Int J Clin Exp Med 2016;9(6):10006-10017
www.ijcem.com /ISSN:1940-5901/IJCEM0021284

Original Article

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

Yuheng Shan[1,2], Xian Chen[1*], Yanchen Lin[1,2*], Yuliang Wang[2], Shijiang Zhong[1], Yanhua Gong[2]

[1]Department of Neurology, Logistic University Affiliated Hospital, Logistic University of Chinese People's Armed Police Force, Tianjin, P. R. China; [2]Department of Biochemistry and Molecular Biology, Logistic University of The Chinese People's Armed Police Force, Tianjin, P. R. China. [*]Equal contributors.

Received December 6, 2015; Accepted April 1, 2016; Epub June 15, 2016; Published June 30, 2016

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 (0.80-0.88), 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

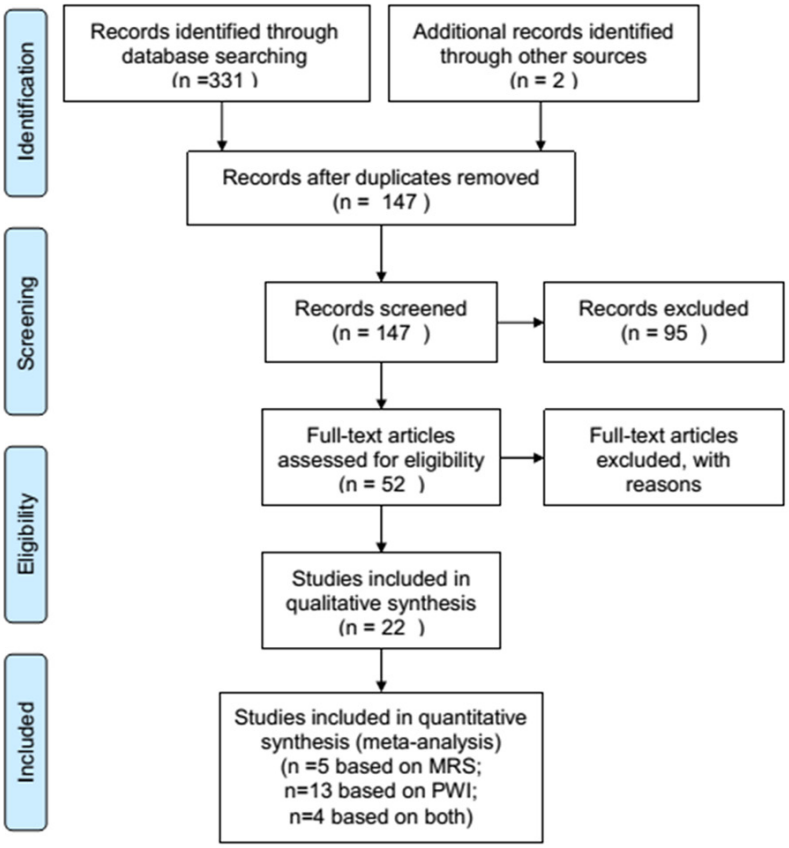

Figure 1. The selection flow diagram of eligible articles.

