Efficacy and Safety of Adjuvant Radiotherapy for Soft Tissue Sarcoma: A Two-Institution Retrospective Observational Study

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Efficacy and Safety of Adjuvant Radiotherapy for Soft Tissue Sarcoma: A Two-Institution Retrospective Observational Study

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Abstract

Background/Objective: The recommended post-operative radiotherapy dose of approximately 60 Gy may be reduced during treatment planning, and the optimal irradiation method and dose remain unclear. We aimed to clarify the usefulness and safety of post-operative radiotherapy for soft tissue sarcomas.

Methods: Forty-five patients with soft-tissue sarcomas who underwent adjuvant radiotherapy at two institutions from June 2014 to August 2020 were included. Patients with a high risk of recurrence underwent post-operative irradiation, with doses of 60–70 Gy and 50 Gy used in patients with positive and negative resection margins, respectively.

Results: The median patient age was 72 (21–88) years. The most common histological types of sarcomas were myxofibrosarcoma (n = 12) and dedifferentiated liposarcoma (n = 11), followed by other sarcomas. Thirty patients were newly diagnosed, and 15 underwent surgery for localized recurrent disease. Thirty-two and 13 patients underwent wide and marginal resection, respectively. Surgical margins were negative in 12 patients and positive in 33 patients. Chemotherapy was administered before or after radiotherapy in 16 patients. The 2-year local control, progression-free survival, and overall survival rates after post-operative radiotherapy were 88%, 78%, and 93%, respectively. In patients with positive resection margins, doses of ≥60 Gy contributed to local control ($p = 0.0002$, log-rank test) and progression-free survival ($p = 0.0033$). Late grade 3 adverse events were observed in 7% of the patients.

Conclusion: Post-operative radiotherapy for soft tissue sarcomas is safe and effective, with high doses (≥60 Gy) contributing to reduced recurrence among patients with positive resection margins.

Keywords: soft tissue sarcoma, post-operative radiotherapy, multidisciplinary therapy, myxofibrosarcoma, dedifferentiated liposarcoma

Introduction

Soft tissue sarcomas are rare malignant neoplasms [1-4]. Although surgery is the main treatment for soft tissue sarcoma, multidisciplinary treatment is often administered, and adjuvant or neoadjuvant radiotherapy is frequently indicated [2-4]. In recent years, recommendations regarding adjuvant therapy after surgery have been published by the European Society for Medical Oncology [3] and the American Society for Radiation Oncology [4]. These guidelines recommend both pre- and post-operative irradiation, with a preference for preoperative irradiation where feasible. However, postoperative radiotherapy is also advised for patients whose localized soft tissue sarcoma was treated with surgery without preoperative radiotherapy and found to have unexpected unfavorable pathologic characteristics [3, 4]. At our institution, for patients deemed to have a high risk of recurrence after surgery owing to tissue invasiveness of the tumor or positive resection margins, the options of reoperation and post-operative radiotherapy are discussed among surgeons, radiologists, and medical oncologists when the risk of recurrence is high; however, reoperation is deemed inappropriate, post-operative radiotherapy is chosen. Overall, while randomized trials have shown that general perioperative radiotherapy reduces the risk of post-operative recurrence [5-9], the literature has been inconsistent in terms of histological tumor grade, method of surgery, method of assessing margins, and radiotherapy method [1, 10].

Previous studies report the recommended dose for post-operative radiotherapy to be approximately 60 Gy; however, the dose may be reduced during treatment planning because of the dose constraint posed by the organs at risk. For example, in patients with retroperitoneal sarcoma in whom the tumor is close to the intestine, the irradiation dose to the target is limited to 50–55 Gy. Moreover, the optimal irradiation method and dose have not yet been determined.

Therefore, this review aimed to examine clinical data and assess the usefulness of post-operative radiotherapy for soft tissue sarcomas while assessing the optimal radiotherapy dose and treatment techniques. We retrospectively reviewed the data of patients treated with post-operative radiotherapy at two institutions and calculated the recurrence, survival, and adverse events. We also examined the differences in local control according to the radiotherapy method and prescribed dose.

Methods

Patients

Forty-five patients with soft tissue sarcomas treated with adjuvant radiotherapy at Kyushu University Hospital and Kyushu Rosai Hospital between June 2014 and August 2020 were included. Adjuvant treatment was considered for each patient after surgery, and those who opted for observation or reoperation were not included in this study.

