Section: Radiodiagnosis

Research

# ROLE OF MR SPECTROSCOPY AND PERFUSION IN GRADING OF GLIOMAS AND TO DIFFERENTIATE GLIOBLASTOMA FROM METASTASES

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## Abstract

**Background:** Conventional magnetic resonance imaging (MRI) is the initial imaging modality of choice for imaging gliomas. Present study was aimed to study role of MR spectroscopy and perfusion in grading of gliomas and to differentiate glioblastoma from metastases. **Materials and Methods:** Present study was single-center, prospective, observational study, conducted in patients with suspected intra axial brain tumour who are referred for imaging of brain tumors. All patients underwent routine MR Brain with contrast, MR spectroscopy and perfusion. **Result:** Mean age of 41.52±17.15 years. Male cases (63.04 %) outnumbered female (36.96 %). DWI restriction was present in 33 cases (71.7%) while minimal DWI restriction noted in 1 case (2.17 %). Other characteristic such as necrosis (69.57 %), hemorrhage (63.04 %) & T2/FLAIR MISMATCH (8.7 %) were also noted. Common Contrast enhancement features observed were irregular ring enhancement (34.78 %), heterogenous enhancement (30.43 %), patchy central enhancement with nodular peripheral enhancement (17.39 %), no enhancement (8.7 %) & intense enhancement of solid components (8.7 %). Sensitivity and specificity of diagnosing low grade gliomas was 90.9% and 75% respectively. The sensitivity and specificity of conventional MR imaging in diagnosing high grade gliomas was 75% and 90.9% respectively. The NPV was 70.5%. The sensitivity of MR perfusion with rCBV>1.5 to diagnose a high-grade glioma was 79.17% with specificity of a 100%. The positive predictive value was 100% with a negative predictive value of 68.75%. The sensitivity and specificity of MR perfusion to diagnose a low-grade glioma was 100% and 79.17% respectively. There was an accuracy of 85.71% in diagnosing a low-grade glioma. **Conclusion:** MR Perfusion and MR Spectroscopy have a very high accuracy of differentiating between glioblastoma and metastases and can be used in everyday practice in the evaluation and grading of gliomas.

## INTRODUCTION

Primary brain tumours such as gliomas arise from the brain's supporting cells and spread throughout the body.[1] Gliomas are the most common type of primary cerebral tumour in adults when it comes to intra axial brain tumours. They are extremely heterogeneous tumours characterized by substantial cellular and nuclear pleomorphism, microvascular proliferation, mitotic activity, and necrosis, among other characteristics.[1]

Gliomas are classified into four categories based on their histological characteristics: WHO grades I-IV. The majority of high-grade gliomas (WHO grades III and IV) are invasive and highly vascular tumours, and patients with high-grade gliomas have a poor prognosis because of their inherent proclivity to undergo progressive genetic alterations and malignant transformation.[2]

In order to retrieve tissue for histopathology, which serves as the foundation for current glioma grading systems, stereotactic brain biopsy or cytoreductive surgery are required. However, both of these procedures have significant limitations in terms of methodology and interpretation.[3] Because of its better soft tissue contrast resolution, conventional magnetic resonance imaging (MRI) is the initial imaging modality of choice for imaging gliomas.[4] Present study was aimed to study role of MR


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spectroscopy and perfusion in grading of gliomas and to differentiate glioblastoma from metastases.

## MATERIALS AND METHODS

Present study was single-center, prospective, observational study, conducted in department of radiodiagnosis, at Madurai Medical College & Govt Rajaji Hospital, Madurai, India. Study duration was of 2 years (January 2020 to December 2021). Study approval was obtained from institutional ethical committee.

**Inclusion Criteria**

- Patients from neurosurgery/ neuromedicine/medicine department, with suspected intra axial brain tumour who are referred for imaging of brain tumors, willing to participate in present study

**Exclusion Criteria**

- Patients with already diagnosed brain tumour
- Allergic to MR contrast
- Surgery, radiation or chemotherapy to the lesion prior to inclusion in the study
- Extra axial brain tumors such as tumors of the meninges, tumors of cranial nerves, tumors of the sellar region.

