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MAGNETIC RESONANCE

Magnetic resonance imaging of pulmonary nodules: accuracy in a granulomatous disease–endemic region

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Abstract
Objective To estimate the diagnostic accuracy of signal intensity of the lesion-to-spinal cord ratio (LSR) and apparent diffusion coefficient (ADC) in diffusion-weighted (DW) magnetic resonance imaging of pulmonary nodules suspicious for lung cancer in granulomatous lung disease-endemic regions.
Methods Forty-nine patients with indeterminate solitary pulmonary nodules detected by chest computed tomography and histopathologically confirmed diagnoses were included in the study. DW images were analysed semiquantitatively by focusing regions of interest on the lesion and spinal cord at the same level (for LSR calculation). ADCs were estimated from ratios of the two image signal intensities. Ratios of T1 and T2 signal intensity between nodules and muscle were calculated for comparison.
Results Mean ADCs±standard deviations for lung cancer and benign lesions were 0.9±0.2 and 1.3±0.2×10^{-3} mm^2/s, respectively. Mean LSRs were 1.4±0.3 for lung cancer and 1 ±0.1 for benign lesions. ADCs and LSRs differed significantly between malignant and benign lesions (P<0.001). Mean T2 signal intensity ratios also differed significantly between benign and malignant lesions (0.8±0.2 vs. 1.6±0.2; P<0.05).
Conclusions DWI can help to differentiate malignant from benign lesions according to ADC and the LSR with good accuracy.
Key Points
- *DW imaging can help differentiate malignant from benign pulmonary nodules.*
- *ADC and LSR signal intensities had only small overlap between malignant and benign pulmonary nodules.*
- *Mean T2 signal intensity ratios differed significantly between benign and malignant lesions.*

Keywords Magnetic resonance imaging · Pulmonary nodules · Granulomatous disease-endemic region · Diffusion weighted · Differentiation of malignant from benign lesions

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Introduction

Since the introduction of magnetic resonance imaging (MRI) in clinical practice, MRI of the chest has had restricted indications because of limited signal caused by low proton density, susceptibility artefacts, and physiological motion (cardiac pulsation, respiration). However, MRI has evolved considerably because of the development of new equipment and more rapid techniques of image acquisition, as well as the introduction of new contrast agents. All of these advances have allowed MRI to gain ground in the study of various pathologies of the chest. MRI is now considered to be the modality of

choice for the evaluation of lesions in the mediastinum and chest wall, as well as of Pancoast tumours [1]. Currently, one of the most relevant clinical applications of MRI of the lung is in lung cancer staging. MRI can also be used for the assessment of pulmonary vascular disease and for the investigation of pulmonary abnormalities in patients who should not be exposed to radiation [2].

At present, computed tomography (CT) is considered to be the best imaging technique for pulmonary nodule detection [3]. However, CT nodule features such as shape, edge characteristics, cavitation, and location have not been found to distinguish accurately benign from malignant nodules [4]. Positron emission tomography (PET) has demonstrated usefulness in this task; several benign conditions have also been noted to have increased metabolic activity including infections, granulomatous disease, and tuberculosis [5]. Use of MRI in the evaluation of pulmonary nodules has thus far been limited [3]. Conventional MRI has been proposed for the evaluation of pulmonary nodules according to their relaxation times, with significant overlap between benign and malignant tumours. More recently, dynamic enhanced MRI has shown better specificity and accuracy than CT and PET-CT in the differentiation between benign and malignant nodules [5–8].

Recently, some papers have demonstrated the use of diffusion-weighted imaging (DWI) in the characterization of pulmonary lesions. The degree of restriction to water diffusion in biologic tissue is inversely correlated to the tissue cellularity and the integrity of cell membranes [5–8]. The motion of water molecules is more restricted in tissues with a high cellular density associated with numerous intact cell membranes [5–8]. DWI of pulmonary nodules has produced good results in terms of differentiation between benign and malignant nodules [5]. However, studies demonstrating the utility of this method in granulomatous disease-endemic regions are not available. Thus, the aim of this study was to estimate the diagnostic accuracy of signal intensity of the lesion-to-spinal cord ratio (LSR) and apparent diffusion coefficient (ADC) in DWI of pulmonary nodules suspicious for lung cancer in regions with endemic granulomatous lung disease.

