Chapter 7

Clinical Application of MR Spectroscopy in Identifying Biochemical Composition of the Intracranial Pathologies

B C Hamsini, Bhavana Nagabhushana Reddy,
Sankar Neelakantan and
Sunitha Palasamudram Kumaran

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Abstract

Magnetic resonance spectroscopy (MRS) provides useful information regarding metabolic composition in the tissues, and advanced spectroscopic methods are used to quantify markers of tumor membrane turnover and proliferation (e.g., choline (Cho)), energy homoeostasis (e.g., creatine (Cr)), intact glioneuronal structures (e.g., N-acetylaspartate (NAA)), and necrosis (e.g., lactate (Lac) or lipids). Results are usually expressed as metabolite ratios rather than absolute metabolite concentrations. Because glial tumors have some specific metabolic characteristics that differ according to the grade of tumor, there is a potential for MR spectroscopy to increase the sensitivity of routinely used diagnostic imaging. MRS also has many diagnostic applications in neurosciences to support the diagnosis in conditions like demyelination, infections, and dementia and in postradiotherapy cases. Biochemical changes in the metabolism of tumor cells related to malignant transformation are reflected in changes of particular metabolite concentration in the tumor tissue. Our prospective study aimed to analyze the usefulness of proton MR spectroscopy in grading of glioma and to correlate various metabolite ratios like choline/creatine, choline/N-acetylaspartate, N-acetylaspartate/creatine, and lactate/creatine with the histopathological grades of glioma.

Keywords: MRS, MRI, grade, glioma, NAA, choline, creatine, ratio

1. Introduction

Magnetic resonance spectroscopy (MRS) is an analytical method used for the identification and quantification of metabolites. It differs from conventional magnetic resonance imaging (MRI) since it provides physiological and chemical information instead of only anatomy [1].

Many of nuclei have been used to obtain MR spectra; few of them include proton (^{1}H), phosphorus (^{31}P), fluorine (^{19}F), carbon (^{13}C), and sodium (^{23}Na).

Proton (^{1}H) MR spectroscopy is most commonly used since hydrogen nucleus is abundant in human tissues [1].

Magnetic field strength clinically used for conventional MRI ranges from 0.2 to 3 T.

For MRS, higher-field strength (1.5 T or more) is required since the main aim of MRS is to detect weaker signals from metabolites. Higher-field strength units have the advantage of higher signal-to-noise ratio (SNR), better resolution, and shorter acquisition times.

2. Metabolites in MRS

2.1. N-Acetylaspartate (NAA)

N-Acetylaspartate (NAA) peak is the most prominent peak in normal adult brain proton MRS which resonates at 2.0 ppm [2] (**Figure 1**).

NAA is a derivative of aspartic acid. It is synthesized and stored primarily in the neurons and hence it is called a neuronal marker or a marker of neuronal density and viability [2].

As a neuronal marker, NAA concentration declines with the destruction of neurons in high-volume lesions, dementia, hypoxia, or multiple sclerosis.

Due to the relationship between the decline in NAA concentration and increasing glioma grade, it is possible to use NAA as a substantial marker [13]. A high level of NAA is associated with a good prognosis [3].

NAA is also helpful for the differentiation of primary brain tumors from metastasis and non-neuronal tumors where the metabolite is lacking in the spectra [4].

2.2. Creatine (Cr)

Creatine (Cr) is synthesized from amino acids primarily in the kidneys and liver and transported to the peripheral organs by blood and is called as energy metabolism marker [3].

Total Cr indicates the quantity of phosphocreatine (PCr) and Cr contained in neurons and glial cells and visualized as a prominent peak in MR spectra at 3.0 ppm; an additional peak for creatine may be visible at 3.94 ppm [3].

A decrease in the Cr level in high-grade gliomas (HGGs) is due to increased metabolic demands of the tumorous tissue in the brain. Cr is a relatively constant element of cellular energetic metabolism of the brain and it is frequently used as a reference metabolite for in vivo MRS, for example, for mainly calculating the metabolite ratios such as choline (Cho)/Cr, NAA/Cr, lipid (Lip)-lactate (Lac)/Cr, or myoinositol/Cr [3].

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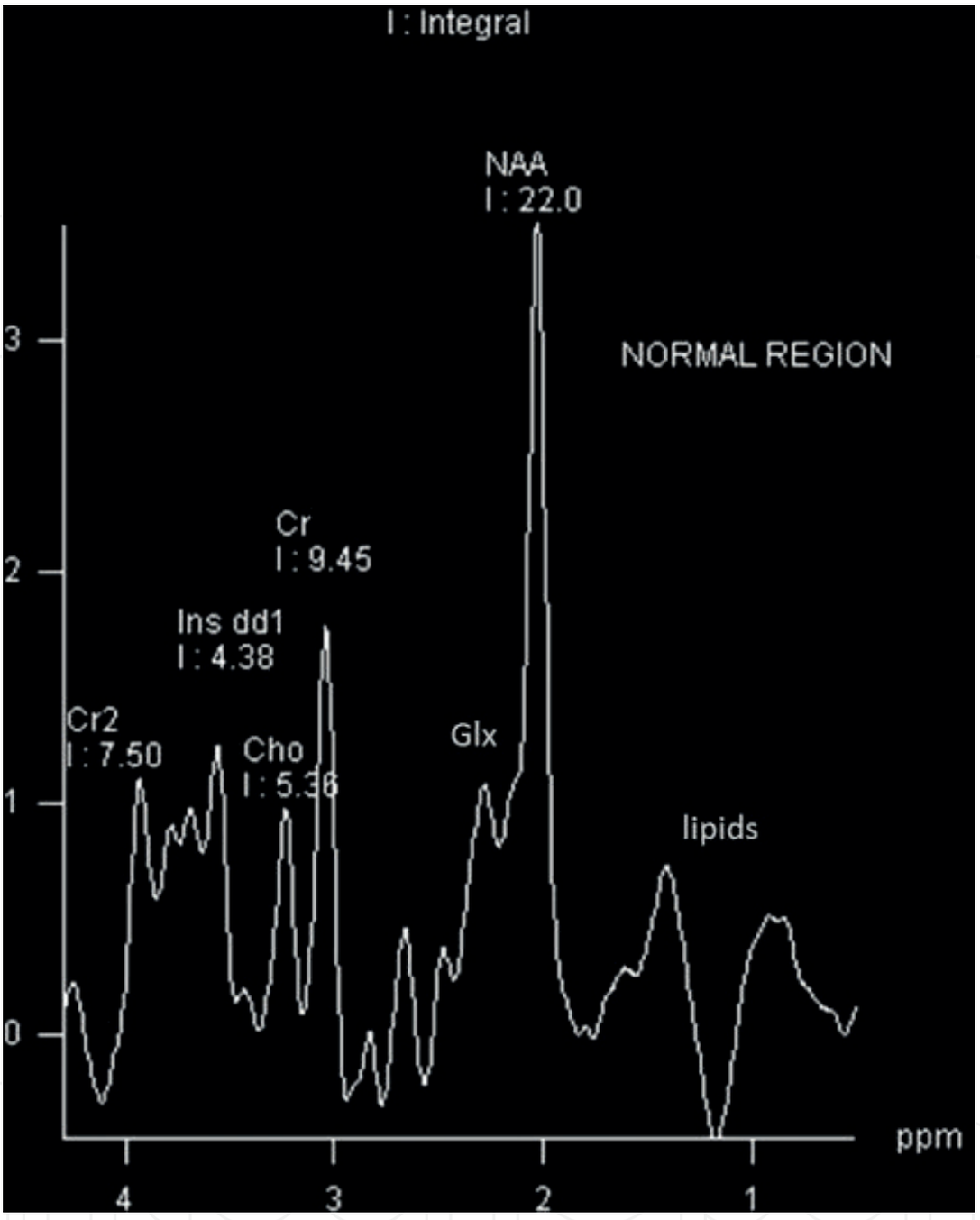


