■ ONCOLOGY

The role of radiotherapy in the treatment of superficial soft-tissue sarcomas

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Aims

The existing clinical guidelines do not describe a clear indication for adjuvant radiotherapy (RT) in the treatment of superficial soft tissue sarcomas (STSs). We aimed to determine the efficacy of adjuvant RT for superficial STSs.

Methods

We retrospectively studied 304 patients with superficial STS of the limbs and trunk who underwent surgical resection at a tertiary sarcoma centre. The efficacy of RT was investigated according to the tumour size and grade: group 1, ≤ 5 cm, low grade; group 2, ≤ 5cm, high grade; group 3, > 5 cm, low grade; group 4, > 5 cm, high grade.

Results

The five- and ten-year local recurrence-free survival (LRFS) for all patients was 88% and 81%, respectively. While the efficacy of adjuvant RT was not proven in local control of all patients (five-year LRFS; RT+, 90% versus RT-, 83%; p = 0.074), the LRFS was significantly improved by adjuvant RT in group 2 (five-year LRFS; RT+, 96% versus RT-, 82%; p = 0.019), and group 4 (five-year LRFS; RT+, 87% versus RT-, 73%; p = 0.027). In groups 2 and 4, adjuvant RT significantly reduced the LR risk if the resection margin was clear but less than 5 mm; the LR rate was 7% with adjuvant RT compared with 26% with surgery alone (p = 0.003). There was no statistical relationship with the use of adjuvant RT and survival in every group.

Conclusion

Adjuvant RT reduces the risk of local recurrence in patients with superficial high-grade STS regardless of tumour size, especially when resection margin is less than 5 mm.

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Introduction

Soft tissue sarcomas (STSs) constitute a diverse group of malignant mesenchymal tumours with over 50 histological entities described.[1-3] The primary treatment of localized STSs is surgical resection, but may involve multimodal treatment, which may include radiotherapy (RT) and/or chemotherapy. The resection margin is generally accepted as a factor for predicting local recurrence (LR), although the adequacy of margin width is controversial.[4] The efficacy of adjuvant RT in the treatment of STSs was demonstrated in a prospective randomized trial,[5] although the tumour location, superficial or deep, was not described. Currently, several guidelines such as the European Society for Medical Oncology (ESMO)[6] and National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines (http://www.nccn.org) advocate that RT should be considered for high-grade, deep tumours > 5 cm in size.

However, the efficacy of adjuvant RT for superficial STSs has rarely been discussed. The ESMO guidelines do not offer a definitive RT indication for tumours other than high-grade, deep, tumours > 5 cm in maximum dimension. They state that the decision should be determined in a multidisciplinary fashion.[2] Thus, the question remains whether or not there is a benefit from administering RT in the treatment of superficial STSs. This study was conducted to investigate the efficacy of adjuvant RT for these tumours.

Methods

We conducted a retrospective study of patients with superficial STSs who underwent surgical

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Table I. Patient demographics.

Variables	Total	Group 1: ≤ 5 cm, low grade	Group 2: ≤ 5 cm, high grade	Group 3: > 5 cm, low grade	Group 4: > 5 cm, high grade
Total patients, n (%)	304	19 (1)	90 (30)	14 (5)	181 (60)
Median age, yrs (range)	65 (8 to 99)	48 (26 to 82)	65 (8 to 94)	50 (35 to 89)	66 (11 to 99)
Sex, n (%)					
Male	157 (52)	8 (42)	53 (59)	13 (93)	83 (46)
Female	147 (48)	11 (58)	37 (41)	1 (7)	98 (54)
Site, n (%)					
Lower limb	183 (60)	9 (47)	53 (59)	7 (50)	114 (63)
Upper limb	61 (20)	4 (21)	25 (28)	2 (14)	30 (17)
Trunk	60 (20)	6 (32)	12 (13)	5 (36)	37 (20)
Diagnosis, n (%)					
Undifferentiated sarcoma	134 (41)	7 (37)	41 (46)	1 (7)	85 (47)
Myxofibrosarcoma	47 (15)	1 (5)	13 (14)	1 (7)	32 (18)
Leiomyosarcoma	29 (10)	4 (21)	14 (16)	0 (0)	11 (6)
Myxoid liposarcoma	25 (8)	2 (11)	5 (6)	4 (29)	14 (8)
Pleomorphic liposarcoma	10 (3)	0 (0)	0 (0)	0 (0)	10 (6)
Angiosarcoma	9 (3)	0 (0)	2 (2)	0 (0)	7 (4)
Synovial sarcoma	9 (3)	1 (5)	4 (4)	0 (0)	4 (2)
MPNST	7 (2)	0 (0)	1 (1)	0 (0)	6 (3)
Others	34 (11)	4 (21)	10 (11)	8 (57)	12 (7)
Adjuvant radiotherapy, n (%)					
Yes	210 (69)	1 (5)	58 (64)	2 (14)	149 (82)
No	94 (31)	18 (95)	32 (36)	12 (86)	32 (18)
Margin, n (%)					
Intralesional	46 (15)	1 (5)	11 (12)	3 (21)	31 (17)
Marginal	158 (52)	9 (47)	42 (47)	9 (64)	98 (54)
Wide	94 (31)	10 (53)	33 (37)	2 (14)	49 (27)
Radical	6 (2)	0 (0)	3 (3)	0 (0)	3 (2)
Local recurrence, n (%)					
Yes	35 (12)	2 (11)	5 (6)	1 (7)	27 (15)
No	269 (88)	17 (89)	85 (94)	13 (93)	154 (85)