Study was explained to patients in local language & written consent was taken for participation & study. Imaging was performed with a 1.5-T Siemens Tim+DOT unit. Routine MRI Brain with contrast, MR perfusion and spectroscopy were done. Conventional grading of each lesion was based on eight criteria such as Contrast material enhancement, Border definition, Mass effect, Signal intensity heterogeneity, Hemorrhage, Necrosis, Degree of edema & Involvement of the corpus callosum or crossing the midline

Dynamic contrast agent–enhanced T2*-weighted gradient-echo echo-planar images were acquired during the first pass of a standard dose (0.1 mmol/kg) bolus of gadolinium contrast.7 Contrast used gadodiamide at a dosage of 0.1mmol/kg7. 7 to 10 sections were acquired for perfusion MR imaging through the tumor based on T2-weighted and FLAIR images as reference. Perfusion data from a set of dynamic contrast-enhanced echo- planar images was used for calculating rCBV3. After construction of an rCBV color map for the selected target regions of maximal abnormality, four region-of-interest measurements was obtained, and the maximum rCBV recorded.

Multivoxel chemical shift imaging (CSI) imaging was performed after gadolinium administration. The volume of interest (VOI) is obtained by using half-Fourier acquisition single-shot turbo spin-echo images. 10 sections with 5-mm slice thickness were obtained in axial, coronal, and sagittal planes for all patients. A volume selective CSI sequence with 1500/144 was used for MR spectroscopic imaging. This multivoxel CSI technique uses a point-resolved spectroscopy (PRESS) sequence for selection of a VOI that includes the abnormality as well as normal-appearing brain tissue. To prevent miscalculations from subcutaneous fat signals, the VOI is placed within the brain. A typical VOI consists of 8 x 8-cm region placed within a 16 x 16-cm field of view on a 1.5 cm axial section. A 16 x 16 phase- encoding matrix is used to attain the 8 x 8 array of spectra in the VOI. The spectroscopy parameters were calculated at the edge of the lesion, indicating the growing edge of the tumour. An increase in choline peak at 3.2ppm, and reduced NAA peak at 2.0ppm, creatinine peak at 3.0-3.9ppm was considered significant for diagnosing brain tumors.

Sensitivity, specificity, PPV, and NPV were calculated for correct identification of high-grade gliomas. Tumors classified as high grade and found at histologic examination to be high grade were considered true-positive findings. Low-grade gliomas that were histologically confirmed as low grade were considered true-negative findings. For rCBV and metabolite ratios, receiver operating characteristic (ROC) curve analyses will be used to evaluate the performance of simple diagnostic tests that declared a glioma to be high grade if and only if the relevant measure (e.g., rCBV) for that patient was greater than or equal to some value K.

## RESULTS

Out of 46 cases studied, majority were from the age group of 41-50 years (23.91 %) followed by age group of 21-30 years (19.57 %). Mean age of 41.52±17.15 years. Male cases (63.04 %) outnumbered female (36.96 %).

**Table 1: Age & gender distribution**

| Characteristics | Frequency | Percentage |
|---|---|---|
| **Age (in years)** | | |
| <10 | 1 | 2.17% |
| 11-20 | 4 | 8.70% |
| 21-30 | 9 | 19.57% |
| 31-40 | 5 | 10.87% |
| 41-50 | 11 | 23.91% |
| 51-60 | 8 | 17.39% |
| 61-70 | 8 | 17.39% |
| Gender | | |
| Male | 29 | 63.04% |
| Female | 17 | 36.96% |


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In present study DWI restriction was present in 33 cases (71.7%) while minimal DWI restriction noted in 1 case (2.17 %). Other characteristic such as necrosis (69.57 %), hemorrhage (63.04 %) & T2/FLAIR MISMATCH (8.7 %) were also noted.

