Journal of Integrative Oncology
ISSN: 2329-6771

Bedi et al., J Integr Oncol 2013, 2:2
DOI: 10.4172/2329-6771.1000109

Review Article

Tumor Increase on MRI after Neoadjuvant Treatment is Associated with Greater Pathologic Necrosis and Poor Survival in Patients with Soft Tissue Sarcoma

Meena Bedi, Jordan Kharofa, Eduardo V Zambrano, Jason Chang, Keith Baynes, Alan P Mautz, Melissa DuBois, David M King, Donald A Hackbarth and Dian Wang*

Department of Radiation Oncology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53045, USA

Abstract

Purpose: MRI is often used to evaluate sarcoma response to neoadjuvant treatment, however its role to predict for pathologic response and survival is unclear.

Methods and materials: From 2003-2010, 116 patients with STS were treated with neoadjuvant therapy (NAT). 62 patients who had an MRI before and after radiotherapy were analyzed. Radiographic change was correlated with survival and necrosis and fibrosis on pathology. ROC curve analysis was used to assess change in volume that best predicted for pathological necrosis.

Results: Median follow-up was 33 months. There was median tumor volume decrease of 15.08 cm^3 after treatment. Increase in tumor size and volume was associated with greater necrosis ($p<0.03$, $p=0.001$, respectively) and less fibrosis ($p<0.001$) on pathology. High-grade tumors had more necrosis ($p<0.001$) and comprised the majority of patients with tumor increases following NAT (88%). Tumor increase of at least 66% predicted for ≥ 70% necrosis with 94% specificity. The 3-year OS was 65% vs. 93% in patients with a decrease in size and volume ($p=0.004$). In tumors with ≥ 70% necrosis, the 3-year OS was 38% vs. 91% if necrosis was <70% ($p<0.001$).

Conclusions: MR-based tumor increase following NAT was associated with greater % necrosis and less fibrosis on pathology. This tumor increase was more likely high-grade and associated with worse survival.

Keywords: Sarcoma; Preoperative radiation therapy; Pathology necrosis; MRI

Introduction

The management of Soft Tissue Sarcomas (STS) of the extremity has evolved overtime. Neoadjuvant radiation with or without chemotherapy followed by limb preserving surgery has been shown to be an effective treatment strategy in the management of primary STS of extremity and trunk. Advantages of neoadjuvant preoperative radiation therapy include a lower treatment dose, decrease in target volume, decreased long-term morbidities and a potential reduction in tumor mass that may facilitate wide resection [1-4].

An MRI is often obtained prior to and after neoadjuvant therapy. It is not uncommon to observe an increase in size of tumor after neoadjuvant therapy; however, the significance of this change is not clear. Radiographic response to therapies has been historically evaluated via the Response Evaluation Criteria in Solid Tumors (RECIST), which evaluates response based on change in tumor size [5]. However, in STS, change in size following neoadjuvant treatment may not always accurately predict tumor response [6]. Some studies have demonstrated that pathologic necrosis of >90% following neoadjuvant therapies is prognostic and correlates with improved outcomes [7-9].

In this study, we retrospectively analyzed a cohort of patients with primary STS of the extremity and body-wall who received neoadjuvant radiotherapy with or without sequential neoadjuvant chemotherapy. The aim of this study was to correlate change in tumor size based on MRI imaging with pathologic findings, including percent necrosis and fibrosis on final pathology, and with Overall Survival (OS) and Disease-Free Survival (DFS).

Materials and Methods

This research was reviewed and approved by the Medical College of Wisconsin Institutional Review Board (IRB) and all investigators completed training in both human research and patient privacy.

Patients

Between May 1999 and October 2010, all stage I-III patients with primary STS of the extremity and body-wall who received preoperative radiation with or without neoadjuvant chemotherapy followed by surgical resection were retrospectively reviewed. Patients were staged according to the 2010 American Joint Committee on Cancer (AJCC) system seventh edition.

