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Radiology

UTILITY OF APPARENT DIFFUSION COEFFICIENTS WITH DIFFUSION-WEIGHTED MRI IN DIFFERENTIATING BENIGN AND MALIGNANT BONE LESIONS

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ABSTRACT **OBJECTIVE:** To evaluate the usefulness of diffusion-weighted MRI with apparent diffusion co-efficients (ADC) cut-off value in differentiating benign and malignant bone lesions.

MATERIALS AND METHODS: 58 patients with suspected bone tumours based on clinical examination and plain radiographs were included in the current study. They were subjected to routine MRI examination with inclusion of diffusion-weighted imaging, followed by histopathology for final diagnosis. All the lesions were assessed to see the presence of diffusion restriction if any. ADC values (mean, minimum and maximum) were obtained by two observers individually. Interobserver measurement and the ADC values in benign and malignant lesions were calculated. Receiver operating characteristic (ROC) analysis was done to determine optimal cut-off ADC values in distinguishing benign and malignant bone lesions.

RESULTS: Of 58 lesions, there were 28 benign lesions and 30 malignant lesions. Diffusion restriction was noted in 83.3% of malignant lesions whereas 57.1% of benign lesions did not show diffusion restriction. There were higher mean, minimum and maximum ADC values in benign lesions when compared with malignant lesions. With cut-off value of minimum ADC as 0.92 x 10-3 mm2/sec to differentiate malignant and benign lesions, the sensitivity of 79% and specificity of 64% was obtained.

CONCLUSIONS: DWI is useful in differentiating between benign and malignant lesions with diffusion restriction favoring malignancy. Higher mean, minimum and maximum ADC values are seen in benign lesions as compared to malignant lesions. Even though, there is slight overlap in ADC values of both benign and malignant lesions, ADC values help in their differentiation.

KEYWORDS : Diffusion, ADC, Differentiation, Tumour, Quantitative

INTRODUCTION

Multimodality approach is used in the evaluation of bone tumours and tumour like lesions - ranging from plain radiography to cross-sectional imaging including Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI). The wide spectrum of the bone tumours and their overlapping pattern on various imaging modalities pose a challenge in the final diagnosis of the tumours. Radiography is the initial imaging technique in the assessment of bone tumours. However, it may be difficult to characterise all lesions on radiographs alone because of overlapping similar findings.[1] CT provides good information on osseous expansion/destruction caused by the tumours, however it is not sensitive in detecting marrow involvement.[2] MRI plays an important role in the assessment of bone tumours, especially in the evaluation of the extent.[3] It is very sensitive in detecting the changes in bone marrow. Pre-operative characterisation of tumours into benign and malignant is important to decide the treatment strategy. Conventional MRI sequences are less specific in tumour characterisation as many tumours show non-specific characteristics and show varying signal intensities on T1/T2 weighted images.[4]

Advanced sequences like Diffusion weighted imaging, Chemical shift imaging etc. can be used to improve the characterisation of the bone tumours and tumour like lesions. Diffusion weighted imaging (DWI) is a functional MRI technique which is quantified by the apparent diffusion coefficient (ADC) values. High ADC values are seen in acellular regions and low ADC values in tumours suggest areas in which there is restriction of diffusion by an abundance of cell membranes.[5] Literature suggests that there is a significant correlation between cellularity and tumour aggressiveness, thus DWI may be used in differentiating benign tumours from malignant tumours.[6] Most studies on DWI in musculoskeletal system were done to characterise soft tissue tumours.[7-9] There are only few studies on the role of DWI in characterisation of bone tumours.[10-12] The purpose of this study was to evaluate the role of DWI (and ADC values) in differentiating benign bone tumours and tumour like lesions from malignant bone tumours.

MATERIALS AND METHODS

Patients

58 patients with suspected bone tumours were involved in the current study. The study was conducted from October 2016 to November 2019 in Government Medical College Hospital, Chandigarh. Approval of Institutional ethical committee was obtained. Informed written consent was obtained from all the participants. They were evaluated with DWI followed by histopathological examination (core needle biopsy). Patients who had contra-indications to MRI like patients with MRI incompatible Prosthetic cardiac valve implants, cochlear implants or any other implants, patients with claustrophobia, biopsied cases and uncooperative patients were excluded from the study.

