

RESEARCH ARTICLE

Diffusion Weighted Imaging Can Distinguish Benign from Malignant Mediastinal Tumors and Mass Lesions: Comparison with Positron Emission Tomography

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Abstract

Background: Diffusion-weighted magnetic resonance imaging (DWI) makes it possible to detect malignant tumors based on the diffusion of water molecules. It is uncertain whether DWI is more useful than positron emission tomography-computed tomography (PET-CT) for distinguishing benign from malignant mediastinal tumors and mass lesions. **Materials and Methods:** Sixteen malignant mediastinal tumors (thymomas 7, thymic cancers 3, malignant lymphomas 3, malignant germ cell tumors 2, and thymic carcinoid 1) and 12 benign mediastinal tumors or mass lesions were assessed in this study. DWI and PET-CT were performed before biopsy or surgery. **Results:** The apparent diffusion coefficient (ADC) value ($1.51 \pm 0.46 \times 10^{-3} \text{mm}^2/\text{sec}$) of malignant mediastinal tumors was significantly lower than that ($2.96 \pm 0.86 \times 10^{-3} \text{mm}^2/\text{sec}$) of benign mediastinal tumors and mass lesions ($P < 0.0001$). Maximum standardized uptake value (SUVmax) (11.30 ± 11.22) of malignant mediastinal tumors was significantly higher than that (2.53 ± 3.92) of benign mediastinal tumors and mass lesions ($P = 0.0159$). Using the optimal cutoff value (OCV) $2.21 \times 10^{-3} \text{mm}^2/\text{sec}$ for ADC and 2.93 for SUVmax, the sensitivity (100%) by DWI was not significantly higher than that (93.8%) by PET-CT for malignant mediastinal tumors. The specificity (83.3%) by DWI was not significantly higher than that (66.7%) for benign mediastinal tumors and mass lesions. The accuracy (92.9%) by DWI was not significantly higher than that (82.1%) by PET-CT for mediastinal tumors and mass lesions. **Conclusions:** There was no significant difference between diagnostic capability of DWI and that of PET-CT for distinguishing mediastinal tumors and mass lesions. DWI is useful in distinguishing benign from malignant mediastinal tumors and mass lesions.

Keywords: Mediastinal tumor and mass lesion - diagnosis - magnetic resonance imaging - diffusion-weighted imaging

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Introduction

Mediastinal tumors and mass lesions span a wide histopathological and radiological spectrum, and remain an interesting diagnostic challenge for radiologists and thoracic surgeons. Thymic epithelial tumors consist of several histologic subtypes, which can be categorized into 3 basic groups in increasing order of malignancy: thymoma types A/AB/B1, types B2/B3, and thymic carcinoma (Travis et al., 2004). Several noninvasive procedures including computed tomography (CT) and positron emission tomography (PET) are widely used for evaluating mediastinal tumors and mass lesions. Magnetic resonance imaging (MRI) is an important adjunctive imaging modality in thoracic oncologic imaging and is used as a problem-solving tool to assess chest wall

invasion, intraspinal extension, and cardiac/vascular invasion (Hayes et al., 2014). Recently diffusion-weighted magnetic resonance imaging (DWI) has been used to detect the restricted diffusion of water molecules. DWI makes it possible to detect malignant tumors based on the difference in the diffusion of water molecules among tissues. The principals of DWI exploit the random motion, or Brownian movement, of water molecules in biologic tissue (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). In

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DWI, blood flow showing high diffusion and normal tissue with fat depression are undetectable, but cancer tissue with low Brownian motion of water molecules is detectable.

