The Role of Diffusion MRI in differentiation between benign and malignant Bone Tumors

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Abstract: Aim of the Work: Is to assess the ability of diffusion MRI in differentiation between benign & malignant bone tumors and to correlate diffusion patterns & Apparent diffusion coefficient (ADC) values of different lesions with their pathological nature. **Patients and Methods:** A prospective study was conducted on thirty patients with clinically suspected and radiologically proven bone tumor. The patients were referred to the MRI unit in Ain Shams University from the surgery and radiotherapy departments. These patients were selected on clinical bases indicating or suggesting presence of bony tumors as a primary diagnosis. The patients were investigated using 1.5 Tesla magnetic resonance device. They were subjected to conventional MRI and dynamic contrast enhancement (DCE) MRI. **Results:** The ADC values of solid malignant tumors (n= 11) ranged from 0.56 to 1.48 x 10-3 mm2/s, with mean ADC (1.04 x 10-3 mm2/s) were significantly lower than that of the benign bony tumors (n=19) which ranged from 1.36 to 2.6 x 10-3mm2/s, with mean ADC (1.96 x 10-3 mm2/s). Diffusion weighed imaging with ADC values measurement were able to discriminate between benign and malignant lesions with sensitivity of 90.9% specificity of 89.5% and diagnostic accuracy of 90%. The results according to ROC curve for the discrimination between benign and malignant lesions using the ADC value showed that the best cut-off criterion is ADC of 1.18 with overall sensitivity of 81.8% specificity of 84.2% and diagnostic accuracy of 83.3%. **Conclusion:** We proved high specificity and sensitivity of DWI as a complementary sequence with conventional MRI and ADC value measurements in discrimination between benign and malignant bone tumors with significant cut-off value, making it a noninvasive tool for increasing the accuracy in identifying bone lesions. Also, they can be used in the follow up of tumors and their response to therapy. However, further studies with larger patient groups are needed to find an optimal cut-off ADC value for differentiation between begin and malignant bone tumors.

1. Introduction

Worldwide, cancer is the second cause of death following heart disease, accounting for 23% of all deaths. Primary malignancy of bone and joints is ranked as third leading cause of death in patient with cancer who is younger than 20 years [1].

Improvement of treatment and outcome of bone tumors requires development of diagnostic tools that can help in differentiation between benign and malignant lesions in a noninvasive and reliable manner [2].

Radiographs provide critical information regarding lesion location, margin, matrix mineralization, cortical involvement and adjacent periosteal reaction [3].

Most bone tumors have classical radiographic appearances and they can be diagnosed and correlated with patient age and clinical data. MRI can detect non-mineralized tumor tissue, evaluate the local extent of a malignant process for staging and assess bone tumor therapeutic responses. However, lesions of high T2 signal and low enhancement constitute diagnostic challenge in daily practice [4 & 5].

In addition, a few benign and malignant tumors show atypical features and need further investigation. Some benign lesions in patients with known primary malignancies also constitute a diagnostic problem [6].

MRI is the most sensitive imaging modality for detection of bony tumors.

It is considered the gold standard for characterization of these lesions and can detect occult intra-medullary lesions with negative bone scan [7].

Diffusion-weighted magnetic resonance imaging (DWI) is a recent addition to the MR sequences conventionally employed. DWI provides qualitative and quantitative functional information concerning the microscopic movements of water at the cellular level [8].

Diffusion MRI measures the random movements of water molecules in the body (Brownian motion). Water molecule motion is assessed in vivo in the extracellular, intracellular, and transcellular

compartments, as well as in the intravascular compartment (microcirculation-perfusion) [9].

Restriction of water-molecule diffusion within biological tissues correlates negatively with tissue cellularity and membrane integrity [10].

Restriction is greater in highly cellular tissues that have intact cell membrane and a small extracellular compartment.

Tumors differ regarding their cellular characteristics and the differences can serve to differentiate tumor types [11 & 12].

The advantage of evaluating diffusion is the ability to probe the Apparent diffusion coefficients (ADC) cellularity of neoplasm, different ADC values corresponding to changes in restricted diffusion [13 & 14].

The purpose of this prospective study is to elucidate the ability of diffusion MRI in differentiation between benign & malignant bone tumors and to correlate diffusion patterns & ADC values of different lesions with their pathological nature.

2. Patients and Methods:

This was a prospective study conducted on 30 patients selected on clinical bases indicating or suggesting presence of bony tumors as a primary diagnosis. The patients were referred from the surgery and radiotherapy departments to MRI unit in Ain Shams University. The patients were investigated using 1.5 Tesla magnetic resonance device. The study was approved by the Ethics Board of Ain Shams University.

