Value of Magnetic Resonance Diffusion-Weighted Imaging for the Prediction of Radiosensitivity in Nasopharyngeal Carcinoma

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. The effectiveness of radiotherapy in nasopharyngeal carcinoma (NPC) is closely related to the radiosensitivity of the carcinoma; however, there is currently no effective method to predict radiosensitivity in NPC. We explored the predictive value of magnetic resonance diffusion-weighted imaging (MR-DWI) for radiosensitivity in NPC.

Study Design. Prospective cohort study.

Setting. Single hospital.

Subjects and Methods. Patients with NPC who received intensity-modulated radiotherapy (IMRT) with or without chemotherapy were enrolled from April 2010 through November 2011. Primary tumor apparent diffusion coefficient (ADC) was measured before treatment (ADC0) and 2 weeks after the start of IMRT (ADC1). ADC change (ΔADC) was calculated as (ADC1 – ADC0)/ADC0 * 100%. Three months after the end of radiotherapy, the short-term effect of radiotherapy was assessed using the World Health Organization’s response evaluation criteria in solid tumors.

Results. Of 134 eligible NPC patients, 121 received combination chemotherapy. Three months after radiotherapy, residual local tumors were detected in 23 (17.2%) cases, and no residual tumors were detected in 111 (82.8%) cases. There was no significant difference in the residual tumor rates of patients receiving combination chemotherapy vs those who did not (P = 1.000). There were no significant differences in the ADC0 or ADC1 values of patients with and without residual tumors (P = .083 and .262). The ΔADC values of patients with (49.77% ± 31.02%) and without (68.35% ± 34.22%) residual tumors were significantly different (t = -2.406, P = .017). Logistic regression analysis indicated that ΔADC was an independent prognostic factor for the short-term effect of IMRT in NPC.

Conclusion. Magnetic resonance diffusion-weighted imaging may potentially have value for predicting radiosensitivity in NPC.

Keywords

diffusion-weighted imaging, apparent diffusion coefficient, nasopharyngeal carcinoma, radiosensitivity

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Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors in southern China and southeastern Asia. Pathologically, most cases of NPC are non-keratinizing carcinoma, with actively growing cancer cells and tumors already at an advanced stage when most patients first present at the hospital. The survival rate of patients with NPC has greatly improved with the development of imaging science and radiotherapy techniques and the wide adoption of combined therapy. However, some patients still have local relapse in the nasopharynx, cervical lymph node drainage area, or both.1,2 In addition to factors related to tumor stage and the therapy modality, recurrence is mainly linked to the biological properties of the tumor, of which the radiosensitivity of the primary tumor plays a major part. The ability to predict the radiosensitivity of...
NPC during the early stages of treatment would be of great significance for the timely and appropriate adjustment of therapeutic strategies. Although it is vital to be able to predict the radiosensitivity of primary tumors, no effective and practical methods have been established to predict the radiosensitivity of NPC.

Magnetic resonance diffusion-weighted imaging (MR-DWI) is a functional imaging technique that indirectly reveals the microstructural features of a tumor by detecting the diffusive state of water molecules in viable tissue. It can provide a quantitative parameter, the apparent diffusion coefficient (ADC), which can indirectly indicate microvascular circulation, cell membrane integrity, and cell density and can also detect local microscopic changes in the tumor before morphological changes are evident. Consequently, MR-DWI could potentially be adopted to predict the radiosensitivity of NPC, which could help to guide treatment planning and the early adjustment of clinical therapy. Clinical research has shown that the quantitative indices provided by MR-DWI can tell whether a tumor is benign or malignant; such assessments have frequently been reported in cases of head and neck squamous cell carcinoma, liver cancer, cervical cancer, and prostate cancer. In addition, the ADC value before treatment and early changes in ADC during treatment are correlated with the sensitivity to radiotherapy and chemotherapy in some tumor types; however, these findings vary, and some are even contradictory. Researchers have also previously tried to apply MR-DWI during the diagnosis and treatment of NPC in China, although only small numbers of cases were assessed. To our knowledge, no studies have applied MR-DWI to predict radiosensitivity in patients with NPC undergoing intensity-modulated radiotherapy (IMRT).

Methods
This study was approved by the Ethics Committee of Fujian Tumor Hospital (approval no. 201011). Informed consent was obtained after the nature of the procedure had been fully explained to each patient.

