The Role of Multimodality Therapy in Soft-tissue Sarcoma

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Soft-tissue sarcomas are uncommon malignancies. The development during a period of 8 years, in one institution, of a prospective data base incorporating more than 1600 patients with these tumors is described. The most common sites for occurrence are the extremities, but they can occur in any of the soft tissues of the body. Liposarcoma and leiomyosarcoma are the most common histopathologic conditions identified. Prognostic factors for both recurrence and survival include site, histopathology, size, grade, and adequacy of resection. A prospective randomized trial of the use of adjuvant radiation by the brachytherapy technique in extremity lesions has shown a decrease in local recurrence, but no impact on survival. Eligible patients not randomized to the trial show no difference in local recurrence or survival, regardless of whether they received adjuvant radiation.

SOFT-TISSUE SARCOMAS are ubiquitous neoplasms that arise in the soft, or connective, tissues of the body. They are diverse in histology and occur at any site throughout the body. Most of them predominate in the extremities. Soft-tissue sarcomas in children, especially the most common form, rhabdomyosarcoma, have been prototypes for multimodality therapy.[1] Children previously treated only by radical and mutilating surgery can now be treated by more function-sparing procedures, chemotherapy and radiation therapy, with the chance for long-term, disease-free survival.[2] The challenge to transfer to adults the improved results seen in children has been one of frustration. The present report documents some of our experiences with these neoplasms and focuses on a recent prospective randomized trial to control local recurrence, by the addition of adjuvant radiation therapy using the brachytherapy technique, in patients with adult extremity soft-tissue tumors.

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Materials and Methods

In 1982 we began a prospective database at Memorial Sloan-Kettering Cancer Center (MSKCC) for all adult (age more than 16 years) patients admitted and treated for soft-tissue sarcoma. This database has been used for the development of prospective evaluations of the management of these tumors and the correlation of clinical and biologic parameters for outcome and survival. All patient tissue biopsies and tumor resections have been reviewed by a single pathologist. All patients have been reviewed and staged on a weekly basis as to extent of disease, and multiple demographic features have been recorded. These include factors known to influence outcome, such as age; sex; tumor site, size, depth, histopathologic grade, and type; and presence or absence of metastasis.

A prospective randomized study of the benefit of brachytherapy (BRT) was begun in July 1982 and is reported here as of closure in July 1987. Patients were ineligible if they had received previous radiation therapy or chemotherapy or if they were foreign nationals, for whom long-term follow-up might be difficult. All patients with localized extremity or superficial truncal lesions were considered eligible, providing they had a limb-sparing operation that would completely remove all gross disease without tumor violation and without the need for resection of major vessels, nerves, or bone. Patients were included if they presented either with a primary untreated but biopsied lesion, or with a locally recurrent but nonmetastatic tumor. All patients had a tissue diagnosis of soft-tissue sarcoma before entrance into the trial.

Signed informed consent was obtained before operation and intraoperative randomization was performed once

we could determine that all gross tumor could be resected. Tumor violation was an intraoperative exclusion, as was the failure to remove the tumor completely as judged by the operating surgeon. Extracapsular excision, in which a defined gross margin of normal tissue could not be obtained, was acceptable. Stratification was used before randomization for known prognostic variables previously identified.[3,4] These included tumor presentation (primary or recurrent), tumor size (less than or more than 5 cm), tumor depth (superficial or deep), and tumor grade (high or low). Once randomized, afterloading catheters were placed in the tumor bed, and on the fifth to sixth postoperative day, these catheters were loaded with Iridium-192 sources. A total dose of approximately 4200 to 4500 cGy was delivered in 4 to 6 days to the isodose contour that incorporated the target volume determined at the time of operation.[5,6] Patients with high-grade tumors were eligible to receive postoperative chemotherapy as part of a further randomized trial of the benefits of adjuvant chemotherapy, with Adriamycin (Adria Laboratories, Dublin, OH) given by either the bolus or continuous-infusion technique.[7] Patient follow-up examinations were performed every 3 months for the first 3 years, then every 6 months thereafter. All nonrandomized patients were followed in the same manner as those who were randomized.

The margin of resection of any tumor situated within 1 mm of an inked surface margin of the surgical specimen was considered microscopically positive.

Statistical evaluation includes the use of chi square, Kaplan–Meier survival curves, and log-rank analysis, performed where indicated.

Results

From 1982 through 1990, we admitted 1685 adults who were more than 16 years old with soft-tissue sarcoma. Most tumors (50%) occurred in the extremities (Fig. 1). The most common histopathologic diagnosis was liposarcoma, followed by leiomyosarcoma and malignant fibrous histiocytoma (MFH) (Fig. 2). In the extremities and superficial trunk, liposarcoma and MFH were most common, whereas in the retroperitoneum and visceral tissues, leiomyosarcoma predominated. Survival rate based solely on site and individual histopathology are shown in Figures 3 and 4. Because tumor grade and site are so important, we documented outcome based on high-grade status alone within a single site, the extremity (Fig. 5).

