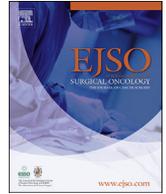




Contents lists available at ScienceDirect

## European Journal of Surgical Oncology

journal homepage: [www.ejso.com](http://www.ejso.com)

## Intermuscular extremity myxoid liposarcoma can be managed by marginal resection following neoadjuvant radiotherapy

Jonathan R. Perera<sup>a, \*</sup>, Meshal AlFaraidy<sup>b</sup>, Izuchukwu Ibe<sup>c</sup>, Ahmed Aoude<sup>d</sup>, Ibtissam Acem<sup>e, f</sup>, Michiel A.J. van de Sande<sup>f</sup>, Mireille Dessureault<sup>d</sup>, Robert E. Turcotte<sup>d</sup>, Sophie Mottard<sup>g</sup>, Georges Basile<sup>g</sup>, Marc Isler<sup>g</sup>, Hugo Saint-Yves<sup>g</sup>, Nicholas Eastley<sup>h</sup>, Jonathan Stevenson<sup>h</sup>, Matthew T. Houdek<sup>i</sup>, Peter W.M. Chung<sup>j</sup>, Anthony M. Griffin<sup>b</sup>, Peter Ferguson<sup>b</sup>, Jay S. Wunder<sup>b</sup>, Kim M. Tsoi<sup>b</sup>

<sup>a</sup> Orthopaedic Oncology, Royal National Orthopaedic Hospital, London, United Kingdom

<sup>b</sup> University Musculoskeletal Oncology Unit, Sinai Health System, Division of Orthopaedic Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada

<sup>c</sup> Orthopaedic Oncology, University of Mississippi Medical Center, USA

<sup>d</sup> Orthopaedic Oncology, McGill University, Montreal, QC, Canada

<sup>e</sup> Surgical Oncology and Gastrointestinal Surgery Erasmus MC Cancer Institute, Rotterdam, the Netherlands

<sup>f</sup> Orthopaedic Oncology Leiden University Medical Centre, Leiden, the Netherlands

<sup>g</sup> Orthopaedic Oncology Université de Montreal, Montreal, QC, Canada

<sup>h</sup> Orthopaedic Oncology, Royal Orthopaedic Hospital, Birmingham, United Kingdom

<sup>i</sup> Orthopaedic Oncology, Mayo Clinic, Rochester, MN, USA

<sup>j</sup> Radiation Oncology, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada

## ARTICLE INFO

## Article history:

Received 25 July 2022

Received in revised form

10 September 2022

Accepted 12 September 2022

Available online xxx

## ABSTRACT

**Background:** Compared with other soft tissue sarcomas, myxoid liposarcoma (MLS) occurs in younger patients, has a propensity for intermuscular locations and is highly radiosensitive. With pre-operative radiotherapy, intermuscular MLS demonstrates substantial volume reduction and can be easily separated from surrounding tissues during resection. However, it is unclear whether marginal excision of MLS is oncologically safe. This study aimed to assess the association between margins and survival in irradiated, intermuscular MLS.

**Methods:** The study identified 198 patients from seven sarcoma centres with a first presentation of localized, extremity, intermuscular MLS that received pre-operative radiotherapy and was diagnosed between 1990 and 2017. Patient and treatment characteristics, radiological and histological responses to neoadjuvant treatment and clinical surveillance were recorded.

**Results:** Margins were microscopically positive in 11% (n = 22), <1.0 mm in 15% (n = 29) and ≥1.0 mm in 72% (n = 143). There was no association between margin status and local recurrence-free, metastasis-free or overall survival. This finding held true even in patients at higher risk of worse overall survival based on multivariable analysis (% round cell ≥5%, percentage ellipsoid tumour volume change ≤ -60.1%).

**Conclusion:** Irradiated, extremity, intermuscular myxoid liposarcoma can safely undergo marginal resection without compromising oncologic control.

© 2022 Published by Elsevier Ltd.

Soft tissue sarcomas (STS) are a heterogeneous group of malignancies of mesenchymal origin, with approximately 70 subtypes included in the latest 5th edition WHO classification [1]. While

\* Corresponding author. Royal National Orthopedic Hospital DOOSHAK Muriel Sands House Brockley Hill Stanmore Middlesex, HA7 4LP, United Kingdom.

E-mail address: [Jonathan.Perera@nhs.net](mailto:Jonathan.Perera@nhs.net) (J.R. Perera).

<https://doi.org/10.1016/j.ejso.2022.09.008>

0748-7983/© 2022 Published by Elsevier Ltd.

historically, STS patients were managed using a uniform algorithm, increased understanding of the biology and natural history of particular subtypes has led to more patient and subtype-specific approaches. As an example, myxoid liposarcoma (MLS) requires unique considerations during staging and treatment. MLS is one of the four types of liposarcoma and accounts for 20–30% of cases [1]. It is characterized by a t(12;16)(q13;p11) translocation which

generates the pathognomonic *FUS-DDIT3* fusion transcript [1]. MLS differs from other STSs in several important ways - it preferentially metastasizes to non-pulmonary sites [2–9] and is much more sensitive to radiation than most other STS subtypes [5,10–14]. Consequently, many centres now perform whole body MRI scans for newly diagnosed MLS patients as standard chest computer tomography scans (CT) alone will fail to detect metastases in many cases [2,9,15]. Furthermore, while most STS tumours can be successfully treated with either pre- or post-operative radiotherapy, MLS patients now typically receive pre-operative radiation followed by surgical resection because of their well-defined radiosensitivity. Adequate surgical margins for STS treated with (neo) adjuvant radiotherapy remains controversial with some reporting a goal of 1–3 cm margins surrounding the tumour [5,16]. It has previously been shown that a <1 mm margin can be safe when adjacent to a critical structure such as a major nerve, blood vessel or bone [17–19].

