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Poor Efficacy of Postoperative Radiotherapy in Infiltrative High-grade Soft Tissue Sarcomas

HIDEYUKI KINOSHITA[1], TAKESHI ISHII[1], HIROTO KAMODA[1], YOKO HAGIWARA[1], TOSHINORI TSUKANISHI[1], MASAHIRO INOUE[2], TORU UETA[2], SEIJI OHTORI[2] and TSUKASA YONEMOTO[1]

[1]*Department of Orthopedic Surgery, Chiba Cancer Center, Chiba, Japan;*
[2]*Department of Orthopedic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan*

Abstract. *Background/Aim: We aimed to investigate the effectiveness of postoperative radiotherapy (RT) on local recurrence-free survival (LRFS) in high-grade infiltrative soft tissue sarcomas (STSs) and determine its prognostic factors. Patients and Methods: This was a retrospective cohort study and included 132 patients with high-grade STSs. Patients were divided into two groups: Group RT (n=48) who underwent postoperative RT and Group No-RT (n=84) who underwent only surgery. We analysed 5-year LRFS and its prognostic factors between these groups. Furthermore, 5-year LRFS in infiltrative and non-infiltrative STSs were evaluated. Results: Five-year LRFS was not significantly different in Group RT (83.6%) and Group No-RT (79.6%) (p=0.698). Overall, significant prognostic factors influencing LRFS were age at diagnosis (p=0.02) and tumour growth pattern (p=0.04). Postoperative RT was less effective in the infiltrative than in non-infiltrative pattern of STSs. Conclusion: Postoperative RT does not influence local recurrence outcomes in infiltrative STSs.*

Overall, soft-tissue sarcomas (STSs) are rare tumours, with an incidence of 5/100,000 cases per year. STSs show mesenchymal differentiation and consist of more than 50 distinct histological subtypes. These subtypes are associated with differing risks of metastases and disease-specific mortality, which makes the treatment of STSs difficult (1, 2). Furthermore, infiltrative STSs have a high local recurrence rate as compared to the non-infiltrative STSs (3).

Correspondence to: Hideyuki Kinoshita, Department of Orthopedic Surgery, Chiba Cancer Center, 666-2 Nitonacho, Chuo-ku, Chiba 260-8717, Japan. Tel: +81 432645431, Fax: +81 432628680, e-mail: kinoshi1783@yahoo.co.jp

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The management of patients presenting with high-grade STSs of the extremity and trunk is done by performing extensive resection and limb-sparing surgery, and adjuvant perioperative radiotherapy (RT) in order to reduce the risk of local recurrence (4, 5). RT is indicated as an adjuvant treatment in all superficial and deep-seated tumours when a wide surgical margin is not achieved (6, 7). Adjuvant RT has been described as an essential contributor in the success of limb-sparing therapy (8, 9). Furthermore, perioperative RT has been used for local control of STSs in various institutions around the world. Recently, however, there have been some sceptical reports about the local control of high-grade STSs in which perioperative RT was performed. Fiore *et al*. reported that the local recurrence-free survival (LRFS) of patients with high-grade STSs who underwent surgery with perioperative RT did not differ from that of patients who underwent surgery alone (10). Teurneau *et al*. reported that the rate of local recurrence in patients with myxofibrosarcoma (MFS) was high and the effect of RT on local control was unclear (11). We previously reported that the infiltrative growth pattern was an adverse prognostic factor for local control, as well as disease-specific survival rate and metastasis-free survival in patients with MFS and undifferentiated pleomorphic sarcoma (UPS). Furthermore, RT could not salvage inadequately resected infiltrative tumours (12).

In the current study, we aim to determine the following: [1] the effect of postoperative RT on LRFS in other high-grade STSs, including UPS and MFS, [2] the prognostic factors for LRFS in STSs, and [3] the effect of postoperative RT on LRFS in different STS growth patterns, such as infiltrative or non-infiltrative pattern.

Patients and Methods

Study design. Approval of the review board of Chiba Cancer Center and written informed consent from each patient prior to inclusion were obtained before beginning this study. We retrospectively reviewed our institution’s database to identify patients who were diagnosed with STSs and underwent extensive resection during the period from 2013 and 2019.

