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Original Article

Diffusion kurtosis imaging for differentiating parotid tumors

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Abstract: Objective: Fine needle aspiration biopsy is invasive and may lead to spread of tumor cells and a higher possibility of local recurrence, especially for pleomorphic adenomas and malignant tumors. The purpose of this study was to elucidate the utility of diffusion kurtosis imaging (DKI) for differentiation of parotid tumors. Methods: 34 parotid tumors were examined with conventional magnetic resonance imaging and DKI. Data of DKI were analyzed with a diffusion kurtosis estimator to calculate mean kurtosis (MK), mean diffusivity (MD), and fractional anisotropy (FA). The diagnostic accuracy of MK, MD and FA values was evaluated, including sensitivity, specificity, and area under receiver operating characteristic (ROC) curve (AUC). Results: There were significant differences of benign and malignant parotid tumors in the values of MK, FA and MD (P=0.003, 0.019 and 0.047). Mean MK value of benign parotid tumors was significantly lower than that of malignant parotid tumors (0.728±0.263 vs. 1.091±0.253, respectively). Mean FA value of benign parotid tumors was significantly lower than malignant parotid tumors, and mean MD value of benign tumors was significantly higher than malignant tumors. The cut-off point between benign and malignant parotid tumors for MK was 1.053. The sensitivity, specificity and AUC for MK were 75.000%, 91.300% and 0.853, respectively. The AUC for FA and MD in differentiating benign and malignant parotid tumor was 0.783 and 0.739. The sensitivity and specificity for FA and MD were 75.000%, 82.610% and 50.000%, 95.650%, respectively. Conclusion: DKI showed higher specificity and sensitivity than conventional diffusion-weighted and tensor imaging for assessment of benign and malignant parotid tumors. MK enables differentiation and characterization of parotid tumors.

Keywords: Parotid tumor, diffusion kurtosis imaging, magnetic resonance imaging

Introduction

80% of parotid tumors are benign tumors, among which about 85% are pleomorphic adenoma [1]. Surgery is the most effective treatment method for parotid tumors [1]. Tumor resection of pleomorphic adenoma without histological confirmation before surgery would result in 20%-45% of risk of local recurrence [2-5], and it would be reduced to about 1.5%-6% by excision of the lateral parotid gland with facial nerve preservation [1, 6-8]. Moreover, the risk of facial paralysis and malignant transformation will be increased by repeated operations [8]. For parotid tumors, preoperative histological diagnosis can help to choose surgical strategy [1]. Fine needle aspiration biopsy is one of the techniques for preoperative histological diagnosis. However, it is invasive and may lead to spread of tumor cells and a higher possibility of local recurrence, especially for pleomorphic adenomas and malignant tumors [9]. Therefore, routine application of fine needle biopsy is not widely accepted [10]. Ultrasonography (US), computed tomography (CT) and conventional magnetic resonance imaging (MRI) are less precise because of overlap in appearance of parotid tumors [9, 11-13]. Diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) assume water diffusion to be Gaussian. In fact, the complexity of the biologic cytoarchitecture, such as cell membranes,

Table 1. MK, FA and MD values in malignant and benign parotid tumors

Pathological diagnosis	MK	FA	MD (10^{-3} mm^2/s)	n
Malignant	1.091±0.253	0.251±0.043	0.738±0.330	11
Benign	0.728±0.263*	0.198±0.047**	1.048±0.323**	23

Notes: Wilcoxon Mann-Whitney test was used to make statistical analysis. *P<0.001, **P<0.05 compared with malignancy. MK: mean kurtosis; MD: mean diffusivity; FA: fractional anisotropy.

intracellular organelles, and the rapid exchange of protons between different compartments causes water diffusion deviating from Gaussian behavior (non-Gaussian distribution) [14]. Diffusion kurtosis imaging (DKI), an extension of DTI with a genuine diffusion technique, could describe the complicated diffusion behavior *in vivo* better and reveal more tissue information about the heterogeneity, vascularity, cellularity, etc [14-16]. In DKI, kurtosis is represented as a new parameter in addition to the diffusion coefficient [17]. Mean kurtosis (MK) was applied for evaluation of cerebral infarction, cerebral gliomas, multiple sclerosis, lung cancer, prostate cancer, nasopharyngeal carcinoma, and head and neck squamous cell carcinoma [15, 18-24], but its application in parotid tumors was rarely reported. This study aimed to elucidate the utility of DKI for differentiation of parotid tumors.

