The Utility of Diffusion-Weighted Magnetic Resonance Imaging for Discriminating and Early Detecting of Nasopharyngeal Carcinoma

Dechun Zheng, Yunbin Chen*, Yuqi Yao, Zhongshi Du and Xiaohong Deng

Department of Radiology, Fujian Medical University Teaching Hospital, Fujian Provincial Tumor Hospital & Institute, Fuzhou, Fujian, China

Abstract

Purpose: To study the utility of Diffusion-Weighted Magnetic Resonance Imaging to distinguish among Nasopharyngeal Carcinoma (NPC), lymphoma, tuberculosis and nasopharyngitis which originates in nasopharynx.

Materials and Methods: Our hospital’s institutional review board approved this retrospective study. Forty-two patients with early stage NPC, sixteen with lymphoma, eleven with tuberculosis, and twenty-six with nasopharyngitis were included in this retrospectively study. All patients underwent both nasopharynx and skull base region MR Imaging and naso-pharyngo-fiberscope biopsy in our hospital, and were finally diagnosed with histopathologically proven (n = 86) and clinical follow-up (n = 9). The Apparent diffusion coefficient (ADC) values were investigated by experienced radiologist, and averaged ADC value of per patient was compared in groups. Mean ADC values between two groups were compared by independent-samples T-test, and one-way Analysis of Variance was used to analyze mean ADC values among four groups.

Results: Mean ADC values of malignant nasopharyngeal lesions (early stage NPC and lymphoma) and benign nasopharyngeal lesions (tuberculosis and nasopharyngitis) were (0.708 ± 0.158) and (0.913 ± 0.168) × 10^-3 mm²/s respectively (t = 6.05, P < 0.01). Mean ADC values of nasopharyngeal lesions of early stage NPC, lymphoma, tuberculosis and nasopharyngitis were (0.753 ± 0.135), (0.590 ± 0.156), (0.855 ± 0.137), and (0.935 ± 0.179) × 10^-3 mm²/s respectively (F = 18.89, P < 0.01), and post multiple comparisons showed that they were all Statistical significance on 0.05 level between NPC, lymphoma, tuberculosis and nasopharyngitis except subgroup tuberculosis and nasopharyngitis (p = 0.55); An ADC value lower than or equal to 0.828 × 10^-3 mm²/s was used as threshold for nasopharyngeal malignancy, with a sensitivity 82.8% and specificity of 70.3%. When the same ADC value ≤ 0.828 × 10^-3 mm²/s was used as threshold to differentiate early stage NPC from nasopharyngitis, sensitivity and specificity were 78.6% and 69.2% respectively. When an ADC value ≤ 0.681 × 10^-3 mm²/s was used as threshold to differentiate lymphoma from early stage NPC, sensitivity and specificity were 81.3% and 71.4% respectively.

Conclusion: MR DWI has a potential value in differentiating nasopharyngeal diseases.

Keywords: Diffusion-weighted magnetic resonance imaging; Nasopharyngeal carcinoma; Lymphoma; Tuberculosis; Nasopharyngitis

Introduction

Nasopharyngeal carcinoma (NPC) is an Epstein-Barr virus-associated malignancy with a marked racial and geographic distribution. Specifically, it is highly prevalent in southern China, Southeast Asia, and the Middle East. It differs significantly from other squamous cell cancers of the head and neck in its clinical presentation, epidemiology, biological behavior, treatment, and prognosis. The five year survival rate of advanced NPC treated with Intensity Modulated Radiotherapy has reached up to 83.3% [1] but not satisfactory. So the early detection of initial and recurrent NPC is important to an earlier therapy and improved outcome.

Symptoms and signs of early stage NPC (Defined as T1 – 2N0 – 1M0, UICC 7th) are nonspecific and often confuse with Nasopharyngeal lymphoma (NPL) and tubercular and other inflammatory nasopharyngeal diseases [they are tuberculosis (NP-TB) and nasopharyngitis (NPNI)]. The lacks of deep peristructures infiltrations in early stage of NPC, such as masticator space, skull base bone, and cranial nerves, have resulted in difficulty for routine CT/MR technique to differentiate NPC from lymphoma, tuberculosis and nasopharyngitis which resemble each other in morphologic performance (Figure 1). Naso-pharyngo-fiberscope biopsy with histopathological examination should be the primary tool and present as the “gold standard”. However, there are some factors that would influence the application and accuracy of nasopharyngo-fiberscope biopsy-including the operator’s technique, location and depth of the mucosa is biopsied, and the amount of tissue have been sampled for histopathology processing. Above all, its accuracy after the first biopsy is remaining a level about 90% to 95% according to the literatures [2-3].

