Fractional Change in Apparent Diffusion Coefficient as an Imaging Biomarker for Predicting Treatment Response in Head and Neck Cancer Treated with Chemoradiotherapy

M. Matoba, H. Tuji, Y. Shimode, I. Toyoda, Y. Kuginuki, K. Miwa and H. Tonami

*AJNR Am J Neuroradiol* 2014, 35 (2) 379-385
doi: https://doi.org/10.3174/ajnr.A3706
http://www.ajnr.org/content/35/2/379
Fractional Change in Apparent Diffusion Coefficient as an Imaging Biomarker for Predicting Treatment Response in Head and Neck Cancer Treated with Chemoradiotherapy

M. Matoba, H. Tuji, Y. Shimode, I. Toyoda, Y. Kuginuki, K. Miwa, and H. Tonami

ABSTRACT

BACKGROUND AND PURPOSE: ADC provides a measure of water molecule diffusion in tissue. The aim of this study was to evaluate whether the fractional change in ADC during therapy can be used as a valid predictive indicator of treatment response in head and neck squamous cell carcinoma treated with chemoradiotherapy.

MATERIALS AND METHODS: Forty patients underwent DWI at pretreatment and 3 weeks after the start of treatment. The pretreatment ADC, fractional change in ADC, tumor regression rate, and other clinical variables were compared with locoregional control and locoregional failure and were analyzed by using logistic regression analysis and receiver operating characteristic analysis. Furthermore, progression-free survival curves divided by the corresponding threshold value were compared by means of the log-rank test.

RESULTS: The fractional change in ADC primary, the fractional change in ADC node, primary tumor volume, nodal volume, tumor regression rate node, N stage, and tumor location showed significant differences between locoregional failure and locoregional control \((P < .05)\). In univariate analysis, the fractional change in ADC primary, fractional change in ADC node, tumor regression rate node, N stage, and tumor location showed significant association with locoregional control \((P < .05)\). In multivariate analysis, however, only the fractional change in ADC primary was identified as a significant and independent predictor of locoregional control \((P = .04)\). A threshold fractional change in ADC primary of 0.24 revealed a sensitivity of 100%, specificity of 78.7%, and overall accuracy of 84.8% for the prediction of locoregional control. Progression-free survival of the 2 groups divided by the fractional change in ADC primary at 0.24 showed a significant difference \((P < .05)\).

CONCLUSIONS: The results suggest that the fractional change in ADC primary is a valid imaging biomarker for predicting treatment response in head and neck squamous cell carcinoma treated with chemoradiotherapy.

ABBREVIATIONS: \(\Delta ADC\) = fractional change in ADC; HNSCC = head and neck squamous cell carcinoma; \(\Delta TV\) = tumor regression rate; LRC = locoregional control; LRF = locoregional failure

Approximately two-thirds of patients with head and neck squamous cell carcinoma (HNSCC) present with advanced-stage disease, and regional lymph node involvement is common.\(^1\) Surgery with or without adjuvant chemotherapy and/or radiation therapy remains a mainstay of treatment in advanced HNSCC, but radical radiation therapy alone or concurrent chemoradiotherapy as a definitive treatment has become a standard management option for many patients with HNSCC to improve the patient’s quality of life via organ preservation. Despite these rigorous treatment methods, however, locoregional disease failure occurs in as many as 30%–40% of cases.\(^2,3\) Therefore, if a reliable indicator of response to radiation therapy or chemoradiotherapy before or at an early stage of treatment could be found, patients whose prognoses are likely to be unfavorable with current approaches might be selected for alternative strategies, improving their chances of success and sparing them from ineffective treatment with unnecessary toxicity. It has been impossible, however, to reliably predict early individual treatment response despite careful evaluation by using traditional clinical predictors such as tumor size, clinical stage, tumor location, and lymph node involvement.\(^4\)

DWI extracts information from the diffusion of water molecules in tissue. Water molecule diffusion motion can be quantified by using the ADC. In general, highly cellular cancers have more restricted diffusion, resulting in lower ADC values, while...
Histologically confirmed HNSCC between January 2008 and September 2012

Inclusion criteria:
- No previous treatment history (primary case)
- Tumor volume and site appropriate to chemoradiotherapy with curative intent
- No history of radiotherapy in the head and neck region
- Performance status of 0–1 (Eastern Cooperative Oncology Group scale)
- Age > 580 years
- Leukocyte ≥ 4000/μL, platelets ≥ 100,000/μL, hemoglobin ≥ 9.5 g/dL, serum creatinine ≤ normal institutional upper limit, 24-hour creatinine clearance ≥ 50 mL/min, bilirubin ≤ 1.5 mg/dL, aspartate aminotransferase and alanine transferase ≤ normal upper limit

Exclusion criteria:
- Active invasive malignancies in the 3 years leading up to protocol entry
- Distant metastases
- Serious complications: active infectious disease, interstitial pneumonia, cardiac failure, renal dysfunction, etc

40 consecutive patients

FIG 1. Patient selection criteria.