Between 1982 and 1987, 997 patients were admitted to MSKCC; of 225 eligible patients, 126 were randomized in the trial of BRT. Failure to randomize was due primarily to patient refusal to accept entrance into an 'ex-

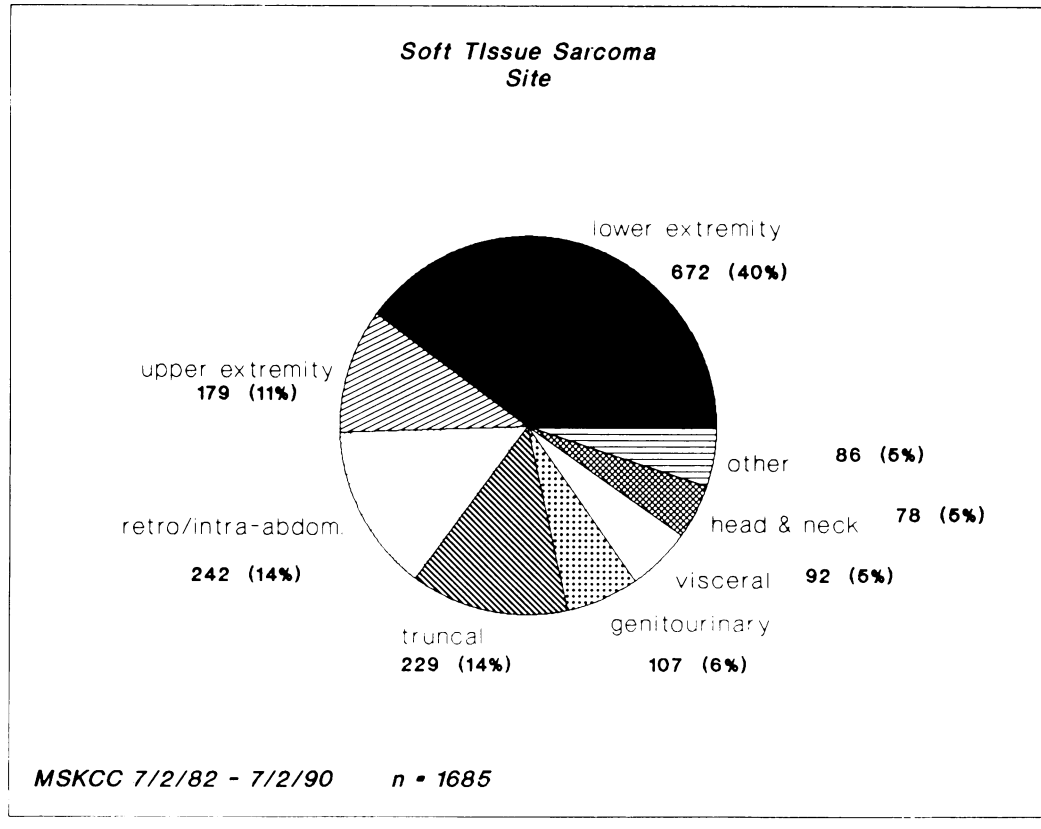

FIG. 1. Site of sarcoma in 1685 patients admitted from 1982 to 1990.

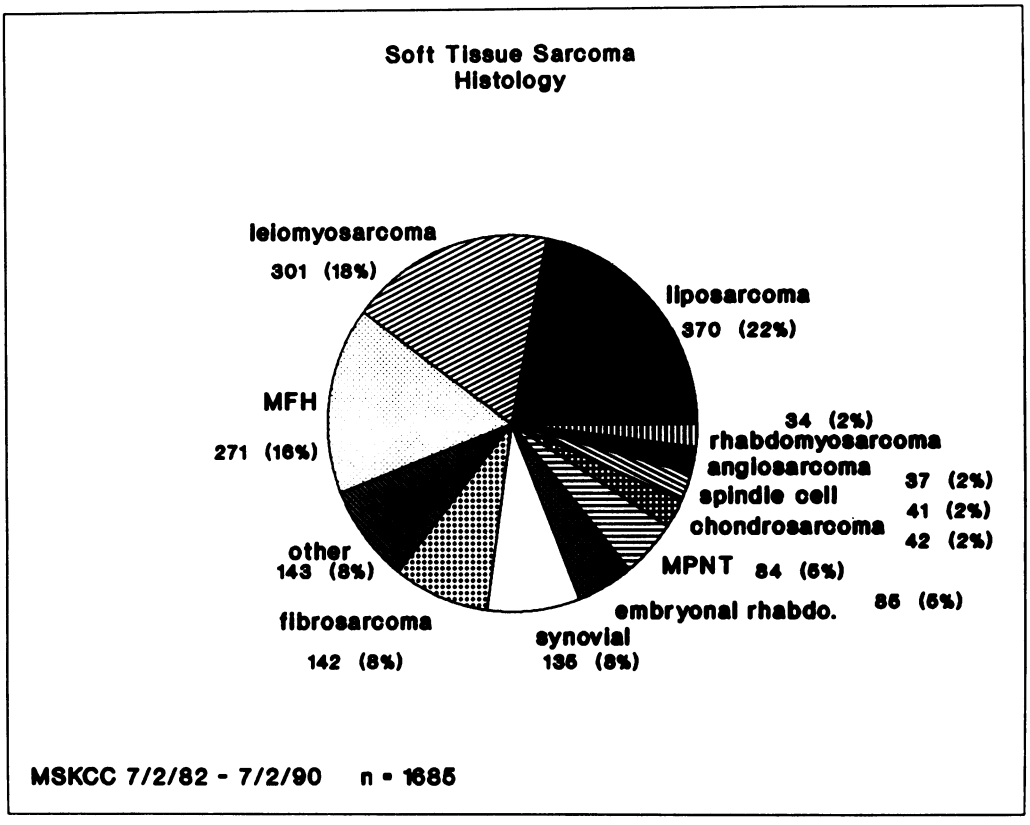

FIG. 2. Histopathology of soft-tissue sarcoma for 1685 patients with soft-tissue sarcoma, admitted from 1982 to 1990.

