Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) values for detection of malignant vertebral bone marrow lesions

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Abstract. – Malignant spinal bone marrow disorders are one of the major causes of significant morbidity and reduction in quality of life in oncological patients. Thus, the characterization of these conditions is of crucial importance in the management of these patients.

Magnetic resonance (MR) imaging plays a vital role in differentiation between benign and malignant spinal bone marrow disorders. However, morphological imaging features, based on T1 and T2 relaxation properties, might fail in differentiating between these conditions because signal characteristics may overlap. Quantitative MR imaging based on diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) values has been proved to help in defining the nature of the lesion. The aims of this paper were: to review basic principles of DWI technique and ADC maps, to describe DWI and ADC maps appearances of normal vertebral bone marrow briefly, to discuss the DWI and ADC maps characteristics in vertebral malignant lesions, to provide indications for differential diagnosis between malignant and benign lesions.

Key Words: Bone marrow, Bone marrow disorders, Bone marrow, Magnetic resonance, Diffusion weighted imaging, Apparent diffusion coefficient.

Introduction

Metastatic bone disease is, unfortunately, a common event in the evolution of cancer. The development of metastases has a key impact on the management of oncological patients, because, once bone metastases occurred, cancer cure is no more possible and palliative therapy is the only viable approach. The commonest site of bone metastases is the vertebral bone marrow. The consequences are often significant morbidity and reduction in quality of life. In some cases, vertebral metastases do not cause symptoms. They often origin severe pain or reduction of mobility due to compression of the spinal cord by a direct mechanism or, indirectly, by causing a vertebral pathologic fracture.

In this scenario, the characterization of spinal bone marrow disorders is of vital importance for the management of oncological patients. Magnetic resonance (MR) imaging plays a crucial role in differentiation. Different T1 and T2 relaxation properties allow distinction of bone marrow lesion from normal bone marrow. However, morphological MR sequences might fail in differentiating between malignant and benign lesion because signal characteristics may overlap. Functional MR imaging based on diffusion weighted imaging (DWI) and the derived apparent diffusion coefficient (ADC) maps may help define the nature of the lesion, offering both qualitative and quantitative information, respectively, on the studied tissue.

The basic principle of DWI is that water molecules in a tissue show a different Brownian motion depending on variations in microstructure. Signal attenuation reflects the degree of water motion with a proportional relationship. ADC value allows the quantification of this Brownian motion, and is calculated from...
DWI and ADC values for detection of malignant vertebral bone marrow lesions

maps derived by diffusional signal attenuation. Briefly, tissues with high free water component, like as those with lower content of membranes and intracellular organelles or high free extracellular water content show lower signal intensity on DWI and higher signal intensity on ADC maps in comparison to muscles. Conversely, tissues with restricted extracellular water content, like those with high cellularity, as tumors, show higher signal intensity on DWI and iso-hypointensity on ADC maps.

DWI has a well-established role in the study of the central nervous system’s pathology. Recently, this MRI technique has been employed also in the musculoskeletal system for detection, characterization and monitoring of soft-tissue and osseous lesions in oncological patients.

When a cancer spreads to new and different site, it very often locates in the axial skeleton, as metastases have a preferential tropism for red marrow contained in skeletal segments. For this reason, some authors have proposed the study of the whole spine for detection and follow-up of bone metastases, particularly those from prostatic cancer.

The aim of this paper was to illustrate the role of DWI imaging in the identification and characterization of malignant vertebral bone marrow lesions. In this study, after the introduction of basic principles of DWI and ADC maps, DWI appearances and ADC values of normal vertebral bone marrow will be described, and DWI and ADC maps characteristics in vertebral malignant lesions will be illustrated. Moreover, indications for differential diagnosis between vertebral malignant vs. benign lesions will be discussed.