¹⁸F-FDG (18-fluoro-2-deoxy-glucose)-PET was reported to be useful in assessing the invasiveness of thymomas (Liu et al., 1995; Kubota et al., 1996). Sasaki et al in 1999 demonstrated that FDG-PET is useful for the differential diagnosis of thymic cancer and thymoma. Kubota et al in 1996 reported the usefulness of FDG-PET for evaluating the malignant nature of primary mediastinal tumors. PET-CT was found to be useful for differentiating subgroups of thymic epithelial tumors and for staging the extent of the disease (Sung et al., 2006). On the other hand, the mean ADC of malignant mediastinal lesions was reported to be significantly lower than that of benign mediastinal lesions (Razek et al., 2009; Gumustas et al., 2011). ADC measurements on DWI may help in differentiating malignant from benign mediastinal masses noninvasively (Gumustas et al., 2011). To the authors' knowledge, there is no paper dealing with diagnostic accuracy of DWI and PET-CT for mediastinal tumors and mass lesions. Although some recent studies comparing DWI with PET-CT have shown that DWI at 1.5 T is comparable with PET-CT for detecting malignant lesions (Mori et al., 2008; Nomori et al., 2008), it is uncertain whether DWI is superior to PET-CT for distinguishing benign from malignant mediastinal tumors or mass lesions. If diagnostic capability of DWI is equivalent to that of PET-CT for benign and malignant mediastinal tumors or mass lesions, DWI will become one of important examination tools in the assessment of benign and malignant mediastinal tumors or mass lesions. The purpose of this study was to compare DWI and PET-CT in distinguishing malignant from benign mediastinal tumors or mass lesions.

Materials and Methods

Eligibility

The study protocol for examining DWI and PET-CT in patients with mediastinal tumors or mass lesions was approved by the Institutional Review Board of Kanazawa Medical University (approval No.189). Written informed consent was obtained from all patients. Patients with mediastinal tumors or mass lesions were enrolled in the analysis, and underwent PET-CT and DWI.

Patients

The clinical prospective study started in January 2010. Most of mediastinal tumors or mass lesions were pathologically diagnosed by resection, and others by percutaneous biopsy under CT. Thymic epithelial tumors are classified into 3 subgroups according to WHO classification (Travis et al., 2004) and Sung et al in 2006: low-risk thymomas (Types A, AB, and B1), high-risk thymomas (types B2 and B3), and thymic carcinomas.

Magnetic resonance imaging (MRI)

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/mm²; 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 (H.T.) with 39 years of MRI experience who was unaware of the patients' clinical data. A ROI was placed around the margin of the tumor using the electronic cursor on the ADC map. The procedure was repeated three times and the minimum ADC value was obtained. The radiologist (H.T.) 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. Mediastinal tumors or mass lesions with an ADC value of the same or less than the OCV were defined as positive. Mediastinal tumor or mass lesions with an ADC value of more than the OCV or those that could not be detected on DWI were defined as negative.

PET-CT

PET-CT scanning was performed with a dedicated PET camera (Biograph Sensation 16, Siemens, Erlangen Germany) before surgery. All patients fasted for 6 hours before the scanning. The dose of ¹⁸F-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 (N.W.) with 29 years of radioisotope scintigraphy and PET-CT 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 (N.W.) 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. Mediastinal tumors or mass lesions with a SUVmax of the same or more than the OCV were defined as positive. Mediastinal tumors or mass lesions 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 \pm 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 mediastinal tumors and mass lesions were compared by using McNemar test. A P value of < 0.05 was considered statistically significant.

Results

From January 2010 to August 2014 twenty-eight mediastinal tumors or mass lesions were enrolled in the study. There were 16 malignant mediastinal tumors (thymoma 7, Thymic cancer 3, malignant lymphoma 3, malignant germ cell tumor 2, and thymic carcinoid 1) and 12 benign mediastinal tumors or mass lesions (bronchogenic, mediastinal, or thymic cyst 7, thymic haperplasia 2, neurinoma 1, teratoma 1 and intrathoracic

Table 1. Number of Patients and Pathological Diagnosis

Diagnosis	Pathology	No. of patients	ADC $\times 10^{-3}$ mm ² /sec	SUV max
Malignant mediastinal tumor	Thymoma	7	1.71 \pm 0.48	3.80 \pm 2.53
	Thymic cancer	3	1.26 \pm 0.74	14.75 \pm 9.99
	Malignant lymphoma	3	1.46 \pm 0.17	21.78 \pm 10.64
	Malignant germ cell tumor	2	1.36 \pm 0.12	4.66 \pm 0.29
	Thymic carcinoid	1	1.26	35.31
	Benign mediastinal tumor & mass lesion	Bronchogenic, mediastinal, or thymic cyst	7	3.57 \pm 0.45
Thymic haperplasia		2	2.35 \pm 0.05	4.26 \pm 0.01
Neurinoma		1	2.55	4.14
Teratoma		1	1.82	2.9
Intrathoracic goiter		1	1.49	13.5