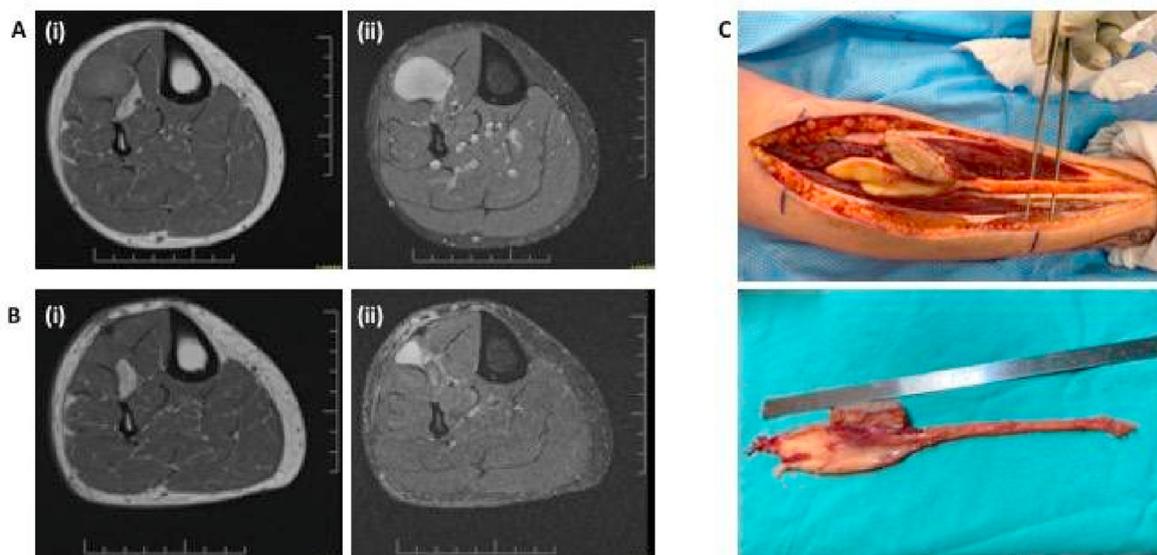
Adequate margins for preoperatively irradiated, extremity MLS is unclear but is a relevant question for two reasons. First, MLS occurs in a relatively young patient population, with a peak incidence in the fifth decade of life [7,16,20]. It is also the most common STS in children and adolescents [21]. Preservation of as much normal tissue as possible to ensure maximal function in these young patients is therefore of significant importance. Second, MLS often arises in intermuscular locations, for example between muscles of the anterior compartment of the lower leg (Fig. 1) [22,23].

When MLS tumours reduce in volume following radiotherapy [10,11,13,14], the intermuscular lesions are often separate from surrounding muscle, fascia and neurovascular structures by a thin pseudocapsule. Given the young age of these patients and with a view of minimizing morbidity in the short-term and optimizing function in the long term, it may be possible to perform a marginal excision in 1 which the irradiated tumour is removed with the pseudocapsule intact and acting as the margin, without the usual surrounding muscle or other soft tissues surrounding the tumour. This is also distinct from the ‘planned close’ margin against a fixed

critical structure [17,24]. The objective of this multicentre, retrospective study was to investigate the association between surgical margin status and oncological outcomes in patients treated with neoadjuvant radiotherapy for localized, extremity, intermuscular MLS. 4.

## 1. Methods

Cases (n = 198 patients) were identified from the prospectively-maintained clinical registries of seven international sarcoma centres located in Canada, the United States, the Netherlands and the United Kingdom. Inclusion criteria were as follows: diagnosis between January 1<sup>st</sup> 1990 and October 1<sup>st</sup> 2017, final pathology confirmed as myxoid/round cell liposarcoma, primary tumour presentation (patients who had a ‘whoops’ procedure and presented with a local recurrence were excluded; while patients that had an open biopsy at another centre that did not compromise definitive management were included), localized disease at presentation, treatment involved pre-operative radiotherapy and limb salvage surgery (patients that received chemotherapy, intra- or post-operative radiotherapy were excluded) and intermuscular tumour location in the extremity. A minimum of 12 months of follow-up was required for patients that survived. Local and/or national ethics board approval was obtained from each institution and/or country. The following variables were collected from each registry: age at surgery, gender, histological diagnosis on final resection specimen, grade (including % round cell), site, radiation dose, percentage necrosis or treatment response on final resection specimen, margins in all six anatomical planes (anterior, posterior, superior, inferior, medial, lateral), surgical date, date and nature of post-operative complications, date of local recurrence, date and location of metastases, status and time to final follow-up. Sites were also asked to measure tumour dimensions (cranio-caudal, X; anterior-posterior, Y; medial-lateral, Z) on MRI both pre- and post-radiotherapy (RT) (pre-RT ellipsoid tumour volume (ETV); post-RT ETV) allowing calculation of the ellipsoid tumour volume ( $ETV = X \times Y \times Z \times \pi/6$ ) [14] as well as the percentage of ellipsoid tumour