Patients age range from 5 to 62 years, patient included in our study were classified according to the pathological and radiological criteria into two groups: Benign bone tumors (19 patients) & malignant bone tumors (11 patients).

Patients

Inclusion Criteria:

Age group: all age group, both sexes were included, bone tumors as a primary diagnosis, which were suspected clinically and were seen on radiographs.

Exclusion Criteria:

Patient with contra indication to MRI: e.g.: pacemaker, metallic implant, severe claustrophobia, patients with contra-indications to contrast media (e.g. severe renal impairment, hypersensitivity).

Methods

The evaluation of patients started with reviewing all patient's clinical data and plain radiographs. Then the patients underwent Conventional and DCE-MRI studies prior to surgery. Sedatives/hypnotics were used in some patients to reduce anxiety and movement.

1.   **Conventional & Diffusion MRI:**

All examinations were performed on a 1.5 Tesla MR scanner (Achieva; Philips Medical Systems, Bothell, WA, USA) using surface array coil & spine radio-frequency. Patients with known primary malignancy received gadolinium as a routine protocol in our MRI unit. The patients were positioned supine. The MR protocol consisted exclusively of the following sequences: conventional TI, T2, STIR and diffusion weighted echoplanar imaging (EPI) and contrast enhanced T1W images.

DW EPI using different b values including 0 s/mm², 500 s/ mm², and 1000 s/ mm². For each DW-EPI sequence and a pixel-by-pixel apparent diffusion coefficient (ADC, unit ×10−3 mm2/s) was automatically calculated with multiple b-values.

2.   **Image interpretation:**

Characterization of different bone tumors will be determined in one lesion per patient by diffusion MRI, correlation with ADC map values, lesion size and relative signal intensity.

The lesion were determined on DWI and ADC map by using the conventional MR images as a guide, Signal intensity of the lesion on DWIs (b1000) is determined: either hypo intense (free diffusion) or hyper intense (restricted diffusion).

Measurements of the apparent diffusion coefficient (ADC) were made using electronic cursor on the ADC map in different regions of interest (ROI) of the lesions and in comparable contralateral regions of normal tissue. The ADC values were expressed in 10^{-3}mm2/s.

The ROI for each lesion was placed 3 times, and then the mean ADC value for the lesion was calculated.

Both solid parts and cystic parts of the tumors were assessed. ROI was placed inside the solid part of the tumor and in the center of the cystic area.

3.   **Correlation of Radiological findings**

With final diagnosis: MRI findings have been correlated with the pathological results of either surgical excision or needle biopsy.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

Receiver-operating characteristic (ROC) curve analysis was used to examine the value of the ADC for discrimination between benign malignant lesions. The diagnostic value of a restricted DWI pattern was examined with classification of lesions into benign or malignant by biopsy.

Independent-samples t-test of significance was used when comparing between two means. Chi-square

(x^2) test of significance was used to compare proportions between qualitative parameters. Evaluation of Diagnostic Performance was used Receiver operating characteristic (ROC curve) analysis.

The following diagnostic indices were then calculated: sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, correct classification rate, and misclassification rate.

