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Original Article

Evaluation of DWI and ADC Sequences' Diagnostic Values in Benign and Malignant Pulmonary Lesions

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Abstract

OBJECTIVE: The gold standard for the diagnosis of lung cancer is conducting a histopathologic study. It is also diagnosed based on some features of a computed tomography (CT) scan. Imposed radiation is a prominent side effect of a CT scan. Diffusion-weighted imaging (DWI) apparent diffusion coefficient (ADC) images have currently been used in the diagnosis of different lesions, including those of the brain and breast, and their uses in lung lesions are being evaluated. In this study, to find a safe, sensitive, and specific method, we aimed to assess DWI imaging to replace the CT scan and the positron emission tomography scan.

MATERIAL AND METHODS: A total of 29 patients were enrolled in the study. In b800 images in DWI, spinal cord and lesion signals were measured, and the lesion-to-cord-signal ratio (LCR) was calculated. The ADC value was measured in a quantitative way. Lesions were also graded qualitatively in b800 DWI sequences.

RESULTS: There was a significant difference between malignant and benign lesions in terms of DWI grading in b800 images ($p<0.001$). There was a significant difference between ADC means of a malignant and benign lesion ($p=0.003$). The mean LCR for malignant lung lesions was significantly higher than that of the benign ones ($p<0.001$). Considering Grade 3 as the cutoff in DWI grading results in sensitivity, specificity, and accuracy of 89%, 90%, and 89.6%, respectively. For ADC values, sensitivity, specificity, and accuracy of 79%, 80%, and 79.3%, respectively, were obtained when the cutoff was 1.027×10^{-3} sec/mm^2. The sensitivity of 84%, the specificity of 90%, and the accuracy of 86.2% were calculated for the LCR in a cutoff of 0.983. In this study, all three parameters had an area under the curve of ≥0.8, meaning that these variables were valuable for the differentiation of benign and malignant lesions.

CONCLUSION: Diffusion-weighted magnetic resonance imaging is a noninvasive tool, with no contrast agent and requiring ionizing radiations, which could be used for the qualitative, quantitative, and semiquantitative assessment of pulmonary lesions.

KEYWORDS: Apparent diffusion coefficient (ADC), diffusion-weighted imaging (DWI) grading, lung lesion, lung-to-cord-signal ratio (LCR)

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INTRODUCTION

Lung cancer, a major disease burden, is the most common type of cancer (except for keratinocyte carcinoma) worldwide [1]. In 2006, in the United States alone, it caused 30% of deaths in the population diagnosed with cancer [2]. It is also considered to be the main cause of mortality among cancer-related deaths [1, 3]. Benign lesions, including 20% of the nodules with a diameter of 2 cm and above, cost many individuals unnecessary, invasive, and often expensive procedures, such as surgical resections [4, 5].

The diagnosis is based on the morphologic features of the lesion, including speculation, notching, calcification, and contrast agent enhancement [6].

The beneficial role of surgical biopsy in the diagnosis of lung lesions is undeniable. However, it has its own contraindications, such as in patients with poor cardiopulmonary function or interstitial lung diseases and limitations in patients with poor compliance [6]. Therefore, computed tomography (CT) is mainly used in the clinical staging of the lesions [6]. A CT scan, as shown in a study by Bastin et al. [7], seems to be a very sensitive diagnostic method, but it also generates overlapping between enhancement patterns of malignant and benign groups. It also has a poor diagnostic value when distinguishing the destruction of a normal pulmonary tissue with fibrosis [6].

Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET), another diagnostic modality, has been used for this purpose in recent years [8], but it is not flawless either. The main issue with an FDG PET and a CT scan is the

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high dose of radiation that these two methods emit on patients. In addition, FDG PET has other limitations, such as lack of sensitivity for the detection of adenocarcinoma and distinguishing malignancies from inflammation [9].

Signal loss caused by the Brownian motion of billions of water molecules within tissues is quantified by the evaluation of an apparent diffusion coefficient (ADC). Diffusion-weighted (DW) magnetic resonance imaging (MRI), which was first used in the brain [10, 11], has been used to distinguish tumors and normal tissues in many organs using ADCs [12, 13].

