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Soft tissue sarcoma: adding diffusion-weighted imaging improves MR imaging evaluation of tumor margin infiltration

Ji Hyun Hong[1,2] · Won-Hee Jee[1] · Chan-Kwon Jung[3] · Joon-Yong Jung[1] · Seung Han Shin[4] · Yang-Guk Chung[4]

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Abstract

Purpose To determine the added value of diffusion-weighted imaging (DWI) to conventional magnetic resonance (MR) imaging in assessment of tumor margin infiltration in soft tissue sarcoma (STS) at 3T.

Materials and methods The institutional review board approved this retrospective study. Forty-five patients who underwent 3T MR imaging including DWI and were pathologically confirmed were included in this study. Two readers retrospectively scored conventional MR imaging alone. Then, they assessed a combination of conventional MR imaging and DWI. At pathology, margin infiltration was retrospectively reviewed by one pathologist blinded to MR findings. Areas under the curve (AUCs) of the receiver-operating characteristic curve were obtained for diagnostic performance. Interobserver agreement for the scoring of margin infiltration of STS was assessed with kappa statistics.

Results Among 45 cases of STS, 33 had infiltrative tumor margin at pathology. Sensitivity, specificity, and accuracy of each reader were 100%, 17%, and 78%; 97%, 25%, and 78% on conventional MR imaging alone and 94%, 67%, and 87%; 94%, 42%, and 80% on conventional MR imaging combined with DWI. AUCs of conventional MR imaging combined with DWI were significantly higher than those of conventional MR imaging alone: 0.890 vs 0.678 ($p = .0123$) and 0.846 vs 0.640 ($p = .0305$) for each reader. Interobserver agreements of conventional MR imaging alone and conventional MR imaging combined with DWI were moderate to substantial ($\kappa = 0.646$, $\kappa = 0.496$).

Conclusion The addition of DWI to conventional MR imaging may improve specificity for assessing tumor margin infiltration in STS at 3T.

Key Points

• *DWI has added value for assessment of tumor margin infiltration in soft tissue sarcoma.*
• *Addition of DWI to conventional MRI at 3T may improve specificity.*
• *Addition of DWI to conventional MRI may help orthopedic surgeon determine the extent of the resection margin.*

Keywords MRI · Diffusion · Sarcoma · Neoplasm staging

Abbreviations

ADC Apparent diffusion coefficient
DWI Diffusion-weighted imaging

Introduction

Soft tissue sarcoma is a heterogeneous group of malignant neoplasms that often shows a high mortality rate [1].

✉ Won-Hee Jee
whjee12@gmail.com

1 Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, South Korea

2 Present address: Department of Radiology, Kangdong Seong-Sim Hospital, College of Medicine, Hallym University, 150 Seongan-ro, Gangdong-gu, Seoul 05355, South Korea

3 Department of Pathology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, South Korea

4 Orthopedic Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, South Korea

Surgery is the mainstay of treatment for soft tissue sarcoma, and the goal of surgery is complete removal of the tumor [2]. Thus, the determination of tumor margin with preoperative imaging studies is important, owing to more widespread use of limb-sparing surgery [3]. Preoperative determination of tumor margin infiltration with magnetic resonance (MR) imaging may help the orthopedic surgeon decide the extent of the resection margin in cases of soft tissue sarcoma. Inadequate resection margin enabling peritumoral infiltration may increase the risk of local tumor recurrence after surgery [4].

MR imaging is the most widely used tool for the detection of soft tissue sarcoma and determination of tumor extent, preoperatively [5–7]. Assessment of tumor extent (i.e., differentiation between peritumoral edema and peritumoral infiltration) is essential for surgical planning. Misjudgment of tumor margin may up-stage or down-stage of soft tissue sarcoma and may influence patient prognosis.

On conventional MR imaging, peritumoral high signal intensities or peritumoral contrast enhancement are common findings. However, it is not clear whether peritumoral high signal intensity represents tumor infiltration or simply reactive change. The applicability of conventional MR imaging alone for the determination of tumor margin is limited.

Previous studies have suggested that diffusion-weighted imaging (DWI) may provide added value to differentiate benign and malignant soft tissue tumors [8, 9]. Similarly, DWI may reveal additional information regarding peritumoral tissue, especially at the cellular level. Therefore, it may provide additional information relevant to the assessment of tumor extent. However, there have been few reports regarding the evaluation of tumor margin infiltration in cases of soft tissue sarcoma by using additional DWI.

Thus, we hypothesized that the addition of DWI to conventional MR imaging may help in the assessment of tumor margin infiltration in soft tissue sarcoma. The purpose of this study was to determine the added value of DWI to conventional MR imaging in assessment of tumor margin infiltration in soft tissue sarcoma at 3T.

