Squamous Cell Carcinoma of the Head and Neck: Comparison of Diffusion-weighted MRI at b-values of 1,000 and 2,000 s/mm² to Predict Response to Induction Chemotherapy

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(Received January 13, 2015; Accepted March 25, 2015; published online June 23, 2015)

Purpose: Recent publications have reported contradictory results of pretreatment diffusion-weighted magnetic resonance imaging (DWI) for the prediction of chemoradiotherapeutic response in primary squamous cell carcinomas of the head and neck (HNSCC). Therefore, we evaluated the diagnostic performance of DWI obtained with both standard (b = 0 and 1,000 s/mm²) and high (b = 0 and 2,000 s/mm²) b-values for predicting response to induction chemotherapy in HNSCCs.

Methods: For 25 patients with primary HNSCC who underwent DWI with both standard and high b-values prior to treatment, we calculated corresponding apparent diffusion coefficient (ADC) maps. Regions of interest containing the tumor were drawn on every section of ADC maps and summed to make volume-based data of the entire tumor. Histogram parameters (mean ADC, kurtosis, and skewness) were correlated with treatment response using unpaired Student t test. Univariate and multivariate analysis of the ADC parameters, patient age, sex, whole tumor volume, and T stage were also performed to predict tumor response to induction chemotherapy.

Results: Response to induction chemotherapy was good in 13 of the 25 patients and poor in 12. The mean ADC values of good responders at standard b-value (ADC1000), 1.23 ± 0.34 (× 10⁻³ mm²/s), and high b-value (ADC2000), 0.62 ± 0.14 (× 10⁻³ mm²/s), were lower than those of poor responders (ADC1000, 1.32 ± 0.28 [× 10⁻³ mm²/s]; ADC2000, 0.76 ± 0.15 [× 10⁻³ mm²/s]), but significant difference was achieved only at the ADC2000 map (P = 0.02). In addition, mean tumor volume prior to treatment of good responders was smaller than that of poor responders. However, at multiple logistic regression analysis, only the mean ADC2000 value remained as a significant predictor of response to induction chemotherapy.

Conclusion: DWI with high b-values (b = 0 and 2,000 s/mm²) as an assessment of ADC values may help predict tumor response to neoadjuvant chemotherapy for primary HNSCCs.

Keywords: diffusion, head and neck cancer, high b-value, magnetic resonance imaging

Introduction

Squamous cell carcinomas of the head and neck (HNSCC) are the sixth most common neoplasm worldwide. About two-thirds of patients present with locally advanced stage disease, and their treatment is aimed at cure.

Such nonsurgical approaches as radiation therapy or concurrent chemoradiotherapy have recently
been accepted as major standard treatment options for these patients because surgery can severely impair quality of life by damaging functions, including speech, eating, and swallowing, and creating cosmetic problems. In the last decade, neoadjuvant induction chemotherapy followed by definitive local therapy has also been considered because induction chemotherapy has the potential to reduce tumor volume, offering a greater opportunity for organ preservation and decreasing the risk of distant failure. In addition, clinicians have been able to choose subsequent individualized definitive treatment modalities according to the response of the tumor to induction chemotherapy. However, recent publications have also reported the questionable efficacy of induction chemotherapy in HNSCC related to locoregional failure. The identification of noninvasive imaging biomarkers that could be used to ascertain which patients might benefit from induction chemotherapy before initiation of treatment is important because not all patients respond to chemotherapy and the cost and toxic side effects induced by induction chemotherapy cannot be ignored. In addition, if we could predict poor treatment response before initiating induction chemotherapy, we could apply alternative therapies or modify therapies early in the course of treatment in individual patients to improve their quality of life and increase survival.

During the last couple of years, researchers have proposed several imaging modalities, including 2-[18F]-fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET), computed tomography (CT) perfusion imaging, and dynamic contrast-enhanced (DCE) magnetic resonance (MR) imaging, as potential imaging biomarkers for predicting and monitoring treatment response before and during treatment in patients with HNSCC. However, lower spatial resolution, specificity (i.e., treatment-related inflammatory condition) and ionizing radiation associated with PET, rigorous processes related with the analysis of data from CT perfusion and DCE-MR imaging limit the routine clinical application of these modalities.