Figure 1. Normal spectra obtained with short TE sequence (TE = 30 ms). Ins dd1, myoinositol; Cho, choline; Cr, creatine; Glx, glutamate glutamine; NAA, N-acetylaspartate [9].

2.3. Choline (Cho)

Choline (Cho) is a metabolic marker of cellular proliferation and cell membrane integrity, that is, phospholipids synthesis and degradation. Choline peak is seen at 3.2 ppm and is the most important metabolic peak for the diagnosis of a glioma [3].

Increased choline reflects increased cell membrane synthesis and degradation. Thus, all processes resulting in increased membrane turnover like primary brain neoplasm and myelin breakdown like demyelinating lesions lead to increased choline concentration [5].

2.4. Myoinositol (Myo)

Myoinositol (Myo) is a simple sugar assigned at 3.56 ppm.

It is considered as a glial marker because it is primarily synthesized in glial cells, almost only in astrocytes. It is also the most important osmolyte in astrocytes [3].

The elevation in Myo detected can be found in cerebral diseases associated with marked gliosis. Myo concentration is higher in low-grade glioma (LGG) when compared to high-grade glioma. Thus, a higher Myo/Cr ratio is seen in low-grade glioma [6].

2.5. Lactate (lac) and lipids (lip)

Lactate (Lac) and lipids (Lip) are known as anaerobic metabolism markers. They are represented as a doublet peak in the MR spectra at 1.31 ppm. It is important to note that lactate is not detected in healthy adult brain tissue. There is direct correlation between Lac level and glioma grade [3].

Malignant transformation of the glial tumors is usually accompanied by an increase in cell density with their relative ischemia resulting in a higher level of Lac. When ischemia of tumorous tissue progresses further, the peaks of Lip increase, indicating the presence of necrosis and the destruction of myelin sheaths [7].

Thus, the level of Lip detected by MRS appears to reflect the severity of tissue damage.

2.6. Glutamate (Glu)-glutamine (Gln) and gamma-amino butyric acid

Glx is a complex peak from glutamate (Glu), glutamine (Gln), and gamma-amino butyric acid (GABA) assigned at 2.05–2.50 ppm [1].

These metabolite peaks are difficult to separate at 1.5 T. Glu is an important excitatory neurotransmitter and plays a role in the redox cycle [8, 9].

An elevated concentration of Gln is found in a few conditions such as hepatic encephalopathy [9].

2.7. Alanine (Ala)

Alanine (Ala) is an amino acid and is a doublet peak assigned at 1.48 ppm.

This peak is located above the baseline in spectra obtained with short or long TE and inverts below the baseline at intermediate TE = 135–144 ms [1].

The function of Ala is uncertain; however, it plays a role in the citric acid cycle. Alanine peak may be obscured by lactate peak [8].

An increased concentration of Ala may occur in oxidative metabolism defects [9].

In tumors, an elevated level of Ala is considered specific for meningiomas [1].

2.8. Other amino acids

In addition to alanine, other amino acids may be seen in various pathologies. Peaks of various amino acids may be seen at many levels, 0.9—valine and 3.6—leucine. Amino acids are also seen in abscesses and neurocysticercosis [10].

3. MRS in tumor grading

This is mainly used for glioma grading. Differentiation between low-grade and high-grade gliomas is important for estimating the prognosis and for therapeutic planning. Proton MRS may indicate the tumor grade with more accuracy because it assesses a larger amount of tissue than what is usually excised during the biopsy.

Gliomas are heterogeneous and their spectra vary depending on the region sampled by MRS. Hence, the region of interest chosen for analysis has a higher influence on the results. Multivoxel spectroscopy is generally considered preferable because it allows metabolic heterogeneity to be evaluated in different components of the tumor.

3.1. Useful metabolites for suggesting the tumor grade

3.1.1. Choline

Statistically significant higher values of Cho/Cr and Cho/NAA are observed in high-grade than in low-grade gliomas.

Although the cutoff values of metabolite ratios for grading of gliomas are not well established, Cho/Cr is the most frequently used ratio. Some institutions use a threshold value of 2.0 for Cho/Cr to differentiate low-grade from high-grade gliomas; others use a cutoff value of 2.5.

