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The Role of Advanced Techniques of MRI in Evaluation of Pediatric Bone Tumors

Abeer Maghawry Abdelhameed *, Ayman Mohamed Ibrahim *, Noha Mohamed Osman *, Sherif Ishak Azmy **, Eman Aly El-Din El-Sayed *

* Radiodiagnosis Department, Faculty of Medicine, Ain Shams University

** Orthopedic Surgery Department, Faculty of Medicine, Ain Shams University

ABSTRACT

Background: Functional magnetic resonance imaging (MRI) improves tissue characterization and staging of bone tumors compared to the information usually supplied by structural imaging. Dynamic MRI and diffusion MRI can be performed in everyday practice. Tumour characterization can benefit from perfusion MRI with dynamic gadolinium injection and enhancement time-intensity curve analysis combined with quantitative and qualitative diffusion MRI.

Aim of the Work: is to elucidate the role of advanced MRI techniques in diagnosis of pediatric bone tumors and to assess the diagnostic potential of Dynamic contrast enhancement (DCE) in conjunction with Diffusion weighted imaging (DWI) in differentiating benign from malignant bone tumors.

Patients and Methods: a prospective study conducted on thirty pediatric patients with clinically suspected and radiologically proven bone tumor or tumor like lesion. The patients were referred from the Department of Orthopedics, Ain Shams University. The patients were investigated using 1.5 Tesla magnetic resonance device. They were subjected to conventional MRI and DCMI.

Results: DWI with measurement of Apparent diffusion coefficient (ADC) values helped in the differentiation of benign and malignant bone tumors, and that the best cut-off criterion is ADC of ≤ 0.9 and this means that ≤ 0.9 indicates malignant result while >0.9 is defined as benign results with overall sensitivity 100% and specificity 100%. A type II curve was seen in 23 cases (one malignant and twenty two benign), type IV was seen in 5 cases (all are malignant) and type V curve was seen in two malignant cases (after chemotherapeutic treatment). ROC analysis for the Dynamic contrast enhancement (DCE) showed a sensitivity of 75 % and specificity of 100%.

Conclusion: DWI and DCE-MRI had been proven to be highly useful in the differentiation of benign and malignant bone tumors. Measurement of ADC values improved the accuracy of the diagnosis of bone tumors. Moreover; they could be used in the follow up of tumors and their response to therapy.

Keywords: Magnetic Resonance Imaging (MRI) - Pediatrics - Bone tumors - Diffusion weighted imaging (DWI) - Apparent diffusion coefficient (ADC) – Dynamic study- Dynamic contrast enhancement (DCE).

INTRODUCTION

The bone tumors can be categorized as benign and malignant, and the latter may be sub-categorized as primary and secondary [1].

All imaging methods play a role in diagnosis of bone tumors. Plain radiography is the primary imaging modality to suggest the diagnosis and judge the nature of different bony lesions. When a lesion is indeterminate or shows signs of aggressiveness, magnetic resonance imaging (MRI) is indicated for further characterisation. It is considered the gold standard for characterization of these lesions [2].

Magnetic resonance imaging (MRI) plays a vital role in the evaluation of skeletal lesions, particularly in defining their composition, extent, compartmental involvement, and relationship to the adjacent structures [3].

T1WI is very important in the evaluation of bone marrow. Most bone tumors will be evident as lesions with low signal against a background of surrounding fatty marrow. T1WI also, provides excellent contrast among the cortical, marrow and surrounding tissues [4].

The use of fat suppression (FS) in MRI can confirm or exclude the presence of fat in a lesion. Water shows higher signal than fat on T2WI, but suppressing the fat signal can allow an even better evaluation of the extent of edema. Suppressing the fat signal in T1WI after injection of gadolinium-based contrast medium increases the conspicuousness when assessing tumor vascularisation. Short T1 inversion recovery (STIR) sequences effectively and homogeneously suppress all fat signals [4].

Improvement of treatment and outcome of bone tumors require development of diagnostic tools that can help in differentiation between benign and malignant lesions in a non invasive and reliable manner. Both diffusion-weighted imaging (DWI) and dynamic contrast enhancement magnetic resonance imaging (DCE-MRI) have been major foci of ongoing research, and are verified as being helpful in differentiating benign from malignant musculoskeletal lesions [5].

