

# An Analysis of Factors Related to Recurrence of Myxofibrosarcoma

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**Objective:** Myxofibrosarcoma is clinically characterized by a high frequency of local recurrence after surgery. To improve the clinical outcome of patients with myxofibrosarcoma, it is imperative to control any postsurgical local recurrence.

**Methods:** In this study, we performed a retrospective clinicopathologic analysis of 100 consecutive patients with myxofibrosarcoma to identify factors related to poor prognosis. All of the patients had been diagnosed, and had undergone surgery at the National Cancer Center Hospital between 1999 and 2008.

**Results:** At the initial visit to our hospital, 64 patients had primary myxofibrosarcoma, whereas 36 had undergone primary unplanned resection at other facilities. Of the 36 patients, 11 consulted our hospital before recurrence and 25 did so after recurrence. A histologically positive margin after surgery was evident in 28% of the cases overall. The estimated 5-year recurrence-free survival rate was 74.8%. Univariate analysis showed that primary unplanned resection at another facility ( $P = 0.0001$ ) and a histologically positive margin ( $P = 0.0224$ ) were significant predictors of local recurrence. When these two factors were subjected to multivariate analysis, only primary unplanned resection at another facility was significantly correlated with the estimated recurrence-free survival rate ( $P = 0.0011$ ). Primary unplanned resection was also significantly related to the 5-year disease-free survival rate ( $P = 0.0401$ ).

**Conclusions:** Our findings indicate that primary unplanned resection at a non-referral hospital is the most important risk factor related to poor prognosis of myxofibrosarcoma. Accurate diagnosis and adequate initial surgery are most important factors for improving the clinical outcomes of myxofibrosarcoma.

*Key words:* myxofibrosarcoma – recurrence – surgery

## INTRODUCTION

Myxofibrosarcoma (MFS) is a common type of adult soft tissue sarcoma, particularly affecting the extremities in the elderly (1). In Japan, it is expected that the number of patients with MFS will increase further as society gradually ages (2), and the tumor is now being recognized more frequently following the latest World Health Organization (WHO) classification (1).

A characteristic clinical feature of MFS is its propensity for persistent local recurrence, even after wide resection (1,3,4).

In previous reports, local recurrence rates have ranged from 22 to 79%, irrespective of grade, depth and size (4–7). In addition, 15–38% of locally recurrent MFS cases progress to a higher grade with an attendant increase of metastatic potential (1,3,7–9).

Although most patients with soft tissue sarcomas can achieve local recurrence-free limb preservation after resection with an adequately wide margin ( $>2$  cm) (10), it remains unclear whether such wide resection for MFS is the optimal

local treatment. In MFS, histologically negative margins after surgery are frequently difficult to achieve because MFS has an unusual infiltrative growth pattern, especially along the fascial planes and muscle bundles, which is often more extensive than initially suggested by magnetic resonance imaging (MRI) (1,11,12). This infiltrative growth pattern of MFS can result in anatomically deceptive boundaries at surgery because of microscopic extension. However, no studies involving large series have yet investigated the factors associated with local recurrence of MFS after surgery.

In the present retrospective study, we examined a large series of 100 patients with MFS to identify the clinicopathological factors associated with poor prognosis after surgery.

## PATIENTS AND METHODS

### PATIENTS

This study included a total of 100 consecutive patients with histologically proven MFS who were treated by surgery with or without adjuvant therapy at the National Cancer Center Hospital (NCCH) between 1999 and 2008. All cases were reviewed and histologically confirmed by a certified pathologist based on the WHO classification of soft tissue tumors (1). The median follow-up period was 65 months (range 1–198 months; mean 62.9 months). This study was approved by the ethical review board of the National Cancer Center.

Clinical data including tumor status at the initial visit, gender, age at surgery, tumor location, tumor depth, histological grade, histological margin of the surgery, adjuvant treatments, period until recurrence, period until metastasis and last follow-up were retrieved from the charts.

Tumor status at the initial visit was classified according to whether the patient received primary wide resection at the NCCH or had undergone primary unplanned resection at a non-specialized facility. The patients who had undergone primary unplanned resection at a non-specialized facility were divided into two groups: those histologically diagnosed as having MFS after surgery and who consulted our hospital immediately before recurrence, and those who consulted our hospital after recurrence without any histological diagnosis. Tumor depth was classified as either superficial MFS located in subcutaneous tissue without invasion of the muscle fascia or deep-seated MFS located in intramuscular tissues beneath the muscle fascia. Histological grade was determined on the basis of the French Federation of Cancer Centers (FNCLCC grade) grading system. This classification is based on the mitotic index, extent of necrosis and degree of histological differentiation of the tumor (13–15).

All patients underwent MRI including gadolinium-enhanced sequences for surgical planning, and the extent of the tumor area was evaluated meticulously from gadolinium-enhanced fat-suppressed T1-weighted images. We then evaluated the surgical margin >3 cm from the distal portion of the area of tumor extension seen in the images. All patients underwent complete resection with a margin of >3 cm. Patients

with primary MFS underwent primary wide resection including amputation, patients histologically diagnosed as having MFS and who consulted our hospital immediately before recurrence underwent additional wide resection and patients who consulted our hospital after recurrence without any histological diagnosis underwent wide resection for the recurrent tumor. Histological margins were evaluated after surgery in all patients. Decisions on whether to administer radiotherapy and/or chemotherapy were made at multidisciplinary sarcoma group meetings. After the meetings, we provided objective data on the risks and benefits related to adjuvant therapies to the patients and conducted therapies only for patients who provided informed consent. For patients considered to have a higher-than-average risk of recurrence on the basis of clinical findings such as anatomical location and an inadequate margin expected on the basis of surgical planning, external beam radiation at doses ranging from 30 to 60 Gy or brachytherapy at a dose of 36 Gy was administered. Systemic chemotherapy was administered at the discretion of the multidisciplinary sarcoma group and based on whether the patient had provided informed consent. Anthracycline-based regimens were used in most patients. The characteristics of the 100 patients are summarized in Table 1.