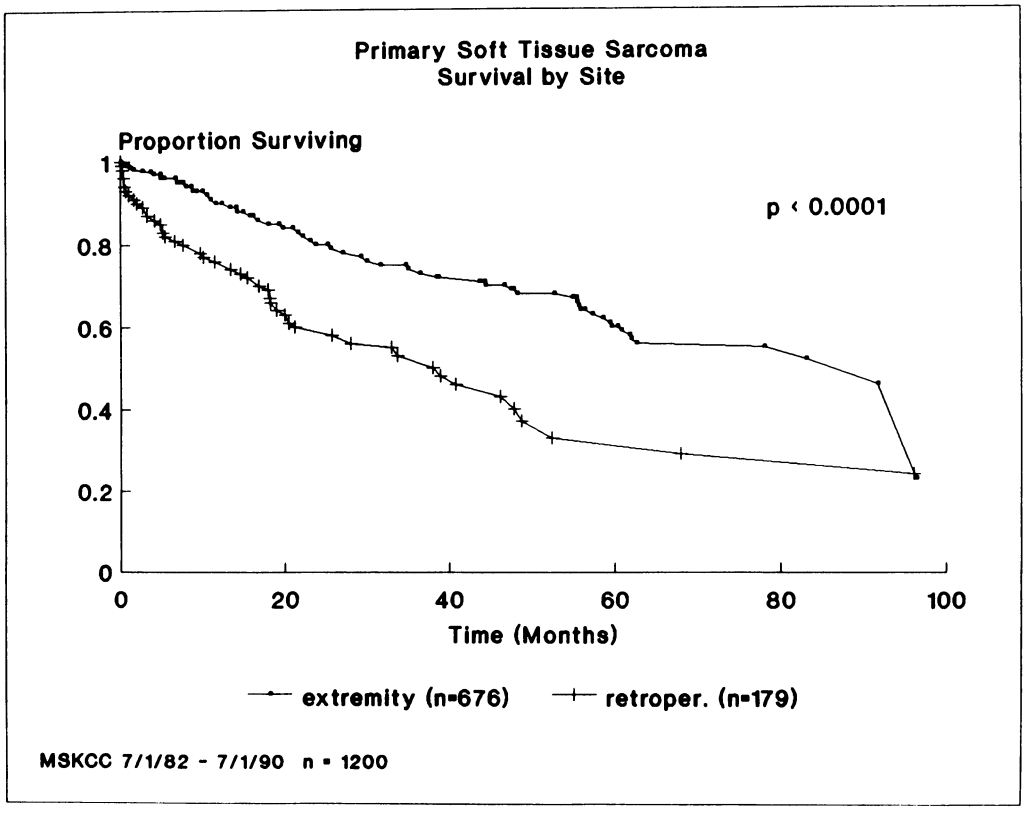

FIG. 3. Survival by site: extremity lesions have a better overall prognosis than retroperitoneal lesions ($p < 0.0001$) for patients presenting with localized disease, for whom complete follow-up is available.

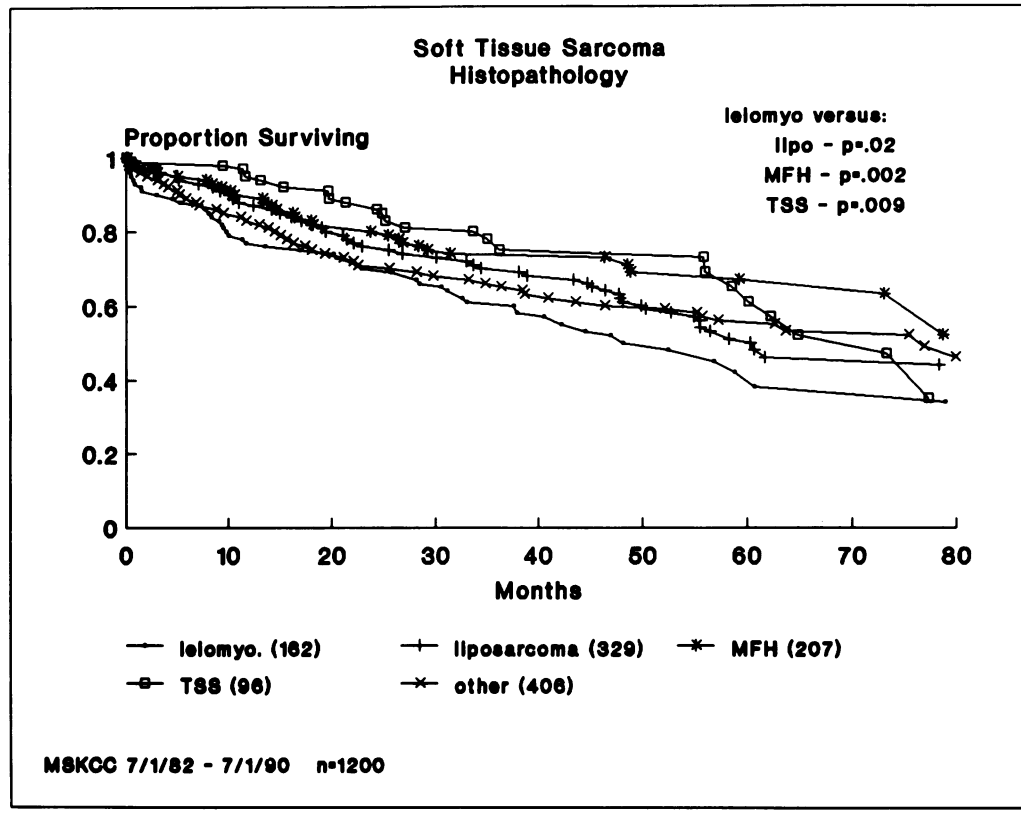

FIG. 4. Survival by histopathology for patients with primary (nonmetastatic) tumors at presentation.

