The Treatment of Soft-tissue Sarcomas of the Extremities

Prospective Randomized Evaluations of (1) Limb-sparing Surgery Plus Radiation Therapy Compared with Amputation and (2) the Role of Adjuvant Chemotherapy

STEVEN A. ROSENBERG, M.D., PH.D.,* JOEL TEPPER, M.D.,† ELI GLATSTEIN, M.D.,† JOSE COSTA, M.D.,‡
ALAN BAKER, M.D.,* MURRAY BRENNAN, M.D.,* ERNEST V. DeMOSS, M.D.,* CLAUDIA SEIPP, R.N.,*
WILLIAM F. SINDELAR, M.D., PH.D.,* PAUL SUGARBAKER, M.D.,* ROBERT WESLEY, PH.D.§

Between May 1975 and April 1981, 43 adult patients with high-grade soft tissue sarcomas of the extremities were prospectively randomized to receive either amputation at or above the joint proximal to the tumor, including all involved muscle groups, or to receive a limb-sparing resection plus adjuvant radiation therapy. The limb-sparing resection group received wide local excision followed by 5000 rads to the entire anatomic area at risk for local spread and 6000 to 7000 rads to the tumor bed. Both randomization groups received postoperative chemotherapy with doxorubicin (maximum cumulative dose 550 mg/m^2), cyclophosphamide, and high-dose methotrexate. Twenty-seven patients randomized to receive limb-sparing resection and radiotherapy, and 16 received amputation (randomization was 2:1). There were four local recurrences in the limb-sparing group and none in the amputation group ($p_1 = 0.06$ generalized Wilcoxon test). However, there were no differences in disease-free survival rates (71% and 78% at five years; $p_2 = 0.75$) or overall survival rates (83% and 88% at five years; $p_2 = 0.99$) between the limb-sparing group and the amputation treatment groups. Multivariate analysis indicated that the only correlate of local recurrence was the final margin of resection. Patients with positive margins of resection had a higher likelihood of local recurrence compared with those with negative margins ($p_1 < 0.0001$) even when postoperative radiotherapy was used. A simultaneous prospective randomized study of postoperative chemotherapy in 65 patients with high-grade soft-tissue sarcomas of the extremities revealed a marked advantage in patients receiving chemotherapy compared with those without chemotherapy in three-year continuous disease-free (92% vs. 60%; $p_1 = 0.0008$) and overall survival (95% vs. 74%; $p_1 = 0.04$). Thus limb-sparing surgery, radiation therapy, and adjuvant chemotherapy appear capable of successfully treating the great majority of adult patients with soft tissue sarcomas of the extremity.

SOFT-TISSUE SARCOMAS are malignant tumors that arise in the extraskeletal connective tissues of the body. Though a large number of different pathologic diagnoses, based on the cell of origin, comprise the soft-tissue sarcomas, these tumors are grouped together because of similarities in pathologic appearance, clinical presentation, and natural history. The clinical behavior of soft-tissue sarcomas is characterized by a tendency to extensively invade surrounding soft tissues as well as early metastatic dissemination, mainly to the lungs.[1,2]

The extensive local invasion of soft-tissue sarcomas along anatomic structures such as fascial layers, blood vessels, nerve sheaths, and muscle fibers has resulted in local recurrence rates of 30 to 50% when local surgical excision is utilized as sole therapy for these lesions.[1-6] These high local recurrence rates have led to the use of radical compartmental excisions or amputations in an attempt to achieve local control and the utilization of these extensive surgical resections has reduced local recurrence rates to 5 to 20%.[7,8] Recently several workers have advocated the use of local surgical excision followed by wide field radiation therapy as a means of obtaining adequate local control of these lesions.[9,10] No comparative studies of these two approaches to achieving local control of soft-tissue sarcomas have been undertaken. The problems of poorly defined criteria for patient selection and the use of historical controls for analysis of treatment results have made reasonable comparison between the efficacy of these two approaches difficult. In this article the authors report the results of a prospective randomized comparison of the role of limb-sparing surgery plus radiation

therapy compared with amputation in the treatment of patients with soft-tissue sarcomas of the extremities.

The tendency of soft-tissue sarcomas to metastasize to the lungs and the poor survival of patients treated for soft-tissue sarcomas (around 40% in most series) has led to a search for systemic treatments that might be applied early in the course of the disease. The authors also present the results of a prospective randomized evaluation of the value of adjuvant chemotherapy in the treatment of patients with soft-tissue sarcomas of the extremities. A more detailed presentation of this latter study has been presented elsewhere.[11]

Methods

All patients with soft-tissue sarcomas of the extremities included in these protocols were evaluated and treated in the Surgery Branch of the National Cancer Institute. To be eligible for these protocols, patients had a diagnosis of either round cell or pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, synovial cell sarcoma, fibrosarcoma, neurofibrosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, or undifferentiated sarcoma. All patients had lesions of the extremities defined as being distal to the shoulder or hip joints.

All patients underwent a standard workup including history, physical examination, blood chemistries, chest radiograph, lung tomograms, liver scan, bone scan, and computerized axial tomography through the area of the primary lesion. All patients in this protocol were free of clinical evidence of metastatic disease, either in regional lymph nodes or more distant sites.

Pathologic material, including biopsies and definitive resection specimens, were reviewed by the same pathologist, and only patients fulfilling the above histologic diagnosis were included.

Patients were excluded from the protocols if they had received any prior chemotherapy or radiation therapy before referral to the National Cancer Institute (NCI) or if they had a history of any other malignant disease except for basal cell carcinoma. Patients who had severe infections, active bleeding disorders, or concomitant severe disease such as cirrhosis, ischemic heart disease or evidence of severe impairment of renal function that made them ineligible to receive the chemotherapy used in the protocols were also excluded. Patients below the age of 30 with a diagnosis of embryonal or alveolar rhabdomyosarcoma were also excluded.

Before randomization in each of the protocols all patients signed an informed consent in accord with the guidelines of the Clinical Research Committee of the National Cancer Institute.