MR imaging are useful to guiding biopsy especial for submucosal lesion, staging, and monitoring treatment response for malignancy. One of the latest advancements in functional MRI technology is the application of Diffusion-weighted Imaging (DWI) to offer quantitative evaluation of Apparent diffusion coefficient (ADC) value. DWI is a powerful imaging tool which noninvasively provides unique information on Brownian motion of water molecules in vivo tissues and allows estimation of cellularity and tissue structure [4]. Restricted

*Corresponding author: Yunbin Chen, Department of Radiology, Fujian Medical University Teaching Hospital, Fujian Provincial Tumor Hospital & Institute, Fuzhou, Fujian, China, E-mail: yunbinchen@126.com

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The axial and coronal T1W were repeated following a bolus injection coronal Short-inversion-time inversion recovery (STIR), axial DWI, axial fat-suppressed Proton Density Weighted Imaging (PDWI) FSE, sequences: sagittal T1-weighted Fast spin echo (FSE), axial T1W FSE, diameter) was used to cover a region from the temporal lobe to the level of 0.2 mmol/kg Gadolinium (Gd-DTPA) with a speed of 1.5 ml/sec. DWI use a SE-EPI-DWI sequences, scan parameters were: Repetition time (TR): 6000 msec; echo time (TE): the default minimum; echo chain length of: 2; field of view: 24 cm × 24 cm; slice thickness 5 mm, intersection gap 1.0 mm; acquisition matrix: 64 × 64; b value: 0.800 s/mm²; single-shot, scan time 48 s, 50 to 54 images available.

Imaging evaluation

First, DWI data was transmitted from PACS to the GE healthcare advanced post-workstation 4.2, and Function2 software packages was used to investigate the Averaged ADC value of nasopharyngeal lesions by experienced radiologist with 5 years experience in head and neck MR imaging. After the largest section of the nasopharyngeal lesion was determined, Region of interest (ROI) was drawn to include lesion entirely. During measurement, if the region of the involved nasopharyngeal wall is too small to identify on DWI map, radiologist would merge routine MR images (axial PDWI or T1W + CE sequence) into DWI map to assist ROI drawing.

Statistical analysis

Statistical analysis was performed by using SPSS15.0 software packages. Averaged ADC value was analyzed by using mean ± standard deviation (SD). For comparison ADC value of malignancy and benign group, the Independent-Samples T-test was used. Comparison of ADC values among four groups was performed by using one-way Analysis of Variance (one-way ANOVA), with post multiple comparisons. Receiver operating characteristic (ROC) analysis was employed to investigate the discriminatory capability of ADC value for distinguishing between: (a). malignant and benign nasopharyngeal diseases. (b). NPC and NPI. (c) NPC and NPL. The area under the ROC curve (AUC(ROC)) was used to give a measure of the global performance of using ADC values as effective indicators for discrimination. The optimal cut off ADC value was determined from coordinates of the curve table with both sensitivity and specificity were considered, then positive and negative predictive value (PV) was calculated. All statistical tests were two sided, and a difference with a P value of less than 0.05 was considered statistically significant.

Result

Clinical and histopathology results

(1). Symptoms and signs, courses are showed in Table 1, We can conclude that only continued low fever is a relative specific symptom for tuberculosis, while others are non-specific symptom. (2). TNM staging for NPC patients: 9 were T1N0M0, 20 were T1N1M0, and 13 were T2N1M0. (3). Histopathology: (a) Among 42 NPC patients: 17

![Figure 1: PDWI images of four different diseases were display on the above picture. They all appeared as thicken mucosa in the nasopharynx. A = Early stage Nasopharyngeal carcinoma, B = nasopharyngeal lymphoma, C = nasopharyngeal tuberculosis, D = nasopharyngitis.](Image)

MR imaging

MR imaging was performed with a 1.5-T unit MR system (GE Signa Excite 1.5T HD Twinspeed). An 8-channel neurovascular coil (30-cm diameter) was used to cover a region from the temporal lobe to the level of thoracic vertebrae one. Imaging protocol consists of the following sequences: sagittal T1-weighted Fast spin echo (FSE), axial T1W FSE, axial fat-suppressed Proton Density Weighted Imaging(PDWI) FSE, coronal Short-inversion-time inversion recovery (STIR), axial DWI, The axial and coronal T1W were repeated following a bolus injection

