Value of magnetic resonance spectroscopy and perfusion-weighted imaging in distinguishing glioma recurrence from PTRE: a meta-analysis

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Abstract: Background and purpose: Nowadays, radiation therapy has become a gold standard treatment for gliomas, especially for high grade gliomas. Unfortunately, posttreatment radiation effect (PTRE) often mimics tumor recurrence, which causes a diagnostic challenge in clinical management. Since traditional magnetic resonance techniques were useless in distinguishing between glioma recurrence and PTRE, advanced magnetic resonance functional imaging methods, for instance magnetic resonance spectroscopy (MRS) and perfusion-weighted imaging (PWI), have been used to distinguish glioma recurrence from PTRE. However, the accuracy of MRS and PWI in distinguishing between glioma recurrence and PTRE is unclear. The purpose of this meta-analysis is to assess the diagnostic value of MRS and PWI in distinguishing glioma recurrence from PTRE. Methods: A comprehensive literature search was accomplished in three databases (PubMed, Web of Science and Embase). Eligible studies were performed in English, aimed to evaluate the performance of MRS, PWI in distinguishing glioma recurrence from PTRE. To assess the quality of included articles, we applied Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) in this meta-analysis. For each study, diagnostic values were extracted or calculated. Sensitivity (SEN), specificity (SPE), likelihood ratio (LR; positive LR/negative LR) and diagnostic odds ratio (DOR) were pooled by using the Stata 13.1 software. Results: 22 eligible articles and 687 patients were included in this meta-analysis. The pooled SEN, SPE, PLR, NLR and DOR for MRS and PWI were 0.92 (0.86-0.96), 0.87 (0.87-0.93), 6.87 (3.86-12.21), 0.09 (0.04-0.17), 48.48 (27.79-221.63) and 0.84 (0.79-0.88), 0.84 (0.79-0.88), 5.51 (3.98-6.89), 0.19 (0.14-0.24), 28.09 (17.63-44.75), respectively. Conclusions: In conclusion, our meta-analysis verified an overall moderate diagnostic performance of MRS and PWI for distinguishing between glioma recurrence and PTRE. Furthermore, both dynamic susceptibility contrast (DSC) perfusion imaging and dynamic contrast enhanced (DCE) perfusion imaging are promising methods in differentiating glioma recurrence from PTRE. In the future, well-designed clinical studies are needed to validate their applicability in differentiating these two lesions.

Keywords: Gliomas, PTRE, MRS, DSC, DCE, meta-analysis

Introduction

Gliomas are the most common type of primary intracranial tumors, represent nearly 31% of all brain and central nervous system (CNS) tumors and 81% of malignant brain and CNS tumors [1]. Despite the large number of potential treatments such as surgical, adjuvant chemotherapy and various forms of radiotherapy have been used, prognosis remains dismal. Glioblastoma (GBM), the most common and serious type of gliomas, suffer a desperate median survival of only 15-18 months [2]. Patients with tumor recurrence, which was widely recognized as a lethal consequence after systematic therapy, have a median survival of 3-6 months [3].

Posttreatment radiation effect (PTRE) is mainly caused by radiation therapy, a therapy which has been shown to be essential to glioma treatment [4]. PTRE can be divided into pseudoprogression (PsP) and radiation necrosis. The former is resulting in the transient interruption of oligodendrocytes myelin synthesis by radiation injury and often appears weeks to months after radiation therapy. On the other hand, radiation
necrosis appears months to years after radiation therapy. Hypoxia, necrosis and immune inflammatory response may be its pathological basis [5]. Both PsP and radiation necrosis share a benign biological behavior, which is dramatically opposite to glioma recurrence. Hence, an early diagnosis of PTRE would allow increased confidence to continue current therapeutic regimen and delay or avoid potentially unnecessary surgery. Unfortunately, it has become a dilemma for many clinicians to distinguish glioma recurrence from PTRE as the similar clinical symptoms including headache, seizures, personality changes and neurologic deficits [6]. Moreover, traditional magnetic resonance (MR) techniques cannot be used for reliable diagnosis because both lesions share the same appearance (increased contrast enhancement, mass effect and peripheral edema) [7]. According to a recent study performed by Shah et al., the sensitivity and specificity in detecting glioma recurrence by traditional MR is 88.9% and 33.4%, which means the inability of differential diagnosis [8]. Therefore, substantial researches have been concentrating on the identification of novel diagnostic techniques to differentiate glioma recurrence from PTRE.