3. Results

According to results of lesion biopsy, 11 (33.6%) patients were proved to be malignant and the other 19 (63.3%) were proved to be benign, in which 12 (40%) patients out of 30 showed restricted diffusion and 18(60%) showed facilitated diffusion. 10 (90.9%) out of the 12 patients, which proved to be malignant according to biopsy results, showed restricted diffusion the P-value is statistically significant (p <0.001) **Table 1**. with median ADC value 1.04 (0.56–1.48). while 17 (89.5%) out of the 19 patients, which proved, to be benign by the biopsy showed facilitated diffusion with median ADC value of 1.96 (1.5–2.6) and the P-value is statistically significant (p < 0.021) **(Cases 1- 4).**
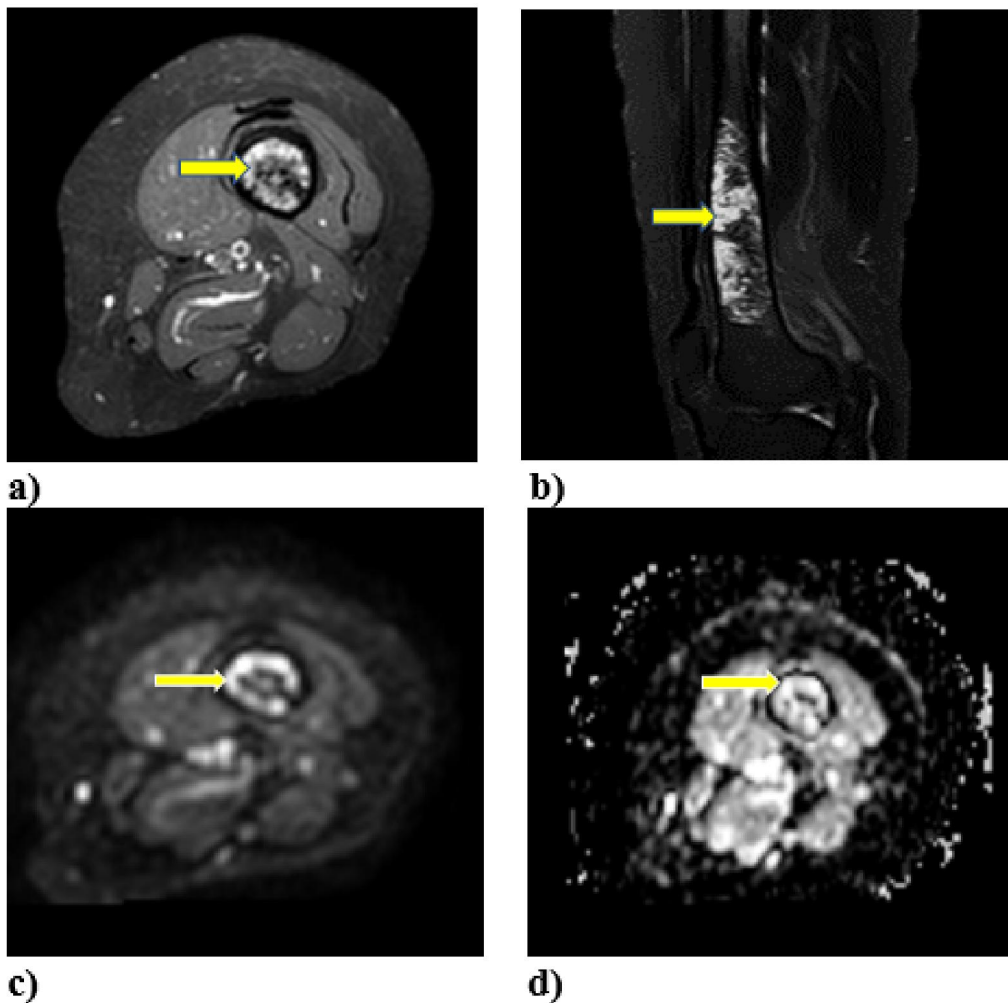

