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What is an adequate margin for infiltrative soft-tissue sarcomas?

Tomohiro Fujiwara [a, b, *], Jonathan Stevenson [a], Michael Parry [a], Yusuke Tsuda [a], Kim Tsoi [a], Lee Jeys [a]

[a] Department of Oncology, The Royal Orthopaedic Hospital, Birmingham, United Kingdom
[b] Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Japan

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ABSTRACT

Objectives: What constitutes an adequate margin of resection for infiltrative subtypes of soft-tissue sarcomas remains unclear. We aimed to determine the prognostic significance of the margin in millimetres for myxofibrosarcoma (MFS) and undifferentiated pleomorphic sarcoma (UPS).
Methods: 305 patients diagnosed with either a high-grade, localised MFS (n = 98) or UPS (n = 207) were included. The relationship of closest margin in millimetres to viable tumour and oncological outcomes was analysed.
Results: The overall local recurrence (LR) rate for all patients were 12%: 19% with positive margin and 10% with negative margin ($p = 0.051$). The LR rate was similar in patients with negative but <10 mm margin; 13%, 6%, 15%, 17% with 0.1–0.9 mm, 1.0–1.9 mm, 2.0–4.9 mm, and 5.0–9.9 mm margin, respectively. However, the LR rate decreased to 3% if the margin was ≥10 mm. By the R- or R+1-classification, the 10-year cumulative probability of LR was 9%, 15%, 48% for R0, R1, R2 resections, respectively, which was not sensitive enough to stratify the LR risk in patients with negative margins. However, the cumulative probability of LR was significantly stratified by metric distance; the 10-year cumulative LR probability was 3%, 14%, 25% with ≥10.0 mm, 0.1–9.9 mm, and 0 mm, respectively ($p = 0.026$). A trend towards improved local control by adjuvant radiotherapy was seen in patients with 0–9.9 mm margin ($p = 0.078$).
Conclusion: The resection margin, when measured as a metric distance, correlates with a reduction in LR, and appears to be more significant on local control than radiotherapy. To minimise the risk of LR, a margin distance of at least 10 mm is advocated for MFS and UPS.

Introduction

The significance of a wide resection margin in local control of soft tissue sarcomas (STSs) has been emphasized for decades [1–8]. While several authors have demonstrated that tumours resected with positive margins have a significantly higher rate of local recurrence [2,3,5,6,9–13], there is no consensus on what is an adequate margin distance for minimizing the risk of local recurrence. To date, several investigations have attempted to quantify the distance associated with a reduced risk of LR. Dickinson et al. stratified patients into five groups (contaminated, < 1 mm but clear, 1–4 mm, 5–9 mm, and 10–19 mm) and concluded that a margin greater than 1 mm was satisfactory for local control of STSs [5]. Sampo et al. reported that the incidence of LR correlated with increasing surgical margin, from 0 to 4 cm, and concluded that a surgical margin of 2–3 cm is 'reasonable' [6]. However, these previous investigations were performed using patient cohorts consisting of a variety of STSs including tumour types with an infiltrative margin, which are associated with higher rates of local recurrence [14].

Myxofibrosarcoma (MFS) and undifferentiated pleomorphic sarcoma (UPS) frequently present with an infiltrative growth pattern [15–18]. This infiltrative growth pattern was first reported in 1999 by Fanburg-Smith et al., where pathological infiltration was observed in patients with 83% of superficial and 24% of deep MFH (now termed UPS) [15]. In a retrospective review of 89 patients diagnosed with MFS or UPS, Iwata et al. observed infiltrative growth in 36% of MFS and 22% of UPS on preoperative MRI, which was defined as a tail-like extensive lesion along the normal fascial plane [17]. Although their surgical protocol was to excise 2–3 cm

* Corresponding author. The Royal Orthopaedic Hospital, Bristol Road South, Birmingham, B31 2AP, UK.
E-mail address: tomomedvn@gmail.com (T. Fujiwara).

