



Low-grade soft-tissue sarcomas: What is an adequate margin for local disease control?

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ABSTRACT

Background: Whilst the resection margin is an established factor predictive of local control of soft-tissue sarcomas (STSs), the adequacy of margin width for low-grade STSs has been rarely described. We aimed to investigate the margin adequacy and its prognostic relevance in low-grade STSs.

Methods: 109 patients who underwent surgical treatment for a low-grade STS were studied. The prognostic value of margin status was evaluated according to the R-, R+1-classification, and width in millimetres.

Results: The 10-year local recurrence (LR) rates were 6%, 27%, 54% in R0, R1, and R2, respectively ($p < 0.001$), according to the R-classification. The R+1-classification resulted in a decreased LR rate in R1, but no major differences in LR rates in R0 and R2; 7%, 14%, 54% in R0, R1, and R2, respectively ($p < 0.001$). When classified by metric distance, 10-year LR rates were 0%, 8%, and 38% by ≥ 2.0 mm, 0.1–1.9 mm, and 0 mm margins, respectively ($p < 0.001$). Patients with close margins (0.1–1.9 mm) who received adjuvant radiotherapy had a trend toward lower LR risk than those without radiotherapy (10-year, 4% vs. 12%; $p = 0.406$). The 5 and 10-year disease-specific mortality was 9% and 13%, respectively; margin width was not associated with disease-specific mortality but LR was a poor prognostic factor for survival ($p = 0.003$).

Conclusion: Whilst negative margin provided local control over 90%, excellent local control was achieved with microscopic margins ≥ 2 mm. The role of margins is more important than radiotherapy in local control. Margins do not determine survival, but LR is associated with a poor prognosis.

1. Introduction

Surgery is the mainstay of treatment for localised soft-tissue sarcomas (STSs) [1,2]. The primary aim of surgery is complete tumour excision with a margin of normal tissue aiming to achieve with wide resection margins [3], and a positive resection margin is a well-established risk factor for local recurrence (LR) [4–6]. However, there is no consensus or guideline on the width of resection margin needed to optimise local control for STSs [3,7]. In the recent decades, several researchers have investigated the extent of resection margins [4, 6–16]. Many descriptions regarding margin adequacy have been found from negative (>0 mm) margin [14,17,18] to 3 cm [11] or even 5 cm [6, 8]. This inconsistency might be due to a selection bias in each study, consisting of a heterogeneous population of low-grade and high-grade STSs, or infiltrative and non-infiltrative STSs. It is worth noting that investigations for low-grade STSs have been rarely performed and, thus,

the question of what margin for low-grade STSs is adequate remains unclear.

The clinical guidelines for low-grade STSs recommend the appropriate resection margins for specific subtypes such as dermatofibrosarcoma protuberans (DFSP) and atypical lipomatous tumour (ALT)/well-differentiated liposarcoma (WDLS) [19]. DFSP is a low-grade cutaneous STS, characterised by infiltrative local invasion associated with a high risk of LR [19]. The National Comprehensive Cancer Network (NCCN) guidelines recommend ‘surgical margins with 2–4 cm to include fascia is preferred when clinically feasible’ [20,21]. ALT/WDLS is a relatively common subgroup of lipomatous STS with no potential for distant metastasis without evidence for dedifferentiation. The European Society for Medical Oncology (ESMO) guidelines advocate that marginal margins can be accepted for this subtype [22]. However, there is no distinct recommendation on the width of resection margin needed for low-grade STSs other than DFSP and ALT/WDLS.

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The purpose of this study was to investigate the prognostic significance of a metric distance of resection margin in low-grade STSs, excluding DFSP and ALT/WDLS, and to clarify the width of margin required for optimising local control for these tumours.

2. Patients and methods

2.1. Patient

A consecutive series of patients who underwent surgical resection for a low-grade STS at a supra-regional, tertiary sarcoma centre between 1996 and 2016 were evaluated. The histological diagnoses were determined by the experienced pathologists according to the latest version of World Health Organization (WHO) classification [23]. Only patients whose tumour was superficial or deep-seated and diagnosed as grade 1 according to French Federation of Cancer Centres Sarcoma Group (FNCLCC)-criteria [24,25] were included. Patients who were diagnosed as ALT/WDLS or DFSP were excluded from this study. Patients whose pathological details including resection margin in millimetres was unavailable or those who were referred for follow-up after initial treatment at another hospital were also excluded.

