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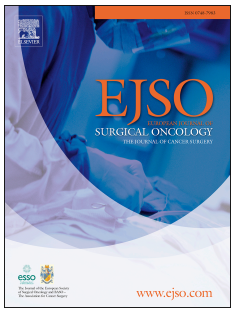

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Tomohiro Fujiwara, Jonathan Stevenson, Michael Parry, Yusuke Tsuda, Yoichi Kaneuchi, Lee Jeys

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Credit Author Statement

Tomohiro Fujiwara: Conceptualization, Methodology, Investigation, Writing - Original Draft; Jonathan Stevenson: Conceptualization, Writing - Review & Editing; Michael Parry: Writing - Review & Editing; Yusuke Tsuda: Investigation; Yoichi Kaneuchi: Investigation; Lee Jeys: Supervision, Conceptualization, Writing - Review & Editing

The adequacy of resection margin for non-infiltrative soft-tissue sarcomas

Tomohiro Fujiwara,[1,2*] Jonathan Stevenson[1], Michael Parry[1],

Yusuke Tsuda,[1] Yoichi Kaneuchi[1], Lee Jeys[1]

[1.] Oncology Service, The Royal Orthopaedic Hospital, Birmingham, UK

[2.] Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

Tomohiro Fujiwara, MD, PhD, Orthopaedic Surgeon
1. The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK
2. Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences

Jonathan D Stevenson, MBChB BMedSci FRCS (Tr&Orth)
Consultant Orthopaedic Oncology and Arthroplasty Surgeon & Honorary Senior Lecturer
1. The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK
2. Aston University Medical School, Aston Express Way, Birmingham, UK

Michael C Parry, BSc, MBChS, MD, FRCS
Consultant Orthopaedic Oncology and Arthroplasty Surgeon & Honorary Senior Lecturer
1. The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK
2. Aston University Medical School, Aston Express Way, Birmingham, UK

Yusuke Tsuda, MD, PhD, Orthopaedic Surgeon
1. The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK

Yoichi Kaneuchi, MD, PhD, Orthopaedic Surgeon
1. The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK

Lee M Jeys, MBChB MSc FRCS (Tr&Orth)
Consultant Orthopaedic Oncology and Arthroplasty Surgeon & Professor
1. The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, UK
2. Life & Health Sciences at University of Aston, Aston Expressway, Birmingham, B4 7ET

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*Corresponding author: Tomohiro Fujiwara; email: tomomedvn@gmail.com

The Royal Orthopaedic Hospital, Bristol Road South, Birmingham B31 2AP, UK

Abstract

Objectives: There remains no consensus on what constitutes an adequate margin of resection for non-infiltrative soft-tissue sarcomas (STSs). We aimed to investigate the role of resection margins in millimetres for non-infiltrative STSs.

Methods: 502 patients who underwent surgical resection for a localized, non-infiltrative, high-grade STSs were studied. The prognostic significance of margin width was analysed and compared with the conventional R- and R+1-classification of surgical margins.

Results: The overall local recurrence (LR) rate was 13%; 9% and 27% with negative and positive margins, respectively (p<0.001). In patients with negative margins, the LR rates were greater than 10% in patients with margins ≤ 5.0 mm but reduced to less than 4% with margins > 5.0 mm. When classified by the R- (or R+1)-classification, the 5-year cumulative LR incidence was 8%, 23% (16%), and 31% for R0, R1, and R2, respectively, which did not stratify the LR risk with negative margins. On the other hand, an accurate risk stratification was possible by metric distance; the 5-year cumulative incidence of LR was 29%, 10%, and 1% with 0mm, 0.1–5.0mm, and >5.0mm, respectively (p<0.001). This classification also stratified the LR risk in patients with or without adjuvant radiotherapy.

Conclusion: While a negative margin is essential to optimize local control in patients with non-infiltrative STSs, surgical margin width greater than 5mm minimises the risk of local failure regardless of the use of adjuvant radiotherapy.

Introduction

The role of surgical margin achieved at resection is critical for the management of bone and soft-tissue tumours [1-5]. However, there is no consensus on how surgical margins are evaluated among different institutes worldwide. The most frequently reported system has been the Musculoskeletal Tumour Society (MSTS) system which records margin status as intralesional, marginal, wide and radical [6]. Whilst there remains no doubt what constitutes an intralesional or radical margin, the interpretation of a wide or marginal margin is subjective and varies depending between investigators and centres [7]. The effect of the closest margin measured in millimetres has been reported for osteosarcoma [7], chondrosarcoma [8], and soft-tissue sarcomas (STSs) [1, 3, 4, 9-16]. This method provides prognostic risk stratification by offering a clear, objective, and reproducible way of interpreting resection margins. For STSs, however, the majority of evidence reports heterogeneous groups of histological subtypes. Since infiltrative STSs, such as myxofibrosarcoma and undifferentiated pleomorphic sarcomas, generally necessitate more extensive surgical margin when compared to non-infiltrative subtypes [15, 17, 18], a more detailed assessment of what constitutes an adequate margin for the non-infiltrative subtypes is required.

