the low number of local recurrences prevented any meaningful comparisons. Similarly, no multivariate analysis was applied because of the low incidence of local recurrences. Statistical analysis was performed using SAS® Version 9.1 statistical package (SAS Institute, Inc, Cary, NC, USA).

Table 3. Patient demographics and treatment characteristics

Characteristic	Number of patients	Number with local recurrence
Total	117 (100%)	4 (3.4%)
Margin size		
< 1 mm	45 (38.5%)	2 (4.4%)
1–5 mm	38 (32.5%)	1 (2.6%)
> 5 mm	26 (22.2%)	1 (3.8%)
No residual tumor	8 (6.8%)	0 (0.0%)
Biopsy		
Outside institution	46 (39.3%)	1 (2.2%)
Home institution	71 (60.7%)	3 (4.2%)
Radiation status		
No radiation	15 (12.8%)	0 (0.0%)
Postoperative	30 (25.6%)	0 (0.0%)
Preoperative	72 (61.5%)	4 (5.6%)
Tumor grade		
1	28 (23.9%)	1 (3.6%)
2	6 (5.1%)	0 (0.0%)
3–4	83 (70.9%)	3 (3.6%)
AJCC stage		
IA	13 (11.1%)	0 (0.0%)
IB	4 (3.4%)	1 (25.0%)
IIA	36 (30.8%)	1 (2.7%)
IIB	11 (9.4%)	1 (9.0%)
III	50 (42.7%)	1 (2.0%)
IV	3 (2.6%)	0 (0.0%)
Metastatic disease	32 (27.4%)	2 (6.2%)
Dead of disease	27 (23.1%)	2 (7.4%)

AJCC = American Joint Committee on Cancer.

Results

Two of 45 patients (4.4%) with less than 1-mm margins locally recurred. Two of 64 patients (3.1%) with 1-mm margins or greater had a local recurrence (Table 3). The 2-year incidence of local recurrence for all patients was 2.92 (95% CI, 0.8–7.6) and the 4-year incidence was 3.93 (95% CI, 1.3–9.0). Due to the low number of local recurrences,

we were unable to determine differences in local recurrence with regard to radiation status, outside biopsy, and sarcoma grade and stage. Sarcoma type had no effect on the local recurrence rate, although two of nine patients with myxofibrosarcomas recurred. We observed no relationship between development of metastatic disease and local recurrence.

Average time to local recurrence for patients was 26 months (median, 22.5 months; range, 17–42 months). Of the four patients with local recurrence, two patients have been cleared of disease with additional wide resections and two patients died of metastatic disease with persistent local disease.

Discussion

The traditional description of a wide margin of resection for sarcoma by Enneking included the pseudocapsule and a cuff of normal tissue surrounding the tumor [5]. No specific guideline has been established for how much normal tissue is required to minimize the risk of local recurrence [13]. Tumor and treatment factors such as tumor grade, radiation, and quality of margin may affect the risk of local recurrence beyond that of the quantitative margin of resection [10–12]. Surgeons are often faced with the difficult decision of whether to perform an ablative procedure that sacrifices neurovascular structures or requires an amputation versus a planned close margin [1, 6]. We therefore determined whether a close resection margin for soft tissue sarcoma resulted in an increased incidence of locally recurrent disease and whether radiation therapy, an outside biopsy, tumor type, grade, and stage at presentation, and the development of metastatic disease influenced the risk of local recurrence.

Our study was limited by a number of factors. First, we had limited power due to the low incidence of local recurrence combined with inadequate patient numbers. Thus, we could not perform a multivariable analysis considering potentially confounding variables, including whether the patient received chemotherapy, differences in outcome between surgeons, and patient age. Second, the outcome of the 14 patients lost to followup is unknown although greater than ½ of those patients were followed for more than 2 years. Our mean time for recurrence was 26 months, so we might presume some of these patients would have had subsequent recurrences. However, the margin status of the patients lost to followup did not differ from the overall patient population. Third, the followup interval was shorter than some historical reports although previous literature has documented the risk of local recurrence decreases after 3 years and our median followup of 44 months compares favorably to existing literature [3, 4, 14, 18]. Fourth, the pathologic specimens were not all evaluated by the same pathologist and were not rereviewed to ensure consistency in reporting. In addition, the margin status of the 13 patients reported as completely excised is unclear and undermines the power of the study. Prospectively evaluating the margins in a more regimented manner by a single pathologist would strengthen future investigations. An additional factor that could have played a role in the study outcome is the percentage of patients with low-grade lesions. Patients with low-grade lesions presumably could have a higher risk of late recurrences and our median followup of 44 months might not capture a number of patients who would eventually recur. Finally, we could not qualitatively evaluate the margins. The importance of qualitative margin, or barrier, has been considered by sarcoma surgeons [7, 10] and attempts have been made to assign quantitative values to anatomic barriers [10]. The difficulty associated with retrospectively evaluating the quality of the margin, as well as the multitude of confounding factors, has prevented meaningful data regarding the quality of the margin and its impact on local recurrence. The complex interplay of quality and quantity of margin will need to be evaluated with a well-controlled prospective evaluation.