### STATISTICAL ANALYSIS

Tumor recurrence after surgery at the NCCH was used as the end point, and calculated from the date of surgery. The recurrence-free survival rate was estimated using the Kaplan–Meier method (16). Relationships between the recurrence-free survival rate and other variables were investigated using the log-rank test for categorical variables and a score test based on the Cox proportional hazards model for continuous variables. Differences at  $P < 0.05$  were considered to be statistically significant. Multivariate analysis using Cox regression was carried out on variables shown to be significant at the univariate level (17) ( $P < 0.05$ ). Statistical computations were done using the Stat-View version 5.0 statistical software package (SAS Institute). The disease-free survival rate was also estimated using the Kaplan–Meier method (16). Primary tumor events including tumor recurrence, metastasis or death due to disease after surgery at the NCCH were used as the end point, and were calculated from the date of surgery. Differences at  $P < 0.05$  were considered to be statistically significant.

## RESULTS

The average age of the 100 patients at surgery was 64 years (range 23–97 years), and there was a male predominance (61 males and 39 females). According to the tumor status at the initial visit, 64 patients had treated primary tumors and 36 had received primary unplanned resection at a non-specialized hospital. Seventy-seven tumors were located in the extremities, including 28 in the upper limbs, 49 in the lower limbs and 23 in the trunk including two in the neck region.

**Table 1.** Clinicopathologic features of the 100 patients with myxofibrosarcoma

Sample no.	Age	Gender	Tumor status	Depth	Size <sup>a</sup> (cm)	Location	Details of surgery <sup>b</sup>	FNCLCC grade <sup>c</sup>	Histological margin	Recurrence	Recurrence free follow-up (months)	Metastasis	Follow-up status	Disease-free follow-up (months)	Adjuvant therapy	Details of adjuvant therapy
1	48	F	Primary wide	Subcutaneous	7	Extremity	Wide	2	—	—	114	—	CDF	114	—	—
2	77	M	Primary non-wide	Subcutaneous	1.5*	Trunk	Wide for rec	2	+	+	1	—	AWD	1	—	—
3	82	F	Primary wide	Subcutaneous	4	Extremity	Wide	2	—	—	3	—	CDF	3	—	—
4	70	M	Primary wide	Deep	8	Extremity	Wide	2	—	—	118	—	CDF	118	—	—
5	69	F	Primary non-wide	Subcutaneous	8	Extremity	Wide for rec	3	—	—	130	—	NED	130	—	—
6	84	M	Primary wide	Subcutaneous	7	Extremity	Wide	2	+	+	8	—	DOD	8	—	—
7	88	F	Primary wide	Deep	8.5	Extremity	Amputation for wide	3	—	—	1	—	CDF	1	—	—
8	63	F	Primary wide	Subcutaneous	7	Extremity	Amputation for wide	3	—	—	96	—	CDF	96	—	—
9	60	M	Primary wide	Subcutaneous	5.5	Extremity	Wide	3	—	—	95	—	CDF	95	—	—
10	63	F	Primary non-wide	Subcutaneous	2.5*	Trunk	Wide for rec	2	—	+	38	—	NED	38	+	Neoadjuvant radiotherapy 60 Gy
11	68	F	Primary non-wide	Subcutaneous	-	Extremity	Add wide	2	+	+	21	—	NED	21	—	—
12	63	M	Primary non-wide	Subcutaneous	-	Extremity	Add wide	/	—	—	137	—	CDF	137	—	—
13	66	M	Primary wide	Subcutaneous	2*	Extremity	Wide	2	+	—	1	—	CDF	1	—	—
14	29	M	Primary wide	Deep	6	Extremity	Wide	1	—	—	1	—	CDF	1	—	—
15	52	M	Primary wide	Subcutaneous	1.5*	Extremity	Wide	2	—	—	4	Lung	AWD	2	+	Adjuvant chemotherapy
16	47	F	Primary wide	Deep	4.5*	Extremity	Wide	1	—	—	145	—	CDF	145	—	—
17	61	F	Primary wide	Subcutaneous	5	Extremity	Wide	/	—	—	148	—	CDF	148	—	—
18	55	M	Primary non-wide	Subcutaneous	3*	Extremity	Wide for rec	2	+	—	1	—	NED	1	+	Neoadjuvant chemotherapy
19	57	M	Primary wide	Deep	12	Extremity	Wide	1	+	—	1	—	CDF	1	—	—

