European Journal of Radiology 83 (2014) 2181–2189

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

Role of magnetic resonance spectroscopy for the differentiation of recurrent glioma from radiation necrosis: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 6 May 2014
Accepted 29 September 2014

Keywords:
Magnetic resonance spectroscopy
Glioma recurrence
Radiation necrosis
Systematic review
Meta-analysis

ABSTRACT

Purpose: Differentiating glioma recurrence from radiation necrosis remains a great challenge. We conducted a meta-analysis to evaluate the diagnostic quality of magnetic resonance spectroscopy (MRS) in differentiating glioma recurrence from radiation necrosis.
Methods: Studies about evaluation of MRS for the differential diagnosis of glioma recurrence from radiation necrosis were systematically searched in PubMed, Embase and Chinese Biomedical databases up to May 4, 2014. The data were extracted to perform heterogeneity test, threshold effect test and to calculate sensitivity (SEN), specificity (SPE) and areas under summary receiver operating characteristic curve (SROC).
Results: Eighteen articles comprising a total sample size of 455 patients (447 lesions) with suspected glioma recurrence after radiotherapy, met all inclusion and exclusion criteria, and were included in our meta-analysis. Quantitative synthesis of studies showed that the pooled SEN and SPE for Cho/Cr ratio were 0.83 (95% CI: 0.77, 0.89) and 0.83 (95% CI: 0.74, 0.90). The area under the curve (AUC) under the SROC was 0.9001. The pooled SEN and SPE for Cho/NAA ratio were 0.88 (95% CI: 0.81, 0.93) and 0.86 (95% CI: 0.76, 0.93). The AUC under the SROC was 0.9185.
Conclusion: This meta-analysis shows that MRS alone has moderate diagnostic performance in differentiating glioma recurrence from radiation necrosis using metabolite ratios like Cho/Cr and Cho/NAA ratio. It is strongly recommended that MRS should combine other advanced imaging technologies to improve diagnostic accuracy. This article underlines the importance of implementing multimodal imaging trials and multicentre trials in the future.

1. Introduction

Differentiating glioma recurrence from radiation necrosis remains a great challenge. The two entities have totally different prognosis, however often share the same symptoms and the same features in conventional morphologic imaging like computerized tomography (CT) and magnetic resonance imaging (MRI) [1]. To solve the problem, numerous innovative imaging technologies focusing on metabolism or blood flow have been introduced, like positron-emission tomography (PET) with different tracers, single photon emission computed tomography (SPECT), and some advanced MRI techniques (diffusion-weighted imaging [DWI], dynamic susceptibility contrast-enhanced perfusion imaging, and magnetic resonance spectroscopy [MRS], etc.) [1–4]. They are believed to contribute a lot to the distinction and the clinical decision-making in the absence of histopathologic confirmation. Some of them are very promising with high sensitivity (SEN) and specificity (SPE). However, MRS might be the most suited noninvasive tool when a new enhancing lesion is first identified since it is an adjunct to MRI and it only requires the imaging time is extended for 15–30 min [5].

Abbreviations: AUC, area under the curve; Cho, choline; CI, confidence intervals; Cr, creatine; CT, computerized tomography; DOR, diagnostic odds ratio; DWI, diffusion-weighted imaging; FN, false negative; FP, false positive; I^2, inconsistency index; Lac, lactate; LR+, positive likelihood ratio; LR−, negative likelihood ratio; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MVS, multi-voxel spectroscopy; NAA, N-acetyl-aspartate; nCr, normalized creatine; PET, positron-emission tomography; QUADAS-2, Quality Assessment Tool for Diagnostic Accuracy Studies version 2; SEN, sensitivity; SPE, specificity; SPECT, single photon emission computed tomography; SROC, summary receiver-operating characteristic curve; SVS, single-voxel spectroscopy; TN, true negative; TP, true positive.

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http://dx.doi.org/10.1016/j.ejrad.2014.09.018
0720-048X/

MRS provides information about metabolic tissue composition, advanced spectroscopic methods have been used to quantify markers of tumor metabolism (e.g. glucose), membrane turnover and proliferation (e.g. choline [Cho]), energy homoeostasis (e.g. creatine [Cr]), intact glioneural structures (e.g. N-acetyl-aspartate [NAA]), and necrosis (e.g. lactate [Lac] or lipids) [5]. Results are usually expressed as ratios between cerebral metabolites, rather than absolute concentrations. Numerous studies have evaluated the diagnostic role of MRS for distinguishing glioma recurrence from radiation necrosis. However, the sample size in each study is relatively small, which may compromise the credibility of results. Thus, we performed the present meta-analysis to evaluate the diagnostic accuracy of MRS for differentiating recurrent glioma from radiation necrosis.

