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

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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 nasopharyngo-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} mm^2/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} mm^2/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} mm^2/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} mm^2/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} mm^2/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 (NPI)]. 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). Nasopharyngo-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

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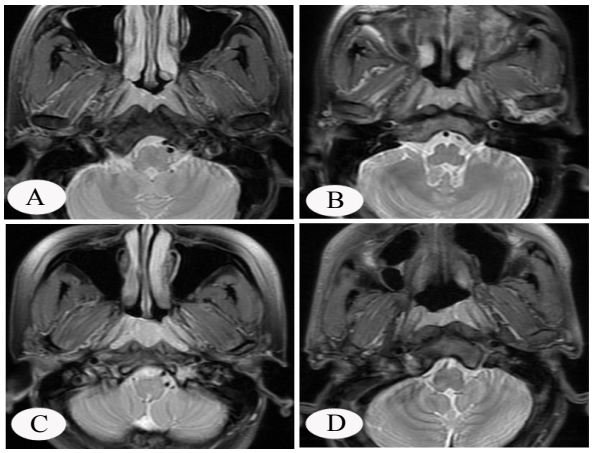

Figure 1: PDWI images of four different diseases were display on the above picture. They all appeared as thicken mucosa in the nasopharynx. A = Early stage Nasopharyngeal carcinoma, B = nasopharyngeal lymphoma, C = nasopharyngeal tuberculosis, D = nasopharyngitis.

water movement in tumors with high cellularity usually leads to higher intensity and lower ADC value [5]. DWI have been proved useful in discriminating, staging, early assess of chemo-radiotherapy response in Oncology [6-9]. There are few reports about the utility of ADC value in discriminating the nasopharyngeal lesions. The aim of this study was to identify the utility of DWI in differentiating early stage NPC, NPL, NP-TB and NPI that happen in nasopharynx.

Materials and Methods

Patients

This retrospective study was performed after institutional review board approval was obtained. From June 2006 to December 2010, a total of 366 patients who were suspected with early stage NPC originally were reviewed in our hospital, among which 309 patients were finally diagnosed with early stage NPC (Group 1), 18 with NPL (Group 2), 11 with NP-TB (Group 3) and 28 with NPI (Group 4). Considered tuberculosis as matched factor (the smallest sample group), Author used matching method 4:1 to randomly include 44 of 309 NPC patients in this study. Among 101 included patients, 2 NPC, 2 NPL and 2 NPI were excluded due to oral metal or magnetic-susceptibility artifact which let to serious deformation of DWI images. All Cases were finally diagnosed either with nasopharyngo-fiberscope biopsy histopathology (n = 86) or with a 6 to 24 months clinical follow-up after discharged (n = 9). In these 9 patients, one nasopharyngitis patient was proved shink by re-examined MRI 6 month later, other three nasopharyngitis patients' symptom disappeared, and five tuberculosis patients were all finally diagnosed and cured in other hospital. The population of male/female for group1 to group4 were 31/11, 10/6, 5/6, 10/16 respectively. Age range (mean age) of each groups were 24 ~ 62(44), 9 ~ 73 (48), 21 ~ 71(37), 17 ~ 65(46) respectively.

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 vertebra 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 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 Functool2 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 T1WI + 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

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

NPC = Nasopharyngeal Carcinoma; NPL = Nasopharyngeal Lymphoma; NP-TB = Nasopharyngeal Tuberculosis; NPI = Nasopharyngitis