### Table 1: Symptoms and signs, courses of different groups.

<table>
<thead>
<tr>
<th>patients</th>
<th>group</th>
<th>NPC</th>
<th>NPL</th>
<th>NP-TB</th>
<th>NPI</th>
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<tbody>
<tr>
<td>number</td>
<td>42</td>
<td>16</td>
<td>11</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td>blood-stain saliva</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>and signs</td>
<td>enlarged nodes</td>
<td>24</td>
<td>8</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>nasal obstruction</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>tinnitus</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>3</td>
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<tr>
<td></td>
<td>headache</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>continued low fever</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>course</td>
<td>range</td>
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<td>0.3-24</td>
<td>0.3-6</td>
<td>0-24</td>
</tr>
<tr>
<td>(month)</td>
<td>mean</td>
<td>3.24</td>
<td>4.2</td>
<td>2</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>standard deviation</td>
<td>3.7</td>
<td>6.1</td>
<td>1.9</td>
<td>7.1</td>
</tr>
</tbody>
</table>

NPC = Nasopharyngeal Carcinoma; NPL = Nasopharyngeal Lymphoma; NP-TB = Nasopharyngeal Tuberculosis; NPI = Nasopharyngitis
were non-keratinizing carcinoma, 25 were undifferentiated carcinoma. (b) Among 16 NPL patients: 15 were non-Hodgkin lymphoma (twelve were B-cell lymphoma, two were T-cell lymphoma, and one was mucosa associated lymphoid tissue (MALT) lymphoma), and 1 was lymphocytic leukemia. (c) Eleven tuberculosis and twenty-six nasopharyngitis patients were proved with histopathology and/or clinical follow-up.

**DWI finding**

Compare means of ADC value for nasopharyngeal lesions: The ADC value of malignancy nasopharyngeal lesions (early stage NPC and lymphoma) ($0.708 \pm 0.158 \times 10^{-3} \text{ mm}^2/\text{s}$) was significantly ($P<0.01$, Independent-Samples T test) lower than that of the benign lesions (tuberculosis and nasopharyngitis) ($0.913 \pm 0.168 \times 10^{-3} \text{ mm}^2/\text{s}$). Graphs (box plots, Figure 2) show that there are a slight overlap between malignancy and benign groups. Mean ADC value of NPC, NPL, NPT and NPI were ($0.753 \pm 0.135$), ($0.590 \pm 0.156$), ($0.855 \pm 0.137$) and ($0.935 \pm 0.179$) $\times 10^{-3} \text{ mm}^2/\text{s}$, respectively; The ADC values were significantly different among these four groups ($p < 0.001$, one-way ANOVA). Post-multiple comparisons depend on LSD method are showed in Table 2. Graphs (box plots, Figure 3) show that there are a slight overlap between early stage NPC and NPL, early stage NPC and NPL group, while seriously overlap between NP-TB and NPI group are discovered.

Diagnostic ability of the ADC value in discriminating nasopharyngeal diseases: ROC analysis is performed to assess diagnostic ability of the DWI in discriminating different nasopharyngeal diseases. Sensitivity, specificity, and positive and negative predictive values were calculated. We first performed ROC analysis in malignant and benign lesions, as showed in Table 3, an ADC value lower than or equal to $0.828 \times 10^{-3} \text{ mm}^2/\text{s}$ was used as threshold to differentiate NPC from NPI, higher sensitivity ($83.3\%$), positive ($81.4\%$) and negative predictive value ($72.0\%$) were obtained, while specificity held at $69.2\%$. When an ADC value $\leq 0.681 \times 10^{-3} \text{ mm}^2/\text{s}$ as threshold to differentiate NPC from NPI, high positive predictive value was obtained ($80.6\%$) and moderate sensitivity, specificity and negative were $66.7\%$, $78.6\%$ and $69.2\%$, respectively. Raising ADC value to $0.851 \times 10^{-3} \text{ mm}^2/\text{s}$ as threshold to differentiate NPC from NPI, sensitivity and specificity were $81.3\%$, $71.4\%$ respectively, and positive and negative predictive value were $50\%$ and $90.9\%$ respectively.

![Figure 2: Graph (box plots) shows mean ADCs of the malignant and benign lesions. The horizontal line is a median(50th percentile) of the measured ADC values, the top and bottom of the box represent 25th and 75th percentiles, respectively, and whiskers indicate the range from the largest to smallest observed data points within 1.5 interquartile range presented by the box. Note that ADCs of early stage NPC and lymphoma are significantly lower than those of benign nasopharyngeal diseases ($P<0.01$, Independent Samples T test).](image1)

![Figure 3: Graph (box plots) shows mean ADCs of the nasopharyngeal wall of early stage NPC, NPL, NP-TB, and NPI. The horizontal line is a median(50th percentile) of the measured ADC values, the top and bottom of the box represent 25th and 75th percentiles, respectively, and whiskers indicate the range from the largest to smallest observed data points within 1.5 interquartile range presented by the box. Further LSD method multiple comparisons are display in table 2.](image2)