**Fig. 1.** Representative case of intermuscular myxoid liposarcoma located in the plane between the tibialis anterior and flexor hallucis longus muscle bellies. Shown are representative T1-weighted (i) and STIR (ii) MRI cuts from scans taken pre- (A) and post-radiotherapy with 50 Gy (B). The tumour shrank with radiotherapy from a pre-radiotherapy ellipsoid tumour volume of 107.4 cm<sup>3</sup> to a post-radiotherapy ellipsoid tumour volume of 7.4 cm<sup>3</sup> for a % change of -93.1%. The tumour was marginally excised with minimal muscle resected as a margin except in the region of the open biopsy (C). Superior, medial, lateral, anterior, and posterior margins were <1 mm and the patient was classified as having multiple <1 mm margins. The patient is alive with no evidence of disease 13 months post-surgery.

volume change [% ETV change = (post-RT ETV – pre RT ETV)/pre-RT ETV) × 100]. Patients were divided into three groups based on the closest margin: Microscopically positive (tumour present at the inked margin), <1.0 mm and ≥1.0 mm. Response to pre-operative radiotherapy was termed 'treatment effect' and was classified as either 'good' or 'poor'. A 'good' treatment effect was noted if the final resection specimen had one of the following: ≥50% necrosis, ≥50% tumour hyalinization/fibrosis, ≤50% viable tumour or if the pathology report commented on 'diffuse' or 'extensive' tumour hyalinization/fibrosis [25]. Overall (OS), local recurrence-free (LRFS) and metastasis-free (MFS) survival were calculated from the date of surgery to the date of the respective event or to the last follow-up. Continuous variables (age, pre-RT ETV, % ETV change) were divided into two groups for survival analysis based on the median value for the entire cohort. Survival curves were obtained using the Kaplan-Meier method and comparisons generated using the log-rank test. The Cox multivariable regression model was utilized to calculate adjusted hazard ratios and their 95% confidence intervals for variables shown to be prognostic in the literature [5,8,26–28].

Multivariable analysis was not conducted for LRFS as there were only two events in the cohort. Correlations were considered statistically significant when the two-tailed alpha p-value was <0.05. The  $\chi^2$  test and two-tailed unpaired Student's t-test or one-way ANOVA were used to measure the association for categorical and continuous variables, respectively. Statistical analysis was performed using SPSS (Version 26, IBM Corporation; Armonk, NY, USA).

## 2. Results

### 2.1. Patients

Demographic and oncologic variables for the 198 patients that met the inclusion criteria are shown in Table 1. Sixty-six percent were male and the median age was 46.0 years (range 17–88). The median follow-up for patients last known to be alive was 60.7 months (range 12.0–255.2). Ninety-seven percent of tumours were located in the lower extremity. The tumour was Grade 1 in 31 cases (16%), Grade 2 in 122 (62%) and Grade 3 in 38 (19%). Thirty (15%) tumours were classified as round cell liposarcoma, based on a round cell component ≥5%. The median pre-radiotherapy ellipsoid tumour volume (pre-RT ETV) was 240.6 cm<sup>3</sup> (inter-quartile range 99.1–592.2).

**Table 1**

Demographic, oncologic and treatment characteristics for the entire patient cohort. Abbreviations – Pre-RT ETV: pre-radiotherapy ellipsoid tumour volume; % ETV change: percentage change in ellipsoid tumour volume after preoperative radiation.

Variable	n	% (n = 198)
Age (years)	Median (Range)	46.0 (17–88)
Gender	Male	131 66%
	Female	67 34%
Site	Upper Extremity	5 3%
	Lower Extremity	193 97%
Grade	1	31 16%
	2	122 62%
	3	38 19%
% Round Cell	<5%	145 73%
	≥5%	30 15%
Pre-RT ETV (cm <sup>3</sup> )	Median (IQR)	240.6 (99.1–592.2)
% ETV Change	Median (IQR)	–60.1% (–75.7% to –35.5%)
Treatment Effect	Good	135 68%
	Poor	33 17%
Closest Margin	Micro Positive	22 11%
	<1.0 mm	29 15%
	≥1.0 mm	143 72%

### 2.2. Treatment

The median dose of pre-operative radiotherapy was 50Gy (range 25–66Gy). The median percentage of ETV change following pre-operative radiation (% ETV change) was –60.1% (IQR –75.7% to –35.5%). Of note, 113 patients (57%) had a reduction in their tumour ETV of >50%, 52 patients (26%) had a reduction in their tumour ETV of ≤50%, 3 patients (1.5%) had unchanged tumour ETVs, and the remainder had growth of their tumours while on neoadjuvant therapy (n = 17; 9%). One hundred and thirty-five patients (68%) had good treatment effect as per the final histological assessment, while 3 (17%) had a poor response. There was a statistically significant association between % ETV change and treatment effect, as defined histologically. Patients with a good treatment effect had a median % ETV change of –62.2% (IQR –77.8% to –43.2%) while patients with a poor treatment effect had a median % ETV change of –46.2% (IQR –64.0% to –2.3%; p = 0.0019). Margins were microscopically positive in 11% (n = 22), <1.0 mm in 15% (n = 29) and ≥1.0 mm in 72% (n = 143). There were no cases of macroscopically positive margins.