Exclusion criteria included metastatic disease on initial presentation, STS of locations other than the extremity or body-wall, recurrent sarcomas, and histopathologic types demonstrating rhabdomyosarcoma, extraosseous primitive neuroectodermal tumor, Ewing's sarcoma, osteosarcoma, Kaposi's sarcoma, angiosarcoma, aggressive fibromatosis, or dermatofibrosarcoma protuberans. Patients who did not have an MRI on the same MRI scanner pre- and post-neoadjuvant therapy as well as those with a follow-up of less than 6

***Corresponding author:** Dian Wang, MD., Ph.D., Department of Radiation Oncology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53045, USA, Tel: (414) 805-4496; Fax: (414) 805-4369; E-mail: dwang@mcw.edu

Received October 11, 2013; **Accepted** November 16, 2013; **Published** November 20, 2013

Citation: Bedi M, Kharofa J, Zambrano EV, Chang J, Baynes K, et al. (2013) Tumor Increase on MRI after Neoadjuvant Treatment is Associated with Greater Pathologic Necrosis and Poor Survival in Patients with Soft Tissue Sarcoma. J Integr Oncol 2: 109. doi:10.4172/2329-6771.1000109

months were excluded. One hundred and sixteen patients received neoadjuvant radiotherapy with or without neoadjuvant chemotherapy followed by resection within the time period and 62 patients were eligible for this analysis.

MR imaging

An MRI of the primary tumor was obtained prior to the initiation of any neoadjuvant therapy, as well as 3-4 weeks after radiation was completed. MRI sequences obtained included T1 and T2-weighted images with contrast. MRI's were re-reviewed by trained musculoskeletal radiologists (KB, APM, and MD). The greatest dimension of each tumor was measured on the pre-treatment and post-radiation MRI's T1 gadolinium contrast sequence. Tumor response on MRI was measured using the RECIST criteria (Table 1) [5]. In addition, we examined the Anterior-Posterior (AP), Craniocaudal (CC), and Medio-Lateral (ML) dimensions, and then estimated tumor volume by multiplying AP x CC X ML

Pathologic assessment

The original pathology report and pathology slides of each case were centrally re-reviewed by a sarcoma pathologist (EVZ) who was blind to clinical outcomes. Histologic type, tumor grade, tumor size, margin status, percent necrosis and percent fibrosis were identified on each specimen of initial biopsy for diagnosis and of surgical resection after neoadjuvant therapy were determined.

Statistical analysis

The change in MRI volume was assessed for correlations with percent necrosis and fibrosis on final pathology using the Spearman correlation coeffecient as well as OS and DFS. The Kaplan-Meier method was used to assess survival outcomes. Receiver Operating Characteristic (ROC) curve analysis was used to examine the change in tumor volume following neoadjuvant treatment that predicted for percent of pathologic necrosis.

Results

Patient characteristics

There are 62 patients included in this analysis. Patient characteristics are located in Table 2. All patients underwent external beam radiotherapy followed by surgical resection. The median dose administered was 50 Gy in 25 fractions. Twenty-two patients (35%) received neoadjuvant chemotherapy. Neoadjuvant chemotherapy was delivered prior to the initiation of radiation. All chemotherapy was doxorubicin and ifosfamide-based regimens. Six of the 22 patients (27.3%) received one cycle, six patients (27.3%) received 2 cycles, and 10 patients (45.4%) received 3 cycles of chemotherapy. Five patients received additional adjuvant chemotherapy in addition to their neoadjuvant chemotherapy regimen.

MRI outcomes

The median pre-treatment tumor size and volume measured on T1-weigted sequences with Gadolinium contrast was 8.6 cm and 1170.7 cm^3, respectively. The median post-treatment tumor size and volume measured from the T1-weigted sequences with contrast was 8.5 cm and 286.2 cm^3, respectively. Median tumor volume decreased 15.08 cm^3 after treatment. According to the RECIST criteria using maximal tumor dimension, 72% of patients had stable disease, 11% of patients had a partial response, 14.5% had progressive disease and 2% had a complete response to neoadjuvant therapy.

Complete Response	Disappearance of all target lesions
Partial Response	30% decrease in sum of longest dimension of target lesions
Stable Disease	Decrease in tumor size of <30% or an increase of <20%
Progressive Disease	Increase of ≥ 20% in the sum of the longest dimensions of target lesions

Table 1: RECIST criteria.

