

Evaluating Efficacy of Dynamic MR Perfusion Imaging in Soft Tissue Tumors

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Abstract

Objective: The aim of this study was to assess the effectiveness of dynamic contrast-enhanced (DCE) MRI perfusion parameters and signal intensity–time curves in distinguishing between benign and malignant soft tissue tumors.

Methods: The study included 51 patients with soft tissue tumors who underwent DCE MRI at 3.0 T. Among these patients, 30 had benign tumors, while 21 had malignant tumors. Perfusion parameters such as k-trans, kep, Ve, and iAUC were measured. Calculations were performed at the most contrast-enhanced areas of the lesions using circular regions of interest measuring 0.2-0.4 cm². The findings were illustrated using signal intensity–time (SIT) curves, which were categorized into 5 types for evaluation.

Results: In the benign group, 19 out of 30 lesions (63.3%) showed contrast enhancement patterns corresponding to type 1-2 SIT curves, and 11 out of 30 lesions (36.7%) exhibited patterns corresponding to type 3-4-5 SIT curves. In contrast, all 21 malignant lesions (100%) displayed type 3-4-5 patterns. Mean values of K-trans ($P < .001$), Ve ($P = .004$), and iAUC ($P < .001$) were significantly higher in malignant lesions compared to benign ones. There was no significant difference in Kep values between the 2 groups ($P = .628$).

Conclusion: The perfusion parameters K-trans, Ve, and iAUC, along with the contrast enhancement patterns observed in DCE MRI, can aid in differentiating between benign and malignant soft tissue tumors.

Keywords: Dynamic contrast-enhanced MRI, soft tissue tumors, MRI perfusion

INTRODUCTION

Magnetic resonance imaging (MRI) is a widely used imaging method in the investigation of soft tissue tumors due to its superiority in soft tissue contrast.^{1,2} Morphological features of tumors, such as size, extension, and relationship with vascular structures can be evaluated with conventional MRI sequences. Administration of paramagnetic contrast material can support the evaluation of these features.¹⁻⁶ These agents pass from the intravascular space to the extravascular space, thus enabling both the detection and characterization of tumors by MRI.⁷

Contrast-enhanced MRI can be applied statically and dynamically. In static contrast MRI, a tissue signal is obtained at a random time point following the injection of contrast material. In contrast to static contrast-enhanced MRI, dynamic contrast-enhanced (DCE) MRI samples the MR signal at multiple time points following the injection of contrast medium. This gives information about the area's enhancement over time. These enhancement characteristics show tissue vascularity and perfusion, which may be associated with tumor angiogenesis.^{1,8}

Differentiating benign and malignant soft tissue tumors is important for patient management and treatment planning. Making this distinction prevents unnecessary surgery in benign lesions. With developing MRI technology, it is becoming a candidate for a non-invasive method in the differential diagnosis of benign and malignant soft tissue tumors. There are some publications showing that perfusion MRI parameters can be used to differentiate benign and malignant tumors.⁹⁻¹²

The aim of this study was to assess the effectiveness of DCE-MRI perfusion parameters and signal intensity–time curves in differentiating benign and malignant soft tissue tumors.

MATERIAL AND METHODS

Patient Selection

This retrospective study received approval from Gazi University ethics committee with decision number: 513, and informed consent was waived. Sixty-four patients who underwent DCE-MRI between January 2011 and November 2014 with the diagnosis of soft tissue tumors were evaluated.

Patient data were collected from the hospital medical recording and data system. Patients with soft tissue tumors that were histopathologically confirmed or diagnosed through clinical and radiological follow-ups were included in this study. Patients whose DCE-MRI was not performed with the appropriate technique and whose images not suitable for evaluation were excluded from the study.

MRI Technique

All cases were examined by a 3.0 T MR system (Magnetom Verio, Siemens, Erlangen, Germany), with body coils or superficial coils depending on the localization of the lesion. Before the administration of the contrast agent, the standard T1W and T2W SE sequence images were acquired, and then DCE-MRI was performed.

