RESEARCH ARTICLE

Diagnostic Performance of Diffusion Weighted Imaging of Malignant and Benign Pulmonary Nodules and Masses: Comparison with Positron Emission Tomography

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Abstract

Background: Diffusion-weighted imaging (DWI) makes it possible to detect malignant tumors based on the diffusion of water molecules. However, it is uncertain whether DWI has advantages over FDG-PET for distinguishing malignant from benign pulmonary nodules and masses. Materials and Methods: One hundred-forty-three lung cancers, 17 metastatic lung tumors, and 29 benign pulmonary nodules and masses were assessed in this study. DWI and FDG-PET were performed. Results: The apparent diffusion coefficient (ADC) value ($1.27\pm0.35\times10^{-3}$ mm^2/sec) of malignant pulmonary nodules and masses was significantly lower than that ($1.66\pm0.58\times10^{-3}$ mm^2/sec) of benign pulmonary nodules and masses. The maximum standardized uptake value (SUVmax: 7.47±6.10) of malignant pulmonary nodules and masses were also significantly higher than that (3.89±4.04) of benign nodules and masses. By using optimal cutoff values for ADC (1.44×10^{-3} mm^2/sec) and for SUVmax (3.43), which were determined with receiver operating characteristics curves (ROC curves), the sensitivity (80.0%) of DWI was significantly higher than that (70.0%) of FDG-PET. The specificity (65.5%) of DWI was equal to that (65.5%) of FDG-PET. The accuracy (77.8%) of DWI was not significantly higher than that (69.3%) of FDG-PET for pulmonary nodules and masses. As the percentage of bronchioloalveolar carcinoma (BAC) component in adenocarcinoma increased, the sensitivity of FDG-PET decreased. DWI could not help in the diagnosis of mucinous adenocarcinomas as malignant, and FDG-PET could help in the correct diagnosis of 5 out of 6 mucinous adenocarcinomas as malignant. Conclusions: DWI has higher potential than PET in assessing pulmonary nodules and masses. Both diagnostic approaches have their specific strengths and weaknesses which are determined by the underlying pathology of pulmonary nodules and masses.

Keywords: Diffusion weighted imaging - positron emission tomography - lung cancer - pulmonary nodules and masses

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Introduction

Positron emission tomography with 18-fluoro-2-deoxy-glucose (FDG-PET) is widely accepted as an imaging modality of choice in tumor staging. Diffusion-weighted magnetic resonance imaging (DWI) has been used to detect the restricted diffusion of water molecules. The principals of DWI exploit the random motion, or so-called Brownian movement, of water molecules in biologic tissue (Le Bihan et al., 1988). The primary application of DWI has been in brain imaging, mainly for the evaluation of acute ischemic stroke, intracranial tumors and demyelinating diseases (Tien et al., 1994; Sorensen et al., 1996). Diffusion of water molecules in malignant tumors is usually restricted compared to that in normal tissue, resulting in a decreased apparent diffusion coefficient (ADC) value (Szafer et al., 1995; Takahara et al., 2004). Some recent studies comparing DWI with FDG-PET have shown that DWI at 1.5 T is comparable with FDG-PET for detecting malignant lesions (Komori et al., 2007; Nomori et al., 2008; Mori et al., 2008), and an meta-analysis has shown that DWI can be used to differentiate malignant from benign pulmonary lesions (Wu et al., 2013). It is uncertain whether DWI has advantages over FDG-PET for distinguishing malignant from benign pulmonary nodules and masses.

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The purpose of this study was to compare the diagnostic performance of DWI and FDG-PET in distinguishing malignant from benign pulmonary nodules and masses, and to clarify the advantages and disadvantages of DWI and FDG-PET.

Materials and Methods

Eligibility

The study protocol for examining DWI and FDG-PET in patients with pulmonary nodules and masses was approved by the ethical committee of Kanazawa Medical University (the approval number: No.189). Five patients who had metal or pacemakers in their body or tattoos on their skin were excluded because of contraindication in MRI examinations. Informed consent was obtained from all patients after discussing the risks and benefits of the examinations with their surgeons. A potential benefit of MRI in this study was considered to be a preoperatively accurate diagnosis to avoid an unnecessary operation in the future.

