Original Article

The Effect of the Setting of a Positive Surgical Margin in Soft Tissue Sarcoma

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BACKGROUND: The objectives of this study were to evaluate the risk of local recurrence and survival after soft tissue sarcoma (STS) resection with positive margins and to evaluate the safety of sparing adjacent critical structures. **METHODS:** One hundred sixty-nine patients with localized STS who had positive resection margins were identified from a prospective database. Patients who had positive margins were stratified into 3 groups, each representing a specific clinical scenario: critical structure positive margin (eg major nerve, vessel, or bone), tumor bed resection positive margin, and unexpected positive margin. The rates of local recurrence-free survival (LRFS) and cause-specific survival (CSS) were calculated and compared with relevant control patients who had negative margins after STS resection. **RESULTS:** After planned close dissection to preserve critical structures, the 5-year LRFS and CSS rates both depended on the quality of the surgical margins (97% and 80.3%, respectively, for those with negative margins vs 85.4% and 59.4%, respectively, for those with positive margins; $P = .015$ and $P = .05$, respectively). Negative margins achieved through resection of critical structures because of tumor invasion or encasement only slightly improved the 5-year rates of LRFS (91.2%) and CSS (63.6%; $P = .8$ and $P = .9$, respectively). The lowest 5-year LRFS and CSS rates were 63.4% and 59.2%, respectively, after an unexpected positive margin during primary surgery. **CONCLUSIONS:** After patients undergo resection of STS with positive margins, oncologic outcomes can be predicted based on the clinical context. Sparing adjacent critical structures in this setting is safe and contributes to improved functional outcomes. ***Cancer* 2014;120:2866-75**. *© 2014 American Cancer Society.*

KEYWORDS: sarcoma, recurrence, survival, morbidity.

INTRODUCTION

The risk of local recurrence in soft tissue sarcoma (STS) relates to the status of the surgical margin after excision.[1-7] Historically, margins were classified as intralesional, marginal, wide, and radical; however, with the advent of adjuvant therapy, margins are now commonly classified as either positive or negative.[8,9] One commonly accepted definition of a positive resection margin is pathologic evidence of neoplastic cells at the excision margin.[7] Gross positive resection margins are accompanied by unacceptably high rates of local recurrence,[10-12] whereas it has been demonstrated that patients who have microscopic positive margins have lower rates of local recurrence as long as the surgical excision is coupled with adjuvant radiation therapy.[2,13,14] This may be especially true when the tumor directly abuts a critical structure such as a major nerve, blood vessel, or bone; to salvage these structures, the plane of dissection is planned to be close to the edge of the tumor using the epineurium, adventitia, or periosteum, respectively, as the margin. Outcome data regarding microscopic positive margins along critical structures are based on a limited number of patients with STS and, as such, the widespread applicability of these data is unknown.

In addition to surgical variables, factors intrinsic to the biology of the tumor influence the likelihood of local or distant recurrence.[15] Specific STS subtypes have an increased likelihood of local recurrence irrespective of the surgical margin.[16,17] Here, even *wide* surgical margins are often accompanied by higher rates of local or distant recurrence than otherwise would be anticipated.[18,19] In comparison, marginal margins in certain STS subtypes are acceptable because of the low risk of recurrence. For example, an excision of low-grade liposarcoma with a microscopically positive surgical margin because of resection along the tumor pseudocapsule is still associated with a low risk of local recurrence.[20,24,25]

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We previously reported on the risk of local recurrence in STS associated with positive surgical margins. In that study, the risk of recurrence was directly related to the setting in which a positive margin was obtained and increased with each category of positive margin status.[13] The use of a microscopically positive surgical margin to preserve a critical structure was not associated with an increased risk of local recurrence in that study. However, those results were based on a group of 28 patients in which there was only 1 local recurrence.

The objectives of the current study were to reevaluate the risk of both local recurrence and cause-specific survival after resection of STS with positive surgical margins in a larger patient cohort and to evaluate the safety of sparing adjacent critical structures in this setting. We hypothesized that the clinical outcome after positive margin resection would be directly related to the setting in which the positive margin occurred.

MATERIALS AND METHODS

After obtaining Research Ethics Board approval and patient informed consent from all patients, we used our prospectively collected database to identify 1371 patients with STS who received treatment between 1986 and 2009, including 169 patients with positive resection margins (study group) and 1202 patients with negative resection margins (control group). Patients with dermatofibrosarcoma protuberans, well differentiated liposarcoma, or abdominal/retroperitoneal sarcomas were excluded; whereas patients with chest wall/paraspinal sarcomas were included. Patients who had received neoadjuvant chemotherapy (n = 112) were excluded. Radiotherapy was delivered using either a preoperative protocol of 50 gray (Gy), or a preoperative protocol of 50 Gy and a postoperative boost of 16 Gy, or a postoperative protocol of 66 Gy.[7,21] A minimum 2 years of follow-up was available for all living patients, and the median follow-up was 61.5 months. These same selection criteria were used to identify the following subgroups from the 1202 control patients with negative surgical margins after STS resection: group 1, 153 patients with tumor adjacent to a critical structure who underwent a planned close excision for preservation of these structures but ultimately had negative margins on final pathologic examination; group 2, 231 patients who had evidence of tumor encasement/invasion of critical structures such that they were resected with the tumor to achieve a negative margin; and group 3, 537 patients who underwent tumor bed resection and had negative margins.