The incidence of local recurrence was similar in patients with less than 1-mm margins and greater than 1-mm margins (two of 45 patients [4.4%] versus two of 64 patients [3.1%], respectively). Local recurrence rates have ranged considerably in previous reports, some of which can be attributed to varying inclusion and exclusion criteria and differences in the categorization of quantitative margin (Table 4). Our overall local recurrence rate of 3.4% for negative-margin patients with extremity soft tissue sarcoma echoes recent findings of other investigators [2, 3, 8, 14, 18, 23, 26]. Despite a number of reports suggesting a higher local recurrence rate associated with close margins of 1–2 mm or less [3, 8, 14, 18], the rate of 4.4% in our study would suggest, as long as oncologic resection principles are followed and radiation is used judiciously, close margins can be tolerated to minimize morbidity and maximize function of the patient with limb salvage.

Our secondary aim was to determine the impact of additional factors, including radiation therapy, outside biopsies, and tumor biology, on risk of local recurrence. There have been varying reports in the literature concerning the effects of radiation therapy on local recurrence, with most reports demonstrating decreased risk of local recurrence in patients who received radiation therapy, in particular patients with narrow or positive margins [9, 14, 15, 21, 25, 26]. The low number of local recurrences in our study and the limited number of patients prevent us from drawing meaningful conclusions from our data. The majority of our patients (102 of 117) (87%) received

Table 4. Comparison of our results with those of other studies in the literature evaluating local recurrence in soft tissue sarcoma

Study	Study period	Number of patients	Selection criteria	Margin categories	Local recurrence at 5 years	Conclusion
Novais et al. [18] (2010)	1995–2008	248	Extremity	+ and ≤ 2 mm	11.6%	> 2-mm margin suggested
			Primary, deep,	> 2 mm	2.4%	
			Intermediate to high grade	> 2 cm	0.0%	
			No outside biopsy			
			No low grade			
Gronchi et al. [8] (2010)	1985–2005	997	Adult	+		> 1-mm margin had low LR
			Extremity	< 1 mm	26.0%	
			Curative intent	> 1 mm	10.0%	
Liu et al. [16] (2010)	1997–2007	181	Extremity	+ or < 1 mm	45% overall	High LR
			> 15 years old	1–4 mm		Recommend >10-m margin
			No LR	5–9 mm		
				10–19 mm		
				20–29 mm		
				> 30 mm		
Kawaguchi et al. [10] (2004)		837	Bone and soft tissue sarcoma	+	79%	High LR overall
				< 1 cm	40%	Recommend 2-cm margin
				1–4 cm	11%	
				5 cm	10%	
McKee et al. [17] (2004)	1979–1998	111	No abdominal or retroperitoneal	+	42%	> 10-mm margin suggested for LR
				1–2 mm	38%	
				3–9 mm	31%	
			No LR or mets	> 10 mm	16%	
Baldini et al. [2] (1999)	1970–1994	74	Primary localized	< 1 cm	8%	XRT not necessary for select patients
			Trunk or extremity	≥ 1 cm	0%	
			No XRT or chemo			
Sadoski et al. [21] (1993)	1974–1988	132	All had preop XRT	+	18%	≤ 1-mm margins had low LR with preop XRT
			Extremity	≤ 1 mm	6%	
			Adult	> 1 mm	3%	
Zagars et al. [26] (2003)	1960–1999	1225	All had XRT	+	36%	+ margins ↑ risk of LR
			No mets at presentation	−	12%	
Pisters et al. [19] (1996)	1982–1994	1041	Extremity	+ or < 1 mm	40%	+ margins ↑ risk of LR
			Localized	> 1 mm	20%	

