

# DIFFUSION AND FUNCTIONAL SEQUENCES: UTILITY IN THE STUDY OF BONE AND SOFT TISSUE TUMORS. PICTORIAL REVIEW



## Key words (MeSH)

Magnetic resonance imaging  
Diffusion  
Bone neoplasms

## Palabras clave (DeCS)

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Difusión  
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Utilidad de las secuencias funcionales por resonancia magnética en el estudio de los tumores óseos y de partes blandas. Revisión imaginológica

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## Summary

Magnetic resonance imaging (MR) is the preferred technique for the diagnosis, characterization, staging, follow-up and assessment of response to treatment of musculoskeletal tumors. Conventional sequences help to classify these lesions. Recently new evolving functional MR sequences with advanced techniques have been implemented, such as phase sequence, opposite phase, diffusion, perfusion and spectroscopy, which provide specific information about the behavior, physiology, metabolism and molecular biology of the tumor. These sequences are non-invasive and provide additional qualitative, quantitative, metabolic and vascular information, making them important for the diagnosis and monitoring of bone and soft tissue tumors. This article reviews the technique of these sequences, particularly the diffusion technique, using illustrative cases from the Hospital Pablo Tobon Uribe (Medellin - Colombia) and the University Hospital Quirón Salud (Madrid - Spain). We aim to review the utility and importance of a combined analysis of these new tools, which will provide additional information for adequate characterization, diagnosis and response to treatment of tumor lesions in the musculoskeletal system.

## Resumen

La resonancia magnética es la técnica de imagen de elección para diagnosticar, caracterizar, estadificar, realizar el seguimiento y valorar la respuesta al tratamiento de los tumores musculoesqueléticos. Para estos fines se utilizan las secuencias

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convencionales. Desde hace algunos años se han comenzado a implementar nuevas técnicas avanzadas, como la secuencia en fase y fase opuesta, difusión, perfusión y espectroscopia, que en conjunto se denominan técnicas funcionales, las cuales proporcionan información más específica del comportamiento, fisiología, metabolismo y biología molecular del tumor. Estas secuencias son no invasivas, aportan información adicional cualitativa, cuantitativa, metabólica y vascular por lo que deberían utilizarse de manera rutinaria en el momento de realizar el diagnóstico y, especialmente, en el seguimiento de los tumores óseos y de partes blandas. En este artículo se revisa la técnica de dichas secuencias, particularmente la secuencia de difusión, mediante casos ilustrativos de nuestros hospitales: Hospital Pablo Tobón Uribe y Hospital Universitario Quirón Salud de Madrid. También se revisarán las aplicaciones e importancia de un análisis combinado de estas nuevas herramientas, que aportarán información adicional para adecuada caracterización, enfoque diagnóstico y respuesta al tratamiento de las lesiones tumorales en el sistema musculoesquelético.

## Introduction

Magnetic resonance imaging (MRI) has excellent resolution, tissue contrast and is the gold technique for diagnosis, preoperative staging and assessment of the response to treatment of bone tumors and soft tissue (1), not forgetting that simple radiography is the preliminary step to any MRI (2). Among the new advanced sequences are: sequences of chemical displacement in phase and opposite phase (POP), which determine the existence of tumor microscopic fat. Diffusion weighted imaging (DWI), which evaluates the random movement of water with a qualitative and quantitative analysis of the cellularity and integrity of the cell membrane. Spectroscopy (MRSI), which reflects tumour metabolic behaviour, of which the most important metabolite is choline (3) -a marker of aggressiveness, given by cell turnover, which is elevated in tumours with a high mitotic index-, and, finally, dynamic sequences with endovenous contrast (ECD), which evaluate the degree of angiogenesis and tumour vascularisation.

## Functional sequences

**Chemical Displacement Sequences:** Normal bone marrow is made up of fat, so that in phase sequences it presents an intermediate signal, and out of phase, homogeneous signal drop.

When the medulla is replaced by tumour lesions, there is no homogeneous drop of the signal by medullary infiltration. In case of edema, osteopenic fractures or spinal cord replacement, the medullary fat will not be affected and there will be a less than normal signal drop in the out-of-phase sequence (figure 1).

