Long-Term Results of a Prospective Randomized Trial of Adjuvant Brachytherapy in Soft Tissue Sarcoma

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Purpose: This trial was performed to evaluate the impact of adjuvant brachytherapy on local and systemic recurrence rates in patients with soft tissue sarcoma.

Patients and Methods: In a single-institution prospective randomized trial, 164 patients were randomized intraoperatively to receive either adjuvant brachytherapy (BRT) or no further therapy (no BRT) after complete resection of soft tissue sarcomas of the extremity or superficial trunk. The adjuvant radiation was administered by iridium-192 implant, which delivered 42 to 45 Gy over 4 to 6 days. The two study groups had comparable distributions of patient and tumor factors, including age, sex, tumor site, tumor size, and histologic type and grade.

Results: With a median follow-up time of 76 months, the 5-year actuarial local control rates were 82% and 69% in the BRT and no BRT groups ($P = .04$), respectively. Patients with high-grade lesions had local control rates of 89% (BRT) and 66% (no BRT) ($P = .0025$). BRT had no impact on local control in patients with low-grade lesions ($P = .49$). The 5-year freedom-from-distant-recurrence rates were 83% and 76% in the BRT and no BRT groups ($P = .60$), respectively. Analysis by histologic grade did not demonstrate an impact of BRT on the development of distant metastasis, despite the improvement in local control noted in patients with high-grade lesions. The 5-year disease-specific survival rates for the BRT and no BRT groups were 84% and 81% ($P = .65$), respectively, with no impact of BRT regardless of tumor grade.

Conclusion: Adjuvant brachytherapy improves local control after complete resection of soft tissue sarcomas. This improvement in local control is limited to patients with high-grade histopathology. The reduction in local recurrence in patients with high-grade lesions is not associated with a significant reduction in distant metastasis or improvement in disease-specific survival.

J Clin Oncol 14:859-868.* © *1996 by American Society of Clinical Oncology.

IN THE 1970s, Suit et al[1,2] published retrospective data that suggested adjuvant external-beam radiation reduced local recurrence after surgical resection of soft tissue sarcomas. Over the next 20 years, adjuvant radiation was widely used against this disease without prospective randomized documentation of its benefit. In addition, there remained significant uncertainty about whether a potential improvement in local control translated into any survival benefit for the patient. Indeed, the relationship between local control and disease-specific survival has been an area of ongoing controversy for physicians who treat patients with sarcoma or other malignancies.[3-5] Such a relationship is conceptually attractive to oncologists who administer local therapies such as surgery and radiation. However, only one prospective trial has addressed this issue in any fashion. A prospective trial from the National Cancer Institute in the United States randomized 43 patients with high-grade extremity sarcomas to receive amputation or limb-sparing surgery combined with postoperative radiation.[6] Although the trial was primarily designed to compare amputation with limb-sparing therapy, it also provided insight into the possible relationship between local control and survival. Despite no local recurrences in the amputation group and a 20% local failure rate in the limb-salvage group, no survival differences were noted. However, other investigators maintain that the power of this study was not sufficient to draw this conclusion.[3]

In an effort to address these questions prospectively, we began a randomized trial of adjuvant radiation for soft tissue sarcoma. The brachytherapy technique of interstitial radiation was attractive because it involved a much smaller total treatment volume than conventional external-beam techniques and could be combined with surgical resection to deliver the patient's entire primary treatment within a short time frame. Results for a smaller cohort of patients accrued over the first 5 years of this trial have been reported.[7,8] Herein we report the long-term results of a 10-year trial with sufficient follow-up data and statistical power to address the relationship between local control and survival. This represents the only prospective randomized trial of adjuvant radiation in the treatment of this rare disease.

PATIENTS AND METHODS

Patients

Over the decade from July 1, 1982, through June 30, 1992, 1986 adult patients with primary or recurrent soft tissue sarcomas were

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Submitted June 5, 1995; accepted October 10, 1995.

Supported by grant no. CA-47179 (M.F.B.) from the National Institutes of Health, Bethesda, MD.

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0732-183X/96/1403-0023$3.00/0

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admitted to our institution and entered prospectively into a sarcoma data base. Of these patients, 1,088 (55%) presented with tumors of the extremities or superficial trunk. Patients who required amputation for local control of an extremity sarcoma (n = 109), who had metastases at the time of presentation (n = 177), who had been previously treated with chemotherapy or radiation therapy (n = 299), or who underwent incomplete resection (positive or indeterminate gross surgical margin, n = 47) were excluded from this study. In addition, foreign nationals treated for soft tissue sarcomas during this period (n = 49) were not offered this protocol because of the difficulty of follow-up evaluation.

Surgery and Randomization

The protocol was approved by the institutional review board for clinical investigation, and written informed consent was obtained from all patients preoperatively. Randomization occurred in the operating room following complete surgical resection. Patients were randomized within strata that were defined by a number of tumor characteristics known to be of prognostic significance, based on an analysis of 423 adult patients with localized extremity soft tissue sarcoma treated at our institution between 1968 and 1978.[9] These factors included high or low histologic grade; tumor size less than 5 cm or ≥ 5 cm; tumor location superficial or deep to the investing fascia; proximal or distal extremity site; and presentation as either a primary or locally recurrent sarcoma.

