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Efficacy of Adjuvant Radiation Therapy in the Treatment of Soft Tissue Sarcoma of the Extremity: 20-year Follow-Up of a Randomized Prospective Trial

Joal D. Beane, MD[1], **James C. Yang, MD**[1], **Donald White, MS**[1], **Seth M. Steinberg, PhD**[2], **Steven A. Rosenberg, MD, PhD**[1], and **Udo Rudloff, MD, PhD**[1]

[1]Surgery Branch, National Cancer Institute, Bethesda, MD;

[2]Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, Bethesda, MD

Abstract

Background.—This update of a randomized, prospective study presents the effect of external beam radiation therapy (EBRT) on long-term overall survival, local control, and limb function following limb-sparing surgery (LSS) for the treatment extremity soft tissue sarcoma (STS).

Methods.—Following LSS, patients with extremity STS were randomized to receive EBRT or surgery alone. All patients with high-grade STS received adjuvant chemo-therapy. Long-term follow-up was obtained through telephone interviews using a questionnaire based on validated methods. Overall survival (OS) was determined by Kaplan–Meier method.

Results.—A total of 141 patients with extremity STS were randomized to receive adjuvant EBRT ($n = 70$) or LSS alone ($n = 71$). Median follow-up was 17.9 years. The 10-and 20-year survival was 77 % (95 % CI 66–85 %) and 64 % (95 % CI 52–75 %) for patients receiving LSS alone and 82 % (95 % CI 72–90 %) and 71 % (95 % CI 59–81 %) for patients receiving EBRT ($p = 0.22$). Of the 54 patients who completed telephone interviews, the incidence of local recurrence during the follow-up period was 4 % (1 of 24) in the LSS alone cohort compared with 0 % (0 of 30) in those who received EBRT ($p = 0.44$). Patients treated with EBRT tended to have more wound complications (17 vs. 12.5 %, $p = 0.72$), clinically significant edema (25 vs. 12 %, $p = 0.31$), and functional limb deficits (15 vs. 12 %, $p = 0.84$).

Conclusions.—Adjuvant EBRT following surgery for STS of the extremity provides excellent local control with acceptable treatment-related morbidity and no statistically significant improvement in overall survival.

The ability of radiation therapy (RT) to improve local control following surgery has made it a cornerstone in the multimodality treatment of common cancers such as primary breast and rectal cancers.[1–4] However, the relationship between the improved local control afforded by RT and overall survival (OS) remains a point of contention. Proponents argue that the prevention of early local recurrences (LR) translates into fewer events of distant spread, and that this may ultimately result in an improvement in OS in sufficiently powered studies with

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longer follow-up. Among others, studies supporting this claim include the Oxford Overview in breast cancer, where a 5 % improvement in OS was observed in women who received RT following mastectomy, and the subgroup analysis of the NSABP rectal cancer trials, where improved OS was associated with adjuvant RT in patients younger than 60 years or who underwent abdominal perineal resection.[2–5]

In 1982, Rosenberg et al.[6] prospectively investigated the relationship between local control and OS in high-grade STS of the extremity. They found that despite increased LR in patients randomized to receive limb-sparing surgery (LSS) plus EBRT, the disease-free survival and OS were similar to patients randomized to undergo amputation. Given these findings, a larger trial from the National Cancer Institute was conducted to address the impact of adjuvant EBRT on LR, OS, and quality of life. The addition of EBRT reduced LR while OS and nonlocal recurrences were similar to patients randomized to LSS alone.[7] Despite being validated by other randomized trials, the relationship between local control and OS remains a point of contention.[8–10] In addition, there are few data to assess the long-term consequences of EBRT, which could offset its benefit on local control in patients at low risk of LR. In order to address the long-term effect of EBRT on OS, LR, and limb function, we present a 20-year follow-up of our randomized prospective study on the use of adjuvant EBRT in the treatment of extremity STS.