MRI protocol

MRI examinations were performed on a 1.5 Tesla scanner (Achieva; Philips medical systems). Appropriate extremity and body coils were used. The following sequences were used - axial and coronal T1 weighted images, T2 weighted images in all planes, axial and coronal Short Tau Inversion Recovery (STIR) images and T1 weighted post contrast images in all 3 planes (if required). Diffusion weighted MR images were acquired using a multi-section single shot spin echo – planar sequence with b values of 0, 500 and 1000 sec/mm^2. Following parameters were used: Repetition time (TR) – 3000-5000 ms, Echo time (TE) – 60-90 ms, Slice thickness - 5 mm with 1 mm of interslice gap, field of view 240 – 400 mm and matrix of 128 x 256. Duration of acquisition was about 1-2 minutes. Four sets of DWIs were acquired and ADC map that is corresponding to the average diffusion images was obtained.

Image Analysis

The images were copied to the Philips workstation (Intellispace Portal v6.0.4.03700) and were then analysed both qualitatively and quantitatively. Image analysis was done by two radiologists who were blinded to the clinical data. On DWI, the areas within the lesion which are of high signal intensity on images with high b-value with

corresponding low signal intensity on ADC maps were characterised as areas with diffusion restriction. The solid and/or homogeneous component of bone tumours were identified on T2W images and post-contrast T1W images (when acquired) and were matched with ADC maps. The elliptical/circular region of interest (ROI) was placed around the margins of the tumour which seemed to have lowest ADC. The largest possible ROI was placed in the solid portion of the tumour (10-80 mm^2). In case of irregular or heterogeneous solid lesions, at least three ROI's (10-55 mm^2) were placed on ADC maps which included areas of enhancement of tumour with lowest ADC. The mean, minimum and maximum ADC values were obtained. The position of ROIs was always compared to conventional MRI sequences to exclude contamination from adjacent bone or soft tissues. A ROI was then placed in the neighbouring normal bone marrow by correlating with T1 weighted images.

Statistical Analysis

After collecting the data, it was entered in Microsoft excel spreadsheet. Mean, Standard deviation and Standard error were calculated for quantitative data. Frequency and percentages were calculated for qualitative data. Data was analyzed by using "IBM SPSS STATISTICS" (version 16.0). Analysis was done by using Student 't' test and chi-square test. All statistical tests were applied at a significance level of "α=.05" (p value < 0.05).

Receiver operating characteristic (ROC) curve analysis was done to determine best cut-off for mean, maximum and minimum ADC values to distinguish benign and malignant tumours. Inter-observer agreement for the calculation of ADC values was analysed by "Bland and Altman method" and Intraclass correlation coefficient (ICC) was calculated.

Table 1. Locations of Bone lesions in participants of the study.

Bone	Count	Percentage (%)
Femur	25	43.1
Tibia	13	22.4
Humerus	7	12
Ilium	4	6
Radius	2	3.4
Ulna	2	3.4
Fibula	1	1.7
Clavicle	1	1.7
Metacarpal	1	1.7
Scapula	1	1.7
Calcaneum	1	1.7

Table 2. Distribution of bone lesions based on presence/absence of diffusion restriction.

		Benign/ Malignant				Total		Chi-Square Value	P Value
		Benign		Malignant					
		N	%	N	%	N	%		
Diffusion Restriction	Present	12	32.4	25	67.6	37	63.8	10.273	<0.001
	Absent	16	76.2	5	23.8	21	36.2		
Total		28	48.3	30	51.7	58	100		

N – Number

Table 3. Mean ADC values of different benign bone lesions.

Benign lesions	No of subjects	Mean of ADC_{mean}	Mean of $ADC_{minimum}$
Aneurysmal Bone cyst	1	1.61	1.6
Chondroblastoma	3	1.54	1.42
Enchondroma	2	1.69	1.67
Fibrous dysplasia	2	1.86	1.77
Giant cell tumour	6	1.17	1.07
Lipoma	1	1.55	0.79
Non ossifying fibroma	1	0.95	0.8
Osteochondroma	3	1.72	1.55
Osteofibrous dysplasia	1	1.08	1.03
Osteoid osteoma	2	1.56	1.53
Osteomyelitis	4	1.06	0.99
Simple Bone cyst	1	2.31	2.23
Spindle cell hemangioma	1	1.14	1

Table 4. Mean ADC values of different malignant bone lesions.