Inclusion Criteria
Patients were included in the study if they (1) had a diagnosis and pathological confirmation of NPC at the Fujian Tumor Hospital between April 2010 and November 2011, (2) were between 18 and 70 years old, (3) had a Karnofsky score more than 80, (4) had no other contraindications on magnetic resonance imaging (MRI) scans, (5) received IMRT, and (6) provided written informed consent.

Exclusion Criteria
Patients were excluded if they (1) had other diseases that may have affected the effects of radiation, (2) were pregnant and lactating women, or (3) did not sign the informed consent form.

Elimination Criteria
Patients were eliminated from the study if (1) IMRT was discontinued for 1 week or more or (2) MR-DWI examinations were not performed before therapy, 2 weeks after the start of radiotherapy, or 3 months after the end of radiotherapy.

Treatment Planning
Radiotherapy. Intensity-modulated radiotherapy was delivered using linear accelerators with a nominal energy of 6 MV and was prescribed as follows: the gross tumor volume (GTV) of the primary tumor was irradiated with a dose of 6600 to 7425 cGy/30 to 33Fx, 6 to 7 W. The GTV was expanded outward by 5 to 10 mm (including the entire mucous membrane of the nasopharynx and 5 mm below the membrane), defined as the high-risk clinical tumor volume (CTV1), and irradiated with a dose of DT6000 to 6270 cGy/30 to 33Fx, 6 to 7 W. Subclinical lesions, including the whole nasopharyngeal cavity, the rear third of the nasal cavity, rear maxillary sinus, pterygopalatine fossa, posterior part of the ethmoid sinus, parapharyngeal space, skull base, part of the cervical vertebra, and clivus, were defined as the low-risk clinical tumor volume (CTV2) and irradiated with a dose of DT5400 to 5610 cGy/30 to 33Fx, 6 to 7 W.

Chemotherapy. Induction chemotherapy was prescribed as follows over a 21-day cycle: 135 to 175 mg/m² paclitaxel on day 1 and 80 mg/m² cisplatin on day 2, or 80 mg/m² cisplatin on days 1, 2, and 3. Concurrent chemotherapy was prescribed as 80 mg/m² cisplatin alone on days 1, 22, and 43. Adjuvant chemotherapy was administered in the same manner as induction chemotherapy.

MRI Scanning Protocol and Parameters
A Signa 1.5T EXCITE III HD magnetic resonance imaging device (GE, Fairfield, Connecticut) was employed. The MRI scans were performed within the week before treatment, 2 weeks after the start of radiotherapy, and 3 months after the end of radiotherapy. A spin echo–echo planar imaging sequence was adopted using the following parameters: b value, 0; 800 s/mm²; repetition time, 6000 ms; echo time, default minimum value; field of view, 24 × 24 cm; matrix, 128 × 128; single shot; and scan time, 48 s.

Measurement of ADC Values
Functool 2, a tool attached to the MRI software (GE, Fairfield, Connecticut), was used to measure the size on maximal cross section of the primary tumor. The region of interest conformed to the primary tumor site as closely as possible. The average ADC value of the primary tumor before treatment was termed ADC0, and the average ADC value 2 weeks after the start of radiotherapy was called ADC1. The change rate in ADC after 2 weeks of the start of radiotherapy (ΔADC) was calculated as (ADC1 − ADC0)/ADC0 * 100%.

Assessment of the Short-Term Curative Effect of Radiotherapy
The short-term curative effect of IMRT was assessed 3 months after the end of radiotherapy. Patients diagnosed with no residual tumor had to meet both of the following...
using logistic regression analysis. Two-tailed factors affecting the short-term curative effect were assessed into 2 new groups based on these optimal cutoff values, and optimal cutoff values. Thereafter, patients were reclassified into 2 new groups based on a positive or negative short-term curative effect, and then receiver operating characteristic (ROC) curves were plotted to determine the negative short-term curative effect, and then receiver operating characteristic (ROC) curves were plotted to determine the optimal cutoff values. Thereafter, patients were reclassified into 2 new groups based on these optimal cutoff values, and the short-term curative effect in the groups was compared. Factors affecting the short-term curative effect were assessed using logistic regression analysis. Two-tailed $P$ values less than .05 were considered statistically significant.