**DWI Basic Principles and Technique**

DWI technique finds its fundamentals in the principles that regulate free water motion in the cellular environments. In all tissues, free and intracellular water molecules show a constant motion (Brownian motion) due to thermal kinetic energy. Whereas this motion is random for free extracellular water molecules, intracellular water’s motion is impeded by cell membranes and organelles. This means that diffusion of water molecules depends strictly by the cellularity of the examined tissue, which influences the Brownian motion of both intracellular and extracellular water. The ability of DWI to detect tumoral foci is explained by the fact that this technique provides visualization and quantification of tissue water content. Tissues, like as cancerous tissue, hypercellular metastases and fibrosis, having increased cellularity, and thus, higher proportions of membranes, intracellular organelles or restricted free extracellular space, show impeded water diffusibility compared with normal surrounding tissues. On the contrary, in tissues with less cellularity or also in necrotic regions of a tumour where disrupted cell membranes are prevalent, diffusion is less restricted.

DWI sequence is a spine-echo T2-weighted single shot sequence that derives from two symmetric motion-probing gradient pulses about a 180° refocusing pulse. The first applied diffusion gradient causes a change of position of the phase shift; in a restricted environment the spins maintain their initial location along the gradient axis during the two pulses. Free water molecules, instead moving in the interval between the first and the second gradient when the second pulse arrive, will be subjected to a different field strength, and will undergo a total phase shift, giving a decreased signal intensity on DWI image. In other words, moving water molecules do not refocus and show a signal loss on DWI. Conversely, water protons impeded by cellular membranes or intracellular organelles retain the signal and show hyperintensity on MR image.

The weighting to diffusion of DWI strictly depends on the b value. The b value is a parameter expressed in seconds per square millimeter that reflects the acquisition setup, i.e., the duration, amplitude, and temporal spacing of the two motion-probing gradients. The b value determines the degree of the diffusion weighting with a direct proportion. The diffusion weighting increases by increasing the b value. Lower b values, which mean higher T2 weighting, provide a high signal-to-noise ratio (SNR), but low definition in the diffusion. Generally, at least two different b values are used to extrapolate quantitative data. At our institution we use for the study of musculoskeletal system the b values of 0 and 800 s/mm.

The quantitative measurement of the Brownian motion is provided by the calculation of the ADC. Tissues with high cellularity and restricted diffusion of free extracellular water molecules exhibit low ADC values. The ADC value is measured by tracing a region of interest (ROI) in the abnormal tissue. Thus, minimum, maximum, and mean ADC values are generated, representing the logarithmic decrease in signal intensity between two or more b values in the selected pixels, expressed in units of $10^{-3}$ × mm$^2$/s.
DWI of Normal Vertebral Bone Marrow

The behavior of normal bone marrow in DWI and ADC maps pass through a deep understanding of the structural composition of this tissue. In adults, the bone marrow is constituted principally by yellow bone marrow containing 80% of fat, 15% of water, and 5% of cellular components. In younger subjects, the prevalence of red bone marrow reflects in a different distribution of the same constituents: 40% of fat and water and 20% of cellular components.

It has been demonstrated that normal yellow bone marrow shows low signal intensity on DWI and low ADC values (Figure 1). This evidence has been explained as due to the prevalence of fat cells, that limits the presence of extracellular water, due to their hydrophobic nature. Moreover, the yellow bone marrow, with its low cellular content, exhibits low perfusion. Conversely, red marrow, with its higher cellularity and extracellular water content, shows higher signal intensity on DWI and higher ADC values than yellow bone marrow. It has to be considered that vertebral metastases are more frequent in older subjects. Red bone marrow atrophy and trabecular bone loss are

Figure 1. 57-year-old man with normal vertebral bone marrow. Sagittal T1-weighted (a) and T2 fat saturated image (b), axial T1 weighted image at the level of D10 (c), show intermediate hyperintensity (a and c) and hypointensity (b) of the vertebral bodies in accordance with the prevalence of yellow bone marrow. Axial DWI image (d) and the corresponding ADC map in D10 at the same level (e) show low signal and high values ($0.15 \times 10^{-3} \text{ mm}^2/\text{s}$), respectively.
more evident after 40 years of age and in woman, probably due to estrogen deficiency and osteoporosis\textsuperscript{26,27}. Both this evidence advantages the detection of hypercellular metastatic tissue.