Malignant lesions	No of subjects	Mean of ADC_{mean}	Mean of $ADC_{minimum}$
Adamantinoma	1	1.46	1.41
Chondrosarcoma	1	1.76	1.53
Ewing's Sarcoma	8	0.86	0.76
Metastatic adenocarcinoma	2	0.64	0.49
Osteosarcoma	18	1.07	0.96

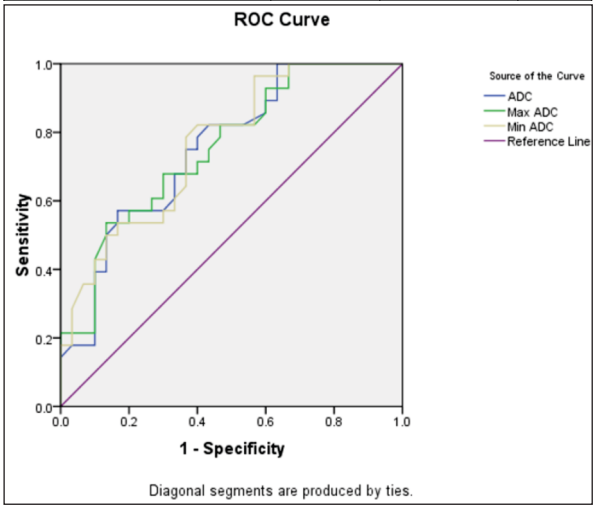
Table 5. Comparison of Mean, minimum and maximum ADC values of bone lesions.

ADC values ($x10^{-3}$ mm^2/sec)	Benign/ Malignant	N	Mean	Std. Deviation	Std. error Mean	" t " Value	P Value
Mean ADC	Benign	28	1.43	0.43	0.08	3.875	<0.001
	Malignant	30	1.02	0.38	0.07		
Max ADC	Benign	28	1.56	0.46	0.09	3.608	<0.001
	Malignant	30	1.15	0.4	0.07		
Min ADC	Benign	28	1.31	0.44	0.08	3.800	<0.001
	Malignant	30	0.91	0.37	0.07		
Mean ADC of normal bone marrow	Benign	28	0.45	0.28	0.05	0.777	0.44 #
	Malignant	30	0.50	0.27	0.05		

** Highly statistically Significant # Not Statistically Significant
Max – Maximum, Min – Minimum, N – Number, Std. – Standard

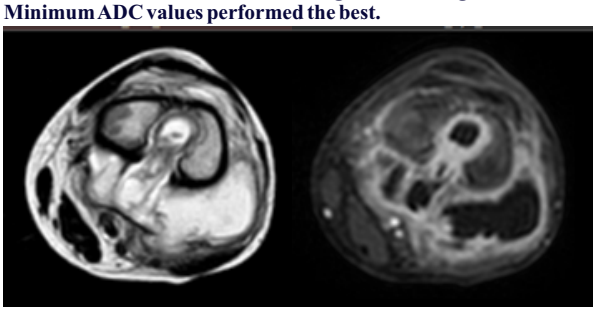
Table 6. Summary of ADC cut-off values of benign and malignant bone lesions.

Cut-off ADC value (x 10^{-3} mm^2/sec)	Sensitivity (%)	Specificity (%)	p-value
Mean ADC value ≥ 1.07	75	64	<0.001
Minimum ADC value ≥ 0.9	79	64	<0.001
Maximum ADC value ≥ 1.19	71.4	60	<0.001

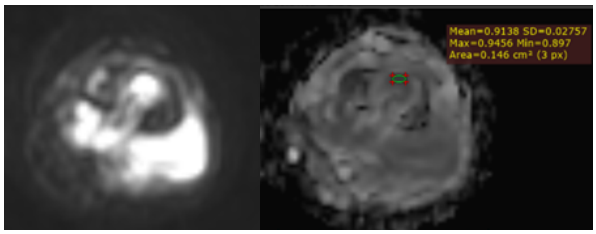


(ADC = Mean ADC value, Max ADC = Maximum ADC value, Min ADC = Minimum ADC value)

Figure 1. ROC analysis of mean, minimum and maximum ADC values for differentiation of benign and malignant lesions. Minimum ADC values performed the best.



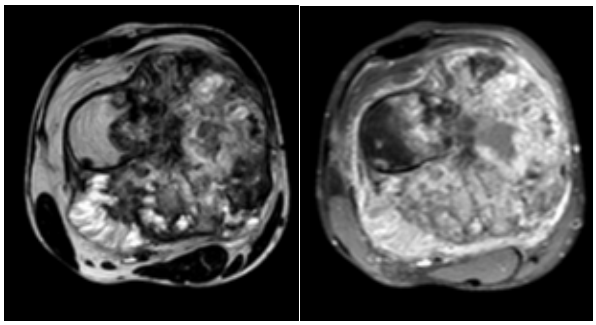
(2 A) (2 B)



(2 C) (2 D)

Figure 2. A 8-year old female child with left distal femoral metaphyseal osteomyelitis and abscess in adjacent soft tissues. (a) Axial T2w image shows ovoid heterogeneously hyperintense lesion with extension into soft tissue plane through cortical breech (cloaca) leading into hyperintense collection.