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

Author	Year	No. of patients	No. of lesions	Design	Mean age (range)	Imaging field strength	Techniques	Index	Cut-off	TP	FP	FN	TN
Hamilton [13]	2015	24	24	R	51±9	3.0T	PWI (DCE)	dsAUC	0.2	14	2	1	7
								V_p	2	10	1	4	8
								K^{trans}	0.2	12	2	3	7
Bulik [14]	2015	24	24	P	52.5 (29-66)	3.0T	MRS	Cho/NAA	1.4	18	1	0	5
Thomas [15]	2015	37	37	R	63 (37-87)	1.5 or 3.0T	PWI (DCE)	V_p	3.7	19	2	5	11
								K^{trans}	3.6	19	4	5	9
Yun [16]	2015	33	33	R	28-82	3.0T	PWI (DCE)	K^{trans}	0.070	14	4	3	12
								v_e	0.182	13	2	4	14
Costanzo [17]	2014	29	29	P	62.5 (38-74)	3.0T	MRS	Cho/Cr	NA	17	2	4	6
							PWI (DSC)	rCBV	NA	18	1	3	7
Alexiou [18]	2014	30	30	P	61.5±11.1	1.5T	PWI (DSC)	rCBV	2.2	24	0	0	6
Sherif [19]	2014	32	32	P	44 (23-65)	1.5T	MRS	NA	NA	24	1	0	7
Young [20]	2013	20	20	R	58 (9-84)	1.5 or 3.0T	PWI (DSC)	rCBV	1.8	12	0	4	4
								rPH	1.7	16	0	0	4
								PSR	0.9	10	0	6	4
Chung [21]	2013	57	57	R	49.9 (35-69)	3.0T	PWI (DCE)	$mAUCR_H$	0.23	30	3	2	22
Seeger [22]	2013	40	40	R	53.6±13.6	1.5T	MRS	Cho/Cr	1.07	14	3	6	11
							PWI (DSC)	rCBV	2.15	17	4	4	13
							PWI (DCE)	K^{trans}	0.058	13	3	8	12
Suh [23]	2013	79	79	R	51.2 (25-69)	3.0T	PWI (DCE)	$mAUCR_H$	0.31	35	4	7	33
Fink [24]	2012	38	40	R	47.6 (28-70)	3.0T	MRS	Cho/NAA	1.05	22	1	1	5
								Cho/Cr	1.54	21	1	2	5
							PWI (DSC)	rCBV	2.08	25	1	4	9
Bisdas [25]	2011	18	19	P	NA	3.0T	PWI (DCE)	K^{trans}	0.19	13	1	0	5
								iAUC	15.35	5	2	2	5
Xu [26]	2011	35	35	P	45.2 (21-65)	3.0T	PWI (DSC)	rCBV	2.15	16	3	4	12
Matsusue [27]	2010	15	15	R	46.9 (30-64)	3.0T	MRS	Cho/NAA	1.30	9	1	1	2
								Cho/Cr	1.29	10	1	0	2
							PWI (DSC)	rCBV	2.10	9	1	1	4
Kim [28]	2010	10	10	R	46.1	1.5 or 3.0T	PWI (DSC)	rCBV	3.69	4	0	0	6
Ozsunar [29]	2009	30	35	R	42 (20-69)	1.5T	PWI (DSC)	rCBV	1.30	19	3	3	7
Nakajima [30]	2009	16	16	R	45 (14-67)	1.5T	MRS	Cho/Cr	2.50	6	2	1	7
Barajas [31]	2009	57	66	R	54.2±10.2	1.5T	PWI (DSC)	rCBV	1.75	34	6	7	14
								rPH	1.38	41	3	5	13
								PSR	0.873	36	4	10	13
Hu [32]	2008	13	40	P	NA	3.0T	PWI (DSC)	rCBV	0.71	22	0	2	16
Zeng [33]	2007	28	28	R	40.25 (23-65)	3.0T	MRS	Cho/NAA	1.71	16	0	1	9
								Cho/Cr	1.41	16	0	1	9
Palumbo [34]	2006	30	30	R	53.47 (25-76)	1.5T	MRS	NA	NA	18	0	2	10

NA, not available; P, prospective; R, retrospective; dsAUC, delayed short area under the signal intensity-time curve; v_p, vascular plasma volume fraction; K^{trans}, endothelial transfer constant; v_e, extravascular; Cho, choline; NAA, N-acetylaspartylglutamate; Cr, creatine; rCBV, relative cerebral blood volume; rPH, relative peak height; PSR, percent signal recovery; $mAUCR_H$, 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 in 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.

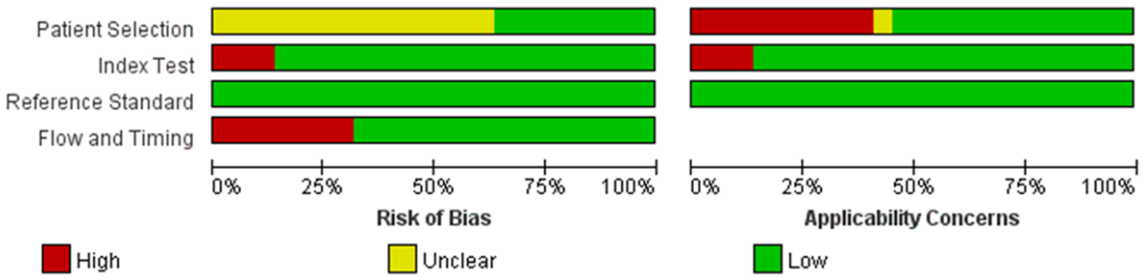

Figure 2. Risk of bias and applicability concerns graph of eligible articles.

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 I^2 statistics. P<0.05 or I^2>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**.

