

## The Added Value of Quantitative DWI MRI in Differentiation between Benign and Malignant Osseous Musculoskeletal Tumours

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### Abstract

**Background:** MRI has a key role in identification of MSK masses, especially in depiction of their nature, borders, regional involvement and their relation to the surrounding organs and neurovascular bundle.

MRI aids clinicians in assessment of osseous tumors to depict the extra-osseous component, and the regional location as well, since both parameters are crucial for the pre-operative assessment.

**Aim of Study:** To evaluate the role of Diffusion Weighted Imaging (DWI) in differentiation of benign and malignant osseous musculoskeletal (MSK) tumors and its added value clinically on patient's management.

**Patients and Methods:** The study included 100 patients; 65 males (65%), and 35 females (35%). Their ages ranged from 3 to 69 years with mean age about 31 years. Patients were selected based on clinical and X-ray image suspicion of MSK tumors. Signal intensity of the lesion on DWI was determined and Attenuation Diffusion Coefficient (ADC) map was measured. The Region of Interest (ROI) for each lesion was placed at least 3 times, and then the mean ADC value for the lesion was calculated. Histopathological findings and clinical follow-up were used as standard of reference.

**Results:** Twenty one 21 (21%) patients had benign tumors, 73 (73%) patients had malignant tumors and 6 (13.6%) patients had tumor like lesion. The cut-off value for mean ADC was  $< 1 \times 10^{-3} \text{ mm}^2/\text{sec}$ . The gold standard of this study was the histopathological correlation and the imaging-clinical relative features for the benign lesions.

**Conclusion:** DWI MRI technique that is easily included in a routine MR study with short scanning time offering valuable data about the cellularity of a MSK lesion and properly differentiating benign and malignant lesions.

**Key Words:** MRI – DWI – ADC map – Musculoskeletal tumors.

### Introduction

**MASSES** of the MSK are not uncommon and variable. Osseous and cartilaginous sarcomas constitute 0.5% of all human malignancies, yet they

occur with a higher frequency in the pediatric population. As regards soft tissue sarcomas, they have 3 to 4 folds higher incidence than osseous and cartilaginous sarcomas and occur in adults after their fifth decade. Benign osseous and soft tissue neoplasms are 100 times more frequent than malignant ones with a total incidence of 300/100,000 [1]. Since the survival rate of cancer patients is increasing, the incidence of bone osseous deposits will also rise as well [2].

MRI has a key role in identification of MSK masses, especially in depiction of their nature, borders, regional involvement and their relation to the surrounding organs and neurovascular bundle [3].

MRI aids clinicians in assessment of osseous tumors to depict the extra-osseous component, and the regional location as well, since both parameters are crucial for the pre-operative assessment [4].

Routine MRI depends mainly on a qualitative interpretation of difference in the T1 and T2 relaxation parameters of normal and affected tissue. Yet, there is a significant overlap between the signal characters of tumors (whether malignant or benign) and non tumors infectious or inflammatory processes. Moreover, it is usually hard to differentiate neoplasms with high signal intensity from reactionary adjacent oedema using fluid-sensitive sequences [5].

The additional value of contrast material enhancement was a turning point for routine MRI in evaluation of tumors as regards distinguishing solid masses from cystic lesions, depiction of tumor borders and determining the extent of tumor necrosis [6].

Yet, contrast material intake is invasive and is relatively avoided in pregnancy and might be

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restricted by hypersensitivity to contrast material or by poor kidney function because of the hazard of nephrogenic system fibrosis [7].

DWI is a functional rapid MRI technique which can be easily included in the conventional MR protocol. Its idea is based on the alterations in the water molecules' Brownian movement made by tissue microstructure. ADC is a quantitative measurement of Brownian motion. The low ADC values generally denotes high cellular packing where diffusion is restricted by cell membranes, whereas low cellular areas show facilitated diffusion and lead to increased ADC values [8].

So, with the help of ADC mapping, we can formulate helpful quantitative data about the cellularity of a MSK mass without using a contrast enhanced technique.

The purpose of this study is to assess the role of DWI in characterization of MSK masses.