Materials and methods

Patient population

The institutional review board approved this retrospective study and waived the requirement for informed consent. From June 2010 through January 2016, 61 patients were referred for the surveillance of soft tissue sarcoma in our institute. Inclusion criteria were (a) patients with soft tissue sarcoma who underwent preoperative 3T MR imaging, including DWI with high *b* values and (b) patients who underwent definite histopathologic confirmation, including the presence or absence of peritumoral infiltration after surgery. Exclusion criteria were patients without preoperative DWI or with poor-quality DWI, and patients who were diagnosed only by biopsy (Fig. 1). Forty-five patients (mean age, 54 years; age range, 3 months to 91 years) who underwent 3T MR imaging including DWI, and who were pathologically confirmed as exhibiting soft tissue sarcoma after surgery, were included in this study. Four patients were treated with neoadjuvant chemotherapy and one patient was treated with neoadjuvant radiation therapy before the surgical resection of soft tissue sarcoma. All patients were imaged both before and after chemotherapy or radiation therapy. Tumor margin was scored based on the last MR imaging before surgery. Mean interval from MR imaging to surgical resection was 12.2 days (1–40 days).

There were 21 men (mean age, 49 years; age range, 3 months–91 years) and 24 women (mean age, 59 years; age range, 23 years–84 years). Table 1 shows histological types of the included patients.

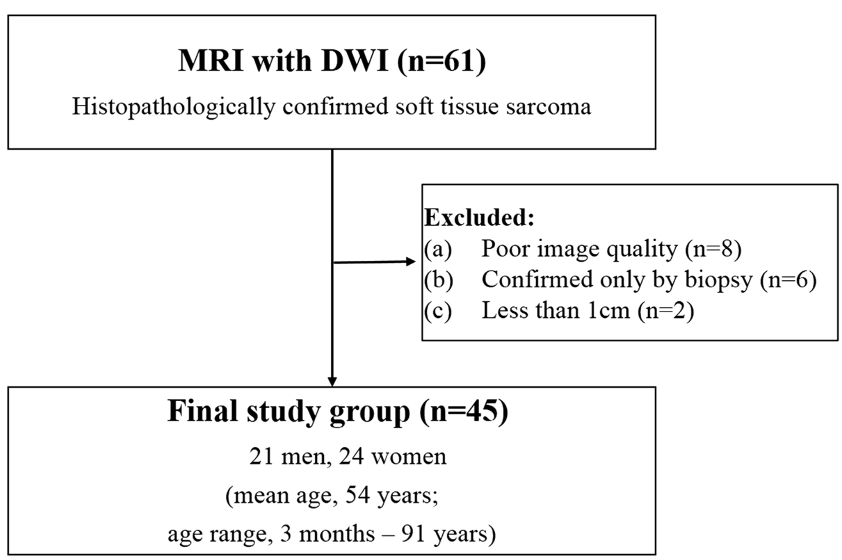

Fig. 1 Flow diagram of the study

Table 1 Histologic types of soft tissue sarcomas

Soft tissue sarcomas	Number of cases
Myxofibrosarcoma	7
Undifferentiated sarcoma	5
Myxoid liposarcoma	5
Synovial sarcoma	4
Well-differentiated liposarcoma	4
Leiomyosarcoma	4
Malignant peripheral nerve sheath tumor	3
Rhabdomyosarcoma	3
Dedifferentiated liposarcoma	3
Fibromyxoid sarcoma	2
Ewing's sarcoma	2
Clear cell sarcoma	1
Fibrosarcoma	1
Angiosarcoma	1

MR imaging protocols

MR examinations were performed with a 3.0T MR imaging unit (Verio; Siemens Healthineers). The conventional MR protocols included longitudinal fat-suppressed T2-weighted turbo spin-echo (TSE) imaging, axial T1-weighted TSE imaging, and axial T2-weighted TSE imaging with and without fat suppression (Table 2). With the exception of one patient, fat-suppressed contrast-enhanced T1-weighted TSE imaging was performed in longitudinal and axial planes in all patients. Before contrast enhancement, a single-shot spine-echo echoplanar DWI sequence was obtained in the axial plane. A parallel imaging technique using GRAPPA (GeneRalized Autocalibrating Partially Parallel Acquisitions) was used with an acceleration factor of 2. Sensitizing diffusion gradients were applied in the x, y, and z directions. Early in the study period DWI was obtained with four b values: 0, 300, 800, and 1400 s/mm^2 ($n = 25$) [10, 11]. Pixel-based apparent diffusion coefficient (ADC) maps were constructed based on mono-exponential calculation from DWI. Subsequently, DWI sequence was changed to Intravoxel Incoherent Motion (IVIM) DWI, which used nine b values: 0, 25, 50, 75, 100, 200, 300, 500, and 800 s/mm^2 ($n = 20$). The acquired DWI data were post-processed to obtain ADC map. Both DWI techniques were post-processed by using prototype software provided by the manufacturer (Leonardo MRWorkplace; Siemens Healthineers). Because DW sequences changed during the study period, ADC maps were obtained from common b values of two DW techniques: 0 and 800 s/mm^2.