MPNST, malignant peripheral nerve sheath tumour.

resection at a tertiary sarcoma centre between April 1996 and December 2015. Patients who were referred after inadvertent excisions at another hospital, that underwent re-excision after primary resection, received any chemotherapy, or were diagnosed as atypical lipomatous tumour/well-differentiated liposarcoma were excluded. A total of 304 patients met the inclusion criteria for the study. The details of demographic and treatment data are shown in Table I. The median age at diagnosis was 65 years (interquartile range (IQR) 52 to 76). There was a slight predominance of males (n = 157/304; 52%).

All the patients were discussed at a multidisciplinary team meeting and the final management plan was developed. The decision to use RT was individualized and variable but in general RT was advised for patients with high-grade and large tumours, close or contaminated surgical margins, or tumours located in areas where LR would be difficult to manage after resection, such as in the axilla. Tumour grade was classified according to the French Federation of Cancer Centres Sarcoma Group (FNCLCCs) grading system[7,8] by pathologists experienced in evaluating STSs; groups with a high-grade tumour included grade 2 and grade 3 tumours and groups with a low-grade tumour included grade 1 tumour by the FNCLCC grading system.

This study was approved by the institutional review board and all data were collected from the clinical and pathological data from an institutional prospective sarcoma database at a single tertiary centre.

Statistical analysis. Outcome measures studied included local-recurrence free survival (LRFS) and disease-specific survival (DSS). The Kaplan-Meier method was used to determine LRFS and DSS with time zero defined as the date of diagnosis and censored at the date of last follow-up or LR and tumour-related death, respectively. Univariate analysis was performed comparing groups with log-rank test and significant variables underwent subsequent multivariate Cox proportional hazard analysis to identify predictors of LRFS and DSS. The variables of each group were compared with use of the chi-squared test or the Fisher's exact test. A p-value ≤ 0.05 was considered significant. Statistical analyses were conducted using SPSS v. 23 (IBM, Armonk, New York, USA).

Results

Demographic and treatment details. In our series, more than half of the tumours were located in the lower limb (n = 183/304; 60%), followed by upper limb (n = 61/304; 20%), and trunk (n = 60/304; 20%). The histological diagnosis was undifferentiated

sarcoma in 134 patients (41%), myxofibrosarcoma in 47 (15%), leiomyosarcoma in 29 (10%), myxoid liposarcoma in 25 (8%), pleomorphic liposarcoma in ten (3%), angiosarcoma in nine (3%), synovial sarcoma in nine (3%), malignant peripheral sheath tumour in seven (2%), and others in 34 (11%). Most tumours were high grade (n = 271/304; 90%) and the median tumour size was 6.3 cm (IQR 4.7 to 9.0). RT was administered to 210 (69%) patients with 206 of these receiving it postoperatively, four had preoperative RT and one patient received preoperative RT with a postoperative boost. After treatment, patients with high-grade tumours were followed every three to four months in the first two or three years, then twice a year up to the fifth year, and once a year thereafter up to ten years postoperatively, with clinical examination and chest radiographs on each visit. Patients with low-grade tumours were followed in a similar way but every four to six months, in the first three to five years, then annually. The median follow-up period was 53 months (IQR 19 to 81 months), which was similar between groups.

