

Research Article

Role of Diffusion-Weighted and Chemical Shift Magnetic Resonance Imaging in Differentiation of Benign and Malignant Spinal Fractures

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Abstract

Atraumatic spinal compression fractures are common clinical problem. Differentiating benign osteoporotic fractures from pathological fractures due to malignant/metastatic lesions affects the management and prognoses in patients with known extraspinal malignancy. **The objective** of the research was to assess the role of conventional magnetic resonance imaging sequences with diffusion-weighted imaging and chemical-shift imaging in differentiating benign and malignant acute spinal compression fractures.

Materials and Methods. The study included 40 patients with acute spinal compression fractures. Patients were evaluated using magnetic resonance imaging with diffusion-weighted imaging and chemical-shift imaging to differentiate benign etiology from malignant one. The results obtained were compared with histopathological follow-up for 6 months for definite clinical diagnoses.

Results. No significant difference was noted in signal characteristics of benign and malignant fractures on T1, T2 and short-tau inversion recovery. However, posterior element involvement, soft tissue component and post-contrast enhancement were seen more frequently in malignant fractures ($p < 0.05$). On diffusion-weighted images, 77.8% of malignant fractures were hyperintense and 59.1% of benign fractures were hypointense ($p < 0.05$). The mean apparent diffusion coefficient value was 0.81 ± 0.19 for malignant and 1.24 ± 0.24 for benign fractures ($p < 0.5$). The mean signal intensity ratio for malignant fractures was 0.91 ± 0.125 , whereas the signal intensity ratio for benign fractures was 0.64 ± 0.096 ($p < 0.001$).

Conclusions. Signal characteristics on T1, T2 and short-tau inversion recovery sequences do not differentiate benign from malignant fractures; however, posterior element involvement, soft tissue and post contrast enhancement help in differentiating the etiology. Diffusion-weighted imaging and apparent diffusion coefficient values, as well as using chemical shift imaging further improve the diagnostic accuracy of magnetic resonance imaging.

Keywords

magnetic resonance imaging; diffusion-weighted imaging; apparent diffusion coefficient; short-tau inversion recovery

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Problem statement and analysis of the latest research

Atraumatic vertebral compression fractures in the spine are a common clinical problem, particularly in

elderly patients. Osteoporosis is the most common cause of compression fractures in elderly age group. The spine is also a common site of metastatic disease and accounts for as much as 39% of all bone metastases which may result in pathologic frac-

tures [1]. Compression fractures due to metastatic malignancy are frequently seen in the same elderly age group, and differentiation from benign compression fractures due to osteoporosis often affects clinical staging, management planning, and determination of prognosis in patients with known nonosseous malignancies [2]. Multiple myeloma, lymphoma, plasmacytoma, chordoma, chondrosarcoma, giant cell tumour, etc. can also present as acute spinal compression fractures. The differentiation between benign and malignant causes of vertebral compression fracture is a common clinical problem. The limitations of plain radiography, bone isotope scanning, myelography, and computed tomography (CT) in the diagnosis of benign and malignant compression fractures have been well documented [3, 4, 5, 6]. Radionuclide bone scanning is highly sensitive, but not specific. Myelography is useful for visualization of cord compression, but it is associated with a significant risk of neurologic complications [7]. As early diagnosis and management of malignant fractures are important to prevent further neurological compromise, a reliable and non-invasive imaging modality is needed. Chronic benign compression fractures can be easily diagnosed due to the absence of abnormal signal intensity in a compressed vertebra [2, 8]; however, acute osteoporotic compression fractures can be difficult to differentiate from malignant compression fractures. Vertebral fractures may be detected on radiographs, CT, or radionuclide studies, but the discrimination between benign and malignant vertebral compression fractures relies heavily on magnetic resonance imaging (MRI) features. Earlier studies carried out around the world showed promising results to differentiate benign and malignant vertebral fractures using MRI, but there are certain pitfalls in the studies carried out. Studies from our part of the world where conditions like malignancies, infections, osteoporotic fractures involving spine are so prevalent are still lacking. Thus, such a study is worth conducting in our part of the world.

