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Research Article

A Comparative Study of Soft Tissue Sarcomas of the Extremities: Brachytherapy versus Radiotherapy

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Abstract

Background: Soft tissue sarcoma (STS) is a wide group of solid tumors with specific features originating from mesenchymal tissue. Radiotherapy (RT) and chemotherapy have been widely applied in the treatment of these tumors to enhance surgical outcomes. This study was performed aiming to compare the results of postoperative brachytherapy (BRT) versus RT in patients who underwent surgical resection of extremity STSs.
Methods: In a prospective study from 2011 to 2015, 166 patients with extremity STS who underwent surgical resection were included. All visible tumors, scars, and drain sites, if present during the surgery, were resected. A number of 79 patients received adjuvant RT, and 87 patients underwent BRT after surgical resection.
Results: In patients who were treated through RT, the two-year local control was 90% in comparison with 87% for those treated through BRT ($P > 0.050$). The total radiation dose was 3869 ± 370 and 3048 ± 465 in the patients who underwent RT and in the BRT group ($P < 0.001$), respectively. The number of radiation sessions in the RT group and BRT group was respectively 27.3 ± 4.5 and 5.8 ± 2.0 ($P = 0.001$).
Conclusion: Not only BRT can lead to similar local control and survival in comparison with the conventional adjuvant RT, but it can also decrease the total dose and number of radiation sessions in patients with STS of the extremity, which is a high grade, in individuals who underwent surgical resection.

Keywords: Sarcoma; Brachytherapy; Radiotherapy

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Background

Soft tissue sarcoma (STS) is a wide group of solid tumors with specific features, originating from mesenchymal tissue with the incidence of about 9000 new cases every year in the U.S (1). Developing management for adults with primary extremity STS accentuate local control with preservation of quality of life (QOL) and limb function. Surgery is considered as the principal treatment for primary extremity STSs. Only surgical resection has led to markedly high incidence of recurrence. Radiotherapy (RT) and chemotherapy have been widely applied in the treatment of these tumors in order to enhance surgical outcomes. In spite of these cases, local recurrence occurs commonly, particularly in patients with large tumors at the beginning, positive surgical margins, close marginal resections, and re-excision in operated patients (2).

On the whole, the one-year and five-year predicted rates of survival are about 80 and 60%, respectively in extremity STSs, when an aggressive surgical treatment as well as amputation is applied. Studies evaluating surgical resection along with external beam radiation therapy (EBRT) showed comparable rates of disease-free survival and overall survival rate. The first randomized prospective trial, about less aggressive surgical approaches revealed no difference between the patients who underwent amputation and those who underwent surgical resection with limb saving procedures combined with EBRT (3). Contrary to EBRT, which covers extensive fields which kindly involve the surgical bed, brachytherapy (BRT) concentrates the dose in the immediate district of the surgical bed. Therefore, BRT can actually better preserve normal tissues and evade complications like lymphedema, fracture of the bone, or fibrosis of subcutaneous tissue (4). In some patients, BRT can be a replacement for EBRT (5). In addition, the use of BRT does not prevent the accumulation of EBRT, which can complement the dose administrated by RT when prescribed (5). Given what was mentioned above, this study was conducted with the aim to compare the outcomes of postoperative BRT with those of RT in patients who underwent surgical resection of extremity STSs.

Methods

This prospective study was carried out from January 2011 to January 2015 on 166 patients with extremity STS referred to Imam Khomeini Hospital Complex in Tehran, Iran, who underwent surgical resection. The study inclusion criteria were primary presentation, high grade in the tumor histology [based on the American Joint Committee on Cancer (AJCC) system], site of the tumor in extremities, limb-sparing surgery, and adjuvant BRT or RT. Moreover, the exclusion criteria were patients with amputation, distant or lymph node metastasis, and recurrent tumors prior RT. The study protocol was revised and approved by the institutional ethics committee of our university with the registration number 315-840-19. Each

patient provided the informed consent before participating in the study.

The demographic, clinical, and pathological information and treatments of the patients were analyzed. The tumor cell extension to the margin less than 1 mm was considered as positive microscopic resection margin. The maximum diameter of the tumor was considered as the tumor size. The depth of the tumor was estimated in relation to the investing fascia of the extremity, with tumors being categorized as either superficial or deep. Our surgical approach in this study was as follows: all visible tumors, scars, and drain sites if present during the surgery were resected. When the tumor was intermuscular or intramuscular, the resection involved one or more of these muscle bundles. A 2 cm margin in all directions was the goal, with limitations (< 2 cm) aimed at preserving all main neurovascular bundles (6).