Patients and clinical characteristics. We identified 257 patients who had been diagnosed with STSs. Myxoid liposarcoma and small round cell sarcoma were excluded because of their significant responsiveness to RT. In addition, patients with less than one year of follow-up, low-grade sarcoma, and R2 resection (macroscopic residual tumour after surgery) diagnosed by postoperative histological analysis were excluded. Finally, 132 patients were included. None of the patients were lost to follow-up. The mean follow-up period and age at diagnosis were 43 months (range=12-101 months) and 66 years (range=13-97 years), respectively. Furthermore, the mean tumour size was 8.6 cm (range=1.3-29 cm). The data regarding tumour-associated factors, such as gender, age at diagnosis, tumour size, tumour depth, tumour location, growth pattern, histology, and histological grading according to the Fédération nationale des centres de lutte contre le cancer (FNCLCC) grading system (13) and American Joint Committee on Cancer (AJCC) TNM system were collected from patient records. Furthermore, the information regarding treatment-associated factors, such as surgical margin, RT status, chemotherapy status, and oncological outcome were also obtained.

Growth pattern. Growth patterns were investigated on preoperative magnetic resonance imaging. We used short TI inversion recovery and gadolinium-enhanced fat-saturated T1-weighted image to evaluate the growth pattern. Infiltrative growth was classified as a tail, which is an extensive lesion along the normal fascial plane with a tumour depth that was either deep-seated or superficial (14, 15). On the other hand, well-demarcated tumours without extension were defined as non-infiltrative growth.

Treatment. All patients were reviewed at our oncology board and treated using appropriate structure- and function-preserving surgical resection. Our general policy regarding the resection margin of an infiltrative tumour was to excise 3 cm away from the edge of the extension of infiltration. In patients with the tumour adjacent to critical structures or neurovascular bundles, an attempt was made to obtain gross tumour-free margin. To evaluate the surgical margin, the tumour specimen at the presumed closest surgical margin after discussing with pathologist was sectioned. Surgical margin was microscopically categorised; positive margin (R1 resection) was defined as the presence of tumour cells at the closest margin, and negative margin (R0 resection) was defined as the absence of tumour cells at the margin. Patients with R1 resection margins were not planned for additional excision. In our institution, we usually perform postoperative RT on patients with R1 resection. Some patients were prescribed postoperative chemotherapy (generally ifosfamide and doxorubicin) based on the prognostic factors predicting higher risk of distant metastasis and local recurrence.

Statistical analysis. Patient data were entered into our database in a consecutive manner. LRFS was defined as the time period from the date of surgery to that of local failure, or the last follow-up of patients without events. Survival probabilities were examined with the Kaplan–Meier analysis. Differences in survivals were evaluated by the log-rank test for univariate analysis. Associations among the indicated factors were assessed with the Fisher's exact test or chi-square test for categorical data and the Wilcoxon rank sum test for continuous data. Differences were defined statistically significant when *p*-values were less than 0.05. All analyses were performed with SAS software, version 14.2 (SAS Institute, Inc.; Cary, NC, USA).

Results

Patient demographics. The data regarding patient and tumour characteristics, and the type of treatment performed are listed in Table I. The number of patients with age ≤65 years at the time of operation was 37.9%, and 56.1% of the patients were male. The tumour size was ≤10 cm in 63.6% cases and deep-seated tumour accounted for 91.7%. Tumours were located in the upper limb (20.5%), lower limb (56%), and trunk (23.5%). Infiltrative tumour growth pattern was present in 55.3% of the cases. The histological tumour subtypes were UPS (37.9%), MFS (18%), liposarcoma (15.9%), synovial sarcoma (6.8%), and malignant peripheral nerve sheath tumour (6.8%). According to the FNCLCC grading, grade 2 and grade 3 tumours accounted for 46.2% and 53.8%, respectively. The distribution of tumours according to the AJCC 7th stage was as follows: IIA (19.7%), IIB (26.5%), III (50%), and IV (3.8%). Surgical margin was R0 and R1 in 53.8% and 46.2% of the cases, respectively. RT was administered in 48 patients (36.4%). The radiation dose ranged from 50 Gy to 66 Gy, with a median dose of 59.3 Gy. Doxorubicin-based chemotherapy regimen was prescribed in 48 patients (36.4%). Complications of postoperative RT were reported in 92% of the cases, which included minor complications, such as tingling or slight erythema, and serious complications. Among these, complications such as infections, burns, and pathological fractures, which required surgery accounted for 11.5% of all cases.

We divided 132 study patients into two groups: Group RT (patients who underwent RT after surgery) and Group No-RT (patients treated with surgery alone). There were significant differences in tumour depth, growth pattern, and surgical margins between the two groups. In our institution, RT was only performed in patients after R1 resection except in cases of wound complication, extreme age, early relapse, and patient's choice. However, RT was administered in 2 patients after R0 resection because of their insistence for its possibility of controlling local recurrence.

