Prediction of Nodal Metastasis in Head and Neck Cancer Using a 3T MRI ADC Map

BACKGROUND AND PURPOSE: The detection of cervical nodal metastases is important for the prognosis and treatment of head and neck tumors. The purpose of this study was to assess the ability of ADC values at 3T to distinguish malignant from benign lymph nodes.

MATERIALS AND METHODS: From July 2009 to June 2010, twenty-two patients (21 men and 1 woman; mean age, 49.8 ± 9.5 years; age range, 28–66 years) scheduled for surgical treatment of biopsy-proved head and neck cancer were prospectively and consecutively enrolled in this study. All patients were scanned on a 3T imaging unit (Verio) by using a 12-channel head coil combined with a 4-channel neck coil. Histologic findings were the reference standard for the diagnosis of lymph node metastasis.

RESULTS: The ADC values derived from the signal intensity averaged across images obtained with b-values of 0 and 800 s/mm² were 1.086 ± 0.222 × 10⁻³ mm²/s for benign lymph nodes and 0.705 ± 0.118 × 10⁻³ mm²/s for malignant lymph nodes (P < .001). When an ADC value of 0.851 × 10⁻³ mm²/s was used as a threshold value for differentiating benign from malignant lymph nodes, the best results were obtained with an accuracy of 91.0%, sensitivity of 91.3%, and specificity of 91.1%.

CONCLUSIONS: The ADC value is a sensitive and specific parameter that can help to differentiate malignant from benign lymph nodes.

ABBREVIATIONS: AUC = area under the ROC curve; ROC = receiver operating characteristic analysis

Nodal metastases are an adverse prognostic factor in patients with head and neck cancer, and accurate detection can help optimize treatment.¹ Anatomic imaging with CT and MR imaging is well-established in the initial diagnostic evaluation of head and neck malignancy and is widely used for treatment planning and monitoring and for posttreatment follow-up.² On anatomic CT and MR images, certain parameters (shape, size, internal architecture, extracapsular extension, and vascular features) are associated with lymph node metastasis, but accuracy is limited, particularly in normalized non-necrotic lymph nodes.³

Cancer metastasis to the regional lymph nodes may be associated with alteration in water diffusivity and microcirculation of the nodes.⁴ DWI, based on intravoxel incoherent motion imaging that allows visualization of molecular diffusion and microcirculation of the blood in the capillary network of biologic tissues is an MR imaging technique that shows the potential for more specific characterization of lesions. The use of DWI to distinguish malignant from benign cervical nodes has been reported in several studies.⁴⁻⁶ All of these studies used 1.5T MR imaging to investigate head and neck nodal lesions and extract ADC values from DWI. After the introduction of 3T MR imaging, ADC values obtained with 3T MR imaging were used to differentiate malignant and benign head and neck cancers,⁹ but not to investigate head and neck lymph nodes. The purpose of this study was to assess whether ADC values from 3T MR imaging could distinguish malignant from benign cervical lymph nodes.

Materials and Methods

Patients
This study was approved by the local institutional review committee. All patients gave their informed consent before MR imaging examinations. From July 2009 to June 2010, thirty-two patients who were scheduled for surgical treatment of biopsy-proved head and neck cancer were prospectively enrolled in this study. MR imaging was then performed on these patients before they underwent surgical neck dissection. Ten patients were excluded from the study cohort: (1) four patients whose images had motion artifacts, (2) three patients whose treatment changed to nonsurgical treatment, and (3) three patients who had surgical excision of neck nodes before MR imaging because of changes in disease status.

The remaining 22 patients (21 men and 1 woman; mean age, 49.8 ± 9.5 years; age range, 28–66 years) underwent combined conventional TSE MR imaging and DWI before undergoing surgery to remove tumors and lymph nodes. The final diagnosis was based on pathologic findings in surgical resection specimens.

