Diffusion-weighted magnetic resonance imaging can be used in place of positron emission tomography for N staging of non-small cell lung cancer with fewer false-positive results

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Objective: One of the deficiencies of positron emission tomography for N staging in lung cancer is a false-positive result caused by concurrent lymphadenitis. Recently, diffusion-weighted magnetic resonance imaging has been reported to be able to image tumors of body organs. The aim of this study is to examine the usefulness of diffusion-weighted magnetic resonance imaging for N staging of non-small cell lung cancer compared with positron emission tomography-computed tomography.

Methods: Both positron emission tomography-computed tomography and diffusion-weighted magnetic resonance imaging were prospectively used in 88 patients before surgical intervention for non-small cell lung cancer to examine 734 lymph node stations. The diagnostic results of positron emission tomography-computed tomography and diffusion-weighted magnetic resonance imaging were compared. The diameters of the metastatic foci within lymph nodes were measured on hematoxylin and eosin-stained sections to compare the detectable size of metastatic foci between positron emission tomography-computed tomography and diffusion-weighted magnetic resonance imaging.

Results: The accuracy of N staging in the 88 patients was 0.89 with diffusion-weighted magnetic resonance imaging, which was significantly higher than the value of 0.78 obtained with positron emission tomography-computed tomography ($P = .012$), because of less overstaging in the former. Among the 734 lymph node stations examined pathologically, 36 had metastases, and the other 698 did not. Although there was no significant difference in the diagnosis of the 36 metastatic lymph node stations between the 2 methods, diffusion-weighted magnetic resonance imaging was more accurate for diagnosing the 698 nonmetastatic stations than positron emission tomography-computed tomography because of fewer false-positive results ($P = .002$). The detectable size of metastatic foci within lymph nodes was 4 mm in both positron emission tomography-computed tomography and diffusion-weighted magnetic resonance imaging.

Conclusions: Diffusion-weighted magnetic resonance imaging can be used in place of positron emission tomography-computed tomography for N staging of non-small cell lung cancer with fewer false-positive results compared with positron emission tomography-computed tomography.

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Several noninvasive diagnostic procedures are used for preoperative N staging in patients with non-small cell lung cancer (NSCLC), including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). However, CT is not sufficiently sensitive or specific for diagnosing lymph node metastases because a size of 1 cm or larger is the only criterion used to differentiate benign from malignant lymph nodes. In recent years fluorodeoxyglucose (FDG)-PET has been reported to be able to detect metastatic lymph nodes smaller than 1 cm.¹⁻⁴ Several meta-analytic studies have demonstrated PET to be superior to CT for N staging in lung cancer.⁵⁻⁷ However, one of the deficiencies of PET for N staging is a false-positive result for concurrent lymphadenitis associated with NSCLC.^{1,8}

Recent advances in MRI gradient technology allow acquisition of diffusion-weighted magnetic resonance imaging (DWI), which provides excellent tissue contrast based on difference in the diffusion of water molecules among tissues and is different from ordinary T1- and T2-weighted images. Because the diffusion of water molecules is restricted by intracellular organelles and macromolecules, any architectural changes in the proportion of extracellular to intracellular water protons will alter the signal intensity of DWI and the apparent diffusion coefficient (ADC).⁹⁻¹¹ Malignant tumors have increased cellularity, larger nuclei with more abundant macromolecular proteins, larger nuclear cytoplasmic ratios, and less extracellular space compared with values in normal tissue. Therefore diffusion of water molecules in malignant tumors is usually restricted compared with that in normal tissue, resulting in a decreased ADC value.^{12,13}

Although the clinical utility of DWI was initially established in the central neural system, application of this technique to body organs has been considered difficult because DWI is highly sensitive to motion artifacts caused not only by breathing but also by the beats of the heart and aorta.¹⁴ However, the recent development of fast imaging techniques, such as echoplanar imaging and parallel imaging, has improved DWI for use in body organs.^{15,16} In addition to these methods, 3-dimensional display of DWI with a reversed gray scale can also produce images similar to PET images.¹² The further recent development in fusion software, which overlays DWI onto ordinary magnetic resonance images, can identify the anatomic location of regions with intense signals on DWI. DWI has been recently reported to be able to show body tumors, including colorectal cancer, prostate cancer, and breast cancer.^{13,17,18} Our recent study has also shown that DWI is useful for differentiating between malignant and benign pulmonary nodules as well as PET-CT (data not shown). However, there have been no reports for N staging of malignancies. In this study we evaluated N staging of NSCLC by using DWI compared with PET-CT.