Fig. 1: Enchondroma: Female patient, 62 years old presented by left knee sub-sequent refereed to left thigh: **(A)** Axial post-contrast T1WI fat sat showing heterogenous enhancement of the lesion with stippled appearance. **(B)** STIR WI showing mixed iso to high SI of the intramedullary lesion. **(C)** Axial DWI reveals non-restricted diffusion at b value 1000. **(F)** ADC map showing the mean ADC value is measuring about 1.9 × 10^{-3} mm^2/s.
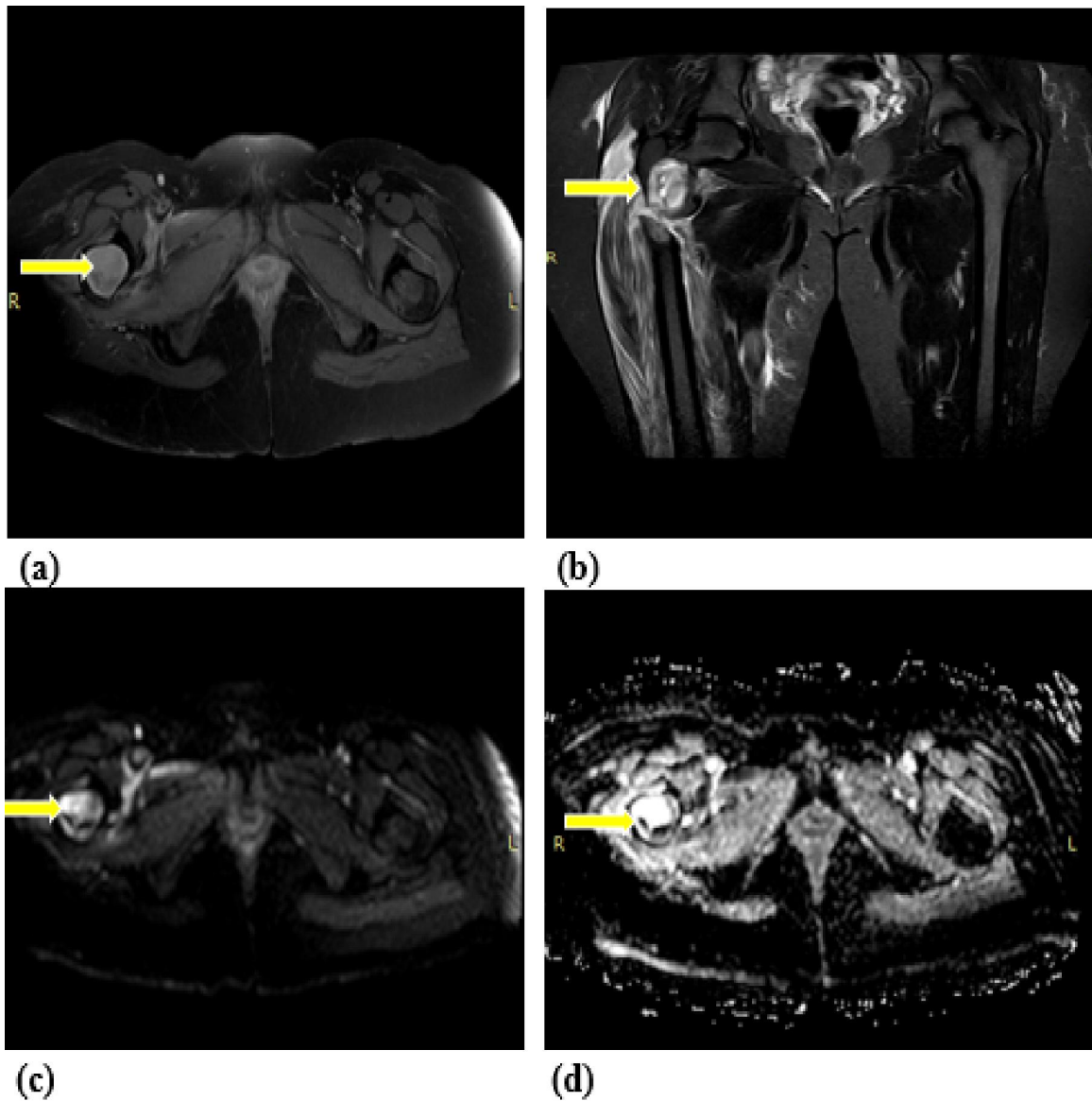
Fig. 2: Simple bone cyst: Female patient, 27 years old discovered accidently after trauma associated with pathological fracture **(A)** Axial post-contrast T1WI showing minimal marginal enhancement of the lesion. **(B)** STIR WI showing the high SI of the lesion. **(C)** Axial DWI reveals that the lesion is restricted diffusion at b value 1000. **(D)** ADC map showing the mean ADC value about 2.58×10^{-3} mm^2/s.
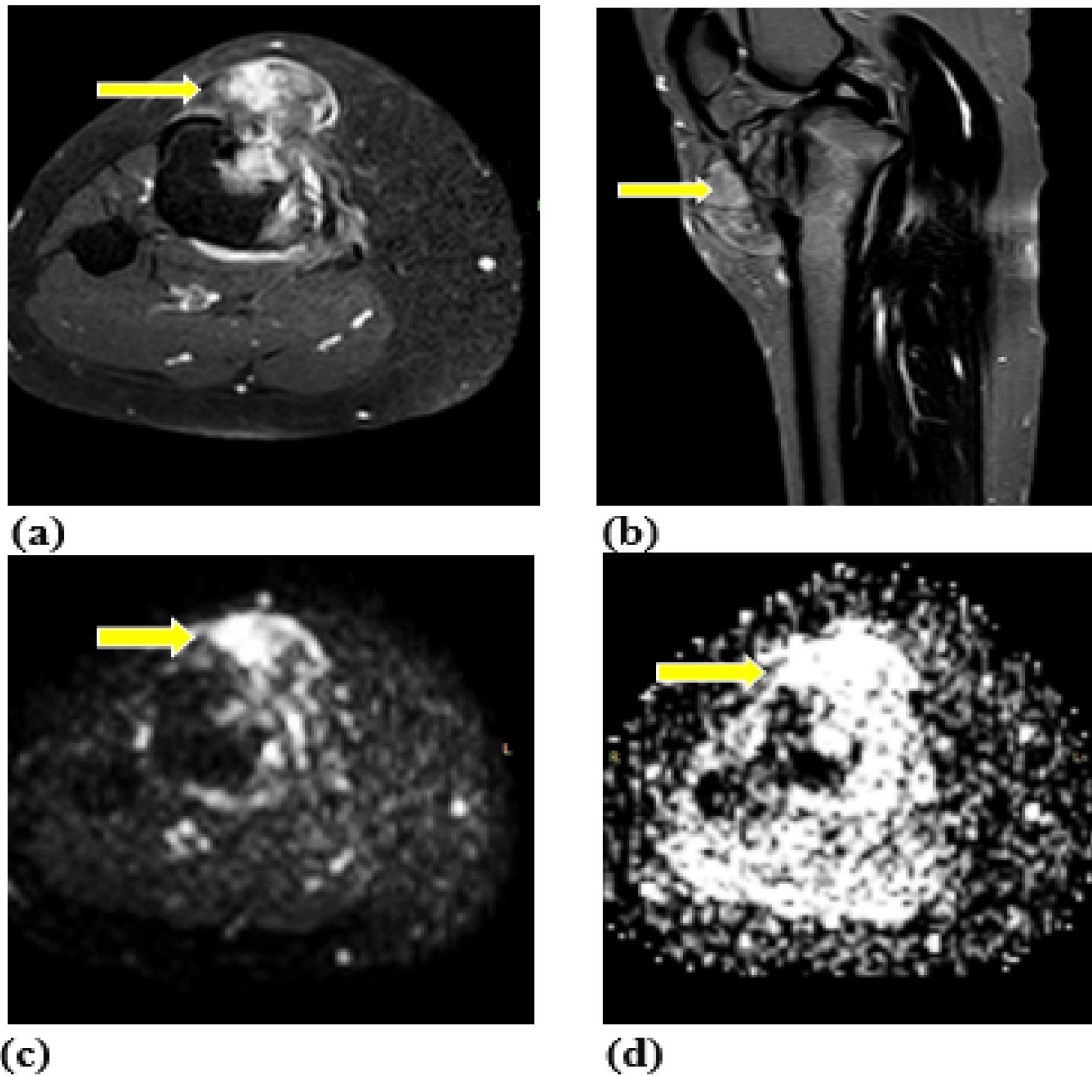
