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MRI surveillance for local recurrence in extremity soft tissue sarcoma☆

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ABSTRACT

Introduction: The role of MRI in surveillance for local recurrence (LR) remains uncertain in extremity soft tissue sarcoma (STS). The aims of this study were 1) to examine the usefulness of MRI in detecting LR, 2) to identify the characteristics of LR detected by MRI, and 3) to examine whether MRI surveillance is associated with oncologic outcome.

Materials and Methods: 477 patients who had regular surveillance for LR after surgery for extremity STS were reviewed. Surveillance was performed by routine MRI in 325 patients or other imaging modalities in 152 patients.

Results: The rate of MRI-detected LR, defined as clinically undetectable LR identified on MRI, was 10.5% in the MRI surveillance cohort. The detection rates of MRI-detected LR were significantly higher in the patients with high risk of LR. MRI-detected LRs were more commonly located in the thigh or buttock ($p = 0.005$), were smaller ($p = 0.001$) and had LRs without mass formation ($p = 0.007$) than non-MRI-detected LRs. On Kaplan-Meier analysis, patients with MRI-detected LR tended to have better post-LR survival ($p = 0.104$).

Conclusion: Routine MRI surveillance can detect a significant number of clinically undetectable LRs in extremity STS especially for LRs in the thigh or buttock, small LRs or LRs without mass formation.

Introduction

Local recurrence (LR) has been associated with increased incidence of distant metastasis and decreased survival in extremity soft tissue sarcoma (STS) [1–3]. Early detection and surgical resection of LR is usually recommended to achieve the best possible oncologic outcome and minimize functional morbidity. Thus, effective surveillance strategy for LR after surgery is needed in extremity STS.

MRI is the most effective modality for evaluation of STS because of its high soft tissue contrast and its capability in imaging superficial and deep soft tissues [4–6]. MRI is routinely used for staging and preoperative planning of extremity STS [7]. However, the role of MRI in surveillance for early detection of LR remains uncertain in extremity STS [8–13]. Moreover, there has been no report about the effect of MRI surveillance on oncologic outcome in extremity STS.

With this regard, this study was performed 1) to examine the usefulness of MRI in detecting LR, 2) to identify the characteristics of LRs detected by MRI, and 3) to examine whether MRI surveillance is associated with oncologic outcome.

Materials and methods

Patients

From the retrospectively collected institutional database, 496 consecutive patients who underwent regular surveillance after surgery for STS of the extremities from 2000 to 2015 were reviewed. The institutional review board of our institute approved

☆ This study was performed at Department of Orthopaedic Surgery, Seoul National University Hospital, Seoul, South Korea.

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this study. Of the 496 patients, 15 patients without sufficient medical records and 4 patients who underwent debulking surgery were excluded, which left 477 patients for analyses.

Surveillance for LR

For surveillance of LR after surgery, patients were followed up every 3–4 months for the 2 years, every 6 months for the next 3 years, and annually after that. The interval of the follow-ups was adjusted based on the risk of LR, such as histologic subtype, histologic grade, or resection margin. At each follow-up, clinical examination and diagnostic imaging were performed.

As for the imaging modality, ultrasonography was primarily used in the early part of our series from 2000 to 2006. Since 2006, the majority of patients undergoing surgery for extremity STS have undergone MRI surveillance. During this period, ultrasonography was selectively offered if the patient had a superficial lesion. MRI was performed when LR was diagnosed in patients who did not undergo MRI surveillance.

All patients underwent MRI examination with a 1.5- or 3-T MR scanner. Spin-echo T1-weighted images, fast spin-echo T2-weighted images (T2WI) with or without fat-suppression, and gadolinium-enhanced T1-weighted images with fat suppression were available in all patients. Gadolinium-enhanced T1-weighted images were obtained in at least two orthogonal planes.

