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RESEARCH ARTICLE

THE ROLE OF PERFUSION MAGNETIC RESONANCE IMAGING IN THE DISCRIMINATION OF BENIGN VS MALIGN CHARACTER OF MUSCULOSKELETAL TUMORS

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ABSTRACT

Purpose: There may be difficulties in diagnosing musculoskeletal system tumors with Magnetic Resonance Imaging (MRI). Advanced MRI imaging techniques may contribute to noninvasive diagnosis.The aim of our study was to evaluate the performance of perfusion magnetic resonance imaging quantitative data in the differentiation of benign and malignant musculoskeletal tumors.
Material and Methods: Thirty-six histologically proven patients were included in the study retrospectively. All patients underwent 1.5-T perfusion MRI (magnetic resonance imaging) with T1 mapping and diffusion MRI. Four quantitative and one semiquantitative parameter were obtained for each tumor using the Toft pharmacokinetic model. ADCmean and ADCmin values were calculated from apparent diffusion coefficient (ADC) maps.
Results: Eighteen of 36 patients (50%) had malignant tumors, and 18 had benign tumors. There were 26 soft tissue tumors and 10 bone tissue tumors. Among malignant and benign tumors, the best performance was found in the Ktrans, Kep, Ve values. (p=0.011, p=0.013, p=0,035).
Conclusion: Ktrans and Kep values, which are indicators of increased permeability in the tumor, are noninvasive parameters for determining the malignant character of the tumor. The 'Ve' value is an indicator of the extracellular volume of the tumor. Ktrans, Kep and Ve maps can also guide the biopsy.

Keywords: ADC, MRI, Kep, Ktrans, ROI, Ve.

INTRODUCTION

Noninvasive characterization of musculoskeletal tumors can be difficult with conventional imaging methods because of their overlapping radiological appearances and their rarity (1). Multiparametric DC-MRI (dynamic contrast-magnetic resonance imaging) and DWI (diffusion weighted imaging) provide information about tissue perfusion, vascularization, vascular permeability, interstitial space value, and cellularity of the lesion (2). DC-MRI; gives a graph of

Table 1. Soft tissue tumor histological subtypes

Soft tissue			
Benign		***Malign***	
Schwannoma	4	Sarcoma	1
Vascular tumors	4	Synovial sarcoma	2
Pseudotumor*	1	Mesenchymal tumor	4
Desmoid tumor	1	Round cell tumor	1
Others**	6	Squamous cell tumor	1
Tenosynovial giant cell tumor	1		
Total: 26			

*Pseudotumor: Gout. **Solid fibrous tumor, neurofibroma, lipomatous tumor

Table 2. Bone tumor histological subtypes

Bone Tumors			
Benign		***Malign***	
Fibrous histiocytoma	1	Osteosarcoma	1
Brown tumor	1	Round cell tumor	1
		Multiple Myeloma	1
		Chordoma	1
		Chondrosarcoma	2
		Metastasis***	2
Total: 10			

***bladder transitional cell cancer, lung adenocarcinoma

the signal intensity over time. It allows the measurement of values such as capillary permeability of tissue, blood flow, blood volume, and extracellular-extravascular volume fraction with quantitative measurements (3).

Permeability MRI quantitative values provide important clues in determining the noninvasive characterization of the tumor. Since the Ktrans value reflects the capillary permeability and the aggressiveness of the tumor, it is the most emphasized parameter in the literature in determining the malignant vs. benign character (4).

Clinical application is not simple because the obtained quantitative parameters are very sensitive depending on the technique used and require additional time to daily MRI practice and long post-processing procedures (5). There have been studies in the literature that it can be used as a biomarker in many tumor groups. Although DC-MRI parameters are thought to be useful in the differentiation of benign and malignant musculoskeletal tumors, there are not enough studies on this subject in the literature (6). The diffusion coefficient "ADC" determined in DWI allows us to predict the cellularity and malignant potential of the tumor (7).