**Table 2: MR Characteristics**

| MR Characteristics | Frequency | Percentage |
|---|---|---|
| Necrosis | 32 | 69.57% |
| Hemorrhage | 29 | 63.04% |
| DWI restriction | | |
| Present | 33 | 71.74% |
| Minimal | 1 | 2.17% |
| T2/FLAIR MISMATCH | 4 | 8.70% |

Common Contrast enhancement features observed were irregular ring enhancement (34.78 %), heterogenous enhancement (30.43 %), patchy central enhancement with nodular peripheral enhancement (17.39 %), no enhancement (8.7 %) & intense enhancement of solid components (8.7 %).

**Table 3: Contrast enhancement features**

| Features | Frequency | Percent |
|---|---|---|
| Irregular ring enhancement | 16 | 34.78% |
| Heterogenous enhancement | 14 | 30.43% |
| Patchy central enhancement with Nodular peripheral enhancement | 8 | 17.39% |
| No enhancement | 4 | 8.70% |
| Intense enhancement of solid components | 4 | 8.70% |

Around 67.4% are having rCBV > 1.5 within the lesion. Around 45.7% have rCBV increased in peritumoral region. Around 52.2% has Cho/NAA>1.9 within the lesion. Around 67.4% has Cho/Cr > 2.3 within the lesion. Around 43.5% has Cho/ Cr is Increased in Peritumoral region.

**Table 4: MR spectroscopy and perfusion**

| MR spectroscopy and perfusion | Frequency | Percentage |
|---|---|---|
| rCBV > 1.5 | 31 | 67.39% |
| rCBV increased in peritumoral region | 21 | 45.65% |
| Cho/NAA>1.9 | 24 | 52.17% |
| Cho/Cr > 2.3 | 31 | 67.39% |
| Cho/ Cr is Increased in Peritumoral region | 22 | 47.83% |

Based on conventional MR imaging alone, that is based on (tumour margins, morphology, hemorrhage, necrosis and contrast enhancement) the sensitivity and specificity of diagnosing low grade gliomas was 90.9% and 75% respectively. The NPV was 94.74% -. The sensitivity and specificity of conventional MR imaging in diagnosing high grade gliomas was 75% and 90.9% respectively. The NPV was 70.5%.

**Table 5: Correlation of Radiological diagnosis based on conventional MR features with HPE**

| Parameter | Correlation of Radiological diagnosis based on conventional MR features with HPE | |
|---|---|---|
| | Low grade glioma | High grade glioma |
| Sensitivity | 90.91% (58.72% to 99.97%) | 75.00% (53.29% to 90.23%) |
| Specificity | 75.00% (53.29% to 90.23%) | 90.91% (58.72% to 99.97%) |
| Positive predictive value | 62.50% (44.85% to 77.36%) | 94.74% |
| Negative predictive value | 94.74% (73.25% to 99.16%) | 62.50% (44.85% to 77.36%) |
| Accuracy | 80.00% (63.06% to 91.56%) | 80.00% (63.06% to 91.56%) |

The sensitivity of MR perfusion with rCBV>1.5 to diagnose a high-grade glioma was 79.17% with specificity of a 100%. The positive predictive value was 100% with a negative predictive value of 68.75%. The sensitivity and specificity of MR perfusion to diagnose a low-grade glioma was 100% and 79.17% respectively. There was an accuracy of 85.71% in diagnosing a low-grade glioma

**Table 6: Correlation of MR perfusion with HPE**

| Parameter | Correlation of MR perfusion features with HPE | |
|---|---|---|
| | Low grade glioma | High grade glioma |
| Sensitivity | 100.00% (71.51% to 100.00%) | 79.17% (57.85% to 92.87%) |
| Specificity | 79.17% (57.85% to 92.87%) | 100.00% (71.51% to 100.00%) |
| Positive predictive value | 68.75% (50.21% to 82.76%) | 100.00% |
| Negative predictive value | 100.00% | 68.75% (50.21% to 82.76%) |
| Accuracy | 85.71% (69.74% to 95.19%) | 85.71% (69.74% to 95.19%) |


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The sensitivity and specificity of MRS (Cho/Cr>2.3 within the tumour core) in identifying a high-grade glioma is 100% and 90.9% with a PPV of 96% and a NPV of 100%. The sensitivity and specificity of MRS(Cho/Cr<2.3) in identifying a low-grade glioma is 90.9% and 100%.