The requirements for randomization were no gross residual tumor, no violation of the tumor during the procedure, and no major bone or neurovascular resection. Thus, patients included in the study were only those with completely resected, localized, superficial trunk sarcomas and those with localized extremity lesions that could be completely resected by a limb-sparing procedure. These patients were randomized intraoperatively to receive either adjuvant radiation therapy in the form of brachytherapy (BRT group) or no adjuvant therapy (no BRT group; control arm).

The surgical technique used in this study has been previously described.[7] In brief, all visible or palpable tumor was resected in an en-bloc fashion. Previous biopsy scars and drain sites, when present, were included in the resection. When the tumor was intermuscular or intramuscular, resection included one or more of the involved muscle bundles. For tumors situated near major neurovascular structures, resection was performed with margins limited by the lack of expendable soft tissues. However, for the patient to be eligible for randomization, the tumor could not have been violated and no visible or palpable residual tumor could be present. The surgical margins were considered to be microscopically positive if tumor was seen within less than one half of a 10× microscopic field (1 mm) from a margin. Patients who were found to have microscopically positive margins at the time of definitive histopathologic examination (n = 29) were not excluded from the study (15 randomized to BRT, 14 to no BRT). During the first 5 years of the trial, postoperative doxorubicin-based chemotherapy was administered to selected patients with high-grade lesions who were believed to be at increased risk for the development of distant metastasis, ie, those with large (≥ 5 cm) high-grade lesions.

Brachytherapy

The brachytherapy technique used afterloading catheters placed intraoperatively in the tumor bed. The tumor bed was evaluated simultaneously by the surgeon and radiation oncologist. A target region to be irradiated was determined by adding 2.0 cm to the superior and inferior dimensions of the tumor bed, with 1.5 to 2.0 cm added in the medial and lateral directions. Afterloading catheters were then implanted percutaneously approximately 1 cm apart in the target area.[10] The catheters were fixed in position in the target region using absorbable sutures and were secured to the skin at the catheter exit site with buttons and nonabsorbable sutures. A drain was placed over the tumor bed, and the wound was closed in layers. Postoperatively, localization films were obtained, and computed dosimetry was performed. A loading plan was designed to deliver 42 to 45 Gy over 4 to 6 days with iridium 192. In patients accrued in or before 1985, loading was performed before the fifth postoperative day. However, interim analysis of wound complication rates showed a relationship between early catheter loading and wound complications.[11] Beginning in 1985, catheters were loaded no sooner than the sixth postoperative day. No special effort was made to treat the surgical scar, the drain site, or the wide margins that are typically included in an external-beam radiation plan. For patients in the BRT group, the total hospital stay for the entire treatment process was 10 to 14 days. Follow-up for the BRT and no BRT groups consisted of physical examination and cross-sectional imaging at 3-month intervals.

Statistical Analysis

Local recurrence, distant recurrence, and disease-specific survival rates were used as end points in the analysis. Local recurrence was defined as any local recurrence with or without synchronous distant metastasis. Analysis was based on the intention-to-treat concept. Clinical and pathologic factors, including age (< or ≥ 60 years), sex, presentation status (primary or recurrent disease), location, histologic subtype, histologic grade, tumor depth, tumor size (< or ≥ 5 cm), and the status of microscopic surgical margins, were correlated with the end points of interest in univariate and multivariate analyses. In modeling the rate of distant metastasis and death from disease, five patients who had low-grade fibrosarcomas of the desmoid subtype were excluded from the analysis because these lesions are known to recur locally but have almost no risk of distant metastasis or disease-related mortality.[12] Deaths that were confirmed to be related to the sarcoma were treated as end points in the study of tumor-related mortality; all other deaths were treated as censored observations.

Summary statistics were obtained using established methods. Associations between categoric variables were studied using Fisher's exact test or χ^2 test, where appropriate. Freedom from local recurrence and survival were calculated from the date of surgery (ie, randomization). The time to recurrence or death was modeled using the method of Kaplan and Meier[13] with the log-rank test for univariate comparison. Five-year actuarial estimates are presented with confidence limits. Cox proportional hazards modeling was used to evaluate the prognostic factors jointly. To arrive at a parsimonious multivariate model, covariates were selected into the model only if they contributed significantly to the fit of the model. The score χ^2 statistic was the criterion used to select covariates into the model. Cox model results are reported with relative risks (RRs) and confidence intervals (CIs).

RESULTS

Four hundred seven patients were eligible for randomization. One hundred sixty-four patients (40%) were randomized. This randomization rate is comparable to that

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Table 1. Distribution of Patient and Tumor Characteristics by Treatment Arm

	No. of Patients	
Characteristic	BRT (n = 78)	No BRT (n = 86)
Age, years		
≥ 60 yr	24	36
< 60 yr	54	50
Sex		
Male	41	53
Female	37	33
Grade		
High	56	63
Low	22	23
Site		
Proximal extremity	59	61
Distal extremity	8	13
Trunk	11	12
Size (cm)		
≥ 5	37	46
< 5	41	40
Depth		
Superficial	25	24
Deep	53	62
Presentation		
Primary	71	76
Recurrent	7	10
Microscopic margin		
Positive	15	14
Negative	63	72
Postoperative chemotherapy		
Yes	34	34
No	44	52
Histopathology		
Liposarcoma	32	35
MFH	19	20
Synovial sarcoma	8	4
MPNT	6	3
Fibrosarcoma	6	4
Leiomyosarcoma	4	8
Rhabdomyosarcoma	1	4
Other	2	8

NOTE. Tests of association were not significant.

