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Original Article

Preliminary study on biexponential diffusion-weighted imaging (dwi) for the prediction of differentiation degree of nasopharyngeal carcinoma

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Abstract: We discussed the value of biexponential diffusion-weighted imaging (DWI) in predicting the differentiation degree of nasopharyngeal carcinoma (NPC). Biexponential DWI was applied to 33 cases of nonkeratinizing NPC, which were classified into differentiated group (14 cases) and undifferentiated group (19 cases). The two groups were compared with respect to DWI parameters (ADC_{stand}, ADC_{slow}, ADC_{fast}, F_{fast}). ADC_{stand}, ADC_{slow}, ADC_{fast} and F_{fast} values of differentiated group were 0.920±0.131×10^{-3} mm^2/s, 0.680±0.115×10^{-3} mm^2/s, 22.3±13.9 mm^2/s and 0.316±0.078, respectively; the corresponding values of undifferentiated group were 0.952±0.203×10^{-3} mm^2/s, 0.672±0.116×10^{-3} mm^2/s, 17.8±20.3 mm^2/s and 0.299±0.120, respectively; ADC_{fast} was significantly different between the two groups (*P<0.05*). The sensitivity and specificity of ADC_{fast} in predicting the differentiation degree of NPC was 85.7% and 63.2%, respectively. ADC_{fast} has a certain value in predicting the differentiation degree of primary NPC.

Keywords: Nasopharyngeal carcinoma, diffusion weighted imaging (DWI), biexponential model

Introduction

Nasopharyngeal carcinoma (NPC) is a common malignancy in south China, and its prognosis is closely associated with pathological staging. Diffusion-weighted imaging (DWI) can detect microscopic structure in organisms and has been widely used to evaluate primary lesions of NPC. DWI is able to diagnose lymph node metastasis, evaluate outcome, and detect recurrent lesions and complications at early stage [1-4]. Apparent diffusion coefficient (ADC) calculated by uni-exponential model cannot realistically reflect the biological features of diffusion in tissues [5]. In contrast, biexponential DWI based on intravoxel incoherent motion requires no injection of contrast medium for precise estimate of diffusion coefficient through tissues and microvessel perfusion. We aimed to find out the difference in DWI parameters for primary lesions of NPC with different differentiation degree and to evaluate the diagnostic value of DWI parameters in differentiated and undifferentiated NPC.

Materials and method

Clinical data

From January to March 2014, 38 NPC cases that satisfied the following inclusion criteria were considered eligible (26 males, 12 females, aged 26-67 years, average 45.8 years), and their pathological and MR data were compared: pathologically confirmed as nonkeratinizing NPC and not having received anti-tumor therapy; in generally good conditions without contraindications for MRI. Exclusion criteria: inaccurate lesion observations due to MR image artifacts or distortion; major diameter less than 1 cm in axial, coronal or sagittal plane which made the delineation of region of interest

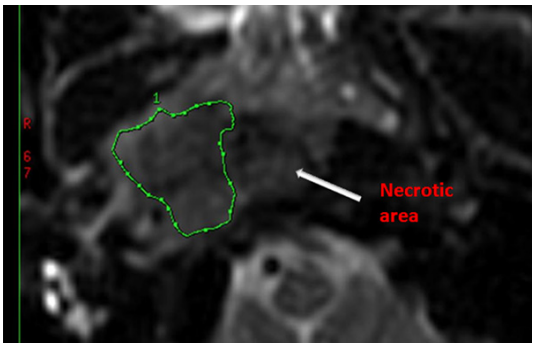

Figure 1. DWI images when b=0 s/mm^2 (the green dashed line box indicates the delineated ROI, and the white arrow indicates the region of tumor necrosis).

(ROI) difficult. The protocol was approved by the hospital ethics committee, and informed consent was obtained from all patients.