Abbreviations and Acronyms

ADC	= apparent diffusion coefficient
CR	= contrast ratio
CT	= computed tomography
DWI	= diffusion-weighted magnetic resonance imaging
FDG	= fluorodeoxyglucose
FN	= false-negative
FP	= false-positive
MRI	= magnetic resonance imaging
NSCLC	= non-small cell lung cancer
PET	= positron emission tomography
STIR	= short tau inversion recovery
SUV	= standard uptake value
TE	= echocardiographic time
TN	= true-negative
TP	= true-positive
TR	= repetition time

Materials and Methods

Eligibility

The study protocol for examining FDG-PET and DWI in patients with suspected NSCLC before undergoing surgical intervention was approved by the Ethics Committee of Kumamoto University Hospital in January 2006. Informed consent was obtained from all patients after discussing the risks and benefits of the study with their surgeons.

Patients

Between February 2006 and May 2007, 93 patients with lung cancer prospectively underwent PET-CT and DWI before pulmonary resection. Of these patients, 88 patients with NSCLC who underwent pulmonary resection and mediastinal lymph node dissection were enrolled in this study. The histologic types of lung cancer were adenocarcinoma in 67 patients, squamous cell carcinoma in 18 patients, and adenosquamous carcinoma in 3 patients (Table 1). The pathologic N stages were N0 in 71 patients, N1 in 9 patients, and N2 in 8 patients. The lymph node stations were classified according to the lymph node map of Naruke, which is approved by the Japan Lung Cancer Society.¹⁹

PET-CT Scanning

Patients were instructed to fast for at least 5 hours before intravenous administration of FDG. The administered dosage of FDG was 100 μ Ci/kg (3.7 MBq/kg) of body weight. PET imaging was performed approximately 60 minutes after intravenous administration of the FDG by using an integrated PET-CT device (Discovery ST; GE Medical Systems) that consisted of a PET scanner (Advance Nx; GE Medical Systems) and an 8-section CT scanner (Light Speed Plus; GE Medical Systems).

The acquisition time for PET in 3-dimensional mode was 3 minutes per table position. CT data were resized from a 512 $\times$ 512 matrix to a 128 $\times$ 128 matrix to match the PET data to allow image fusion, and a CT transmission map was generated. PET image

TABLE 1. Patient characteristics

Mean age, y (range)	70 ± 9 (38–82)
Male sex	47
Female sex	41
Mean tumor size, cm (range)	2.1 ± 1.0 (0.5–8.0)
Tumor location	
Right upper lobe	29
Right middle lobe	5
Right lower lobe	25
Left upper lobe	20
Left lower lobe	9
Histologic type	
Adenocarcinoma	62
Squamous cell carcinoma	14
Adenosquamous carcinoma	2
Pathologic N stage	
N0	71
N1	9
N2	8
Total	88

data were reconstructed iteratively by using the ordered subsets expectation maximization algorithm with segmented attenuation correction (4 iterations, 28 subsets) and the CT data. The 3.75-mm-thick transaxial CT images were reconstructed at 3.27-mm intervals (transaxial) for fusion with the transaxial PET images. The PET, CT, and fused images were available for review in axial, coronal, and sagittal planes by using software (Xeleris; GE Medical Systems) on a computer workstation.

DWI

All magnetic resonance images were obtained with a 1.5-T superconducting system (Gyrosan Intera Achieva Nova Dual; Philips Medical Systems). Conventional magnetic resonance images and DWI were acquired during the same procedure. The conventional magnetic resonance images consisted of a coronal T1-weighted sequence (repetition time [TR] in milliseconds/echocardiographic time [TE] in milliseconds/excitations: 234/4/1), a coronal and axial single-shot spin echocardiographic T2-weighted (800/90/1) sequence, and a coronal and axial short tau inversion recovery (STIR; TR/TE/inversion time, 4600/90/160) sequence. The T1-weighted, T2-weighted, and STIR sequences were acquired at a section thickness of 6 mm with a 1-mm intersection gap, a 128 × 128 – 256 matrix, and a 40- to 45-cm field of view.