### Sample Size Calculation

Sample size was estimated using the following formula: $n = \frac{(Ua/\delta)^2}{P(1 – P)}$. The allowable error ($\delta$) was set to 10%. The local residual tumor rate ($P$) was set to 18%, according to our previous findings. The significance level ($\alpha$) was set to 0.05, and the critical value of $U(U_{0.05})$ was 1.96; therefore, $n = 133$. The final sample size was 147, allowing for loss of up to 10% of the cases.

### Statistical Analysis

SPSS software for Windows 13.0 (SPSS, Inc, and IBM Company, Chicago, Illinois) was employed. The Pearson $\chi^2$ test or Fisher exact test was used for comparing clinical characteristics. The $t$ test was used for comparing mean values. Patients were first divided into groups based on a positive or negative short-term curative effect, and then receiver operating characteristic (ROC) curves were plotted to determine the optimal cutoff values. Thereafter, patients were reclassified into 2 new groups based on these optimal cutoff values, and the short-term curative effect in the groups was compared. Factors affecting the short-term curative effect were assessed using logistic regression analysis. Two-tailed $P$ values less than .05 were considered statistically significant.

### Results

#### Patient Recruitment

In total, 151 patients were considered for the study; however, 17 patients were excluded because they did not meet the inclusion criteria: 4 patients stopped radiotherapy or switched to conventional radiotherapy during treatment, 7 patients did not have an MRI examination 2 weeks after the start of IMRT, and 6 patients did not have an MRI examination 3 months after the end of radiotherapy. As a result, 134 patients qualified for the study. The MRI images of 1 patient were presented in Figure 1.

#### Clinical Characteristics

The median age of the 134 patients with NPC at disease onset was 47 years (range, 18-79 years). The radiation doses prescribed to the primary site were as follows: all 134 patients received an initial radical irradiation dose of 6600 to 7425 cGy/30 to 33Fx, 6 to 7 W; 15 patients also received supplementary irradiation after planning radiotherapy with a median supplementary irradiation dose of 675 cGy (200-900 cGy). The median total irradiation dose to the primary site was 6975 cGy (6600-7875 cGy). Chemotherapy was administered as follows: 90.3% (121/134) of the patients received combination chemotherapy, of whom 80.6% (108/121) received induction chemotherapy (1 cycle in 7 patients, 2 cycles in 91 patients, 3 cycles in 8 patients, 4 cycles in 1 patient, and 6 cycles in 1 patient). In total, 55.2% (74/131) of the patients received concurrent chemoradiotherapy, and 59.0% (79/131) received adjuvant chemotherapy (1 cycle in 17 patients, 2 cycles in 41 patients, 3 cycles in 10 patients, and 4 cycles in 1 patient).

Three months after the end of radiotherapy, residual local tumors were detected in 23 (17.2%) cases, and 111 (82.8%) cases had no detectable residual tumor; the clinical characteristics of these groups of patients are presented in Table 1.

### Relationship Between Primary Tumor ADC Value and Short-Term Curative Effect of Radiotherapy

The ADC0 values of the primary tumor in the group with and without residual tumors were $0.864 \pm 0.159 * 10^{-3}$ mm$^2$/s and $0.808 \pm 0.137 * 10^{-3}$ mm$^2$/s, respectively; this difference was not significant ($t = 1.747, P = .083$). The ADC1 values of the group with and without residual tumors were $1.274 \pm 0.258 * 10^{-3}$ mm$^2$/s and $1.336 \pm 0.237 * 10^{-3}$ mm$^2$/s, respectively; this difference was not significant ($t = -1.127, P = .262$). The $\Delta$ADC values of the group with and without residual tumors were $49.77\% \pm 31.02\%$ and $68.35\% \pm 34.22\%$, respectively; this difference was statistically significant ($t = -2.406, P = .017$).

Patients were divided into 2 groups on the basis of a positive or negative short-term curative effect. The cut point for $\Delta$ADC was determined to be 52.70%, which had a sensitivity of 0.640 (95% confidence interval [CI], 0.444-0.836), a specificity of 0.697 (95% CI, 0.612-0.783), and an area under the ROC curve of 0.675 (95% CI, 0.546-0.803) (see Figure 2). An $\Delta$ADC value of 52.70% had a positive predictive value of 0.286 (16/56; 95% CI, 0.167-0.404), a negative predictive value of 0.910 (71/78; 95% CI, 0.847-0.974),
and an accuracy of 0.649 (87/134; 95% CI, 0.569-0.730) for prediction of a residual tumor. Then, the patients were reclassified into 2 new groups on the basis of the ΔADC values (>52.70% or <52.70%); the residual tumor rates of the groups with a ΔADC value >52.70% and ≤52.70% were 9.0% (7/78) and 28.6% (16/56), respectively. A significant difference was observed between the residual tumor rates of these groups (χ² = 8.805, P = .003).

