RESEARCH ARTICLE

Diagnostic Performance of Whole-Body Diffusion-Weighted Imaging Compared to PET-CT Plus Brain MRI in Staging Clinically Resectable Lung Cancer

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Abstract

Background: Precise staging of lung cancer is usually evaluated by PET-CT and brain MRI. Recently, however, whole-body diffusion-weighted magnetic resonance imaging (WB-DWI) has be applied. The aim of this study is to determine whether the diagnostic performance of lung cancer staging by WB-DWI is superior to that of PET-CT+brain MRI. Materials and Methods: PET-CT + brain MRI and WB-DWI were used for lung cancer staging before surgery with 59 adenocarcinomas, 16 squamous cell carcinomas and 6 other carcinomas. Results: PET-CT + brain MRI correctly identified the pathologic N staging in 67 patients (82.7%), with overstaging in 5 (6.2%) and understaging in 9 (11.1%), giving a staging accuracy of 0.827. WB-DWI correctly identified the pathologic N staging in 72 patients (88.9%), with overstaging in 1 (1.2%) and understaging in 8 patients (9.9%), giving a staging accuracy of 0.889. There were no significant differences in accuracies. PET-CT + brain MRI correctly identified the pathologic stages in 56 patients (69.1%), with overstaging in 7 (8.6%) and understaging in 18 (22.2%), giving a staging accuracy of 0.691. WB-DWI correctly identified the pathologic stages in 61 patients (75.3%), with overstaging in 4 (4.9%) and understagings in16(19.7%), giving a staging accuracy of 0.753. There were no significant difference in accuracies. Conclusions: Diagnostic efficacy of WB-DWI for lung cancer staging is equivalent to that of PET-CT + brain MRI.

Keywords: Lung cancer - staging - whole body diffusion-weighted magnetic resonance imaging - MRI - PET-CT

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Introduction

Staging of lung cancer is very important because several therapies are administered based on which stage of cancer the patient is in. The current methods being used to stage of lung cancer involve 18-fluoro-2-deoxy-glucose positron emission tomography- computed tomography (PET-CT) and brain MRI. Brain MRI is necessary for stage evaluation of lung cancer because PET-CT has a limitation in detecting brain metastasis. Recently whole-body diffusion-weighted magnetic resonance imaging (WB-DWI) has begun to be applied for the staging of lung cancer. WB-DWI provides functional information and is able to highlight oncological lesions throughout the entire body. 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). An MRI examination carries no risk of radiation exposure (Kim et al., 2015), has easier accessibility in hospitals and is relatively cheaper compared with PET-CT. In addition, in a DWI examination patients do not have to fast before the examination, do not need exogenous contrast medium, and less time is required for the examination.

Diagnostic performance of WB-DWI has so far been inconclusive compared to PET-CT: Some research has shown that diagnostic efficacy of WB-DWI is equivalent to that of PET-CT (Ohno et al., 2008; Takenaka et al., 2009; Sommer et al., 2012), superior than that of PET-CT (Laurent et al., 2010), and inferior than that of PET-CT (Plathow et al., 2008). It is not clear whether diagnostic performance for lung cancer by WB-DWI is higher than that of PET-CT+ brain MRI. In this study, diagnostic performance of WB-DWI was compared to that of PET-CT + brain MRI. If diagnostic performance of WB-DWI is shown to be equivalent or superior to that of PET-CT + brain MRI, WB-DWI would become a useful examination tool for the staging of lung cancer.

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Materials and Methods

Eligibility

The study protocol for examining DWI and PET-CT in patients with thoracic diseases was approved by the Institutional Review Board in Kanazawa Medical University (the approval number: No.189). 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 each patient after discussing the risks and benefits of the study with their surgeons.

Patients

From September 2013 to December 2015, 81 patients with operable lung cancer and from whom written informed consents were obtained were enrolled in this study. 51 patients were male and 30 were female. Their mean age was 69.4 years old (range 43 to 82). There were 59 adenocarcinomas, 16 squamous cell carcinomas, 3 adenosquamous carcinomas, 2 large cell neuroendocrine carcinomas and 1 small cell carcinoma. For resection, 68 patients underwent lobectomy with lymph node dissection, and other 13 patients underwent wedge resection or segmentectomy of the lung. TNM classification and the lymph node stations of lung cancer were classified according to the new definition of UICC 7 (International Union Against Cancer, 2009). They underwent PET-CT, brain MRI and WB-DWI within two weeks. Clinical TNM staging of lung cancer by PET-CT + brain MRI and clinical TNM staging by WB-DWI were determined preoperatively through general consensus in the surgical conference by doctors in our department. They underwent pulmonary resection, and the pathological stages of the lung cancers were determined.