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from the edge of the tumour extension on imaging studies, the surgical margin was positive in 48% (n = 43/89) and 5-year local recurrence-free survival was 81%. These outcomes underscore the difficulty of achieving wide margins for infiltrative subtypes of soft-tissue sarcomas [19]. Therefore, it would be preferable to analyse margin adequacy based on the narrower view focusing on the STS subtypes with infiltrative nature, which has been unclear to date.

In this study, we aimed to determine the significance of margin adequacy in millimetres on local control for the infiltrative subtypes of STS, namely MFS and UPS.

Patients and methods

This study was approved by the institutional review board and all data was collected from the clinical records and imaging systems as part of routine patient follow-up.

We conducted a retrospective review of patients diagnosed with MFS and UPS who underwent surgical treatment between 1996 and 2016. The histological diagnoses of these subtypes were determined by experienced pathologists and defined according to the latest version of World Health Organization (WHO) classification [20,21]. Only patients with a primary, high-grade sarcoma without metastatic disease at presentation were included. A minimum of two years follow-up was required for patients who remained alive. Those with low-grade and/or metastatic disease at presentation were excluded. Patients whose pathological details, including resection margin in millimetres, was unavailable were also excluded from this study.

All cases were discussed at a multidisciplinary team meeting in order to develop final management plans. Our policy for defining the area of resection was to undertake wide excision, including the tail-sign region identified on the preoperative magnetic resonance (MR) images, with the surrounding normal tissue. The decision to use radiotherapy was individualised and varied from patient to patient; however, radiotherapy was generally advised for patients with large or high-grade tumours, close or contaminated surgical margins or tumours located in areas where LR would be difficult to manage after resection, such as the axilla. Tumour-related factors including age at diagnosis, sex, histopathological diagnosis, tumour site, tumour size, tumour depth, histological grade, and tumour stage were collected from the patient records. Treatment-related factors obtained included surgical margin, adjuvant therapy (chemotherapy and radiotherapy), follow-up data including local recurrence and distant metastasis, follow-up period, and oncological outcome. Tumour size was determined as the greatest diameter of the tumour measured on the resected specimens. Tumour grade was classified according to the Trojani grading system [22]. Tumour stage was classified according to the UICC classification [23]. The closest resection margin was evaluated by pathologists highly experienced in bone and soft-tissue sarcomas following gross and microscopic examinations of the specimen. The resection margin in millimetres was classified according to the conventional R-classification (R0, macroscopic and macroscopic negative margin; R1, microscopically positive margin or marginal resection along a pseudo-capsule; R2, macroscopically positive margin) [24] and R+1-classification (R0, margin with $\geq$ 1 mm; R1, margin with <1 mm; R2, macroscopic positive margin) [25], and also categorised according to the results regarding the correlation between the margin and LR.

The primary end point of the analysis in this study was LR. Crude cumulative incidence was estimated for LR using a competing risk analysis. Death or metachronous distant metastases, whichever occurred first, was regarded as a competing event to LR. Multivariate analysis was performed using Fine and Gray model and calculated subdistribution hazard ratios (HRs) for the final predictor variables [26–29]. Statistical analyses were performed using the R version 3.5.5. Differences were considered to be statistically significant at $p < 0.05$.

Results

Patient characteristics

A total of 305 patients were available for analysis. The patient demographics, tumour characteristics and treatments received summarised in Table 1. The mean age at diagnosis was 67 years (range, 9–99 years). There was a slight male predominance (n = 160; 52%). 183 tumours (60%) were located in the lower extremity and 66 tumours (22%) were located in the upper extremity. Most tumours were grade 3 (82%), with the remaining 18% grade 2. Approximately half of the patients (54%) had tumours located deep to the fascia. The histopathological diagnosis was myxofibrosarcoma in 98 patients (32%) and undifferentiated pleomorphic sarcoma in 207 (68%). The mean tumour size defined as the greatest diameter of the tumour as measured from the excised specimen, was 9.2 cm (range, 2–31 cm). The stage of disease at presentation was IIA in 67 patients (22%), IIB in 115 (38%), and III in 123 (40%). Adjuvant chemotherapy and/or radiotherapy was performed in 13 patients (4%) and 245 (80%), respectively.