DWI was performed for the thorax in the transverse plane by using a spin echocardiographic, echoplanar imaging sequence with the following parameters: TR/TE/flip angle, 5900/60/90; diffusion gradient encoding in 3 orthogonal directions; b value, 1000 s/mm²; field of view, 400 mm; matrix size, 112 × 100; section thickness, 6 mm; section gap, 1 mm; and number of signals acquired, 6. DWI data were evaluated semiquantitatively by using the ADC. The ADC was calculated as follows: $ADC = -[ln(S/S_0)]/b$, where S is the signal intensity of the region of interest obtained through 3 orthogonally oriented DWIs and b is the gradient b factor with a value of 1000 s/m².

N Staging by Means of PET-CT Scanning

Two radiologists (KK and SS, with 14 and 11 years, respectively, of radioisotope scintigraphy and PET interpretation experience) evaluated the PET-CT data before the operation. N staging by means of PET-CT was determined as follows. The region of interest was placed on the lymph nodes more than 1 cm in the long axis, for which the standard uptake value (SUV) was measured. The contrast ratio (CR) of SUV (SUV-CR) was calculated as the SUV of the lymph nodes divided by the SUV of the cerebellum in each lymph node, as reported previously.¹

N Staging by means of DWI

One radiologist (KK, with 14 years of MRI interpretation experience) evaluated the MRI data before the operation. N staging by means of DWI was determined as follows: the region of interest was placed on the lymph nodes more than 1 cm in the long axis, and the minimum ADC value (ADC-min) was measured.

Determining the Cutoff Values of SUV-CR and ADC-min

A receiver operating characteristic curve was constructed from the SUV-CR and ADC-min data by using SPSS software (SPSS 15.0 J for Windows, SPSS, Inc), and the cutoff values for a diagnosis of metastasis were determined. Lymph nodes with SUV-CR values of greater than the cutoff value were defined as positive by means of PET-CT. Lymph nodes with SUV-CR values of less than the cutoff value or those that could not be detected on PET-CT were defined as negative by means of PET-CT. By using DWI, lymph nodes with ADC-min values of less than the cutoff value were defined as positive by means of DWI. Lymph nodes with ADC-min values of greater than the cutoff value or those that could not be detected on DWI were defined as negative by means of DWI.

Measuring the Size of Metastatic Foci

The long-axis diameters of metastatic foci within lymph nodes were measured on hematoxylin and eosin–stained sections with a microscope to compare the detectable size of metastatic foci between PET-CT and DWI.

Statistical Analysis

True-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) results of PET-CT and DWI images for the diagnosis of lymph node metastasis were compared with the results of the pathologic diagnosis. Sensitivity was calculated as $TP/TP+FN$, specificity as $TN/TN+FP$, and accuracy as $TP+TN/Total$. The sensitivity, specificity, and accuracy of PET-CT versus DWI for N staging and diagnosing each lymph node station were compared by using a McNemar test. The size of the metastatic foci was analyzed by using the 2-tailed Student *t* test. All values in the text and tables are given as means ± standard deviation.

Results

DWI identified metastatic lymph nodes, as well as primary tumors, like PET images (Figure 1). Eighty lymph nodes in the 88 patients that were greater than 1 cm in their longest axis were studied to determine the cutoff values with the receiver operating characteristic curves. The receiver operating

Figure 1. Diffusion-weighted magnetic resonance imaging with a reversed gray scale in adenocarcinoma of the right lower lobe with hilar lymph node metastases, which shows similar images of positron emission tomography.

characteristic curves for the diagnosis of metastasis in these 80 lymph nodes showed an optimal cutoff value of SUV-CT on PET-CT to be 0.26 and ADC-min on DWI to be $1.6 \times 10^{-3} \text{ mm}^2/\text{s}$ (Figures 2 and 3).

