Metastases in mediastinal and hilar lymph nodes in patients with lung carcinoma: Quantitative assessments with Diffusion-Weighted (DW) Magnetic Resonance (MR) imaging. What is the appropriate method for detection of metastases in lymph nodes on the DW MR images?

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Purpose

Lung cancer is the leading cause of cancer death in both men and women worldwide (1). Mortality rates and the success of therapeutic approaches depend on the histologic type of cancer, the involvement of mediastinal and hilar lymph nodes, and the presence of remote metastases. Therefore, accurate tumor staging is essential for choosing the appropriate treatment strategy for patients with lung cancer, and mainly, tumor staging depends on imaging procedures.

Various diagnostic techniques and procedures, such as CT, MRI, bronchography, mediastinoscopy, and PET-CT, are used for preoperative staging of lung cancer. CT is the most commonly used method for staging of lymph nodes. However, CT is limited in the evaluation of nodal status because it provides only presumptive evidence of metastatic disease on the basis of size criteria. Sensitivity and specificity of CT in this regard are approximately 60%, which is not optimal for clinical decision making (2-8). A more accurate noninvasive method for determining lymph node status in patients with early-stage NSCLC would be useful for assigning patients to the most appropriate staging procedure.

Promising results have been reported for PET-CT performed with fluorine 18 fluorodeoxyglucose (FDG). PET-CT has been used to differentiate lymph nodes with metastasis from those without on the basis of the biochemical mechanisms of increased glucose metabolism and duplication tumor cells (9-12); however, elevated glucose metabolism may be secondary to tumor, infection, or inflammation (13, 14). Moreover, the diagnostic capability of FDG-PET is limited because standard uptake values at FDG-PET are affected by lymph node size (11).

Some investigators have discussed the utility of STIR MR imaging for detection of lymph nodes with metastasis in various malignant cancers (15-19).

DW MR images and ADC values add important information to findings obtained with conventional MR imaging and have been widely used in brain imaging, primarily for the evaluation of acute ischemic stroke, intracranial tumors, and demyelinating disease (20-22). With the advent of the echo-planar MR imaging technique, DW MR imaging of the abdomen and thoracic cavity has become possible with fast imaging times, which minimize the effects of gross physiologic motion from respiration and cardiac movement (23). The application of DW echo-planar MR imaging has extended to the breast and prostatic regions and allows for differentiation between tumor and normal tissue (24, 25). DW MR imaging has also been used in the hepatic and thoracic lesion to help differentiate between malignant and benign lesions (26, 27). Therefore, we hypothesized that Quantitative analysis and qualitative analysis of DW MR images enable characterization of lymph nodes. ADC measurement may be useful for differentiating between lymph nodes with metastasis and those without metastasis.
Thus, the purpose of our study was to evaluate DW MR imaging for detection of metastases in lymph nodes by using quantitative analysis.
Methods and Materials

This study was approved by the institutional review board, and informed consent was waived.

Patient

78 patients suspected of having lung tumor on the basis of findings at postanterior and lateral chest radiographs or CT were examined with contrast material-enhanced CT, DW and MR imaging at Hokkaido University Hospital within two weeks before anterior thoracotomy, or VATS, during the period of (2007 and 2008). These 78 patients (mean age, 68 years; age range, 46-84 years) included 44 men and 34 women. The final diagnosis of lung tumor and lymph node was based on pathologic findings in resected specimens. 54 of 70 patients had adenocarcinoma, 17 patients had squamous cell carcinoma, 4 patients had small cell carcinoma, 2 patients had adenosquamous carcinoma, and 1 patient had pleomorphic carcinoma. There were no patients with large cell carcinoma, or other histologic types of lung cancer in this series.

MR Imaging Examination

All MR examinations were performed with a 1.5-T clinical imager (Avanto; Siemens, Erlangen, Germany) by using a body phased-array coil. Patients were in the supine position throughout the examination. Prior to DW MR imagings, T1-and T2-weighted images were obtained in the transverse plane in each patient. Transverse DW MR images were obtained with b values of 50 and 1000 sec/mm$^2$. The components of the applied gradients for diffusion weighting, which consisted of three orthogonal gradients, were equal in read, phase, and section orientation obtain maximum total gradient strength. DW half-Fourier single-shot turbo spin-echo imaging was used in this study. Other parameters were as follows: repetition time msec/echo time msec, 3000/69; effective band width, 2056Hz/pixel; number of signals acquired, two; matrix, 78 × 128; field of view, 45 × 28.1 cm; and section thickness, 6mm.