**Spectroscopy:** Allows the study of metabolism in vivo and provides non-invasive biochemical information of the tissues. Hydrogen (H1) or proton spectroscopy is the most commonly used technique in clinical practice. The most useful metabolite detected in musculoskeletal tumors is choline, which participates in the formation of the phospholipid structure of cell membranes, and is a marker of proliferative activity. For its calculation, the ROI (region of interest) is placed in the solid part of the tumour, avoiding calcified, haemorrhagic or necrotic areas (4). When there is an increase in cell membrane turnover, there is an increase in choline levels (figure 2).

**Dynamic sequences with endovenous contrast and perfusion:** This is done with echo gradient sequences in several phases, following the administration of endovenous contrast medium (figure 3). The semiquantitative analysis is carried out by subjectively evaluating the enhancement and the change in intensity; the qualitative analysis is done by ROI in order to generate enhancement curves, which are classified as: type I, progressive enhancement; type II, intense enhancement; plateau and type III, intense enhancement and subsequent washing (5).

**Diffusion sequences:** Uses the physical property describing the microscopic random movement of water molecules in intracellular, transcellular, interstitial and intravascular spaces, in response to thermal energy (Brownian movement) (6-8). It employs pulse sequences sensitive to small movements of water molecules at the microscopic level and is affected by the biophysical properties of the tissue, such as tissue cellularity (cell density, nucleus-cytoplasm ratio), cell membrane integrity, the extracellular space (stroma) of the tumour and tissue perfusion.

The most widely used diffusion sequences are EPI (Echo Planar Imaging) (8-11), FAST, which have fewer motion artifacts; however, they have more susceptibility artifacts in soft bony interfaces and fundamentally in air-soft tissue interfaces.

Usually the diffusion images are obtained using two values of b, one with values of b between 0-100 s/mm<sup>2</sup> and another b greater than 100 s/mm<sup>2</sup>, and two images are obtained simultaneously with these two values b. The greater the value of b, the greater the attenuation of the signal of the water molecules with worse signal-to-noise ratio and more artifacts.

In our protocol we use a b factor with values of b<sub>0</sub>, b<sub>1000</sub> mm<sup>2</sup>/s, fat suppression, matrix of 128 x 128 and 8 NEX (number of acquisitions).

The remaining parameters depend on the extent of the tumor and the amplitude of the anatomical region to be studied; also, the type of antenna and MRI equipment if it is 1.5 or 3T. The indicative parameters are: TR > 3000 ms (normally between 3000-5000 ms, although it can be greater if the area to be studied is very wide and there are more cuts); minimum TE 75-90 ms; cutting thickness: 3-6 mm; GAP: < 1 mm with an acquisition time of 3-4 minutes (12).