Continued

Table 1. Continued

Sample no.	Age	Gender	Tumor status	Depth	Size <sup>a</sup> (cm)	Location	Details of surgery <sup>b</sup>	FNCLCC grade <sup>c</sup>	Histological margin	Recurrence	Recurrence free follow-up (months)	Metastasis	Follow-up status	Disease-free follow-up (months)	Adjuvant therapy	Details of adjuvant therapy
20	67	M	Primary non-wide	Subcutaneous	7.5	Extremity	Wide for rec	/	—	+	4	—	NED	4	—	—
21	63	F	Primary wide	Deep	7.5	Extremity	Wide	3	—	—	122	—	CDF	122	—	—
22	72	M	Primary wide	Deep	14	Extremity	Wide	3	—	—	1	—	CDF	1	—	—
23	50	M	Primary non-wide	Subcutaneous	5.5	Extremity	Wide for rec	2	—	+	3	—	NED	3	—	—
24	84	F	Primary wide	Subcutaneous	11	Trunk	Wide	2	+	—	1	—	CDF	1	—	—
25	48	F	Primary non-wide	Deep	8	Extremity	Wide for rec	2	+	+	49	—	NED	49	—	—
26	58	M	Primary non-wide	Subcutaneous	4.5*	Extremity	Wide for rec	2	—	+	43	—	NED	43	—	—
27	70	M	Primary non-wide	Subcutaneous	-	Trunk	Add wide	2	+	+	4	—	NED	4	—	—
28	63	M	Primary non-wide	Subcutaneous	8.5	Extremity	Wide for rec	2	+	+	62	—	AWD	62	+	Brachytherapy 36 Gy
29	58	M	Primary non-wide	Subcutaneous	4.8*	Extremity	Wide for rec	2	+	—	105	—	NED	105	+	Brachytherapy 37 Gy
30	62	M	Primary non-wide	Subcutaneous	8	Extremity	Wide for rec	1	+	—	88	—	NED	88	+	Brachytherapy 38 Gy
31	46	F	Primary wide	Subcutaneous	8.3	Extremity	Wide	/	—	—	112	Lung	AWD	19	—	—
32	71	F	Primary wide	Deep	12	Extremity	Wide	1	—	—	110	—	CDF	110	+	Adjuvant radiotherapy 40 Gy
33	79	F	Primary non-wide	Subcutaneous	2*	Extremity	Wide for rec	2	—	—	69	—	NED	69	—	—
34	78	M	Primary non-wide	Deep	15	Extremity	Wide for rec	2	+	+	10	Lung	DOD	9	+	Neoadjuvant radiotherapy 40 Gy
35	58	M	Primary wide	Subcutaneous	3.5*	Extremity	Wide	3	—	—	102	—	CDF	102	—	—
36	77	M	Primary wide	Deep	2.5*	Extremity	Wide	2	+	—	84	—	CDF	84	—	—
37	60	M	Primary wide	Subcutaneous	9	Trunk	Wide	1	—	—	2	—	CDF	2	—	—
38	80	M	Primary wide	Subcutaneous	10	Extremity	Wide	2	+	—	58	—	CDF	58	—	—

39	88	F	Primary wide	Deep	20	Extremity	Wide	3	+	—	8	—	DOD	8	+	Neoadjuvant radiotherapy 40 Gy
40	50	M	Primary wide	Deep	17	Extremity	Wide	/	+	—	108	—	CDF	108	+	Neoadjuvant chemotherapy
41	72	M	Primary wide	Subcutaneous	5	Extremity	Amputation for wide	2	—	—	105	—	CDF	105	—	—
42	69	M	Primary wide	Subcutaneous	5.5	Extremity	Wide	3	—	—	29	Lung	DOD	19	—	—
43	35	M	Primary non-wide	Deep	9	Extremity	Wide for rec	1	—	—	100	—	NED	100	+	Neoadjuvant radiotherapy 30 Gy
44	60	M	Primary non-wide	Subcutaneous	—	Extremity	Add wide	/	+	+	48	—	NED	48	—	—
45	77	M	Primary non-wide	Subcutaneous	10	Extremity	Wide for rec	/	—	—	1	—	NED	1	—	—
46	78	M	Primary wide	Deep	14	Extremity	Wide	/	—	—	1	—	CDF	1	+	Neoadjuvant radiotherapy 30 Gy
47	67	M	Primary wide	Subcutaneous	2.2*	Extremity	Wide	1	—	—	1	—	CDF	1	—	—
48	71	F	Primary wide	Subcutaneous	4.5*	Extremity	Wide	2	—	+	34	—	NED	34	—	—
49	67	F	Primary wide	Deep	15	Extremity	Wide	2	—	—	103	—	NED	103	—	—
50	72	M	Primary non-wide	Subcutaneous	3*	Extremity	Wide for rec	/	+	+	76	—	NED	76	+	Brachytherapy 36 Gy
51	56	F	Primary wide	Subcutaneous	6.5	Extremity	Wide	2	—	—	103	—	CDF	103	—	—
52	62	M	Primary non-wide	Subcutaneous	5.7	Extremity	Wide for rec	/	—	—	95	—	NED	95	—	—
53	67	F	Primary wide	Subcutaneous	5.5	Extremity	Wide	2	+	—	96	—	CDF	96	+	Brachytherapy 36 Gy
54	52	M	Primary wide	Deep	3.5*	Extremity	Wide	2	+	—	87	—	CDF	87	+	Brachytherapy 37 Gy
55	57	M	Primary wide	Deep	7	Extremity	Wide	2	—	—	85	—	CDF	85	—	—
56	71	M	Primary wide	Subcutaneous	2*	Extremity	Wide	2	—	—	100	—	CDF	100	—	—
57	71	M	Primary wide	Deep	4.4*	Trunk	Wide	3	—	—	24	Lung	DOD	5	+	Adjuvant chemotherapy and radiotherapy*
58	60	M	Primary wide	Subcutaneous	4*	Extremity	Wide	2	+	—	1	—	CDF	1	—	—
59	62	M	Primary non-wide	Subcutaneous	—	Extremity	Add wide	/	—	+	16	Lung	AWD	16	+	Brachytherapy 36 Gy