Although increased Cho is related to tumor grade, few of grade IV gliomas have lower levels of Cho than grade II or grade III gliomas [11]. This may be due to the presence of necrosis in high-grade tumors, because necrosis is associated with a prominent lipid peak along with the reduction of rest other metabolites [12].

3.1.2. Lipids and lactates

The presence of lipids and lactates correlates with the necrosis in high-grade gliomas. High-grade and low-grade tumors and their margins could be differentiated based on the lactate/lipid peaks.

Lipids peak is also found in metastasis. When lipids peak is observed in solid tumors, lymphoma should also be considered.

An increase in the lipid peak is inversely correlated to prognosis [12].

3.1.3. Myoinositol

Useful information on tumor grade can be obtained by assessing the myo levels at short TE (30–35 ms).

Myo/Cr ratio is typically higher in low-grade than in high-grade gliomas. This may be due to a low mitotic index leading to lack of activation phosphatidylinositol metabolism resulting in the accumulation of myo in low-grade gliomas.

In gliomas without alteration in Cho/Cr ratio, increased levels of Myo have been reported to be useful in the identification of low-grade tumors [12].

3.1.4. NAA and Cr

A greatest reduction in NAA and Cr levels has been observed in higher-grade tumors. As the grade of the tumor increases, NAA/Cr ratio decreases and Cho/NAA ratio increases.

4. Other applications of MRS in brain

4.1. Response to radiotherapy

Differentiation between recurrent brain tumor and radiation change/injury is an important concern in postradiotherapy patients with brain tumors and particularly when fresh contrast-enhancing lesions are seen in previously operated and/or irradiated regions.

Proton MRS is useful in differentiating radiation-induced tissue injury from tumor recurrence. Significantly reduced Cho and Cr levels suggest radiation necrosis; increased lipid and lactate signals can also be seen in necrotic areas.

Increased Cho levels relative to the normal tissue suggest recurrence of the tumor. Cho/Cr and/or Cho/NAA ratios are significantly higher in recurrent tumor than in radiation injury [12].

4.2. Infections

Pyogenic abscess: Amino acid peak at 0.9 ppm is useful in differentiating pyogenic abscess from tumors. Abscess from anaerobic organism in addition has acetate and succinate peaks at 1.9 and 2.4 ppm, respectively [13] .

Tuberculous abscess: Spectra from tuberculous abscess shows lipid-lactate peak at 1.3 ppm. No amino acid peak is observed in tubercular abscess, which helps to differentiate it from pyogenic abscess [14].

Fungal abscess: A spectrum in fungal abscesses shows amino acids and lactate peak along with multiple peaks between 3.6 and 4.0 ppm. These peaks have been assigned to trehalose sugar present in the fungal wall [15].

4.3. Metabolic brain disorder

Proton MR spectroscopy is a useful tool in diagnosing metabolic brain disorders when used as an adjunct to conventional MRI.

In most of the inherited metabolic disorders, MRS findings are abnormal but are not specific for a single metabolic disease or syndrome.

Few metabolic diseases have specific MRS findings, either abnormal elevation or reduction of a single normal peak or detection of abnormal metabolite peak.

Specific MRS patterns are mainly found in Canavan's disease with prominently increased NAA peak and creatine deficiency with a characteristic reduced creatine peak. In nonketotic hyperglycemia, there is an appearance of glycine peak at 3.55 ppm and there is detection of branched-chain amino acids in maple syrup urine disease [16].

4.4. Dementia

Neurodegenerative dementia is characterized by elevated myoinositol and decreased N-acetylaspartate levels.

An increase in myoinositol occurs before the reduction of NAA levels in Alzheimer's disease. An NAA/myo ratio in the posterior cingulate gyri decreases with an increasing burden of Alzheimer's disease.

In patients with mild cognitive impairment, 1H MRS is sensitive in the detection of the pathophysiologic processes associated with the risk of dementia [17].

4.5. Brain ischemia

The characteristic spectroscopic finding in acute brain ischemia is the early appearance of a lactate peak, a decrease of NAA, and a slight increase of choline. Lactate is observed within few minutes following brain ischemia and its concentration reduces in sub-acute phase. The intensity of these peaks in the infracted area is related to the prognosis [18].

4.6. Epilepsy

The role of 1H–MRS in epilepsy is to help in characterizing and localizing the epileptogenic focus, especially in patients with refractory focal epilepsy without clear MR imaging findings.

Temporal lobe epilepsy (TLE) is the most common cause of focal epilepsy; reduction in NAA concentration and NAA/Cho + Cr ratio is observed in TLE, which reflects the neuronal damage [1].

5. Materials and methods

5.1. Study site

The study was conducted at the Department of Radio Diagnosis, Sri Sathya Sai Institute of Higher Medical Sciences, Whitefield, Bangalore 560066.

5.2. Study population

Initially, all patients suspicious for glioma and fulfilling the inclusion and exclusion criteria were imaged with conventional MRI and proton MR spectroscopy. All these patients underwent histopathological examination. Specimens were obtained via surgical resection/biopsy. Patients who had histopathological confirmation of glioma were included in the study. Histopathological grading was done according to WHO classification of brain tumors 2007 [19]. Grades I and II were graded as low-grade and grades III and IV were graded as high-grade tumors.

5.3. Study design

The study design was a prospective study.

5.4. Sample size

$$\text{Sample size} = \frac{Z^2_{1-a/2}\, SD^2}{d^2} \tag{1}$$

where $Z_{1\text{-}a/2}$ is the standard normal variant; SD is the standard deviation of variable; d is the absolute error of precision.

The standard deviation of Cho/Cr for high-grade glioma is 1.92; Cho/Cr ratio is taken because for other ratios the sample size becomes very low. Absolute error of precision was 0.5.

$$\begin{aligned} \text{Sample size} &= (1.96)^2 \times (1.92)^2/0.5 \\ &= 3.8 \times 3.6/0.25 \\ &= 54.72(\text{rounded to } 55) \end{aligned} \tag{2}$$

The minimum sample size was around 55; we have included 70 patients.

5.5. Duration of the study

The duration of study was over a period of 14 months from 01-10-2014, to 01-02-2016.