It is universally accepted from the available literature that a microscopically negative margin following resection is associated with a lower risk of local recurrence [11, 19-23]. These studies were performed using the Enneking system [6], R-classification [24], or R+1-classification by the Union for International Cancer Control (UICC) [25]. In the R-classification, R2 resection describes intralesional resection; R1 resection is defined as a resection with microscopically contaminated margins or marginal resection along a pseudo-capsule; R0 resection is defined as a resection with macroscopically and microscopically negative margins [24]. In the R+1 classification, R2 involves macroscopic tumour contamination, R1 describes a margin with < 1 mm; R0 is defined

as a margin with ≥ 1mm [25]. Whilst the R or R+1 classification offers a metric 1 mm cut-off [26], fewer publications have discussed the effect of margins over 1 mm. Furthermore, the prognostic significance of margin width remains undefined, which could be attributed to the heterogeneity in histological diagnoses, and the small numbers reviewed. Thus, there remains no consensus on what how wide of a margin is necessary in opitimising local disease control for STSs.

The aim of this study, therefore, was to investigate the role of resection margins in millimetres for non-infiltrative STSs and to determine what constitutes an adequate margin for optimising local control.

Patients and methods

Patients were identified from a prospectively maintained database at a single tertiary referral sarcoma centre. All patients treated with a diagnosis of STS surgically treated between 1996 and 2016 were eligible. The study population comprised 2,984 patients, of which 2,177 underwent surgical treatment at our institute. Inclusion criteria included primary, localised, intermediate- or high-grade STSs. Exclusion criteria included patients with secondary sarcoma, locally recurrent or metastatic disease at presentation, low-grade STS such as well-differentiated liposarcoma and dermatofibrosarcoma protuberans, and infiltrative histological subtypes including myxofibrosarcoma and undifferentiated pleomorphic sarcoma. Having applied these criteria, 902 eligible patients were identified of whom 502 had complete histological data included resection margin, in millimetres.

Treatments for all patients were managed by a formally constituted sarcoma multiple disciplinary team, in which decisions about surgery, chemotherapy, radiotherapy and the timing of all these modalities was made. Chemotherapy was considered for borderline resectable tumours, which was also guided by the histological diagnosis. Radiotherapy was considered preoperatively for

myxoid liposarcoma in a recent decade and postoperatively for those with large, deep tumours with close or intralesional margin.

Clinical data collected included age at diagnosis, sex, histopathological diagnosis, tumour site, size, depth, grade, stage, surgical margin, adjuvant therapy, and oncological outcome. Tumour stage was classified according to the UICC classification (8th edition) [27]. The closest resection margin was evaluated by an experienced pathologist after gross examination of the formalin-fixed specimens. The resection margin was recorded in millimetres, and also classified according to two conventional classifications; the R-classification and R+1 mm classification. 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.

The primary endpoints in this study were LR and disease-specific mortalities. The cumulative incidence of LR and disease-specific mortality were estimated using a competing risk analysis. Death or metachronous distant metastases, whichever occurred first, was regarded as a competing event to LR. Deaths by nononcological causes were regarded as competing risks to disease-specific mortality. Multivariate analysis was performed using the Fine–Gray model and subdistribution hazard ratios were calculated for the final predictor variables. Statistical analyses were performed using R software version 3.5.5. Differences were considered statistically significant at $p < 0.05$.

Results

Patient characteristics

A total of 502 patients with primary, localised STS were available for analysis after exclusion criteria. Baseline patient characteristics are summarised in **Table 1**. The median age at diagnosis was 52

years (range, 2 to 92 years), 300 males (60%) and 202 females (40%). Of these, 339 (68%) presented with lower extremity and 91 (18%) with upper extremity tumours. Most tumours were high-grade (FNCLCC grade 3, 61%; grade 2, 39%). The majority of tumours were located deep to the fascia (72%). The most frequent histopathological diagnosis was synovial sarcoma (n=122; 24%), followed by myxoid liposarcoma (n=119; 24%), leiomyosarcoma (n=88; 18%), and malignant peripheral nerve sheath tumor (MPNST) (n=66; 13%) (**Table 1**). The median tumour size, the greatest diameter measured in the excised specimen, was 9 cm (range, 0.4 to 42 cm). The tumour stage of disease at presentation was IIA in 124 patients (25%), IIB in 75 (15%), and III in 300 (60%), classified according to the AJCC criteria [28]. Chemotherapy was performed in 79 patients (16%); preoperatively in 33 patients, postoperatively in 38 patients, and both before and after operative treatment in 5 patients. The use of radiotherapy was common (75%), which was administered preoperatively in 40 patients, postoperatively in 330 patients, and both before and after operative treatment in 3 patients.