For the DCE-MRI, all cases were administered gadopentetate dimeglumine (Magnevist, Bayer-Schering, Berlin, Germany) 0.1 mmol/kg intravenously. Following the administration of the intravenous contrast agent, 15 mL of physiological saline solution was given at the same rate. Dynamic contrast-enhanced-MRI sequencing started simultaneously with the administration of the IV contrast media injection. Dynamic contrast-enhanced-MRI was performed using 3-dimensional fat-suppressed T1W GRE (VIBE – Volumetric Interpolated Breath-hold Examination) sequences. The following parameters were used for the T1W VIBE sequences: TR: 4.29, TE: 1.47, NEX: 1, flip angle: 9°, FOV: 280 mm, matrix: 183 × 288, and slice thickness: 4 mm. Images were acquired in 35 consecutive sequences, each lasting 10-15 seconds and covering all lesions on the axial plane.

The computations were performed at the highest contrast-enhanced areas of the lesions using circular region of interests (ROIs) of 0.2-0.4 cm². The results were demonstrated by the signal intensity–time (SIT) curves. Signal intensity–time curves were evaluated in 5 categories.¹¹

- Type 1: No contrast enhancement.
- Type 2: Slow contrast enhancement.
- Type 3: Plato phase following the rapid enhancement at the beginning.
- Type 4: Wash-out phase following the rapid enhancement at the beginning.
- Type 5: Increasingly contrast enhancement following the initial rapid enhancement.

The following DCE-MRI perfusion parameters were *K-trans* (volume transfer constant), *kep* (transfer rate constant, which is the reflux of contrast agent from the extravascular extracellular space to the plasma compartment), *Ve* (fractional volume of the extravascular extracellular space), and *iAUC* (the initial area under the contrast uptake curve) values computed at the highest contrast-enhanced areas of the

lesions using circular ROI of 0.2-0.4 cm². Simultaneously, circular ROI were placed in the arteries and muscles to compute the perfusion parameters.

Statistical Analysis

The statistical tests were performed in SPSS version 20 (IBM SPSS Corp.; Armonk, NY, USA). Primarily, descriptive analyses were utilized. The Shapiro–Wilk normality test was used to determine whether the data followed a normal distribution. For continuous variables, descriptive statistics were presented as mean ± SD or as median values (minimum–maximum). Categorical variables were expressed as numbers of observations and percentages (%). The Mann–Whitney *U* test was used to evaluate the differences between the benign and malignant lesion groups. The cut-off points for the parameters were determined by receiver operating characteristic (ROC) analysis to assess the values of the T1W dynamic perfusion MRI parameters useful for the differential diagnosis of benign and malignant lesions. Using these cut-off points of the parameters, the values for sensitivity and specificity, as well as the positive predictive values (PPV) and negative predictive values (NPV) were determined according to Youden's index. To evaluate whether the *k-trans*, *kep*, *Ve*, and *iAUC* values were determinants for the differential diagnosis of malignant and benign lesions, the areas under the curve were calculated by ROC analysis. If the value of the area under the curve was found to be significant, the best cut-off point was calculated using Youden's index. In addition, the sensitivity, specificity, and reliability values, as well as the positive and negative predictive values were calculated for this point. *P* < .05 was considered statistically significant.

RESULTS

A total of 51 cases were included in the study, comprising 24 (47.1%) female and 27 (52.9%) male patients. The patients' ages ranged 12-84 years, with a mean age of 42.2 ± 19.5. Of the cases, 30 (58.8%) were diagnosed with benign soft tissue tumors, 16 (31.4%) with malignant tumors, and 5 (9.8%) were diagnosed with intermediate–borderline soft tissue tumors. The diagnoses were made histopathologically in 34 patients and through clinical and radiological follow-up findings in 17 patients. Intermediate-borderline tumors were included in the malignant tumors group. Finally, 30 (58.8%) cases with benign soft tissue lesions and 21 (41.2%) malignant tumor cases, making up a total of 51 cases, were included in our study. Histopathological subtypes of tumors are presented in Table 1.

No statistically significant differences were found in age, gender, and the mean dimension of the lesions between the malignant and benign soft tissue lesion groups (*P* > .05). The comparisons of the benign and malignant cases in terms of age, gender, and the mean dimension of the lesions are presented in Table 2.

The distribution of the SIT curve categories is detailed in Table 3. Nineteen (63.3%) lesions demonstrated contrast enhancement patterns of types 1 and 2; however, 11 (36.7%) cases demonstrated type 3, 4, and 5 SIT curve categories out of the 30 benign lesions. On the other hand, all 21 (100%) malignant soft tissue tumors showed type 3, 4, and 5 contrast agent enhancement patterns. Therefore, the NPVs of type 1 and 2 SIT curve patterns were found to be 100% in diagnosing malignant lesions.