Abbreviations: MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral nerve tumor.

observed in other phase III trials performed in our referral-based population. Reasons for lack of randomization included patient refusal to participate in a clinical trial and reluctance on the part of some treating physicians to participate in the trial. Seventy-eight patients were randomized to the BRT arm and 86 were randomized to the no BRT arm. One patient randomized to receive brachytherapy had his afterloading catheters removed before loading because of deep vein thrombosis in the ipsilateral extremity and thus did not receive adjuvant radiation. However, because the analysis was performed on an intention-to-treat basis, this patient was included in the BRT arm for analysis. The median follow-up time among survivors as of June 1, 1994, was 76 months.

Table 1 lists patient and tumor characteristics by treatment arm. These factors, including age, sex, histologic tumor grade, extremity tumor site (proximal or distal), tumor depth, presence of microscopically positive margins, presentation as either a primary or recurrent lesion, and administration of postoperative doxorubicin-based chemotherapy, were evenly distributed between the two groups. The predominant histopathologic diagnosis was liposarcoma, which accounted for 41% of the lesions in each group. The remaining histopathologic subtypes were comparably distributed between the two treatment arms.

Local Recurrence

Table 2 lists recurrence and mortality data for both groups. We observed 13 local recurrences in the BRT group compared with 25 in the no BRT group ($P < .04$). This represents a significant improvement in local control when all local recurrences are included in the analysis. When the analysis was confined strictly to local recurrence (excluding patients with synchronous local and distant recurrences), the improvement approached but did not reach statistical significance ($P = .055$). An actuarial plot of freedom from any local recurrence is shown in Fig 1. Actuarial estimates of freedom from local recurrence at 60 months were 82% (range, 73% to 92%) and 69% (range, 59% to 80%) for the BRT and no BRT groups ($P = .04$), respectively. Analysis of local control by histologic grade demonstrated that the improvement in local control was limited to patients with high-grade lesions (Fig 2). Among 56 patients with high-grade lesions randomized to receive brachytherapy, five local recurrences were noted, versus 19 local recurrences among 63 patients with high-grade lesions in the no BRT arm ($P = .0025$). Consequent actuarial local control rates for those with high-grade tumors were 89% (BRT arm) and 66% (no BRT arm). There was no demonstrable impact of brachytherapy on local control in patients with low-grade lesions ($P = .49$; Fig 3).

Table 2. Absolute Recurrence and Mortality Results

	No. of Patients		
	BRT (n = 78)	No BRT (n = 86)	P*
Any local recurrence	13	25	.040
Local recurrence only	12	21	.055
Distant recurrence	15	21	.600
Disease-specific mortality	12	16	.650

*By log-rank analysis.

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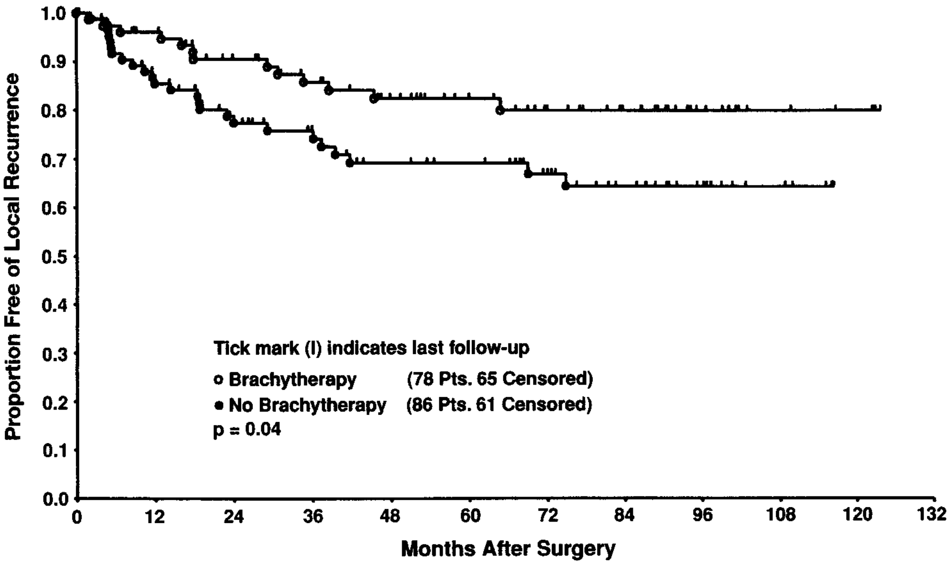
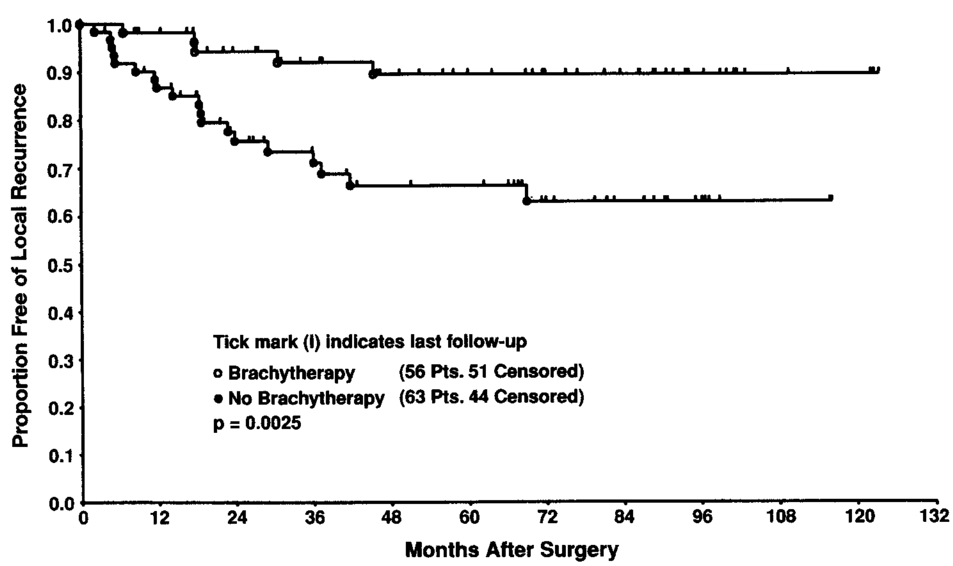