(b) Axial Post contrast fat-supressed T1w image shows peripheral enhancement of the lesion and also the collection. (c) and (d) Axial diffusion weighted images show restricted diffusion with mean, minimum and maximum ADC values (x 10^{-3} mm^2/sec) of 0.91, 0.89 and 0.94 respectively.



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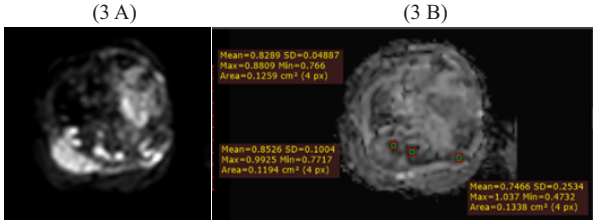
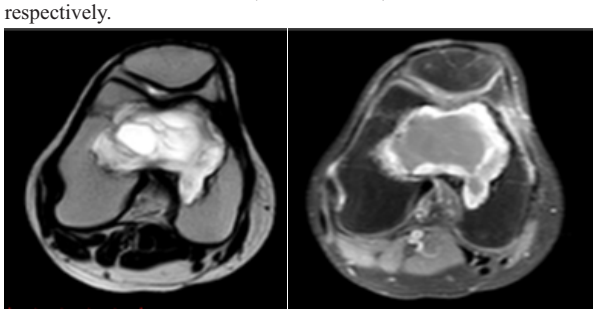


(3 C) (3 D)

Figure 3. A 15-year old male child with left distal diametaphyseal osteosarcoma. (a) Axial T2w image shows large heterogeneously hyperintense lesion with extraperiosteal extension along posterior aspect (b) Axial Post contrast fat-supressed T1w image shows heterogeneous enhancement (c) and (d) Axial diffusion weighted images show patchy areas of restricted diffusion with mean, minimum and maximum ADC values (x 10^{-3} mm^2/sec) of 0.80, 0.66 and 0.96 respectively.



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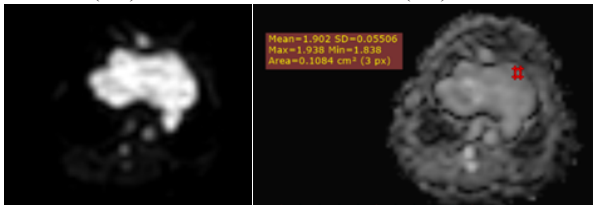

(4 A) (4 B)

Figure 4. A 20-year old female adult with left distal epiphyseal chondroblastoma. (a) Axial T2w image shows hyperintense lesion with multiple internal septae (b) Axial Post contrast fat-supressed T1w image shows peripheral enhancement of the lesion. (c) and (d) Axial diffusion weighted images show lack of diffusion restriction with mean, minimum and maximum ADC values (x 10^{-3} mm^2/sec) of 1.9, 1.83 and 1.93 respectively.

RESULTS

The mean age of the participants was 22.67±13.87 years. There were 20 (34%) females and 38 (66%) males in the study. On histopathological examination of 58 bone tumours/tumour like conditions, 28 (48%) were benign and 30 (52%) were malignant. Femur was the most common bone involved in the study subjects (43.1%), followed by tibia (22.4%) and humerus (12%) as mentioned in Table 1. Majority of tumours were Osteosarcoma (31%), followed by Ewing's sarcoma (14%) and Giant cell tumour (10%) and so on. Diffusion restriction was present in 83.3% (25/30 cases) of malignant lesions and 57.1% (16/28 cases) of benign lesions did not show diffusion restriction (Table 2). This difference in diffusion restriction between malignant and benign lesions was statistically significant (p value < 0.001).