Comparison of Patients Receiving Limb-sparing Surgery Plus Radiation Therapy with Patients Receiving Amputation

Patients with soft-tissue sarcoma of the extremities meeting the above eligibility criterion who had lesions that were amenable to local treatment by either amputation or by limb-sparing surgery were offered entrance into this protocol. A criteria of eligibility for this protocol was the clinical judgment that a limited operation would be capable of removing all gross disease from the involved extremity without sacrifice of vessels or nerves essential for even limited function of the extremity. When tumor was abutting or adjacent to vessels or nerves, the tumor was carefully dissected from these structures even if the pseudocapsule of the tumor was in intimate apposition to these structures. Approximately 15% of patients presenting with soft-tissue sarcomas of the extremities had local lesions so extensive that no limited surgical option existed that was capable of eliminating gross tumor, and these patients were not eligible for this protocol.

Patients were prospectively randomized to receive either amputation or to receive limb-sparing resection followed by radiation therapy. Patients were randomly assigned to one of the two treatment groups using a schema design to enter twice as many patients in the limb-sparing surgical arm as in the amputation arm. Patients were stratified on the basis of the histology of the primary lesion, the degree of differentiation (grade), the time from initial diagnosis, and whether the lesion was proximal or distal in the extremity.

Patients randomized to receive amputation underwent amputation at or above the joint proximal to the lesion including all involved muscle groups. In this protocol the following amputations were performed: three hemipelvectomies, seven hip disarticulations, three above-knee amputations, two forequarter amputations, and one below-elbow amputation.

Patients randomized to receive limb-sparing surgery plus radiation therapy underwent wide local excision designed to remove all gross tumor with several centimeters of surrounding normal tissue. In cases where the pseudocapsule of tumor was in close apposition to essential vessels or nerves, tumor was dissected free of those anatomic structures even if positive surgical margins resulted. All patients randomized to the limb-sparing arm of the protocol underwent removal of all gross disease at the time of surgery. No attempt was made to perform radical compartmental excisions in these patients. The patient routinely had metallic clips placed around the borders of the resected specimen to guide the radiation therapist in the treatment of the tumor

bed. Four of the 27 patients randomized to the limb-sparing treatment arm of the protocol had a resection margin pathologically positive for tumor cells. No patients who underwent amputation had a positive pathologic margin. All patients who underwent limb-sparing surgery also received radiation therapy designed to treat all areas at risk for tumor spread between the joints proximal and distal to the tumor including all involved muscle groups. Daily treatments were given at 180 to 200 rads per treatment to a dose of 4500 to 5000 rads. A "shrinking field" technique was then used, and a total of 6000 to 7000 rads was delivered to the tumor bed and completed in the sixth and seventh week of radiation therapy. The radiation therapy used in these patients has been presented in detail elsewhere.[12] When possible, some portion of the circumference of the limb was excluded from the treatment portals. When possible the adjacent joint space was also eliminated from the radiation portal, however, this was often not feasible because of the location of the tumor. Radiation therapy was begun as soon as the wound was healed. Wedge filters, compensator filters, complex field arrangements, wedged pairs, tangential fields, and rotational therapy were all used in an attempt to maximize radiation exposure to tissues at risk and to minimize radiation of normal tissues.

All patients in this protocol received chemotherapy beginning in the immediate postoperative period. Patients receiving radiation therapy received the first chemotherapy dose three days before the first radiation dose. Patients received doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan) intravenously on day 21 of a 28-day cycle. Doxorubicin was begun at a dose of 50 mg/m² and was escalated by 10 mg/m² to a maximum of 70 mg/m² depending on bone marrow toxicity. A maximum cumulative dose of doxorubicin of 550 mg/m² was given. Cyclophosphamide was started at a dose of 500 mg/m² and was escalated by 100 mg/m² in conjunction with doxorubicin to a maximum of 700 mg/m². When the maximum cumulative dose of doxorubicin was reached, patients received high-dose methotrexate with leukovorin rescue, again on a 28-day cycle for a total of six doses. The initial dose of methotrexate was 50 mg/kg in a six-hour infusion followed two hours after completion of the infusion by 15 mg/m² of leukovorin intravenously. Intravenous leukovorin was repeated every six hours for a total of eight doses. Methotrexate dosage was escalated by 50 mg/kg in each cycle to a maximum dose of 250 mg/kg. Patients were well hydrated, and urine was alkalinized before each drug infusion. Forty-eight-hour blood levels of methotrexate were determined by radioimmunoassay, and all patients with methotrexate levels greater than 4×10^{-7} Molar received additional leukovorin.

Comparison of Patients Receiving Adjuvant Chemotherapy with Patients Receiving No Adjuvant Chemotherapy

In a study separate from that described above, patients with soft-tissue sarcoma of the extremities were prospectively randomized to be treated by either surgery alone or by surgery followed by adjuvant chemotherapy. All patients in this protocol received either amputation or limb-sparing surgery plus radiation therapy as described above. Patients were prospectively randomized to receive either adjuvant chemotherapy with doxorubicin, cyclophosphamide, and high-dose methotrexate as described above or randomized to receive no chemotherapy.

To assure comparability of the patient groups in this protocol, randomized patients were stratified based on the degree of differentiation of the primary lesion, whether patients received an amputation or limb-sparing surgery, and whether the lesions were in a proximal or distal portion of the involved extremity.

Patient Follow-up

All patients were seen at least every two months for the first three years after surgery and at three monthly intervals thereafter for the first five years. Complete blood chemical evaluation and chest radiographs were obtained at each visit. Full lung tomography was obtained every six months for the first three years. Histologic confirmation of recurrent disease was obtained in all patients who recurred.