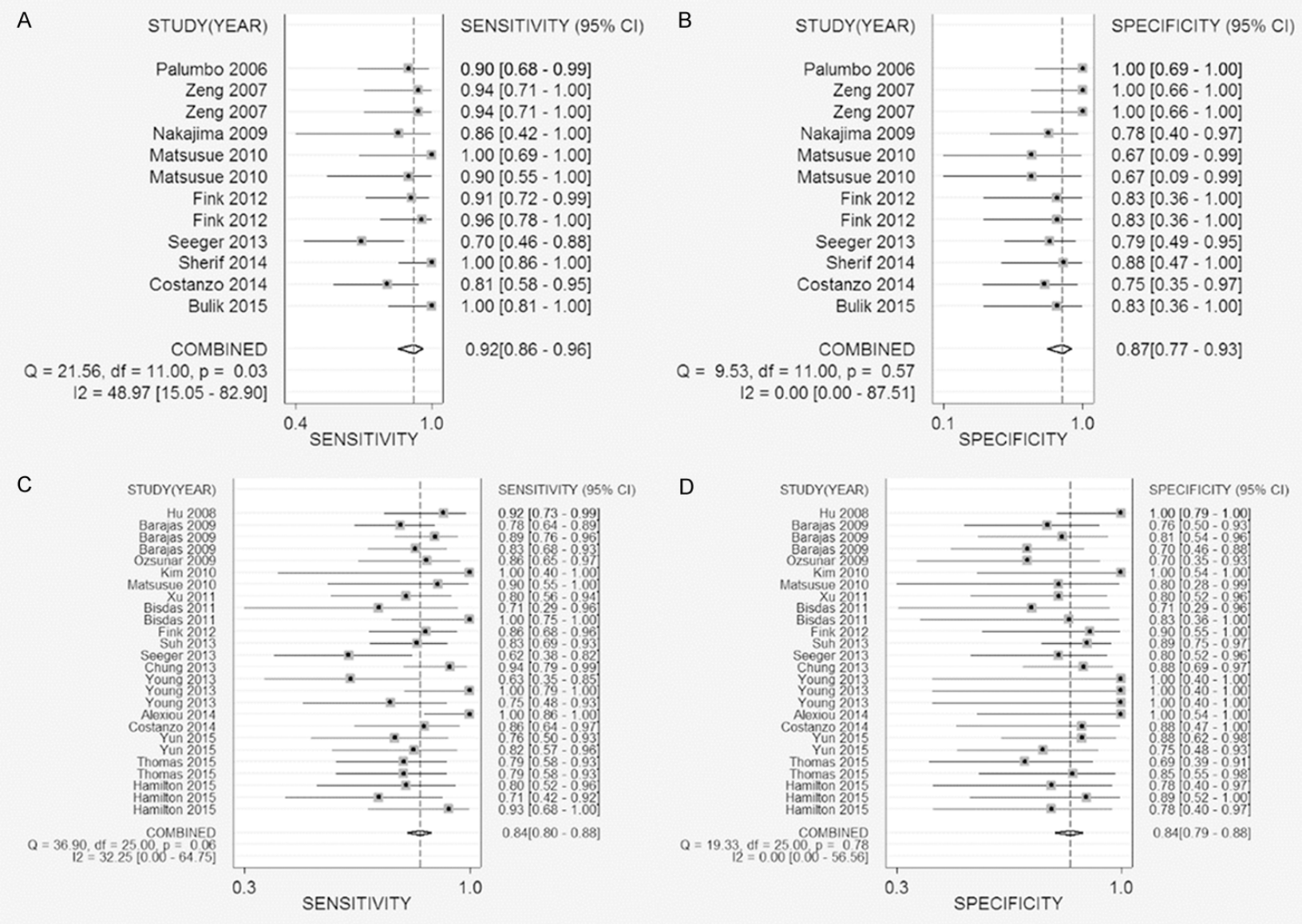

Figure 3. The pooled sensitivity and specificity of MRS and PWI for differentiate glioma recurrence from PTRE. A. Forest plots of sensitivity for MRS; B. Forest plots of specificity for MRS; C. Forest plots of sensitivity for PWI; D. Forest plots of specificity for PWI.