Continued

Table 1. *Continued*

Sample no.	Age	Gender	Tumor status	Depth	Size <sup>a</sup> (cm)	Location	Details of surgery <sup>b</sup>	FNCLCC grade <sup>c</sup>	Histological margin	Recurrence	Recurrence free follow-up (months)	Metastasis	Follow-up status	Disease-free follow-up (months)	Adjuvant therapy	Details of adjuvant therapy
60	67	F	Primary wide	Subcutaneous	4.5*	Extremity	Wide	/	+	+	21	—	NED	21	—	—
61	50	F	Primary non-wide	Subcutaneous	—	Extremity	Add wide	/	—	+	20	—	NED	20	—	—
62	23	M	Primary wide	Deep	11.5	Extremity	Wide	1	—	—	73	—	CDF	73	+	Neo- and adjuvant chemotherapy
63	66	F	Primary wide	Subcutaneous	5.6	Trunk	Wide	1	—	—	76	—	CDF	76	—	—
64	40	F	Primary wide	Deep	20	Extremity	Wide	1	—	—	88	—	CDF	88	—	—
65	77	M	Primary non-wide	Subcutaneous	6	Extremity	Wide for rec	3	—	—	59	—	NED	59	—	—
66	63	M	Primary non-wide	Deep	8	Extremity	Wide for rec (amputation)	/	—	—	1	—	NED	1	—	—
67	67	M	Primary non-wide	Deep	1.4*	Trunk	Wide for rec	2	—	—	88	—	NED	88	—	—
68	75	M	Primary wide	Subcutaneous	11	Extremity	Wide	1	—	—	59	—	CDF	59	—	—
69	44	F	Primary wide	Deep	14	Extremity	Wide	1	—	—	77	—	CDF	77	—	—
70	90	F	Primary non-wide	Subcutaneous	2.5*	Trunk	Wide for rec	2	—	+	4	—	NED	4	—	—
71	77	M	Primary non-wide	Subcutaneous	4.2*	Extremity	Wide for rec	2	—	—	78	—	NED	78	—	—
72	69	M	Primary wide	Subcutaneous	4*	Trunk	Wide	2	—	—	81	—	CDF	81	+	Neoadjuvant chemotherapy
73	62	F	Primary non-wide	Subcutaneous	4*	Trunk	Wide for rec	/	—	—	1	—	NED	1	+	Neoadjuvant chemotherapy
74	60	M	Primary wide	Deep	10	Extremity	Wide	/	—	—	72	—	CDF	72	+	Neo- and adjuvant chemotherapy
75	70	M	Primary wide	Deep	10	Extremity	Wide	2	—	—	73	—	CDF	73	—	—
76	46	F	Primary non-wide	Subcutaneous	—	Extremity	Add wide	1	—	—	88	—	NED	88	—	—
77	70	M	Primary wide	Subcutaneous	10	Trunk	Wide	2	+	—	62	—	CDF	62	—	—
78	70	F	Primary wide	Subcutaneous	4.5*	Extremity	Wide	2	—	—	88	—	CDF	88	—	—

79	75	F	Primary non-wide	Subcutaneous	—	Extremity	Add wide	/	—	—	67	—	NED	67	—	—
80	97	M	Primary wide	Deep	15	Extremity	Wide	2	—	—	7	—	CDF	7	—	—
81	41	M	Primary non-wide	Subcutaneous	3*	Trunk	Wide for rec	/	—	—	58	Lung	AWD	1	—	—
82	81	M	Primary non-wide	Subcutaneous	—	Extremity	Add wide	/	—	—	57	—	NED	57	—	—
83	77	F	Primary non-wide	Subcutaneous	—	Trunk	Add wide	2	—	+	30	—	NED	30	—	—
84	63	M	Primary non-wide	Subcutaneous	—	Extremity	Add wide	3	—	—	44	—	NED	44	—	—
85	33	F	Primary wide	Deep	16.4	Extremity	Wide	2	+	—	10	—	CDF	10	+	Adjuvant radiotherapy 50 Gy
86	58	M	Primary wide	Deep	12.8	Extremity	Wide	1	+	—	63	—	CDF	63	—	—
87	75	M	Primary wide	Deep	8	Extremity	Wide	3	+	—	40	—	CDF	40	—	—
88	69	M	Primary wide	Subcutaneous	14	Trunk	Wide	3	—	—	1	—	CDF	1	—	—
89	57	F	Primary wide	Subcutaneous	6.5	Trunk	Wide	3	—	—	63	—	CDF	63	—	—
90	66	M	Primary wide	Subcutaneous	10	Trunk	Wide	3	—	—	40	Lung	DOD	3	—	—
91	73	F	Primary wide	Deep	5.5	Extremity	Wide	3	—	+	3	—	NED	3	+	Adjuvant radiotherapy 50 Gy
92	61	F	Primary non-wide	Deep	21	Trunk	Wide for rec	2	—	—	5	—	NED	5	+	Adjuvant chemotherapy
93	86	F	Primary wide	Subcutaneous	16	Trunk	Wide	3	+	—	20	Lung	AWD	8	—	—
94	70	M	Primary wide	Deep	11	Trunk	Wide	3	—	—	2	Lung	AWD	1	+	Adjuvant radiotherapy 37.5 Gy
95	73	M	Primary wide	Deep	8	Trunk	Wide	3	—	+	7	—	NED	7	—	—
96	67	F	Primary wide	Deep	16	Trunk	Wide	2	—	—	9	—	AWD	9	—	—
97	68	M	Primary wide	Subcutaneous	5	Extremity	Wide	3	—	—	3	—	CDF	3	—	—
98	71	M	Primary wide	Subcutaneous	6	Trunk	Wide	/	—	—	2	—	CDF	2	—	—
99	69	F	Primary wide	Deep	4*	Extremity	Wide	2	—	—	62	Lymph node	CDF	9	—	—