DWI provides qualitative and quantitative functional information concerning the microscopic movements of water at the cellular level, using ADC map as the quantitative measurement [5].

Dynamic imaging provides physiologic information that cannot be determined from conventional MR imaging, including information regarding tissue vascularization and perfusion, capillary permeability, and the volume of the interstitial space. MR imaging is performed with fast

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GE sequences after gadolinium-based contrast medium injection [6].

AIM OF THE WORK

The purpose of this study is to elucidate the role of advanced techniques of MRI in diagnosis of pediatric bone tumors and to assess the diagnostic potential of MR-DCE in conjunction with MR-DWI in differentiating benign from malignant bone tumors.

PATIENTS AND METHODS

This was a prospective study conducted on 30 pediatric patients with clinically suspected and radiologically proven bone tumor or tumor like lesion. The patients were referred from the Department of Orthopedics, 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

Inclusion Criteria:

1- Age group: pediatric age group (up to 18 years old).
2- Both sexes were included.
3- Bone tumors or tumor like lesions, which were suspected clinically and were seen on radiographs.

Exclusion Criteria:

1- Patients with contra-indications to MR imaging (e.g. pacemaker, metallic implant, severe claustrophobia).
2- Patients with contra-indications to chloral hydrate (e.g. hypersensitivity).
3- Patients with contra-indications to contrast media (e.g. severe renal impairment, hypersensitivity).

METHODS

The evaluation of patients started with reviewing full 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 MRI:

All examinations were performed on a 1.5-Tesla superconductive Magnetic Resonance MR system, with high-gradient performance.

The patients were positioned supine in the magnet bore. The MR protocol consisted exclusively of the following sequences:

First, Coronal T1 spin echo -weighted images were obtained with the following parameters: TR/TE, 490/11; number of signals acquired (averages), 6; matrix, 192 × 256; FOV, 320 × 320 mm; and section thickness, 3 mm.

Second, Coronal T2 weighted images, with short time inversion recovery (STIR) sequences. STIR images were obtained with the following parameters:7020/87; inversion time, 150 ms; echo-train length, 15; averages, 4; matrix, 192 × 256; FOV, 320 × 320 mm; and section thickness, 3 mm.

Third, Axial T1 spin echo weighted images were obtained with the following parameters: TR/TE, 430/12; number of signals acquired (averages), 6; matrix, 192 × 256; FOV, 160 × 160 mm; and section thickness, 3 mm.

Fourth, Axial T2 weighted images TR/TE, 2000/95; number of signals acquired (averages), 6; matrix, 192 × 256; FOV, 160 × 160 mm; and section thickness, 3 mm.

1- Diffusion weighted MR imaging (DWI)

2- Dynamic contrast enhanced technique (DCE)

3- MRI Interpretation

a. Interpretation of Diffusion weighted images
b. Interpretation of Dynamic contrast enhanced images

4- Correlation of Radiological findings with final diagnosis of patients

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

RESULTS

Table (1): Demographic data distribution of the study group (Number of patients =30).

	Demographic Data	Total (N=30)	Malignant (N=8)	Benign (N=22)	p-value
Sex	Female	13 (43.3%)	4 (50.0%)	9 (40.9%)	0.657
	Male	17 (56.7%)	4 (50.0%)	13 (59.1%)	
Age(Years)	Range	4-18	6-18	4-18	0.563
	Mean±SD	11.03 ± 4.37	10.25 ± 4.30	11.32 ± 4.45	

Table (1) showed no statistical significant difference between benign and malignant lesions in terms of demographic data of patients' (age and sex)

Table (2): Histopathological distribution of bone lesions among the study group (N=30)

Histopathology	No.	%
Osteochondroma	7	23.3%
Non-ossifying fibroma	6	20.0%
Simple bone cyst	5	16.7%
Aneurysmal bone cyst	4	13.3%
Osteosarcoma	5	16.7%
Ewing's sarcoma	2	6.7%
Metastasis to Skull from Neuroblastoma	1	3.3%
Total	30	100.0%

The histopathological diagnosis (Table 2) revealed that Osteochondroma was the predominant benign lesion (7 cases) (23.3%), followed by Non-ossifying fibroma (6 cases) (20.0%), then Simple bone cyst (5 cases) (16.7%), and the Aneurysmal bone cyst (4 cases) (13.3%), while that the predominant malignant lesion was Osteosarcoma (5 cases) (16.7%), followed by Ewing's sarcoma (2 cases) (6.7%), then metastasis to the skull from Neuroblastoma (1 case) (3.3%).