The tumor stage was determined according to the size of the tumor, the muscle invasion, and the involvement of adjacent structures as per the American Joint Committee on Cancer staging system.¹⁰

MR Imaging Technique
All MR imaging studies were performed by using a 3T imaging unit (Verio; Siemens, Erlangen, Germany) with a 12-channel head coil combined with a 4-channel neck coil. During MR imaging sequences, patients were instructed to hold still and not to swallow to avoid motion artifacts.

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The following protocols were used in all patients. Before contrast administration, the patients underwent 3 scanning sequences: 1) transverse T2-weighted TSE MR imaging (TR/TE, 3500/88 ms; section thickness, 3 mm; FOV, 230 mm; intersection gap, 0.9 mm; image matrix, 314 × 314; number of signals acquired, 1); 2) transverse T1-weighted TSE MR imaging (TR/TE, 700/10 ms; section thickness, 3 mm; FOV, 230 mm; intersection gap, 0.9 mm; image matrix, 314 × 448; number of signals acquired, 1); 3) DWI of the head and neck in the transverse plane by using a spin-echo single-shot echo-planar imaging sequence (TR/TE, 8000/77 ms; section thickness, 3 mm; intersection gap, 0.9 mm; FOV, 230 mm; image matrix, 122 × 144; number of signals acquired, 3). DWI images were obtained at b factors of 0 and 800 s/mm² for each section in the same sequence. The scan range was from the skull base to the suprasternal notch. The ADC maps were then automatically reconstructed on the scanner console.

After a bolus injection of 0.1 mmol/kg of gadodiamide (Omniscan; GE Healthcare, Cork, Ireland), the patients underwent 1 scanning sequence: transverse fat-suppressed T1-weighted TSE MR imaging (TR/TE, 700/10 ms; section thickness, 3 mm; FOV, 230 mm; intersection gap, 0.9 mm; image matrix, 314 × 448; number of signals acquired, 1).

**Image Analysis**

One radiologist (C.-K.L.) with 6 years of experience in MR imaging of the head and neck region interpreted MR images on the basis of T2- and T1-weighted contrast-enhanced MR images. A lymph node was considered to be metastatic on the basis of the nodal size, contour irregularity, or heterogeneous contrast enhancement. The sizes of all lymph nodes were measured by the radiologist (C.-K.L.) in their minimal transverse diameter. The nodal size criteria larger than 2 mm were used.10

**Pathologic Evaluation**

Histologic findings from surgical resection were the reference standard for primary tumor metastasis to the lymph nodes. Surgeons carefully reviewed MR images on the PACS, and intraoperatively, the specimens were matched with the lymph nodes as imaged on T2- and T1-weighted contrast-enhanced MR images. To ensure that the node removed surgically during neck dissection was the same node seen at imaging, the lymph nodes were excised adjacent to reference structures to determine the relationship between the excised nodes and the surrounding structures. After surgery, each node was carefully delineated and tagged for pathologic diagnosis. The histopathologic and radiologic findings were correlated on an individual nodal basis.

After the histopathologic and radiologic findings for each lymph node were correlated, the optimal ADC₀₉₀₀ threshold for differentiating malignant from benign lymph nodes was determined by using ROC analysis. The sensitivity and specificity of the DWI method were then calculated. For pathologic metastatic lymph nodes, the ratio of intranodal
tumor deposits was measured by an experienced pathologist according to the lymph node size (short-axis diameter) and the size of intranodal tumor deposits (maximum diameter of metastatic foci in each lymph node).

**Statistical Analysis**

Statistical analyses were performed by using statistical software MedCalc for Windows (Version 9.4; MedCalc Software, Mariakerke, Belgium). Numeric data are reported as means ± SD. A box-and-whisker plot was used to depict the scatterplot of mean ADC values in benign and malignant lymph nodes. The ROC curve was performed to evaluate the diagnostic capability of the ADC value and to determine the cutoff values for differentiating malignant from benign lymph nodes.

The AUC was used to measure the performance of using the ADC values as effective indicators for discrimination. An independent-sample t test was used to compare the mean diameters of the benign and malignant lymph nodes.