5.6. Inclusion criteria

- All cases with neuroparenchymal space occupying lesions suspicious for gliomas on MRI.
- All age groups.

- Both male and female patient population.

5.7. Exclusion criteria

- Postoperative and postradiotherapy patients.
- Unavailability of histopathological examination.
- MR spectroscopy with artifact, baseline noise, and uninterruptable spectra.
- MRI contraindicated patients:
  - Patients with cardiac pace maker
  - Patients with aneurysm clips in the brain
  - Patients with a metallic foreign body in the eye
  - Patients with severe claustrophobia
  - Pregnant patients
  - Mentally ill patients.

5.8. Methodology

- Concurrence was taken from the chairman, academic committee, scientific committee, and ethical committee for the study.
- Written informed consent was obtained prior to subject enrolment into the study.
- All the patients were subjected to conventional MRI and proton MR spectroscopy.

5.9. Magnetic resonance imaging

For all patients, initially MR imaging was performed with Siemens 1.5 T Magnetom Aera.

A localizing sagittal T1-weighted image was obtained followed by non-enhanced axial and coronal T2-weighted (4500/102 [TR/TE]), axial fluid-attenuated inversion-recovery (FLAIR, 8500/86/2500 [TR/TE/TI]), and T1-weighted axial (600/9 [TR/TE]) images, Susceptibility weighted imaging (50/40 [TR/TE]). Contrast material-enhanced axial T1-weighted imaging was performed.

5.10. Magnetic resonance spectroscopy

After the conventional MRI volume of interest from the lesion (VOI) was selected from T1 post-contrast images, VOI was selected from the solid part of lesion with edges of the voxel well within the mass and in most of the cases perilesional edema was included within the VOI. VOI was carefully selected so that it will not include areas of hemorrhage or calcification and unintended areas like ventricles, calvarium, and so on.

In our institution, we used Multivoxel MR spectroscopy technique (chemical shift method) at intermediate TE of −135 ms.

A typical VOI consisted of an 8 × 8 cm region placed within a 16 × 16 cm field of view on a 1.5-cm transverse section. A 16 × 16 phase-encoding matrix was used to obtain 8 × 8 arrays of spectra in the VOI, with an in-plane resolution of 1 × 1 cm and a voxel size of 1 × 1 × 1.5 cm^3. The time taken to acquire spectra was around 8 min.

The metabolite peaks were assigned as follows: Cho, 3.22 ppm; Cr, 3.02 ppm; NAA, 2.02 ppm; lactate was identified at 1.33 ppm by its characteristic doublet and inversion at intermediate TE. Lipid peak was demonstrated at 0.9–1.3 ppm without inversion at intermediate TE. Metabolite ratios were obtained for Cho/Cr, Cho/NAA, NAA/Cr, and lactate/Cr. Maximal Cho/Cr, Cho/NAA and lactate/Cr and minimum NAA/Cr ratios were obtained from spectral maps. Lactate/Cr was used instead of lipid-lactate/Cr used by other studies in literature because lipid peak was not consistently seen in most of the cases at intermediate TE.

5.11. Statistical methods

The data collected were entered into a Microsoft excel spreadsheet and analyzed using IBM SPSS Statistics, Version 22 (Armonk, NY: IBM Corp). Descriptive data were presented in the form of frequency, percentage, mean, median, standard deviation, and quartiles. The metabolite ratios of Cho/Cr, Cho/NAA, NAA/Cr, and lactate/Cr were calculated. The metabolite ratios between the low-grade and high-grade gliomas were compared using Mann–Whitney *U*-test. Comparisons of the categorical variables between the two groups were performed using the chi-squared test. Receiver-operating characteristic (ROC) curve analysis was done to evaluate the performance of the metabolite ratios in differentiating high-grade and low-grade gliomas. The area under the ROC curve was calculated to summarize the performance of each metabolite in differentiating the two grades of glioma. The sensitivity, specificity, positive-predictive value (PPV), negative-predictive value (NPV), and diagnostic accuracy with each metabolite were assessed using the cutoff value obtained with minimum C1 error from the ROC analysis. A *P*-value of <0.05 was considered as statistically significant. In the same way, ROC curve analysis was done to evaluate the performance of metabolite ratios in differentiating grade II and grade III glioma. By similar way, sensitivity, specificity, positive-predictive value, negative-predictive value, and diagnostic accuracy with each metabolite were assessed using the cutoff value obtained with minimum C1 error from the ROC analysis in differentiating grade II and grade III gliomas.

6. Results

Seventy histopathologically proved cases of gliomas were included in the study. Grade I [14] and grade II [19] gliomas were classified as low-grade and grade III [22] and grade IV [15] were classified as high-grade tumors.

All patients underwent conventional MRI sequences and proton MR spectroscopy. Quantitative values were calculated for Cho/Cr, Cho/NAA, NAA/Cr, and lactate/Cr ratios. Grading by conventional MRI was also done to know the additional usefulness of MRS in grading of gliomas.

The sensitivity, specificity, PPV, and NPV of conventional MRI in grading of gliomas were 62.2, 78.8, 76.7, and 65%, respectively, with the total diagnostic accuracy of 70%.

The sensitivity, specificity, PPV, and NPV of proton MR spectroscopy in differentiating the grades of glioma were high in comparison to conventional MRI indicating that proton MRS spectroscopy is a useful tool in differentiating grades of glioma.

Lac/Cr ratio had a total diagnostic accuracy of 95.12%. Cho/NAA and Cho/Cr ratios had a total diagnostic accuracy of 88.57 and 88.43%, respectively.

Metabolite ratio that had the highest diagnostic value was lactate/Cr followed by Cho/NAA and Cho/Cr in differentiating low- and high-grade gliomas.

NAA/Cr ratio had poor diagnostic significance in differentiating the grades of gliomas.

The presence of lipid peak was found to be suggestive of high-grade gliomas and was found in about 46% of high-grade gliomas.

Other metabolite peaks like myoinositol and glutamate could not be evaluated.

MRS had the added advantage in combination with conventional MRI with good diagnostic accuracy in differentiating grade II and grade III gliomas. Lactate/Cr had the highest diagnostic value followed by Cho/NAA and Cho/Cr in differentiating the two grades.