Advanced magnetic resonance functional imaging methods, for instance magnetic resonance spectroscopy (MRS) and perfusion-weighted imaging (PWI), have been used to distinguish glioma recurrence from PTRE. Till now, many studies have confirmed the diagnostic value of these promising advanced MR techniques in differentiating glioma recurrence from PTRE. However, the accuracy of MRS and PWI to guide clinical decision making have not been widely accepted and further investigations involving large samples should be executed to verify their reliability. Therefore, this study aims to assess the value of MRS and PWI in distinguishing between glioma recurrence and PTRE through a synthesis of published clinical researches by meta-analysis.

Materials and methods

Search strategy

A comprehensive literature search was accomplished independently by two investigators in three common international electronic databases (PubMed, Web of Science and Embase) from January 2006 to November 2015. The following retrieval strategy was applied: ("gliomas" OR "glioblastoma" OR "GBM" OR "astrocytoma") AND ("radiation injury" OR "radiation necrosis" OR "pseudoprogression" OR "treatment effect" OR "radiation change" OR "post-treatment radiation effect" OR "PTRE") AND ("diagnosis" OR "sensitivity" OR "specificity" OR "ROC curve") AND ("dynamic susceptibility contrast" OR "dynamic contrast enhanced" OR "perfusion MR imaging" OR "perfusion weighted imaging" OR "magnetic resonance spectros-
Table 1. Characteristics and diagnostic results of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of patients</th>
<th>No. of lesions</th>
<th>Design</th>
<th>Mean age (range)</th>
<th>Imaging field strength</th>
<th>Techniques</th>
<th>Index</th>
<th>Cut-off</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
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<tbody>
<tr>
<td>Hamilton [13]</td>
<td>2015</td>
<td>24</td>
<td>24</td>
<td>R</td>
<td>51±9</td>
<td>3.0T</td>
<td>PWI (DCE)</td>
<td>iAUC</td>
<td>0.13</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Bulik [14]</td>
<td>2015</td>
<td>24</td>
<td>24</td>
<td>P</td>
<td>52.5 (29-66)</td>
<td>3.0T</td>
<td>MRS</td>
<td>K&lt;sub&gt;trans&lt;/sub&gt;</td>
<td>0.2</td>
<td>10</td>
<td>1</td>
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<td>Thomas [15]</td>
<td>2015</td>
<td>37</td>
<td>37</td>
<td>R</td>
<td>63 (37-87)</td>
<td>1.5 or 3.0T</td>
<td>PWI (DCE)</td>
<td>iAUC</td>
<td>3.7</td>
<td>19</td>
<td>2</td>
<td>9</td>
<td>5</td>
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<td>Yun [16]</td>
<td>2015</td>
<td>33</td>
<td>33</td>
<td>R</td>
<td>28-82</td>
<td>3.0T</td>
<td>PWI (DCE)</td>
<td>K&lt;sub&gt;trans&lt;/sub&gt;</td>
<td>0.07</td>
<td>14</td>
<td>4</td>
<td>12</td>
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<tr>
<td>Costanzo [17]</td>
<td>2014</td>
<td>29</td>
<td>29</td>
<td>P</td>
<td>62.5 (38-74)</td>
<td>3.0T</td>
<td>MRS</td>
<td>Cho/Cr</td>
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<td>13</td>
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<td>Alexiou [18]</td>
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<td>30</td>
<td>30</td>
<td>P</td>
<td>61.5±11.1</td>
<td>1.5T</td>
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<td>32</td>
<td>P</td>
<td>44 (23-65)</td>
<td>1.5T</td>
<td>MRS</td>
<td>NA</td>
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<td>0</td>
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<td>Young [20]</td>
<td>2013</td>
<td>20</td>
<td>20</td>
<td>R</td>
<td>58 (9-84)</td>
<td>1.5 or 3.0T</td>
<td>PWI (DSC)</td>
<td>iAUC</td>
<td>1.8</td>
<td>12</td>
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<td>57</td>
<td>R</td>
<td>49.9 (35-69)</td>
<td>3.0T</td>
<td>PWI (DCE)</td>
<td>mAUCR</td>
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<td>30</td>
<td>3</td>
<td>22</td>
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<td>Seeger [22]</td>
<td>2013</td>
<td>40</td>
<td>40</td>
<td>R</td>
<td>53.6±13.6</td>
<td>1.5T</td>
<td>MRS</td>
<td>Cho/Cr</td>
<td>1.07</td>
<td>14</td>
<td>3</td>
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<td>11</td>
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<tr>
<td>Suh [23]</td>
<td>2013</td>
<td>79</td>
<td>79</td>
<td>R</td>
<td>51.2 (25-69)</td>
<td>3.0T</td>
<td>PWI (DCE)</td>
<td>mAUCR</td>
<td>0.31</td>
<td>35</td>
<td>4</td>
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<tr>
<td>Fink [24]</td>
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<td>38</td>
<td>40</td>
<td>R</td>
<td>47.6 (28-70)</td>
<td>3.0T</td>
<td>MRS</td>
<td>Cho/Cr</td>
<td>1.05</td>
<td>22</td>
<td>1</td>
<td>1</td>
<td>5</td>
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<td>18</td>
<td>19</td>
<td>P</td>
<td>NA</td>
<td>3.0T</td>
<td>PWI (DCE)</td>
<td>K&lt;sub&gt;trans&lt;/sub&gt;</td>
<td>0.19</td>
<td>13</td>
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<td>Xu [26]</td>
<td>2011</td>
<td>35</td>
<td>35</td>
<td>P</td>
<td>45.2 (21-65)</td>
<td>3.0T</td>
<td>PWI (DCE)</td>
<td>rCBV</td>
<td>2.15</td>
<td>16</td>
<td>3</td>
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<td>Matsusue [27]</td>
<td>2010</td>
<td>15</td>
<td>15</td>
<td>R</td>
<td>46.9 (30-64)</td>
<td>3.0T</td>
<td>MRS</td>
<td>Cho/Cr</td>
<td>1.30</td>
<td>9</td>
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<td>R</td>
<td>46.1</td>
<td>1.5 or 3.0T</td>
<td>PWI (DCE)</td>
<td>rCBV</td>
<td>3.69</td>
<td>4</td>
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<td>Ozsunar [29]</td>
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<td>R</td>
<td>42 (20-69)</td>
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<td>PWI (DCE)</td>
<td>rCBV</td>
<td>1.30</td>
<td>19</td>
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<td>Nakajima [30]</td>
<td>2009</td>
<td>16</td>
<td>16</td>
<td>R</td>
<td>45 (14-67)</td>
<td>1.5T</td>
<td>MRS</td>
<td>Cho/Cr</td>
<td>2.50</td>
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<td>Barajas [31]</td>
<td>2009</td>
<td>57</td>
<td>66</td>
<td>R</td>
<td>54.2±10.2</td>
<td>1.5T</td>
<td>PWI (DSC)</td>
<td>rCBV</td>
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<td>Hu [32]</td>
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<td>NA</td>
<td>3.0T</td>
<td>PWI (DCE)</td>
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<td>MRS</td>
<td>Cho/Cr</td>
<td>1.71</td>
<td>16</td>
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<td>Palumbo [34]</td>
<td>2006</td>
<td>30</td>
<td>30</td>
<td>R</td>
<td>53.47 (25-76)</td>
<td>1.5T</td>
<td>MRS</td>
<td>NA</td>
<td>18</td>
<td>2</td>
<td>10</td>
<td></td>
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</table>