On the basis of a previous study by Gerrand et al,[13] the 169 patients who had positive STS resection margins were stratified into groups, each representing a specific clinical scenario thought to be associated with increasing risk: those with a critical structure positive margin (eg major nerve, blood vessel, or bone), those with a tumor bed resection positive margin, and those with an unexpected positive margin during primary resection.[13] Positive margins were defined pathologically as the presence of tumor cells at the inked margin of the resection specimen. Most tumors in the study group were removed with microscopically positive resection margins (R1) (n = 160), whereas grossly positive margins (R2) (n = 9) were uncommon.

The primary outcomes of this study were the 5-year local recurrence-free and cause-specific survival rates after resection of STS with positive margins. Survival estimates were generated for each patient group using the Kaplan-Meier method and were compared using the log-rank test. A P value $\leq .05$ was considered statistically significant. Data were analyzed using SPSS version 19 software (SPSS Inc., Chicago, Ill).

RESULTS

Patient demographics and treatments are listed in Table 1. Figure 1 illustrates the Kaplan-Meier local recurrence-free survival curves for all 3 study groups and for the control group with negative margins (n = 1202). The risk of local relapse increased progressively with each of the positive margin treatment scenarios ($P < .01$). The 5-year local recurrence-free survival rate was 85.4% for the group with critical structure positive margins, 78.9% for the group with tumor bed resection positive margins, and 63.4% for the group with unexpected positive margins. Figure 2 illustrates 5-year cause-specific survival and demonstrates the worst outcomes for the groups with critical structure positive margins (59.4%) or unexpected positive margins (59.2%).

The critical structure positive margin group consisted of patients who had planned close margins used to preserve a major nerve, blood vessel, or bone but who ultimately ended up having microscopically positive margins on pathologic examination (73 patients, 7 local recurrences). Four recurrences developed after positive margins were used to preserve a major nerve, 1 developed after preservation of a major long bone, and 2 developed after the femoral vessels were salvaged. Of the 7 patients who developed local recurrences, 3 had received preoperative radiation therapy, 2 had received preoperative radiation with a postoperative boost, and 2 had received postoperative radiotherapy. These 7

TABLE 1. Patient Demographic and Treatment and Oncologic Outcome Characteristics

	Group			
Characteristic	Critical Structure-Positive Margin	Tumor Bed Resection-Positive Margin	Unexpected Positive Margin	Negative Margins
Total no. of patients	73	53	43	1202
No. of local recurrences (%)	7 (9.6)	13 (24.5)	15 (34.9)	78 (6.5)
Mean follow-up, mo	49.6	61.1	46.5	57.7
Mean age, y	61	64.6	63.3	55.6
Sex, no. of patients				
Men	34	26	18	672
Women	39	27	25	530
Average greatest tumor dimension, cm	11.2	5.2	9.5	7.8
Grade of tumor, no. of patients				
1	5	9	3	139
2	31	18	15	410
3	37	26	25	652
Depth, no. of patients				
Superficial	4	20	4	388
Deep	69	33	39	814
Histologic type, no. of patients				
MFH	24	24	20	409
Myxoid liposarcoma	11	7	2	144
Intermediate/high-grade liposarcoma	21	10	4	250
Other	17	12	15	321
Location, no. of patients				
Upper extremity	25	26	11	338
Lower extremity	44	22	26	812
Pelvic girdle	4	5	6	52
Radiation, no. of patients				
Preoperative	27	20	17	576
Preoperative and postoperative	21	14	9	24
Postoperative	25	19	17	220
None	0	0	0	382
Metastasis, no. of patients	34	13	21	332

Abbreviations: MFH, malignant fibrous histiocytoma.

local recurrences developed at an average of 27.9 months after resection (range, 2-58 months). The 5-year local recurrence-free survival rate for group 2 was 85.4%.

We identified 2 additional subgroups from the 1202 control patients for comparison to explain how the quality of the surgical margin affects local recurrence when the tumor is close to critical structures. Patients in the first comparison control subgroup also had tumor adjacent to a critical structure and underwent a planned close excision for preservation of these structures, but they ultimately had negative margins on final pathologic examination (n = 153) (Fig. 3). This group with planned close but ultimately negative margins along critical structures demonstrated a significantly improved 5-year local recurrence-free survival rate of 97% compared with 85.4% for the group with critical structure positive margins ($P = .015$) (Fig. 3). Patients in the second comparison control subgroup had either preoperative radiographic or intraoperative evidence of tumor encasement or invasion of critical structures such that they were resected with the tumor to achieve a negative margin (n = 231 patients). This group had a 5-year local recurrence-free survival rate of 91.2%, which was only slightly better than the group with critical structure positive margins ($P = .8$) (Fig. 3).

To understand the influence of margins close to critical structures on cause-specific survival, we compared the critical structure positive margin group and the 2 comparison control subgroups described above (Fig. 4). These 2 control subgroups were similar to the critical structure positive margin group in terms of tumor size ($P = .1$), depth ($P = .3$), and tumor grade ($P = .06$). After preservation of a major nerve, blood vessel, or bone but ultimately with microscopic positive margins, the 5-year cause-specific survival rate was 59.4% (Figs. 2 and 4). Tumors with invasion or encasement of critical structures that were resected with negative margins had a cause-specific survival rate of 63.6% ($P = .9$) (Fig. 4). In contrast, the cause-specific survival rate after a planned close but ultimately negative margin excision for preservation of critical structures was 80.3% ($P < .005$).