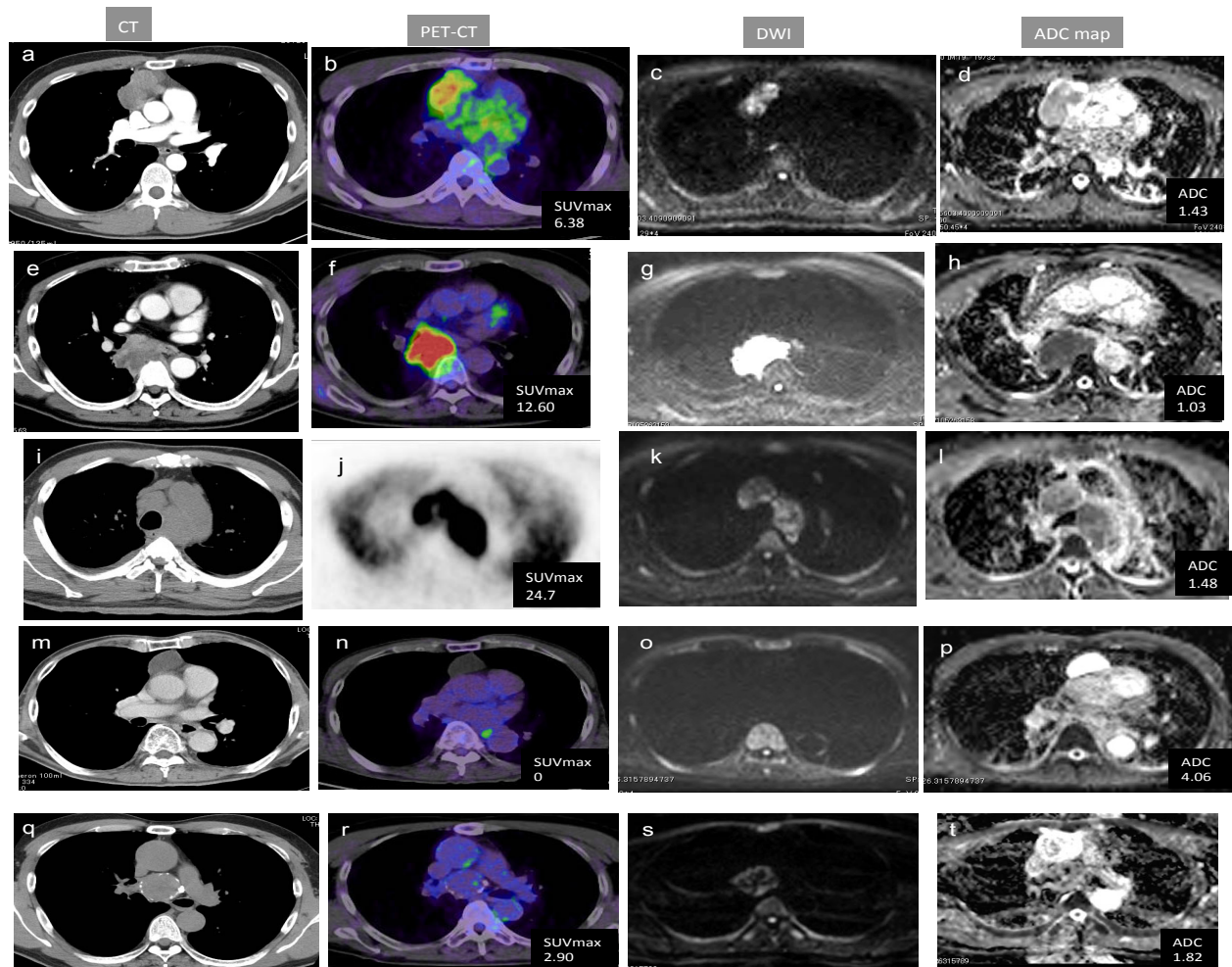


Figure 1. Chest CT (a), PET-CT (b), DWI (c) and ADC map (d) of a patient with thymoma. SUVmax 6.38, ADC 1.43×10^{-3} mm²/sec; Chest CT (e), PET-CT (f), DWI (g) and ADC map (h) of a patient with thymic cancer. SUVmax 12.6, ADC 1.03×10^{-3} mm²/sec; Chest CT (i), PET-CT (j), DWI (k) and ADC map (l) of a patient with malignant lymphoma. SUVmax 24.7, ADC 1.48×10^{-3} mm²/sec; Chest CT (m), PET-CT (n), DWI (o) and ADC map (p) of a patient with thymic cyst. SUVmax 0, ADC 4.06×10^{-3} mm²/sec; Chest CT (q), PET-CT (r), DWI (s) and ADC map (t) of a patient with teratoma. SUVmax 2.90, ADC 1.82×10^{-3} mm²/sec