The distributions of the perfusion parameters, computed from T1W dynamic perfusion MRI, in benign and malignant lesion groups are presented in Table 4.

MAIN POINTS

- This study evaluates the effectiveness of dynamic contrast-enhanced (DCE) MRI perfusion parameters and signal intensity–time (SIT) curves in differentiating benign and malignant soft tissue tumors.
- Significant differences in *K-trans*, *Ve*, and *iAUC* values were found between benign and malignant tumors, with higher values observed in malignant tumors, aiding in their differentiation.
- DCE MRI provides useful quantitative parameters and SIT curves for distinguishing between benign and malignant soft tissue lesions.

Table 1. Histopathological Subtypes of Tumors

Histopathological Subtypes	n
Benign (n=30)	
Lipoma	8
Hemangioma	6
Schwannoma	3
Neurofibroma	3
Myxoma	1
Myoepithelioma	1
Giant cell tumor of tendon sheet	1
Elastofibroma dorsi	1
Pigmented villonodular synovitis	1
Tumor-like structures	
Intramuscular hematoma	1
Crural abscess	1
Focal synovitis	1
Epidermal-type keratinous cyst	1
Myositis ossificans	1
Malignant (n=16)	
Malignant mesenchymal tumor	3
Synovial sarcoma	2
Liposarcoma	2
Leiomyosarcoma	2
Undifferentiated pleomorphic sarcoma	2
Pleomorphic malignant fibrous histiocytoma	1
Malignant giant cell tumor	1
Metastasis	3
Intermediate-borderline (n=5)	
Desmoid tumor	3
Fibromatosis	1
Angiomatous fibrous histiocytoma	1

The *K-trans* and *iAUC* values of malignant soft tissue lesions were found to be significantly higher statistically compared to those of the benign lesions ($P < .001$). Similarly, *Ve* values of the malignant tumors were found to be statistically significantly higher compared to those of the benign lesions ($P < .05$). There was no significant difference between malignant and benign lesion groups in terms of *Kep* values ($P > .05$) (Figure 1).

Table 2. The Demographic Characteristics of the Patients and the Lesion Dimensions by Group

	Benign (n=30)	Malignant (n=21)	P
Age	41 ± 17 (18-82)	44 ± 23 (13-84)	.674
Gender (male/female)	14/16	13/8	.288
Mean dimension (cm)	7.7 ± 4.7 (1.7-20)	9.0 ± 4.9 (2.5-24)	.224

Data: mean ± standard deviation.

Table 3. Distributions in the Benign and Malignant Lesion Groups According to the SIT Curve Categories

Type of the SIT Curves	Benign (n=30)	Malignant (n=21)
Type 1	9 (30.0%)	—
Type 2	10 (33.3%)	—
Type 3	6 (20.0%)	4 (19.0%)
Type 4	—	4 (19.0%)
Type 5	5 (16.7%)	13 (62.0%)

Receiver operating characteristic curve analysis demonstrated that when the cut-off point of *k-trans* was determined to be 0.111, the sensitivity was found to be 85.7%, the specificity was 73.3%, PPV was 69.2%, and NPV was 88.0% for differentiating between benign and malignant lesions. When the cut-off point for *Ve* was determined to be 0.406, the sensitivity was found to be 76.2%, the specificity was 70.0%, PPV was 64.0%, and NPV was 80.8% for differentiating between benign and malignant lesions. When the cut-off point for *iAUC* was determined to be 10.606, the sensitivity, specificity, PPV, and NPV were found to be similar to the values found for *k-trans* as 85.7%, 73.3%, 69.2%, and 88.0%, respectively (Figures 2 and 3).

There were significant differences between SIT curve types and the values of *k-trans*, *Ve*, and *iAUC* ($P < .001$). In terms of the *k-trans*, *Ve*, and *iAUC* values, no differences were found between the type 1 and 2 SIT curves representing the benign lesions, whereas individual differences with statistical significance were noted between the type 1 curve and each of the type 3, type 4, and type 5 curve representing the malignant lesions ($P < .05$). In addition, the Type 2 SIT curve was observed to be significantly higher in the benign group and the type 5 curves representing the malignant lesions in terms of *k-trans*, *Ve*, and *iAUC* values ($P < .05$). However, in terms of *k-trans*, *Ve*, and *iAUC* values, no significant differences were detected between the Type 2 SIT curves and type 3 and 4 SIT curves representing the malignant lesions ($P > .05$).

