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Multiparametric evaluation of bone tumors utilising diffusion weighted imaging and dynamic contrast enhanced magnetic resonance imaging

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ABSTRACT

Aim: This study aimed to use multiparametric magnetic resonance imaging (MRI) techniques, namely, diffusion-weighted imaging (DWI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) to evaluate bone tumors.

Methods: Thirty-three patients with primary untreated bone tumors were assessed utilizing DWI and DCE-MRI. Various parameters like ADC values from DWI and percentage peak signal intensity (%PSI), the maximum slope of increase (MSI), and time to peak signal intensity (TTP) values were assessed in different cases, and the final correlation was drawn with histopathological findings.

Result: Parameters of semi-quantitative DCE-MRI, i.e., %PSI, MSI and, TTP, correlated significantly with the histopathological characteristics of the tumor (p values < 0.001). Minimum ADC value in the tumor also showed a strong correlation with the tumor characteristic (p values < 0.001). Also, the correlation between parameters of DWI and DCI-MRI is well correlated with each other.

Conclusion: The results of this study provide grounds for the integration of multiparametric pre-treatment evaluation of bone tumors. In our study, we not only tried to utilize different parameters of functional MRI in bone tumors as well as re-explored the semi-quantitative analysis of DCE-MRI.

1. Introduction

In musculoskeletal imaging, radiography is the modality of choice in characterizing and diagnosing primary as well as secondary bony lesions. Magnetic resonance imaging (MRI) has become a highly efficient imaging modality in oncological imaging in modern-day practice. Its role in pre-treatment and post-treatment evaluation continues to expand with the development of newer imaging sequences and image processing tools. The primary role of conventional MRI is to evaluate the anatomical extent of the disease and its relationship with adjacent structures.[1,2] However, several functional and metabolic MR techniques have become a part of imaging protocol in many tumors, notably that of Breast, prostate, and brain. These techniques not only have a role in tumor characterization but also help in post-treatment assessment by providing baseline data for response assessment. The characterization has a special role in differentiating tumors of similar morphological characteristics, e.g., between a chondroma and chondrosarcoma. Functional MRI techniques, although being increasingly studied, have still not formed a part of routine imaging protocol in bone tumors, as compared to breast and prostate cancer imaging, where it is an essential criterion for staging. Various advanced MRI techniques, such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI), and magnetic resonance spectroscopy (MRS), are being used for the evaluation of tumors and tumor-like lesions.[3] Of these, DWI and DCE-MRI are of particular significance since these can depict the microvascular and cellular environment of the lesion, respectively. DWI is an MRI technique that accesses variation in the Brownian motion of water as a result of differences in tissue microstructure. The apparent diffusion coefficient (ADC) is its quantitative measure, i.e., Low ADC values indicate highly cellular micro-environments in which diffusion is limited, whereas high ADC values are seen in acellular or necrotic regions.[4,5] Hence, DWI has the potential to differentiate

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between benign and malignant lesions. DCE-MRI is a time-resolved perfusion study to understand the microvascular environment of the tumor. It analyzes the temporal enhancement characteristics of a tumor by a series of images following injection of a contrast into the vascular system over a few minutes. Neo-angiogenesis is the pathophysiological basis of this technique, wherein, the tumor after growing to a certain extent induces the surrounding vessels for the neo-angiogenetic process by release of growth factors. This leads to the formation of neoangiogenic vessels are characterized by permeability, chaotic flow patterns, and fragility.[6,7]

The purpose of the study was to assess the correlation between the histopathology and pattern of mean time-intensity curve characteristics of various bone tumors on dynamic contrast-enhanced MR (DCE-MRI) utilizing semi-quantitative analysis and to find a correlation between the nature of the lesion and quantitative ADC values. Also, the correlation between these two functional techniques was assessed.

2. Materials and Methods

Study design: A cross-sectional study was conducted for 1.5 years.

Study population: 38 patients with clinically or radiographically diagnosed bone tumors were included in the study. Patients with surgically removed lesions or patients on chemotherapy and/or radiotherapy were excluded from the study.