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Patients (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>66.2</td>
</tr>
<tr>
<td>Range</td>
<td>33–79</td>
</tr>
<tr>
<td>Male/female</td>
<td>30:5</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
</tr>
<tr>
<td>Supraglottis</td>
<td>3</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>9</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>9</td>
</tr>
<tr>
<td>Larynx</td>
<td>10</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>4</td>
</tr>
<tr>
<td>T stage (UICC 2002)</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1</td>
</tr>
<tr>
<td>T2</td>
<td>14</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
</tr>
<tr>
<td>T4</td>
<td>12</td>
</tr>
<tr>
<td>N stage (UICC 2002)</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>3</td>
</tr>
<tr>
<td>N1</td>
<td>7</td>
</tr>
<tr>
<td>N2</td>
<td>20</td>
</tr>
<tr>
<td>N3</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: - UICC indicates Union for International Cancer Control.

4. Cancer treatments causing cell death increase water diffusion and lead to a rise in ADC. In HNSCC, recent clinical studies have applied DWI to the prediction of treatment response to neoadjuvant chemotherapy, radiation therapy, or chemoradiotherapy before or at an early stage of treatment, revealing that pretreatment ADC correlates with treatment response and that ADC changes at 1, 2, and 4 weeks after the start of treatment can predict treatment response. In addition, it has been reported that ADC changes at 3 weeks posttreatment can predict treatment response with higher accuracy than morphologic imaging assessment. Studies evaluating the predictive value of DWI for treatment response post-radiation therapy and/or chemotherapy are limited, however, and the optimal timing of the evaluation of the DWI and ADC analysis method for predicting the treatment response has not been established, to our knowledge.

The aim of this study was to evaluate the usefulness of the fractional change in ADC (ΔADC) during therapy for prediction of treatment response in patients with HNSCC treated with chemoradiotherapy compared with the other clinical variables and to identify whether the ΔADC during therapy can be used as a valid imaging biomarker for prediction of treatment response.

MATERIALS AND METHODS

Patient Population

This prospective study was approved by the Committee on Clinical Study at our institution, and written informed consent was obtained from all patients. The study population consisted of patients with histologically confirmed primary HNSCC who were treated with chemoradiotherapy between January 2008 and September 2012 at our institution. Patient selection was performed according to the inclusion and exclusion criteria for this study, summarized in Fig 1. Forty patients who met these criteria were enrolled in this study. Five patients were excluded from the data analysis: 2 who refused the proposed treatment, 2 for whom the MR image quality was poor due to a low signal-to-noise ratio or artifacts, and 1 who died within 3 months after therapy with unknown disease status. Eventually, 35 patients were eligible for the present analysis. Patient characteristics are displayed in Table 1. All tumors were staged according to the 2002 Union for International Cancer Control Tumor, Node, Metastasis staging system.

Treatment and Follow-Up

All patients underwent concurrent chemoradiotherapy. External radiation therapy was administered in 2-Gy daily standard fractions by using 4-MV x-ray, and CT-based 3D conformal radiation therapy was mandatory. The gross tumor volume and the bulky lymph nodes were treated with up to 60–70 Gy (median, 68.4 Gy). A prophylactic nodal area was irradiated with up to 40–50 Gy (median, 44.6 Gy). Patients received concurrent chemotherapy by using S-1 and cisplatin: S-1 at the dose of 60 mg/m² for 3 weeks followed by 1 week of rest plus weekly cisplatin at the dose of 30 mg/m² for 3 weeks followed by 1 week of rest with cisplatin, 100 mg/m², at weeks 1 and 4 (n = 25) or cisplatin, 100 mg/m², at weeks 1 and 4 (n = 10). Chemotherapy was repeated every 4 weeks for 2 courses.