Positron emission tomography – computed tomography (PET-CT)

PET-CT scanning was performed with a dedicated PET camera (SIEMENS Biograph Sensation 16, Erlangen Germany). All patients fasted for 6 hours before the cscanning. 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 a radiologist (N.W.) with 29 years of radioisotope scintigraphy and PET-CT experience who was unaware of the patients' clinical data. 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 PET-CT data. A consensus was reached if there were any differences of opinion. The optimal cutoff value (OCV) of SUVmax for diagnosing malignancy in FDG-PET was determined to be 4.45 using the receiver operating characteristics curve as previously reported (Usuda et al., 2013). Hilar, mediastinal lymph nodes or other metastatic lesions with SUVmax of the same or more than the OCV was defined as positive. Hilar, mediastinal lymph nodes or other metastatic lesions with SUVmax less than the OCV, or those that could not be detected on FDG-PET were defined as negative.

Brain MRI

Brain MR images were obtained with a 1.5 T superconducting magnetic scanner (Magnetom Avanto; Siemens, Erlangen, Germany). They consisted of T1 weighted images, T2 weighted images, FLAIR (Fluid Attenuated Inversion Recovery) and MRA (Magnetic Resonance Angiography). The parameters were as follows. T1 weighted images [TR/TE/flip angle/ field of view/ slice thickness/ matrix size: 580/12/75/220 x 198/23/ 320 x 256]. T2 weighted images [TR/TE/flip angle/ field of view/ slice thickness/slice number/ matrix size: 4200/92/150/220 x 198/23/38 x 346]. FLAIR [TR/TE/flip angle/ field of view/ slice thickness/slice number/ matrix size: 9000/110/150/220 x 198/23/320 x 240], MRA [TR/TE/flip angle/ field of view/ slice thickness/slice number/ matrix size : 24/7/20/200 x 166/144/320 x 320]. A radiologist (H.T.) with 39 years of MRI experience who was unaware of the patients' clinical data assessed the MRI data.

Whole - body MRI

The MR image was performed on a 1.5 T superconducting magnetic scanner (Magnetom Avanto; Siemens, Erlangen, Germany) using single-shot echo planar imaging (EPI) sequence with phased-array coils including head, neck and body matrix coils. The sequences employed were T1-weighted spin echo sequences. WB-DWI was performed with slice thickness of 6mm under SPAIR (spectral attenuated inversion recovery) with respiratory triggered scans 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. WB-DWI was used to scan from the skull to the pelvis of the patient. Total examination time was about 30 minutes. 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 T1-weighted or CT image by the radiologist (H.T.) with 39 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 (H.T.) and a pulmonologist (K.U.) with 28 years of experience evaluated the MRI data. A consensus was reached if there were any differences of opinion. The OCV of ADC for diagnosing malignancy in DWI was determined to be 1.70×1D-^{3}mm^2/sec using the receiver operating characteristics curve as previously reported (Usuda et al., 2013). Hilar, mediastinal lymph nodes or other metastatic lesions with ADC value of the same or less than the OCV was defined as positive. Hilar, mediastinal lymph nodes or other metastatic lesions with ADC value of more than the OCV or those that could not be detected on DWI 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, accuracy of whole body DWI versus PET-CT + brain MRI for lung cancer staging were compared using McNemar test, and positive predictive value (PPV) and negative predictive value (NPV) of DWI versus PET-CT for lung cancer staging by using Chi-square test. P value of <0.05 was considered statistically significant.

Results

Diagnostic images between PET-CT +brain MRI and WB- DWI of lung cancer cases are shown in Figure 1-3.