The aim of this study was to evaluate the correlation of histopathological diagnosis with parameters ADC, Ktrans, Kep, Ve, Vp, and IAUC (incremental area under the curve) obtained from multiparametric MRI in the differentiation of benign and malignant soft tissue and bone tumors.

MATERIAL AND METHODS

Ethical Considerations

This study was approved by Dokuz Eylul University, Non-Interventional Research Ethics Committee (Date: 14.09.2020, Decision No: 2020/21-19).

Population

In this single-center study, between July 2018 and December 2020, patients diagnosed with bone and soft tissue tumors as a result of biopsy or excision and imaging with DC-MRI were retrospectively scanned, and 36 patients were identified. This study was approved by Dokuz Eylul University, Non-Interventional Research Ethics Committee (Date: 14.09.2020, Decision No: 2020/21-19). All patients were over the age of 18. Informed consent was waived due to the retrospective nature of the study. Patients whose MRI images are not suitable for evaluation due to metallic artifacts (prosthesis, etc.) and patients who received treatment before MRI for the tumor for their current diagnosis were excluded. Thus, the study population consisted of 10 bone and 26 soft tissue tumor patients (Tables 1, 2).

MRI Protocol

All patients were captured on a 1.5 A Tesla MRI device (Philips Healthcare/Philips Medical Systems B. V, The Netherlands), DWI and DC-MRI sequences were taken in addition to routine sequences.

In dynamic imaging, the shooting was taken with TR: 4.01 msec, TE: 1.94 msec, matrix: 192x192, GE (T1 Single Shot Turbo Field Echo) sequence, and the shooting time was approximately 6 minutes. The contrast agent gadoterat meglumin (Dotarem,

