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Review

Role of Radiological Intervention in Brain Tumor: A Meta-Analysis

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Background: This meta-analysis highlights the diagnostic efficacy of computed tomography (CT), computed tomography angiography (CTA), magnetic resonance image (MRI), as well as magnetic resonance spectroscopy (MRS). This paper assesses the detection of the primary outcome comprising choline/creatine ratio, relative cerebral blood volume (rCBV), as well as choline/N-acetyl aspartate. Cochrane, Medline, ScienceDirect, Google Scholar, and EMBASE databases were searched for extracting the relevant studies.

Methods: A sample of 12 studies on radiologic assessment of brain tumors was selected.

Results: The evidence provides that the heterogeneity exists concerning the CBV of 311.623, I2 = 96.12%, with a significance value of $P < 0.001$. The pooled difference showed rCBV mean (as 2.18, 95% confidence interval = 0.85 to 3.50) substantially enhances lesion.

Conclusion: The study concluded that radiological interventions, particularly the combination of MRS and MRI, help in the brain patient's precise diagnosis and treatment.

Key words: Brain tumor – Meta-analysis – MRI – MRS – Radiological intervention

Studies highlight brain tumor as the primary cause of mortality for patients with cancer.[1,2] Florian *et al*[2] reports that about 238,000 new cases are diagnosed, with a global mortality ratio of 175,000. Most studies indicate that the recent growth in the cancer imaging analytic methods has added new insights for treating the brain tumors, reducing its risk factors and tailoring techniques for optimal results.[3,4] Various studies have termed radiotherapy as the best option for treating unresectable brain tumor.[1,5] Chuang *et al*[5] highlight that the radiotherapy ratio is 78% for the non-surgical treatments provided to cancer patients. This method aims to provide a high dose of radiation to tumor volume (TV) with adjacent tissues sparing. The use of advanced treatment techniques helps in accomplishing it such as the intensity-modulated radiotherapy and 3-dimensional (3D) conformal radiation treatments.[6,7]

The aggressive management of the brain tumor has led to the emergence of new neoadjuvant strategies, including stereotactic radiosurgery and

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gamma knife. However, the difference of the radiation necrosis from recurrent/progressive tumor is integral as well as difficult, given the difference in the treatment options and prognosis. To identify the difference between the two and be certain of the diagnosis, a surgical biopsy with reoperation is needed.[5] This has led various studies for identifying more advanced imaging methods that help monitor tumor physiologic as well as metabolic properties.[8]

Generally, these include magnetic resonance (MR) perfusion,[5] computed tomography (CT) perfusion,[9] single-photon emission CT (SPECT),[10,11] diffusion-weighted imaging (DWI),[12] positron emission tomography (PET),[13,14] and MR spectroscopy (MRS),[15,16] though each technique has certain limitations. For example, magnetic resonance imaging (MRI) might not provide enough details for differentiation of the delayed radiation effects from tumor reoccurrence, while false-positive results for tumor might appear for PET, MR spectroscopy, and other radiologic intervention.[17]

Although brain biopsy is used for diagnosing brain tumors, increased choline (Cho) levels are found for areas that have a high turnover of the cellular membrane. It also has increased cerebral blood volume (rCBV) for reflecting neovascularization of tumors.[5,18] Other metabolic observations include N-acetyl aspartate (NAA) and creatine (Cr). Although these have been evaluated empirically, the review on these radiologic interventions with highlighting metabolic has remained limited. Either it has remained central to a certain type of radiology or included outcomes.[5] Thereby, this study is intended to assess the diagnostic efficacy of MRI, CT, CT angiography (CTA), and MRS concerning detection of the outcome including rCBV, choline/N-acetyl aspartate (Cho/NAA), and choline/creatine (Cho/Cr) ratio. The findings of this meta-analysis are likely to assist reduce the recurrent of tumors in brain tissues following a radiologic intervention.

Methods

Search strategy

The studies published between 2009 and 2019 were selected from databases including Cochrane, Medline, ScienceDirect, Google Scholar, and EMBASE. The search strategy was modified for suiting the different databases. Medical subject headings were used for searching along with free text key terms. Search terms classified includes target participants, radiologic interventions, and the outcome. The key words comprise magnetic resonance spectroscopy OR MR spectroscopy magnetic resonance perfusion AND brain tumors, MR perfusion, CTA, brain metastasis, recurrence, radiological intervention, MRS.

Eligibility criteria

This meta-analysis included only prospective and retrospective studies related to primary brain tumor patients and brain metastasis. Participants' characteristics, details of the interventions (evaluation of the tumor using at least one among 4 diagnostic tests including MRI, CT, CTA, or MRS) and study characteristics and outcomes were the primary information extracted from each of the studies. The articles included are all in English and have evaluated at least one of the measure outcomes, such as ratio of Cho/Cr, rCBV, and the Cho/NAA ratio. Only human intervention studies were selected. The excluded articles were either letters, proceedings, case reports, editorials, along with personal communications. The studies that did not have any quantitative measures or outcomes were also excluded. The available individual patient data from all included studies were accessed and retrieved.