Pretreatment diagnostic examinations included contrast-enhanced CT in all patients, [18F]FDG-PET/CT in 20 patients, and panendoscopy with biopsy in all patients. For routine pretreatment examinations, MR imaging with DWI was performed in all patients. Pretreatment MR imaging with DWI was performed from 1 to 10 days before the start of treatment, and a second MR imaging with DWI was performed at 3 weeks after the start of treatment. In the previous study of the usefulness of DWI in predicting the response to neoadjuvant chemoradiotherapy for...
imaging with DWI performed from 1 to 10 days after the start of treatment and MR imaging with DWI performed at 3 weeks after the start of treatment, respectively. Because the images of HNSCC are subject to artifacts induced by continuous physiologic motion such as breathing and swallowing as well as susceptibility artifacts, automated evaluation of serial changes in ADC, such as a histogram-based or voxel-wise approach incorporating registered image datasets between treatment interval examinations, may be needed to decrease interpretation error. Therefore, in this study, the mean value of ADC of the whole tumor and the mean change in ADC during treatment were used. ROIs were independently placed over all targeted lesions on every section of the ADC map, and the ADC values for the sections were averaged to obtain the mean value of ADC of the whole tumor for each of the patients at each measurement time point. For region-of-interest placements in the lesions, care was taken to include the solid portions of the lesions and to exclude any obviously cystic or necrotic areas in reference to the T2WI. In addition, these ROIs were used to measure the whole tumor volume. In each primary tumor and metastatic node, whole tumor volume was calculated by multiplying each cross-sectional area by the section thickness. These procedures were performed separately and independently by 2 observers (M.M. and Y.K., with 15 and 20 years of experience in head and neck MR imaging, respectively) who were blinded to the information regarding local failure or control. All ADC and tumor volume measurements were performed twice by each observer.

The ΔADC at 3 weeks for each primary tumor and metastatic node was calculated on the basis of the ADC values at pretreatment and 3 weeks after the start of treatment by using the formula

$$\Delta ADC = (ADC_{SW} \cdot \Delta ADC_{pre})/ADC_{pre}$$

where $ADC_{pre}$ represents the pretreatment ADC values and $ADC_{SW}$ represents the ADC values at 3 weeks after the start of treatment.

In addition, the tumor regression rate (ΔTV) for each primary tumor and metastatic node was calculated on the basis of the tumor volume at pretreatment and 3 weeks after the start of treatment by using the formula

$$\Delta TV = (TV_{pre} - TV_{3W})/TV_{pre}$$

where $TV_{pre}$ represents the pretreatment tumor volume and $TV_{3W}$ represents the tumor volume at 3 weeks after the start of treatment.

**Statistical Analysis.** The intraobserver and interobserver variability of region-of-interest placement for the measurement of ADC and tumor volume of primary tumors and metastatic nodes was analyzed by calculating the interclass correlation coefficient for single measurements (0–0.20 is considered poor; 0.21–0.40, as fair; 0.41–0.60, good; 0.61–0.80, excellent; 0.81–1.0, perfect).
as moderate; 0.61–0.80, as good; and 0.81–1.00, as excellent correlation). The pretreatment ADC; ΔADC; primary tumor volume; primary nodal volume; ΔTV; and the other clinical variables such as age, T stage (T1–2 versus T3–4), N stage (N0–1 versus N2–3), and tumor location (hypopharynx or oral cavity versus others) were compared with LRC and locoregional failure (LRF) by using a Mann-Whitney U test. The univariate/multivariate nominal logistic analysis was used to assess the correlation between LRC and the same variables described above. Then, a receiver operating characteristic analysis with the area under the curve was used to investigate the discriminatory capability of the significant predictive value of LRC. For calculation of the sensitivity, specificity, and accuracy of the significant predictive value of LRC, the optimal threshold was determined by giving equal weighting to sensitivity and specificity on the receiver operating characteristic curve.

Finally, to determine the usefulness of ΔADC for the prediction of prognosis after chemoradiotherapy, we compared progression-free survival for the 2 groups divided by the optimal threshold value by using the Kaplan-Meier method followed by the log-rank test.