The relationships between clinical N factors (cN factors) diagnosed by PET-CT or whole-body DWI and pathologic N factors (pN factors) are shown (Table 1). Concerning clinical N factor by PET-CT, there were 73 N0 diseases, 1 N1 disease, 4 N2 diseases and 3 N3 diseases. Concerning clinical N factor by WB- DWI, there were 74 N0 diseases, 4 N1 diseases, 2 N2 diseases and 1 N3 disease. Concerning pathological N factor, there were 69 N0 diseases, 8 N1 diseases, and 4 N2 diseases. PET-CT correctly identified the pathologic N staging in 67 patients (82.7%), with overstaging in 5 patients (6.2%) and understaging in 9 patients (11.1%), giving a staging accuracy of 0.827. On the other hand, whole-body DWI correctly identified the pathologic N staging in 71 patients (87.6%), with overstaging in 1 patients (1.2%) and understaging in 8 patients (9.9%), giving a staging accuracy of 0.876. The accuracy for N staging (0.876) by WB-DWI tended to be higher than that (0.827) by PET-CT, but there were no significant differences between them (p = 0.125). And there were no significant differences in sensitivities, specificities, positive predictive values and negative predictive values between PET-CT and WB-DWI (Table 2).

Table 1. Relationships between Clinical N Factors by PET-CT or Whole-body DWI and Pathologic N Factors

Clinical N factor		Pathologic N factor				Total
		pN0	pN1	pN2	pN3	No.
PET-CT	cN0	65	7	1	0	73
	cN1	0	0	1	0	1
	cN2	2	0	2	0	4
	cN3	2	1	0	0	3
Whole-body DWI	cN0	67	6	1	0	74
	cN1	1	2	1	0	4
	cN2	0	0	2	0	2
	cN3	1	0	0	0	1
Total No.		69	8	4	0	81

The relationships between clinical stages (cStage) diagnosed by PET-CT+brain MRI or whole-body DWI and pathologic stages (pStage) are shown (Table 3). Concerning clinical stage by PET-CT+Brain MRI, there were 56 stage IA, 12 stage IB, 5 stage IIA, 1 stage IIB, 4 stage IIIA and 3 stage IIIB. Concerning clinical stage by WB-DWI, there were 57 stage IA, 11 stage IB, 7 stage IIA, 3 stage IIB, 2 stage IIIA and 1 stage IIIB. Concerning pathologic stage, there were 47 stage IA, 16 stage IB, 8 stage IIA, 5 stage IIB, 4 stage IIIA and 1 stage IV.

PET-CT and brain MRI correctly identified the pathologic stages in 56 patients (69.1%), with overstaging in 7 patients (8.6%) and understaging in 18 patients (22.2%), giving a staging accuracy of 0.691. On the other hand, WB-DWI correctly identified the pathologic stages in 61 patients (75.3%), with overstaging in 4 patients (4.9%) and understaging in16 patients(19.7%), giving a

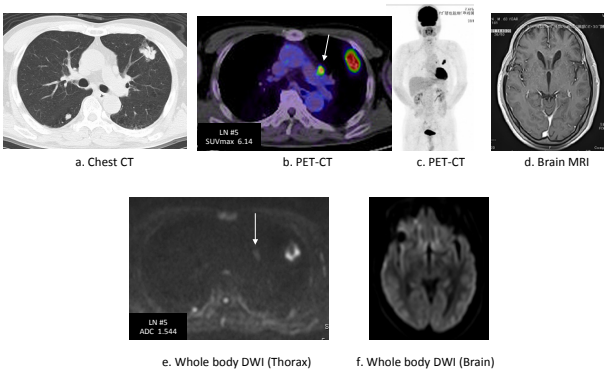

Figure 1. 72 y.o. Male with Pulmonary Adenocarcinoma. The lung cancer was diagnosed clinically as cT2aN2M0 (cStage IIIA) by PET-CT and brain MRI. The lung cancer was also diagnosed clinically as cT2aN2M0 (cStage IIIA) by whole body DWI. The lung cancer had #5 station lymph node metastasis and was pathologically diagnosed as pT2aN2M0 (pStage IIIA)