The BRT technique was applied after loading the catheters into the tumor site intraoperatively by MultiSource®, Bebig (Cobalt-60 source). A radiation oncologist and a surgeon assessed the tumor site concurrently. A target region to be exposed was defined by adding 15 to 20 mm in the lateral and medical dimensions and 20 mm to the inferior and superior dimensions of the excised tumor bed. The afterloading catheters were inserted intraoperatively, about 10 mm separately, in the tumor bed. The catheters were fixed in the mentioned site through absorbable sutures and to the skin at the catheter exit place with non-absorbable sutures. A drain was placed in the surgery site. The dosage of BRT in the current study was 47 Gray (Gy; eight patients received 49 Gy) with a median dosage of 0.41 Gy/h. The BRT started after two weeks of surgery (7).

In our institute, chemotherapy is not advised particularly for all patients with high grade STS. The median time of follow up in our patients was 30 months. Local recurrence was considered as any recurrence in the primary site irrespective of distant recurrence. The Kaplan-Meier product limit method was used for measuring the survival rates (7). The statistical analysis was carried out using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA) and the chi-square test was used for analysis of correlations of the variables. Besides, the Cox stepwise regression analysis was used for independent prognostic factors (8). The probability values of less than 0.050 were considered significant.

Results

The mean age at the time of diagnosis was 48 years with the range of 18 to 70 years. 84 (50.6%) and 82 (49.4%) of the patients were women and men, respectively. The tumor in 75 (45.2%) and 91 (54.8%) patients was in the upper extremity and in the lower extremity, respectively. Malignant fibrous histiocytoma (MFH) was seen in 77 (46.3%) of the patients, which is the most common histology, followed by synovial sarcoma in 29 (17.4%), liposarcoma in 23 (13.9%), and miscellaneous in 37 (22.4%) of the patients. Manipulation of bone, which was considered as periosteal stripping (28 patients), or resection of bone (11 patients) was necessary in 39 (23.4%) patients. Manipulation of the nerve which was considered as neurolysis (18 patients) or nerve resection (21 patients), was necessary in 39 (23.4%) patients. 79 patients received adjuvant RT and 87 patients underwent BRT after surgical resection in a randomly assigned method by closed envelopes. Postoperative RT was administrated to 79 patients six weeks after the surgical resection to a median dose of 59 Gy by VARIAN CLINAC 600C/D Linear accelerator (Table 1).

Table 1. Demonstrates patients characteristics

Parameters		n	%
Sex			
	Male	82	49.4
	Female	84	50.6
Site	Upper extremity	75	45.2
	Lower extremity	91	54.8
Histology			
	MFH	77	46.3
	Synovial sarcoma	29	17.4
	Liposarcoma	23	13.9
	Miscellaneous	37	22.4
Bone manipulation			
	Periosteal stripping	28	16.9
	Bone resection	11	6.6
	No	127	76.5
Nerve manipulation			
	Neurolysis	18	10.8
	Nerve resection	21	12.6
	No	127	76.6
RT			
	Yes	79	47.6
	No	87	52.4
BRT			
	Yes	87	52.4
	No	79	47.6

MFH: Malignant fibrous histiocytoma; RT: Radiotherapy; BRT: Brachytherapy

The analysis of the RT and BRT groups demonstrated that there was no significant differences regarding age, sex, depth, location (upper or lower extremity), and histologic type between the two groups (P > 0.050 for all of them) (Table 2). The prevalence of tumors > 10 cm was 44% in the RT group in comparison with 47% in the BRT group. In the RT group, the necessity of periosteal stripping/bone resection (30.3% versus 17.2%, P > 0.050) and neurolysis/nerve resection (27.8% versus 19.5%, P > 0.050) was not considerably greater than in the BRT group. The percentage of positive/close margin was 42% for the RT group versus 39% for the BRT group (P > 0.050). The mean follow-up period for the BRT group was 32 months in comparison with 30 months for the RT group.

Table 2. Summarized outcomes in both groups

Parameters	Radiotherapy	Brachytherapy	P
Numbers	79	87	0.980
Female (%)	40 (50.6)	44 (50.1)	
Male (%)	39 (49.4)	43 (49.9)	
Age	49.23 ± 12.16	47.42 ± 17.64	0.440
Site			
Upper extremity (%)	35 (44.3)	40 (45.9)	0.920
Lower extremity (%)	44 (55.7)	47 (54.1)	
Histology of the tumor			
MFH (%)	38 (48.2)	39 (44.8)	0.220
Synovial sarcoma (%)	15 (18.9)	14 (16.2)	
Liposarcoma (%)	14 (17.7)	9 (10.3)	
Miscellaneous (%)	12 (15.2)	25 (28.7)	
Bone Manipulation			
Yes (%)	24 (30.3)	15 (17.2)	0.140
No (%)	55 (69.7)	72 (82.8)	
Nerve manipulation			
Yes (%)	22 (27.8)	17 (19.5)	0.210
No (%)	57 (72.2)	71 (80.5)	
Tumor size			
≤10 cm	44 (55.7)	41 (47.1)	0.210
>10 cm	35 (44.3)	47 (52.9)	
Margin			
Positive/close	33 (41.8)	34 (39.1)	0.380
Negative	46 (58.2)	57 (60.9)	
2-year survival rate (95% CI)	53 (47-69)	59 (55-73)	0.620
2-year local control	90 (85-95)	87 (80-93)	0.470
Radiation dose (Gy)	3869 ± 370	3048 ± 465	< 0.001
Number of sessions of radiation	27.3 ± 4.5	5.8 ± 2	< 0.001