Fig 1. Actuarial plot of freedom from local recurrence for the entire study group.

Among patients who had local recurrences in the BRT group, correlation of the treatment films with those of the subsequent local recurrence site showed that the majority of recurrences were in-field. One of the local recurrences in the BRT group was in the patient whose afterloading catheters were removed before loading because of ipsilateral deep vein thrombosis.

For the entire cohort of patients, age ≥ 60 years was a significant predictor of local recurrence by univariate analysis (P = .0001). No other significant adverse prognostic factors were identified by univariate analysis. Table 3 lists the observed proportion of patients who developed local recurrences by patient characteristic and treatment arm. In a multivariate regression analysis of the entire group of patients, the only factor that significantly predicted local recurrence was age ≥ 60 years (P = .0001, RR = 3.8, CI = 1.9 to 7.7). Regression analysis of 119 patients with high-grade lesions demonstrated that age ≥ 60 years (P = .0001, RR = 5.8, CI = 2.3 to 14.8) and randomization to the no BRT arm (P = .006, RR = 3.7, CI = 1.4 to 10.0) were adverse prognostic factors for local recurrence. Other factors such as size (< 5 *v* ≥ 5 cm), histologic margin (positive *v* negative), location (extremity *v* trunk), depth (superficial *v* deep), and status

Fig 2. Actuarial plot of freedom from local recurrence for the 119 patients with histopathologic high-grade lesions.



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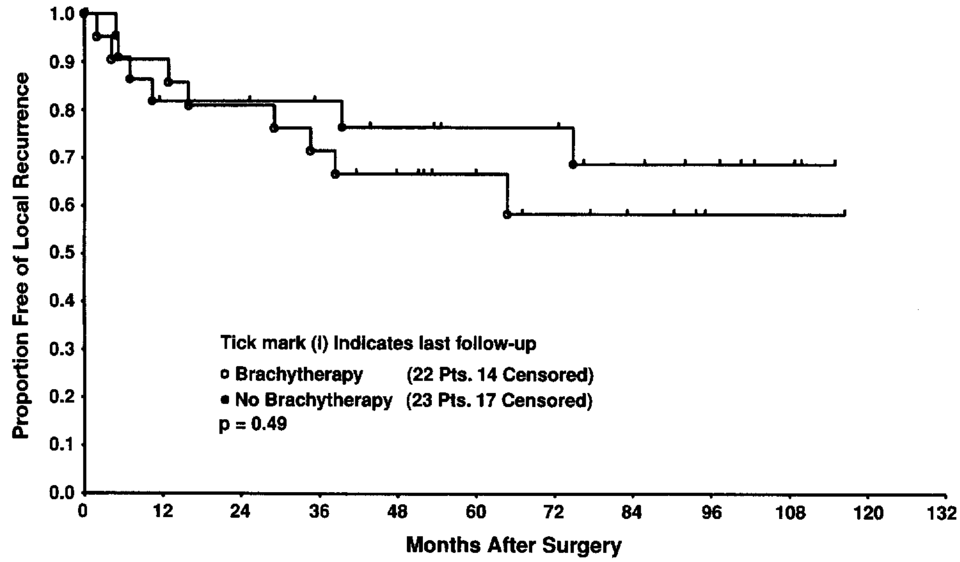

Fig 3. Actuarial plot of freedom from local recurrence for the 45 patients with histopathologic low-grade lesions.

at presentation (primary *v* recurrent) had no significant effect on local recurrence.

The relationship between histologic margin status and local control is of interest. Among patients with negative margins, eight of 63 developed local recurrence in the BRT group compared with 20 of 72 in the no BRT arm (Table 3; $P = .04$). A total of 29 patients with microscopically positive margins were randomized: 15 to the BRT arm and 14 to the no BRT arm. Five local failures were noted in each group (Table 3; $P = .99$). Among patients with high-grade lesions, two of 10 with microscopically positive margins who received brachytherapy developed local recurrences, compared with four of 10 in the control arm ($P = .63$).