The objective of this research was to evaluate which conventional MRI features are useful to differentiate benign and malignant vertebral fracture, as well as the role of quantitative diffusion-

weighted imaging (DWI) and advance sequences like chemical-shift imaging (CSI) in differentiating the same. We assessed the value of apparent diffusion coefficient (ADC) in osteoporotic and malignant fractures and determined a cut-off value of ADC which have a good accuracy in differentiating the two processes. We assessed the signal intensity ratio (SIR) of benign osteoporotic and malignant spinal fractures with a cut-off value with acceptable accuracy to differentiate the two processes. Most of the studies conducted so far have assessed the qualitative aspects of DWI and CSI in differentiating the acute osteoporotic and malignant fractures of spine only.

Diffusion-weighted MRI is a well-recognized technique with various roles in neuroradiology, especially in stroke evaluation [9, 10, 11, 12]. Water molecules in body undergo a random motion called Brownian motion which is uniform in all directions. Diffusion of water in body depends on many different factors like restriction, hindrance, membrane permeability, and tissue inhomogeneity [9, 13]. In case of malignant tumours, the cells are densely packed with large nuclei and scanty cytoplasm which results in restricted diffusion. On the other hand, in benign pathologies, cells are loosely packed with abundant cytoplasm resulting in comparatively free diffusion [14]. All DWI sequences use a dephasing and rephasing gradient which are of equal magnitude, but opposite in direction. The water molecules with restricted motion will be subjected to both gradients at the same place and the two gradients will neutralize each other. Therefore, these water molecules will be in phase to produce a strong signal. This information can be used for tissue characterization.

In-phase/opposed-phase CSI assesses the presence of water and fat in a tissue voxel at the molecular level, as hydrogen nuclei associated with fat resonate at a frequency that is different from hydrogen nuclei which are part of water molecules. CSI has been used extensively in evaluation of the adrenals and liver; however, only a few studies have assessed the benefit of this technique in MRI of the spine [15]. Based on the fact that benign vertebral fractures still have normal fatty marrow and

that it has been replaced and infiltrated in malignant fractures by malignant cells, the differentiation of these two processes should be possible with in-phase/opposed-phase CSI [16].

1. Materials and Methods

It was a prospective observational study conducted at Sher-i-Kashmir Institute of Medical Sciences, Srinagar in the Department of Radiodiagnosis between October 2016 to January 2018, and 40 patients were included in the study. In all cases, informed consent was taken from the patient before participating in the study. The study was approved by the Institutional Ethics Committee.

All patients without history of trauma underwent imaging performed with 1.5-T MRI scanner (Magnetom, Avanto, Siemens Healthcare). The imaging protocol consisted of:

- Unenhanced sagittal T1-weighted sequence (TR/TE: 450/10);
- Sagittal short-tau inversion recovery (STIR) sequence (TR/TE, 3000/35, TI: 160);
- Sagittal T2-weighted sequence (TR/TE: 4160/114);
- Contrast-enhanced fat suppressed axial and sagittal images (TR/TE, 450/10);
- Echo-planar sagittal diffusion-weighted images/ADC maps (b=50, 400, 800).
- Chemical-shift sagittal MR images: in-phase (TR/TE: 100/2.2) & out-of-phase (TR/TE: 100/4.9).

Histopathological confirmation was done in eight patients in which seven turned out to be malignant and one was reported as benign. Follow-up MRI was done in seven patients. Rest of the patients were followed clinically for a period of 6 months and final clinical diagnosis was taken as ultimate diagnosis. ADC measurement was done on ADC maps created using combined b-values of 50, 400, 800 with region of interest (ROI) placed at the compression level. For ADC measurement of normal vertebrae, ROI was placed on apparently normal vertebral bodies.

All in-phase/out-of-phase images were evaluated and areas that were of abnormal signal intensity

on the T1, T2 and STIR sequences were identified on the in-phase/opposed-phase sequences. A spherical region of interest cursor was placed over the abnormal area on the in-phase, as well as opposed-phase images. Three measurements of the signal intensity were made, and the average was recorded. A computation of the SIR of the marrow on the opposed phase to signal intensity measured on the in-phase images was made.

Clinically suspected cases of spinal fractures presenting within 2 months, cases of spinal fractures diagnosed by using other modalities like x-rays or CT scans and cases with suspected metastasis to spine presenting with backache or radiculopathies were included in the study. Patients having claustrophobia, metallic stents or MRI incompatible cardiac pacemakers, or any other prosthesis, patients presenting more than 2 months after spinal fracture, pregnant patients, patients with traumatic or sclerotic fractures were excluded from the study.