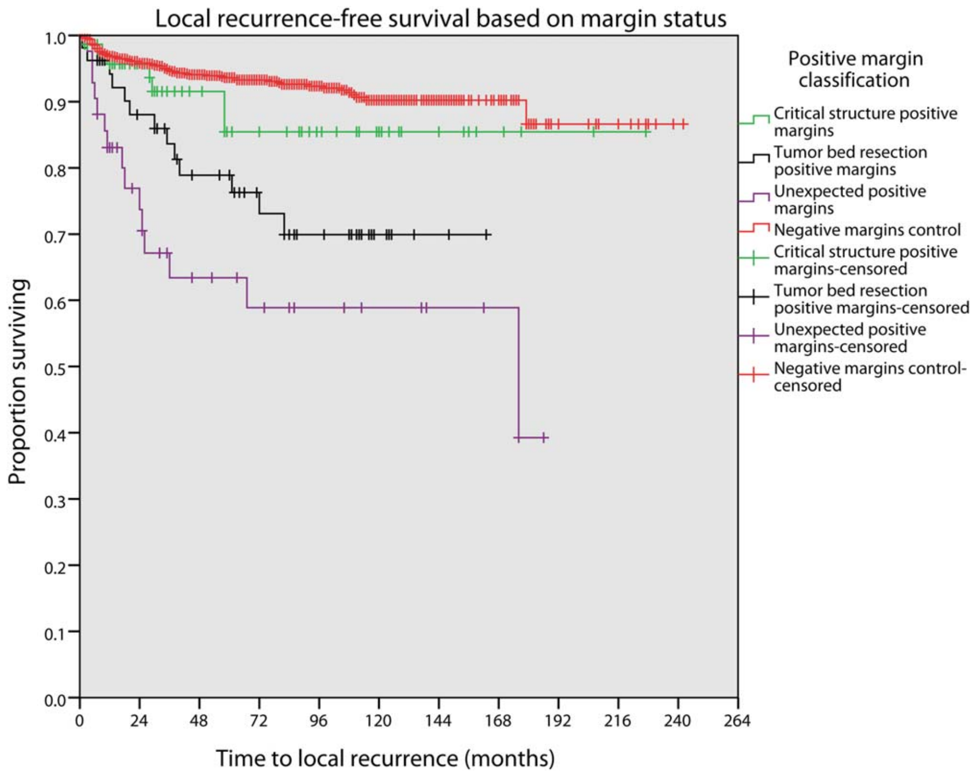

Figure 1. Local recurrence-free survival based on margin status is illustrated.

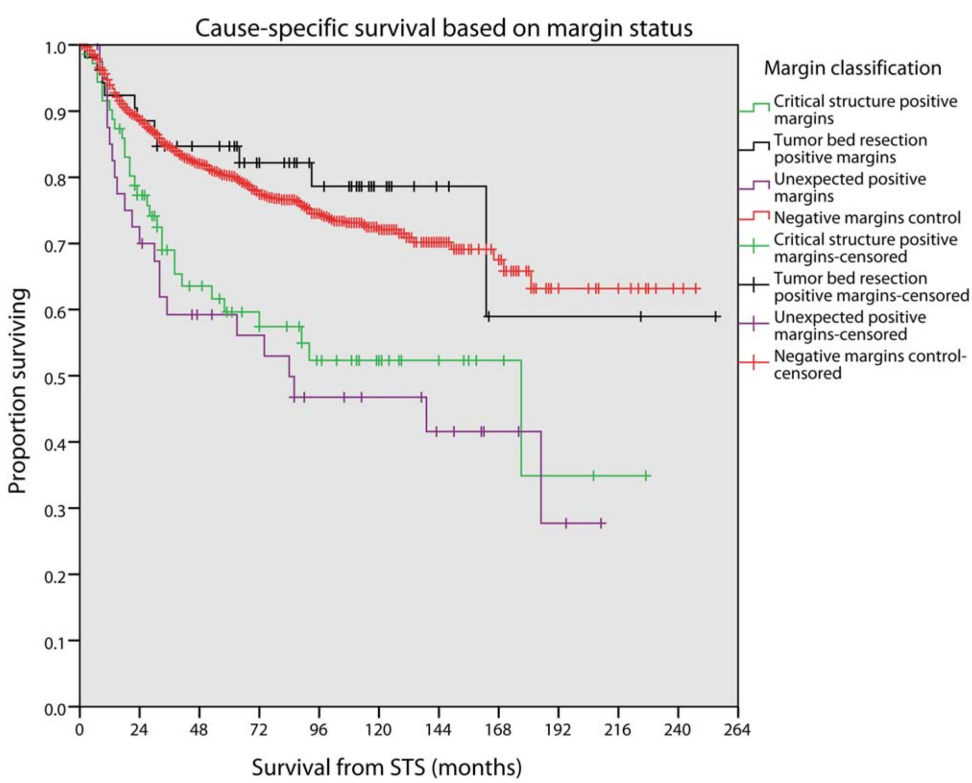

Figure 2. Cause-specific survival based on margin status is illustrated. STS indicates soft tissue sarcoma.

