Received: 28 May 2013 Revised: 13 January 2014

Accepted: 29 April 2014

 $\mathit{B\!J\!R}$   $\blacksquare$   $\bl$ 

#### Cite this article as:

Koyama H, Ohno Y, Nishio M, Takenaka D, Yoshikawa T, Matsumoto S, et al. Diffusion-weighted imaging vs STIR turbo SE imaging: capability for quantitative differentiation of small-cell lung cancer from non-small-cell lung cancer. Br J Radiol 2014;87:20130307.

## FULL PAPER

# Diffusion-weighted imaging vs STIR turbo SE imaging: capability for quantitative differentiation of small-cell lung cancer from non-small-cell lung cancer

<sup>1</sup>H KOYAMA, MD, PhD, <sup>2,3</sup>Y OHNO, MD, PhD, <sup>2,3</sup>M NISHIO, MD, PhD, <sup>4</sup>D TAKENAKA, MD, <sup>2,3</sup>T YOSHIKAWA, MD, PhD,<br><sup>2,3</sup>S MATSUMOTO, MD, PhD, <sup>1</sup>S SEKI, MD, <sup>5</sup>Y MANIWA, MD, PhD, <sup>6</sup>T ITO, MD, PhD, <sup>7</sup>Y NISHIMURA, MD, PhD a <sup>2,3</sup>S MATSUMOTO, MD, PhD, <sup>1</sup>S SEKI, MD, <sup>5</sup>Y MANIWA, MD, PhD, <sup>6</sup>T ITO, MD, PhD, <sup>7</sup>Y NISHIMURA, MD, PhD and <sup>1</sup>K SUGIMURA, MD

<sup>1</sup> Division of Radiology, Department of Radiology, Kobe University Graduate School of Medicine, Kobe, Japan

2Advanced Biomedical Imaging Research Center, Kobe University Graduate School of Medicine, Kobe, Japan

<sup>3</sup>Division of Functional and Diagnostic Imaging Research, Department of Radiology, Kobe University Graduate School of Medicine, Kobe, Japan

4Department of Diagnostic Radiology, Hyogo Cancer Center, Akashi, Japan

5Division of Thoracic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

6Division of Diagnostic Pathology, Department of Pathology, Kobe University Graduate School of Medicine, Kobe, Japan

<sup>7</sup>Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

Address correspondence to: Dr Hisanobu Koyama E-mail: [hkoyama@med.kobe-u.ac.jp](mailto:hkoyama@med.kobe-u.ac.jp)

Objective: To compare the capability of differentiation of small-cell lung cancer (SCLC) from non-SCLC (NSCLC) between diffusion-weighted imaging (DWI) and short tau inversion recovery (STIR) turbo spin-echo imaging.

Methods: The institutional review board of Kobe University Hospital, Kobe, Japan, approved this study, and written informed consent was obtained from each patient. 49 patients with NSCLC (30 males and 19 females; mean age, 66.8 years) and 7 patients with SCLC (5 males and 2 females; mean age, 68.6 years) enrolled and underwent DWI and STIR. To quantitatively differentiate SCLC from NSCLC, apparent diffusion coefficient (ADC) values on DWI and contrast ratios (CRs) between cancer and muscle on STIR were evaluated. ADC values and CRs were then compared between the two cell types by Mann–Whitney's U-tests,

Lung cancer is the most common cause of cancer-related death among both males and females worldwide.<sup>1</sup> Lung cancers are divided into non-small-cell cancer (NSCLC) and small-cell lung cancer (SCLC), and the differentiation between SCLC and NSCLC is important in clinical practice because their therapeutic strategies, clinical course and prognoses are different.<sup>2</sup> In general, SCLC is usually determined with extensive hilar and mediastinal lymphadenopathy, $3$  and these cancers are mainly treated by chemotherapy or chemoradiotherapy. $2,4$ 

On the other hand, 5–10% of patients with SCLC were diagnosed as having solitary pulmonary nodules.<sup>[5](#page-6-0),[6](#page-6-0)</sup> In this and the diagnostic performances were compared by McNemar's test.

Results: There were significant differences of mean ADC values ( $p < 0.001$ ) and mean CRs ( $p = 0.003$ ). With adopted threshold values, the specificity (85.7%) and accuracy (85.7%) of DWI were higher than those of STIR (specificity, 63.3%;  $p = 0.001$  and accuracy, 66.1%;  $p = 0.001$ ). In addition, the accuracy of combination of both indexes (94.6%;  $p = 0.04$ ) could significantly improve as compared with DWI alone.

Conclusion: DWI is more useful for the differentiation of SCLC from NSCLC than STIR, and their combination can significantly improve the accuracy in this setting.