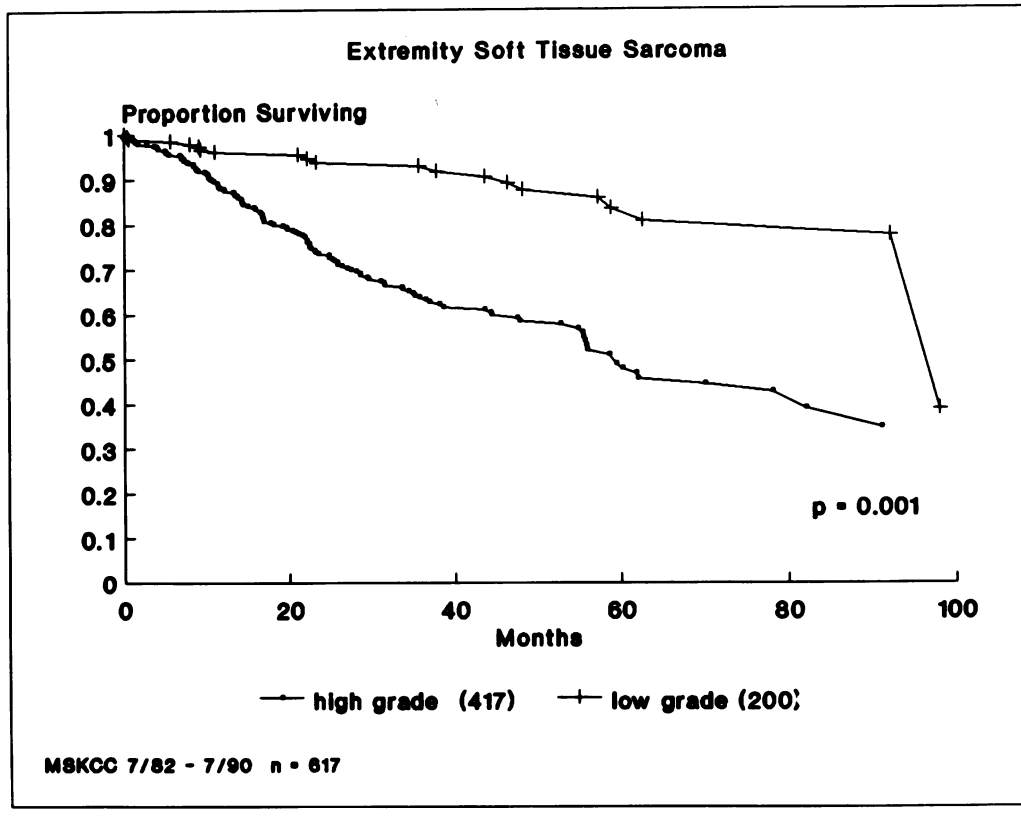

FIG. 5. Extremity soft-tissue sarcoma. Patients with primary localized lesions at presentation. Influence of grade is shown.

