Whole-tumor histogram analysis of apparent diffusion coefficient maps in grading diagnosis of ependymoma

Huiyu Huang · Yong Zhang · Jingliang Cheng · Mengmeng Wen

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Abstract

Objective  To study the value of whole-tumor histogram analysis which is based on apparent diffusion coefficient maps in grading diagnosis of ependymoma.

Methods  71 patients with ependymal tumors were retrospectively analyzed, including 13 cases of WHO grade I, 28 cases of WHO grade II, and 30 cases of WHO grade III. Mazda software was used to draw the region of interest (ROI) in the apparent diffusion coefficient maps of three groups on every layer of tumor level. The whole-tumor gray histogram analysis was carried to obtained nine characteristic parameters, including mean, variance, kurtosis, skewness, Perc.01%, Perc.10%, Perc.50%, Perc.90%, and Perc.99%. When the parameters satisfy the test of normal distribution and homogeneity of variance, single factor analysis of variance (ANOVA) was carried to compare the three groups and LSD t test was performed to compare the two groups. Besides, the ROC curve was used to analyze the diagnostic efficacy of the parameters.

Results  Variance, Perc.01%, and Perc.10% had significant differences among the three groups (all $P < 0.05$). The remaining six parameters had no significant difference among the three groups (all $P > 0.05$). And, between WHO I and WHO II, the sensitivity and specificity of the Perc.10% were 85.7% and 100.0%, the AUC was 0.872, and the cut-off was 126.5. Between WHO I and WHO III, the sensitivity and specificity of the Perc.10% were 85.7% and 87.7%, the AUC was 0.835, and the optimum critical value was 131.3. Besides, the sensitivity, specificity, and AUC of variance between WHO II and WHO III are 68.4%, 76.9%, 0.794, and 2645.7, respectively. They had higher identification efficiency.

Conclusion  Whole-tumor histogram analysis of apparent diffusion coefficient (ADC) maps could provide ancillary diagnostic value in grading diagnosis of ependymoma. Perc.10% had a high diagnostic efficiency.

Keywords  Magnetic resonance imaging · Ependymoma · Whole-tumor histogram analysis · Diagnosis

Introduction

Ependymoma originates from ependymal cells and glial epithelial cells in the ventricular system and the lining of the central spinal canal. The main clinical manifestations of patients with ependymoma are headache, dizziness, vomiting, and standing instability. According to the classification of 2016 WHO nervous system, ependymoma can be classified into grade I–III [1]. WHO type I ependymoma is a benign tumor, and WHO type II is between benign and malignant [2]. WHO type III, also known as anaplastic ependymoma, is a malignant ependymoma and the tumor cells are easily disseminated along the cerebrospinal fluid. And WHO type III of ependymoma has the characteristics of strong invasiveness, poor prognosis, and easy recurrence. Therefore, the preoperative classification of ependymoma is very important for treatment and prognosis. Previous literatures have used imaging features, ADC values, or dynamic enhancement curves to identify different grades of ependymoma [3–5]. However, the imaging features of benign and malignant ependymoma are often insignificant, which have little value in differentiating the type and grade of tumors. Histogram analysis is a new image analyzing method based on voxel distribution, which can provide more quantitative information, thus reflecting the heterogeneity and the diffusion characteristics of tumors in many aspects [6]. In this...
study, the ADC images of different grades of ependymoma were collected to explore the value of the whole-tumor histogram analysis based on ADC images in the classification and diagnosis of ependymoma.

**Materials and methods**

**Clinical data**

A retrospective analysis was carried on MRI of 71 ependymoma cases confirmed by pathology in our hospital from February 2012 to December 2018. The age of the participants ranged from 1 to 74 years, with an average of \(46.8 \pm 3.5\) years. Among them, there are 13 cases of WHO grade I, 28 cases in grade II and 30 cases were in grade III. And the basic data and tumor types of the participants are shown in Table 1. The inclusion criteria were: (1) the ependymoma confirmed by operation and pathology; (2) the patient did not undergo intracranial decompression, chemotherapy, or radiotherapy before conventional MRI examination. Besides, this study was approved by the Medical Ethics Committee of our hospital, and all the subjects signed the informed consent.

**MR examination method**

Using German Siemens Skyra 3.0 T magnetic resonance imaging system and standard head coil. The patient was relaxed naturally in supine position and maintained the forehead and face in horizontal position and. Besides, the nose root was in the central line of the coil. Plain scan in sagittal and axial position \(T_1WI, T_2WI, FLAIR\) sequence, and \(b\) value of axial DWI \(0.800 \, \text{s/mm}^2\) were performed. Enhanced scan in sagittal, axial, and coronal positions \(T_1WI\) were performed with \(0.1 \, \text{mmol/kg}\) of Gd-DTPA as a contrast medium. Scanning parameters were: \(T_1WI: TR \, 260.0 \, \text{ms}, TE \, 2.46 \, \text{ms}; T_2WI: TR \, 3800 \, \text{ms}, TE \, 93.0 \, \text{ms}; \text{FLAIR: TR} \, 4500 \, \text{ms}, \text{and TE} \, 93.0 \, \text{ms.} \) DWI scanning was carried out by SE-EPI sequence, with \(b = 0\) and \(1000 \, \text{s/mm}^2\) \([2]\), TR \(3500 \, \text{ms}, \text{TE} \, 119 \, \text{ms}; 23 \times 23\)-cm field of vision, 5-mm-layer thin, 0.3-mm-layer spacing, and 20 layers.