On the other hand, diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps, which provides a quantitative index of water diffusivity for each voxel that allows visualization of the microscopic motion of water molecules within tissues, can facilitate data acquisition and processing steps without the use of ionizing radiation or contrast agents. Therefore, in recent years, DWI has been considered a good candidate as a noninvasive biomarker for predicting and monitoring treatment responses. Consequently, many studies have assessed DWI parameters (ADC values) with tumor response to chemoradiation therapy, but the results of those studies have been conflicting. The studies have used DWI with standard b-values (b = 1,000 s/mm² or lower), and most have not considered such clinical factors as age, sex, tumor stage, and tumor volume. Furthermore, quite recently, substantial advances in diffusion MR technology have made the acquisition of DWI with higher b-values feasible, and DWI with high b-values (b = 0 and 2,000 s/mm²) has been applied successfully to HNSCC for tumor grading and work-up for recurrence following treatment.

In addition, a histogram-based approach with ADC maps has been used in neuro-oncologic imaging to differentiate tumor progression from pseudo-progression and to evaluate tumor grades and even gene mutations. Histogram analysis is considered to represent tumor heterogeneity, which is well known to affect tumor response to chemoradiation therapy. Therefore, analysis of the spatial heterogeneity of the tumor cellularity by histogram analysis of ADC maps could help evaluate and predict tumor response to treatment.

We evaluated the usefulness of DWI with high b-values (b = 0 and 2,000 s/mm²) comparing to DWI with standard b-values (b = 0 and 1,000 s/mm²) to predict tumor response to induction chemotherapy using histogram analysis along with the influence of other clinicopathologic factors.

Materials and Methods

Our institutional review board approved this retrospective study, and informed consent was waived.

Study population

Seventy-nine patients were diagnosed with HNSCC in our hospital between September 2008 and March 2012 and received neoadjuvant chemotherapy. We excluded 54 of these 40 patients without either pre-treatment or post-treatment MR examinations, seven with MR examination without a relevant DWI protocol, three with primary masses too small to allow measurement of ADC values (less than 1.0 cm³ of volume) on MR images, two with severe artifacts on both standard and high b-value DWI, and two with an interval greater than 30 days between initial MR imaging and pathologic tissue confirmation.

We finally included 25 patients (18 men, 7 women; mean age, 53.8 ± 10.4 years) in this study. The 25 primary tumor sites were the oral cavity (n = 8), oropharynx (n = 10), nasopharynx (n = 5), larynx (supraglottis, n = 1), and maxillary sinus (n = 1).
The mean volume of primary tumors was 20.3 ± 30.0 cm³, and T stages were T1 (n = 1), T2 (n = 5), T3 (n = 4), and T4 (n = 15).

Treatment response

Tumor response was classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) as complete (n = 2), partial (n = 11), stable disease (n = 7), and progressive disease (n = 5). The good responder group (n = 13) comprised tumors with complete and partial response and the poor responder group (n = 12), tumors with stable disease and progressive disease, after neoadjuvant chemotherapy.

Chemotherapeutic regimens used for neoadjuvant chemotherapy were docetaxel with 5-fluorouracil and cisplatin (n = 8) or docetaxel and cisplatin with (n = 12) or without (n = 5) cetuximab. All patients underwent 2 or 3 cycles of the above regimens of neoadjuvant treatment. Response was evaluated approximately 2 weeks (mean 14.9 ± 3.4 days, 10 to 24 days) after the second cycle of induction chemotherapy in all patients.

MR and DWI

All patients underwent MR imaging using a 1.5-tesla system (Signa Excite, GE Medical Systems, Milwaukee, WI, USA) with an 8-channel head and neck coil before induction chemotherapy and 2 weeks after the second cycle of induction chemotherapy.

Conventional MR images were obtained using a transverse spin-echo T₁-weighted sequence (repetition time [TR], 550 to 650 ms; echo time [TE], 8 to 11 ms; matrix, 320 × 192; section thickness, 4.0 mm; gap, 1.2 mm; field of view [FOV], 24 × 24 cm; number of acquisitions [NEX], 1.5; pixel resolution, 0.7 × 1.1 × 4.0 mm) and a transverse fast spin-echo T₂-weighted sequence (TR, 3200 to 5800 ms; TE, 60 to 100 ms; matrix, 320 × 192; section thickness, 4.0 mm; gap, 1.2 mm; FOV, 24 × 24 cm; NEX, 2; echo train length, 16; pixel resolution, 0.7 × 1.1 × 4.0 mm) with fat suppression.

Contrast-enhanced multiplanar MR images using the fat suppressed spin-echo T₁-weighted sequences were obtained after intravenous injection of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist; Schering AG, Berlin, Germany).