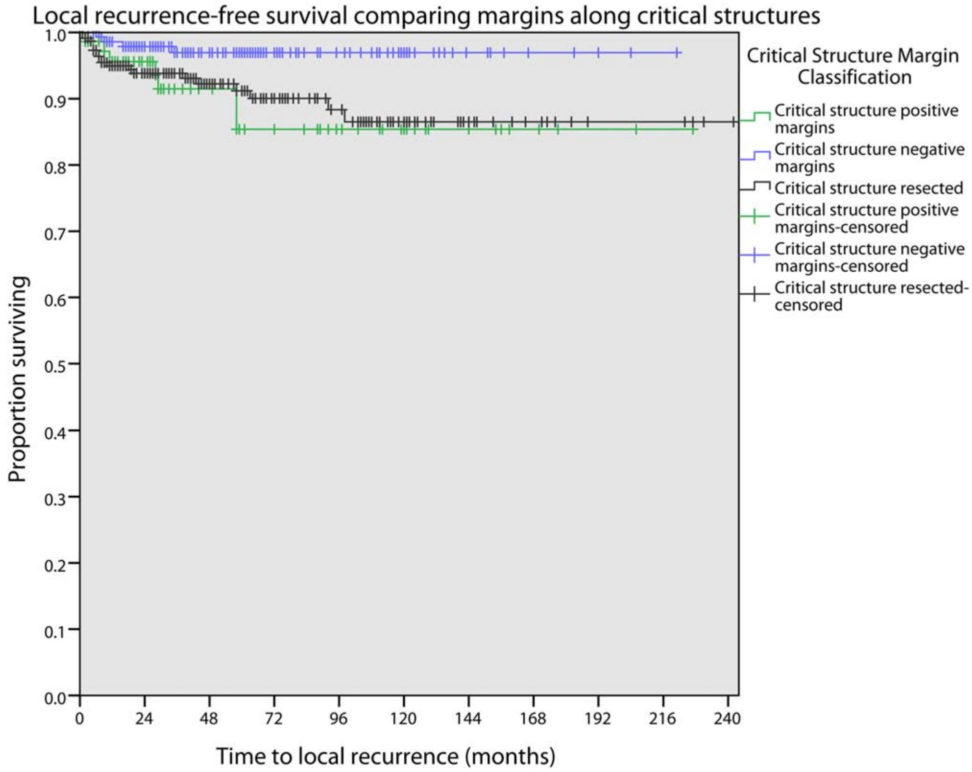

Figure 3. Local recurrence-free survival is illustrated in a comparison of margins along critical structures.

The group with tumor bed resection positive margins consisted of patients who had positive margins on re-excision after a prior, unplanned excision elsewhere (53 patients, 13 local recurrences). These patients were compared with 537 control patients who had negative margins after tumor bed resection. Of the patients who developed a local recurrence after achieving a positive margin on tumor bed resection, 5 had received preoperative radiation therapy, 4 had received preoperative radiation with a postoperative boost, and 4 had received postoperative radiotherapy. These 13 local recurrences occurred at an average of 32.7 months after resection (range, 1-82 months). Patients in this group had smaller tumors (mean, 5.2 cm), more low-grade tumors (9 of 53 patients; 17%), more superficial tumors (20 of 53 patients; 38%), and more upper extremity lesions (26 of 53 patients; 49%). The 5-year local recurrence-free and cause-specific survival rates for this group were 78.9% and 84.7%, respectively, versus 92.3% and 87.1% ($P = .0001$ and $P = .5$, respectively) for the control group with tumor bed resection negative margins.

The group with unexpected positive margins during primary resection at our center included 43 patients and 15 local recurrences. These were compared with a control group of patients who underwent resection of STS with negative margins (1202 patients, 78 local recurrences). The positive margins were caused either by unrecognized tumor extension along or through a fascial plane or by disruption of the tumor pseudocapsule during dissection. Of the patients who developed a local relapse, 4 had received preoperative radiation therapy, 6 had received preoperative radiation with a postoperative boost, and 5 had received postoperative treatment. The 15 local recurrences occurred at a mean 29.1 months after resection (range, 3-176 months). The 5-year local recurrence-free and cause-specific survival rates for patients who had unexpected positive margins were 63.4% and 59.2%, respectively, versus 93.6% and 80.2%, respectively, for patients in the negative margin control group (Figs. 1 and 2).

DISCUSSION

A microscopically positive surgical resection margin (R1) in the setting of STS is a concerning situation; however, not all positive margins should be considered equal in their risk to the patient.[1] Understanding the nature of a positive margin and its potential impact on disease control, survival, and patient function is imperative for the

