Differential diagnosis between benign and malignant soft tissue tumours using multi-b diffusion weighted images and dynamic contrast enhanced MRI

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Aims and objectives

Magnetic Resonance (MR) is the method of choice for diagnostic work-up of soft tissue tumors [1-3].

Conventional MR is based of qualitative interpretation of morphological parameters such as size, margins demarcation, involvement of adjacent viscera and neuro-vascular structures, variations of T1 and T2 relaxation properties, homogeneity in signal intensity and enhancement after contrast agent administration [4,5]. However, in several cases, conventional MR provides limited information regarding tissue characterization with a considerable overlap in the signal characteristics of soft tissue tumors (both benign and malignant) and non-neoplastic reactive or inflammatory lesions [2].

Previous researches have utilized advanced MR techniques such as Dynamic Contrast Enhancement study (DCE) and Diffusion-weighted imaging (DWI) in association with conventional MR for improving lesion characterization and the evaluation of tumor response after therapy of soft tissue tumors [6-11].

Diffusion-weighted magnetic resonance imaging is a non-enhanced functional MR imaging technique that reflects intravoxel incoherent motion (IVIM) [12]. In biological tissue, motion includes Brownian motion of extra, intra and trans-cellular individual water molecules (true diffusion) as well as microcirculation of blood (perfusion). The apparent diffusion coefficient (ADC) is a quantitative measure of Brownian motion [13]. Both true diffusion and perfusion contribute to apparent diffusion coefficient ADC [14].

DCE MR imaging depends on contrast medium kinetics and offers the advantage of providing physiologic and hemodynamic information [15]. DCE MR imaging is able to detect tumor neovascularization with an objective evaluation of tumor vascularity measuring the pharmacokinetics of the contrast agent [7,16].

The aim of the present study is evaluating the role of functional MRI techniques, such as DCE and DWI IVIM, in the differential diagnosis of soft tissue lesions.
Methods and materials

From January 2012 to October 2013, 30 patients were enrolled for the study. All of them underwent MR imaging with the indication of characterization and staging of a soft tissue mass.

Patients with clearly clinical benign lesions, such as subcutaneous lipomas were not included; patient with bone lesions were not included.

The cohort included 30 patients (20 male and 10 female, mean age 55.96 years [range age 23-84 years]).

Among the 30 soft tissue masses, there were 13 benign lesions and 17 malignant; tumor histology is summarized in table 1:
Table 1: Table 1 shows the list of confirmed histology of the 30 soft tissue masses.

References: Radiology and Diagnostic Imaging Department, Regina Elena National Cancer Institute, Rome, Italy

Diagnosis was confirmed by surgical specimen or by core-needle biopsy.

MR imaging was performed with a 1.5 T superconductive system (OptimaTM MR450w, GE Medical System), using a eight-channels cardiac array coil.

The protocol was performed with the following sequences: coronal T2-weighted FSE, axial T2-weighted FSE, axial T1-weighted FSE, IDEAL T2-weighted FSE with fat
suppression, spin echo EPI DWI (TR = 4500 ms, TE = 77ms, section thickness = 4mm, matrix size = 128x128) with multiple b-values (b= 0, 25, 50, 75, 100, 150, 300, 500, 800 s/mm²).

After the administration of gadobenate dimeglumine (MultiHance 0,5 M, Bracco), 0,2 ml/kg, dynamic contrast enhanced MRI was obtained by a fast SPGR sequence (TR = 7ms, TE = 4.2ms, section thickness = 5mm, matrix size = 160x96); a series of 50 of these fast SPGR sequences were performed after the bolus of Gadobenate dimeglumine with a time of interval or temporal resolution of 3-5 seconds depending on the size of the lesion. Total scanning time ranged from 150 to 250 seconds. At last an enhanced gradient echo LAVA FLEX with fat suppression sequence was obtained.

Quantitative analysis of DWIs was performed using the Matlab code (Release 7.10.0, The Mathworks Inc., Natick, Massachusetts).

ADC and IVIM diffusion parameters were obtained on the basis of a pixel by pixel analysis.

The signal variation with increasing b values was modeled by using the following bi-exponential function (Fig. 1) [17]:

$$S_b / S_0 = (1 - f) \cdot e^{-bD} + f \cdot e^{-b(D+D^*)}$$

**Fig. 1**: Function of signal variation: Sb is the signal intensity with diffusion weighting b, S0 is the signal intensity for b-value of 0 s/mm2, f is the perfusion fraction, D the diffusion coefficient related to pure molecular diffusion (in mm²/s) and D* the perfusion-related diffusion coefficient (in mm²/s).


Assuming that the contribution of D* to the signal ratio S_b/S_0 can be neglected for b values greater than 150-200 s/mm², an estimation of D was derived from formula in Fig.1 simplifying the bi-exponential to a mono-exponential function (Fig. 2):
considering only measurements from three b-values: 300, 500, and 800 s/mm².

The perfusion fraction \( f \) was obtained from an asymptotic fitting [18, 19], extrapolating to \( b = 0 \) s/mm² the signal intensity \( S^{\text{extr}} \) from the above mono-exponential fit of \( D \), as followed:

\[
\text{f (\%) = } \left( \frac{S^{\text{meas}} - S^{\text{extr}}}{S^{\text{meas}}} \right) \times 100,
\]

where \( S^{\text{meas}} \) is the measured signal intensity for b-value of 0 s/mm².

Finally, global ADC was calculated from formula in Fig.2 using data at b-values of 0, 300, 500, and 800 s/mm². The Levenberg-Marquardt algorithm was used to perform the mono-exponential fits of both \( D \) and \( \text{ADC} \).

