Follow-up After Primary Treatment of Soft Tissue Sarcoma of Extremities: Impact of Frequency of Follow-Up Imaging on Disease-Specific Survival

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Background and Objectives: We explored the impact of frequency of surveillance imaging on disease-specific survival (DSS) in patients with extremity soft tissue sarcoma (STS).

Methods: Locoregional imaging (LRI) and chest imaging (CI) were used to detect local recurrence (LR) and distant metastasis (DM), respectively. Relapsing patients were retrospectively assigned to more frequent surveillance (MFS) or less frequent surveillance (LFS) groups, according to the median interval for each follow-up modality. Outcome measures included overall DSS (O-DSS), post-LR DSS, and post-DM DSS.

Results: We assigned 165 patients to three distinct risk groups according to tumor size ($\leq$5 vs. >5 cm), depth (superficial- vs. deep-seated), grade (I vs. II or III), and surgical margin ($\geq$10 vs. <10 mm). Data for 80 patients who relapsed were analyzed. Among 50 high-risk (with all four risk factors) relapsing patients, those in the MFS group for either LRI or CI had better O-DSS (LRI, median 44.07 vs. 27.43 months, $P = 0.008$; CI, median 43.60 vs. 36.93 months, $P = 0.036$), post-LR DSS (median 27.20 vs. 10.63 months, $P = 0.028$) and post-DM DSS (median 13.20 vs. 6.24 months, $P = 0.031$).

Conclusion: More frequent follow-up were associated with improved survival in high-risk relapsing patients with extremity STS by providing greater opportunities for adequate reoperation.

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KEY WORDS: disease-specific survival; radiological imaging; soft tissue sarcoma

INTRODUCTION

Soft tissue sarcomas (STSs) are a heterogeneous group of tumors that arise in the connective tissues. Approximately 50–60% of STSs occur in the extremities [1,2]. Limb-sparing wide excision is the standard primary treatment [3,4], and a 5-year distant metastasis-free survival of over 60% can be achieved [5–9]. However, recurrence remains a major threat and is responsible for treatment failures in extremity STS [10].

Several risk factors associated with recurrence have repeatedly been reported in the literature, including histologic subtype; tumor location, size, depth, and grade; and surgical margin [5–9]. Risk assessment based on these prognostic factors may therefore help to establish an optimal follow-up protocol. Both the National Comprehensive Cancer Network (NCCN) (http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf) and the European Society of Medical Oncology (ESMO) guidelines [11] suggest a more intensive follow-up protocol within the first 2–3 years for high-risk/high-stage patients. In 2 questionnaire surveys, most physicians, although varying greatly in their practice pattern, also generally adopted a risk-stratified surveillance strategy [12–14]. However, there is much debate on the available data regarding the benefit of close surveillance [15–21].

In our previous study, we found that the surgical margin prognostically influences survival in both patients undergoing primary surgery and those undergoing reoperation for relapse, in a cohort of 181 patients with extremity STS [5]. In this study, we aimed to explore the patterns of follow-up practice in this patient cohort. We focused on characterizing the frequencies of different follow-up

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modalities [including locoregional imaging (LRI) and chest imaging] and their association with outcome after primary treatment for STS of the extremity.

PATIENTS AND METHODS

Study Design, Patient Population, and Data Collection

This study, approved by the Institutional Review Board of Taipei Veterans General Hospital, was a retrospective cohort analysis of consecutive adult patients (≥16 years old) with STS of the extremity, who did not have synchronous metastasis or local recurrence (LR) on presentation, and who received primary surgery at Taipei Veterans General Hospital from January 1997 through January 2007. The diagnosis, treatment, and characteristics of the study cohort have been previously described [5]. Four factors were used to categorize patients and identify those at high risk of relapse: tumor size (>5 cm), tumor depth (deep-seated), Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grade (II and III), and tumor margin (<10 mm). These factors have been identified previously as predictors of recurrence [5]. Reoperation was defined as surgery for locally or distally recurrent tumors during follow-up, and the margin status after reoperation was determined microscopically and documented as microscopically negative (R0) or positive (non-R0) [5]. The demographic data and clinical characteristics of the study population were acquired from clinical chart review, tumor registry information, and physicians' records.