### 2.3. Oncologic outcomes

Overall survival for the entire cohort was 94.2% at 5 years. Both % ETV change and % round cell composition were significantly associated with overall survival in multivariable analysis. A % ETV change of less than the median of –60.1% had a hazard ratio of 5.14 (95% CI 1.07–24.73; p = 0.041) while having greater than 5% round cell had a hazard ratio of 6.28 (95% CI 1.57–25.13; p = 0.009) (Table 2).

Metastasis-free survival for the entire cohort was 77.2% at 5 years. Pre-RT ETV (≥240.6 cm [3]; HR 3.08, 95% CI 1.48–6.42, p = 0.003), % ETV change (≥–60.1%; HR 3.00, 95% CI 1.42–6.37; p = 0.004) and % round cell (≥5%; HR 4.24, 95% CI 1.69–10.62, p = 0.002) were significantly associated with metastasis-free survival in multivariable analysis. Location of first metastasis was most commonly soft tissue (21/48; 44%), multisystem (12/48; 25%), bone (7/48; 14%) and lung (4/48; 8%). Only two patients (1.0%) developed a local recurrence for a five-year local control rate of 98.9%. Both patients had tumours of the lower extremity that shrank by greater than the median %ETV change (–64.7% and 86.6%, respectively) and showed good treatment effect on final pathology. One patient had a margin of <1.0 mm and the other of ≥1.0 mm while both had greater than 5% round cell component. Both were treated with pre-operative radiotherapy and excision of the local recurrence. While both patients recurred around 17 months post-operatively (17.6 and 17.1 months, respectively), one died of metastatic disease at 36.9 months and the other was alive at last follow-up (26.0 months).

### 2.4. Post-operative outcomes

Thirty-five patients (18%) developed post-treatment complications that required surgical intervention at a median of 1.8 months (range 0.7–28.1 months). The most common complications were due to surgical site infection or hematoma, requiring debridement only (28/35) or soft tissue coverage (3/35). Complications were not associated with any studied variables in univariable analysis.

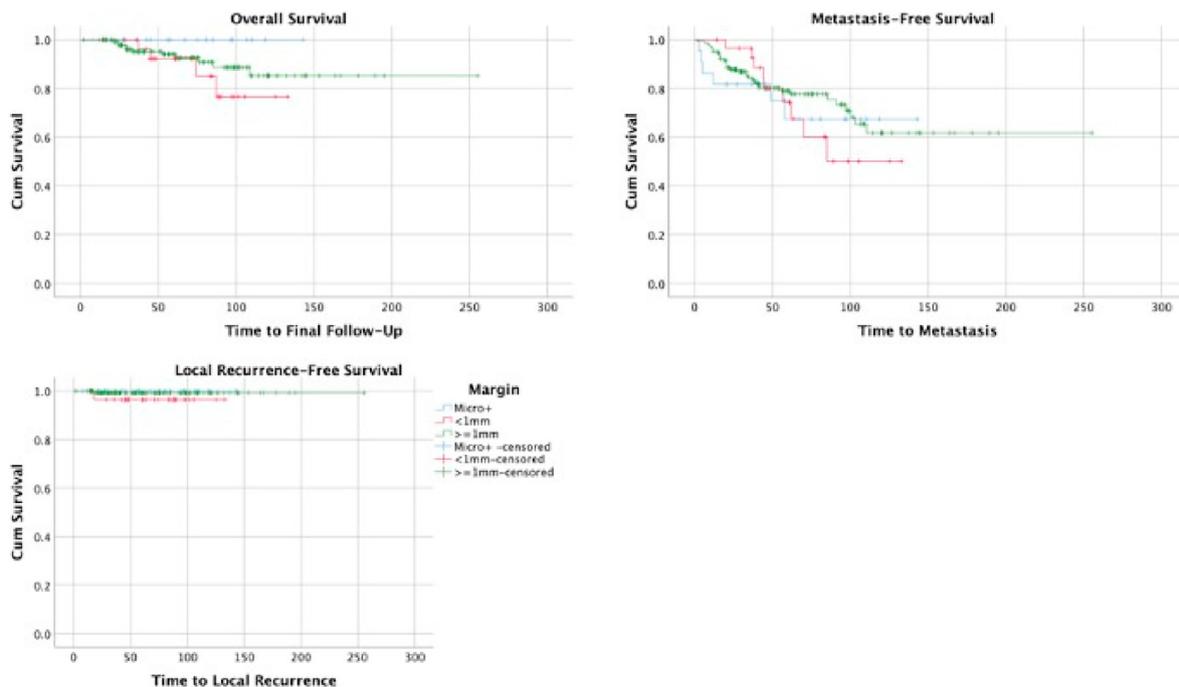
### 2.5. Impact of surgical margins

Surgical margins were not associated with overall, metastasis-free, or local recurrence-free survival (Table 2; Fig. 2). Margins were not associated with the risk of developing a post-treatment 20 complication that required surgical intervention (data not shown).