Lymph Node Sampling and Histopathologic Examination

All operations were systematically performed by the surgeon. All resected lymph nodes were fixed in 10% buffered formalin and were routinely processed before histologic examination. Each histologic specimen contained the largest cut surface of each lymph node and evaluated by at least two pathologists. In addition, all lymph nodes were histologically reviewed for confirmation independently by a single pathologist.

Analysis of DW MR images
Quantitative analysis of DW MR images

On DW MR images obtained with high b values, all signal intensities were measured in circular or oval regions of interest drawn over each lymph node, lung cancer, spinal cord, and saline phantom of 100 mL of 0.9% saline by a chest radiologist with 14 years of experience (J.N.). The regions of interest drawn over the lymph node, lung cancer, spinal cord, and saline phantom encompassed the entire cross-sectional area of the lymph node and saline phantom (3-10 mm in diameter). All signal intensities of lymph nodes were normalized by comparing them with the signal intensities of the spinal cord and the 0.9% saline phantom to produce lymph node-spinal cord (LnScR) and lymph node-saline ratio (LnSR). And ratios of signal intensity in lung cancer to that in spinal cord (LcScR) and to that in 0.9% saline phantom (LcSR).

The LnScR was the formula LnScR = SI_{LN}/SI_{SC}, where SI_{LN} is the signal intensity of the lymph node, SI_{SC} is the signal intensity of the spinal cord.

The LnSR was the formula LnSR = SI_{LN}/SI_{SP}, where SI_{LN} is the signal intensity of the lymph node, SI_{SP} is the signal intensity of the saline phantom.

The LcScR was the formula LcScR = SI_{LC}/SI_{SC}, where SI_{LC} is the signal intensity of the lung cancer, SI_{SC} is the signal intensity of the spinal cord.

The LcSR was the formula LcSR = SI_{LC}/SI_{SP}, where SI_{LC} is the signal intensity of the lung cancer, SI_{SP} is the signal intensity of the saline phantom.

The difference of LcScRs and LnScRs (D1), that of LcSRs and LnSRs (D2).

The D1 was the formula D1 = |LcScR - LnScR|.

The D2 was the formula D2 = |LcSR - LnSR|.

ADC values were calculated with a linear regression analysis of the natural log of signal intensity versus the gradient factor according to the following equation: ADC = \[-\ln (S_h / S_i) / (b_h - b_i)\]. S_h and S_i were the signal intensities in the region of interest obtained with two different gradient factors (b_h and b_i). In this study, b_h was 1000 sec/mm2 and b_i was 50 sec/mm2. Regions of interest with a diameter of 3-10 mm were positioned for the measurement of ADC in each lymph node and lung cancer. The regions of interest...
were placed on the multiple areas of lymph nodes and lung cancers. $\text{ADC}_{\text{LC}}$ is the ADC of the lung cancer, $\text{ADC}_{\text{LN}}$ is that of the lymph node.

The $\textbf{D3}$ was the formula $\textbf{D3} = |\text{ADC}_{\text{LC}} - \text{ADC}_{\text{LN}}|$.

**Data and Statistical Analysis**

To determine the effect of short-axis diameter on $\text{LnScRs}$, $\text{LnSRs}$, $\text{ADC}_{\text{LN}s}$, $\text{D1s}$, $\text{D2s}$, and $\text{D3s}$, the lymph nodes were classified into the following **Six** size groups:

- **Size group A** : #0.5cm
- **Size group B** : #0.5cm and #1cm
- **Size group C** : #1cm and #2cm
- **Size group D** : #2cm and #3cm
- **Size group E** : #3cm
- **Size group F** : lymph nodes directly invaded by a primary tumor mass

$\text{LnScRs}$, $\text{LnSRs}$, $\text{ADC}_{\text{LN}s}$, $\text{D1s}$, $\text{D2s}$, and $\text{D3s}$ of lymph nodes with metastasis and those of nodes without metastasis were compared among short-axis diameter groups by using analysis of variance followed by Tukey honestly significant difference multiple comparison testing.