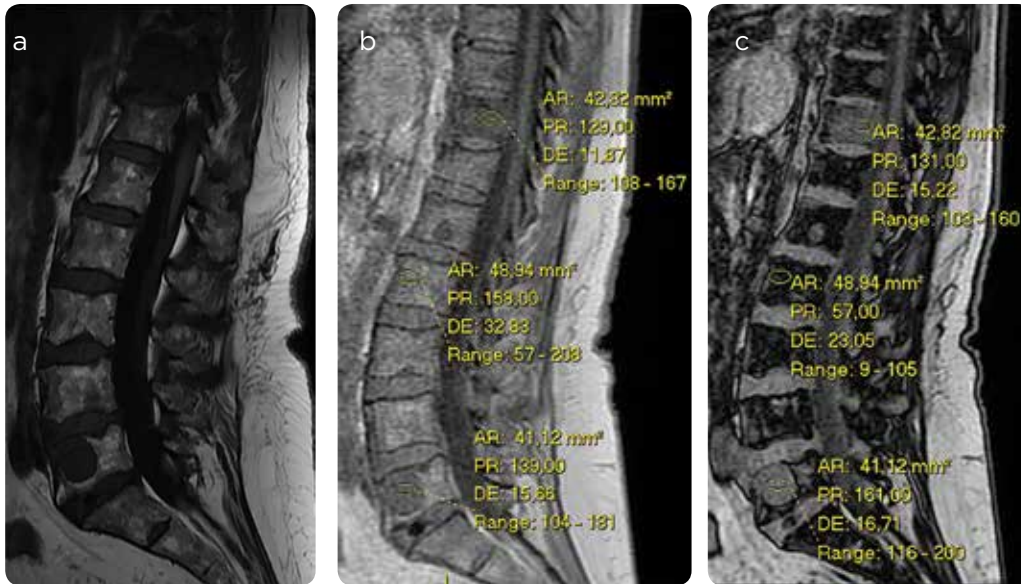


Figure 1. MRI. 64 year old woman, with breast cancer, with low back pain. a) Sagittal with information T1, lesions in T11 and L5. b) Sagittal with information T2 fat suppression. c). Sagittal in phase D. Sagittal out of phase. Lesions of T11 and L5 have medium signal in T1, high signal in T2 and no signal drop in opposite phase (< 20%), typical of metastases, unlike L3, which is a normal vertebra, and if it presents signal drop in opposite phase.

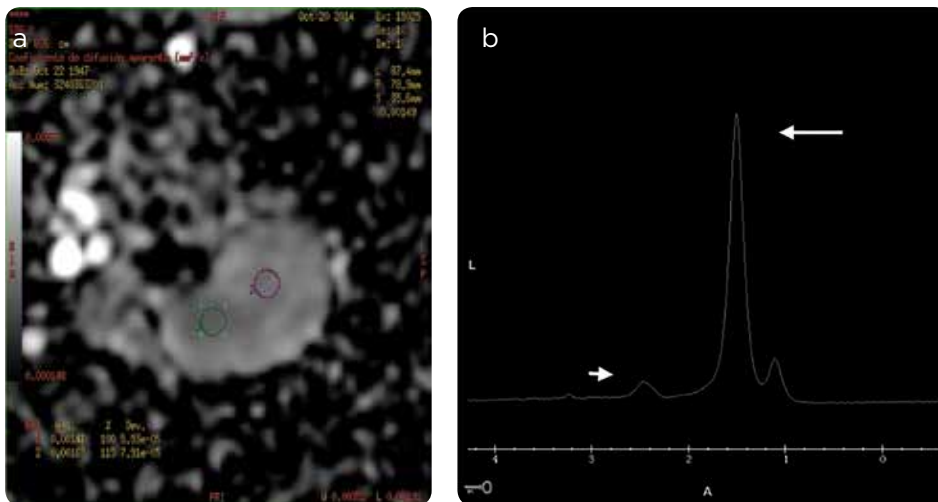


Figure 2. Spectroscopy. 64-year-old female, with peripheral nerve tumor evolving for 5 years. a) ADC map, diffusion, with an ADC value of  $1.43 \times 10^{-3} \text{ mm}^2/\text{s}$  see ROI. b) Spectroscopic curve with lipid peak (white arrow) and small hill peak (at 3.2 ppm) (arrowhead).