The following data were extracted from records: age at diagnosis, sex, histopathological diagnosis, tumour site, size, depth, and stage, use of adjuvant therapy, resection margin, follow-up data including local recurrence (LR) and oncological outcome. Tumour size was determined as the greatest diameter of the tumour measured on the resected specimens. Tumour stage was classified according to the UICC 8th classification [26]. The closest resection margin in millimetres was evaluated by an experienced sarcoma histopathologist after gross and microscopic examination of the specimen. The resection margin width was classified according to the conventional R-classification (R0, macroscopic and microscopic negative margin; R1, microscopically positive margin or marginal resection along a pseudo-capsule; R2, macroscopically positive margin) [27], and R+1-classification (R0, margin with ≥ 1 mm; R1, margin with <1 mm; R2, macroscopic positive margin) [28], and also categorised according to the results regarding the correlation between the margin width and LR.

Biopsy was routinely performed preoperatively at our institution. Diagnosis and treatment decisions were discussed and determined at a weekly multidisciplinary team meeting. Our basic policy for low-grade STSs was wide excision with the surrounding normal tissues. If the resection margin was intralesional, marginal, or close to marginal, adjuvant radiation therapy was indicated. 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.

2.2. Statistical analysis

Outcome measures included LR and disease-specific mortality. Crude cumulative incidence for LR and a disease-specific death was estimated using a competing risk analysis. Death or metachronous distant metastases, whichever occurred first, was regarded as a competing event to LR. Other causes of death were regarded as competing risks to disease-specific mortality. Multivariate analysis was performed using Fine and Gray model and calculated sub-distribution hazard ratios (HRs) for the final predictor variables [29–31]. All statistical analyses were performed using the R version 3.5.5. Differences were considered to be statistically significant at $p < 0.05$.

3. Results

3.1. Patient characteristics

The study cohort consisted of 109 patients. The details of patient demographics and treatments are summarised in Table 1. The median age at diagnosis was 49 years (Interquartile range [IQR], 37–65 years).

There was a slight male predominance ($n = 66$; 61%). The most common primary site was upper extremity ($n = 67$; 61%), followed by trunk ($n = 23$; 21%) and lower extremity ($n = 19$; 17%). The histological diagnosis included myxoid liposarcoma in 42 patients (39%), undifferentiated/unclassified sarcoma in 19 (17%), myxofibrosarcoma in 16 (15%), low-grade fibromyxoid sarcoma in 9 (8%), leiomyosarcoma in 8 (7%), and others (Table 1). The median size of the tumour was 7.1 cm (IQR, 4.5–13.0 cm). Adjuvant radiotherapy was performed in 46 patients (42%).

3.2. Resection margin width in millimetres and local control

The correlations between LR and resection margin in millimetres are summarised in Table 2. The LR rate in this cohort was 15% ($n = 16$); 38% ($n = 12$) in patients with positive margin and 5% ($n = 4$) with negative margin ($p < 0.001$). In patients with negative margin, the LR rate was 6% and 8% in 0.1–0.9 mm and 1.0–1.9 mm, respectively, but no LR was observed in ≥ 2.0 mm margin.

The 5 and 10-year crude cumulative incidence of LR in this cohort was 15% and 16%, respectively. By the R-classification, the 10-year cumulative incidence of LR was 6%, 27%, 54% in R0, R1, and R2 margin, respectively ($p < 0.001$; Fig. 1A). By the R+1-classification, the 10-year cumulative incidence of LR was 7%, 14%, and 54% in R0, R1, and R2 margin, respectively ($p < 0.001$; Fig. 1B). The cumulative LR incidence with R0 resection by R- and R+1-classification was similar, indicating that the margin width less than 1 mm could not distinguish the risk of LR in patients with negative margin. When we divide patients into three groups of resection margin according to the results in Table 1, the 10-year cumulative incidence of LR was 0%, 8%, and 38% by ≥ 2.0 mm, 0.1–1.9 mm, and 0 mm, respectively ($p < 0.001$; Fig. 1C).