**Multivariate Analysis of Factors Affecting the Short-Term Curative Effect of IMRT**

When the presence of a residual local tumor was assessed as the dependent variable, logistic regression analysis (backward stepwise, conditional; probability for stepwise entry, 0.05; removal, 0.1) indicated that both clinical stage and ΔADC were independent prognostic factors for the short-term effect of IMRT in NPC (Table 2). An advanced T stage was associated with an increased risk of a local residual tumor, and a larger ΔADC was associated with a reduced risk of a local residual tumor 3 months after the end of IMRT.

**Discussion**

This study indicates that the presence of a residual tumor at the primary site three months after the end of radiotherapy
correlates with the \( \Delta ADC \) two weeks after the start of IMRT in patients with NPC.

Magnetic resonance diffusion-weighted imaging is a functional imaging process that takes advantage of the Brownian motion of water molecules in biotic tissues. It is highly sensitive to the motional change of water molecules at a microscopic scale and capable of detecting differences in tissue form and volume before changes visible to the naked eye occur. The general diffusion of water in tumor tissues occurs due to extracellular diffusion, diffusion across cell membranes, and intracellular diffusion, yet with each of these processes contributing differently to overall diffusion. The diffusion coefficient of the integral tissue changes when alterations in the cellular microstructure occur. The ADC value reflects all factors that influence the movement of water molecules in a tissue and is determined by tissue perfusion and the ability of extracellular water molecules to diffuse. In this study, the ADC values of some patients with NPC increased more than those of other patients, and a large \( \Delta ADC \) value 2 weeks after the start of IMRT was shown to correlate with a higher tumor radiosensitivity, which indicates that, 2 weeks after the start of radiotherapy, water molecules diffused more freely in the radiosensitive tumors due to increased tissue necrosis and cell disruption.

Over the past 10 years or so, a number of reports have applied MR-DWI for the prediction and evaluation of the effects of radiotherapy and chemotherapy in a range of tumor types; however, the ADC parameters used, response criteria assessed, and results have varied significantly. From studies of ADC values before treatment as the observation index, it has been reported that the response of rectal carcinoma to chemotherapy, the response of glioma to radiotherapy, and the effect of radiochemotherapy in head and neck cancer are inversely proportional to the ADC value before treatment. Other studies have assessed early changes in the ADC value after treatment. Theilmann et al reported that a large change in the ADC value after 4 to 7 days of chemotherapy indicated a better response to chemotherapy in metastatic breast cancer. Moffat et al found that a large change in the ADC value in the third week of chemotherapy indicated a higher local remission rate in glioma. Recently, Fu et al claimed that the response to neoadjuvant chemotherapy in locally advanced cervical carcinoma was related to the change in the ADC value after 2 weeks of chemotherapy. The findings of these 3 studies are similar to the results of this study in NPC, as a larger \( \Delta ADC \) 2 weeks after the start of IMRT correlated with a higher tumor radiosensitivity. However, this study also showed that the pretreatment ADC values are not related to the response to chemotherapy/radiotherapy in NPC. This observation is similar to the report by Sanjeev et al about head and neck cancer but in contrast to Dzik-Jurasz et al, who reported that a low pretreatment tumor ADC value was predictive of a larger percentage change in the size of rectal tumor after chemotherapy.