Based on the tumour size and grade, patients were divided into four groups (Table I); ≤ 5 cm and low-grade tumours (group 1); ≤ 5 cm, high-grade tumours (group 2); > 5 cm, low-grade tumours (group 3); and > 5 cm, high-grade tumours (group 4).

Local tumour control according to tumour size and grade. Surgical margins were negative in 258 patients (85%) and positive in 46 (15%). LR occurred in 35 patients (12%). The five- and ten-year LRFS for all patients was 88% and 81%, respectively. In the univariate analysis, tumour size > 5 cm (p = 0.023, log-rank test) and positive resection margin (p < 0.001, log-rank test) were significant prognostic factor for LRFS (Supplementary Fig. a). There was a trend toward better local control in patients with adjuvant RT (p = 0.074, log rank test); the five- and ten-year LRFS was 94% and 84% in patients with adjuvant RT and 84% and 77% in those without it (Figure 1). In the multivariate analysis, tumour size (> 5 cm hazard ratio (HR) 2.405; 95% confidence interval (CI) 1.024 to 5.646; p = 0.044 vs ≤ 5 cm HR 1), surgical margin (positive, 3.286; 95% CI 1.635 to 6.602; p = 0.001 vs negative HR, 1), and use of adjuvant RT (RT- HR, 2.960; 95% CI 1.463 to 5.987; p = 0.003 vs RT+ HR, 1) were independent prognostic predictors for LRFS (Table II).

In group 1 (≤ 5 cm, low-grade tumours; n = 19), surgical margin was negative in 18 patients (95%) and positive in one (5%). LR occurred in two (11%) patients and the five- and ten-year LRFS was 93% and 83%, respectively (Figure 2). No patient treated with RT (n = 0/1) developed LR compared to 11% (n = 2/18) of those who did not have RT, but the difference was not statistically significant due to limited number of patients (p = 0.673, log-rank test; Figure 3a, Table III).

In group 2 (≤ 5 cm, high-grade tumours; n = 90), resection margin was negative in 79 patients (88%) and positive in 11 (12%). The five- and ten-year LRFS was 92% at both intervals (Figure 2). LR occurred in five patients (5%) including one patient with RT and four without RT. The LRFS was significantly better in patients treated with adjuvant RT than those without it (p = 0.019, log-rank test; Figure 3b, Table III).

In group 3 (> 5 cm, low-grade tumours; n = 14), LR occurred in one patient (7%) who had positive margin but declined further treatment. The five- and ten-year LRFS was 100% and 88%, respectively (Figure 2). There was no significant difference in LRFS between patients with or without adjuvant RT (p = 0.564, log-rank test; Figure 3c, Table III).

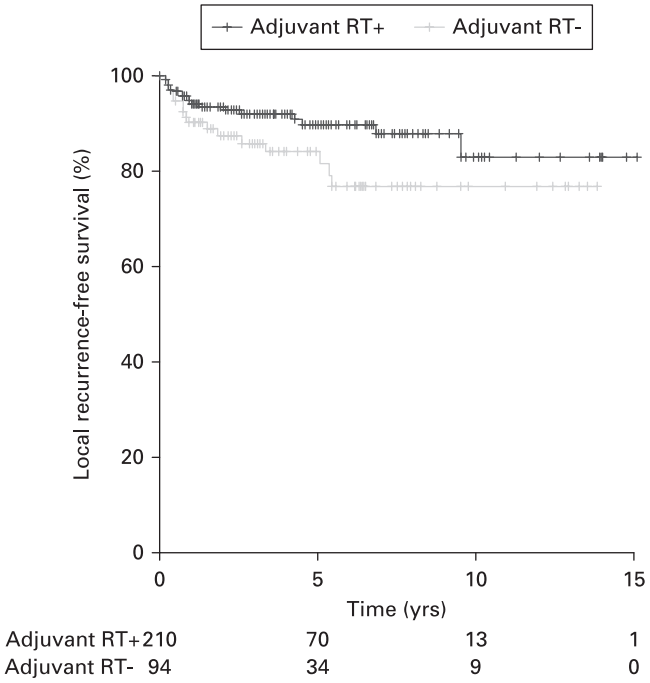

Fig. 1

Kaplan-Meier curves showing local recurrence-free survival in all patients stratified by the use of adjuvant radiotherapy (RT). p = 0.074, log-rank test.