Resection margin of millimetres and local control

The relationship of margin in millimetres and LR is summarised in Table 2. The overall LR rate for all patients was 12% (n = 35/304). The incidence of LR for patients in whom a positive resection margin was achieved was 19% (n = 11/59), whilst for those in whom a negative margin was achieved, the rate of LR was 10% (n = 24/245) ($p = 0.051$). The LR rate was higher in macroscopically positive patients (R2) (33%; n = 7/21) when compared to microscopically positive patients (11%; n = 8/76). In patients with negative margin, the LR rate was not significantly different among patients with margin <10 mm when compare to those with a margin of 0.1–0.9 mm (13%), a margin of 1.0–1.9 mm (6%), a margin of 2.0–4.9 mm (15%), and a margin of 5.0–9.9 mm (17%). However, the LR rate decreased to less than 5% if the margin was >10 mm (Table 2).

When classified according to the R- and R+1-system, the crude cumulative probability of LR at 10 years was 9%, 15%, and 48% in R0, R1, and R2 resections, respectively ($p < 0.001$; Fig. 1A and B). No significant differences in the cumulative probability of LR were observed with regards to R0 or R1 resection using either system ($p = 0.643$, R-classification; $p = 0.535$; R+1-classification), indicating that this system is not sensitive enough to stratify the LR risk for patients with clear margin in these infiltrative subtypes of STS. On the other hand, when margins were categorised into three groups; positive margin (group 1), negative margin <10 mm (group 2), or negative margin >10 mm (group 3); based on the outcomes summarised in Table 2, a significant difference was observed between groups in terms of the cumulative probability of LR. The 10-year probability of 25% in group 1, 14% in group 2, and 3% in group 3 ($p = 0.026$; Fig. 1C).

Multivariate analysis was performed separately for R-classification, R+1-classification, and the three-group classification using Fine and Gray subdistribution hazard model. In all cases, the resection margin was identified as a significant factor, whereas tumour size, depth, grade and adjuvant radiotherapy did not have a significant influence (Table 3). In terms of R-classification, R2 resection was a significant hazard for LR (R2: HR, 5.923; 95% CI, 2.393–14.660; $p < 0.001$ versus R0 HR, 1). In R+1-mm classification, R2 resection was still a significant hazard for LR (R2: HR,

Table 1
Patient characteristics.

Variables	Definition	No. of patients	%, range
Total		305	–
Age at diagnosis	(median)	67	9–99
Gender	Male	160	52%
	Female	145	48%
Site	Lower extremity	183	60%
	Upper extremity	66	22%
	Trunk	53	17%
	Head and neck	3	1%
Depth	Deep	166	54%
	Superficial	139	46%
Diagnosis	Myxofibrosarcoma	98	32%
	Undifferentiated pleomorphic sarcoma	207	68%
Grade (FNCLCC)	Grade 2	55	18%
	Grade 3	250	82%
Tumour size	≤5 cm	66	22%
	>5 cm, ≤10 cm	152	50%
	>10 cm	87	29%
UICC stage	IIA	67	22%
	IIB	115	38%
	III	123	40%
Adjuvant chemotherapy	Yes	13	4%
	No	292	96%
Adjuvant radiotherapy	Yes	245	80%
	No	62	20%

Table 2
Local recurrence according to the surgical margin width and the use of radiotherapy.

Margin width	Total			No RT			Adjuvant RT		
	LR		%LR	LR		%LR	LR		%LR
	Yes	Total		Yes	Total		Yes	Total	
0 mm	11	59	19%	2	8	25%	9	51	18%
0.1–0.9 mm	9	72	13%	2	9	22%	7	63	11%
1.0–1.9 mm	4	70	6%	0	5	0%	4	65	6%
2.0–4.9 mm	8	55	15%	2	13	15%	6	42	14%
5.0–9.9 mm	2	12	17%	1	5	20%	1	7	14%
≥10.0 mm	1	36	3%	0	22	0%	1	14	7%
Total	35	304	12%	7	62	11%	28	242	12%

6.300; 95% CI, 2.445–16.230; $p < 0.001$ versus R0: HR, 1). However, no significant hazards for LR were observed for the R0 and R1 resections ($p = 0.650$ by R classification; $p = 0.460$ by R+1 classification). On the other hand, macro-/microscopic positive margins were significant hazards for LR with reference to ≥10 mm margin (0 mm: HR, 12.730; 95% CI, 1.055–153.500; $p = 0.045$ versus ≥ 10 mm: HR, 1). We identified a trend toward better local control in patients receiving adjuvant radiotherapy in group 1 and 2 patients with a 10-year cumulative LR probability of 14% in patients receiving adjuvant radiotherapy and 20% in patients who did not receive adjuvant radiotherapy (p = 0.078; Fig. 2).