METHODS

Between 1983 and 1991, 141 patients with extremity STS who had undergone LSS were randomized to receive or not receive adjuvant EBRT. Patients with gross residual tumor, evidence of metastatic disease, history of a second malignancy, or contraindications to receiving doxorubicin, cyclophosphamide, or EBRT were excluded. Tumor grading was performed by 1 pathologist as previously described.[7] Randomization was performed using a computer program to assign treatment on the basis of a random number selected from a uniform distribution, used fixed blocks, and was stratified for tumor grade, proximal limb tumors versus distal limb tumors, and positive surgical margins versus negative margins.[7]

Treatment

Patients with high-grade STS received doxorubicin and cyclophosphamide that was given concurrently with EBRT within 4 months of LSS. Doxorubicin 70 mg/m^2 and cyclophosphamide 700 mg/m^2 IV were given on day 1 of a 28-day cycle for 5 cycles. Also, 4,500 cGy of radiation were delivered to a wide field followed by a 1,800-cGy boost to the tumor bed; 180-cGy fractions were administered 5 days a week for 6–7 weeks. Irradiation of joints and tissues not at risk was minimized as described.[11]

Long-Term Follow-Up

A questionnaire based on validated methods including the Erdman's scale of activities of daily living (ADL) and the tool for the short-term prospective trial was used to conduct telephone interviews.[12,13] Interviews were blinded and focused on the treated extremity. Data collected includes employment status and age at retirement, pain severity (from 1, no pain, to 10, most severe), need for routine use of pain medication (>3 days/week). Questions were objective in nature, and grading was based on the need for medical intervention such as the use of diuretics or support stockings for edema or the use of an orthotic or assist device (cane) to grade functional limb deficits. The need for wound care was graded: (1) subclinical wound management; (2) outpatient wound care or a surgical intervention requiring general anesthesia; (3) multiple surgical procedures requiring anesthesia or amputation. The presence of limb edema was graded: (1) subclinical edema; (2) requiring routine use of prescribed compression stockings or diuretics; (3) edema or complications thereof resulting in hospitalization. Functional limb deficits were graded: (1) independent in ADL and ambulatory; (2) need of self-help devices for ADL or an assist device for ambulation; (3) requiring minimal assistance from others for ADL or ambulation; (4) completely dependent on others for ADL or nonambulant.

Local recurrence data was obtained during telephone interviews and ascertained based on a diagnosis from the patient's provider and treatment history. Median follow-up was defined as the median interval from the on-study date to the date of patient contact or death. Patients were censored at the time of death. Date of death was confirmed using the social security death index, local obituaries, medical records, and family-provided data.

Statistics

Overall survival was analyzed by Kaplan–Meier method. The difference between treatment arms was compared using the log-rank test. Dichotomous outcomes were compared using the Fisher exact test, while an exact Wilcoxon rank sum test was used to compare continuous age and pain levels between the arms. Trends across grades were compared using an exact Cochran-Armitage trend test.[14] All p values are 2-tailed and reported without adjustment for multiple comparisons. Institutional Review Board approval was obtained, and the study conducted under Protocol 83C0212.

RESULTS

A total of 141 patients with extremity STS were randomized to receive ($n = 70$) or not receive ($n = 71$) adjuvant EBRT (Table 1).[7] Median follow-up was 17.9 years overall (range 1–29 years) and 20.9 years (range 18–29) for survivors. Since our original publication 55 patients have died (39 %), 19 (13 %) have been lost to follow-up, and 76 (48 %) confirmed living. Of the patients confirmed living, 54 (71 %) completed telephone interviews (Table 2). A total of 22 patients (29 %) did not complete the questionnaire because they were unwilling to participate or were unable to be contacted by telephone and thus excluded.

Overall Survival

The 10- and 20-year survival was 77 % (95 % confidence interval 95 % CI 66–85 %) and 64 % (95 % CI 52–75 %) for patients receiving LSS alone and 82 % (95 % CI, 72–90 %) and 71 % (95 % CI 59–81 %) for patients receiving adjuvant EBRT. There was no difference in OS in patients treated with EBRT compared with LSS alone ($p = 0.22$, Fig. 1). Furthermore, there was no difference in OS between treatment arms when analyzing patients with high-grade ($p = 0.59$) or low-grade ($p = 0.14$) STS separately (Figs. 2 and 3).