goiter 1) (Table 1) . Two malignant lymphomas were diagnosed by biopsy, and the other 26 mediastinal tumors or mass lesions were diagnosed by resection. Their ADC values and SUVmax are shown in Table 1.

Findings of chest CT, PET-CT, DWI, and ADC map for calculating ADC of patients with mediastinal tumors and mass lesions are shown in Figure 1. ADC value ($1.51 \pm 0.46 \times 10^{-3} \text{mm}^2/\text{sec}$) of malignant mediastinal tumors was significantly lower than that ($2.96 \pm 0.86 \times 10^{-3} \text{mm}^2/\text{sec}$) of benign mediastinal tumors and mass lesions ($P < 0.0001$) (Figure 2a) . The SUVmax (11.30 ± 11.22) of malignant mediastinal tumors was significantly higher than that (2.53 ± 3.92) of benign mediastinal tumors and mass lesions ($P = 0.0159$) (Figure 2b).

The 16 malignant mediastinal tumors were classified into 3 low-risk thymomas, 4 high-risk thymomas, and 9 other malignant mediastinal tumors (thymic cancer,

malignant lymphoma, malignant germ cell tumor and thymic carcinoid).

Concerning differences in ADC values among several pathological types of mediastinal tumors and mass lesions, ADC value ($2.96 \pm 0.86 \times 10^{-3} \text{mm}^2/\text{sec}$) of benign mediastinal tumors and mass lesions was higher than that ($2.01 \pm 0.16 \times 10^{-3} \text{mm}^2/\text{sec}$) of low-risk thymomas ($p = 0.888$), significantly higher than that ($1.49 \pm 0.53 \times 10^{-3} \text{mm}^2/\text{sec}$) of high-risk thymomas ($p = 0.0067$), and significantly higher than that ($1.35 \pm 0.39 \times 10^{-3} \text{mm}^2/\text{sec}$) of the other malignant mediastinal tumors ($p < 0.0001$) (Fig.3a). The ADC value of low-risk thymomas was higher than that of high-risk thymomas, but there was no significant difference ($p = 0.162$). Concerning differences in SUVmax among several pathological types of mediastinal tumors and mass lesions, the SUVmax (2.53 ± 3.92) of benign mediastinal tumors or mass lesions