MR imaging analysis

To determine the added value of DWI to conventional MR imaging to assess tumor margin infiltration in soft tissue sarcoma at 3T, the diagnostic performances of conventional MR imaging alone and conventional MR imaging combined with DWI were compared. Two musculoskeletal radiologists (W.H.J., J.H.H., with 19 years and 2 years of respective experience in musculoskeletal radiology) retrospectively interpreted MR imaging independently, with respect to tumor margin infiltration. The two readers reviewed images, blinded to clinical information, information from other imaging modalities, and pathologic reports. First, the two readers retrospectively reviewed preoperative conventional MR imaging. Tumor margin infiltration was scored with a 5-level confidence score based on the presence or absence of peritumoral T2-weighted high signal intensity or peritumoral contrast enhancement and tumor margin itself (step 1): 0, definitely circumscribed; 1, probably circumscribed; 2, indeterminate; 3, probably infiltrative; 4, definitely infiltrative. After a 4-week washout period, the same readers scored tumor margin infiltration with conventional MR imaging combined with DWI in a random order that differed from the order of the first step (step 2). During the first and second steps, tumor margin was scored based on the tumor margin itself and peritumoral signals. Tumor margin was classified as infiltration if it was ill-defined or irregular, whereas it was classified as

Table 2 MR imaging parameters

Parameters	Conventional sequences	DWI (single shot)
Field of view	100–400 mm	100–400 mm
Matrix size	512 × 256	70 × 42–128 × 128
TR (msec)/TE (msec)	T1-weighted images, 680–870/11–21 T2-weighted images, 4000–5600/63–83	3400–10,800/49–90
Fat suppression	CHESS pulse	CHESS pulse
Section thickness	3–10 mm	3–10 mm
Intersection gap	No	No
Turbo factor or EPI factor	T1-weighted images, 3 T2-weighted images, 13	56
Number of excitation	1	3–5

TR repetition time, *TE* echo time, *EPI* echoplanar imaging, *CHESS* chemical shift selective, *DWI* diffusion-weighted imaging circumscribed if it was completely well-defined. Peritumoral signal intensity and peritumoral enhancement were analyzed by visual assessment to determine tumor margin infiltration on conventional MR imaging and DWI. In all cases, qualitative analysis of DWI was performed. In equivocal cases, quantitative ADC measurement of peritumoral soft tissue was combined in addition to qualitative analysis.

One radiologist (W.H.J., with 19 years of respective experience in musculoskeletal radiology) repeated scoring of tumor margin infiltration for the assessment of intraobserver agreement.

Pathological analysis

One pathologist (C.K.J., 15 years of experience in musculoskeletal pathology) assessed tumor margin infiltration, blinded to MR findings. Tumor margin was classified into two groups based on surgical specimens from our institution: circumscribed and infiltrative.

Statistical analysis

Pathologic findings were used as the standard of reference. Based on image findings, score 0–1 tumors were regarded as circumscribed and score 2–4 tumors were regarded as infiltrative. McNemar's test was used for comparisons of sensitivity, specificity, and accuracy between conventional MR imaging alone and conventional MR imaging combined with DWI. Interobserver and intraobserver agreement was evaluated by kappa coefficient (κ). κ values were interpreted as follows: < 0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, very good [12]. A receiver-operating characteristic curve with area under the curve (AUC) was constructed for evaluating diagnostic performance. Statistical analysis was performed with commercial software (SPSS, version 19; IBM corporation and MedCalc, version 11.3.0.0; MedCalc Software). P values of < 0.05 were considered indicative of statistically significant differences.

Results

Among a total of 45 patients with soft tissue sarcoma, 33 lesions showed infiltrative margin and 12 lesions showed circumscribed margin on histopathology. On conventional MR imaging alone, tumor margin was scored as 1 ($n = 2$), 3 ($n = 14$), and 4 ($n = 29$)