**Results**

A total of 169 cervical lymph nodes were detected in 22 untreated patients (21 men and 1 woman; mean age, 49.8 ± 9.5 years; age range, 28–66 years). There were 17 patients with unilateral neck dissection and 5 patients with bilateral neck dissection. The specimens were divided into level I to level V, and then resected lymph nodes were carefully matched with MR images and pathologic evaluation. The location and clinical tumor stage were based on physical examinations and preoperative MR images. The nodal stage was determined by the conventional TSE MR images, DWI images, and histopathology for each patient. The tumor stages and nodal stages are shown in Table 1. Of 169 cervical lymph nodes, 146 were benign and 23 were malignant. The sizes of 23 malignant lymph nodes ranged from 0.36 to 1.84 cm (in minimal transverse diameter), and ADC values ranged from 0.437 to 0.884 × 10⁻³ mm²/s (Table 2). The box-and-whisker plot (Fig 1) presents the distribution of mean ADC values in benign and malignant lymph nodes. All lymph nodes were placed in 1 of 2 groups according to their diameters: supracentimeter (n = 58) or subcentimeter (n = 111) lymph nodes. The mean ADC values for the benign and malignant lesions were 1.086 ± 0.222 and 0.705 ± 0.118 × 10⁻³ mm²/s for all lymph nodes, 1.076 ± 0.238 and 0.705 ± 0.141 × 10⁻³ mm²/s for subcentimeter lymph nodes, and 1.105 ± 0.188 and 0.705 ± 0.077 × 10⁻³ mm²/s for supracentimeter lymph nodes. The detailed data are summarized in Table 3.

Figure 2 shows corresponding ROC curves of ADC values used for differentiating malignant from benign lymph nodes (P < .0001). Patients with hypopharynx squamous cell carcinoma who had supracentimeter and subcentimeter metastatic lymph nodes are shown in Figs 3 and 4, respectively.

One patient (Table 1, patient 19) with pathologically proved squamous cell carcinoma of the right tongue had a right level I lymph node metastasis. Conventional TSE MR images showed a normal regular contour, a minimal trans-
verse diameter of 0.55 cm, and homogeneous enhancement. The DWI ADC value was lower than the cutoff value though, representing malignancy (Fig. 5).

The mean diameters of the benign and malignant lymph nodes were 0.89 $\pm$ 0.38 cm (range, 0.27–2.89 cm) and 0.98 $\pm$ 0.46 cm (range, 0.36–1.84 cm), respectively. Although the mean diameter of the malignant lymph nodes was slightly greater than that of the benign lymph nodes, comparison of the groups of benign and malignant nodes by using an independent-samples $t$ test revealed that the difference did not reach statistical significance ($P = .192$).

The conventional TSE MR imaging findings based on morphology and size were correlated with pathologic findings for each patient. The sensitivity and specificity of conventional TSE MR imaging findings to detect malignant nodal involvement were 87.5% and 57.1%, respectively. The mean percentage of the tumor deposit within the affected nodes measured by a pathologist was 74.3% $\pm$ 30.2%.

Discussion

Differentiation of benign from malignant nodes is essential for tumor staging, treatment planning, prognostication, and follow-up both during and after treatment. Diffusion imaging enables characterization of tissue at a microscopic level, emphasizing a mechanism that is different from T1 and T2 relax-
ation and potentially improving the performance of MR imaging.\textsuperscript{13,14}

Differences in ADC values between benign and malignant processes of the head and neck have been demonstrated in several studies.\textsuperscript{4-9,12,13,17-19} The On-line Table summarizes the studies that have investigated head and neck lesions with 1.5T or 3T MR imaging. These studies determined the cutoff ADC values for differentiating malignant from benign head and neck cancers or lymph nodes. For example, Srinivasan et al\textsuperscript{9} used 3T MR imaging to determine an ADC cutoff value of \(1.3 \times 10^{-3}\) mm\(^2\)/s for differentiating malignant (0.85 to 1.09 mm\(^2\)/s) from benign (1.19 to 1.64 mm\(^2\)/s) head and neck tumors.