MRI

Plain scan, biexponential DWI and contrast-enhanced MR imaging were performed sequentially using MRGE MR360 1.5T MR scanner and CP head//neck array coil. The patients took supine position. Conventional scan sequence: axial T1WI (TR=568 ms, TE Min Full, slice thickness 6 mm, slice interval 1 mm, FOV 22 cm, NEX 2), axial T2WI (TR=6289 ms, TE=85 ms, slice thickness 6 mm, slice interval 1 mm, FOV 22 cm, NEX 2). Spin echo-diffusion weighted echo planar imaging (EPI) was performed for the cross section of the nasopharynx; 9 b-values were taken (b=0, 50, 80, 100, 150, 200, 400, 600, 800, 1000 s/mm^2), with TR=4225 ms, TE minimum, slice thickness 5 mm, slice interval 1 mm, FOV 22 cm, NEX 4). Contrast-enhanced scan sequence: axial T1WI (TR=365 ms, TE minimum, slice thickness 6 mm, slice interval 1 mm, FOV 22 cm, NEX2) and coronal T1WI (TR=205 ms, TE 80, slice thickness 5 mm, slice interval 1 mm, FOV 27 cm, NEX2).

Analysis of DWI data

According to the principle of biexponential DWI, the relationship between intensity in DWI image and b-value is expressed as $S_b/S_0=(1-F_{fast})\cdot exp(-b\cdot ADC_{slow})+ F_{fast}\cdot exp(-b\cdot ADC_{fast})$, where S_0 and S_b are the intensity in DWI images when b=0 and b value is not equal to 0, respectively; ADC_{fast} is the diffusion coefficient due to microcirculation perfusion (fast component of diffusion); ADC_{slow} is the diffusion coefficient due to simple diffusion of water molecules (slow component of diffusion); F_{fast} is the contribution of perfusion to diffusion signals; ADC_{stand} is the diffusion coefficient calculated by uni-exponential DWI model according to $S_b/S_0=exp(-b\cdot ADC_{stand})$.

The raw DWI images were uploaded to GE Advantage Windows Workstation (version 4.6). ADC_{stand}, ADC_{slow}, ADC_{fast} and F_{fast} were calculated automatically by MADC software in FuncTool. ROI was delineated by 2 experienced head and neck radiologists. With reference to axial T2WI, plain T1WI and enhanced T1WI, the slice not covering necrosis, cystic lesion, air-bearing region or vessels and with lesion area as large as possible was chosen for the measurement. Then ROI was delineated on DWI image with b=0 s/mm^2 (**Figure 1**). This ROI was replicated in all other images of the same slice.

Statistical analysis

ADC_{stand}, ADC_{slow}, ADC_{fast} and F_{fast} values were expressed as mean ± standard deviation ($\overline{x}$ ±S), and analyzed using SPSS19.0 software. P<0.05 was considered statistically significant. Non-parametric Mann-Whitney U test was used for inter-group comparisons. The diagnostic accuracy of DWI parameters was evaluated by ROC curve, and the optimal cut-off was determined according to Youden's index.

Results

Pathology

DWI image distortion was serious in 2 out of 38 cases; the lesions of NPC were too small for the measurement of DWI parameters in 3 cases and therefore were excluded. Finally 33 cases were included for the analysis, all belonging to nonkeratinizing NPC (14 differentiated lesions and 19 undifferentiated lesions); 8 cases had lesions in the superior lateral wall, 9 in the superior posterior wall, 11 in lateral wall, 4 in half cavity and 1 in the whole cavity. The maximum superior-inferior diameter of the lesions was 21.6±6.7 mm; the major diameter in the axial plane was 32.1±12.3 mm, and the minor diameter was 18.6±8.6 mm.

Comparison of DWI parameters

DWI parameters for differentiated and undifferentiated NPC are shown in **Table 1**, and the typical parameters are in **Figures 2** and **3**. ADC_{fast} was significantly different between the

Table 1. DWI parameters for differentiated and undifferentiated NPC

Pathology	ADC_{stand} ($\times10^{-3}$ mm^2/s)	ADC_{slow} ($\times10^{-3}$ mm^2/s)	ADC_{fast} ($\times10^{-3}$ mm^2/s)	F_{fast}
Differentiated (n=14)	0.920±0.131	0.680±0.115	22.3±13.9	0.316±0.078
Undifferentiated (n=19)	0.952±0.203	0.672±0.116	17.8±20.3	0.299±0.120
U value*	131	123	74	105
P value*	0.957	0.733	0.032	0.321

Note: *Mann-Whitney U test.