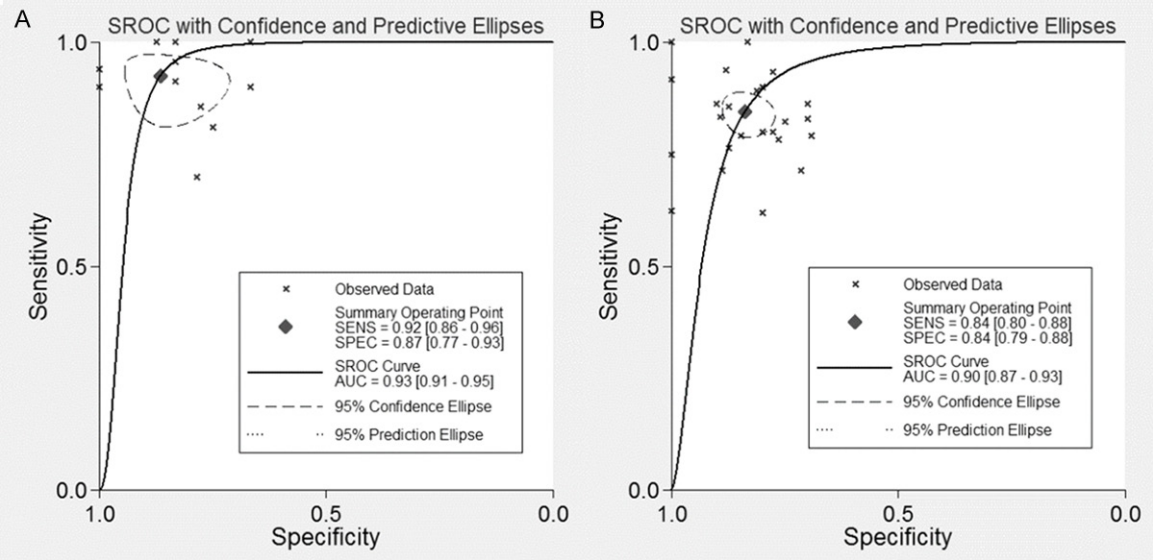

Figure 4. Summary receiver operating characteristic (SROC) curve of MRS and PWI for differentiate glioma recurrence from PTRE. A. SROC curve of MRS; B. SROC curve of PWI.

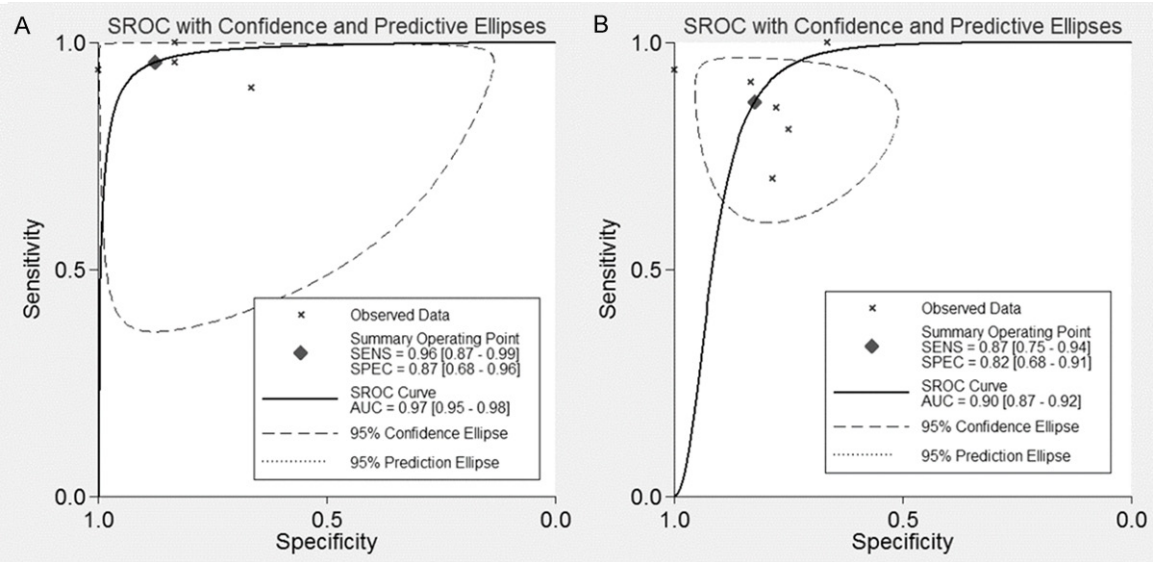

Figure 5. Summary receiver operating characteristic (SROC) curve of Cho/NAA and Cho/Cr for differentiate glioma recurrence from PTRE. A. SROC curve of Cho/NAA; B. SROC curve of Cho/Cr.