7. Discussion

Tumor grade is the most important key factor in determining treatment plan. Treatment plan for low-grade glioma is surgical resection; adjuvant radio chemotherapy is only recommended for patients with incompletely resected grade II tumors or for patients older than age of 40 years. Whereas high-grade glioma always require chemotherapy and/or radiotherapy following surgery; therefore, preoperative grading of glioma is necessary for good patient care and to reduce the morbidity and mortality [19].

The current "gold standard" for the determination of glioma grade is histopathological examination. It has few limitations; the most significant one is limited number of samples which creates potential errors in determining the glioma grade. When samples are not taken from the most malignant region of tumor during biopsy or when the tumor has not been completely resected, histopathological grading becomes inaccurate. This problem is particularly observed in glioma because of the infiltrative and heterogeneous nature of these tumors; the region of highest malignancy may then be within the peritumoral or perilesional-enhancing region [20, 21].

Because histopathological examination requires biopsy/surgical resection which are invasive, it has morbidity of up to 3.6%, hemorrhage rate of up to 8%, and mortality of up to 1.7%, as assessed over a large number of studies [22].

Alternatively, many noninvasive or minimally invasive imaging technologies have been used to evaluate the malignancy of brain tumors [20, 21].

In our study, grades I and II were graded as low grade and grades III and IV were graded as high grade [19].

We have used the following criteria for grading gliomas by conventional MRI: margins of the lesion, perilesional edema, heterogeneity of lesion, mass effect, crossing the midline, hemorrhage, necrosis, and enhancement pattern. Other studies have also used the similar criteria [21].

Sensitivity, specificity, PPV, and NPV of conventional MRI in grading of gliomas were found to be 62.2, 78.8, 76.7, and 65%, respectively, with the total diagnostic accuracy of 70%.

In other studies conducted by Law et al. [21], Zou et al. [19], and Ellika et al. [23], the sensitivity ranged from 72 to 86% and the specificity ranged from 60 to 67%.

Other studies in literature have shown sensitivity ranging from 55 to 83% [19, 21].

A study conducted by Dean et al. [24] and Atkinson et al. [25] showed that a high-grade glioma may be mistaken for a low-grade when it demonstrates minimal edema, no contrast enhancement, no necrosis, and no mass effect. Conversely, low-grade gliomas sometimes can be mistaken for a high-grade when it demonstrates peritumoral edema, contrast material enhancement, central necrosis, and mass effect.

Low diagnostic accuracy in our study was because of the overlapping imaging features in low- and high-grade gliomas, predominantly between grades II and grade III. Fourteen cases of grade III tumors were classified as low grade because they had imaging features favoring low grade such as minimal perilesional edema, no significant mass effect, no contrast enhancement, no necrosis, and no hemorrhage.

Seven cases of low-grade gliomas were classified as high grade since they had imaging features favoring high grade such as significant perilesional edema, mass effect, presence of necrosis or hemorrhage, and heterogeneous contrast enhancement.

In our study, the most consistent characteristics on MRI to predict the grade were necrosis, mass effect, and crossing the midline.

A study conducted by Dean et al. [24] has shown that mass effect and necrosis are the most important characteristic for predicting tumor grade by conventional MRI.

Because of the limitations of conventional MRI in differentiating high- from low-grade gliomas, advanced multi-parametric magnetic resonance techniques have been used in grading of gliomas and they are diffusion-weighted imaging (DWI), proton MR spectroscopy, and perfusion imaging [19].

Magnetic resonance spectroscopy is one of the advanced adjuvant MR techniques and because of its safe and noninvasive nature it is of great advantage in characterizing gliomas.

Because glial tumors have some specific metabolic characteristics which further differ according to the grade, there is growing interest in MR spectroscopy that could further increase the sensitivity of routinely used diagnostic imaging [3].

In our study, we have used Cho/Cr, Cho/NAA, NAA/Cr, and lactate/Cr ratios for grading since the study was done at intermediate TE, prominent peaks seen were Cho, Cr, NAA, and lactate.

In literature, Cho/Cr, Cho/NAA, and NAA/Cr were the commonly used metabolites [19, 21]. Lipid-lactate ratio was used for grading of gliomas in few studies [26]; we have used lactate/Cr ration since lipid peak was not consistently seen in a majority of cases at intermediate TE.

In our study, the values of mean and median for Cho/Cr, Cho/NAA, and NAA/Cr had statistically significant difference between low- and high-grade gliomas.

Other studies have also shown significant difference of mean for Cho/Cr, Cho/NAA, and NAA/Cr between low- and high-grade gliomas [10].

NAA is a neuronal marker and decreases in all gliomas since the neurons are destroyed and/or substituted by the malignant cells. The elevation of choline is due to the increased cellularity and cell membrane turnover. The decrease in creatine is due to the altered energy metabolism in the cells and can be attributed to the low energy status of the glycolyzing tumors. Therefore, the typical MRS characteristics of a glioma are elevated Cho with reduction in NAA and Cr signals. This results in an absolute increase in Cho/Cr and Cho/NAA and a decrease in NAA/Cr ratios [1].

Lac/Cr ratio in our study had significant difference in mean between low- and high-grade gliomas.

Studies conducted by Yoon et al. [26] and Kim et al. [27] showed significant difference in mean values for lipid-lactate/Cr between low- and high-grade gliomas.

Since lactate is a marker of anaerobic glycolysis, malignant transformation of glial tumors is accompanied by an increase in cell density with relative ischemia resulting in a higher level of lactate. There is a direct correlation between Lac levels and glioma grade with higher peaks seen in higher-grade tumors [3]. Therefore, Lac/Cr ratio increases with an increase in the malignant potential of tumor.

In a clinical setting, where decisions such as the extent of tumor resection, the dose of post-operative chemo radiation, and the interval of follow-up must be made, cutoff values can be used as important supplementary information in noninvasive grading of gliomas [21].

In our study, we have provided cutoff values for Cho/Cr, Cho/NAA, and lactate/Cr ratios to differentiate low- from high-grade gliomas.