Patients

The clinical study started in May 2009. Patients included in the study had pulmonary nodules and masses with a maximum size of 10cm or less, and which had no definitive calcification. Patients with pulmonary nodules and masses prospectively underwent FDG-PET and DWI. Most of pulmonary nodules and masses were pathologically diagnosed by resection, or through flexible bronchoscopy. The other remaining pulmonary nodules and masses were diagnosed by bacterial culture or roentgenographical follow-up study. Indeterminate pulmonary nodules and masses went to surgery when they fulfilled one or more of the following criteria: (1) a growing lesion, (2) a lesion of 5mm or larger with no calcification, (3) a lesion with a hot FDG accumulation, or (4) a lesion with increased DWI signals. The remaining pulmonary nodules and masses, which fulfilled none of the criteria, were diagnosed as benign when the pulmonary nodules and masses decreased in size or didn't increase in size for more than two years upon review of retrospective chest x-ray films or CT. Pure ground-glass-opacity (GGO)-type lung cancers were excluded in this study because all pure GGO-type lung cancers were negative on FDG-PET (Mori et al., 2008; Chun et al., 2009). According to the percentage of bronchioloalveolar carcinoma (BAC) component within maximally cut surface specimens of the tumor, presented in the pathological reports, adenocarcinomas were classified into four types based on the definition of Higashiyama M (Higashiyama et al., 1999): type I (BAC 0%), type II (BAC 1% to 49%), type III (BAC 50% to 99%), and type IV (BAC 100%: pure GGO-type lung cancer). The TNM classification and cell types of lung cancers were classified according to the definition of UICC 7 (International Union Against Cancer, 2009).

MR Imaging

All MR images were obtained with a 1.5 T superconducting magnetic scanner (Magnetom Avanto; Siemens, Erlangen, Germany) with two anterior six-channel body phased-array coils and two posterior spinal clusters (six-channels each). The conventional MR images consisted of a coronal T1-weighted spin-echo sequence and coronal and axial T2-weighted fast spin-echo sequences. DWIs using a single-shot echo-planar technique were performed with slice thickness of 6mm under SPAIR (spectral attenuated inversion recovery) with respiratory triggered scan with the following parameter: TR/TE/flip angle, 3000-4500/65/90; diffusion gradient encoding in three orthogonal directions; b value = 0 and 800 s/mm^2; field of view, 350 mm; matrix size, 128x128. After image reconstruction, a 2-dimensional (2D) round or elliptical region of interest (ROI) was drawn on the lesion which was detected visually on the ADC map with reference to T2-weighted or CT image by the radiologist (Y.K.) with 22 years of MRI experience who was unaware of the patients' clinical data. Areas with necrosis were excluded from the ADC measurement. The procedure was repeated three times and the minimum ADC value was obtained. The radiologist (Y.K.) and one pulmonologist (K.U.) with 28 years of experience evaluated the MRI data. A consensus was reached if there were any differences of opinion. A receiver operating characteristics curve (ROC curve) was constructed according to the ADC value, and the optimal cutoff value (OCV) of the ADC value for diagnosing malignancy were determined. Pulmonary nodules and masses with an ADC value of the same or less than the OCV were defined as positive. Pulmonary nodules and masses with an ADC value of more than the OCV or those that could not be detected on DWI were defined as negative.

FDG-PET

FDG-PET scanning was performed with a dedicated PET camera (SIEMENS Biograph Sensation 16, Erlangen Germany) before surgery. All patients fasted for 6 hours before scanning. The dose of ^{18}F-FDG administered was 3.7MBq/Kg of body weight. After a 60- min uptake period, an emission scan was acquired for 3 min per bed position and a whole-body scan (from head to pelvis) was performed. After image reconstruction, a 2-dimensional (2D) round region of interest (ROI) was drawn on a slice after visual detection of the highest count on the fused CT image by the radiologist (M.T.) with 12 years of radioisotope scintigraphy and FDG-PET experience who was unaware of the patients' clinical data. For the lesions with negative or faintly positive PET findings, the ROI was drawn on the fusion image with the corresponding CT. From those ROI, the maximum standardized uptake value (SUVmax) was calculated. The radiologist (M.T.) and one pulmonologist (K.U.) with 28 years of experience evaluated the FDG-PET data. A consensus was reached if there were any differences of opinion. A ROC curve was constructed according to the SUVmax, and the OCV of the SUVmax for diagnosing malignancy were determined. Pulmonary nodules and masses with a SUVmax of the same or more than the OCV were defined as positive. Pulmonary nodules and masses with a SUVmax less than the OCV or those that could not be detected on FDG-PET were defined as negative.