Advances in knowledge: Pulmonary MRI, including DWI and STIR, had a potential of the suggestion of the possibility as SCLC.

situation, the assessments of distant metastases before treatment play an important role in deciding the treatment. At present, although there are some different reports for patients with NSCLC regarding the assessment of distant metastases before surgery, $7-9$  $7-9$  $7-9$  it is important to assess the distant metastases of these patients with SCLC because SCLC is known for its rapid doubling time, high growth fraction and early development of metastatic disease.<sup>[10](#page-6-0)-[12](#page-6-0)</sup> If patients with SCLC are diagnosed at Stage I or possibly Stage II, clinicians consider their treatment as surgery and/ or neoadjuvant chemotherapy.[13](#page-6-0)–[15](#page-6-0) Therefore, the differentiation between SCLC and NSCLC and the suggestion of the possibility of SCLC may be important in routine clinical practice. However, the differentiation of SCLC from NSCLC is difficult on CT and positron emission tomography (PET) or PET/CT,<sup>[5,6](#page-6-0),[16](#page-6-0)</sup> and fiberoptic bronchoscopy and percutaneous biopsy are recommended, although their diagnostic sensitivities range from 67% to 100%.<sup>[17](#page-7-0)-[19](#page-7-0)</sup>

Recently, the image quality and diagnostic capability of chest MRI has improved because of the advancement of MR systems and sequences, and short tau inversion recovery (STIR) turbo spin-echo (SE) imaging and diffusion-weighted imaging (DWI) have been reported as useful in differentiating malignant nod-ules and lymph nodes from benign ones in several articles.<sup>[20](#page-7-0)-[25](#page-7-0)</sup> Meanwhile, the utilities of chest MRI, including STIR and DWI, have been reported, $26$  and, in addition, meta-analysis report for pulmonary nodules by means of DWI have been published.<sup>[27](#page-7-0)</sup> However, to the best of our knowledge, there have been only reports of chest DWI regarding the differentiation between SCLC and NSCLC,<sup>[22](#page-7-0)</sup> but no major studies have reported a direct comparison of the use of DWI and STIR in chest MRI for the assessment of differentiation between SCLC and NSCLC. We hypothesized that both DWI and STIR were useful MR sequences for differentiation of SCLC from NSCLC and their combination might improve the differentiation capabilities. The aim of this study was to evaluate the diagnostic performances of DWI and STIR for differentiating between SCLC and NSCLC.

#### METHODS AND MATERIALS

#### **Subjects**

The institutional review board of Kobe University Hospital, Kobe, Japan, approved this study, and written informed consent was obtained from every subject before his or her enrolment in this study.

Between January 2006 and December 2011, 221 patients (139 males and 82 females; mean age, 65.3 years) who had been referred to our hospital, had been radiologically and pathologically diagnosed as having lung cancer and were considered to be candidates for surgical resection underwent chest MRI, including DWI and STIR. Of these 221 patients, 7 patients (5 males and 2 females; mean age, 68.6 years; age range, 62–73 years) were diagnosed with SCLC via pathological examinations of surgical specimens, and these patients were enrolled in this study. On the other hand, 60 patients with NSCLC were consecutively selected, and patients meeting the following criterion were excluded. The criterion was the air-containing lung adenocarcinoma (AD) based on CT appearance, because of the inability to measure the apparent diffusion coefficient (ADC) values of lesions located adjacent to air-containing organs because of susceptibility artefact in these cancers.[28](#page-7-0) Finally, according to this criterion 49 patients with NSCLC (30 males and 19 females; mean age, 66.8 years; age range, 42–82 years) were also enrolled in this study. All MR examinations were performed before the surgery treatment, and all MR images were not influenced by the therapeutic effect of radiation and/or chemotherapy. The details of these patients are shown in [Table 1,](#page-2-0) and their pathological diagnoses were as follows: 30 ADs, 14 squamous cell carcinomas (SQs) and 5 large-cell neuroendocrine carcinomas (LCNECs). There was no significant difference of ages and diameters between

patients with SCLC and patients with NSCLC by means of Mann–Whitney's U-test.

#### Chest MRI

Images of MR were obtained by a 1.5-T MRI machine (Gyroscan Intera; Philips Medical Systems, Best, Netherlands) and a fourchannel sensitivity encoding body coil was used.

The sequentially re-ordered, half-Fourier, single-shot STIR SE echo-planar imaging sequence was performed for acquisition of DWI. The details of the sequence are as follows: free breathing acquisition; repetition time (TR), 5000 ms; echo time (TE), 70 ms; inversion time (TI), 180 ms; number of excitations (NEX), 5; echo train length, 41; slice thickness, 5 mm; slice gap, 1.5 mm; matrix size,  $96 \times 96$ ; reconstruction matrix,  $256 \times 256$ ; and b-values, 0 and 1000 s mm<sup>-2</sup>. Acquisition time was 5.0 min.

Yet, a centrically re-ordered, multishot, black blood STIR turbo SE sequence was performed for acquisition of STIR. The details of the sequence are as follows: breath holding acquisition; TR,  $2-3 < R-R$  ms; effective TE (TEeff), 8 ms; TI, 165 ms; NEX, 2; echo train length, 27; slice thickness, 5 mm; slice gap, 1.5 mm; matrix size,  $256 \times 256$ ; reconstruction matrix size,  $512 \times 512$ ; field of view, 320 mm; and reduction factor, 4. Mean acquisition time was 3.0 min (range, 2.5–3.5 min).

#### Pathological examinations and gold standard for pulmonary adenocarcinomas

Each resected lung specimen was fixed at end-inspiration volume. Owing to correlation of radiological findings with histopathological examinations, the specimens were cut into serial 1-mmthick sections by referring to the axial radiological images. By pathologists with more than 15 years' experience, the specimens were stained with haematoxylin–eosin and diagnosed by the same pathologists.