Unlike other soft tissue cancer localizations, metastatic tissue colonizing yellow bone marrow displaces fat cells; the result is an increase of signal intensity on DWI and an increment of ADC value (Figure 2).

**DWI and ADC Maps in Vertebral Malignant Bone Marrow Disorders**

MR imaging is the reference standard imaging modality for evaluating spinal lesions. The reason is mainly related to its excellent capacity of differentiating soft from bone tissue. Vertebral metastases are generally classified as mostly destructive or osteolytic and mostly bone forming or osteoblastic (e.g., from prostatic carcinoma). Both types of vertebral metastasis appear on T1-weighted sequences as hypointense lesions compared to fatty tissue, due to the replacement of adipose cells by tumor cells (Figure 2). On T2-weighted images the signal characteristics are more variable in relation to the water content of the metastases. However, they generally appear as more or less hyperintense lesions\textsuperscript{15} (Figure 2). In addition, around the lesion a hyperintense halo is visible, due to perilesional edema\textsuperscript{28,29}. Nevertheless, morphological sequences are often insufficient in distinguishing malignant from benign vertebral bone marrow lesions, due to overlapping features, or the coexistence of bone marrow edema caused for example by fractures, infection, bone marrow hyperplasia related to therapy.

DWI and ADC maps have been proposed for the discrimination of malignant lesions, especially in these particular conditions\textsuperscript{30-32}.

Generally, bone marrow vertebral metastases appear on DWI as high signal intensity areas in an otherwise hypointense vertebral soma. These areas correspond to low signal intensities on ADC maps (Figure 2).

It is well known that bone metastases can be prevalently lytic or sclerotic. Although in both types of metastases the bone turnover is more pronounced than in normal bone marrow, in osteolytic metastases, the osteoclastic activity is prevalent as it is stimulated by the adjacent metastatic tumor cells. Conversely, the osteoblastic metastases origin from the prevalent stimulation of osteoblasts.

Osteolytic lesions are better detected on DWI imaging, due to the higher content of water and cells with respect to the sclerotic ones\textsuperscript{33}.

It has to be considered, as mentioned above, that the behavior of vertebral malignant lesion on DWI and ADC map against normal tissue is different from that of other soft tissue malignant lesions. In fact, whereas in soft tissue malignant lesions show high signal intensity on DWI and lower ADC values than the corresponding normal tissue, malignant yellow bone marrow lesions show high signal intensity on DWI, but higher ADC values than normal yellow bone marrow\textsuperscript{22,23,33-35} (Figures 1, 2). As explained above, this is due to the fact that tumor cells infiltrating bone marrow displace fat cells, thus increasing cellular and water proton density, and augmenting blood perfusion\textsuperscript{19,24,36-38}.

Padhani et al\textsuperscript{35} in 2013 and other previous studies\textsuperscript{22,24,39} demonstrated statistically significant