Distant Metastasis

Distant metastases developed in 15 patients who received brachytherapy compared with 21 patients in the control arm (Table 2). Freedom from distant recurrence is plotted in Fig 4, with no differences observed between the two treatment groups. Five-year actuarial estimates of freedom from distant metastasis were 83% (range, 74% to 92%) and 76% (range, 67% to 86%) in the BRT and no BRT groups ($P = .60$), respectively. Analysis by histologic grade did not demonstrate an impact of adjuvant brachytherapy on the development of distant metastasis in patients with high-grade tumors (Fig 5). Only one distant metastasis was observed among patients with low-grade tumors and, hence, actuarial plots for distant metastasis in this population are not presented. Univariate analysis demonstrated that high grade ($P = .0005$), size $\geq$ 5 cm ($P = .0006$), and age $\geq$ 60 years ($P = .04$) were adverse prognostic factors for distant recurrence.

The Cox proportional hazards model selected high grade ($P = .0006$, RR = 11.2, CI = 1.5 to 82.7) and size $\geq$ 5 cm ($P = .097$, RR = 2.6, CI = 1.2 to 5.6) as unfavorable prognostic factors for the development of distant metastasis. Other factors tested, including status at presentation, age, tumor location, tumor size, tumor depth, and margin status, were not selected. Only one of 40 patients with low-grade sarcomas developed a distant metastasis (the five patients with low-grade fibrosarcomas of the desmoid type were not considered). No differences in metastasis-free survival were observed between the BRT and no BRT groups, whether patients were stratified by grade or considered as a single group.

Disease-Specific Survival

Disease-specific survival rates for both groups are plotted in Fig 6. No difference in disease-specific survival was observed ($P = .65$). The 5-year disease-specific survival rates for the BRT and no BRT groups were 84% (range, 76% to 93%) and 81% (range, 72% to 90%), respectively. There was no demonstrable impact of brachytherapy on either the high-grade ($P = .26$; Fig 7) or low-grade ($P = .52$) groups of patients. By univariate analysis, the following factors were found to be adverse prognostic factors for disease-specific survival: high histologic grade ($P = .015$), size $\geq$ 5 cm ($P = .0002$), and age $\geq$ 60 years ($P = .017$). The Cox model selected tumor size $\geq$ 5 cm ($P = .0002$, RR = 5.2, CI = 1.9 to 13.7) as the sole adverse prognostic factor for disease-specific survival.

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Table 3. Observed Proportion of Patients With Local Recurrence Distributed by Treatment and Clinicopathologic Characteristic

	No. With Local Recurrence/ No. With Characteristic		
Clinicopathologic Characteristic	BRT (n = 78)	No BRT (n = 86)	P*
Local recurrence	13/78	25/86	
Age, years			
≥ 60	8/24	16/36	.43
< 60	5/54	9/50	.25
Sex			
Male	8/41	14/53	.47
Female	5/37	11/33	.09
Grade			
High	5/56	19/63	.01
Low	8/22	6/23	.53
Site			
Proximal extremity	10/59	15/61	.51
Distal extremity	0/8	5/13	.11
Trunk	3/11	5/12	.67
Size (cm)			
≥ 5	6/37	14/46	.20
< 5	7/41	11/40	.30
Depth			
Superficial	7/25	8/24	.76
Deep	6/53	17/62	.04
Presentation			
Primary	11/71	21/76	.11
Recurrent	2/7	4/10	.99
Microscopic margin			
Positive	5/15	5/14	.99
Negative	8/63	20/72	.04
Histopathology			
Liposarcoma	4/32	12/35	.05
Fibrosarcoma	1/6	0/4	.99
MFH	3/19	6/20	.45
MPNT	3/6	1/3	.99
Synovial sarcoma	2/8	0/4	.51
Leiomyosarcoma	0/4	3/8	.49
Other	0/3	3/12	.99
Postoperative chemotherapy			
Yes	4/34	10/34	.13
No	9/44	15/52	.47

*By Fisher's exact test (BRT group *v* no BRT group).

Complications

The major acute morbidity associated with the combination of surgery and early postoperative adjuvant radiation therapy was related to healing of the surgical wound. Major complications were defined as delayed healing that required further operative intervention for wound closure or threatened loss of a functional limb. Moderate complications were defined as delay with persistent seroma that required repeated aspiration or debridement, wound separation ≥ 2 cm, hematoma ≥ 25 mL, and/or purulent wound discharge. Analysis of our experience with wound complications during the first 3 years of the trial (1982 to 1985) showed statistically significantly more major and moderate wound complications in patients in the BRT group (11 of 23 patients) compared with the no BRT arm (five of 31; $P = .03$).[14] During this period, the afterloading catheters were loaded within the first 5 postoperative days, which correspond to the proliferative phase of wound healing. This timing appeared to account for the higher incidence of wound complications. On the basis of these data, in 1985 the treatment policy was modified so that radioactive sources were not loaded until after the fifth postoperative day. Reanalysis of wound complications after 50 subsequent patients had been randomized demonstrated a substantial reduction in wound complications with major or moderate wound complications in only three of 21 and three of 29 patients in the BRT and no BRT groups ($P = .67$), respectively.[14] Over the remainder of the trial, there were no statistical differences in wound complication rates between the two treatment arms.