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 I^2=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

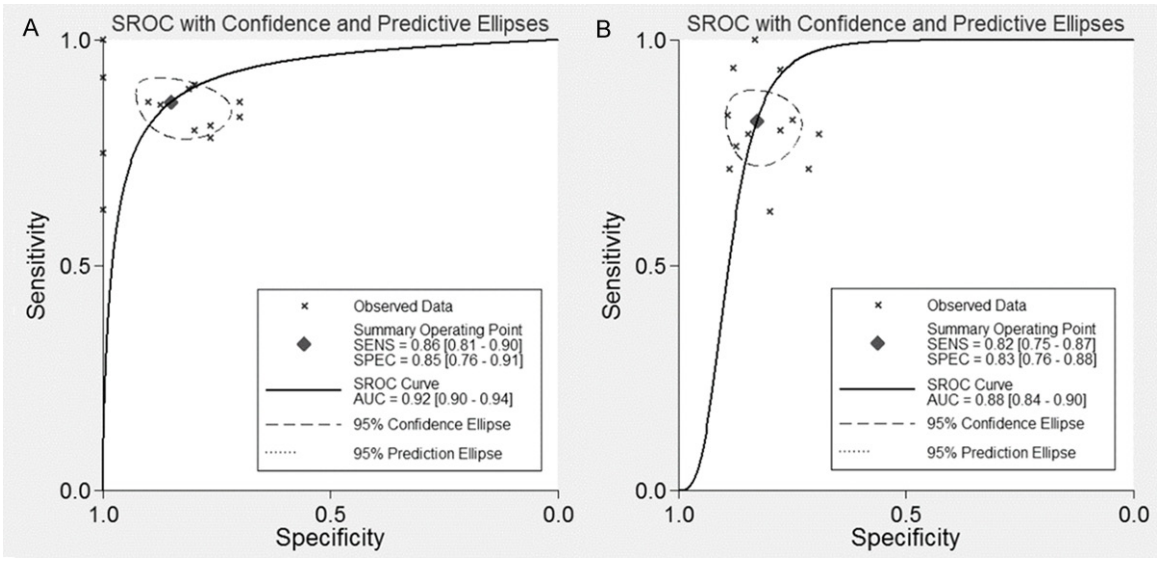

Figure 6. Summary receiver operating characteristic (SROC) curve of DSC perfusion imaging and DCE perfusion imaging for differentiate glioma recurrence from PTRE. A. SROC curve of DSC perfusion imaging; B. SROC curve of DCE perfusion imaging.

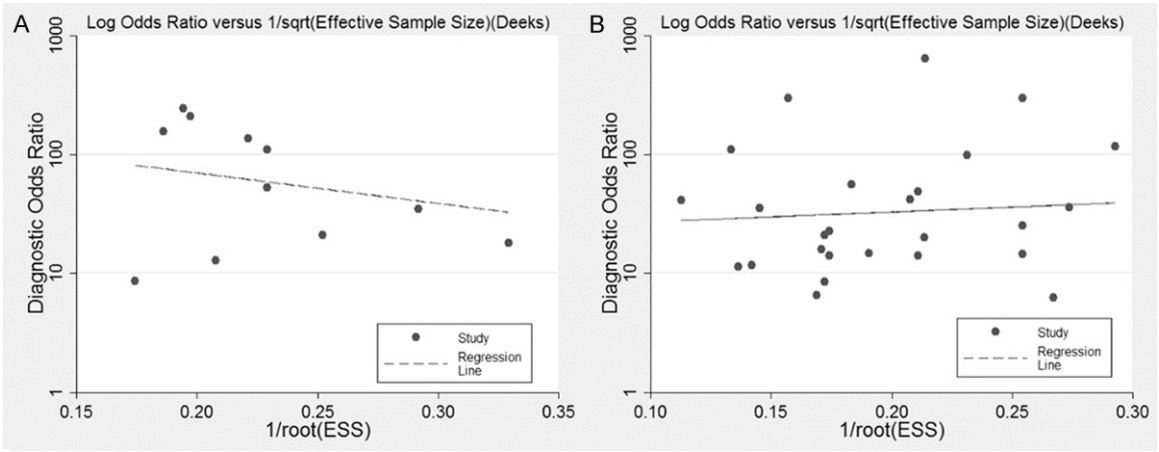

Figure 7. Funnel plot for the assessment of potential publication bias in MRS and PWI studies. A. Funnel plot for MRS; B. Funnel plot for PWI.

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 4**.

Sub-group analysis

Subgroup analysis for MRS was conducted according to two major imaging interpretations: choline/N-acetylaspartylglutamate (Cho/NAA) andcholine/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

(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-radiotharapy, 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 andCr [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/creatine (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

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 indexto 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 (K^{trans}), vascular plasma volume fraction (v_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.

Address correspondence to: Dr. Shijiang Zhong, Department of Neurology, Logistic University Affiliated

Hospital, Logistic University of Chinese People's Armed Police Force, Tianjin 300162, P. R. China. Tel: 131-0229-6029; E-mail: zhongshijiang1@163.com; Dr. Yanhua Gong, Department of Biochemistry and Molecular Biology, Logistic University of the Chinese People's Armed Police Force, Tianjin 300309, P. R. China. Tel: 135-1281-9772; E-mail: bigchock@vip.sina.com

References

[1] Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, Stroup NE, Kruchko C and Barnholtz-Sloan JS. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. Neuro Oncol 2013; 15 Suppl 2: ii1-56.