Statistical Analysis

For comparing the disease-free survival and overall survival, the test of Mantel and Haenszel was used.[13] In comparisons in which there were fewer than five total failures, the exact version of the Mantel–Haenszel test as described by Thomas was used to compute p values.[14] Estimates of the "survival" curves were computed using the method of Kaplan and Meier.[15] In looking at these curves the reader should keep in mind that toward the right hand side of these curves, where relatively few patients are at risk, the estimates are not very reliable. In comparing proportions in two groups the authors have used the Fisher exact test.[16]

During the course of the adjuvant chemotherapy trial, interim analyses were performed at approximately six-month intervals. In order to guard against prematurely stopping the study, the method of monitoring

TABLE 1. *Soft-tissue Sarcomas of the Extremities*

		Amputation	Limb-Sparing Surgery + Radiotherapy
		Number of Patients (%)	
Sex:	Male	10 (63)	23 (85)
	Female	6 (37)	4 (15)
Age:	0–20 years	2 (13)	4 (15)
	21–40 years	9 (56)	9 (33)
	41–65 years	5 (31)	14 (52)
Race:	Caucasian	13 (81)	22 (81)
	Black	3 (19)	5 (19)
Site:	Arm	2 (12)	3 (11)
	Forearm-hand	1 (6)	2 (7)
	Thigh	10 (63)	17 (63)
	Leg-foot	3 (19)	5 (19)
Histology:	Fibrosarcoma	0 (0)	1 (4)
	Malignant fibrous histiocytoma	1 (6)	3 (11)
	Liposarcoma	7 (44)	4 (15)
	Leiomyosarcoma	1 (6)	4 (15)
	Rhabdomyosarcoma	0 (0)	3 (11)
	Synoviosarcoma	4 (25)	7 (25)
	Neurofibrosarcoma	1 (6)	3 (11)
	Undifferentiated	2 (13)	5 (19)
Grade:	1	1 (6)	0 (0)
	2	4 (24)	3 (11)
	3	11 (70)	24 (89)
Total		16	27

described by Peto, et al. was employed.[17] An overall test of disease-free survival for all patients randomized to chemotherapy or no chemotherapy was performed at

each interim analysis using the test of Mantel and Haenszel. At none of the interim analyses was the value of the chi square statistic extreme enough to warrant stopping the trial.

Results

Comparison of Patients Receiving Limb-Sparing Surgery Plus Radiation Therapy with Patients Receiving Amputation

Between May 1975 and April 1981, 43 patients with soft-tissue sarcoma of the extremities were randomized into this treatment protocol. Follow-up is complete in all patients as of October 1981 with a median follow-up of four years and eight months. The characteristics of the patients randomized in this protocol are presented in Table 1. Sixteen patients randomized to receive amputation and 27 patients randomized to receive limb-sparing surgery and radiotherapy. Only about one third of eligible patients with soft-tissue sarcomas of the extremities agreed to enter this protocol and only these patients are considered here. There were no significant differences in patient characteristics in the two treatment arms with regard to sex, race, site, histology, or histologic grade of the primary lesions. Patients randomized to receive amputation tended to be younger than patients randomized to receive limb-sparing surgery plus radiation therapy.

The results of treatment as a function of site, histology, and grade of the primary lesion is presented in Table 2. Three patients randomized to the amputation

TABLE 2. *Soft-tissue Sarcomas of the Extremities*

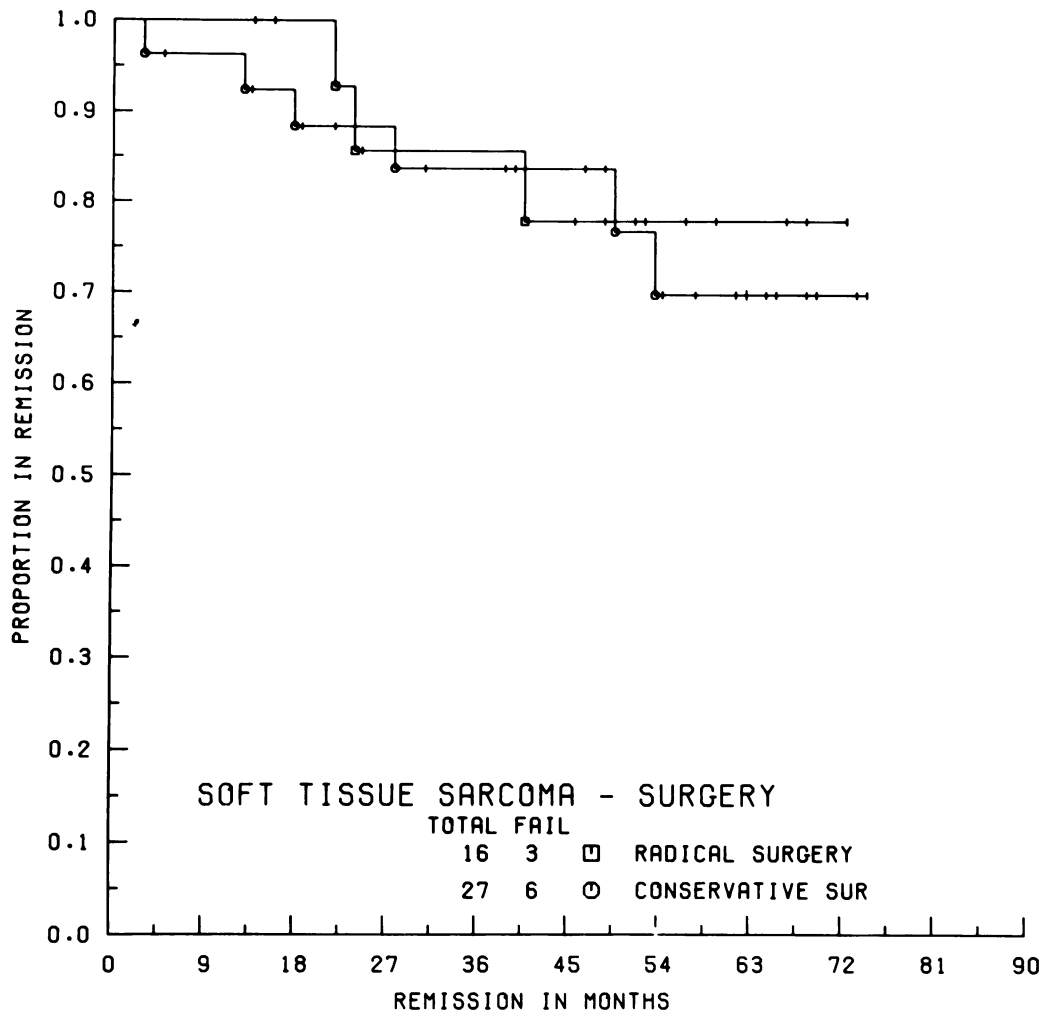|	Amputation (Number of Patients)					Limb-Sparing Surgery + Radiotherapy (Number of Patients)				
		Recurred					Recurred			
	Total	Local	Distant	Local + Distant	Dead	Total	Local	Distant	Local + Distant	Dead
Arm	2	0	0	0	0	3	0	0	0	0
Forearm-hand	1	0	0	0	0	2	0	0	0	0
Thigh	10	0	2	0	2	17	1	2	3	3
Leg-foot	3	0	1	0	0	5	0	0	0	0
Fibrosarcoma	0	0	0	0	0	1	0	0	0	0
Malignant fibrous histiocytoma	1	0	1	0	1	3	0	0	0	0
Liposarcoma	7	0	0	0	0	4	0	1	1	1
Leiomyosarcoma	1	0	1	0	0	1	0	0	0	0
Rhabdomyosarcoma	0	0	0	0	0	3	1	0	1	1
Synoviosarcoma	4	0	1	0	1	7	0	0	1	1
Neurofibrosarcoma	1	0	0	0	0	3	0	1	0	0
Undifferentiated	2	0	0	0	0	5	0	0	0	0
Grade: 1	1	0	0	0	0	0	0	0	0	0
2	4	0	1	0	0	3	0	0	0	0
3	11	0	2	0	2	24	1	2	3	3
Total	16	0	3	0	2	27	1	2	3	3