Materials and methods

Patients

This study received institutional review board approval, and all patients provided written informed consent. Patients with pulmonary nodules detected by chest CT between October 2010 and February 2015 from a single centre from an endemic region of granulomatous disease were included. The inclusion criteria were: indeterminate solitary pulmonary nodule visible on CT, solid nodule, nodule diameter>8 mm, and histopathology confirmation obtained or planned by surgical resection or transbronchial or transthoracic biopsy. All patients with inconclusive biopsy results were followed for 2 years. Lesions were considered to be benign (a) with histopathologic confirmation, (b) when the lesion subsequently disappeared or decreased in size, or (c) when the lesion appeared stable on follow-up (≥24 months) CT. Identification of organisms in culture was also considered to be a benign finding.

MRI

MRI was performed using a 1.5-T scanner (Magnetom AERA; Siemens, Erlangen, Germany). For signal reception, a dedicated 8-element integrated matrix coil system that covered the whole thorax was used. This system consisted of one anterior and one posterior flexible phased-array coil, each containing a set of six receiver elements. A half-Fourier single-shot turbo spin-echo sequence was used, and the field of view (FOV) was patient adapted. The sequence was performed using respiratory gating, with a navigator signal that monitored the diaphragm position. The following sequence parameters were used: repetition time (TR)/echo time (TE)/flip angle, infinite/92 ms/150°; parallel acquisition factor, 2; slice thickness, 5 mm; distance factor, 20 %; transversal (matrix, 380×256) and coronal (matrix, 400×320) orientations; and acquisition time, approximately 90 s. A volumetric interpolated breath-hold examination (VIBE) sequence was chosen for fast T1-weighted MRI. Imaging parameters for the VIBE sequence were: TR/TE, 5.12/2.51 ms; flip angle, 10°; partition thickness, 5 mm with no interslice gap; and matrix size, 256×116 with a three-dimensional breath-hold imaging technique. A T2-weighted fat-saturated BLADE (proprietary name for periodically rotated overlapping parallel lines with enhanced reconstruction in MR systems from Siemens Healthcare) sequence was also used, with the following imaging parameters: TR/TE, 4670/113 ms; and partition thickness, 5 mm with no interslice gap. DWI was performed using a single-shot echo-planar technique with a slice thickness of 5 mm under spectral attenuated inversion recovery, with respiratory-triggered scanning. The DWI parameters were: TR/TE/flip angle, 3000–4500 ms/65 ms/90°; diffusion gradient encoding in three orthogonal directions; b=0 and 800 s/mm^2; field of view, 350 mm; and matrix size, 128×128. The overall time spent in the MRI room was approximately 15 min. No patient required sedation. Contrast medium was not used.

Image analysis

Mean signal intensity on DWI was analysed semiquantitatively by focusing the region of interest (ROI) on the lesion with two gradient factors (b_h and b_l), as well as on the spinal cord at the same level. When a lesion seemed to be heterogeneous, the ROI was placed at the location of highest signal intensity. Two

radiologists with 24 and 12 years of experience, respectively, in chest MRI defined DWI section locations.

The ADC was estimated from the ratio of the two image signal intensities, according to the following equation: $ADC = -[\ln (SI_h/SI_l)]/(b_h - b_l)$, where SI_h and SI_l are the signal intensities in the lesion of interest obtained with two mean pressure gradients (b_h and b_l, respectively). In this study, b_h was 800 s/mm^2 and b_l was 0 s/mm^2.

The LSR of signal intensity was measured on the same DW image with a diffusion gradient of b_h=800 s/mm^2. An ROI of the same size as that placed on the spinal cord was positioned on the lesion. The ROIs placed on the thoracic spinal cord were 50–80 mm^2, which was equivalent to 14–22 pixels. We used DW images with averaged multiple signal intensities obtained during quiet breathing, instead of performing no averaging of signal intensity obtained during breath holding. Accordingly, the signal-to-noise ratio was reasonably good and the LSRs obtained were reproducible.

Signal intensity on T1 and T2 images was measured in an ROI of 30–40 mm^2 in the inner space of the nodule. The same ROI was used to measured T1 and T2 signal intensity in the longissimus dorsi muscle. The nodule:muscle ratios of T1 and T2 signal intensity were calculated for comparison.

No problematic motion artefact that resulted in poor image quality or instance of image distortion due to susceptibility occurred in this series.