Materials and methods

Patients

The study has been approved by the Ethics Committee of Shandong Provincial Hospital Group, Shandong University and informed consent form was obtained from each patient. 32 patients with 34 parotid tumors confirmed by pathology were included in this study (15 males and 17 females; age range: 18-76 years old; mean age: 47.7±5.5 years old). The course of diseases was from 3 months to 15 years. Inclusion criteria were as follows: 1) parotid tumors confirmed by pathology; 2) patients without any invasive examinations or any treatments including biopsy, radiation and chemotherapy before MRI examination.

MR imaging and evaluation

All patients were examined with conventional MRI and DKI on a MAGNETOM Skyra 3.0 T MRI scanner (Siemens AG, Erlangen, Germany). Conventional MRI is helpful for localization and characterization of parotid tumors and valuable in differentiation of benign and malignant tumors. Besides, conventional MRI can provide important clues for diagnosis. DKI could describe the complicated diffusion behavior in parotid tumor tissues and reveal more tissue information about heterogeneity, vascularity and cellularity, etc. MK and fractional anisotropy (FA) value of lesions could be calculated. DKI might be more helpful in differentiating parotid tumors. DKI parameters were as follows: TR=3700 ms, TE=95 ms, FOV=210 mm×210 mm, slice thickness=3 mm with 0 mm gap, b-values =0, 1000 and 2000 mm^2/s, 20 orthogonal directions, and acquisition time 13 min 39 s.

Data of DKI was analyzed by using in-house software (Diffusion and Kurtosis Estimator) in Matlab, Version Release 2012a/7.14 (MathWorks, Natick, Massachusetts) into MK, mean diffusivity (MD), FA maps. A standardized ROI size about 20 voxels was drawn in the solid part of tumor, and mean values of MK, MD and FA were evaluated. All images were evaluated by two experienced radiologists with double-blind method (15 and 20 years of experience in head and neck radiology respectively).

Statistical analysis

Statistical analysis was performed with the Statistical Package for Medical Statistics (Medcalc 15.6). Values of MK, MD and FA were presented in a form of mean ± standard deviation. Data were compared between benign and malignant parotid tumors by using Mann-Whitney test. Receiver operating characteristic curve analysis was in mean kurtosis (MK), MD and FA, and area under the receiver operating characteristic curve (AUC) was calculated for assessment of optimal parameter between benign and malignant parotid tumors. P<0.05 was considered significant.

Results

Patients' data

32 patients with 34 parotid tumors were enrolled in this study. One patient with adeno-