FIG. 1. Prospective randomized evaluation of continuous disease-free survival in patients receiving either amputation or limb-sparing surgery plus radiation therapy.

SOFT TISSUE SARCOMA - SURGERY

TOTAL FAIL

16   3   □   RADICAL SURGERY

27   6   ⊙   CONSERVATIVE SUR

REMISSION IN MONTHS

PROPORTION IN REMISSION

arm recurred, and two of these patients have died. All three patients had distant metastases to the lungs, and there were no local recurrences in this treatment group. One patient had all pulmonary metastases resected and remains alive and disease-free eight months later.

Six patients have recurred in the limb-sparing surgery plus radiation therapy arm of the protocol, and three of these patients have died. There were a total of four local recurrences in these patients. One patient developed a local recurrence in the distal thigh. This patient subsequently underwent a hip disarticulation and remains disease-free 35 months later. Three patients developed simultaneous local recurrence and distant metastases, and two patients developed only distant metastases. These latter two patients underwent resection of all pulmonary metastases and remain alive 28 and 30 months later.

Actuarial analysis of the time to recurrence for all patients in the protocol is presented in Figure 1. There was no significant difference in time to recurrence in patients randomized to receive amputation compared with those randomized to receive limb-sparing surgery

plus radiation therapy (p_2 = 0.75). Actuarial five-year disease-free survival was 78% in the amputation group and 71% in the limb-sparing group. Similarly there was no difference in overall survival between these two patient groups as shown in Figure 2 (p_2 = 0.99). Actuarial five-year overall survival in the amputation group was 88% compared with 83% in the group undergoing limb-sparing surgery. When analyzed for local recurrence there is a suggestion that patients undergoing limb-sparing surgery plus radiation therapy have a higher local recurrence rate than patients undergoing amputation as shown in Figure 3 (p_1 = 0.06). This difference in local recurrence rates did not result in improved survival in patients in this protocol though the number of patients in this comparison is small and this conclusion is a tentative one.

Detailed studies of the quality of life of patients in these two treatment arms have been performed and presented elsewhere.[18] The authors found no significant differences in the quality of life parameters that were evaluated between these two patient groups.

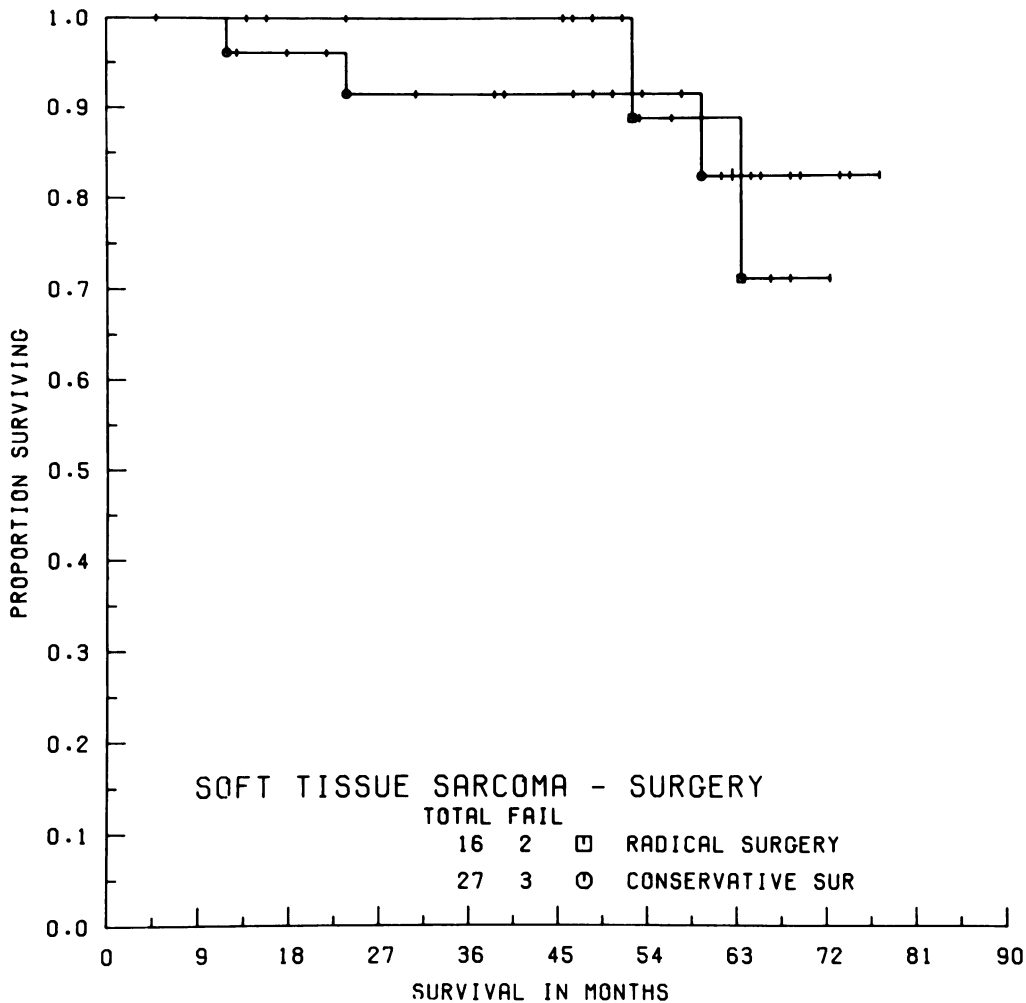The disease-free and overall survival of patients in