MRI protocol: MRI was performed using a 3 T MRI machine (GE, Discovery 750 W). Apart from conventional sequences, DWI with ADC quantification and DCE-MRI were done. An image plane showing the lesion along with surrounding normal tissue and a large vessel was selected for the DCE-MRI study. A bolus intravenous (IV) injection of gadolinium-based contrast agent (gadobenate dimeglumine) at a concentration of 0.1–0.2 ml/kg was injected using an auto-injector. A Liver Acquisition with Volume Acceleration (LAVA) sequence was started at the time of the bolus IV injection and was repeated at 10 s intervals for the next 5 min to create 30 three-dimensional datasets.

Data Analysis: All the conventional MRI sequences were interpreted by two radiologists. Data obtained from DCE-MRI for all patients was analyzed by the mean curve engine of the in-house software (READY View MR standard protocol – GE Advantage 3.2 workstations) (Fig. 1). A region of interest ROI within the tumor tissue was selected using the ADC map image, such that it contains a significant tumor area showing low ADC values. Another ROI was placed in the enhancing arterial vessel visualized in the section for the determination of the first pass. One more ROI was placed in the uninvolved soft tissue/musculature as reference enhancement. A signal intensity v/s time curve was generated with signal intensity plotted on the y-axis and time plotted on the x-axis. The part of the curve corresponding to the first pass was utilized for determining the parameters. The parameters were computed over the enhancement image range, i.e., between the first last pre-contrast and the first post-contrast images.

The percentage peak enhancement value (%PSI), the maximum slope of increase (MSI), and the time to peak enhancement (TTP) were calculated from the ROI.

Percentage signal intensity (%SI) is defined as $[SI^T - SI^0]/SI^0$, where SI^T = Average signal intensity of the ROI at time = T after administration of IV contrast is started. SI^0 = average signal intensity at time = 0 (signal intensity at the time the bolus IV administration of contrast is started).

The %PSI value is defined as the $\%SI^T$ value at the peak of the signal intensity-time curve (within the first pass), after which the $\%SI^T$ value reaches a plateau or shows a decreasing trend. The MSI is the slope of the time course values at each time course index i ($Slope_i = s_{i+1} - s_i$). The single value parameters returned by the MSI algorithm is the maximum value of the $slope_i$ function. The time to peak enhancement (TTP) is the time after the bolus IV administration of contrast is started, at which $\%SI^T$ value reaches a peak or a descending trend is observed in the signal intensity-time curve. While %PSI was determined directly from the curve, MSI and TTP values were based values on the same ROIs on the color-coded map generated by the software.

ADC values were determined from the ROI drawn in the ADC images. Both minimum and average values were determined.

Statistical analysis

%PSI values among benign and malignant lesions were compared using an Independent *t*-test, while for MSI, TTP, ADC average, and ADC minimum, Mann Whitney *U* test was used. Receiver Operator Curve (ROC) curves were determined for each of the parameters. 'p'-value was calculated and compared with the level of significance to reach an inference. Pearson's correlation was used to determine the correlation coefficient between the ADC minimum and each parameter of DCE-MRI.

3. Results

Out of 38 patients enrolled in the study, 3 had acute on chronic osteomyelitis and necrotizing granulomatous infection, 2 had recurrent/residual disease; hence these cases were excluded from the study. Of the remaining 33 patients, 15 had benign bone tumors, and 18 had malignant bone tumors on histopathology. Many tumors of chondroid origin were also included in the study (Table 1). The semi-Quantitative analysis of DCE-MRI revealed:

- **%PSI -** Mean value in benign lesions was 0.80 ± 0.65, and malignant lesions were 1.64 ± 0.46 with the statistically significant difference among the benign and malignant lesions ($p < 0.001$).
- **MSI-** A statistically significant difference was found in the MSI between the two groups ($p < 0.001$). The mean value in benign lesions was 270, while for malignant lesions was 1090.
- **TTP-** Statistically significant difference was found in the TTP values between the two groups ($p = 0.002$). The mean TTP in benign diseases was 259.73 s and in malignant diseases was 116.17 s.
- Both ADC average and ADC minimum values showed a statistically significant difference between benign and malignant disease ($p = 0.009$ *and* $p = 0.003$, *respectively*). The mean ADC minimum value among benign lesions was $1.12 \times 10^{\wedge -6}$ mm^2/sec, and for malignant lesions was $0.52 \times 10^{\wedge -6}$ mm^2/sec. Results are summarized in Table 2.