### Patients and Methods

#### Patients:

This study is prospective one and was conducted in Radiology Department of governmental hospital in collaboration with the Orthopedics and Oncology Departments, from November 2018 till March 2019. It included 100 patients 65 males (65%) and 35 females (35%). Their ages ranged from 3 to 69 years with median age 31 years. The study was approved by the Local Ethics Committee.

An informed consent was signed by all patients or their guardians for the pediatric patients.

Patients' selection was based on clinical and X-ray imaging suspicion of musculoskeletal tumors.

#### Inclusion criteria:

- Males and females.
- All age groups.
- Patients presented with MSK tumors.

#### Exclusion criteria:

- Contraindications to MRI examination, e.g. magnetic implants, pacemakers or claustrophobia.

#### Methods:

No special patient preparation was needed. Detailed explanation of imaging procedure was done. The patient was placed in a supine position. Scan time was about 20 to 30 minutes. The procedure was done using a 1.5-T unit (Achieva, Philips)

with a dedicated extremity coil and the following spin echo sequences: Coronal T1, coronal T2, coronal STIR, axial T1, axial T2 and axial diffusion (with diffusion sensitivities of b-value=0, 200 and 800s/mm<sup>2</sup>). Post contrast axial and coronal FAT SAT sequences were also obtained. Signal intensity of the lesion on DWIs (b800) was determined and ADC map was also measured using ROI for the suspicious lesion. The ROI for each lesion was placed at least 3 times, and then the mean ADC value for the lesion was calculated. The MR scans were reported by one general radiologist and one MSK specialized radiologist.

#### Statistical analysis:

The results were analyzed using a Student *t*-test. Statistical significance was put at *p* 0.05. Results were evaluated as means of Standard Deviation (SD).

### Results

Among 100 patients, 21 (21%) patients had benign tumors, 73 (73%) patients had malignant tumors and 6 (6%) patients had tumor like lesion.

Nine females (9%) and 12 male (12%) patients had benign MSK lesions. The average ADC value of benign tumors was above  $1 \times 10^{-3}$  /sec as illustrated in (Table 1).

Benign MSK tumors have ADC values ranging from  $1_3$  to  $3_2 \times 10^{-3}$  mm<sup>2</sup>/sec with a mean of  $2.14 \times 10^{-3}$  mm<sup>2</sup>/sec. The highest ADC<sub>3</sub> value is seen in unicameral bone cyst ( $2.8 \times 10^{-3}$  mm<sup>2</sup>/sec) and intraosseous lipoma ( $2.79 \times 10^{-3}$  mm<sup>2</sup>/sec) followed by aneurysmal bone cyst ( $2.37 \times 10^{-3}$  mm<sup>2</sup>/sec) Fig. (1).

Thirty females (30%) and 43 male (43%) patients had malignant MSK lesions. The average ADC value of malignant lesions was below  $1 \times 10^{-3}$  mm<sup>2</sup>/sec as illustrated in (Table 2).

Malignant MSK tumors have ADC values ranging from 0 to  $1 \times 10^{-3}$  mm<sup>2</sup>/sec with a mean ADC value of  $0.88 \times 10^{-3}$  mm<sup>2</sup>/sec. The lowest ADC<sub>2</sub> value is seen in lymphoma Fig. (2) ( $0.6 \times 10^{-3}$  mm<sup>2</sup>/sec) and Ewing sarcoma ( $0.63 \times 10^{-3}$  mm<sup>2</sup>/sec) Fig. (3).

Three females (3%) and 3 males (3%) had tumor like lesions Fig. (4). Their average ADC was variable as illustrated in (Table 3).

The ADC values of benign and malignant MSK tumors were analyzed. ROC analysis of both mean ADC values of malignant and benign lesions yield-

ed an area under the curve of  $0.958$  and a cut-off value of mean ADC  $\leq 1 \times 10^{-3} \text{ mm}^2/\text{sec}$  Fig. (5).

Sensitivity and specificity for malignancy in this study group was 96.4% and 90.48% respectively. There was a highly significant statistical difference between benign and malignant tumors in ADC values ( $p$ -value=0.000).

Table (1): Spectrum of benign MSK lesions and their mean ADC values.