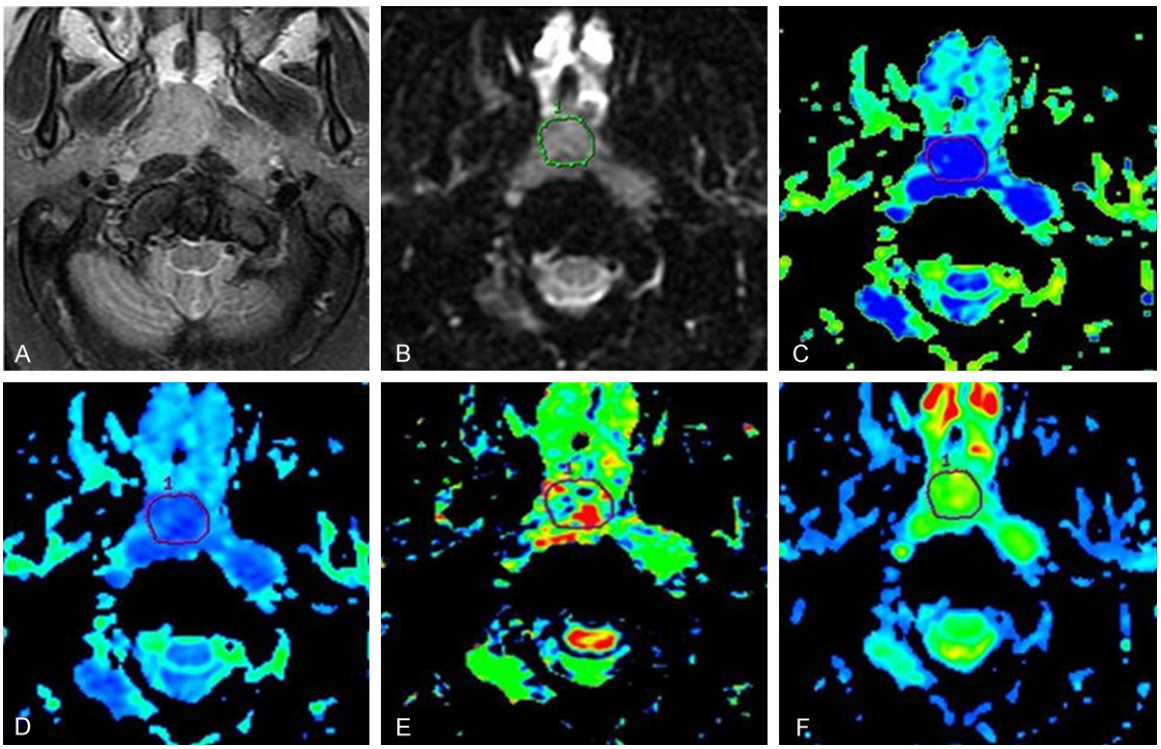

Figure 2. A male case with undifferentiated NPC and aged 51 years. The slice with the maximum lesion was selected by reference to T2WI (A). ROI was delineated manually on DWI image with b=0 s/mm^2 (B). ADC stand (C), ADC slow (D), ADC fast (E) and F fast (F) were generated automatically by the software. Their values were 0.957×10^{-3} mm^2/s, 0.695×10^{-3} mm^2/s, 17.3×10^{-3} mm^2/s and 0.322, respectively.

two groups, but ADC_{stand}, ADC_{slow} and F_{fast} showed no significant differences. The diagnostic accuracy of ADC_{fast} in discriminating differentiated and undifferentiated NPC was evaluated by ROC curve. When the area under curve (AUC) was 0.722 (**Figure 4**) and ADC_{fast} cut-off was 11.7×10^{-3} mm^2/s, Youden's index was the largest (0.489). At this time, the diagnostic sensitivity and specificity of ADC_{fast} were 85.7% and 63.2%, respectively.

Discussion

The untreated NPC lesions are mostly of nonkeratinizing type in districts of high incidence of NPC in China. To ensure the homogeneity of subjects, we only included cases with nonkeratinizing NPC, which were further divided into differentiated and undifferentiated type. These two types of nonkeratinizing NPC were different in pathological features and prognosis. An accurate pathological staging of NPC is crucial for the choice of therapies, particularly ROI delineation and dose allocation. Although biopsies can determine the pathological type of NPC, they cause trauma and cannot be performed repeatedly. For recurrent cases, the lesions are usually located deeper and are difficult to be sampled by biopsies. Conventional imaging techniques lack specificity in pathological staging of NPC. In recent years, DWI has been widely applied to preoperative pathologi-