Table 2 shows the results of N staging with PET-CT and DWI. Among the 88 patients, PET-CT correctly identified the pathologic N stage in 69 patients, with overstaging in 12 patients and understaging in 7 patients, giving a staging accuracy of 0.78. DWI images correctly identified the pathologic N stage in 78 patients, with overstaging in 4 patients and understaging in 6 patients, giving a staging accuracy of 0.89.

Tables 3 to 6 show the data for the analysis by using the McNemar test. Both PET-CT and DWI gave correct N staging in 68 patients but incorrect staging in 9 patients (Table 3). Although N staging was correct by means of PET-CT but incorrect by means of DWI in 1 patient, it was correct by means of DWI but incorrect by means of PET-CT in 10 patients. DWI diagnosed N staging significantly more accurately than PET-CT because of a reduction in overstaging (McNemar test, $P = .02$).

Of the 734 lymph node stations examined, 36 had metastases, and the other 698 did not. In the 36 metastatic lymph node stations, both PET-CT and DWI produced TP results in 24 and FN results in 10 (Table 4). Although results for 2 metastatic lymph node stations were TP with PET-CT but

Figure 2. Receiver operating characteristic curve and standard uptake value–contrast ratio value for diagnosing lymph node metastasis on positron emission tomography–computed tomography shows the optimal cutoff value to be 0.26. Area under the curve, 0.79; 95% confidence interval, 0.69 to 0.89.

FN with DWI, results of none of the metastatic lymph nodes were TP with DWI but FN with PET-CT. The sensitivities of PET-CT and DWI were 0.72 (95% confidence interval, 0.65–0.87) and 0.67 (95% confidence interval, 0.52–0.82), respectively. There was no significant difference in the diagnosis of metastatic lymph node stations between PET-CT and DWI (McNemar test, $P = .5$).

In the 698 nonmetastatic lymph node stations, results of both PET-CT and DWI were FP in 3 and TN in 678 (Table 5). Although results with 15 nonmetastatic lymph node stations were FP with PET-CT but TN with DWI, 2 were FP with DWI but TN with PET-CT. The specificities of PET-CT and DWI were 0.97 (95% confidence interval, 0.962–0.986) and 0.99 (95% confidence interval, 0.987–0.996), respectively. DWI showed a greater specificity than PET-CT (McNemar test, $P = .002$). The 18 lymph node stations that had FP results on PET-CT showed histologic findings of nonspecific lymphadenitis ($n = 15$) or tuberculosis ($n = 3$), with a mean size on CT of $12 \pm 2 \text{ mm}$ (range, 10–14 mm). The 5 lymph node stations that had FP results on DWI showed tuberculosis ($n = 3$) or nontuberculosis ($n = 2$) granulation, with a mean size on CT of $12 \pm 2 \text{ mm}$ (range, 10–14 mm). The results of DWI were not FP for the 15 stations with nonspecific lymphadenitis, which were FP with PET-CT.

In the overall 734 lymph node stations, both PET-CT and DWI gave correct diagnoses in 702 stations but incorrect

Figure 3. Receiver operating characteristic curve and apparent diffusion coefficient value for diagnosing lymph node metastasis on diffusion-weighted magnetic resonance imaging shows the optimal cutoff value to be $1.6 \times 10^{-3} \text{ mm}^2/\text{s}$. Area under the curve, 0.82; 95% confidence interval, 0.71 to 0.94.

diagnoses in 13 stations (Table 6). Although the diagnosis was correct by means of PET-CT but incorrect by means of DWI in 4 lymph node stations, it was correct by means of DWI but incorrect by means of PET-CT in 15 stations. DWI diagnosed lymph node stations significantly more accurately than PET-CT because of fewer FP results (McNemar test, $P = .019$).

The sizes of the metastatic foci in the lymph nodes that had FN results on PET-CT ranged from 0.5 to 3 mm, with a mean value of 1.2 ± 0.9 mm, whereas those with TP results ranged from 3 to 13 mm, with a mean value of 9 ± 4 mm (Figure 4). There was a significant difference in the size of metastatic foci between the FN and TP lymph nodes ($P < .001$). PET was unable to detect any of the metastatic foci smaller than 4 mm, except for one foci with 3 mm, but detected all those larger than 4 mm.