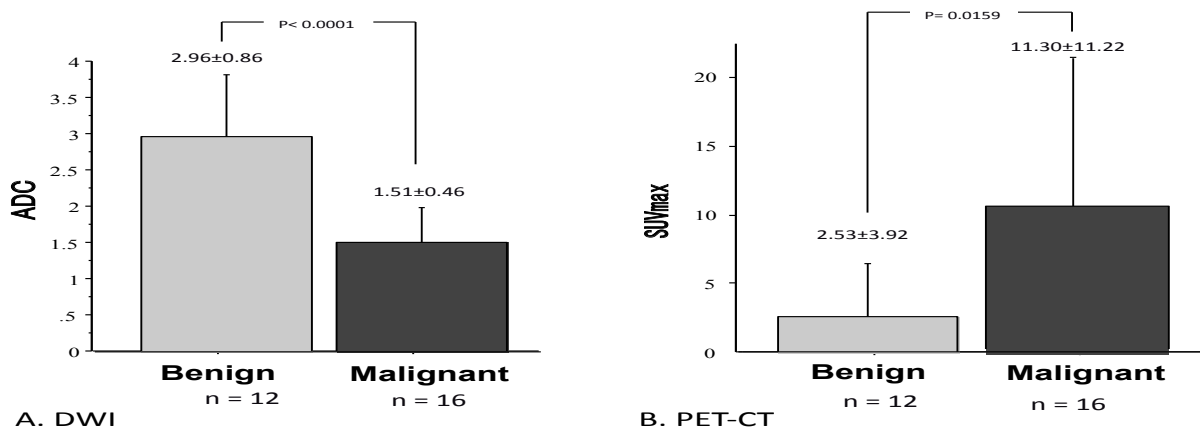


Figure 2. Differences in ADC values and differences in SUVmax between malignant and benign mediastinal tumors and mass lesions. (A) The ADC value ($1.51 \pm 0.46 \times 10^{-3} \text{mm}^2/\text{sec}$) of malignant mediastinal tumors was significantly lower than that ($2.96 \pm 0.86 \times 10^{-3} \text{mm}^2/\text{sec}$) of benign mediastinal tumors and mass lesions ($P < 0.0001$). (B) The SUVmax (11.30 ± 11.22) of malignant mediastinal tumors was significantly higher than that (2.53 ± 3.92) of benign mediastinal tumors and mass lesions ($P = 0.0159$)

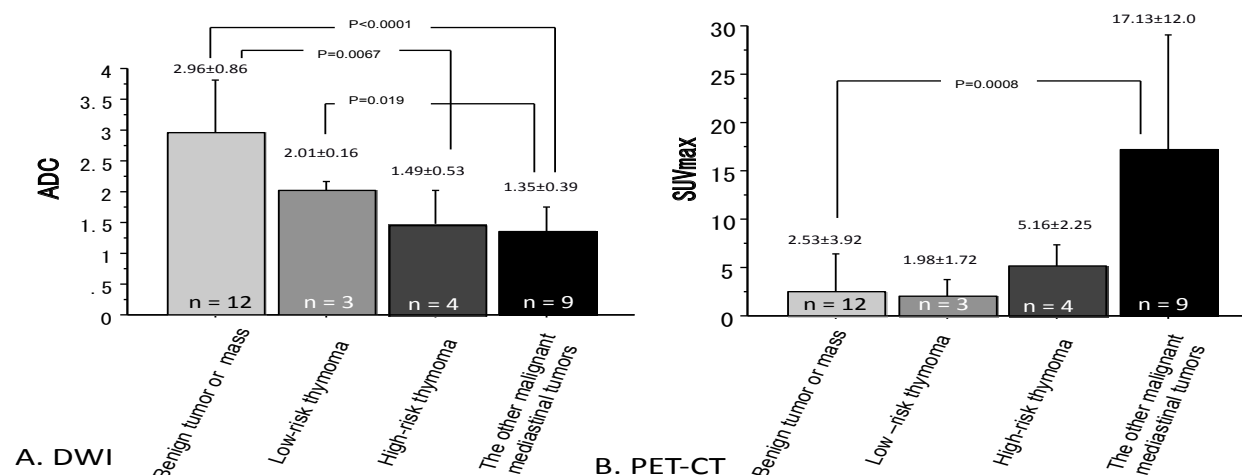


Figure 3. Differences in ADC values and differences in SUVmax among several pathological types of mediastinal tumors and mass lesions. (A) The ADC value ($2.96 \pm 0.86 \times 10^{-3} \text{mm}^2/\text{sec}$) of benign mediastinal tumors or mass lesions was higher than that ($2.01 \pm 0.16 \times 10^{-3} \text{mm}^2/\text{sec}$) of low-risk thymomas, significantly higher than that ($1.49 \pm 0.53 \times 10^{-3} \text{mm}^2/\text{sec}$) of high-risk thymomas and significantly higher than that ($1.35 \pm 0.39 \times 10^{-3} \text{mm}^2/\text{sec}$) of the other malignant mediastinal tumors. (B) The SUVmax (2.53 ± 3.92) of benign mediastinal tumors and mass lesions was lower than that (5.16 ± 2.25) of high-risk thymomas and significantly lower than that (17.13 ± 12.0) of the other malignant mediastinal tumors