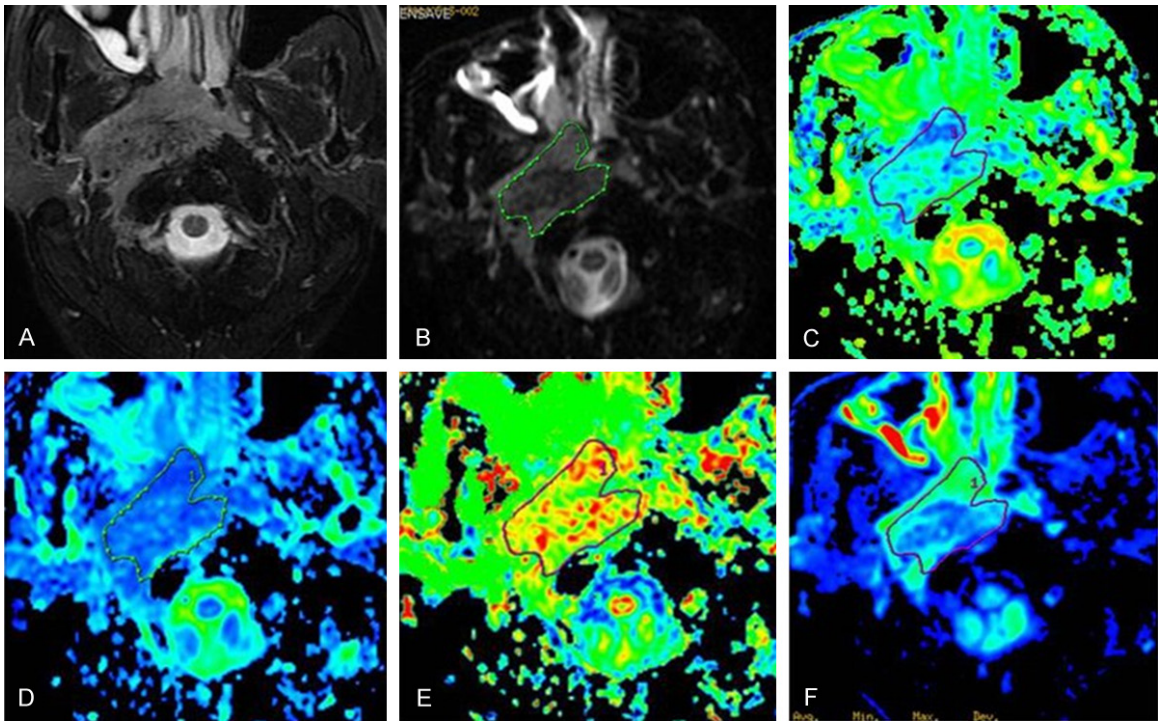

Figure 3. A male case with differentiated NPC and aged 47 years. The slice with the maximum lesion was selected by reference to T2WI (A). Then ROI was delineated manually on DWI image with b=0 s/mm^2 (B). ADC stand (C), ADC slow (D), ADC fast (E) and F fast (F) were calculated using the software. The values were 1.020×10^{-3} mm^2/s, 0.763 ×10^{-3} mm^2/s, 21.4×10^{-3} mm^2/s and 0.265, respectively.