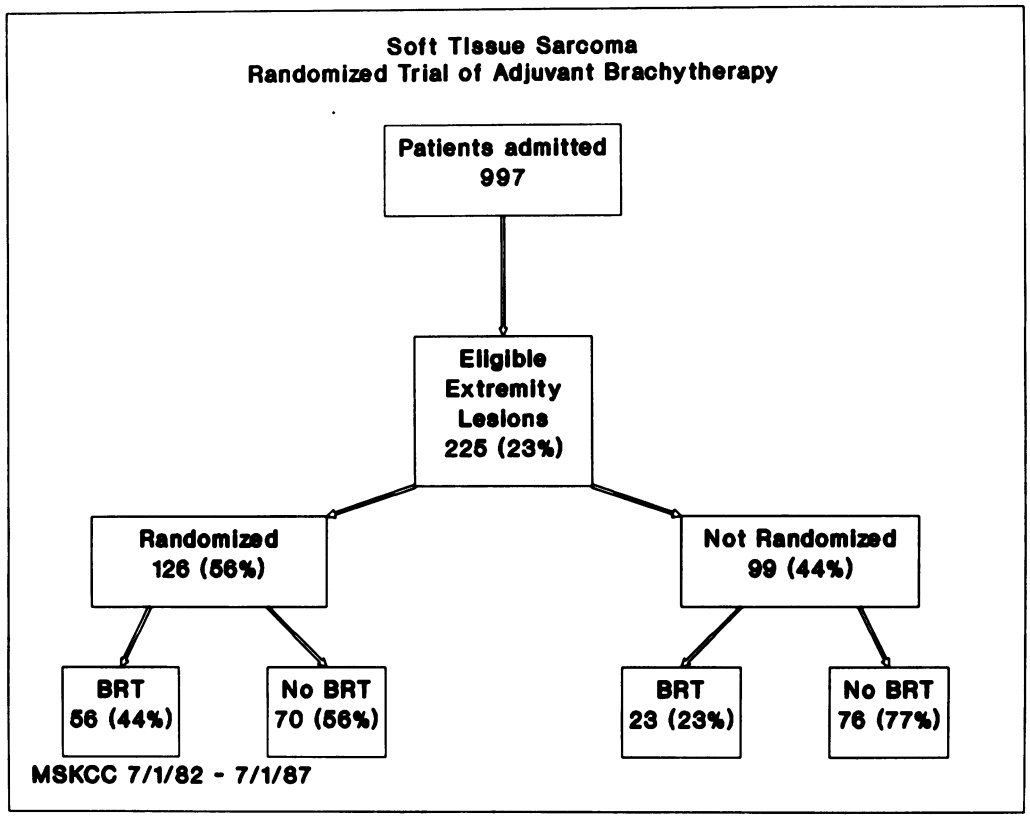

FIG. 6. Schematic showing randomization of patients for adjuvant brachytherapy.

periment.' Of those patients not randomized, approximately 25% received BRT and 75% did not (Fig. 6). Follow-up data dates from March 1, 1991, with a median of 40.75 months for all patients, and 46.5 months for survivors.

The appropriateness of our preoperative stratifications are indicated in Table 1, showing patients equally distributed between the two groups according to risk factors. The differences between the numbers entered for the two groups was a consequence of our initial expectation that we would need 250 patients to show effectiveness, and because of multiple prerandomization stratifications, group allocation was performed such that a balance for each stratum would be achieved when 30 patients were entered into each stratum. The fact that 30 patients were not entered into every stratum at the time of closure confirmed the appropriateness of the stratification strategy but resulted in a slight disparity in the total number of patients in each group. The patients were equally distributed by histopathologic diagnosis (Table 2). There were no differences within the two groups between patients with high-grade lesions who received adjuvant Adriamycin, and no difference in the number with positive microscopic margins (Table 3). As expected, nonrandomized patients who received BRT had a greater proportion of large, deep, high-grade lesions than those not receiving BRT (Table 4).

The results of the impact on local recurrence are illustrated in Figure 7, in which any local recurrence is demonstrated to be diminished by the addition of BRT. This is true also when local-only recurrence is examined (Fig. 8). No effect on survival has yet been demonstrated (Fig. 9). Interestingly subset analysis, analyzing only high-grade

TABLE 1. *Soft-tissue Sarcoma: Randomized Trial of Adjuvant Brachytherapy*

Patient and Tumor Characteristics		BRT (n = 56)		no BRT (n = 70)	
Age (years)	>50	33	59%	39	56%
	<=50	23	41%	31	44%
Sex	Female	25	45%	24	34%
	Male	31	55%	46	66%
Site	Proximal	50	89%	59	84%
	Distal	6	11%	11	16%
Initial size	>5 cm	40	71%	52	74%
	<=5 cm	16	29%	18	26%
Depth	Superficial	24	43%	21	30%
	Deep	32	57%	49	70%
Grade	High	45	80%	52	74%
	Low	11	20%	18	26%
Presentation	Primary	50	89%	60	86%
	Recurrent	6	11%	10	14%

MSKCC 7/82-7/87.
All not significant by chi square test.
Patients are equally distributed according to risk factors.

TABLE 2. *Soft-tissue Sarcoma: Randomized Trial of Adjuvant Brachytherapy*

	Histopathology	
	BRT (n = 56)	no BRT (n = 70)
Liposarcoma	22 (39%)	27 (39%)
MFH	13 (23%)	17 (24%)
MPNT	6 (11%)	3 (4%)
Synovial	4 (7%)	4 (6%)
Leiomyosarcoma	4 (7%)	6 (9%)
Other	7 (13%)	13 (19%)

Patients are randomized by histopathology.
MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral nerve tumor.

lesions, suggests that the effect is due to the impact on local recurrence in high-grade lesions alone. Currently the benefit of adjuvant BRT for low-grade lesions has not been demonstrated, although the numbers are small. Interestingly one would expect the high-grade lesions to be accompanied by subsequent metastatic disease, yet the impact on long-term survival has not been demonstrated. This important observation is addressed further in the Discussion.

When we examine the characteristics of patients who did have a local recurrence as the first demonstration of recurrence, there was no difference in the distribution by risk factors. Microscopically positive margins did not appear to be a factor. Nonrandomized patients showed no apparent benefit from BRT (Fig. 10), which emphasizes the importance of randomized trials. Of 22 patients with positive microscopic margins (Table 3), three in the BRT group experienced local recurrence, as did three patients in the non-BRT group. Equal numbers of patients received or did not receive Adriamycin in the groups that experienced local recurrence.

Discussion

Several major questions exist about the management of soft-tissue sarcoma. Some address the entire biology of the management of malignancy. The issue of whether more conservative, *i.e.*, less radical, surgery can be performed and preserve limb function without sacrificing long-term freedom from local and distant recurrence is an important biologic concept. It has been addressed primarily in the management of breast carcinoma. However, to show that control of the local lesion can affect long-term survival, which many believe is predetermined, requires that a randomized trial can demonstrate decreased local recurrence by the use of an adjuvant modality. Once this is established in a trial setting, follow-up data on patients with diminished local recurrence can be examined in terms of survival. The current study addresses this issue. It would appear that at the present time, decrease in local recurrence is not accompanied by an improvement in the long-term survival rate. This important observation required continuation and long-term follow-up study.

