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RESEARCH ARTICLE

Accuracy of diffusion-weighted magnetic resonance imaging in diagnosing malignant musculoskeletal tumours

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ABSTRACT

Background: Conventional magnetic resonance imaging (MRI) lacks specificity for differentiating several tumours. Combining advanced techniques like diffusion-weighted imaging (DW-MRI) with conventional MRI may enhance diagnostic accuracy. However, we do not have such data for Bangladeshi patients. This study aimed to examine the diagnostic accuracy of apparent diffusion coefficient values obtained by DW-MRI.

Methods: A cross-sectional study was conducted from July 2022 to June 2023 in the Department of Radiology and Imaging, Bangabandhu Sheikh Mujib Medical University (BSMMU). After collecting their baseline data, thirty-five patients with musculoskeletal tumours underwent DW-MRI and histopathology tests or fine needle aspiration cytology (FNAC). The apparent diffusion coefficient (ADC) values obtained by DW-MRI were examined for diagnostic accuracy against a standard of histopathology/FNAC.

Results: According to the gold standard (histopathology/FNAC), there were 28 patients with malignancy, and 7 had benign tumours. Their mean age was 33 (standard deviation, 17) years (range, 4 to 74 years). The mean ADC value was 0.86 ± 0.30×10-3 mm^2/s. The malignant musculoskeletal tumour group had significantly lower ADC (0.79 ± 0.24 $\times 10^{-3}$ mm^2/s) compared to the benign tumour group (1.15 ± 0.37$\times 10^{-3}$ mm^2/s.) (P = 0.04). The DW-MRI ADC categories correctly diagnosed 27 malignant and five benign tumours using a cut-off value of ≤ 1.1$\times 10^{-3}$ mm^2/s. DW-MRI had a sensitivity of 96.4% and a specificity of 71.4%. Diagnostic accuracy was 91.4% for detecting malignant musculoskeletal tumours.

Conclusions: Malignant musculoskeletal tumours have lower DW-MRI-derived ADC levels, demonstrating good diagnostic accuracy. However, a larger and more representative sample is needed before it is recommended for clinical practice.

Keywords: *musculoskeletal tumours, diffusion-weighted-magnetic resonance imaging, apparent diffusion coefficient*

INTRODUCTION

Musculoskeletal tumours are prevalent in young patients, comprising 3–5% of all tumours diagnosed under 15 years and 7–8% in Europe's age group 15-19 years.[1] They constitute an important component of early deaths, with a 50-60% five-year survival rate for cancers originating in soft tissue and bones.[2] Primary care physicians rarely see these tumours because of their rarity and nonspecific symptoms, leading to delayed referral diagnosis.[3]

Magnetic resonance imaging (MRI) plays an important role in characterising musculoskeletal lesions by providing comprehensive insights into their composition, compartmental involvement, extent, and relationships with adjacent viscera and neurovasculature.[4,5] Conventional MRI mainly relies on the qualitative interpretation of variations in the T1 and T2 relaxation properties within normal and pathological tissues. However, confusion may occur due to considerable overlaps in signal characteristics between benign and malignant neoplasms and non-neoplastic

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HIGHLIGHTS

1. Typically, malignant musculoskeletal tumours show lower apparent diffusion coefficient (ADC) values than benign ones.
2. When combined with traditional magnetic resonance imaging (MRI), diffusion-weighted magnetic resonance imaging can enhance standard MRI features and improve the ability to differentiate between different types of musculoskeletal tumours.
3. Due to occasional overlaps in ADC values, relying solely on diffusion-weighted MRI ADC values may not provide adequate differentiation between different types of benign and malignant musculoskeletal tumours.

reactive or inflammatory lesions. As a result, it may prove challenging to distinguish fluid-sensitive sequences from reactive peritumoral oedema when using conventional MRI to distinguish hyperintense tumours.[6]