A cutoff value of 1.76 for Cho/Cr and 2.22 for Cho/NAA ratio provided good sensitivity, specificity, PPV, and NPV with a total diagnostic accuracy of 78.05 and 82.93%, respectively, in differentiating low- from high-grade gliomas.

Other studies in literature have given a cutoff value ranging from 1.56 to 2.04 for Cho/Cr and 1.6 to 2.49 for Cho/NAA. These values provided good sensitivity, specificity, PPV, and NPV with a total diagnostic accuracy ranging from 81 to 88% [21].

Even though the cutoff value for Cho/Cr and Cho/NAA provided by our study was comparable with other studies in literature [21], the small variation in cutoff value between studies is possibly because of differences in the MRS imaging methods, including magnetic resonance field strength, acquisition parameters, voxel size and location, heterogeneity of tumor, and sample size and distribution.

A cutoff value of 0.68 for Lac/Cr ratio provided an excellent diagnostic accuracy of 95.12% which was the most useful metabolite ratio in differentiating low- from high-grade gliomas in our study.

Limited studies in literature have given cutoff for lipid-lactate/Cr ratio in grading of gliomas. A study performed by Kim et al. gave a cutoff value of 0.59 for lipid-lactate/Cr [28]. A study performed by Yoon et al. gave a cutoff of 1.39 with a sensitivity of 64.6% and a specificity of 91.7% [26].

There was no cutoff value given for NAA/Cr ratio in our study even though the mean values were statistically significant in differentiating high- and low-grade gliomas because of overlapping of NAA/Cr values between the grades; out of 37 people in high-grade gliomas, 29 (78% of high-grade glioma cases) had values higher than the lowest value in low grade.

Zeng et al. [28] and Liu et al. [29] have given cutoff values of 0.72 and 0.97 for NAA/Cr ratio to differentiate low- and high-grade gliomas with a diagnostic accuracy of 73–75%.

In our study, lipid peak was found in 46% of high-grade and 12% of low-grade gliomas. A prominent lipid peak in high-grade gliomas was due to necrotic component.

Other studies have also shown that gliomas are heterogeneous tumors and they include areas of viable tumor, necrosis, and hemorrhage. Elevated lipid peaks are often found in high-grade gliomas due to the necrotic portion [30, 31].

Since our study is carried out at intermediate TE (135 ms), we could not evaluate other peaks like myoinositol and glutamate. Few cases had myoinositol peak but the peak was not consistently seen to comment upon.

Differentiation between grade II and III gliomas is clinically important since the treatment plan and prognosis are different but it is difficult to differentiate them on conventional MRI because of the overlapping imaging characteristics [32].

Literature review showed limited studies to differentiate grade II and grade III gliomas. In our study, we analyzed and tried to establish cutoff values to differentiate grade II and grade III gliomas.

Lactate/Cr had excellent diagnostic value followed by Cho/NAA and Cho/Cr ratios. NAA/Cr had poor diagnostic value in differentiating the grade II and grade III because of the overlapping of values.

Cutoff values for Cho/Cr, Cho/NAA, and lactate/Cr ratios were 1.76, 2.22, and 0.685 with good sensitivity, specificity, PPV, and NPV. Diagnostic accuracy was 78.05, 82.93, and 95.12% for Cho/Cr, Cho/NAA, and lactate/Cr, respectively.

Stadlbauer et al. [23] found that there was significant difference in Cho, Cr, and NAA levels between grade II and grade III gliomas, and all patients with a grade II glioma had a Cho/NAA ratio of less than 0.8, whereas all patients with a grade III glioma had a Cho/NAA ratio of greater than 0.8.

Zonari et al. [33] found the sensitivity, specificity, PPV, and NPV for Cho/Cr ratio to be 75.6 45, 60.7, and 62.1 and NAA/Cr ratio to be 64.4, 65, 67.4, and 61.9 in differentiating grade II from grade III gliomas by a logistic regression analysis.

Advanced multi-parametric magnetic resonance techniques, including DWI, DTI, and MR perfusion and multimodal imaging including PET/SPECT, also compliment MRS to distinguish HGGs from LGGs. Though it is controversial which imaging technique is superior, most authors concluded that combined techniques would improve the diagnostic accuracy [19].

8. Limitations

1. Our study was done at a magnetic field strength of 1.5 T. A higher-field strength of 3 T or more would have yielded a better spatial resolution and high SNR.
2. Small sample size may reduce or bias the power of the results. Further studies with a larger sample size are necessary to extend these results.
3. Our sample volume predominantly consists of astrocytomas, and other glial tumors like oligodendrogliomas and ependymomas were less frequent.
4. Our study was carried at intermediate TE, so we could not evaluate smaller metabolite peaks like myoinositol and glutamate. MRS at short TE would have given spectra with multiple metabolite peaks.
5. Comparison of MRS with other advanced MR techniques like perfusion and DTI would have given additional value in grading of gliomas.