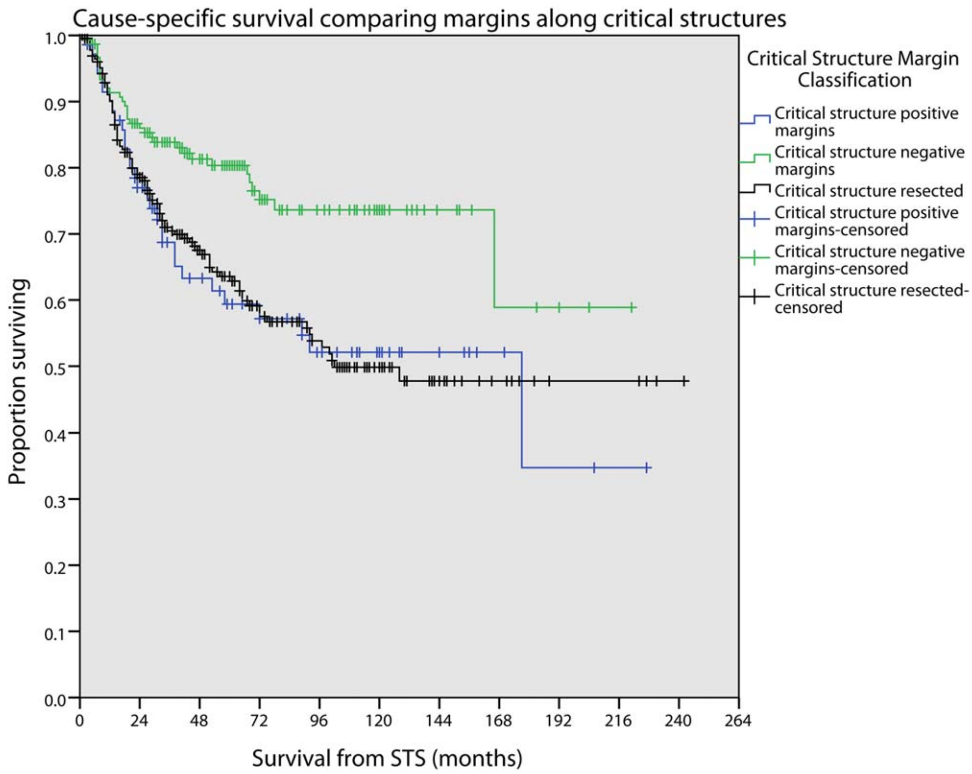

Figure 4. Cause-specific survival is illustrated in a comparison of margins along critical structures. STS indicates soft tissue sarcoma.

treatment team. Therefore, we characterized the nature of positive surgical margins after resection of STS in an effort to better understand the risks associated with various clinical scenarios. We used a previously described classification of positive margins: critical structure positive margin (eg major nerves, vessels, or bone); tumor bed resection positive margin, and unexpected positive margin after primary resection at our center.[13] In this study, the 5-year local recurrence-free survival rate decreased incrementally in these groups (from 85.4% to 63.4%; $P < .01$).

Several limitations of this study exist. First, this study was performed in a retrospective fashion, although we used a prospectively collected database. The second limitation relates to the small number of patients in each cohort and the small number of local recurrences observed in some of these groups. This relates to the infrequency of STS and the low rate of positive surgical margins (169 of 1371 patients; 12.3%) in our series. However, we were able to almost triple the enrolment compared with the previous study by Gerrand et al.[13] Finally there is no widely accepted definition of a positive resection margin for sarcomas. For example, the American Joint Committee on Cancer/International Union Against Cancer defines an R1 resection as having microscopic residual tumor after treatment (ie, microscopic positive margin). In the current study, we defined a microscopic positive or R1 resection by the presence of tumor cells at the inked margin of the resected specimen. However, other recent studies have used different definitions, making a direct comparison of results difficult.[3,4,19,22,23]

STS located adjacent to major vessels, nerves, or bone presents a unique challenge to the treating surgeon. Before the use of adjuvant radiotherapy, wide surgical excision of STS often required resection of these critical structures to obtain appropriate surgical margins and decrease the chance of local recurrence.[8] However, radiotherapy concepts regarding the necessity of *wide* surgical margins have evolved to allow closer surgical margins to preserve critical structures and thereby maximize patient function.[2,14] Because poor functional outcomes after STS resection are directly related to bone or major nerve resection,[26,27] and because vascular resection is associated with high rates of wound complications and lymphedema,[28] preservation of these critical structures needs to be closely weighed against the potential for decreased local recurrence-free and cause-specific survival.[2,14,29,30]