Fig.3: Tibial paraosteal Osteosarcoma: Female patient, 30 years old presented by small painful swelling increased in size in the upper third of the right leg. **(A)** Axial post-contrast T1WI showing heterogeneous enhanced bony lesion with extra-osseous soft tissue component. **(B)** STIR WI detects the bone alteration and provides a better depiction of the associated extra-osseous mass. **(C)** Axial DWI reveals restricted diffusion at b value 1000. **(D)** ADC map showing the mean ADC value is measuring about 1.12×10^{-3} mm2/s.
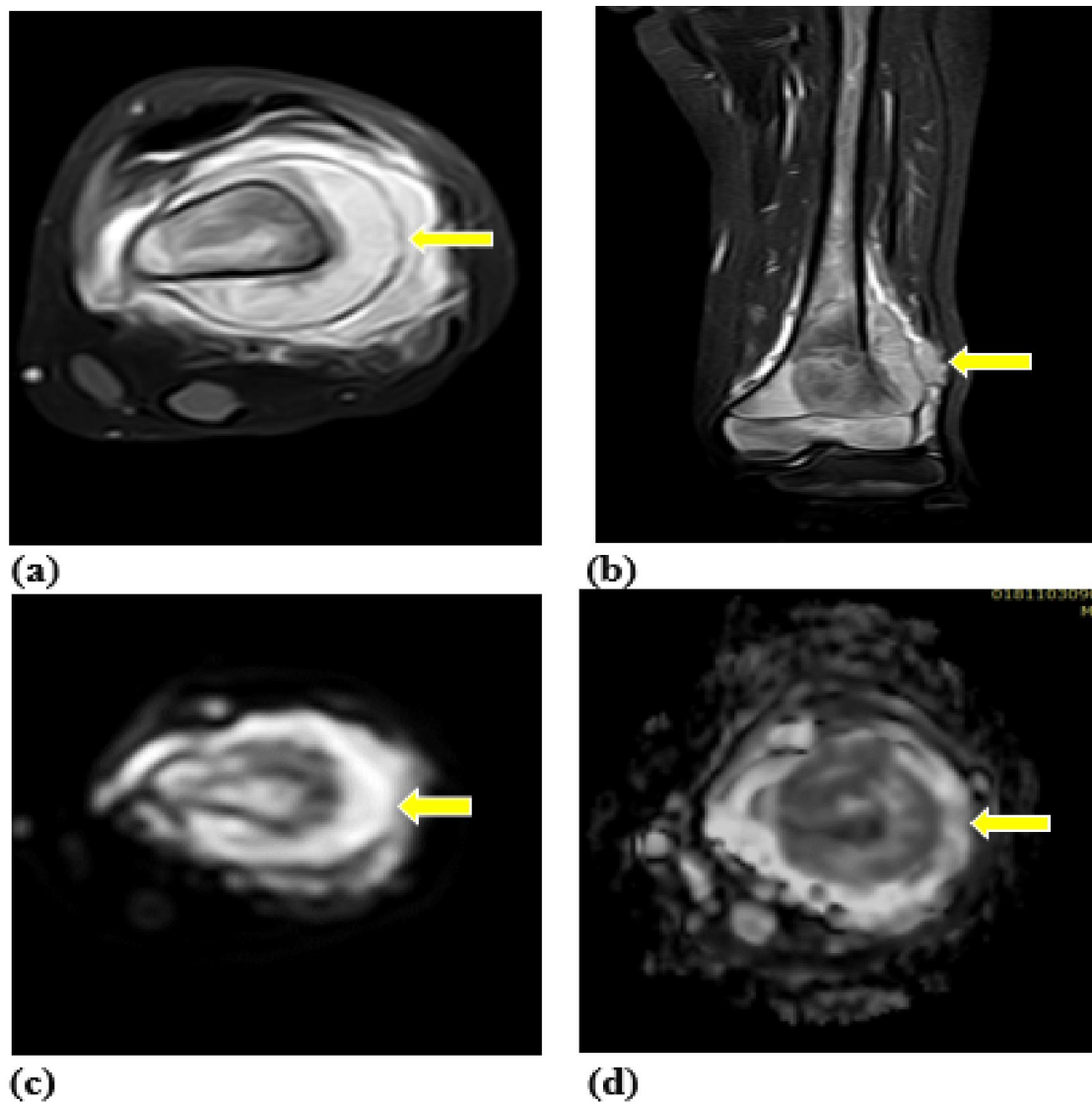
Fig.4: Osteosarcoma: Female patient, 10 years old presented by pain and swelling of the left femur **(A)** Axial post-contrast T1WI showing heterogeneous enhanced lesion with extra-osseous soft tissue component. **(B)** STIR WI detects the bone alteration and provides a better depiction of the associated extra-osseous soft tissue component. **(C)** Axial DWI reveals restricted diffusion at b value 1000. **(D)** ADC map showing the mean ADC value is measuring about 0.97 × 10-3 mm2/s.