**Table 2**

Prognostic factors for local recurrence-free, metastasis-free and overall survival. Abbreviations – Pre-RT ETV: pre-radiotherapy ellipsoid tumour volume; % ETV change: percentage change in ellipsoid tumour volume after preoperative radiation.

Variable	Metastasis-free survival			Overall survival				
	Univariable	Multivariable		Univariable	Multivariable			
	p	HR	95%CI	p	p	HR	95%CI	p
Age $\geq$ 40 years	0.49	–	–	–	0.050	3.24	0.40–26.15	0.27
Grade 2	0.0010	0.84	0.36–1.96	0.68	0.84	1.33	0.28–6.28	0.72
Grade 3		1.13	0.34–3.74	0.84		0.20	0.015–2.65	0.22
% Round Cell $\geq$ 5%	<0.0001	4.24	1.69–10.62	<b>0.002</b>	0.097	6.28	1.57–25.13	<b>0.009</b>
Pre-RT ETV $\geq$ 240.6 cm <sup>3</sup>	0.0010	3.08	1.48–6.42	<b>0.003</b>	0.11	1.39	0.41–4.76	0.60
% ETV change $\geq$ –60.1%	0.00021	3.00	1.42–6.37	<b>0.004</b>	0.012	5.14	1.07–24.73	<b>0.041</b>
Poor Treatment Effect	0.40	–	–	–	0.16	–	–	–
$\geq$ 1 mm Margin	0.76	–	–	–	0.28	–	–	–
<1.0 mm Margin	–	–	–	–	–	–	–	–
Micro Positive Margin	–	–	–	–	–	–	–	–



**Fig. 2.** Overall, metastasis-free, and local recurrence-free survival are comparable for patients with microscopically positive, <1.0 mm and  $\geq$ 1.0 margins. P-values are 0.28, 0.76 and 0.38, respectively.

Demographic and oncologic characteristics were compared between patients with microscopically positive, <1.0 mm and  $\geq$ 1.0 mm margins (Table 3). The groups differed only with regards to grade; patients with microscopically positive margins had a higher rate of low-grade tumours (36% vs 10% and 13% for <1.0 mm and  $\geq$ 1.0 mm, respectively;  $p = 0.012$ ). Five-year overall survival for patients with microscopically positive, <1.0 mm and  $\geq$ 1.0 mm margins was 100%, 92.1% and 93.9%, respectively ( $p = 0.28$ ). Five-year metastasis-free survival for patients with microscopically positive, <1.0 mm and  $\geq$ 1.0 mm margins was 67.5%, 74.4% and 79.0%, respectively ( $p = 0.76$ ). Five-year local recurrence-free survival for patients with microscopically positive, <1.0 mm and  $\geq$ 1.0 mm margins was 100%, 96.4% and 99.3%, respectively ( $p = 0.38$ ). Of the 29 patients with margins <1.0 mm, details regarding individual margins were available from the pathology reports of 27 patients. There were 11 patients with a single margin <1.0 mm and 16 patients with two or more margins <1.0 mm. Not surprisingly, given the fact that even microscopically positive margins were not negatively associated with survival, patients with

multiple <1.0 mm margins did not have increased risk of death compared with patients with either a single <1.0 mm or  $\geq$ 1.0 mm margins (5-year OS of 92.8%, 90.9% and 93.9%, respectively;  $p = 0.38$ ). Of the 143 patients with  $\geq$ 1.0 mm margins, numeric values for additional margins were available for 104 patients. The median closest margin was 1.5 mm (range 1.0–15 mm) while the median widest margin was 33 mm (range 1.0–100.0 mm).

We further examined whether microscopically positive or margins <1.0 mm in 'high risk' tumours were associated with worse outcomes. An association between margins and overall survival was not found even when the analysis was repeated for patients in these higher risk groups: % ETV change  $\geq$  –60.1% ( $p = 0.48$ ) and % round cell $\geq$ 5% ( $p = 0.86$ ). Given the low number of events, subgroup analysis was not appropriate for local recurrence-free survival.

### 3. Discussion

This study aimed to assess whether intermuscular extremity MLS tumours treated with pre-operative radiotherapy can be

**Table 3**

Comparison of demographic, oncologic and treatment characteristics between patients with microscopically positive, <1.0 mm and  $\geq$ 1.0 mm margins. Abbreviations – Pre-RT ETV: pre-radiotherapy ellipsoid tumour volume; % ETV change: percentage change in ellipsoid tumour volume after preoperative radiation.