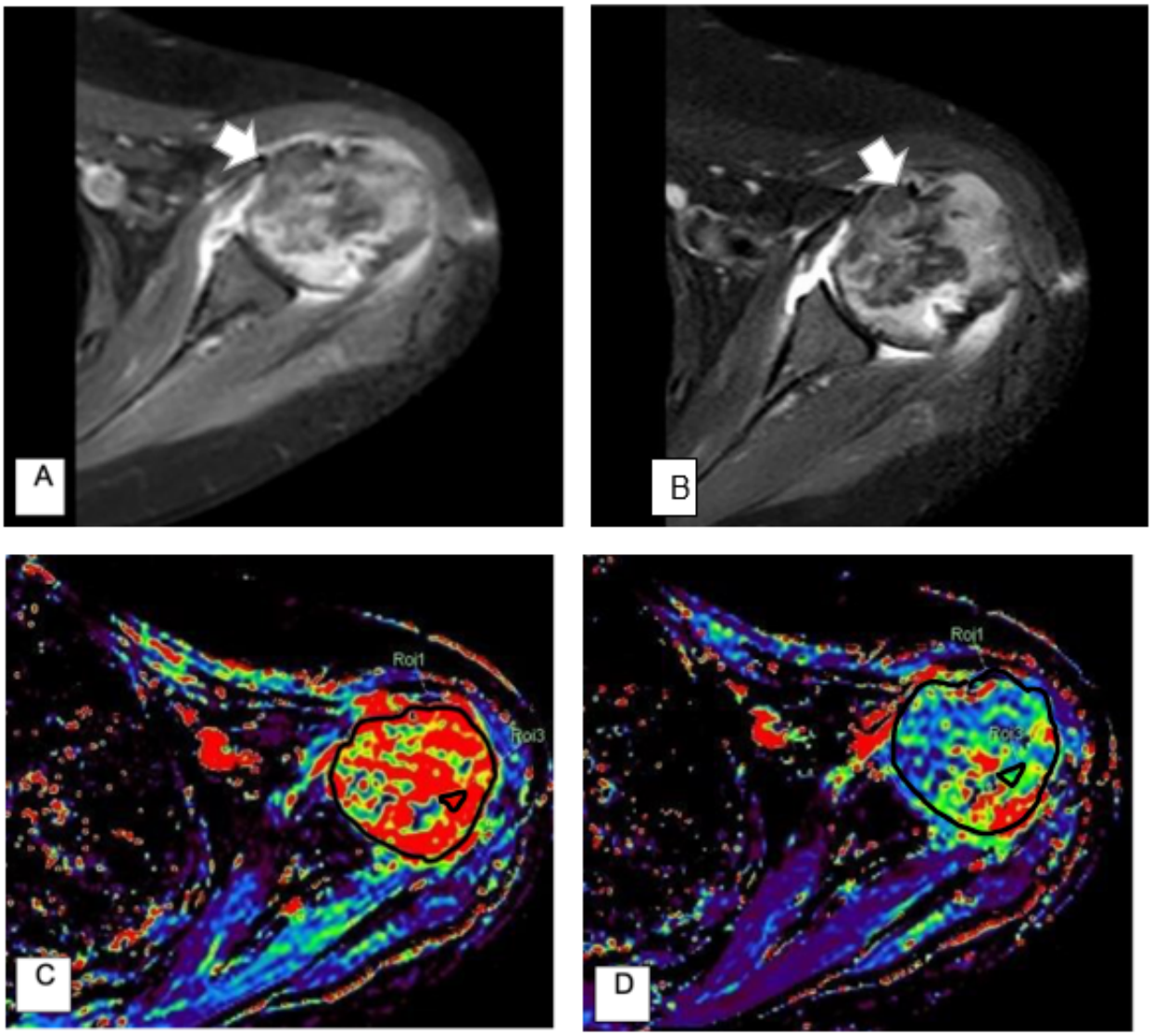

Figure 1. Measurement samples of T2W, postcontrast T1W and DC-MRI quantitative parameters of a patient with osteosarcoma. **A:** Postcontrast T1 weighted images (left arrow) **B:** On T2 weighted images, lesion located in the humeral epiphysometaphysis causing cortical destruction (right arrow) **C:**Ktrans, **D:** Kep maps, measurements were made with the ROI placed on the widest (ROI 1) section and the narrow ROI (ROI 3) (highlighted by black drawing).

Guerbet Medicine Medical Materials and Devices Industry and Trade Inc.) was administered intravenously from the forearm with an automatic injector at a dose of 0.2 mmol/kg at a rate of 2 ml/s. After the contrast agent injection, 20 ml of saline was injected.

To provide sufficient data for pharmacokinetic analysis data, the examination will typically continue for more than 5 minutes (3-4 min for Kt alone, 6 min for Ve and Vp). High temporal resolution is essential (3-6 seconds) to obtain high-quality images and to clearly show the hemodynamic process in the tissue. The temporal resolution can be enhanced using the parallel imaging method. High temporal resolution may require sacrificing the signal-to-noise ratio (SNR). Mapping DC-MRI dynamic parameters requires an optimal balance between temporal and spatial resolution and volumetric area to be imaged and SNR. In diffusion-weighted imaging, b=500 s/mm2 and b=1000 s/mm2 values were used.

Analysis of images

Images of all patients were transferred to the workstation (IntelliSpace Portal V8.2.20820, Philips Medical Systems, Netherlands), and all measurements were made at the workstation. DC-MRI images were obtained by means of dynamic series and T1 maps. AIF (arterial input function);

Table 3. DC-MRI data of malignant and benign tumor tissue comparison

	Malign Tumor		Benign Tumor		P value
	Median	**Minimum-Maximum**	**Median**	**Minimum-Maximum**	
Wide ROI Ktrans (min -1)	45,3	0,009-366,06	34,42	0,001-50,4	0,018
Standart ROI Kep (min -1)	578,32	0,005-1485,74	222,96	0,001-589,92	0,013
Standart ROI Ktrans	254,86	0,011-1,850	39,86	0,001-404,74	0,011
Wide ROI Ve	308,96	0,023-452,63	20,45	0,00-109,77	0,035

modeled using an intermediate mode provided by the software. Diffusion images and ADC maps of each B value were used to evaluate the diffusion-weighted images. Necrotic and solid areas of the tumor were determined with the help of available T2W (weighted), non-contrast and contrast-enhanced T1W (weighted), images.