Other important observations have been made as a consequence of examination of these interesting lesions, particularly as they relate to size and depth of the primary tumor in predicting survival. Previously no one group or institution has had enough patients to examine specifically outcome in terms of local recurrence or survival for individual sites or individual histopathologic diagnoses. As a consequence of the development of this data base, we have consistently tried to answer a number of questions about these patients and their tumors.

Initially, in a retrospective review of patients seen from 1968 to 78 and followed for more than 8 years, we identified factors that predicted both local recurrence and survival. These included patient age and tumor site, size, depth, histopathologic type, and histopathologic grade.[8-10] Careful dissection within the histopathologic determination, *e.g.*, liposarcoma, permitted the finding

TABLE 3. *Soft-tissue Sarcoma: Randomized Trial of Adjuvant Brachytherapy*

	BRT (n = 56)	no BRT (n = 70)
Pathologic margins		
Micropositive	11 (20%)	11 (16%)
Micronegative	45 (80%)	59 (84%)
High grade only	45 (80%)	52 (73%)
Adriamycin	34 (76%)	31 (60%)
No adriamycin	11 (24%)	21 (40%)

MSKCC 7/82–7/87.
All not significant by chi square test.
Pathologic margins and chemotherapy in each group.

TABLE 4. *Soft-tissue Sarcoma: Nonrandomized Patients*

Characteristic		BRT (n = 23)		no BRT (n = 76)	
Age	>50	9	39%	26	34%
	<=50	14	61%	50	66%
Sex	Female	12	52%	32	42%
	Male	11	48%	44	58%
Site	Proximal	20	87%	55	72%
	Distal	3	13%	21	28%
Initial size	>5 cm	13	56%	15	20%
	<=5 cm	10	44%	61	80%
Depth	Superficial	4	17%	48	63%
	Deep	19	83%	28	37%
Grade	High	16	70%	42	55%
	Low	7	30%	34	45%
Presentation	Primary	19	83%	60	79%
	Recurrent	4	17%	16	21%

MSKCC 7/82–7/87.

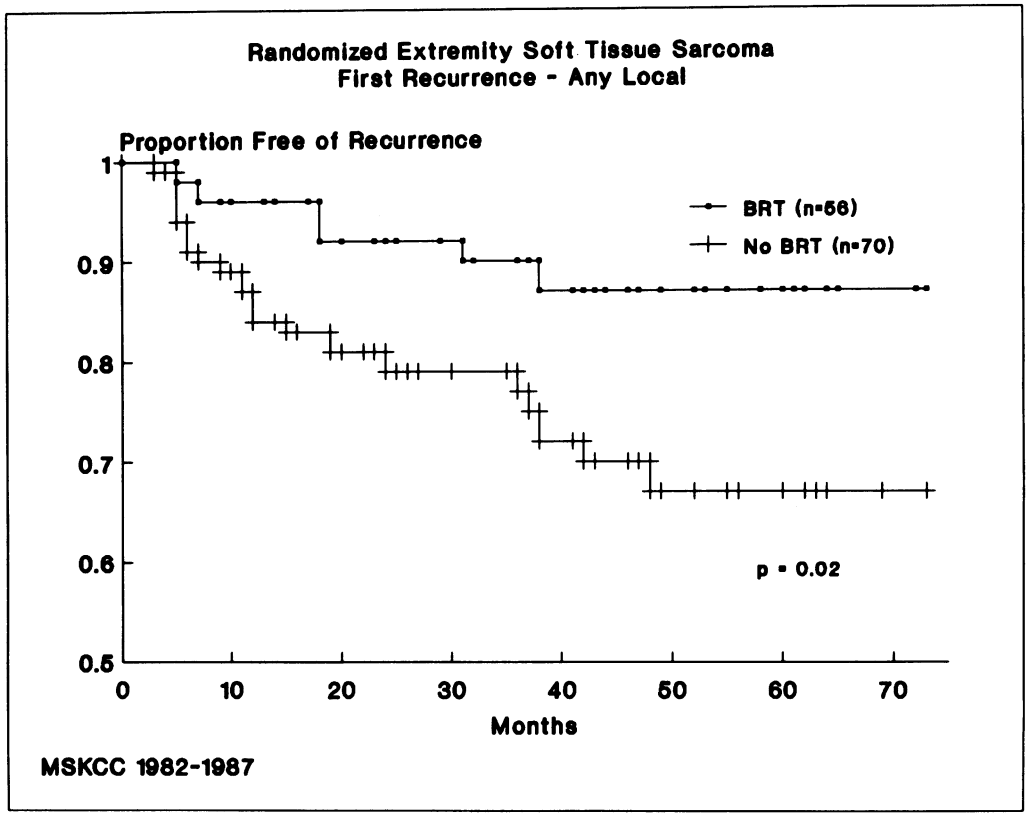

FIG. 7. Local recurrence is diminished by the addition of brachytherapy (follow-up March 1, 1991).