Statistical analysis

Statistical analysis was performed with SPSS software (version 15.0 for Windows; SPSS Inc., Chicago, IL, USA). To compare ADCs and LSRs between lung cancer and benign lesions, the Mann–Whitney *U* test was used. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic capabilities of ADC and LSR in the differentiation of benign lesions and lung cancer. Cut-off values were calculated using the JMP IN statistical programme (version 5.1.1 for Windows; SAS Institute, Cary, NC, USA). The accuracy of the two parameters was compared statistically using the McNemar test. *P* values <0.05 were considered to be significant in all analyses.

Results

Forty-nine patients (20 men; mean age 65.4±14.2 years) with solitary pulmonary nodules were included in the study. The mean nodule size was 1.2 cm (range, 0.8–2.9). Pathologic confirmation was obtained by surgical resection in 30 patients and by transbronchial or transthoracic biopsy in 19 patients. Biopsy demonstrated the inconclusive presence of inflammatory tissue in 10 patients, who were followed for 24 months. Lesion regression was demonstrated in seven of these patients (Fig. 1). The sample comprised 31 cases of lung cancer (adenocarcinoma, *n*=21; squamous cell carcinoma, *n*=9; small cell carcinoma, *n*=1) and 18 benign lesions (inconclusive inflammatory lesions, *n*=7; fungal infection, *n*=7; tuberculous mycobacterial infection, *n*=3; cryptogenic organizing pneumonia, *n*=1).

ADCs

ADCs were obtained for all patients. The calculated mean ADCs±standard deviations for lung cancer and benign lesions were 0.9±0.2 and 1.3±0.2×10^{-3} mm^2/s, respectively (P< 0.001).

LSRs

LSRs were obtained for all patients. The mean LSRs for lung cancer and benign lesions were 1.4±0.3 and 1±0.1, respectively (P<0.001).

T1 and T2 ratios

The overall mean T2 signal intensity ratio was 1.1±0.4. This ratio differed significantly between benign and malignant lesions (0.8±0.2 vs. 1.6±0.2; P<0.05). The T1 signal intensity ratio did not differ according to lesion type (overall, 0.9±0.2; malignant, 1±0.2; benign, 0.9±0.2).

ROC findings

ROC curves for ADCs, LSRs, and T2 signal are shown in Fig. 2. The area under the ROC curve was 0.9 (95 % confidence interval, 0.8–1) for LSR and 0.9 (95 % confidence interval, 0.8–1) for ADC; this difference was not significant. Table 1 shows results for the diagnostic capability of ADC and LSR. With a cut-off value of 1.08×10^{-3} mm^2/s, the ADC had a positive predictive value of 88.2 %, a negative predictive value of 90.6 %, and an accuracy of 89.8 % in the detection of lung cancer. With a cut-off value of 1.20×10^{-3} mm^2/s, the LSR had a positive predictive value of 94.1 %, a negative predictive value of 93.8 %, and an accuracy of 93.9 % for the detection of lung cancer.

Discussion

Many recent studies have explored the role of DWI in the differentiation of benign from malignant pulmonary nodules or masses, but some inconclusive or conflicting results have been published. Liu et al [6] suggested that ADC values could aid the differentiation of lung cancer from benign lesions, but Uto et al [7] reported no significant difference in ADC values for lung cancer and benign lesions in 28 patients with pulmonary nodules. They found that the LSR was more effective