DISCUSSION

The present report, with a median follow-up time of 76 months, confirms the findings noted in the smaller cohort of 126 patients entered in the first 5 years of the trial.[7,8] This study demonstrates that adjuvant radiation in the form of brachytherapy improves local control following complete resection of soft tissue sarcomas of the extremity and superficial trunk. However, this improvement in local control is confined to patients with high-grade histopathology. Among 119 patients with high-grade lesions, only five local recurrences were noted among 56 patients randomized to receive adjuvant brachytherapy. This represents an absolute local control rate of 91%, which is comparable to local control rates reported in retrospective series using postoperative external-beam radiation.[15,16]

Notwithstanding comparable local control rates, brachytherapy has substantial logistical, economic, and functional advantages over conventional external-beam radiotherapy. First among these is the fact that a patient's entire primary local therapy, ie, surgery and radiation, is completed in a 10- to 14-day window. In contrast, typical external-beam radiotherapy plans necessitate daily therapy for 6 to 7 weeks, with an additional 4- to 6-week interval before or after surgery. Protracted time commitments for such therapy are inconvenient and have obvious economic implications for the patient in terms of return to work and to a normal daily routine. The short period required for surgery combined with brachytherapy has advantages for patients who present with synchronous local and distant disease, since it facilitates completion

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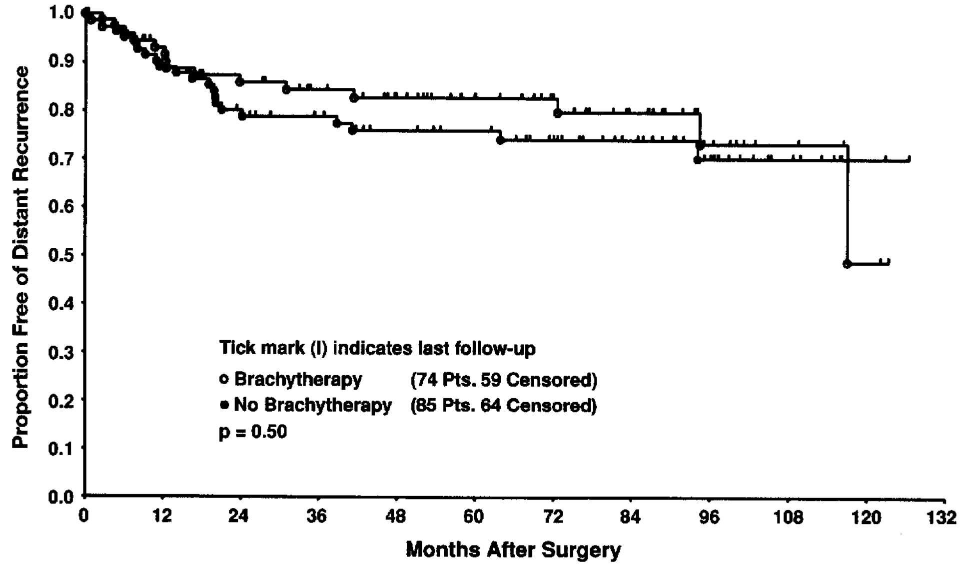

Fig 4. Actuarial plot of freedom from distant metastasis for the entire study group.

of the entire local therapy within a short time frame and thereby allows attention to be promptly focused on the management of the more life-threatening distant disease. In addition, brachytherapy treats a defined and more limited volume of tissue than external-beam radiation does. This may have functional advantages. Indeed, we have compared the functional outcomes of our brachytherapy patients with those managed by surgery alone.[17] Comparison of objective outcomes such as muscle strength, ambulation velocity, stride length, and stride cadence showed no differences in the BRT group compared with the no BRT group treated with surgery alone. This suggests that the limited field of radiation did not introduce long-term functional morbidity. Last, but of significant import in this era, recent data that document the lower cost of brachytherapy versus external-beam radiotherapy make a compelling argument for brachytherapy's use in clinical settings in which its long-term results are known to be comparable to those of external-beam approaches.[18]

Patients with low-grade histopathology do not appear to receive the same local control benefit from adjuvant brachytherapy. Among 45 patients with low-grade lesions, eight of 22 randomized to the BRT arm developed subsequent local recurrences versus six of 23 in the no