[2] Darefsky AS, King JT Jr and Dubrow R. Adult glioblastoma multiforme survival in the temozolomide era: a population-based analysis of Surveillance, Epidemiology, and End Results registries. Cancer 2012; 118: 2163-2172.

[3] Gruber ML and Buster WP. Temozolomide in combination with irinotecan for treatment of recurrent malignant glioma. Am J Clin Oncol 2004; 27: 33-38.

[4] Oike T, Suzuki Y, Sugawara K, Shirai K, Noda SE, Tamaki T, Nagaishi M, Yokoo H, Nakazato Y and Nakano T. Radiotherapy plus concomitant adjuvant temozolomide for glioblastoma: Japanese mono-institutional results. PLoS One 2013; 8: e78943.

[5] Parvez K, Parvez A and Zadeh G. The diagnosis and treatment of pseudoprogression, radiation necrosis and brain tumor recurrence. Int J Mol Sci 2014; 15: 11832-11846.

[6] Alexiou GA, Tsiouris S, Kyritsis AP, Voulgaris S, Argyropoulou MI and Fotopoulos AD. Glioma recurrence versus radiation necrosis: accuracy of current imaging modalities. J Neurooncol 2009; 95: 1-11.

[7] Ryken TC, Aygun N, Morris J, Schweizer M, Nair R, Spracklen C, Kalkanis SN, Olson JJ; AANS/CNS Joint Guidelines Committee. The role of imaging in the management of progressive glioblastoma: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2014; 118: 435-460.

[8] Shah AH, Snelling B, Bregy A, Patel PR, Tememe D, Bhatia R, Sklar E and Komotar RJ. Discriminating radiation necrosis from tumor progression in gliomas: a systematic review what is the best imaging modality? J Neurooncol 2013; 112: 141-152.

[9] Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155: 529-536.

[10] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.

[11] Zamora J, Abraira V, Muriel A, Khan K and Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol 2006; 6: 31.

[12] Deeks JJ, Macaskill P and Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005; 58: 882-893.

[13] Hamilton JD, Lin J, Ison C, Leeds NE, Jackson EF, Fuller GN, Ketonen L and Kumar AJ. Dynamic contrast-enhanced perfusion processing for neuroradiologists: model-dependent analysis may not be necessary for determining recurrent high-grade glioma versus treatment effect. AJNR Am J Neuroradiol 2015; 36: 686-693.

[14] Bulik M, Kazda T, Slampa P and Jancalek R. The Diagnostic Ability of Follow-Up Imaging Biomarkers after Treatment of Glioblastoma in the Temozolomide Era: Implications from Proton MR Spectroscopy and Apparent Diffusion Coefficient Mapping. Biomed Res Int 2015; 2015: 641023.

[15] Thomas AA, Arevalo-Perez J, Kaley T, Lyo J, Peck KK, Shi W, Zhang Z and Young RJ. Dynamic contrast enhanced T1 MRI perfusion differentiates pseudoprogression from recurrent glioblastoma. J Neurooncol 2015; 125: 183-190.

[16] Yun TJ, Park CK, Kim TM, Lee SH, Kim JH, Sohn CH, Park SH, Kim IH and Choi SH. Glioblastoma treated with concurrent radiation therapy and temozolomide chemotherapy: differentiation of true progression from pseudoprogression with quantitative dynamic contrast-enhanced MR imaging. Radiology 2015; 274: 830-840.

[17] Di Costanzo A, Scarabino T, Trojsi F, Popolizio T, Bonavita S, de Cristofaro M, Conforti R, Cristofano A, Colonnese C, Salvolini U and Tedeschi G. Recurrent glioblastoma multiforme versus radiation injury: a multiparametric 3-T MR approach. Radiol Med 2014; 119: 616-624.

[18] Alexiou GA, Zikou A, Tsiouris S, Goussia A, Kosta P, Papadopoulos A, Voulgaris S, Tsekeris P, Kyritsis AP, Fotopoulos AD and Argyropoulou MI. Comparison of diffusion tensor, dynamic susceptibility contrast MRI and (99m)Tc-Tetrofosmin brain SPECT for the detection of recurrent high-grade glioma. Magn Reson Imaging 2014; 32: 854-859.

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

Qanet M. Hammad. Role of magnetic resonance spectroscopy in differentiation between recurrence of glioma and post radiation injury. J Radiology and Nuclear Med 2014; 45: 1233-1240.