NA, not available; P, prospective; R, retrospective; dsAUC, delayed short area under the signal intensity-time curve; v<sub>trans</sub>, vascular plasma volume fraction; K<sub>trans</sub>, endothelial transfer constant; v<sub>p</sub>, extravascular; Cho, choline; NAA, N-acetylaspartylglutamate; Cr, creatine; rCBV, relative cerebral blood volume; rPH, relative peak height; PSR, percent signal recovery; mAUCR, mean value at the higher curve of the bimodal histogram; iAUC, initial area under the signal intensity-time curve.

Copy” OR “MR spectroscopy” OR “MRS”). Articles were limited to English, and humans were defined as the subjects for these studies. To achieve additional studies, reference lists of review papers and other relevant articles were searched independently.

**Inclusion and exclusion criteria**

Studies were brought into this meta-analysis according to the following selection criteria: (a) patients were diagnosed as gliomas by histopathology, and has a history of treatment with radiotherapy; (b) diagnostic imaging was performed by MRS or PWI; (c) histological confirmation and/or follow-up by MR imaging were used as the gold standard; (d) the diagnostic results of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) were available; (e) each individual study involved two treatment groups, namely, the glioma recurrence and PTRE.
We included both retrospective and prospective studies, while case series (<10 patients), case control studies, conferences, unpublished data, reviews, letters, editorials and comments were excluded.