The univariate analysis for Fine and Gray sub-distribution hazard model revealed that surgical margin (R-, R+1-classification, and our classification) was significantly associated with the LR (Supplementary Table 1). We then performed multivariate analysis separately for R-classification, R+1-classification, and the three-group classification using the Fine and Gray subdistribution hazard model. In all cases, the resection margin and tumour depth were identified as a significant

Table 1
Patient characteristics.

Variables	Definition	No. of patients	%, range
Total		109	–
Age at diagnosis	(median, IQR)	49	37–65
Gender	Male	66	61%
	Female	43	39%
Site	Upper extremity	67	61%
	Lower extremity	19	17%
	Trunk	23	21%
Depth	Deep	74	68%
	Superficial	35	32%
Diagnosis	Myxoid liposarcoma	42	39%
	Undifferentiated/unclassified sarcoma	19	17%
	Myxofibrosarcoma	16	15%
	Low-grade fibromyxoid sarcoma	9	8%
	Leiomyosarcoma	8	7%
	MPNST	6	6%
	Dedifferentiated liposarcoma	5	5%
	Myxoinflammatory fibroblastic sarcoma	4	4%
	Others	5	5%
Tumour size	≤ 5 cm	39	36%
	>5 cm, ≤ 10 cm	33	30%
	>10 cm	37	34%
Chemotherapy	Yes	1	1%
	No	108	99%
Radiotherapy	Yes	46	42%
	No	63	58%

Table 2

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

Margin width	Total			Adjuvant RT-			Adjuvant RT+		
	LR+	Total	%LR	LR+	Total	%LR	LR+	Total	%LR
0 mm	12	32	38%	6	16	38%	6	16	38%
0.1–0.9 mm	2	33	6%	1	14	7%	1	19	5%
1.0–1.9 mm	2	25	8%	2	20	10%	0	5	0%
≥2.0 mm	0	19	0%	0	13	0%	0	6	0%
Total	16	109	15%	9	63	14%	7	46	15%

factor, whereas age, sex, tumour size, tumour site, inadvertent treatment, and the use of radiotherapy were not significantly associated with LR (Supplementary Table 2). Among three margin classifications, positive margin or 0.1–1.9 mm margin versus ≥2 mm margin showed the most significant hazards for LR compared with R1 or R2 margin versus R0 margin in the R- or R+1-classification, respectively (Supplementary Table 2).

3.3. Adjuvant radiotherapy

Patients with close margins of 0.1–1.9 mm who received adjuvant radiotherapy had a trend towards fewer local recurrences than those without radiotherapy (10-year, 4% vs. 12%; $p = 0.406$; Supplementary Fig. 1A), despite no significant difference. The efficacy of radiotherapy was not seen in patients with positive margins: the 10-year cumulative incidence of LR was 39% and 38% in patients with and without radiotherapy, respectively ($p = 0.934$; Supplementary Fig. 1B). Regardless of the use of radiotherapy, the cumulative LR incidence was clearly stratified by ≥ 2.0 mm, 0.1–1.9 mm, and 0 mm margin (Fig. 2A and B).

3.4. Resection margin width of millimetres and cause-specific mortality

The 5 and 10-year cumulative incidence of disease-specific mortality was 9% and 13%, respectively, with a median follow-up of 67 months (IQR, 39–103 months). The univariate analysis for Fine and Gray sub-distribution hazard model revealed that presence of LR was a poor prognostic factor for disease-specific mortality (HR 4.580, 95% CI 1.665–12.600, versus no LR: HR 1; $p = 0.003$). Resection margin width, however, was not significantly correlated with disease-specific mortality; the 10-year cumulative disease-specific mortality was 23%, 6%, and 13% in 0 mm, 0.1–1.9 mm, and ≥2.0 mm, respectively ($p = 0.414$; Supplementary Fig. 2).