Variable		Micro Positive		<1.0 mm		$\geq$ 1.0 mm		p
		n	% (n = 22)	n	% (n = 29)	n	% (n = 143)	
Age (years)	Median (Range)	42.0	(21.0–87.5)	42.6	(17.3–68.9)	46.7	(18.9–84.0)	0.13
Gender	Male	13	59%	20	69%	96	67%	0.72
	Female	9	41%	9	31%	47	33%	
Site	Upper Extremity	2	9%	0	0%	3	2%	0.10
	Lower Extremity	20	91%	29	100%	140	98%	
Grade	1	8	36%	3	10%	19	13%	0.012
	2	7	32%	22	76%	93	65%	
	3	4	18%	4	14%	29	20%	
% Round Cell	<5%	13	59%	23	79%	108	76%	0.84
	$\geq$ 5%	3	14%	6	21%	21	15%	
Pre-RT ETV (cm <sup>3</sup> )	Median (IQR)	201.1	(96.4–723.9)	393.0	(240.1–879.3)	206.0	(89.3–565.8)	0.33
% ETV Change	Median (IQR)	–60.0%	(–82.8% to –17.4%)	–58.6%	(–80.9% to –44.4%)	–60.2%	(–73.9% to –35.5%)	0.88
Treatment Effect	Good	13	59%	24	83%	96	67%	0.53
	Poor	5	23%	4	14%	23	16%	

excised marginally without compromising local recurrence-free, metastasis-free, and overall survival. Patients from seven sarcoma referral centres in four different countries were pooled, yielding a cohort of 198 cases after exclusions. Twenty-nine patients had sub-1 mm margins, 22 patients had microscopically positive margins and the remaining 143 patients had margins that were 1 mm or greater. In this cohort, patients with microscopically positive as well as sub-1 mm margins had comparable local control and survival to patients with wider margins.

The relationship between margins and disease-free and overall survival in MLS has been mixed in the literature. Certain studies report an association between the surgical margin and a risk for local recurrence [16,20,28,29], while others, like the current work, did not find such a relationship [5,6,27]. Similarly, some found an association between positive margins and worse overall survival [27], while others did not [3,6,16,28]. These conflicting findings may be partially explained by the heterogeneity of the patient cohorts, a common confounding factor in analyzing rare malignancies such as sarcoma. For instance, many studies included patients not treated with radiotherapy [20,28,29] or patients with other subtypes of liposarcoma [16,27]. Furthermore, margin classification systems varied between studies with some defining an R1 margin as we did and as per the AJCC manual, based on the presence of tumour at the inked resection margin [4,12] while others considered R1 as tumour present within 1 mm of the resection margin [17,27,28,30]. As our study was designed to ask a specific question – 'Is it oncologically safe to marginally resect irradiated, intermuscular MLS?', it had much more restrictive inclusion criteria than any other investigations and makes direct comparisons challenging.

We were particularly interested in patients whose tumours were resected relying on the pseudocapsule as the margin instead of a cuff of normal tissue, which is the more usual planned margin when resecting extremity STS. While it is difficult in a retrospective, multicentre study to ascertain the surgeon's intent, we inferred that patients with multiple margins <1.0 mm had likely undergone this marginal type of procedure using the tumor pseudocapsule as the resection margin. These patients had comparable survival to those with a single margin <1.0 mm, which may have occurred against a fixed critical structure [17], as well as to those with wider margins. Additional indirect evidence of the oncologic safety of a marginal resection in this particular setting is the fact that even patients with microscopically positive margins had excellent local control and overall survival that did not differ from the outcomes of patients with wider margins.

In multivariable analysis, tumours with greater than 5% round cell component and greater than the median % ETV change (i.e. less volumetric tumour shrinkage) were significantly associated with worse overall survival. We therefore performed a sub-group analysis, examining the relationship between margins and overall survival for patients with these higher risk tumours (i.e.  $\geq$ 60.1% ETV change and  $\geq$ 5% round cell component). We did not identify an association between margins and overall survival even in these higher risk patients, suggesting that marginal excision is safe even in poorly responding and more biologically aggressive tumours.

While most patients in our study were treated with 50Gy, the question of pre-operative radiation dosing is pertinent given the recent publication of results from the Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcomas (DOREMY) trial. This prospective, single-group, phase 2, multi-centre trial administered 36Gy pre-operatively and found a local control rate of 100% in short-term follow-up [25]. Margins were classified as either positive (5 of 77 patients) or negative (72 of 77 patients) without specific values given. Though it is encouraging that none of the patients with microscopically positive margins developed a local recurrence in the median follow-up time of 25 months, further analysis will be required to determine whether a marginal excision is oncologically safe at this reduced radiation dose with longer follow-up.

While it is intuitive that resecting less muscle should reduce surgical morbidity, we were unable to demonstrate this by examining post-operative complications. As this was a retrospective study and most centres only include complications requiring surgical intervention in their databases, this was the only metric available for analysis. Using this data, no association between margin status and complication-free survival was noted.

This study had some limitations. We did not re-review the pathology and instead used the histologic diagnosis from the resection specimen report. While all included centres are sarcoma referral sites with sub-specialty pathologists, the differential diagnosis of myxoid-rich sarcomas is wide and if cases were not confirmed molecularly, they may include other types of STS. Similarly, only a subset of MRIs were re-reviewed and when not re-reviewed, cases were included based on the database noting that the tumour was intermuscular. It is possible that some intramuscular and subcutaneous tumours were included in the analysis. When assessing additional margins for the  $\geq$ 1.0 mm group, only margins with an available numeric value were included. Many pathology reports included the descriptor 'wide' and therefore values for the widest margin are likely an underestimate. We did not capture all complications, particularly those related to wound

healing as only those requiring a return to the operating room were included. While the multicentre nature of this report is one of its strengths, there may have been some variability in imaging studies and treatment modalities. The DOREMY trial published in 2020 has led to the opening of an international prospective registry on local treatment approaches in MLS to gain real-life prospective data on not only surgical differences but radiotherapy dosing schedules [32].