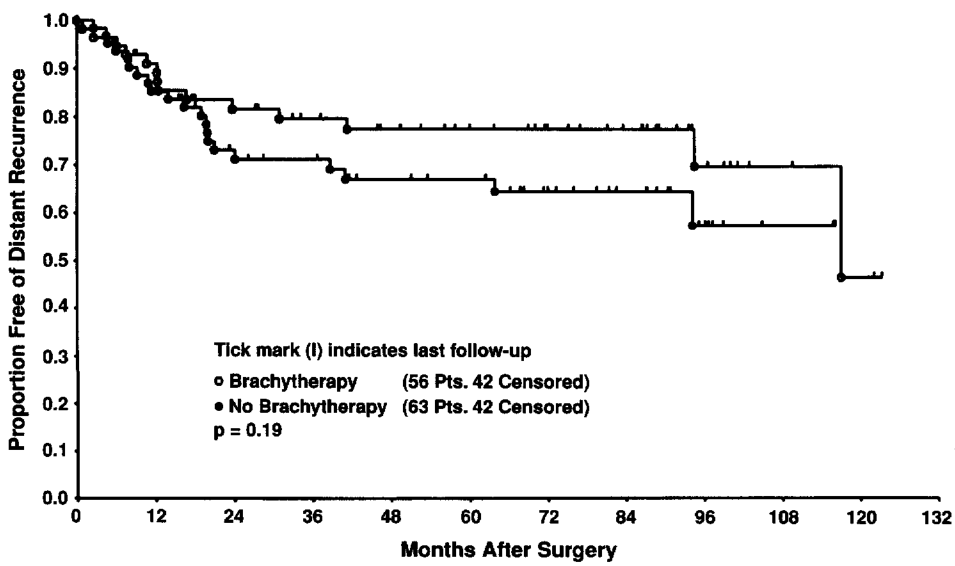

Fig 5. Actuarial plot of freedom from distant metastasis for the 119 patients with high-grade lesions.

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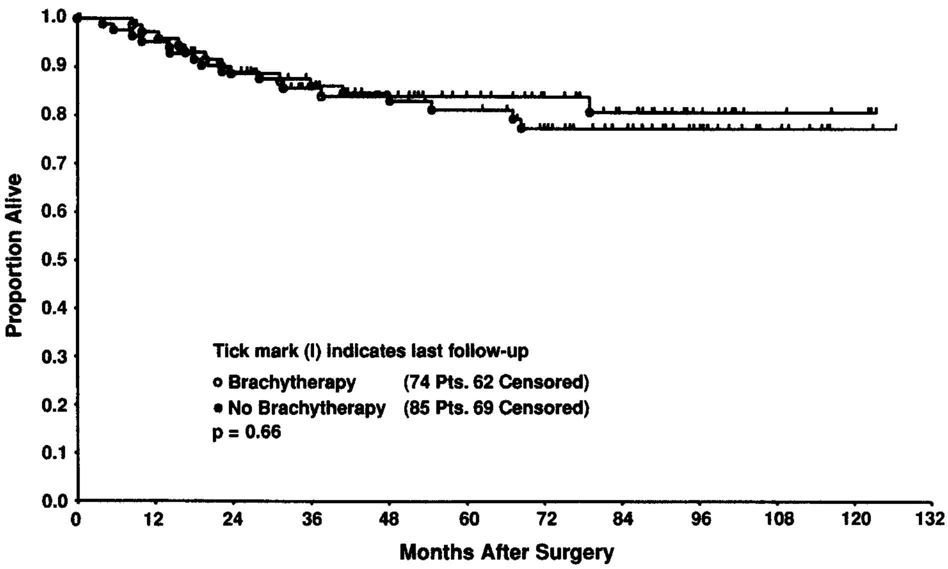

Fig 6. Actuarial plot of disease-specific survival for the entire study group.

BRT arm (P = .53). While it is possible that a type II error may exist in drawing this conclusion, the practical reality is that an additional 85 patients would need to be randomized to detect a difference in local control as large as 20% with 80% power. At present rates of accrual, it would take an additional 20 years to randomize this number of patients with low-grade lesions. A smaller difference between the treatment groups would require even more patients to detect with good power. These statistical considerations combined with data that suggest low-grade lesions may be more sensitive to external-beam radiation[15,19] have prompted us to use external-beam radiation as the standard adjuvant radiation technique for patients with large (≥ 5 cm) low-grade soft tissue sarcomas.

The putative relationship between local control and distant metastasis/disease-specific survival has engendered significant controversy. In the present report, the improvement in local control associated with adjuvant brachytherapy did not translate into any significant change in the rates of distant metastasis or disease-specific survival. Subset analysis among patients with high-grade lesions, where the local control benefit of brachytherapy was confined, did not demonstrate any significant impact on distant metastasis or disease-specific mortality

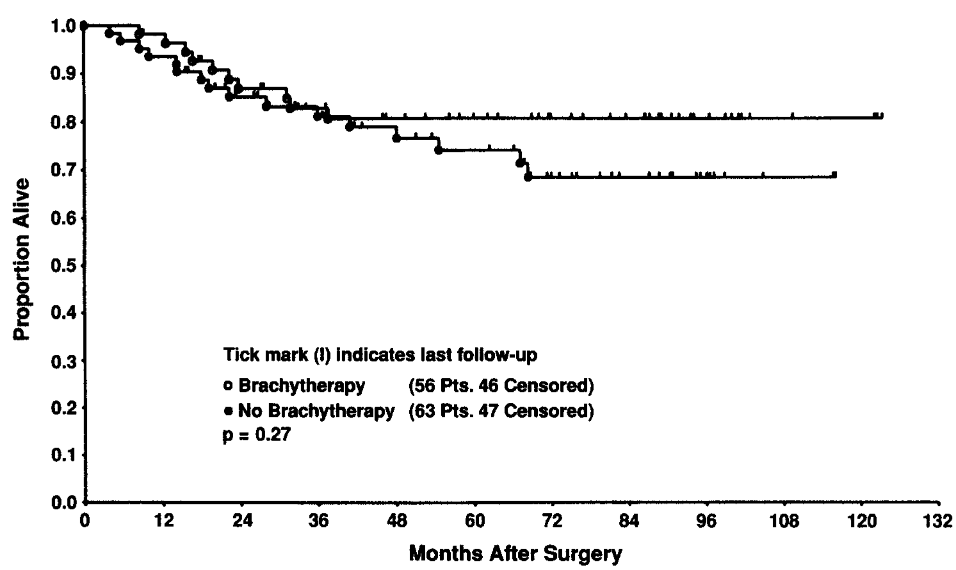

Fig 7. Actuarial plot of disease-specific survival for the 119 patients with high-grade lesions.

