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FULL PAPER

Multiparametric quantitative analysis of tumor perfusion and diffusion with 3T MRI: differentiation between benign and malignant soft tissue tumors

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Objective: To evaluate multiparametric MRI for differentiating benign and malignant soft tissue tumors.

Methods: This retrospective study included 67 patients (mean age, 55 years; 18–82 years) with 35 benign and 32 malignant soft tissue tumors. Intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI)-derived parameters (D , D^* , f), apparent diffusion coefficient (ADC), and dynamic contrast-enhanced (DCE)-MRI parameters (K^{trans} , K_{ep} , V_e , iAUC) were calculated. Myxoid and non-myxoid soft tissue tumors were divided for subgroup analysis. The parameters were compared between benign and malignant tumors.

Results: ADC and D were significantly lower in malignant than benign soft tissue tumors (1170 ± 488 vs $1472 \pm 349 \mu\text{m}^2/\text{s}$; 1132 ± 500 vs $1415 \pm 374 \mu\text{m}^2/\text{s}$; $p < 0.05$). K^{trans} , K_{ep} , V_e , and iAUC were significantly different between malignant and benign soft tissue tumors (0.209 ± 0.160 vs $0.092 \pm 0.067 \text{ min}^{-1}$; 0.737 ± 0.488

vs $0.311 \pm 0.230 \text{ min}^{-1}$; 0.32 ± 0.17 vs 0.44 ± 0.28 ; 0.23 ± 0.14 vs 0.12 ± 0.09 , $p < 0.05$, respectively). ADC (0.752), D (0.742), and K_{ep} (0.817) had high AUCs. Subgroup analysis showed that only K^{trans} , and iAUC were significantly different in myxoid tumors, while, ADC, D , K^{trans} , K_{ep} , and iAUC were significantly different in non-myxoid tumor for differentiating benign and malignant tumors. D , K_{ep} , and iAUC were the most significant parameters predicting malignant soft tissue tumors.

Conclusion: Multiparametric MRI can be useful to differentiate benign and malignant soft tissue tumors using IVIM-DWI and DCE-MRI.

Advances in knowledge: 1. Pure tissue diffusion (D), transfer constant (K^{trans}), rate constant (K_{ep}), and initial area under time-signal intensity curve (iAUC) can be used to differentiate benign malignant soft tissue tumors. 2. K^{trans} and iAUC enable differentiation of benign and malignant myxoid soft tissue tumors.

INTRODUCTION

It is not uncommon to encounter problems distinguishing benign from malignant soft tissue tumors in routine practice. It can be difficult to differentiate between benign and malignant soft tissue tumors with conventional MRI alone because morphologic features and signal intensities of benign and malignant soft tissue tumors may overlap.^{1–5} Recently, diffusion-weighted imaging (DWI) has been used to evaluate soft tissue tumors. Calculation of apparent diffusion coefficient (ADC) values for random water movement in tissues can reflect the pathologic status of diseased tissue.^{6–10} DWI based on an intravoxel incoherent motion (IVIM) biexponential model by Le Bihan et al¹¹ can more accurately separate

microcapillary perfusion from pure tissue diffusion (D). Perfusion characteristics (pseudodiffusion coefficient, D^*) and their volume fraction (perfusion fraction, f) can be obtained simultaneously. IVIM-DWI has been applied in soft tissue tumors to demonstrate the feasibility of differentiation between benign and malignant soft tissue tumors.^{12,13} Dynamic contrast-enhanced (DCE)-MRI has been reported as potentially helpful in characterizing soft tissue tumors.^{14–16} When a pharmacokinetic model by Tofts¹⁷ is applied, DCE-MRI can derive three main quantitative parameters: transfer constant (K^{trans}), rate constant (K_{ep}), and extravascular extracellular volume fraction (V_e), as well as the semi-quantitative parameter of initial area under the time-signal intensity curve

Figure 1. Study flowchart. DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; IVIM-DWI, intravoxel incoherent motion diffusion-weighted imaging

(iAUC). The values of these pharmacokinetic parameters for DCE-MRI have rarely been evaluated in soft tissue tumors.^{18,19}

Despite these developments, there have been inconsistent reports about using DWI, IVIM, or DCE-MRI for differentiating benign and malignant soft tissue tumor and few reports fully evaluating quantitative multiparametric MRI including IVIM-DWI and DCE-MRI for differentiating benign and malignant soft tissue tumors. Therefore, the purpose of our study was to determine the value of multiparametric MRI for differentiation between benign and malignant soft tissue tumors.