On MRI, LR was suspected when there was a newly appearing discrete lesion of increased signal intensity on T2WI, with or without contour deformity in adjacent tissues. Areas of low to medium signal intensity on both T1 and T2-weighted images without discrete configuration, whether or not these areas were well defined, were considered postsurgical changes without LR. The possibility of LR was excluded if no or minimal diffuse enhancement occurred after administration of gadolinium [14,15]. LR was diagnosed when the suspected lesion became larger and more discrete on follow-up MRI. Diagnosis of LR was determined by the discussion of two senior orthopaedic oncologists (HSK and IH) and two experienced musculoskeletal radiologists (HSH and JYC). All suspicious LRs were either resected or underwent core needle biopsy for histological examination. LR was defined as the first recurrence of disease at the site of the primary tumor, occurring after at least 3 months after surgery.

Characteristics of MRI-detected LR

To identify the clinicopathologic characteristics of the MRI-detected LRs, patients with LR were divided into MRI-detected LR group and non-MRI-detected LR group. MRI-detected LR group included the patients whose LRs were clinically undetectable and were identified by MRI (Supplementary Fig. 1). Non-MRI-detected LR group included the patients with LRs were clinically detectable either by symptoms or physical examinations or with LRs detected by imaging modalities other than MRI, mainly ultrasonography (Supplementary Fig. 1) [11]. Of note, symptomatic LRs in patients on MRI surveillance were classified as non-MRI-detected LRs. The two groups were compared with regard to the following characteristics: (1) patient demographics, (2) STS characteristics, (3) treatment, and (4) LR characteristics.

For patient demographics, age, gender, and presentation status were investigated. The mean age at the time of surgery was 46.2 years (range 1.0–85.0) (Table 1). Two hundred and fifteen patients (45%) were female and 262 patients (55%) were male. One hundred and eight patients (22%) presented after an unplanned removal of an STS and 72 patients (15%) presented with locally recurrent tumors. Thirty-four patients (7%) had metastatic disease at the time of diagnosis of STS.

Table 1
Characteristics of study population.

Characteristics	Value
Age, years [mean (range)]	46.2 (1.0–85.0)
Gender	
Female	215 (45%)
Male	262 (55%)
Follow-up duration, months [mean (range)]	48.6 (6–196)
Primary tumor size, cm [mean (range)]	6.3 (0.2–36.0)
Presentation	
Fresh	297 (63%)
Unplanned excision	108 (22%)
Recurred	72 (15%)
Location	
Thigh or buttock	247 (52%)
Knee or lower leg	103 (22%)
Shoulder or upper arm	69 (14%)
Elbow or forearm	41 (9%)
Trunk wall	17 (3%)
Depth	
Superficial	69 (15%)
Deep	408 (85%)
Histological type	
Undifferentiated pleomorphic sarcoma	95 (20%)
Liposarcoma	59 (12%)
Synovial sarcoma	57 (12%)
Myxofibrosarcoma	40 (8%)
Leiomyosarcoma	24 (5%)
Others	202 (43%)
FNCLCC grade	
1	109 (23%)
2	152 (32%)
3	180 (38%)
Undetermined	36 (7%)
Pathologic margin	
Negative	412 (86%)
Positive	65 (14%)
Radiation therapy	
Not done	254 (53%)
Done	223 (47%)
Radiation therapy dose, Gy [mean (±SD)]	58.4 (±14.3)
Chemotherapy	
Not done	381 (80%)
Done	96 (20%)
Metastasis at diagnosis	
Absent	443 (93%)
Present at diagnosis	34 (7%)

Data are expressed as *n* (%) unless otherwise specified.
FNCLCC, Federation Nationale des Centers de Lutte Contre le Cancer; SD, standard deviation.

For STS characteristics, tumor location, histological type, histologic grade, tumor size, and tumor depth were investigated. The most common locations of tumors were thigh (n = 207, 43%), lower leg (n = 59, 12%) and buttock (n = 40, 8%). Four hundred and eight tumors (85%) were deep-seated and 69 (15%) were superficial. The most common histologic types were undifferentiated pleomorphic sarcoma (UPS, n = 95, 20%), liposarcoma (n = 59, 12%), synovial sarcoma (n = 57, 12%), and myxofibrosarcoma (n = 40, 8%). As for histologic grading of the primary tumor, there were 109 grade 1 (23%), 152 grade 2 (32%), and 180 grade 3 (38%) tumors according to the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) classification system [16]. Mean size of the primary tumor, defined as the largest diameter on the pathology report or preoperative MRI, was 6.3 cm (range, 0.2–36.0) (Table 1).