Low proton density, B0 inhomogeneity, and physiologic motion are the factors that seem to make the diagnosis based on the ADC inapplicable [6]; Takahara et al. [14] and Kwee et al. [15] reported different results.

In a study by Shen et al. [16], the ADC proved to be a reliable parameter in evaluating the subtypes of lung lesions. The lesion-to-cord-signal ratio (LCR), which is calculated by signals of the spinal cord and lesions, is also a method for the differentiation of different lung cancers [17, 18].

Comparing the LCR and ADC, there are some studies [17], which prove that there is no significant difference between these methods in terms of the diagnosis of different lung lesions. Nevertheless, in another study by Concatto et al. [18], the LCR was found to be significantly more practical than the ADC.

Diffusion-weighted imaging (DWI), which depicts the restriction degree of random thermal motion of water molecules within biologic tissues, also seems to be valuable and has acceptable accuracy in discriminating benign and malignant pulmonary tumors according to Shen et al. [19] and Broncano et al. [20].

Considering the controversy and data shortage on such modalities worldwide, lack of related studies in our country, and in order to provide a safer and more sensitive method to diagnose such lesions, our goal was to evaluate the diagnostic values of DWI and ADC in distinguishing benign and malignant lesions in the pulmonary system.

MATERIAL AND METHODS

A cross-sectional study was conducted at Qaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran between January and November 2017.

MAIN POINTS

- Diffusion-weighted magnetic resonance imaging (DWI) grading showed a significant difference between benign and malignant lesions and its accuracy was 89.6%.
- ADC values and LCR also showed an accuracy of 79.3% and 86.2%, respectively.
- Our results suggest that all three parameters are valuable for the differentiation of benign and malignant lesions.
- DWI grading could be a safe and non-invasive tool for assessment of lung lesions.

Table 1. DWI signal (b800) grading of the lung lesion

Grade	Description
1	Lung signal
2	The signal between lung and cord
3	cord signal
4	More than cord signal
5	Very more than cord signal

Patients

In all, 29 patients (20 males and 9 females) who were admitted to Qaem hospitals and met the inclusion criteria of the study were enrolled. Mean ages of male and female patients were 53 and 63 years, respectively. Inclusion criteria were finding a pulmonary nodule larger than 1 cm in the largest diameter in the high-resolution CT scan and performing or planning a pathologic study of lesion biopsy. Three patients who were not able to be taken into the MRI ward were excluded. A written informed consent was provided by all cases.

MRI Study

We used the Avanto magnetom Tim 32[8] 1.5-T magnetic resonance (MR) imager (Siemens, Erlangen, Germany) for all MR examinations by using a phased-array body coil. Patients were in the supine position. T1- and T2-weighted MR images were obtained from patients before obtaining DWI MR images. The following parameters were applied to obtain T1-weighted spin-echo images: repetition time/echo time 485/8.9 msec; flip angle 150°; field of view 488´488 mm; matrix 384´512; and section thickness 4.5 mm, with a 0.45-mm gap. In addition, T2-weighted, single-shot, fast spin–echo images were obtained using the following parameters: repetition time/echo time 3300/82 msec; matrix 320´256; and section thickness 5 mm, with a 1-mm gap. Both T1- and T2-weighted MR images were obtained in a transverse plane.

Using T1- and T2-weighted images as the basis, DWI MR images were obtained only on the lesions in the transverse plane. Patients were asked to breathe quietly, and DWI MR images were obtained with a motion-probing gradient of *b* values of 800, 400, and 0 sec/mm^2 in *x*, *y*, and *z* directions, respectively: section thickness 3.6 mm (gapless); field of view 260´260 mm; matrix 95´160; echo space 0.91 msec; and base resolution 160 Hz/pixel.

Radiologic Analysis

MRI images were interpreted by an expert radiologist who was blinded to the pathological reports in standard conditions in terms of light and image quality by Radiant software. In *b*800 images in DWI, signals of the spinal cord and lesions were measured, and the LCR was calculated. In heterogeneous lesions, the highest signal was used. Lesions were also graded qualitatively in *b*800 DWI sequences. Lesions with the same signals as the lung signal were labeled as Grade 1 and those with a signal higher than the cord signal were labeled as Grade 5. Grading signals are listed in Table 1.