Two different measurements were made for the quantitative analysis of the images. First, for the evaluation of DC-MRI, with the help of T1W and T2W images, areas of necrosis were avoided ,and the widest section of the tumor was determined. Ktrans, Kep, Ve, Vp ,and iAUC measurements were made with the free ROI placed in this section. In the second method, in lesions larger than 1 cm in diameter, three standard ROIs of approximately 0.35 square centimeters, which do not intersect with each other as much as possible, were used from the most solid areas of the tumor. In lesions smaller than 1 cm (with approximately 0.35 square centimeters ROI), Ktrans, Kep, Ve, Vp, iAUC ,and ADC data from the ADC map were measured and recorded from DC-MRI sections. The highest Ktrans, Kep, Ve, Vp ,and iAUC values and the lowest ADC values were chosen to reflect the solid part of the tumor in lesions with three measurements. A single measurement was used in patients who could not have three measurements. In addition, DC-MRI data of normal tissue were obtained with ROIs placed in normal tissues.

Pharmacokinetic analysis was performed according to the Toft model (8). The contrast agent in the vein passes into the EES depending on the concentration difference and permeability. The volume transfer constant (Ktrans) reflects the rate of flow of gadolinium contrast from the blood plasma into the extracellular-extravascular space (EES). In cases where permeability is limited, Ktrans becomes an indicator of permeability (9). It has been reported that blood flow and vascular permeability may increase in cancer angiogenesis compared to normal tissue, and therefore, Ktrans may be higher in primary tumor localization (10). Kep is the flow rate constant between the plasma and the EEB. Ve is the volume of the EES cavity, and Vp is the plasma volume. Vp; indicates how much of the unit tissue volume is the plasma volume. The area under the signal intensity time curve (IAUC) does not require AIF and is an independent parameter from pharmacokinetic modeling calculations. It reflects both tumor perfusion and permeability (11).

For the evaluation of diffusion, measurements were made with the ROI placed similarly in the same section, and ADCmean, min, and max data were recorded.

Measurements were made by two radiologists at different times, one with 5 years of experience (s, s.) and the other with 3 years of experience (s, e.a.). The observer with 5 years experience was accepted as standard while analyzing benign and malignant tumor differentiation. Interobserver compliance was assessed.

Statistics

The Kolmogorov-Smirnov test was performed to determine whether the data were normally distributed. The Spearman correlation test was used

Table 4. Concordance of interobserver DC-MRI data valuation

Compared metrics	SCC	95% CI
$G1_{Ktrans}$ -G2 Ktrans	0.918	0.840 to 0.958
$G1_{Kep}$ -$G2_{Kep}$	0.955	0.913 to 0.977
$G1_{Ve}$ -$G2_{Ve}$	0.936	0.875 to 0.967
$G1_{Vp}$ -$G2_{Vp}$	0.731	0.476 to 0.862
$G1_{iAUC}$ -$G2_{iAUC}$	0.665	0.348 to 829

SCC: Standard correlation coefficient; CI: Confidence interval

to evaluate the correlation of nonnormally distributed data. The Mann-Whitney U test was used to evaluate the differences between DC-MRI and DWI data in the differentiation of benign vs. malignant tumors. In addition, the Wilcoxon signed rank test was used to determine whether there was a significant difference between DC-MRI data from tumor tissue and DC-MRI data from normal tissue. The chi-square test was used to compare qualitative data.

The intraclass correlation coefficient (ICC) was used to evaluate the correlation of DC-MRI and diffusion parameters between the two observers.

SPSS 24 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, and the results with $p<0.05$ in all analyses were considered statistically significant.