4. Discussion

Although the extent of resection margin for STSs has been investigated in a recent decade [4,6–16], most of these studies are done using the patient cohort which consists of a mixture of low-grade and high-grade STSs, and studies focusing on low-grade STSs are limited (Table 3). Marcus et al. reported that the 5-year probability of LR in 76 patients with low-grade STSs was 21.4% in patients with positive margins and 9.8% in patients with negative margins, although this did not reach statistical difference ($p = 0.076$) [32]. Only reports by Kawaguchi et al. analysed the adequacy of margin width in low-grade sarcomas. They defined a margin with ≥5 cm, more than 1–4 cm, 1 cm, and pericapsular reactive zone as a ‘curative’, ‘adequate wide’, ‘inadequate wide’, and ‘marginal’ margin [6,8]. In low-grade sarcomas, the adequate wide and curative margins achieved >90% local curability (97% and 91%, respectively), while inadequate wide, marginal, and intralesional margins resulted in <80% local curability (76%, 78%, and 48%, respectively). However, this study cohort consisted of a mixture of bone sarcomas and STSs, including chordoma, parosteal and periosteal osteosarcoma and conventional chondrosarcoma, which provides ambiguous conclusion regarding the margin adequacy for low-grade STSs. In addition, this method applies ‘round-up’ system from millimetres to

centimetres; resection margin was finalized, for example, as 1 cm if the closest margin was 0.1–0.9 cm. Thus, the value of margin in millimetres has been unclear to date. This study is, to the best of our knowledge, the largest series on low-grade STSs to demonstrate the margin adequacy in a metric distance. Our investigation demonstrated that local control after 10 years was achieved in 62%, 92%, and 100% in intralesional, 0.1–1.9 mm, and ≥2.0 mm, respectively. Our data indicates that, although local control is expected in >90% of cases with clear margins, a resection margin width ≥2.0 mm provides optimal local control.

Studies suggest the disparate surgical margin width of resection specimens between the unfixed and fixed state. Horn et al. investigated the possible shrinkage effects of formalin fixation on breast cancer specimens. They found that there were significant changes in the distance to all surgical resection margins from the unfixed to fixed state, resulting in a 15%–22% loss of mean distance [33]. Goldstein et al. investigated the shrinkage of the resected colorectal specimens and reported that these specimens shrank by 57% of the *in vivo* length after formalin fixation [34]. Given that this shrinkage also occurs in STSs, the microscopic ‘2 mm’ margin, which minimised the risk of LR in this study, could be equivalent to ‘4–5 mm’. In addition, there is also shrinkage of normal muscle or adipose tissue around the tumour just after resecting out from the tumour site. Therefore, aiming for an at least 1 cm margin in the surgical field, considering a possible shrinkage down to the microscopic 2 mm margin, could be safer to minimise the risk of local failure for low-grade STSs.

In this study, we identified a trend toward better local control with adjuvant radiotherapy in patients with margins of 0.1–1.9 mm. In a retrospective study of 132 patients with low-grade STSs, Choong et al. described a beneficial effect of radiotherapy on tumours that had been excised with marginal margins; LR occurred in 6 of 9 patients (67%) who did not receive radiotherapy while no LR in 24 patients who received radiotherapy ($p = 0.0008$) [35]. The definition of marginal and wide resections was not described, and are inherently subjective and may vary depending on reporter, it is difficult to make clear conclusions on what width of margin is rescued by adjuvant radiotherapy. Although further investigation is needed, adjuvant radiotherapy might play a role on tumours which is excised with very close margins. Of note, our data demonstrated no benefit of adjuvant radiotherapy in patients with intralesional margin, indicating that the role of surgical margin appears to be more crucial than radiotherapy for low-grade STSs.

We acknowledge several limitations to this study. First, the details of adjuvant radiotherapy including radiation dose or radiated field were not fully available and could not be assessed, because our institute is a supra-regional surgical centre for bone and soft-tissue tumours. Second, this study has a retrospective nature with a limited number of patients. Thus, further analyses based on a larger cohort of patients would be necessary for more precise analysis. Third, this study cohort consists of a variety of histological diagnosis, even focused on low-grade tumours. Fourth, the margin quality was not analysed in this study. Further analysis considering with margin quality would provide more precise stratification for low-grade STSs.