DISCUSSION

Dynamic contrast-enhanced MRI is based on the PWI technique, reflecting the functional condition of the tumoral vasculature indirectly. The pathological basis of perfusion is associated with the number of vessels in the tumor tissue and their functional modifications. In malignant tumors, the contrast agent diffuses into the extracellular space swiftly, and a fast staining of the tumor, as well as its wash-out, is observed. In contrast, in benign tumors, the vascular intensity is relatively lower and the infusion effect of the contrast agent is not significant. Used by Tofts, the two-compartment kinetic model (microvascular and extravascular interstitium) is commonly used during the DCE-MRI. The acquired results are analyzed, and the *K-trans*, *kep*, *Ve*, and *iAUC* values, which are the vascular function parameters, are found.¹⁰

Table 4. The Comparison of the Quantitative Perfusion Parameters at T1W Dynamic Perfusion MRI in Benign and Malignant Lesion Groups

	Benign (n=30)	95% CI	Malignant (n=16)	95% CI	P
<i>K-trans</i>	0.107 ± 0.120	0.062-0.151	0.250 ± 0.192	0.163-0.397	.000*
<i>Kep</i>	2.633 ± 3.718	1.244-4.021	0.826 ± 0.939	0.398-1.253	.628
<i>Ve</i>	0.294 ± 0.294	0.184-0.403	0.515 ± 0.205	0.422-0.608	.004*
<i>IUAC</i>	8.096 ± 9.008	4.732-11.459	18.874 ± 9.469	14.563-23.184	.000*

Data: mean ± standard deviation.

* $P < .05$.

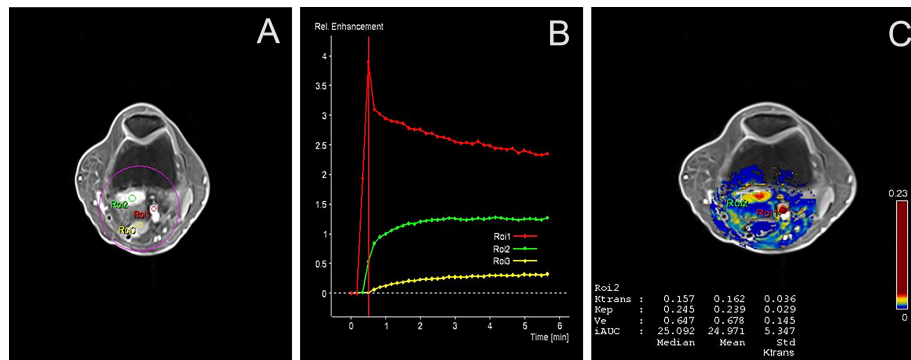


Figure 1. A 20-year-old-woman with a painful and locked knee. A soft tissue lesion with lobulated contours is present at the supracondylar level in the knee joint space posteromedially (A). The lesion demonstrates a type 3 curve (B), which is characterized by initial fast contrast enhancement followed by a plateau phase. On the parametric perfusion mapping of the lesion (C), K-trans, Kep, Ve, and iAUC values of 0.162, 0.239, 0.678, and 24.971, respectively, have been obtained. The k-trans, Ve, and iAUC values of this lesion have been found to be higher than the cut-off points for the differential diagnosis of benign and malignant lesions. The lesion has been diagnosed with pigmented villonodular synovitis histopathologically.

Costa et al⁹ compared the diagnostic efficacy of proton MRI spectroscopy and DCE perfusion MRI investigations in 55 musculoskeletal tumor cases, consisting of 27 malignant and 28 benign cases. This study reported robust associations of the type 1-2 curves with benign lesions and of the Type 4 curves with malignant lesions. In addition, it was noted that Type 3 curves were not useful in differentiating benign and malignant lesions. In our study, all the lesions with Type 1 and 2

SIT curve patterns were in the benign group. We believe that this pattern is a reliable indicator of benign lesions. Similar to the above-mentioned study, the SIT curve Type 3 pattern was found in the benign and malignant groups at similar rates (20.0% and 19.0%, respectively) in our study. The Type 5 curve pattern was identified in 62% of the malignant cases and in 16% of the benign cases in our study, this pattern was found to be an important finding in the diagnosis of malignancies and