Local Control

Of the 54 patients who completed telephone interviews, the incidence of LR during the follow-up period was 4 % (1 of 24) in the LSS alone cohort compared with 0 % (0 of 30) in those who received EBRT ($p = 0.44$). This patient underwent resection of the local recurrence followed by EBRT and remains fully ambulatory. Taken together with the previously reported early recurrences, the rate of LR in our study was 25 % following LSS alone ($n = 18$; 17 reported initially and 1 late recurrence) and 1.4 % ($n = 1$ reported initially) in those having received EBRT ($p = 0.0001$).

Wound Complications

The majority of patients (75 %, 41 of 54) had no wound complications. Of 30 patients in the EBRT cohort, 8 (27 %; 95 % CI 12–46 %) required routine wound care or subsequent major surgical interventions compared with 5 of 24 (20 %; 95 % CI 7–42 %) patients who had LSS alone ($p = 0.75$). The rate of pathologic fractures was 10 % (3 of 30; 95 % CI 2–27 %) in patients with EBRT compared with 4 % (1 of 24; 95 % CI 0–21 %) in patients with LSS alone ($p = 0.62$). Two patients (6.7 %, $n = 30$; 95 % CI 1–22 %) who required amputation following complications related to EBRT. One patient developed a nonhealing wound and osteomyelitis, and the second patient had recurrent pathologic fractures in the irradiated field complicated by nonunion that required amputation. Average time from EBRT to amputation was 23.7 years (range 21.7–25.7 years).

Presence of Edema

Patients with limb loss were excluded ($n = 2$, EBRT). Of 28 patients who received EBRT, 5 (18 %; 95 % CI 0–37 %) developed grade 2 edema compared with 3 of 24 patients (12 %; 95 % CI 3–32 %) having LSS alone. There were 2 patients (7 %) with grade 3 edema, both in the EBRT group. In 1 patient, the degree of edema interferes with their ability to perform ADL, and the other has been hospitalized on multiple occasions for lymphedema related cellulitis. Overall, there was no difference in edema between the 2 groups ($p = 0.21$; Table 2).

Functional Limb Deficits—Upper and lower extremity STS was analyzed separately. There were no functional limb deficits observed in patients with upper extremity STS (100 % grade 1, $n = 9$). Of those with lower extremity STS ($n = 45$), 17 patients (85 %, $n = 20$; 95 % CI 83–100 %) who had LSS alone and 22 patients (88 %, $n = 25$; 95 % CI 80–100 %) who received EBRT were classified as grade 1 (Table 2). Also, 3 of 20 (15 %; 95 % CI 3–38 %) of those treated with LSS alone compared with 2 of 25 (8 %; 95 % CI 1–27 %) treated with adjuvant EBRT require an assist device to ambulate ($p = 0.065$). One patient (2 %) who underwent EBRT developed wound complications, required a below the knee amputation, and is wheelchair bound. The second patient who had recurrent pathologic fractures and required amputation uses a prosthesis, but is completely independent in ADL.

DISCUSSION

This study presents the longest follow-up of the effects of limb irradiation for STS on OS, LR, and limb function. While OS was greater in patients treated with adjuvant EBRT, this difference failed to reach statistical significance. As with most sarcoma trials, the size of this study does not permit the detection of small differences in an effect of EBRT on OS. With 71 patients in each arm, the study would have had 80 % power to detect a difference between 2 arms with 85 and 64 % survival probabilities at 10 years, using a 2-sided 0.05 significance level log-rank test. Thus, this study does not have sufficient power to detect an OS benefit of <21 %. Another limitation of this study is the inability to determine the effect of EBRT on disease-free survival and disease-specific survival rates and their association with OS.