Twenty four cases in our study had no diffusion restriction giving high ADC value; 4 cases of aneurysmal bone cyst showing T2 shine through effect and 2 malignant cases after chemotherapy indicating a good response to the therapy, while the other 18 cases were proved to be benign bone lesion. The remaining 6 cases in our study showed diffusion restriction as they were malignant cases giving low ADC value (Table 3, 4).

Table (3): Diffusion and ADC value results among the study group (N=30).

	No.	%
Diffusion		
Unrestricted	24	80%
Restricted	6	20%
ADC value		
High value	24	80%
Low value	6	20 %

Table (4): Comparison between malignant and benign bone lesions according to diffusion results and ADC value (N=30).

	Malignant (N=8)	Benign (N=22)	p-value
Diffusion Unrestricted Restricted	 2 (25 %) 6 (75 %)	 22 (100 %) 0	<0.001
ADC ($x10^{-3}$) High Low	 2 (25 %) 6 (75 %)	 22 (100 %) 0	<0.001
ADC value ($x10^{-3}$)	**Malignant (N=8)**	**Benign (N=22)**	**p-value**
Mean ± SD	0.78 ± 0.44	1.69 ± 0.54	0.007
Range	0.4-1.5	0.7-2.6	

Table (4) showed statistically significant difference between malignant and benign bone lesions according to diffusion results (P value <0.001) and ADC values (P value = 0.007).

DISCUSSION

Magnetic resonance imaging (MRI) plays a vital role in the evaluation of skeletal lesions, particularly in defining their composition, extent, compartmental involvement, and relationship to the adjacent structures [7].

The purpose of this study was to elucidate the role of advanced techniques of MRI in diagnosis of pediatric bone tumors or tumor like lesions and to assess the diagnostic potential of MR-DCE in conjunction with MR-DWI in differentiating benign from malignant bone tumors.

To achieve this; a prospective study was carried on 30 patients, age range 4–18 years old, mean age 11.03 years, 17 male and 13 female. Conventional and dynamic MRI were performed. Then, they were compared to the reference standard for final diagnosis through post-operative histopathological results.

DWI is an unenhanced functional MRI technique based on how the tissue microenvironment affects the Brownian motion of water. The ADC value is a quantitative measure of this movement: low ADC values in a lesion reflect a highly cellular microenvironment, whereas high ADC values are observed in acellular regions [8].

During our study, we noticed that cystic lesions like ABC cysts had high signal on DWI effect, but usually had high mean ADC values (more than 2 x 10^{-3} mm^2/s). This was similar to the results of **Kotb *et al.*** [9] who attributed this result to T2 shine through effect.

Similar to **Lang *et al.*** [10] we found low signal intensity in necrotic tumors who received chemotherapy on DWIs, indicating rapid diffusion of water molecules because of loss of membrane integrity. This was demonstrated in two cases (osteosarcoma and metastatic neuroblastoma) in which the signal intensity of the lesion decreased on DWIs (at b =1000 s/mm^2) indicating more free water diffusion caused by cell necrosis. Similarly ADC values significantly increased. These findings are similar to those observed by **Einarsdottir *et al.*** [8] and **Hayashida *et al.*** [11].

In our study, we found that, the ADC values of solid malignant tumors (n= 8) ranged from 0.4 to 1.5 x 10^{-3} mm^2/s, with mean ADC (0.78 x 10^{-3} mm^2/s) were significantly lower than that of the benign bony tumors (n=22) which ranged from 1.26 to 2.6 x 10^{-3} mm^2/s, with mean ADC (1.69 x 10^{-3} mm^2/s). 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 values may be an effective criterion for predicting the presence of benign disease. **Ahlawat *et al.*** [12] found that quantitative ADC values have predictive value for the characterisation of bone lesions, which is consistent with our study.

Pekcevik *et al.* [13] stated a cut-off value of 1.37 x 10^{-3} mm^2/s for distinguishing benign and malignant bone tumors with a sensitivity of 90 %, a specificity of 92.9%, and an accuracy of 92% resulting from 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 $\leq$0.9 x 10^{-3} mm^2/s, and this means that less than or equal to 0.9 x 10^{-3} mm^2/s is indicating malignant result while >0.9 x 10^{-3} mm^2/s is defined as benign results, with overall sensitivity 100%, specificity 100%, and accuracy 100%.