Continued

Table 1. Continued

Sample no.	Age	Gender	Tumor status	Depth	Size <sup>a</sup> (cm)	Location	Details of surgery <sup>b</sup>	FNCLCC grade <sup>c</sup>	Histological margin	Recurrence	Recurrence free follow-up (months)	Metastasis	Follow-up status	Disease-free follow-up (months)	Adjuvant therapy	Details of adjuvant therapy
100	66	F	Primary wide	Subcutaneous	5	Extremity	Wide	2	—	—	52	—	CDF	52	—	—

+, present; —, absent.  
CDF, continuously disease free; MFS, myxofibrosarcoma; NED, no evidence of disease; AWD, alive with disease; DOD, died of disease; FNCLCC, French Federation of Cancer Centers; wide, wide resection; wide for rec, wide resection for recurrence tumor; add wide, additional wide resection.  
<sup>a</sup>Primary tumor size was only evaluated for primary tumor.  
<sup>b</sup>Details of surgery at our hospital. Patients wide for rec consulted to our hospital after recurrence without any histological diagnosis; patients with add wide histologically diagnosed as MFS and consulted to our hospital immediately before recurrence.  
<sup>c</sup>FNCLCC grade was only evaluated for 80 cases.  
\*Asterisk show that tumor size is <5 cm.

Sixty-four of the patients presented with superficial tumors and 36 with deep-seated tumors. Histological grades according to the FNCLCC grading system were Grade 1 in 15 patients, Grade 2 in 44 patients and Grade 3 in 21 patients. Tumor resection with a histologically negative margin was achieved in 72 patients. A total of 25 patients received adjuvant therapy (radiotherapy in 16, chemotherapy in 8, and both radiotherapy and chemotherapy in one).

Twenty-one patients developed local recurrence within a median period of 20 months (1–76 months; average 24 months). Figure 1 shows the local recurrence-free survival curves for the 100 patients as a whole. The 5-year local recurrence-free survival rate was 74.8%.

When the patients were stratified according to the status at the initial visit, the estimated 5-year recurrence-free survival rate was 89.0% for those with primary tumors and 55.0% for those who had undergone initial unplanned surgery at the previous non-specialized hospital ( $P = 0.0001$ , Fig. 2A). We further investigated whether the difference in local tumor status after unplanned primary resection was significantly correlated with the 5-year recurrence-free survival rate. Of the 36 patients with primary unplanned resection, 11 underwent additional wide resection before recurrence, and 25 underwent wide resection after recurrence. The estimated 5-year recurrence-free survival rate was 43.6% for those with additional wide resection and 61.2% for those with wide resection for recurrence. The difference in local tumor status after primary unplanned resection did not significantly correlate with the 5-year recurrence-free survival rate ( $P = 0.6303$ ).

There were also significant differences in the estimated 5-year recurrence-free survival rates between patients with a histologically positive margin (61.5%) and those with a histologically negative margin (79.8%) ( $P = 0.0224$ , Fig. 2B).

No other factors examined, including age at surgery, gender, tumor depth, tumor location, adjuvant therapy and FNCLCC grade, were associated with an increased risk of local recurrence (Table 2). Multivariate analysis revealed that primary unplanned resection at a previous non-specialized hospital was the only factor significantly correlated with the

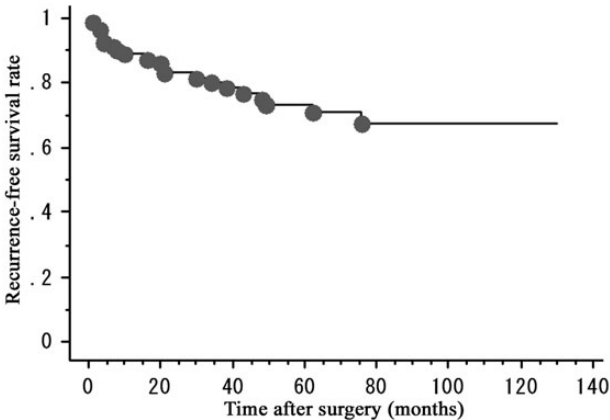
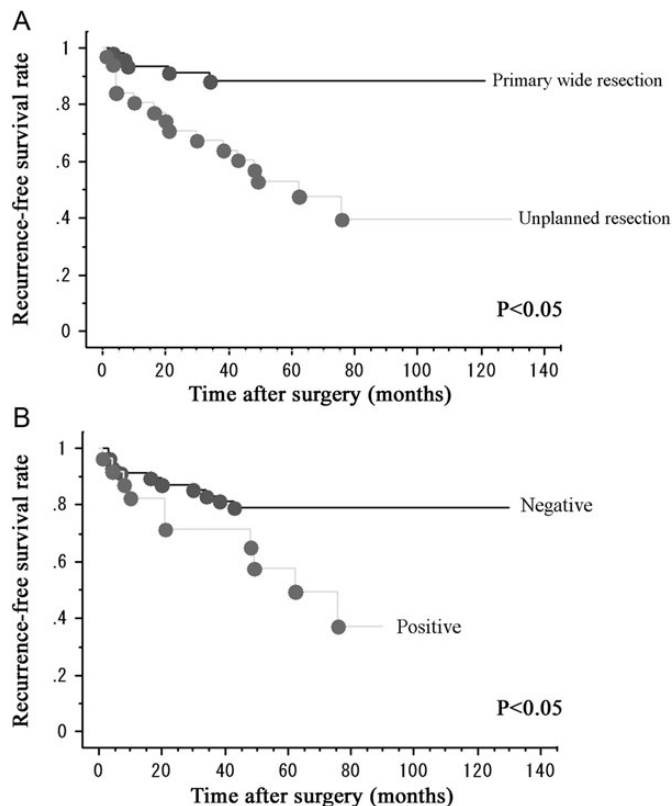