Statistical analysis

Statistical analysis was performed using StatView for Windows (Version 5.0; SAS Institute Inc. Cary, NC, USA). The data is expressed as the mean±standard deviation. A two-tailed Student t test was used for comparison of ADC values or SUVmax in several pathological factors. The sensitivity, specificity, and accuracy of DWI versus FDG-PET for pulmonary nodules and masses were compared by using McNemar test. A P value of<0.05 was considered statistically significant.

Results

Between May 2009 and February 2012, 208 patients with pulmonary nodules and masses prospectively underwent FDG-PET and DWI. Of these 208 patients, 17 patients with a pure GGO-type lung cancer were excluded in this study. A patient with encapsulated effusion was excluded in this study. Another patient was also excluded because a definitive diagnosis could not be obtained. As a result, 189 patients who had pulmonary nodules and masses were enrolled in this study. 124 patients were male and 65 were female. Their mean age was 68.5 years old (range 37 to 87). There were 143 lung cancers, 17 metastatic lung tumors, and 29 benign pulmonary nodules and masses. Out of 143 lung cancers, there were 97 adenocarcinomas, 36 squamous cell carcinomas, 3 large cell carcinomas, 3 small cell carcinomas, 1 adenosquamous carcinoma, 1 large cell neuroendocrine carcinoma, 1 carcinoid, and 1 carcinosarcoma. Concerning the 17 metastatic lung tumors, the primary sites were colon in 6 patients, rectum in 6, breast in 1, thyroid in 1, kidney in 1, uterus in 1, and ethmoidal sinus in 1 patient. Twenty-nine benign pulmonary nodules and masses consisted of 10 chronic pneumonias, 4 nontuberculous mycobacterias, 4 hamartomas, 3 pulmonary tuberculosises, 2 granulomas, 2 sarcoidosises, 2 lung abscesses, and 2 pulmonary scars. The details are as follows: pathological diagnoses were made in 16 benign pulmonary nodules and masses; bacterial diagnoses from cultured samples were made in 3 benign pulmonary nodules and masses, and roentgenographical diagnoses were made in the remaining 10 benign pulmonary nodules and masses.

The mean size of the malignant pulmonary nodules and masses in chest CT was 31.8±21.3 mm (from 5 to 100mm), which was not significantly higher than that [21.1±13.1 mm (from 6 to 55mm)] of the benign pulmonary nodules and masses (p= 0.061). Findings of chest CT, DWI, and FDG-PET of patients with pulmonary nodules and masses are shown in Figure 1. The ROC curve for the ADC value for diagnosing malignancy in DWI revealed the OCV was 1.44×10^{-3} mm^2/sec (Figure 2a). The ROC curve for the SUVmax for diagnosing malignancy in FDG-PET revealed the OCV was 3.43 (Figure 2b).

The ADC value ($1.27\pm0.35\times10^{-3}$mm^2/sec) of the 160 malignant pulmonary nodules and masses was significantly lower than that ($1.66\pm0.58\times10^{-3}$mm^2/sec) of the 29 benign pulmonary nodules and masses (p=0.0003). The SUVmax (7.47±6.10) of the malignant pulmonary nodules and masses was significantly higher than that (3.89±4.05) of the benign pulmonary nodules and masses (p=0.027). The ADC value was $1.33\pm0.47\times10^{-3}$mm^2/sec