Data extraction and quality assessment

Data were independently refined by two reviewers (YCL and XC) from the relevant studies. Inconsistencies were re-reviewed and disagreements were resolved by a third reviewer (YHS) who assessed all of the included items. Data collected included the followings: (a) study characteristics (first author, publication year, number of patients, mean age, design method, imaging field strength, techniques and index); (b) diagnostic results (TP, FP, FN and TN).

The quality assessment of studies eligible for this meta-analysis were evaluated by Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2), which is recognized as a reliable tool for the quality assessment to test diagnostic studies [9].

Statistical analysis

All statistical analyses were performed using Stata 13.1 and metadisc 1.4. P<0.05 indicated statistical significance. The between-study heterogeneity was assessed by Q test and I² statistics. P<0.05 or I²>50% suggested significant heterogeneity. If significant heterogeneities were identified, the test performance was summarized applying a random-effects model; otherwise a fixed-effects model was applied [10]. The sensitivity (SEN), specificity (SPE), likelihood ratio (LR; positive LR/negative LR), diagnostic odds ratio (DOR) and their 95% confidence intervals (CIs) were pooled from the original data. The overall diagnostic accuracy of included studies was assessed by areas under summary receiver operating characteristic curve (SROC). The Spearman correlation coefficient was used to evaluate the threshold effect [11]. Finally, Deeks’ funnel plot asymmetry test was used to investigate publication bias, with P<0.10 indicating the existence of significant publication bias [12].

Results

Literature search

The systematic search initially yielded a total of 333 results, 186 of which were removed as duplicated publications. 95 results were excluded after reviewing the titles and abstracts because of the irrelevance. With 52 articles obtained for full-text review, 22 were included according to the inclusion criteria. The main reasons for exclusion were as follows: (1) can’t extract data to create 2×2 table; (2) same author’s similar studies in short period; (3) less than 10 patients included. The flow diagram of article selection is presented in Figure 1.

Study characteristics and quality assessment

In the 22 studies included for this meta-analysis, a total of 687 glioma patients were included. The main characteristics and diagnostic results of 22 studies were summarized in Table 1. Among all the studies included, 5 studies (23%) focused on the diagnostic value of MRS, 13 studies (59%) investigated the diagnostic value of PWI and 4 studies (18%) pointed at both. All the included articles in this meta-analysis met at least 4 items in QUADAS-2, which indicated an overall high quality of involved articles. Results of quality assessment according to the QUADAS-2 tool for the 22 articles were summarized in Figure 2.
Distinguishing glioma recurrence from PTRE by MRS and PWI

Figure 3. The pooled sensitivity and specificity of MRS and PWI for differentiate glioma recurrence from PTRE. A. Forest plots of sensitivity for MRS; B. Forest plots of specificity for MRS; C. Forest plots of sensitivity for PWI; D. Forest plots of specificity for PWI.
Threshold effect

Spearman correlation coefficient was evaluated to be -0.181 (P=0.574) and -0.230 (P=0.259) for MRS and PWI respectively, indicating the absence of the threshold effect in our meta-analysis.

Overall analysis

Notable heterogeneities were absent in both sensitivity and specificity data ($I^2=48.97\%$ and $P=0.00\%$, respectively) in MRS studies. Similarly, as for studies on PWI, no substantial heterogeneities were observed in sensitivity and specificity data ($I^2=32.25\%$ and $I^2=0.00\%$, respectively). So the fixed-effects model was used for our meta-analysis. The pooled values for studies on MRS were SEN 0.92 (0.86-0.96), SPE 0.87 (0.87-0.93), PLR 6.87 (3.86-12.21), NLR 0.09 (0.04-0.17), DOR 48.48 (27.79-221.63) and area under curve (AUC) 0.93 (0.91-0.95). The pooled values for studies on
PWI were SEN 0.84 (0.80-0.88), SPE 0.84 (0.79-0.88), PLR 5.51 (3.98-6.89), NLR 0.19 (0.14-0.24), DOR 28.09 (17.63-44.75) and AUC 0.90 (0.87-0.93). Forest plots of sensitivity and specificity are shown in Figure 3. SROC curve is shown in Figure 6.

Sub-group analysis

Subgroup analysis for MRS was conducted according to two major imaging interpretations: choline/N-acetylaspartylglutamate (Cho/NAA) and choline/creatine (Cho/Cr). The pooled SEN, SPE and AUC of Cho/NAA were 0.96 (0.87-0.99), 0.87 (0.68-0.96) and 0.97 (0.95-0.98). The pooled SEN, SPE and AUC of Cho/Cr were 0.87 (0.75-0.94), 0.82 (0.68-0.91) and 0.90 (0.87-0.92). SROC curve for Cho/Cr and Cho/NAA is shown in Figure 5.

