Review Article

Value of DWI Combined with Magnetic Resonance Spectroscopy in the Differential Diagnosis between Recurrent Glioma and Radiation Injury: A Meta-Analysis

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Received 3 September 2022; Revised 16 October 2022; Accepted 19 October 2022; Published 25 October 2022

To analyse the value of the apparent diffusion coefficient (ADC) in diffusion-weighted imaging (DWI) and the choline (Cho)/creatine (Cr) ratio and Cho/N-acetyl-aspartate (NAA) ratio in magnetic resonance spectroscopy (MRS) in the differential diagnosis between recurrent glioma and radiation injury. Chinese and English studies related to the diagnosis of recurrent glioma and radiation injury using DWI and MRS and published before 15 October 2022 were retrieved from PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure, China Biomedical Literature Database, VIP Journal Database, and Wanfang Database for a meta-analysis. A total of 11 articles were included in this study. ADC was lower in the recurrent glioma group than in the radiation injury group (standardized mean difference $\bar{d} = -1.29$, 95% confidence interval (CI) ($-1.87$, $-0.71$), $P < 0.001$). The Cho/Cr ratio was higher in the recurrent glioma group than in the radiation injury group (weighted mean difference $\bar{d} = 0.65$, 95% CI (0.40, 0.90), and $P < 0.001$). The Cho/NAA ratio was higher in the recurrent glioma group than in the radiation injury group, as evidenced by the sensitivity analysis. The sensitivity and specificity of the Cho/Cr ratio were 0.85 (0.73–0.92) and 0.82 (0.67–0.91), respectively, and the area under the curve was 0.86. The sensitivity and specificity of the Cho/NAA ratio were 0.82 (0.66–0.91) and 0.94 (0.69–0.99), respectively, and the area under the curve was 0.93. This meta-analysis showed that ADC, Cho/Cr, and Cho/NAA ratios all had high sensitivity and specificity. Therefore, DWI combined with MRS can effectively improve the diagnosis of recurrent glioma and radiation injury.

1. Introduction

Glioma is the most common primary intracranial tumour, and it exhibits infiltrating growth. Therefore, it is often treated with surgical resection, supplemented with postoperative radiotherapy and targeted chemotheraphy [1]. Conventional postoperative radiotherapy kills tumour cells and inhibits tumour cell growth while causing brain tissue damage, leading to radiation injury. Clinically, radiation-induced brain injury has become one of the serious complications of radiotherapy. Approximately 20% of patients with glioma will have different degrees of radiation-induced brain injury after radiotherapy. The higher the radiation dose, the earlier the occurrence of radiation-induced brain injury and the more obvious the brain oedema and clinical symptoms [2]. Radiation injury can cause demyelination, degeneration, and even death of glial cells and can damage the blood–brain barrier, so it is difficult to determine whether a new enhanced lesion in the resected site or irradiated site is recurrent glioma or radiation injury by conventional imaging techniques [3, 4].

Diffusion-weighted imaging (DWI) visualizes anatomical structures by detecting the diffuse movement of water molecules and reflects the structural changes of a tissue at the cellular level. A hypointense signal on DWI indicates more diffuse movement of water molecules, apparent diffusion coefficient (ADC), which is the diffusion coefficient of water molecules in a voxel and a commonly used quantitative
2.2. Inclusion and Exclusion Criteria.

Inclusion criteria were as follows: (1) the subjects in the included studies were patients with definite diagnosis of glioma; (2) the diagnostic method in the literature was DWI combined with MRS; (3) the outcome measures of the study included (1) ADC, (2) Cho/Cr (metabolite Cho/(Cr/phosphocreatine)) ratio, (3) Cho/NAA (metabolite Cho/NAA) ratio, (4) the diagnostic efficacy of the Cho/Cr ratio, and the diagnostic efficacy of the Cho/NAA ratio; (4) the data in the literature were complete.

Exclusion criteria were as follows: (1) incomplete statistical results or incomplete relevant data; (2) repeated publications; (3) diagnostic methods other than DWI combined with MRS; and (4) conference papers, meta-analyses, and literature reviews.

2.3. Literature Screening and Data Extraction. Two researchers first independently screened the retrieved studies based on the inclusion and exclusion criteria and then cross-checked the studies. If they had controversial opinions on a paper, the paper was evaluated by a third researcher, and then all three of them would discuss it to reach a consensus. Two researchers extracted relevant data from the included studies, including first author(s), publication year, country of publication, sample size, ADC, the Cho/Cr ratio, the diagnostic efficacy of the Cho/NAA ratio, the Cho/Cr ratio, and the diagnostic efficacy of the Cho/NAA ratio.

2.4. Evaluation of Literature Quality. A quality assessment was conducted, adapting to this particular review the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. The QUADAS-2 format includes four domains: (1) patient selection; (2) index testing; (3) reference standard; and (4) flow and timing. For each domain, the risk of bias and concerns about applicability (the latter not applying to the domain of flow and timing) were analysed. The results of the quality assessment were used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to investigate potential sources of heterogeneity.