Blood volume (BV) maps were derived from DCE-MRI using a commercial software and then normalized with respect to the mean BV inside a healthy muscle region (nBV). All sections containing the lesion were manually outlined for each patient on both DWIs and perfusion maps, using morphological images as guide to the lesion location. Median values of all parameters were calculated based on a volumetric analysis of the entire lesion.

Statistical analysis: the distribution of the two groups was calculated for each parameter (\( D \), \( \text{ADC} \), \( f \), \( \text{nBV} \)). Mann Whitney test was used to establish the differences between the two groups. A p-value < 0.05 was considered signficative.
Results

Malignant lesions showed lower median D value respect to benign tumors that have a higher median D value (D=1.44 [95%CI 0.97-2.07] ·10^{-3} mm²/s vs. 1.68 [95%CI 1.12-2.30] ·10^{-3} mm²/s, respectively). As opposite the median nBV value was higher for malignant lesions respect to benign lesions (median nBV=4.60 [95%CI 2.8-6.9] vs. 3.2 [95%CI 0.4-13.7], respectively). However the differences detected were not statistically significant (P=0.43 and 0.26, respectively).

Similarly, no differences were found between median ADC (benign lesions: ADC=1.83 [95%CI 1.33-2.35] ·10^{-3} mm²/s; malignant lesions: 1.92 [95%CI 1.02-2.90] ·10^{-3} mm²/s; p=0.74) and median perfusion fraction f (benign lesions: f=12.2% [95%CI 9.78-15.49] ; malignant lesions: 12.42% [95%CI 5.42-21.79] ; p=0.82) among the two patient groups.
Fig. 3: Boxplot summarizes the results obtained; in A, nBV boxplot of the two group shows a higher blood support of malignant masses. In B and C the perfusion fraction (f) and the ADC between the two groups are comparable. In D the diffusion coefficient (D) is higher in benign soft tissue masses than malignant. For any of the four parameters was obtained a significative p value.

References: Radiology and Diagnostic Imaging Department, Regina Elena National Cancer Institute, Rome, Italy

Some examples of clinical cases with morphological MR images and related diffusion and perfusion maps:

Fig. 4: Male, 80 years. Patient affected by a high grade undifferentiated pleomorphic soft tissue sarcoma of right leg. Pre-treatment MRI shows a mass with heterogeneous T1 and T2 signal (A and B, respectively); enhanced T1 fat sat sequence (C: coronal plane; D: axial plane) shows the enhancement of solid components and a central hypovascular area corresponding to necrosis.

References: Radiology and Diagnostic Imaging Department, Regina Elena National Cancer Institute, Rome, Italy
**Fig. 5:** Same patient than Fig. 4. A: \( b=800 \) s/mm\(^2\); B. ADC maps (median value = \( 1,085 \times 10^{-3} \) mm\(^2\)/s), C: D maps (median value \( 0,921 \times 10^{-3} \) mm\(^2\)/s) and D: f maps (median value \( 10,31\% \)). Low values of D and ACD are likely related to high cellularity of the lesion.

**References:** Medical Physics Laboratory, Regina Elena National Cancer Institute, Rome, Italy
**Fig. 6**: Same patient than Fig. 4 and Fig. 5. Positive enhancement integral map is shown. nBV maps show an increased vascularization compared to a normal muscle (value: 2.6).

**References**: Medical Physics Laboratory, Regina Elena National Cancer Institute, Rome, Italy
**Fig. 7**: Female, 43 years. Patient affected by a myxoma of the left leg. Morphological T1 (A) and T2 (B) pre-contrast images are shown. The lesion has a hypointense signal in T1 and hyperintense signal in T2 weighted sequences. Margins are well defined. Contrast enhanced T1 with fat saturation (C: coronal and D axial) shows a faint vascularization within the lesion.

**References**: Radiology and Diagnostic Imaging Department, Regina Elena National Cancer Institute, Rome, Italy
Fig. 8: Same patient of Fig. 7: myxoma. Maps of b=800 s/mm², ADC maps (median value = $2.9 \times 10^{-3}$ mm²/s), D maps (median value $2.77 \times 10^{-3}$ mm²/s) and f maps (median value 6.1 %) are shown. The increased signal in D and ADC maps is due to the myxoid component.

References: Medical Physics Laboratory, Regina Elena National Cancer Institute, Rome, Italy
Fig. 9: Same patient than Fig 7 and 8: myxoma. nBV maps show a poor vascularization compared to a normal muscular tissue.

References: Medical Physics Laboratory, Regina Elena National Cancer Institute, Rome, Italy
Fig. 10: Female, 39 years. Biopsy proven villonodular synovitis of left feet. T1 weighted images show a hypointense mass; contrast enhanced MRI show a homogeneous enhancement of the lesion. Positive enhancement integral map demonstrate an increased vascularisation of the lesion (nBV value: 59); ADC maps (median value = 1.7 x 10^-3 mm2/s), D maps (median value 1.1 x 10^-3 mm2/s) and f maps (median value 23.7 %) are shown.

References: Radiology and Diagnostic Imaging Department and Medical Physics Laboratory, Regina Elena National Cancer Institute, Rome, Italy
Conclusion

This study provides an accurate analysis of the entire volume of the mass, not only of a single slice, taking into account the common heterogeneous appearance of these lesions. Despite the accuracy of pixel by pixel analysis we didn't find a significative difference between the group of benign masses and the malignant one, thus preventing the possibility of finding any cut-off value of ADC, D and f.

This was an expected result in agreement to previous results described in the literature. What it was innovative in our study is the application of a pixel by pixel analysis, rather than ROI approach that is limited by sampling errors and inter-operator variability.

The limit of this study is the number of patients, due to the rarity of this type of tumors.

In our study multi-b DWI and DCE-MRI did not improve differentiation between benign and malignant soft tissue tumors.
References