On the other hand, subgroup analysis for PWI was based on two type of sequences applied in PWI: dynamic susceptibility contrast (DSC) perfusion imaging and dynamic contrast enhanced (DCE) perfusion imaging. The pooled SEN, SPE and AUC of DSC perfusion imaging were 0.86...
Distinguishing glioma recurrence from PTRE by MRS and PWI

(0.81-0.90), 0.85 (0.76-0.91) and 0.92 (0.90-0.94). The pooled SEN, SPE and AUC of DCE perfusion imaging were 0.82 (0.75-0.87), 0.83 (0.76-0.88) and 0.88 (0.84-0.90). SROC curve is shown in Figure 6.

Publication bias

Deeks’ funnel plots asymmetry test was conducted to investigate the potential publication bias of included studies in this meta-analysis. P-value of MRS and PWI was 0.598 and 0.722 respectively, which suggested the absence of publication bias. The Funnel plots were shown in Figure 7.

Discussion

Since the therapeutic effect of postoperative radiation treatment was first demonstrated in a randomized trial in the 1970s, radiation therapy has become a gold standard treatment for gliomas, especially for high grade gliomas [35]. According to a latest study, not only progression-free survival was prolonged but also health-related quality of life was improved in newly diagnosed GBM under adjuvant temozolomide combined with radiotherapy after surgery [36]. However, PTRE, the main side effect after cranial radiotherapy, often mimic tumor recurrence, which causes a diagnostic challenge in clinical management. The incidence of PTRE depends on dose, volume and location of irradiation [37]. What’s more, treatments with antiangiogenic targeted therapies such as bevacizumab and temozolomide also increase the risk of PTRE [38]. Chamberlain et al. reported that in GBM patients treated with chemo-radiotherapy, incidence of PTRE approached nearly 14% [39]. With antithetical treatments required, the distinction between PTRE and glioma recurrence should be evaluated correctly and timely. Therefore, an accurate, noninvasive diagnostic technique is required since traditional strategies such as conventional MRI were useless in distinguishing between glioma recurrence and PTRE.

Advanced MRI is a series of powerful imaging techniques evolved from traditional MRI. By providing a much deeper insight into metabolic composition, vascularity and many other valuable information, advanced MRI is playing a significant role in glioma diagnosis [40]. MRS, one of the earliest techniques of advanced MRI, provides information about proliferation, energy homoeostasis and necrosis through detecting metabolic compositions such as Cho, NAA and Cr [41]. Gliomas, especially high grade gliomas show a significant elevation in Cho [42], while low Cho is more consistent with PTRE [43]. As a result, relative value of Cho/NAA and Cho/Cr may have a promising diagnostic potential to differentiate these two entities. In this meta-analysis, 9 studies and 252 glioma patients detected by MRS were included according to the inclusion criteria. The sensitivity and specificity yielded weighted averages of 0.92 and 0.87 respectively. MRS technique displayed a moderate test performance with an AUC of 0.93 when differentiating between glioma recurrence and PTRE. The mean cut-off value of Cho/NAA and Cho/Cr to detect glioma recurrence from PTRE was 1.12 (range: 1.05-1.71) and 1.56 (range: 1.07-2.50) respectively. According to sub-group analysis, Cho/NAA determined to be a more reliable text index with an AUC of 97%. Apart from these two most common used metabolite ratios, Bulik et al. reported lactate + lipid containing compounds/creatinine (Lac + Lip/Cr) ratio as a new statistically significant parameter with a cut-off value of 1.9 (sensitivity 0.92, specificity 0.75) to distinguish between GBM relapse and PsP [14]. Another type of parameter also be used is normalized ratios. However, Elias et al. documented that among the normalized metabolite ratios, Cho/nNAA was the only one to yield significant values with a relatively low diagnostic accuracy (sensitivity 0.73, specificity 0.40) [44]. These data indicated that unnormalized ratios had better discriminating ability than their corresponding normalized ratios.