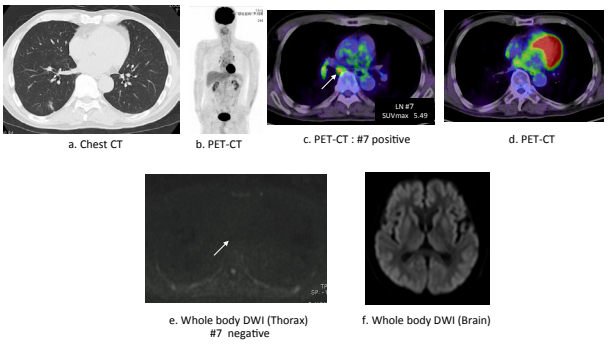

Figure 2. 72 y.o. Male with Pulmonary Adenocarcinoma. The lung cancer was diagnosed as cT1aN2M0 (cStage IIIA) by PET-CT and brain MRI, but pT1aN0M0(pStage IA) by whole body DWI. The lung cancer did not have metastasis of #7 lymph node station and was pathologically diagnosed as pT1aN0M0 (pStage IA)

Table 2. Comparison of Diagnostic Accuracy in the Assessment of Hilar and Mediastinal Lymph Nodes in Lung Cancer of PET-CT and WB-DWI in the McNemar Test or χ^2 Test

Modality	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Negative predictive value (%)
PET-CT	16.7% (2/12)	94.2% (65/69)	82.7% (67/81)	25% (2/8)	89% (65/73)
WB-DWI	33.3% (4/12)	97.1% (67/69)	87.6% (71/81)	57.1% (4/7)	90.5% (67/74)
McNemar test	P=0.179	P=0.5	P=0.125		
χ^2 test				P=0.204	P=0.764

Table 3. Relationships Between Clinical Stages by PET-CT+ Brain MRI or Whole-Body DWI and Pathologic Stages

Clinical stage (cStage)		Pathologic stage (pStage)						Total No.
		pIA	pIB	pIIA	pIIB	pIIIA	pIV	
PET-CT+ brain MRI	cIA	44	7	3	0	1	1	56
	cIB	1	7	2	2	0	0	12
	cIIA	0	1	2	1	1	0	5
	cIIB	0	0	0	1	0	0	1
	cIIIA	1	0	0	1	2	0	4
	cIIIB	1	1	1	0	0	0	3
Whole-body DWI	cIA	46	7	2	0	1	1	57
	cIB	1	7	1	2	0	0	11
	cIIA	0	1	4	1	1	0	7
	cIIB	0	0	1	2	0	0	3
	cIIIA	0	0	0	0	2	0	2
	cIIIB	0	1	0	0	0	0	1
Total No.		47	16	8	5	4	1	81

Table 4. Comparison of the Accuracy of Staging between PET-CT + Brain MRI and WB-DWI in the McNemar Test

		PET-CT + brain MRI		Total
		Correct	Incorrect	
WB-DWI	Correct	56	5	61
	Incorrect	0	20	20

P=0.0625

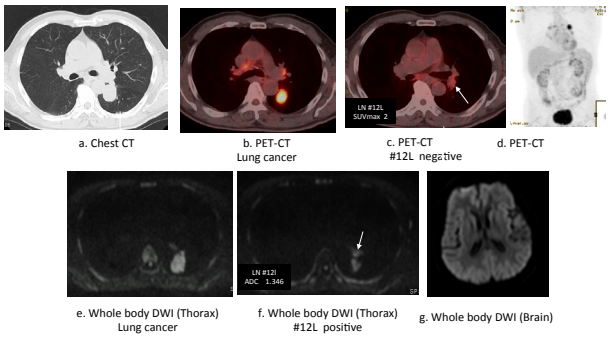

Figure 3. 64 y.o. male with small cell carcinoma. The lung cancer was diagnosed as cT2aN0M0 (cStage IB) disease by PET-CT and brain MRI, but cT2aN1M0(cStage IIA) disease by whole body DWI. Whole body DWI showed lymph node station #12L as positive (f), but not negative by PET-CT. The lung cancer was diagnosed as pT2aN1M0(pStage IIA) disease pathologically.

staging accuracy of 0.753. The accuracy for stages (0.753) by WB-DWI tended to be higher than that (0.691) by PET-CT + brain MRI, but there were no significant differences between them (p = 0.0625) (Table 4).