Diagnosis	Number of cases	Mean ADC value $\times 10^{-3} \text{ mm}^2/\text{sec}$
Aneurysmal bone cyst	5	2.37
Enhcondroma	1	1.97
Eosinophilic granuloma	1	1.35
Lipoma	1	2.79
Non ossifying fibroma	3	2.16
Unicameral bone cyst	1	2.8
Osteochondroma	5	1.63

Table (2): Spectrum of malignant MSK lesions and their mean ADC values.

Diagnosis	Number of cases	Mean ADC value $\times 10^{-3} \text{ mm}^2/\text{sec}$
Osteosarcoma	2	0.68
Fibrosarcoma	1	0.78
Spindle cell sarcoma	3	0.87
Lymphoma	1	0.6
Melanoma	1	0.73
Ewing sarcoma	2	0.63
Metastasis	1	0.83

Table (3): Spectrum of tumor like MSK lesions and their mean ADC value.

Diagnosis	Number of cases	Mean ADC $\times 10^{-3} \text{ mm}^2/\text{sec}$
Chronic expanding hematoma	2	2.2
Subacute hematoma	1	0.35
Chronic osteomyelitis	1	1.75

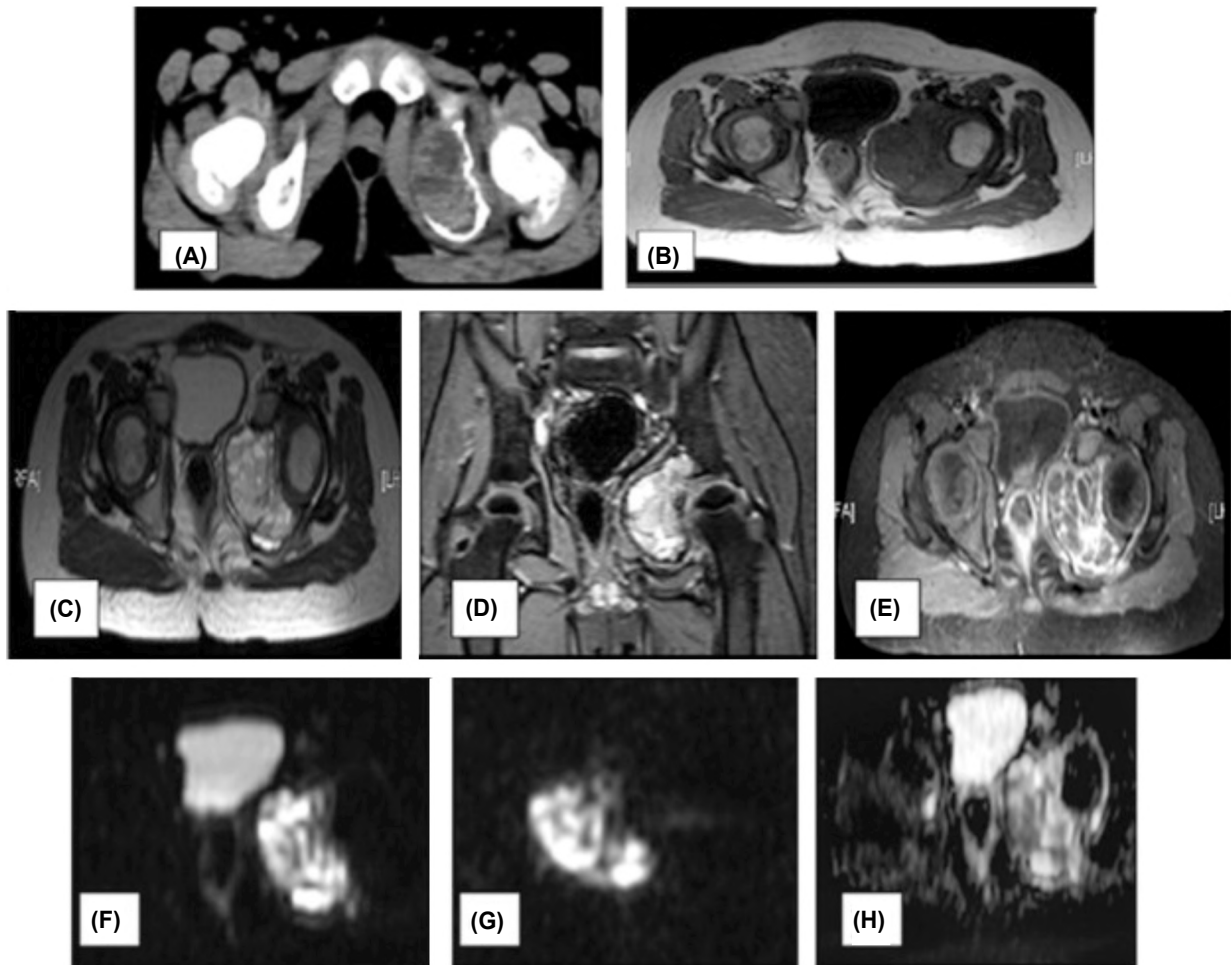


Fig. (1): Aneurysmal bone cyst (ABC): 15 year old male complaining of pain of the left hip: CT scan of the pelvic bones: Showing an expansile bony lesion affecting the left acetabulum. Axial T1 WI showing intermediate SI of the lesion which has intra-pelvic extension, with mild compression of the urinary bladder and rectum. (C and D) Axial T2WI and coronal T2 fat suppressed image: Showing mixed high SI of the bony lesion with the presence of fluid-fluid levels. (E) Post contrast axial T1 WI with fat suppression showing the enhancing septae of the lesion. (F) Diffusion-weighted images at different b values (0 and 800): Showing high signal at b 1000 diffusion weighted image. (H) ADC map showing the mean ADC value about ( $2.37 \times 10^{-3}$ )  $\text{mm}^2/\text{s}$ .