In group 4 (> 5 cm, high-grade tumours; n = 181), LR occurred in 27 patients (17%). This included 11 patients with a positive margin and 16 who had a negative margin, respectively. Among these patients, 18 patients had adjuvant RT and nine did not. The five- and ten-year LRFS was 84% and 76%, respectively (Figure 2). LRFS was significantly better in patients treated with adjuvant RT than without it (p = 0.027, log-rank test; Figure 3d, Table III).

Local control according to use of adjuvant RT and measured resection margins. The width of surgical margins was clearly described for 282 patients (93%) of the patients studied. The relationship between resection margin width and LR stratified according to use of adjuvant RT is shown in Tables IV and V, and Supplementary Table i, ii.

In high-grade tumours, the LR rate in tumours with a positive resection margin was lower in patients with adjuvant RT than those without it, despite no significant difference; 21% and 38%, respectively (p = 0.374, chi-squared test). In tumours resected with a clear margin, adjuvant RT significantly reduced the LR rate if the resection margin was less than 5 mm; 7% with and 26% without adjuvant RT (p = 0.003, chi-squared test; Table IV). However, the LR rate was similar in tumours with and without adjuvant RT if the resection margin was over 5 mm; 6% and 5%, respectively (p = 0.400, chi-squared test). The histological subtypes for patients with margins over 5 mm who developed LR were myxofibrosarcoma (n = 1; RT+) and undifferentiated pleomorphic sarcoma (UPS) (n = 1; RT-).

Table II. Multivariate analysis for local recurrence-free survival and disease-specific survival.

Variable	LRFS		DSS	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Size		0.044		0.006
≤ 5 cm	1		1	
> 5 cm	2.405 (1.024 to 5.646)		2.286 (1.261 to 4.143)	
Grade		0.071		0.034
Low	1		1	
High	2.578 (0.746 to 8.908)		8.790 (1.176 to 65.689)	
Radiotherapy		0.003		0.555
Yes	1		1	
No	2.960 (1.463 to 5.987)		0.834 (0.457 to 1.522)	
Resection margin		0.001		0.412
Negative	1		1	
Positive	3.286 (1.635 to 6.602)		1.271 (0.717 to 2.252)	

CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; LRFS, local recurrence-free survival.

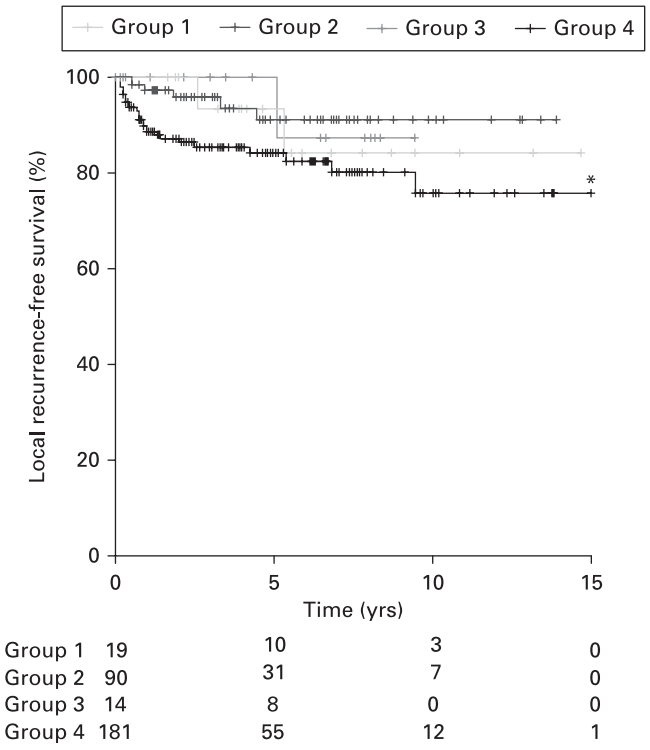

Fig. 2

Kaplan-Meier curves showing local recurrence-free survival in all patients stratifying by tumour size and grade (p = 0.102). *p = 0.024 (compared to group 2), log-rank test.

In low-grade tumours, no LR occurred in the three patients treated with adjuvant RT. Of those who did not received adjuvant RT, LR occurred in two of three patients (67%) with positive margin and one of 13 patients (8%) with margin less than 2 mm (Table V). The efficacy of adjuvant RT did not reach statistical significance (p = 0.629, chi-squared test).