[20] Young RJ, Gupta A, Shah AD, Graber JJ, Chan TA, Zhang Z, Shi W, Beal K and Omuro AM. MRI perfusion in determining pseudoprogression in patients with glioblastoma. Clin Imaging 2013; 37: 41-49.

[21] Chung WJ, Kim HS, Kim N, Choi CG and Kim SJ. Recurrent glioblastoma: optimum area under the curve method derived from dynamic contrast-enhanced T1-weighted perfusion MR imaging. Radiology 2013; 269: 561-568.

[22] Seeger A, Braun C, Skardelly M, Paulsen F, Schittenhelm J, Ernemann U and Bisdas S. Comparison of three different MR perfusion techniques and MR spectroscopy for multiparametric assessment in distinguishing recurrent high-grade gliomas from stable disease. Acad Radiol 2013; 20: 1557-1565.

[23] Suh CH, Kim HS, Choi YJ, Kim N and Kim SJ. Prediction of pseudoprogression in patients with glioblastomas using the initial and final area under the curves ratio derived from dynamic contrast-enhanced T1-weighted perfusion MR imaging. AJNR Am J Neuroradiol 2013; 34: 2278-2286.

[24] Fink JR, Carr RB, Matsusue E, Iyer RS, Rockhill JK, Haynor DR and Maravilla KR. Comparison of 3 Tesla proton MR spectroscopy, MR perfusion and MR diffusion for distinguishing glioma recurrence from posttreatment effects. J Magn Reson Imaging 2012; 35: 56-63.

[25] Bisdas S, Naegele T, Ritz R, Dimostheni A, Pfannenberg C, Reimold M, Koh TS and Ernemann U. Distinguishing recurrent high-grade gliomas from radiation injury: a pilot study using dynamic contrast-enhanced MR imaging. Acad Radiol 2011; 18: 575-583.

[26] Xu JL, Shi DP, Dou SW, Li YL and Yan FS. Distinction between postoperative recurrent glioma and delayed radiation injury using MR perfusion weighted imaging. J Med Imaging Radiat Oncol 2011; 55: 587-594.

[27] Matsusue E, Fink JR, Rockhill JK, Ogawa T and Maravilla KR. Distinction between glioma progression and post-radiation change by combined physiologic MR imaging. Neuroradiology 2010; 52: 297-306.

[28] Kim YH, Oh SW, Lim YJ, Park CK, Lee SH, Kang KW, Jung HW and Chang KH. Differentiating radiation necrosis from tumor recurrence in high-grade gliomas: assessing the efficacy of 18F-FDG PET, 11C-methionine PET and perfusion MRI. Clin Neurol Neurosurg 2010; 112: 758-765.

[29] Ozsunar Y, Mullins ME, Kwong K, Hochberg FH, Ament C, Schaefer PW, Gonzalez RG and Lev MH. Glioma recurrence versus radiation necrosis? A pilot comparison of arterial spin-labeled, dynamic susceptibility contrast enhanced MRI, and FDG-PET imaging. Acad Radiol 2010; 17: 282-290.

[30] Nakajima T, Kumabe T, Kanamori M, Saito R, Tashiro M, Watanabe M and Tominaga T. Differential diagnosis between radiation necrosis and glioma progression using sequential proton magnetic resonance spectroscopy and methionine positron emission tomography. Neurol Med Chir (Tokyo) 2009; 49: 394-401.

[31] Barajas RF Jr, Chang JS, Segal MR, Parsa AT, McDermott MW, Berger MS and Cha S. Differentiation of recurrent glioblastoma multiforme from radiation necrosis after external beam radiation therapy with dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. Radiology 2009; 253: 486-496.

[32] Hu LS, Baxter LC, Smith KA, Feuerstein BG, Karis JP, Eschbacher JM, Coons SW, Nakaji P, Yeh RF, Debbins J and Heiserman JE. Relative cerebral blood volume values to differentiate high-grade glioma recurrence from posttreatment radiation effect: direct correlation between image-guided tissue histopathology and localized dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging measurements. AJNR Am J Neuroradiol 2009; 30: 552-558.

[33] Zeng QS, Li CF, Zhang K, Liu H, Kang XS and Zhen JH. Multivoxel 3D proton MR spectroscopy in the distinction of recurrent glioma from radiation injury. J Neurooncol 2007; 84: 63-69.