5. Conclusion

This study, the largest study that reports the margin adequacy for

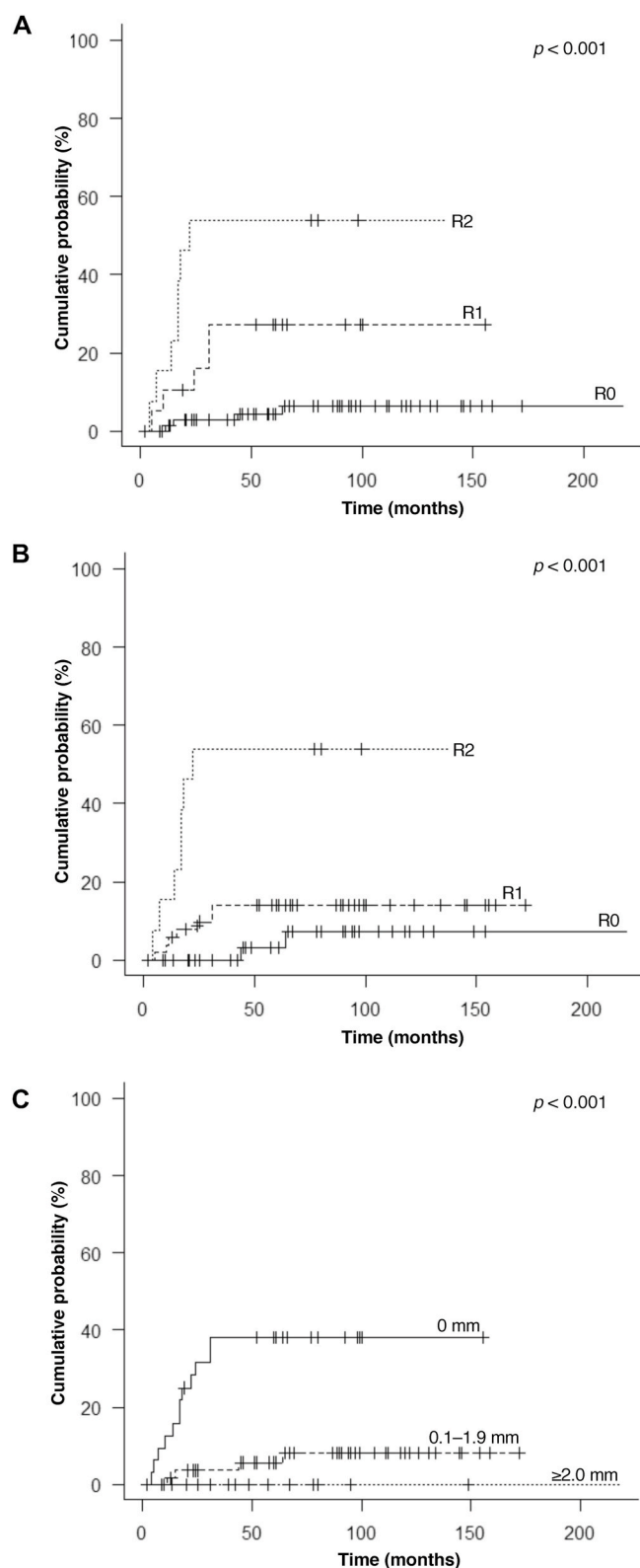


Fig. 1. Cumulative probability of local recurrence stratified by margin classification; R-classification (A), R+1-classification (B), three-group classification by metric distance (C).

low-grade STSs, demonstrated that excellent local control was achieved with margins greater than 2 mm, although negative margins provided local control of over 90%. The role of margins is more important than radiotherapy in local control for low-grade STSs. Margins do not