Regions of interest (ROIs) were placed on lesion signal points at the center of the lesion, and their size was 50% of the

Table 2. Pathologic diagnosis, gender, and mean age in the malignant and benign groups

Group (N)	Mean age±SD (Y)	Gender (M/F)	Histopathology (N)	Mean lesion volumes
Malignant (19)	59.9±10.9	12/7	Squamous cell carcinoma (4), adenocarcinoma (8), small-cell lung carcinoma (3), Non–small-cell carcinoma (4)	72.5 mL
Benign (10)	48.8±16.5	8/2	Pneumonia (3), papillary adenoma (1), hamartoma (1), COP (1), reactive lymphadenitis (1), inflammatory granuloma (1), hydatid cyst (1), Wegener granulomatosis (1)	42.8 mL
Total (29)	60±13.8	20/9	-	-

COP: cryptogenic organizing pneumonia; SD: standard deviation

Table 3. Diagnostic capability of ADC, LCR, and DWI grading

Parameter	Cutoff value (%)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
ADC	1.027	79	80	67	88	79.3 (23/29)
LCR	0.983	84	90	75	94	86.2 (25/29)
DWI grading	Grade 3	89	90	82	94	89.6 (26/29)

ADC: apparent diffusion coefficient; DWI: diffusion-weighted imaging; LCR: lesion-to-cord ratio; NPV: negative predictive value; PPV: positive predictive value

lesion size. Necrosis or air around the lesions was not included. The ADC was calculated in the place where the lesion signal was measured in b800 DWI images using Radiant software. ROIs were placed symmetrically in DWI b800 and ADC images.

Ethical Approval

This study was approved by Medical Ethics Committee, Medical Faculty, Mashhad University of Medical Sciences. The approval code is IR.MUMS.FM.REC.1394.381.

Statistical Analysis

The Statistical Package for Social Sciences software, version 21.0 for Windows (IBM SPSS Corp.; Armonk, NY, USA), was used in the statistical analysis. To compare DWI grading, the ADC, and the LCR between lung cancer and benign lesions, an independent samples *t* test and a chi-square test were used. A receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic capabilities of DWI grading, ADC, and LCR in the differentiation of benign and malignant lesions. The cutoff value was calculated using R statistical software. The accuracy of the three parameters was obtained.

The ROC curve shows sensitivity versus specificity. Thus, the area under the curve (AUC) is a measure to evaluate the performance of the outcome with respect to any variable. However, the problem is determining which value of the variable can provide the best value of sensitivity and specificity. Here, we obtained the cutoff, which maximizes the sum of sensitivity and specificity, by using R statistical software.

A difference with a p value less than 0.05 is considered as a significant difference.

RESULTS

MRI procedures were done without any adverse effect. Pathologic diagnoses, gender, mean age, and mean lesion volume in the malignant and benign groups are shown in Table 2.

DWI Grading Analysis

It was possible to obtain DWI grading for all patients. There was a significant difference between malignant and benign lesions using DWI grading in *b*800 images. ($p<0.001$).

ADC Analysis

We obtained ADCs for all patients. Mean ADC±SD was $0.864\pm0.232\acute{}10^{-3}$ mm^2/sec for malignant lung lesions and $1.212\pm0.243\acute{}10^{-3}$ mm^2/sec for benign lesions. There was a significant difference in the ADC mean between a malignant and benign lesion ($p=0.003$).

LCR Analysis

LCRs for all cases were obtained. The mean LCR was 1.204±0.313 for malignant lung lesions and 0.632±0.325 for benign ones. The LCR in the cancerous lesions of the lung was significantly higher than that of the benign ones ($p<0.001$).

DW *b*800 and ADC images of benign and malignant lesions are shown in Figures 1 and 2, respectively.