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

were non-keratinizing carcinoma, 25 were undifferentiated carcinoma. (b) Among 16 NPL patients: 15 were non-Hodgin 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) ($0.708 \pm 0.158 \times 10^{-3}$ mm^2/s) was significantly (P<0.01, Independent-Samples T text) lower than that of the benign lesions (tuberculosis and nasopharyngitis) ($0.913 \pm 0.168 \times 10^{-3}$ mm^2/s). Graphs (box plots, Figure 2) show that there are a slightly overlap between malignancy and benign groups. Mean ADC value of NPC, NPL, NPT and NPI were (0.753 ± 0.135), (0.590 ± 0.156), (0.855 ± 0.137) and (0.935 ± 0.179) $\times 10^{-3}$ mm^2/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 NPI, 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 0.828×10^{-3} mm^2/s was used as threshold for malignancy, we obtained high sensitivity 82.8% and positive predictive value 81.4%, and moderate specificity 70.3% and positive predictive value 72.2%. Then we further applied ROC analysis on early stage NPC with NPL and with NPI. When ADC value ≤ 0.828×10^{-3} mm^2/s was used 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 0.851×10^{-3} mm^2/s 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 ≤ 0.681×10^{-3} mm^2/s was used as threshold to differentiate NPL from NPC, sensitivity and specificity were 81.3%, 71.4% respectively, and positive and negative predictive value were 50% and 90.9% respectively.

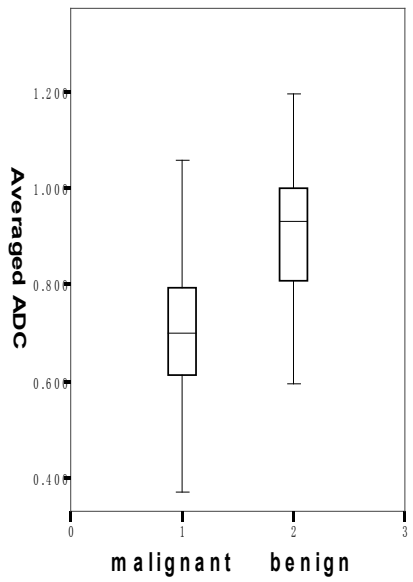

Figure 2: Graph (box plots) shows mean ADCs of the malignant and benign lesions. The horizontal line is a median(50th percentile) of the measured ADC values, the top and bottom of the box represent 25th and 75th percentiles, respectively, and whiskers indicate the range from the largest to smallest observed 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 text).

(I) group	(J) group	Mean Difference (I-J)	Std. error	Sig.	95% Confidence interval	
					Lower bound	Higher bound
NPC	NPL	.162625(*)	0.045	0.000	0.074	0.251
	NP-TB	-.111841(*)	0.051	0.032	-0.214	-0.010
	NPI	-.181769(*)	0.038	0.000	-0.257	-0.107
NPL	NPC	-.162625(*)	0.045	0.000	-0.251	-0.074
	NP-TB	-.274466(*)	0.059	0.000	-0.392	-0.157
	NPI	-.344394(*)	0.048	0.000	-0.440	-0.249
NP-TB	NPC	.111841(*)	0.051	0.032	0.010	0.214
	NPL	.274466(*)	0.059	0.000	0.157	0.392
	NPI	-0.069928	0.055	0.203	-0.178	0.038
NPI	NPC	.181769(*)	0.038	0.000	0.107	0.257
	NPL	.344394(*)	0.048	0.000	0.249	0.440
	NP-TB	-0.069928	0.055	0.203	-0.038	0.178

Note: LSD statistical method was used. Labeled with (*) corresponded statistical significant (P<0.05). In this table, we can see that there are Statistical significant on 0.05 level between NPC, lymphoma, tuberculosis and nasopharyngitis except tuberculosis and nasopharyngitis (p = 0.20).

Table 2: Multiple comparisons.

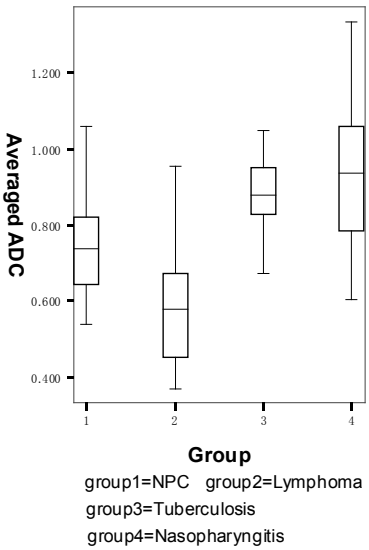

Figure 3: Graph (box plots) shows mean ADCs of the nasopharyngeal wall of early stage NPC, NPL, NP-TB, and NPI. The horizontal line is a median(50th percentile) of the measured ADC values, the top and bottom of the box represent 25th and 75th percentiles, respectively, and whiskers indicate the range 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.