For treatment of STS, tumors were removed with a wide margin in 395 cases (82%), a marginal margin in 79 cases (17%) and an intralesional margin in 3 cases (1%). Histologically negative margins were achieved in 412 patients (86%). Postoperative radiation therapy was administered in 223 patients (47%), all of whom received external beam radiation with the mean dose of 58.4Gy (±14.3Gy).

Postoperative chemotherapy was administered in 96 patients (20%) (Table 1).

Of the 477 patients who underwent regular surveillance for LR, 94 LRs (20%) were detected. All LRs were confirmed by pathologic assessment. Time to LR was recorded as the time from resection of the primary tumor until the development of first LR. Mean time to LR was 19.7 months (range, 3.0–150.0). Of the 94 patients with LRs, 73 patients did not have metastases prior to LR. Of the 73, 4 patients developed concomitant metastases with LR. All 4 had high grade STS (2 patients with FNCLCC grade 2 and 2 patients with FNCLCC grade 3). Morphology of LR was categorized as mass-forming LR or non-mass-forming LR based on MRI findings. MRI was performed for all LR cases. Mass-forming LR was defined as LRs forming discrete mass of any shape. Non-mass-forming LR was defined as a diffuse enhancement or tapered thick fascial enhancement without discrete nodular mass inside of the enhancing area (Fig. 1). Mean number of LRs was 1.5 (range, 1 to 7) and 44 of 94 patients (46.8%) had more than one episode of LR.

MRI surveillance for LR and oncologic outcome

To examine whether MRI surveillance for LR is associated with patient survival in STS, patients with LR (n = 94) were divided into two groups on the basis of mode of LR detection: MRI-detected LR (n = 34) and non-MRI-detected LR (n = 60). Oncologic outcome was analyzed using disease-specific death as the clinical endpoint. The time to disease-specific death was calculated from the date of detection of local recurrence to the date when the disease-specific death was first recorded. Deaths confirmed to be due to STS were treated as an endpoint for disease-specific survival, and deaths due