Definitions of Follow-Up Modalities and Frequencies of Follow-Up

In this study, we focused on the impact of follow-up frequency on the outcome of patients who suffered from relapse. LRI, which consisted of magnetic resonance imaging (MRI) and/or ultrasonography of the limbs, was used to detect LR. Chest imaging (CI), which included computed tomography (CT) and/or chest roentgenogram (CXR), was used to identify distant metastasis (DM). The investigative imaging or workups of suspicious findings either on clinical or previous radiologic examinations were all excluded, and only imaging studies scheduled for regular follow-up (surveillance imaging) were counted in for calculation of frequency of surveillances. Among relapsing patients, the follow-up intervals (FUIs) for LRI and CI were calculated as the time from completion of all primary therapies to first relapse, divided by the number of follow-ups for that modality. Patients were categorized according to the median length of each FUI into more frequent surveillance (MFS, FUI shorter than the median) or less frequent surveillance (LFS, FUI longer than the median) groups.

Statistical and Survival Analysis

The outcome measures included LR-free survival (LRFS), distant metastasis-free survival (DMFS), overall disease-specific survival (O-DSS), post-LR DSS, and post-DM DSS. LRFS and DMFS were measured from the date of diagnosis to the first LR or distant relapse, respectively. O-DSS, post-LR DSS, and post-DM DSS were measured from the date of diagnosis, LR, and distant metastasis, respectively, to the date of death from cancer or the last follow-up. Survival was estimated using the Kaplan–Meier method, and the log-rank test was used for comparison of survival curves. The Cox proportional hazards model was used for univariate analysis to determine the impact of follow-up frequency on outcome and the prognostic influence of clinicopathological factors. A P-value <0.05 was regarded as statistically significant in two-sided tests. Power analysis was performed for each outcome, and a power value more than 0.8 was regarded as adequate. Data were analyzed using SPSS software (version 17.00, SPSS, Chicago, IL).

RESULTS

Clinicopathological Characteristics and Outcome of Sarcoma Patients

During the study interval, a total of 461 adult STS patients received treatment at our institute. Among them, 265 patients with non-extremity STS and 15 patients with extremity STS who had synchronous metastasis on presentation were excluded. Of the remaining 181 patients, only 165 had detailed follow-up data and were therefore included in further analysis.

The general characteristics of these patients are summarized in Table I. Briefly; the median age was 54 years. Most of the tumors were high grade (76.4%), > 5 cm in size (84.2%), and deep-seated (61.2%). Limb-sparing surgery was the surgical treatment of choice for most of the patients, with only four patients undergoing amputations. Sixty-three patients (38.2%) received radiotherapy, and 66 patients (40.0%) received anthracycline-based chemotherapy. Among the chemotherapy recipients, 7 patients (4.2%) had preoperative chemotherapy alone, 44 (26.7%) had postoperative chemotherapy alone, and 15 (9%) had both.

TABLE I. Characteristics of the 165 Patients Enrolled in This Study

	No.	(%)
Total	165	100
Age		
≥60	72	43.6
<60	93	56.4
Gender		
Male	95	57.6
Female	70	42.4
Histology subtype		
MFH	46	27.9
Liposarcoma	48	29.1
Leiomyosarcoma	16	9.7
Synovial sarcoma	18	10.9
Others	37	22.4
FNCLCC grade		
Grade 1	39	23.6
Grade 2	60	36.4
Grade 3	66	40
Tumor depth		
Superficial	64	38.8
Deep	101	61.2
Tumor size (mm)		
≤5	26	15.8
>5 and ≤15	106	64.2
>15	33	20
Surgical margin		
<10 mm	98	59.4
≥10 mm	67	40.6
Preoperative chemotherapy		
Yes	22	13.3
No	143	86.7
Postoperative chemotherapy		
Yes	59	35.8
No	106	64.2
Radiotherapy		
Yes	63	38.2
No	102	61.8

MFH, malignant fibrous histiocytoma; FNCLCC, French Federation Nationale des Centres de Lutte Contre le Cancer.