Another type of advanced MRI widely used is PWI. This Developing technique using DSC perfusion imaging and DCE perfusion imaging provides information about vascular microenvironment. High levels of proangiogenic cytokines expression and microvascular formation are closely related to glioma invasion, proliferation and also recurrence. Thus, detecting parameters about hemodynamic may have great value in the diagnosis of glioma recurrence from PTRE [45]. In this meta-analysis, 17 studies and 565 glioma patients detected by PWI were included according to the inclusion criteria. An AUC of 0.90 showed that PWI may be a promising technique to discriminate glioma recurrence
Distinguishing glioma recurrence from PTRE by MRS and PWI

from PTRE with a pooled sensitivity of 0.84 and specificity of 0.84.

T2 and/or T2* weighted DSC perfusion imaging have been substantially applied in clinical practice to differentiate gliomas from brain metastasis, high grade gliomas from low grade gliomas and also glioma recurrence from PTRE. According to Barajas’s study, both relative cerebral blood volume (rCBV) and relative peak height (rPH) were significantly higher while percentage of signal intensity recovery (PSR) was lower in patients with recurrent GBM than in patients with radiation necrosis [31]. As a result, rCBV/PSR or rPH/PSR may have a better index to discriminate glioma recurrence from PTRE. However, diagnostic accuracy of DSC perfusion imaging is less reliable due to blood-brain barrier (BBB) disruption and contrast leakage effects. To solve this problem, preload dosing (PLD) and baseline subtraction (BLS) techniques have been used. Hu et al. have demonstrated that with combination of PLD (0.1-mmol/kg amount, 6-minute incubation time) and BLS correction methods, diagnostic value of rCBV (AUC, 0.99) was much higher compared with uncorrected rCBV (AUC, 0.85) [46]. On the other hand, the recent emergence of T1 weighted DCE perfusion imaging have shown great value in distinguishing glioma recurrence from PTRE since firstly reported by Bisdas et al. at 2011. With better estimations of hemodynamic status and less interference from sources of susceptibility, DCE perfusion imaging is becoming more and more attractive. DCE perfusion imaging highlights on hemodynamic parameters such as endothelial transfer constant (Ktrans), vascular plasma volume fraction (v\text{p}) and area under the signal intensity-time curve (AUC). Based on sub-group analysis, both DSC and DCE perfusion imaging applied in PWI had a moderate test performance with an AUC of 0.92 and 0.88 respectively.

Although these methods have been extensively studied to differentiate between glioma recurrence and PTRE, there are still many issues to be solved. First of all, there is no consensus about which technique(s), which parameter(s) and/or which threshold level(s) ensure the better discrimination accuracy. Second, as gliomas is a kind of heterogeneity disease. The diagnostic performance may differ from various types and grades. According to Kong’s study, value of DSC perfusion MR imaging in detecting glioma recurrence with PTRE is associate with methylation of O6-methylguanine-DNA methyltransferase (MGMT) gene promoter [47]. Third, the ability to detect early glioma recurrence is critical to responding timely with a change of treatment strategy in this deadly progressive tumor. Forth, one issue can’t be overlooked is that glioma recurrence and PTRE are rarely an all-or-nothing phenomenon but frequently coexist. Reddy et al. demonstrated that the spectra of both recurrent glioma and necrosis ranges from 0 to 100%, with most reoperation specimens comprising a mixture of both [48]. To what extent can we identify a lesion as true glioma recurrence or complete PTRE is the key point on both diagnosis and treatment afterwards.

In terms of this meta-analysis, some potential limitation exists. First, the included studies were mostly retrospective with small sample size, which is a remarkable problem in diagnostic studies [49]. Second, Various types and grades of gliomas were involved in this meta-analysis. Third, relative studies available in this meta-analysis using both histopathology and follow-up MRI as the “gold standard”. Fourth, the imaging equipments and cut-off values used in the included studies varies. All these inherent shortcomings lead to low level of evidences.

In conclusion, a limited number of studies included in our meta-analysis indicated an overall moderate diagnose performance of MRS and PWI for distinguishing between glioma recurrence and PTRE. Furthermore, both dynamic susceptibility contrast (DSC) perfusion imaging and dynamic contrast enhanced (DCE) perfusion imaging are promising methods in differentiating these two lesions. In the future, well-designed prospective studies comparing the available imaging techniques and using histopathology as the “gold standard” reference test are needed to validate their potential applicability in differentiating between glioma recurrence and PTRE.

Disclosure of conflict of interest

None.

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Distinguishing glioma recurrence from PTRE by MRS and PWI

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References


[19] Mohamed Fouad Sherif FMS, Magdy A. Almahallawy, Ahmad Mohamed Abd Algawad and