Median age		54.5 (range 18-92)
Median Follow-up		33 months
Tumor Stage	I	16%
	II	8%
	III	76%
Histology	Undifferentiated/MFH	26%
	Other	21%
	Myxofibrosarcoma	19%
	Leiomyosarcoma	13%
	Liposarcoma	11%
	Synovial Cell Sarcoma	10%
Location	Proximal Lower Extremity	61%
	Upper Extremity/Trunk	24%
	Distal Lower Extremity	15%
Grade	Intermediate	3.2%
	Low	19.4%
	High	77.4%

Table 2: Patient Characteristics.

Thirty-seven of the 62 patients (60%) had an absolute decrease in tumor volume after radiation. Of these, 26 patients (70.3%) were high grade, 2 (5.4%) were intermediate grade, and 9 (24.3%) were low grade.

Twenty-five of the 62 patients (40%) had an absolute increase in tumor volume after radiation. Of these, 22 patients (88%) had high grade, 0 (0%) had intermediate grade, and 3 (12%) had low grade disease.

When evaluating the 25 patients who had an increase in tumor volume after neoadjuvant treatment using a similar rule as in the RECIST criteria, 17 of the 25 patients (68%) had stable disease, 8 (32%) had progressive disease and no patients had either a complete response or partial response. Of the patients with stable disease, 15 of the 17 (88%) were high grade, no patients had intermediate grade, and 2 patients (12%) had low grade disease. Of the patients with progressive disease, 7 of the 8 (87.5%) had high grade, no patients had intermediate grade, and 1 patient (12.5%) had low grade disease.

Pathologic outcomes

Percent necrosis was documented in all patients and percent fibrosis was documented in 79% of patients. Eleven (17.7%) patients had ≥ 70% necrosis, with a median percent necrosis of 13.5%. Ten (91%) of the 11 patients had high-grade disease and 1 had low grade disease. Four (6.4%) patients had ≥ 90% necrosis.

An absolute increase in MRI tumor volume after neoadjuvant therapy was associated with greater pathologic necrosis (R=0.39, p=0.001) and less fibrosis (R=-0.51, p<0.001) on the final pathology. This was similar when looking at tumor size (maximal tumor dimension), where an increase in size corresponded to greater necrosis (R=0.26, p<0.03) and less fibrosis (R=0.55, p<0.001). High grade tumors had more pathologic necrosis (R=0.42, p<0.001) and comprised the majority of patients with increases in volume following neoadjuvant treatment (87%). On ROC

analysis, a tumor volume increase of at least 66% predicted for ≥ 70% necrosis on final pathology with 94% specificity (CI 88-99%).

Clinical outcomes

The cumulative incidence of local failure and distant metastases were 3.2% and 27.4% in this cohort, respectively. The 3-year DFS and OS were 70% and 82%, respectively. In patients with an increase in tumor volume following neoadjuvant treatment, the 3-year DFS was 42% versus 85% in those that had a decrease in tumor volume following neoadjuvant therapy (p=0.006) (Figure 1A). In patients with an increase in tumor volume following neoadjuvant treatment, the 3-year OS was 65% compared to 93% in patients with a decrease in tumor volume (p=0.004) (Figure 1B).

In tumors with ≥70% pathologic necrosis, the 3 year DFS was 43% compared to 75% if pathologic necrosis was <70% (p=0.047) (Figure 2A) and the 3 year OS was 38% compared to 91% if pathologic necrosis was <70% (p<0.001) (Figure 2B). Of interest, there were no deaths in the 12 patients that had ≥ 70% fibrosis of their tumor, however, this was not statistically significant in prediction for DFS and OS (p=0.2).

Discussion

Studies have shown that MRI changes may be prognostic for tumor response to therapy in certain malignancies. Historically, the response of solid tumors to interventions such as chemotherapy and radiation has been evaluated by the change in tumor size. The RECIST criteria use size as a basis for tumor response, in which a measurement in one dimension of the maximum tumor diameter in the axial plane of CT or MRI is needed [5]. The advancement of imaging techniques, however, allow one to identify more minute changes in tumors, including tumor density, which may be a prognostic indicator of response to therapies. The CHOI criteria was reported to incorporate not only size, but change in attenuation in Gastrointestinal Stromal Tumors (GIST), but the role of the CHOI criteria is uncertain in STS [10,11]. Due to the image acquisition and sequences obtained, only the RECIST criteria could be employed to assess treatment response in this study.