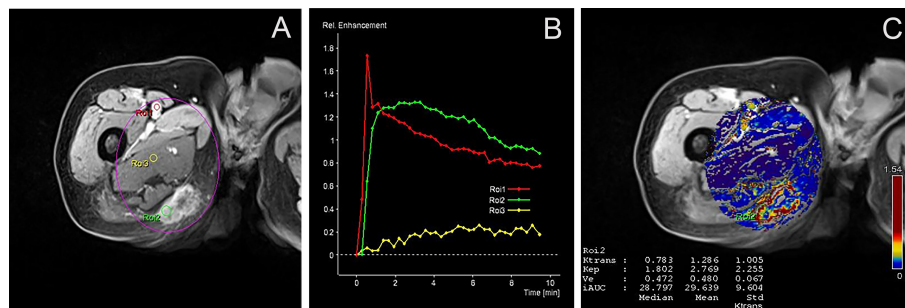


Figure 2. An 84-year-old male with a diagnosis of squamous cell malignant tumor of the lung with a mass located behind the femur. The lesion, with irregularly lobulated contours, is observed in the subcutaneous fat tissue of the right thigh posteriosuperiorly (A). The lesion demonstrates a type 4 curve, which is characterized by initial fast contrast enhancement followed by a wash-out phase (B). On the parametric perfusion mapping of the lesion (C), k-trans, kep, Ve, and iAUC values of 1.286, 2.769, 0.480, and 29.639 have been obtained, respectively. The k-trans, Ve, and iAUC values of this lesion have been found to be significantly higher than the cut-off points of these parameters for the differential diagnosis of benign and malignant lesions. The lesion has been diagnosed with metastasizing malignant neoplasm of the lung histopathologically.

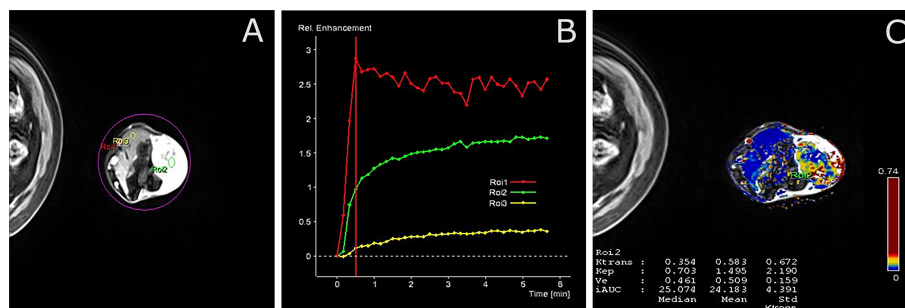


Figure 3. A 41-year-old male with a soft tissue mass in the left elbow. The soft tissue mass, with irregularly lobulated contours, is present in the left elbow posteriorly in the skin and subcutaneous tissue (A). The lesion demonstrates a Type 5 curve (B). On the parametric perfusion mapping of the lesion (C), the following k-trans, kep, Ve, and iAUC values of 0.583, 1.495, 0.509, and 24.183 have been obtained. The k-trans, Ve, and iAUC values of this lesion have been found to be significantly higher than the cut-off points for the differential diagnosis of benign and malignant lesions. A high-grade malignant mesenchymal tumor has been the histopathological diagnosis.

in deciding biopsy procedures. However, it is not considered to be a reliable indicator individually when used alone.

Van Rijswijk et al¹¹ reported that the demonstration of a plateau or wash-out phase following early and intense contrast enhancement (SIT curves Type 3 and 4) in soft tissue tumors supported the diagnosis of malignant tumors. Van der Woude et al¹³ found that SIT curve typing had 86% sensitivity and 81% specificity for differentiating malignant from benign tumors from each other by demonstrating the progression of contrast enhancement. However, they did not observe a statistically significant difference using this method for the differential diagnosis of bone tumors. In our study, all of the 4 cases with SIT curve Type 4 patterns were in the malignant group, whereas the Type 3 pattern was found at similar rates in both the benign and malignant lesion groups (20.0% and 19.0%, respectively) in our study. The Type 3 pattern was not found to be reliable for differential diagnosis.