To evaluate the ability of $\text{LnScR}$, $\text{LnSR}$, $\text{ADC}_{\text{LN}}$, $\text{D1}$, $\text{D2}$, and $\text{D3}$ to enable the differentiation of lymph nodes with metastasis from those without metastasis, the feasible thresholds of $\text{LnScR}$, $\text{LnSR}$, $\text{ADC}_{\text{LN}}$, $\text{D1}$, $\text{D2}$, and $\text{D3}$ on a per-mass basis was determined by using a receiver operating characteristic- positive test. Receiver operating characteristic analysis was used to evaluate the effectiveness of $\text{LnScR}$, $\text{LnSR}$, $\text{ADC}_{\text{LN}}$, $\text{D1}$, $\text{D2}$, and $\text{D3}$ for revealing lymph nodes with metastasis. Sensitivity, specificity were calculated for each level of $\text{LnScR}$, $\text{LnSR}$, $\text{ADC}_{\text{LN}}$, $\text{D1}$, $\text{D2}$, and $\text{D3}$ by varying $\text{LnScR}$, $\text{LnSR}$, $\text{ADC}_{\text{LN}}$, $\text{D1}$, $\text{D2}$, and $\text{D3}$ that signified a positive test (i.e., the threshold value). Feasible threshold values at quantitative analyses of DW MR images were tested for ability to enable a correct diagnosis on a per-patient basis. Overlapping lesions evaluated with the feasible threshold value were also histologically reviewed. The abilities of quantitative analyses of DW MR images to enable a correct diagnosis were compared among quantitative analyses of DW MR images on a per-patient basis by using the McNemar test.
For all statistical analyses, a $P$ value of less than 0.05 was considered to indicate a statistically significant difference.
Results

Diagnosis of 460 lesions in 78 patients: At pathologic examination, 15 of 78 patients were pN positive (pN1:9, pN2:6). 424 nodes without metastastic carcinoma included nodes with anthracosillicotic nodes, silicotic nodes, hyalinized nodes, epithelioid cell granulomas such as sarcoid reaction or sarcoidosis, and reactive lymph nodes not otherwise specified nodal involvement of malignant lymphoma was also found in lymph nodes.

The number of each size lymph nodes (n=460)

Size group A #0.5cm#402
B #0.5cm and #1cm#12
C #1cm and #2cm#35
D #2cm and #3cm#2
E #3cm#0

F lymph nodes directly invaded by a primary tumor mass: 9

The numbers of each size lymph nodes with metastasis are shown in Table 1.
Table 1: The number of each size lymph nodes with metastasis (n=36)

<table>
<thead>
<tr>
<th>Size group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>Total</th>
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<td>8</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
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<td>0</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>From small cell carcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>From pleomorphic carcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>36</td>
</tr>
</tbody>
</table>

References: Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP

On DW MR images obtained with high b values, 47 of 460 lymph nodes (10.2%) were able to be detected, and LnScRs, LnSRs, ADC_LNs of each group were able to be measured.; 16 of 36 lymph nodes (44.4%) with metastasis were able to be detected and LnScRs, LnSRs, ADC_LNs of each group were able to be measured.

The number of each size group detected lymph nodes (n=460)

Size group A #0.5cm#0 / 402 (0%)

B #0.5cm and #1cm#11 / 12 (91.7%)

C #1cm and #2cm#34 / 35 (97.1%)

D #2cm and #3cm#2 / 2 (100%)

E #3cm#0 / 0

F lymph nodes directly invaded by a primary tumor mass: 0 / 9 (0%)
The number of each size detected lymph nodes with metastasis (n=36)

Size group A #0.5cm#0 / 11 (0%)

B #0.5cm and #1cm#0 / 0

C #1cm and #2cm#14 / 14 (100%)

D #2cm and #3cm#2 / 2 (100%)

E #3cm#0 / 0

F lymph nodes directly invaded by a primary tumor mass: 0 / 9 (0%)

The lymph nodes that were not able to be detected were lymph nodes with a long-axis diameter of less than 5 mm and/or lymph nodes without metastasis that is not detected as abnormal signal intensity lesion.

And lymph nodes directly invaded by a primary tumor mass were not able to be detected.

Quantitative analysis of DW MR image

The numbers and mean \( \text{LnScR, LnSR, ADC}_{\text{LN}}, \text{D1, D2, D3} \) with metastasis and those without metastasis are shown in Table 2.
Table 2: Number and mean LnScRs, LnSRs, ADCs, D1s, D2s, and D3s of Lymph nodes

References: Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP

**In each size group**, the mean LnScR, LnSR, ADC$_{LN}$, D1, D2, and D3 for lymph nodes with metastasis was significantly different from that for the lymph nodes without metastasis (**P < 0.05**).