The use of RT following LSS for STS has reduced the rate of LR from historic levels of 30–50 % to less than 10 %.[6] While we do not have LR data for 74 patients (55 patients who died during the follow-up period; 19 patients lost to follow-up), which could introduce significant bias, the rate of LR in our study was at least 25 % following LSS alone ($n = 18$; 17 reported initially and 1 late recurrence) and 1.4 % in those having received EBRT ($n = 1$ reported initially; $p = 0.0001$). It is intriguing to speculate whether this large difference in LR rates could have contributed to the trend toward improved OS in those treated with EBRT.

Because STS is a disease frequently afflicting young patients, it was important to assess whether there were additional limb deficits over a 20-year period that might alter the advisability of administering EBRT in patients with a low risk of LR.[6,9,10] Complications range from 17 to 48 % and have a significant impact on limb function and quality of life.[7,13,15,16] Previously, we reported significant differences in muscle strength, edema, and joint motion that favored patients not having EBRT. Over time, these improved and did not affect ADL.[13] Within the limits of the study size, longer follow-up of surviving patients did not show a significant difference in our assessment of limb function. It is important to note that 29 % of patients confirmed alive were unable to contribute to this analysis, leaving 54 of the original 141 (38 %) to be queried, which could bias the results. Clinicopathologic variables of those who did not complete the questionnaire including age ($p = 0.18$), tumor size ($p = 0.62$), and grade ($p = 0.24$) were compared with those who completed the interview and did not differ. More so, for patients with high-grade STS, we cannot comment on the effect of concurrent adjuvant chemotherapy and EBRT on the complications revealed in our study.

From our follow-up a number of important events were uncovered. Long bone fractures are reported in retrospective series in as many as 7.6 % of patients and, given their high nonunion rate, are major causes of morbidity.[17–19] In our series, the rate of fracture was 10 % in patients with EBRT compared with 4 % in patients with LSS alone ($p = 0.62$). No patient treated with LSS alone required amputation, while 2 patients treated with EBRT required amputation; 1 due to nonunion of a pathologic fracture and the other secondary to osteomyelitis.

In light of these complications, investigators have explored ways to minimize toxicity and refine patient selection. Brennan et al.[10,20] prospectively investigated the use of BRT. They found this more local therapy was not associated with increased functional deficits or wound complications compared with those managed by surgery alone, but a subsequent randomized trial revealed that the improvement in local control following LSS with BRT was limited to those with high-grade STS. As such, patients with low-grade STS at increased risk of LR are treated with EBRT.[9,20] The same authors recently reported a comparison of LSS and intensity-modulated radiation therapy (IMRT) versus LSS and BRT for high-grade STS of the extremity.[21] IMRT improved local control compared with BRT and was associated with reduced morbidity compared with historic controls of EBRT.[21–23] Though not as precise as current methods, patients in our study were treated with complex field planning, and surrounding tissue irradiation was minimized using filters, compensatory wedges, and electrons.[11] While modern techniques such as IMRT appear to have improved short-term functional outcomes, their superiority to complex conventional EBRT over the long-term is unknown.[23]

Pisters et al.[24] have focused on refining patient selection for EBRT and found similar LR and OS rates for patients with T1 STS treated with LSS alone compared with those treated with LSS and EBRT. Others have retrospectively identified patients at risk for LR following LSS.[25–30] The tool that informs best based on clinicopathological variables for both the risk of LR following LSS alone and decision-making on the gain of adjuvant RT is a recently published nomogram that predicts the 3- and 5-year risk of local recurrence after LSS in the absence of adjuvant RT with a CI of 0.73.[31] Combining a risk-prediction model derived from a high-volume center with the information from our study on the small provides an important source for patients and physicians to guide their decision on adjuvant RT. The risk of specific RT-related complications such as pathological fracture of the femur in those with lower extremity STS can be calculated and also assist in the decision-making process.[17,32]

In summary, the initial results of this study demonstrated that adjuvant EBRT for extremity STS improves local control without a statistically significant improvement in overall survival. Although it is possible an OS benefit exists but was not detected due to limited power, this has remained true on long-term follow-up. Our recommendation has been that adjuvant EBRT be reserved for those with significant risk of local recurrence to avoid multiple surgeries and limb loss from such preventable recurrences. In our study some late limb-loss events occurred in patients who had undergone EBRT, and we maintain that its use for patients at low risk of recurrence should be selective.