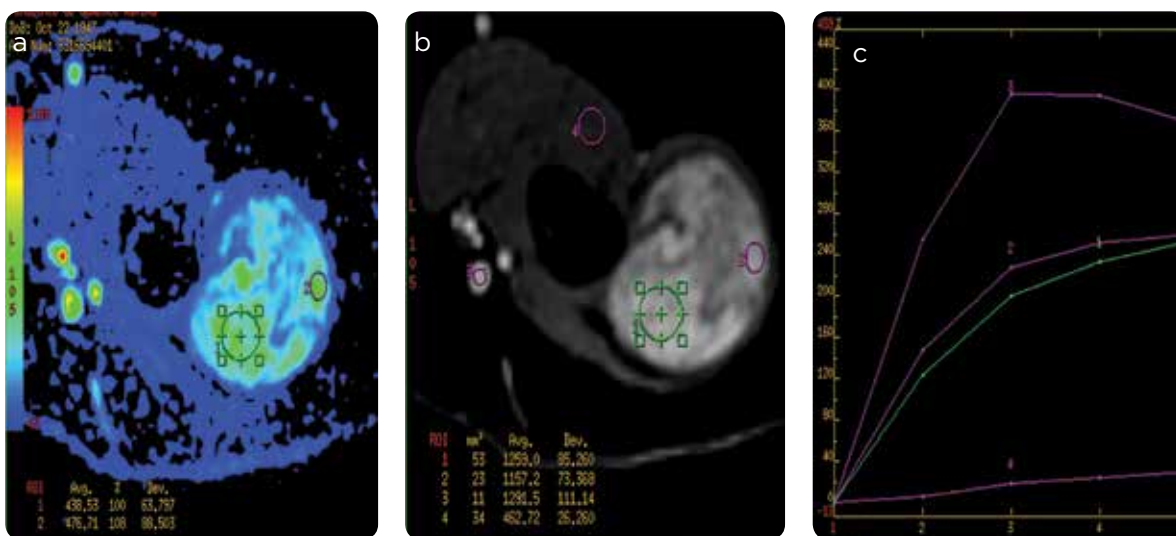


Figure 3. Dynamic sequences and perfusion. They correspond to the case of figure 2. a) Parametric semi-quantitative axial map with color map indicating the areas of greatest perfusion where the ROI is placed. b) Dynamic sequence T1 axial gradient echo with fat suppression, which is obtained at the same time as the color map. c) Curve type I, with progressive enhancement in the area of greatest enhancement of the tumor (green curve).

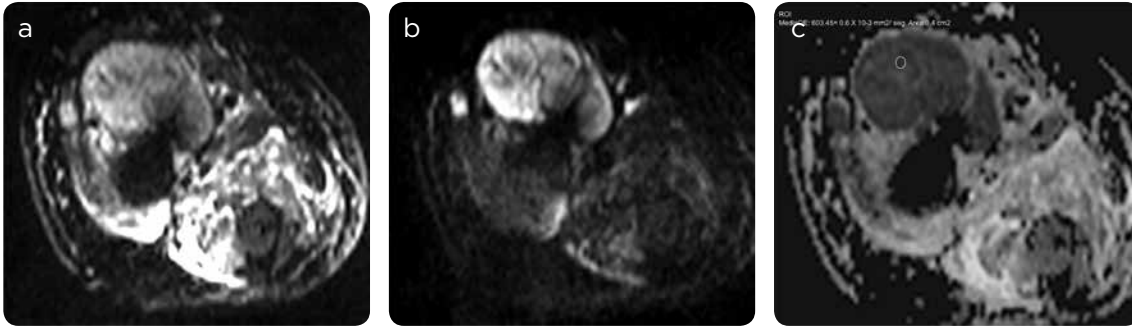


Figure 4. Image processing. a and b) Axial diffusion with values of b0 and b1000. c) ADC map. ROI of small size, in the area of the tumour where the signal is less intense, an average of 603.45 is obtained, which is equivalent to  $0.6 \times 10^{-3} \text{ mm}^2/\text{s}$ .