The relationship between resection margin in millimetres and local control

Details of resection margin obtained are summarised in **Table 2**. When classified by the R-classification, a total of 52 patients (10%), 42 (8%), and 408 (81%) were resected with macroscopically positive (R2), microscopically positive (R1), and microscopically negative margin (R0). When classified by the R+1 system, the number of microscopically negative margin (R0) decreased to 360 patients (72%), with an increase in the number of patients with microscopically positive margins (n=90; 18%).

The overall LR rate for all patients was 13% (n=64). The relationship between margin in millimetres and local recurrence is shown in **Table 2**. The LR rates were 27% and 9% in patients

with positive and negative margin, respectively (p<0.001). In patients with a negative margin, the LR rates were greater than 10% with margins ≤ 5.0 mm but the rates decreased to less than 4% with margins > 5.0 mm. Patients were therefore categorised according to the margin achieved, measured in millimetres, into three groups for further analysis; group 1, 0 mm; group 2, 0.1–5.0 mm; group 3, > 5.0 mm.

The cumulative incidence of LR was 8% (95% CI, 6–11%), 12% (95% CI, 9–15%), and 16% (95% CI, 12–20%) at 2, 5, and 10 years, respectively. The cumulative incidence of LR at 5 years according to the R-classification was 8% (95% CI, 6–11%) for R0 margins, 23% (95% CI, 10–39%) for R1 margins, and 31% (95%CI, 19–44%) for R2 margins (p<0.001; **Figure 1A**). The 5-year cumulative incidence of LR when classified according to the R+1-classification was 8% (95% CI, 8–12%) for R0 margins, 16% (95% CI, 8–27%) for R1 margins, and 31% (95%CI, 19–44%) for R2 margins (p<0.001; **Figure 1B**). No significant differences in the cumulative LR incidence were observed with regard to R0 or R1 resection using R+1-classification in patients with negative margin (p=0.425; **Supplementary Figure 1A**). On the other hand, when margins were classified according to the three-group classification, the cumulative incidence of LR at 5 years was 29% (95% CI, 19–39%) for group 1, 10% (95% CI, 7–14%) for group 2, and 1% (95% CI, 0.1–6%) for group 3 (p<0.001; **Figure 1C**). This classification stratified the risk of LR with statistical significance in patients with negative margin (p=0.003; **Supplementary Figure 1B**).

When including the use of adjuvant radiotherapy with the novel classification system, the 5-year cumulative LR incidence was 29% (95% CI, 19–40%) for group 1, 9% (95% CI, 6–13%) for group 2, and 0% for group 3 (p<0.001; **Figure 2A**). In patients who underwent surgical resection alone, the cumulative LR incidences at 5 years were 28% (95% CI, 5–57%), 14% (95% CI, 5–26%), and 2% (95% CI, 0.1–8%) for group 1, group 2, and group 3, respectively (p=0.004; **Figure 2B**).

In the univariate analysis, a significant association between tumour size, R-classification, R+1-classification, and the novel margin classification system was seen with respects to LR. There was no significant association between the cumulative incidence of LR and gender, tumour site, grade, unplanned excision ('whoops' surgery), and the use of adjuvant therapy. The multivariate analysis was performed using Fine–Gray subdistribution hazard model based on the R-classification, R+1-classification, and the novel margin classification system. The R-classification demonstrated that R2 and R1 resections had 4.8× (HR, 4.818; 95% CI, 2.655–8.742; $p<0.001$) and 2.9× (HR, 2.907; 95% CI, 1.227–6.886; $p=0.015$) LR risk compared to R0 resection. According to the R+1-classification, R2 and R1 resections had 5.2× (HR, 5.237; 95% CI, 2.813–9.750; $p<0.001$) and 2.3× (HR, 2.301; 95% CI, 1.118–4.737; $p=0.024$) LR risk, compared to R0 resection. When analysing the novel classification system, a positive margin or a margin of ≤ 5 mm, compared to > 5 mm, had 68.8× (HR 68.840, 95% CI 8.250–574.500, $p<0.001$) and 19.9× (HR 19.990, 95% CI 2.522–158.400, $p=0.005$), respectively (**Table 3**). This demonstrates an increase in accuracy of risk stratification when compared to the conventional R- or R+1-classifications. Other independent risk factors for LR, other than margin status included unplanned excision (unplanned excision HR 5.016, 95% CI 2.451–10.270, $p<0.001$, versus planned excision HR, 1), and tumour size (≥ 10 cm HR 2.375, 95% CI 1.165–4.631, $p=0.017$, versus < 5 cm HR 1; 5–9.9 cm HR 3.077, 95%CI 1.423–6.653, $p=0.004$, versus < 5 cm HR 1) (**Table 3**).