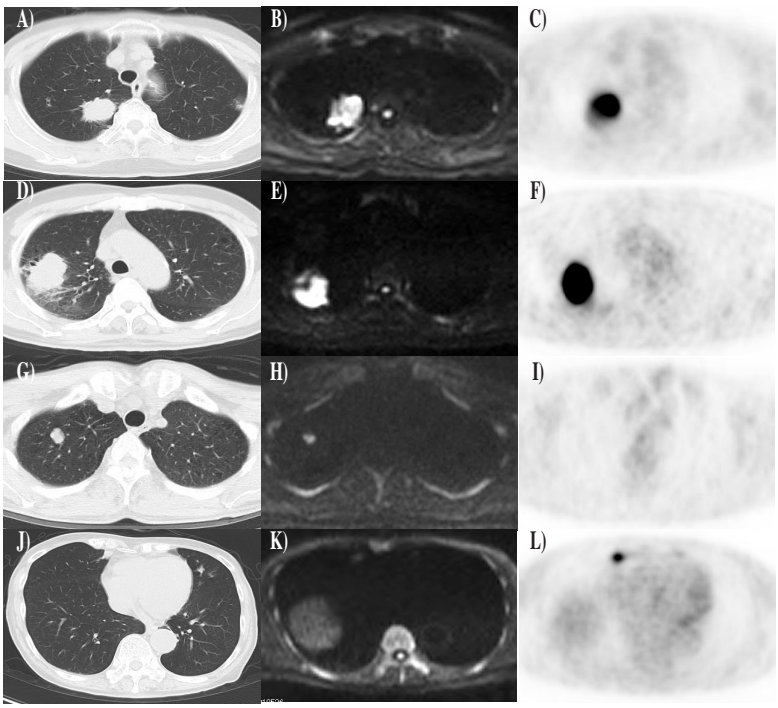

Figure 1. Findings of Chest CT, DWI, and FDG-PET of Patients with Pulmonary Nodules and Masses. Chest CT **(A)**; DWI **(B)**; FDG-PET **(C)** of one patient with adenocarcinoma. ADC value of the lung cancer was 1.07×10^{-3} mm^2/sec, and its SUVmax was 12.9; Chest CT (**D**); DWI **E**); FDG-PET (**F**) of one patient with squamous cell carcinoma. ADC value of the lung cancer was 0.98×10^{-3} mm^2/sec, and its SUVmax was 16.9; Chest CT (**G**); DWI (**H**); FDG-PET (**I**) of one patient with hamartoma. ADC value of the hamartoma was 1.97×10^{-3} mm^2/sec, and accumulation of FDG was not seen; Chest CT (**J**); DWI (**K**), and FDG-PET (**L**) of one patient with nontuberculous mycobacteria. ADC value of the nontuberculous mycobacteria was 2.19×10^{-3} mm^2/sec, and its SUVmax was 7.48

in metastatic lung tumors, 1.27±0.34×10^{-3}mm^2/sec in lung cancers. The ADC value of lung cancers was significantly lower than that of the benign pulmonary nodules and masses (p=0.0002). The SUVmax were 7.71±6.84 in the metastatic lung tumors, 7.44±6.03 in the lung cancers. The SUVmax of the lung cancers was significantly higher than that of the benign pulmonary nodules and masses (p=0.0273).

Assessment of DWI and FDG-PET in pulmonary nodules and masses is shown in Table 1. The sensitivity [80.0% (128/160)] of DWI was significantly higher than that [70.0% (112/160)] of FDG-PET for the malignant pulmonary nodules and masses (p=0.0389). The specificity [65.5% (19/29)] of DWI was equal to that [65.5% (19/29)] of FDG-PET for the benign pulmonary nodules and masses (p=0.80). The accuracy [77.8% (147/189)] of DWI was not significantly higher than that [69.3% (131/189)] of FDG-PET for all pulmonary nodules and masses (p=0.0621).