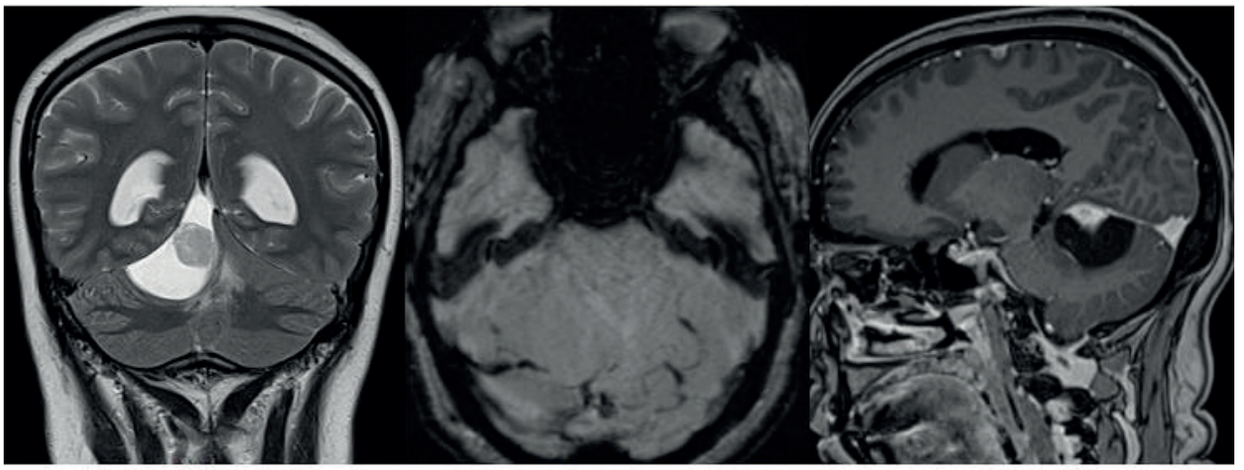
9. Conclusion

MRS is an important diagnostic and research tool in clinical neuroscience. MRS is a very useful tool in combination with conventional MRI for grading of gliomas. Lactate/creatine ratio has highest diagnostic accuracy followed by choline/NAA and choline/creatine ratios. NAA/creatine has least diagnostic significance in grading of gliomas. Lipid peak on MRS is more frequently found in high-grade gliomas. MRS could differentiate grade II and grade III gliomas more effectively in comparison to only conventional MRI. Apart from tumor grading, MRS can support the diagnosis in many brain infections by showing the specific metabolite peaks. It is also helpful in diagnosis of post-radiotherapy patients when differentiation between recurrent brain tumor and radiation change/injury is the concern. It also has a significant role in narrowing the differential diagnosis of metabolic brain disorders. MRS is also important in the diagnosis of stroke and demyelination in brain.

A. Appendix A

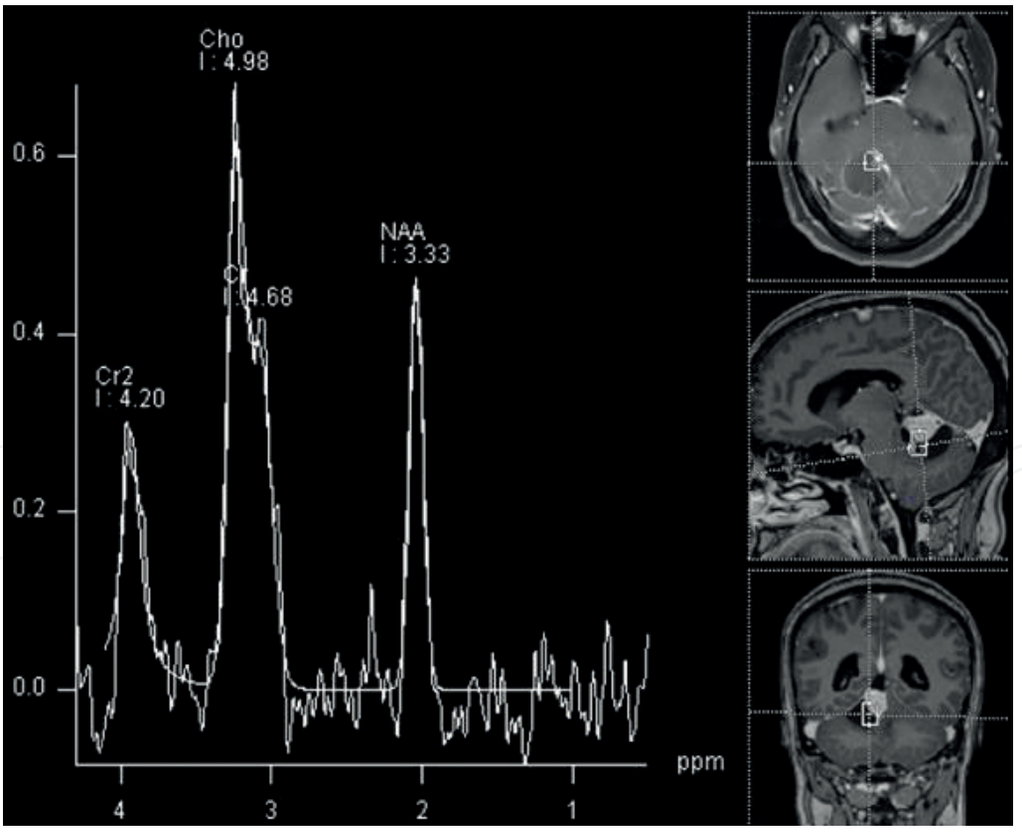
A.1. Representative cases

Case 1. A 46-year-old female presented with headache since 1 year.



MRI shows well-defined cystic lesion with enhancing peripheral mural nodule in the right cerebellar hemisphere with mild perilesional edema. Local mass effect on the adjacent neuroparenchyma. No areas of hemorrhage on SWI. No areas of necrosis.

Diagnosed as low-grade glioma on conventional MRI.



MRS: Elevated choline, reduced NAA, and Cr. Cho/Cr: 1.63; Cho/NAA: 1; NAA/Cr: 1.09; lactate/Cr: 0.18. No lipid peak.

Histopathological diagnosis: Pilocytic astrocytoma (grade I glioma).

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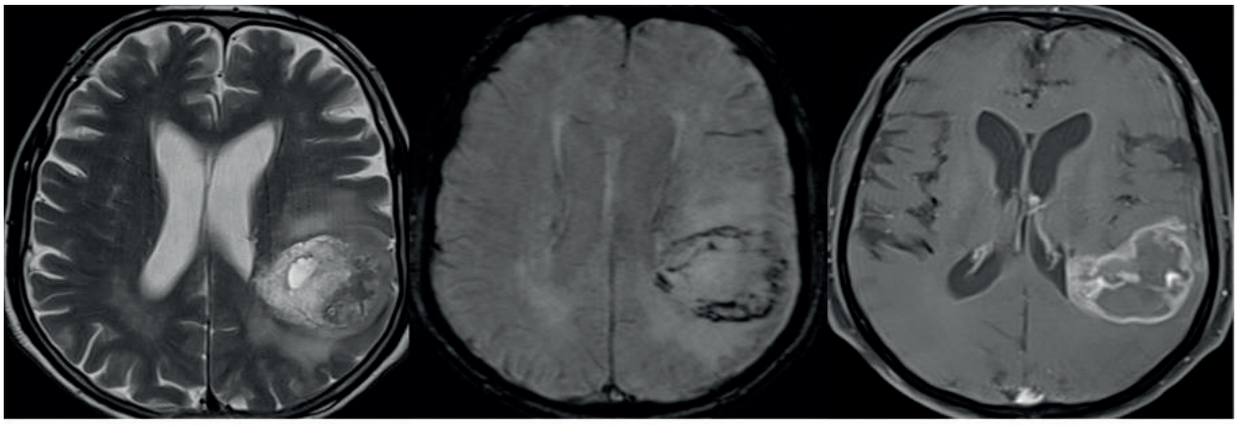
Case 2: A 70-year-old male presenting with seizures since 2 months.