The recorded data were compiled and entered in a spreadsheet (Microsoft Excel) and then, exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were summarized in the form of the means and standard deviations (SD) and categorical variables were expressed as frequencies and percentages. Graphically, the data were presented by bar diagrams and scatter plot. The Student's independent t-test was employed for comparing continuous variables. The Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. Receiver-operating characteristic (ROC) analysis was performed to determine the optimal cut-off of "ADC at fracture site" for predicting the malignant fracture. The Karl Pearson's coefficient of correlation was applied to determine correlation between ADC and age. A p-value of less than 0.05 was considered statistically significant. All p-values were two-tailed.

2. Results

2.1 Patient Profile

During the course of our study, 40 vertebral compression fractures were considered. Proper MRI protocol was followed in all cases. All the cases were interpreted under the guidance of senior radiologists with years of experience in MRI. The mean age of patients with benign compression fractures was 54.2 ± 16.73 SD; the mean age of patients with malignant compression fractures was 56.4 ± 12.49 SD as shown in Table 1.

Table 1. Age distribution of patients.

Age (years)	Malignant		Benign		p-value
	No.	%age	No.	%age	
<30	1	5.6	0	0.0	0.639
30-60	12	66.7	13	59.1	
>60	5	27.8	9	40.9	
Total	18	100	22	100	
Mean±SD	54.2±16.73		56.4±12.49		

Ten out of eighteen patients in malignant category were males and 8 were females, whereas 9 out of twenty-two patients in benign category were males and 13 were females. Malignant compression fractures were more prevalent in male patients and benign compression fractures were more prevalent in female patients, although the value was not statistically significant.

2.2 Signal Intensity on Conventional T1-, T2-Weighting and STIR Sequence

Seventeen malignant and 18 benign fractures were hypointense on T1-weighted images (T1WI), and 1 malignant and 4 benign fractures were isointense on T1WI with respect to presumed normal marrow on T1WI. On T2-weighted images (T2WI), 15 malignant and 17 benign fractures were hyperintense, 3 malignant and 4 benign fractures were isointense and 1 benign fracture was hypointense. All benign and malignant compression fractures were hyperintense on STIR sequence as shown in Table 2.

Table 2. Signal intensity on conventional MRI sequences in benign and malignant compression fractures.

	Malignant		Benign		p-value
	No.	%age	No.	%age	
T1WI Hypointense	17	94.4	18	81.8	0.356
T1WI Isointense	1	5.6	4	18.2	
T1WI Hyperintense	0	0.0	0	0.0	
T2WI Hypointense	0	0.0	1	4.5	0.645
T2WI Isointense	3	16.7	4	18.2	
T2WI Hyperintense	15	83.3	17	77.3	
STIR Hypointense	0	0.0	0	0.0	-

2.3 Signal on DWI

Fourteen fractures in malignant category were hyperintense, 3 were isointense, 1 was hypointense, whereas in the benign category, 13 were hypointense, 7 were hyperintense, 2 were isointense as shown in Table 3. The values were statistically significant.

Table 3. Signal intensity on DWI in benign and malignant fractures.

Signal Intensity	Malignant		Benign		p-value
	No.	%age	No.	%age	
Hypointense	1	5.6	13	59.1	0.002*
Isointense	3	16.7	2	9.1	
Hyperintense	14	77.8	7	31.8	

Note: * - statistically significant difference ($p < 0.05$)

2.4 MRI Characteristics

In our study, posterior element involvement was seen in 14 malignant fractures and 3 benign fractures; paraspinal soft tissue was seen in 9 malignant and 1 benign fracture; epidural compression was seen in 18 malignant and 8 benign fracture, gadolinium enhancement was seen in 17 malignant and 8 benign fractures (Fig. 1). There was a statistically significant difference for all characteristics studied between malignant and benign fractures as shown in Table 4.

2.5 Quantitative Analysis of DWI/ADC Value

Mean ADC value for metastatic fractures was 0.81 ± 0.19 (range; 0.45-1.3) and mean ADC value

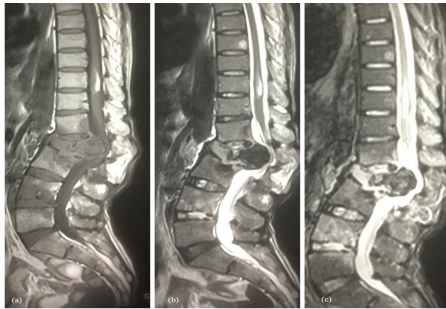


Figure 1. T1WI(a), T2WI(b), STIR(c) images of a patient with compression fracture of L2 vertebrae with associated soft tissue.