Because the purpose of this study was to investigate the efficacy of adjuvant therapy, one patient with a gross residual tumor after surgery (R2 resection) was excluded. This study was conducted in accordance with the Japanese Ethical Guidelines for Medical and Biological Research Involving Human Subjects [11] and was approved by the institutional review boards of Kyushu University Hospital (Approval number: 22279-00) and Kyushu Rosai Hospital (Approval number: 22-17). Informed consent was obtained in the form of opt-out on the website.

Tumor grading and staging

Histological grade and stage were classified according to the French Federation Nationale des Centers de Lutte Contre le Cancer and the 8th edition of the Union for International Cancer Control classification, respectively.

Treatment

The decision regarding post-operative radiation was made after a discussion at a joint conference or direct discussion between the attending physician and the radiation oncologist. In general, irradiation was performed in patients with positive margins and those with negative margins but a high risk of recurrence owing to high tissue invasiveness. The clinical target volume (CTV) was defined as >2 cm from the tumor bed. When the extremities were involved, a longitudinal margin of ~4–7 cm was added, and after 40–50 Gy of irradiation, the longitudinal CTV margin was shrunk to ~3–4 cm to avoid irradiation of the hip and shoulder joints. When the tumor bed was close to the normal organs at risk, the target volume was reduced according to the location of the organs. The total dose was 50 Gy for negative resection margins and 60–70 Gy for positive resection margins and was selected on a case-by-case basis, with consideration of irradiation history and surrounding normal organs. Chemotherapy was not administered concurrently with radiotherapy but was administered before or after radiotherapy.

Evaluation and statistical analysis

Post-treatment follow-up evaluations were typically performed at intervals of 3 to 6 months. When necessary, CT and MRI were performed at least annually during the follow-up. The local control, progression-free survival, and overall survival, after post-operative radiotherapy were evaluated using Kaplan–Meier survival curve analysis, and the results were compared using the log-rank test. Adverse events were evaluated in terms of acute and late

effects according to Common Terminology Criteria for Adverse Events version 5.0. Fisher's exact test was used to evaluate the correlation between age and other factors to investigate why age was a prognostic factor for local control. Statistical analyses were performed using JMP Pro, Version 16 (SAS Institute Inc., Cary, NC, USA). Kaplan–Meier curves were drawn using GraphPad Prism version 9.4.1 for MacOS (GraphPad Software, San Diego, CA, USA).

Results

Patients and treatments

Patient characteristics are shown in Table 1. The median patient age was 72 (21–88) years. Thirty patients were newly diagnosed, and 15 were surgically treated for localized recurrence. The histological types of sarcomas were myxofibrosarcoma (12 patients), dedifferentiated liposarcoma (11 patients), myxoid liposarcoma (6 patients), leiomyosarcoma (5 patients), undifferentiated pleomorphic sarcoma (4 patients), synovial sarcoma (2 patients), malignant peripheral nerve sheath tumor (1 patient), rhabdomyosarcoma (1 patient), extraosseous myxoid chondrosarcoma (1 patient), hemangiosarcoma (1 patient), and epithelioid sarcoma (1 patient) (Online Resource 1). Thirty-two patients underwent wide resection, and 13 underwent marginal resection. Surgical margins were negative (R0) in 12 patients and positive (R1) in 33.

Post-operative radiotherapy was administered as three-dimensional conformal radiotherapy in 41 patients and intensity-modulated radiotherapy in 4 patients. The X-ray beam energies were 4–10 MV, and the dose was 50 Gy, 60 Gy, and 70 Gy in 9, 33, and 3 patients, respectively. Details of the patients who received less than 60 Gy are shown in Online Resource 2. Radiotherapy was started 2 to 24 weeks (median, 6 weeks) postoperatively. Chemotherapy was administered to 16 patients as follows: doxorubicin/ifosfamide (10 patients), gemcitabine/docetaxel (2 patients), docetaxel (2 patients), eribulin (1 patient), and trabectedin (1 patient).