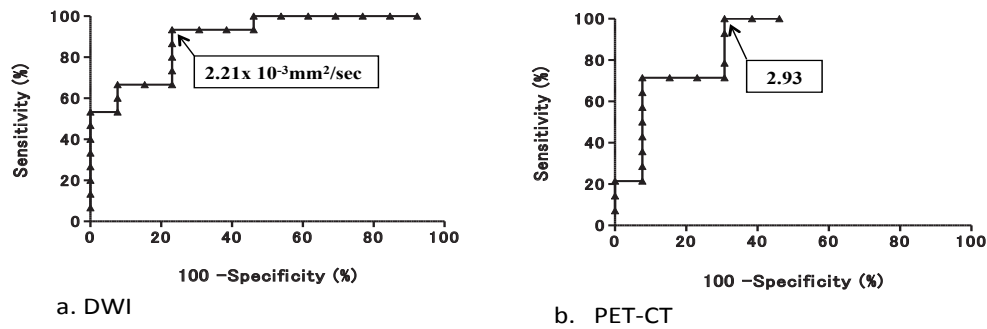


Figure 4. (A) Receiver Operating Characteristic Curve for the ADC value for Diagnosing Malignancy in DWI Revealed that the Optimal cutoff value was $2.21 \times 10^{-3} \text{mm}^2/\text{sec}$. Area under the curve, 0.90; 95% confidence interval, 0.78 to 1.01. Sensitivity was 0.93 and specificity was 0.77. (B) Receiver operating characteristic curve for the SUVmax for diagnosing malignancy in PET-CT revealed that the optimal cutoff value was 2.93. Area under the curve, 0.87; 95% confidence interval, 0.73 to 1.01. Sensitivity was 1.0 and specificity was 0.69

Table 2. Comparison of Sensitivities between DWI and PET-CT for 16 Malignant Mediastinal Tumors in the McNemar Test (P=1.0)

		PET-CT		Total
		True-positive	False-negative	
DWI	True-positive	15	1	16
	False-negative	0	0	0
Total		15	1	16

Table 3. Comparison of Sensitivities between DWI and PET-CT for 12 Benign Specificities Mediastinal Tumors and Mass Lesions in the McNemar Test (P=0.683)

		PET-CT		Total
		True-negative	False-positive	
DWI	True-negative	6	4	10
	False-positive	2	0	2
Total		8	4	12

Table 4. Comparison of Accuracies between DWI and PET-CT for 28 Mediastinal Tumors and Mass lesions in the McNemar test (P=0.453)

		PET-CT		Total
		Correct	Incorrect	
DWI	Correct	21	5	26
	Incorrect	2	0	2
Total		23	5	28

was lower than that (5.16 ± 2.25) of high-risk thymomas and significantly lower than that (17.13 ± 12.0) of the other malignant mediastinal tumors (Figure 3b).

The ROC curve for the ADC value for diagnosing malignancy in DWI revealed the OCV was $2.21 \times 10^{-3} \text{mm}^2/\text{sec}$ (Figure 4a). The ROC curve for the SUVmax for diagnosing malignancy in PET-CT revealed the OCV was 2.93 (Figure 4b).

Concerning sensitivities between DWI and PET-CT for 16 malignant mediastinal tumors, 15 (93.8%) were true-positive (TP) with DWI and PET-CT, 1 (6.2%) were TP with DWI but false-negative (FN) with PET-CT. The sensitivity (100%) by DWI was not significantly higher than that (93.8%) by PET-CT for malignant mediastinal

tumors in the McNemar test (P=1.0) (Table 2). Concerning specificities between DWI and PET-CT for the 12 benign mediastinal tumors and mass lesions, 6 (50%) were true-negative (TN) with DWI and PET-CT, 4 (33.3%) were TN with DWI but false-positive (FP) with PET-CT, 2 (16.7%) were TN with PET-CT but FP with DWI (Table 3). The specificity (83.3%) by DWI was not significantly higher than that (66.7%) by PET-CT for benign mediastinal tumors and mass lesions in the McNemar test (P=0.683). Concerning accuracies between DWI and PET-CT for all 28 mediastinal tumors and mass lesions, 21 (75%) were correct with DWI and PET-CT, 5 (17.9%) were correct with DWI but incorrect with PET-CT, 2 (7.1%) were correct with PET-CT but incorrect with DWI (Table 4). The accuracy (92.9%) by DWI was not significantly higher than that (82.1%) by PET-CT for mediastinal tumors and mass lesions in the McNemar test (P=0.453).