Discussion

Concerning diagnostic performance of WB-DWI compared to that of PET-CT, there have been several review studies (Kim et al., 2015; Kwee et al., 2009; Lambregts et al., 2011; Li B et al., 2014). WB-DWI was reported to have better performance than PET-CT for detecting brain and hepatic metastases because some lesions were obscured by high physiological FDG uptake of these organs (Kim et al., 2015; Schmidt et al., 2005). On the other hand, WB-DWI seemed to be less sensitive than PET-CT for abdominal and pelvic sites (Stecco et al., 2009). The combined use of WB-DWI and PET-CT may be complementary and improve the diagnostic performance of WB-DWI or PET-CT alone (Li B et al., 2014). WB PET/MRI, which combines PET with MRI, was reported to be more accurate and demonstrated less understaging than PET/CT plus brain MRI (12.6% vs 23.3% respectively) (Plathow et al., 2008). Our study revealed that diagnostic performance of the staging of lung cancer by WB-DWI tended to be higher than that of PET-CT+brain MRI, although there were no significant differences between them. Diagnostic performance of WB-DWI has been shown to be equivalent to that of PET-CT + brain MRI, and WB-DWI will become a useful examination tool for the staging of lung cancer.

Concerning malignancy other than lung cancer, diagnostic performance of WB-DWI has not been determined yet. WB-DWI has shown advantages for the detection of distant metastatic disease (Schmidt et al., 2007; Schmidt et al., 2009), melanoma (Laurent et al., 2010), malignant pheochromocytoma and paraganglioma (Takano et al., 2008). WB-DWI shows high accuracy for characterizing primary tumors, peritoneal and distant staging compared with CT and FDG-PET/CT in ovarian cancer patients (Michielsen et al., 2015). Although diagnostic performance of PET-CT is equivalent to that of WB-DWI, WB-DWI has advantages in the treatment of children because there is no chance of radiation (Darge et al., 2008). In other reports, diagnostic performance of WB-DWI is equivalent to that of PET-CT in lymphoma (Abdulqadhr et al., 2011), and in gastrointestinal cancer (Li B et al., 2014; Gong et al., 2014). However, diagnostic performance of WB-DWI was reported to be inferior to that of PET-CT in lymphoma (van Ufford et al., 2011) and breast cancer (Heusner et al., 2010).

Although PET-CT is widely accepted as the imaging modality of choice in tumor staging, false positive results of hilar and mediastinal lymph nodes by PET-CT were reported to be due to pneumoconiosis, silicosis, pulmonary tuberculosis, and sarcoidosis (Usuda et al., 2013; Konishi et al., 2003; Jain et al., 2011; Lin et al., 2012; Maturu et al., 2014). Evaluation by DWI for patients with multiple hilar and mediastinal lymph nodes with FDG accumulation is useful for distinguishing benignity and malignancy

(Usuda et al., 2015). In PET-CT, care should be taken in lymph node staging for patients who have other pulmonary complications, including interstitial pneumonitis, previous pulmonary tuberculosis and silicosis (Konishi et al., 2003). PET had also some limitations for evaluating sarcoidosis (Jain et al., 2011). PET gives false-negative results for well-differentiated pulmonary adenocarcinoma (Higashi et al., 1998; Cheran et al., 2004), and false-positive results for inflammatory nodules (Goo et al., 2000; Nomori et al., 2004). PET-CT is likely to show false-positive results when lymph nodes contain inflammation, and is likely to show false-negative results when the lymph nodes contain a small amount of cancer cells.

Recently, there have been advancements in MR gradient technology. DWI was reported to be a new promising technique for differentiating inflammatory from metastatic lymph nodes on animal models (Xue et al., 2008). Some reports indicate the superiority of DWI over PET-CT. First, DWI was reported to be superior to PET-CT in detection of primary lesions and 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 with ADC value and signal intensity can be useful in the differentiation of malignant and benign mediastinal lymph nodes (Kosucu et al., 2009). The superiority 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 PET-CT (Nomori et al., 2008), but DWI also gave fewer false-negative results for N staging of non-small cell lung cancer compared with PET-CT (Usuda et al., 2011) .

In conclusions, WB-DWI may become a more useful examination tool in the assessment of lung cancer. WB-DWI is an efficient imaging modality, adding diagnostic performance to PET-CT.

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