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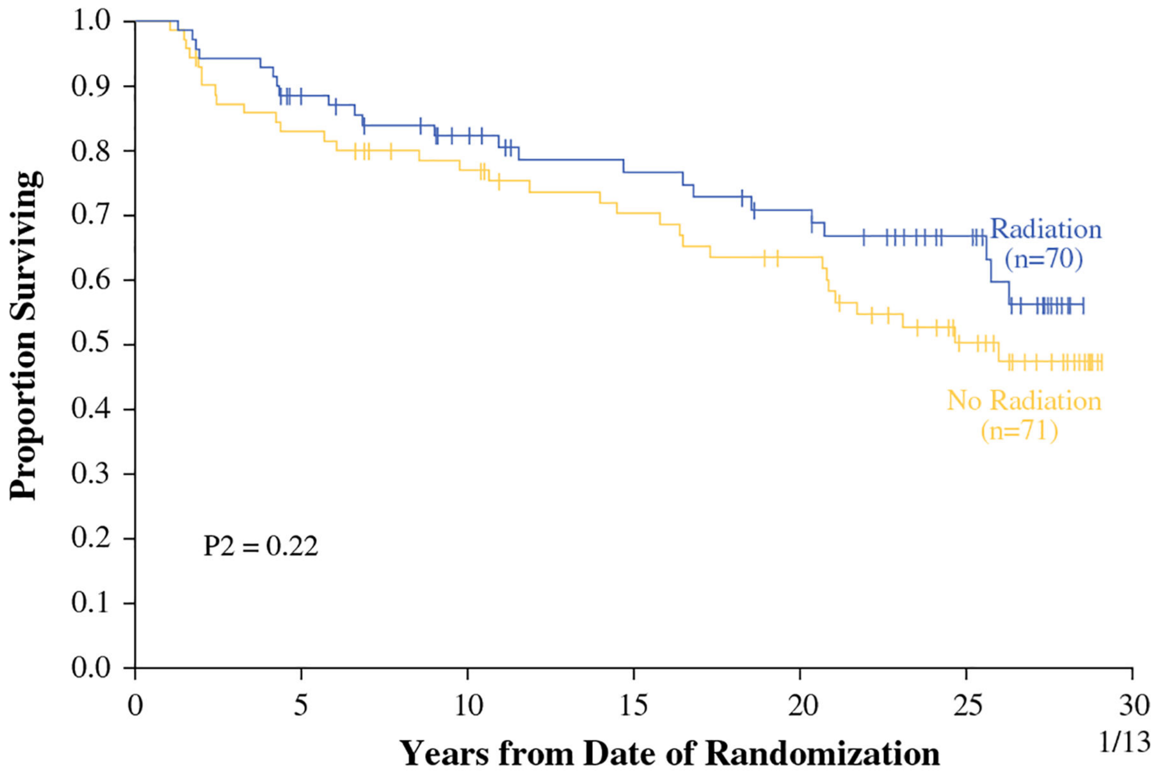

FIG. 1.

Overall survival of all patients with extremity sarcoma randomized to treatment with surgery and adjuvant chemotherapy versus surgery, chemotherapy, and EBRT