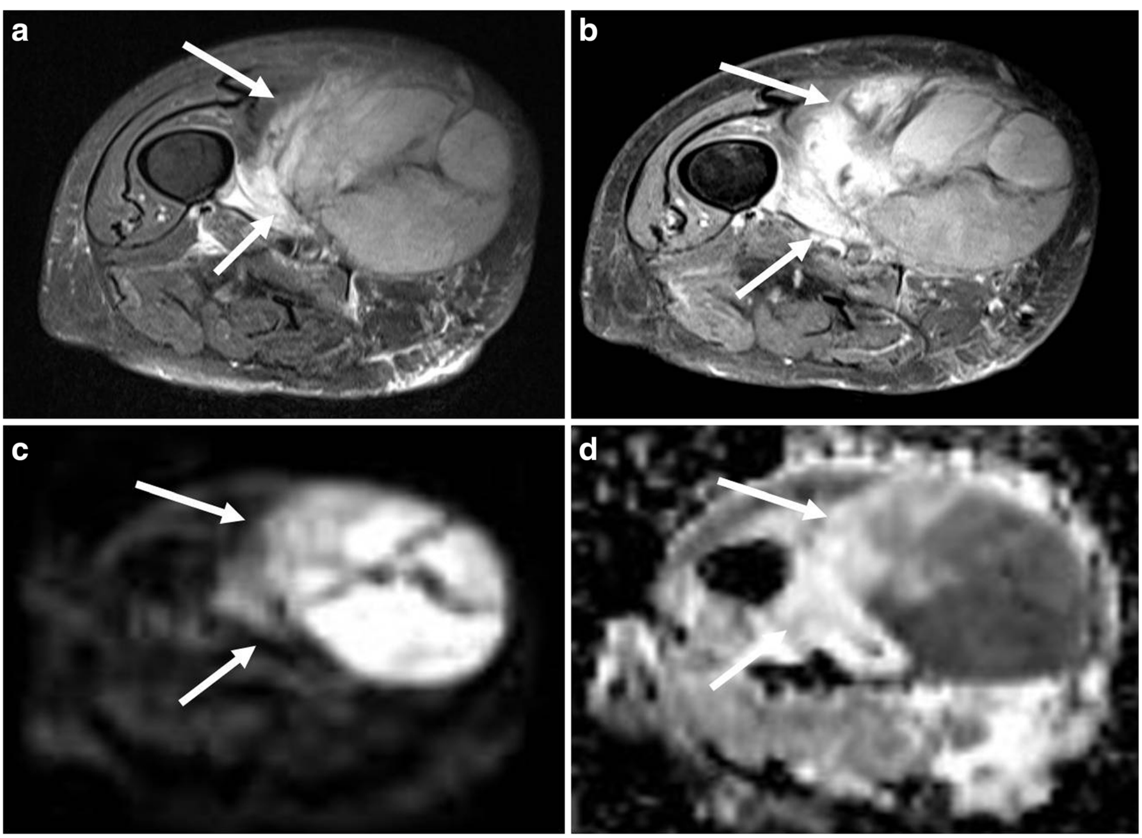

Fig. 2 A 77-year-old woman with fibrosarcoma. There is an ill-defined soft tissue mass in the thigh. Peritumoral abnormal signal (arrows) is present on axial fat-suppressed T2-weighted imaging (**a**). There is peritumoral contrast enhancement (arrows) on axial fat-suppressed contrast-enhanced T1-weighted imaging (**b**). Peritumoral abnormal signal is slightly hyperintense (arrows) on diffusion-weighted imaging with high b value (**c**). On an apparent diffusion coefficient map, it reveals diffusely hyperintense signals (arrows) (**d**). The score of tumor margin changed from 4 on conventional MR imaging alone to 1 on diffusion-weighted imaging combined with conventional MR imaging by reader 1, and from 4 to 2 by reader 2. At pathology, the tumor was confirmed as fibrosarcoma with circumscribed margin

by reader 1, and 1 ($n = 4$), 2 ($n = 3$), 3 ($n = 13$), and 4 ($n = 25$) by reader 2. With the addition of DWI to conventional MR imaging, tumor margin was scored as 1 ($n = 10$), 3 ($n = 9$), and 4 ($n = 26$) by reader 1, and 1 ($n = 8$), 2 ($n = 13$), 3 ($n = 9$), and 4 ($n = 15$) by reader 2. In our study, most (43/45, reader 1) soft tissue sarcomas showed peritumoral high signal intensity or peritumoral enhancement on conventional MR imaging alone. Among these cases that showed peritumoral high signal intensity and peritumoral enhancement, 12 cases were finally confirmed to show circumscribed margin on pathology (Fig. 2). In nine of 12 cases, high signal was not observed on DWI with high *b* value at the site, consistent with peritumoral high signal intensity or peritumoral enhancement on conventional MR imaging alone (Fig. 2). There were 32 cases that showed peritumoral abnormal signals on conventional MR imaging, as well as peritumoral high signals on DWI combined with low signals on ADC map. Thirty (30/32, 94%) of these cases were confirmed to exhibit an infiltrative margin (Fig. 3) on histopathology. Two (2/32, 6%) cases were confirmed to exhibit a circumscribed margin (Fig. 4).

Two cases were false-positive for both readers: malignant peripheral nerve sheath tumor and undifferentiated sarcoma. A case that was false-negative for both readers was leiomyosarcoma. For reader 1 only, a case that was false-positive was liposarcoma; a false-negative case was undifferentiated sarcoma. For reader 2 only, false-positive cases were liposarcoma, myxofibrosarcoma, and fibrosarcoma; a false-negative case was liposarcoma.

Five patients who were treated with neoadjuvant chemotherapy or radiation therapy were included in this study. Four patients underwent neoadjuvant chemotherapy: rhabdomyosarcoma ($n =$