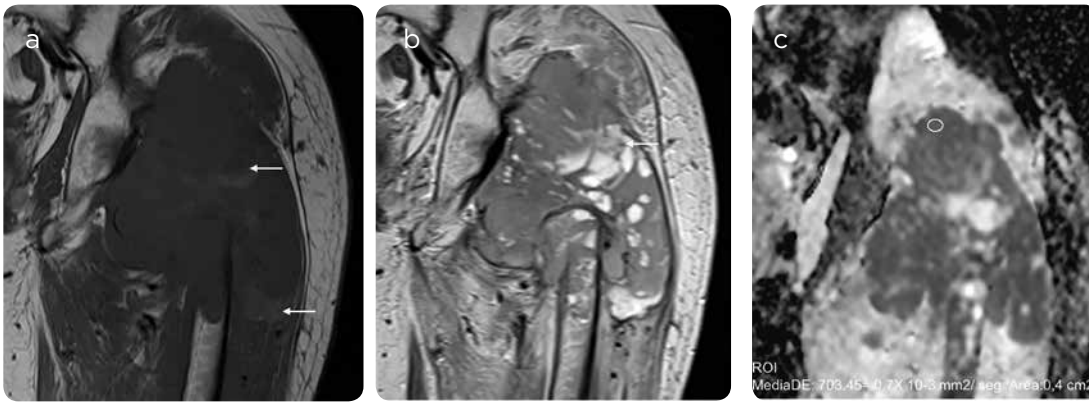


Figure 5. High-grade fusocellular sarcoma. 39-year-old female with left hip pain and mass sensation. In the MRI, voluminous mass is observed in the left iliac with heterogeneous aspect in the anatomical sequences and low values in diffusion, which suggests tumoral type lesion. a, b and c) Coronal with information T1, T2 and ADC map. a) Low signal mass with T1 information and high signal area (arrows) compatible with bleeding areas. b) Heterogeneous signal with T2 information (arrow). c) ADC map with diffusion restriction and an ROI with ADC value of  $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$ , low, suggesting sarcoma.

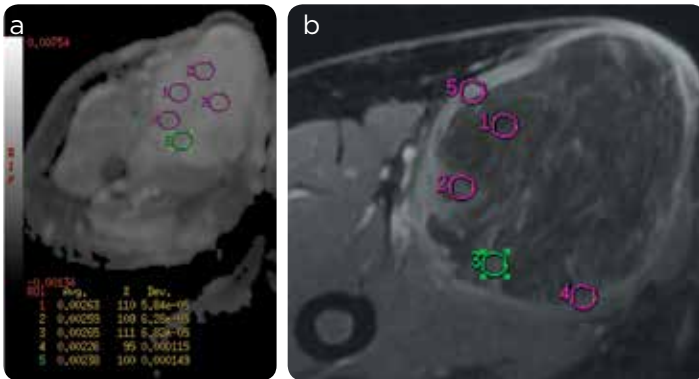
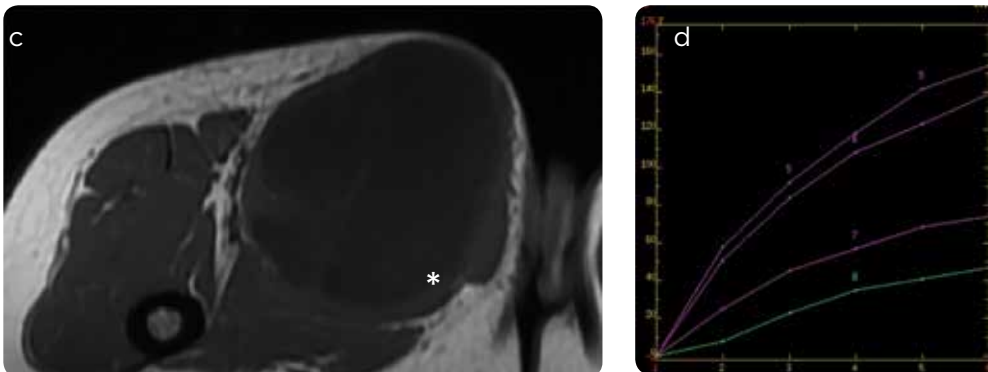


Figure 6. Mixofibrosarcoma. 38-year-old female, with intermuscular cystic appearance in anterior compartment of right thigh. a) ADC map, placing 5 ROI with high values of ADC, without restriction of diffusion, ranging from  $2.3\text{-}2.6 \times 10^{-3} \text{ mm}^2/\text{s}$ . b) Dynamic axial sequence T1 gradient echo with several ROI, with a progressive enhancement shown in graph d. c) Axial with T1 information, with low signal lesion of cystic aspect and periphery with slightly high signal (star). d) Type I curves with slight progressive enhancement.