FIG 3. A 68-year-old man with hypopharyngeal cancer (poorly differentiated squamous cell carcinoma). A, Pretreatment transverse T2-weighted MR image shows a primary hypopharyngeal cancer (arrow). B, The pretreatment ADC map derived from the DWI shows that the corresponding ADC value was 1.11 × 10⁻³ mm²/s for the manually placed region of interest covering the tumor. C, At 3 weeks after the start of treatment, the T2-weighted MR image shows a mass with marked regression (arrow). D, The ΔADCprimary at 3 weeks of treatment is 0.69.

Analysis of Variables for Treatment Response
All DWI examinations of eligible patients for the present analysis were performed successfully. A representative case is shown in Fig 3.

Comparison of variables in LRC and LRF and univariate and multivariate analysis of variables in association with LRC are summarized in Table 2. The ΔADCprimary, ΔADCnode, ΔTVprimary, primary tumor volume, primary nodal volume, ΔTVnode, N stage, and tumor location revealed significant differences between LRC and LRF; however, there was no significant difference in ADCprimary, ADCnode, ΔTVprimary, age, and T stage. In univariate logistic analysis, ΔADCprimary, ΔADCnode, ΔTVnode, N stage, and tumor location showed significant association with LRC. Primary tumor volume and primary nodal volume showed no significant association. In multivariate logistic analysis after variable selection with the use of the forward stepwise method, only ΔADCprimary was identified as a significant and independent predictor of LRC.

The receiver operating characteristic analysis resulted in a threshold ΔADCprimary of 0.24 and an area under the curve of 0.9.
The median progression-free survival period of patients with \( \Delta ADC_{\text{primary}} = 0.24 \) was significantly longer than that of patients with \( \Delta ADC < 0.24 \) \((P < .05)\).

The 2-by-2 contingency table based on a \( \Delta ADC_{\text{primary}} \) of 0.24 revealed a sensitivity of 100\%, specificity of 78.7\%, positive predictive value of 76.7\%, negative predictive value of 100\%, and overall accuracy of 84.8\% for the prediction of LRC.

The progression-free survival curves in patients with \( \Delta ADC_{\text{primary}} \geq 0.24 \) and \( \Delta ADC_{\text{primary}} < 0.24 \) are shown in Fig 4. The median progression-free survival period of patients with \( \Delta ADC_{\text{primary}} < 0.24 \) was 11.5 ± 7.6 and that of patients with \( \Delta ADC_{\text{primary}} \geq 0.24 \) was 32.8 ± 8.2. The difference in progression-free survival between the 2 groups divided by the threshold value of \( \Delta ADC_{\text{primary}} \) was significant \((P < .05)\).

DISCUSSION

In previous clinical studies evaluating the use of DWI to predict treatment response to radiation therapy or chemoradiotherapy in HNSCC, 2 ADC parameters—namely, pretreatment ADC and the change in ADC during or early after treatment—have been shown to be useful. Kim et al\(^6\) reported the usefulness of pretreatment ADC for predicting the treatment response of neck lymph nodes at the end of treatment. In addition, Hatakenaka et al\(^7\) reported the usefulness of pretreatment ADC for predicting local failure during follow-up after chemoradiotherapy or radiation therapy. On the other hand, Vandrecaqey et al\(^8\) reported that the change in ADC at 2 and 4 weeks of treatment correlated significantly with the LRC and was more accurate than volumetric changes for the prediction of treatment outcome. In addition, King et al\(^9\) reported that a strong significant correlation was found between LRF and serial change in ADC. Thus, the optimal timing of the evaluation of ADC and its analysis method for predicting the treatment response to chemotherapy or chemoradiotherapy in HNSCC have not been established.

In the current study, the \( \Delta ADC_{\text{primary}} \) at 3 weeks of treatment was significantly lower for lesions with LRF than for those with LRC, and in the multivariate analysis, only \( \Delta ADC_{\text{primary}} \) revealed a significant association with LRC. By contrast, pretreatment ADC\(_{\text{primary}}\) was not statistically correlated with LRC. In addition, the \( \Delta ADC_{\text{primary}} \) threshold value of 0.24 resulted in 100\% sensitivity and 100\% negative predictive value for the prediction of LRC. The high negative predictive value of \( \Delta ADC_{\text{primary}} \) may help to predict patients with LRF of chemoradiotherapy at the early phase of treatment. Furthermore, in comparison of progression-free survival by using the \( \Delta ADC_{\text{primary}} \) threshold value of 0.24 for distinguishing the LRC group from the LRF group, the patients with \( \Delta ADC_{\text{primary}} \geq 0.24 \) showed better prognosis than those with \( \Delta ADC_{\text{primary}} < 0.24 \). Therefore, our results indicate that \( \Delta ADC_{\text{primary}} \) is a potential predictive indicator of treatment response to chemoradiotherapy but that pretreatment ADC\(_{\text{primary}}\) is not. However, further studies that prospectively use the thresholds obtained in this study are necessary to determine the real significance of \( \Delta ADC_{\text{primary}} \) for prediction and management of patients with HNSCC treated with chemoradiotherapy.