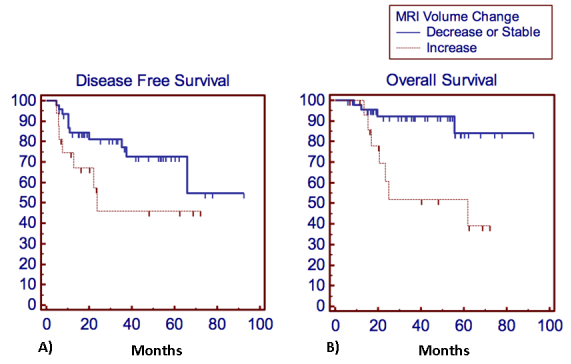

Figure 1: Relationship between MR-based volume change and survival [disease free survival (1A) and overall survival (1B)].

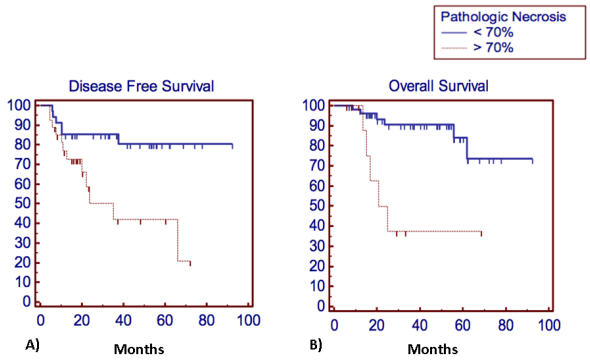

Figure 2: Relationship between percent pathologic necrosis and survival [disease free survival (2a) and overall survival (2b)].

There is a known correlation between a decrease in tumor size and pathologic necrosis following neoadjuvant chemotherapy in osteosarcomas [8,12]. Response to neoadjuvant chemotherapy is considered successful if there is >90% necrosis seen on pathology [6,7]. Kim, et al., retrospectively reviewed 151 patients with stage II osteosarcomas who were treated with neoadjuvant chemotherapy followed by surgery. This study showed a correlation between volume change and necrosis, such that a decrease in tumor volume predicted increased necrosis and thus a good pathologic response [9].

Although several studies have shown a correlation between radiographic and pathologic outcomes to neoadjuvant chemotherapy for osteosarcomas, this relationship has not been consistently reported in STS [11,12]. Eilber et al. assessed 496 patients with intermediate-to-high grade STS who underwent neoadjuvant therapy followed by resection. Greater than ninety-five percent necrosis predicted for improved local control and survival rates than those patient with <95% necrosis [8]. Similarly, other studies have shown improved surgical, local control and survival outcomes in patients who underwent neoadjuvant chemotherapy [9,13]. However, other studies have not demonstrated this correlation. Lucas et al. reviewed histologic response to neoadjuvant chemotherapy in STS and found no difference in OS or event-free survival in patients with excellent, moderate or poor responses [14]. In addition, Pisters et al. reviewed 76 patients with stage IIIB STS of the extremity who received neoadjuvant chemotherapy and found no differences in local-recurrence free, distant-metastasis free, disease-free and overall survival in responders and non-responders radiographically to neoadjuvant chemotherapy [15].

While there have been attempts to correlate tumor response to neoadjuvant chemotherapy and outcomes, the clinical significance of changes in tumor size and volume following neoadjuvant radiation is not well characterized. Increases in tumor size and/or volume after radiation therapy were generally assumed to be due to hemorrhage, radiation-induced swelling, or necrosis, rather than tumor growth. However, previous investigations attempting to correlate radiographic response and pathologic response after preoperative radiotherapy with clinical outcomes failed to provide a consistent result [16-18].