LRFS and prognostic factors. Next, we evaluated the efficacy of postoperative RT in high-grade STSs. Figure 1 shows that 5-year LRFS was not significantly different between Group RT (83.6%) and Group No-RT (79.6%) (p=0.698). The results of univariate analysis showed that significant prognostic factors for LRFS were age at diagnosis (p=0.02) and tumour growth pattern (p=0.04) (Table II). Figure 2 indicates the efficacy of postoperative RT on LRFS of infiltrative and non-infiltrative patterns. In the infiltrative pattern, 5-year LRFS was not significantly different between Group RT (75.9%) and

Table I. *Patient demographics and disease characteristics*.

Characteristics		RT (n=48)		No RT (n=84)		Overall (n=132)		*p*-Value
		N	%	N	%	N	%	
Gender	Male	27	56.3	47	55.9	74	56.1	0.973
	Female	21	43.7	37	44.1	58	43.9	
Age at diagnosis	65 years or less	15	31.3	35	41.7	50	37.9	0.232
	Over 65 years	33	68.7	49	58.3	82	62.1	
Tumor size. cm	10 cm or less	34	70.8	59	70.2	84	63.6	0.942
	Over 10 cm	14	29.2	25	29.8	48	36.4	
Tumor depth	Superficial	1	2.1	10	11.9	11	8.3	0.031*
	Deep-seated	47	97.9	74	88.1	121	91.7	
Tumor location	Upper limb	10	20.8	17	20.2	27	20.5	0.938
	Lower limb	26	54.2	48	57.2	74	56	
	Trunk	12	25	19	22.6	31	23.5	
Growth pattern	Infiltrative	33	68.8	40	47.6	73	55.3	0.018*
	Non-infiltrative	15	31.2	44	52.4	59	44.7	
Histology	UPS	18	37.5	32	38.1	50	37.9	0.831
	Myxofibrosarcoma	11	22.9	13	15.5	24	18	
	Liposarcoma	9	18.7	12	14.3	21	15.9	
	Synovial sarcoma	2	4.2	7	8.3	9	6.8	
	MPNST	2	4.2	7	8.3	9	6.8	
	Leiomyosarcoma	2	4.2	5	6	7	5.5	
	Other	4	8.3	8	9.5	12	9.1	
FNCLCC Grade	Grade 2	23	47.9	38	45.2	61	46.2	0.766
	Grade 3	25	52.1	46	54.8	71	53.8	
AJCC 7th stage	IIA	9	18.8	17	20.2	26	19.7	0.783
	IIB	14	29.2	21	25	35	26.5	
	III	24	50	42	50	66	50	
	IV	1	2	4	4.8	5	3.8	
Surgical margins	R0	2	4.2	69	82.1	71	53.8	<0.0001*
	R1	46	95.8	15	17.9	61	46.2	
Radiotherapy	Yes	48	100	0	0	48	36.4	NA
	No	0	0	84	100	84	63.6	
Chemotherapy	Yes	13	27.1	35	41.7	48	36.4	0.094
	No	35	72.9	49	58.3	84	63.6	

UPS: Undifferentiated pleomorphic sarcoma; RT: radiotherapy; MPNST: malignant peripheral nerve sheath tumour; FNCLCC: Fédération nationale des centres de lutte contre le cancer; AJCC: American Joint Committee on Cancer. *Statistically significant.

Group No-RT (70.3%) (p=0.729) (Figure 2A). Similarly, in the non-infiltrative pattern, there was no significant difference in 5-year LRFS between Group RT (100%) and Group No-RT (85.7%) (p=0.226) (Figure 2B).

Discussion

Our results showed that postoperative RT was not effective in preventing local recurrence of high-grade STSs except for myxoid liposarcoma and small round cell sarcomas, and overall significant prognostic factors for LRFS were age at diagnosis and tumour growth pattern. When the results were evaluated with respect to tumour growth patterns, it was observed that RT had a poor local control effect in infiltrative patterns (5-year LRFS in Group RT and Group No-RT was 75.9% and 70.3%, respectively). However, in the non-infiltrative pattern, although there was no significant difference in 5-year LRFS between Group RT (100%) and Group No-RT (85.7%), postoperative RT showed a relative effectiveness as compared to surgery alone. The reasons for the poor effect of RT on high-grade STSs will be discussed in terms of pre- or postoperative RT, histological type, growth pattern, and inclusion criteria of adequate margin for RT.