METHODS AND MATERIALS

Study population

This retrospective study was approved by our Institutional Review Board, and the requirement for informed consent was waived. From May 2014 to February 2018, a total of 130 patients was enrolled in the study with the following criteria: (i) first diagnosis of a soft tissue mass (images were examined before histologic biopsy and/or initiation of treatment), (ii) soft tissue tumors with pathologic confirmation using histologic biopsy and/or examination of the surgical specimens, and (iii) underwent 3 T MRI including IVIM-DWI and DCE-MRI. Among these 130 patients, 63 were excluded based on the following exclusion criteria: (i) 30 non-neoplastic lesions (21 ganglion cysts, 6 epidermoid inclusion cysts, and 3 metastases), (ii) 24 well-differentiated adipocytic tumors (20 lipomas and 4 well-differentiated liposarcomas), (iii) 4 soft tissue tumors less than 0.5 cm in diameter (2 fibromatosis and 2 glomus tumors), (iv) 4 with unsatisfactory image quality in most sequences due to artifacts (three tenosynovial giant cell tumors and one fibromatosis), and (v) one intermediate malignancy (dermatofibrosarcoma protuberans). Finally, the remaining 67 patients (mean age, 55 ± 15 years; range, 18–82 years) with soft tissue tumors constituted the study population of 30 males (mean age, 54 ± 16 years; range,

18–82 years) and 37 females (mean age, 57 ± 15 years; range, 26–82 years). Part of the population of this study ($n = 17$) originates from a previous study²⁰ with different measurements and aims to determine the diagnostic value of multiparametric MRI for differentiating benign from malignant soft tissue tumors. Of these patients, six patients (angioleiomyoma, fibroma, fibromatosis, glomus tumor, tenosynovial giant cell tumor, and malignant melanoma) were further excluded from IVIM-DWI analysis due to artifacts. The DCE-MRI analysis included all 67 patients (Figure 1).

Since it has been reported that a myxoid tumor matrix forms parts of many benign and malignant soft tissue tumors,²¹ we decided to compare quantitative parameters between patients with and without myxoid tumor matrix. For these reasons, the tumors were divided into 19 myxoid and 48 non-myxoid soft tissue tumors for subgroup analysis. Myxoid soft tissue tumors included myxoid liposarcomas ($n = 3$) and myxofibrosarcomas ($n = 3$), schwannomas ($n = 8$), myxomas ($n = 2$), a neurofibroma ($n = 1$), a low grade fibromyxoid sarcoma ($n = 1$), and a malignant peripheral nerve sheath tumor ($n = 1$).

MRI acquisition

Images were obtained using a 3 T system (MAGNETOM Verio, Siemens Healthineers, Erlangen, Germany). Field of view varies by body part. Conventional MRI was obtained with coil adjustments. Axial turbo spine echo (TSE) T_1 weighted and TSE T_2 weighted images with and without fat suppression, at least one fat suppressed T_2 weighted longitudinal scan, and contrast-enhanced longitudinal and axial TSE T_1 weighted images with fat suppression were obtained.

IVIM-DWI was obtained using single-shot spin echo echoplanar imaging. Encoding was performed in three orthogonal directions. A series of nine b -values (0, 25, 50, 75, 100, 200, 300, 500, and 800 s/mm²) was applied. The acquired imaging data were post-processed to obtain ADC, and the IVIM-derived parameters including D (diffusion coefficient), D^* (pseudodiffusion), and f (perfusion fraction of proton linked to microcirculation) were determined using prototype software (Siemens Healthineers). Pixel-based ADC maps were created based on monoexponential calculation from DWI with b -values of 0 and 800 s/mm².

For DCE-MRI, unenhanced axial T_1 weighted volumetric interpolated breath-hold examinations (VIBE) images were acquired for baseline T_1 maps with flip angles of 2° and 15° before injecting contrast material. Images were then obtained immediately after a bolus injection of gadobutrol (Gadovist, Bayer Healthcare, Leverkusen, Germany) at a rate of 2 ml s⁻¹ for a dose of 0.1 mmol/kg followed by a 20 ml normal saline flush. Total acquisition time was 5 min. The Tofts pharmacokinetic model was applied to calculate perfusion parameters including rate transfer constant between blood plasma and extracellular/extravascular space (K^{trans}), volume fraction of extracellular/extravascular space (V_e), and rate intravascular constant (K_{ep}) calculated as K^{trans}/V_e .¹⁷ Population-averaged arterial-input function (AIF) was applied with intermediate type.²² Semiquantitative parameters of the

Figure 2. ROI analysis. A, Axial fat-suppressed contrast-enhanced TSE T_1 weighted image shows ROI placed manually within solid tumor portion on representative axial plane. B, IVIM-DWI parametric map and C, DCE-MRI parametric map show ROIs copied and pasted in the same place and shape on selective slice. DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; IVIM-DWI, intravoxel incoherent motion diffusion-weighted imaging; ROI, region of interest; TSE, turbo spine echo

initial area under the time–signal intensity curve (iAUC) were also provided from the time-to-signal intensity curve as iAUC in 60 s.