**Discussion**

Our study showed that mean ADC value of malignant lesions (NPC...
and lymphoma) was lower than that of benign lesions (tubercular and other inflammatory diseases). Pathologic study findings, as shown in Figure 4A,4B revealed that there are notable cancerous cells with high cellular density, large cellular shape along with magnified Nuclear cytoplasm (N/C) ratio in cancerous tissue (nasopharyngeal carcinoma and lymphoma). On the other hand, in inflammatory tissue (tuberculosis and nasopharyngitis), there exist a great number lymphocytes (though different in types) infiltration in the nasopharyngeal mucosal tissue, in which there are more microabscess and granulomas with more lymphocytes density, this may result in a seriously overlapped in the inflammatory disease. The weakened effect within pairwise comparison of tuberculosis and nasopharyngitis may be attributable to several factors, alone or in combination. Purulent fluid in abscesses is known to restrict water diffusion evidently [16]. Granulomas are more frequently detected in Tubercular lesion than inflammatory lesion, in which there are more microabscess and granulomas with more lymphocytes density, this may result in a lower ADC value in tubercular lesion than inflammatory lesion. Other pathological changes in inflammatory tissue include tissue swelling, lymphocytes infiltrating, protein contents increasing, microabscess and granulomas forming, which may decrease ADC value too. Inherent measurement error between different cases may be a contributing factor, particularly with a small sample study. More patients should be including in future study in order to feature ADC value between tubercular and inflammatory diseases.

**Limitation**

Although we often noted some anatomic distortion in the nasopharynx due to magnetic-susceptibility artifact, we found that also find out that ADC value of early stage NPC was significantly lower than nasopharyngitis (P<0.01) in our study. Differences in cellularity, N/C ratio, and perfusion may account for differences in diffusion restriction in NPC and nasopharyngitis. Wang et al. [11] applied diffusion-weighted MR imaging to head and neck lesions and found that the mean ADC value of carcinomas was less than that of benign solid masses. Belli et al. [12] reported that ADC value appears a promising adjunctive parameter in distinguishing malignant from benign breast lesions. The present study has extended these preceding findings to show that ADC value assessment can help differentiate malignancy from benign nasopharyngeal lesions. The important value in investigating ADC value of nasopharyngeal lesions has a potential in locating the true nasopharyngeal diseases where in fact present as lower ADC value, and hence is useful to conduct the nasopharyngoscopy biopsy, for those have a negative result during the first biopsy. This may avoid unnecessary lymphadenopathy aspiration biopsy which is an important factor that influences the outcome and prognosis of NPC.

Despite existing overlap in ADC value between NPC and lymphoma, a subset of lymphoma (15 of 16 cases were histopathologically proved non-Hodgin lymphoma in our study) showed a significantly decreased ADC value (P<0.01) than NPC. Supporting a theory of markedly restricted diffusion within lymphoma lesions. Lymphoid lesion elsewhere in the head and neck regions have been reported to be lower ADC value than HNSCC too [13]. As showed in Figure 4A,4B, we can learn that there higher cellular density and higher N/C ratio in non-Hodgin lymphoma than in keratinizing undifferentiated type carcinoma, which could in turn results in stronger restricted diffusion and lower ADC value when measured. We assume that DWI analysis would discriminate the difference of cellular density among malignancy in a way.

**ROC analysis**

shows a promising result for DWI in discriminating different nasopharyngeal diseases. The utility of ADC value of discriminating lymphoma from NPC (AUC = 0.795) and of discriminating NPC from nasopharyngitis (AUC = 0.794) is similar to that of discriminating malignant from benign lesion (AUC = 0.818). The evaluation of ADC value and contrast-enhanced forms of lymphadenopathy in the neck regions may be beneficial in discriminating lymphoma, NPC from benign lesions which happen in nasopharyngeal region [14-15].
DWI images were adequate for evaluation. The ADC value assessment requires relatively large target areas to obtain reliable ADC values with high Signal-to-noise ratios (SNR). ADC value measurements on smaller lesions in our study would be hampered by low signal-to-noise ratios. The diagnostic test may be biased by the fact that only early stage of NPC was included in present study. Finally, despite Levene’s test before statistic analysis show a homogeneity of variances, either one-way ANOVA (p=0.28) or independent-samples T test (p=0.55), that permit parametric analysis as did in our study. The sample size available in this analysis is somehow small.

Conclusion

ADC value determination on diffusion-weighted MR imaging may be potential for discriminating malignant lesions in the nasopharyngeal region. It could locate the true nasopharyngeal diseases, and hence is valuable to conduct the epipharyngoscope biopsy.

References