RESULTS

In measurements made with standard and wide ROIs, in Ktrans and Ve values with large ROIs, a statistically significant difference was observed in malignant lesions compared to benign lesions in Ktrans and Kep values performed with standard ROIs ($p<0.05$) (Table 3). There was no significant difference between benign and malignant tumors in the diffusion MRI parameters ADCmean, ADCmin and ADCmax. The sensitivity and specificity of the cut-off values in the ROC analysis remained below 50%.

In the measurement of DC-MRI data, in the measurement of Ktrans, Kep, Ve, and Vp, the agreement between the observers was excellent-good, and the iAUC was moderate (Table 4).

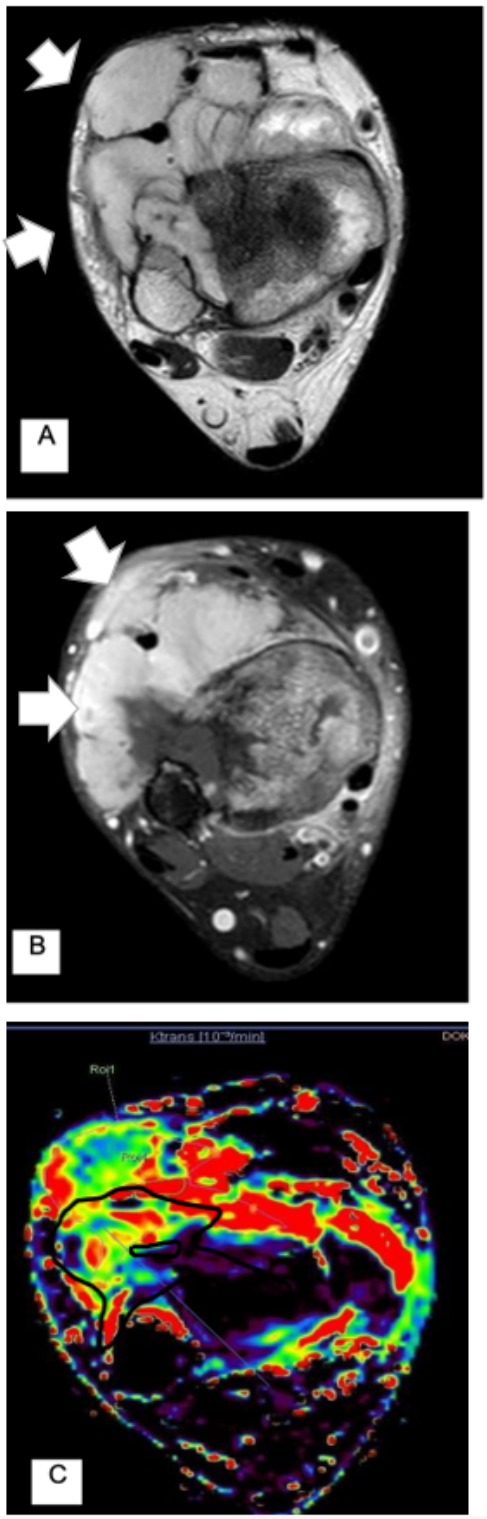

Figure 2. Measurement samples of T2W, postcontrast T1W, DC-MRI quantitative parameters of a patient with osteosarcoma. A: T2W B: Mass lesion in the ankle that destroys bone and extends into soft tissues on postcontrast T1W images (white arrows) C: Illustration of the measurement of dynamic contrast-enhanced MRI quantitative parameters with large (ROI 1) and standard ROIs (ROI 4) (highlighted by black drawing).