The distinctive features of contrast material enhancement play a crucial role in the traditional MRI evaluation of masses. These characteristics are critical for identifying solid tumours from cysts, delineating mass boundaries, and assessing the degree of tumour necrosis.[7, 8] Diffusion-weighted MRI (DW-MRI) is a non-enhanced functional MRI technique that utilises the phenomenon of the random movement of water molecules in the soft tissues of the musculoskeletal system.[9] This Brownian motion, or proton diffusion, happens randomly in unrestricted environments (isotropic diffusion). However, it results in restricted diffusion or anisotropic diffusion, inside the human body due to restrictions imposed by biological tissue structures such as cell membranes and macromolecules.[10] The apparent diffusion coefficient (ADC) is a quantitative indicator of Brownian motion. A low ADC value indicates densely cellular microenvironments where multiple cell membranes limit diffusion. In contrast, high ADC values are linked to acellular regions that permit unrestricted water molecule diffusion.[11] Because of this feature, DW-MRI can provide assessments of intra-tumoral cellularity that consider both qualitative and quantitative factors.[12]

Numerous previous studies have demonstrated the additional benefits of DW-MRI and ADC mapping in distinguishing diverse musculoskeletal tumours, diffuse bone marrow infiltrative lesions, and distinguishing between benign and pathological vertebral collapses compared to traditional MRI sequences.[12, 13, 14] As such, DW-MRI may serve as a dependable tool in differentiating various bone and soft tissue tumours compared to conventional MRI findings.[13, 15, 16, 17, 18] However, tumour cellularities and extracellular substances may influence the overlap of ADC values in benign and malignant musculoskeletal tumours, making tumour differentiation difficult in certain cases.[19]

Despite numerous studies highlighting the benefits of DW-MRI in differentiating musculoskeletal tumours, there is a distinct lack of data of this modality in Bangladesh. Therefore, this study aimed to bridge this knowledge gap by ascertaining the diagnostic accuracy of DW-MRI with ADC mapping in the characterisation of musculoskeletal tumours.

METHODS

This cross-sectional study was conducted in the Department of Radiology and Imaging, Bangabandhu Sheikh Mujib Medical University (BSMMU), after obtaining approval of the Institutional Review Board. All patients with clinically suspected musculoskeletal tumours who fulfilled the selection criteria were purposively included in the study.

The patients with suspected musculoskeletal lesions and those willing to undergo DW-MRI and histopathology tests were included in this study. Exclusion criteria were: (i) patients having strong contraindications to MRI, including those with cardiac pacemakers, prosthetic heart valves, cochlear implants, brain aneurysm clips or coils, operated or on treatment, (ii) known hypersensitivity to contrast medium, and (iii) who were mentally unable to give consent.

Finally, 35 patients participated in this study. After informing the participants regarding the purpose of the study, informed written consent was obtained from each participant. In the case of minors, informed written consent was obtained from their guardian and assent forms were obtained from the participants. Age, sex, clinical and previous laboratory and imaging data were collected by a trained interviewer-administered

questionnaire. DW-MRI was performed following standard procedural protocol, images were analysed, and ADC value was calculated from the DW-MRI sequences by experienced radiologists. After evaluating the MRI features of the lesion, patients went through either fine needle aspiration cytology (FNAC) or biopsy procedures for histopathology, depending on the type of lesion. Patients with limitations such as the inability to lay down on a prone stereotactic table and body habitus were dealt with accordingly. Subsequently, the accuracy of DW-MRI ADC values was determined and compared with the gold standard of histopathology/FNAC results.

MRI protocol

MRI was done by a Siemens Magnetom Skyra 3T MRI Machine with 3 Tesla (T) magnetic strengths. MRI images were obtained for all patients using the following parameters.