The ROC obtained for %PSI showed an area-under-curve (AUC) of 0.907. The cut-off was determined at the value of approximately 1.090 with a sensitivity of 88.9% and specificity of 86.7%.

The AUC for MSI and TTP were 0.919 and 0.809. The cut-off value for the two groups was kept at 498 for MSI with a sensitivity of 88.9% specificity of 86.7% and 132 for TTP with a sensitivity of 88.3 and specificity of 66.7%. AUC for ADC average and ADC minimum were approximately 0.761 and 0.709, respectively. Cut off value was kept at $0.71 \times 10^{\wedge -6}$ mm^2/sec for ADC minimum with a sensitivity of 88.3% and specificity of 66.7%.

ADC minimum values were correlated with each of the parameters of the DCE-MRI. Pearson's correlation coefficient for %PSI was found to be −0.582 with $p < 0.001$, suggestive of moderate to strong correlation. For MSI, the correlation coefficient was −0.498 with $p = 0.003$, suggestive of weak to moderate correlation. For TTP, the coefficient value was 0.205 with $p = 0.250$, suggestive of no statistically significant correlation.

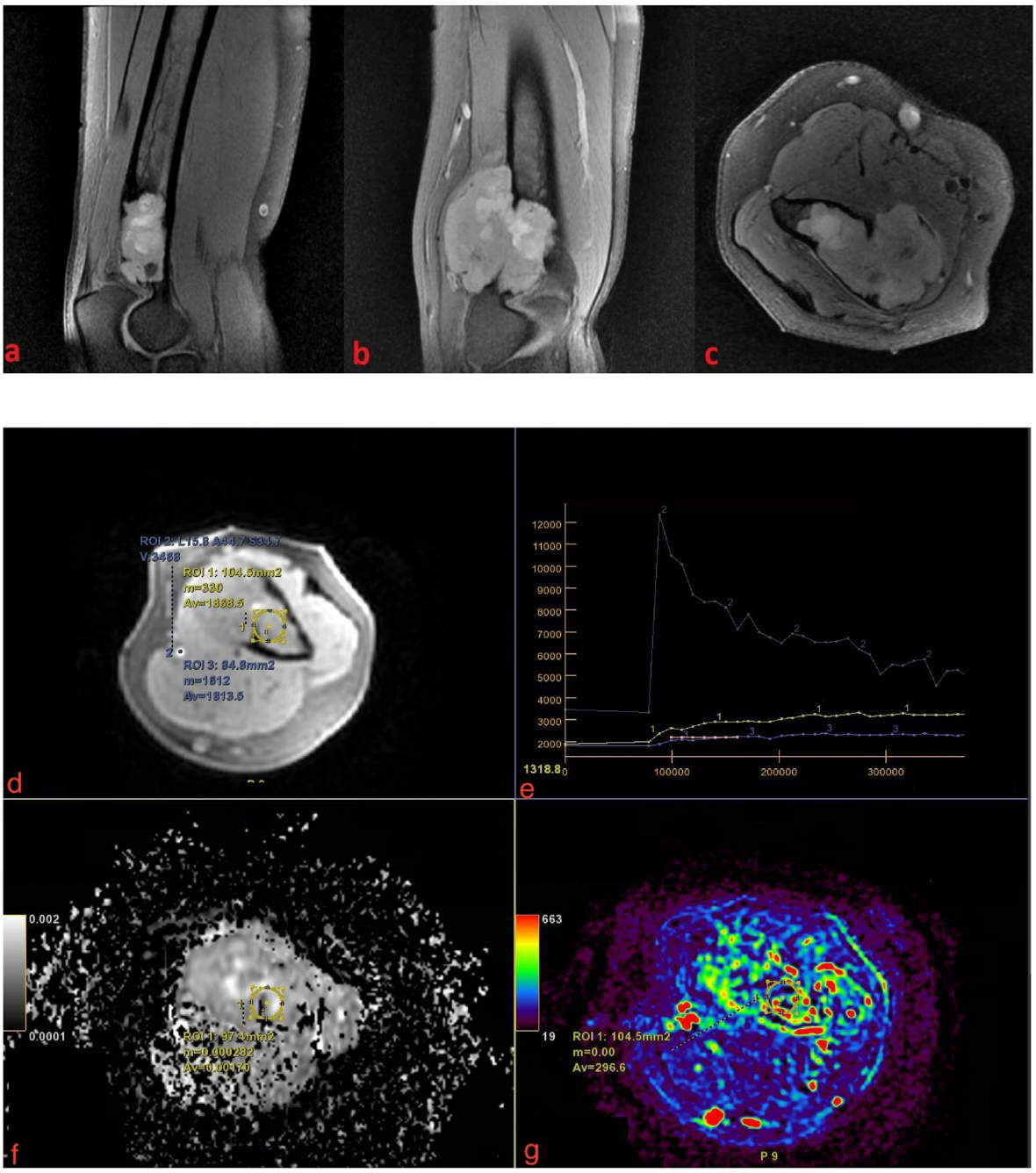

Fig. 1. Conventional MRI images of a 22- year-old male patient presenting with pain in elbow. Sagittal T2 image (a) and coronal proton density fat suppressed (PDFS) (b) showing a hyperintense expansile lesion in distal metaphysis of humerus. Axial PDFS (c) image showing cortical thinning at the lateral margin of the lesion.
Fig. 1 (continued): READY View MR standard protocol – GE Advantage 3.2 workstation. Left upper panel (d) shows the T1 weighted fat saturated sequence image used for DCE-MRI ROI 1 placed within the tumor, ROI 2 placed within the artery, and ROI 3 placed in an involved soft tissue (muscle in this case). Left lower panel