Figure 1. Kaplan–Meier estimated recurrence-free survival curves for all 100 patients.



**Figure 2.** Kaplan–Meier estimated recurrence-free survival curves based on (A) tumor status at initial visit and (B) histological margin. Primary unplanned resection at a non-specialized facility ( $P = 0.0001$ , log-rank test) and a histologically positive margin ( $P = 0.0224$ , log-rank test) were significant predictors of local recurrence.

estimated recurrence-free survival rate ( $P = 0.0011$ , relative risk 5.35, 95% confidence interval 0.068–0.513; Table 2).

We further investigated whether primary unplanned resection, identified as a significant predictor of recurrence by univariate and multivariate analyses, was significantly correlated with the estimated disease-free survival rate. From the 100 patients included in this study, 50 remained continuously disease-free (CDF), 35 showed no evidence of disease (NED), 9 were alive with disease (AWD) and 6 died of disease (DOD) (Table 1). Eleven patients had metastases after surgery (10 in the lung and one in the lymph nodes, Table 1). The estimated 5-year disease-free survival rate for the 100 patients was 63.9% (Fig. 3A). Primary unplanned resection was significantly related to the 5-year disease-free survival rate ( $P = 0.0401$ , Fig. 3B). Meanwhile, primary unplanned resection was not significantly associated with overall survival. DOD occurred in only six patients during the follow-up period. Remarkably, two of those six patients died because of local failure after surgery despite the absence of metastases. Of these two patients, one died because of uncontrollable local recurrence after surgery (Case 6, Table 1), and the other died due to local infection after surgery without any disease recurrence (Case 39, Table 1).

## DISCUSSION

MFS is clinically characterized by a high frequency of local recurrence after surgery because of its potential for unusual infiltrative growth (11,12). Previous reports have documented local repeated recurrences after surgery in up to 50–60% of cases (3,6,7). In the present study, primary unplanned resection at another facility and a histologically positive margin after surgery were factors significantly related to poor prognosis of MFS. At present, the only established radical treatment for MFS is primary wide resection with a histologically negative margin. The rate of local recurrence is strongly affected by the quality of primary surgery. Merk et al. (7) reported that the local failure rate for primary wide resections was 17%, in comparison with 79% for non-wide resections. Therefore, primary wide resection with an accurately assessed surgical margin is most important for local control of MFS.

Thirty-six of the present cases were treated by primary unplanned resection at a non-specialized facility without any doubt as to the diagnosis. One of the reasons for these inadequate resections may have been that about two-thirds of MFS cases develop in subcutaneous tissue. In fact, 30 (83.3%) of the 36 cases treated at a non-specialized facility were located in subcutaneous tissue, as were 34 (53.1%) of the 64 cases treated primarily at the NCCH. Another reason for inadequate surgery was that the MFS tumors were comparatively small and asymptomatic initially. The tumor diameter was  $< 5$  cm in 16 of the 64 cases (25%) in our series.

Our present findings indicate that MFS should be consistently considered in the differential diagnosis of soft tissue tumors located in subcutaneous tissue. Huang et al. (4) indicated that MFS is prone to misinterpretation as benign or malignant myxoid mimickers such as myxoid liposarcoma, low-grade fibromyxoid sarcoma, cellular myxoma and nodular fasciitis. A significant feature to consider in the differential diagnosis of MFS is the presence of an infiltrative growth pattern on MRI. It has been reported that such an infiltrative growth pattern is especially obvious in gadolinium-enhanced fat-suppressed T1-weighted images (12,18). Accordingly, a careful evaluation using MRI imaging should be performed before primary surgery.

Malignant bone and soft tissue sarcomas are rare, accounting for  $< 1\%$  of all tumors (19,20), and orthopedic surgeons who are not specialized in musculoskeletal tumors encounter, on average, less than one patient with a tumor of the musculoskeletal system every 3 years (20,21). Therefore, non-specialized clinicians generally cannot be expected to possess basic knowledge of the diagnostic and therapeutic principles for MFS (21). In a study of 1460 musculoskeletal tumors, Grimer concluded that those exceeding golf ball (4.27 cm) size had a potential for malignancy (22). His study serves as an example that effective education about MFS is important for avoiding primary unplanned resection of this tumor.