Discussion

This study demonstrates the effect of resection margin in millimetres on the risk of LR in infiltrative variants of STSs. Previous investigations regarding the clinical significance of margin width have been based on heterogeneous groups of STSs. King et al. retrospectively reviewed 117 patients with STSs, comprising pleomorphic sarcoma (26.5%), myxoid liposarcoma (13.7%), leiomyosarcoma (9.4%), synovial sarcoma (9.4%), MFS (7.7%), MPNST (6.0%), and others [30]. The incidence of LR was similar in patients with less than 1 mm margin and greater than 1 mm margins, and the half of the LRs (2/4) occurred in MFS patients with <1 mm and

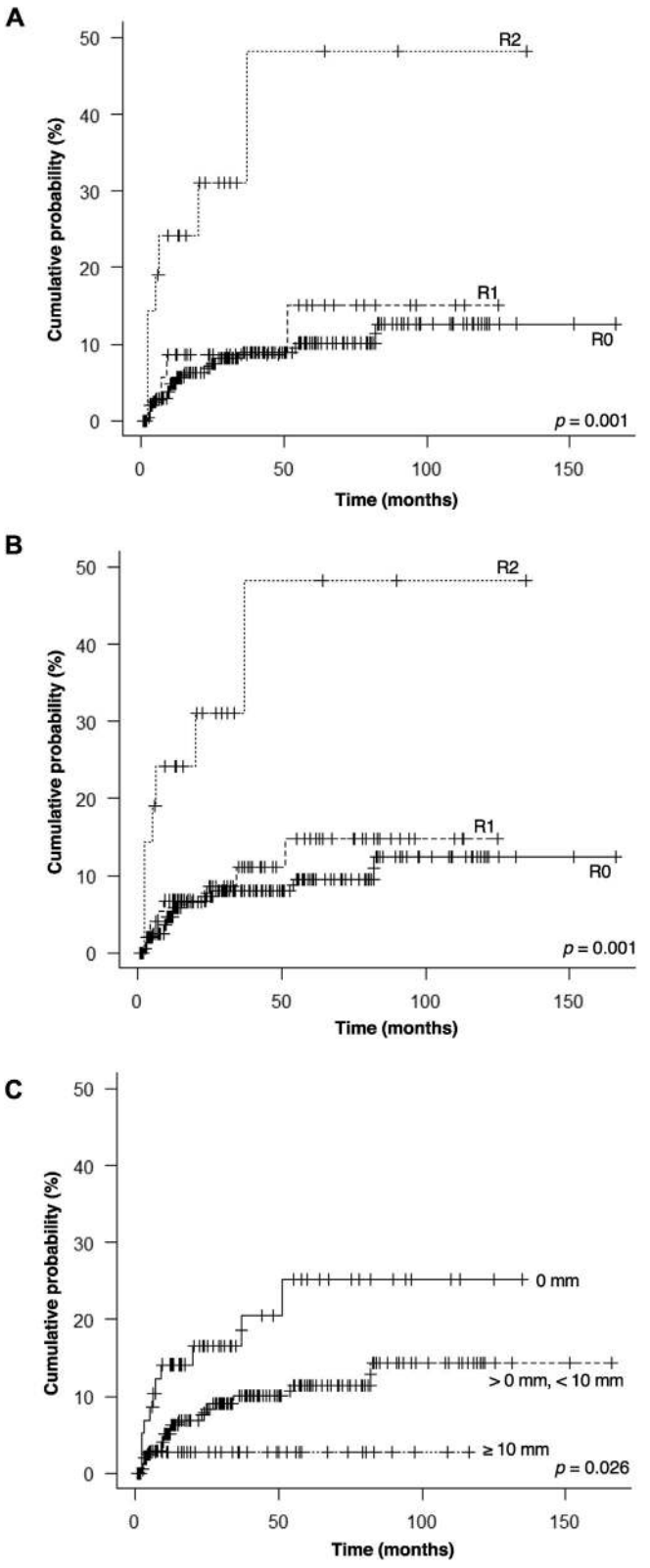

Fig. 1. Cumulative probability of local recurrence stratified by margin classification; R-classification (A), R+1-classification (B), three-group classification by metric distance (C).

>5 mm margin, respectively [30]. Sampo et al. reported that a surgical margin of 2–3 cm provided reasonable local control in STSs by the investigation of 270 STS patients [6]. In this report, MFH was

Table 3
Results of the Fine and Gray subdistribution hazards for local recurrence.

R-classification				R+1-classification				Three-group classification			
Variable	HR	95% CI	*p* value	Variable	HR	95% CI	*p* value	Variable	HR	95% CI	*p* value
Size				Size				Size			
5–10 cm vs ≤ 5 cm	2.067	0.793–5.385	0.140	5–10 cm vs ≤ 5 cm	2.098	0.797–5.525	0.130	5–10 cm vs ≤ 5 cm	1.979	0.754–5.199	0.170