Survival analysis of post-operative radiotherapy

Of the 45 patients who received post-operative radiotherapy, 15 (33%) had recurrence during the observation period (7–88 months, median 27 months): 7 (16%) had local recurrence, 2 (4%) had regional lymph node recurrence, and 7 (16%) had distant metastasis (Fig. 1A). Five (11%) patients died, all owing to primary disease. Survival curves showed a 2-year local control rate of 88%, a 2-year progression-free survival rate of 78%, and a 2-year overall survival rate of 93% (Fig. 1B–D). Five of the local recurrences occurred outside or on the edge of the irradiated field, and two occurred within the irradiated field (Online Resource 3).

In a univariate analysis based on patient characteristics and treatment strategy, local control was significantly better in patients younger than 70 years, newly diagnosed patients, and patients with a low histological grade (Table 2, Fig. 2). While this was not significant, all patients with local recurrence had positive resection margins (Table 2, S3). Therefore, we next performed a subgroup analysis of patients with positive resection margins, which may contribute to local recurrence, and found that patients younger than 70 years, those with early-stage disease, and those who received a high dose (>60 Gy) exhibited significantly better local control (Table 3, Fig. 3).

In univariate analysis of progression-free survival, newly diagnosed patients and those with a low histological grade had a better prognosis (Table 2, Online Resource 4). In a subgroup analysis similar to that for local control, doses ≥ 60 Gy contributed to improvement in progression-free survival in patients who underwent R1 resection (Table 3, Online Resource 5).

To determine the reason for poor prognosis in the older group, we applied Fisher's exact test and found that the number of patients with recurrence and pathologically high grade was higher, and that of those treated with chemotherapy was lower in the older group than in the younger group (Online Resource 6).

Adverse events

Acute adverse events included grade 3 dermatitis in three patients (7%). Late adverse events included one case of grade 3 dermatitis, one case of dermatitis and ileus, and two cases of histological fractures. All adverse events improved with medical treatment (Online Resource 7).

Discussion

In this retrospective review of patients treated with post-operative radiotherapy for soft tissue sarcoma at two institutions, the 2-year local control, progression-free survival, and overall survival rates were 88%, 78%, and 93%, respectively. Despite the short observation period of 2 years, the local control and overall survival rates were comparable to those reported in previous randomized trials with variable histological grades (8, 9). Furthermore, although 7% of adverse events were grade 3, they were treatable and were thus considered acceptable.

In the univariate analysis, dose prescriptions ≥60 Gy were found to contribute to local control and progression-free survival in the recurrence factor analysis in a subgroup of patients who underwent R1 resection,

suggesting that a sufficient prescribed dose is necessary for post-operative irradiation in patients undergoing R1 resection.

According to previous studies, the recommended dose of post-operative radiotherapy is approximately 60 Gy [1, 3, 4]. Therefore, a prescribed dose of 60 Gy for post-operative irradiation was used for this research. However, in cases where organs at risk, such as the digestive tract, spinal cord, or joints, were close to the surgical bed, irradiation of up to 50 Gy has been used, with consideration of the tolerable dose to the surrounding organs (Online Resource 2). However, advanced radiotherapy techniques such as intensity-modulated radiotherapy or adaptive radiotherapy can deliver increased doses to the target while reducing the dose to at-risk organs. Therefore, using such techniques, it may be possible to prescribe doses ≥ 60 Gy for post-operative irradiation of sites where the dose has been reduced to 50 Gy.

This analysis also included patients in whom radiotherapy was administered after reoperation for recurrence. Recurrence after radiotherapy was significantly more frequent in patients who had undergone reoperation, suggesting that the potential for malignancy was higher in these patients than in newly diagnosed patients. It has been suggested that an increase in treatment intensity is necessary in patients with recurrence. However, the optimal use of treatment methods such as dose escalation and concurrent chemotherapy are is yet to be established.

Age was also a prognostic factor for local control because of the higher number of patients with recurrence, higher histological grade, and lower number of patients treated with chemotherapy in the older group than in the younger group (Online Resource 6). These factors may have influenced the prognosis in older patients.