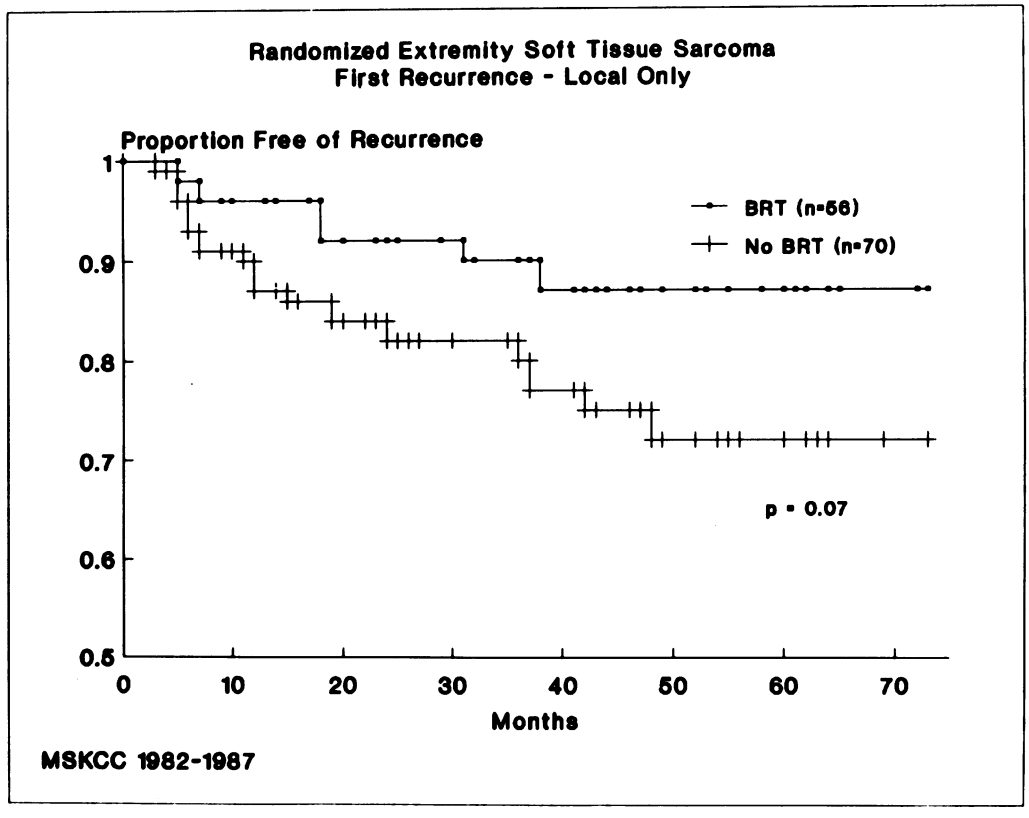

FIG. 8. Local-only recurrence is diminished by the addition of brachytherapy (follow-up March 1, 1991).

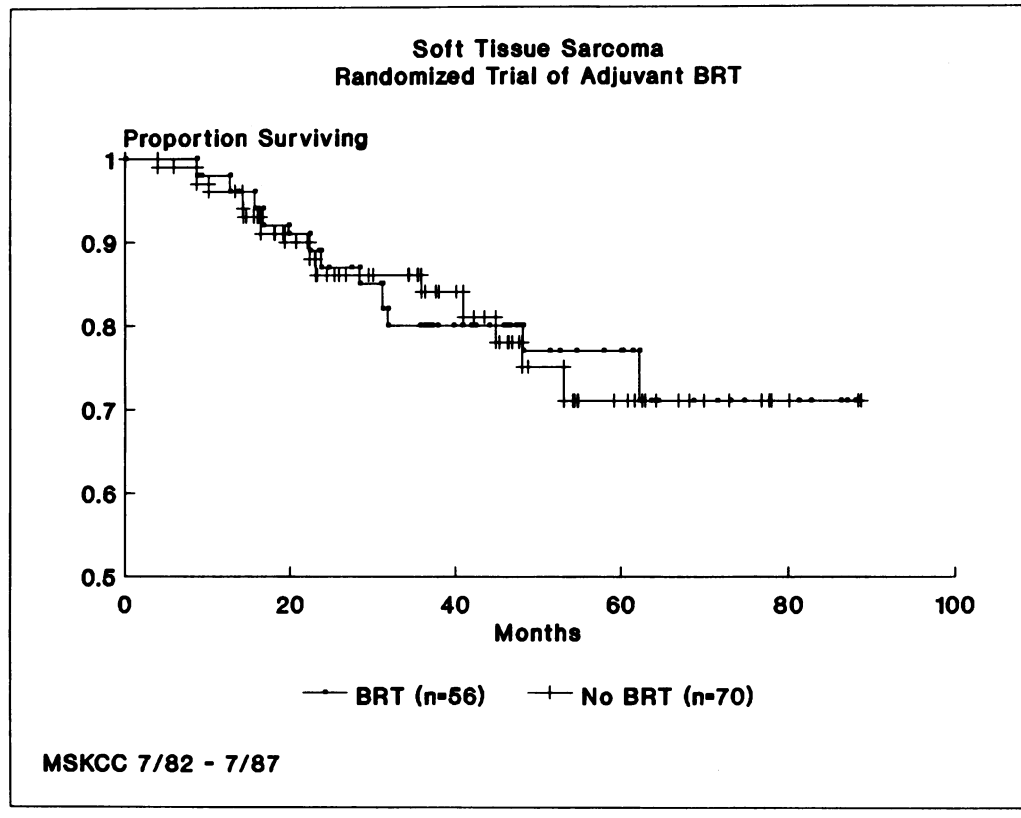

FIG. 9. No effect on survival has been demonstrated (follow-up March 1, 1991).