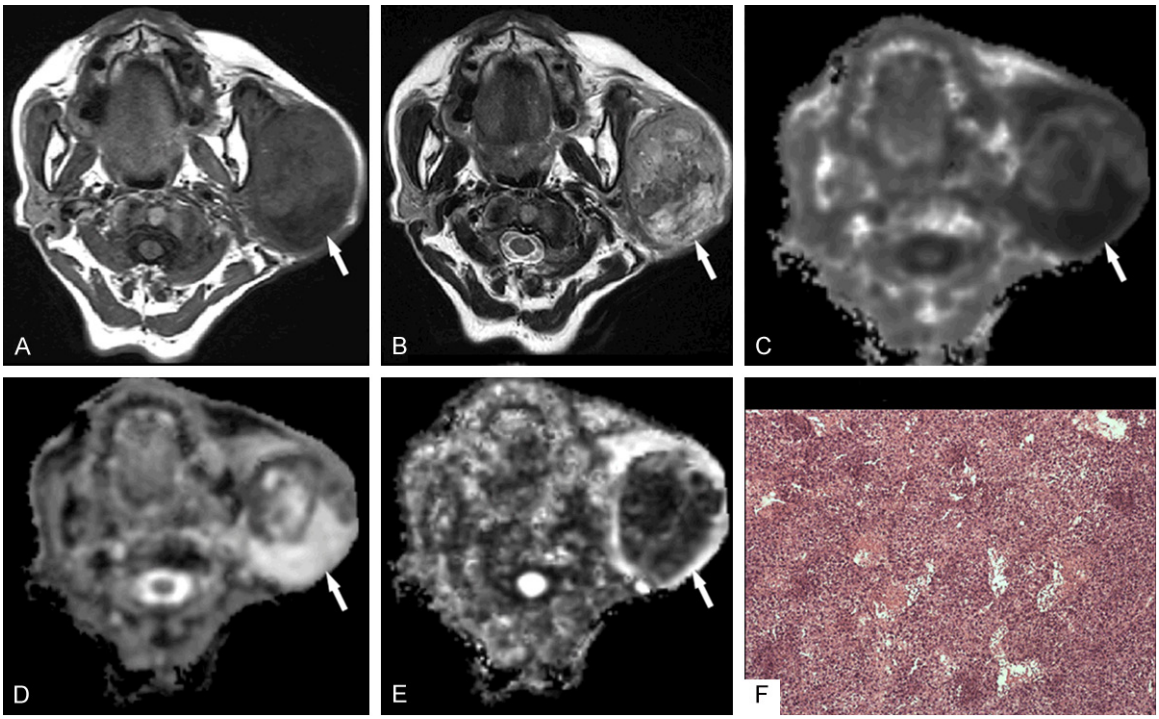

Figure 1. A 76 Years male, pleomorphic adenoma. A. Traverse T1WI showed an iso-intense with hypo-intense signal mass in superficial parotid lobe (arrow). B. Traverse T2WI showed an inhomogenous hyper-intense mass with incomplete capsule. C-E. MK, MD and FA maps showed solid region of the mass with MK value of 1.351, MD value of 0.511×10^{-3} mm^2/s and FA of 0.302 respectively. F. HE staining (×100). MK: mean kurtosis; MD: mean diffusivity; FA: fractional anisotropy.

lymphoma had two bilateral masses, and one patient with mucoepidermoid carcinoma had two masses in right parotid gland. In 23 benign parotid tumors, there were 10 pleomorphic adenomas, 9 adenolymphomas, 2 basal cell adenomas, 1 multiple nodular acidophil adenoma, and 1 myoepithelioma. In 11 parotid malignant tumors, there were 4 mucoepidermoid carcinomas, 3 acinic cell carcinomas, 2 basal cell carcinomas, 1 adenoid cystic carcinoma, and 1 carcinoma ex pleomorphic adenoma.

MK, FA and MD in benign and malignant parotid tumors

The diffusion kurtosis metric values MK, FA and MD in the solid region of the parotid tumors are shown in **Table 1** and **Figures 1** and **2**. Mean MK value was significantly lower in benign than that in malignant tumors (P=0.003). Mean FA was significantly lower in benign than that in malignant tumors (P=0.019), whereas the mean MD values was significantly higher in benign than that in malignant tumors (P=0.047).

Diagnostic accuracy of MK, FA and MD values in benign and malignant parotid tumors

In order to measure the diagnostic accuracy of MK, FA and MD values for differentiating benign from malignant tumors, receiver operating characteristic (ROC) analysis was performed, and the cut-off value was calculated. The diagnostic accuracy of MK, FA and MD was evaluated in terms of sensitivity, specificity and AUC. The diagnosis of cut-off point between benign and malignant parotid tumors for MK, FA and MD was 1.053, 0.240 and 0.647 (**Table 2**). The AUC for MK showed the highest value of 0.853 for the differentiation between benign and malignant parotid tumor. AUC was 0.783 for FA and 0.739 for MD.

The sensitivity and specificity for differential diagnosis of benign from malignant tumors was 75.000% and 91.300% for MK, 75.000% and 82.610% for FA, and 50.000% and 95.650% for MD (**Table 2** and **Figure 3**). ROC analysis of MK showed increased AUC and Youden index