Table 4. MRI characteristics in benign and malignant compression fractures.

MRI Characteristics	Malignant No.	Malignant %age	Benign No.	Benign %age	p-value
Posterior Element Involvement	14	77.8	3	16.7	<0.001*
Paraspinal Soft Tissue	9	50.0	1	5.6	0.002*
Epidural Compression	18	100.0	8	44.4	<0.001*
Gadolinium Enhancement	17	94.4	8	44.4	<0.001*

Note: * - statistically significant difference (p<0.05)

for benign fractures was 1.24 ± 0.24 (range; 0.81-1.6). The values were statistically significant.

2.6 Optimal Cut-Off Value for ADC

Our results, according to the ROC curve for discriminating malignant and benign fractures using ADC value, showed that the best cut-off criterion is ADC of ≤ 0.93 with area under the ROC curve (AUC) 0.943, and this means that ≤ 0.93 indicates malignant result, while > 0.93 was defined as benign result with a sensitivity of 88.9%, specificity of 95.5% and accuracy of 92.5% as shown in Table 5.

2.7 ADC of Normal Vertebral Bodies with Age

No significant correlation of normal vertebral bodies with age was found in our study as shown in Fig. 2.

Table 5. ADC at fracture site in benign and malignant fractures.

Fracture	N	Mean	SD	Range	p-value
Malignant	18	0.81	0.19	0.45-1.3	<0.001*
Benign	22	1.24	0.24	0.81-1.6	

Note: * - statistically significant difference (p<0.05).

2.8 SIR (Out-Of-Phase/In-Phase Imaging)

The mean SIR for malignant fractures was 0.91 ± 0.125 , whereas the SIR for benign fractures was 0.64 ± 0.096 (Fig. 3). Although there was some overlapping in the range, the values were statistically significant as shown in Table 6.

Table 6. SIR (out-of-phase/in-phase) in benign and malignant fractures.

Fracture	N	Mean	SD	Range	P-value
Malignant	18	0.91	0.125	0.78-1.3	<0.001*
Benign	22	0.64	0.096	0.44-0.82	

Note: * - statistically significant difference (p<0.05).

2.9 Optimal Cut-Off Value for SIR (Opposed-Phase/In-Phase)

In our study, if a cut-off value of 0.75 was chosen for the SIR with > 0.75 defined as malignant and < 0.75 defined as benign, the SIR predicted the correct nature of fracture with sensitivity - 100%, specificity - 90.9%, accuracy - 95% and area under a curve - 0.989 on the ROC curve as shown in Table 7.

3. Discussion

The differentiation between the benign and malignant causes of vertebral compression fracture is a common clinical problem. The plain radiography, bone isotope scanning, myelography and CT have many shortcomings in the diagnosis of benign and malignant compression fractures, and these have been well-documented [3, 4, 5, 6]. Radionuclide bone scanning is sensitive, but it lacks specificity. Myelography visualises cord compression, but it has associated risk of neurologic complications [7].

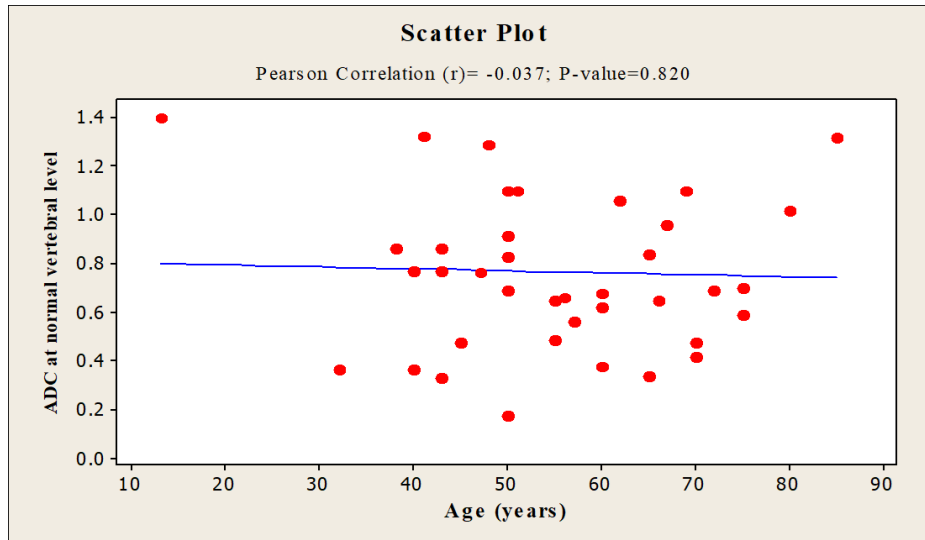


Figure 2. Scatter plot showing relationship of ADC at normal vertebral bodies with age.