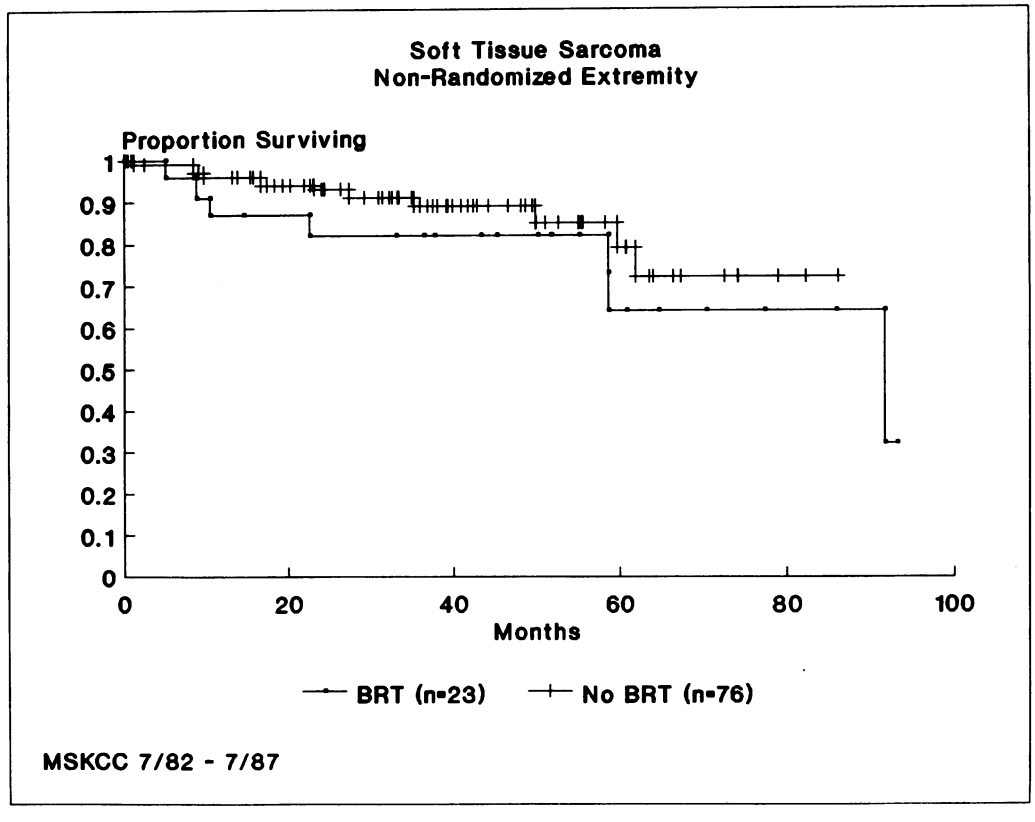

FIG. 10. Nonrandomized patients who received BRT showed no apparent benefit in effect on local recurrence.

that histologic subtype and grade could be predictors of local and systemic recurrence.[11] Careful examination of patients with low-grade lesions has allowed some insight into the possibility (less than 25%) of metastases from these lesions.[12]

Staging systems for soft-tissue sarcoma have focused on size and grade in the presence or absence of metastasis. Historically we have used tumor size and grade, as well as presence of invasion, to help characterize the potential outcome of patients. Grade has been used widely in either four levels or three. We have used only the high- or low-grade designation, a distinction that is easier to manage and circumvents the difficulty of interpreting individual histopathologic variation in what is considered a grade II or grade III lesion when three or four categories are used. With the combination of tumor size, depth, and grade, we have been able to achieve excellent separation of outcome. The only other available data are from the American Joint Commission on Cancer published some years ago by Russell et al.[13] Our definition of tumor within 1 mm of any inked margin as a positive microscopic margin exaggerates the possibility of positive microscopic margins, but it does allow consistency. Certainly such a limited margin would be considered inadequate or marginal in any analysis of local resection.

In our trial we learned the consequences of early (less than 5 days) application of BRT to a large healing wound,[6] as would be predicted by previous animal wound-healing studies.[14] The insistence that afterloading catheters not be loaded until the fifth or subsequent postoperative day has ameliorated the additive effect of wound-healing impairment by radiation.[5]

The current database has great potential for the use and correlation of alternative prognostic variables. An excellent example is the ability to examine the significance of biologic variables identified in the tumor with respect to outcome. We and others have demonstrated that tumors in which the expression of retinoblastoma-susceptibility gene product was decreased were more aggressive than tumors in which it was expressed by nearly all cells in patients with soft-tissue and bone sarcoma.[15,16] The diagnostic significance of cytogenetic differences in adult soft-tissue sarcoma also could be tested with such a data base.[17] We have suggested that these kinds of analyses have potential for further identification of high-risk groups within tumor grades.

Acknowledgments

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Discussion

DR. EDWARD M. COPELAND, III (Gainesville, Florida): When I joined the faculty of the M. D. Anderson Hospital in 1972, convincing data from that institution had shown that adequate local excision of extremity soft tissue sarcomas followed by radiation therapy resulted in survival figures equal to those of amputation. Dr. Steven Rosenberg and his group several years later proved this observation in a randomized prospective trial, the data from which were presented before this Association.

Brachytherapy interests me because the time required for delivery is only 5 days rather than the 5 to 6 weeks required for adequate external beam radiation therapy. It is thus shorter and possibly less expensive. Please comment on the expense, because a prolongation of hospitalization to deliver brachytherapy may offset any cost savings by the shorter time