The 165 patients were categorized into three distinct risk groups on the basis of tumor size, depth, grade, and margin: low risk (presence of 0–1 risk factors), intermediate risk (presence of 2–3 risk factors), and high risk (presence of all 4 risk factors). As shown in Figure 1, patients in the three different risk groups had significantly different LRFS, DMFS, and O-DSS.

Associations Between Frequency of Different Follow-Up Modalities and Clinicopathological Characteristics of Patients With Recurrence

A total of 80 patients suffered recurrence, with a median follow-up duration of 52.8 months. Twenty-three patients (13.9%) had LR alone, 27 (16.4%) had pulmonary metastasis alone, and 30 (18.2%) had both LR and pulmonary metastasis. The median FUIs for LRI and CI were 25 weeks and 22 weeks, respectively, and patients were evenly divided into MFS and LFS groups accordingly. All 57 pulmonary metastases were identified by either chest X-ray (31, median FUI = 18 weeks) or chest CT scan (26, median FUI = 27 weeks). On the other hand, 16 (30.2%) of the LRs were first identified clinically and only subsequently confirmed by LRI. This confirmatory diagnostic imaging was not counted as surveillance imaging in this study.

The median time to first LRI was 36 days in the MFS group and 29 days in the LFS group ($P = 0.470$). The median time to first CI was 34.5 days in the MFS group and 33.0 days in the LFS group ($P = 0.817$). There was also no significant difference between the LFS and MFS groups regarding the median size of either pulmonary metastases detected by CI (4.0 vs. 3.5 cm, $P = 0.522$) or local recurrent tumors detected by LRI (5.0 vs. 5.0 cm, $P = 0.862$). In clinical practice, physicians may increase follow-up frequency for patients with small pulmonary nodular lesions, which may bias results. However, we did not find a significant difference in the percentage of cases with lung tumor sizes $\leq$1 cm between the MFS and LFS groups (14.8% vs. 23.3%, $P = 0.512$).

The associations between follow-up frequency and clinicopathological factors for each follow-up modality are shown in Table II. The data shows that patients in the MFS groups tended to have higher-grade disease and a greater chance of receiving preoperative chemotherapy.

Impact of Frequencies of Follow-Up Modalities on DSS

Among the 80 relapsing patients, there was no overall difference in O-DSS between the MFS and LFS groups for LRI ($P = 0.279$) or CI ($P = 0.869$). For patients in the low and intermediate risk groups, there was also no difference in O-DSS between the MFS and LFS groups for LRI ($P = 0.785$) or CI ($P = 0.242$). However, among patients with high-risk features (n = 50), those in the MFS groups for LRI or CI had a significantly better O-DSS than those in the LFS groups (LRI, median 44.07 vs. 27.43 months, $P = 0.008$; CI, median 43.60 vs. 36.93 months, $P = 0.036$, Fig. 2).

We then further explored the possible influence of follow-up frequency in relapsing patients with high-risk characteristics. As shown in Figure 3A,B, there was no significant difference in LRFS or DMFS between the MFS and LFS groups for LRI or CI in high-risk patients. However, the power of these analyses were <0.8, probably due to the limited sample size and relatively frequent relapse events. On the other hand, patients suffering LR who were in the MFS group for LRI had a significantly better post-LR DSS than patients in the LFS group (median 27.20 vs. 10.63 months, $P = 0.028$; Fig. 3C). A similar result was seen in patients with lung metastasis (MFS vs. LFS median post-DM DSS: 13.20 vs. 6.24 months, $P = 0.031$, Fig. 3D). We also analyzed the association of follow-up frequency with known prognostic clinicopathological factors that may influence the difference in survival. As shown in Table III, there were no differences regarding histology, recurrent tumor size, number of pulmonary metastases, post-relapse chemotherapy, or radiotherapy between the MFS and LFS groups for either of the two modalities. However, patients in the MFS group, particularly those with lung metastasis, had a greater chance of undergoing reoperation after detection of recurrence (60.9% vs. 15.0%, $P = 0.004$). In addition, patients in the MFS group, especially those with LR, had a better chance of achieving R0 at reoperation (71.4% vs.14.3%, $P = 0.006$; Table III).