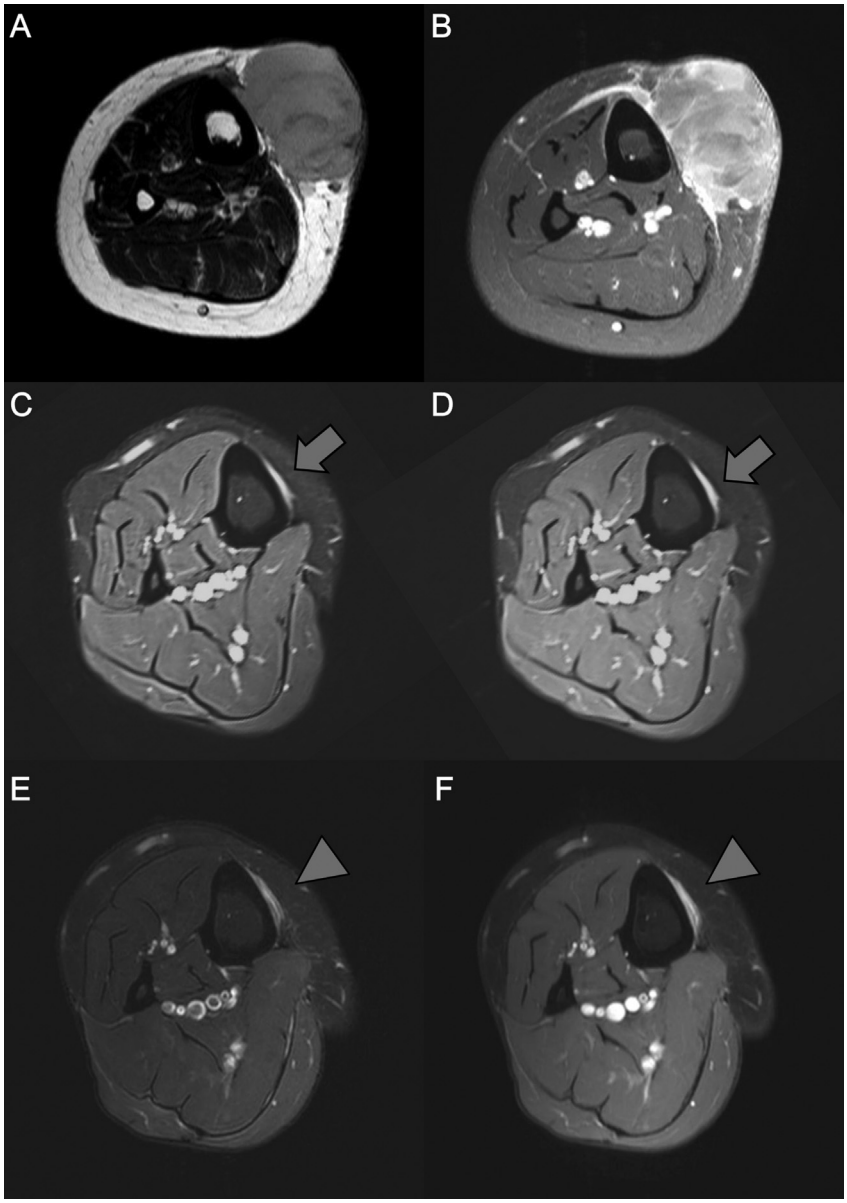

Fig. 1. Representative case of MRI-detected local recurrence. A 44-year-old woman with undifferentiated pleomorphic sarcoma in the pretibial area was diagnosed of local recurrence with non-mass forming morphology. A and B, Preoperative axial MRI shows a large soft tissue mass in the pretibial area with deep fascial thickening adjacent to the main mass. The soft tissue defect was reconstructed with a sural fasciocutaneous flap. C and D, At postoperative 32 months, thick curvilinear T2 hyper-intense lesion was observed (arrows). E and F, On follow-up MRI 3 month later, the lesion became thicker (arrowheads) and was confirmed as local recurrence by biopsy. A, C, E: T2-weighted images, B, D, F: Gadolinium-enhanced T1-weighted images.

to other causes were regarded as censored observations. To address the lead time bias that was caused by early detection of local recurrence by MRI, disease-specific survival was investigated. For the analysis of disease-specific survival, the survival time was calculated from the date of the diagnosis of the primary tumor to the date when the disease-specific death was first recorded. Actuarial survival curves were constructed using the Kaplan-Meier method.

Statistics

The significance of differences between frequencies was calculated using chi-square or Fisher's exact tests. Differences in means were evaluated using the independent *t*-test. Differences between Kaplan-Meier survival curves were evaluated using the log-rank test. Statistical analysis was performed using SPSS v.22.0 software (IBM Inc., Armonk, New York). All reported P values were two-tailed and P values of <0.05 were deemed statistically significant.

Results

MRI surveillance and MRI-detected LR

In 325 patients of the MRI surveillance cohort, a total of 2391 MRIs was performed. The mean number of MRI per patient was 7.4 (range 1–19). In 309 patients who had more than 2 surveillance MRIs, the mean interval between MRIs was 5.9 months (range 2–12). Of the 325 patients on MRI surveillance, 56 patients (17.2%) developed LR. Of the 56 LRs, 34 LRs (61%) were MRI-detected LRs. The remaining 22 LRs (39%) were detected by symptoms such as palpable mass or pain and then confirmed by MRI. The rate of MRI-detected LR of the MRI surveillance cohort was 10.5% (34/325) (Supplementary Table 1).

Further analyses of MRI-detected LR rate based on the clinicopathologic characteristics were performed to examine which patients would benefit from MRI surveillance. Patients with the following characteristics had significantly higher MRI-detected LR rate: presentation with locally recurrent tumors ($p = 0.014$), aged over 40 years ($p = 0.007$), FNCLCC grade 3 tumors ($p = 0.035$) or tumors located in the buttock or thigh ($p = 0.033$) (Table 2).

Table 2
Rate of MRI-detected LR by clinicopathologic characteristics.