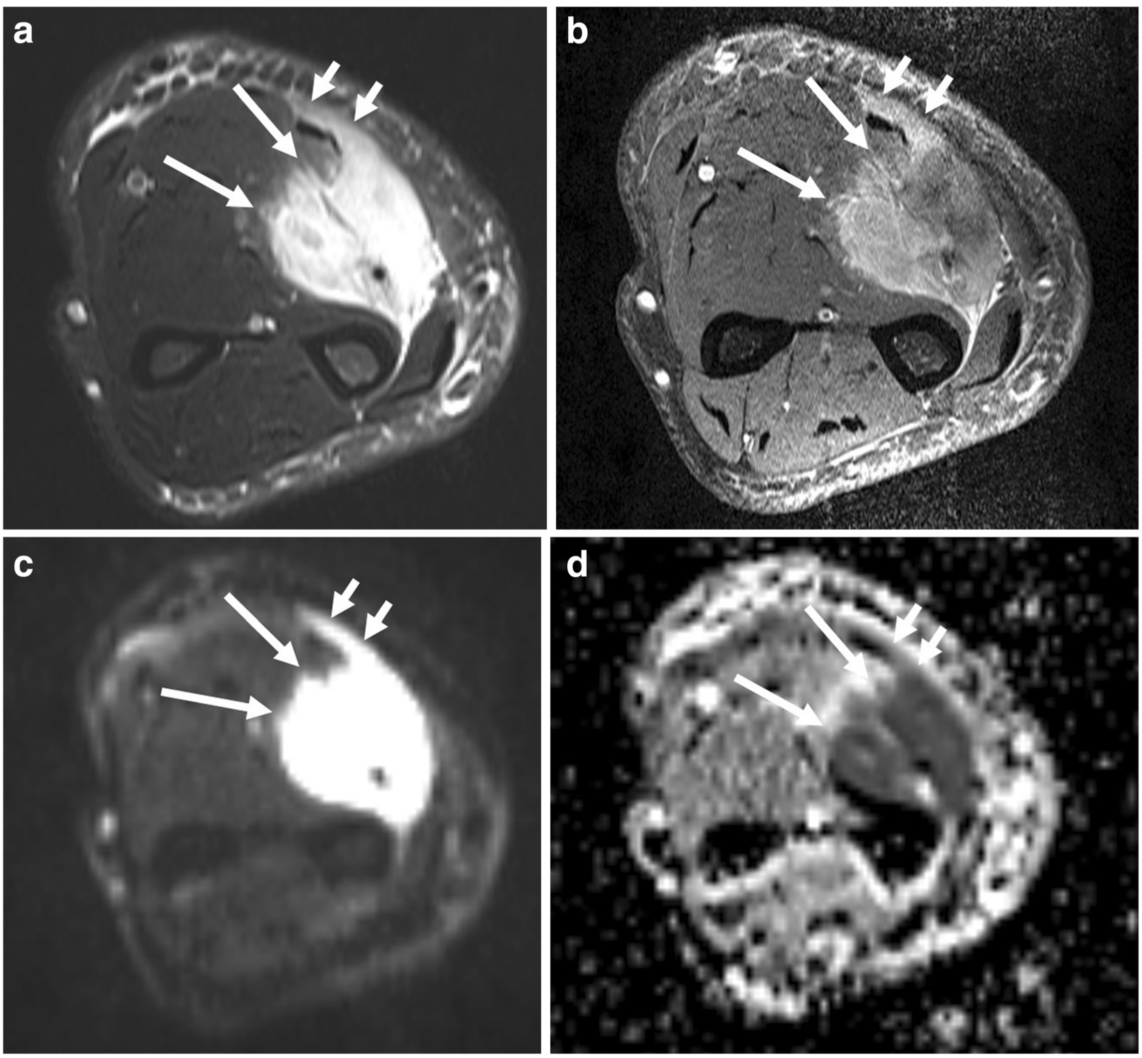

Fig. 3 A 20-year-old man with rhabdomyosarcoma in the forearm. There is a soft tissue mass in the forearm. There are focally irregular tumor margin (long arrows) and peritumoral abnormal signals (short arrows) on axial fat-suppressed T2-weighted image (**a**) and fat-suppressed contrast-enhanced T1-weighed image (**b**). More extensive irregular margin (long arrows) and peritumoral high signals (short arrows) can be observed on diffusion-weighted image with high *b* value (**c**). These reveal hypointense signals (long and short arrows) on apparent diffusion coefficient map (**d**). Tumor margin was graded as 4 based on conventional MR imaging alone and diffusion-weighted imaging combined with conventional MR imaging by readers 1 and 2. At pathology, it was confirmed as rhabdomyosarcoma with infiltrative margin