**In lymph nodes with metastasis**, results of analysis of variance revealed no significant difference among the mean LnScR, LnSR, ADC$_{LN}$, D1, D2, and D3 of the size groups (**P > 0.05**).

**In lymph nodes without metastasis**, results of analysis of variance revealed no significant difference among the mean LnScR, LnSR, ADC$_{LN}$, D1, D2, and D3 of the size groups (**P > 0.05**).

Results with the receiver operating characteristic-based positive test for LnScR, LnSR, ADC$_{LN}$, D1, D2, and D3 on a per-node basis are shown in **Figures 1-6**.
**Fig. 1:** Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the LnScR on a per-node basis. $\# = \text{sensitivity}$, $\# = \text{specificity}$. An LnScR of 0.629 was adopted as the threshold for a positive test.

**References:** Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP

An LnScR of 0.629 was adopted as the threshold for a positive test (i.e., an LnScR greater than 0.629 indicated that a lymph node contained metastasis). The sensitivity and specificity for differentiating lymph nodes with metastasis from those without metastasis by using this threshold LnScR were 87.5% and 83.9%, respectively.

Overlapped lesions
The LnScRs of 2 (12.5%) of 16 lymph nodes with metastasis were overlapped with those without metastasis (ie, the LnScRs were less than or equal to 0.629). For One overlapped lymph node had metastasis from well-differentiated adenocarcinoma. One overlapped lymph node with metastasis, causes that had become the false negatives was uncertain.

And the LnScRs of 5 (16.1%) of 31 lymph nodes without metastasis were overlapped with those with metastasis (ie, the LnScRs were greater than 0.629). For Three overlapped lymph nodes without metastasis, cause that had become the false positives were uncertain. Two overlapped lymph nodes without metastasis were anthracosillicotic nodes.
**Fig. 2:** Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the LnSR on a per-node basis. # = sensitivity, # = specificity. An LnSR of 0.774 was adopted as the threshold for a positive test.

**References:** Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP

An LnSR of 0.774 was adopted as the threshold for a positive test (ie, an LnSR greater than 0.774 indicated that a lymph node contained metastasis). The sensitivity and specificity for differentiating lymph nodes with metastasis from those without metastasis by using this threshold LnSR were 87.5% and 87.1%, respectively.

**Overlapped lesions**

The LnSRs of 2 (12.5%) of 16 lymph nodes with metastasis were overlapped with those without metastasis (ie, the LnSRs were less than or equal to 0.774). For two overlapped lymph nodes with metastasis, cause that had become the false negatives were uncertain.

And the LnSRs of 4 (12.9%) of 31 lymph nodes without metastasis were overlapped with those with metastasis (ie, the LnSRs were greater than 0.774). For two overlapped lymph node without metastasis were **anthracosillicotic nodes. One overlapped lymph node without metastasis was a hyalinized nodule. One overlapped lymph nodes without metastasis was Malignant lymphoma.**
Fig. 3: Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the ADCLN on a per-node basis. # = sensitivity, # = specificity. An ADCLN of $1.681 \times 10^{-3}$ mm$^2$/sec was adopted as the threshold for a positive test.

**References:** Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP

An $\text{ADC}_{\text{LN}}$ of $1.681 \times 10^{-3}$ mm$^2$/sec was adopted as the threshold for a positive test (ie, an $\text{ADC}_{\text{LN}}$ less than $1.681 \times 10^{-3}$ mm$^2$/sec indicated that a lymph node contained metastasis). The sensitivity and specificity for differentiating lymph nodes with metastasis from those without metastasis by using this threshold $\text{ADC}_{\text{LN}}$ were 93.8% and 87.1%, respectively.
Overlapped lesions

The $\text{ADC}_{\text{LN}}$ of 1 (6.3%) of 16 lymph node with metastasis was overlapped with that without metastasis (ie, the $\text{ADC}_{\text{LN}}$ was greater than or equal to $1.681 \times 10^{-3} \text{mm}^2/\text{sec}$). One overlapped lymph node had metastasis from well-differentiated adenocarcinoma.