TABLE 2. N staging by means of positron emission tomography and diffusion-weighted magnetic resonance imaging

	Correct, n (%)	Incorrect, n (%)		Total
		Overstaging, n (%)	Understaging, n (%)	
PET-CT	69 (78)	12 (14)	7 (8)	88
DWI	78 (89)	4 (5)	6 (7)	88

PET-CT, Positron emission tomography–computed tomography; DWI, diffusion-weighted magnetic resonance imaging.

TABLE 3. Correlation of accuracy for N staging between positron emission tomography and diffusion-weighted magnetic resonance imaging

	PET-CT		Total
	Correct	Incorrect	
DWI			
Correct	68	10	78
Incorrect	1	9	10
Total	69	19	88

PET-CT, Positron emission tomography–computed tomography; DWI, diffusion-weighted magnetic resonance imaging. McNemar test: $p = .012$.

The sizes of the metastatic foci that had FN results on DWI ranged from 0.5 to 8 mm, with a mean value of 2.0 ± 2.3 mm, whereas those with TP results ranged from 3 to 13 mm, with a mean of 10 ± 4 mm (Figure 5). There was a significant difference in the size of metastatic foci between the lymph nodes with FN and TP results ($P < .001$). DWI was unable to detect any of the metastatic foci smaller than 4 mm, except for one focus with 3 mm, but detected all those larger than 4 mm except for one focus of adenocarcinoma 8 mm in size.

Discussion

This study showed a superiority of DWI to PET-CT for N staging in patients with NSCLC because of fewer FP diagnoses in the former. FP diagnosis with PET-CT caused by concurrent lymphadenitis is well known for N staging in patients with NSCLC.^{1,8} Most of the lymph nodes with FP results on PET-CT in this study also showed histologic findings of lymphadenitis, whereas DWI did not show FP results for them. We therefore conclude that DWI can be used in place of PET-CT for N staging of NSCLC and that it is also associated with a reduction in the number of overstagings compared with PET-CT.

The difference in the ADC value between metastatic and nonmetastatic lymph nodes is considered to be caused by the difference in cellularity and structural features between

TABLE 4. Correlation between positron emission tomography and diffusion-weighted magnetic resonance imaging for diagnosis of the 36 metastatic lymph node stations

	PET-CT		Total
	True-positive	False-negative	
DWI			
True-positive	24	0	24
False-negative	2	10	12
Total	26	10	36

PET-CT, Positron emission tomography–computed tomography; DWI, diffusion-weighted magnetic resonance imaging. Sensitivity of PET-CT, 0.72 (95% confidence interval, 0.65–0.87); sensitivity of DWI, 0.67 (95% confidence interval, 0.52–0.82). McNemar test: $P = .5$.

TABLE 5. Correlation between positron emission tomography and diffusion-weighted magnetic resonance imaging for diagnosis of the 698 nonmetastatic lymph node stations

	PET-CT		Total
	False-positive	True-negative	
DWI			
False-positive	3	2	5
True-negative	15	678	693
Total	18	680	698

PET-CT, Positron emission tomography–computed tomography; *DWI*, diffusion-weighted magnetic resonance imaging. Specificity of PET-CT, 0.97 (95% confidence interval, 0.962–0.986); specificity of DWI, 0.99 (95% confidence interval, 0.987–0.996). McNemar test: *P* = .002.

them. Malignant lymph nodes have increased cellularity, larger nuclei with more abundant macromolecular proteins, nuclear cytoplasmic ratios, and less extracellular space than benign nodes, which reduce diffusion of water molecules on DWI, resulting in decreased ADC values.^{12,13} The significant decrease in FP results on DWI might be due to the following reasons: although the nonspecific lymphadenitis increases FDG uptake, this would not change the basic architecture of lymph nodes, resulting in a similar ADC value between lymphadenitis and normal lymph nodes. However, granulation tissue in tuberculosis or nontuberculosis lymph nodes showed FP results on DWI because an architectural change with granulation tissue decreases the diffusion of water molecules on DWI.

