Original Article

Potential role of fractional anisotropy derived from diffusion tensor imaging in differentiating high-grade gliomas from low-grade gliomas: a meta-analysis

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Abstract: Background and purpose: It is crucial to accurately differentiate high-grade gliomas (HGGs) from low-grade gliomas (LGGs) preoperatively, as treatment strategies vary. So we performed a meta-analysis to assess the sensitivity and specificity of fractional anisotropy (FA) value derived from diffusion tensor imaging (DTI) in differentiating HGGs from LGGs. Materials and methods: Between January 2005 and June 2014, relevant articles were searched from the Embase and Medline databases for analysis. Statistical analyses were performed using Meta-Disc 1.4. Results: A total of 221 patients included in the FA analysis: 127 with HGGs and 94 LGGs. The pooled sensitivity, specificity and diagnostic odds ratio (DOR) for differentiating HGGs from LGGs were 93% (95% CI 0.87-0.97), 85% (95% CI 0.76-0.92), and 55.41 (95% CI 16.77-183.07), respectively. And computation of heterogeneity metrics revealed an acceptable level of the between-study heterogeneity of DOR ($I^2=30.9\%$). Conclusions: The results of our meta-analysis present that the FA derived from DTI act as a useful diagnostic marker could be used in distinguishing the HGGs from LGGs in the preoperative and the clinical application values are to be confirmed by further larger case-control studies.

Keywords: Diffusion tensor imaging, fractional anisotropy, high grade gliomas, low grade gliomas

Introduction

Gliomas are the most frequent brain neoplasms of the central nervous system (CNS). The prognosis for patients with gliomas relies on the histopathologic grading, whereas the prognosis for those with high-grade gliomas (HGGs) remains very poor compared to the low-grade gliomas (LGGs) [1]. In patients with HGGs, surgical resection followed by adjuvant chemoradiotherapy represents the standard of care [2]. As for those with LGGs, the optimal therapeutic measure likely includes offering extensive resection of the tumor, if possible, and postoperative delaying adjuvant radiotherapy until the time of glioma progression [3]. So, it is crucial to accurately differentiate HGGs from LGGs preoperatively. As an advanced magnetic resonance images (MRI) technique, diffusion tensor imaging (DTI) provides visibility into the motion of water molecules. Fractional anisotropy (FA) is the commonly used key metric of DTI, which represents a metric of the directionality of molecular movement [4]. Some studies have tried to distinguish HGGs from LGGs by analyzing the characteristics of FA, but with mixed results [5-12]. So, the purpose of this study was to assess the sensitivity and specificity of FA in discriminating HGGs from LGGs.

Materials and methods

We searched the Embase and Medline databases from January 2005 to June 2014, using the following strategy: (diffusion tensor imaging or fractional anisotropy or DTI or FA) and (brain tumor or glioma). Language restriction to English was performed.

And the relevant articles from the reference lists of all identified studies were searched.
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Two independent observers (R.F.L., X.W. and M. L.) included those articles that satisfied the inclusion criteria of this study by evaluating the full text of the rest studies.

The inclusion criteria were: (1) before treatment with surgery or biopsy all patients underwent DTI; (2) the gliomas cases were confirmed by pathological examination.

The exclusion criteria were: (1) the studies could not provide enough data for sensitivity and specificity; (2) the patients were included in other studies; (3) the article type was a case report, letter, editorial or review. We resolved disagreements by consensus.

Two independent observers (R.F.L. and X.W.) evaluated the quality of each included study according to the QUADAS criteria [13], and disagreements were also resolved by discussion and consensus if any. The QUADAS tool, which contains 14 items and each item could be answered as “unclear”, “yes”, or “no”. We defined that all items were equal-weighted and scored 0.5 for “unclear”, 1 for “yes”, and 0 for “no”.

The same independent observers (R.F.L. and X.W.) extracted data from each included study and solved disagreement by consensus. Information extracted included the authors, patients, the nation of origin, the year of publication, study design, b values, MRI field strength, QUADAS score, and the numbers of true negative (TN), false negative (FN), true positive (TP), false positive (FP).
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**Statistical analysis**

We calculated the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) of each included study, and their DOR were also counted. Heterogeneity was tested by using the $I^2$, Cochran-Q tests and Chi-square tests. An $I^2$ value ranges from 0% to 40% is considered as “heterogeneity might not be important”, value ranges from 30% to 60% is considered as “moderate heterogeneity”, value ranges from 50% to 90% is considered as “substantial heterogeneity”, [14] and value ranges from 75% to 100% is considered as “considerable heterogeneity”. We pooled sensitivities, specificities and DOR by the fix-effect

**Figure 2.** Forest plot of the sensitivity, specificity, and DOR of FA for discriminating HGGs from LGGs of initial meta-analysis.
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In the model when the heterogeneity was not statistically significant. In addition, the random-effect model was performed if the heterogeneity was statistically significant. All of the above-mentioned statistical analyses were performed using Meta-Disc 1.4 [15].