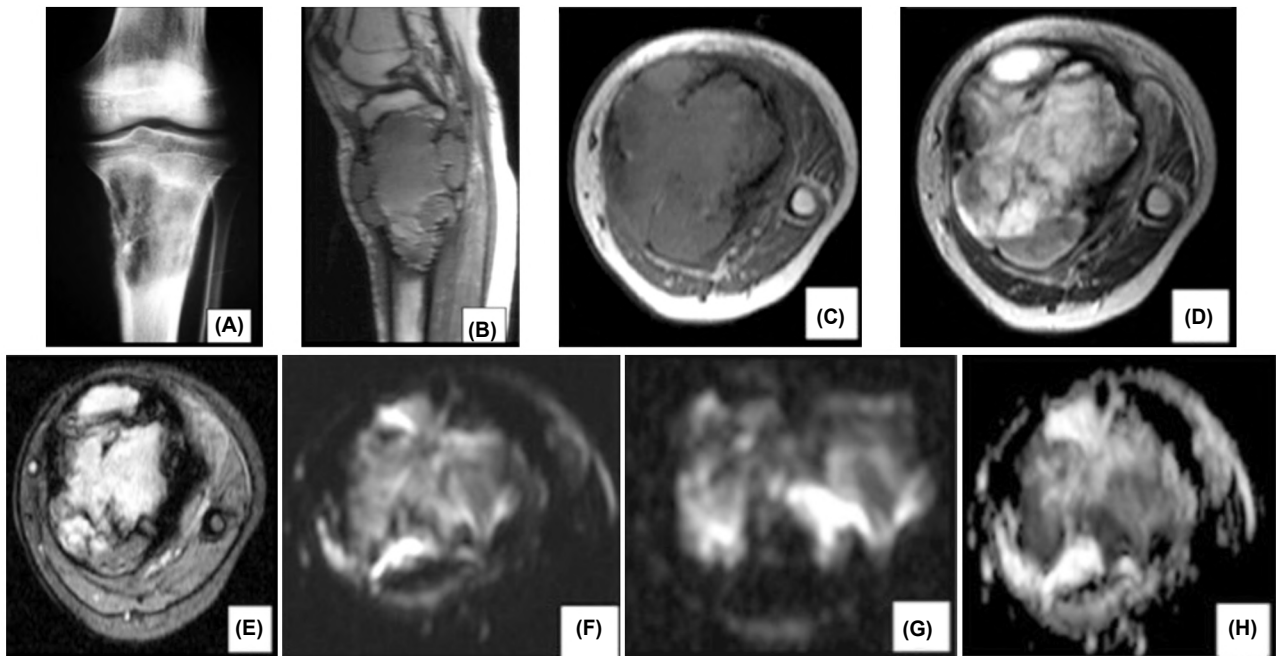


Fig. (2): Lymphoma: 17 year old male complaining of swelling and pain of the left knee: (A) Plain X-ray (AP view) of the left tibia: Showing diffuse patchy sclerotic lesion mixed with osteolytic areas. (B and C) Sagittal and axial T1WIs intermediate SI of the lesion and the associated soft tissue component. (D and E) Axial T2WI and GRE images showing mixed high SI of the bony lesion and the associated soft tissue mass. (F and G): Diffusion-weighted images at different b values (0 and 800): Showing high signal at b 800 (restricted diffusion). (H) ADC map showing the mean ADC value about  $(0.6 \times 10^{-3})$  mm<sup>2</sup>/s.



Fig. (3): Ewing's sarcoma: 21 year old female complaining of swelling and pain of the left radius: (A) Plain X-ray (AP and lateral views) of the left radius: Showing diffuse sclerosis and periosteal reaction. (B and C) Sagittal and axial T1WIs showing lesion of intermediate SI and the cortical defect through which the lesion is passing outside the medullary cavity to form a soft tissue mass. (D and E) Sagittal STIR and axial T2WI showing high SI of the bony lesion and the associated soft tissue mass. (F and G): Diffusion-weighted images at different b values (0 and 800): Showing high signal at b 800 (restricted diffusion). (H) ADC map showing the mean ADC value about  $(0.63 \times 10^{-3})$  mm<sup>2</sup>/s.