Imaging analysis

MRI images were analyzed with region of interest (ROI) in a blind fashion by two musculoskeletal radiologists. Quantitative analysis of IVIM-DWI and DCE-MRI were obtained by manually placing a ROI within as much of the solid portion of the soft tissue tumor as possible, excluding cystic, hemorrhagic, or necrotic areas on the representative axial plane (Figure 2). Each ROI was placed on the T_1 weighted images after gadolinium injection, and this ROI was propagated automatically on each of the parametric maps by software Syngo Via (Siemens Healthineers).

The mean values of the parametric maps from the pixels within the ROIs were calculated. ROIs were visually corrected if any image distortions or artifacts were identified.

Statistical analysis

χ^2 test and Student's t -test were used to compare the findings between the two groups. The Mann–Whitney U test was used to compare the findings for subgroup analysis. Receiver operating characteristic (ROC) analysis with area under the curve (AUC) was used to calculate sensitivity, specificity, and accuracy according to a defined cut-off value. Logistic regression analysis was performed to determine independent parameters for predicting a malignant lesion. Multiple ROC comparison was performed for prediction models representing the ROC AUC. Interobserver agreement for the measurement was evaluated by intraclass correlation coefficient (ICC) using a two-way mixed model with absolute agreement. Results were evaluated within a 95% confidence interval (CI), and significance level was set at $p < 0.05$. Statistical analysis was conducted using software packages (SPSS v. 20.0, Chicago, IL; and MedCalc, v. 12.7, Mariakerke, Belgium).

RESULTS

Final diagnoses were established on the basis of histopathology, and the cases were composed of 35 benign and 32 malignant lesions. Detailed demographic and histopathological information of the two groups are described in Table 1. Interobserver agreement of IVIM-DWI was considered excellent for ADC and D (ICC = 0.95–0.98), good for D^* and f (ICC = 0.58–0.65). For DCE-MRI, interobserver agreements for K^{trans} , K_{ep} and iAUC were considered good (ICC = 0.72–0.74) and that for V_e was poor (ICC = 0.38).

Table 1. Demographic and histologic information for benign and malignant soft tissue tumors

Demographic data	Benign group ($n = 35$)	Malignant group ($n = 32$)	p value
Age (years)	53 ± 16	58 ± 14	0.227
Gender (m : f)	16 : 19	14 : 18	0.872
Histologic results (n)	Schwannoma (8)	Undifferentiated sarcoma (8)	
	Hemangioma (6)	Synovial sarcoma (4)	
	Angioleiomyoma (4)	Myxoidliposarcoma (3)	
	Fibromatosis (4)	Myxofibrosarcoma (3)	
	Nodular fasciitis (3)	Lymphoma (3)	
	Fibroma (2)	Epithelioidhemangioendothelioma (2)	
	Glomus tumor (2)	Leiomyosarcoma (2)	
	Tenosynovial giant cell tumor (2)	Angiosarcoma (1)	
	Myxoma (2)	Low grade fibromyxoid sarcoma (1)	
	Neurofibroma (1)	Myeloid sarcoma (1)	
	Neuroma (1)	Extraskeletalmesenchymalchondrosarcoma (1)	
		Malignant melanoma (1)	
		Malignant peripheral nerve sheath tumor (1)	
		Malignant solitary fibrous tumor (1)	

Figure 3. A 50-year-old male with myeloid sarcoma. *A*, Axial fat-suppressed contrast-enhanced TSE T_1 weighted image shows 2.5cm enhancing mass (arrows) along radial nerve in the elbow, mimicking schwannoma. *B*, Mass demonstrates high signal with hypointense portion (arrows) on DWI with b value of 800s/mm². *C*, Impeded water diffusivity (arrows) on ADC map. IVIM-DWI parameters and DCE-MRI parameters suggest malignant soft tissue tumor. This case was pathologically confirmed as myeloid sarcoma. *D*, Results of quantitative multiparametric MRI. ADC, apparent diffusion coefficient; DCE-MRI, dynamic contrast enhanced magnetic resonance imaging; DWI, diffusion-weighted imaging; IVIM-DWI, intravoxel incoherent motion diffusion-weighted imaging; TSE, turbo spin echo.