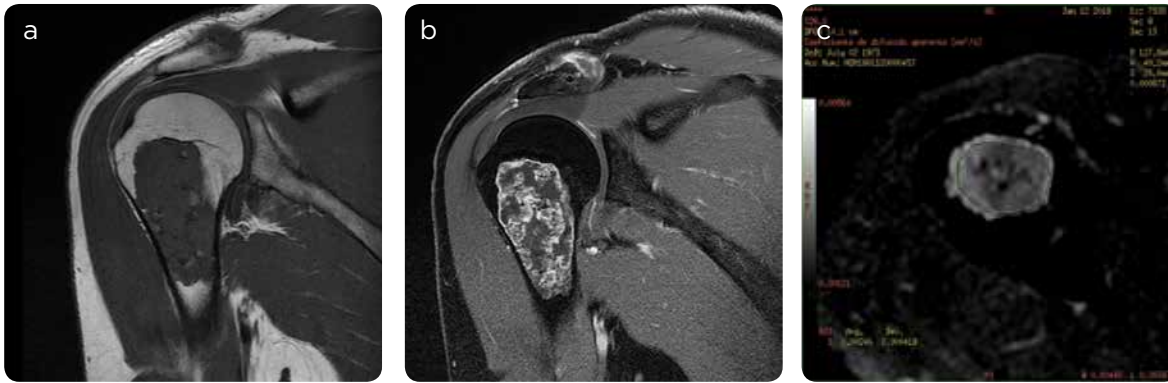


Figure 7. Low grade, cartilaginous, atypical chondral tumors. A 45-year-old male, with incidental occurrence of subacromial pain of low-grade chondral tumour or atypical cartilage in the proximal diaphysis of the right humerus, with well-defined edges, which does not cause rupture of the cortex or endosteal recession, 6.3 cm in length. Small calcifications and small areas of fat inside are observed. a) Sagittal with T2 information fat suppression. b) Sagittal with T1 information without fat suppression. c) Sagittal with T1 information with fat suppression, with typical cathedral enhancement. d) Axial Diffusion, average ADC calculation of  $2.46 \times 10^{-3} \text{ mm}^2/\text{s}$ .

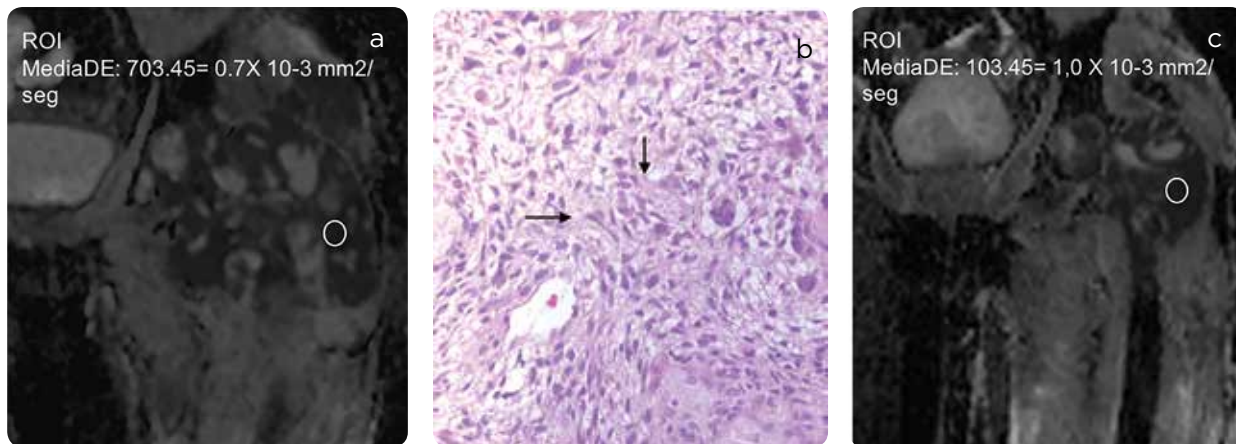


Figure 8. Control MRI of high-grade fusocellular sarcoma. Chemotherapy was used for 3 months. In the control MRI, an increase in ADC values and a decrease in tumour volume was observed, a finding that confirms that diffusion sequences make it possible to estimate cell death, damage to membranes and a decrease in tumour density. a) Map of ADC at diagnosis with an ADC value of  $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$ . b) Histological cuts with hematoxylin eosin staining, in which undifferentiated mesenchymal cells, some pleomorphic and multinucleated cells with atypical mitosis (arrows) are observed. c) Control ADC map: at 3 months the ADC value rises to  $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ , which suggests a decrease in tumor density and response to treatment.