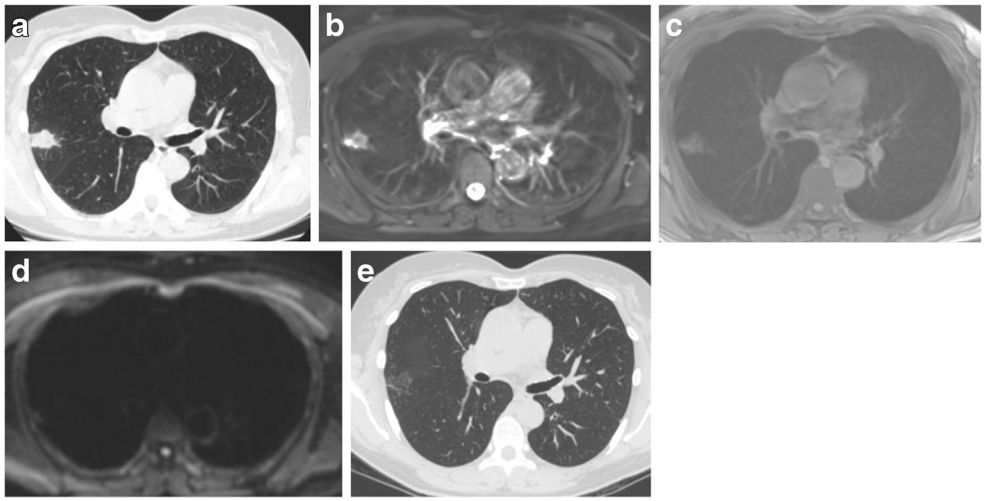

Fig. 1 Images from a 59-year-old asymptomatic male smoker. **a** CT demonstrated the presence of a spiculated solid pulmonary nodule with a diameter of 2.4 cm in the right upper lobe. **b** A T2-weighted sequence showed hypointense signal in the nodule. **c** A T1-weighted sequence showed hyperintense signal in the nodule. **d** A diffusion-weighted sequence showed no restriction. CT-guided biopsy evidenced a nonspecific inflammatory process and follow-up CT (**e**) indicated reduction of lesion size. (ADC: 1.56x 10^{-3} mm^2/s; LSR: 0.85; T1 index 0.87; T2 index 0.67)

than the ADC for differentiation. Based on qualitative evaluation, Kanauchi et al [8] suggested that the LSR was useful for the prediction of tumour invasiveness in clinical stage IA non-small cell lung cancer. Considering these reports and our results, the ADC and LSR appear to be useful for the differentiation of lung lesions.

Lung MRI is limited by several shortcomings, including low signal-to-noise ratios due to low proton density in inflated lungs, artefacts related to prominent differences in the magnetic susceptibility of air and soft tissue, and motion artefacts and loss of signal related to cardiac pulsation and respiratory motion [7, 9]. However, advances in MRI technology have addressed these issues. In addition to technologic improvements in MRI systems, dynamic administration of gadolinium contrast medium further improves image quality and yields functional information about pulmonary nodules [9]. Recent developments of echo planar imaging, high-gradient amplitudes, multichannel coils, and parallel imaging have reduced image distortion and increased the signal-to-noise ratio, rendering body DWI a potential and more feasible approach for pulmonary imaging [10]. The principle of DWI exploits the random motion, or Brownian movement, of water protons in biologic tissue. This motion causes phase dispersion of the spins, resulting in signal loss in images of diffusion-sensitive sequences and in spin echo-based, echo planar-imaging sequences [11]. DWI can help to differentiate malignant from benign lesions on the basis of tissue cellularity according to two criteria: the ADC and LSR [9].

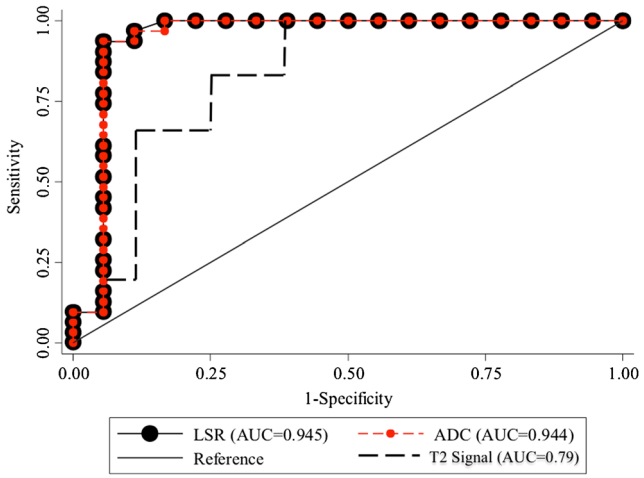

Fig. 2 Results of receiver operating characteristic analysis for the ADC, LSR, and T2 signal. ADC, apparent diffusion coefficient; LSR, lesion-to-spinal cord ratio; AUC, area under the curve

Signal loss can be quantified by calculating the ADC, which depends largely on the presence of barriers to diffusion (cell membranes and macromolecules) within the water microenvironment [11]. Compared with normal tissue, malignant tumours have increased cellularity, larger nuclei with more abundant macromolecular proteins, larger nuclear cytoplasmic ratios, and less extracellular space. Thus, diffusion of water molecules in malignant tumours is restricted compared with that in normal tissue, resulting in a decreased ADC value [12]. It remains uncertain, however, whether the ADC can reliably differentiate malignant disease from other lung abnormalities, as in other organs, because of low proton density, B_0 heterogeneity, and physiologic motion [7].