The results of this study have implications for the management of patients with localized, intermuscular, extremity myxoid liposarcoma. Consideration should be given to administering pre-operative radiotherapy and a typical protocol is 50Gy in 25 fractions, followed by surgery 4–6 weeks later [31]. Our results suggest that it is oncologically safe to perform a marginal resection – removing the tumour en-bloc with only the pseudocapsule as the margin. While it is hard to advocate for microscopically positive margins, our results suggest that for this pathologic entity and when radiation is given pre-operatively, an R1 resection does not compromise local control or survival.

### Funding

None

### Disclosure

None of the authors report any commercial interest or financial/material support with regards to the subject of study.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Acknowledgements

None.

### References

- [1] WHO Classification of Tumours: Soft Tissue and Bone Tumours. Vol 3. 5th ed. International Agency for Research on Cancer; 2020.
- [2] Visgauss JD, Wilson DA, Perrin DL, et al. Staging and surveillance of myxoid liposarcoma: follow-up assessment and the metastatic pattern of 169 patients suggests inadequacy of current practice standards. *Ann Surg Oncol* 2021;28(12):7903–11. <https://doi.org/10.1245/s10434-021-10091-1>.
- [3] Fuglø HM, Maretty-Nielsen K, Hovgaard D, Keller JØ, Safwat AA, Petersen MM. Metastatic pattern, local relapse, and survival of patients with myxoid liposarcoma: a retrospective study of 45 patients. *Sarcoma* 2013;2013:548628. <https://doi.org/10.1155/2013/548628>.
- [4] Dürr HR, Rauh J, Baur-Melnyk A, et al. Myxoid liposarcoma: local relapse and metastatic pattern in 43 patients. *BMC Cancer* 2018;18(1):304. <https://doi.org/10.1186/s12885-018-4226-8>.
- [5] Guadagnolo BA, Zagars GK, Ballo MT, et al. Excellent local control rates and distinctive patterns of failure in myxoid liposarcoma treated with conservation surgery and radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;70(3):760–5. <https://doi.org/10.1016/j.ijrobp.2007.07.2337>.
- [6] Haniball J, Sumathi VP, Kindblom LG, et al. Prognostic factors and metastatic patterns in primary myxoid/round-cell liposarcoma. *Sarcoma* 2011;2011:538085. <https://doi.org/10.1155/2011/538085>.
- [7] Spillane AJ, Fisher C, Thomas JM. Myxoid liposarcoma—frequency and the natural history of nonpulmonary soft tissue metastases. *Ann Surg Oncol* 1999;6(4):389–94. <https://doi.org/10.1007/s10434-999-0389-5>.
- [8] Muratori F, Bettini L, Frenos F, et al. Myxoid liposarcoma: prognostic factors and metastatic pattern in a series of 148 patients treated at a single institution. *Int J Surg Oncol* 2018;2018:8928706. <https://doi.org/10.1155/2018/8928706>.
- [9] Gorelik N, Reddy SMV, Turcotte RE, et al. Early detection of metastases using whole-body MRI for initial staging and routine follow-up of myxoid liposarcoma. *Skeletal Radiol* 2018;47(3):369–79. <https://doi.org/10.1007/s00256-017-2845-9>.
- [10] O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002;359(9325):2235–41. [https://doi.org/10.1016/s0140-6736\(02\)09292-9](https://doi.org/10.1016/s0140-6736(02)09292-9).
- [11] Chung PWM, Deheshi BM, Ferguson PC, et al. Radiosensitivity translates into excellent local control in extremity myxoid liposarcoma. *Cancer* 2009;115(14):3254–61. <https://doi.org/10.1002/cncr.24375>.
- [12] Chowdhry V, Goldberg S, DeLaney TF, et al. Myxoid liposarcoma: treatment outcomes from chemotherapy and radiation therapy. *Sarcoma* 2018;2018:8029157. <https://doi.org/10.1155/2018/8029157>.
- [13] Engström K, Bergh P, Cederlund CG, et al. Irradiation of myxoid/round cell liposarcoma induces volume reduction and lipoma-like morphology. *Acta Oncol* 2009;46(6):838–45. <https://doi.org/10.1080/02841860601080415>.
- [14] Pitson G, Robinson P, Wilke D, et al. Radiation response: an additional unique signature of myxoid liposarcoma. *Int J Radiat Oncol Biol Phys* 2004;60(2):522–6. <https://doi.org/10.1016/j.ijrobp.2004.03.009>.
