Original Article

1H-MR spectroscopy in grading of cerebral glioma: A new view point, MRS image quality assessment

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Abstract

Background: Noninvasive preoperative prediction of histological grading is essential for clinical management of cerebral glioma.

Purpose: This study aimed to investigate the association between the image quality assessment of 1H magnetic resonance spectroscopy and accurate grading of glioma.

Materials and Methods: 98 glioma patients confirmed by pathology were retrospectively recruited in this single-center study. All patients underwent 1H-MRS examination at 3.0T before surgery. According to WHO standards, all cases were divided into two groups: low-grade glioma (grade I and II, 48 cases) and high-grade glioma (grades III and IV, 50 cases). The metabolite ratios in both grades were calculated before and after image quality assessment. The area under the receiver operating characteristic (ROC) curve was used to evaluate the capacity of each ratio in glioma grading.

Results: The Cho/Cr, Cho/NAA and NAA/Cr metabolite ratios had certain differences in each glioma group before and after MRS image quality assessment. In the low-grade glioma group, there was a dramatic difference in the Cho/Cr ratio before and after image quality assessment ($p = 0.011$). After MRS image quality assessment, the accuracy of glioma grading was significantly improved. The Cho/Cr ratio with 83.3% sensitivity and 93.7% specificity is the best index of glioma grading, with the optimal cutoff value of the Cho/Cr ratio being 3.72.

Conclusion: The image quality of MRS does affect the metabolite ratios and the results of glioma grading. MRS image quality assessment can observably improve the accuracy rate of glioma grading. The Cho/Cr ratio has the best diagnostic performance in differentiating high-grade from low-grade glioma.

Keywords
1H-MRS, glioma grading, quality assessment

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Introduction

Glioma is the most common primary tumor of the central nervous system (CNS), and the incidence rate is increasing every year.[1] The malignancy degree of gliomas is critical to the treatment regimens and prognosis. Noninvasive preoperative prediction of histological grading is essential for the clinical management of cerebral glioma, and is closely related to survival probability.[2–4] Conventional magnetic resonance imaging (MRI) is considered to be a useful tool

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for differentiating between high-grade glioma and low-grade glioma, but provides only limited information on the biological behavior of the tumor.[5] Proton 1H magnetic resonance spectroscopy (1H-MRS), which is a noninvasive functional imaging method providing complementary information to anatomical imaging, has been proposed as an additional technique for cerebral glioma grading. Several studies have proven that the MRS technique has the potential to accurately predict cerebral glioma grading than conventional MRI.[6–10] A meta-analysis of 30 articles comprising a total sample size of 1228 patients showed that MRS demonstrated moderate diagnostic performance in glioma grading by using metabolite ratios including Cho/Cr, Cho/NAA, and NAA/Cr.[11] Recent studies support the use of MRS in tumor grading. Extensive literature demonstrates that the metabolite ratios of Cho/Cr, NAA/Cr, and *myo*-inositol/Cr, and the presence of lipids and lactate are useful in tumor grading and predicting of tumor malignancy.[12–15] Other studies also support the use of MRS as a powerful tool in the characterization of metabolic changes associated with tumor grading and progression. Specially, elevation in choline with depression of N-acetylaspartate is a reliable indicator of tumor characterization.[6,16]

There has been no consensus on the best metabolite indicators and cutoff value in glioma grading. We believe that the reason for this phenomenon is the lack of MRS image quality assessment, resulting in uneven quality of the spectrum.