DISCUSSION

In this study, we examined the possible impact of the frequency of follow-up LRI and CI on the outcome of patients with localized STS who relapse. Among high-risk (tumor size > 5 cm, deep-seated tumor, FNCLCC grades II and III, and tumor margin < 10 mm) relapsing patients, those in the MFS group had better O-DSS than those in the LFS group (Fig. 2). Further analysis revealed that relapsing patients with high-risk features who were in the MFS groups for either LRI or CI had significantly better post-LR DSS and post-DM DSS than those in the LFS groups, and that these survival advantages may be due to a greater opportunity to receive reoperation and thereby achieve R0 (Table III).

Most physicians believe that routine follow-up for STS is beneficial. In a survey of 318 members of the Society of Surgical Oncology

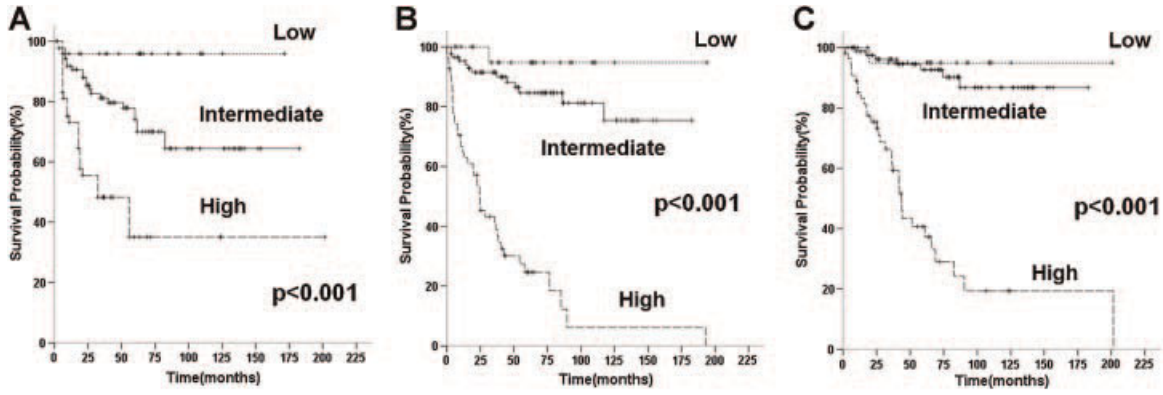

Fig. 1. Survival analysis of 165 patients with different risk features. Significant differences in (**A**) LRFS, (**B**) DMFS, and (**C**) DSS were seen between the low-risk (presence of 0–1 risk factors), intermediate-risk (presence of 2–3 risk factors), and high-risk (presence of all 4 risk factors) groups.

TABLE II. Association of MFS Versus LFS Groups With Clinicopathological Factors in Each Follow-Up Modality Among 80 Relapsing Patients