Characteristics	MRI-detected LR rate	p value
Overall	11% (34/325)	
Age		0.007*
≤40	5% (6/127)	
>40	14% (28/198)	
Sex		0.643
Female	10% (14/146)	
Male	11% (20/179)	
Presentation		0.014*
Fresh	8% (16/213)	
Unplanned excision	13% (9/72)	
Reccured	23% (9/40)	
Primary tumor size		0.774
≤5 cm	11% (13/117)	
>5 cm	10% (21/208)	
Primary tumor depth		0.586
Superficial	8% (4/48)	
Deep	11% (30/277)	
Tumor location		0.033*
Thigh	9% (15/158)	
Buttock	21% (7/33)	
Others	9% (12/134)	
FNCLCC grade		0.035*
1 or 2	8% (14/186)	
3	14% (20/139)	
Pathologic margin		0.536
Negative	10% (30/295)	
Positive	13% (4/30)	
Radiation therapy		0.195
Done	8% (14/168)	
Not done	13% (20/157)	
Tumor type		0.348
Undifferentiated pleomorphic sarcoma	14% (8/51)	
Leiomyosarcoma	12% (2/15)	
Liposarcoma	11% (5/40)	
Synovial sarcoma	9% (3/32)	
Myxofibrosarcoma	6% (2/33)	
Others	9% (14/150)	

LR, local recurrence.
*Statistically significant.

Characteristics of MRI-detected LR

In 477 patients who underwent regular surveillance for LR, 94 LRs were detected. Of the 94 LRs, 34 LRs were MRI-detected LRs. The remaining non-MRI detected LRs ($n = 60$) were detected either by clinical examinations ($n = 33$) or by ultrasonography ($n = 27$). When MRI-detected LRs were compared with non-MRI detected LRs, the size of the MRI-detected LR was significantly smaller than that of the non-MRI detected LR (2.3 ± 1.3 cm vs. 4.0 ± 3.4 cm, $p = 0.001$) (Fig. 2). MRI-detected LRs were more likely to be located in the thigh or buttock ($p = 0.005$) (Fig. 2). In addition, MRI-detected LRs were more likely to show non-mass-forming morphology on MRI ($p = 0.007$) (Fig. 1). MRI-detected LRs were detected earlier, as the time from surgery to LR tended to be shorter in MRI-detected LR than non-MRI detected LRs (15.5 ± 14.9 months vs. 22.0 ± 29.0 months, $p = 0.157$) (Table 3).

MRI surveillance for LR and survival

As for the survival outcome, seven patients (21%) with MRI-detected LR died of disease whereas 28 patients (47%) with non-MRI-detected LR died of disease. On Kaplan-Meier analysis, patients with MRI-detected LR tended to have better post-LR survival, however the difference between curves was not significant ($p = 0.104$) (Fig. 3A). For the disease-specific survival, patients with MRI-detected LR showed a trend toward a better survival, however the difference between curves was not significant ($p = 0.072$) (Fig. 3B).

Discussion

Due to its high soft tissue contrast and capability in imaging superficial and deep soft tissues, MRI is being increasingly performed for surveillance of LR in extremity STS. However, the role of MRI in surveillance for LR remains controversial in extremity STS. This study showed that MRI can detect a significant number of clinically undetectable LRs in extremity STS and is especially useful for detecting LRs in the thigh or buttock, small LRs or LRs without mass formation. In survival analysis, the MRI surveillance cohort tended to have better post-LR survival. However the survival difference between cohorts was not significant ($p = 0.104$).

Conflicting results have been reported regarding the usefulness of MRI in detecting clinically undetectable LRs in STS. In comparison to the detection rate of 11% (34/325) in this study, studies by Cheney et al. [11] and Labarre et al. [15], reported the detection rate of only 1% (1/114) and 2% (2/124) respectively, suggesting the limited role of MRI surveillance in extremity STS. The exclusion of patients with high risk of LR in these studies, such as patients with recurrent disease, metastasis at diagnosis or histologic types such as angiosarcoma, might have contributed to this finding. In agreement with this study, Watts et al. reported detection rate of 12% (6/