The American College of Radiology defined the practice parameter and technical standard of MRS, and proposed that it can be useful in the diagnosis and management of patients, but its findings may be misleading due to many reasons. MRS inspection process is relatively complex, and many technical factors can affect the spectral quality and metabolite ratios. Among them, MRS scanning has a harsh requirement for magnetic field uniformity and water suppression of the MR imaging equipment. Shimming and water suppression are key technologies for achieving high-quality MRS.[17] According to clinical experiences and results from previous studies, the main factors affecting the quality of the MRS image include the water linewidth (WBW), full-width at half-maximum peak height (FWHM), water suppression (WS), signal-to-noise ratio (SNR), spectral baseline, spectral lineshape, and all kinds of artifacts.[18–23] We speculate that poor quality of the MRS image may result in glioma grading errors, reducing its reliability and diagnostic performance, and also affecting the clinical application and promotion. Therefore, access to a high-quality spectrum image is a prerequisite to improve the accuracy of glioma grading. Although many studies have begun to focus on MRS quality assessment, there is still a lack of clinical application research on quality assessment[18,24,25] Accurate diagnostic imaging rely on high-quality images. The success standard of MRS is the ability to get high-quality images to meet the requirements of clinical diagnosis.

In this study, we preliminarily established a spectral image quality assessment flow path to screen out high-quality MRS data. Before and after MRS image quality assessment, we compared the spectrum characteristics in gliomas to investigate the relationship between image quality and glioma grading. This research aims to raise awareness regarding quality assessment and strict control of the spectral quality, and maximizing the accuracy of MRS for glioma grading.

Materials and methods

Patients

A cohort of 98 glioma patients was evaluated after pathological confirmation. For this purpose, a retrospective study was conducted from January 2015 to February 2017. Histopathology diagnosis was graded by the 2016 World Health Organization (WHO) criteria. All the patients were recruited according to following inclusion criteria: (a) All patients underwent 1H-MRS examination before surgery and (b) the clinical record and MRS image data of the patient were available.

Patient's demographics

All the cases were divided into two groups based on histopathology reports: low-grade glioma group and high-grade glioma group. A total of 48 cases in the low-grade glioma group, 26 cases of males and 22 cases of females, with an average age of 39.2 ± 13.5 years. There were 50 cases in the high-grade glioma group, 22 cases of males and 28 cases of females, with an average age of 48.6 ± 15.5 years.

Data acquisition

All 1H-MR spectroscopy studies were performed according to routine clinical protocols at each center on a 3T scanner (Signa HDxt; GE Medical Systems, Waukesha, WI, USA). The 8-channel head phase array coil was used for multi-sequence, multi-directional, and multi-parameter imaging. Axial T2-weighted fast spin-echo sequences (5200/109; 24-cm field of view; thickness, 5 mm; slice spacing, 1.5 mm; scanning time, 1.08 sec) or fluid-attenuated inversion recovery (FLAIR) (8725/165; 24-cm field of view; thickness, 5-mm; slice spacing, 0.5 mm; scanning time, 53 sec) were obtained to define the volume of interest (VOI). VOI size ($20\times20\times20$ mm^3 $150\times150\times150$ mm^3) was set according to the area of VOI which varied depending on the tumor size. The size and location of the voxel were carefully adjusted to include as much of the solid tumor portion as possible. The data was not very significant in relation to the size of the VOI was excluded which also includes some large VOI data.

We intended to avoid voxels with obvious necrosis, hemorrhage, and calcification. All 1H spectroscopic

acquisition methods were applied to combine the point-resolved spectroscopy sequence (PRESS) with chemical shift selective water suppression (TR/TE, 1100 ms/144 ms).

Spectral analysis

MRS raw data were automatically evaluated via the Functool package on the GE ADW4.4 workstation. The T2 fast spin-echo (FSE) image including the largest lesion level was used as the positioning image of the MRS, and the axial, coronal, and sagittal planes were co-located. The VOI changes according to the size of the tumor, including as much of the solid tumor as possible, and the region of interest (ROI) of the same size was selected as a control in the symmetrical part of the normal brain tissue area and the lesion on the opposite side. MRS pre-scan was routinely preceded with shimming and water suppression, and the water WBW and WS were evaluated for each patient. The image processing included spectral phase correction, baseline correction, and calculating the area under each metabolite peak. The peak area corresponding to each compound was determined according to the chemical shift used to estimate the concentration of the compound. Chemical shift of major metabolites choline (Cho) at 3.22 ppm, N-acetylaspartic acid (NAA) at 2.02 ppm, creatine (Cr) at 3.03 ppm, lactate at 1.32 ppm, and lipid at 0.9–1.30 ppm in each area were recorded, and then ratio of Cho/Cr, Cho/NAA, and NAA/Cr was calculated. Among them, Cho/Cr and Cho/NAA had the maximum value, while NAA/Cr had the minimum value.