FIG. 2. Prospective randomized evaluation of overall survival in patients receiving either amputation or limb-sparing surgery plus radiation therapy.

SOFT TISSUE SARCOMA - SURGERY

TOTAL	FAIL		
16	2	⊡	RADICAL SURGERY
27	3	⊙	CONSERVATIVE SUR

this protocol was markedly improved compared with virtually all reported series of patients with soft-tissue sarcomas of the extremities.[1-10] All patients in this protocol received adjuvant chemotherapy and this is the likely explanation for the improved disease-free and overall survival seen in these patients as will be addressed in the next section.

Adjuvant Chemotherapy in Patients with Soft-Tissue Sarcomas of the Extremities

Between May 1975 and June 1977 all patients with soft-tissue sarcomas of the extremities treated in the Surgery Branch of the National Cancer Institute in the protocol described in the previous section, as well as patients not eligible or refusing randomization in the above protocol, were treated with adjuvant chemotherapy. Preliminary results of this treatment in 26 patients with extremity soft-tissue sarcomas were reported in 1978.[19] Despite the short follow-up at that time, it appeared that disease-free and overall survival in the patients receiving chemotherapy was prolonged compared with 46 historical controls from our own institution treated by surgery alone. In June 1977, therefore, we began a prospective randomized trial of the value of adjuvant chemotherapy in patients with soft-tissue sarcomas of the extremities. Patients underwent local therapy by either amputation or limb-sparing surgery plus radiation therapy and were then prospectively randomized to receive chemotherapy with doxorubicin, cyclophosphamide, and high-dose methotrexate as described above or to receive no adjuvant chemotherapy. This patient population differs from that previously described in the protocol comparing amputation and limb-sparing surgery plus radiation therapy though 16 of the 92 total patients in these protocols overlap the two protocols.

Sixty-five patients were evaluated in this randomized protocol before its termination in July 1981. Follow-up is presented here as of October 1981 with a median
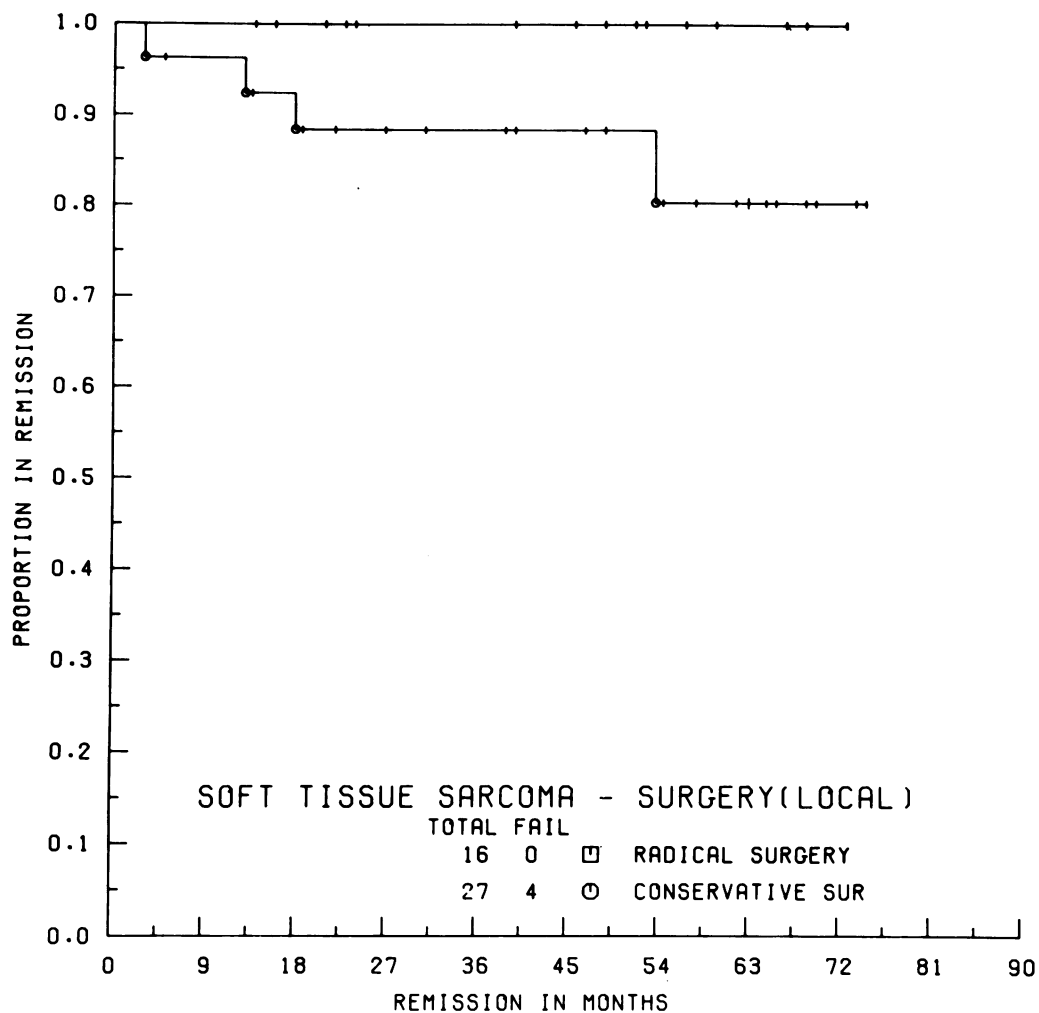
FIG. 3. Prospective randomized evaluation of local recurrence in patients receiving either amputation or limb-sparing surgery plus radiation therapy.