#### Image analysis

All MR data were analysed with picture archiving and communication systems (ShadeQuest; Yokogawa, Tokyo, Japan).

For quantitative assessment of DWI, the ADC values were used. Meanwhile, the assessment of STIR was by using contrast ratios (CRs) for each nodule or mass and the muscle. The details of these methods are given in the following paragraphs.

Regions of interest (ROIs) were placed over each pulmonary lesion on DWI by one chest radiologist (HK) according to the consensus of two readers who had no knowledge of the pathological type of the lung cancer (HK and DT). A ROI was placed over the nodule or mass and encompassed the entire cross-sectional area of the nodule or mass, making it as large as possible and excluding necrotic lesions. The mean ADC value was then calculated using the following formula:

$$
ADC value = -\left[\ln(S_h/S_l)\right]/(b_h - b_l) \tag{1}
$$

where  $S_h$  and  $S_l$  are the signal intensities in the ROI obtained with two different gradient factors  $(b<sub>h</sub>$  and  $b<sub>l</sub>$ ). In this study,  $b<sub>h</sub>$ was 1000 s mm<sup>-2</sup> and  $b_1$  was 0 s mm<sup>-2</sup>.

Characteristics	<b>SCLC</b>	Non-small-cell lung cancer	Large-cell neuroendocrine carcinoma	Squamous cell carcinoma	Adenocarcinoma
Male/female	5/2	30/19	5/0	10/4	15/15
Mean age (years)	68.6	66.8	73.6	66.5	65.9
Range (years)	$62 - 73$	$43 - 82$	$68 - 78$	$43 - 82$	$45 - 81$
		$p = 0.46^a$	$p = 0.81^{b}$	$p = 0.97^b$	$p = 0.91^b$
Mean diameter (mm)	35.0	34.2	38.0	33.4	33.9
Range (mm)	$25 - 56$	$11 - 69$	$25 - 56$	$11 - 56$	$13 - 69$
		$p = 0.34^a$	$p = 0.98^a$	$p = 0.99^a$	$p = 1.00^a$
Location					
Right upper lobe	$\overline{2}$	19	3	$\overline{4}$	12
Right middle lobe	N/A	$\mathbf{1}$	N/A	N/A	1
Right lower lobe	$\mathbf{1}$	14	$\overline{2}$	6	6
Left upper lobe	$\mathbf{1}$	11	N/A	$\mathbf{1}$	10
Left lower lobe	3	$\overline{4}$	N/A	3	

<span id="page-2-0"></span>Table 1. Details of the subjects in this study

N/A, not applicable; SCLC, small-cell lung cancer.

<sup>a</sup>Difference with SCLC by using Mann-Whitney's U-test.

 $b$ Difference with SCLC by using the Tukey honest-significance test.

STIR assessment was performed based on past literature.<sup>[24,25](#page-7-0)</sup> ROIs were placed over each pulmonary lesion and the rhomboid muscle by the same chest radiologist (HK) based on the consensus of two readers who lacked information on the pathological type of lung cancer (HK and DT). A ROIwas placed over pulmonary lesions in a similar way as with DWI, whereas the ROI placed over the muscle was fixed at 120 mm<sup>2</sup>. The CR was then acquired following the formula:

$$
CR = \frac{SI_{\text{pulmonary nodule or mass}}}{SI_{\text{rhomboid muscle}}}
$$
 (2)

where SI<sub>pulmonary nodule or mass</sub> is the lung lesion signal intensity and  $SI$ <sub>rhomboid muscle</sub> is the muscle signal intensity.

#### Statistical analysis

#### Comparison of ADC values and CRs between SCLC and NSCLC

The ADC values between SCLCs and NSCLCs were compared by using Mann–Whitney's U-test. CRs of SCLCs and NSCLCs were also compared by same test. In addition, the ADC values and CRs of SCLCs were compared with those of the other pathological types by the Tukey honest-significance test.

### Comparison of quantitatively differentiated capability

Receiver operating characteristic (ROC) analysis was used to evaluate the usefulness of ADC values and CRs as markers for distinguishing SCLCs from NSCLCs. Diagnostic capabilities, such as sensitivity, specificity, positive predictive value, negative predictive value and accuracy, were calculated for each level by varying the levels of indexes that signified a positive test (threshold value). $^{2}$ 

To distinguish SCLCs from NSCLCs on DWI, sensitivity and specificity were defined as follows: sensitivity was the percentage of SCLCs with levels of indexes equal to or less than the given threshold level and specificity was the percentage of NSCLCs with levels of indexes greater than the threshold levels, $^{29}$  because low ADC values are suggestive of hypercellularity.<sup>[30](#page-7-0)</sup> On the other hand, to distinguish SCLCs from NSCLCs on STIR, sensitivity and specificity were defined as follows: sensitivity was the percentage of SCLCs that had levels of indexes equal to or greater than the given threshold level and specificity was the percentage of NSCLCs that had levels of indexes less than the threshold levels,<sup>29</sup> because many pathological lesions demonstrate increases in both  $T_1$  and  $T_2$ .<sup>[23,31,32](#page-7-0)</sup> Therefore, the addition of these two types of contrasts to the STIR sequence produces a higher net tissue contrast.<sup>23,31,[32](#page-7-0)</sup> In the results, lung nodules or masses with high signal intensity on STIR are suggestive of malignant tumours, excluding necrosis and cystic change.