Functool software was used to calculate the Cho/Cr, Cho/NAA, and NAA/Cr ratios. After obtaining the spectrum, we observed and recorded the baseline, linetype, signal-to-noise ratio, and artifacts of each spectrum.

Data extraction

We extracted the patient's basic information (age, gender, and hospital number), MRS data (Cho/Cr, Cho/NAA, NAA/Cr, and LL peak), imaging results, pathological results (tumor type and WHO classification) and other information. The ratio of Cho/Cr, Cho/NAA, and NAA/Cr in the tumor area and the normal brain tissue were recorded, respectively. The Cho/Cr and Cho/NAA ratios had the maximum value, and the NAA/Cr ratio had the minimum value.

MRS image quality assessment flow chart

Through extensive literature review and clinical practice, we explored the MRS image quality factors and preliminarily established MRS image quality assessment flow chart. We divided the MRS image quality assessment into objective evaluation and subjective evaluation as two parts. Objective evaluation included WBW, FWHM, and WS. Subjective evaluation included signal-to-noise ratio (SNR), spectral baseline, spectral lineshape, and artifact recognition. Among them, high-quality MRS data were based on the following conditions: at the same time to meet the WBW < 10 Hz, WS > 98%, FWHM < 0.1 ppm, high signal-to-noise ratio SNR >10, smooth baseline, linear symmetry, and few or no artifacts.[24,26,27] Through the MRS quality assessment flow chart, high-quality MRS data were screened out. The glioma patients with high-quality MRS images were used as new subjects to carry out the next study. A flow chart to determine whether the spectrum was adequate for clinical use is shown in Figure 1.

Statistical analysis

SPSS 18.0 statistical software package was used for the statistical analysis. Metabolite ratios of Cho/Cr, Cho/NAA, and NAA/Cr were calculated in low-grade glioma and high-grade glioma. The measured metabolite ratio results are expressed as mean ± standard deviation ($\overline{X} \pm S$). The statistical methods used included two-independent-sample *T*-test and receiver operating characteristic (ROC) curve analysis, where the test level was $\alpha = 0.05$. *T*-tests were performed to evaluate the MRS differences between the low-grade glioma and high-grade glioma groups. Screening of high-quality MRS images was done by the image quality assessment flow chart. After the image quality assessment, Cho/Cr, Cho/NAA, and NAA/Cr ratios of low-grade glioma and high-grade glioma were recalculated. The metabolite ratio differences before and after MRS image quality assessment in the same-grade glioma groups were evaluated by *T*-tests. Receiver operating characteristic (ROC) curve analysis was done to evaluate the diagnostic performance of the metabolite ratios. The cutoff value was used to calculate the diagnostic positive rate of the MRS grading of glioma, respectively, so as to compare the value of image quality assessment.

ROC analysis before MRS image quality assessment

Ninety-eight cases of gliomas (48 cases of low-grade glioma and 50 cases of high-grade glioma) were used in the ROC curve study. The cutoff point of Cho/Cr for identifying glioma grading was set at 3.63 with 68% sensitivity and 70.8% specificity (Figure 2). The area under the curve (AUC) of Cho/NAA for identifying glioma grading was 0.599 by the ROC analysis. The cutoff point of Cho/NAA for identifying glioma grading was set at 3.19 with 70% sensitivity and 52.1% specificity. The area under the curve (AUC) of NAA/Cr for identifying glioma grading was 0.540 via the ROC analysis. The cutoff point of NAA/Cr for identifying glioma grading was set at 0.94 with 50% sensitivity and 64% specificity. It can be seen that the Cho/Cr ratio with high sensitivity and high specificity is the best