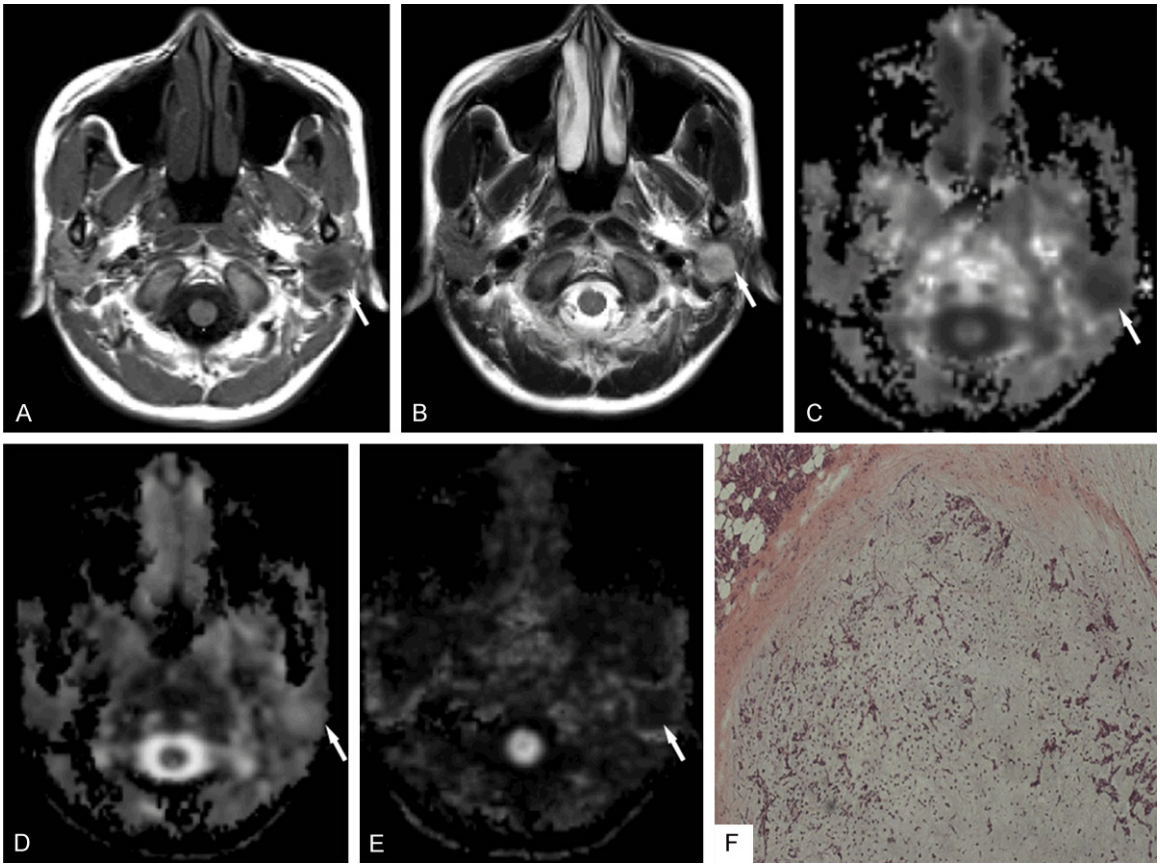

Figure 2. 23 Years female, pleomorphic adenoma. A. Traverse T1WI showed a hypo-intense signal mass in superficial parotid lobe with well-defined borders (arrow). B. Traverse T2WI showed homogenous hyper-intense mass with incomplete capsule. C-E. MK, MD and FA maps showed tumor with MK value of 1.168, MD value of 1.209×10^{-3} mm^2/s and FA of 0.169, respectively. F. HE staining (×100). MK: mean kurtosis; MD: mean diffusivity; FA: fractional anisotropy.

Table 2. Variables of ROC analysis of MK FA and MD for differentiating benign and malignant parotid tumors

Variables	MK	FA	MD
AUC	0.853	0.783	0.739
Cut-off point	1.053	0.240	0.647 (10^{-3} mm^2/s)
Sensitivity (with 95% CI)	75.000	75.000	50.000
Specificity% (with 95% CI)	91.300	82.610	95.650
P (AUC=0.5)	<0.0001	0.002	0.030
Youden index (J)	0.663	0.576	0.457

Notes: All the variables were obtained with ROC analysis. MK: mean kurtosis; MD: mean diffusivity; FA: fractional anisotropy.

compared with FA and MD (**Table 2** and **Figure 3**).