The feasible threshold values of ADC values and CRs for distinguishing SCLCs from NSCLCs were tested for their diagnostic capabilities and were compared using McNemar's test. In addition, diagnostic capabilities were obtained by a combination of both sequences for assessment of the utility of these sequences.



Table 2. Comparison of apparent diffusion coefficient (ADC) values and contrast ratios (CRs)

ADC, apparent diffusion coefficient; CR, contrast ratio; SCLC, small-cell lung cancer; SD, standard deviation.

a<br>Significant difference with SCLC.

 $b$  Difference with SCLC by using Mann–Whitney's U-test.

Difference with SCLC by using the Tukey honest-significance test.

A p-value of  $<$ 0.05 was considered to indicate a statistically significant difference for all statistical analyses. All statistical analyses were performed in Excel 2003 (Microsoft; Redmond, WA) and in statistical software based on Excel 2003 (StatMate III; ATMS Co. Ltd, Tokyo, Japan).

#### RESULTS

#### Comparison with ADC values and CRs between SCLC and NSCLC

The results of the comparison of the ADC values and CRs are shown in Table 2. The mean ADC values of SCLCs and NSCLCs were  $0.79 \times 10^{-3}$  mm<sup>2</sup> s<sup>-1</sup> (n = 7) and  $1.33 \times 10^{-3}$  mm<sup>2</sup> s<sup>-1</sup>  $(n = 49)$ , respectively. The ADC values of SCLCs were significantly lower than those of NSCLCs ( $p < 0.001$ ). On the other hand, the mean CRs of SCLC and NSCLC were 1.59 ( $n = 7$ ) and 1.30 ( $n = 49$ ), respectively. There were also significant differences between the CRs of SCLCs and NSCLCs ( $p = 0.003$ ).

Regarding the pathological type, the ADC values of SCLC were significantly different from those of LCNEC ( $p = 0.02$ ) and AD  $(p = 0.005)$ ; however, there were no significant differences between those of SCLC and SQ ( $p = 0.06$ ). On the other hand, CRs of SCLC were significantly different from those of SQ ( $p = 0.03$ ) and AD ( $p = 0.004$ ); yet, there were no significant differences between those of SCLC and LCNEC ( $p = 0.92$ ).

#### Comparison of quantitatively differentiated capability

Two-dimensional scattergram of ADC values and CRs of SCLCs and NSCLCs, including LCNEC, SQ and AD, are shown in Figure 1. Based on the results of the ROC-based positive test that quantitatively distinguished SCLCs from NSCLCs, the feasible threshold values of qualitatively assessed DWI and STIR were determined to be  $0.95 \times 10^{-3}$  mm<sup>2</sup> s<sup>-1</sup> and 1.40, respectively. The threshold values for distinguishing SCLCs

from NSCLCs were then adopted; the diagnostic capabilities are shown in [Table 3](#page-4-0). The specificity [85.7% (42/49)] and accuracy [85.7% (48/56)] of DWI were significantly higher than those of STIR [specificity, 63.3% (31/49) and accuracy, 66.1% (37/56)].

When these threshold values were adopted, the accuracy of the combination of both sequences was significantly higher than that of only DWI [accuracy, 94.6% (53/56)].

Representative cases are shown in [Figures 2](#page-4-0)–[5.](#page-6-0)

#### **DISCUSSION**

In this study, we assessed the diagnostic capability of differentiating SCLC from NSCLC. The result was that the diagnostic capability of DWI was higher than that of STIR on the assessment of quantitative differentiation between SCLC and NSCLC. In addition, the combination of these two sequences increased diagnostic capability, and the specificity and accuracy were

Figure 1. Two-dimensional scattergram of apparent diffusion coefficient (ADC) values and contrast ratios (CRs) of small-cell lung cancers (SCLCs) and non-SCLCs. AD, adenocarcinoma; LCNEC, large-cell neuroendocrine carcinoma; SQ, squamous cell carcinoma.





<span id="page-4-0"></span>Table 3. Different capabilities of quantitatively distinguishing small-cell lung cancer from non-small-cell lung cancer

ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; STIR, short tau inversion recovery.

a Significant difference with STIR.

<sup>b</sup>Significant difference with DWI.

remarkably high. These facts indicate that chest MRI, particularly the DWI, could provide additional information in routine clinical practice.

Regarding the comparison of SCLC and NSCLC ADC values, SCLC ADC values were significantly lower than those of NSCLC. This may be explained by the fact that the tumour cellularity of SCLC seemed to be relatively high because tumour cellularity is an important factor influencing ADC values in viable tumour tis-sue.<sup>[30](#page-7-0)</sup> The ADC value is estimated to be lower in viable tumour tissue with densely packed, diffusion-hindering obstacles than that in tissue with less densely packed obstacles. $30$  In fact, Sugahara et al $^{33}$  have reported that the ADC value of gliomas correlates significantly with tumour cellularity and that ADC values of highgrade gliomas are significantly lower than those of low-grade gliomas. Yet, Guo et  $a^{34}$  have revealed that tumour cellularity has a significant influence on ADC values obtained in both benign and malignant breast tumours. Considering these findings, our results were compatible with these studies, and ADC values might reflect the characteristics of lung tumours.