**Image processing**

1. Image selection: All patients’ MRI images were exported from PACS workstation in “.BMP” format, and the window width and window position were adjusted to keep the consistency when exported. All images were saved on the hard disk. The axial ADC was selected to carry on the global histogram analysis.

2. ROI selection and global histogram analysis: The Mazda software used in this study was developed by Materka and his team. It was easier for the experimenter to learn how to use, and the software ran stably in Windows 8. Before Mazda software analysis, unified window width and window location were used to ensure the reliability of the research. The ROI was manually drawn along the edge of the tumor on every slice in axial ADC image by three MRI experts. The gray histogram of ROI is automatically generated by the software and the average values of the parameters of each lesion were calculated, respectively. Three samples were randomly selected from different grades of ependymoma, respectively, and the ROI of one layer in each sample was drawn, filling with red. The corresponding images before and after marking are shown in Figs. 1, 2, and 3.

**Statistical methods**

SPSS 21.0 statistical software was applied to analyze the data. Statistical descriptions of measurement data were made by mean ± standard deviation (mean ± SD). If the data conformed to normal distribution and the variance is homogeneous, one-way ANOVA is used for multigroup comparisons and LSD \(t\) test was used for two-group comparisons. When the data did not satisfy normal distribution or homogeneity of variance, Kruskal–Wallis test was used for multigroup comparisons and Bonferroni test was used for comparisons between two groups. We defined that \(P < 0.05\) had significant difference. The ROC curve was established to determine the optimal threshold for differentiating the three groups of tumors. The AUC was calculated and the diagnostic efficiency of the parameters was analyzed by ROC curve.

**Result**

The histograms of tumors run by the MaZda software are shown in Figs. 4, 5, and 6. The statistical results of the histogram parameters of the three groups are shown in Table 2. Among the nine parameters, Variance, Perc.01%, and Perc.10% had significant difference among the three groups (all \(P < 0.05\)), while the other six parameters had
Fig. 1 a The primary axis ADC image of WHO grade I; b the marked axis ADC image of WHO grade I

Fig. 2 a The primary axis ADC image of WHO grade II; b the marked axis ADC image of WHO grade II

Fig. 3 a The primary axis ADC image of WHO grade III; b the marked axis ADC image of WHO grade III
no significant difference among the three groups (all $P > 0.05$). Meanwhile, comparisons between the two groups showed that there were significant differences in the variance, Perc.01%, and Perc.10% between WHO I and WHO II, and between WHO II and WHO III ($P < 0.05$), and Perc.10% had significant difference between WHO I and WHO III ($P < 0.05$).

ROC curves were used to analyze the diagnostic efficacy of the parameters of Variance, Perc.01%, and Perc.10% in differentiating the three-group tumors. And the sensitivity, specificity, and the optimal threshold are given in Tables 3, 4, and 5. Between WHO I and WHO II, the sensitivity and specificity of the Perc.10% were 85.7% and 100.0%, the AUC was 0.872, and the cut-off was 126.5. Between WHO I and WHO III, the sensitivity and specificity of the Perc.10% were 85.7% and 87.7%, the AUC was 0.835, and the optimum critical value was 131.33. Besides, the sensitivity, specificity, and AUC of variance between WHO II and WHO III are 68.4%, 76.9%, 0.794, and 2645.7, respectively. They had higher identification efficiency.

**Discussion**

Texture analysis, as a new technology, is more and more widely used in extracting features from medical images. Texture analysis of medical images can provide quantitative information for differential diagnosis, grading, and predicting therapeutic effect [7, 8]. Histogram is the most commonly used tool in texture analysis of medical images. Mazda software can generate histograms about given regions of interest in the images [9], and calculate a lot of texture parameters from histograms, such as mean, variance, percentile, etc. Mean value shows the absolute value of the diffusion amount, reflecting the heterogeneity and invasiveness of tumors to a certain extent. Low mean values indicate limited diffusion, while high mean values indicate increased diffusion. The variance reflects the discrete degree of the average gray value. The smaller the