Selection of study and extraction of data

The guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were used for selecting studies. Data extraction was based on the first author's name, publication year, design, participants' numbers, participants' ages, gender, primary outcomes, and follow-up time.

Data extraction and management

The appropriate population and intervention attributes were extracted by the 2 researchers using standard data extraction template to maximize the information added in this study through assessment of all available data for avoiding included duplication publication.

Quality assessment

In this research, the Newcastle-Ottawa Scale was used. This scale is valid for assessing non-randomized researches.[19]

Risk of bias assessment

The selected studies were examined by 2 independent reviewers, wherein case of uncertainty the consultation was held with another reviewer. The risk of bias of the study was determined using the Cochrane Collaboration tool.[20] According to the Cochrane Handbook for Systematic Review of Intervention,[20] the risk of bias criteria is presented as follows:

- Low risk
- Moderate risk
- Unclear risk
- Severe risk

The investigation regarding effect of individual bias domains was done based on study endpoint results and study level.

Statistical assessment

The Comprehensive Meta-Analysis V.3 software (Biostat, Inc., Englewood, NJ, USA) was used for statistical assessment. This included the outcomes difference, such as rCBV and ratios of Cho/Cr and Cho/NAA. If median and IQR (interquartile ranges) are provided, it is assumed that the outcome variable median is equivalent to the mean response, and IQR range is 1.35 times of SD. In case no mean and standard deviation is found, then median, range, and sample size are calculated for mean and variance. The mean difference of 95% confidence interval (CI) is measured for every study.

Results and Discussion

Initially, the eligibility of 157 studies was assessed from their abstracts and inclusion and exclusion criteria. Based on this, 78 studies were included in this research. The full-text review of research led to the exclusion of 49 studies based on their lack of interesting outcomes or for their characteristics of being one-arm studies (Fig. 1). The final sample included 12 studies that assessed the brain metastasis for the tumor using CT scan, MRI, MRS, and CTA.

Study characteristics and clinical outcomes

Table 1 shows that the number of prospective studies was 4, while the number of retrospective studies was 8. The number of patients in the included studies ranged from 7 to 58. The number

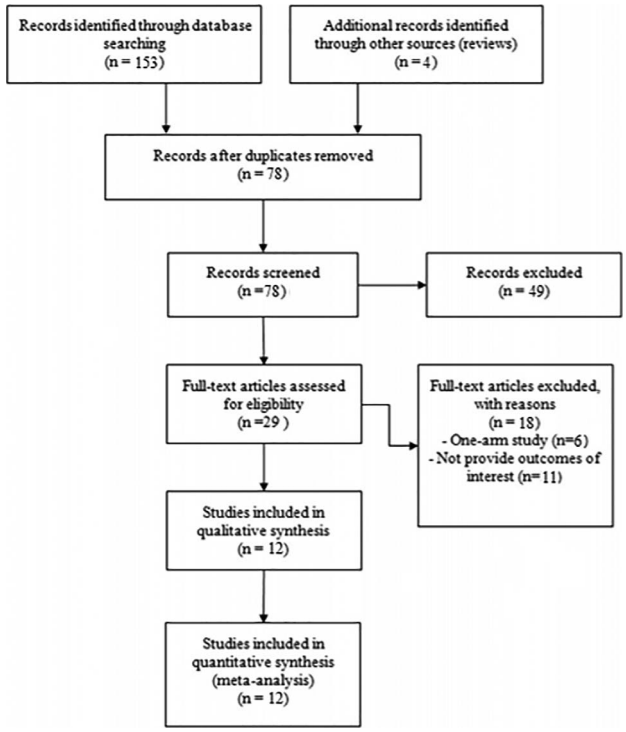

Fig. 1 Study inclusion.

of studies on MRI was 10, while that of MRS was 2, which evaluated the brain tumor among patients.

Table 2 presents the functional outcomes of the selected study. It shows the different ratios present in the studies. Vallée *et al*,[21] Di Costanzo,[22] Huang,[23] and Matsusue[18] radiologic findings reported results for rCBV, Cho/NAA, and Cho/Cr, while Elias[24] and Kirov *et al*[25] reported on Cho/Cr and Cho/NAA. Whereas Alexiou *et al*,[26] Prager *et al*,[27] Shin *et al*,[28] and Xu *et al*[29] stated results for rCBV. The Mitsuya *et al*[17] and Barajas[30] study also reported on rCBV.