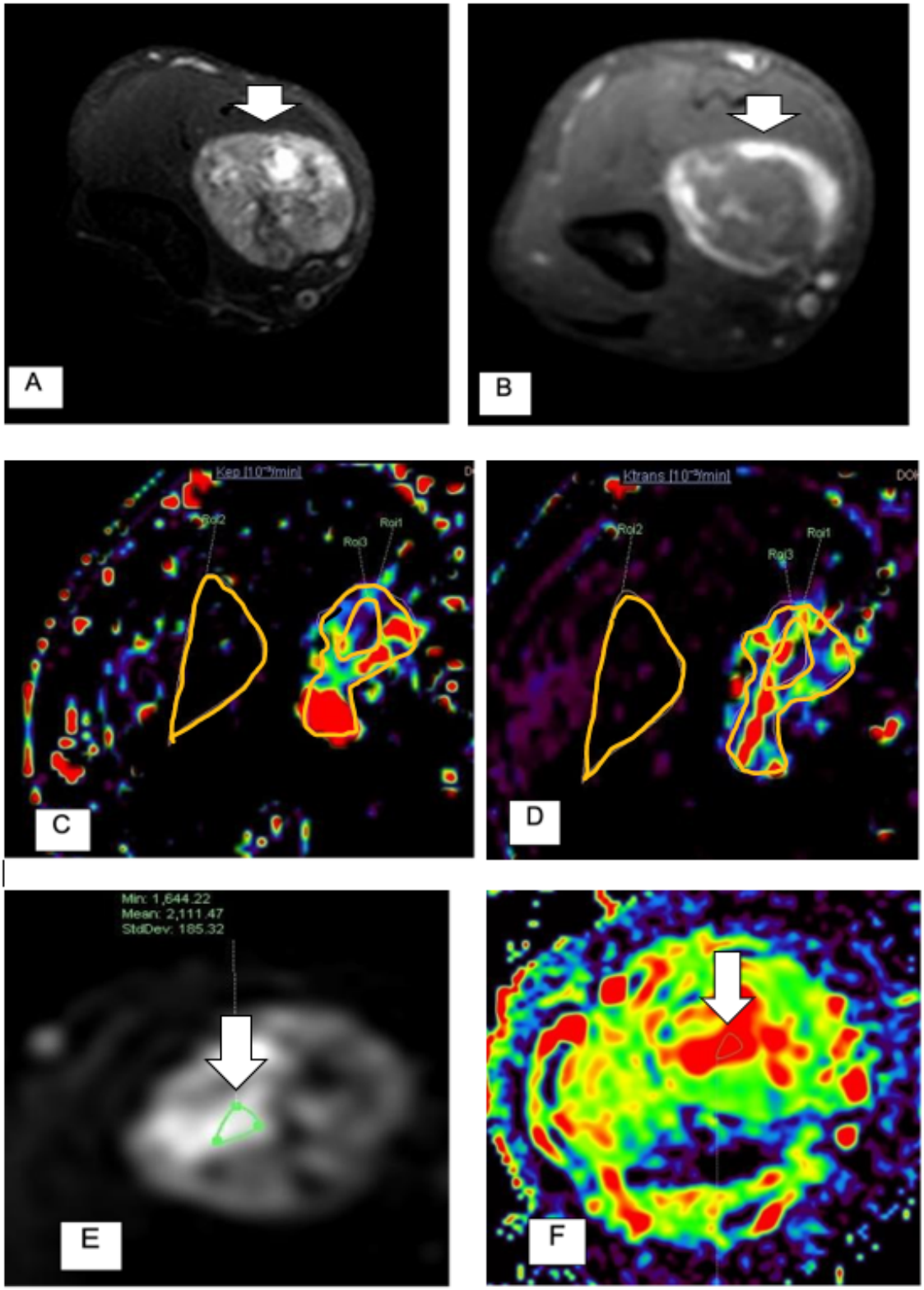

Figure 3. Measurement samples of T2W, postcontrast T1W, DC-MRI quantitative parameters of the patient with osteosarcoma and diffusion-weighted images **A:** T2W **B:** Deeply located heterogeneous mass lesion between muscle planes on postcontrast T1W images (white arrows) **C and D**: Wide and wide range of dynamic contrast-enhanced MRI quantitative parameters display of measurement with a standard ROI (ROI 3). (ROI 2: normal tissue, ROI 1: large ROI from the tumor) (highlighted by yellow drawing) **E:** Diffusion weighted image (left arrow) **F:** ADC (apparent diffusion coefficient); measurements were made from the area where diffusion restriction was observed in the lesion (right arrow)

DISCUSSION

In our study, we found Ktrans and Kep values in standard ROI in musculoskeletal tumors to be significantly higher in the malignant group and Ktrans and Ve values to be higher in our measurements with large ROI. Interobserver correlation in Ktrans, Kep, Ve and Vp values was good-excellent.