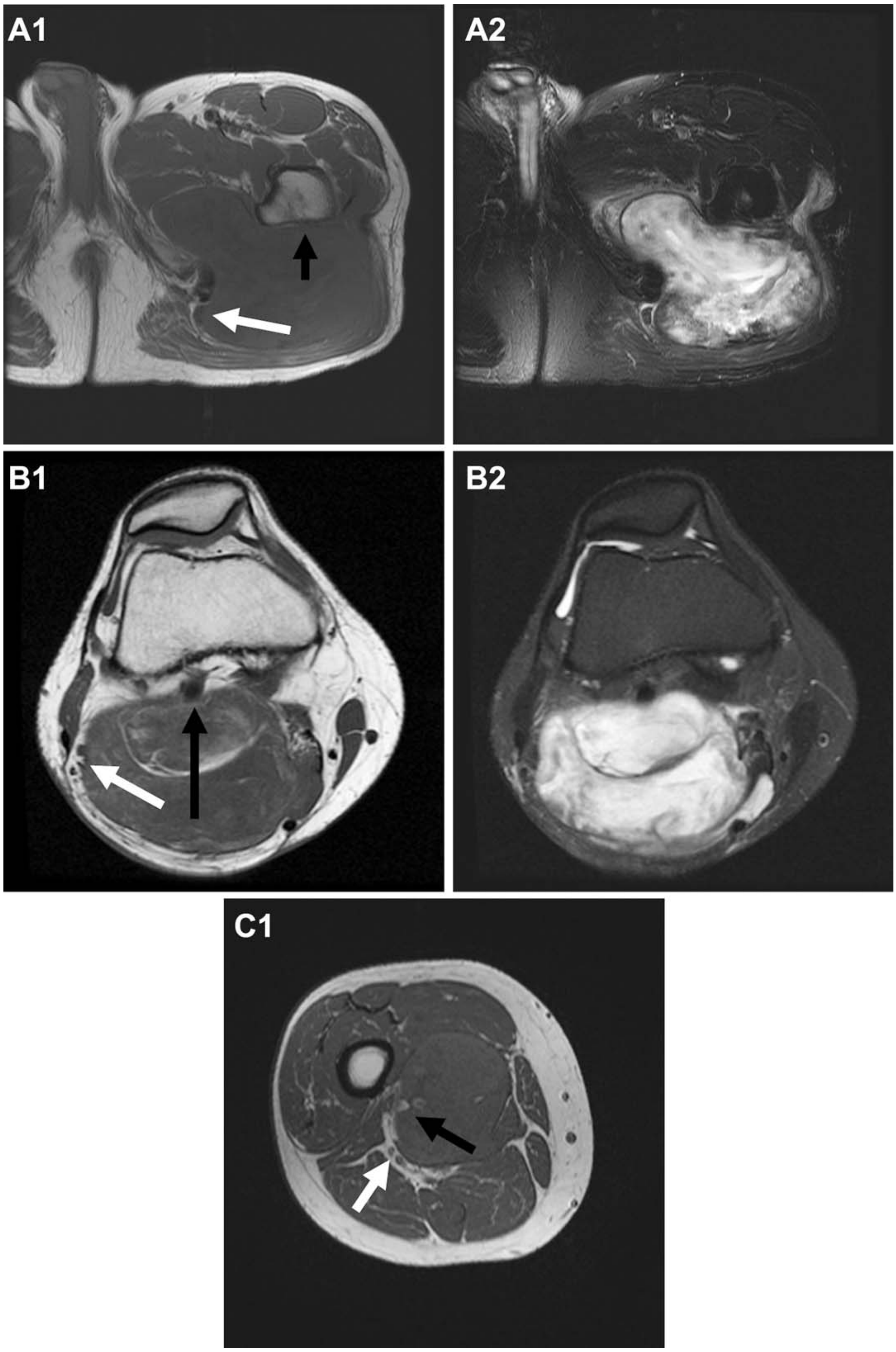

Figure 5.

The results of this study directly support the practice of close dissection for the preservation of major vessels, nerves, or bone even when sparing these adjacent critical structures may lead to microscopically positive margins. Kawaguchi et al[31] previously suggested that using major vessel adventitia, epineurium, or periosteum as a margin for sarcoma was safe, because these tissues had inherent resistance to tumor invasion. Compared with the 5-year local recurrence-free survival rate of 97% for patients with planned close but ultimately negative margins along critical structures, a critical structure positive margin was associated with a lower 5-year local recurrence-free survival rate of 85.4% ($P = .015$). However, for another comparison group in which a critical structure was encased or invaded by tumor and, thus, was resected en bloc with the tumor to achieve negative margins, the 5-year local recurrence-free survival rate of 91.2% was only slightly better than that for patients who had a critical structure positive margin ($P = .8$). These results may be explained on the basis of tumor-specific or biologic factors. If the increased risk of local recurrence in patients with a critical structure positive margin was only because of the presence of residual microscopic disease, then resection of critical structures when invaded or encased by tumor should lower the rate of local recurrence. However, that was not the case. Therefore, the ability of a tumor to encase or invade critical structures, even if only microscopically, may indicate a biologic aggressiveness associated with an increased risk of local recurrence that is not significantly lessened even after resection of the involved critical structure (Fig. 5).

The data presented here regarding survival for patients in the critical structure positive margin group are intriguing but, again, may simply reflect biology. The 5-year cause-specific survival rate for patients who had critical structure positive margins was significantly worse compared with that for patients who had planned close but negative margins along critical structures (59.4% vs 80.3%, respectively; $P = .05$). However resection of critical structures because of invasion or encasement by tumor to facilitate negative margins only slightly improved the 5-year cause-specific survival rate to 63.6% ($P = .9$). This follows the similar trend observed with local relapse and suggests that STSs that can directly invade bone periosteum, vessel adventitia, or nerve epineurium are high-risk tumors both locally and systemically (Fig. 5). Therefore, the biologic aggressiveness inherent to an STS that invades critical structures portends a worse overall prognosis, regardless of the quality of the surgical margin or the morbidity associated with achieving that margin.[26,27,29,30]

Unplanned excision of STS is an all-too-frequent occurrence and something the treating oncologic surgeon must be skilled at handling. Tumor bed re-excision to salvage this situation, although potentially a morbid procedure, has been accepted as necessary to minimize local recurrence in STS.[32,33] The likelihood of achieving negative margins after tumor bed re-excision is related to a combination of: 1) the extent of contamination caused by the initial surgery, 2) tumor biology, and 3) aggressiveness of the re-excision procedure.[34,35] Other authors have observed that unplanned excision of STS resulted in increased rates of local recurrence despite tumor bed re-excision and even radiation.[32,36]