**Table 7: Correlation of MRS with HPE**

| Parameter | Correlation of MRS features with HPE | |
|---|---|---|
| | Low grade glioma | High grade glioma |
| Sensitivity | 90.91% (58.72% to 99.77%) | 100.00% (85.75% to 100%) |
| Specificity | 100.00% (85.75% to 100.00%) | 90.91% (58.72% to 99.77%) |
| Positive predictive value | 100% | 96.00% (78.74% to 99.36%) |
| Negative predictive value | 96.00% (78.74% to 99.36%) | 100.00% (95.00% to 100%) |
| Accuracy | 97.14% (85.08% to 99.93%) | 97.14% (85.08% to 99.93%) |

In differentiating glioblastoma from metastases MR Perfusion (peritumoural increase in perfusion) showed a sensitivity and specificity of 100% and 90.9% respectively in identifying glioblastomas. The positive predictive value was 88.8% with negative predictive value of 100%.

**Table 8: Distribution of correlation of MR perfusion with HPE**

| Parameter | Correlation of MR perfusion features with HPE | |
|---|---|---|
| | HPE Glioblastoma | HPE metastasis |
| Sensitivity | 100% (63.06% to 100%) | 90.91% (58.72% to 99.77%) |
| Specificity | 90.91% (58.72% to 99.77%) | 100% (63.06% to 100%) |
| Positive predictive value | 88.89% (55.25% to 98.11%) | 100% (95% to 100%) |
| Negative predictive value | 100% (95% to 100%) | 88.89% (55.95% to 98.11%) |
| Accuracy | 94.74% (73.97% to 99.87%) | 94.74% (73.97% to 99.87%) |

The sensitivity and specificity of MRS (peritumoural increase in choline) in identifying glioblastomas was 100% and 90.9% respectively

**Table 9: Distribution of correlation of MRS with HPE**

| Parameter | Correlation of MRS features with HPE | |
|---|---|---|
| | HPE Glioblastoma | HPE metastasis |
| Sensitivity | 100% (63.06% to 100%) | 90.91% (58.72% to 99.77%) |
| Specificity | 90.91% (58.72% to 99.77%) | 100% (63.06% to 100%) |
| Positive predictive value | 88.89% (55.25% to 98.11%) | 100% (95% to 100%) |
| Negative predictive value | 100% (95% to 100%) | 88.89% (55.95% to 98.11%) |
| Accuracy | 94.74% (73.97% to 99.87%) | 94.74% (73.97% to 99.87%) |

## DISCUSSION

Obtaining an appropriate grading of gliomas is critical since the grading has an impact on the treatment strategy, responsiveness to therapy, and prognosis of the patient.[5] In our study total sample size was 46 with 11 cases being histopathologically diagnosed as metastases. Hasan et al,[5] consisted of 50 patients aged 3 to 70 years. As in the clinical setting, the incidence of high-grade glioma (58%) was higher than that of Low grade glioma (42%). Glioblastoma was the commonest type of all gliomas and accounted for 34%. Our study also concurred with high grade gliomas (43.5%) being more common than low grade glioma 23.9%. These results are consistent with the estimated international incidence of gliomas.[6,7,8]

Our study showed that a Cho/Cr >2.3 within the tumour core is able to identify high grade gliomas with a sensitivity of 100% and a specificity of 90.9%. This clearly compares better to conventional MR imaging, where the sensitivity in identifying a high-grade glioma was only 75%.

Our study also concurs with Ginsberg et al,[9] who showed that lack of enhancement of gliomas does not equate with low-grade glioma. They also showed that the peritumoural hyperintensity in T2 and FLAIR which could be misconstrued as vasogenic edema could sometimes be due to tumour infiltration, which is accurately picked up by MRS showing an increase in choline metabolites. Conventional MRI showed a sensitivity of 91% in diagnosing low grade gliomas indicating very few low-grade gliomas were misclassified as high grade. However, since most of the gliomas in the real world are infact high grade, it is very important that no high-grade gliomas are misclassified as low grade leading to increased mortality and hence additional sequences are required to minimize the C2 error. By using MR spectroscopy as an adjunct tool, the C2 error is minimized and the sensitivity of detecting a high-grade glioma increases.