Table 4. continued

Study	Study period	Number of patients	Selection criteria	Margin categories	Local recurrence at 5 years	Conclusion
Dickinson et al. [3] (2006)	1987–2002	279	No LR No Mets	+ < 1 mm 1–4 mm 5–9 mm 10–19 mm > 20 mm	+ and < 1 mm had higher rate of LR	> 1-mm margins adequate for local control
Kim et al. [14] (2010)	2000–2006	56	All with preop XRT No LR Adults	+ + and < 1 mm > 1 mm	55.6% 33% 0% Overall 11.5%	≥ 1-mm margin with preop XRT adequate for local control
Stojadinovic et al. [24] (2002)	1982–2000	2084	> 16 years old Localized	+ −	35% 18%	+ margins doubled risk of LR
Kim et al. [15] (2008)	1980–2003	150	Extremity and trunk Postop XRT patients No mets	+ or < 10 mm > 10 mm	24.5% 21.4%	No difference in LR based on margin if XRT given but high LR overall
Tanabe et al. [25] (1994)	1970–1987	95	Intermediate to high grade Extremity Preop XRT	+ −	38% 9%	+ margins had ↑ LR despite preop XRT
Al Yami et al. [1] (2010)	1986–2003	58	Extremity and trunk No chemo Planned + margin patients	Planned + microscopic	10.3%	planned + microscopic margins have low LR rates
Current study (2011)	2001–2007	117	Adult Extremity No LR No mets	< 1 mm 1–5 mm > 5 mm	4.4% 2.6% 3.8%	No differences Low LR even with narrow margins

LR = local recurrence; mets = metastatic lesions; XRT = radiation therapy; chemo = chemotherapy; preop = preoperative; postop = postoperative.

radiation therapy and our local recurrence rate was acceptably low. We will continue to radiate high-risk patients, including patients we believe have sarcoma types at higher risk of local recurrence such as myxofibrosarcomas, patients biopsied at outside facilities, and patients with planned close margins due to anatomic constraints. The low local recurrence rate for the subset of patients who did not receive radiation therapy is likely due to appropriate clinical judgment, avoiding the morbidity of radiation therapy in a subset of patients deemed by the multidisciplinary sarcoma group to be at low risk for local recurrence, such as those with superficial, low-grade, and widely excised lesions.

Patients biopsied in outside facilities by a nonsarcoma specialist reportedly have higher complication rates and increased risk of local recurrence despite wide reexcisions [10]. Our local recurrence rate for the 40% of our patients biopsied by nonspecialists did not differ from the patients biopsied by the multidisciplinary sarcoma group. These findings may be attributable to both lower-stage lesions and an aggressive approach to this patient population that generally includes preoperative radiation therapy, wider resection with 2- to 3-cm margins whenever possible, and plastic surgery reconstruction.

Tumor biology, or aggressiveness of the tumor, plays a role in the development of both local recurrence and metastatic disease [13–15]. More aggressive tumor biology is seen with high-grade and undifferentiated tumors and in patients who present with or develop metastatic disease. Eighty-nine of 117 tumors in our study were intermediate to high grade (76%) and three of the four local recurrences were in patients with high-grade tumors. We did not identify differences in the incidence of local recurrence based on sarcoma type, grade, or stage or in patients who presented with or developed metastatic disease. Nevertheless, any meaningful comparison of recurrence data between studies should include an evaluation of lesion grade and followup interval. Twenty-four percent of our patients had low-grade tumors, a higher percentage than those in studies by Novais et al. [18], Tanabe et al. [25], McKee et al. [17], Zagars et al. [26], and Kim et al. [14]. Studies by Gronchi et al. [8], Baldini et al. [2], Pisters et al. [19], Stojadinovic et al. [24], Kim et al. [15], and Al Yami et al. [1] included a higher percentage of low-grade tumors than our study, and Kawaguchi et al. [10], Sadoski et al. [21], and Dickinson et al. [3] did not report specific grade of the lesions.

We found a low incidence of local recurrence in patients with extremity soft tissue sarcoma regardless of the quantitative extent of the negative margin. The low recurrence rates are consistent with other reports [1, 2, 14, 21, 25] of selected populations of sarcoma patients treated with radiation therapy and wide surgical resection. The low number of recurrences and inadequate power of the study prevent us from making conclusions from our data regarding the appropriate quantitative margin of resection for an extremity soft tissue sarcoma. Nevertheless, based on our findings and those of other investigators [1, 21], it is evident, for primary extremity soft tissue sarcomas, relatively low local recurrence rates can be achievable with planned close margins of less than 1 mm if the resection is approached with oncologically sound principles by a sarcoma specialist. An honest discussion with the patient regarding the increased risk of local recurrence versus the increased morbidity and functional impairment of a wider resection is warranted.

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