<i>a</i>	<i>b</i>	<i>c</i>

ADC ($\mu\text{m}^2/\text{sec}$)	D ($\mu\text{m}^2/\text{sec}$)	D^* ($\mu\text{m}^2/\text{sec}$)	f (%)
837	881	275	133
K^{trans} ($\text{min}^{-1}\times 10^3$)	K_{ep} ($\text{min}^{-1}\times 10^3$)	V_e (%)	iAUC (%)
116	824	14	12

Benign vs malignant soft tissue tumors

Among the IVIM-DWI parameters, ADC ($1170 \pm 488 \mu\text{m}^2/\text{s}$) and D ($1132 \pm 500 \mu\text{m}^2/\text{s}$) in malignant tumors were significantly lower than those of benign tumors ($1472 \pm 349 \mu\text{m}^2/\text{s}$ and $1415 \pm 374 \mu\text{m}^2/\text{s}$; $p = 0.007$ and 0.015 , respectively) (Figures 3 and 4). There were no significant differences in D^* and f between the two groups (Table 2). ROC analysis demonstrated that ADC and D

showed the highest sensitivities of 74 and 71%, respectively (specificities of 73 and 83%, cut-offs of $\leq 1310 \mu\text{m}^2/\text{s}$ and $\leq 1190 \mu\text{m}^2/\text{s}$ indicating malignancy) with AUC values of 0.752 and 0.742 with statistical significance ($p = 0.005$ and 0.006) (Table 2).

Among the DCE-MRI parameters, K^{trans} ($209 \pm 160 \text{ min}^{-1}\times 10^3$), K_{ep} ($737 \pm 488 \text{ min}^{-1}\times 10^3$), and iAUC ($23 \pm 14\%$) in malignant tumors were significantly higher than those in benign tumors ($92 \pm 67 \text{ min}^{-1}\times 10^3$, $311 \pm 230 \text{ min}^{-1}\times 10^3$, and $12 \pm 9\%$ respectively; $p < 0.001$ for all), while V_e ($32 \pm 17\%$) in malignant tumors was significantly lower than that in benign tumors ($44 \pm 28\%$, $p = 0.043$) (Table 2). ROC analysis found that K^{trans} had the highest sensitivity of 81% (specificity of 77%, cut-off of $> 110 \text{ min}^{-1}\times 10^3$ indicating malignancy) with an AUC of 0.792 with statistical significance ($p < 0.001$). K_{ep} showed the highest AUC of 0.817 with statistical significance ($p < 0.001$), with a value greater than $368 \text{ min}^{-1}\times 10^3$ indicating malignancy (sensitivity of 78% and specificity of 71%). The iAUC also showed an AUC of 0.771 with statistical significance ($p < 0.001$), with a value greater than 14% indicating malignancy (sensitivity of 72% and specificity of 69%) (Table 2).

Subgroup analysis for myxoid soft tissue tumors

There were no significant differences in IVIM-DWI to differentiate between benign and malignant myxoid soft tissue tumors. There was no parameter in IVIM-DWI showing an AUC with statistical significance (Table 3).

Of the DCE-MRI parameters, K^{trans} ($122 \pm 73 \text{ min}^{-1}\times 10^3$) and iAUC ($17 \pm 12\%$) in malignant myxoid soft tissue tumors were significantly higher than those in benign myxoid soft tissue tumors ($63 \pm 37 \text{ min}^{-1}\times 10^3$ and $8 \pm 5\%$ respectively; $p = 0.035$ and 0.037). ROC analysis showed K_{ep} to have the highest sensitivity of 87% (specificity of 63%, cut-off of $> 220 \text{ min}^{-1}\times 10^3$ indicating malignancy) with an AUC of 0.750 with statistical significance ($p = 0.001$). Better specificity was achieved with iAUC (specificity of 90%, sensitivity of 62%, cut-off of $> 14\%$ indicating malignancy) with an AUC of 0.761 with statistical significance ($p = 0.001$) (Table 3).

Subgroup analysis for non-myxoid soft tissue tumors

The ADC ($979 \pm 300 \mu\text{m}^2/\text{s}$) and D ($938 \pm 296 \mu\text{m}^2/\text{s}$) in malignant non-myxoid soft tissue tumors were significantly lower than in benign non-myxoid soft tissue tumors ($1365 \pm 238 \mu\text{m}^2/\text{s}$ and $1294 \pm 249 \mu\text{m}^2/\text{s}$, respectively; $p < 0.001$). ROC analysis found that ADC and D showed the highest sensitivity of 87% (specificities of 73 and 79%, cut-offs of $\leq 1261 \mu\text{m}^2/\text{s}$ and $\leq 1183 \mu\text{m}^2/\text{s}$ indicating malignancy, respectively) with AUCs of 0.835 and 0.831 with statistical significance ($p = 0.001$) (Table 4).