Survival outcome. The five- and ten-year DSS for all patients was 75% and 66%, respectively. Univariate analysis revealed that the tumour size over 5 cm, high grade, and the presence of LR were significantly associated with poorer DSS (Supplementary Figure b). The five- and ten-year DSS was 100%, 100% for group 1, 86%, 76% for group 2, 100%, 76% for group 3, and 64%, 55% for group 4. Although there was a trend toward better survival in patients with clear resection margin, it did not reach statistical difference in DSS (p = 0.177, log-rank test). The efficacy of adjuvant RT for DSS was not proven in every group (Supplementary Figure c). The multivariate analysis revealed that tumour size (> 5 cm HR, 2.286; 95% CI 1.261 to 4.143; p = 0.006 vs ≤ 5 cm HR, 1), grade (high HR, 8.790; 95% CI 1.176 to 65.689; p = 0.034 vs low HR, 1), and the presence of LR (present HR, 3.137; 95% CI, 1.818 to 5.415; p < 0.001 vs absent HR, 1) were independent prognostic factors for DSS (Table II).

Discussion

There is no consensus whether or not the use of adjuvant RT provides benefit for patients with superficial STS, while the efficacy of adjuvant RT is proven in other types of sarcomas such as Ewing sarcoma.[9] In a study of 367 patients from the French Sarcoma Group database, the use of adjuvant RT had no significant correlation with LRFS and overall survival.[10] In contrast, Rydholm et al[11] and Tsagozis et al[12] indicated the efficacy of adjuvant RT in local control. Rydholm et al[11] reviewed 129 patients with superficial STSs and reported that the LR rate was 11% (n = 1/9) and 67% (n = 22/33) for marginal resections with and without adjuvant RT, respectively. In a report from Scandinavian Sarcoma Group, Tsagozis et al[12] demonstrated that LR rate was 7% (n = 8/115) in patients with adjuvant RT and 12% (n = 36/298) in those without it, but there was no analysis regarding tumour size. In our study, we identified that adjuvant RT significantly reduced the risk of LR in patients with superficial high-grade STSs regardless of tumour size. These outcomes confirm the positive efficacy of adjuvant RT for high-grade, superficial STS.

To date, the significance of resection margin width according to the use of adjuvant RT in superficial STSs has been unknown. In the study by the Scandinavian Sarcoma Group, adjuvant RT was associated with a superior local control in patients with high-grade tumours and marginal margin.[12] However, the classification of margins categorized as radical, wide, marginal, and intralesional by Enneking et al,[13] is inherently subjective and the answer to the question of what is a marginal margin varies