follow-up of 653 days. Thirty-seven patients randomized to receive chemotherapy and 28 patients randomized to receive no chemotherapy. Actuarial analysis reveals a marked improvement in continuous disease-free survival in patients randomized to receive chemotherapy compared with those receiving no chemotherapy as shown in Figure 4 (p_1 = 0.0008). The actuarial three-year disease-free survival for patients randomized to receive chemotherapy was 92% compared with 60% for patients receiving no chemotherapy. Improved survival in patients receiving chemotherapy was seen in patients who underwent either amputation or limb-sparing resection plus radiation therapy (Table 3). The overall survival of patients receiving chemotherapy was also improved compared with those randomized to receive no chemotherapy (Table 3) with actuarial three-year survivals of 95% and 74%, respectively (p_1 = 0.04).

Three patients randomized to receive chemotherapy recurred with disease confined to the lung. Two of these patients underwent resection of all pulmonary disease

and remain alive and free of disease without further recurrence eight and 23 months later. Nine patients who randomized to receive no chemotherapy recurred. Five patients recurred solely in the lung and four of these patients underwent resection of all known pulmonary disease, though only one has remained disease-free four months later. The remaining three patients recurred in the lungs a second time and were all rendered disease-free at repeat thoracotomy and are alive with no evidence of disease at one, two, and three months later. Though follow-up in this randomized trial is short, it appears that adjuvant chemotherapy is of benefit in the treatment of patients with soft-tissue sarcomas of the extremities. This prospective randomized trial confirms the results of the authors' pilot, historically controlled trial conducted in the Surgery Branch of the National Cancer Institute between 1975 and 1977.[19] Updated analysis of the 26 patients entered into that pilot trial as of October 1981 with a minimum follow-up of over four years continues to show benefit
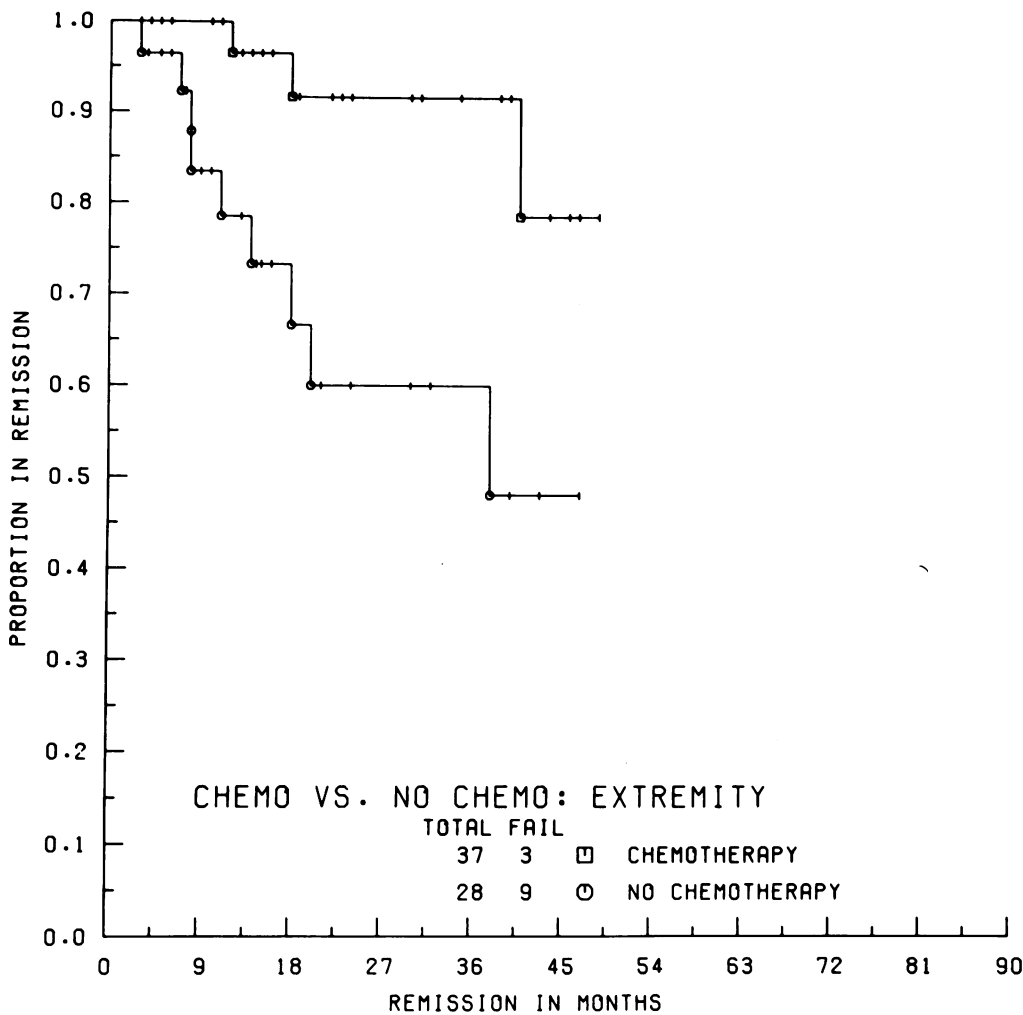
FIG. 4. Prospective randomized evaluation of continuous disease-free survival in patients randomized to receive adjuvant chemotherapy or no chemotherapy.

for patients who received chemotherapy compared with historical controls who did not receive chemotherapy (p < 0.001).