shows an ADC map for ROI corresponding to the tumor. The right upper panel (e) shows the corresponding signal intensity versus the time curve. The right lower panel shows the color-coded map for DCE-MRI parameters (g). Type II enhancement curve on DCE-MRI (e) is seen with ADC (minimum) value of 1.61 $\times$ 10^{-3} cm/s (f). The final histopathological diagnosis came out to be chondromyxoid fibroma.

4. Discussion

The two basic properties of tumors, cellularity, and microvascular structure can be studied by utilizing MRI techniques, i.e., DWI and DCE imaging, respectively.

The results of our study showed that malignant tumors have significantly lower ADC values as compared to benign lesions. The mean value for ADC minimum among the malignant lesion was 0.52 $\times$ 10^-6 mm^2/sec and for benign lesions was 1.12 $\times$ 10^-6 mm^2/sec. Also, it was found that ADC minimum values are better predictors as compared to the ADC average based on the AUC. Baur et al.[8] proposed DWI as a parameter discriminating pathologic from benign compression fractures in the spine. Multiple studies[11–15] have been conducted in the past to determine the minimum, maximum, and cut-off ADC values for benign and malignant lesions. The region of interest drawn on an ADC map image shows

Table 1
Distribution of lesions in each group.

Diagnosis On HPE	Number Of Cases
Osseous tumors:	
Fibrous Dysplasia	1
Osteosarcoma	9
Cartilaginous:	
Enchondroma	2
Chondromyxoid Fibroma	1
Osteochondroma	2
Chondrosarcoma	1
Miscellaneous:	
Ewing's Sarcoma	8
Non-ossifying fibroma	1
Giant Cell Tumor	5
Aneurysmal Bone Cyst	2
Simple Bone cyst	1

Table 2
Summary of mean values and cut-off values of each parameter of dynamic contrast enhanced MRI and Diffusion weighted imaging.