	LRI			CI		
	MFS (N = 39)	LFS (N = 41)		MFS (N = 40)	LFS (N = 40)	
	N (%)	N (%)	P^a	N (%)	N (%)	P^a
Age						
≥60	19 (48.7)	20 (48.8)	0.996	21 (52.5)	18 (45.0)	0.502
<60	20 (51.3)	21 (51.2)		19 (47.5)	22 (55.0)	
Gender						
Male	25 (64.1)	26 (63.4)	0.949	25 (62.5)	26 (65.0)	0.816
Female	14 (35.9)	15 (36.6)		15 (37.5)	14 (35.0)	
Histology						
MFH	10 (25.6)	17 (41.5)	0.114	15 (37.5)	12 (30.0)	0.130
Liposarcoma	5 (12.8)	7 (17.1)		2 (5.0)	10 (25.0)	
Leiomyosarcoma	6 (15.4)	1 (2.4)		5 (12.5)	2 (5.0)	
Synovial sarcoma	7 (17.9)	3 (7.3)		5 (12.5)	5 (12.5)	
Others	11 (28.2)	13 (31.7)		13 (32.5)	11 (27.5)	
FNCLCC						
Grade 1	1 (2.6)	8 (19.5)	0.052	3 (7.5)	6 (15.0)	0.256
Grade 2	11 (28.2)	11 (26.8)		9 (22.5)	13 (32.5)	
Grade 3	27 (69.2)	22 (53.7)		28 (70.0)	21 (52.5)	
Tumor size(cm)						
≤5	0 (0)	5 (12.2)	0.078	3 (7.5)	2 (5.0)	0.792
>5 and ≤15	31 (79.5)	28 (68.3)		30 (75.0)	29 (72.5)	
>15	8 (20.5)	8 (19.5)		7 (17.5)	9 (22.5)	
Depth						
Superficial	8 (20.5)	12 (29.3)	0.366	8 (20.0)	12 (30.0)	0.302
Deep	31 (79.5)	29 (70.7)		32 (80.0)	28 (70.0)	
Surgical margin						
<10 mm	35 (89.7)	36 (87.8)	1.000	38 (95.0)	33 (82.5)	0.154
≥10 mm	4 (10.3)	5 (12.2)		2 (5.0)	7 (17.5)	
Risk group						
Low-intermediate	11 (28.2)	19 (46.3)	0.094	12 (30.0)	18 (45.0)	0.166
High	28 (71.8)	22 (53.7)		28 (70.0)	22 (55.0)	
Preoperative C/T						
Yes	8 (20.5)	1 (2.4)	0.013*	6 (15.0)	3 (7.5)	0.481
No	31 (79.5)	40 (97.6)		34 (85.0)	37 (92.5)	
Postoperative C/T						
Yes	18 (46.2)	12 (29.3)	0.119	19 (47.5)	11 (27.5)	0.065
No	21 (53.8)	29 (70.7)		21 (52.5)	29 (72.5)	
Radiotherapy						
Yes	21 (53.8)	14 (34.1)	0.076	18 (45.0)	17 (42.5)	0.822
No	18 (46.2)	27 (65.9)		22 (55.0)	23 (57.5)	

MFS, more frequent follow-up; LFS, less frequent follow-up; LRI, locoregional regional imaging; CI, chest imaging; MFH, malignant fibrous histiocytoma; FNCLCC, French Federation Nationale des Centres de Lutte Contre le Cancer; C/T, chemotherapy.

[a]Chi square test comparing MFS and LFS groups within each follow-up modality.

*$P < 0.05$.

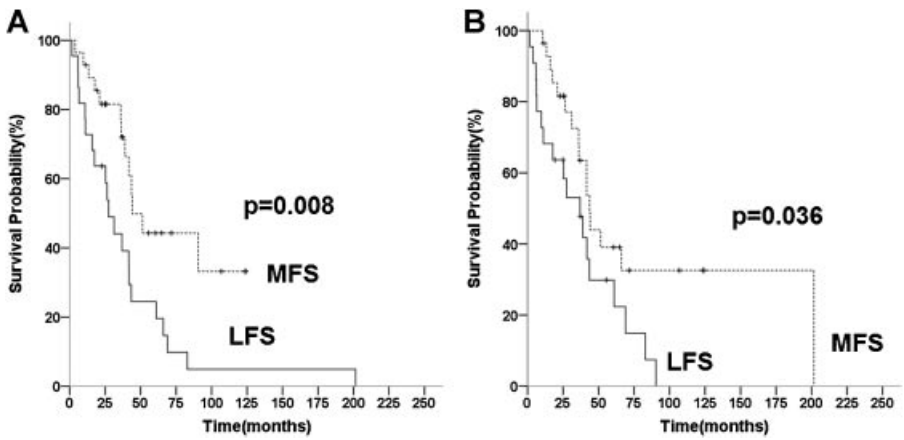

Fig. 2. O-DSS in all relapsing patients with high-risk features (n = 50). Patients in the high-frequency follow-up group (MFS, dotted line) had a better O-DSS than patients in the low-frequency follow-up group (LFS, solid line) for both (**A**) LRI and (**B**) CI.