Discussion

Soft-tissue sarcomas are malignant tumors of the extraskeletal connective tissues that are characterized by an aggressive tendency to invade into surrounding soft tissues and by a tendency for early metastatic spread to the lungs. There are about 4500 new cases of soft-tissue sarcomas in the United States each year. Soft-tissue sarcomas represent about 0.7% of cancers

and about 6.5% of all cancers in individuals below the age of 25.[1] Many different diagnoses comprise the soft-tissue sarcomas, though all have a similar clinical behavior and can be considered as a single entity in evaluating proper therapy. The degree of differentiation (histologic grade) of the lesion is the major prognostic factor in patients with soft-tissue sarcomas.

The extensive local invasion of soft-tissue sarcomas into surrounding tissues has led to local recurrence rates of approximately 30 to 50% when wide local excision alone is used as treatment of these lesions.[1-6] Two approaches that have been used to attempt to improve local control rates are the use of extensive radical compartmental excisions or amputations and the use of local excisional surgery to remove gross tumor followed by aggressive radiation therapy to all areas at risk for local tumor spread.[7-10] Though this latter approach is effective in the control of childhood rhabdomyosarcomas, the application of this combined modality treatment to adult patients with soft-tissue sarcomas has not been evaluated in well designed clinical trials in the adult.

TABLE 3. *Soft-tissue Sarcomas of the Extremities*

	Chemotherapy	No Chemotherapy	
	(number of patients)		
Total recurred	3/37	9/28	$p_1 = 0.0008$
Total dead	1/37	4/28	$p_1 = 0.04$
Amputation-recurred	3/16	6/11	$p_1 = 0.006$
Limb sparing-recurred	0/21	3/17	$p_1 = 0.04$

The current clinical trial was undertaken in an attempt to compare the standard treatment for extremity sarcomas, *i.e.,* amputation to treatment with limb-sparing resectional surgery followed by radiation therapy.

In virtually all reported series of patients with soft-tissue sarcomas, five-year survival is in the range of 40%.[1-10] Several chemotherapeutic agents exist with proven effectiveness in the treatment of adult patients with soft-tissue sarcomas, including doxorubicin, cyclophosphamide, DTIC, methotrexate, and vincristine.[1,20-25] Objective response rates of approximately 30 to 45% can be achieved in patients with metastatic soft-tissue sarcomas when appropriate combinations of these chemotherapeutic agents are utilized. The use of aggressive adjuvant chemotherapy following surgery in the treatment of patients with soft-tissue sarcomas of the extremities has not been subjected to rigorous clinical evaluation. In the studies reported here the authors have evaluated the combination of doxorubicin, cyclophosphamide, and high-dose methotrexate in patients following definitive resection for the treatment of soft-tissue sarcomas. Though follow-up is limited in this latter protocol, previous studies have shown that 80% of all sarcoma patients who recur, manifest a recurrence within two years of definitive therapy.[3,7,8] This allows for relatively rapid evaluation of new therapies in this disease.

Between 1975 and 1981, the authors conducted a prospective randomized evaluation in adult patients with soft-tissue sarcomas of the extremities, comparing amputation with limb-sparing resection followed by radiation therapy. Only about one third of all patients with soft-tissue sarcomas of the extremities seen in the Surgery Branch of the NCI suitable for entrance into this protocol consented to join the protocol, and the data presented here deals only with this patient group. Although many patients refused amputation, a smaller number insisted on this treatment compared with the more experimental limb-sparing surgical treatment combined with radiation therapy. All patients included, however, were prospectively randomized. Patients randomized to receive amputation had removal of all involved tissues in the compartment of the tumor. Patients randomized to receive limb-sparing resection all underwent resection of all gross disease with maintenance of a functional extremity as a primary goal. In four of 27 patients undergoing limb-sparing surgery, positive margins of resection were present at the completion of surgery because of the proximity of tumor to essential nerves and vessels. Approximately 15% of patients presented with extremity lesions that were so extensively invasive into local tissues that local resection of all gross disease with maintenance of reasonable function of the extremity was not thought to be possible. These patients

all underwent amputation and were not entered into this randomized protocol.

Appropriate stratification for prognostic factors resulted in a similar distribution of patients in the two treatment arms with respect to sex, age, race, site, histology, and histologic grade. Actuarial analysis of the results of this protocol with a median follow-up of four years and eight months revealed no difference in disease-free or overall survival between the two patient groups. The local recurrence rate was somewhat higher in the group receiving limb-sparing surgery plus radiation therapy ($p_1 = 0.06$) though this difference did not result in decreased survival of patients undergoing limb-sparing surgery plus radiation therapy. Though the lack of impact of increased local recurrence on survival may be due to the small number of patients involved in this comparison, it may also indicate that patients with lesions that locally recur are also patients that are highly likely to develop disseminated disease even if local control were achieved by more radical surgery.

In a further attempt to analyze the prognostic factors responsible for recurrence the authors performed a multivariate analysis of the treatment results of all patients who received chemotherapy for the treatment of soft-tissue sarcomas in both protocols considered in this article. No correlation existed with local recurrence, overall recurrence or survival with respect to site, histology, grade, sex, race, age, time from surgery to onset of chemotherapy and nadir white count or platelet counts during chemotherapy. However, a high correlation did exist with local recurrence and the final margin of surgical resection with a marked increase in local recurrence in patients whose final surgical margins were positive for tumor ($p < 0.0001$). In this combined group patients with negative surgical margins had an improved survival compared with those with positive surgical margins ($p_1 = 0.007$). This analysis, however, includes patients from the chemotherapy randomization study who were not randomized to the surgical treatments, and it is thus possible that this survival difference is caused by factors other than the surgical treatment performed. Patients who had positive surgical margins who recurred might well have recurred if amputative surgery to achieve negative margins had been performed. On the basis of the authors' randomized trial it does not appear essential that negative surgical margins be achieved if radiation therapy and chemotherapy are administered in the postoperative period. However, this conclusion is based on a small number of patients and must be considered tentative. A very conservative interpretation of these results, however, would indicate that if negative surgical margins can be obtained with limb-sparing surgery, and radiation therapy and chemotherapy are used in the postoperative period, these

patients will have a long-term, disease-free and overall survival comparable with those patients who undergo amputation.