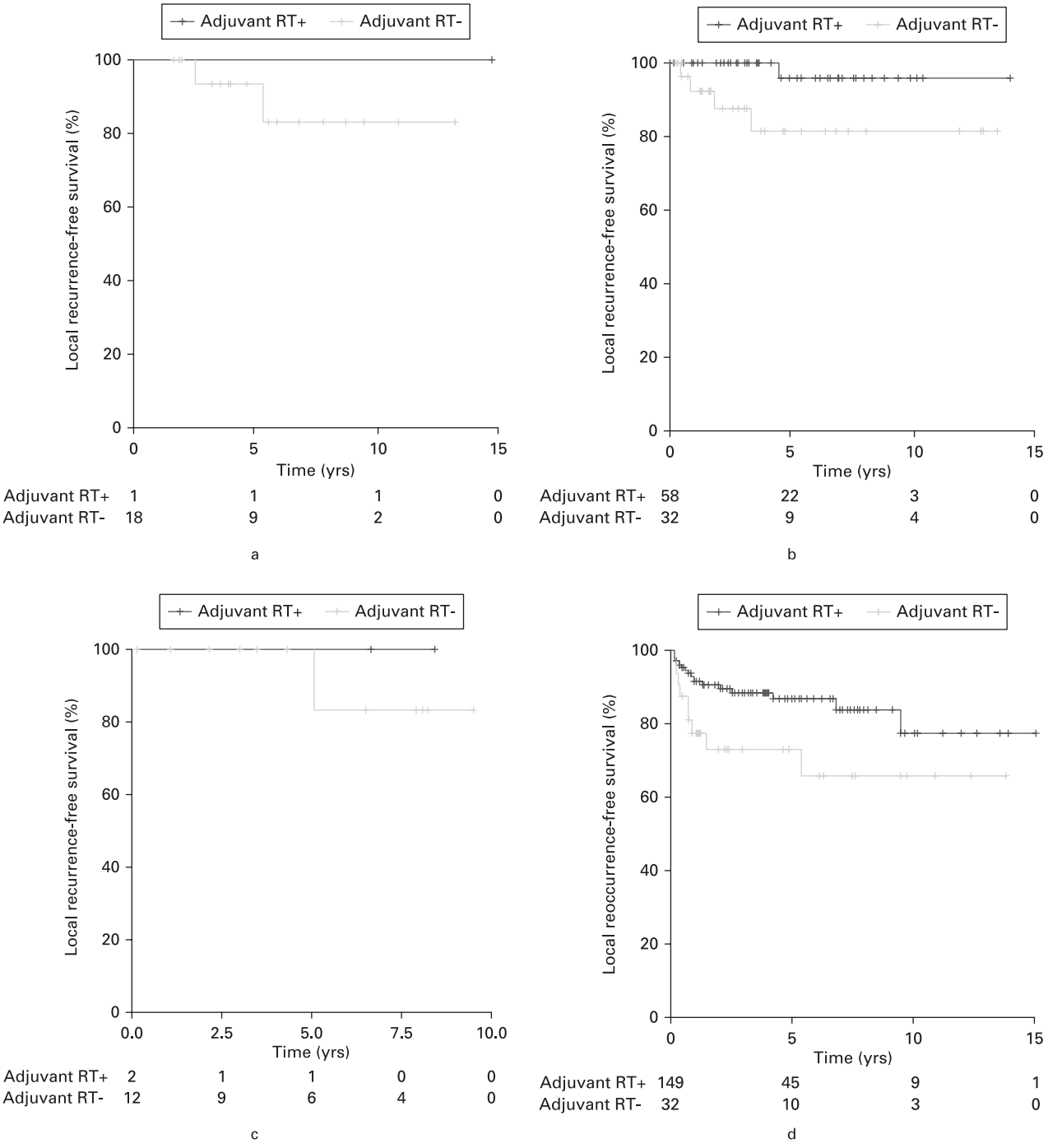

Fig. 3

a) Kaplan-Meier curves showing local recurrence-free survival stratified by the use of adjuvant radiotherapy (RT) in group 1 (≤ 5 cm, low-grade); p = 0.673. b) Kaplan-Meier curves showing local recurrence-free survival stratified by the use of adjuvant radiotherapy in group 2 (≤ 5 cm, high-grade); p = 0.019, c) Kaplan-Meier curves showing local recurrence-free survival stratified by the use of adjuvant radiotherapy in group 3 (> 5 cm, low-grade); p = 0.564. d) Kaplan-Meier curves showing local recurrence-free survival stratified by the use of adjuvant radiotherapy in group 4 (> 5 cm, high-grade); p = 0.027, log-rank test.

depending on the surgeons and investigators. In our study, adjuvant RT significantly reduced the LR rate of high-grade STSs if the resection margin was less than 5 mm. The efficacy of adjuvant RT was not evident if the resection margin was over 5 mm. The histological subtypes associated with LR despite a margin greater than 5 mm were myxofibrosarcoma and UPS. Myxofibrosarcoma and UPS frequently present an infiltrative growth pattern,[14-17] and the difficulty in local control even in the patients with wide resection margins has been noted.[15,16] Thus, adjuvant RT may contribute to decreased LR risk regardless of

Table III. Local recurrence-free survival according to use of radiotherapy.

Groups by tumour size and grade	Adjuvant RT-			Adjuvant RT+			p-value*
	n	5-yr, %	10-yr, %	n	5-yr, %	10-yr, %	
Group 1: ≤ 5 cm, low grade	18	93	83	1	100	100	0.673
Group 2: ≤ 5 cm, high grade	32	82	82	58	96	96	0.019
Group 3: > 5 cm, low grade	12	100	83	2	100	100	0.564
Group 4: > 5 cm, high grade	32	73	66	149	87	78	0.027

*Log-rank test.
RT, radiotherapy.

Table IV. Local recurrence rate in patients with superficial high-grade soft-tissue sarcoma stratified by resection margin in millimetres.