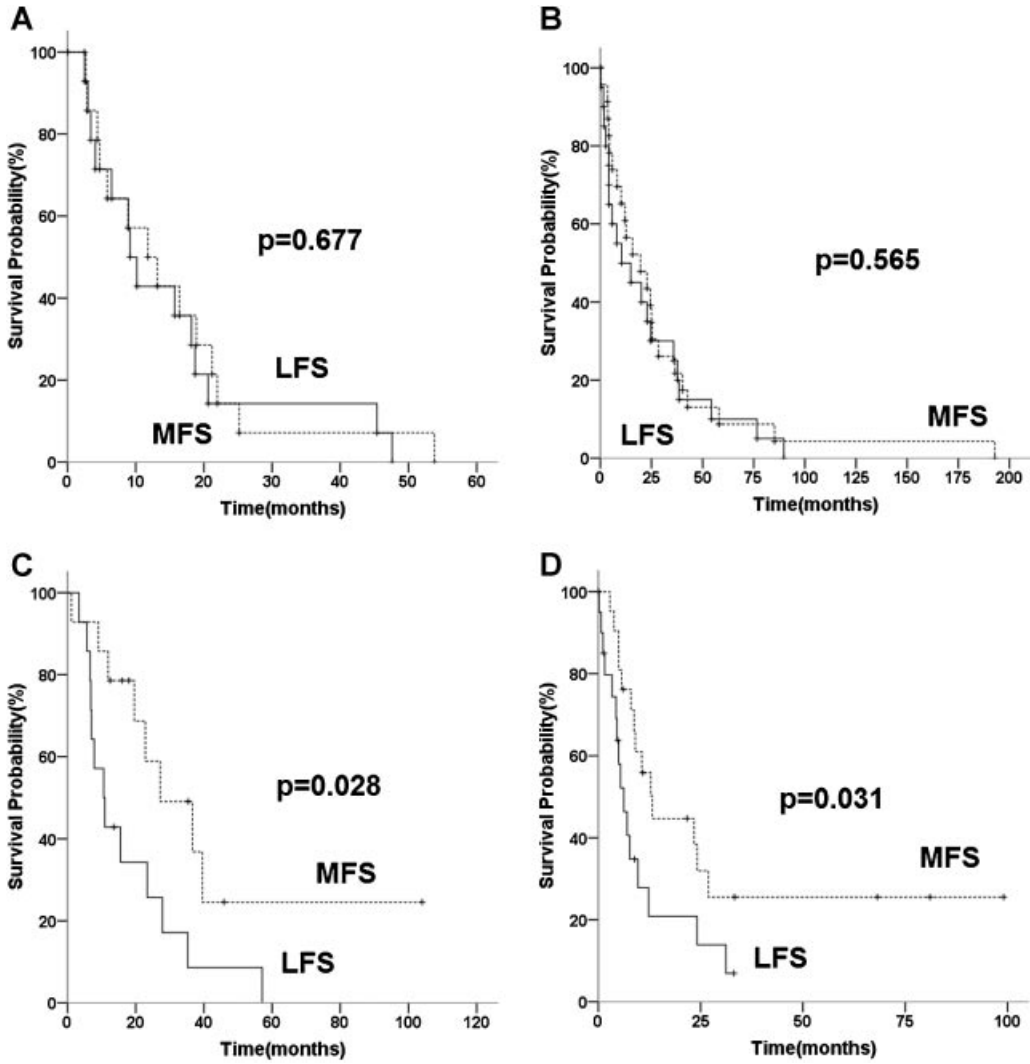

Fig. 3. Survival analysis of patients with high-risk characteristics suffering from local recurrence (LR, n = 28) or distant lung metastasis (DM, n = 43). **A**: There was no significant difference in LRFS between patients with LR detected by LRI in the high-frequency follow-up (MFS, n = 14) and low-frequency follow-up (LFS, n = 14) groups. **B**: Similarly, there was no significant difference in DMFS between patients with DM identified by chest imaging in the MFS (n = 23) and LFS (n = 20) groups. **C**: Patients suffering LR in the MFS group had a significantly better post-LR DSS than those in the LFS group. **D**: Similarly, patients suffering lung metastasis in the MFS group had a significantly better post-DM DSS than those in the LFS group.

(SSO) regarding surveillance strategies for STS, 74% believed that routine follow-up examinations would lead to early detection of recurrence and subsequent cure [12]. In another questionnaire study, 83% of respondents thought that regular follow-up was of benefit for patients with STS [13]. However, most did not think that there was substantial evidence in the literature supporting this belief [12], and their own clinical practice pattern varied greatly [12,13]. Therefore, the survival benefit of routine surveillance requires further confirmation.