In many previous clinical and animal model studies, tumors showing a rise in the ADC at an early phase of treatment showed a better treatment response than those with little or no ADC rise.\(^{12,13}\) Although the mechanism of rise in the ADC at an early phase of treatment following cytotoxic and radiation treatment in experimental and human tumors is not fully understood, it has been speculated that a rise in ADC might be attributed to an increase in the fractional volume and diffusion of water molecules in the extracellular space that occurs with the disorganized micro-

---

Table 2: Comparison of variables in LRC and LRF/univariate and multivariate analysis of variables in association with LRC

<table>
<thead>
<tr>
<th>Comparison of Variables</th>
<th>LRC</th>
<th>LRF</th>
<th>( P ) Value</th>
<th>( P ) Value</th>
<th>( P ) Value</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta ADC_{\text{primary}} )</td>
<td>1.18 ± 0.29</td>
<td>1.24 ± 0.3</td>
<td>NS</td>
<td>NS</td>
<td>( 0.004 )</td>
<td>6.85 ( \times 10^{-4} )</td>
<td>0.48 ( \times 10^{-1} )</td>
<td>0.1</td>
<td>0.14 ( \times 10^{-3} )</td>
</tr>
<tr>
<td>( \Delta ADC_{\text{node}} )</td>
<td>0.19 ± 0.05</td>
<td>1.35 ± 0.03</td>
<td>NS</td>
<td>NS</td>
<td>( 0.03 )</td>
<td>1.78 ( \times 10^{-2} )</td>
<td>0.46 ( \times 10^{-3} )</td>
<td>0.69</td>
<td>NS</td>
</tr>
<tr>
<td>( \Delta TV_{\text{primary}} )</td>
<td>0.04 ± 0.01</td>
<td>0.32 ± 0.04</td>
<td>NS</td>
<td>NS</td>
<td>( 0.04 )</td>
<td>1.13 ( \times 10^{-2} )</td>
<td>0.52 ( \times 10^{-3} )</td>
<td>0.40</td>
<td>NS</td>
</tr>
<tr>
<td>( \Delta TV_{\text{node}} )</td>
<td>0.11 ± 0.09</td>
<td>0.56 ± 0.19</td>
<td>NS</td>
<td>NS</td>
<td>( 0.02 )</td>
<td>1.23 ( \times 10^{-3} )</td>
<td>0.52 ( \times 10^{-5} )</td>
<td>0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>69.3</td>
<td>66.9</td>
<td>( 0.29 )</td>
<td>( 1.24 )</td>
<td>( 0.03 )</td>
<td>1.3</td>
<td>2.15</td>
<td>( 0.03 )</td>
<td>1.3</td>
</tr>
<tr>
<td>TV primary</td>
<td>7,106</td>
<td>11,048</td>
<td>( 0.03 )</td>
<td>0.29</td>
<td>( 0.01 )</td>
<td>NS</td>
<td>NS</td>
<td>( 0.03 )</td>
<td>0.29</td>
</tr>
<tr>
<td>TV node</td>
<td>32,122</td>
<td>4,788</td>
<td>( 0.03 )</td>
<td>NS</td>
<td>( 0.01 )</td>
<td>NS</td>
<td>NS</td>
<td>( 0.03 )</td>
<td>NS</td>
</tr>
<tr>
<td>Primary nodal volume (mm(^3))</td>
<td>32,122</td>
<td>4,788</td>
<td>( 0.03 )</td>
<td>NS</td>
<td>( 0.01 )</td>
<td>NS</td>
<td>NS</td>
<td>( 0.03 )</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor location (hypopharynx or oral cavity vs others)</td>
<td>4/17</td>
<td>9/5</td>
<td>( 0.003 )</td>
<td>( 0.03 )</td>
<td>( 0.22 )</td>
<td>( 0.05–0.88 )</td>
<td>NS</td>
<td>NS</td>
<td>( 0.03 )</td>
</tr>
</tbody>
</table>

Note:—NS indicates a \( P \) value > .05.  