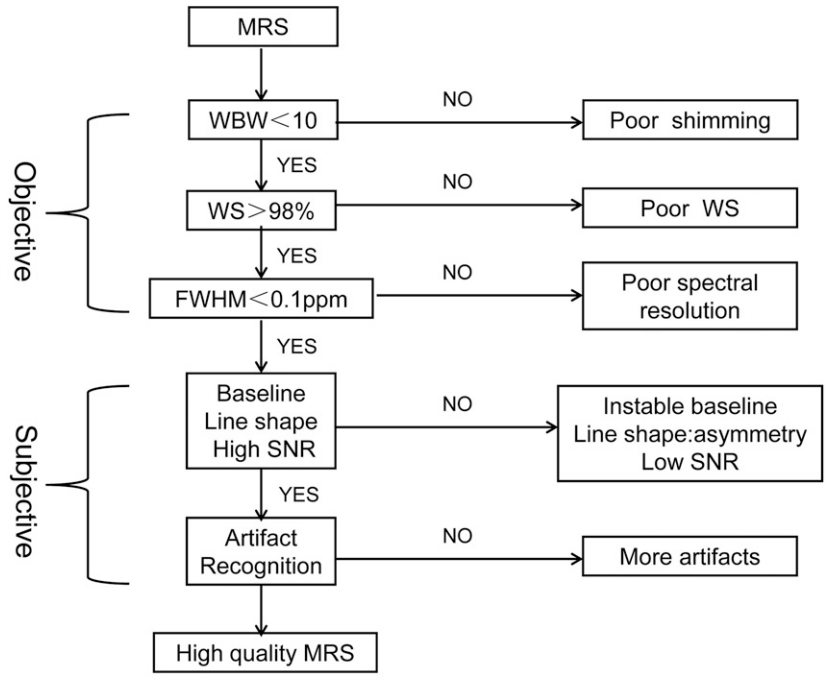

Figure 1. Flow chart showing the process of MRS image quality assessment. MRS, magnetic resonance spectroscopy; WBW, water linewidth; WS, water suppression; FWHM, full-width at half-maximum peak height; SNR, signal-to-noise ratio.