- [15] Stevenson JD, Watson JJ, Cool P, et al. Whole-body magnetic resonance imaging in myxoid liposarcoma: a useful adjunct for the detection of extrapulmonary metastatic disease. *European J Surg Oncol Ejsso* 2016;42(4):574–80. <https://doi.org/10.1016/j.ejsso.2015.12.011>.
- [16] Zagars GK, Goswitz MS, Pollack A. Liposarcoma: outcome and prognostic factors following conservation surgery and radiation therapy. *Int J Radiat Oncol Biol Phys* 1996;36(2):311–9. [https://doi.org/10.1016/s0360-3016\(96\)00265-9](https://doi.org/10.1016/s0360-3016(96)00265-9).
- [17] Gundle KR, Kafchinski L, Gupta S, et al. Analysis of margin classification systems for assessing the risk of local recurrence after soft tissue sarcoma resection. *J Clin Oncol* 2018;36(7). <https://doi.org/10.1200/jco.2017.74.6941>. JCO.2017.74.694.
- [18] Gerrand CH, Wunder JS, Kandel RA, et al. Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. *Bone Joint Lett J* 2001;83-B(8):1149–55. <https://doi.org/10.1302/0301-620x.83b8.12028>.
- [19] Clarkson PW, Griffin AM, Catton CN, et al. Epineural dissection is a safe technique that facilitates limb salvage surgery. *Clin Orthop Relat Res* 2005;438(NA):92–6. <https://doi.org/10.1097/01.blo.0000180057.22712.53>.
- [20] Antonescu CR, Tschernyavsky SJ, Decuseara R, et al. Prognostic impact of P53 status, TLS-CHOP fusion transcript structure, and histological grade in myxoid liposarcoma: a molecular and clinicopathologic study of 82 cases. *Clin Cancer Res Official J Am Assoc Cancer Res* 2001;7(12):3977–87.
- [21] Alaggio R, Coffin CM, Weiss SW, et al. Liposarcomas in young patients. *Am J Surg Pathol* 2009;33(5):645–58. <https://doi.org/10.1097/pas.0b013e3181963c9c>.
- [22] Ouni FE, Jemni H, Trabelsi A, et al. Liposarcoma of the extremities: MR imaging features and their correlation with pathologic data. *Orthop Traumatology Surg Res* 2010;96(8):876–83. <https://doi.org/10.1016/j.otsr.2010.05.010>.
- [23] Sung MS, Kang HS, Suh JS, et al. Myxoid liposarcoma: appearance at MR imaging with histologic correlation. *Radiographics* 2000;20(4):1007–19. <https://doi.org/10.1148/radiographics.20.4.g00j021007>.
- [24] O'Donnell PW, Griffin AM, Eward WC, et al. The effect of the setting of a positive surgical margin in soft tissue sarcoma. *Cancer* 2014;120(18):2866–75. <https://doi.org/10.1002/cncr.28793>.
- [25] Lansu J, Bovée JVMG, Braam P, et al. Dose reduction of preoperative radiotherapy in myxoid liposarcoma. *JAMA Oncol* 2021;7(1):e205865. <https://doi.org/10.1001/jamaoncol.2020.5865>.
- [26] Heuvel SE ten, Hoekstra HJ, Ginkel RJ van, Bastiaannet E, Suurmeijer AJH. Clinicopathologic prognostic factors in myxoid liposarcoma: a retrospective study of 49 patients with long-term follow-up. *Ann Surg Oncol* 2007;14(1):222–9. <https://doi.org/10.1245/s10434-006-9043-7>.
- [27] Fiore M, Grosso F, Vullo SL, et al. Myxoid/round cell and pleomorphic liposarcomas. *Cancer* 2007;109(12):2522–31. <https://doi.org/10.1002/cncr.22720>.
- [28] Moreau LC, Turcotte R, Ferguson P, et al. Myxoid/Round cell liposarcoma (MRCLS) revisited: an analysis of 418 primarily managed cases. *Ann Surg Oncol* 2012;19(4):1081–8. <https://doi.org/10.1245/s10434-011-2127-z>.
- [29] Kilpatrick SE, Doyon J, Choong PFM, Sim FH, Nascimento AG. The clinicopathologic spectrum of myxoid and round cell liposarcoma: a study of 95 cases. *Cancer* 1996;77(8):1450–8. [https://doi.org/10.1002/\(sici\)1097-0142\(19960415\)77.8<1450::aid-cncr5>3.0.co;2-g](https://doi.org/10.1002/(sici)1097-0142(19960415)77.8<1450::aid-cncr5>3.0.co;2-g).
- [30] Dalal KM, Kattan MW, Antonescu CR, Brennan MF, Singer S. Subtype specific prognostic nomogram for patients with primary liposarcoma of the retroperitoneum, extremity, or trunk. *Transactions Meet Am Surg Assoc* 2006;124(NA):47–57. <https://doi.org/10.1097/01.sla.0000234795.98607.00>.
- [31] Griffin AM, Dickie CI, Catton CN, et al. The influence of time interval between preoperative radiation and surgical resection on the development of wound healing complications in extremity soft tissue sarcoma. *Ann Surg Oncol* 2015;22(9):2824–30. <https://doi.org/10.1245/s10434-015-4631-z>.
- [32] International prospective registry on local treatment approaches in MLS. <https://clinicaltrials.gov/ct2/show/NCT04699292>.