The study by Yao et al¹² compared the microvascular intensities using DCE-MRI in 26 histopathologically proven rectal cancer cases. They calculated the following parameters: k-trans, kep, and Ve. They found that the values of these parameters were significantly higher in the tumoral tissue compared to those values found in the normal rectal wall. The study reported that k-trans values were positively correlated with Duke and TNM stagings, serosal involvement, and lymphatic metastases to a moderate to high extent; however, kep values were reported to demonstrate a moderate degree of correlation. No correlations were found with the Ve values. In our study as well, the k-trans values were observed to be significantly higher in the malignant lesion group of soft tissue tumors.

A study by Jackson et al¹⁴ compared histopathologically proven prostate cancer lesions in 18 patients by DCE-MRI pharmacokinetic parameters and T2W image findings, aiming to identify a malignant lesion located at each pixel. The sensitivity and specificity of DCE-MRI to diagnose the lesions were found to be 50% and 85%, respectively. For the T2W images, the sensitivity was 21% and the specificity was 89%. When the authors compared the DCE-MRI parameters, namely, the k-trans, kep, and Ve values found for the cancer tissue in the prostate gland, they found these values significantly higher compared to those obtained in the benign peripheral zone. Finally, the authors reported that DCE-MRI was superior to the T2W section images in determining the locations of the lesions in prostate cancers.

Ma et al¹⁰ investigated the efficacy of the T1W imaging by dynamic perfusion MRI in a total of 44 breast lesions. Of these lesions, 30 were malignant lesions. The authors reported that k-trans, kep, and iAUC values were found to be statistically significantly different in differentiating malignant and benign lesions from each other, while the Ve values were not statistically significant. The non-significantly different Ve values, representing the contrast agent percentages in the tissue spaces, were associated with the increased k-trans and kep values due to the increased neovascular permeability in the malignant lesions. Therefore, according to the “ $Ve = k\text{-trans}/kep$ ” formula, they explained that the Ve values did not show any differentiation. In contrast to the findings of the study described above, Ve values in our study were found to be statistically significantly different in differentiating malignant and benign lesions. We believe that this result may be associated with the statistically significantly different k-trans values and with the non-significant differences found with the kep values.

In 36 breast cancer cases, Li et al¹⁵ compared the pathological response to the first cycle of neoadjuvant chemotherapy by comparing the

tumor sizes, DCE-MRI, apparent diffusion coefficient (ADC) values acquired by the diffusion-weighted imaging (DWI) and the kep/ADC ratios. Consequently, they reported that the kep/ADC ratio was more statistically significant. They reported that the area under the curve (AUC) for the kep/ADC was 0.88, superior to kep (AUC: 0.76) and ADC (AUC: 0.82) values in predicting the pathological response after chemotherapy. They suggested that the combined use of DCE-MRI and DWI might be beneficial in evaluating the response to chemotherapy and in assessing treatment results during follow-ups in cases with breast cancer. On the other hand, in our study, the kep parameter was not found to be useful in differentiating benign and malignant soft tissue lesions from each other. We suggest that this finding might be associated with the heterogeneous microvascular intensity found in soft tissue tumors.

Baik et al¹⁶ investigated the efficacy of the tissue permeability factor acquired by the DCE-MRI in differentiating between benign and malignant pulmonary lesions in 30 cases of pulmonary lesions. They evaluated the k-trans, kep, and Ve parameters as the tissue permeability factors. Their study reported that the perfusion parameter of k-trans acquired by the DCE-MRI might be beneficial in determining whether the pulmonary nodules or masses were benign or malignant. Similarly, in the differential diagnosis, our study determined the k-trans value to be the most beneficial parameter together with the iAUC values.

The limitations of our study might include the relatively insufficient number of cases and their variabilities, as well as the unavailability of the histopathological diagnoses for some cases. Perfusion parameters may be affected by tumor grade. The lack of tumor stages is another limitation of this study. We conclude that further studies should be conducted with larger sample sizes and more variable cases to better demonstrate the efficacy of the DCE-MRI perfusion parameters in differentiating malignant from benign soft tissue tumors.

In conclusion, our study showed that the quantitative perfusion parameters and the contrast-enhanced curve types acquired by the DCE-MRI provided useful contributions to the diagnosis in determining whether the soft tissue lesions were benign or malignant. We suggest that further studies in broader patient groups with more diagnostic variability should be conducted to better demonstrate the efficacy of this technique in the malignant versus benign differentiation of soft tissue tumors.

Availability of Data and Materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: Ethical approval was received from the local Ethics Committee of Gazi University Faculty of Medicine, approval number 513, date november 11, 2014.

Informed Consent: N/A.

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