In MFS patients who undergo primary unplanned resection and are thus at high risk of local recurrence, it is thought necessary to consider additional resections. Merk et al. (7)

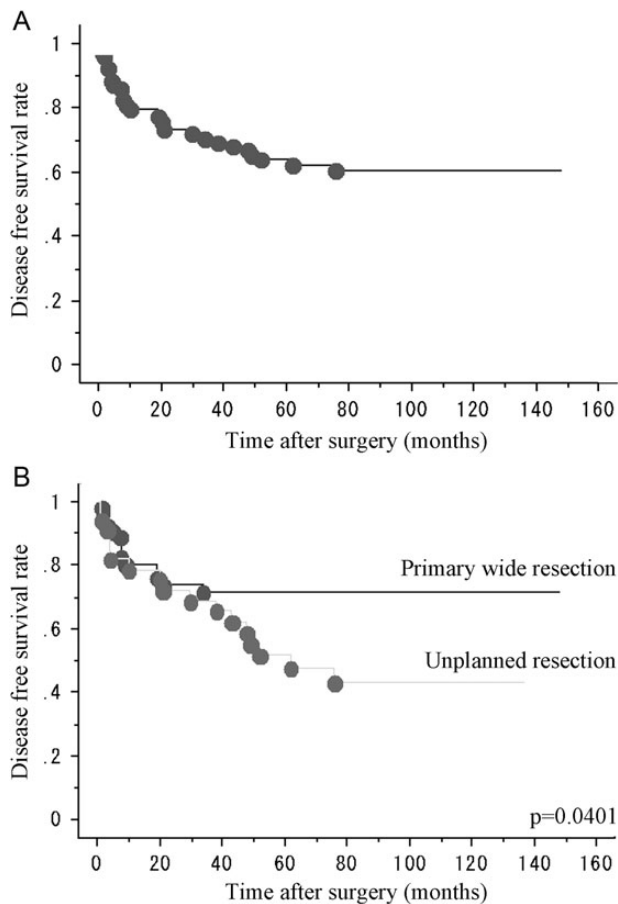
**Table 2.** Univariate- and multivariate analyses of the prognostic factors

Variable	Univariate survival analysis				Multivariate survival analysis		
	Number of cases	Number of recurrence	5-year recurrence-free survival rate (%)	Log-rank <i>P</i> value	<i>P</i> value	Relative risk	95% Confidence interval
Age at surgery (year)				0.2874			
<60	25	4	80.4				
≤60	75	17	72.9				
Gender				0.9729			
M	61	12	77.5				
F	39	9	70.9				
Tumor status at initial visit				0.0001	0.0011		0.068–0.513
Primary wide resection	64	5	89			1	
Primary unplanned resection	36	16	55			5.35	
Depth				0.1162			
Subcutaneous	64	17	70.3				
Deep-sheated	36	4	84.3				
Location				0.1156			
Extremity	77	15	78.4				
Trunk	23	6	39.9				
Histological margin				0.0224	0.0563		0.184–1.023
Positive	28	10	61.5			2.31	
Negative	72	11	79.8			1	
Adjuvant therapy				0.6328			
+	25	6	77.2				
–	75	15	74				
FNCLCC grade <sup>a</sup>							
G1	15	0	100				
G2	44	13		0.1914 <sup>b</sup>			
G3	21	2					

<sup>a</sup>FNCLCC grade was only evaluated for 80 cases.<sup>b</sup>There were no recurrent cases in Grade 1. We analyzed the prognostic value between G2 and G3 for 5-year recurrence-free survival rate.

reported that if non-radical excisions preceded a radical resection, the local failure rate was up to 33%, in comparison to 17% for primary wide resection because of the unusual infiltrative growth of MFS. It is known that MFS is often more extensive than initially suggested by MRI (18). Primary non-wide resection leads to dissemination of tumor cells via hemorrhage and edema beyond the primary site of the tumor. Such hemorrhage and edema after surgery make it more difficult to identify the total extent of the tumor by MRI. These clinical conditions explain the high rate of local recurrence after additional wide resection. Our findings also indicated a higher rate of local recurrence after additional wide resection (54.5%; 6 of 11 cases) than after primary wide resection (7.8%; 5 of 63 cases). As was the case for additional wide

resection, patients who underwent wide resection for recurrent tumors had a high recurrence rate after surgery, presumably for similar reasons. Furthermore, Waters et al. reported that recurrent MFS had a particular propensity for infiltrative growth and poorly defined margins on MRI because it did not show an apparent pseudocapsule in the images, unlike other types of soft tissue sarcomas. Given this infiltrative tendency of recurrent MFS, the full extent of the tumor is difficult to determine or may be overlooked. If the radiologic description of the tumor is limited to its extent, and surgery is planned on that basis, then the resection margins may be inadequate and recurrence imminent (11). These findings highlight the clinical features of MFS that make it different from other types of soft tissue sarcomas, and also indicate the importance of



**Figure 3.** Kaplan–Meier estimated disease-free survival curves for all 100 patients (A) and based on the tumor status (B). Primary unplanned resection at a non-specialized facility ( $P = 0.0401$ , log-rank test) was a significant predictor of recurrence.

primary planned resection with an accurately assessed surgical margin for local control.