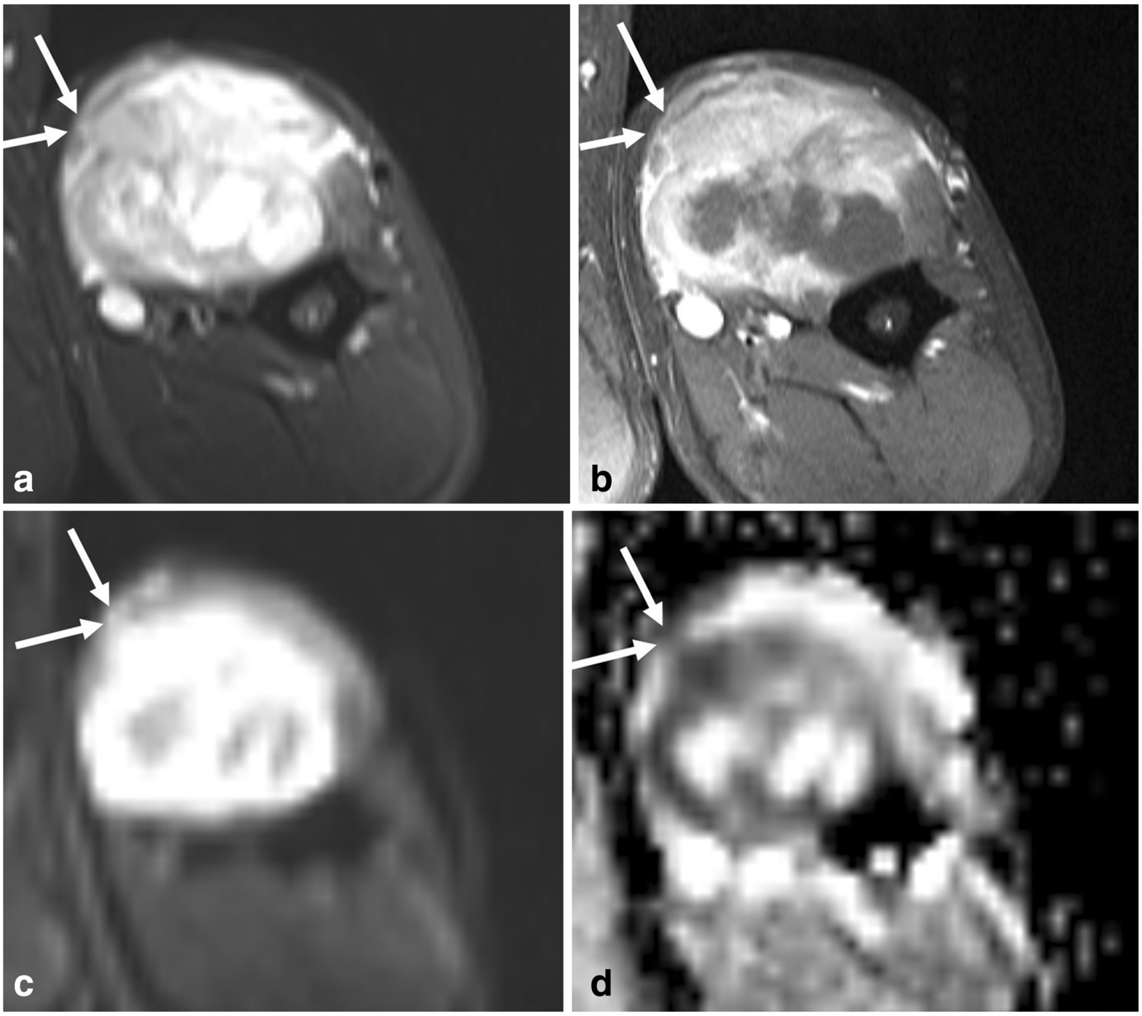

Fig. 4 A 54-year-old man with a malignant peripheral nerve sheath tumor. There is a soft tissue mass in the upper arm. The tumor margin is focally irregular along the medial side (arrows) on axial fat-suppressed T2-weighted image (**a**) and more irregular on fat-suppressed contrast-enhanced T1-weighted image (**b**). The irregular margin appears hyperintense (arrows) on diffusion-weighted image with high *b* value (**c**). It is hypointense (arrows) on apparent diffusion coefficient map (**d**). The score of tumor margin changed from 4 to 4 by reader 1 and from 4 to 3 by reader 2. At pathology, it was confirmed as malignant peripheral nerve sheath tumor with circumscribed margin

2), synovial sarcoma ($n = 1$), and Ewing's sarcoma ($n = 1$). In these four patients, the margins were interpreted as infiltrative on conventional MR imaging alone and conventional MR imaging combined with DWI. After resection of soft tissue sarcoma, the margin was confirmed as infiltrative on histopathology of all four patients. One patient with undifferentiated sarcoma underwent preoperative radiation therapy. The margin was interpreted as infiltrative on both conventional MR imaging alone and conventional MR imaging combined with DWI. However, on histopathology, the margin was confirmed to be a circumscribed margin.

Table 3 Diagnostic performance in assessment of tumor margin infiltration in soft tissue sarcomas

Diagnostic performance	Conventional MRI alone		Combined DWI and conventional MRI	
	Reader 1	Reader 2	Reader 1	Reader 2
Sensitivity	100% (33/33)	97% (32/33)	94% (31/33)	94% (31/33)
Specificity	17% (2/12)	25% (3/12)	67% (8/12)	42% (5/12)
Accuracy	78% (35/45)	78% (35/45)	87% (39/45)	80% (36/45)
AUC	0.678 [0.487, 0.869]	0.640 [0.442, 0.839]	0.890 [0.764, 1]	0.846 [0.728, 0.964]

Note: Numbers in brackets are 95% confidence intervals

AUC area under the operating characteristic curve, *DWI* diffusion-weighted imaging