Concerning the percentage of BAC component in the 97 adenocarcinomas, there were 32 type I adenocarcinomas, 38 type II adenocarcinomas, and 27 type III adenocarcinomas (Table 2). The sensitivities of DWI were similar to each other based on the percentage of BAC component. On the other hand, the FDG-PET sensitivity [25.9% (7/27)] of type III adenocarcinomas was significantly lower than that [81.3% (26/32)] of type I adenocarcinomas (p<0.001), and that [65.8% (25/38)] of type II adenocarcinomas (p<0.01). As the percentage of BAC component in adenocarcinoma increased, the sensitivity of FDG-PET decreased. The ADC value (1.30±0.30×10^{-3}mm^2/sec) of the 65 adenocarcinomas with BAC features (type II-III adenocarcinomas) was similar to that (1.25±0.39×10^{-3}mm^2/sec) of the 95 solid malignant pulmonary nodules and masses, and was significantly lower than that (1.66±0.58×10^{-3}mm^2/sec) of the 29 benign pulmonary nodules and masses (p=0.0014) (Figure 3). Conversely, the SUVmax (4.18±3.55) of the adenocarcinomas with BAC features was significantly lower than that (9.72±6.46) of the solid malignant pulmonary nodules and masses (p<0.0001), but similar to that (3.89±4.05) of the benign pulmonary nodules and masses (p=0.779). The sensitivity [76.9% (50/65)] of DWI was significantly higher than that [49.2% (32/65)] of FDG-PET for the 65 adenocarcinomas with BAC features (p=0.0014). FDG-PET could not help in the diagnosis of adenocarcinomas with BAC features as malignant.

In the 143 lung cancers, there were 6 mucinous adenocarcinomas. The ADC value (1.95±0.30×10^{-3}mm^2/sec) of the 6 mucinous adenocarcinomas was significantly higher than that (1.24±0.31×10^{-3}mm^2/sec) of the 137 lung cancers except the mucinous adenocarcinomas (p<0.0001), and was slightly higher than that (1.66±0.58×10^{-3}mm^2/sec) of the 29 benign pulmonary nodules and masses (p=0.30). On the other hand, the SUVmax (6.44±3.56) of the mucinous adenocarcinomas was not significantly lower than that (7.49±6.12) of the lung cancers except the

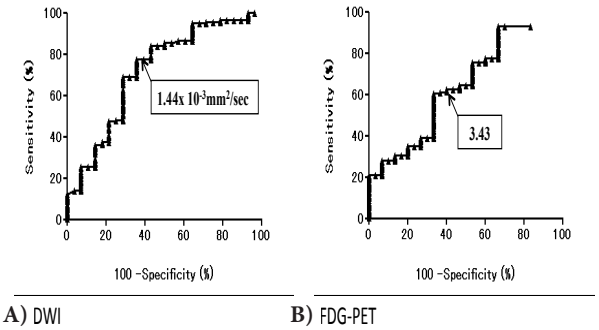

Figure 2. Receiver Operating Characteristics Curve (ROC curves) for Diagnosing Malignancy. A) ROC curve for the ADC value for diagnosing malignancy in DWI revealed that the optimal cutoff value was 1.44x10^{-3} mm^2/sec. Area under the curve, 0.72; 95% confidence interval, 0.61 to 0.83. Sensitivity was 0.77 and specificity was 0.64. **B)** ROC curve for the SUVmax for diagnosing malignancy in FDG-PET revealed that the optimal cutoff value was 3.43. Area under the curve, 0.68; 95% confidence interval, 0.57 to 0.79. Sensitivity was 0.68 and specificity was 0.60

Table 2. Sensitivity Based on Percentage of BAC Component in the 97 Adenocarcinomas

Adenocarcinoma	DWI			FDG-PET		
	TP	FN	Sensitivity	TP	FN	Sensitivity
Type I (BAC 0%)	24	8	75%	26	6	81.3%
Type II (BAC 1-49%)	30	8	78.9%	25	13	65.8%
Type III (BAC 50-99%)	20	7	74.1%	7	20	25.9%

*TP=true-positive, FN=false-negative

Table 1. Assessment of DWI and FDG-PET in Malignant and Benign Pulmonary Nodules and Masses

		DWI				FDG-PET				Total
		TP	FN	TN	FP	TP	FN	TN	FP	
Malignant	Lung cancer	115	28			99	44			143
	Metastatic lung tumor	13	4			13	4			17
Benign	Chronic pneumonia			7	3			6	4	10
	Nontuberculous mycobacteria			2	2			2	2	4
	Hamartoma			4	0			4	0	4
	Pulmonary tuberculosis			0	3			3	0	3
	Granuloma			2	0			2	0	2
	Sarcoidosis			2	0			0	2	2
	Lung abscess			2	0			0	2	2
	Pulmonary scar			0	2			2	0	2
Total		128	32	19	10	112	48	19	10	189