K^{trans} ($238 \pm 172 \text{ min}^{-1}\times 10^3$), K_{ep} ($832 \pm 510 \text{ min}^{-1}\times 10^3$), and iAUC ($26 \pm 15\%$) in malignant non-myxoid soft tissue tumors were significantly higher than in benign non-myxoid soft tissue tumors ($105 \pm 72 \text{ min}^{-1}\times 10^3$, $333 \pm 207 \text{ min}^{-1}\times 10^3$, and $14 \pm 10\%$ respectively; $p = 0.001$, < 0.001 , and 0.002). ROC analysis determined that K^{trans} , K_{ep} , and iAUC showed the same sensitivity of 87% (specificities of 66%, 66%, and 62%, cut-offs

Figure 4. A 71-year-old female with myxoma. *A*, Axial fat-suppressed contrast-enhanced TSE T_1 weighted image shows 4 cm heterogeneously enhancing mass (arrows) in proximal thigh. *B*, Bright signal is not demonstrated on DWI with b value of 800s/mm². *C*, The mass is hyperintense (arrows) on ADC map. IVIM-DWI parameters and DCE-MRI parameters suggest a benign soft tissue tumor. The mass was pathologically confirmed as myxoma. *D*, Results of quantitative multiparametric MRI. ADC, apparent diffusion coefficient; DCE-MRI, dynamic contrast enhanced magnetic resonance imaging; DWI, diffusion-weighted imaging; IVIM-DWI, intravoxel incoherent motion diffusion-weighted imaging; TSE, turbo spin echo.

<i>a</i>	<i>b</i>	<i>c</i>

ADC ($\mu\text{m}^2/\text{sec}$)	D ($\mu\text{m}^2/\text{sec}$)	D^* ($\mu\text{m}^2/\text{sec}$)	f (%)
2173	2179	212	33
K^{trans} ($\text{min}^{-1}\times 10^3$)	K_{ep} ($\text{min}^{-1}\times 10^3$)	V_e (%)	iAUC (%)
78	191	41	14

Table 2. Comparison of parameters between benign and malignant soft tissue tumors

Parameters	Benign group	Malignant group	<i>p</i> value	Cut-off values	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
IVIM DWI	<i>n</i> = 30	<i>n</i> = 31						
<i>D</i> ($\mu\text{m}^2/\text{s}$)	1415 $\pm$ 374	1132 $\pm$ 500	0.015a	≤ 1190	71 (22/31)	83 (25/30)	77 (47/61)	0.742a
<i>Da</i> ($\mu\text{m}^2/\text{s}$)	297 $\pm$ 96	258 $\pm$ 83	0.094	≤ 274	58 (18/31)	57 (17/30)	57 (35/61)	0.638
<i>f</i> (%)	101 $\pm$ 58	83 $\pm$ 36	0.149	≤ 82	55 (17/31)	57 (17/30)	56 (34/61)	0.576
ADC ($\mu\text{m}^2/\text{s}$)	1472 $\pm$ 349	1170 $\pm$ 488	0.007a	≤ 1310	74 (23/31)	73 (22/30)	74 (45/61)	0.752a
DCE-MRI	<i>n</i> = 35	<i>n</i> = 32						
K^{trans} ($\text{min}^{-1} \times 10^3$)	92 $\pm$ 67	209 $\pm$ 160	<0.001a	>110	81 (26/32)	77 (27/35)	79 (53/67)	0.792a
K_{ep} ($\text{min}^{-1} \times 10^3$)	311 $\pm$ 230	737 $\pm$ 488	<0.001a	>368	78 (25/32)	71 (25/35)	75 (50/67)	0.817a
V_e (%)	44 $\pm$ 28	32 $\pm$ 17	0.043a	≤ 35	69 (22/32)	54 (19/35)	61 (41/67)	0.616
iAUC (%)	12 $\pm$ 9	23 $\pm$ 14	<0.001a	>14	72 (23/32)	69 (24/35)	70 (47/67)	0.771a

AUC, area under the curve; DCE-MRI, Dynamic contrast enhanced magnetic resonance imaging; IVIM DWI, intravoxel incoherent motion diffusion-weighted imaging.

All data are means ($\pm$ standard deviation).