Discussion

PET-CT has been reported to be useful for differentiating subgroups of thymic epithelial tumors and for staging the extent of the disease (Sung et al., 2006). Also, SUVmax has been connected to malignancy of anterior mediastinal masses (Luzzi et al., 2009). FDG-PET has demonstrated the ability to differentiate malignant from benign pulmonary nodules (Could et al., 2001; Usuda et al., 2014). It is well known that PET gives false-negative results for well-differentiated pulmonary adenocarcinoma (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).

Recently, there have been advancements in magnetic resonance (MR) gradient technology. DWI has been reported to be potentially useful for the assessment of anterior mediastinum solitary tumors as well as CT (Seki et al., 2014). DWI has been also reported to be superior to PET-CT in the detection of primary lesions and the nodal assessment of non-small cell lung cancers (Usuda et al., 2011). DWI has higher potential than PET in assessing pulmonary nodules and masses (Usuda et al., 2014). DWI has been known to be able to distinguish benign from malignant lesions in the head and neck (Wang et al., 2001), lung (Mori et al., 2008; Ohba et al., 2009), thorax (Tondo

et al., 2011), prostate (Yamamura et al., 2011), breast (Fornasa et al., 2011), liver (Koike et al., 2009), kidney (Zhang et al., 2008), retroperitoneum (Nakayama et al., 2004), and mediastinum (Razek et al., 2009; Gumustas et al., 2011; Seki et al., 2014).

In this paper, diagnostic capability of DWI was not significantly higher than that of PET-CT for distinguishing benign from malignant mediastinal tumors and mass lesions. DWI will become one of important examination tools in the assessment of benign and malignant mediastinal tumors or mass lesions because of high sensitivity (100%), specificity (83.3%), and accuracy (92.9%). DWI has already been reported to have several advantages over PET-CT in dealing lung cancer (Usuda et al., 2013); compared to PET-CT, DWI shows higher sensitivity and accuracy for diagnosing metastatic lymph node stations, and is relatively cheaper and easy to handle. Furthermore, in the DWI examination patients do not have to fast, do not need exogenous contrast medium, and less time is required.

This study shows that DWI could distinguish not only benign from malignant mediastinal tumors and mass lesions, but also may distinguish among low-risk thymoma, high-risk thymoma, and the other malignant mediastinal tumors. Thymoma types A and AB generally behave like benign tumors, and thymoma type B1 is a low-grade malignant tumor (10-y survival rates of >90%). However, thymoma type B2 shows a higher degree of malignancy, and thymoma type B3 in the advanced stage shows a poor prognosis, similar to that of thymic carcinoma and the malignant tumors of other organs (Travis et al., 2004).

This study has some limitations. First, this study included small number of mediastinal tumors and mass lesions. ADC value ($2.01 \pm 0.16 \times 10^{-3} \text{mm}^2/\text{sec}$) of low-risk thymomas was higher than that ($1.49 \pm 0.53 \times 10^{-3} \text{mm}^2/\text{sec}$) of high-risk thymomas, but a significant difference was not found because of the small number. A large number of mediastinal tumors and mass lesions should be analyzed for comparison between low-risk thymomas and high-risk thymomas. Second, the evaluation of several areas such as the spinal cord, spleen, kidney, and bone marrow may be insufficient using DWI because an impeded diffusion can also be seen in these normal structures (Kwee et al., 2010). Third, benign mediastinal tumor or mass lesions with histopathological necrosis may show restricted diffusion and lower ADC values, and be misdiagnosed as malignant. For malignant pulmonary lesions, the ADC value of the lung cancers with necrosis was significantly lower than that of the lung cancers without necrosis (Usuda et al., 2014). Abscesses and thrombi are believed to impede the diffusivity of water molecules because of their hyperviscous nature (Kwee et al., 2010).

PET-CT provides quantitative information regarding cellular glucose metabolism, while DWI provides quantitative information regarding tissue cellularity and the diffusion of water molecules (Liu et al., 2009). 18F-FDG-PET and DWI may offer complementary information for the evaluation of treatment response in lymph node metastases of non-small cell lung cancer using hybrid 18F-FDG PET/MRI (Schaarschmidt et al., 2015).

We have come to the conclusion that DWI can be used routinely for distinguishing benign from malignant mediastinal tumors and mass lesions. There was no significant difference between diagnostic capability of DWI and that of PET-CT for distinguishing mediastinal tumors and mass lesions.

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