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YL, MPG, SC, MAM, RY, JT, AR, JPM: Nothing to Disclose

INTRODUCTION

- Soft tissue sarcomas mostly occur in the extremities and local recurrence (LR) rate often directly correlates with the oncological prognosis of the patient.
- An important predictor of the risk of LR is the status of the surgical resection margins. Positive margins in these patients show both increased LR and decreased overall survival (OS).
- Myxofibrosarcoma is notorious for its infiltrative growth pattern, making wide excisions difficult to achieve when compared to other soft tissue sarcomas, and it is associated with increased LR (30%).
- We performed a retrospective study to determine (1) What is the LR rate after multimodal treatment of myxofibrosarcomas treated in a sarcoma center? (2) Which factors are associated with LR? (3) What is the distant metastatic and OS rate in patients affected by this tumor and what are the contributing factors? (4) What is the accuracy of intra-operative assessment of surgical resection margins ?

METHODS

- Medical records of 209 patients with appendicular soft tissue sarcomas between the years 2012 – 2018 were retrospectively reviewed. Of these, 29 patients (14%) were diagnosed with myxofibrosarcoma. These patients underwent a total of 33 resections between the years of 2012 - 2018. The pathological analyses were conducted by an experienced musculoskeletal pathologist.
- We analyzed **demographic variables**: age, gender, race, stage, tumor location (upper vs lower extremity), laterality (left vs right), follow-up time; **tumor characteristics**: depth (subcutaneous vs intramuscular), size, necrosis, margin status (negative (≤ 0.1 cm, 0.1-0.49 cm, ≥ 0.5 cm) vs positive), **adjuvant therapy**: radiation therapy and chemotherapy; **oncological outcomes**: LR rate and OS; and accuracy of intra-operative analysis of surgical resection margins.
- Kaplan-Meier curves were created to evaluate the LR, metastatic, and OS rates based on 2-year local recurrence-free rate. Cox regression analysis was performed to determine independent predictors of LR and OS. Statistical analysis was performed using SPSS (version 26).

Tables & Figures

Table 1: Demographics and Tumor Descriptions for Each Patient									
Patient ID	Gender	Race	Age	Location Left/Right	Location Upper/Lower	Tumor Depth	Tumor Character	Tumor Grade	Tumor Stage
1	F	W	57	Left	Lower	Sub-Q	Inf	3/3	Stage IIIA
2	M	W	74	Right	Lower	IM	WC	3/3	Stage II
3	M	W	66	Left	Lower	Sub-Q	Inf	3/3	Stage IIIB
4	M	H	77	Right	Upper	IM	WC	3/3	Stage IIIA
5	M	W	56	Left	Lower	Sub-Q	WC	3/3	Stage IIIB
6	F	W	64	Left	Lower	Sub-Q	WC	3/3	Stage IIIB
7	F	W	67	Right	Lower	IM	WC	3/3	Stage IIIA
8	M	AA	46	Left	Lower	IM	WC	3/3	Stage II
9	F	W	82	Left	Upper	IM	Inf	2/3	Stage IIIB
10	M	W	90	Left	Lower	Sub-Q	WC	3/3	Stage IV
11	F	AA	65	Right	Lower	Sub-Q	WC	3/3	Stage IIIB
12	M	W	54	Right	Lower	Sub-Q	Inf	3/3	Stage IIIB
13	F	As	54	Left	Lower	Sub-Q	WC	3/3	Stage II
14	M	W	66	Left	Lower	Sub-Q	Inf	3/3	Stage IIIB
15	F	W	83	Left	Lower	IM	WC	3/3	Stage IIIB
16	M	AA	62	Right	Upper	IM	WC	2/3	Stage II
17	F	W	53	Left	Lower	IM	WC	2/3	Stage IIIB
18	M	W	59	Left	Lower	IM	Inf	3/3	Stage II
19	F	W	88	Left	Lower	IM	WC	2/3	Stage IIIB
20	M	W	47	Left	Lower	Sub-Q	Inf	3/3	Stage IIIA
21	M	W	47	Left	Lower	Sub-Q	Inf	3/3	Stage II
22	M	AA	67	Left	Lower	IM	WC	3/3	Stage IIIB
23	M	W	78	Right	Lower	IM	Inf	3/3	Stage IIIB
24	F	W	85	Left	Lower	IM	Inf	3/3	Stage II
25	F	W	64	Left	Lower	IM	WC	3/3	Stage II
26	F	W	67	Right	Lower	IM	WC	3/3	Stage II
27	M	AA	46	Left	Lower	IM	WC	3/3	Stage II
28	M	W	55	Right	Upper	Sub-Q	WC	3/3	Stage II
29	M	W	63	Right	Lower	Sub-Q	Inf	2/3	Stage IIIB