Single-shot echo-planar DWI was obtained in the transverse plane prior to contrast injection at both standard (b = 0 and 1,000 s/mm²) and high (b = 0 and 2,000 s/mm²) b-values with following parameters: TR, 9,000 to 10,000 ms and TE, 61.6 to 77.6 ms at standard b-value and TR, 9,325 to 12,000 ms and TE, 73.8 to 90.4 ms at high b-value; matrix, 160 × 160; 30 to 45 slices; slice thickness, 4.0 mm; intersection gap, 1.2 mm; bandwidth, 1,953 Hz/pixel; FOV, 24 × 24 cm; NEX, 2; and pixel resolution, 1.5 × 1.5 × 4.0 mm. DWI data were acquired in 3 orthogonal directions and combined into a trace image. The average duration of DWI at b = 0 and 1,000 s/mm² was 1 min 23 s and of b = 0 and 2,000 s/mm², 2 min 50 s.

We derived ADC maps from the following equation on the GE Medical Systems workstation: 

\[
ADC = -\ln(S(b)/S(0))/b,
\]

where S(b) is the signal intensity with diffusion-sensitizing gradients, and S(0) is the intensity without diffusion-sensitizing gradients.

Image analysis

We reviewed MR images on a picture archiving and communication system workstation (m-view, version 5.4; Infinitt Healthcare, Seoul, Korea).

Regions of interest (ROIs) that contained the entire tumor were drawn in each section of the ADC₁₀₀₀₀ maps (ADC values of DWIs obtained with b = 0 and 1,000 s/mm²) and copied to the ADC₂₀₀₀ maps (ADC values of DWIs obtained with b = 0 and 2,000 s/mm²). A neuroradiologist with 6 years of experience interpreting head and neck MR images (I.R.) defined tumor boundaries with reference to the contrast-enhanced T₁-weighted images and T₂-weighted images (Figs. 1, 2). The data acquired from each section were summed to derive voxel-by-voxel ADCs for the entire tumor volume using software developed in house.

From the ADC histograms, we derived following parameters: (a) mean; (b) standard deviation; (c) kurtosis, the degree of peakedness of a distribution; and (d) skewness, a measure of the degree of asymmetry of a distribution.

Statistical analysis

All statistical analyses were performed using MedCalc® software for Windows (Version 12.6.1.0, Mariakerke, Belgium), with a 2-tailed P value equal to or less than 0.05 considered to indicate a statistically significant difference.

We used unpaired Student t test to compare age, tumor volume, and ADC values of all tumors with the standard and high b-values between good and poor responders to induction chemotherapy. Fischer’s exact test was used to compare sex, and χ² test was used to compare T stages of the tumors between the 2 groups.

Furthermore, we performed a receiver operating characteristic (ROC) curve analysis to correlate ADC values and tumor response to induction che-
Fig. 1. A 58-year-old man with right tonsillar cancer with good response to induction chemotherapy. (a) Transverse T1-weighted postcontrast magnetic resonance image. (b) Transverse apparent diffusion coefficient (ADC) map obtained with $b = 0$ and $1,000 \text{s/mm}^2$ (ADC$_{1000}$); mean ADC$_{1000}$, $1.24 \times 10^{-3} \text{ mm}^2/\text{s}$. (c) Transverse ADC map obtained with $b = 0$ and $2,000 \text{s/mm}^2$ (ADC$_{2000}$); mean ADC$_{2000}$, $0.53 \times 10^{-3} \text{ mm}^2/\text{s}$. (d) Histogram of ADC$_{1000}$ with a normal distribution curve (dashed line); kurtosis, 0.3; skewness, 0.5. (e) Histogram of ADC$_{2000}$ with a normal distribution curve (dashed line); kurtosis, 0.16; skewness, 0.46.

Fig. 2. A 39-year-old man with left nasopharyngeal cancer with poor response to induction chemotherapy. (a) Transverse T1-weighted postcontrast magnetic resonance image. (b) Transverse apparent diffusion coefficient (ADC) map obtained with $b = 0$ and $1,000 \text{s/mm}^2$ (ADC$_{1000}$); mean ADC$_{1000}$, $1.19 \times 10^{-3} \text{ mm}^2/\text{s}$. (c) Transverse ADC map obtained with $b = 0$ and $2,000 \text{s/mm}^2$ (ADC$_{2000}$); mean ADC$_{2000}$, $0.82 \times 10^{-3} \text{ mm}^2/\text{s}$. (d) Histogram of ADC$_{1000}$ with a normal distribution curve (dashed line); kurtosis, 2.47; skewness, 1.65. (e) Histogram of ADC$_{2000}$ with a normal distribution curve (dashed line); kurtosis, 0.59; skewness, 0.96.
Diffusion Imaging in Head and Neck Cancer