Miki et al. retrospectively reviewed 91 cases with STS of the extremity and trunk treated with preoperative radiation followed by wide local excision. There was no difference in local control and overall survival between those that had an increase compared to those that had a decrease or stable tumor size [19]. DeLaney et al. reviewed 48 patients with high-grade, large STS of the extremity with preoperative chemotherapy and radiation. Six patients had an increase in tumor size in response to neoadjuvant therapy. However, upon pathologic review, it was found that most of the tumors in these patients showed ≥ 70% necrosis. As such, it was determined that the progression seen radiographically was actually secondary to swelling from the osmotic effect of necrosis [16]. Roberge et al. retrospectively assessed the correlation between radiographic and pathologic response, as defined by necrotic tumor, and fibrotic or hyalinized stroma in 50 patients with

STS of the extremity and trunk treated with neoadjuvant radiation. In this study, a volume decrease of ≥ 50% on MRI was predictive of a good pathologic response. However, progression on imaging did not predict poor pathological response partial response on MRI [20].

In our study, an increase in tumor volume following neoadjuvant treatment as measured on MRI lead to decreased DFS (42% vs. 85%, p=0.006) and OS (65% vs 93%, p=0.004) compared to those that had a decrease in volume. However, high grade tumors had more pathologic necrosis and comprised the majority of patients with increases in volume following neoadjuvant treatment (87%). Moreover, in patients who had tumors with ≥ 70% pathologic necrosis, the 3 years OS was 38% versus 91% if pathologic necrosis was <70% (p<0.001). Results of this study may indicate that certain high grade STS tend to have tumor necrosis that are not treatment-related. Greater than 70% tumor necrosis following neoadjuvant radiotherapy may suggest aggressive tumor behavior that requires aggressive adjuvant chemotherapy. Certainly our observation may be secondary to the sample size bias or other factors. However, the authors make all efforts to eliminate potential pitfalls in this retrospective study, such as central pathology review to eliminate variations among individual pathologic reports and central review of MR images from all patients in this study. We have also excluded those patients who did not have an MRI on the same MRI scanner pre- and post-neoadjuvant therapy.

As opposed to chemotherapy, radiation causes cellular fibrosis and stromal hyalinization data. Pezzi et al. reported on 46 patients treated with neoadjuvant chemotherapy. Forty-eight percent of patients had some histologic evidence of response, which was deemed as decreased cellularity, fibrosis, cellular fibrosis, foam cells, cellular gigantism, hyalinization, and coagulative necrosis. A significant improvement in survival was seen in patients who had evidence of some form of histologic response (p=0.04) [21]. Our study was able to evaluate the role of fibrosis defined by decreased cellularity and stromal hyalinization, as opposed to necrosis, might play with regard to predicting clinical outcomes. The finding that patients with >70% fibrosis of their resection specimen had improved clinical outcomes is interesting and suggests the pathologic tumor response to radiation may differ from the response to chemotherapy. It also may suggest that increased percent fibrosis following preoperative radiotherapy predicts for less aggressive tumor biology and good disease control outcomes.

The limitations of this study include the small sample size, variation in histologic types of sarcomas and the retrospective nature of the study that leads to inherent biases. Moreover, the Choi criteria could not be employed with our institution's MRI sequence acquisitions, which would allow for better delineation of tumor response to neoadjuvant therapies.

Conclusions

MR-based increase in tumor volume and size after neoadjuvant radiotherapy is associated with greater percent necrosis and less fibrosis on pathology. Patients with a high percentage of necrosis following neoadjuvant radiotherapy with or without sequential neoadjuvant chemotherapy are more likely to have high grade tumors and worse survival. Further evaluation of post-radiotherapy fibrosis might be useful to predict survival outcomes.