Note: M = male; F = female; W = White; AA = African American; H = Hispanic; As = Asian; Sub-Q = subcutaneous; IM = intramuscular; Inf = infiltrative; WC = well circumscribed

Table 2: Relationship between oncological outcomes and 2-year local recurrence-free rates					
Oncological Outcomes		2-year LR over Total	2-year LRFR	HR	95% CI
Tumor Type	Myxofibrosarcoma	7/33	79%		
Gender	Male	4/17	76%	2.33	0.24-22.44
	Female	1/12	92%		
Age	≤ 60 years old	1/11	91%	0.50	0.05-4.80
	> 60 years old	4/18	78%		
Tumor Size	≤ 10 cm	7/20	65%	N/A**	44-86%**
	> 10 cm	0/13	100%		
Margin Size	Negative ≤ 0.1 cm	3/8	63%	7.97	0.83-76.79
	Negative > 0.1 cm	1/18	94%		
Surgical Margins	Positive	3/7	57%	-	-
	Close Margins*	3/8	63%	0.95	0.19-4.73
	Negative > 0.1 cm	1/18	94%	0.11	0.01-1.07
Grouped Surgical Margins	Positive or Close*	6/13	54%	11.74	1.41-97.74
	Negative > 0.1 cm	1/20	95%		
Tumor Depth	Subcutaneous	5/17	71%	2.56	0.50-13.21
	Intramuscular	2/16	88%		
Tumor Character	Well-Circumscribed	2/18	89%	0.30	0.06-1.54
	Infiltrative	5/15	67%		
Re-Resections	Yes	2/7	71%	1.51	0.29-7.78
	No	5/26	80%		
Adjuvant Therapy	Chemotherapy and Radiotherapy	0/17	100%	N/A**	100%**
	Chemotherapy Alone	3/4	25%		
	Radiotherapy Alone	2/8	75%		
	No Treatment	2/4	50%		

Note: LRFR = 2-year local recurrence free rate; LR = local recurrence; HR = hazard ratio; CI = confidence interval
* Close margins = negative margins ≤ 0.1 cm
** Kaplan Meier log ranked test was used to assess statistical significance