Our study had some limitations. First, it was a retrospective analysis that only included patients who underwent post-operative irradiation, and there was no control group to determine the usefulness of this irradiation. Second, the number of cases was small, and the observation period was short. Owing to the low prevalence of this disease, large-scale prospective studies are not feasible. Third, detailed comparisons according to histological type or site of occurrence were not performed because of the small sample size. Certain histological types, such as liposarcomas, show better results with radiotherapy than other sarcomas [3, 10, 12], and in the future, it may be necessary to select treatment according to histological type. In addition, clinical target volume settings must be unified. Radiation coverage was based on the clinical target volume with a margin of ≥2 cm from the tumor bed; however, this varied from case to case, and detailed comparisons are yet to be made. Finally, as marginal

recurrence accounts for most local recurrences, the appropriate post-operative irradiation range remains controversial.

Conclusions

In this study, we found that post-operative radiotherapy for soft tissue sarcomas is beneficial and safe.

In patients with positive resection margins, doses of ≥60 Gy contributed significantly to local control and progression-free survival.

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Declarations

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Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval: This study was approved by the institutional review boards of Kyushu University Hospital (Approval number: 22279-00) and Kyushu Rosai Hospital (Approval number: 22-17).

Consent to participate: Informed consent was obtained in the form of opt-out on the website.

Consent for publication: Informed consent was obtained in the form of opt-out on the website.

Availability of data and materials: The authors confirm that all data supporting the findings of this study are available within the article.

Code availability: Not applicable.

Author's contributions: All authors contributed to the study conception and design. Data collection was perfoemed by OH and SN. Data were analyzed by OH, and interpreted by OH, TY, SN. KM, HW, RU, MT, TO, YM, ME, AN, TM, AM, and KI supervised and critically revised the manuscript. The first draft of the manuscript was written by OH, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Abbreviations:
CTV: clinical target volume
UICC: Union for International Cancer Control

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Figure Legends

Fig. 1 Recurrent disease and survival

Venn diagram showing recurrence patterns and the number of cases (A). Kaplan–Meier survival curves for local control (B), progression-free survival (C), and overall survival (D)

Fig. 2 Prognostic factors for local control in all patients

Kaplan–Meier survival curves for local control after post-operative radiotherapy divided by radiation dose (A), age (B), occurrence (C), histological grade (French Federation Nationale des Centers de Lutte Contre le Cancer, FNCLCC) (D), and stage (Union for International Cancer Control, UICC 8th edition) (E)

Fig. 3 Prognostic factors for local control in patients who underwent R1 resection

Kaplan–Meier survival curves for local control after post-operative radiotherapy divided by radiation dose (A), age (B), occurrence (C), histological grade (French Federation Nationale des Centers de Lutte Contre le Cancer, FNCLCC) (D), and stage (Union for International Cancer Control, UICC 8th edition) (E)

Reporting guidelines checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2	Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	Introduction: paragraphs 1, 2, 3
Objectives	3	State specific objectives, including any prespecified hypotheses	3	Introduction: paragraphs 4
Methods				
Study design	4	Present key elements of study design early in the paper	3	Methods: section 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3	Methods: section 1
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	3,4	Cohort study: Methods: section 1, 4
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case		Cohort study: Methods: section 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3,4	Methods: section 4
Data sources/8* measurement		For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3,4	Methods: section 4
Bias	9	Describe any efforts to address potential sources of bias	3	Methods: section 1
Study size	10	Explain how the study size was arrived at	3	Methods: section 1

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3	Methods: section 4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	3.	Methods: section 4
		(b) Describe any methods used to examine subgroups and interactions	3.	Methods: section 4
		(c) Explain how missing data were addressed	3.	Methods: section 4
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	Not applicable.	
		(e) Describe any sensitivity analyses	Not applicable.	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	4	Result:section 1
		(b) Give reasons for non-participation at each stage	4	Result:section 1
		(c) Consider the use of a flow diagram	Not applicable.	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4	Result:section 1
		(b) Indicate number of participants with missing data for each variable of interest	4	Result:section 1
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	4	Result:section 1
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time Case-control study—Report numbers in each exposure category, or summary measures of exposure Cross-sectional study—Report numbers of outcome events or summary measures	4,5	Result:section 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4,5	Result:section 2
		(b) Report category boundaries when continuous variables were categorized	4,5	Result:section 2
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable.	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable.	
Discussion				
Key results	18	Summarise key results with reference to study objectives	5	Discussion: paragraphs 1
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	5	Discussion: paragraphs 6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5	Discussion: paragraphs 2-5
Generalisability	21	Discuss the generalisability (external validity) of the study results	5	Discussion: paragraphs 1-3
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	6	Declarations