ROC Curve Analysis

ROC curves for the ADC and LCR are shown in Figure 3 (left), and ROC curves for DWI grading are shown in Figure 3 (right). AUCs for the LCR (AUC=0.873 and 95% confidence interval [0.717-1.000]), DWI grading (AUC=0.0.900 and 95% confidence interval [0.770-1.000]), and the ADC (AUC=0.800 and 95% confidence interval [0.613-0.987]) were measured. The diagnostic capability results of ADC, LCR, and DWI grading are

Table 4. Comparing the parameters in our study and similar ones

Studies	Parameters	Cutoff value (%)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
Our results	ADC	1.027	79	80	67	88	79.3 (23/29)
	LCR	0.983	84	90	75	94	86.2 (25/29)
Uto et al. (6)	ADC	0.913	38.9	80	25	60	50 (14/28)
	LCR	0.953	88.9	80	80	88.9	85.7 (24/28)
Cakmak et al. (17)	ADC	1.78	86	95	76	97	89
	LCR	0.86	69	85	-	-	74

ADC: apparent diffusion coefficient; DWI: diffusion-weighted imaging; LCR: lesion-to-cord ratio; NPV: negative predictive value; PPV: positive predictive value

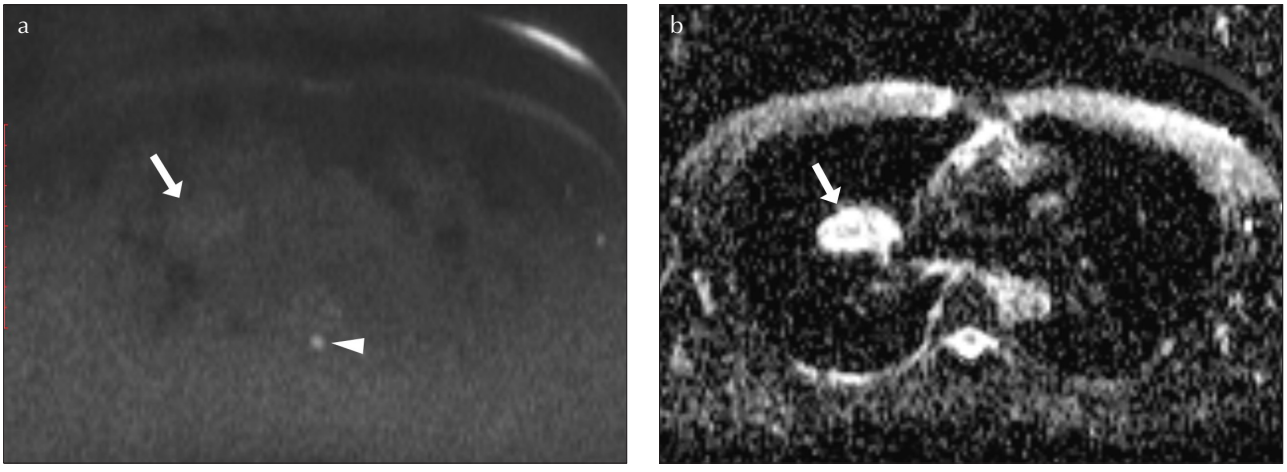

Figure 1. a, b. Benign lesion. A papillary adenoma in the histopathologic examination. a: DWI b800. The DWI grading is 2. The lesion (arrow) signal to spinal cord (arrow head) signal ratio was obtained as 0.365. b: ADC. The signal for this lesion (arrow) was obtained as 1.511×10^{-3} mm^2/s