A. Pre-contrast

T1-weighted pulse sequence imaging was acquired in axial, coronal, and sagittal view following the parameters of repetition time (TR) 800 ms, time to echo (TE) 9.5 ms, slice thickness 3 mm, field of view (FOV) 160 mm, and matrix 205×256. T2-STIR sequence imaging parameters were TR 3400 ms, TE 41 ms, slice thickness 3.5 mm, FOV 140 mm, and matrix 307×384.

B. Post-contrast

After administrating a 10 ml bolus dose of Gadodiamide, all contrast studies were obtained with the following parameters: TR 800 ms, TE 9.5 ms, slice thickness 3 mm, FOV 156 mm and matrix 205×256.

C. Diffusion-weighted magnetic resonance images

Diffusion-weighted MR images were obtained in the axial plane with TR 4400 ms, TE 72 ms, slice thickness 3.5 mm, FOV 150 mm and matrix 140×140. The strength of MPG is usually defined by the gradient factor b. The b-values used in this study were 0 and 800s/mm^2. The ADC is determined as a numerical number by manually placing a region of interest (ROI) over the solid part of the tumour. The workstation generated ADC maps automatically based on the three b values using the formula $ADC=\ln(S_0/S_1)/(b_1-b_0)$, where S_0 and S_1 represent the signal intensity before and following the application of diffusion gradients, respectively, and b_1 and b_0 represent the various b-values applied.

Image analysis

The images were uploaded onto the workstation. Three radiologists (MS, MSS and SAA) with more than ten years of experience reviewed the MRI images. The review process was independent, with readers being unaware of clinical histories, pathologic results, and results from other imaging modalities. In the qualitative analysis, disagreements were resolved through consensus among the three radiologists. Each radiologist independently measured size and ADC values; the mean values were utilised for the final results.

A. Analysis of conventional magnetic resonance images

A variety of lesions' characteristics, such as tumour sizes, margins, locations, involvement of neurovascular bundles, tumour necrosis, periosteal reaction, extension of lesion, involvement of other organs, pathological fracture, and the presence of diffusion within the lesion or extension of lesion were evaluated by analysing conventional MRI. The largest dimension determined tumour size, and margins were categorised as capsulated, non-capsulated or irregular. A capsulated margin indicated clear differentiation from surrounding structures, irrespective of peritumoral oedema. Non-capsulated margins were mostly well-defined. Peri-tumor necrosis was defined as non-enhanced areas on post-contrast images. Periosteal lesions were analysed in non-contrast-enhanced images, whereas involvement of neurovascular bundles was observed in contrast images. Extension of the lesion was determined by measuring the extent of enhancement in contrast image.

B. ADC calculation analysis

ADC values were generated pixel by pixel. Minimum, maximum, and mean ADC values were calculated using round or elliptical regions of ROIs, with mean ADC values chosen for statistical analysis. ADC values were

expressed in 10^{-3} × mm²/second. Multiple uniform-sized ROIs (area, minimum ten mm², maximum 50 mm²) were placed, with three ROIs in the central non-necrotic portion and three in the peripheral portion of the tumour. ROIs were selectively placed in solid, enhancing, non-necrotic, and/or DWI-restricted regions, avoiding contamination from adjacent normal-appearing bone or soft tissue. ROI position was verified with reference to conventional MRI images to avoid artefacts, distortions, partial volume effects, and the most peripheral margin of the tumours. In the case of multiple lesions, the largest lesion was selected to calculate the mean ADC value.

Histopathological examination

The definitive diagnosis was established through histopathologic findings after performing FNAC (n=8) or biopsy (n=27). Ultrasonogram-guided FNAC and image-guided core biopsy procedures were conducted in the Department of Radiology and Imaging, while the surgical open biopsy procedure was conducted in the Departments of Orthopedic Surgery, and Surgical Oncology of BSMMU; and National Institute of Cancer Research and Hospital (NICRH). Two experienced pathologists examined all specimens in the Department of Pathology, BSMMU, and the final results were determined by consensus. Biopsies were conducted to determine the lesion type, as requested by the clinician.