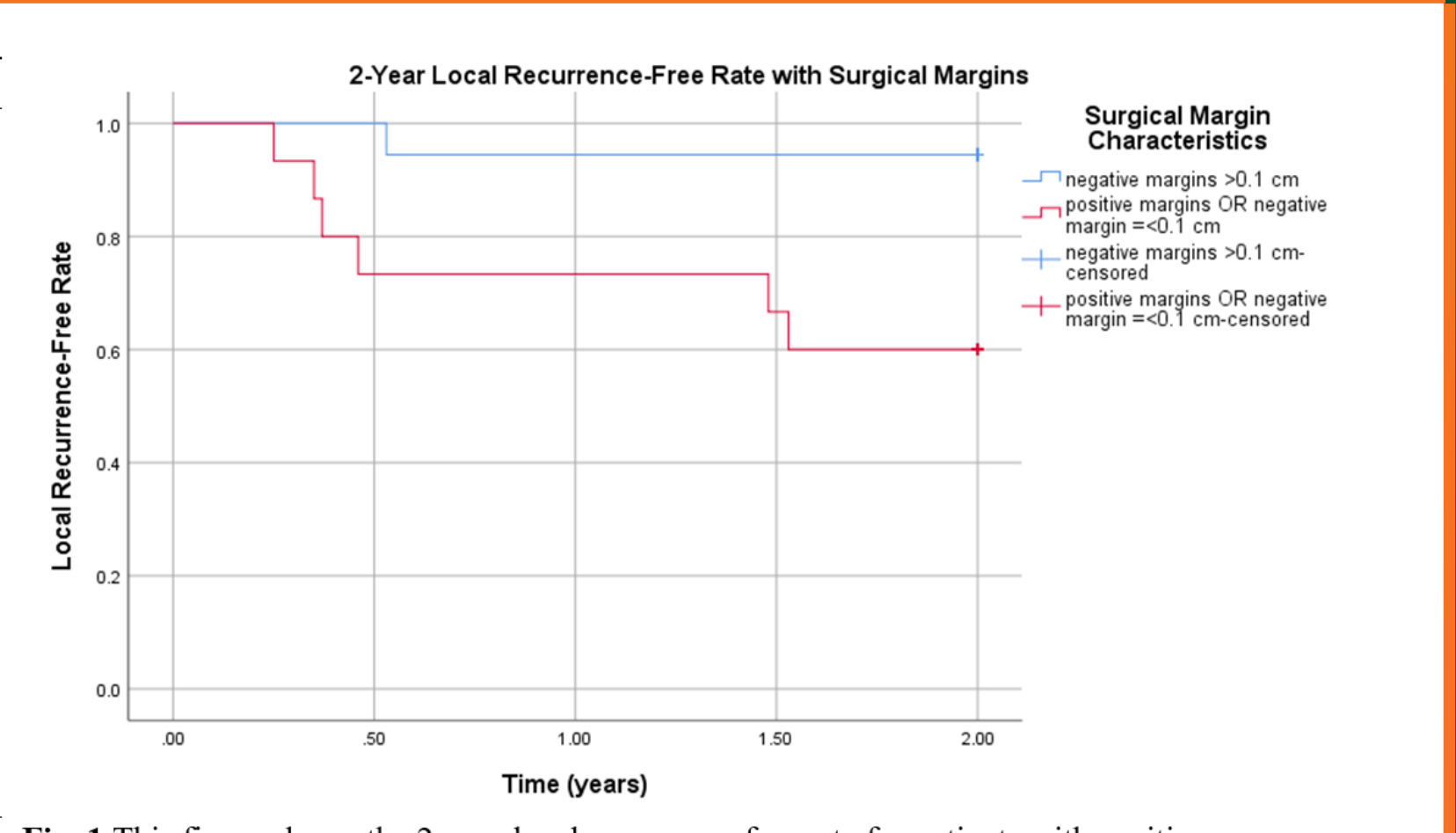


Fig. 1 This figure shows the 2-year local recurrence-free rate for patients with positive or negative margins ≤ 0.1 cm versus negative margins > 0.1 cm