Therefore, in our study, we found that ADC value was able to distinguish benign from malignant high signal intensity on DWI and this was in agreement with **Padhani *et al.*** [14] 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 was able to monitor tumor response to therapy as agreed by **Einarsdottir *et al.*** [8].

DCE-MRI can reflect the dynamic changes of intra-tumour blood flow and perfusion. The analysis of the DCE-MRI can be performed either using semi-quantitative analysis (e.g. visual assessment of the TIC curves, parametric analysis of the time dependent MRI signal), or quantitatively (calculated by a pharmacokinetic model) [15].

In our study, we used the visual assessment of the shape of the TIC as it was easy to perform and it was easily applied in daily clinical routine, that is, merely considering the shape of the uptake and washout of contrast agent as agreed by **Lavini *et al.*** [16].

Concerning TIC type in our study, 22 cases of benign lesions were type II, 5 cases of malignant lesions were type IV, two malignant cases after chemotherapeutic treatment were type V, and one malignant case was type II which is a false negative result. Therefore, type II curve is highly suggestive of benign lesions, and type IV curve is highly suggestive of malignancy.

Our results are in agreement with **Lang *et al*.**[10] who found that the active moiety of malignant bone tumors and infiltrated muscle tissue often rapidly increase earlier, resulting in type IV curve, whereas benign lesions, oedema, and other non-active small areas are the opposite, resulting in type II curve.

In our study, we noticed that the two malignant cases that received chemotherapeutic treatment resulted in type V curve. According to **Kajihara *et al*.**[17] this is a good response to the treatment as he stated that an accurate evaluation of the tumour response during the initial treatment phase is of the utmost importance to assess treatment effectiveness, plan the rest of the treatment strategy, and predict the outcome. During follow-up in poor responders, the time-intensity curve remained unchanged (type IV). Changes in the time-intensity curve to be type V curve with rapid early enhancement followed by slow gradual enhancement defines a good treatment response. Dynamic perfusion MRI makes a major contribution to patient follow-up during chemotherapy.

TIC reflects lesion vascularisation; however, because sometimes there is an overlap between benign and malignant bone diseases, it could not be used alone for the differential diagnosis of benign and malignant lesions. As we noticed in our results that there was a malignant case resulted in type II curve, which is in agreement with **Geirnaerdt *et al*.**[18] who stated that in dynamic imaging, the first pass of the contrast agent serves to evaluate tissue vascularisation and tumour perfusion. However, qualitative overlap sometimes occurs between the time intensity curves of highly vascular benign tumors and those of poorly vascularised malignant tumors.

Our study showed that DCE has a diagnostic value in the discrimination between benign and malignant bone lesions with overall sensitivity 75%, specificity 100%, and accuracy 93.3%. While **Cao *et al*.**[19] reported that the overall sensitivity was 95.5%, specificity 85.7%, and an accuracy 90.6% for DCE in the discrimination between benign and malignant bone lesions.

In our study, all the benign cases corresponded to high ADC values with type II curve (true negative cases). The two malignant cases who received chemotherapeutic treatment corresponded to high ADC values and type V curve indicating good response to the treatment. The other six malignant cases corresponded to low ADC values from which five of them showed type IV curve (true positive cases), while one of them showed type II curve (false negative case). So, there was a malignant case misdiagnosed by DCE.

Therefore, we agree with **Cao *et al*.**[19] who stated that a combination of both DWI and DCE-MRI is a promising method for differentiating malignant from benign bone lesions and that the combination of DWI with DCEMRI is more valuable than either one alone.

CONCLUSION

In summary, combination of both DWI and DCE-MRI had been proven to be highly useful in the differentiation of benign and malignant bone tumors. When combined as a complementary sequence with conventional MRI together with the measurement of ADC values. With significant cut-off value, the accuracy of the diagnosis of bone tumors and tumor like lesions will be improved making it a non-invasive tool in diagnosis of bone tumors and differentiating benign from malignant lesions. Moreover, they can be used in the follow up of tumors and their response to therapy.