Table (1): List of the bone tumors and mean ADC values.

Bone tumors	ADC value range (10−3 mm2/s)	Mean ADC value (10−3 mm2/s)	Total mean ADC value (10−3 mm2/s)	Chi-square test	
				x2	p-value
Benign tumors					
Simple Bone cyst	2.5-2.58	2.54	1.96±0.44	4.557	0.021*
Aneurysmal bone cyst	2.1-2.6	2.42			
Non‑ossifying fibroma	1.36- 2.1	1.62			
Enchondroma	1.9	1.9			
Chondroblastoma	1.5- 2.25	1.78			
Malignant tumors					
Osteosarcoma	0.56- 1.39	0.9	1.04±0.34		
Paraosteal osteosarcoma	1.12-1.2	1.16			
Ewing sarcoma	0.56- 1.09	0.82			
Lymphoma	1.39-1.48	1.43			

ADC: Apparent diffusion coefficient.
ROI: Region of interest. No SD values are mentioned in the table. (They are the mean ADC values obtained with ROI measurements. Not the median value with interquartile range).

Tables & figures show the diagnostic value of a restricted pattern by DWI for the discrimination between benign and malignant lesions. Receiver operating characteristics (ROC) curve was used to define the best cut off value of ADC value which was <1.18 with sensitivity of 81.8%, specificity of 84.2%, positive predictive value of 75%, negative predictive value of 88.9% and diagnostic accuracy of 83.3%, also diffusion weighed imaging show sensitivity of 90.9%, specificity of 89.5%, positive predictive value of 83.3%, negative predictive value of 94.4% and diagnostic accuracy of 90%.

Table (2): Comparison between malignant and benign lesions according to diffusion weighted imaging

Diffusion weighted imaging	Type of tumor				Chi-square test	
	Malignant (n=11)		Benign (n=19)			
	N	%	N	%	x2	p-value
Restricted	10	90.9%	2	10.5%	18.756	<0.001**
Unrestricted	1	9.1%	17	89.5%		

DWI & ADC values are used in discrimination between benign and malignant bone tumors, as malignant bone tumors usually have mean ADC values less than 1.04 x 10 -3 mm2/s. While benign tumors have mean ADC value 1.96 x 10 -3 mm2/s.

Also, they can be used in evaluation of cystic lesions (without the use of contrast media) as cystic lesions usually have mean ADC value more than 2.38 x10 -3 mm2/s.