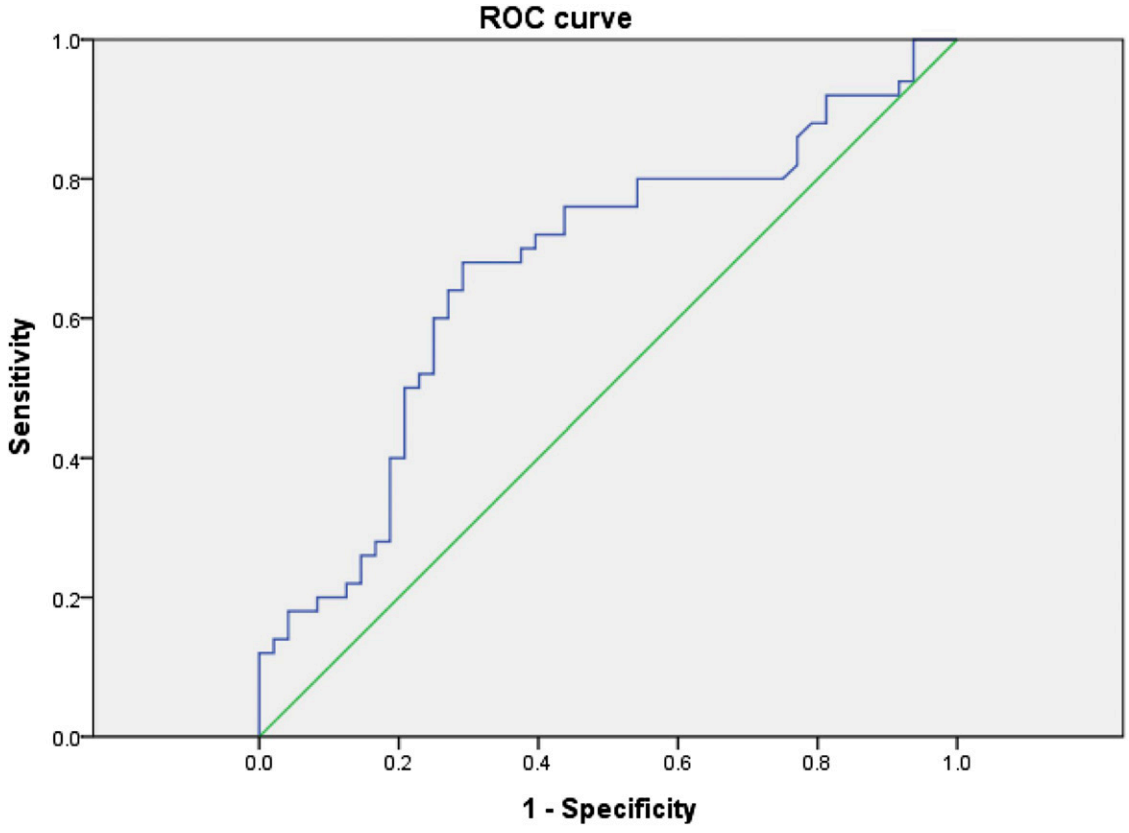

Figure 2. ROC curves of the Cho/Cr ratio before quality assessment. The green line is the main diagonal, and the blue line for the ROC curve. ROC, receiver operating characteristic