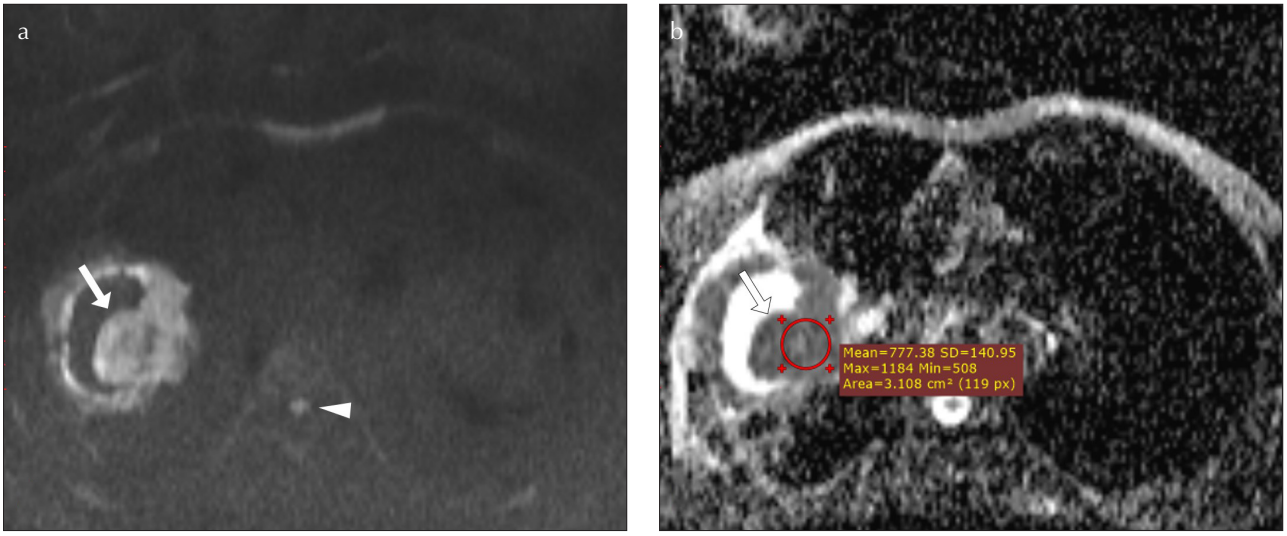

Figure 2. a, b. Malignant lesion. A squamous cell carcinoma in the histopathologic examination. a: DWI b800. The DWI grading is 4. The lesion (arrow) signal to spinal cord (arrow head) signal ratio was obtained as 1.222. b: ADC. The signal for this lesion (arrow) was obtained as 0.777×10^{-3} mm^2/s

shown in Table 3. Using a cutoff value of $1.027\acute{}10^{-3}$ sec/mm^2, the ADC showed a positive predictive value of 88%, a negative predictive value of 67%, and an accuracy of 79.3% in the detection of cancer lesions. However, by using a cutoff value of 0.983, the LCR had a positive predictive value of 94%, a negative predictive value of 75%, and an accuracy of 86.2% for the detection of lung malignancies.

By using grade 3 for the cutoff value of DWI grading, there was a positive predictive value of 94%, a negative predictive value of 82%, and an accuracy of 89.6% for the detection of lung cancers.

In this study, all three parameters have an AUC ≥0.8, which means these variables have a good value for the differentiation of benign and malignant lesions.