However, some reports have different results concerning ADC values of lung cancers. One study reported that the differentiation capabilities of pathological subtype classifications of pulmonary ADs using ADC values were low.<sup>[25](#page-7-0)</sup> Generally, avoiding susceptibility artefacts on DWI of lung cancers is difficult. Wang et  $al<sup>28</sup>$ reported that air-containing areas within lung cancers could be considered to influence the measurement of ADC values because of inhomogeneities of the magnetic field; they were unable to

measure the ADC values of lesions located adjacent to aircontaining organs because of susceptibility artefacts. Considering these findings, as written in the report by Koyama et al,  $2^5$  there is a limit to subtype classification, including AD in situ. However, the measurement of ADC values was actually higher, because the subjects did not have an air-containing nodule or mass in their CTs in this study.

Matoba et al<sup>[20](#page-7-0)</sup> reported that a significant negative linear correlation was found between tumour cellularity and the mean ADC value. However, the mean ADC value of SCLC tended to be higher than that of SQ and large-cell carcinoma in their study, and the mean ADC value was  $2.09 \times 10^{-3} \pm 0.3$  mm<sup>2</sup> s<sup>-1</sup>. They suspected that the higher ADC values of SCLC were owing to the degree of necrosis and/or microstructural change.<sup>[20](#page-7-0)</sup> On the other hand, the ADC values of SCLC were low in other reports, and the ADC values were  $1.06 \times 10^{-3} \pm 0.20$  mm<sup>2</sup> s<sup>-1</sup>.<sup>[22](#page-7-0)</sup> While the ADC value was  $0.79 \times 10^{-3} \pm 0.30$  mm<sup>2</sup> s<sup>-1</sup> in our study. Presuming the reason for the varying results is difficult; however, the setting of the b-value and the subject might have been factors. ADC values tended to be higher when low b-values were used because ADC values are greatly influenced by tissue perfusion and  $T_2$  time.<sup>20</sup> In our study, because high *b*-values  $(1000 \text{ s mm}^{-2})$  were used, the ADC values of SCLC might be lower than those found in the previous report. $20,21$  Regarding the subject problem, all subjects were enrolled based on diagnosis by surgical and pathological examinations in our study, and the selection of the subjects might have influenced the results. However, the presumption of the difference was not enough, and the patient population was

Figure 2. A 64-year-old male patient with small-cell lung cancer (SCLC) in the right upper lobe. (a) Thin-section CT shows a cancer with a diameter of 26 mm in the right upper lobe. (b) Diffusion-weighted imaging (DWI) shows remarkably high signal intensity. The apparent diffusion coefficient value for the cancer is 0.94  $\times$  10 $^{-3}$  mm $^2$  s $^{-1}$ . The quantitative assessment of DWI identified this case as SCLC. (c) Short tau inversion recovery (STIR) also shows a remarkable high intensity. The contrast ratio for the cancer is 1.47. Quantitative assessment of STIR identified this case as SCLC.



Figure 3. A 75-year-old male patient with large-cell neuroendocrine carcinoma in the right upper lobe. (a) Thin-section CT shows a cancer with a diameter of 38 mm in the right upper lobe. (b) Diffusion-weighted imaging (DWI) shows slightly high signal intensity. The apparent diffusion coefficient value for the cancer is 2.07  $\times$  10 $^{-3}$  mm<sup>2</sup> s $^{-1}$ . Quantitative assessment of DWI identified this case as non-small-cell lung cancer. (c) Short tau inversion recovery (STIR) also shows remarkable high intensity. The contrast ratio for the cancer is 1.46. This is a false-positive case on the quantitative assessment of STIR.



relatively small. Therefore, further studies are needed to determine the factors influencing the ADC values of lung cancers.

STIR had a lower potential than that of DWI on the assessment of the difference between SCLC and NSCLC. Generally, many pathological lesions demonstrate an increase in both  $T_1$  and  $T_2$ ; the addition of these two types of contrasts to the STIR sequence produces a higher net tissue contrast.<sup>[23,31,32](#page-7-0)</sup> In addition, one study reported that the differentiation capabilities of pathological subtype classification of pulmonary ADs by STIR were higher than those of DWI.<sup>[25](#page-7-0)</sup> STIR seemed to be limited in its ability to reflect tumour cellularity of a solid nodule or mass in comparison with DWI on the assessment of differentiation between SCLC and NSCLC. However, STIR is also an important sequence in clinical practice, just as DWI is; $^{23,24}$  $^{23,24}$  $^{23,24}$  in fact, the combination of DWI and STIR had a remarkably high diagnostic capability for the purposes of this study.