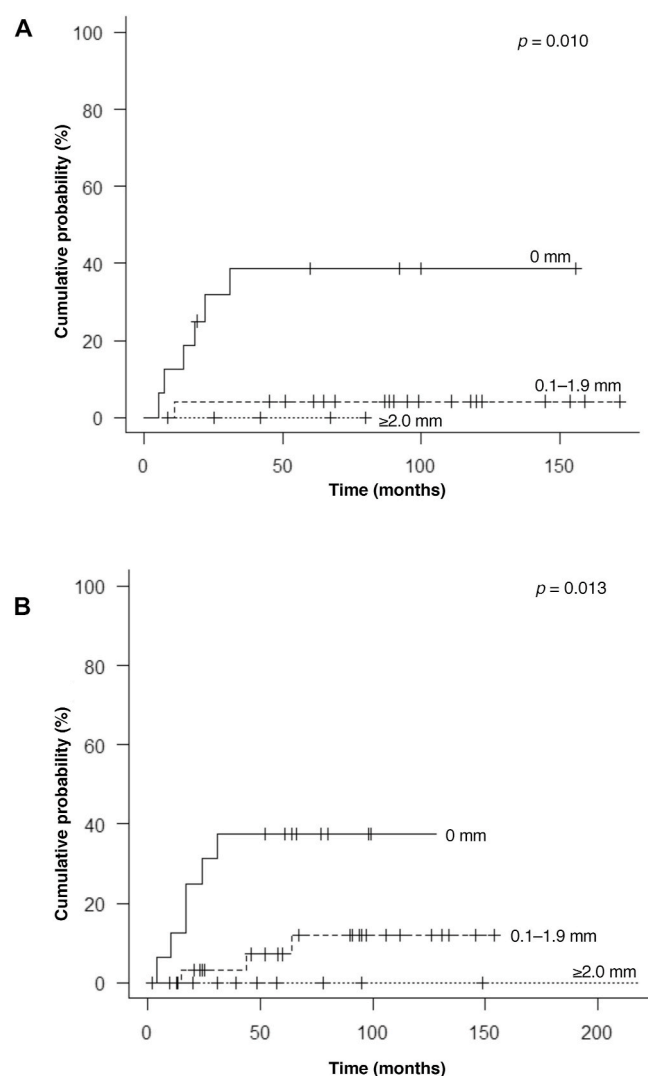


Fig. 2. Cumulative probability of local recurrence stratified by the metric distance of margin in patients who received adjuvant radiotherapy (A) and did not (B).

determine survival, but LR is associated with a poor prognosis.

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Tomohiro Fujiwara: Conceptualization, Methodology, Investigation, Writing - Original Draft, Funding acquisition.

Yoichi Kaneuchi: Investigation, Validation.

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Table 3
Summary of the comparative literature.

Reference	Years	N	Surgical margin	LR	Survival	Significant prognostic factor
Marcus et al. ²⁷	1993	80	Positive	5yr PR of LR = 21.4%	10yr OS = 94%	RT for LR
Kawaguchi et al. ³	2004	87 ^a	Negative	5yr PR of LR = 9.8%		
			Curative (5 cm or more)	10yr LRFS = 91%	15yr OS = 86%	Margin for LRFS
			Adequate wide (1–4 cm)	10yr LRFS = 97%		
			Inadequate wide (1 cm)	10yr LRFS = 76%		
			Marginal	10yr LRFS = 78%		
			Intralesional	10yr LRFS = 48%		
Current study	2019	109	Positive	10yr CI of LR = 38%	10yr CI of mortality = 23%	Age, margin for LR
			Negative with margin 0.1–1.9 mm	10yr CI of LR = 8%	10yr CI of mortality = 6%	LR for disease-specific death
			Negative with margin ≥2.0 mm	10yr CI of LR = 0%	10yr CI of mortality = 13%	

Abbreviations: STS, soft-tissue sarcoma; LR, local recurrence; LRFS, local recurrence-free survival; DSS, disease-specific survival; RT, radiotherapy; PR, probability rate; CI, cumulative incidence; N/A, not available.

^a Number of patients with low-grade bone and soft tissue sarcomas.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.suronc.2020.08.022>.

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