*TP=true-positive; FN=false-negative; TN=true-negative; FP=false-positive

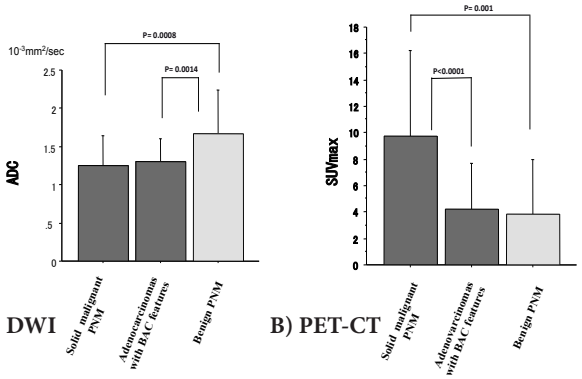

Figure 3. Differences in ADC values and SUVmax in Pulmonary Nodules and Masses (PNM). A) Differences in ADC values in PNM. The ADC value (1.30±0.30×10^{-3} mm^2/sec) of the 65 adenocarciniomas with BAC features was significantly lower than that (1.66±0.58×10^{-3} mm^2/sec) of the 29 benign PNM (p=0.014). The ADC value (1.25±0.39×10^{-3} mm^2/sec) of the 95 solid malignant PNM was significantly lower than that of the 29 benign PNM (p=0.0008). **B)** Differences in SUVmax in PNM. The SUVmax (4.18±3.55) of adenocarciniomas with BAC features was significantly lower than that (9.72±6.46) of the 95 solid malignant PNM (p<0.0001), but similar to that (3.89±4.05) of the 29 benign PNM (p=0.779)

mucinous adenocarcinomas (p=0.68), and not significantly higher than that (3.89±4.05) of the 29 benign pulmonary nodules and masses (p=0.19). The sensitivity [83.3% (5/6)] of FDG-PET was higher than that [0% (0/6)] of DWI for the mucinous adenocarcinomas (p=0.063). DWI could not help in the diagnosis of mucinous adenocarcinomas as malignant.

The ADC value (1.11±0.25×10^{-3} mm^2/sec) of the 34 lung cancers with necrosis was significantly lower than that (1.30±0.33×10^{-3} mm^2/sec) of the 104 lung cancers without necrosis (p=0.0027). The SUVmax (11.89±6.31) of the lung cancers with necrosis was significantly higher than that (5.72±4.96) of the lung cancers without necrosis (p<0.0001).

Discussion

FDG-PET has helped differentiate malignant from benign pulmonary nodules (Lowe et al., 1998; Gould et al., 2001). However, FDG-PET has given false-negative results for well-differentiated pulmonary adenocarcinoma (Higashi et al., 1998; Cheran et al., 2004), or small volumes of metabolically active tumor (Satoh et al., 2011), and false-positive results for inflammatory nodules (Goo et al., 2000; Nomori et al., 2004). In addition, FDG-PET is not widely available because of its high cost.

The MR signal intensity of pulmonary cancer nodules was significantly higher than that of benign lesions (Uto et al., 2009). DWI can be used to distinguish benign from malignant lesions in the lung (Mori et al., 2008; Ohba et al., 2009; Wu et al., 2013), in the thorax (Tondo et al., 2011), in the prostate (Yamamura et al., 2011), in the breast (Fornasa et al., 2011), and in the liver (Koike et al., 2009; Wu et al., 2013). DWI was reported to be superior to FDG-PET in the detection of primary lesions and the nodal assessment of non-small cell lung cancers (Usuda et al., 2011; Wu et al., 2012). The advantages of DWI can be explained not only by DWI giving fewer false-positive results for N staging of non-small cell lung cancer compared with FDG-PET (Nomori et al., 2008), but also by DWI giving fewer false-negative results (Usuda et al., 2011). To the authers' knowledge, there is only one paper which deals with diagnostic accuracy between DWI and FDG-PET for pulmonary nodules and masses (Mori et al., 2008). This study has shown that the sensitivity of DWI was significantly higher than that of FDG-PET, and the accuracy of DWI was higher than that of FDG-PET in pulmonary nodules and masses.