References

1. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, et al. (2002) Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 359: 2235-2241.
2. Nielsen OS, Cummings B, O'Sullivan B, Catton C, Bell RS, et al. (1991) Preoperative and postoperative irradiation of soft tissue sarcomas: effect of radiation field size. Int J Radiat Oncol Biol Phys 21: 1595-1599.
3. Sadoski C, Suit HD, Rosenberg A, Mankin H, Efird J (1993) Preoperative radiation, surgical margins, and local control of extremity sarcomas of soft tissues. J Surg Oncol 52: 223-230.
4. Wilson AN, Davis A, Bell RS, O'Sullivan B, Catton C, et al. (1994) Local control of soft tissue sarcoma of the extremity: the experience of a multidisciplinary sarcoma group with definitive surgery and radiotherapy. Eur J Cancer 30A: 746-751.
5. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247.
6. Stacchiotti S, Collini P, Messina A, Morosi C, Barisella M, et al. (2009) High-grade soft-tissue sarcomas: tumor response assessment--pilot study to assess the correlation between radiologic and pathologic response by using RECIST and Choi criteria. Radiology 251: 447-456.
7. Uhl M, Saueressig U, van Buiren M, Kontny U, Niemeyer C, et al. (2006) Osteosarcoma: preliminary results of in vivo assessment of tumor necrosis after chemotherapy with diffusion- and perfusion-weighted magnetic resonance imaging. Invest Radiol 41: 618-623.
8. Eilber FC, Rosen G, Eckardt J, Forscher C, Nelson SD, et al. (2001) Treatment-induced pathologic necrosis: a predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. J Clin Oncol 19: 3203-3209.
9. MacDermed DM, Miller LL, Peabody TD, Simon MA, Luu HH, et al. (2010) Primary tumor necrosis predicts distant control in locally advanced soft-tissue sarcomas after preoperative concurrent chemoradiotherapy. Int J Radiat Oncol Biol Phys 76: 1147-1153.
10. Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, et al. (2007) Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinibmesylate: proposal of new computed tomography response criteria. J Clin Oncol 25: 1753-1759.
11. Tuma RS (2006) Sometimes size doesn't matter: reevaluating RECIST and tumor response rate endpoints. J Natl Cancer Inst 98: 1272-1274.
12. Holscher HC, Bloem JL, van der Woude HJ, Hermans J, Nooy MA, et al. (1995) Can MRI predict the histopathological response in patients with osteosarcoma after the first cycle of chemotherapy? Clin Radiol 50: 384-390.
13. Meric F, Hess KR, Varma DG, Hunt KK, Pisters PW, et al. (2002) Radiographic response to neoadjuvant chemotherapy is a predictor of local control and survival in soft tissue sarcomas. Cancer 95: 1120-1126.
14. Lucas DR, Kshirsagar MP, Biermann JS, Hamre MR, Thomas DG, et al. (1997) Histologic alterations from neoadjuvant chemotherapy in high-grade extremity soft tissue sarcoma: clinicopathological correlation. Oncologist 13: 451-458.
15. Pisters PW, Patel SR, Varma DG, Cheng SC, Chen NP, et al. (1997) Preoperative chemotherapy for stage IIIB extremity soft tissue sarcoma: long-term results from a single institution. J Clin Oncol 15: 3481-3487.
16. DeLaney TF, Spiro IJ, Suit HD, Gebhardt MC, Hornicek FJ, et al. (2003) Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys 56: 1117-1127.
17. van Rijswijk CS, Geirnaerdt MJ, Hogendoorn PC, Peterse JL, van Coevorden F, et al. (2003) Dynamic contrast-enhanced MR imaging in monitoring response to isolated limb perfusion in high-grade soft tissue sarcoma: initial results. Eur Radiol 13: 1849-1858.
18. Panicek DM, Casper ES, Brennan MF, Hajdu SI, Heelan RT (1991) Hemorrhage simulating tumor growth in malignant fibrous histiocytoma at MR imaging. Radiology 181: 398-400.
19. Miki Y, Ngan S, Clark JC, Akiyama T, Choong PF (2010) The significance of size change of soft tissue sarcoma during preoperative radiotherapy. Eur J Surg Oncol 36: 678-683.
20. Roberge D, Skamene T, Nahal A, Turcotte RE, Powell T, et al. (2010) Radiological and pathological response following pre-operative radiotherapy for soft-tissue sarcoma. Radiother Oncol 97: 404-407.
21. Pezzi CM, Pollock RE, Evans HL, Lorigan JG, Pezzi TA, et al. (1990) Preoperative chemotherapy for soft-tissue sarcomas of the extremities. Ann Surg 211: 476-481.