The qualitative study is based on the signal presented by the lesions. In very cellular tissues, such as malignant tumors, barriers to diffusion are generated (diffusion is restricted) and signal attenuation will be lower (low signal in diffusion images-low ADC). In hypocellulars, such as benign tumors and cysts (13), there is no barrier to diffuse (increased diffusion) and the attenuation of the signal will be greater (high signal in high diffusion-ADC images).

It is necessary to take into account the “T2 shine through effect” which consists of an increase in signal intensity in the diffusion images, which simulates a restricted diffusion; however, in the ADC there is no drop in signal intensity, this is because the signal strength depends not only on the diffusion of the water but also on the relaxation time T2. Thus, a lesion with a very long relaxation time in T2 can be clearly manifested.

The T2 effect can be partially eliminated by increasing the b-value and the possibility of quantification by calculating the ADC (Apparent Diffusion Coefficient). The ADC is independent of the magnetic field, is not affected by the T2 effect (14) and varies with the value b,

although there are authors who claim that for technical reasons there are variations of the ADC value due to the magnetic field (12). In order to determine the quantitative value of the ADC, the studies in different stations were evaluated: Syngo Vía, from Siemens, at the Pablo Tobón Uribe Hospital and General & Electric, at the Quirón Salud Hospital in Madrid. A small ROI (figure 4) is located in the most solid and homogeneous portion of the tumor, to avoid necrotic or cystic areas, hence the importance of performing an adequate analysis of these tumor components in the morphological sequences.

### Analysis of the qualitative and quantitative diffusion value

As mentioned, there is greater restriction on the movement of water molecules in tissues with high cellularity, intact cell membranes and reduction of extracellular space or stroma. On the contrary, there is less restriction or facilitation of the movement of water molecules, in tissues

with less cellularity, damage to cell membranes and more extracellular space. The degree of restriction on diffusion is directly proportional to tissue cellularity and membrane integrity and inversely proportional to extracellular space. These differences may be useful to estimate the histological composition of tumors and establish approximate ADC values in some of them (9,15).

Generally, malignant tumors are more cellular than benign tumors and offer greater restriction on diffusion (figure 5); however, not all malignant tumors have greater cellularity when compared to benign tumors (figure 6) (2). This variability in the histology of tumours means that, in general, the diffusion sequence cannot be used in isolation to assess the benign or malignant behaviour of all tumours, nor does it allow the specific type of tumour to be specified in all cases, due to the overlap in the ADC values they present. The patient's age, location, radiological aspect and signal intensity in the morphological sequences must be taken into account, as well as the qualitative and quantitative analysis of the diffusion, which constitutes an additional tool that allows a diagnostic impression to be supported or discarded.

In this case, the absence of diffusion restriction, high ADC and progressive curves indicate lesions not very suspicious of sarcoma, but it is a myxoid tumour that cannot be differentiated by calculating the ADC due to the important myxoid matrix in benign and malignant tumours (13).

### Differentiation of benignity versus malignity

With respect to the ADC values, there are some authors (5,7,11,12,16-19) who try to establish a cutoff value, most with statistically significant differences and some not. The latter, because they

have not established an initial differentiation between myxoid and non-myxoid tumors, as described by Nagata in 2008 (17), given that these tumors, (due to the large amount of mucin and extracellular stroma), do not present a significant difference between malignant and benign myxoid tumors. This initial differentiation is useful; however, groups of tumors with common histological characteristics and similar ADC values should be established. However, it should be borne in mind that there are tumours which, due to their histological heterogeneity, cannot be classified into specific groups. The tumours can be grouped into: myxoids, round cells, giant cells, fusiform cells, with specialised stroma and abscesses-haematomas (12,19,20). A summary of the values is given in Table 1.