It was interesting to observe that, although patients who had positive margins after tumor bed re-excision had higher rates of local relapse (Fig. 1), this did not translate into worse cause-specific survival. In fact, the 5-year cause-specific survival rate for this group with positive margins after tumor bed re-excision was nearly identical to that for the entire negative margin control group of 1202 patients (Fig. 2) and for the tumor bed resection negative margin control group of 527 patients. The

Figure 5. The involvement of critical structures by soft tissue sarcoma predicts for worse local control and survival. (A1,A2) Planned close but ultimately positive margins to salvage critical structures are shown. (A1) An axial, T1-weighted MRI image and (A2) a corresponding T2-weighted image with fat suppression reveal a high-grade, large, and deep fibrosarcoma in the buttock adjacent to the sciatic nerve (white arrow) and the proximal femur (black arrow). The sciatic nerve was dissected from the tumor, leaving the epineurium as a margin, and this was the only area in which the final resection margin was microscopically positive. The patient developed metastases 2 years after resection of the primary tumor with no evidence of local recurrence. (B1,B2) Planned close but ultimately negative margins to salvage critical structures are shown (control subgroup). (B1) An axial, T1-weighted MRI image and (B2) a corresponding T2-weighted image with fat suppression reveal a high-grade, large, and deep pleomorphic liposarcoma in the popliteal fossa adjacent to the peroneal and tibial nerves (white arrow) and the popliteal vessels (black arrow). The nerves and vessels were dissected free of the tumor, leaving the epineurium and adventitia behind, respectively, and the final margins were negative. At 5-year follow-up, the patient had no local recurrence but developed metastases. (C1) Critical structures encased by tumor and resected with negative margins are shown (control subgroup). The MRI image reveals a grade 2, large, and deep myxoid liposarcoma in the distal posterior thigh encasing the popliteal vessels (black arrow) and adjacent to the peroneal and tibial nerves (white arrow). The vessels were resected en bloc with the tumor and reconstructed, and the nerves were dissected from the tumor with negative margins. The patient developed metastases 8 months later but never had local a recurrence.

explanation for this may simply be biologic, in that tumors in the tumor bed resection positive margin group were more likely to be superficial (38%), low grade (17%), and small (mean, 5.2 cm).[37]

Unexpected positive margins not along critical structures but, instead, affecting the soft tissues surrounding the excised STS may occur because of surgical error or extension of tumor beyond what is evident on cross-sectional imaging. In these patients, positive margin errors occurred most frequently when a proposed surgical boundary such as fascia did not represent a true barrier to tumor spread or because of incorrect assessment of the peripheral extent of cancer cells in the reactive zone surrounding the tumor.[38] These scenarios lead to the worst results for patients, with a 63.4% 5-year local recurrence-free survival rate and a 59.2% cause-specific survival rate.[10-12]