REFERENCES

1. **Eyre R, Feltbower RG, Mubwandarikwa E, Eden T(2011):**Epidemiology of bone tumors in children and young adults. Pediatr Blood Cancer,53(6):941–52.
2. **Kung JW, Yablon CM, Eisenberg RL(2016):** Bone marrow signal alteration in the extremities. AJR .,196:492–510.
3. **Bourillon C, Rahmouni A, Lin C(2015):** Intra-voxel incoherent motion diffusion-weighted imaging of multiple myeloma lesions: correlation with whole-body dynamic contrast agent-enhanced MR imaging. Radiology ,277:773-83.
4. **Davies AM, Sundaram M, James SLJ(2012)** Imaging of Bone Tumors and Tumor Like Lesions (Techniques and Applications). Springer, Berlin Heidelberg, 6(4):211–24.
5. **Khoo MY, Tyler PA, Saifuddin A, Padhani AR (2015)** Diffusion weighted imaging (DWI) in musculoskeletal MRI: a critical review. Skeletal Radiol.,40: 665–81.
6. **Fayad LM, Jacobs MA, Wang X, Carrino JA, Bluemke DA(2013)** Musculoskeletal tumors: how to use anatomic, functional, and metabolic MR techniques. Radiology, 265(2):340–56
7. **Subhawong TK, Jacobs MA, Fayad LM (2016)** Diffusion-weighted MR imaging for characterizing musculoskeletal lesions. Radiographics, 34:1163-77.
8. **Einarsdottir H, Karlssom M, Wejde J (2014)** Diffusion-weighted MRI of bone and soft tissue tumors. Eur Radiol., 14:959–63.
9. **Kotb SZ, Sultan AA, Elhawary GE, Taman SE (2014)** Value of diffusion weighted MRI in

differentiating benign from malignant bony tumors and tumor like lesions. Egyptian Journal of Radiology and Nuclear Medicine, 45:467-76.

10. **Lang P, Honda G, Roberts T (2017)** Musculoskeletal neoplasm: peri-neoplastic edema versus tumor on dynamic post-contrast MR imaging with spatial mapping of instantaneous enhancement rates. Radiology, 197:831-39.
11. **Hayashida Y, Yakushiji T, Awai K, Katahira K, Nakayama Y, Shimomura O (2016)** Monitoring therapeutic responses of primary bone tumors by diffusion-weighted image: initial results. Eur Radiol., 16(12):2637–43.
12. **Ahlawat S, Khandheria P, Subhawong TK(2015):** Differentiation of benign and malignant skeletal lesions with quantitative diffusion weighted MRI at 3T. Eur J Radiol .,84:1091-7.
13. **Pekcevik Y, Kahya MO, Kaya A(2014)** Diffusion weighted magnetic resonance imaging in the diagnosis of bone tumors: preliminary results. J Clin Imag Sci., 3:63.
14. **Padhani AR, Khoo MY, Tyler PA, Saifuddin A (2017)** Diffusion weighted imaging (DWI) in musculoskeletal MRI: a critical review. Skeletal Radiol., 40:665–81.
15. **Biffar A, Dietrich O, Sourbron S (2014):** Diffusion and perfusion imaging of bone marrow. Eur J Radiol. ,76:323-28.
16. **Lavini C, Pickaart BC, De Jonge MC, Schaap GR, Maas M (2016)** Region of interest and pixel-by-pixel analysis dynamic contrast enhanced magnetic resonance imaging parameters and time–intensity curve shapes: a comparison in chondroid tumors. Magn Reson Imaging,27:62–68.
17. **Kajihara M, Sugawara Y, Sakayama K, Kikuchi K, Mochizuki T, Murase K (2014)** Evaluation of tumor blood flow in musculoskeletal lesions: dynamic contrast-enhanced MR imaging and its possibility when monitoring the response to preoperative chemotherapy. Radiat Med., 25(3):94–105.
18. **Geirnaerdt MJ, Van Rijswijk CS, Hogendoorn PC (2016)** Soft tissue tumors: value of static and dynamic gadopentetate dimeglumine-enhanced MR imaging in prediction of malignancy. Radiology,233(2):493—502.
19. **Cao J, Xiao L, Zhang G, Dong J (2017)** Diagnostic value of combined diffusion-weighted imaging with dynamic contrast enhancement MRI in differentiating malignant from benign bone lesions. Clin Radiol., 250:1-9.