Parameter		Mean Value	*p* value
%PSI	Benign	0.80	<0.001
	Malignant	1.64	
MSI	Benign	270	<0.001
	Malignant	1090	
TTP	Benign	259.73	0.002
	Malignant	116.17	
ADC average	Benign	$1.18 \times 10^{\wedge -6}$ mm^2/sec	0.009
	Malignant	$0.78 \times 10^{\wedge -6}$ mm^2/sec	
ADC minimum	Benign	$1.12 \times 10^{\wedge -6}$ mm^2/sec	0.003
	Malignant	$0.52 \times 10^{\wedge -6}$ mm^2/sec	

mean and minimum ADC values. Different authors used either of these values for determining the cut-off. The comparative conclusion of these studies is summarized in Table 3. Compared to previous studies, our study showed lower ADC cut-off values. This can be attributed to less number of chondroid tumors, which show higher ADC values. ADC value depends on whether there are myxomatous, cystic, and cartilaginous components within the lesion. Hayashida et al.[9] found that (n = 20) T2-hyperintense bone lesions (bone cysts, fibrous dysplasia, and chondrosarcoma), solitary bone cysts had higher mean ADC values than fibrous dysplasia and chondrosarcoma. In another study, Yakushiji et al.[10] found that minimum ADC values could help in differentiating between chondroblastic osteosarcoma and chondrosarcoma despite the similarities in histologic features. Nagata et al.[16] found that, in cartilaginous tumors, malignant tumor ADC values (2.33 ± 0.44) were higher than those of benign tumors. Likewise in our study, cartilaginous tumors had higher ADC values and helped in negating the sarcomatous transformation of an osteochondroma into chondrosarcoma (Fig. 2).

DCE-MRI can be utilized using either qualitative, semi-quantitative, or quantitative methods. A semi-quantitative method of DCE-MRI analysis was utilized in our study, and it was found that all three parameters, i.e., %PSI, MSI, and TTP, showed a significant difference between the benign and malignant lesions. Also, the part of the curve which was used to determine these values corresponded to the first pass of the contrast. The first pass method is based on the assumption that part of the curve in the initial increment phase represents kinetics of the contrast agents with the vessels, whereas peak enhancement determined from the whole curve represents kinetics of both intravascular and extravascular cellular spaces.[19] Also, the use of %PSI further increases the sensitivity since it uses a baseline value, which acts as a normalizing factor for variations in the biological environment and imaging parameters.

Considering the sensitivity of the parameters in differentiating benign and malignant lesions, %PSI had the highest AUC in ROC analysis, followed by MSI and TTP.

Quantitative analysis requires the determination of pre-contrast T1 parametric map, arterial input function, and measurement of signal intensity changes with the injection of contrast. Many studies have shown problems associated with pharmacokinetic models, e.g., the need for high temporal resolution sampling, accurate arterial input function definition, and curve fitting-based analysis, which introduces a degree of uncertainty into parameter estimation.[17]

Despite the widespread incorporation of semi-quantitative parameters in clinical radiology, particularly oncology, they are avoided for clinical trial applications in considering that they are biologically and physiologically less relatable and more prone to variations than the pharmacokinetic models. Jackson et al.[18] showed that semi-quantitative parameters have a relatively higher tolerance to poor signal-to-noise ratio compared to pharmacokinetic parameters and demonstrated equivalent therapy-induced changes.

In our study, the ROI for the generation of the curve was based on the ADC map and was placed in the tumor area showing low ADC values, irrespective of the enhancement in that region. It was found that ADC minimum values significantly correlated with %PSI and MSI with negative correlation coefficient values. The correlation between %PSI and ADC minimum was moderate to strong and between MSI and ADC minimum was moderate to weak. TTP did not show any significant correlation with ADC values. This can be explained by the fact that MSI and TTP are dependent on scan parameters, while %PSI is independent of these factors.

Multiparametric evaluation of different tumors using various combinations of functional MRI techniques has been attempted by many studies in the past. Arlinghaus et al.[20] found no statistically significant correlation between ADC and v_e in the breast cancer patient. In a study by Chu et al.[21] it was found that irrespective of brain tumor type, there is an inverse correlation between ADC and K^{trans}. In a Study by Ji Hyun Koo et al.[22], *a* significant correlation was found between ADC and K^{trans} in primary bone tumors; however, this relationship was not consistent in all cases. E Oh et al.[3] found that all pharmacokinetic parameters except v_e were significantly different between benign and malignant bone tumors. Also, the ratio K^{trans}/ADC had the best sensitivity and specificity for differentiating them. In contrast to previous studies, our study combined the ROI for the calculation of both functional techniques so that the

Table 3
Comparative summary of various studies on Diffusion Weighted Imaging for differentiating between benign and malignant lesions.