The mean of ADC_{mean} values in malignant lesions was 1.02±0.38 x 10^{-3} mm^2/sec and in benign lesions was 1.43±0.43 x 10^{-3} mm^2/sec (Tables 3 and 4). The mean $ADC_{maximum}$ values in malignant lesions was 1.15±0.4 x 10^{-3} mm^2/sec and in benign lesions was 1.56±0.46 x 10^{-3} mm^2/sec. The mean of $ADC_{minimum}$ values in malignant lesions was 0.9±0.37 x 10^{-3} mm^2/sec and in benign lesions was 1.31±0.44 x 10^{-3} mm^2/sec (Table 5). This difference in mean, maximum and minimum ADC values between malignant and benign lesions was statistically significant (p value < 0.001). Chondrosarcoma had the highest ADC value (mean ADC - 1.76 x 10^{-3} mm^2/sec) and Breast metastases (mean ADC - 0.32 x 10^{-3} mm^2/sec) had the lowest ADC values in malignant lesions. Osteochondroma had the highest ADC value (mean ADC - 2.31 x 10^{-3} mm^2/sec) and Giant cell tumour (mean ADC - 0.87 x 10^{-3} mm^2/sec) had the lowest ADC values in benign lesions. The interobserver agreement (ICC 0.93, 95% CI 0.84, 0.97) was excellent.

ROC curves were analyzed and areas under the curve were obtained which were 0.75, 0.76 and 0.75 for mean, minimum and maximum ADC values respectively (Figure 1). ROC analysis showed that minimum ADC provided best sensitivity and specificity in differentiating benign and malignant lesions (Table 6). Optimal cut-off value of 1.07 x 10^{-3} mm^2/sec (mean ADC) to differentiate benign and malignant lesions had 75% sensitivity and 64% specificity. Optimal cut-off value of 0.92 x 10^{-3} mm^2/sec (minimum ADC) to differentiate benign and malignant lesions had 79% sensitivity and 64% specificity. Figures 2, 3 and 4 are examples of the lesions included in our study.

The mean ADC value of normal bone marrow was 0.45 ± 0.27 x 10^{-3} mm^2/sec in cases with malignant lesions and 0.5 ± 0.2 x 10^{-3} mm^2/sec in cases with benign lesions. This difference in mean normal bone marrow ADC values of in cases with benign and malignant bone lesions was statistically not significant (p value = 0.44). The mean ADC value of normal bone marrow was 0.47 ± 0.24 x 10^{-3} mm^2/sec. The mean ADC values of all normal bone marrow were low in comparison to those of bone tumours.

DISCUSSION

Bone tumours are relatively uncommon. The incidence of benign bone tumours is more in comparison to malignant bone tumours, however benign bone tumours are underestimated as they are frequently asymptomatic.[13] Conventional X-rays are the first line of imaging modality for detection of the tumour.[14] MRI is often the next imaging modality. Most of the bone tumours show non-specific characteristics on conventional MRI sequences and thus it may not be possible to characterize bone tumours on conventional MRI alone. Advanced MRI sequences like DWI may be required which can aid in the diagnosis of bone tumours. DWI is an unenhanced functional MRI technique. It is based on the variations in the Brownian movement of water molecules due to variations in the tissue microenvironment. ADC is the quantitative measure of Brownian motion. Malignant lesions with high cellularity restrict diffusion and exhibit low ADC values. Benign lesions with less cellularity allow free diffusion of water molecules and exhibit high ADC values.[15] Hence, it can be utilized in the differentiation of benign and malignant bone tumours. However, some overlap of the ADC values among benign and malignant lesions can be observed. It needs short time for acquisition (approximately 3 minutes) and there is no need for intravenous contrast administration hence can be easily incorporated into the

routine scanning protocol of musculoskeletal tumours. DWI is a very good technique for characterization of the lesions throughout the body. It is most commonly used in intracranial pathologies.[16] It is also used in detection of whole body metastases and in abdomen and pelvis scans.[17-19] However, there is a limited literature on the role of DWI in characterizing the bone tumours.[20,21] This study adds to the current limited literature on the usefulness of DWI (and ADC values) in the characterization of bone tumours.

In our study, the mean of ADC_{mean} values in malignant lesions was $1.02\pm0.38 \times 10^{-3}$ mm^2/sec and in benign lesions was $1.43\pm0.43 \times 10^{-3}$ mm^2/sec. This difference was statistically significant with 1.07×10^{-3} mm^2/sec as a cut-off to differentiate benign and malignant lesions. The sensitivity and specificity for the differentiation were 75% and 64% respectively. In a study investigated by Wang et al (2014), 1.10×10^{-3} mm^2/sec was the cut-off to differentiate benign from malignant lesions.[10] They obtained 89.7% sensitivity and 84.5% specificity. ADC cut-off value was almost similar to that obtained in our study, but our study had less sensitivity and specificity as compared to their study. In another study conducted by Rao et al (2019), 1.31×10^{-3} mm^2/sec was the cut-off to differentiate benign from malignant lesions.[11] They obtained sensitivity of 73.3% and specificity of 77.1%. They had higher cut-off ADC value as compared to our study with similar sensitivity and more specificity as compared to our study.