The relationship between resection margin in millimetres and disease-specific mortality

The 5-year cumulative incidence of disease-specific death was 31% (95% CI, 26–35%) with a median follow-up of 61 months (range, 1 to 203 months). According to univariate analysis, increasing tumour size, higher grade, and the presence of LR were poor prognostic factors. In

multivariate analysis using Fine–Gray subdistribution hazard model, tumour grade (grade-3 HR 1.630, 95% CI 1.174–2.263, p=0.005, versus grade-2 HR 1), tumour size (≥ 10 cm HR 2.786, 95% CI 1.638–4.738, p<0.001, versus < 5 cm HR 1; 5–9.9 cm HR 2.065, 95% CI 1.238–3.445, p=0.005, versus < 5 cm), and presence of LR (presence HR 2.437, 95% CI 1.637–3.627, p<0.001, versus absence HR 1) were independent prognostic predictors for disease-specific survival, but the none of the margin classification showed significant association with survival outcomes (**Figure 3** and **Supplementary Figure 2**).

Discussion

This study has confirmed the margin status, defined by conventional R- or R+1-classification, is an independent prognostic factor for LR, in agreement with previous publications [3, 26]. In a recent study of 2,217 patients with localised STS, Gundle et al. reported that these classifications were both independent predictors for LR, with the 10-year LR rates for R0, R1, and R2 margins being 8%, 21% (or 12%), 44% by the R- (or R+1)-classification, respectively [3]. Our investigation reported 5-year LR rates with R0, R1, and R2 margins of 8%, 23% (16%), and 31% for R0, R1, and R2 by R- (or R+1)-classifications, respectively. However, the 9% risk of LR in patients with R0 resections identified in this study suggests these classification systems lack the detail to truly predict LR risk. Furthermore, these classifications were not sensitive enough to stratify the risk of LR with statistical significance in patients with negative margin. Using the novel classification system proposed in this study, the risk of LR significantly decreased if a clear margin was obtained but was similar to the risk of LR with resection margins less than 5mm, at 10%. However, the LR risk markedly decreased to approximately 1–2% with margins over 5 mm, suggesting that this metric measure of margins is a more accurate descriptor than the R- and R+1-classification. The risk of LR was clearly stratified by

the margin width of 5 mm in patients with negative margin.

The effect of margin on local control has been well documented in the literature. Dickinson *et al*. stratified patients into five groups; contaminated, < 1 mm but clear, 1–4 mm, 5–9 mm, and 10–19 mm. They observed the highest local control rates in patients with 1–4 mm, concluding that a margin greater than 1 mm was satisfactory [11]. Novais *et al.* classified margins into four groups; positive, < 2 mm but clear, 2–20 mm, and > 20 mm, and demonstrated that a margin ≤ 2mm was significantly associated with a higher risk for LR [13]. Liu *et al.* stratified patients into six groups; 0−1 mm, 1−4 mm, 5–9 mm, 10−19 mm, 20−29 mm, and ≥ 30 mm. They described that margin ≥ 10 mm was one of the independent prognostic factors for LR-free survival [29]. However, the study populations in these studies comprised a mixture of infiltrative and non-infiltrative sarcomas. In general, wider margins are necessary for local control in infiltrative STSs such as myxofibrosarcoma and undifferentiated pleomorphic sarcoma [15], which has a high LR rate as tumours typically spread extensively along fascial planes [30]. Indeed, cases with LR in these published series included substantial numbers of infiltrative subtypes, which may explain the discrepancy in the accepted metric margin among these studies. Our group recently reported the role of margin in millimetres in infiltrative STSs [31]; the LR risk was lowest if the resection margin was ≥ 10mm. Thus, the extent of margin width for optimising local control seems to be less in non-infiltrative STSs (> 5mm) than in infiltrative subtypes (≥ 10mm). We believe that our analysis, focusing on the non-infiltrative entity, would provide more precise information for surgical planning and postoperative surveillance.