In this study, the combination of DWI and STIR increased diagnostic capability, and the diagnostic capabilities were remarkably high. These facts indicate that DWI and STIR provide additional information in routine clinical practice. For example, before biopsy and/or when adequate material has not been obtained for tissue diagnosis by means of fiberoptic bronchoscopy and percutaneous biopsy, radiologists can suggest the

possibilities of SCLC. This might lead to better management for patients.

Our study has some limitations. First, the patient population was relatively small, and the patient selection was biased because the entry criteria were based on a surgical and pathological diagnosis of SCLC. Patients diagnosed with SCLC usually exhibited extensive hilar and mediastinal lymphadenopathy and distant metastases. Therefore, the SCLC patient population with solitary pulmonary nodules was relatively small. However, further studies involving a larger number of patients without potential selection bias should be performed. In addition, because this study was performed for a single centre cohort, multicentre studies will be needed in the near future.

Second, avoiding susceptibility artefacts on DWI of lung cancers is difficult, and the merit of ADC values is different according to the choice of  $b$  factors because they are influenced by tissue perfusion and  $T_2$  time.<sup>[20](#page-7-0)</sup> Although in this study two *b* factors  $r^{2}$  and  $r_2$  and  $r_3$  and  $r_4$  and  $r_5$  and  $r_6$  in this study two *v* factors were used as in previous reports,<sup>[20,22,25](#page-7-0)</sup> it may be desirable for accurate ADC measurement that one of the b-values is not 0 and that multiple b factors are used in the acquisition of  $DWI$ <sup>[35](#page-7-0)–[37](#page-7-0)</sup> In addition, although we chose the mean ADC value in this study, a minimal ADC value was chosen in some previous reports because the value within the entire tumour might not

Figure 4. A 54-year-old male patient with squamous cell carcinoma in the right upper lobe. (a) Thin-section CT shows a cancer with a diameter of 26 mm in the right upper lobe. (b) Diffusion-weighted imaging (DWI) shows high signal intensity. The apparent diffusion coefficient value for the cancer is 1.07  $\times$  10 $^{-3}$  mm $^2$  s $^{-1}$ . Quantitative assessment of DWI identified this case as non-small-cell lung cancer. (c) Short tau inversion recovery (STIR) also shows remarkable high intensity. The contrast ratio for the cancer is 1.48. This is a false-positive case on the quantitative assessment of STIR.



<span id="page-6-0"></span>Figure 5. A 59-year-old male patient with adenocarcinoma in the left upper lobe. (a) Thin-section CT shows a cancer with a diameter of 25 mm in the right upper lobe. (b) Diffusion-weighted imaging (DWI) shows high signal intensity. The apparent diffusion coefficient value for the cancer is  $1.08 \times 10^{-3}$  mm<sup>2</sup> s<sup>-1</sup>. Quantitative assessment of DWI identified this case as non-small-cell lung cancer (NSCLC). (c) Short tau inversion recovery (STIR) shows a high intensity. The contrast ratio for the cancer is 1.28. Quantitative assessment of STIR identified this case as NSCLC.



characterize the tumour because of its heterogeneity.<sup>[38](#page-7-0)</sup> Results might differ when these problems are solved.

Third, an analysis of the tumour cellularity was not performed in this study. Generally, ADC tumour cellularity is an important factor influencing the ADC values of viable tumour tissue.[30](#page-7-0) Although tumour cellularity of SCLC seemed to be relatively high, the result might not be strictly accurate. Meanwhile, some NSCLCs had high tumour cellularity according to the degree of tumour differentiation. In fact, the ADC values of NSCLC were broad in this study. Therefore, analysis should be performed in the future.

In conclusion, DWI and ADC values had high diagnostic capabilities on the quantitative assessment of differentiation between SCLC and NSCLC in comparison with STIR and CRs. Yet, the combination of ADC values and CRs increased diagnostic capability. DWI is a sensitive sequence for the

differentiation of SCLC from NSCLC, and the combination of DWI and STIR served as a reliable diagnostic indicator for this purpose.

#### ACKNOWLEDGMENTS

Kazuyuki Kobayashi, MD, PhD, Yasuhiro Funada, MD, PhD, Yoshikazu Kotani, MD, PhD (Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan), Yasuhiro Sakai, MD, PhD (Division of Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe, Japan), Nobukazu Aoyama, BS and Hideaki Kawamitsu, BS (Division of Radiology, Kobe University Hospital, Kobe, Japan) are acknowledged for their contribution to this work.

#### FUNDING

This work was supported by Philips Healthcare.

### **REFERENCES**

- 1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74–108.
- 2. Stupp R, Monnerat C, Turrisi AT 3rd, Perry MC, Leyvraz S. Small cell lung cancer: state of the art and future perspectives. Lung Cancer 2004; 45: 105–17. [doi: 10.1016/](http://dx.doi.org/10.1016/j.lungcan.2003.12.006) [j.lungcan.2003.12.006](http://dx.doi.org/10.1016/j.lungcan.2003.12.006)
- 3. Fraser R, Müller N, Colman N, Paré P. Diagnosis of disease of the chest. 3rd edn. Philadelphia, PA: W.B. Saunders; 1999. pp. 1067–250.
- 4. Ihde D, Souhami B, Comis R, Gregor A, Hansen H, Johnson B, et al. Consensus report. Small cell lung cancer. Lung Cancer 1997; 17(Suppl. 1): S19–21.
- 5. Quoix E, Fraser R, Wolkove N, Finkelstein H, Kreisman H. Small cell lung cancer presenting as a solitary pulmonary nodule. Cancer 1990; 66: 577–82.
- 6. Yabuuchi H, Murayama S, Sakai S, Hashiguchi N, Murakami J, Muranaka T, et al. Resected

peripheral small cell carcinoma of the lung: computed tomographic-histologic correlation. J Thorac Imaging 1999; 14: 105–8.