>10 cm vs ≤ 5 cm	1.334	0.424–4.196	0.620	>10 cm vs ≤ 5 cm	1.358	0.423–4.355	0.610	>10 cm vs ≤ 5 cm	1.597	0.512–4.982	0.420
Depth				Depth				Depth			
Deep vs superficial	1.143	0.562–2.324	0.710	Deep vs superficial	1.143	0.562–2.324	0.710	Deep vs superficial	1.259	0.591–2.680	0.550
Histological grade				Histological grade				Histological grade			
Grade 2 vs grade 3	1.611	0.726–3.573	0.240	Grade 2 vs grade 3	1.638	0.739–3.631	0.220	Grade 2 vs grade 3	1.362	0.622–2.983	0.440
Radiotherapy				Radiotherapy				Radiotherapy			
Used vs not used	0.644	0.277–1.501	0.310	Used vs not used	0.635	0.271–1.489	0.300	Used vs not used	0.419	0.159–1.103	0.078
Margin				Margin				Margin			
R1 vs R0	1.280	0.437–3.746	0.650	R1 vs R0	1.381	0.582–3.278	0.460	0–10 mm vs ≥ 10 mm	5.624	0.488–64.750	0.170
R2 vs R0	5.923	2.393–14.660	<0.001	R2 vs R0	6.300	2.445–16.230	<0.001	0 mm vs ≥ 10 mm	12.730	1.055–153.500	0.045

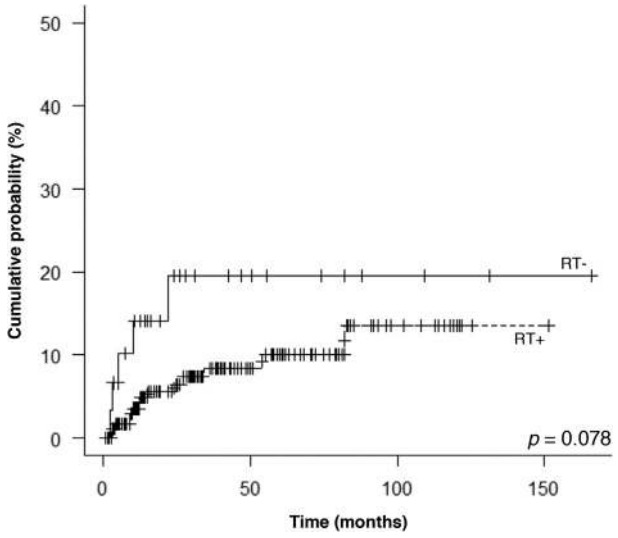

Fig. 2. Cumulative probability of local recurrence in patients with less than 10 mm margins, stratified by the use of adjuvant radiotherapy.

the commonest histological subtype (32%) with the poorest 5-year LR-free survival (69%) when compared to the other subtypes. This suggests that a wider resection margin is required to reduce the incidence of LR in tumour types known to have an infiltrative growth pattern, and that what constitutes an adequate margin for one histological variant may not apply to all histological variants.