| Groups          | Mean   | Variance | Skewness  | Kurtosis | Perc.01%  | Perc.10%  | Perc.50%  | Perc.90%  | Perc.99%  |
|-----------------|--------|----------|-----------|----------|-----------|-----------|-----------|-----------|-----------|
| WHO grade I     | 179.65 ± 42.00 | 1156.48 ± 753.26 | −0.33 ± 0.73 | 0.62 ± 0.64 | 100.86 ± 40.00 | 137.86 ± 45.23 | 181.44 ± 50.62 | 217.94 ± 29.13 | 242.86 ± 10.78 |
| WHO grade II    | 147.47 ± 31.27 | 3183.36 ± 1333.37 | 0.41 ± 0.67 | 0.32 ± 1.74 | 57.72 ± 28.53 | 80.61 ± 23.92 | 146.37 ± 43.03 | 221.49 ± 34.54 | 245.59 ± 20.20 |
| WHO grade III   | 154.38 ± 43.90 | 1664.72 ± 1429.54 | 0.20 ± 0.39 | 0.74 ± 1.18 | 83.69 ± 17.90 | 105.75 ± 23.29 | 158.97 ± 55.53 | 196.10 ± 54.28 | 217.84 ± 43.64 |

*For $X^2$ values: $P < 0.05$.*

Table 2 Histogram data of each group with ependymoma ($X ± s$)

| Parameters | AUC | The optimal threshold | Sensitivity (%) | Specificity (%) | $P$ |
|------------|-----|-----------------------|-----------------|-----------------|-----|
| Variance   | 0.060 | 1217.5               | 42.9            | 6.3             | $<0.05$ |
| Perc.01%   | 0.865 | 86.25                | 85.7            | 89.5            | $<0.05$ |
| Perc.10%   | 0.872 | 126.5                | 85.7            | 100             | $<0.05$ |

Table 3 The efficacy of variance, Perc.01%, and Perc.10% in differentiating WHO grade II from WHO grade I of ependymoma

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*Means when compared with WHO grade I, $P < 0.05$; $^a$means when compared with WHO grade II, $P < 0.05$
Table 4  The efficacy of Perc.01% and Perc.10% in differentiating WHO grade III from WHO grade I of ependymoma

| Parameters | AUC The optimal threshold | Sensitivity (%) | Specificity (%) | P    |
|------------|---------------------------|----------------|----------------|------|
| Perc.10%   | 0.835 131.33              | 85.7           | 87.7           | 0.016|

Table 5  The efficacy of variance, Perc.01%, and Perc.10% in differentiating WHO grade III from WHO grade II of ependymoma

| Parameters | AUC The optimal threshold | Sensitivity (%) | Specificity (%) | P    |
|------------|---------------------------|----------------|----------------|------|
| Variance   | 0.794 2645.7              | 68.4           | 76.9           | <0.05|
| Perc.01%   | 0.178 44.3                | 63.2           | 7.7            | 0.002|
| Perc.10%   | 0.186 85.9                | 52.6           | 15.4           | 0.003|

In this study, we are aiming to explore the value of ADC-based whole-tumor histogram analysis in the grading diagnosis of ependymomas. By analyzing the nine parameters, we found that the Variance, Perc.01% and Perc.10% were significantly different among the three groups. ROC curve showed that the Perc.10% between WHO I and WHO II, WHO I and WHO III had high diagnostic efficiency. Also, the Perc.10% value of WHO grade I ependymoma was the highest, indicating that the voxel value of WHO grade I ependymoma was higher than that of other two grades. Lu et al. [20] found that the percentile of ADC histogram can be used to distinguish primary central nervous system lymphoma from active demyelinating lesions of tumors, similar to the results of this study. The variance between WHO II and WHO III has a high diagnostic efficiency. In this study, WHO I ependymoma had the smallest variance, and WHO II ependymoma and WHO III ependymoma had relatively larger variance. This was due to that the texture of WHO I ependymoma was relatively homogeneous, and those of WHO II and WHO III are relatively complex and heterogeneous. Wang et al. [21] found that histogram variance had a high diagnostic efficiency in grading and differentiating prostate cancer, which was similar to the results of this study.

Histogram analysis can provide non-invasive diagnostic information for grading diagnosis of ependymoma. In addition, the ROIs in this study include not only the parenchymal part of the tumor, but also the necrosis, cystic degeneration, and hemorrhage that reflect the heterogeneity of the tumor. Thus, the method of whole-tumor histogram analysis based on voxel distribution is more accurately and reliably in reflecting the heterogeneity of tumors, and it can avoid the sampling error caused by ROI in local area in the greatest extent, and provide more quantitative information for the identification or classification of tumors [22, 23].

There are some limitations in our research. First, it is a small-scale retrospective study in which the number of patients in three groups was unbalanced, especially the group of WHO I only had 13 cases, and we will collect more cases in the future studies; second, because of the low resolution of ADC maps, it is difficult to clearly define the edge of tumors on ADC maps. Our study defines the edge of tumors by referring T₁WI and T₂ enhanced images. However, there are still some problems in image registration between different sequences. It is expected that image fusion or computer intelligent image registration will be introduced to solve these problems in the future research.

Conclusions

To sum up, our research shows that the whole-tumor histogram analysis based on ADC maps is a non-invasive method that synthesizes all voxels of the entire tumor volume to
obtain histogram parameters. Thus, the results are more objective variability and are helpful in grading diagnosis of ependymoma.

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