Although SUV has frequently been used for evaluation of FDG-PET, it has been reported that several factors can affect the SUV, such as body size,²⁰ blood glucose level,²¹ and time after injection.²² We previously compared the results of SUV-max, SUV-CR with contralateral lung, and SUV-CR with cerebellum for pulmonary nodules and reported that SUV-CR with contralateral lung or cerebellum showed significantly higher sensitivity than SUV-max,²³ a result supported by Obrzut and associates.²⁴

TABLE 6. Correlation of accuracy for diagnosis of over all lymph node stations between positron emission tomography and diffusion-weighted magnetic resonance imaging

	PET-CT		Total
	Correct	Incorrect	
DWI			
Correct	702	15	717
Incorrect	4	13	17
Total	706	28	734

PET-CT, Positron emission tomography–computed tomography; *DWI*, diffusion-weighted magnetic resonance imaging. Correct: true-positive + true-negative results; incorrect: false-positive + false-negative results. McNemar test: *P* = .019.

Figure 4. The distribution of sizes of metastatic foci in false-negative and true-positive lymph nodes with positron emission tomography–computed tomography (*PET-CT*). The difference between them was a *P* value of less than .001.

Although the present study showed the cutoff value of ADC-min for diagnosing metastatic lymph nodes to be $1.6 \times 10^{-3} \text{ mm}^2/\text{s}$, our recent study for diagnosing malignant pulmonary nodules by means of DWI showed the cutoff value of ADC-min to be $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$. The reason why the cutoff value of ADC for diagnosing metastatic lymph nodes was higher than that for diagnosing malignant pulmonary nodules could be due to the fact that the ADC value of lymph nodes might increase with motion artifact by the beats of the heart and great vessels in the hilum and

Figure 5. The distribution of sizes of metastatic foci in false-negative and true-positive lymph nodes with diffusion-weighted imaging (*DWI*). The difference between them was a *P* value of less than .001.

mediastinum, whereas the ADC value of peripheral pulmonary nodules should be little affected by these motion artifacts. The cutoff value of SUV-CR on PET-CT for differentiating metastatic lymph nodes was 0.26 in this study, which was similar to our previous report and others.^{1,24}

FN results were similar between PET-CT and DWI. Both diagnostic tools had very limited ability to detect lymph nodes with metastatic foci smaller than 4 mm. Considering the spatial resolution of the PET scanner, artifacts resulting from respiratory movements, and image reconstruction, it is difficult to evaluate such small metastatic foci. Even on DWI, STIR sequences were acquired at a section thickness of 6 mm, causing lymph nodes with small metastatic foci to be missed. We previously reported that 32% of metastatic lymph nodes of NSCLC had metastatic foci smaller than 4 mm.¹ Because neither PET-CT nor DWI was able to detect metastatic foci smaller than 4 mm, which were not unusual sizes of metastatic lymph nodes in NSCLC, lymph node dissection cannot be reduced for patients with N0 stage NSCLC diagnosed by means of either PET-CT or DWI.

Our study had the following limitations: (1) because the patients in the present study were referred to surgical intervention, 71 (81%) of 88 patients had N0 disease, which might cause a group-specific bias and a superiority of DWI to PET, and (2) DWI in the present study just examined the thorax and not the whole body, whereas PET-CT showed the whole body. Recently, whole-body DWI has become available. Lichy and colleagues²⁵ compared the tumor detection between whole-body DWI and PET-CT for 19 patients with various kinds of tumors, showing a feasibility of the former for clinical practice. We believe that whole-body DWI will be used routinely for TNM staging of patients with lung cancer in the near future.

MRI has the following advantages over PET: (1) patients do not have to fast before examination; (2) there is no radiation exposure; (3) less time is required for examination (30 minutes for DWI vs 90 minutes for PET-CT); and (4) there is less cost (\$100 for DWI vs \$700 for PET-CT in Japan). Although PET-CT is still superior to DWI on whole-body imaging, this study showed that that DWI can be used in place of PET-CT for N staging of NSCLC and is associated with significantly fewer FP results compared with PET-CT. In the future, a multicenter study with a larger dataset will be necessary.

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