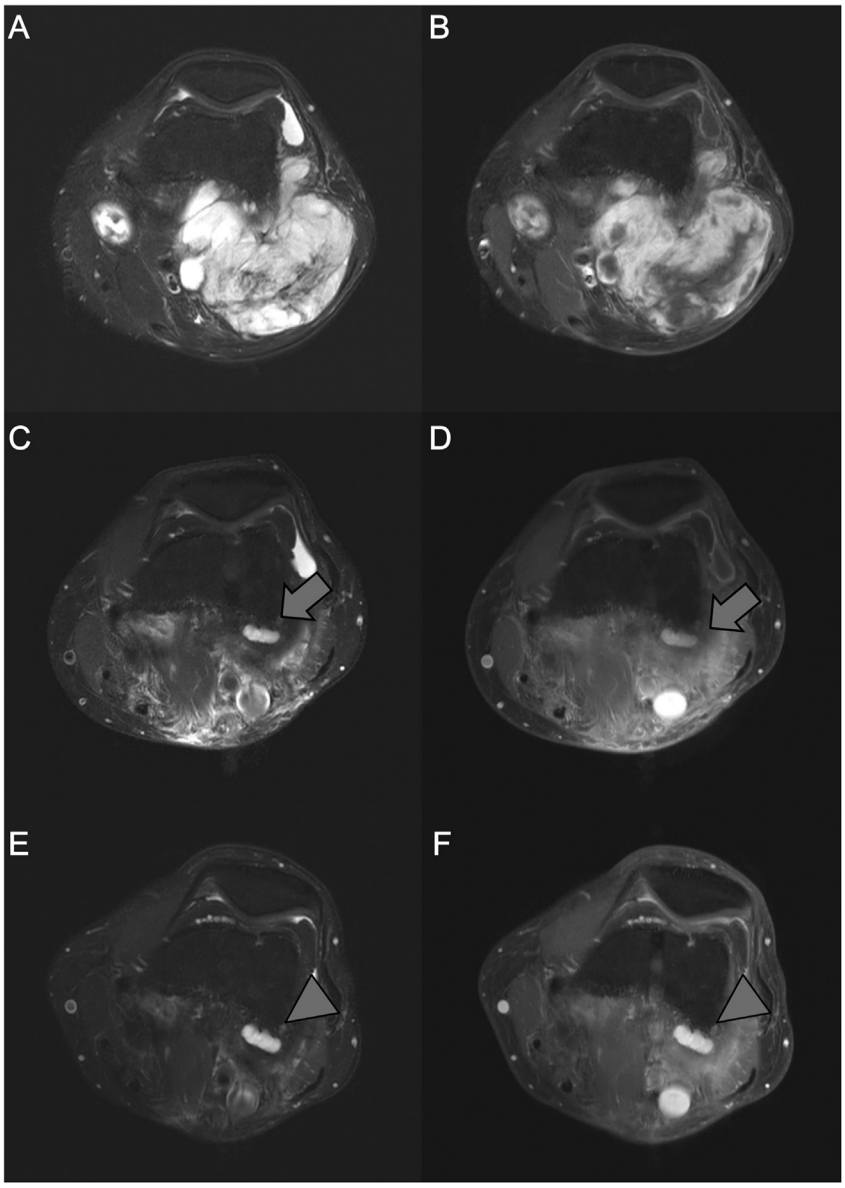

Fig. 2. Representative case of MRI-detected local recurrence. A 55-year-old man with extraskeletal myxoid chondrosarcoma in the posterior thigh was diagnosed of small local recurrence. A and B, Preoperative axial MRI shows a large multi-lobulated soft tissue mass in posterior thigh. C and D, At postoperative 12 months, a small T2 hyper-intense enhancing lesion was detected at the lateral supracondylar area (arrows). E and F, On follow-up MRI 3 month later, the lesion increased in size (arrowheads) and was confirmed as local recurrence by biopsy. A, C, E: T2-weighted images, B, D, F: Gadolinium-enhanced T1-weighted images.

47) in unselected patients with extremity STS [10]. The authors believe that this study is the largest study to date encompassing a broad spectrum of extremity STS patients.