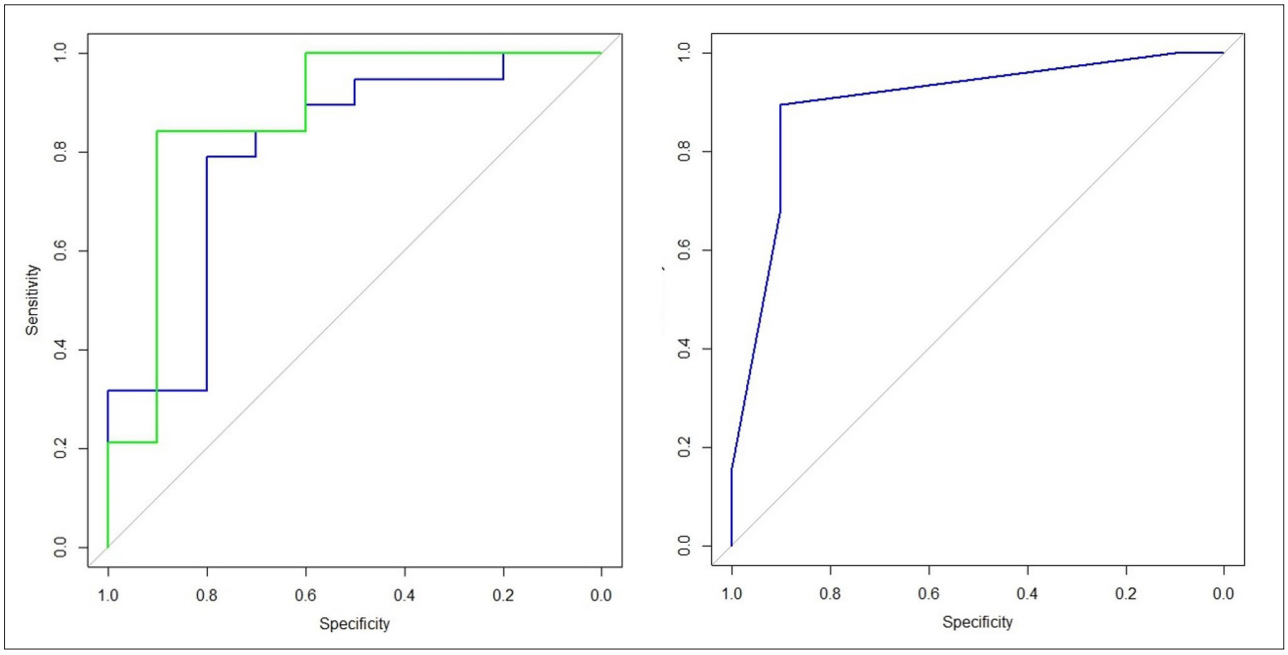

Figure 3. Left: ROC curve for the LCR (green line) and the ADC (blue line). Right: ROC curve for DWI grading

For the LCR, there was one false-positive case of Wegener granulomatosis (LCR=1.447), two false-negative cases of adenocarcinoma (LCR=0.702 and 0.675, respectively), and one false-negative case of non–small-cell carcinoma (LCR=0.712).

For the ADC, there were two false-positive cases of Wegener granulomatosis and hydatid cyst (ADC=0.761 and 0.760, respectively), four false-negative cases, including one case of adenocarcinoma (ADC=1.213), one false-negative case of non–small-cell carcinoma (ADC=1.130), and two cases of small-cell carcinoma (ADC=1.167 and 1.334, respectively).

DISCUSSION

In this discussion, we aimed to investigate the diagnostic values of DWI and ADC in the differentiation of the benign and malignant lesions in the pulmonary system. We also assessed the lesion-to-spinal cord signal intensity ratio (LCR) for all 29 lesions. The ratio is also abbreviated as LSR in some literature [6, 17].

DWI grading as a qualitative, ADC as a quantitative, and LCR as a semiquantitative evaluation showed reasonable accuracies in differentiating the lesions.

There were significant differences between benign and malignant lesions in values of ADC, LCR, and DWI grading. Cutoff values for the ADC and LCR were 1.027 and 0.982, respectively. The grade of DWI modality was 3 with an accuracy of 89.6%. Furthermore, the accuracies of the ADC and LCR were 79.3% and 86.2%, respectively.

DWI is an important diagnostic tool to distinguish benign and malignant lesions in multiple organs [8], but it seems that there is a lack of studies about thoracic and intrathoracic lesions, and only a few investigations discussed this issue [6, 21, 22].

In our study, there was a significant difference in the mean ADC values between a lung cancer and benign lesion (p=0.003). In another study, Gümüştaş et al [8] found different results. They observed that differences between benign and malignant groups were not considerable (p<0.675) regardless of the fact that the ADC of the malignant lesions was lower than that of the benign group. However, the findings regarding *b*1000 DWI images were similar in both investigations, showing that there was a significant difference in the signals of malignant and benign lesions in this modality.

According to our study, the LCR of lung cancer was significantly higher than that of benign lesions (p<0.001). In a study by Uto et al. [6] they also found that the LCR differences between malignant and benign lesions were significant with a p value <0.00. We also found a considerable LCR difference between malignant and benign lesions, which was surprisingly higher compared with the difference in relation to the ADC.