And the $\text{ADC}_{\text{LNS}}$ of 4 (12.9%) of 31 lymph nodes without metastasis were overlapped with those with metastasis (ie, the $\text{ADC}_{\text{LNS}}$ were less than $1.681 \times 10^{-3} \text{mm}^2/\text{sec}$). Two overlapped lymph nodes without metastasis were infiltrated by inflammatory cells including many eosinophils, suggesting a specific inflammatory process of uncertain etiology in these cases. One overlapped lymph node without metastasis was Malignant lymphoma. One overlapped lymph node without metastasis, causes that had become the false positives was uncertain.
Fig. 4: Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the D1 on a per-node basis. # = sensitivity, # = specificity. An D1 of 0.598 was adopted as the threshold for a positive test.

References: Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP
An D1 of 0.598 was adopted as the threshold for a positive test (i.e., an D1 less than 0.598 indicated that a lymph node contained metastasis). The sensitivity and specificity for differentiating lymph nodes with metastasis from those without metastasis by using this threshold D1 were 81.3% and 80.6%, respectively.

Overlapped lesions
The D1s of 3 (18.7%) of 16 lymph nodes with metastasis were overlapped with those without metastasis (ie, the D1s were greater than or equal to 0.598). For two overlapped lymph nodes with metastasis, cause that had become the false negatives were uncertain. One overlapped lymph node had metastasis from well-differentiated adenocarcinoma.

And the D1s of 6 (19.4%) of 31 lymph nodes without metastasis were overlapped with those with metastasis (ie, the D1s were less than 0.598). Two overlapped lymph nodes without metastasis were infiltrated by inflammatory cells including many eosinophils, suggesting a specific inflammatory process of uncertain etiology in these cases. Two overlapped lymph nodes without metastasis were Malignant lymphoma. One overlapped lymph node without metastasis was anthracosillicotic node. One overlapped lymph node without metastasis, causes that had become the false positives was uncertain.
Fig. 5: Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the D2 on a per-node basis. # = sensitivity, # = specificity. An D2 of 0.761 was adopted as the threshold for a positive test.

References: Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP
An D2 of 0.761 was adopted as the threshold for a positive test (ie, an D2 less than 0.761 indicated that a lymph node contained metastasis). The sensitivity and specificity for differentiating lymph nodes with metastasis from those without metastasis by using this threshold D2 were 68.8% and 67.7%, respectively.

Overlapped lesions
The D2s of 5 (31.2%) of 16 lymph nodes with metastasis were overlapped with those without metastasis (i.e., the D2s were greater than or equal to 0.761). For three overlapped lymph nodes with metastasis, cause that had become the false negatives were uncertain. One overlapped lymph node had metastasis from well-differentiated adenocarcinoma. One metastatic adenocarcinoma was producing abundant intra- and extra-cellular mucin.

And the D2s of 10 (32.3%) of 31 lymph nodes without metastasis were overlapped with those with metastasis (i.e., the D2s were less than 0.761). Two overlapped lymph nodes without metastasis were infiltrated by inflammatory cells including many eosinophils, suggesting a specific inflammatory process of uncertain etiology in these cases. Two overlapped lymph nodes without metastasis were Malignant lymphoma. One overlapped lymph node without metastasis was anthracosillicotic node. One overlapped lymph node without metastasis was a hyalinized nodule. Four overlapped lymph nodes without metastasis, cause that had become the false positives were uncertain.
Fig. 6: Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the D3 on a per-node basis. # = sensitivity, # = specificity. An D3 of 0.296 was adopted as the threshold for a positive test.

References: Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP

An D3 of 0.296×10^{-3} mm^{2}/sec was adopted as the threshold for a positive test (ie, an D3 less than 0.296×10^{-3} mm^{2}/sec indicated that a lymph node contained metastasis). The sensitivity and specificity for differentiating lymph nodes with metastasis from those without metastasis by using this threshold D3 were 93.8% and 96.8%, respectively.

Overlapped lesions
The D3 of 1 (6.2%) of 16 lymph node with metastasis was overlapped with that without metastasis (ie, the D3 was greater than or equal to $0.296 \times 10^{-3} \text{mm}^2/\text{sec}$). One overlapped lymph node with metastasis, causes that had become the false negatives was uncertain.

And the D3 of 1 (3.2%) of 31 lymph node without metastasis was overlapped with that with metastasis (ie, the D3 was less than $0.296 \times 10^{-3} \text{mm}^2/\text{sec}$). One overlapped lymph node without metastasis, causes that had become the false positives was uncertain.