MFH: Malignant fibrous histiocytoma

Of the 166 patients, 38 (22.9%) suffered from local recurrence during a mean follow-up time of 15 months with the range of 9 to 24 months since the date of the surgery. A total number of 14 local recurrences in the RT

group and 25 local recurrences in the BRT group was seen (P = 0.090) The local recurrence management (n = 380) consisted of wide local excision (WLE) in 23, WLE and RT in 5, WLE and BRT in 3, and amputation in 2 of our patients, and the last 5 cases were followed because of the presence of distant metastasis. Of the 14 local recurrences in the RT group, 9 were in-field and 5 were marginal. A number of 18 in-field and seven marginal local recurrences was seen in the BRT group. The two-year overall local control rate was 89% [95% confidence interval (CI), 82-93]. In patients who were managed by RT, the two-year local control was 90% (95% CI, 85-95) in comparison with 87% (95% CI, 80-93) for those managed by BRT (P > 0.050) The two-year survival rate in the patients managed by RT was 53% (95% CI, 47-69) compared with 59% (95% CI, 55-73) in the patients managed with BRT (P > 0.050). The total radiation dose of the patients who underwent RT (3869 ± 370) was significantly greater than that in the BRT group (3048 ± 465) (P < 0.001). Moreover, the number of sessions of radiation in the RT group (27.3 ± 4.5) was significantly greater than that in the BRT group (5.8 ± 2.0) (P = 0.001). The total duration of treatment in the RT and BRT groups was 43.7 ± 8.7 versus 6.3 ± 1.9 weeks, respectively (P = 0.001). Of the 79 patients in the RT group, 11 (13.9%) patients suffered from infection, while of the 87 patients in the BRT group, 27 (31.0%) patients suffered from infection (P > 0.050). There were no statistically significant differences between the groups regarding seroma/hematoma formation, bleeding, and fibrosis.

With a mean follow-up of 32 months in the BRT group and 28 months in the conventional RT group, the two-year local control rate was 90% with conventional RT, when compared with 87% in the BRT (P > 0.050).

Discussion

Given the findings of this study, we suggest that with high-grade non-metastatic STS of the extremities, BRT can lead to a significant decrease in the total dosage and sessions of radiation in these special group of patients with equal rate of local recurrence and survival compared with conventional RT. However, BRT may increase the risk of postoperative infection.

Based on the literature review, two prospective randomized trials were found, with one using BRT (6) and the other using adjuvant RT (9), which showed the local control advantage of adjuvant RT or BRT over surgical resection alone in STSs. RT before the surgery has also been compared with postoperative RT in a randomized approach (10). While there was no randomized trial, a prospective study compared adjuvant BRT to RT in high grade extremity STSs. In the present study, we compared adjuvant RT with BRT, in a randomized manner to increase its validity and feasibility. There were no statistically significant differences between the groups in terms of bone manipulation (stripping/resection) and nerve in the BRT group in comparison with the conventional RT. Moreover, there were no significant differences between the groups relating to patients with positive/close (< 1 mm) margin in the BRT group compared with the conventional RT. Despite the greater frequency of postoperative complication including infection in the BRT group, the local control was comparable with BRT on univariate as well as multivariate analysis (90% in the RT group versus 87% in the BRT group). In a randomized trial, the five-year local control frequency for STSs (High grade) was 89% in the BRT group (6). However, in another study by reviewing BRT data in 233 patients with high grade STS of the limbs, a five-year local control of 83% was presented, which is in line with our results (11).

In another study, Bean et al. demonstrated that EBRT could amend local recurrence, but it should be performed in patients with high risk of local recurrences and in patients with low risk, it should be selective (12). Folkert et al. showed about 7.6% of their patients with primary STS had local recurrence who were managed with RT, which was lower than in patients with BRT (5). Conventional RT is presently the preferred protocol of delivering adjuvant RT in most of the cancer treatment centers all over the world considering the great proportion of local control achieved (5). Possibly with better modifications and improvements in the BRT techniques, similar to what occurred in prostate BRT (13, 14), one might use a renaissance in the efficacy of BRT in STSs of the extremity in the future.

The results of this study indicated that, not only that BRT can lead to similar local control and survival in comparison with conventional adjuvant RT, but can also decrease total dose and number of radiation sessions in patients with STSs of the extremity which is high grade, who underwent surgical resection. This may increase the possibility of postoperative complications, especially surgical site infection.

Conclusion

Not only BRT can lead to similar local control and survival in comparison with conventional adjuvant RT, but it can also decrease the total dose and number of radiation sessions in patients with STS of the extremity, which is high grade, who underwent surgical resection.

Conflict of Interest

The authors declare no conflict of interest in this study.

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