Sensitivity, specificity, and accuracy of each reader were 100%, 17%, and 78%; 97%, 25%, and 78% on conventional MR imaging alone; and 94%, 67%, and 87%; 94%, 42%, and 80% on conventional MR imaging combined with DWI (Table 3). With conventional MR imaging alone, specificity and accuracy were low for each reader (17% and 78% in reader 1 and 25% and 78% in reader 2). With addition of DWI to conventional MR imaging, specificity was increased for each reader. The specificity for reader 1 was statistically different between conventional MR imaging alone and conventional MR imaging combined with DWI ($p = .008$). The proportion of correct diagnosis by each reader increased with added information from DWI: 8.9% (4/45) for reader 1; 2.2% (1/45) for reader 2. For readers 1 and 2, the AUC of conventional MR imaging combined with DWI was significantly higher than the AUC of conventional MR imaging alone: 0.890 vs 0.678 ($p = .0123$) for reader 1 and 0.846 vs 0.640 ($p = .0305$) for reader 2 (Fig. 5). Interobserver agreement of conventional MR imaging alone was substantial ($\kappa = 0.646$), while that of conventional MR imaging combined with DWI was moderate ($\kappa = 0.496$). Intraobserver agreement of conventional MR imaging alone was substantial ($\kappa = 0.656$); that of conventional MR imaging combined with DWI was very good ($\kappa = 0.871$).

There were 10 low-grade tumors and 35 high-grade tumors: grade 1 ($n = 10$), grade 2 ($n = 13$), and grade 3 ($n = 22$). Among 12 soft tissue sarcomas with circumscribed margin, there were grade 1 ($n = 6$), grade 2 ($n = 1$), and grade 3 ($n = 5$). Among 33 soft tissue sarcomas with infiltrative margin, there were grade 1 ($n = 4$), grade 2 ($n = 12$), and grade 3 ($n = 17$) (Table 4).

Discussion

Our study showed that specificity in assessing the tumor margin infiltration of soft tissue sarcomas was improved by adding DWI to conventional MR imaging at 3T. The differentiation of peritumoral edema and tumor infiltration by preoperative MR imaging may help the orthopedic surgeon determine the extent of the resection margin in cases of soft tissue sarcoma. Local control with R0 resection and preservation of function are two critical aspects for better prognosis [13].

However, if peritumoral edema is misinterpreted as tumor infiltration, the tumor is up-staged and undergoes unnecessarily wide resection. Conversely, if peritumoral infiltration is misinterpreted as edema, the tumor is down-staged and may be removed with an inadequate resection margin; the remaining peritumoral infiltration may increase the risk of local tumor recurrence after surgery. In our study, with the addition of DWI, sensitivity decreased slightly, but remained high: 100% vs. 94% in reader 1 and 97% vs 94% in reader 2. In contrast, specificity greatly increased with the addition of DWI for the assessment of tumor margin infiltration: 17% vs. 67% in reader 1 and 25% vs. 42% in reader 2. Thus, DWI does not detect additional cases of infiltration; however, it improves reader confidence when in positive cases. Limb-sparing surgery has been the standard of care in cases of soft tissue sarcoma for decades [3]. The observation that specificity increased with addition of DWI for assessing tumor margin infiltration may help to preserve adjacent essential structures in limb salvage surgery. The therapeutic goal of soft tissue sarcoma is to maintain function while achieving a cure.