**Figure 2.** 45-year-old woman with breast carcinoma. T1 (a) and T2 fat saturated (b) images show the presence of two lumbar metastatic lesion respectively hypo- and hyperintense with respect to the surrounding tissue. The corresponding DWI image (c) demonstrates hyperintense lesions, that show on ADC map, values of 0.78-0.82 × 10\textsuperscript{-3} mm\textsuperscript{2}/s.
differences in signal intensity and ADC values of metastatic and normal yellow bone marrow. Particularly, Padhani et al\(^3\) demonstrated that the 95\(^{th}\) percentile and maximum values for mean tumor ADC distribution were 1.2 \(\times\) \(10^{-3}\) mm\(^2\)/s and 1.4 \(\times\) \(10^{-3}\) mm\(^2\)/s. The ADC cut-off value for distinguishing between normal and malignant bone marrow was settled at 0.774 \(\times\) \(10^{-3}\) mm\(^2\)/s by Padhani et al\(^3\), and at 0.655 \(\times\) \(10^{-3}\) mm\(^2\)/s by Messiou et al\(^2\). This means that when the presence of a vertebral lesion is suspected in an oncological patient, the high signal intensity on DWI and ADC values above at least 0.655 \(\times\) \(10^{-3}\) mm\(^2\)/s suggests the malignant nature of the alteration. However, it has to be specified that this is truer for yellow bone marrow. In younger patient, with an higher proportion of red bone marrow, or in patients treated with stimulating factors like G-CSF, because of higher signal intensity and ADC values of normal bone marrow related to higher cellular density and perfusion, the differences in DWI signal intensity and ADC values between malignant and normal bone marrow are narrower.

Another major problem in oncological patients is the differentiation between pathological vs. osteoporotic fracture. Also in this case, the use of DWI and ADC maps can be useful for differentiation. Bone marrow edema, that means the water proton density and interstitial space, is supposed to be superior in non-pathological fractures than in pathological ones. In fact, in pathological fractures, tumor cells infiltrating bone marrow cause restriction of interstitial space and displacement of water molecules. The result is the evidence of higher DWI signal intensity and lower ADC values in pathological fractures with respect to what observed in osteoporotic fractures\(^4\)\(^4\).

In a comprehensive review of the literature, Dietrich et al\(^4\)\(^2\) suggested the following differentiating ADC values: the ADC value of normal vertebral bone marrow is typically found to be between 0.2 and 0.6 \(\times\) \(10^{-3}\) mm\(^2\)/s, ADC value in osteoporotic fractures are generally between 1.2 and 2.0 \(\times\) \(10^{-3}\) mm\(^2\)/s, superior to that of malignant fractures or lesions, typically between 0.7 and 1.3 \(\times\) \(10^{-3}\) mm\(^2\)/s (Figure 3).

About the differentiation between malignant and benign lesions, the literature offers some indications (Figure 4). Dietrich et al\(^4\)\(^1\) summarizing the results of some studies on the issue\(^2\)\(^3\)\(^4\)\(^3\)\(^4\)\(^6\)\(^4\)\(^3\)\(^4\)\(^6\) identified a mean value of 1.2 \(\times\) \(10^{-3}\) mm\(^2\)/s for inflammatory vertebral lesions such as lesions caused by spondylitis or tuberculosis. Thus, intermediate ADC values are identified for such lesions, between those of osteoporotic fractures and malignant vertebral lesions.

**Conclusions**

DWI and ADC maps are able to detect differences in cellularity of malignant bone marrow disorders with respect to the normal bone marrow. This ability allows the diagnosis of vertebral metastases with a high level of confidence, so that DWI and its ADC maps could be effectively applied for the routine MR imaging analysis in oncological patients for the diagnosis of vertebral metastases. Some limitations for the daily application of DWI in the study of oncological patients are the presence of high cellularity lesions such as sclerotic vertebral metastases\(^4\)\(^7\) and the presence of red bone marrow, for example in younger subjects or in those patients treated with bone marrow stimulating factors such as G-CSF. These

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**Figure 3.** 44-year-old man with lung cancer. A vertebral collapse appears iso-hypointense on T1 weighted image (a), shows hyperintensity on DWI image (b), and ADC value on the related map (c) of 0.82 \(\times\) \(10^{-3}\) mm\(^2\)/s.
last conditions, in fact, increase basal bone marrow signal intensity on DWI imaging, thus rendering eventual malignant lesions less evident on the normal background.

Conflict of interest
The authors declare no conflicts of interest.

References