Because of the improved survival that was observed in the early pilot trials utilizing chemotherapy in patients with soft-tissue sarcomas of the extremities,[19] the authors undertook a prospective randomized trial of the value of chemotherapy. The adjuvant chemotherapy regimen selected was a combination of doxorubicin, cyclophosphamide, and high-dose methotrexate that appeared successful in the early pilot trials.

A recent analysis of the results of treatment in the 26 patients in the pilot chemotherapy trial treated between May 1975 and June 1977 compared with our historical controls, with a minimum follow-up of four years, revealed an improvement in survival because of the adjuvant chemotherapy ($p = 0.001$). The prospective randomized trial comparing patinets receiving chemotherapy with those receiving no chemotherapy conducted between June 1977 and July 1981 revealed a marked improvement in disease-free and overall survival for those patients receiving chemotherapy. This trial has been analyzed in more detail elsewhere. It should be emphasized, however, that follow-up in this trial is short (one year, eight months), and further follow-up will be necessary to verify this conclusion.

In summary it appears that limb-sparing surgery plus radiation therapy is effective treatment for most patients with soft-tissue sarcomas of the extremities. Postoperative adjuvant treatment with the combination chemotherapy regimen that has been described appears capable of significantly improving disease-free and overall survival of these patients.

References

1. Rosenberg SA, Suit HD, Baker LH, Rosen G. Sarcomas of the soft tissue and bone. In: DeVita VT, Hellman S, Rosenberg SA, eds. Principles and Practice of Oncology. Philadelphia: JB Lippincott, 1982; 1037-1093.
2. Rosenberg SA, Glatstein EJ. Perspectives on the role of surgery and radiation therapy in the treatment of soft tissue sarcomas of the extremities. Semin Oncol 1981; 8:190-200.
3. Cantin J, McNeer GP, Chu FC, et al. The problem of local recurrence after treatment of soft tissue sarcoma. Ann Surg 1968; 168:47-53.
4. Gerner RE, Moore GE, Pickren JW. Soft tissue sarcomas. Ann Surg 1975; 181:803-808.
5. Shieber W, Graham P. An experience with sarcomas of the soft tissues in adults. Surgery 1962; 52:295.
6. Hare HF, Cerny MF. Soft tissue sarcoma: a review of 200 cases. Cancer 1963; 16:1332.
7. Shiu MH, Castro EB, Hajdu SI, et al. Surgical treatment of 297 soft tissue sarcomas of the lower extremity. Ann Surg 1975; 182:597.
8. Simon MA, Enneking WF. The management of soft-tissue sarcomas of the extremities. J Bone Joint Surg 1976; 58-A:317.
9. Suit HD, Russell WO, Martin RG. Sarcoma of soft tissue: clinical and histopathologic parameters and response to treatment. Cancer 1975; 35:1478-1483.
10. Lindberg RD, Martin RG, Romsdahl MM. Surgery and postoperative radiotherapy in the treatment of soft tissue sarcomas in adults. Am J Roentgenol Ther Nucl Med 1975; 123:123-129.
11. Rosenberg SA, Tepper J, Glatstein E, et al. Prospective randomized evaluation of adjuvant chemotherapy in adults with soft tissue sarcomas of the extremities. Cancer 1982 (in press).
12. Tepper J, Rosenberg SA, Glatstein E. Radiation therapy technique in soft tissue sarcomas of the extremity—policies of treatment at the National Cancer Institute. Int J Radiat Oncol Biol Phys 1981; 8:263-273.
13. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22:719-748.
14. Thomas D. Exact and asymptomatic methods for the combination of 2 × 2 tables. Computers Biomedical Res 1975; 8:423-446.
15. Kaplan E, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958; 8:423-446.
16. Armitage P. Statistical Methods in Medical Research. New York: John Wiley & Sons, 1971; 135-138.
17. Peto R, Pike M, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Introduction and design. Br J Cancer 1976; 34:611-612.
18. Sugarbaker PH, Barofsky I, Rosenberg SA, Bianola FJ. Quality of life assessment of patients in extremity sarcoma clinical trials. Surgery 1982; 91:17-23.
19. Rosenberg SA, Kent H, Costa J, et al. Prospective randomized evaluation of the role of limb-sparing surgery, radiation therapy, and adjuvant chemoimmunotherapy in the treatment of adult soft-tissue sarcomas. Surgery 1978; 84:62-69.
20. O'Bryan RM, Luce JK, Talley RW, et al. Phase II evaluation of adriamycin in human neoplasia. Cancer 1973; 32:1-8.
21. O'Bryan RM, Baker LH, Gottlieb JE, et al. Dose response evaluation of adriamycin in human neoplasia. Cancer 1977; 39:1940-1948.
22. Gottlieb JA, Benjamin RS, Baker LH, et al. Role of DTIC (NSC-45388) in the chemotherapy of sarcomas. Cancer Treat Rep 1976; 60:199-203.
23. Korst DR, Johnson D, Frenkel EP, et al. Preliminary evaluation of the effect of cyclophosphamide on the course of human neoplasms. Cancer Chemother Rep 1960; 7:1-12.
24. Subramanian S, Wiltshaw E. Chemotherapy of sarcoma—a comparison of three regimens. Lancet 1978; 683-686.
25. Selawry OS, Holland JF, Wolman IJ. Effect of vincristine (NSC-67574) on malignant solid tumors in children. Cancer Chemother Rep 1968; 52:497-499.

DISCUSSION

DR. LASALLE D. LEFFALL, JR. (Washington, D.C.): I would like to compliment Dr. Rosenberg and his colleagues on this paper, in particular for their continued study on a very important area in surgical oncology, and that is the management of soft sarcomas. Even though we don't see very many of these malignant tumors, very often when we do see them, some of these patients have been subjected to amputations, and I think, based on the study of Dr. Rosenberg and others who he has alluded to in his manuscript, we have evidence to show that we do not need to perform some of these amputative procedures.

In the manuscript, he gives recognition to the work of Suit and Lindberg; both of these men called attention to the role that radiotherapy plays in the management of soft sarcomas. At one time we