Statistical analysis for the ADC values measured in the solid part of the bone tumor, revealed that there was a significant statistical difference between benign and malignant lesions (P =<0.021).

Table(3): Receiver-operating characteristic(ROC) curve for of lesions using ADC value and diffusion weighted imaging

Items	Sen.	Sps.	PPV	NPV	Accuracy
ADC value	81.8%	84.2%	75.0%	88.9%	83.3%
Diffusion weighted imaging	90.9%	89.5%	83.3%	94.4%	90.0%
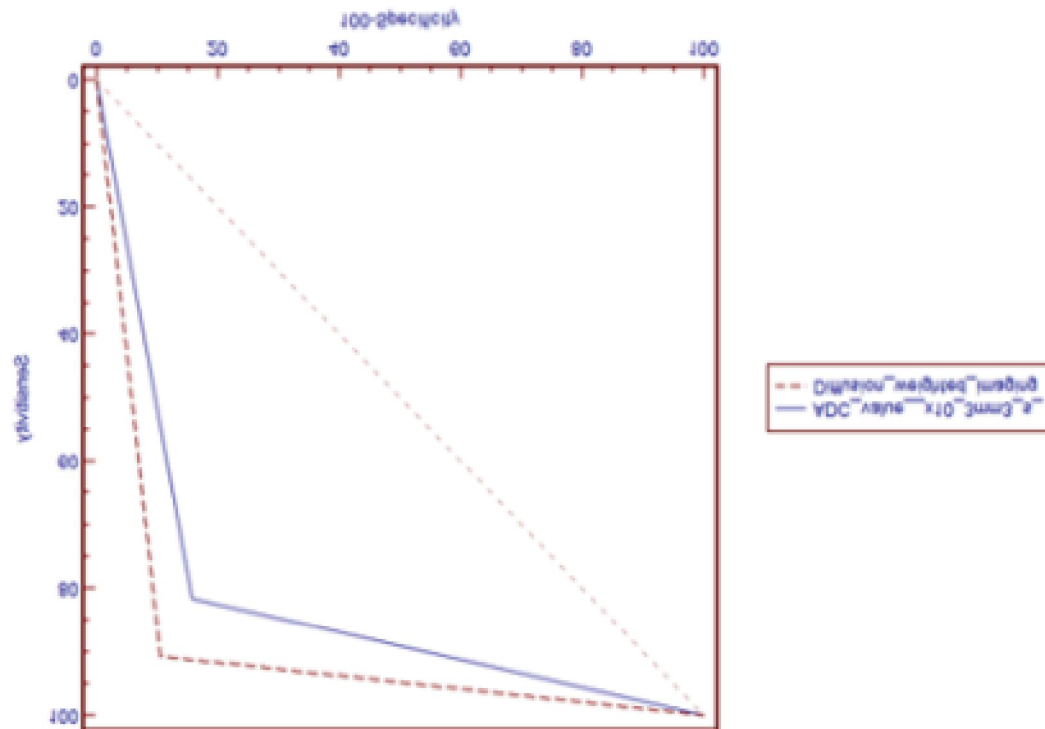
Fig. 5: Receiver-operating characteristic (ROC) curve for prediction of lesions using ADC value and diffusion weighted imaging.

4. Discussion

Magnetic resonance (MR) imaging is considered the most advanced and sensitive imaging technique for evaluating changes in bone marrow, characterization of musculoskeletal lesions particularly in defining their composition, extent, compartmental involvement, and relationship to the adjacent viscera and neuro vasculature. This permits the precise evaluation of the aggressiveness of different lesions through detection of their extent.

DW-MRI is no enhanced functional MR imaging technique. Diffusion relies on selective excitation of the water resonance and generation of a contrast image that depends on differential nuclear relaxation times

and self-diffusion coefficients. It reflects the microstructural characteristics, physiological state of the tissues and reflects microscopic water diffusion using a pair of strong diffusion gradients **(Zampa et al., 2010)** [15].

DWI was developed to map the apparent diffusion coefficient (ADC)**,** which is a quantitative measure of the Brownian motion, low ADC values in a lesion reflect a highly cellularity, where as high ADC values reflects a cellular regions **(Subhawong et al., 2016)** [16].

The potential additional value of diffusion lies in that it provides functional tissue information which can be combined with MR imaging anatomy to improve lesion characterization. Many tumors have certain entities on multimodal diagnostic imaging, however surgical biopsy is so far the only way to establish diagnosis with confidence.

The purpose of this study was to assess the ability of diffusion MRI in differentiation between benign & malignant bone tumors, also to correlate diffusion patterns, ADC values of different lesions & to guide invasive diagnostic measures for limiting the number of patients with benign diseases who undergo biopsy.