Statistical analysis

Descriptive statistics (means, standard deviations, frequencies, percentages) were computed to present person and disease-related variables. The quantitative variables between the two groups were compared using *t* test. Statistical significance was set at $P < 0.05$, where the confidence interval level was 95%. The diagnostic performance of DW-MRI to detect malignancy was done for ADC cut-off value of $\leq 1.1 \times 10^{-3}$ mm²/s.

Based on the cut-off value, a 2 × 2 contingency table was created, and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPP) were calculated. The accuracy was calculated as the number of true positives plus true negatives divided by the number of all subjects. The data were analysed using SPSS software (SPSS Inc. Version 23.0TM; IBM Corporation, Chicago, USA).

RESULTS

There were 28 patients with malignancy and seven with benign tumours. The mean age of the patients was 32.9 (17.3), ranging from 5 to 74 years. Twenty-two of them were males, and 13 were females. The most common clinical presentation was swelling with pain in 26 (74.3%) patients.

The most frequently affected sites were the thigh and leg, present in 10 (28.6%) patients each. The majority of the lesions had irregular margins (82.9%). The neurovascular bundle was involved in 7 (20.0%) cases, necrosis in 9 (25.7%) cases, 25 (71.4%) patients had an extension of the lesion, and the periosteal reaction was present in 10 (28.6%) cases. Restricted diffusion within the lesion was present in 34 (97.1%) patients, while 4 (11.4%) patients had restricted diffusion in the extension of the lesion. Overall, DW-MRI detected 29 (82.9%) malignant lesions and 6 (17.1%) benign lesions among the enrolled patients **(TABLE 1)**.

TABLE 1 Clinical characteristics of the lesions in magnetic resonance imaging (n=35)

Characters	Frequency	Percentage
Site of lesion		
Thigh, leg	10*	28.6
Pelvis, shoulder	3*	8.6
Abdomen, spine	2*	5.7
Neck, elbow, forearm, back, ankle	1*	2.9
Margin of the lesion		
Irregular	29	82.9
Capsulated	9	25.7
Non-capsulated	8	22.9
Necrosis	9	25.7
Periosteal reaction	10	28.6
Extension of lesion	25	71.4
Involvement of other organs	1	2.9
Involvement of neurovascular bundle	7	20.0
Pathological fracture	1	2.9
Diffusion		
Restriction within the lesion	34	97.1
Restriction in the extension of lesion	4	11.4
Nature of the lesion in MRI		
Benign	6	17.1
Malignant	29	82.9

* values are for each entity

TABLE 2 **Histopathological findings of the musculoskeletal tumours (n=35)**

Findings	Frequency	Percentage
Benign (n=7)		
Neurofibroma	2	5.7
Lipoma, intramuscular abscess, intramuscular myxoma, giant cell tumour of bone, Fibromatosis	1*	2.9
Malignant (n=28)		
Ewing's Sarcoma	8	22.9
Synovial sarcoma	5	14.3
Spindle cell sarcoma, chondrosarcoma, other soft tissue sarcoma	3*	8.6
Undifferentiated pleomorphic sarcoma	2	5.7
Fibrosarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumour, osteosarcoma	1*	2.9

* Values are for each entity

Among the patients, 28 (80.0%) had malignant lesions, while 7 (20.0%) had benign lesions. The most frequent malignant lesion was Ewing's sarcoma in 8 (22.9%) patients, followed by synovial sarcoma in 5 (14.3%) patients. Among benign lesions, two patients had neurofibroma, while lipoma, abscess, myxoma, fibromatosis, and Giant cell tumour of bone were present in 1 patient each **(TABLE 2)**.