Difference of rCBV in tumor

Figure 2 shows the difference concerning the rCBV means. It is observed that among the 12 studies, the numeric evaluation was provided by 10 studies only. The heterogeneity evidence suggests that rCBV values for studies, *i.e.*, Q statistics is 311.623, I2 = 96.12%, with a significance value of $P < 0.001$, so the analysis was conducted using the random effect model. The pooled difference mean of rCBV (as 2.18, 95% CI = 0.85 to 3.50), for lesion enhancement substantial.

Table 1 Study characteristics

Author	Years	Study design	Patients	Intervention
Vallée *et al*[20]	2018	Retrospective	55	MRI
Kirov *et al*[21]	2017	Retrospective	27	MR Spectroscopy
Prager *et al*[22]	2015	Retrospective	58	MRI
Alexiou *et al*[23]	2014	Prospective	24	MRI
Shin *et al*[24]	2014	Retrospective	19	MR
Di Costanzo[25]	2014	Prospective	21	MRI
Xu *et al*[26]	2011	Prospective	20	MR
Huang[27]	2011	Retrospective	23	MR
Elias[28]	2011	Prospective	25	MR Spectroscopy
Matsusue[18]	2010	Retrospective	10	MR
Mitsuya[17]	2010	Prospective	7	MR
Barajas[29]	2009	Retrospective	27	MR

Table 2 Functional outcomes among studies selected

Authors	Relative cerebral blood volume	Cho/Cr ratio	Cho/NAA ratio
Vallée *et al*[20]	0.960 (.001)	3.22 (3.02)	0.835 (0.05)
Kirov *et al*[21]	NA	5.5 (0.4)	7.7 (0.5)
Prager *et al*[22]	6.71 (0.41)	NA	NA
Alexiou *et al*[23]	4.40 (3.07)	NA	NA
Shin *et al*[24]	1.73 (0.56)	2.12 (0.64)	2.84 (1.40)
Di Costanzo[25]	1.81 (1.46, 2.58)	NA	NA
Xu *et al*[26]	4.36 (1.98)	NA	NA
Huang[27]	4.36 (1.98)	1.72 (1.10)	1.32 (1.25)
Elias[28]	NA	1.84 (0.58)	1.39 (0.46)
Matsusue[18]	3.33 (1.16)	1.87 (0.39)	1.56 (0.82)
Mitsuya[17]	3.5 (2.1–10)	NA	NA
Barajas[29]	2.38 (0.95)	NA	NA

Ratios for Cho/NAA and Cho/Cr

Figure 3 shows Cho/Cr ratio difference. It shows that there exists no heterogeneity evidence concerning the assessment of ratio for Cho/Cr ratio, including use of a fixed-effect analysis model (Q statistic = 8.211, I2 = 39.32%, $P = 0.1298$). Also, Cho/Cr ratio is found to be substantially high, given the pool difference in means). Whereas, Fig. 4 shows the difference concerning the Cho/NAA ratio, which depicts the numerical data concerning the Cho/NAA ratio. The evidence suggests that ratio of Cho/NAA were heterogeneous (Q statistic = 12.98, I2 = 76.32%, $P = 0.002$), thereby, using the random effect model. The studies showed a substantial difference concerning the Cho/NAA ratio (1.02, 95% CI = 0.03 to 2.00, $P = 0.044$) (Fig. 4).

Sensitivity analysis

The sensitivity analysis results were obtained with the use of the leave-one-out approach. In it, rCBV and ratios of Cho/NAA and Cho/Cr were considered. For the ratio of Cho/Cr and rCBV, the magnitude and direction estimates did not show substantial changes, indicating that every study did not overly impact the data. Concerning the mean of Cho/NAA, the differences were found to be significant. The pooled forecast might be impacted due to the study of Di Costanzo,[22] where the Cho/NAA ratio changed to non-significant.

Publication bias

The present study aimed to study radiologic intervention in brain tumors. A meta-analysis was conducted, which showed that MRS serves as the most reliable method for the accurate diagnosis of the brain tumor. This diagnosis helps to implement the information related to biochemical information, which relates to the total choline compounds (Cho), neutral tissue displacement (N-acetyl-aspartate [NAA]), as well as energy metabolism (Creatine

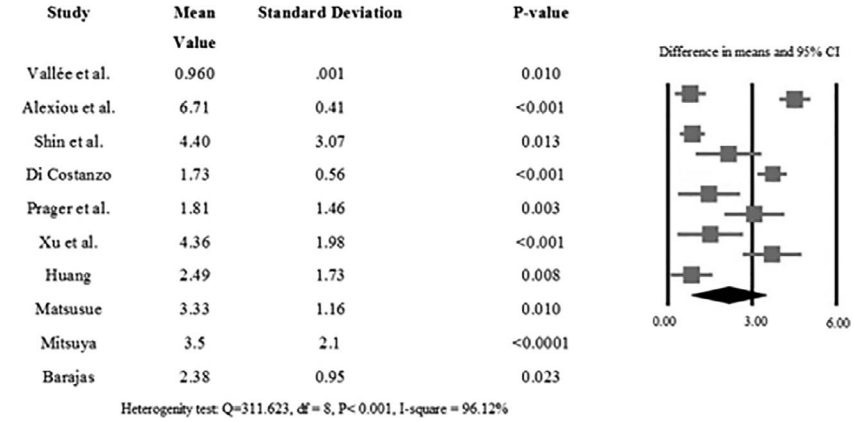

Fig. 2 Studies with rCBV mean.