Ahmad *et al.* recently investigated the relationship of the width of surgical margin and radiotherapy for localized STS patients who underwent limb-sparing surgery, stratified by three groups; ≤ 1mm, 1–5 mm, and > 5mm [16]. Although they observed a significant difference in LR

rate between positive and negative margin, there was no difference in LR rates among groups with negative margins and concluded that the width of margin does not influence outcomes in STS treated with RT. However, there was a clear trend towards improved outcomes in patients with > 5 mm margins which failed to achieve statistical significance, attributed to the limited number of patients in that group (n=28) compared to those with ≤ 1mm (n=128) and 1–5 mm (n=79) margins. Our analyses, focusing on the non-infiltrative subtypes, identified clear stratification of LRFS between positive margin, 0.1–5.0 mm, and > 5.0 mm with statistical significance in both patients either with or without adjuvant radiotherapy. These data indicate the crucial role of resection margins regardless of the use of adjuvant radiotherapy for these subtypes.

There is no consensus regarding the efficacy of adjuvant RT for patients with positive margins [1]. In this study, we observed no significant difference in the LR rates between patients with and without adjuvant RT when resection margins were positive (5-year cumulative LR incidence: 29% with RT versus 28% without RT; p = 0.617). Alkektiar et al. and Sadoski et al. reported that positive margins were associated with poor LR-free survival even with adjuvant RT [32, 33]. In contrast, Kim et al. reported that positive or close margins had no negative effect on local failure when adjuvant RT was performed [34]. There is no consensus regarding the RT dose for local control in patients with positive margins. Delaney et al. described that a RT dose >64 Gy could provide better local control in STS patients with positive margins [35]. Conversely, Levy et al. analysed differences in LR rates between ≥55 Gy and <55 Gy in patients with positive margins (defining a surgical margin < 1 mm as a “positive” margin) and reported no significant difference (5-year LR rate; 23% with ≥55 Gy versus 11% with <55 Gy; p = 0.200) [36]. They also included specific analyses of patients with R1 margins (defined as microscopically positive margins), observing that patients with R1 margins who received higher RT doses had an increased LR rate

(5-year LR rate; 15% with ≥55 Gy versus 4% with <55 Gy; $p < 0.001$) [36]. Zagars et al. demonstrated that higher RT doses were not able to fully overcome the adverse effects of positive margins [37]. We observed no significant advantage of adjuvant RT in patients with positive margins, supporting previous evidence that achieving a negative margin remains critical, even in patients receiving adjuvant RT.

The influence of surgical margins on survival is also not clear. In a retrospective study with 2,084 adult patients with localized STSs, Stojadinovic *et al.* stated that microscopically positive margins significantly decreased LR-free survival, metastasis-free survival, and disease-specific survival [20]. Similarly, Dickinson *et al.* reported that patients with contaminated margin had significantly higher risk of mortality compared to those with 20 mm or greater margins, although there was no significant difference for those with uncontaminated margins of up to 19 mm [11]. In contrast, Bonvalot *et al.* investigated 531 patients with extremity STSs and reported that neither margin status nor LR had an effect on overall survival while margins < 1 mm affected the risk of LR [38]. In this study, no statistically significant correlation between margin status and overall survival was seen. However, the development of LR was associated with poorer survival outcomes. Whilst we cannot directly attribute the margin status to the effect on overall survival, it can be inferred that where margin status effects LR, and LR effects overall survival, margin status has an indirect effect on overall survival. Further investigation with a larger cohort is clearly required to more accurately assess this risk.

We acknowledge several limitations to this study. First, the quantitative margin width in millimetres was not available in approximately half the patients with negative margins in this study period. Thus, the proportion of positive margins in this cohort was higher than the actual data. Second, the data on the quality of surgical margin were not available in all patients. Therefore, we

cannot make meaningful conclusions about the nature of the margin material and the effect this may have on LR and overall survival. Previous investigations have suggested that some margin tissues such as fascia or periosteum function as barriers against tumour infiltration. Further analysis considering the margin quantitative width and the margin quality would provide better risk stratification in local control for STSs. Third, the detailed information from the record regarding positive margins was unavailable. Gundle et al. previously classified positive margins into three categories: inadvertent positive margin; planned close but with an ultimately positive microscopic margin along a critical structure; and positive margin after a tumour bed re-excision in patients treated initially with inadequate surgery elsewhere [3]. In their study, no significant differences were observed in the 10-year LR rates between positive margins on critical structures and R0 margins (11% versus 8%), however inadvertent positive margins (35%) and positive margin after a tumour bed re-excision (24%) both exhibited higher LR rates [3]. Further research into positive margins in the present study cohort may provide information contributing to further categorization of the margin system for STSs. Fourth, radiotherapy details such as such as radiation field and dose were unavailable, as the delivery of radiotherapy was performed at outside institutions. This variation in dose and radiation field may explain the discrepancy we see in the effect of adjuvant radiotherapy on LR, particularly for patients with narrow or involved margins. Finally, the study population comprised various histological subtypes, though we attempted to harmonise the cohort by excluding tumour types known to have an infiltrative growth pattern. We believe this offers a more accurate assessment of the effect of margin on LR when compared to other studies which included all histological variants, including infiltrative myxofibrosarcoma and undifferentiated pleomorphic sarcomas, subtypes known to have a high risk of LR [17].