^aindicates statistical significance.

of $>110 \text{ min}^{-1} \times 10^3$, $>358 \text{ min}^{-1} \times 10^3$, and $>12\%$ indicating malignancy, respectively) with AUCs of 0.798, 0.855, and 0.766 with statistical significance ($p < 0.001$ for all)(Table 4).

Multivariate logistic regression analysis for predicting malignant soft tissue tumors

IVIM-DWI parameters were analyzed by stepwise multivariate logistic regression analysis, and *D* (OR, 0.998; 95% CI, 0.997–0.999) was an independent factor for predicting malignancy. The DCE-MRI with multivariate logistic regression analysis showed that K_{ep} (OR, 1.004; 95% CI, 1.001–1.006) and iAUC (OR, 1.064;

95% CI, 1.001–1.131) were independent factors for predicting malignancy.

Three prediction models were designed as follows – first model, *D* alone; second model, *D* combined with K_{ep} ; third model, *D* combined with K_{ep} and iAUC. ROC analyses of the three logistic regression models showed that the ROC AUC of predicted probability increased by adding parameters to *D* (AUC of first model, 0.750; second model, 0.809; third model, 0.838) without statistically significant differences ($p = 0.415$, 0.406 , and 0.184 between first vs second, second vs third, and first vs third, respectively) (Figure 5).

Table 3. Comparison and diagnostic performance of parameters between benign and malignant myxoid soft tissue tumors

Parameter	Benign group	Malignant group	<i>p</i> - value	Cut-off values	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
IVIM DWI	<i>n</i> = 11	<i>n</i> = 8						
<i>D</i> ($\mu\text{m}^2/\text{s}$)	1623 $\pm$ 466	1687 $\pm$ 565	0.791	≤ 1416	50 (4/8)	63 (7/11)	57 (11/19)	0.511
<i>Da</i> ($\mu\text{m}^2/\text{s}$)	268 $\pm$ 38	232 $\pm$ 44	0.077	≤ 233	50 (4/8)	81 (9/11)	68 (13/19)	0.739
<i>f</i> (%)	77 $\pm$ 46	68 $\pm$ 34	0.662	≤ 65.5	75 (6/8)	54 (6/11)	63 (12/19)	0.545
ADC ($\mu\text{m}^2/\text{s}$)	1656 $\pm$ 438	1720 $\pm$ 524	0.776	≤ 1407	50 (4/8)	81 (9/11)	68 (13/19)	0.545
DCE-MRI	<i>n</i> = 11	<i>n</i> = 8						
K^{trans} ($\text{min}^{-1} \times 10^3$)	63 $\pm$ 37	122 $\pm$ 73	0.035a	>110	62 (5/8)	100 (11/11)	84 (16/19)	0.744
K_{ep} ($\text{min}^{-1} \times 10^3$)	262 $\pm$ 279	454 $\pm$ 279	0.158	>220	87 (7/8)	63 (7/11)	73 (14/19)	0.750a
V_e (%)	57 $\pm$ 35	34 $\pm$ 14	0.100	≤ 43	87 (7/8)	63 (7/11)	73 (14/19)	0.693
iAUC (%)	8 $\pm$ 5	17 $\pm$ 12	0.037a	>14	62 (5/8)	90 (10/11)	78 (15/18)	0.761a

AUC, area under the curve; DCE-MRI, Dynamic contrast enhanced magnetic resonance imaging; IVIM DWI, intravoxel incoherent motion diffusion-weighted imaging

All data are means ($\pm$ standard deviation).

^aindicates the statistical significance.

Table 4. Comparison and diagnostic performance of parameters between benign and malignant non-myxoid soft tissue tumors

Parameter	Benign group	Malignant group	<i>p</i> value	Cut-off values	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
IVIM DWI	<i>n</i> = 19	<i>n</i> = 23						
<i>D</i> ($\mu\text{m}^2/\text{s}$)	1294 $\pm$ 249	938 $\pm$ 296	<0.001a	≤ 1183	87 (20/23)	79 (15/19)	83 (35/42)	0.831a
<i>Da</i> ($\mu\text{m}^2/\text{s}$)	312 $\pm$ 114	266 $\pm$ 92	0.152	≤ 279	65 (15/23)	57 (11/19)	62 (26/42)	0.634
<i>f</i> (%)	114 $\pm$ 61	88 $\pm$ 36	0.081	≤ 88	60 (14/23)	68 (13/19)	64 (27/42)	0.638
ADC ($\mu\text{m}^2/\text{s}$)	1365 $\pm$ 238	979 $\pm$ 300	<0.001a	≤ 1261	87 (20/23)	73 (14/19)	81 (34/42)	0.835a
DCE-MRI	<i>n</i> = 24	<i>n</i> = 24						
K^{trans} ($\text{min}^{-1} \times 10^3$)	105 $\pm$ 72	238 $\pm$ 172	0.001a	>110	87 (21/24)	66 (16/24)	77 (37/48)	0.798a
K_{ep} ($\text{min}^{-1} \times 10^3$)	333 $\pm$ 207	832 $\pm$ 510	<0.001a	>358	87 (21/24)	66 (16/24)	77 (37/48)	0.855a
<i>V_e</i> (%)	38 $\pm$ 22	31 $\pm$ 18	0.303	≤ 33	62 (15/24)	50 (12/24)	56 (24/48)	0.584
iAUC (%)	14 $\pm$ 10	26 $\pm$ 15	0.002a	>12	87 (21/24)	62 (15/24)	75 (36/48)	0.766a