Patients with MRI-detected LR showed a trend toward better post-LR survival than those with non-MRI-detected LR. The treatment of LR did not differ between the MRI-detected LR cohort and non-MRI-detected LR cohort as the proportion of patients undergoing curative surgery for LR were similar (28/34, 82% and 49/60, 82% respectively, $p = 0.934$). Seventeen patients did not undergo surgery because of the presence of lung metastases ($n = 11$), unresectable LR ($n = 3$) or patient refusal ($n = 3$). Of note, all 3 unresectable LRs were non-MRI-detected LRs. The administration of chemotherapy (14/34, 41% and 32/60, 53% respectively, $p = 0.257$) or radiation therapy (14/34, 41% and 34/60, 57% respectively, $p = 0.149$) for LR was not different between the two groups. We postulate that the ability of MRI to find LRs at an early stage, by detecting deep-seated or non-mass forming morphology, may have resulted in treating LRs with favorable biology, resulting in better survival in the MRI-detected LR cohort. Further analyses in a larger group of patients in a prospective setting are warranted to verify whether MRI surveillance for LR translates into better survival.

In 325 patients whose surveillance for LR was performed by MRI, 60 patients developed suspicious LRs on MRI. Of the 60 patients, 56 patients (93.3%) were found to have histologically confirmed LRs. MRI surveillance showed a sensitivity of 100.0%, a specificity of 98.5%, a positive predictive value (PPV) of 93.3% and a negative predictive value of 100%, with an overall diagnostic

Table 3
Comparison between MRI-detected LR and non-MRI detected LR.

Characteristic	MRI-detected LR	Non-MRI-detected LR	p value
Patient demographics			
Patients	34 (36%)	60 (64%)	
Age, years [mean (±SD)]	53.0 (±20.3)	49.3 (±19.1)	0.374
Sex			0.719
Female	14 (41%)	27 (45%)	
Male	20 (59%)	33 (55%)	
Primary tumor chracteristics			
Presentation			0.502
Fresh	16 (46%)	27 (45%)	
Unplanned excision	9 (27%)	11 (18%)	
Recurred	9 (27%)	22 (37%)	
Primary tumor size, cm [mean (±SD)]	9.1 (±9.0)	7.2 (±5.4)	0.294
Primary tumor depth			0.249
Superficial	4 (12%)	3 (5%)	
Deep	30 (88%)	57 (95%)	
FNCLCC grade			0.071
1	9 (27%)	10 (17%)	
2	5 (15%)	22 (37%)	
3	20 (59%)	28 (46%)	
Tumor type			0.178
Undifferentiated pleomorphic sarcoma	8 (24%)	22 (37%)	
Synovial sarcoma	3 (9%)	6 (10%)	
Liposarcoma	5 (15%)	5 (8%)	
Myxofibrosarcoma	2 (6%)	4 (7%)	
Leiomyosarcoma	2 (6%)	1 (2%)	
Others	14 (40%)	22 (36%)	
Treatment for primary tumor			
Pathologic margin			0.805
Negative	30 (88%)	50 (83%)	
Positive	4 (12%)	10 (17%)	
Radiation therapy			0.353
Not done	20 (59%)	41 (68%)	
Done	14 (41%)	19 (32%)	
Chemotherapy			0.732
Not done	25 (74%)	45 (75%)	
Done	9 (26%)	15 (25%)	
LR chracteristics			
Time to LR, months [mean (±SD)]	15.5 (±14.9)	22.0 (±29.0)	0.157
Size of LR, cm [mean (±SD)]	2.3 (±1.3)	4.0 (±3.4)	0.001*
Number of LRs, n [mean (±SD)]	1.5 (±1.2)	1.5 (±0.8)	0.791
Tumor location			0.005*
Thigh or buttock	22 (65%)	21 (35%)	
Others	12 (35%)	39 (65%)	
Depth of LR			0.408
Superficial	7 (21%)	17 (28%)	
Deep	27 (79%)	43 (72%)	
Morphology of LR			0.007*
Mass-forming	25 (73%)	57(95%)	
Non-mass-forming	9 (27%)	3 (5%)	

Data are expressed as *n* (%) unless otherwise specified.
SD, standard deviation; LR, local recurrence.
FNCLCC, Federation Nationale des Centers de Lutte Contre le Cancer.
*Statistically significant.

accuracy of 98.8%. The PPV of 93.3% in this study is higher than those of previous studies [15,17]. Strict and improved interpretation of suspicious LR using interval follow-up MRIs, may have contributed to the superior diagnostic accuracy of this study.