The mean $ADC_{minimum}$ values in malignant lesions were $0.9\pm0.37 \times 10^{-3}$ mm^2/sec and in benign lesions was $0.45.23\pm0.28 \times 10^{-3}$ mm^2/sec in our study. Minimum ADC value provided highest sensitivity and specificity in differentiating malignant lesions from benign lesions. This was also observed in studies conducted by Ahlawat S et al (2015) and Pekcevik et al (2013) who found that minimum ADC value had highest accuracy in differentiating malignant and benign lesions. Optimal cut-off value of 0.92×10^{-3} mm^2/sec to differentiate malignant and benign lesions had 79% sensitivity and 64% specificity. Pekcevik et al (2013) conducted a study which revealed mean $ADC_{minimum}$ value of 1.37×10^{-3} mm^2/sec as a cut-off with 77.8% sensitivity and 82.4% specificity in differentiating benign and malignant lesions.[12] Sensitivity was similar in both the studies, while they had higher specificity as compared to our study. Another study conducted by Ahlawat et al (2015), found cut-off mean $ADC_{minimum}$ value as 0.9×10^{-3} mm^2/sec in differentiating benign and malignant lesions with a 92% sensitivity and 78% specificity.[22] Cut-off was similar as obtained in our study; however their study had higher sensitivity and specificity.

ADC value also helps in differentiation of certain histologies. Cysts (Simple bone cysts, Aneurysmal bone cyst) and Chondrogenic lesions (Osteochondroma, Chondroblastoma, Enchondroma and even Chondrosarcoma) had higher mean, minimum and maximum ADC values as compared to other bone lesions. This can be attributed to differing degrees of cellularity and more fluid content in cysts and cartilaginous matrix.[23,24] Mean value of chondrogenic lesions was $1.68\pm0.38 \times 10^{-3}$ mm^2/sec and of cysts was $1.6\pm0.4 \times 10^{-3}$ mm^2/sec. Osteomyelitis had low mean of ADC_{mean} ($1.06\pm0.25 \times 10^{-3} mm^2$/sec) and mean $ADC_{minimum}$ ($0.91\pm0.25 \times 10^{-3} mm^2$/sec) values.

In comparison to previous studies, current study shows similar cut-off values of mean ADC as obtained by Wang et al. Their study obtained mean cut-off ADC value as 1.10×10^{-3} mm^2/sec and our study obtained 1.07×10^{-3} mm^2/sec as cut-off value. Chondrosarcoma had highest ADC value ($2.99 \times 10^{-3} mm^2$/sec) in the category of malignant lesions in their study which is also similar in our study. Ewing's sarcoma had least ADC value (0.56×10^{-3} mm^2/sec) among malignant lesions in their study, while breast metastases had lowest ADC value in the current study. Simple bone cyst had highest ADC value ($2.72 \times 10^{-3} mm^2$/sec) and Non-ossifying fibroma (NOF) had lowest ADC value (1.01×10^{-3} mm^2/sec) in the benign lesions category in their study, while Osteochondroma had highest ADC value and Giant cell tumour had least ADC value in the present study.

In the current study, Diffusion restriction was noted in 83.3% (25/30 cases) of malignant lesions and 57.1% (16/28 cases) of benign lesions did not show diffusion restriction. Most of the malignant lesions and few of the benign lesions showed diffusion restriction.

Mean ADC values of normal bone marrow are low as compared with bone tumours (both benign and malignant). This is due to the fact that fat-suppression is used in the acquisition of DWI images and hence the predominantly fat containing normal yellow bone marrow is suppressed. So, all bone tumours are easily detected against normal bone marrow.[25] Less water content, absence of significant extracellular matrix can also contribute to restricted diffusion and low ADC values in normal bone marrow.[26]

Limitation

The sample size is comparatively small and hence further studies with large sample sizes need to be conducted to corroborate these findings and the ADC cut-off value.

CONCLUSIONS

DWI (with ADC values) is a useful non-contrast technique to differentiate benign and malignant bone lesions, although there is some overlap in ADC values among benign and malignant lesions. Diffusion restriction favours malignancy. It can be incorporated into routine MRI protocol of bone tumours as duration of acquisition is less.

Declaration of Conflicting Interests

The authors declare that there are no potential conflicts of interests.

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