Discussion

DKI was thought to be valuable for quantitatively measuring histological properties of tissues. In this study, it was proved to be useful in differential diagnosis of parotid tumors. Compared with previous reports evaluating DWI in parotid tumors, two prominent findings were revealed in this study. Firstly, in addition to MD and FA, MK was another valuable parameter for differential diagnosis of benign and malignant tumors. Secondly, compared with MD and FA, MK was superior for differentiating malignant and benign parotid tumors.

Traditional diffusion (DWI and DTI) assumes that water molecule diffusivity has a Gaussian distribution [14, 25]. The deviation from Gaussian distribution can be quantified by using diffusion kurtosis which can be regarded as index of tissue microstructural complexity [16]. Thereby, DKI is considered to be more suitable than conventional diffusion weighted and tensor imaging for the detection of microstructural changes [26]. By acquiring

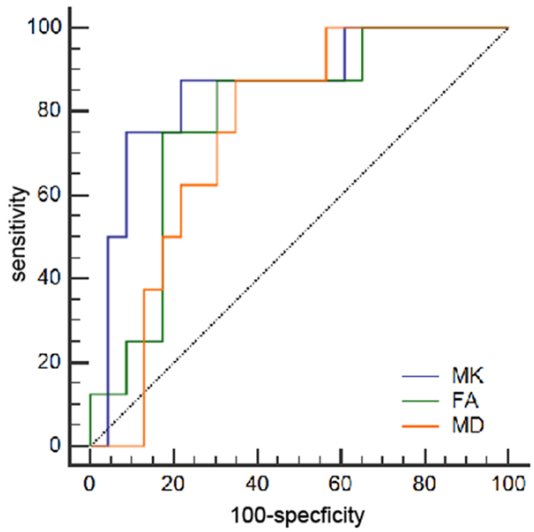

Figure 3. ROC analysis of three parameters for differentiating benign and malignant parotid tumors. AUC below the black dotted line was less than 0.5. MK had the largest AUC, while MD had the smallest AUC. MK: mean kurtosis; MD: mean diffusivity; AUC: area under curve.

data for at least two nonzero diffusion gradient factors (*b* value) in more than 15 nonlinear directions, MK and conventional diffusion metrics (including MD and FA) are obtained simultaneously. MK is the average kurtosis of all diffusion directions. MK value is a new parameter in addition to the diffusion coefficient (FA and MD), measured by using higher b-value than conventional diffusion weighted and tensor imaging [21]. The highest b-value applied in this study was 2000 s/mm^2. MK was found to be able to reflect histological changes of cerebral infarction, cerebral gliomas, multiple sclerosis, lung cancer, prostate cancer, nasopharyngeal carcinoma and head and neck squamous cell carcinoma, etc. [15, 18-24] There was a tendency of increasing MK values of malignant tumors with higher grades [15]. In consistent with previous studies, MK of malignant parotid tumors was significantly higher than benign parotid tumors, and the higher MK values may not be caused by increased viscosity in the tissue but by increased cellular density [15, 16].

MK is shown to be the most promising imaging markers for differentiation of parotid tumors in the present study. A series of changes caused by malignant parotid tumors greatly increase the heterogeneity and complexity of the microstructure of tissues and cells. MK is more sensitive and accurate for the detection of microstructural changes, hence, these changes can be detected by MK at the early stages but are not sufficiently evident enough for MD or FA to recognize them. There was a tendency of higher MK values for highly malignant tumors in this study. Higher-grade malignant parotid tumors with increasing MK values are characterized by higher cellularity, more nuclear atypia, higher pleomorphism, and more vascular hyper-plasia and necrosis [27]. Therefore, MK could be used as another effective parameter for differentiation of parotid tumors.

In this study, there were some limitations. We measured the regions of most solid parts of the tumors based on T2 weighted imaging instead of the whole tumors, which may lead to bias of selection. In addition, the total amount of patients was relatively small, especially the amount of patients with malignant tumors, which may introduce a statistical deviation. Therefore these results are preliminary and need to be confirmed by further investigation.

In conclusion, these results demonstrate significant differences in mean MK between benign and malignant parotid tumors. It is better to differentiate benign and malignant parotid tumors by mean MK instead of conventional diffusion weighted and tensor imaging parameters. This new technique can be used as a non-invasive biomarker for preoperative diagnosis of benign and malignant parotid tumors.

Disclosure of conflict of interest

None.

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