FIG 4. Progression-free survival of patients with head and neck squamous cell carcinoma assessed by \( \Delta ADC \). The graph shows that the median progression-free survival period of patients with \( \Delta ADC \geq 0.24 \) was significantly longer than that of patients with \( \Delta ADC < 0.24 \) \((P < .05)\).
structure in necrosis and apoptosis in response to treatment.\(^{14}\)
Therefore, \(\Delta\text{ADC}\) at an early phase of treatment seems to reflect
the degree of tumor cell damage resulting from the treatment. However,
because the treatment response may be attributed to
differences in tumor aggressiveness, the treatment method, or
the intensity of treatment, the use of only a single ADC measurement
at pretreatment appears to be inadequate for the prediction of
treatment response. Therefore, evaluating the \(\Delta\text{ADC}\) may be nec-
essary for the prediction of treatment response.

The induction of tiny regions of liquefaction necrosis at the
early phase of treatment may interfere with ADC measurement.\(^{15}\)
For this reason, there may be a misleading and misrepresentative
rise in ADC despite the persistence of viable tumor components.
In the ADC measurement in our study, it may have been difficult
to distinguish tiny liquefaction necrosis from lesions at 3 weeks of
treatment because the lesions were visually associated on the ADC
map in reference to T2WI for tumor heterogeneity. Therefore, we
used the mean value of ADC of the whole tumor and the mean
change in ADC during treatment. The use of the mean change in
ADC may be explained by the fact that the specificity and positive
predictive value of \(\Delta\text{ADC}\) were low in the current study. In brain
tumor, quantification of diffusion changes has evolved from the
mean change in ADC to a voxel-by-voxel approach, termed the
“functional diffusion map,” as a biomarker for treatment re-
sponse.\(^{16}\) In the functional diffusion map, treatment response is
evaluated on the basis of the fractional volume of significantly
increased ADC within the tumor. In the study by Galbán et al\(^{17}\) of
the functional diffusion map of HNSCC, the change in ADC assessed
by the functional diffusion map was superior to the percentage
change of the mean ADC in prediction of disease control after
chemoradiotherapy. Therefore, in the future, more automated
evaluations, such as a voxel-by-voxel approach, may be needed to
estimate the change in ADC during treatment more accurately.
However, it may be difficult to implement it in routine examina-
tions for organs outside the brain due to differences in the orien-
tation of images and artifacts induced by continuous physiologic
motion.

In many previous studies that used DWI to examine the treat-
ment response in HNSCC, a maximum b-value of 1000 s/mm\(^2\)
was used.\(^{6-10}\) Preferentially, a standardized ADC calculation by
using at least 3 b-values, including a maximum b-value exceeding
500 s/mm\(^2\), should be performed.\(^{18}\) In the current study, a max-
imum b-value of 800 s/mm\(^2\) was used to limit the possible effects
of distortion due to susceptibility artifacts and to reduce the sig-
nal-to-noise ratio on the ADC value; such factors are problems at
high b-values. In this study, only 2 patients were excluded from
this study due to a low signal-to-noise ratio or artifacts of DWI.
The merit of ADC values differs with b-values because they are
influenced by tissue perfusion and T2 time, and it may be desir-
able for accurate ADC measurement that 1 of the b values not be
zero. Therefore, in this study, ADC values were calculated from
b-values of 90 and 800 s/mm\(^2\), and DWI with a b-value of zero was
used for image registration.

With regard to the relationship between the ADC of metastatic
nodes and treatment response, Kim et al\(^{8}\) reported that the change
in ADC of metastatic nodes within the first week of chemoradio-
therapy was more useful for predicting treatment response than
pretreatment ADC. In addition, Vandecaveye et al\(^{8}\) reported that
the change in the ADC of metastatic nodes at 2 and 4 weeks after
the start of treatment correlated significantly with 2-year LRC. In
this study, \(\Delta\text{ADC}_{\text{node}}\) revealed a significant difference between
LRC and LRF and showed a significant association with LRC in
univariate analysis. Therefore, our results were comparable with
theirs, and it was suggested that the change in ADC of metastatic
nodes during treatment may be useful for the prediction of treat-
ment response and/or LRC. The primary sites of HNSCC are gen-
erally located at the air-tissue interface and in areas prone to mo-
tion artifacts induced by physiologic motion such as breathing
and swallowing. Therefore, in DWI, the primary sites seem to be
more influenced by physiologic motion and susceptibility arti-
facts than cervical lymph nodes. In addition, in variability analysis
of region-of-interest placement for measurements of ADC, intra-
observer and interobserver agreement of the metastatic nodes
tended to be higher than those of the primary tumors in this study.
Therefore, although only the \(\Delta\text{ADC}_{\text{primary}}\) was identified as a sig-
nificant and independent predictor of LRC in this study, the pos-
sibility that ADC values from the metastatic nodes may predict
LRC in patients with HNSCC treated with chemoradiotherapy
was thought to have great clinical significance.