TABLE 3 **Mean (standard deviation) of apparent diffusion coefficients (ADC) values derived from diffusion-weighted magnetic resonance imaging (n=35)**

Musculoskeletal tumours	ADC value (10^{-3} mm²/s)
Benign	
Lipoma	0.72
Neurofibroma	1.20 (0.0)
Abscess	1.20
Myxoma	1.40
Giant cell tumour of bone	0.62
Fibromatosis	1.70
Malignant	
Spindle cell sarcoma	0.81 (0.15)
Ewing's Sarcoma	0.76 (0.10)
Synovial sarcoma	0.94 (0.43)
Fibrosarcoma	0.75
Malignant fibrous histiocytoma	1.00
Malignant peripheral nerve sheath tumour	0.75
Undifferentiated pleomorphic sarcoma	0.79 (0.05)
Other soft tissue sarcoma	0.63 (0.37)
Chondrosarcoma	0.78 (0.19)
Osteosarcoma	0.55
Combined	
All	0.86 (0.30)
Benign	1.15 (0.37)
Malignant	0.79 (0.24)
P-value	0.04

The mean ADC value of the total 35 study subjects was 0.86 ± 0.30×10^{-3} mm²/s. The ADC values vary largely depending on the specific tumour. In general, the malignant musculoskeletal tumour group had significantly lower ADC (0.79 ± 0.24×10^{-3} mm²/s) compared to the benign tumour group (1.15 ± 0.37×10^{-3} mm²/s) (P = 0.04) **(TABLE 3)**.

Among the 35 patients (diagnosed with histopathology or FNAC), DW-MRI successfully diagnosed 27 out of 28 cases of malignant tumours. However, they falsely diagnosed two instances with a benign nature as malignant and one case of malignant to a benign nature **(TABLE 4)**. With a cut-off ADC value of ≤ 1.1 × 10^{-3} mm²/s, DW-MRI has a sensitivity of 96.4%, specificity of 71.4%, and overall accuracy of 91.4% for diagnosing malignant musculoskeletal tumours. An analysis limited to those diagnosed with histopathology (n=28) yielded almost the same results (data not shown).

TABLE 4 **Performance of the apparent diffusion coefficients (ADC) derived from diffusion-weighted magnetic resonance imaging compared to the gold standard of histopathology or fine needle aspiration cytology**

ADC* categories (10^{-3} mm²/s)	Histopathology/FNAC	
	Malignant	Benign
≤1.1	a (27)	b (2)
>1.1	c (1)	d (5)
Sensitivity, a/(a+c)	96.4%	
Specificity, d/(b+d)	71.4%	
Positive predictive value, a/(a+b)	93.1%	
Negative predictive value, d/(c+d)	83.3%	
Accuracy, (a+d)/(a+b+c+d)	91.43%	

DISCUSSION

MRI is widely regarded as the modality of choice to evaluate and characterise musculoskeletal soft tissue and bone tumours and create an effective management protocol.[20, 21, 22] While conventional MRI is crucial for revealing tumour details such as size, depth, composition, and relationships with surrounding structures, it faces challenges in distinguishing hyperintense tumours from reactive peritumoral oedema, which leads to a significant overlap in the signal properties of both benign and malignant neoplasms, and non-neoplastic reactive or inflammatory lesions.[4, 6] With minimal extra scanning

time, the DW-MRI technique, can be added to the standard MRI protocols to provide a way to assess musculoskeletal tumours according to their histological composition. DW-MRI ADC mapping quickly generates quantitative data regarding the tumour cellularity.[4]

Our finding of lower ADC values in malignant tumours aligns with those of Romeih *et al.*, who discovered that benign lesions had a higher ADC level.[22] Similar findings were also observed by Nassef *et al.*, Neubauer *et al.*, Li *et al.*, and Nagata *et al.*, where the mean ADC value of malignant tumours was lower than that of benign tumours.[17, 20, 21, 23] This applies to other studies findings of most common lesion of Ewing's Sarcoma. Romeih *et al.*[22] and Nassef *et al.*[20] also reported similar results.[22]