Previous studies\textsuperscript{4-8} investigated neck lymph nodes at 1.5T. The cutoff values were from 0.94 to 1.38 \(\times 10^{-3}\) mm\(^2\)/s.\textsuperscript{5-7} Mean ADC values for benign (1.19 to 1.64 \(\times 10^{-3}\) mm\(^2\)/s) were higher than malignant (0.85 to 1.09 \(\times 10^{-3}\) mm\(^2\)/s) lymph nodes. Sumi et al,\textsuperscript{4} however, found that metastatic nodes (0.410 \(\pm 0.105 \times 10^{-3}\) mm\(^2\)/s) had higher ADC values than benign nodes (0.302 \(\pm 0.062 \times 10^{-3}\) mm\(^2\)/s). These differences cannot be attributed solely to the different b-value setting for ADC calculations. The higher number of necrotic metastatic lymph nodes included in the Sumi et al study may have contributed to the discrepancy.\textsuperscript{4} In our study, the ADC cutoff value (0.851 \(\times 10^{-3}\) mm\(^2\)/s) is lower than the values found in other studies\textsuperscript{5-7} for the detection of malignant head and neck lymph nodes. The ADC value is calculated by the equation, \(\text{ADC} = \ln (\text{SI}_1 / \text{SI}_2) / b_2 - b_1\), where \(\text{SI}_1\) is the signal intensity when the \(b_1\) value is 0, and \(\text{SI}_2\) is the signal intensity when the \(b_2\) value is 800. The other studies used \(b\)-values of 0 and 1000, a much higher \(b\) factor than that in our study. According to the equation, the ADC value for \(b = 0-1000\) is higher than the value for \(b = 0-800\) because of the signal loss in DWI with the increasing \(b\)-value.\textsuperscript{20} Different MR imaging units may also have different ranges of ADC values as shown in the On-line Table.

In our study, the mean ADC values of benign lymph nodes were higher than the provided cutoff ADC value (Fig 1). However, some benign lymph node ADC values were lower than the cutoff value. Perrone et al\textsuperscript{7} indicated that the ADC values of benign lymph nodes in patients with tuberculosis are lower than the cutoff value, for example, for the malignant group. In future studies, a larger number of cases should be included to clarify the correlation between the ADC values of benign lymph nodes that are lower than the cutoff value and histopathologic findings.

DWI ADC calculation and ROC analysis (all lymph nodes, subcentimeter, and supracentimeter) presented higher sensitivity and specificity than conventional TSE MR imaging findings.
The size of the node and the size of intranodal tumor deposits varied widely in affected lymph nodes in the study of Ng et al.\textsuperscript{21} They showed that the mean percentage of tumor deposit within the affected nodes was 69.31% ± 27.7%, which is similar to the result (74.3% ± 30.2%) in our study. Previous studies\textsuperscript{22,23} indicated that there was a strong correlation between the intranodal tumor deposit and the size of the metastatic lymph node.\textsuperscript{24} This supports the use of nodal size as an index to evaluate preoperative nodal metastasis, but it remains a nonspecific feature of tumor-involved lymph nodes.

A potential problem of using the ADC cutoff value to distinguish malignant lymph nodes was that metastatic nodes with necrotic areas might have higher ADC values due to necrosis and might be incorrectly identified as benign. To avoid this bias, we calculated the ADC value from the region of interest drawn on the solid part of lymph nodes.

Conclusions
A cutoff ADC value of 0.851 × 10\textsuperscript{−3} mm\textsuperscript{2}/s best differentiated malignant from benign lymph nodes on 3T MR imaging in the setting of head and cancer, with 91.3% sensitivity and 91.1% specificity to detect tumor-involved lymph nodes. Adding DWI to routine MR imaging neck protocols is suggested because it may provide useful information. The results in our study can be used as reference values for studies investigating head and neck lymph nodes by using 3T MR imaging.

References