In summary, achieving a negative margin is essential to optimise local control regardless of

the use of adjuvant radiotherapy in patients with non-infiltrative subtypes of STS. Surgical margins greater than 5 mm minimise the risk of LR, regardless of adjuvant radiotherapy. This system more accurately predicted this risk of LR when compared to the conventional R- and R+1- classifications. The role of resection margin for survival prognosis remains unclear, requiring further investigation with a larger patient cohort.

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Figure Legend

Figure 1. Cumulative incidence of local recurrence stratified by margin classification; R-classification (A), R+1-classification (B), three-group classification by metric distance (positive; clear, ≤5 mm; clear, > 5 mm; C).

Figure 2. Cumulative incidence of local recurrence stratified by three-group margin classification by metric distance (positive; clear, ≤5 mm; clear, > 5 mm) in patients with (A) and without (B) adjuvant radiotherapy.

Figure 3. Cumulative incidence of disease-specific death stratified by three-group margin classification by metric distance (positive; clear, ≤5 mm; clear, > 5 mm).

Table 1. Patient characteristics

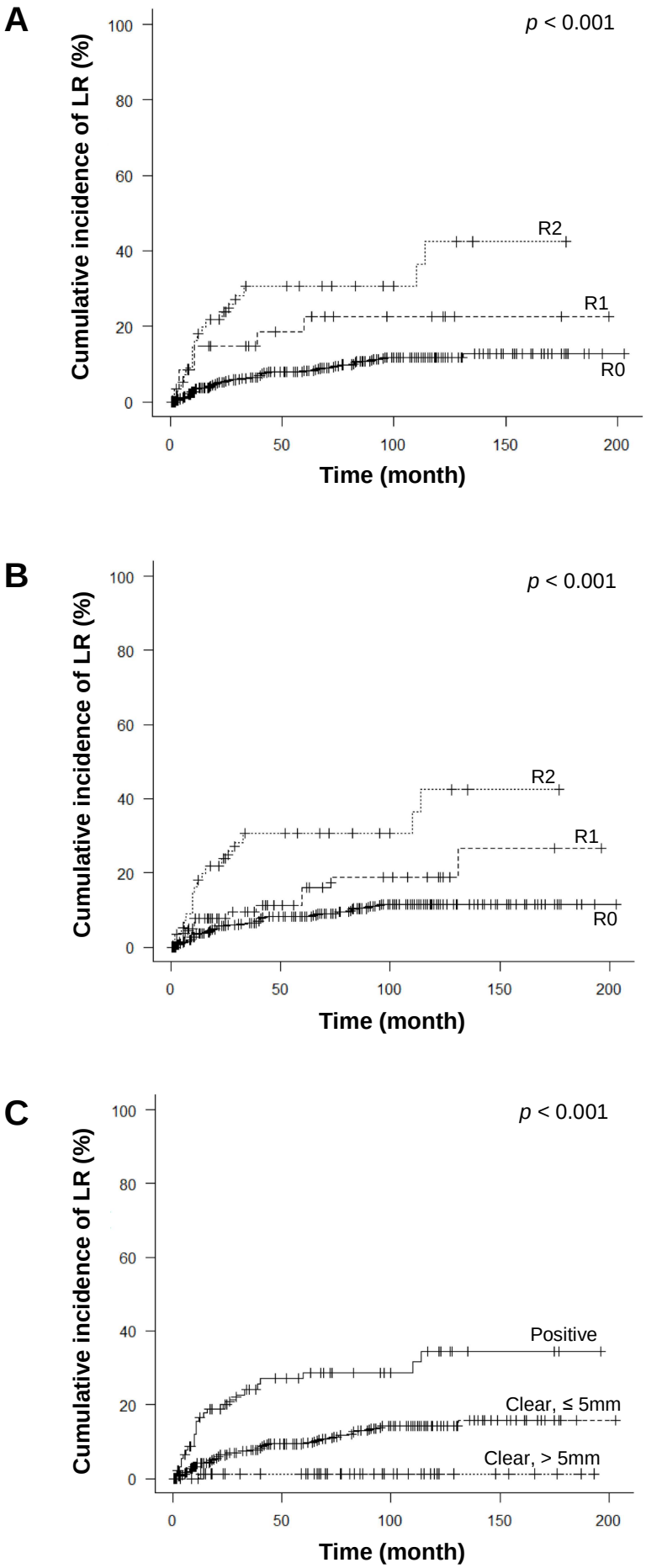
Variable	Definition	No. of patients	%, range
Total		502	–
Age at diagnosis	(median)	52	2–92
Gender	Male	300	60%
	Female	202	40%
Site	Lower extremity	339	68%
	Upper extremity	91	18%
	Trunk/neck	44	9%
Depth	Deep	361	72%
	Superficial	141	28%
Diagnosis	Synovial sarcoma	122	24%
	Myxoid liposarcoma	119	24%
	Leiomyosarcoma	88	18%
	MPNST	66	13%
	Dedifferentiated liposarcoma	16	3%
	Clear cell sarcoma	13	3%
	Pleomorphic liposarcoma	12	2%
	Extraskeletal myxoid chondrosarcoma	12	2%
	Alveolar soft part sarcoma	6	1%
	Others	48	9%
Grade (FNCLCC)	Grade 2	194	39%
	Grade 3	308	61%
Tumour size	≤5cm	142	28%
	>5cm, ≤10cm	195	39%
	>10cm	165	33%
UICC stage	IIA	124	25%
	IIB	75	15%
	III	300	60%
Unplanned excision	Yes	75	15%
	No	427	85%
Chemotherapy	Yes	79	16%
	No	423	84%
Radiotherapy	Yes	375	75%
	No	127	25%