Since the structures surrounding the nasopharynx are complex and often involve various pathways of the skull

### Table 2. Logistic regression analysis of factors affecting the short-term effect of intensity-modulated radiotherapy in patients with nasopharyngeal carcinoma.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Assignment</th>
<th>B</th>
<th>SE</th>
<th>( \chi^2 )</th>
<th>P Value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1: Male</td>
<td>0.857</td>
<td>.355</td>
<td></td>
<td>.355</td>
<td></td>
<td></td>
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<td></td>
<td>2: Female</td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>1: ( \leq 47 ) years</td>
<td>3.515</td>
<td>.061</td>
<td></td>
<td>.061</td>
<td>2.156</td>
<td>1.274-3.648</td>
</tr>
<tr>
<td></td>
<td>2: &gt;47 years</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Pathological type</td>
<td>1: Keratinizing squamous cell carcinoma</td>
<td>1.227</td>
<td>.268</td>
<td></td>
<td>.268</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2: Differentiated nonkeratinizing carcinoma</td>
<td></td>
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<td></td>
<td>3: Undifferentiated nonkeratinizing carcinoma</td>
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<tr>
<td>2010 AJCC stage</td>
<td>1: T1</td>
<td>0.768</td>
<td>.268</td>
<td>8.191</td>
<td>.004</td>
<td>2.156</td>
<td>1.274-3.648</td>
</tr>
<tr>
<td></td>
<td>2: T2</td>
<td></td>
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<td></td>
<td>3: T3</td>
<td></td>
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<td></td>
<td>4: T4</td>
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<tr>
<td>Anemia</td>
<td>0: No</td>
<td>0.439</td>
<td>.508</td>
<td></td>
<td>.508</td>
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<tr>
<td></td>
<td>1: Yes</td>
<td></td>
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</tr>
<tr>
<td>Treatment model</td>
<td>0: Radiotherapy alone</td>
<td>0.009</td>
<td>.925</td>
<td></td>
<td>.925</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1: Chemoradiotherapy</td>
<td></td>
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<tr>
<td>Irradiation dose to nasopharynx</td>
<td>1: ( \leq 6975 ) cGy</td>
<td>0.031</td>
<td>.860</td>
<td></td>
<td>.860</td>
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<td></td>
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<tr>
<td></td>
<td>2: &gt;6975 cGy</td>
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</tr>
<tr>
<td>( \Delta ADC^a )</td>
<td>1: ( \leq 52.70% )</td>
<td>-1.627</td>
<td>.546</td>
<td>8.883</td>
<td>.003</td>
<td>0.196</td>
<td>0.067-0.573</td>
</tr>
<tr>
<td></td>
<td>2: &gt;52.70%</td>
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**Abbreviations:** ADC, apparent diffusion coefficient; AJCC, American Joint Committee on Cancer; CI, confidence interval; OR, odds ratio.

\( \Delta ADC = (ADC1 - ADC0)/ADC0 \times 100\% \).
base, the primary tumors often shrink asymmetrically, and it is difficult to confirm whether a residual local tumor exists in patients with NPC, we adopted combined criteria based on nasopharyngoscopy and MRI scans to determine the short-term curative effect of IMRT in NPC. In this study, the short-term effect of IMRT was not related to chemotherapy, the irradiation dose, or pathological type or anemia; however, this may due to the relatively imbalanced features of the group of patients involved in this study. All patients involved in this study received a radical irradiation dose, with only 11.2% (15/134) receiving supplementary irradiation after initial radiotherapy (median supplementary irradiation dose, 6.75 Gy). In addition, 90.3% (121/134) of the patients received combined chemotherapy, 93.3% (125/134) had undifferentiated nonkeratinizing carcinoma, and 84.3% (113/134) did not have anemia.

Limitations of This Study

The MR-DWI scans were performed only before treatment and 2 weeks after the start of IMRT; therefore, the ADC values were not determined after chemotherapy and before radiotherapy. It still remains to be identified whether 2 weeks after the start of IMRT is the best timing for the assessment of ΔADC. In addition, a longer follow-up period is required to determine whether MR-DWI could be used to predict the long-term effect of radiotherapy in patients with NPC.

Conclusion

A high ΔADC value 2 weeks after the start of IMRT is associated with a reduced risk of a residual local tumor 3 months after radiotherapy in patients with NPC, indicating that the ΔADC 2 weeks after the start of radiotherapy may potentially have value for predicting radiosensitivity of the primary tumor to IMRT in NPC.

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Author Contributions

Jinsheng Hong, analyzed data, wrote article; Yiqi Yao, analyzed data, wrote article; Yu Zhang, collected data, revised article; Tianlan Tang, collected data, wrote article; Hao Zhang, collected data, wrote article; Daoliang Bao, collected data, wrote article; Yunbin Chen, collected data, revised article; Jianji Pan, designed study, revised article.

Disclosures

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