Table 1. Pretreatment apparent diffusion coefficient (ADC) histogram values for squamous cell carcinomas of the head and neck

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Whole group</th>
<th>Good responders</th>
<th>Poor responders</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>13</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Standard b-value (b = 0 and 1,000 s/mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ADC*</td>
<td>1.27 ± 0.31</td>
<td>1.23 ± 0.34</td>
<td>1.32 ± 0.28</td>
<td>0.46</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.34 ± 1.18</td>
<td>0.14 ± 1.01</td>
<td>0.57 ± 1.35</td>
<td>0.37</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.55 ± 0.50</td>
<td>0.41 ± 0.41</td>
<td>0.71 ± 0.55</td>
<td>0.14</td>
</tr>
<tr>
<td>High b-value (b = 0 and 2,000 s/mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ADC*</td>
<td>0.68 ± 0.16</td>
<td>0.62 ± 0.14</td>
<td>0.76 ± 0.15</td>
<td>0.02</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.32 ± 0.83</td>
<td>0.29 ± 0.69</td>
<td>0.36 ± 0.99</td>
<td>0.83</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.51 ± 0.43</td>
<td>0.50 ± 0.40</td>
<td>0.52 ± 0.47</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Note: Unless otherwise specified, the data are the means ± standard deviations.

*ADC value: × 10⁻³ mm²/s
†P value for the comparison of means was calculated using unpaired Student t test.

Results

Analysis of DWI

The mean ADC₁₀₀₀ (1.23 ± 0.34 [× 10⁻³ mm²/s]) and mean ADC₂₀₀₀ (0.62 ± 0.14 [× 10⁻³ mm²/s]) values of the good responder group were lower than those of the poor responders (ADC₁₀₀₀, 1.32 ± 0.28 [× 10⁻³ mm²/s]; ADC₂₀₀₀, 0.76 ± 0.15 [× 10⁻³ mm²/s]). However, statistical significance was achieved only with ADC₂₀₀₀ (P = 0.02) (Figs. 1, 2).

In the histogram analysis, skewness and kurtosis were lower for good responders than for poor responders on both standard and high b-value ADC maps, but the results of neither standard nor high b-value reached statistical significance (Table 1) (Figs. 1, 2).

In the ROC curve analysis, the area under the ROC curve (Az) value of ADC₁₀₀₀ was 0.628 and of ADC₂₀₀₀, 0.769, for predicting good response to induction chemotherapy. The cutoff values were 1.37 (× 10⁻³ mm²/s) for ADC₁₀₀₀ and 0.68 (× 10⁻³ mm²/s) for ADC₂₀₀₀. For ADC₁₀₀₀, the corresponding sensitivity was 84.6% and specificity was 41.7%, and for ADC₂₀₀₀, sensitivity was 84.6% and specificity was 66.7% (Table 2).

Univariate and multivariate analysis

The good responder group comprised 4 women and 9 men with mean age 55.1 ± 7.7 (range: 35–65) years and the poor responder group, 3 women and 9 men with mean age 52.4 ± 13.0 (range: 32–71) years. The mean tumor volume of good responders was 8.1 ± 5.7 cm³ and of poor responders, 33.4 ± 39.6 cm³. One tumor in the good responder group was stage T1, three were T2, three were T3,
and six were T4. Two tumors in the poor responder group were stage T2, one was T3, and nine were T4 (Table 3).

Univariate analysis demonstrated no significant difference among sex, age, and pretreatment tumor stage as predictors of response to neoadjuvant chemotherapy. The mean tumor volume of good responders was also smaller than that of poor responders ($P = 0.05$) (Table 3). However, at multiple logistic regression analysis, only the mean ADC$_{2000}$ value remained as a significant predictor of response to neoadjuvant chemotherapy ($P = 0.04$, $P$ value for the mean tumor volume in multivariate analysis was 0.13).

**Table 3.** Comparison of demographic and clinicopathologic features between good and poor responders to induction chemotherapy in patients with squamous cell carcinoma of the head and neck

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Good responders</th>
<th>Poor responders</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>55.1 ± 7.7 (range, 35 to 65)</td>
<td>52.4 ± 13 (range, 32 to 71)</td>
<td>0.54*</td>
</tr>
<tr>
<td>Sex (Male:Female)</td>
<td>9:4</td>
<td>9:3</td>
<td>1.0†</td>
</tr>
<tr>
<td>Tumor volume (cm$^3$)</td>
<td>8.1 ± 5.7 (range, 1.8 to 22.5)</td>
<td>33.4 ± 39.6 (range, 4.0 to 135.3)</td>
<td>0.05*</td>
</tr>
<tr>
<td>T stage 1/2/3/4 (No.)</td>
<td>1/3/3/6</td>
<td>0/2/1/9</td>
<td>0.17‡</td>
</tr>
</tbody>
</table>

Note: Unless otherwise specified, the data are the means ± standard deviations.