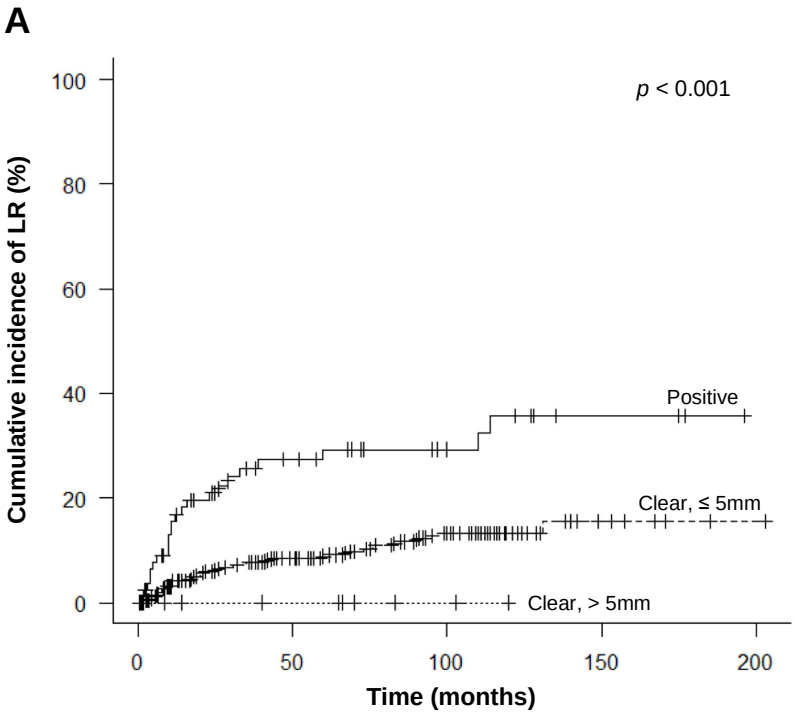
Table 2. Local recurrence according to the surgical margin width and the use of radiotherapy

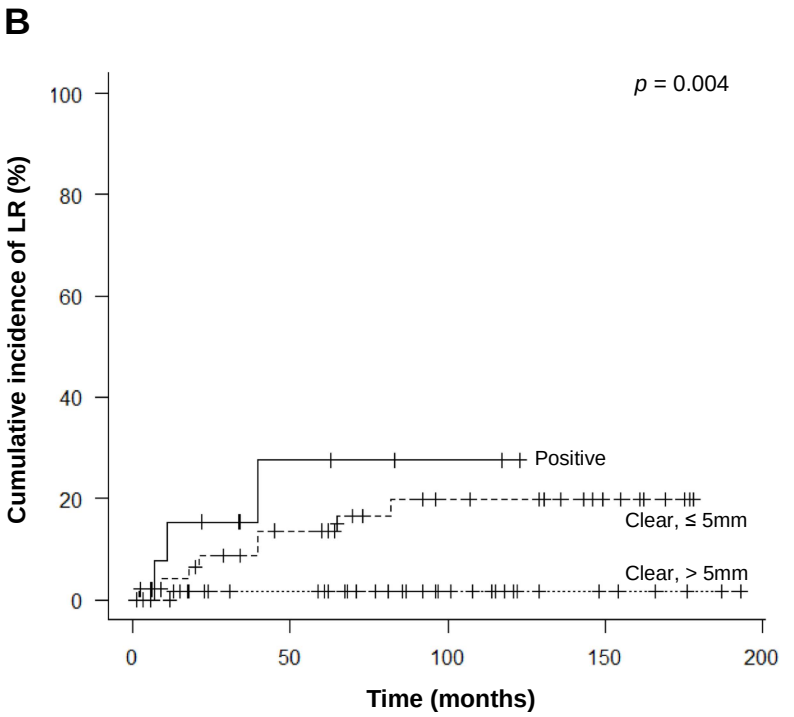
Margin width (mm)	Total			Adjuvant RT-			Adjuvant RT+		
	LR		%	LR		%	LR		%
	Yes	Total		Yes	Total		Yes	Total	
0	26	95	**27%**	3	14	**21%**	23	58	**28%**
0.1–1.0	27	236	**11%**	5	25	**20%**	22	211	**10%**
1.1–2.0	6	49	**12%**	1	10	**10%**	5	39	**13%**
2.1–5.0	4	37	**11%**	2	14	**14%**	2	23	**9%**
5.1–20.0	1	25	**4%**	1	12	**8%**	0	13	**0%**
>20.0	0	60	**0%**	0	55	**0%**	0	5	**0%**
Total	64	502	**13%**	12	130	**9%**	52	372	**14%**