AUC, area under the curve; DCE-MRI, Dynamic contrast enhanced magnetic resonance imaging; IVIM DWI, intravoxel incoherent motion diffusion-weighted imaging.

All data are means ($\pm$ standard deviation).

^aindicates the statistical significance.

False negative and false positive cases

D demonstrated a significantly high AUC value among IVIM-DWI parameters, and the *D* cut-off value resulted in seven false positive cases (two angioleiomyoma, two nodular fasciitis, fibromatosis, a fibroma, and a tenosynovial giant cell tumor and eight false negative cases (three myxoid liposarcomas, a fibromyxoid sarcoma, a malignant peripheral nerve sheath tumor, an epithelioid hemangioendothelioma, a leiomyosarcoma, and a synovial sarcoma).

Among DCE-MRI parameters, K^{trans} and K_{ep} revealed significantly high AUC values. Based on K^{trans} cut-off value, there were eight false positive cases (two hemangiomas, two glomus tumors, a fibromatosis, a nodular fasciitis, a tenosynovial giant cell tumor, and an angioleiomyoma) and six false negative cases (two myxoid

liposarcomas, a synovial sarcoma, an epithelioid hemangioendothelioma, a leiomyosarcoma, and a low-grade fibromyxoid sarcoma), while based on K_{ep} cut-off value, there were 10 false positive cases (three hemangiomas, two nodular fasciitis cases, a schwannoma, a glomus tumor, a myxoma, a neuroma, and a tenosynovial giant cell tumor) and 7 false negative cases (two myxoid liposarcomas, a myxofibrosarcoma, a malignant peripheral nerve sheath tumor, a malignant solitary fibrous tumor, an epithelioid hemangioendothelioma, and a synovial sarcoma).

DISCUSSION

Our study showed that *D*, ADC, K^{trans} , K_{ep} , and iAUC can be used to differentiate benign and malignant soft tissue tumors. Only the DCE-MRI parameters of K^{trans} , and iAUC enabled differentiation of benign and malignant myxoid soft tissue tumors, whereas *D*, ADC, K^{trans} , K_{ep} , and iAUC can be used to differentiate benign and malignant non-myxoid soft tissue tumors.

Although we did not assess capacity of conventional MRI to characterize soft tissue tumors, Chung et al²³ reported the diagnostic values of conventional MRI using depth, size, and heterogeneity to differentiate between benign and malignant soft tissue tumors, resulting in a sensitivity of 64%, a specificity of 85%, and an accuracy of 77%. By comparing the results of that study using conventional MRI by Chung et al²³ and the results presented in this study using multiparametric MRI, we can infer that addition of multiparametric MRI to conventional MRI can improve the diagnostic performance in distinguishing malignant from benign soft tissue tumors, as it increased the sensitivity (71 to 81%) while maintaining similar levels of specificity (69 to 83%) and accuracy (70 to 79%).

D and ADC were significantly different between malignant and benign soft tissue tumors with good diagnostic performance, consistent with previous studies.^{12,13} We expected that *D* would be better than ADC for differentiating soft tissue tumors because *D* eliminates the contributions of tissue perfusion to reflect tissue