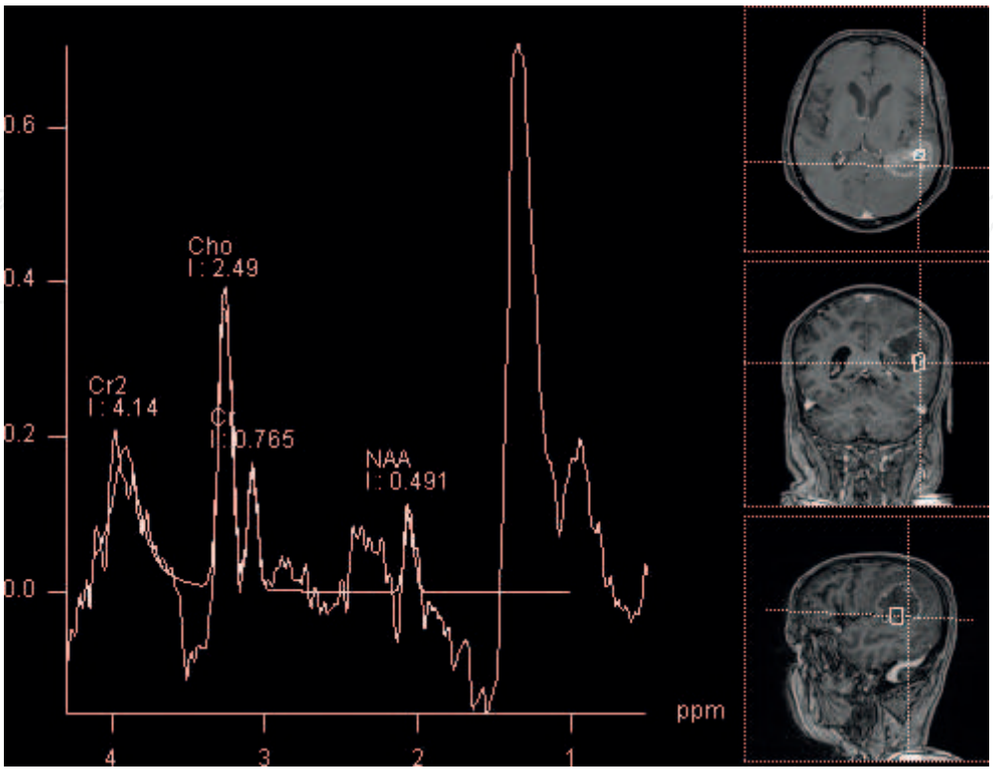


MRI shows relatively well-defined heterogeneous lesion noted in the left parietal lobe with moderate perilesional edema. There is mass effect on the adjacent neuroparenchyma without midline shift. Areas of necrosis and hemorrhage noted within the lesion. Peripheral nodular enhancement is seen.

Diagnosed as high-grade glioma on conventional MRI.

Relatively well-defined heterogeneous lesion noted in the left parietal lobe with moderate perilesional edema. There is mass effect on the adjacent neuroparenchyma without midline shift. Areas of necrosis and hemorrhage noted within the lesion. Peripheral nodular enhancement is seen.

Diagnosed as high-grade glioma on conventional MRI.

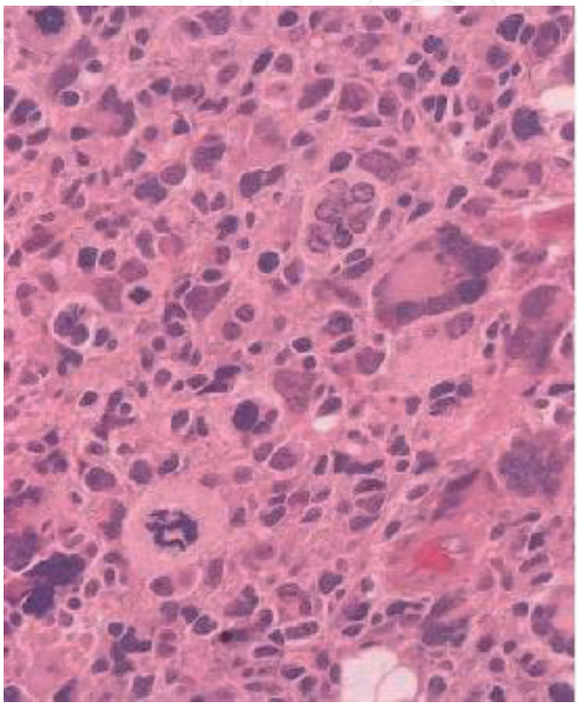


MRS: Elevated choline, reduced NAA, and Cr.

Cho/Cr: 2.47; Cho/NAA: 3.5; NAA/Cr: 0.7; lactate/Cr: 1.

Lipid peak present.

Histopathological diagnosis: GBM (grade IV glioma).



Paraffin section with hematoxylin and eosin stain showing marked nuclear pleomorphism and mitotic figures.

Author details

B C Hamsini[1], Bhavana Nagabhushana Reddy[2], Sankar Neelakantan[2] and Sunitha Palasamudram Kumaran[1,2]*

*Address all correspondence to: drsunitha27@gmail.com

1 Neuroimaging, Toronto Western hospital, Toronto, Ontario, Canada

2 Department of Radiology, Sri Sathya Sai Institute of higher medical sciences, Bangalore, India

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