Quantitative analyses of DW MR images by using D3s enable differentiation of lymph nodes with metastasis from lymph nodes without metastasis with sensitivity- and specificity-values that are greater than or equal to quantitative analyses by using LnScRs, LnSRs, ADCs, D1s, and D2s.

However, there was no significant difference ($P > 0.05$) among quantitative analyses of LnScRs, LnSRs, ADCs, D1s, D2s, and D3s for differentiating lymph nodes with metastasis from those without metastasis.

Representative examples are shown in Figures 7-10, respectively.

**Fig. 7:** Images in 58-years-old man with lymph nodes containing metastasis from adeno carcinoma. a. Transverse contrast-enhanced CT scan shows a right hilar node. b. Transverse DW MR image obtained with diffusion gradient 50sec/mm2 shows a lymph node as high-signal-intensity area. c. Transverse DW MR image obtained with
diffusion gradient 1000sec/mm² also shows a lymph node as high-signal-intensity area. On DW MR image obtained with diffusion gradient 1000sec/mm², the LnScR was 1.120. The LnSR was 1.321. And the ADC of the lymph node was 1.325×10⁻³mm²/sec. The D₁, D₂, and D₃ were 0.160, 0.500, and 0.057×10⁻³mm²/sec, respectively. Analysis of histologic specimen from right hilar node revealed nodular lesion composed of metastasizing adeno carcinoma.

**References:** Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP

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**Fig. 8:** Images in 64-years-old woman with lymph nodes free of metastasis from adenocarcinoma. a. Transverse contrast-enhanced CT scan shows a right pretracheal node. b. Transverse DW MR image obtained with diffusion gradient 50sec/mm² shows a lymph node slightly high-signal-intensity area. c. Transverse DW MR image obtained with diffusion gradient 1000sec/mm² also does not show lymph node as high-signal-intensity area. On DW MR image obtained with diffusion gradient 1000sec/mm², the LnScR was 0.270. The LnSR was 0.175. And the ADC of the lymph node was 1.760×10⁻³mm²/sec. The D₁, D₂, and D₃ were 1.114, 0.836, and 0.350×10⁻³mm²/sec, respectively. Analysis of histologic specimen from right pretracheal node revealed no evidence of metastatic cell nests.

**References:** Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP
Fig. 9: Images in 71-years-old man with lymph nodes containing metastasis from well-differentiated adeno carcinoma. a. Transverse contrast-enhanced CT scan shows a subaortic node. b. Transverse DW MR image obtained with diffusion gradient 50sec/mm² shows a lymph node as high-signal-intensity area. c. Transverse DW MR image obtained with diffusion gradient 1000sec/mm² also shows a lymph node as high-signal-intensity area. On DW MR image obtained with diffusion gradient 1000sec/mm², the LnScR was 0.628. The LnSR was 0.889. And the ADC of the lymph node was 1.711×10⁻³mm²/sec. The D₁, D₂, and D₃ were 0.782, 1.103, and 0.087×10⁻³mm²/sec, respectively. Analysis of histologic specimen from right hilar node revealed nodular lesion composed of metastasizing well-differentiated adeno carcinoma.

References: Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP
**Fig. 10**: Images in 71-years-old woman with lymph nodes free of metastasis from squamous cell carcinoma. a. Transverse contrast-enhanced CT scan shows a right hilar node. b. Transverse DW MR image obtained with diffusion gradient 50sec/mm² shows a lymph node as high-signal-intensity area. c. Transverse DW MR image obtained with diffusion gradient 1000sec/mm² also shows a lymph node as high-signal-intensity area. On DW MR image obtained with diffusion gradient 1000sec/mm², the LnScR was 0.587. The LnSR was 0.556. And the ADC of the lymph node was $1.621 \times 10^{-3}$mm²/sec. The D1, D2, and D3 were 1.058, 1.002, and 0.212×10⁻³mm²/sec, respectively. Analysis of histologic specimen from right hilar node revealed no evidence of metastatic cell nests.