2.5. Statistical Methods. All the data were analysed in Stata 16.0. Measurement data are represented as the weighted mean difference (WMD), and the 95% confidence interval (CI) was used as the indicator of the effect size. Interstudy heterogeneity was determined by combining the chi-sq test and I² quantitative analysis. If P > 0.1 and I² < 50%, the interstudy heterogeneity was acceptable, and the fixed-effects model was used for meta-analysis; if P < 0.1 and I² > 50%, the interstudy heterogeneity was large, and the random-effects model was used for analysis [10].

3. Results

3.1. Flowchart of Literature Retrieval and Results. A total of 431 relevant original articles were identified in this meta-analysis. After carefully reading the titles and abstracts and screening the articles according to the inclusion and exclusion criteria, 32 articles were left. Then, after reading the whole articles, 11 available articles were included and all the research was retrospective studies (see Figure 1).
3.2. Methodological Quality of Included Studies. We extracted this data using a modified QUADAS-2 criteria proforma that focused on four domains of methodological quality: patient selection; index test; reference standard; and flow and timing. The domain with the highest level of risk for bias across all studies was that of patient selection (>50%) (Figure 2).

3.3. Basic Information and Quality Evaluation of the Included Articles. A total of 11 articles were included in this study, involving 320 patients [11–21]. The basic characteristics and quality evaluation of the included studies are given in Table 1.

3.4. Meta-Analysis of Relative ADC (rADC). The rADC of the included studies had a high degree of heterogeneity ($I^2 = 79.4\%$, $P < 0.001$). The random-effects model was used to combine the effect size. The Cho/Cr ratio was significantly elevated in the recurrent glioma group than in the radiation injury group (WMD = 0.65, 95% CI (0.40, 0.90), $P < 0.001$). The subgroup analysis based on ethnicity showed that the Cho/Cr ratio was significantly higher in the recurrent glioma group than in those radiation injury group (see Figure 3).

3.5. Meta-Analysis of the Cho/Cr Ratio. The Cho/Cr ratio of the included studies had moderate heterogeneity ($I^2 = 73.0\%$, $P < 0.001$). The random-effects model was used to combine the effect size. The Cho/Cr ratio was significantly elevated in the recurrent glioma group than in the radiation injury group (WMD = 0.80, 95% CI (0.39, 1.21), $P < 0.001$). Additionally, stratified analysis by ethnicity demonstrated that the abovementioned results could only be identified in East Asian groups (WMD = 0.92, 95% CI (0.46, 1.38), $P < 0.001$) but not in Caucasian populations (WMD = 0.44, 95% CI ($-0.44, 1.31$), $P < 0.001$) (Figure 5).

3.6. Meta-Analysis of the Cho/NAA Ratio. The Cho/NAA ratio of the included studies had high heterogeneity ($I^2 = 83.1\%$, $P < 0.001$). The random-effects model was used to combine the effect sizes. The results indicated that the Cho/NAA ratio was significantly increased in the recurrent glioma group than in the radiation injury group (WMD = 0.80, 95% CI (0.39, 1.21), $P < 0.001$). Additionally, stratified analysis by ethnicity demonstrated that the abovementioned results could only be identified in East Asian groups (WMD = 0.92, 95% CI (0.46, 1.38), $P < 0.001$) but not in Caucasian populations (WMD = 0.44, 95% CI ($-0.44, 1.31$), $P < 0.001$) (Figure 5).
### Table 1: Basic characteristics and quality evaluation of the included studies.

| Author                  | Year | Country | Ethnicity | Study design | Comparator imaging tests | N (radiation injury) | Outcome measures |
|-------------------------|------|---------|-----------|--------------|--------------------------|----------------------|------------------|
| Meng et al. [11]        | 2010 | China   | East Asian| Retrospective| DWI + MRS                | 12                   | 6                |
| Liu et al. [12]         | 2019 | China   | East Asian| Retrospective| DWI + MRS                | 15                   | 17               |
| Li et al. [13]          | 2015 | China   | East Asian| Retrospective| DWI + MRS                | 14                   | 16               |
| Liu and Zheng [14]      | 2016 | China   | East Asian| Retrospective| DWI + MRS                | 25                   | 15               |
| Zhang et al. [15]       | 2013 | China   | East Asian| Retrospective| DWI + MRS                | 12                   | 13               |
| Meng et al. [16]        | 2011 | China   | East Asian| Retrospective| DWI + MRS                | 15                   | 7                |
| Matsusue et al. [17]    | 2010 | USA     | Caucasian | Retrospective| DWI + MRS                | 10                   | 5                |
| Bobek-Billewicz et al. [18] | 2010 | Poland  | Caucasian | Retrospective| DWI + MRS                | 4                    | 4                |
| Zeng et al. [19]        | 2007 | China   | East Asian| Retrospective| DWI + MRS                | 32                   | 23               |
| Feng et al. [20]        | 2014 | Italy   | Caucasian | Retrospective| DWI + MRS                | 21                   | 8                |
| Di Costanzo et al. [21] | 2022 | China   | East Asian| Retrospective| DWI + MRS                | 31                   | 15               |

#### Figure 2: The risk of bias in the studies conducted was measured by using the QUADAS-2 tool.

#### Figure 3: Forest plot of the rADC of the radiation injury group and the recurrent glioma group detected by DWI combined with MRS.
The Cho/Cr ratio and Cho/NAA ratio had high accuracies in the differential diagnosis between recurrent glioma and radiation injury. The Fagan nomograms of the Cho/Cr ratio and Cho/NAA ratio showed that when the test result was positive, the probability of accurate detection increased from 20% (pretest probability) to 77% (post-test probability) (Figure 8). When the test result was negative, the probability of accurate detection decreased from 20% (pretest probability) to 5% (post-test probability), further indicating that the Cho/Cr ratio and Cho/NAA ratio can improve the identification efficiency of recurrent glioma and radiation injury.