The findings of this study should be interpreted in the context of some limitations. First, the patient population in this study may represent STS patients with high risk of LR as 38% of the patients presented either with recurred tumors or after unplanned excision. Indeed, the LR rate of 20% (94/477) in this study was higher than the typical <15% rate in modern era studies. The utility of MRI surveillance may not be as distinct in STS patients with fresh presentation. Second, the survival advantage of MRI surveillance needs to be interpreted with caution, as the propensity score analyses are subject to biases from unobserved differences despite reducing bias in causal estimates due to observed differences between the groups [18]. Finally, this study is limited by its retrospective design and relatively small number of patients included. A prospective comparative study of a larger group of patients is needed to examine the advantage of MRI over other imaging modalities such as ultrasonography or CT.

Conclusions

In conclusion, routine MRI surveillance can detect significant number of clinically undetectable LRs in extremity STS. Patients presenting with recurred tumors, high grade tumors or tumors in the thigh or buttock may benefit from MRI surveillance. MRI is especially effective in detecting small LRs or LRs without mass formation.

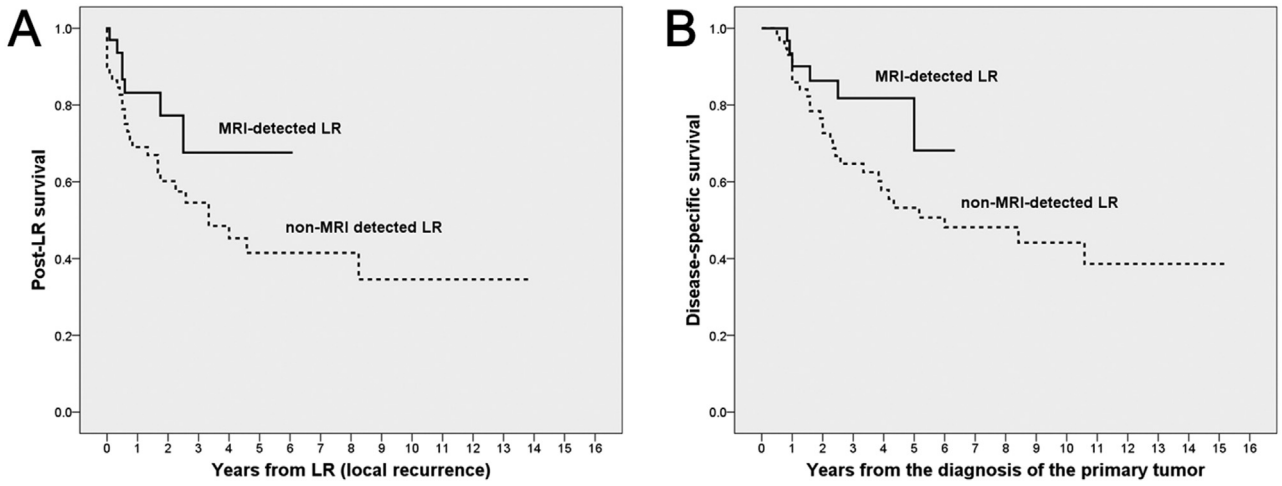

Fig. 3. Comparison of survival between the MRI-detected LR cohort and non-MRI-detected LR cohort. A, On Kaplan-Meier analysis, patients with MRI-detected LR showed a trend toward better post-LR survival than patients with non-MRI-detected LR ($p = 0.104$). B, On Kaplan-Meier analysis, patients with MRI-detected LR showed a trend toward better disease-specific survival than patients with non-MRI-detected LR ($p = 0.072$).

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Disclosure

The authors declare that they have nothing to disclose.

Conflict of interest statement

We declare that we have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.08.032.

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