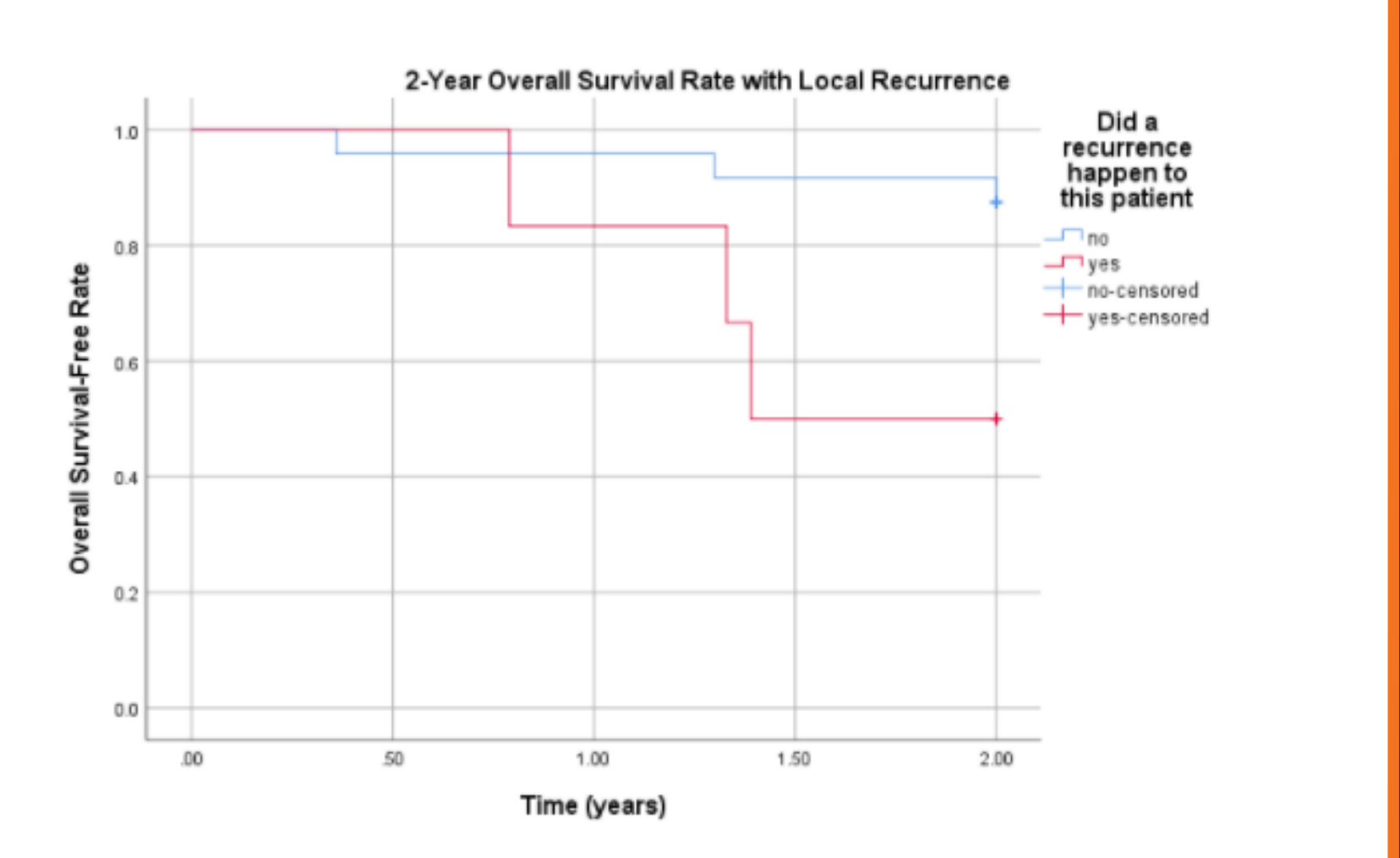
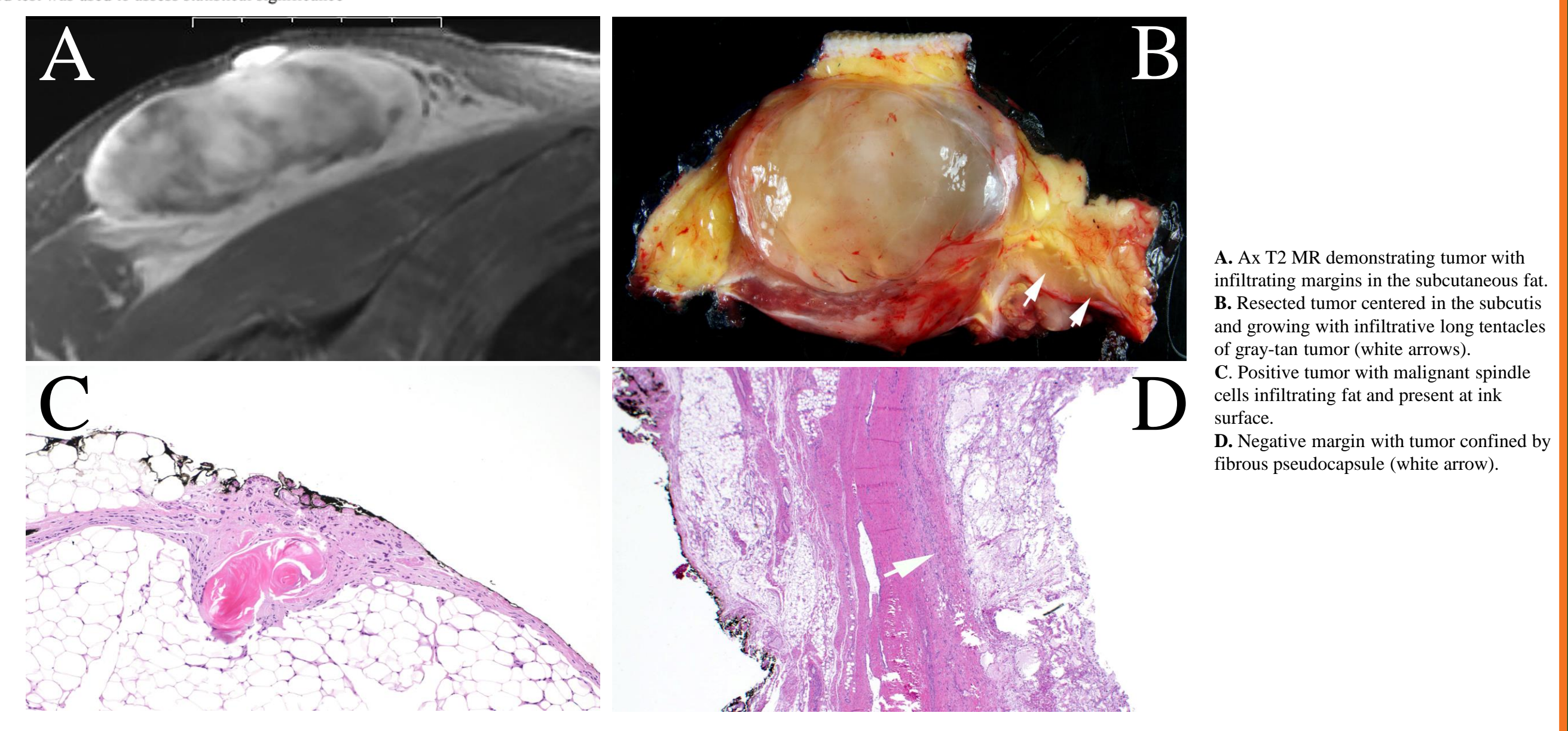