The current results demonstrate that the risk of local recurrence after resection of a STS with positive margins can be predicted by the clinical context of the positive margin. Classification of different positive margins is useful when evaluating a patient's individual risk of recurrence and cause-specific survival. This information carries important decision-making implications for the management of patients at risk of positive margin resection of an STS.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol.* 1996;14:1679-1689.
2. Dagan R, Indelicato DJ, McGee L, et al. The significance of a marginal excision after preoperative radiation therapy for soft tissue sarcoma of the extremity. *Cancer.* 2012;118:3199-3207.
3. Zagars GK, Ballo MT, Pisters PW, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. *Cancer.* 2003;97:2530-2543.
4. Stojadinovic A, Leung DH, Hoos A, Jaques DP, Lewis JJ, Brennan MF. Analysis of the prognostic significance of microscopic margins in 2084 localized primary adult soft tissue sarcomas. *Ann Surg.* 2002;235:424-434.
5. Tanabe KK, Pollock RE, Ellis LM, Murphy A, Sherman N, Romsdahl MM. Influence of surgical margins on outcome in patients with preoperatively irradiated extremity soft tissue sarcomas. *Cancer.* 1994;73:1652-1659.
6. Liu CY, Yen CC, Chen WM, et al. Soft tissue sarcoma of extremities: the prognostic significance of adequate surgical margins in primary operation and reoperation after recurrence. *Ann Surg Oncol.* 2010;17:2102-2111.
7. Al Yami A, Griffin AM, Ferguson PC, et al. Positive surgical margins in soft tissue sarcoma treated with preoperative radiation: is a postoperative boost necessary? *Int J Radiat Oncol Biol Phys.* 2010;77:1191-1197.
8. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. 1980. *Clin Orthop Relat Res.* 2003;415:4-18.
9. Enneking WF, Spanier SS, Malawer MM. The effect of the anatomic setting on the results of surgical procedures for soft parts sarcoma of the thigh. *Cancer.* 1981;47:1005-1022.
10. Enneking WF, Maale GE. The effect of inadvertent tumor contamination of wounds during the surgical resection of musculoskeletal neoplasms. *Cancer.* 1988;62:1251-1256.
11. Han D, Deneve J, Gonzalez RJ. Recurrence risk after resection of gastrointestinal stromal tumors: size is not all that matters... the consequences of tumor rupture. *Am Surg.* 2012;78:74-79.
12. Chen Y, Hao J, Yang Y, Yang J, Hao X. Tumor rupture predicts early metastasis and poor prognosis in stage III soft tissue sarcomas. *World J Surg.* 2011;35:1002-1009.
13. Gerrand CH, Wunder JS, Kandel RA, et al. Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. *J Bone Joint Surg (B).* 2001;83:1149-1155.
14. King DM, Hackbarth DA, Kirkpatrick A. Extremity soft tissue sarcoma resections: how wide do you need to be? *Clin Orthop Relat Res.* 2012;470:692-699.
15. Biau DJ, Ferguson PC, Chung P, et al. Local recurrence of localized soft tissue sarcoma: a new look at old predictors. *Cancer.* 2012;118:5867-5877.
16. Koea JB, Leung D, Lewis JJ, Brennan MF. Histopathologic type: an independent prognostic factor in primary soft tissue sarcoma of the extremity? *Ann Surg Oncol.* 2003;10:432-440.
17. Wong WW, Hirose T, Scheithauer BW, Schild SE, Gunderson LL. Malignant peripheral nerve sheath tumor: analysis of treatment outcome. *Int J Radiat Oncol Biol Phys.* 1998;42:351-360.
18. Sawamura C, Springfield DS, Marcus KJ, Perez-Atayde AR, Gebhardt MC. Factors predicting local recurrence, metastasis, and survival in pediatric soft tissue sarcoma in extremities. *Clin Orthop Relat Res.* 2010;468:3019-3027.
19. Gronchi A, Lo Vullo S, Colombo C, et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. *Ann Surg.* 2010;251:506-511.
20. Mavrogenis AF, Lesensky J, Romagnoli C, Alberghini M, Letson GD, Ruggieri P. Atypical lipomatous tumors/well-differentiated liposarcomas: clinical outcome of 67 patients [serial online]. *Orthopedics.* 2011;34:e893-e898.
21. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet.* 2002;359:2235-2241.
22. Gronchi A, Verderio P, De Paoli A, et al. Quality of surgery and neoadjuvant combined therapy in the ISG-GEIS trial on soft tissue sarcomas of limbs and trunk wall. *Ann Oncol.* 2013;24:817-823.
23. Trovik CS, Bauer HC, Alvegard TA, et al. Surgical margins, local recurrence and metastasis in soft tissue sarcomas: 559 surgically treated patients from the Scandinavian Sarcoma Group Register. *Eur J Cancer.* 2000;36:710-716.
24. Dei Tos AP. Liposarcoma: new entities and evolving concepts. *Ann Diagn Pathol.* 2000;4:252-266.
25. Gaskin CM, Helms CA. Lipomas, lipoma variants, and well-differentiated liposarcomas (atypical lipomas): results of MRI evaluations of 126 consecutive fatty masses. *AJR Am J Roentgenol.* 2004;182:733-739.
26. Bell RS, O'Sullivan B, Davis A, Langer F, Cummings B, Fornasier VL. Functional outcome in patients treated with surgery and irradiation for soft tissue tumours. *J Surg Oncol.* 1991;48:224-231.
27. Davis AM, O'Sullivan B, Bell RS, et al. Function and health status outcomes in a randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma. *J Clin Oncol.* 2002;20:4472-4477.
28. Ghert MA, Davis AM, Griffin AM, et al. The surgical and functional outcome of limb-salvage surgery with vascular reconstruction for soft tissue sarcoma of the extremity. *Ann Surg Oncol.* 2005;12:1102-1110.
29. Ferguson PC, Griffin AM, O'Sullivan B, et al. Bone invasion in extremity soft-tissue sarcoma: impact on disease outcomes. *Cancer.* 2006;106:2692-2700.

30. Panicek DM, Go SD, Healey JH, Leung DH, Brennan MF, Lewis JJ. Soft-tissue sarcoma involving bone or neurovascular structures: MR imaging prognostic factors. *Radiology.* 1997;205:871-875.
31. Kawaguchi N, Ahmed AR, Matsumoto S, Manabe J, Matsushita Y. The concept of curative margin in surgery for bone and soft tissue sarcoma. *Clin Orthop Relat Res.* 2004;419:165-172.
32. Qureshi YA, Huddy JR, Miller JD, Strauss DC, Thomas JM, Hayes AJ. Unplanned excision of soft tissue sarcoma results in increased rates of local recurrence despite full further oncological treatment. *Ann Surg Oncol.* 2012;19:871-877.
33. Arai E, Nishida Y, Tsukushi S, Wasa J, Ishiguro N. Clinical and treatment outcomes of planned and unplanned excisions of soft tissue sarcomas. *Clin Orthop Relat Res.* 2010;468:3028-3034.
34. Nurkin SJ, Kane JM 3rd. Margin status, local recurrence, and survival: correlation or causation? *Surg Oncol Clin North Am.* 2012;21:255-267.
35. Han I, Kang HG, Kang SC, Choi JR, Kim HS. Does delayed re-excision affect outcome after unplanned excision for soft tissue sarcoma? *Clin Orthop Relat Res.* 2011;469:877-883.
36. Potter BK, Adams SC, Pitcher JD Jr, Temple HT. Local recurrence of disease after unplanned excisions of high-grade soft tissue sarcomas. *Clin Orthop Relat Res.* 2008;466:3093-3100.
37. Lachenmayer A, Yang Q, Eisenberger CF, et al. Superficial soft tissue sarcomas of the extremities and trunk. *World J Surg.* 2009;33:1641-1649.
38. White LM, Wunder JS, Bell RS, et al. Histologic assessment of peritumoral edema in soft tissue sarcoma. *Int J Radiat Oncol Biol Phys.* 2005;61:1439-1445.