Our finding of higher levels of ADC in benign tumours is in agreement with Romeih *et al.*[22] Typically, benign tumours demonstrate high ADC values, except for some instances, such as giant cell tumours and osteoblastoma, etc. Thus, ADC value can be vital in differentiating benign and malignant musculoskeletal tumours.[4, 24]

There was some overlap in the ADC value of benign and malignant lesions. Two patients with low ADC values (0.72×10^{-3} mm²/sec and 0.21×10^{-3} mm²/sec) were diagnosed as lipoma and giant cell tumour of bone, respectively. These results are considered false positives. In the case of lipoma, a possible explanation may be that a large amount of fatty tissue has resulted in restricted diffusion and, thus, low ADC value.[22] The histologic characteristics of giant cell tumours of bone include multinucleated giant cells and a moderately vascularised network of stromal cells, which might contribute to decreasing the extracellular space and the resulting low ADC value.[4] Several previous studies have similarly encountered the overlapping of ADC value between benign and malignant musculoskeletal tumours.[16, 20, 22]

In this study, DW-MRI accurately identified 28 malignant and five benign lesions, achieving an overall diagnostic accuracy of 91.4% using a cut-off ADC value of 1.1×10^{-3} mm²/s, the sensitivity and specificity were determined to be 96.4% and 71.4%, respectively. Similar findings were observed by Romeih *et al.*, who found a sensitivity of 83.3% and specificity of 72.7%.[22] With a cut-off mean ADC value of 1.058×10^{-3} mm²/s, Boruah *et al.* observed that DW-MRI demonstrated a sensitivity of 83.3%, specificity of 66.7%, and accuracy of 78.7% in distinguishing benign from malignant bone tumours. Furthermore, for distinguishing benign from malignant soft tissue tumours, it exhibited a sensitivity of 83.3%, specificity of 87.5%, and accuracy of 84.6% with a cut-off mean ADC value of 1.198×10^{-3} mm²/s.[16] Neubauer *et al.*, employing a similar cut-off point, reported a sensitivity of 90% and specificity of 91% for characterising musculoskeletal tumours.[23] Therefore, the determination of the cut-off point for each population might be important. Larger studies are warranted for it.

This study has several limitations. First, the generalizability of the findings is constrained by the purposive nature of a small sample of subject selection in a tertiary-level hospital in Dhaka, potentially not reflecting the representative national perspectives. Second, the ROI occasionally included very minute necrotic spots or cysts, which possibly affected ADC analysis performance. Third, not all study subjects underwent open biopsy. For some patients, histopathological analysis was performed using FNAC. This variation in diagnostic procedures could introduce inconsistencies in the histopathological confirmation of the tumour types and may impact the overall accuracy and comparability of the diagnostic results.

Conclusion

In summary, when combined with conventional MRI sequences, DW-MRI ADC mapping plays a valuable role in assessing musculoskeletal tumours. As reported by other studies, we report a higher ADC value in benign patients than in malignant musculoskeletal tumours. DW-MRI demonstrated high diagnostic accuracy in differentiating musculoskeletal tumours, enhancing the capabilities of conventional MRI. However, due to overlapping ADC values, DW-MRI ADC mapping alone is insufficient for distinguishing between benign and malignant musculoskeletal tumours. Further studies with larger and more representative samples are necessary to corroborate these findings.

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Author contributions

Conception and design: MS, SR. *Acquisition, analysis, and interpretation of data:* MS, PC. *Manuscript drafting and revising it critically:* MS, SR, PC, SAA, BPK, MSS. *Approval of the final version of the manuscript:* MS, SR, PC, SAA, BPK, MSS. *Guarantor of accuracy and integrity of the work:* MS.

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Conflict of interest

We do not have any conflict of interest.

Ethical approval

The study was approved by the IRB of BSMMU (Memo no- BSMMU/2022/8439, Date- 25/08/2022)

Data availability statement

We confirm that the data supporting the findings of this study will be shared upon reasonable request.

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