Figure 3. In-phase (a) and opposed-phase (b) images in a patient with D4 vertebral compression showing no significant drop of signal on opposed-phase image. On follow up a diagnosis of metastatic compression was made. Patient was a case of lung carcinoma.

Table 7. Diagnostic accuracy at optimum cut-off values (in predicting malignant fracture).

Parameter	Optimal Cut-Off [#]	Sensitivity	Specificity	Accuracy	AUC
ADC at Fracture Site	≤0.93	88.9	95.5	92.5	0.943
SIR (Out-Of-Phase/In-Phase)	>0.75	100	90.9	95.0	0.989

Note: # – the cut-off recommended by ROC model.

Since early diagnosis and management of malignant fractures are important to prevent further neurological compromise, a reliable and non-invasive imaging modality is the need of hour. In our study, we took 40 patients, considered solitary vertebral compression fracture in each case and performed imaging to differentiate whether the fracture was benign or malignant. Age distribution and gender distribution were not statistically significant in our study. On the conventional imaging sequences, 17 (94.4%) out of 18 malignant fractures were hypointense on T1WI and 18 (81.8%) out of 22 benign fractures were hypointense on T1WI. Fifteen (83.3%) out of 18 malignant and 17 (77.3%) out of 22 benign fractures were hyperintense on T2WI. The T1WI and T2WI were statistically insignificant to differentiate benign and malignant fractures in our study in accordance with previous study [17]. All the patients showed hyperintense signal on STIR sequence in our study as expected for the acute compression fractures. We took certain characteristics like posterior element involvement, associated paraspinal soft tissue, epidural compression, gadolinium enhancement and evaluated their role in differentiating benign and malignant compression fractures. Posterior element involvement was seen in 77.8% of malignant fractures against 16.7% of benign fractures. Paraspinal soft tissue was associated in 50% of malignant fractures against 5.6% of benign fractures. Epidural compression was present in 100% of malignant fractures against 44.4% of benign fractures. Gadolinium enhancement was seen in 94.4% of malignant fractures, while in benign fractures, enhancement was seen in 44.4% of cases. There was a statistically significant difference among all the characteristics chosen to differentiate malignant and benign fractures in our study. This was in accordance with the previous studies [17, 18]. DW-MRI of the vertebral body has proved its value and has been successfully implemented for the differentiation of benign and malignant fracture oedema (due to tumour infiltration) [19]. DWI provides unique tissue characterisation that is complementary to that provided by conventional MRI and is sensitive to micro-structural changes. The reduced mobility of water in pathologic fractures is the re-

sult of tumour cell accumulation and subsequent reduction in the interstitial spaces that results in high signal intensity as compared to normal bone marrow. On the other hand, the increased mobility of water attributed to an increase in the interstitial space in relation to oedema or haemorrhage [20] in benign fractures [21, 22, 23] results in low signal intensity in benign osteoporotic and traumatic fractures. On this basis, DWI has been suggested to be useful particularly in the evaluation of vertebral lesions. Bauer *et al.* [24] found 100% accuracy in the diagnosis of malignant compression fractures using steady-state free precession (SSFP) DWI. They also showed that even though T1W spin-echo and T2W STIR scans detected all fractures, there was no discriminating power based on signal intensity or bone marrow contrast ratio. In our study, we found that 77.8% of malignant fractures showed high signal on DWI against 31.8% of benign fractures showing high signal on DWI. We also carried out quantitative DWI measuring ADC at the fracture site on ADC maps created at b-values of 50, 400, 800 and found that the mean ADC of malignant fractures ($0.81 \pm 0.19 \times 10^{-3} \text{mm}^2/\text{s}$) was lower than the mean ADC of benign fractures ($1.24 \pm 0.24 \times 10^{-3} \text{mm}^2/\text{s}$) with a p-value of < 0.001 which is statistically significant. Most of previous studies have shown that ADC in the benign fractures was considerably higher than ADC in malignant fractures [21, 25, 26, 27] which is also in accordance with our study. To our knowledge, there has been one study by Pozzi *et al.* [28] which conflicts with our study and the other previous studies. We assume that this discrepancy may be related to difference in location and size of ROI. ROI placement is of utmost importance particularly with low spatial resolution imaging techniques such as DWI. Using ROC analysis, we identified an ADC cut-off value of 0.93 between benign and malignant vertebral marrow lesions, which is higher than that reported by Wonglaksanapimon S *et al.* [29] and Tadros MY *et al.* [30]. In our study, an ADC cut-off value of 0.93 resulted in 88.9 % sensitivity, 95.5% specificity and 92.5% accuracy in the discrimination between benign and malignant vertebral marrow lesions. Though our cut-off was higher than