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(Figs 5 and 7). These observations are consistent with the findings of the randomized trial from the National Cancer Institute in which patients with high-grade extremity sarcomas were randomized to receive either amputation or conservative surgery plus radiation therapy.[6] Despite a 20% difference in local control between the treatment groups, no survival differences were noted. In the present trial, comparable improvements in local control were noted with adjuvant brachytherapy, with 5-year actuarial local control rates in the patients with high-grade lesions of 66% and 89% in the no BRT and BRT groups, respectively. Notwithstanding this improvement in local control, no significant impact on distant metastasis or disease-specific survival was demonstrable. With 119 patients in the high-grade subset, the power of this observation is 80% to detect a 20% difference in the 5-year rate of distant metastasis between the two arms.

In the analysis of these data and examination of the relationship between local control and survival, two issues are of critical importance: (1) does a specific local treatment modality impact on the rates of local recurrence, distant metastasis, or tumor-related mortality; and (2) when patients with similar prognoses are given identical treatment, does subsequent local failure result in increased risk of distant metastasis or tumor-related mortality? The present randomized trial allowed examination of the first question by regression analyses that incorporated clinicopathologic factors and a specific treatment factor (BRT *v* no BRT) as covariates. In these analyses, adjuvant radiation in the form of brachytherapy improved local control, but did not have any significant impact on distant metastasis or tumor-related mortality. The second question was addressed by additional multivariate analyses in which the development of a local recurrence was treated as a time-dependent covariate and its value in predicting the development of distant metastasis or tumor-related mortality examined. In this regression analysis, which adjusted for all the patient, tumor, and treatment (BRT *v* no BRT) factors, the rates of distant metastasis and disease-specific survival were examined in patients with and without a local recurrence. This multivariate analysis showed the rates of distant metastasis and disease-specific mortality to be significantly increased in patients who developed a local recurrence ($P = .001$ for both events). This is in contrast to the results derived from Cox regression analysis of the relationship between the two treatment modalities (BRT *v* no BRT) and the same end points. Similar types of analysis using time-dependent covariates in nonrandomized populations have suggested a relationship between local failure and distant recurrence/tumor-related mortality.[5] However, such associations are imperfect, as demonstrated in the subset of patients with high-grade lesions who received adjuvant brachytherapy: nine of 14 who developed distant metastasis did not have a previous local recurrence. This fact may partially explain why the local control advantage did not translate into significantly improved metastasis-free or disease-specific survival rates in the patients with high-grade lesions who received adjuvant brachytherapy. With these clear distinctions in mind, we conclude that improvements in local control in this referral-based population did not translate into significant decreases in rates of distant metastasis or tumor-related mortality. However, once a local recurrence is manifest, patients are at increased risk for subsequent distant metastasis and tumor-related mortality. Although the relationship between local control and disease-specific survival is statistically complex and difficult to examine in clinical research, it is in the patient's best interest to have local control. Whether this will have an impact on survival is unclear, but given the results of the randomized data, any positive effect is likely to be small in the context of large cohorts of sarcoma patients.

The short-term complications of brachytherapy and its impact on healing of the surgical wound have been previously reported.[11,14] Within the first 3 years of the trial, a clear relationship between the time of isotope loading and the incidence of wound breakdown emerged, and analysis of the perioperative wound complications showed a higher incidence of moderate and major wound complications in the BRT group. This prompted us to institute a policy of waiting until at least the sixth postoperative day before loading the radioactive sources. This approach allows the proliferative phase of wound healing to take place without the concurrent cytotoxic effects of high-dose radiation. With this temporal change in the administration of the adjuvant radiation dose, wound complication rates can be minimized as would be predicted from animal studies.[20] Unfortunately, when a wound complication does occur in the presence of recent or prior irradiation, the duration of that complication is prolonged.

In summary, this randomized prospective trial demonstrates that adjuvant brachytherapy improves local control in patients with completely resected high-grade soft tissue sarcomas. This improvement in local control does not have an impact on rates of distant recurrence or disease-specific survival. There is no evidence that patients with low-grade histopathology derive the same local control benefit from this form of adjuvant radiation. Indeed, we currently recommend that patients with large, low-grade lesions receive adjuvant external-beam radiation. However, two thirds of all extremity soft tissue sarcomas are

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high-grade lesions. For these patients, adjuvant brachytherapy provides a simple, convenient means to complete the entire primary local therapy within a short period with no long-term functional sequelae and with a local control benefit comparable to that obtained with more protracted courses of adjuvant external-beam radiation.

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