The findings show that determining quantitative permeability values, which are closely related to neovascularization of the tumor, will be beneficial in addition to conventional MRI findings in making a non-invasive diagnosis. It can also guide the biopsy by creating permeability maps such as Ktrans, Kep and Ve. Since there is no clear consensus regarding the measurement, we wanted to show two different measurement results. In the standard ROI, Ktrans and Kep values, which show the permeability of the tumor, reflect the measurement made from the most solid part of the tumor; We found the Ve value, which is a quantitative indicator of extracellular volume, to be significantly higher in the wide ROI, reflecting the largest area of the tumor.

Clinical application of perfusion MRI does not require extra doses of gadolinium and does not increase the cost of conventional MRI examination for standard characterization of musculoskeletal tumors. For this reason, it is thought that its routine use will contribute to the diagnosis.

The results of studies conducted on musculoskeletal tumors, generally with soft tissue tumors, have shown that the use of quantitative parameters to examine tumor perfusion may be useful (12).In studies conducted with the soft tissue tumor group, Ktrans and Kep values, which are associated with tumor aggressiveness and neoangiogenesis, were found to be significantly higher in the malignant tumor group (13,14,2).

Although we obtained a significant difference in permeability quantitative values in the malignant group, we obtained low sensitivity and specificity. The limitations of the study are due to the small number of patients, the fact that the patient population is a very heterogeneous group including both bone and soft tissue tumors, the lack of a standardized protocol of DC-MRI applied in the same way in every center and the chosen pharmacokinetic model. It is thought that there are factors affecting the perfusion image quality and causing interpatient variation in quantitative perfusion parameters depending on the technique. Many factors during data acquisition and analysis, such as the characteristics of the MRI device, T1 analysis method, AIF measurement method, ROI and parameter selection, and pharmacokinetic model variability, were considered. It can affect the reliability of the results of studies with MRI, which causes different results in different institutions (6). Intraobserver compliance was not measured, which may be considered as a limitation.

DWI, in addition to contributing to the diagnosis of musculoskeletal tumors, it also provides an idea about the structure and behavior of the tumor. Diffusion MRI makes great contributions to early diagnosis, staging and evaluation of response to treatment (15). In our study, no significant difference was observed in the ADCmean and ADCmin values in the group in which the majority (n=26) of 36 patients had soft tissue tumors ($p>0.05$). Some studies have shown a correlation between ADC values and tumor grade (16). High ADC values in tumors with dominant necrotic or cystic components may reduce the relationship between ADC and cell density. High ADC values can be detected in bone tumors with a high chondroid matrix and soft tissue tumors with a high myxoid matrix, even if they are malignant (17).

Limitations

We also showed in our study that there may be overlaps in diffusion studies in musculoskeletal tumors. More meaningful results can be obtained in a more homogeneous patient group.

The distinction between benign and malignant soft tissue and bone tumors, which have a very heterogeneous spectrum, is not always easy. In addition to conventional magnetic resonance imaging and other imaging modalities, it has become possible to obtain more data about these lesions with newly developed techniques.

CONCLUSION

Our work has shown that the use of perfusion MRI quantitative data can be useful in the differential diagnosis of tumors, similar to many studies in the literature. DC-MRI quantitative parameters have the potential to be a noninvasive biomarker in determining the malignant character of the tumor. In future studies, it is thought that the contribution of the method will be clearer with the standardization of measurement methods and techniques and a wider patient group.

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