Discussion

Our study showed that mean ADC value of malignant lesions (NPC

Positive group(I)	negative group(J)	valid N (I/J)	AUCa	Cutoff (≤Vb)	Sensi-tivity	Speci-ficity	Positve PV	Negative PV
malignancy	benign	58/37	0.818	0.828	82.8%	70.3%	81.4%	72.2%
NPC	NPI	42/26	0.794	0.828	78.6%	69.2%	80.5%	66.7%
				0.851	83.3%	69.2%	81.4%	72.0%
NPL	NPC	16/42	0.795	0.681	81.3%	71.4%	52.0%	90.9%

Note: ROC = Receiver Operating Characteristic; PV = Predictive Value; V = Value
a. AUC = Area Under the ROC Curve, under the nonparametric assumption.
b. cutoff value defined as ≤ Value × 10^{-3} mm^2/s.

Table 3: ROC and PV analysis between different groups.

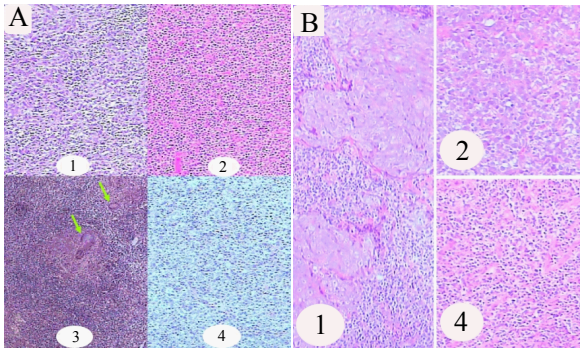

Figure 4 (A-B): These two graph show the micrograph findings of the 4 different diseases under ×40 (Figure4-A) and ×100 times (Figure 4-B). No.1 = Early stage Nasopharyngeal Carcinoma, No.2 = nasopharyngeal lymphoma, No.3=nasopharyngeal tubercular, No.4 = nasopharyngitis.
4-A1: displays a micrograph of keratinizing undifferentiated type carcinoma. Numerous cancerous cells presented with keratin or "keratin pearls" under ×100 times micrograph was found out in figure 4-B1.
4-A2: and figure4-B2 shows a diffuse large B cells chronic lymphocytic leukemia/small lymphocytic lymphoma. Under×100 times micrograph, as showed in figure 4-B2, higher cellular density, larger nucleio shape, and greater nuclear cytoplasm (N/C) ratio were found than NPC tissue (Figure 4-B1).
4-A3: shows a tuberculosis micrograph with a typical caseation granuloma in the middle field under ×40 times micrograph. The green arrows show Langhans giant cells in granuloma.
4-A4: show a nasopharyngitis pathology with moderate abundance lymphocytes infiltration. Its celluar shape and N/C ratio are normal, as showed in figure4-B4.

and lymphoma) was lower than that of benign lesions (tubercular and other inflammatory diseases). Pathologic study findings, as show 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 their cellular shape and N/C ratio are normal. Our finding of restricted diffusion in malignant disease is consistent with expectations. In general, the increased hypercellularity and N/C ratio reduce the extracellular matrix and the diffusion space of water protons in the extracellular and intracellular dimensions, with a resultant decrease in ADC value. A significant correlation between the ADC value and cell density was reportedly found in human melanoma xenografts [10]. So ADC value measurement could reflect differences in the histopathologic features of the malignant and inflammatory diseases. This notion was substantiated by the ROC analysis on the diagnostic ability of ADC value in discriminating malignant nasopharyngeal lesions from benign ones, which yielded an AUC value of 0.818.

Further analyze of these four processes show a significance between groups ($p<0.05$, one-way ANOVA). Pairwise comparison 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 nasopharyngofiberscope biopsy, especially 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 tern 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].

In benign groups, graph analysis (Figure 3) showed that tuberculosis 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 gramulomas 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

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 text (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.

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