Fig. (4): Osteomyelitis: Male patient aged 30 years old complaining of right lower thigh painful, swelling and fever: (A) Plain X-ray (lateral view) of the left distal femur showing an ill defined osteolytic lesion. (B) Sagittal T1WI showing the low SI of the lesion and the surrounding bone marrow. (C) Sagittal T2WI, with fat suppression showing the high SI of the lesion and the surrounding bone marrow. (D and E) Axial CT scan (bone window) showing small bony sequestra. (F and G) diffusion weighted images at b-values (0 and 800): Showing non restricted diffusion in the peripheral parts (bone marrow edema) and high signal in the central part of the lesion (restricted diffusion). (H) ADC map showing the mean ADC value in the central part ( $0.9 \times 10^{-3}$ )  $\text{mm}^2/\text{s}$ , while in the solid part ( $1.75 \times 10^{-3}$ )  $\text{mm}^2/\text{s}$ .

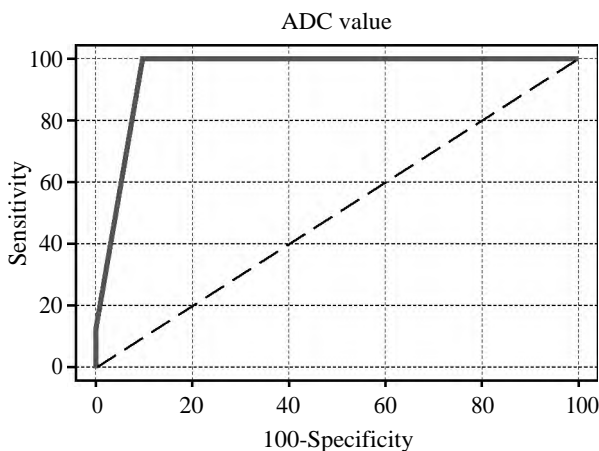


Fig. (5): ROC analysis of ADC in malignant VS benign lesions.

### Discussion

Reliable differentiation of MSK osseous tumors into benign and malignant entities by imaging modalities alone is difficult since malignant sarcomatous lesions may have well defined margins and show a homogenous enhancement exactly like benign tumors. The rationale that malignant lesions should demonstrate a lower ADC values was illustrated in many reports with different outcomes [8].

In this study, a significant difference was found in mean ADC value between benign and malignant MSK tumors. Malignant tumors tend to have lower ADC values than benign ones. With a cut off ADC value  $1 \times 10^{-3} \text{ mm}^2/\text{sec}$ , this study had 96.4% sensitivity and about 94% specificity, which can readily differentiate between benign and malignant tumors.