### Response to treatment

The response to treatment with chemotherapy and radiotherapy is traditionally based on an anatomical approach by measuring tumour size.

Morphological and diffusion sequences make it possible to assess the efficacy of chemotherapeutic management, the presence of tumour recurrence, as well as the appearance of tumour necrosis and changes in vascularisation (21) induced by treatment (figure 8).

One of the first applications of diffusion in musculoskeletal tumors was to assess the efficacy of neoadjuvant chemotherapeutic treatment in osteosarcomas (21-23), which, although satisfactory, does not significantly reduce the size of the lesion, since the treatment does not affect the mineralized matrix of the tumor, but does affect cellularity. The response to treatment is of prognostic value, as it indicates greater disease-free survival.

**Table 1. Classification of bone tumours. ADC values according to composition and types of tumours**

| Primary bone tumors                     | Types   | Composition  | ADC   |
|---|---|--|---|
| Mixoids.<br>Tumors of cystic appearance | Juxtaarticular myxoma, myxofibrosarcoma, intramuscular myxoma, myxoid liposarcoma, myxoid leiomyosarcoma  | They present a high content of mucin or extracellular mixoid matrix, low content of collagen and a large amount of water | High ADC values 2.08 +/- 0.51 x 10 <sup>-3</sup> mm <sup>2</sup> /s (12) a PIADC value of 2.92 x 10 <sup>-3</sup> mm <sup>2</sup> /s (4)  |
| Round cells                             | Non-Hodgkin's lymphomas, Ewing's sarcoma, PNET, myelomas, neuroblastomas, and rhabdomyosarcomas   | Formed by cells with a rounded morphology and a high nucleus/cytoplasm ratio   | Very low ADC.<br>In our experience: the mean lymphomas is 0.77 x 10 <sup>-3</sup> mm <sup>2</sup> /s and in general round cell tumors 0.84 x 10 <sup>-3</sup> mm <sup>2</sup> /s (12).<br>PIADC of lymphomas 0.64 +/- 0.18 x 10 <sup>-3</sup> mm <sup>2</sup> /s (4).<br>Spectroscopy: high choline |
| Giant cells                             | Bony tumors and soft tissue tumors of the tendon sheath   | High cellularity and low stroma  | ADC of 0.96 x 10 <sup>-3</sup> mm <sup>2</sup> /s vs. 0.85 bone and sheath GCTs, respectively (12)  |
| Fusiform cells                          | Aggressive fibromatosis, malignant fibrohistiocytoma, leiomyoma, leiomyosarcoma. Other non-tumour entities: nodular fasciitis and ossifying myositis. | Fusiform cells: fibroblasts, myofibroblasts and smooth muscles   | 1.56 x 10 <sup>-3</sup> mm <sup>2</sup> /s for benign and intermediate and 0.89 for malignant (12)  |
| Atypical Cartilaginous Chondrales       | Low-grade chondroma chondrosarcoma  | Chondroid matrix (figure 7)  | ADC between 2.3-2.5 x 10 <sup>-3</sup> mm <sup>2</sup> /s, (12)   |
| Inflammation-infection                  | Hematomas, abscesses  | Abscesses with marked decrease in ADC values   | Low ADC.<br>In cases of HPTU 1 to 1.28 x 10 <sup>-3</sup> mm <sup>2</sup> /s  |

Source: Carrascoso and collaborators (12).

## Conclusions

Functional sequences are useful tools that complement conventional sequences, provide quantitative and qualitative information on tumour tissue and also allow a diagnostic approximation of the type of tumour.

With regard to diffusion sequences, there is not yet a standardized and validated cut-off value to determine benign and malignant lesions, due to tumour heterogeneity. So far, studies have been carried out in different teams and with different quantification protocols, which allow values to be reported, such as those described, by means of the imaging review and, in table 1, from cases from both institutions.

It is considered that more studies should be carried out to support a cut-off value. Among these, we expect to present the series of cases obtained at the Pablo Tobón Uribe Hospital, Medellín, Colombia, which began in January 2015.

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