Oncologists often adopt a risk-stratified surveillance strategy for STS. The SSO survey showed that risk factors such as tumor grade or size might impact upon the follow-up intensity. Most physicians almost never use chest CT for patients with low-grade tumors, and use it fairly infrequently for those with high-grade tumors [14]. Two consecutive studies from The University of Texas MD Anderson Cancer Center evaluated the cost-effectiveness of routine chest CT scan in detecting lung metastasis of extremity STS. Their studies showed that routine use of chest CT in T1 disease is not cost-effective due to the relatively low yield [16]. However, for T2 tumors, the yield of chest CT was higher when used routinely than when used selectively based on chest X-ray findings (19.2% vs. 16%), and routine chest CT was most cost-effective in patients with high-grade lesions or extremity lesions [17]. These studies revealed that it is worthwhile, in terms of cost-effectiveness, to employ expensive chest CT in high-risk STS patients.

In this study, our goal was to determine the survival benefit of frequent surveillance imaging for localized STS in a risk-stratified manner. We first created our own recurrence-predicting categorization system based on the four risk factors identified in our previous study (tumor size, depth, grade, and margin) [5]. These were similar to other reports [6–9], and our system worked well (Fig. 1).

Next, we divided patients into MFS and LFS groups according to the median value of follow-up for each modality. One could argue that this approach may obscure the fact that some patients may have

TABLE III. Association of Recurrence Characteristics With Frequency of Follow-Up With Locoregional and Chest Imaging in High Risk Patients With Recurrence

	LR detected by LRI			Lung metastasis detected by CI		
	MFS (N = 14)	LFS (N = 14)		MFS (N = 23)	LFS (N = 20)	
	N (%)	N (%)	P^a	N (%)	N (%)	P^a
Histology						
MFH	7 (50.0)	9 (64.3)	0.704	12 (52.2)	8 (40.0)	0.544
Non-MFH	7 (50.0)	5 (35.7)		11 (47.8)	12 (60.0)	
Recurrent tumor size						
<5 cm	4 (28.6)	4 (28.6)	1.000	—	—	—
≥5 cm	10 (71.4)	10 (71.4)		—	—	
Pulmonary tumor no.						
1	—	—	—	3 (13.0)	6 (30.0)	0.366
2–3	—	—		7 (30.4)	4 (20.0)	
>3	—	—		13 (56.5)	10 (50.0)	
Post relapse chemotherapy						
Yes	7 (50.0)	5 (35.7)	0.704	15 (65.2)	14 (70.0)	1.000
No	7 (50.0)	9 (64.3)		8 (34.8)	6 (30.0)	
Post LR radiotherapy						
Yes	3 (21.4)	1 (7.1)	0.596	2 (8.7)	2 (10.0)	1.000
No	11 (78.6)	13 (92.9)		21 (91.3)	18 (90.0)	
Reoperation						
Yes	12 (85.7)	8 (57.1)	0.209	14 (60.9)	3 (15.0)	0.004*
No	2 (14.3)	6 (42.9)		9 (39.1)	17 (85.0)	
R0 resection						
Yes	10 (71.4)	2 (14.3)	0.006*	4 (17.4)	3 (15.0)	0.832
No	4 (28.6)	12 (85.7)		19 (82.6)	17 (85.0)	

MFS, more frequent follow-up; LFS, less frequent follow-up; LRI, locoregional imaging; CI, chest imaging; MFH, malignant fibrous histiocytoma.
[a]Chi square test comparing MFS and LFS groups within each follow-up modality.
*$P < 0.05$.

a relatively long interval before the first follow-up, but many subsequent follow-up visits with short intervening periods. However, although an individualized surveillance approach was allowed based on physicians' preferences, which may result in variable FUIs, we still applied a standard follow-up protocol, as most guidelines suggest, preventing these extreme situations. In addition, as shown in the results, there were no significant differences in the times to first follow-up between the different surveillance groups for either modality. Consequently, we believe our approach should provide similar results to a weighted approach.