The specificity of MRS in identifying low grade tumours was 100 percent, showing that the less severe tumours were correctly distinguished from the more severe ones. However not all high Cho/Cr ratios were HGG which lead to a drop in specificity to 90.9 percent, suggesting that they had a high rate of true positives and a low rate of false negatives; as a result, they are extremely useful for diagnosing high-grade cancers. In this investigation, rCBV was found to be capable of distinguishing significantly


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between low grade glioma and high-grade glioma, with a P value of 0.0001.

All of these findings are consistent with those of Fatima et al,[10] who discovered that the proportion of LG and HG that could be distinguished from rCBV at the cut-off of 1.33 was 100% and 67% respectively. Soliman et al,[11] and Sparacia et al.,12 have found nearly identical rCBV values with relatively high specificity and sensitivity in the distinction between low- and high-grade gliomas, indicating the reliability of rCBV in this regard.[12]

We also discovered that rCBV has the ability to discriminate between LGG and HGG within the peritumor region, with a P value of 0.0001 within the peritumor region, which was unexpected as this parameter was to be used only for differentiating GBM vs metastases.

Soliman et al,[11] which revealed a threshold value more than 0.7 with a sensitivity of 100%, a specificity of 66.7%, a PPV of 88.2%, a NPV of 100%, and an accuracy 90.5% best distinguish high- and low-grade gliomas. On the other hand, Server et al,[13] also reported this. The most obvious conclusion emerging from the analysis is that the combination of MRS and MR perfusion with conventional MRI improves the accuracy of the distinction between low- and high-grade gliomas up to 100%. This result was also reported by Zonari P et al,[14] and Di Costanzo et al.[15]

In our investigation, two factors were employed to distinguish between solitary metastases and glioblastoma: an increase in peritumoural perfusion and an increase in peritumoural choline. We discovered that nearly all patients of glioblastoma had enhanced perfusion as well as choline in the non enhancing peritumoural region. Another study by Law et al,[16] which concluded that the difference in peritumoural perfusion between the two tumour types was attributable to the inherent pathophysiological variations in vascularity of the two tumour types, supports this enhanced peritumoural rCBV. Kelley et al,[17] demonstrated that the peritumoural zone of GBM contains a high proliferation of neoplastic arteries and infiltrating glial cells, which may account for the perfusion and spectroscopic characteristics of this tumour form.

In our investigation, we also found that both peritumoural rCBV and peri tumoural MRS indicating choline increase were equally accurate in distinguishing between metastases and glioblastoma in terms of accuracy in differentiation and both showing same sensitivity and specificity of 100% and 90.9% respectively.

Limitations of the study were our study used Cho/Cr>2.3 and Cho/NAA >1.9 as high-grade tumour. In the study by Hasan et al,[5] the cut-off values useful for intermediate TE Cho metabolite ratios were used to differentiate high- grade tumours from low-grade tumours. The Cho/NAA ratio to a cut-off value greater than 1.8 and the Cho/Cr ratio to a cut-off value greater than 1.7 An explanation for these variations could be attributed to the changes in MRS imaging methods, which could include differences in MRI field strength, acquisition settings, voxel size, and location, among others. There is a need for further research into the standardization of these cut off values, in the need for a more uniformity in reporting.

## CONCLUSION

Grading of gliomas based on just conventional MR imaging is often inaccurate with few high-grade gliomas being misclassified as low grade. rCBV or MRS alone or in combination may be used as an adjunct to conventional MR. MR Perfusion and MR Spectroscopy also have a very high accuracy of differentiating between glioblastoma and metastases with 96% each. They are an easy tool, with good reproducibility and can be used in everyday practice in the evaluation of brain tumours.

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