In MFS patients who are at a high risk of local recurrence after surgery, it is necessary to consider additional therapeutic approaches such as radiotherapy or chemotherapy. The impact of radiotherapy in an adjuvant setting on relapse-free survival of MFS patients remains to be proven (23,24). In a previous series reported by Karl et al., radiotherapy was given to 28 MFS patients pre- and/or postoperatively, and 11 of them later developed local recurrence, suggesting that radiotherapy had no significant impact (23). Sanfilippo et al. (24) also reported that radiotherapy had apparently only limited value for reducing the risk of local recurrence, although the patients in their series who received radiotherapy already had unfavorable prognostic factors such as a large tumor size, deep location, and high histological grade. In addition, the role of adjuvant chemotherapy in the treatment of soft tissue sarcoma is still debatable (25,26). Also in our present study, radiotherapy (which was used in 16 cases) seemed to be only of limited value for reducing the risk of local recurrence, and adjuvant chemotherapy (which was used in 9 of these patients) proved not to be an independent prognostic factor. Therefore, primary

wide resection for MFS is considered to be the only reliable treatment that can offer local tumor control.

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### Conflict of interest statement

None declared.

### References

- Mentzel T, van den Berg D, Molenaar WM. Myxofibrosarcoma. In: Fletcher CDM, Unni KK, Mertens F, editors. *WHO Classification of Tumors—Pathology and Genetics, Tumors of Soft Tissue and Bone*. Lyon: IARC Press, 2002; 102–3.
- Muramatsu N, Akiyama H. Japan: super-aging society preparing for the future. *Gerontologist* 2011;51:425–32.
- Weiss SW, Enzinger FM. Myxoid variant of malignant fibrous histiocytoma. *Cancer* 1977;39:1672–85.
- Huang HY, LAL P, Qin J, Brennan MF, Antonescu CR. Low-grade myxofibrosarcoma: a clinicopathologic analysis of 49 cases treated at a single institution with simultaneous assessment of the efficacy of 3-tier and 4-tier grading systems. *Human Pathol* 2004;35:612–21.
- Angervall L, Kindblom L, Merck C. Myxofibrosarcoma: a study of 30 cases. *Acta Pathol Microbiol Scand* 1977;85:127–40.
- Mentzel T, Calonje E, Wadden C, et al. Myxofibrosarcoma: clinicopathologic analysis of 75 cases with emphasis on the low-grade variant. *Am J Surg Pathol* 1996;20:391–405.
- Merk C, Angervall L, Kindblom LG, Oden A. Myxofibrosarcoma. A malignant soft tissue tumor of fibroblastic-histiocytic origin. A clinicopathologic and prognostic study of 110 cases using multivariate analysis. *Acta Pathol Microbiol Immunol Scand Suppl* 1983;282:1–40.
- Willems SM, Debiec-Rychter M, Suzhai K, Hoogendoorn PC, Sciort R. Local recurrence of myxofibrosarcoma is associated with increase in tumour grade and cytogenetic aberrations, suggesting a multistep tumour progression model. *Mod Pathol* 2006;19:407–16.
- Lin CN, Chou SC, Li CF, et al. Prognostic factors of myxofibrosarcomas: implications of margin status, tumor necrosis, and mitotic rate on survival. *J Surg Oncol* 2006;93:294–303.
- Rosenberg SA, Tepper J, Glastein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg* 1982;196:305–15.
- Waters B, Panicek DM, Letkowitz RA, Healey JH, Athanasian EA, Brennan MF. Low-grade myxofibrosarcoma: CT and MRI pattern in recurrent disease. *Am J Roentgenol* 2007;188:193–8.
- Manoso MW, Pratt J, Healey JH, Boland PJ, Athanasian EA. Infiltrative MRI pattern and incomplete initial surgery compromise local control of myxofibrosarcoma. *Clin Orthop* 2006;450:89–94.
- Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading system in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol* 1997;15:350–62.
- Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. *Cancer* 2001;91:1914–26.
- Roberta S, Rosalba M, Federica G, et al. Myxofibrosarcoma: prognostic factors and survival in a series of patients treated at a single institution. *Ann Surg Oncol* 2011;18:720–5.

16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
17. Cox DR. Regression models and life tables. *JR Stat Soc* 1972;34:187–220.
18. Kaya M, Wada T, Nagoya S, et al. MRI and histological evaluation of the infiltrative growth pattern of myxofibrosarcoma. *Skelet Radiol* 2008;37:1085–90.
19. Delling G. Diagnostik von knochentumoren. *Verh Dtsch Ges Path* 1998;82:121–32.
20. Steinau HU, Homann HH, Drucke D, Torres A, Soimaru D, Vogt P. Resektionsmethodik und funktionelle Wiederherstellung bei Weichgewebssarkomen der Extremitäten. *Chirurg* 2001;72:501–13.
21. Springfield DS, Rosenberg A. Editorial: biopsy: complicated and risky. *J Bone Joint Surg* 1996;78:639–43.
22. Grimer RJ. Size matters for sarcomas! *Ann R Coll Surg Engl* 2006;88:519–24.
23. Kark EH, Chandrajit PR, Alessandra FN, Qian W, Suzanne G, Elizabeth HB. Recurrence patterns and survival for patients with intermediate- and high-grade myxofibrosarcoma. *J Radiat Oncol* 2010;82:361–7.
24. Sanfilippo R, Miceli R, Grosso F, et al. Myxofibrosarcoma: prognostic factors and survival in a series of patients treated at a single institution. *Ann Surg Oncol* 2011;18:720–5.
25. Frustachi S, Gherlinzoni F, De Paoli A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. *J Clin Oncol* 2001;19:1238–47.
26. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systemic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer* 2008;113:573–81.