First, the administration of pre- or post-operative RT has been reported to provide similar local control effects and survival rates (16). Yang *et al*. evaluated oncologic outcomes of pre- and post-operative RT in resectable STSs through a systematic review and meta-analysis (17). The results of this meta-analysis suggested that LRFS, overall survival, and distant metastasis were not significantly different between the pre- and post-operative RT groups in resectable STS cases. Although postoperative RT has been commonly used,

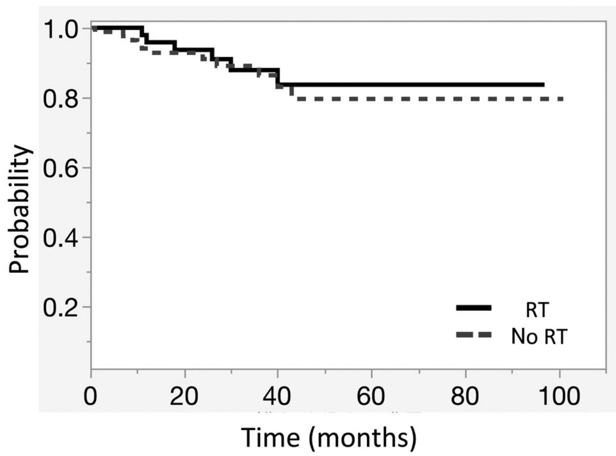

Figure 1. *Kaplan–Meier curves for evaluating local recurrence-free survival in high-grade soft tissue sarcomas after undergoing surgery and radiotherapy (Group RT), or surgery alone (Group No-RT).*

Table II. *Univariate analysis for investigating prognostic factors of local recurrence-free survival in high-grade soft tissue sarcomas.*

Factors		N	%	5-year LRFS (%)	*p*-Value
Gender	Male	74	56.1	83.5	0.29
	Female	58	43.9	79.1	
Age at diagnosis	65 years or less	50	37.9	92.4	0.02*
	Over 65 years	82	62.1	70.9	
Tumor size. cm	10 cm or less	84	63.6	81.3	0.64
	Over 10 cm	48	36.4	78.8	
Tumor depth	Superficial	11	8.3	100	0.28
	Deep-seated	121	91.7	80.3	
Growth pattern	Infiltrative	73	55.3	74	0.04*
	Non-infiltrative	59	44.7	89.4	
FNCLCC Grade	Grade 2	61	46.2	85.2	0.46
	Grade 3	71	53.8	78.5	
AJCC 7th stage	II	61	46.2	84.7	0.64
	III and IV	71	53.8	78.3	
Surgical margins	R0	71	53.8	78.4	0.76
	R1	61	46.2	83.4	
Radiotherapy	Yes	48	36.4	83.6	0.69
	No	84	63.6	79.6	
Chemotherapy	Yes	48	36.4	75.8	0.42
	No	84	63.6	85.3	

FNCLCC: Fédération nationale des centres de lutte contre le cancer; LRFS: local recurrence-free survival; AJCC: American Joint Committee on Cancer. *Statistically significant.

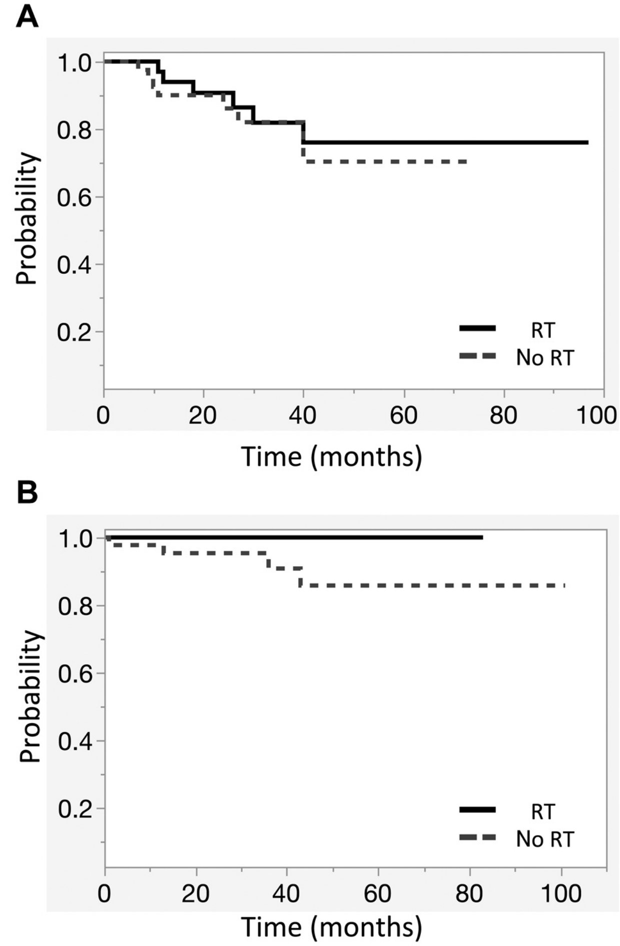

Figure 2. *Kaplan–Meier curves for evaluating local recurrence-free survival in high-grade infiltrative soft tissue sarcomas (A) and high-grade non-infiltrative soft tissue sarcomas (B) after surgery and radiotherapy (Group RT), or surgery alone (Group No-RT).*