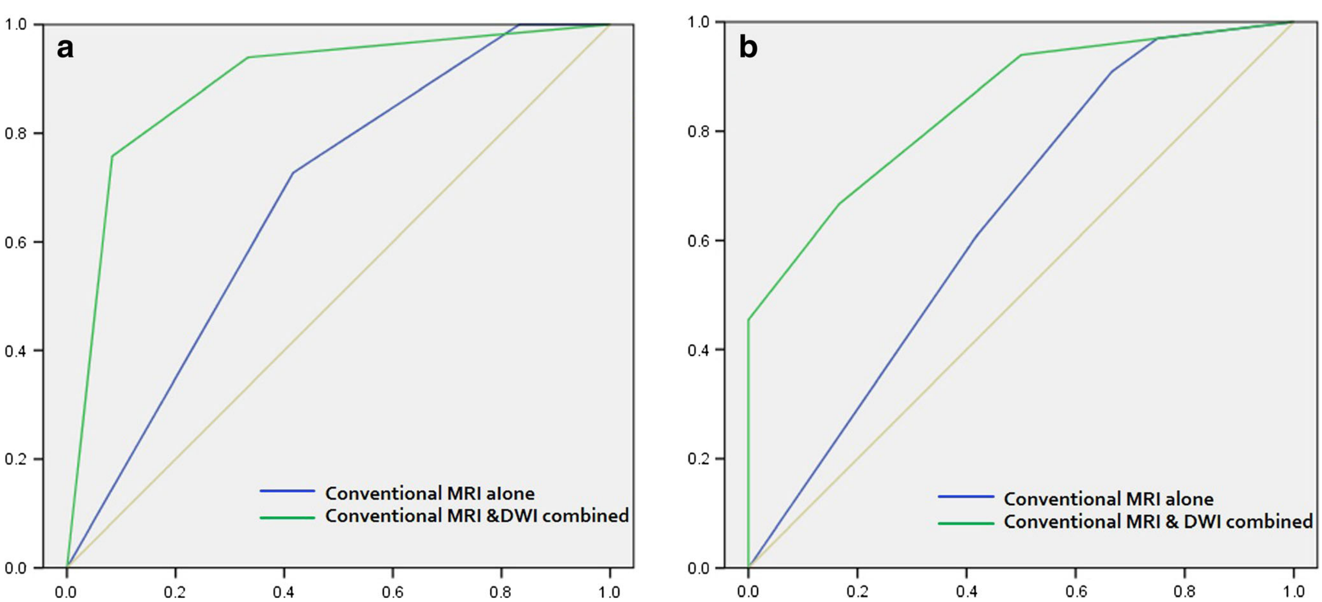

Fig. 5 Receiver-operating characteristic (ROC) curves demonstrating the comparison of diagnostic performances of conventional MR imaging alone and conventional MR imaging combined with diffusion-weighted imaging (DWI) for reader 1 (**a**) and reader 2 (**b**) in assessment of tumor margin. For both readers, area under the curve of conventional MR imaging combined with DWI was significantly higher than that of conventional MR imaging alone: 0.678 vs 0.890, $p = .0123$ for reader 1; 0.640 vs 0.846, $p = .0305$ for reader 2

Table 4 Grades of soft tissue sarcomas

	Soft tissue sarcoma with circumscribed margin	Soft tissue sarcoma with infiltrative margin
Grade 1	6	4
Grade 2	1	12
Grade 3	5	17

According to previous studies [14, 15], the meaning of peritumoral high signal intensity on a pathologic basis remains controversial and T2-weighted peritumoral high signal intensity may be caused by peritumoral edema, tumor infiltration, or both. In our study, of 12 soft tissue sarcomas with circumscribed margin, nine showed T2-weighted peritumoral high signals. In these cases, T2 peritumoral high signals were not related to tumor infiltration. Peritumoral high signal intensity on T2-weighted images may be enhanced after contrast infusion due to various possible causes, including perilesional inflammatory infiltration, vascular congestion and hyperperfusion, and increased extracellular fluid or edema [14, 16–20]. White et al [15] evaluated the histopathology of peritumoral high signal intensity in 15 patients with extremity or truncal soft tissue sarcoma. Peritumoral soft tissue in all planes was sampled to evaluate peritumoral infiltration. Peritumoral malignant cell infiltrations were pathologically confirmed within areas of peritumoral high signal intensity in 9 of 15 cases.

Tumor margin itself is also important to assess tumor infiltration. Zhao et al [21] reported that poorly defined tumor margin on conventional MR imaging suggests tumor infiltration in peritumoral tissue and high-grade soft tissue sarcoma. High-grade tumors tended to show poorly defined margins on all images, peritumoral high signal intensity on T2-weighted images, and peritumoral contrast enhancement. We found that irregular or poorly defined tumor margin on DWI indicates infiltrative tumor margin. Our results are consistent with a previous report [21] where higher tumor grade was related with poorly defined margin, peritumoral high signal intensity, and peritumoral enhancement. In our study, among 33 soft tissue sarcomas with infiltrative margin, 88% (29/33) were high-grade.

Lang et al [22] attempted to differentiate between peritumoral edema and tumor cell infiltration with dynamic contrast-enhanced MR imaging. They reported that tumor infiltration showed rapid and prominent enhancement with high initial slope, whereas peritumoral edema showed slow enhancement with low initial slope in 14 tumors.

Previous studies [8–10] found that DWI with high *b* value was useful for distinguishing malignant and benign soft tissue tumors, and that benign tumors tended to show hyperintensity on ADC maps. We found that T2 peritumoral high signal intensity and peritumoral contrast enhancement do not always suggest infiltrative tumor margin. With the addition of DWI, specificity to assess tumor margin infiltration increased in two readers and the proportion of correct diagnosis increased. The diagnostic performance was significantly higher in conventional MR imaging combined with DWI, compared with conventional MR imaging alone, for each reader. However, interobserver agreement of conventional MR imaging alone ($\kappa = 0.646$) was higher than that of conventional MR imaging combined with DWI ($\kappa = 0.496$). In our study, tumor margin grade was determined by visual assessment on DWI, rather than by quantitative analysis. Thus, we suspect that, the difference in the reader's clinical experience on DWI resulted in lower interobserver agreement in MR with DWI, compared with MR without DWI.

Our study has several limitations. First, this is a retrospective study. Although we recruited consecutive patients who satisfied the inclusion criteria, there remains the possibility of selection bias. Second, the study population was relatively small. Third, we could not perform pathologic mapping due to the retrospective design of the study. Although one pathologist assessed tumor margin infiltration, MR imaging findings and surgical specimens could not be matched one-to-one. Further prospective studies for pathologic mapping are needed. Fourth, the possibility of a recall bias should be considered, although we attempted to avoid it by using a washout period.

In conclusion, the addition of DWI to conventional MR imaging may improve specificity for assessing tumor margin infiltration in soft tissue sarcoma at 3T.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Won-Hee Jee.

Conflict of interest The authors declare that they have no conflict of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
• retrospective
• diagnostic or prognostic study
• performed at one institution

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