Using these categorization systems for risk of recurrence and surveillance frequency, we then analyzed the associations between frequency of follow-up imaging and patients' characteristics. Patients in the MFS group tended to have high-grade tumors and a greater chance of receiving preoperative chemotherapy. This was consistent with the SSO survey, which indicated that the severity of the patient's disease may increase the follow-up intensity [14]. We then explored the impact of follow-up frequency on DSS, and found no difference in DSS between the MFS and LFS groups in all patients or in patients with low or intermediate risk features. However, for high-risk patients, the MFS group had a significantly better O-DSS than the LFS group (Fig. 2). This is one of the few studies to demonstrate the survival benefit of frequent follow-up imaging for localized extremity STS.

Next, we studied the possible factors causing this survival benefit. We found that relapsing patients with all four risk factors who received MFS for either LRI or CI had significantly better post-LR DSS or post-DM DSS than the equivalent LFS group (Fig. 3). By comparing the characteristics of these two groups, we found that patients in the MFS group had a greater opportunity to receive reoperation after recurrence was detected and had a better chance of achieving R0 at reoperation (Table III). These results suggested that the survival benefit of more frequent follow-up among relapsing patients in the high-risk group could be attributed to a greater chance of tumor resection with a safe margin.

This study, however, is limited by its retrospective design, which may result in differences in factors such as disease characteristics, primary treatments, follow-up decisions, and post-recurrence management between the MFS and LFS groups, and therefore bias the analysis. This study only provides evidence to show that high-risk relapsing patients receiving a more intensive surveillance may have a better DSS, based on our subjective definitions of high risk and intensive surveillance. The optimal follow-up frequency for patients with extremity STS remains to be determined and requires further investigation in future studies. Whether a small 1–2 month difference in the interval between each imaging follow-up would affect outcome remains unclear. Additionally, the individual contribution of each imaging modality, such as ultrasonography, MRI, CXR, or CT, was not delineated. The current study also did not explore the cost-effectiveness of close surveillance. Moreover, owing to the small sample size, the statistical power might not have been sufficient to reach significance for small, but potentially relevant, differences between groups; for example, in the outcome analyses and the association analyses shown in Tables II and III.

It is possible that smaller/less suspicious recurrences will require more imaging to clarify their malignant or benign status, whereas a larger recurrence can be clearly detected with a single imaging modality, which may skew the conclusion toward a better outcome for MFS groups. In order to minimize this potential bias, only imaging studies scheduled for regular follow-up (surveillance imaging) were counted in for calculation of frequency of surveillances. Moreover, we did not find any significant difference in the median size of LRs or pulmonary metastases or in the proportion of lung metastasis cases with tumor sizes ≤1 cm between MFS and LFS groups.

Another issue is that patients with indeterminate pulmonary lesions that are eventually proven to be benign might have received more frequent follow-up imaging. Nonetheless, all patients with chest recurrence (n = 57) in this study were clinically or pathologically proven cases of metastasis.

One may argue that the differences of survival could be lead-time bias of surveillances. One way to evaluate this issue is to look at the actual long-term survivors. For high-risk relapsing patients, the percentage of actual 4-year survivors were 0% (0/20) and 13% (3/23), respectively, in the LFS and MFS groups of CI, and were 0% (0/14) and 14.3% (2/14), respectively, in the LFS and MFS groups of LRI. In addition, if lead-time bias exists, the improvement in post-recurrence survival occurs at the expense of primary progression-free survival with no overall survival benefit [22]. However, our study has demonstrated significant better O-DSS in MFS than LFS groups (Fig. 2). Moreover, further analysis showed that the LRFS and DMFS were similar in MFS and LFS groups of both modalities (Fig. 3A,B), and O-DSS benefits in MFS groups were most likely due to increased post-LR DSS and post-DM DSS (Fig. 3C,D). In summary, it suggests that the survival benefit associated with more frequent follow-up were not likely due to lead-time bias.

In conclusion, our findings suggest that more frequent follow-up using LRI or CI is associated with better DSS in high-risk extremity STS patients who experience relapse after primary treatment. These results provide evidence in favor of a close surveillance strategy for patients with high-risk features, as most guidelines suggest. Moreover, our analysis indicated that the survival benefit of intense follow-up in this specific subgroup of patients may be attributable to an increased opportunity for surgical management (reoperation) for relapsed lesions.

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