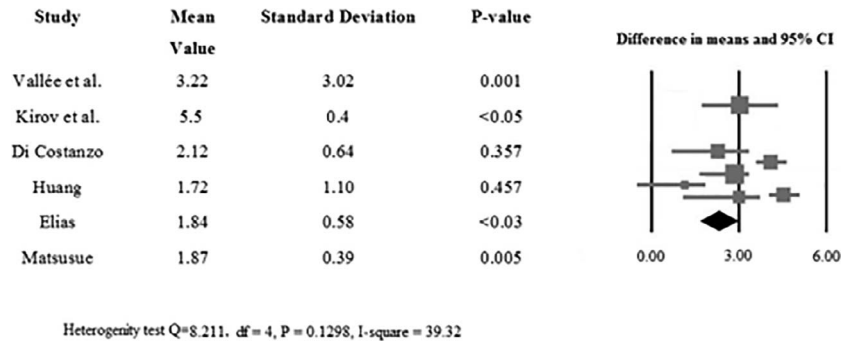

Fig. 3 Studies with Cho/Cr ratio.

[Cr]). It is also found to be linked to predict therapy response and identify the border's viable tumor as well as brain parenchyma. The radiologic intervention analysis predicts that the use of the combination of MRS and MRI can help in precise brain tumor diagnosis and detection. For radiologic intervention, the use of MRI and MRS substantially increased due to its metabolic and functional information supply.

Meta-analysis results show that average of rCBV, the Cho/Cr and Cho/NAA ratios are high for the case of a brain tumor in contrast to another. The study also carried out sensitivity analysis and conducted a homogeneity test. The homogeneity test results were achieved through Cochran's Q statistic and I2. The homogeneity was found to be good for the students who had ratios of Cho/Cr. This meta-analysis findings help contribute by highlighting the versatility as well as the effective diagnosis of the MRS. The inclusion of different radiologic and various types of brain tumors helps establish the clinical self-efficacy of the study results.

Similar to the current meta-analysis findings, the earlier researches using the radiologic evaluations of the meta-analysis also showed the effectiveness of the rCBV,[5,31] Cho/NAA, and Cho/Cr ratios,[32,33] for predicting brain tumor. For example, the findings of Guo *et al*[32] indicated that an increased Cho/NAA level was able to predict tumor infiltration. Also, Durmo[34] further highlighted that an increased level of the Cho/NAA ratio was linked with a brain tumor. However, the change in the ratio of the Cho/NAA may account for the difference in the sample size as a result of inconsistent results across different research. Although the majority of the studies conclude the high efficiency of the MRI, these cannot be generalized, as most of the included studies are small, heterogeneous, and retrospective.

Conclusions

The results depict that advanced MRI use should be implemented for the follow-up procedures concerning the brain tumor treatment. Although the performance of the diagnosis can be increased with adequate implementation and interpretation, the 100% accuracy of the techniques cannot be ensured. The diagnosis results can be further improved with the use of postprocessing, quantitative MRI, as well as computer-aided diagnostic technology. The findings of the study are limited due to the inclusion of minimal research in meta-analysis. Also, operators who evaluate rCBV or others were blinded to the clinical data. The finding suggests that an update of this review is needed with more rigorous methodologic design and availability of more data.

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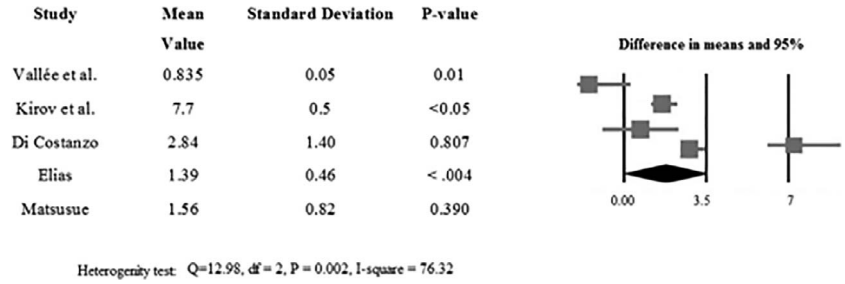

Fig. 4 Studies with Cho/NAA ratio.

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