We have demonstrated that neither the R-classification nor the R+1-classification were able to stratify the risk of LR in patients with negative margins, indicating that these classification systems are not sufficiently sensitive to stratify what constitutes an adequate margin of resection for infiltrative subtypes of STS. However, when the margin was stratified according to the metric distance from the tumour as 0 mm, 0.1–9.9 mm, and 10.0 mm, we were able to demonstrate that the risk of LR was significantly decreased when the margin of resection was ≥10 mm. Therefore, we can recommend from these findings that for tumours with an infiltrative growth pattern (eg MFS and UPS), a minimum resection margin of at least 10 mm should be the aim to minimise the risk of LR.

When exploring the effect of adjuvant radiotherapy on the risk of LR, we observed a trend towards improvement in the cumulative probablility of LR in patients with a margin of less than 10 mm, although this did not reach statistical significance. This could be attributed to the fact that the majority of patients (80%) in the present study received adjuvant RT; therefore, the number of patients in the untreated cohort was small. In a prospective randomised study of 91 STS patients, Yang et al. demonstrated a significant reduction in the probability of LR in those receiving adjuvant radiotherapy [31]. However, this study comprised a cohort of heterogeneous histological subtypes, which makes it difficult to extrapolate the effect of margin and radiotherapy on the risk of LR. Odei et al. reviewed 52 patients with MFS and reported that the use of RT (preoperative, 19%; postoperative, 50%; and both, 2%) had no significant effect on LR ($p = 0.4675$) or overall survival ($p = 0.7377$) [32]. Similarly, Sanfillippo et al. investigated 158 MFS patients and identified no correlation between the use of RT and LR ($p = 0.753$) or overall survival ($p = 0.342$) [33]. Imanishi et al. investigated the effect of preoperative RT in 8 superficial MFS and 10 superficial UPS. The pathological response was a near-complete response (≥95% non-viable area) in 60% of UPS but none of MFS. Of note, a total of 8 patients (62%; 7 MFS and 1 UPS) among 13 patients whose tail was pathologically detected had viable or possibly viable tumour cells in the tail [18]. Whether this represents an error in radiotherapy planning in that the tails seen on MRI are misinterpreted as oedema rather than tumour infiltration, or this represents a relative resistance of these tumour types to radiotherapy, is not clear. However, what we can infer from our own findings, which support the findings of others, is that the only modifiable variable which has the most significant effect on the risk of LR is the margin that is achieved at resection.

We acknowledge several limitations to this study. First, we did not attempt to correlate the histological findings with the preoperative radiological findings, particularly the margin dimension in relation to the radiological tail. Further analyses regarding this tumour-related factor would provide more detailed information on the margin adequacy for these subtypes. Second, the data of margin in millimetres were not available in all patients with negative margin in the study period. Thus, the overall incidence of positive marginal resections in this study appears higher than the actual figure. Third, the details of radiotherapy, including dose and exact field, could not be assessed, as radiotherapy was often administered in regional centres whilst surgical resection was undertaken at a single, supra-regional sarcoma centre. Forth, the margin quality was not analysed in this study. Further analysis considering with margin quantity, particularly in relation to the margin tissue in deep MFS and UPS, would provide better a more accurate prognostic indicator. If the quality of the margin could be predicted prior to resection, particularly when the resection may require the close dissection or even excision of nearby vital structures, it may be possible to give more accurate information for preoperative planning.

In conclusion, this study identified that in the case of MFS and UPS, a margin in excess of 10 mm was associated with the lowest

risk of LR. For these tumour types, a margin less than 10 mm is associated with a greater than 10% risk of LR, which does not show a linear relationship. When assessing the effect of radiotherapy in these specific tumour types, it appears that radiotherapy has a far inferior effect on LR than the dimensions of the margin achieved at surgical resection.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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