The LSR of signal intensity on high b-value DWI may be more useful for differentiating between benign and malignant lung nodules [7]. Use of the LSR for qualitative evaluation is advantageous because it is simple. However, the reproducibility of the LSR may be limited, as it relies on subjective

Table 1 Diagnostic Capability of T2, ADC, and LSR*

Parameter	Cut-off Value	Sensitivity	Specificity	PPV	NPV	Accuracy
T2	1.3	78.9 %	69.7 %	78.2 %	80.6 %	79.5 %
ADC	1.0	83.3 %	93.5 %	88.2 %	90.6 %	89.8 %
LSR	1.2	88.8 %	96.7 %	94.1 %	93.7 %	93.9 %

PPV, positive predictive value; NPV, negative predictive value; ADC is measured as $x10^{-3}$ mm^2/s

*ADC vs. LSR (P=.688); T2 vs. ADC or LSR (P<0.005)

evaluation [8]. The LSR of cancer nodules is significantly higher than that of benign lesions [7].

PET combined with fludeoxyglucose F-18 (FDG) is recommended for the non-invasive diagnosis of pulmonary nodules suspicious for lung cancer [13]. However, the use of FDG-PET/CT is less specific in diagnosing malignancy in populations with endemic infectious lung disease compared with those from non-endemic regions [13]. Lung nodules that are fungal in origin may be metabolically active and appear similar to malignancy on FDG-PET/CT. A regional endemic prevalence of fungal disease confounds the diagnosis of infection or cancer in asymptomatic individuals with pulmonary lesions [14]. In contrast, these lesions may show low DWI signal intensity when they are hypocellular, which reduces the number of false-positive findings. Other reasons to select DWI instead of FDG-PET/CT are the lack of need for specialized devices, lower cost, and avoidance of exposure to ionizing radiation [7].

Our data demonstrate that DW sequences enable the accurate differentiation of lung lesions in granulomatous disease-endemic regions. The LSR showed reasonably good sensitivity, specificity, and accuracy for the detection of lung cancer, and is thus useful for the differentiation of pulmonary nodules. The diagnostic capability of the ADC did not differ significantly from that of the LSR, but LSR calculation is more useful and practical than ADC calculation in routine clinical practice.

Malignant lesions show high signal intensity on DWI due to their increased cellularity, high degree of tissue disorganization, and increased extracellular space tortuosity compared with benign lesions. Generally, DWI (and thus LSR methods) is influenced by diffusion restriction and T2 elongation. The signal from the spinal cord, which effectively acts as an intrinsic calibrating factor, can be used as a qualitative surrogate for the assessment of the b-value signal-to-noise ratio. The combined effects of diffusion restriction and T2 elongation play an important role in differentiating benign and malignant lesions [11]. Lung cancer is characterized by elongated T2 values, which makes malignant tumours more conspicuous on DWI. T2 elongation alone, however, is not a main factor improving the ability to differentiate between malignant and benign lesions [7]. In addition, our data demonstrate that malignant lesions have larger T2 signal ratios than do benign lesions.

Our study has some limitations. First, we included only indeterminate nodules with diameters>8 mm and pathology confirmation; the inclusion of all nodules encountered in clinical practice may have yielded different results. However, small nodules are more frequently benign, and follow-up of patients with pulmonary nodules is a standard recommendation of the Fleischner Society [15]. In this context, additional examination is not necessary. Second, although the LSR has been established as the better DWI method for the diagnosis of pulmonary lesions, these results cannot be extrapolated to areas in which granulomatous diseases are not endemic. Also, the spatial resolution in our study was not constant since the field of view (FOV) was patient adapted keeping the imaging matrix constant.

In conclusion, DWI can help to differentiate malignant from benign lesions on the basis of tissue cellularity according to the ADC and the LSR, with an accuracy of at least 93.9 %. In addition, the T2 signal intensity ratio differed significantly between benign and malignant lesions, with malignant lesions having larger T2 signal ratios than to benign lesions.

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One of the authors has significant statistical expertise. Institutional Review Board approval was obtained. Written informed consent was obtained from all subjects (patients) in this study. Methodology: cross sectional study, performed at one institution.

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