3.8. Heterogeneity Test and Sensitivity Analysis. Significant heterogeneity between these studies was observed among the outcome measures (Figures 3–5). The results of our subgroup analysis confirmed that ethnicity was the primary sources of heterogeneity. Additionally, sensitivity analysis was conducted to evaluate the effect of an individual study on the pooled results. The pooled effects were not affected by removing any study.

3.9. Publication Bias. Because rADC, the Cho/Cr ratio, the Cho/NAA ratio, and other outcome measures were analysed using conventional meta-analytical methods, fewer than 10 included studies had rADC, the Cho/Cr ratio, or the Cho/NAA ratio. This meant the publication bias could not be effectively evaluated through the symmetry of the funnel plot, so it was evaluated using Egger’s test. The results showed no publication bias (P > 0.05) in rADC (P = 0.574), Cho/Cr ratio (P = 0.339), and Cho/NAA ratio (P = 0.47). The results of the Deeks funnel plots of the Cho/Cr ratio and Cho/NAA ratio did not show any publication bias in the diagnostic efficiency of the Cho/Cr ratio (P = 0.289) or in the diagnostic efficiency of the Cho/NAA ratio (P = 0.253).

4. Discussion

Glioma is characterized by diffuse growth and is the most refractory tumour with the highest recurrence rate [22, 23]. On the one hand, patients need postoperative radiotherapy to prolong their survival, but on the other hand, they must tolerate the tissue damage caused by radiotherapy. Conventional non-contrast-enhanced magnetic resonance imaging (MRI) and contrast-enhanced MRI are the most commonly used MRI techniques. However, both recurrent glioma and radiation injury show enhancement of the lesion area during enhanced MRI [4, 24] and thus are extremely difficult to differentially diagnose. In addition, the lesion area has a complex composition, with tumour cells and the radiation-damaged tissue coexisting or existing alone. The application of DWI combined with MRS in the diagnosis of
recurrent glioma and radiation injury can reduce the misdiagnosis rate, thereby providing clinicians with information with which to develop treatment plans.

The results of our meta-analysis showed that ADC was lower in the recurrent glioma group than in the radiation injury group. ADC can be used to quantitatively study the diffuse movement of intracellular water molecules. Tissues of recurrent tumors have a high cell density, relatively narrow intercellular space, restricted intracellular diffusion of water molecules, and low movement ability, resulting in a decrease in ADC [25, 26]. Tissues of radiation-induced lesions have a low cell density, an enlarged intercellular space, and active diffusion of water molecules due to necrosis and liquefaction of cells and degeneration and dissolution of myelin sheaths and axons in the lesions, leading to a high ADC value [27–29]. Although ADC had high heterogeneity, sensitivity analysis and subgroup analysis did not reveal the main cause of the heterogeneity, so ADC was relatively stable. Cells in recurrent glioma proliferate vigorously and have accelerated metabolism; their cell membranes and organelles are disintegrated to release free Cho; tumour cells show infiltrating growth; and nerve cells are destroyed. The MRS manifestations of recurrent glioma include decreased NAA peaks, differently increased Cho peaks, slightly decreased Cr, and increased Cho/Cr and Cho/NAA ratios [30, 31]. Radiation-induced brain injury is a complication of radiotherapy, which is related to the radiation dose, the size of the radiation field, the radiation frequency during the treatment process, and the survival time of the patient [32]. Radiation injury can lead to cell necrosis, inflammatory repair, neuronal damage, and reduced metabolism, which manifests as the diminution or disappearance of Cho and NAA peaks. When the brain tissue is permanently damaged, the MRS parameters are all low [33, 34]. Therefore, the Cho/Cr and Cho/NAA ratios were lower in radiation injury than in recurrent glioma. The sensitivity and specificity of the Cho/Cr and Cho/NAA ratios in the diagnosis of glioma recurrence were both moderate to high.
Figure 6: Summary ROC (SROC) curves of the diagnostic efficacy of the Cho/Cr ratio of the radiation injury group and the recurrent glioma group.

Figure 7: Summary ROC (SROC) curves of the diagnostic efficacy of the Cho/NAA ratio of the radiation injury group and the recurrent glioma group.
Data Availability

All data and codes are available upon request to the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors would like to thank all the authors that tried to provide us with additional data upon our request. This work was supported by the Shenyang Science and Technology Program Public Health R&D Special Project (22-321-32-02).

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