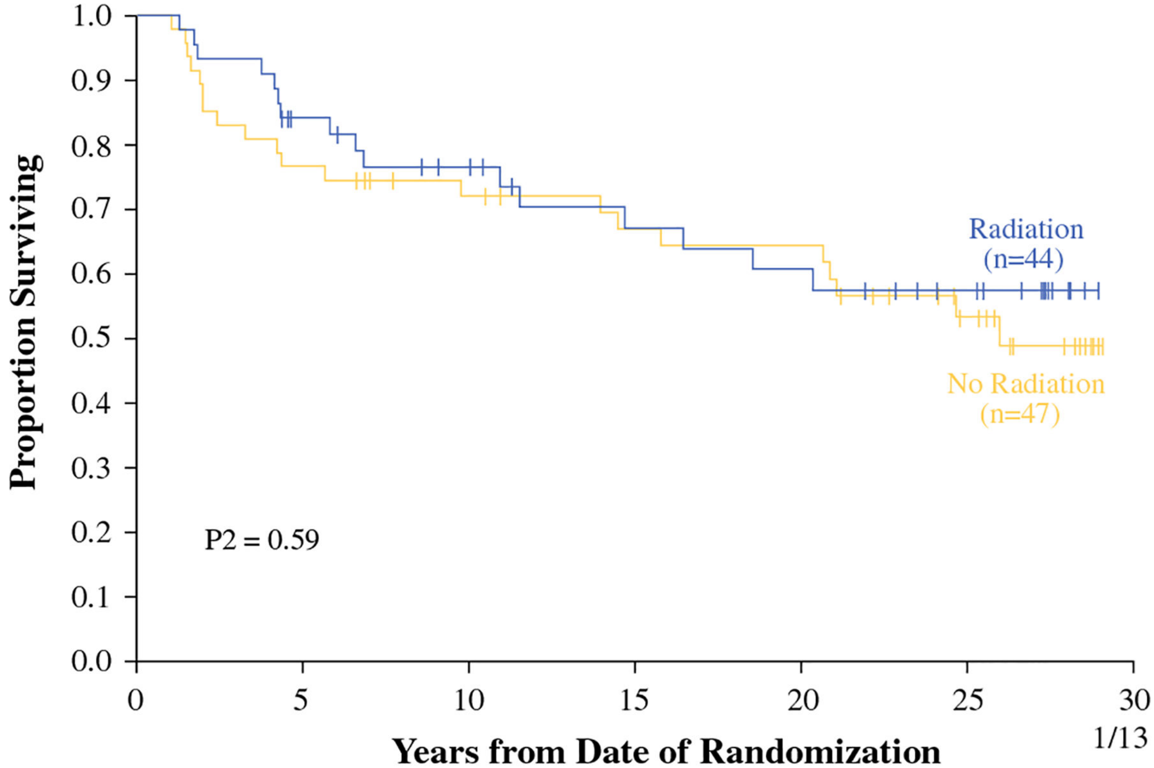

FIG. 2.

Overall survival of patients with high-grade extremity sarcoma randomized to treatment with surgery and adjuvant chemo-therapy versus surgery, chemotherapy, and EBRT