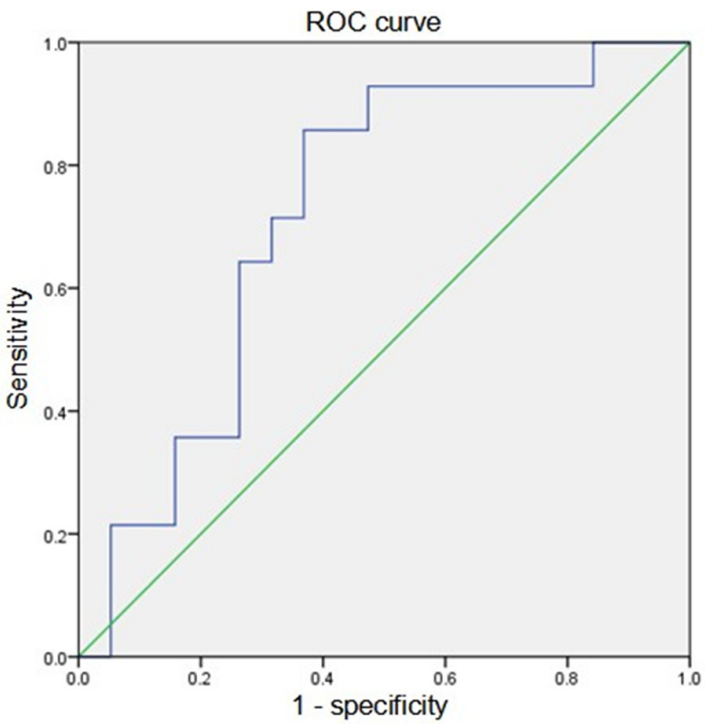

Figure 4. ROC curve of ADC fast for discriminating differentiated and undifferentiated NPC.

cal staging of tumors, including brain tumors [6], but it is rarely used in NPC.

Conventional DWI uses uni-exponential model which is based on isotropic motion of water molecules without taking into account the factor of microcirculation perfusion in live tissues. Therefore, the calculated ADC is usually larger than the true value. Biexponential DWI is based on the assumption that the water molecules diffuse at two different rates in live tissues, either slowly or fast. ADC_{slow} represents the slow diffusion of water molecules due to thermal energy (i.e., Brownian motion); ADC_{fast} represents the rapid diffusion of water molecules due to blood pressure gradient, thus reflecting the displacement of water molecules in capillary network. Biexponential DWI applies to live tissues that contain diffu-

sion of water molecules (Brownian motion) and microcirculation perfusion. However, tumor voxels contain both diffusion and perfusion, and biexponential DWI can separate diffusion of water molecules from perfusion, which is not possible with uni-exponential DWI. Therefore, ADC calculated by biexponential DWI is closer to real value and better represents the microscopic features of tissues.

Biexponential DWI is now used for differential diagnosis of benign and malignant nasopharyngeal lesions. Zhang et al. [7] found that perfusion-related diffusion coefficient of primary lesion of NPC (ADC_{fast}) was higher than that of inflammatory disease, while real diffusion coefficient (ADC_{slow}) and the perfusion fraction (F_{fast}) were lower than those of inflammatory disease. Lai V et al. [8] found that perfusion-related diffusion coefficient of primary lesion of NPC was higher than that of fibrosis after radiotherapy, while the real diffusion coefficient and perfusion fraction were lower than those of fibrosis after radiotherapy. These findings demonstrated the feasibility of biexponential DWI in detecting the microscopic differences between benign and malignant nasopharyngeal lesions and thus in making differential diagnosis.

Lai V et al. [9] indicated that the real diffusion coefficient decreased with higher TNM stage of NPC. The reason may be that the tumor cells proliferate more rapidly at higher TNM stage with more compact arrangement, larger nuclei and fewer cytoplasm. This means reduced extracellular space, lower cell membrane permeability and limited diffusion of water molecules. However, we did not discover significant differences in ADC_{slow} and ADC_{stand} between differentiated and undifferentiated NPC. Thus ADC_{slow} and ADC_{stand} may be less accurate in discriminating the two types of NPC, and more studies are needed to confirm this.

In theory, ADC_{fast} and F_{fast} will increase with increased capillary density and perfusion as verified by clinical trials. Lai V et al. [9] found that both ADC_{fast} and F_{fast} declined with higher TNM stage of NPC. Huang B et al. [10] showed that Krans value (an index characterizing capillary perfusion and permeability) increased with higher overall stage, T stage and M stage of NPC. Thus the higher the stage of NPC, the stronger the microcirculation perfusion will be (ADC_{fast} and F_{fast} increase with increasing Krans value). As indicated by our data, ADC_{fast} of undifferentiated NPC was lower than that of differentiated NPC, which was suggestive of the correlation between ADC_{fast} and pathological staging of NPC (i.e., the higher the malignancy degree, the lower the ADC_{fast}). Therefore the microcirculation perfusion tends to vary for different stage or differentiation degree of NPC. Undifferentiated NPC may be associated with more rapid tumor cell proliferation, higher pressure of extracellular fluid, and hence greater compression of capillaries and lower microcirculation perfusion. This finally leads to lower ADC_{fast} in undifferentiated NPC than in differentiated NPC. We did not find significant differences in F_{fast} between differentiated and undifferentiated NPC, possibly indicating the limited value of F_{fast} in discriminating the two types of NPC.

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Disclosure of conflict of interest

None.

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