Pure BAC is a subtype of adenocarcinoma, which manifests as lepidic growth of tumor cells along the alveoli without stromal, vascular, lymphatic, or pleural invasion (Travis et al., 2005), and appears as GGO on CT scans. The SUVmax of pure ground-glass-opacity (GGO)-type lung cancers was reported to be 0.64±0.19 (Chun et al., 2009). Although pure BACs are uncommon, adenocarcinomas with BAC features are common (Ebright et al., 2002). Adenocarcinomas with BAC features have been increasing in incidence in the past two decades (Read et al., 2004). For assessment of non-solid solitary pulmonary nodules, the cutoff of 1.5 was used for SUVmax (Tsushima et al. 2008). Although a meta-analysis (Gould et al., 2001) of studies published between January 1966 and September 2000 in the MEDLINE and CANCERLIT databases showed FGD-PET sensitivity over 90% for malignant pulmonary lesions, the studies mainly looked at solid lung cancers, which are easier to detect by FGD-PET than pure BACs and adenocarcinomas with predominantly BAC features. Now, CT examinations are widely used and make it easy to detect pure BACs, adenocarcinomas with predominantly BAC features, or smaller lung cancers under 10 mm. They are likely to be false-negative by FDG-PET because of their lower metabolism and small volumes of metabolically active tumor. One of the reasons for the lower sensitivity (70.0%) of pulmonary nodules and masses on FDG-PET in this study was thought to be associated with increased adenocarcinomas with predominantly BAC features.

There are two important limitations of DWI. First, pulmonary lesions with histopathological necrosis showed restricted diffusion and lower ADC values. Abscesses and thrombi are believed to impede the diffusivity of water molecules because of their hyperviscous nature (Desprechins et al., 1999; Kwee et al., 2010). The pus structure itself is responsible for the low ADC values, and the heavily impeded water mobility of pus may be related to its high cellularity and viscosity (Ebisu et al.,1996). In the interpretation of DWI, 22% of benign lesions can exhibit restricted diffusion in images with high b values (Feuerlein et al., 2009). These previous reports on the properties of abscesses and thrombi can explain our false-positive results using DWI for the assessment of some benign pulmonary nodules and masses which have abscesses.

Second, mucinous carcinomas were hypointense in DWI and had higher ADC values, which could be misdiagnosed as benign lesions in DWI. Mucinous carcinomas have higher ADC values and lower DWI

signal intensity than tubular adenocarcinoma in the anorectal region, because mucinous carcinomas have far lower cellularity than tubular adenocarcinomas (Nasu et al., 2012).

The difference found in diagnosing pulmonary nodules and masses can be explained by the fact that FDG-PET provides quantitative information regarding cellular glucose metabolism, while DWI provides quantitative information regarding tissue cellularity and the diffusion of water molecules.

FDG-PET/CT and DWI were reported to have diagnostic merit in treatment and survival of lung cancer patients. Concerning survival of patients with locally advanced non-small lung cancer, staging with PET-CT was reported to be superior to conventional staging methods (Mutlu et al., 2013). Radiotherapy adaptive to tumor shrinkage determined by repeated FDG-PET/CT after 40 Gy during treatment course might be feasible to spare more normal tissues, and had the potential to allow dose escalation and increased local control (Ding et al., 2013). DWI was reported to have better potential than FDG-PET/CT for prediction of tumor response to therapy in non-small cell lung cancer patients before chemoradiotherapy (Ohno et al., 2012). Further studies are necessary to evaluate the diagnostic performance of FDG-PET/CT and DWI for treatment and survival of lung cancer patients.

In conclusion, the sensitivity of DWI was significantly higher than that of FDG-PET in distinguishing malignant from benign pulmonary nodules and masses. DWI has advantages over FDG-PET in assessing pulmonary nodules and masses.

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