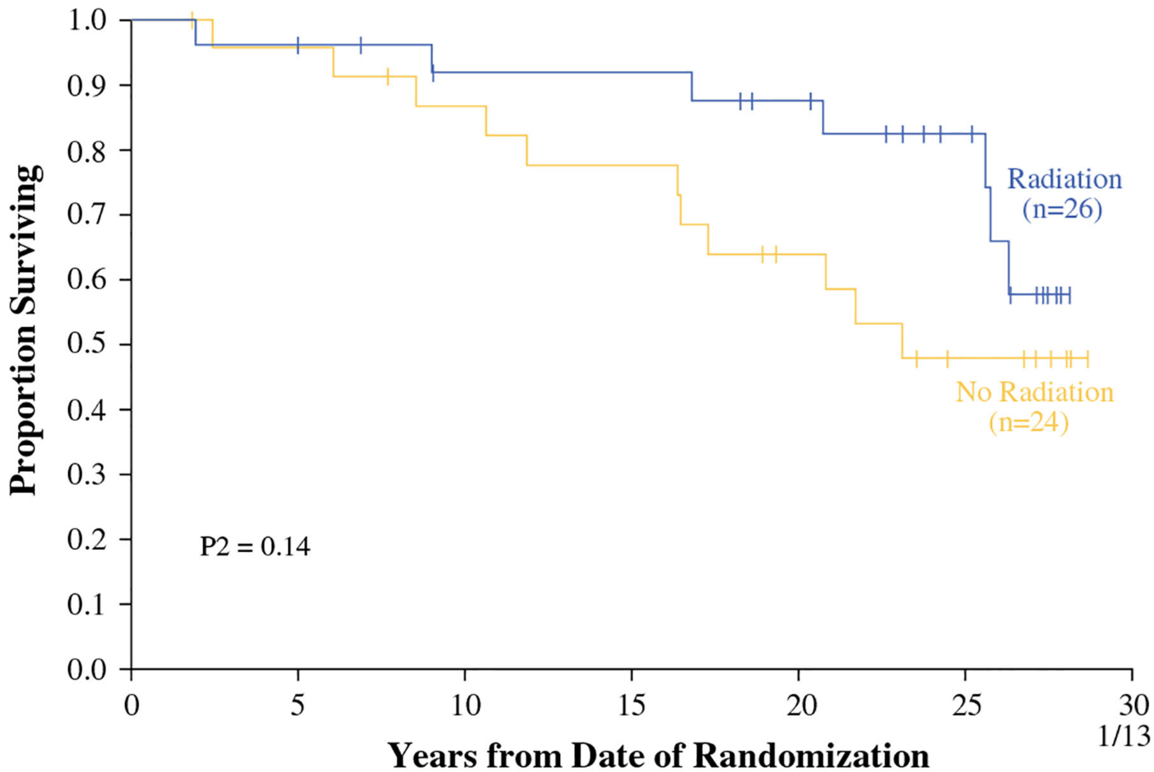

FIG. 3.
Overall survival of patients with low-grade extremity sarcoma randomized to treatment with surgery and adjuvant chemo-therapy versus surgery, chemotherapy, and EBRT

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TABLE 1

Patient demographics

	No EBRT		Adjuvant EBRT	
	No.	**%**	**No.**	**%**
Total patients randomized	71		70	
Known protocol violators	4	6	1	1
Sex				
Male	43	61	35	50
Female	28	39	35	50
Site				
Proximal upper extremity	12	17	13	19
Distal upper extremity	6	8	3	4
Proximal lower extremity	40	56	33	47
Distal lower extremity	13	18	21	30
Tumor				
Benign	5	7	4	6
Grade 1	19	27	22	31
Grade 2	26	37	24	34
Grade 3	21	30	20	29
Tumor size (cm; maximum diameter)				
0–1.9	6	8	5	7
2–4.9	19	27	24	34
5–9.9	25	35	27	39
≥10.0	21	30	13	19
Not available	0	0	1	1
Surgical resection margin				
Positive (<1 mm)	11	15	7	10
Negative; close (1–10 mm)	20	28	12	17
Negative; wide (>10 mm)	5	7	13	19
Negative; not specified	7	10	11	16
No tumor in re-resection	27	38	27	39
Not available	1	1	0	0

TABLE 2

Functional and quality of life assessment in surviving patients

	No EBRT		Adjuvant EBRT		*p* value
	No.	**%**	**No.**	**%**	
Employment status					
Yes	10	42	9	30	0.57
No	13	54	17	57	
Never employed	1	4	4	13	
Age at retirement (mean ± SEM years)	59.9 ± 2.2		58.6 ± 3.2		0.76
Pain score (mean ± SEM)	2.1 ± 0.4		2.5 ± 0.4		0.44
Routine use of pain medication					
Yes	3	13	5	17	1.00
No	21	88	25	83	
Wound complications					
None	19	79	22	73	0.68
Grade 1	2	8	3	10	
Grade 2	2	8	3	10	
Grade 3	1	4	2	7	
Presence of edema					
None	15	63	14	50	0.21
Grade 1	6	25	7	25	
Grade 2	3	12	5	18	
Grade 3	0	0	2	7	
Lower extremity function					
Grade 1	17	85	22	88	0.84
Grade 2	3	15	2	8	
Grade 3	0	0	0	0	
Grade 4	0	0	1	4	