In 2012, Razek et al., reported that malignant tumors have a lower mean ADC value than benign tumors and suggested to use a threshold mean ADC value of  $1.34 \times 10^{-3} \text{ mm}^2/\text{sec}$  to differentiate benign from malignant tumors. This yielded a sensitivity of 94%, a specificity of 88%, and an overall accuracy of 91% [9]. Moreover, more aggressive sarcomas showed lower mean ADC values than less aggressive ones and this is compatible with our results where histopathologic findings were of more aggressive nature in lower ADC values as illustrated in (Table 2).

There are many parameters that influence ADC values other than the lesion cellular content, such as the nature of the lesion matrix, the existence of necrotic tissue and variable imaging techniques for DWI-ADC mapping. That's why there is a controversy in specifying the ADC cut off value to differentiate benign from malignant tumors in the available literature [11].

In 2004, Einarsdóttir and his colleagues depicted a significant similarity between the ADC value of 13 sarcomatous lesions (mean ADC  $1.7 \times 10^{-3} \text{ mm}^2/\text{sec}$ ) and that of 16 benign ones (mean ADC  $=1.8 \times 10^{-3} \text{ mm}^2/\text{sec}$ ). They reported that a subject presented with osseous liposarcoma had one of the greatest ADC values for a sarcoma. This is consistent with our results where we encountered a case of non myxoid soft tissue sarcoma showing a mean ADC value of  $(0.99 \times 10^{-3} \text{ mm}^2/\text{s})$  [10].

Drapé, 2013 noted that both malignant and benign lesions have a greater ADC values than those in non myxoid lesions. The ADC values are high due to the high mucin content in these lesions [12].

In this study, we had only one subject presenting with benign myxoma with a high mean ADC value  $(2.31 \times 10^{-3} \text{ mm}^2/\text{sec})$ , yet we didn't encounter any myxoid malignant lesions.

Hayashida et al., [13] found that for a small sample ( $n=20$ ) of T2-hyperintense bone lesions (bone cysts, fibrous dysplasia, and chondrosarcoma), ADC maps were not helpful in differentiating malignant from benign lesions, since the mean ADC for chondrosarcomas  $(2.29 \times 10^{-3} \text{ mm}^2/\text{sec})$  was intermediate between that of simple bone cysts  $(2.57 \times 10^{-3} \text{ mm}^2/\text{sec})$  and that of fibrous dysplasia  $(2 \times 10^{-3} \text{ mm}^2/\text{sec})$ .

In another series, Yakushiji et al., [14] showed that minimum ADC values allowed good discrimination between chondroblastic osteosarcoma and chondrosarcoma, despite their having similar chondroid-type matrix enhancement patterns.

The authors found that the minimum ADC values of chondroblastic osteosarcoma  $(1.24 \pm 0.10 \times 10^{-3} \text{ mm}^2/\text{sec})$  were higher than those of other types of osteosarcoma  $(0.84 \pm 0.15 \times 10^{-3} \text{ mm}^2/\text{sec})$  and lower than those of conventional chondrosarcoma  $(1.64 \pm 0.20 \times 10^{-3} \text{ mm}^2/\text{sec})$ .

However, the literature says little about the ability of DW imaging to ameliorate the ongoing diagnostic dilemma of distinguishing low-grade chondrosarcomas from enchondromas, since it is generally not helpful in characterizing bone lesions as malignant. The same conclusion has been elicited in this study. This difference highlights the utility of DW imaging as a technique for tumor detection against a background of normal marrow, although the role of DW imaging in tumor characterization remains unclear.

Current study have confirmed that low ADC values are related to malignancy and propose that ADC values are mainly beneficial in differentiating between solid and cystic lesions when contrast media are contraindicated.

This overlap in DWI parameters accentuates the urgency for a global MR sequence selection and the value of clinical data in evaluation of different lesions. The use of intravenous contrast material is still preferred for standard evaluation of associated soft tissue lesions especially if there is a high possibility of an infectious process [15].