2. Materials and methods

2.1. Search strategy

A comprehensive computer literature search of the PubMed, Embase and Chinese Biomedical databases was conducted to find relevant published articles (up to May 4, 2014). The search terms were as follows: ("Magnetic resonance spectroscopy" or "MR spectroscopy" or "MRS") AND (glioma or brain neoplasm) AND recurrence. The equivalent Chinese terms were used in the Chinese databases. Additionally, the reference lists of all retrieved articles were checked for other eligible reports that have not been identified as aforementioned.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) MRS was used to differentiate glioma recurrence from radiation necrosis; (2) the diagnostic criteria of glioma recurrence or radiation necrosis were clearly stated; (3) at least one single metabolite ratio was reported; (4) values of true positive (TP), false positive (FP), false negative (FN), true negative (TN), SEN, SPE, positive likelihood ratio (LR+) and negative likelihood ratio (LR−) could be calculated from the data reported; (5) at least eight patients were included; (6) pathological analysis and/or clinical follow-up were used as the reference standard; (7) no overlapping data, if studies had the same or overlapping data, only the largest study should be included in the final analysis; and (8) only English and Chinese language publications included. Studies were excluded based on the following criteria: animal studies, abstracts, reviews, case report, letters, editorials, comments and conference proceedings.

Two authors (H. Zhang and Q. Wang) evaluated potentially relevant articles independently using the inclusion criteria and exclusion criteria. If these two authors could not reach a consensus, disagreements were discussed and resolved by a third author (B.N. Xu).

2.3. Data extraction and quality assessment

The final articles were assessed independently by the same two authors (L. Ma and C. Wu). For each included study basal characteristics (authors, year of publication, and country of origin), patient characteristics (mean age, sex, number, type of glioma, and type of radiotherapy) and technical aspects (imaging field strength, techniques of spectrum acquisition, metabolite ratios, cut-off value, and reference standard) were noted. The numbers of TP, FP, FN and TN results were recorded. The methodological quality of the studies was assessed using Quality Assessment Tool for Diagnostic Accuracy Studies version 2 (QUADAS-2) [6]. This revised tool is a considerable improvement over the original one as it allows for more transparent rating of bias and applicability of primary diagnostic accuracy studies.

Disagreements were discussed among the authors until a consensus was reached.

2.4. Statistical analysis

Standard methods recommended for diagnostic accuracy meta-analysis were used [7,8].

First, we needed to evaluate the heterogeneity between each study that was caused by threshold effect. The Spearman correlation coefficient between the logit of SEN and the logit of (1− SPE) was computed to assess the threshold effect. A strong positive correlation would suggest a threshold effect with $P < 0.05$.

Furthermore, we conducted heterogeneity analysis in each study to assess the extent of heterogeneity by using the chi-squared value test and the inconsistency index (I^2) of the diagnostic odds ratio (DOR). In brief, if $P < 0.1$ or $I^2 > 50\%$, significant heterogeneity was considered to exist. Existence of significant heterogeneities required using a random-effects coefficient binary regression model when the test performance was summarized; otherwise, a fixed-effects coefficient binary regression model was used [9,10].

Pooled SEN, SPE, LR+, LR−, and diagnostic odds ratios (DOR) with their 95% confidence intervals (CIs) were calculated in each study. A value of 0.5 was added to all cells of studies that contained a count of zero to avoid potential problems in odds calculations for studies with SENs or SPEs of 100%. The summary receiver-operating characteristic curve (SROC), area under the curve (AUC) and Q^* index (Q^* index is the point on the SROC at which SEN and SPE are equal and is the best statistical method assessing diagnostic performance) were calculated. AUC values less than 0.50 indicated that the diagnostic test was meaningless. AUC values ranging from 0.51 to 0.70 meant that the diagnostic accuracy was lower. AUC values from 0.71 to 0.90 represented moderate diagnostic accuracy. AUC more than 0.90 illustrated high diagnostic accuracy that was closer to the higher accuracy of diagnostic tests for the top left corner of the coordinate axes.

Subgroup analysis was performed when some homogenous set of studies adopted similar design variables. Subgroups were constructed only when ≥3 studies could be included. Tests of interaction were performed to assess differences between subgroups [11]. The above mentioned statistical analyses were performed using Meta-DiSc statistical software version 1.4 [8].

Publication bias was assessed visually by using a scatter plot of the inverse of the square root of the effective sample size ($ESS^{1/2}$) versus the diagnostic log odds ratio. The scatter plot would have a symmetric funnel shape if publication bias was absent. Formal testing for publication bias was conducted by using a regression of the diagnostic log odds ratio against $ESS^{1/2}$ and weighting according to the effective sample size, with $P < 0.1$ indicating significant asymmetry [12]. This statistical analysis was performed using Stata 12.0 (StataCorp LP, College Station, TX).

3. Results

3.1. Study selection and characteristics

The study selection process is detailed in Fig. 1. Eighteen articles [13–30] comprising a total sample size of 455 patients (447 lesions) with suspected glioma recurrence after radiotherapy, met all inclusion and exclusion criteria, and were included in our meta-analysis. The characteristics of the included studies are presented in Table 1.

Fifteen studies were retrospective cohort studies, and only three were prospective cohort studies. The sample size in each study was