STUDY	MEAN ADC VALUE FOR BENIGN DISEASE ($\times 10-3$ mm^2/s)	MEAN ADC VALUE FOR MALIGNANT DISEASE ($\times 10-3$ mm^2/s)	CUT OFF VALUE ($\times 10-3$ mm^2/s)
Pekcevik et al.	1.99 ± 0.57	1.02 ± 1.0	1.37 s
Wang et al.	1.17 ± 0.36	0.87 ± 0.20	1.10
Kotb et al.	1.43	1.31	–
Shivani et al.	1.27	0.68	–
Rao et al.	1.62	1.092	–

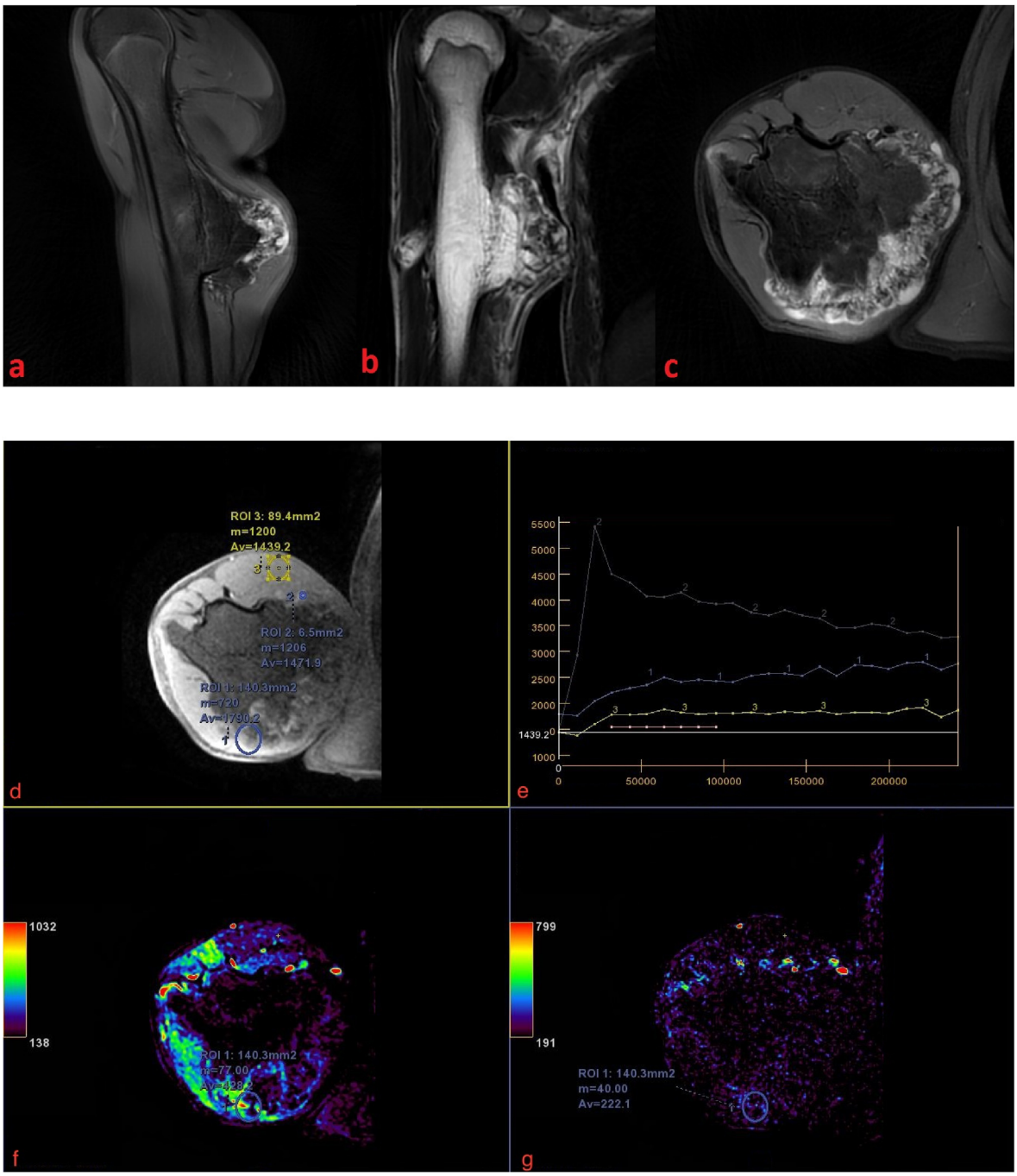

Fig. 2. Conventional MRI images of a 13-year-old patient presented with a recent increase in the size of a previously stable lesion. Sagittal PDFS (a), coronal T2FS (b) and axial PDFS (c) shows a board based lesion arising from the diaphyseal region of humerus with medullary continuity with the shaft. Overlying cartilage cap is seen which appears thickened (3 cm in maximum thickness) and shows heterogeneous signal intensity on T2/PDFS images.
Fig. 2 (continued): READY View MR standard protocol – GE Advantage 3.2 workstation. Multiparametric imaging showed a type II enhancement curve (e) and ADC (minimum) value of 1.85 × 10-3 cm/s, (f) suggesting the contrary. On pathology, features were suggestive of osteochondroma without any evidence of malignant transformation.

same tumor area is being assessed. Hence, the ROI served as a connecting link between DWI and DCE-MRI. This can be highly helpful in biopsy planning. In most cases of malignant and few benign cases, the ROI site was marked while multiparametric evaluation was utilized for obtaining biopsy samples and yielded diagnostic samples. (Fig. 3). Also, it is the first study to utilize semi-quantitative method of assessment of DCE-MRI in bone tumors. These modification in our study helped multiparametric evaluation of bone tumors more incorporable in routine imaging protocol and more useful for surgeons in biopsy planning and surgical resection.

The goal of this study was beyond predicting the histopathological nature of bone tumors using multiparametric techniques. The fact that radiology is as important as histology in bone oncology, our approach was to use the wealth of information provided by MRI in their evaluation.

There were several limitations in the study. The study was a single-center study with a limited number of cases. The tumors included were radiologically and histopathologically different.