The analysis of DWI in bone masses varies from that in soft tissues as ADC masses with high cellularity. This is most probably because yellow marrow has poor water content with minimal extracellular matrix. Moreover, big lipid laden cells in yellow marrow hinder water mobility much more than smaller cells of red marrow.

Fat itself is not hydrophilic and acts as an obstacle to diffusion. In addition, the higher intramedullary blood outflow in red marrow augments the perfusion-weighted parameter of the ADC obtained from lower b-values. These rules are vital when assessing the pediatric population, as the regular skeletal maturity will lead in a gradual decreasing ADC value of marrow as it is gradually replaced by fat.

Moreover, this indicates that ADC values of worrisome bone lesions will be greater than the suggested cutoff values for discriminating tumor from normal bone marrow [8].

In our study, we had two intra-medullary lesions, the first was non Hodgkin's lymphoma with a mean ADC value of  $0.84 \times 10^{-3} \text{ mm}^2/\text{sec}$  and the second one was metastatic with a mean ADC value of  $0.83 \times 10^{-3} \text{ mm}^2/\text{sec}$ .

Padhani et al., 2013 concluded that the 95<sup>th</sup> percentile  $\text{ADC}_2$  value in bone secondaries was  $1.21 \times 10^{-3} \text{ mm}^2/\text{sec}$ , and applying a cutoff value of  $0.77 \times 10^{-3} \text{ mm}^2/\text{sec}$  led to specificity of 90% and sensitivity of 85% and in discriminating malignant marrow infiltration from regular marrow [16].

In this study, we found a highly significant statistical difference in ADC of benign and malignant primary bone tumors.

Unfortunately, DWI has some drawbacks. First, DWI has a low sensitivity for sclerotic osseous deposits which are devoid of water leading to false negative results. This dilemma is responsible for

the debate in literature about the role of DWI in evaluation of vertebral body deposits.

Moreover, false positive results can also occur when there are incidental blood products in the lesion leading to low ADC values, equally, abscess or infectious process with low ADC values can pose the same problem and can be misinterpreted as a malignant sarcoma.

Finally, since fat in normal bone marrow has a diffusion coefficient much lower than water, so any ROI contaminated with fatty marrow, false negative low ADC values can be expected [8].

#### Conclusion:

DWI is a non contrast enhanced functional MRI tool which can be smoothly integrated in the conventional MRI procedure with minimal extra scanning duration and can add beneficial value of differentiation between benign and malignant lesions in special cases like those with renal impairment.

It provides essential data about the cellular content of musculoskeletal lesion and accurately differentiates between benign and malignant lesions and therefore minimizing the demand for unneeded biopsies.

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## دور الرنين المغناطيسي بخاصية الانتشار في تقييم أورام العظام الحميدة والسرطانية

يلعب الرنين المغناطيسي دور جوهري في تقييم الأورام العظمية المختلفة خاصة من ناحية طبيعتها وحدودها ودرجة إنتشارها خاصة قبل إجراء الجراحات المختلفة.

وقد عزز الرنين المغناطيسي بخاصية الانتشار هذا الدور وطوره.

وقد كان الهدف من البحث هو تقييم دور الرنين المغناطيسي بخاصية الانتشار في التفرقة بين الأورام الحميدة والسرطانية ودراسة تأثيره على خطة العلاج.

تضمن البحث عينة من ١٠٠ مريض تتراوح أعمارهم بين ٣-٦٩ سنة ممن يعانون من أورام عظمية مختلفة، حيث تم إجراء فحص الرنين المغناطيسي لهم قبل وبعد حقن الصبغة وتضمن أيضاً خاصية الانتشار وقياس معاملها.

وقد جاءت النتيجة بأن الحد الفاصل بين طبيعة الأورام المختلفة هو ١ \* ١٠-.

وقد أوصى البحث بضرورة عمل الرنين المغناطيسي وإضافة تقنية خاصية الانتشار مع قياس معامل الانتشار في حالات أورام العظام المختلفة لما في ذلك من أهمية كبرى في التفرقة بين الأورام الحميدة والخبيثة، بالإضافة إلى قدرة هذا الفحص على تحديد حجم الورم وأبعاده ودرجة إنتشاره ومن ثم تأثيره على الأنسجة المحيطة به.