Figure 5. Graph showing ROC comparison between prediction models (*D* alone, *D* combined with K_{ep} , and *D* combined with K_{ep} and iAUC; AUC, 0.750, 0.809, 0.838, respectively) for predicting malignancy. (AUC, area under the curve; ROC, receiver operating characteristic curve)

diffusivity more precisely than ADC.²⁴ However, the AUCs of ADC and D were similar based on ROC analysis (ADC, 0.752; D , 0.742) and multivariate logistic regression analysis, in agreement with the recent study by Lim et al.¹³ Our results were contrary to the previous study by Rijswijk et al.⁶ Rijswijk et al⁶ investigated soft tissue tumors using early IVIM-DWI with five b -values (0–701 s/mm²) at 1.5 T and reported that D was significantly different between benign and malignant soft tissue tumors, whereas ADC was not. Early IVIM-DWI with fewer b -values at 1.5 T might be one of the reasons for the difference. We also assume that microcapillary perfusion might be heterogeneous or higher in benign soft tissue tumors than in malignant soft tissue tumors, which seems to contribute to there being no significant difference between ADC and D for differentiating soft tissue tumors. This assumption is reinforced by our result that there were no differences in D^* and f between malignant and benign soft tissues, similar to the previous study by Lim et al.¹³

We found significant differences in K^{trans} , K_{ep} , and iAUC between malignant and benign soft tissue tumors with good diagnostic performances. Our results are similarly to that of Leplat et al,¹⁹ who found only K^{trans} was only different between malignant and benign soft tissue tumors. However, we observed some discrepancies in K_{ep} , iAUC, and K^{trans} , which might be due to different AIF selection and ROI measurement techniques. Leplat et al¹⁹ used automatic software AIF selection, and ROIs were placed on the tumor areas that were most intensely enhancing on the AUC map. Our study found that among quantitative DCE-MRI parameters, K_{ep} had the highest AUC by ROC analysis (K_{ep} , 0.817; K^{trans} , 0.792; iAUC, 0.771) and multivariate logistic regression analysis, similar to a previous study.²⁵ Oto et al²⁵ found the best correlation between quantitative perfusion parameters and histologic angiogenesis parameters were noted between K_{ep} and microvessel density. K_{ep} is an index of K^{trans} / V_e , and the compounding effect of K^{trans} and V_e may contribute to better correlation of K_{ep} and microvessel density.²⁵

Our study found that soft tissue tumors are distinguished better when evaluated with a combination of IVIM-DWI and DCE-MRI than when evaluated by IVIM-DWI alone. The subgroup analysis of our study classified benign and malignant soft tissue tumors into two groups each: myxoid and non-myxoid subgroups, and showed that ADC and D were not significantly different between benign and malignant myxoid soft tissue tumors. Although a classification of myxoid soft tissue tumors based on the WHO classification²⁶ did not include peripheral nerve sheath tumors in myxoid soft tissue tumors, we categorized peripheral nerve sheath tumors as myxoid soft tissue tumors because they histologically contained a small myxoid component.^{26,27} As illustrated by the subgroup analysis

results, IVIM-DWI has limitations in differentiation of soft tissue tumors because ADC is affected by the extracellular matrix as well as by cellularity.^{9,21,27} Regardless of benign or malignant behavior, soft tissue tumors contain varying degrees of myxoid matrix, which causes overlap in ADC values between benign and malignant soft tissue tumors. This was demonstrated by subgroup analysis in our study and previous studies.^{9,21,27} The ADC and D of malignant myxoid soft tissue tumors were slightly higher than those of benign myxoid soft tissue tumors, although there was no significant difference ($p > 0.05$). We thought these results were affected by inclusion of peripheral nerve sheath tumors in the subgroup of myxoid soft tissue tumors. As schwannoma, which has a relatively small myxoid component, was included as a benign subgroup, the ADC and D of the benign subgroup were demonstrated to be lower than those of the malignant subgroup.

Our study had several limitations. First, it was conducted retrospectively at a single institution with a limited study population. Although we enrolled consecutive patients with clear inclusion criteria, the possibility of selection bias remains. Second, the study population and range of tumors were relatively small because surgeons at our institution (Seoul St. Mary's Hospital) do not perform surgery on tumors that are definitely benign on imaging studies. Third, ROIs may contain calcifications of soft tissue tumors that affect ADC values because calcifications cannot be completely excluded on MRI. Finally, we did not assess conventional MRI because it is subjective and our purpose was to provide an objective quantitative value to differentiate benign and malignant soft tissue tumors in clinical practice. Since the usefulness of IVIM-DWI and DCE-MRI in addition to conventional MRI was not been addressed in our study, it is not known how useful is multiparametric MRI for diagnosis of soft tissue tumors compared to conventional MRI alone. We expect this evaluation to be performed in future studies.

In summary, quantitative analysis of multiparametric MRI including IVIM-DWI and DCE-MRI enables better differentiation of benign and malignant soft tissue tumors. Particularly in myxoid tumors, the DCE-MRI parameters of K^{trans} , and iAUC enable differentiation of benign and malignant myxoid soft tissue tumors.

CONFLICT OF INTEREST

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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