especially in Europe, technical improvements in RT, such as intensity-modulated RT are associated with a better management of postoperative wounds. These apparent benefits have resulted in an increased preference for the use of preoperative RT. However, pre-operative RT is associated with a significantly increased risk for complications compared to postoperative RT. The role of pre- and postoperative RT for the treatment of resectable STSs has remained controversial.

Second, there are many different histological subtypes of STS, which increase difficulties in its treatment. Some histological subtypes of STS, such as small cell sarcoma, show higher radiosensitivity. Additionally, myxoid liposarcoma is a common STS of the mediastinum and retroperitoneum, which is known to have good radiosensitivity (18). In the current study, we excluded myxoid liposarcoma and small cell sarcoma, owing to their higher sensitivity to RT. However, future studies are warranted to separately evaluate the effect of RT on individual histological subtypes of high-grade STSs.

Third, local recurrence rate depends on tumour growth pattern. Dadrass *et al*. reported that infiltrative STSs have a relatively high rate of local recurrence compared to other STS subtypes (19). We have previously reported that infiltrative growth pattern was an adverse prognostic factor for LRFS in patients with MFS and UPS. Furthermore, RT could not salvage inadequately resected infiltrative tumours (12). In the current study, 5-year LRFS after postoperative RT was 83.6% in overall STSs, 75.9% in infiltrative STSs, and 100% in non-infiltrative STSs. Conversely, 5-year LRFS without postoperative RT was 79.6% in overall STSs, 70.3% in infiltrative STSs, and 85.7% in non-infiltrative STSs. Zhao *et al*. reported that postoperative RT was related with a significant reduction in local recurrence risk compared to surgery alone, with a 5-year LRFS in the postoperative RT group of 81.1% and in the surgery alone group of 63.6% (20). Compared to many reports in the literature, our results showed that postoperative RT could control local recurrence in non-infiltrative STSs. However, RT showed limited efficacy in preventing local recurrence in infiltrative high-grade STSs, thereby necessitating alternate treatment protocol or modality for the local control of infiltrative STSs.

Finally, there is a need for determining quantitative criteria for adequate margin before considering any case for RT. According to the National Comprehensive Cancer Network (NCCN) Guideline, 10 mm can be accepted as an adequate margin (21). A margin width of less than 2 mm results in a marginal excision (22). Novais *et al*. evaluated quantitative margins, which were defined as a tumour on ink (positive), ≤2 mm, >2 mm–≤2 cm, and >2 cm (23), and reported that patients with ≤2 mm margins have decreased overall survival. However, in a cohort study of 387 patients who underwent wide resection with RT, no difference in survival rate and local recurrence was noted with any width of the resection margin (≤1 mm, >1–≤5 mm, and ≥5 mm) (24). As there is no clear guideline or consensus in the existing literature regarding an adequate quantitative margin width for RT, surgeons need to determine acceptable margin on an individual basis with efforts to preserve critical structures and maximise postoperative functionality.

Recently, treatment modalities other than RT have been reported to control local recurrence of STSs. Mateusz *et al*. reported that hypofractionated RT combined with hyperthermia is a feasible treatment option for marginally resectable or unresectable STSs, especially in patients for whom chemotherapy in contraindicated (25). Furthermore, the proton quad-shot regimen is reported to serve as a feasible alternative treatment for patients with previously treated recurrent or metastatic STSs, in which overall treatment options may be limited (26).

In conclusion, the postoperative RT does not influence local recurrence outcomes in infiltrative STSs. The future policy in our institution is to consider postoperative RT for infiltrative STSs with a close margin of ≤2 mm, and adding other modalities such as hyperthermia in the perioperative period. Further prospective studies evaluating the efficacy of RT on local recurrence are necessary.

Conflicts of Interest

The Authors have no conflicts of interest directly relevant to the content of this article.

Authors' Contributions

H.K, T.Y, and T.I designed and performed experiments, analyzed data and wrote the article; H.K, Y.H, T.T, M.I, T.U, S.O gave technical support and conceptual advice.

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