Cakmak et al. [17] conducted a study, which demonstrates that the LCR and ADC have good predictor values in the diagnosis of malignant and benign pulmonary lesions with the accuracy of 74% and 89%, respectively. In our investigation, both the LCR and ADC are acceptable predictors, but the LCR is more favorable due to its better discriminative specificities between lesions.

Different *b* values could be the reason of the difference between our result and these studies [6, 17]. Table 4 compares the parameters between recent similar studies and this study.

Using a qualitative grading of DWI in *b*1000 images, Shiro et al. [23] found a significant difference (p<0.01) between malignant and benign pulmonary lesions. With the same DWI grading and cutoff value as in our study, our accuracy was 89.6%, 10% higher than that in Shiro et al's [23] study.

Although according to some studies [7, 24], the risk of the artifacts and distortion will rise significantly with higher *b* val-

ues, we found a significant difference between malignant and benign lesions by using DWI grading in *b*800 images ($p<0.001$). It is also noteworthy that DWI cannot assess the lesion's contour characteristics in comparison with CT images, which seems to be its downside. However, these characteristics cannot be trusted in the discrimination of benign and malignant lesions; hence, it does not seem to be important after all [8].

In the study by Matoba et al. [21], the ADCs of hypocellular well-differentiated adenocarcinoma were higher than those in other types of lung malignancies. Due to the perfusion effect, ADCs may not be the reflection of diffusion phenomena at low *b* values of less than 600 sec/mm^2 (68.46 and 577.05 sec/mm^2 in the study by Matoba et al. [21]).

As shown in many studies [6, 25-27], the role of FDG PET in the diagnosis of different tumors and cancers, including lung cancer, is inevitable. The problem is the primary dependency of FDG PET on metabolic characteristics of the specific tissue. So, the new LCR method described earlier, which lacks this flaw, could be a useful tool in assessing benign and malignant lung lesions. It has also been proposed that the LCR is more accurate than mean ADC values [28].

Nevertheless, because of the effect of the T2 value of the lesions on signal intensity on DWI [29-31], using the LCR creates a concern about the effects of both the diffusion capacity and T2 value of the lesions.

Using the LCR, our misdiagnosed cases were one false-positive case of Wegener granulomatosis (LCR=1.447), two false-negative cases of adenocarcinoma (LCR=0.702 and 0.675), and one false-negative case of non–small-cell carcinoma (LCR=0.712).

There were also six misdiagnosed cases within patients who were assessed by ADC mapping, including two false-positive cases of Wegener granulomatosis and hydatid cyst (ADC=0.761 and 0.760, respectively) and four false-negative cases, which comprised one case of adenocarcinoma (ADC=1.213), one false-negative case of non-small-cell carcinoma (ADC=1.130), and two cases of small-cell carcinoma (ADC=1.167 and 1.334).

We consider the hemorrhage in lesions as a probable cause of false-positive results for Wegener granulomatosis lesions in the LCR analysis. In addition, cellularity is a suspicious role player in false-negative results of adenocarcinoma reported using the LCR. The ADC analysis reported the hydatid cyst as a malignant lesion because of the presence of air in the cyst, which we believe is responsible for this result.

Our study has several limitations. The small number of patient groups is the first one. In addition, in a tertiary center, where we conducted the study, most of the admitted patients have malignant diagnoses. Cultural properties of the region, including smoking, could affect the severity and histopathology of the lesions. In our study, a blinded radiologist assessed all the images, so interobserver variations could have been missed. The most important limitation to the use of ADC values is that the monoexponential calculation is heavily influenced by the *b* value.

In conclusion, DWI MRI could be noninvasive, with no contrast agent and an ionizing radiation tool for the qualitative, quantitative, and semiquantitative assessment of pulmonary lesions. DWI should be evaluated in multicenter studies with more patients and extensive reviews. In addition, using different imaging settings and details may lead to more reliable results.

Ethics Committee Approval: Ethics Committee approval for the study was obtained from the Medical Ethics Committee, Medical Faculty, Mashhad University of Medical Sciences (IR.MUMS.FM.REC.1394.381).

Informed Consent: Written informed consent was obtained from all patients who were enrolled in this study.

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