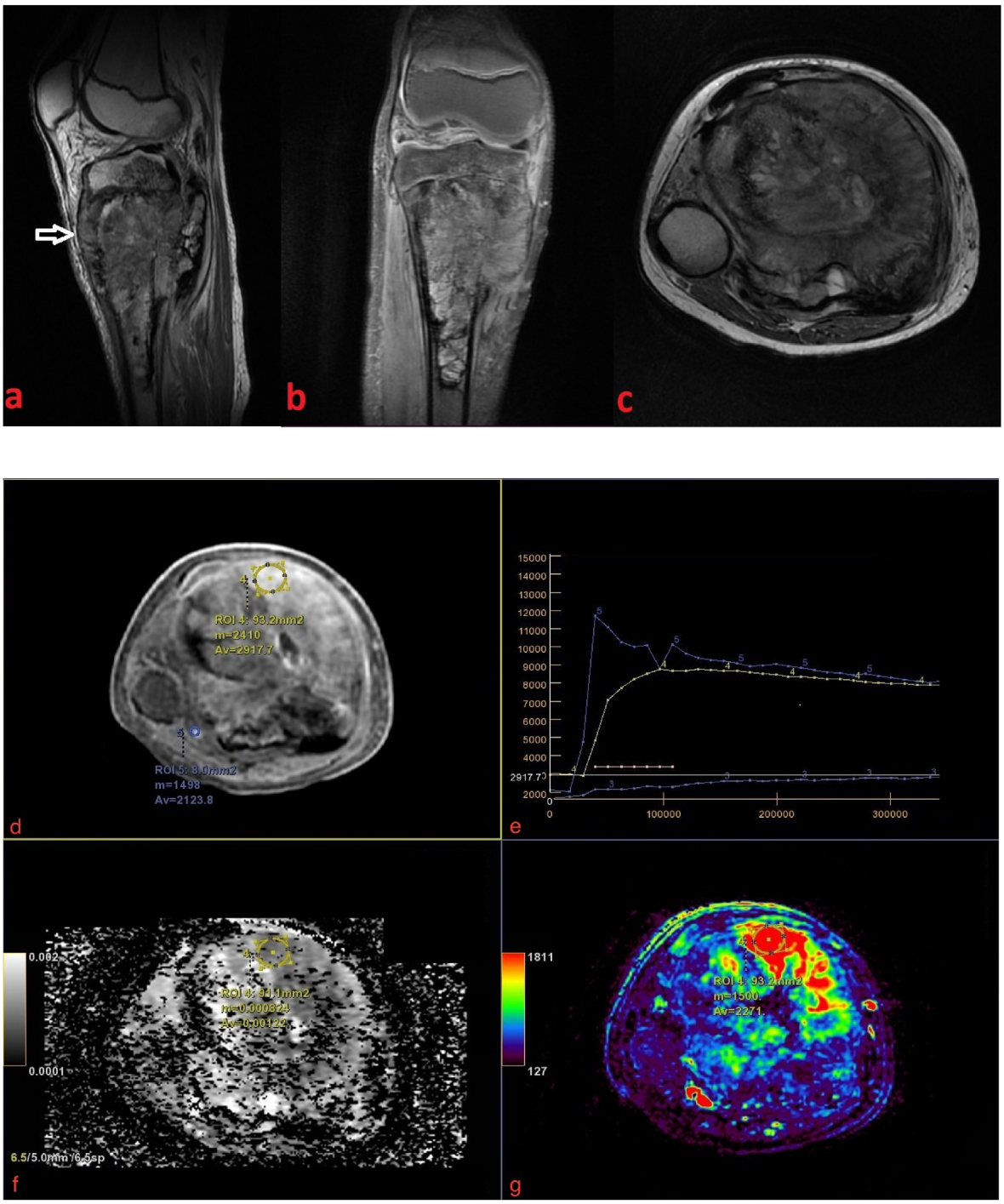

Fig. 3. MRI imaging of a 12-year-old male patient. Sagittal T2 weighted (a), coronal PDFS (b) and axial T2 weighted images show an ill defined lesion involving the meta-diaphyseal region of tibia, crossing the growth plate to involve the epiphysis as well. Periosteal elevation is seen along anterior tibial cortex (white open arrow in a). Extension in surrounding tissue is seen.
Fig. 3 (continued): READY View MR standard protocol – GE Advantage 3.2 workstation. Multiparametric imaging showed a type III enhancement curve (e) and ADC (minimum) value of 0.47 $\times$ 10^{-3} cm/s (f). The ROI site was utilized for biopsy planning (d). Diagnosis of osteosarcoma was made on hispothapathological examination.

Pathological markers of cellularity and vascularity were not correlated with the radiological parameters representing the same. Only final histopathological diagnosis as the benign or malignant lesion was taken into consideration. Furthermore, since only pre-treatment cases were included in the study, the role of multi-parametric assessment in post-treatment evaluation was not attempted.

5. Conclusion

Multiparametric MRI plays an important role in oncological imaging, especially when two or more techniques are combined. Benign and malignant lesions showed a significant difference in parameters of semi-quantitative DCE-MRI and DWI. There was an inverse relationship between ADC values and parameters of DCE-

MRI in both groups of lesions. These functional MRI techniques can help in tumor characterization, biopsy planning, and post-treatment response assessment.

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Authorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication.

Authorship contributions

(The authors' initials followed by their surnames).

Category 1

Conception: G. S., Sharma; S. S., Saxena; S.S., Saran; T.G., Goyal, **Acquisition of data:** G. S., Sharma; S. S., Saxena; S.S., Saran, **Analysis and/or interpretation of data:** G. S., Sharma; S. S., Saxena; S.S., Saran.

Category 2

Drafting the manuscript: G. S., Sharma, S.S., Saran, **Revising the manuscript critically for important intellectual content:** G. S., Sharma, S.S., Saran.

Category 3

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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