The value of the primary tumor volume and T stage as a prog-
nostic factor in HNSCC has been reported in published studies for
multiple subsites and different treatment modalities.\(^{2,19}\) How-
ever, in the current study, primary tumor volume and T stage did
not show a significant correlation with LRC. Most previously
published studies included patients treated with single-technique
therapy (radiation therapy or surgery alone). However, in this
study, all patients were treated with definitive concurrent chemo-
radiotherapy. There have been many reports that definitive con-
current chemoradiotherapy leads to better clinical outcome than
single-technique therapy in HNSCC.\(^{20}\) Therefore, it was specu-
lated that clinical outcome after definitive concurrent chemora-
diotherapy might not be significantly influenced by primary tu-
mor volume or T stage.

In patients with HNSCC treated with chemoradiotherapy,
controversies remain concerning the role of neck dissection for
the management of the neck with bulky lymph node involve-
ment.\(^{21}\) There is no consensus on the treatment of patients with a
complete regional response after treatment. With regard to the
regional recurrence after chemoradiotherapy, it has been re-
ported that lymph node residual size and the regression rate of
nodal maximal diameter or nodal volume after treatment might
be useful for the prediction of regional recurrence.\(^{22,23}\) In
this study, we evaluated the usefulness of the tumor regression ratio
at 3 weeks after the start of chemoradiotherapy for prediction of
LRC. As a result, \(\Delta\text{TV}_{\text{node}}\) revealed a significant difference be-
tween LRC and LRF and showed significant association with LRC
in univariate analysis. Therefore, if prediction of regional recur-
rence is possible by the tumor regression rate of metastatic nodes
during treatment, it has great clinical significance. In the future, it
would be interesting to evaluate whether \(\Delta\text{TV}_{\text{node}}\) may be a useful
criterion to guide clinical decisions regarding neck dissection after
chemoradiotherapy.

There are limitations to our study. First, the patient popula-
tion was relatively small and heterogeneous, including those with
tumors from various head and neck sites. Also, in this study, patients with oral cavity cancer were included. Surgery is usually the preferred treatment option in patients with oral cavity carcinoma, but these patients whose disease was considered inoperable because of tumor extent and/or medical reasons were enrolled in this study. Therefore, further studies with a large number of patients without potential selection bias are needed because direct comparison among DWI and other predictive or prognostic factors is necessary to show the actual clinical significance of our findings. Second, the biologic differences in squamous cell carcinomas due to differences in smoking and alcohol use as well as molecular markers such as epidermal growth factor receptor expression and human papillomavirus infection have been suggested as prognostic factors. In particular, human papillomavirus–positive oropharyngeal carcinoma has emerged as a new entity with an excellent overall survival rate, but the patients in this study were not tested for human papillomavirus infection.

CONCLUSIONS

DWI provides information that may be used as a predictive imaging biomarker of LRC in patients with HNSCC treated by chemoradiotherapy. The $\Delta$ADC$_{prim}$ at 3 weeks during treatment is a valid predictive clinical factor, showing a significant association with LRC. Thus, sequential DWI may help to avoid ineffective treatment and unnecessary toxicity, allowing chemoradiotherapy to be selectively used for appropriate patients.

REFERENCES

2. Horiot JC, Bontemps P, van den Bogaert W, et al. Accelerated fractionation (AF) compared with conventional fractionation (CF) improves locoregional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol 1997;44:111–21
8. Vandeaveye V, Dirix P, De Keyzer F, et al. Predictive value of diffusion-weighted magnetic resonance imaging during chemoradiotherapy and unnecessary toxicity, allowing chemoradiotherapy to be a valid predictive clinical factor, showing a significant association during treatment is