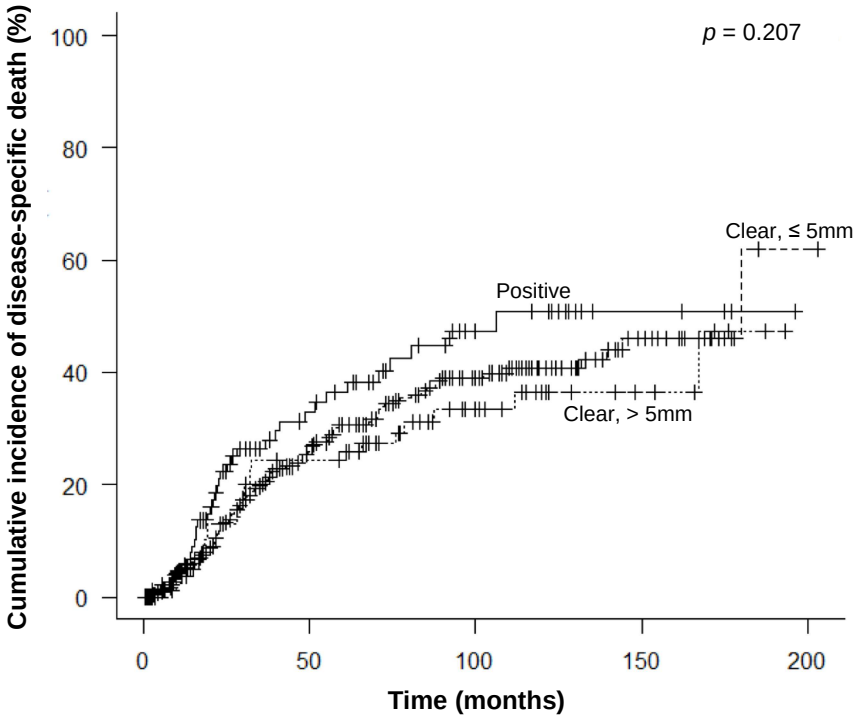
Table 3. Multivariate analysis using Fine–Gray subdistribution hazard model for LR and disease-specific mortality

Variable	Detail	LR			Disease-specific death		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Size	≤5cm	1			1		
	>5cm, ≤10cm	2.375	1.165–4.631	0.017	2.065	1.238–3.445	0.005
	>10cm	3.077	1.423–6.653	0.004	2.786	1.638–4.738	<0.001
Depth	Superficial	1			1		
	Deep	1.12	0.611–2.171	0.660	0.834	0.554–1.254	0.380
Grade	Grade 2	1			1		
	Grade 3	1.601	0.931–2.753	0.089	1.630	1.174–2.263	0.004
Unplanned excision	No	1			1		
	Yes	5.016	2.451–10.270	<0.001	1.057	0.645–1.732	0.830
Chemotherapy	Yes	1			1		
	No	1.287	0.665–2.491	0.450	0.771	0.474–1.254	0.290
Radiotherapy	Yes	1			1		
	No	0.769	0.375–1.578	0.470	1.232	0.773–1.963	0.380
Resection margin	>5mm	1			1		
	>0mm, ≤5mm	19.990	2.522–158.400	0.005	1.013	0.599–1.712	0.960
	0mm	68.840	8.250–574.500	<0.001	1.252	0.678–2.312	0.469









Conflict of interest statement

The authors have no conflicts of interest to declare.