- 7. Ichinose Y, Hara N, Ohta M, Motohiro A, Maeda T, Nobe T, et al. Preoperative examination to detect distant metastasis is not advocated for asymptomatic patients with stages 1 and 2 non-small cell lung cancer. Preoperative examination for lung cancer. Chest 1989; 96: 1104–9.
- 8. Michel F, Soler M, Imhof E, Perruchoud AP. ` Initial staging of non-small cell lung cancer: value of routine radioisotope bone scanning. Thorax 1991; 46: 469–73.
- 9. Hatter J, Kohman LJ, Mosca RS, Graziano SL, Veit LJ, Coleman M. Preoperative evaluation of stage I and stage II non-small cell lung cancer. Ann Thorac Surg 1994; 58: 1738–41.
- 10. Johnson DH. Management of small cell lung cancer: current state of the art. Chest 1999; 116(Suppl. 6): 525S–30S.
- 11. Elias AD. Small cell lung cancer: state-of-theart therapy in 1996. Chest 1997; 112(Suppl. 4): 251S–8S.
- 12. Sher T, Dy GK, Adjei AA. Small cell lung cancer. Mayo Clin Proc 2008; 83: 355–67. [doi: 10.4065/83.3.355](http://dx.doi.org/10.4065/83.3.355)
- 13. Waddell TK, Shepherd FA. Should aggressive surgery ever be part of the management of small cell lung cancer? Thorac Surg Clin 2004; 14: 271–81. [doi: 10.1016/S1547-4127\(04\)](http://dx.doi.org/10.1016/S1547-4127(04)00004-0) [00004-0](http://dx.doi.org/10.1016/S1547-4127(04)00004-0)
- 14. Nakamura H, Kazuyuki S, Kawasaki N, Taguchi M, Kato H. History of limited resection for nonsmall cell lung cancer. Ann Thorac Cardiovasc Surg 2005; 11: 356–62.
- 15. Coolen L, Van den Eeckhout A, Deneffe G, Demedts M, Vansteenkiste J. Surgical treatment of small cell lung cancer. Eur J Cardiothorac Surg 1995; 9: 59–64.
- 16. Bradley JD, Dehdashti F, Mintun MA, Govindan R, Trinkaus K, Siegel BA. Positron emission tomography in limited-stage small-

<span id="page-7-0"></span>cell lung cancer: a prospective study. J Clin Oncol 2004; 22: 3248–54. [doi: 10.1200/](http://dx.doi.org/10.1200/JCO.2004.11.089) [JCO.2004.11.089](http://dx.doi.org/10.1200/JCO.2004.11.089)

- 17. Johnston WW. Cytologic diagnosis of lung cancer. Principles and problems. Pathol Res Pract 1986; 181: 1–36. [doi: 10.1016/S0344-](http://dx.doi.org/10.1016/S0344-0338(86)80184-4) [0338\(86\)80184-4](http://dx.doi.org/10.1016/S0344-0338(86)80184-4)
- 18. Michel RP, Lushpihan A, Ahmed MN. Pathologic findings of transthoracic needle aspiration in the diagnosis of localized pulmonary lesions. Cancer 1983; 51: 1663–72.
- 19. Delgado PI, Jorda M, Ganjei-Azar P. Small cell carcinoma versus other lung malignancies: diagnosis by fine-needle aspiration cytology. Cancer 2000; 90: 279–85.
- 20. Matoba M, Tonami H, Kondou T, Yokota H, Higashi K, Toga H, et al. Lung carcinoma: diffusion-weighted MR imaging—preliminary evaluation with apparent diffusion coefficient. Radiology 2007; 243: 570–7.
- 21. Satoh S, Kitazume Y, Ohdama S, Kimula Y, Taura S, Endo Y. Can malignant and benign pulmonary nodules be differentiated with diffusion-weighted MRI? AJR Am J Roentgenol 2008; 191: 464–70. [doi: 10.2214/](http://dx.doi.org/10.2214/AJR.07.3133) [AJR.07.3133](http://dx.doi.org/10.2214/AJR.07.3133)
- 22. 1Liu H, Liu Y, Yu T, Ye N. Usefulness of diffusion-weighted MR imaging in the evaluation of pulmonary lesions. Eur Radiol 2010; 20: 807–15. [doi: 10.1007/s00330-009-1629-6](http://dx.doi.org/10.1007/s00330-009-1629-6)
- 23. Ohno Y, Hatabu H, Takenaka D, Higashino T, Watanabe H, Ohbayashi C, et al. Metastases in mediastinal and hilar lymph nodes in patients with non-small cell lung cancer: quantitative and qualitative assessment with STIR turbo spin-echo MR imaging. Radiology 2004; 231: 872–9. [doi: 10.1148/](http://dx.doi.org/10.1148/radiol.2313030103) [radiol.2313030103](http://dx.doi.org/10.1148/radiol.2313030103)
- 24. Koyama H, Ohno Y, Kono A, Takenaka D, Maniwa Y, Nishimura Y, et al. Quantitative

and qualitative assessment of non-contrastenhanced pulmonary MR imaging for management of pulmonary nodules in 161 subjects. Eur Radiol 2008; 18: 2120–31. [doi: 10.1007/s00330-008-1001-2](http://dx.doi.org/10.1007/s00330-008-1001-2)