Closest margin	Total			Adjuvant RT-			Adjuvant RT+			p-value*
	LR+, n	Total, n	LR, %	LR+, n	Total, n	LR, %	LR+, n	Total, n	LR, %	
0 mm	11	46	24	3	8	38	8	38	21	0.374
0.1 to 4.9 mm	18	175	10	8	31	26	10	144	7	0.003
≥ 5.0 mm	2	35	6	1	19	5	1	16	6	0.400
Total	31	256	13	12	58	21	19	198	5	0.038

*Chi-squared test.
LR, local recurrence; RT, radiotherapy.

Table V. Local recurrence rate in patients with superficial low-grade soft-tissue sarcoma stratified by resection margin in millimetres.

Closest margin	Total			Adjuvant RT-			Adjuvant RT+			p-value*
	LR+, n	Total, n	LR, %	LR+, n	Total, n	LR, %	LR+, n	Total, n	LR, %	
0 mm	2	4	50	2	3	67	0	1	0	0.600
0.1 to 1.9 mm	1	14	7	1	13	8	0	1	0	0.929
≥ 2.0 mm	0	9	0	0	7	0	0	1	0	N/A
Total	3	26	12	3	23	13	0	3	0	0.629

*Chi-squared test.
LR, local recurrence; N/A, not applicable; RT, radiotherapy

the margin extent for myxofibrosarcoma and UPS, considering their local aggressiveness by infiltrative behaviour, although the radio-responsiveness of these tumours may not be the same as other histiotypes.[15,18]

The rate of LR and tumour-related death in this study was comparable to the previously published results. The reported LR rates were 9% to 23%[10,12,19,20] and five-year overall survival were 75% to 81%.[10,12,20] In general, superficial STSs are associated with superior survival compared to deep-seated STSs.[21,22] Tsagozis et al[12] described that the good prognosis of superficial STSs could be attributed to the low proportion of patients presenting with metastatic disease, which is lower than the rate of patients with deep-seated STSs. The rate of metastatic disease at presentation was 5% (n = 12/222) in their study, while the reported rate in deep-seated STSs was 8%.

The prognostic significance of adjuvant RT in STSs has been unclear. A retrospective study from the Surveillance, Epidemiology, and End Results (SEER) database with 6,960 patients with high-grade STSs involving the extremities found that three-year overall survival was increased by up to 10% ($p < 0.001$) with RT,[23,24] although randomized trials of adjuvant external-beam RT have not confirmed this survival benefit.[24] For superficial STSs, no study has demonstrated a survival benefit of adjuvant RT.[10-12] In this study, we observed no survival difference between patients treated with or without adjuvant RT in both low-grade and high-grade tumours. Collectively, adjuvant RT seems to be beneficial for local control but not for survival in patients with superficial STS.

We acknowledge several limitations to this study. Firstly, this study has a retrospective nature. Secondly, the number of patients, especially with low-grade STS, was relatively small for statistical analysis. Further analysis based on the larger cohorts would clarify the efficacy of adjuvant RT for low-grade tumours. Thirdly, the details regarding RT including radiation field and dose were unavailable for analysis, as RT is administered outside our institution. Fourthly, RT-related complications were not fully documented because of the reasons above and could not be discussed. Fifthly, this study did not compare functional outcomes between patients who received RT to those who did not. The reason is that the tumour sites varied from upper limb, lower limb, to trunk wall, and the extent of the resection also varied according to the tumour size and surrounding tissues, which made it difficult to perform a precise comparison between patients with and without the use of RT. Lastly, this study has an inherent selection bias in terms of the RT-treated patients as there was no randomization. In the absence of clear guidance regarding RT in superficial STSs, patients receiving RT were deemed to be high risk by the multidisciplinary team meeting. This could be a possible confounding factor in interpreting the outcomes of RT.

In conclusion, this study confirmed the efficacy of adjuvant RT in local control for high-grade superficial STSs regardless of the tumour size. LR risk was significantly reduced by adjuvant RT if the resection margin was less than 5 mm. The use of adjuvant RT had no relationship with tumour-related mortality in patients with superficial STS.

Take home message

- Adjuvant radiotherapy reduces the risk of local recurrence in patients with superficial high-grade STS regardless of the tumour size.
- The risk of local recurrence in superficial high-grade STSs is reduced by adjuvant radiotherapy, when the resection margin is less than 5 mm.

Supplementary material

Further Kaplan–Meier curves showing LRFS and DSS stratified by tumour- and treatment-related variables, and more detailed information on the LR rate according to the resection margin in millimetres.

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