* $P$ value for the comparison of means was calculated using unpaired Student t test.
† Fisher’s exact test
‡ X$^2$ test

However, King’s group could not corroborate these positive results using a b-value of 500 s/mm$^2$ or could Vandecaveye’s team using a b-value of 1,000 s/mm$^2$. These conflicting results might suggest that the potential of DWI for predicting tumor response to definitive radiation therapy and concurrent chemoradiation therapy might not be so strong in DWI with a standard b-value of 1,000 s/mm$^2$ or less.

With regard to neoadjuvant chemotherapy, 2 studies have related DWI parameters (b-value of 1,000 s/mm$^2$) with tumor response to induction chemotherapy.16,19 Kato and associates demonstrated positive correlation between the rate of tumor regression and signal intensities on DWI and inverse correlation between the rate of tumor regression and ADC values.19 Berrak and colleagues showed significant difference in the percentage of change of ADC values of metastatic nodes before and after induction chemotherapy between live patients and
patients who died of HNSCC, but they did not show any potential of pretreatment ADC values to predict outcome. In this regard, our study showed the potential of pretreatment ADC values to reflect the treatment response to induction chemotherapy, which was not revealed in standard b-value DWI.

Several reports have described the decrease in ADC values when the b-value increases beyond 1,000 s/mm². Such a decrease could be explained by the biexponential signal decay. Fast and slow diffusion components have been described in a human brain model, and the fast diffusion components have been reported to be the main source of signal at a relatively low b-value, whereas the slow diffusion components dominate the signal intensity at a high b-value. Increased cellularity of the tumor leads to a greater proportion of intracellular compared to extracellular water components, whereas decreased cellularity indicates a greater proportion of relatively easily diffusible extracellular water components. Even though intracellular water components are not exactly the same as the slow diffusion components and extracellular water components are not the same as the fast diffusion components, the components are considered to correspond.

Regarding the better response to chemoradiation therapy of solid tumors with high cell density in the highly proliferating state than those with low cellularity (including areas with necrotic components that represent tumor hypoxia with low oxygen tensions that render the tumor more resistant to chemotherapy or radiation therapy), tumors with high intracellular water components that dominate signal intensity at high b-value DWI rather than extracellular water components can show better response to induction chemotherapy. In other words, the ADC values of a tumor with a high b-value can better predict the response to induction chemotherapy than those with a standard b-value.

Therefore, it is relevant that our results showed significant correlation between tumor response to induction chemotherapy and ADC_{2000} rather than ADC_{1000} in patients with HNSCC. Even at multivariate analysis, only ADC_{2000} showed significant results. ADC_{1000} and pretreatment tumor volume, which a very recent study using DWI with standard b-values (b = 0, 100, 200, 300, 400, and 500) reported as the only potential predictor of tumor response in HNSCCs, were not independent predictors in this study.

Our study has several other limitations aside from those intrinsic limitations in any retrospective study. Our sample size was rather small to generalize study results. Further investigations with a larger population are warranted to strengthen our results. Second, we excluded 2 patients because of MR artifacts or poor visualization of the primary lesion. Although we optimized scanning parameters to reduce artifacts and increase the signal-to-noise ratio, the intrinsic limitations of DWI in head and neck imaging, such as low acquirable signal, motion, air-tissue interfaces, presence of dental work, and anatomic heterogeneity of the area, were still challenging in interpreting DWI. Third, human papilloma virus (HPV) infection is major risk factor for HNSCC, and patients with HPV-positive HNSCC have a better prognosis and response to therapy than patients with HPV-negative HNSCC. However, we only had the HPV status of 7 patients in this study, so we could not evaluate the correlation between imaging findings or clinical outcome and HPV status. Further studies with correlation between tumor response and HPV status in HNSCC would be needed.

## Conclusion

DWI with high b-values (b = 0 and 2,000 s/mm²) as a tool to assess ADC values may help predict tumor response to neoadjuvant chemotherapy for HNSCC. If we can predict the response to neoadjuvant chemotherapy before treatment is started, appropriate therapeutic strategies can be selected for individual patients to preserve functions of head and neck region and improve quality of life.

## References