that in previous studies, our results were in concordance with previous studies [29, 31, 32]. We also tried to find out the relationship between ADC of normal vertebral bodies and age. Although a previous study by Lavdas I *et al.* [33] has shown that ADC of bone marrow change significantly with age and the ADC of bone marrow in women are significantly higher than those of men and correlate strongly with fat fraction, however we could not find out any significant correlation of ADC of vertebral bodies with age. We assume that it is because we carried out our study on patients in whom the vertebral bodies, other than the fractured vertebra, were only apparently normal. We recommend that future studies should be carried out on normal volunteers to draw any conclusion on relationship between ADC and age. We also calculated the SIR (opposed-phase/in-phase) on CSI and found that the mean SIR for malignant fractures was 0.91 ± 0.125 (range 0.78-1.3) and the mean SIR for benign fractures was 0.64 ± 0.096 (range 0.44-0.82) with a p-value of < 0.001 which is statistically significant. The ROC curve for discrimination between benign and malignant lesions using the SIR showed that the best cut-off criterion is the SIR of > 0.75 with AUC 0.989, this means that > 0.75 indicates malignant result, while < 0.75 was defined as benign result with a sensitivity of 100%, specificity of 90.9% and accuracy of 95%. A previous study [33] showed that there was a significant difference ($p < 0.001$, Student's t-test) in the mean SIR for benign lesions (mean, 0.58; SD, 0.02) as compared to malignant lesions (mean, 0.98; SD, 0.095); if the SIR of 0.80 was chosen as a cut-off, with > 0.8 defined as malignant and < 0.8 defined as a benign result, in-phase/opposed-phase imaging correctly identified 19 of 20 malignant lesions and 26 of 29 benign lesions (sensitivity, 0.95; specificity, 0.89). Our results were in concordance with previous studies [32, 34].

There were few limitations in our study. Firstly, pathological confirmation was not available in all the cases. However, we believed that the clinical and imaging follow-up criteria of our study would be sufficient to conclude the benignity and malignancy of the fractures. Secondly, the study popula-

tion was small. Although there was some overlap in ADC and the SIR of collapsed vertebrae in our study, studies with larger population could reveal more overlap. Thirdly, DWI was evaluated in combination with standard MRI, not alone. However, to draw ROI on the lesion that best represents the character of the compression fracture itself and to overcome the insufficient resolution of DWI, it must be examined with conventional MRI.

4. Conclusions

We conclude that MRI is a useful tool in differentiating benign and malignant spinal fractures. Signal intensity on conventional MRI alone may not be able to differentiate benign and malignant vertebral fractures. Certain MR characteristics like posterior element involvement, paraspinal soft tissue mass, epidural compression, gadolinium enhancement allow early differentiating between benign and malignant vertebral fractures.

Quantitative ADC mapping in addition to qualitative DWI represent a useful complementary tool in differentiating between acute benign fractures from malignant fractures. CS-MRI is a valuable addition to standard MRI techniques and represent a rapid problem-solving tool in differentiating benign from malignant vertebral compression fractures.

Based on the results of our study we recommend the routine use of DWI/ADC maps and the SIR on CSI in complicated cases in addition to the conventional MR sequences to differentiate acute benign and malignant vertebral compression fractures. Future studies in normal volunteers are needed to draw any conclusion between ADC of normal vertebral bodies and age.

Compliance with Ethical Standards

The study was conducted in accordance with the ethical standards of the Institutional Ethics Committee according to WMA declaration of Helsinki – ethical principles for medical research involving human subjects.

Informed Consent

Written informed consent was obtained from all patients before participating in the study.

Conflict of Interest

No conflict of interest is noted.

Financial Disclosure

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