- 25. Koyama H, Ohno Y, Aoyama N, Onishi Y, Matsumoto K, Nogami M, et al. Comparison of STIR turbo SE imaging and diffusion-weighted imaging of the lung: capability for detection and subtype classification of pulmonary adenocarcinomas. Eur Radiol 2010; 20: 790–800. [doi: 10.1007/s00330-009-1615-z](http://dx.doi.org/10.1007/s00330-009-1615-z)
- 26. Koyama H, Ohno Y, Seki S, Nishio M, Yoshikawa T, Matsumoto S, et al. Magnetic resonance imaging for lung cancer. J Thorac Imaging 2013; 28: 138–50. [doi: 10.1097/](http://dx.doi.org/10.1097/RTI.0b013e31828d4234) [RTI.0b013e31828d4234](http://dx.doi.org/10.1097/RTI.0b013e31828d4234)
- 27. Chen L, Zhang J, Bao J, Zhang L, Hu X, Xia Y, et al. Meta-analysis of diffusion-weighted MRI in the differential diagnosis of lung lesions. J Magn Reson Imaging 2013; 37: 1351–8. [doi: 10.1002/jmri.23939](http://dx.doi.org/10.1002/jmri.23939)
- 28. Wang J, Takashima S, Takayama F, Kawakami S, Saito A, Matsushita T, et al. Head and neck lesions: characterization with diffusionweighted echo-planar MR imaging. Radiology 2001; 220: 621–30. [doi: 10.1148/](http://dx.doi.org/10.1148/radiol.2202010063) [radiol.2202010063](http://dx.doi.org/10.1148/radiol.2202010063)
- 29. Rosner BA. Fundamentals of biostatistics. 2nd edn. Boston, MA: Dexbury; 1986. pp. 584.
- 30. Herneth AM, Guccione S, Bednarski M. Apparent diffusion coefficient: a quantitative parameter for in vivo tumor characterization. Eur J Radiol 2003; 45: 208–13.
- 31. Wiener JI, Chako AC, Merten CW, Gross S, Coffey EL, Stein HL. Breast and axillary tissue MR imaging: correlation of signal intensities and relaxation times with pathologic findings. Radiology 1986; 160: 299–305. [doi: 10.1148/radiology.160.2.3726104](http://dx.doi.org/10.1148/radiology.160.2.3726104)
- 32. Fossel ET, Brodsky G, deLayre JL, Wilson RE. Nuclear magnetic resonance for the differentiation of benign and malignant breast tissues and axillary lymph nodes. Ann Surg 1983; 198: 541–5.
- 33. Sugahara T, Korogi Y, Kochi M, Ikushima I, Shigematu Y, Hirai T, et al. Usefulness of diffusion-weighted MRI with echoplanar technique in the evaluation of cellularity in gliomas. J Magn Reson Imaging 1999; 9: 53–60.
- 34. Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, et al. Differentiation of clinically benign and malignant breast lesions using diffusionweighted imaging. J Magn Reson Imaging 2002; 16: 172–8. [doi: 10.1002/jmri.10140](http://dx.doi.org/10.1002/jmri.10140)
- 35. Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology 1988; 168: 497–505. [doi: 10.1148/](http://dx.doi.org/10.1148/radiology.168.2.3393671) [radiology.168.2.3393671](http://dx.doi.org/10.1148/radiology.168.2.3393671)
- 36. Turner R, Le Bihan D, Maier J, Vavrek R, Hedges LK, Pekar J. Echo-planar imaging of intravoxel incoherent motion. Radiology 1991; 177: 407–14. [doi: 10.1148/](http://dx.doi.org/10.1148/radiology.177.2.2217777) [radiology.177.2.2217777](http://dx.doi.org/10.1148/radiology.177.2.2217777)
- 37. Yamada I, Aung W, Himeno Y, Nakagawa T, Shibuya H. Diffusion coefficients in abdominal organs and hepatic lesions: evaluation with intravoxel incoherent motion echo-planar MR imaging. Radiology 1999; 210: 617–23. [doi: 10.1148/radiology.210.3.](http://dx.doi.org/10.1148/radiology.210.3.r99fe17617) [r99fe17617](http://dx.doi.org/10.1148/radiology.210.3.r99fe17617)
- 38. Mori T, Nomori H, Ikeda K, Kawanaka K, Shiraishi S, Katahira K, et al. Diffusionweighted magnetic resonance imaging for diagnosing malignant pulmonary nodules/ masses: comparison with positron emission tomography. J Thorac Oncol 2008; 3: 358–64.