**References:** Diagnosis Center, Medical image Lab, Inc. - Sapporo/JP
### Table 1: The number of each size lymph nodes with metastasis (n=36)

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<th>Size group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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### Table 2: Number and mean LnScRs, LnSRs, ADCs, D1s, D2s, and D3s of Lymph nodes

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<td>Lymph nodes without metastasis (n=31)</td>
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**Note.**
- Data are means ± SDs.
- Data are means ± SDs (×10⁻⁶ mm²/sec).
- Mean LnScR of Lymph nodes with metastasis was significantly higher (P < 0.000005) than that of lymph nodes without metastasis.
- Mean LnSR of Lymph nodes with metastasis was significantly higher (P < 0.000005) than that of lymph nodes without metastasis.
- Mean ADC of Lymph nodes with metastasis was significantly lower (P < 0.000005) than that of lymph nodes without metastasis.
- Mean D1 of Lymph nodes with metastasis was significantly lower (P < 0.05) than that of lymph nodes without metastasis.
- Mean D2 of Lymph nodes with metastasis was significantly lower (P < 0.05) than that of lymph nodes without metastasis.
- Mean D3 of Lymph nodes with metastasis was significantly lower (P < 0.05) than that of lymph nodes without metastasis.
Fig. 1: Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the LnScR on a per-node basis. # = sensitivity, # = specificity. An LnScR of 0.629 was adopted as the threshold for a positive test.
Fig. 2: Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the LnSR on a per-node basis. # = sensitivity, # = specificity. An LnSR of 0.774 was adopted as the threshold for a positive test.

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Fig. 3: Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the ADCLN on a per-node basis. $\# = $ sensitivity, $\# = $ specificity. An ADCLN of $1.681 \times 10^{-3}$ mm$^2$/sec was adopted as the threshold for a positive test.

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**Fig. 4:** Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the D1 on a per-node basis. # = sensitivity, # = specificity. An D1 of 0.598 was adopted as the threshold for a positive test.
Fig. 5: Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the D2 on a per-node basis. # = sensitivity, # = specificity. An D2 of 0.761 was adopted as the threshold for a positive test.

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**Fig. 6:** Graph shows results with receiver operating characteristic-based positive test at quantitative analysis with the D3 on a per-node basis. $\# = $ sensitivity, $\# = $ specificity. An D3 of 0.296 was adopted as the threshold for a positive test.

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Fig. 7: Images in 58-years-old man with lymph nodes containing metastasis from adeno carcinoma. a. Transverse contrast-enhanced CT scan shows a right hilar node. b. Transverse DW MR image obtained with diffusion gradient 50sec/mm² shows a lymph node as high-signal-intensity area. c. Transverse DW MR image obtained with diffusion gradient 1000sec/mm² also shows a lymph node as high-signal-intensity area. On DW MR image obtained with diffusion gradient 1000sec/mm², the LnScR was 1.120. The LnSR was 1.321. And the ADC of the lymph node was 1.325×10⁻³mm²/sec. The D1, D2, and D3 were 0.160, 0.500, and 0.057×10⁻³mm²/sec, respectively. Analysis of histologic specimen from right hilar node revealed nodular lesion composed of metastasizing adeno carcinoma.

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Fig. 8: Images in 64-years-old woman with lymph nodes free of metastasis from adenocarcinoma. a. Transverse contrast-enhanced CT scan shows a right pretracheal node. b. Transverse DW MR image obtained with diffusion gradient 50sec/mm² shows a lymph node slightly high-signal-intensity area. c. Transverse DW MR image obtained with diffusion gradient 1000sec/mm² also does not show lymph node as high-signal-intensity area. On DW MR image obtained with diffusion gradient 1000sec/mm², the LnScR was 0.270. The LnSR was 0.175. And the ADC of the lymph node was 1.760×10⁻³mm²/sec. The D1, D2, and D3 were 1.114, 0.836, and 0.350×10⁻³mm²/sec, respectively. Analysis of histologic specimen from right pretracheal node revealed no evidence of metastatic cell nests.
**Fig. 9:** Images in 71-years-old man with lymph nodes containing metastasis from well-differentiated adeno carcinoma. a. Transverse contrast-enhanced CT scan shows a subaortic node. b. Transverse DW MR image obtained with diffusion gradient 50sec/mm² shows a lymph node as high-signal-intensity area. c. Transverse DW MR image obtained with diffusion gradient 1000sec/mm² also shows a lymph node as high-signal-intensity area. On DW MR image obtained with diffusion gradient 1000sec/mm², the LnScR was 0.628. The LnSR was 0.889. And the ADC of the lymph node was 1.711×10⁻³mm²/sec. The D1, D2, and D3 were 0.782, 1.103, and 0.087×10⁻³mm²/sec, respectively. Analysis of histologic specimen from right hilar node revealed nodular lesion composed of metastasizing well-differentiated adeno carcinoma.