In our study subcentimetric lesions were omitted due to small ROI which would not give valuable results. **(Park et al., 2007)** [17] discussed that small lesions have degree of diffusively similar to surrounding normal tissue & may not be distinguished by DWIs & ADC. This was in agreement with **Padhiani et al., 2017**[18]**,** most recent studies which suggest a cut off value of 2 cm as minimum diameters of lesion.

In our study one of the pitfalls of visual assessment of DWI is that an area with long T2relaxation time may remain high signal and mistaken for restricted diffusion. This false impression was corrected with ADC value measurement which proved to be more accurate in judging lesions.

In our study, we noticed that benign cysticlesions that showed high signal intensity which persist with high b values due shine through effect simulate more aggressive tumors with true restriction, but usually had high mean ADC values (2.38 x 10-3 mm2/s). This result was attributed to T2 shine through effect similar to the results of **(Kotb et al, 2014)** [19].

Similar to **Lang et al.,2017**[10] we found low signal intensity in necrotic tumors in patients who received chemotherapy on DWIs, indicating rapid diffusion of water molecules because of loss of membrane integrity. In our study this was demonstrated in one case of Ewing sarcoma in which the signal intensity of the lesion decreased on DWIs (at b =1000 s/mm2) indicating more free water diffusion caused by cell necrosis, similarly, ADC

values significantly increased. Our finding is like that observed by **Einarsdottir et al., 2004**[20]**, Hayashida et al., 2016** [21] **& Abeer et al., 2018**[22]**.**

In our study, we had 2 cases of lymphoma showed restricted & non-restricted diffusion. The mean ADC value was 1.43. This was not in agreement with **Guo et al., 2002**[23] who stated that lymphoma has lower ADC values in comparison with other tumors.

In our study, we found that, the ADC values of solid malignant tumors (n= 11 ranged from 0.56 to 1.48 x 10-3 mm2/s, with mean ADC (1.04 x 10-3 mm2/s) were significantly lower than that of the benign bony tumors (n=19) which ranged from 1.36 to 2.6 x 10-3 mm2/s, with mean ADC (1.96 x 10-3 mm2/s).

Diffusion weighed imaging was also able to discriminate between benign and malignant lesions with sensitivity of 90.9% specificity of 89.5% with diagnostic accuracy of 90%. The results according to ROC curve for the discrimination between benign and malignant lesions using the ADC value showed that the best cut-off criterion is ADC of 1.18 with overall sensitivity of 81.8% specificity of 84.2% with diagnostic accuracy of 83.3%.

This finding indicated that a lower ADC value with high signal intensity on DWI of solid components can serve as a useful criterion for predicting malignancy in bone lesions, and that higher ADC value may be an effective method for predicting the presence of benign lesions. **Ahlawat et al.,2015** [24] found that quantitative ADC values have predictive value for the characterization of bone lesion in agreement with **Khoo et al., 2015**[8]**.**

According to **Neubauer et al., 2012**[25], mean ADC value 1.03 x 10-3 mm2/s is a strong indicator of malignancy at the first diagnosis; which match with our study results. **Pekcevik et al., 2014**[4] noted some overlap in distinguishing benign and malignant lesion and stated acut-off value of 1.37 with a sensitivity of 90 %, a specificity of 92.9%, and an accuracy of 92% using ADC values in the discrimination between benign and malignant bone lesions. However, our study showed that for the discrimination between benign and malignant bone tumors using the ADC, the best cut-off value was<1.18x 10-3 mm2/s, and this means that less than or equal to1.18 x 10-3 mm2/s is indicating malignant result. Therefore, in our study, we found that ADC value was able to distinguish benign from malignant high signal intensity on DWI and this was agreement with **Padhani et al., 2017**[25] who highlighted the necessity of correlating high b-value DW images with corresponding ADC values to prevent misinterpretation due to T2 shine-through.

In addition, we found that the ADC value could monitor tumor response to therapy as agreed by **Einarsdottir et al., 2004.** [22]

The development of specific guidelines for diffusion imaging & ADC measurement checklists for results reporting may facilitate comparison of study results and help in applying ADC measurement for characterization of tumors in clinical sitting **(Vermoolen et al., 2012)** [26].

In conclusion, we proved high specificity and sensitivity of DWI as a complementary sequence with conventional MRI and ADC value measurements in discrimination between benign and malignant bone tumors with significant cut-off value, making it a noninvasive tool for increasing the accuracy in identifying bone lesions.

However, further studies with larger patient groups are needed to find an optimal cut⬜off ADC value for differentiation ADC value for differentiation between begin and malignant bone tumors.

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