[34] Palumbo B, Lupattelli M, Pelliccioli GP, Chiarini P, Moschini TO, Palumbo I, Siepi D, Buoncristiani P, Nardi M, Giovenali P and Palumbo R. Association of 99mTc-MIBI brain SPECT and proton magnetic resonance spectroscopy (1H-MRS) to assess glioma recurrence after radiotherapy. Q J Nucl Med Mol Imaging 2006; 50: 88-93.

[35] Walker MD, Alexander E Jr, Hunt WE, MacCarty CS, Mahaley MS Jr, Mealey J Jr, Norrell HA, Owens G, Ransohoff J, Wilson CB, Gehan EA and Strike TA. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. J Neurosurg 1978; 49: 333-343.

[36] Taphoorn MJ, Henriksson R, Bottomley A, Cloughesy T, Wick W, Mason WP, Saran F, Nishikawa R, Hilton M, Theodore-Oklota C, Ravelo A and Chinot OL. Health-Related Quality of Life in a Randomized Phase III Study of Bevacizumab, Temozolomide, and Radiotherapy in

Newly Diagnosed Glioblastoma. J Clin Oncol 2015; 33: 2166-2175.
[37] McDonald MW, Linton OR and Calley CS. Dose-volume relationships associated with temporal lobe radiation necrosis after skull base proton beam therapy. Int J Radiat Oncol Biol Phys 2015; 91: 261-267.
[38] Fink J, Born D and Chamberlain MC. Pseudoprogression: relevance with respect to treatment of high-grade gliomas. Curr Treat Options Oncol 2011; 12: 240-252.
[39] Chamberlain MC, Glantz MJ, Chalmers L, Van Horn A and Sloan AE. Early necrosis following concurrent Temodar and radiotherapy in patients with glioblastoma. J Neurooncol 2007; 82: 81-83.
[40] Guzman-De-Villoria JA, Mateos-Perez JM, Fernandez-Garcia P, Castro E and Desco M. Added value of advanced over conventional magnetic resonance imaging in grading gliomas and other primary brain tumors. Cancer Imaging 2014; 14: 35.
[41] Dhermain FG, Hau P, Lanfermann H, Jacobs AH and van den Bent MJ. Advanced MRI and PET imaging for assessment of treatment response in patients with gliomas. Lancet Neurol 2010; 9: 906-920.
[42] Schlemmer HP, Bachert P, Herfarth KK, Zuna I, Debus J and van Kaick G. Proton MR spectroscopic evaluation of suspicious brain lesions after stereotactic radiotherapy. AJNR Am J Neuroradiol 2001; 22: 1316-1324.
[43] Isobe T, Akutsu H, Yamamoto T, Shiigai M, Masumoto T, Nakai K, Takano S, Anno I and Matsumura A. [Usefulness of quantitative H-MR spectroscopy for the differentiation between radiation necrosis and recurrence of anaplastic oligodendroglioma]. No Shinkei Geka 2011; 39: 485-490.
[44] Elias AE, Carlos RC, Smith EA, Frechtling D, George B, Maly P and Sundgren PC. MR spectroscopy using normalized and non-normalized metabolite ratios for differentiating recurrent brain tumor from radiation injury. Acad Radiol 2011; 18: 1101-1108.
[45] Batchelor TT, Reardon DA, de Groot JF, Wick W and Weller M. Antiangiogenic therapy for glioblastoma: current status and future prospects. Clin Cancer Res 2014; 20: 5612-5619.
[46] Hu LS, Baxter LC, Pinnaduwage DS, Paine TL, Karis JP, Feuerstein BG, Schmainda KM, Dueck AC, Debbins J, Smith KA, Nakaji P, Eschbacher JM, Coons SW and Heiserman JE. Optimized preload leakage-correction methods to improve the diagnostic accuracy of dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging in posttreatment gliomas. AJNR Am J Neuroradiol 2010; 31: 40-48.
[47] Kong DS, Kim ST, Kim EH, Lim DH, Kim WS, Suh YL, Lee JI, Park K, Kim JH and Nam DH. Diagnostic dilemma of pseudoprogression in the treatment of newly diagnosed glioblastomas: the role of assessing relative cerebral blood flow volume and oxygen-6-methylguanine-DNA methyltransferase promoter methylation status. AJNR Am J Neuroradiol 2011; 32: 382-387.
[48] Reddy K, Westerly D and Chen C. MRI patterns of T1 enhancing radiation necrosis versus tumour recurrence in high-grade gliomas. J Med Imaging Radiat Oncol 2013; 57: 349-355.
[49] Rutjes AW, Reitsma JB, Di Nisio M, Smidt N, van Rijn JC and Bossuyt PM. Evidence of bias and variation in diagnostic accuracy studies. CMAJ 2006; 174: 469-476.