Results

A total of 824 articles, [5-12, 16-28] 21 full texts were assessed and reference lists were searched for additional includable papers. Finally, 7 studies [6-12] were included the analysis. The study selection flow diagram was listed in Figure 1. The key information of the studies included in this meta-analysis was listed in Tables 1 and 2.

The initial meta-analysis included FA measure in a population of 246 subjects (n=142 HGGs, n=104 LGGs). We found that the FA value owned a high differential diagnostic value for differentiation HGGs from LGGs. The pooled sensitivity, specificity and DOR for differentiating HGGs from LGGs were 87% (95% CI 0.81-0.92), 85% (95% CI 0.76-0.91), and 37.75 (95% CI 0.07-0.98).
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CI 9.55-149.19), respectively (Figure 2). However, we found a moderate level of the between-study heterogeneity of DOR ($I^2=57.9\%$).

To assess for potential reasons of the observed moderate variability of study results, we repeated the analysis after exclusion of the study [11] that had the lowest QUADAS score among included studies. This reduced the between-study heterogeneity of DOR to an acceptable level ($I^2=30.9\%$) for the 6 finally included studies with 221 subjects (n=127 HGGs, n=94 LGGs). And the pooled sensitivity, specificity and DOR for differentiating HGGs from LGGs were 93% (95% CI 0.87-0.97), 85% (95% CI 0.76-0.92), and 55.41 (95% CI 16.77-183.07), respectively (Figure 3).

Discussion

HGGs present heterogeneous contrast enhancement patterns, haemorrhage, cystic or necrotic areas, and infiltrative edema. However, the imaging feature of the two main glioma categories is not always grade specific, as in some cases HGGs may show similar morphological characteristics to LGGs and the latter may present relatively malignant imaging features [9]. Therefore, these imaging similarities may potentially result in inaccurate glioma staging merely based on conventional MRI [29].

Hence these lesions may be indistinguishable. Since the advent of DTI, the ability to distinguish HGGs from LGGs has been a source of interest. Studies of the relationship between DTI metrics and pathological grading of gliomas showed that FA values can differentiate HGGs from LGGs [6-12], thus be useful for deciding on the surgery tactics or the selected biopsy site of stereotactic biopsy [6].

In this meta-analysis, the FA derived from DTI, which had 93% (87-97%) sensitivity, 85% (76-92%) specificity and 55.41 (16.77-183.07) DOR, is confirmed to own a high diagnostic value for the grading of gliomas in the preoperative. It means that a significantly increased FA in the HGGs group when compared with the metric in the LGGs group [9].

The potential limitations in our meta-analysis should be acknowledged. Firstly, we solely focused on published articles which tend to present significant and/or positive findings; whereas, some journals are much more prone to rejecting those studies with insignificant and/or negative consequences. Therefore, the diagnostic accuracy and value of FA value may be overestimated and less applicable to current clinical practice. Secondly, this study was restricted to articles published in English that may have introduced bias into this meta-analysis. Thirdly, although the tumor cases were confirmed by pathological examination in included studies, the results may be variable, on some level, due to the different reference standard of histopathologic diagnosis in various institutions. And this also may have introduced bias into this study. Fourthly, some included studies provided multiple different sensitivity and specificity based on different criteria, such as the classification of the region of interest, the threshold value and the index used to describe the FA (minimum, maximum, range or mean). We only extracted the relatively lower values and did not perform subgroup analyses, because of the limited number of studies, so the diagnostic value of FA value may be underestimated. Furthermore, due to the limited number of studies in this study, the publication bias was not evaluated, and the summary receiver operating characteristic (SROC) curve and the funnel plots was not draw.

Conclusion

In conclusion, the results of our meta-analysis present that the FA derived from DTI act as a useful diagnostic marker could be used in distinguishing the HGGs from LGGs in the preoperative and the clinical application values are to be confirmed by further larger case-control studies.

Disclosure of conflict of interest

None.

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