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**Fig. 10:** Images in 71-years-old woman with lymph nodes free of metastasis from squamous cell carcinoma. a. Transverse contrast-enhanced CT scan shows a right hilar node. b. Transverse DW MR image obtained with diffusion gradient 50sec/mm² shows a lymph node as high-signal-intensity area. c. Transverse DW MR image obtained with diffusion gradient 1000sec/mm² also shows a lymph node as high-signal-intensity area. On DW MR image obtained with diffusion gradient 1000sec/mm², the LnScR was 0.587. The LnSR was 0.556. And the ADC of the lymph node was 1.621×10⁻³mm²/sec. The D1, D2, and D3 were 1.058, 1.002, and 0.212×10⁻³mm²/sec, respectively. Analysis of histologic specimen from right hilar node revealed no evidence of metastatic cell nests.

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Conclusion

Accurate evaluation of the presence or absence of metastases in mediastinal and hilar lymph nodes is a critical factor which may determine the appropriate treatment strategy for patients with lung cancer. CT and FDG-PET are most commonly used method for staging of lymph nodes. However, CT and MRI are limited in the evaluation of nodal status because it provides only presumptive evidence of metastatic disease on the basis of size criteria (2-8).

Recently, DW MR imaging has also been used in the hepatic and thoracic lesion to help differentiate between malignant and benign lesions (26, 27). Although the total number of patients in this study was small, we found that quantitative analyses by using ADC, LnScR, LnSR, D1, D2, and D3 enable characterization of lymph nodes. And quantitative analyses of DW MR images by using D3 enable differentiation of lymph nodes with metastasis from lymph nodes without metastasis with sensitivity- and specificity- values that are greater than or equal to quantitative analyses by using LnScR, LnSR, D1, D2, and D3.

ADC refers to the specific diffusion capacity of a biologic tissue. ADC depends largely on the presence of barriers to diffusion within the water microenvironment, namely, cell membranes, tight junctions, fibers, macromolecules, and cell organelles (28). Consequently, compartments within different cellular structures may exhibit dissimilar ADCs, and the ADC can therefore aid in determining different tissue types and tissue characteristics (29, 30). Therefore, significant differences between benign- and malignant- lesions in the mediastinum and hilar were observed in this study.

When $0.24 \times 10^{-3} \text{mm}^2/\text{sec}$ was adopted as the feasible D1 threshold value, the D3 of 1 (6.2%) of 16 lymph node with metastasis was overlapped with that without metastasis. One overlapped lymph node with metastasis, causes that had become the false negatives was uncertain. And the D3 of 1 (3.2%) of 31 lymph node without metastasis was overlapped with that with metastasis. One overlapped lymph node without metastasis, causes that had become the false positives was uncertain. Previous studies have revealed a significant correlation between ADC and tumor cellularity (24, 27, 31, 32). Tumor cellularity may be an important factor influencing ADCs in viable tumor tissue. In this study, it was thought that the degree of such pathologic changes as size of metastatic cell nests, amount of mucin production, necrosis, and infiltrating eosinophils within a lymph node affected the changes in ADC and result in some overlap between lymph nodes with metastasis and those without. Oppositely, it was thought that the degree of such pathologic changes as hyalinization and anthracosis, as well as epithelioid cell granulomas did not affect the changes in ADC. Therefore, these results suggest that the ADCs of the lymph nodes with a high ratio of metastatic cell nests is approximated to
ADCs of the primary lung cancer. And D3s of lymph nodes with metastasis were lower than D3s of those without.

There were several limitations to our study. Lymph nodes with a long-axis diameter of less than 5 mm were not able to be detected on DW MR images. And, there were lymph nodes with micrometastasis that were not detected as abnormal signal intensity lesion. And, ADCs of necrotic lymph nodes with metastasis are relatively higher. In addition, lymph nodes directly invaded by a primary tumor mass were not able to be detected by separating the lymph nodes from the lung cancer.

In conclusion, Quantitative analyses by using LnScRs, LnSRs, ADC, D1s, D2s and D3s of DW MR images enable characterization of lymph nodes. D3s measurement may be especially useful for differenting between lymph nodes with metastasis and those without metastasis.
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