Fig. 2 This figure shows the 2-year overall survival for patients with a recurrence of MFS.



RESULTS

- Patient Demographics (**Table 1**): Mean patient age was 68 years (range 46-90 years); there were 17 females and 12 males. Of the 29 patients (33 resections), 17 (52%) cases were treated with a combination of radiation and chemotherapy, 8 (24%) were treated with radiation only, 4 (12%) were treated with chemotherapy only, and 4 (12%) were treated with neither radiation nor chemotherapy. Patient follow-up time ranged from 0.36 to 6.63 years (median, 3.38 years).
- Local Recurrence Data (**Table 2**): The overall LR rate was 27% (9/33). 2-year LR rate was 21%. Factors associated with significantly decreased local recurrence free rates (LRFRs) were: tumor size ≤ 10 cm (2-year LRFR, 65%; 95% confidence interval (CI), 44-86%; $p = 0.02$) and surgical margins ≤ 0.1 cm (2-year LRFR, 63%; 95% CI, 29-97%; $p = 0.033$). Chemotherapy and radiotherapy together (2-year LRFR, 100%; 95% CI, 100%, $p = 0.001$) positively increased the LRFR.
- Positive surgical margins grouped with negative margins ≤ 0.1 cm was a factor predictive of LR on univariate analysis (**Fig. 1**). (Hazard ratio [HR], 11.74; 95% CI, 1.41-97.74; $p = 0.02$). Even though there was not a statistical significance, subcutaneous location [29% (5/17) vs 13% (2/16), $p=0.2$], re-resections of the surgical bed [29% (2/7) vs 19% (5/26), $p=0.6$] showed a tendency for higher local recurrence rates.
- Overall 2-year distant metastasis and overall survival were 15% and 86%, respectively. Predictor of distant metastasis was female gender. Local recurrence had a negative impact on the overall survival (**Fig. 2**).
- Intra-operative analysis of resection margins accuracy was 75% (12/16) when non-MSK pathologists were involved; however, when the specimen was analyzed by an MSK pathologist, accuracy was 100% (12/12).

DISCUSSION

- Myxofibrosarcomas showed high local recurrence rates after treatment.
- Close margins (≤ 0.1 cm) should be considered as a risk factor for local recurrence, and re-resections of the surgical bed do not decrease this risk. Neoadjuvant therapy in terms of combined chemotherapy and radiation therapy seems to decrease LR rates.
- The overall survival at 2-years is 86% and is negatively affected by local recurrence. Finally, if intra-operative assessment of margins is to be done, it should be performed by an experienced MSK pathologist.
- Level of Evidence: Level III Retrospective Comparative Study