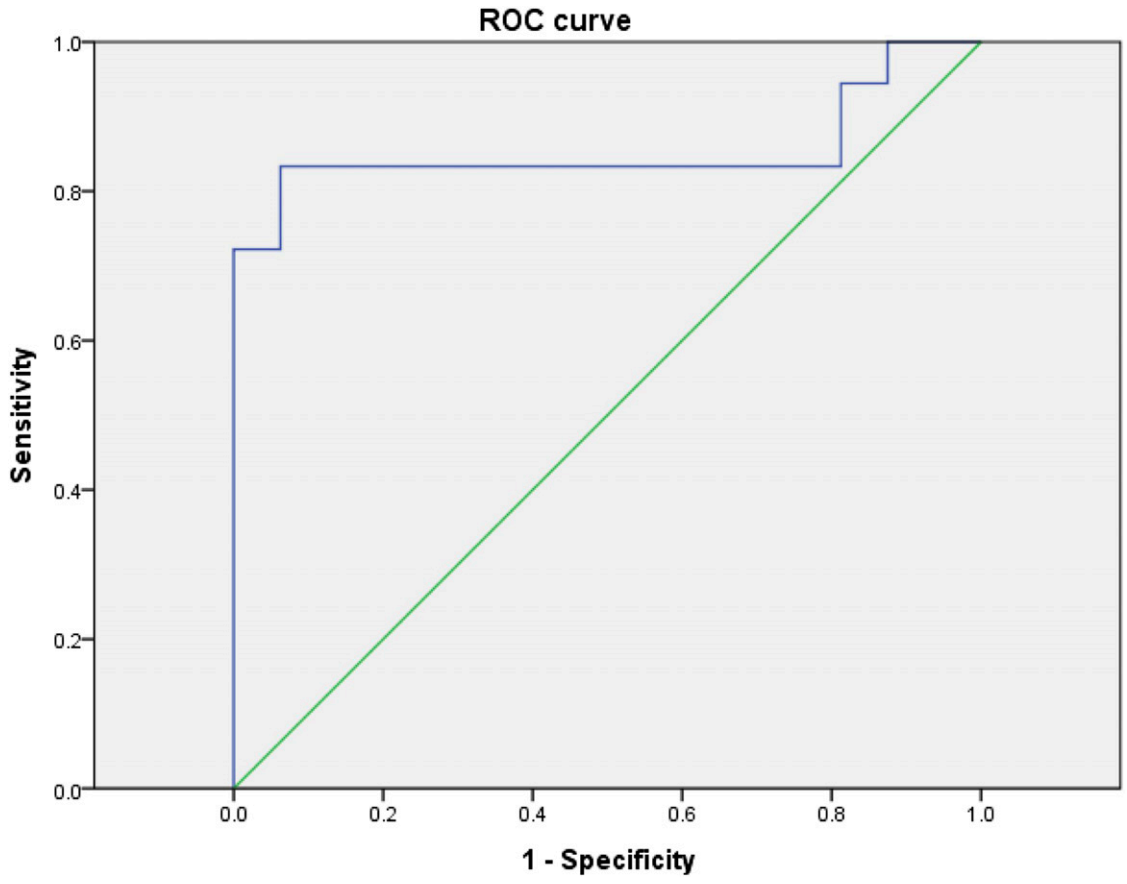

Figure 3. ROC curves of the Cho/Cr ratio after quality assessment. The green line is the main diagonal, and the blue line for the ROC curve. ROC, receiver operating characteristic

index of glioma grading. The cutoff point of Cho/Cr was 3.63.

ROC analysis after MRS image quality assessment

Thirty-four cases of gliomas (16 cases of low-grade glioma and 18 cases of high-grade glioma) were used in the ROC curve study. The cutoff point of Cho/Cr for identifying glioma grading was set at 3.72 with 83.3% sensitivity and 93.7% specificity (Figure 3). The AUC of Cho/NAA and NAA/Cr were at 0.637 and 0.514. The cutoff point of Cho/NAA was set at 3.14 with 88.9% sensitivity and 43.7% specificity. The cutoff point of NAA/Cr was set at 0.42 with 100% sensitivity and 31.2% specificity.

Results

Pathological diagnosis confirmed 98 patients with brain glioma. There were 48 cases in the low-grade glioma group, including 7 cases of grade I glioma (pilocytic astrocytoma, choroid plexus papilloma, nodular cell tumor, and ganglion cell glioma) and 41 cases of grade II glioma (diffuse astrocytoma). There were 50 cases in the high-grade glioma group, including 25 cases of grade III glioma (anaplastic oligodendroglioma and anaplastic astrocytoma) and 25 cases of grade IV glioma (medulloblastoma and gliosarcoma).

After the MRS image quality assessment, 34 (34.7%) cases of glioma patients with high-quality MRS images were screened. There were 16 cases in the low-grade glioma group, 11 cases of males and 5 cases of females, with an average age of 38.8 ± 14.8 years. There were 18 cases in the high-grade glioma group, 7 cases of males and 11 cases of females, with an average age of 49.8 ± 15.8 years.

Comparison of MRS performance in different-grade gliomas

The MRS of the glioma generally showed a Cho peak that was significantly increased, NAA peak was decreased, Cr peak had no obvious change, and with the increase in the glioma malignancy degree, the Cho peak increased even more. Some cases could also detect an abnormal increase in the Lac peak or Lip peak.

With 98 cases of glioma patients as the research subjects, the results showed that the metabolite ratios for different

levels of gliomas were indeed different. The ratio of Cho/Cr in the low-grade glioma group was 3.81 ± 2.40, the ratio of Cho/NAA was 4.70 ± 3.71, and the ratio of NAA/Cr was 1.17 ± 0.98. The ratio of Cho/Cr in the high-grade glioma group was 5.85 ± 4.45, the ratio of Cho/NAA was 6.21 ± 5.27, and the ratio of NAA/Cr was 1.03 ± 0.87. The difference in the Cho/Cr ratio between high- and low-grade gliomas was statistically significant ($p < 0.05$). There was no obvious difference in the ratio of Cho/NAA and NAA/Cr between the two groups ($p > 0.05$) (Table 1).

Comparison of metabolite ratios before and after image quality assessment (QA)

Cho/Cr ratio in low-grade glioma had a remarkable difference before and after the image quality assessment (3.81 ± 2.40 vs 2.76 ± 0.80 [$p < 0.05$]). Cho/NAA (4.70 ± 3.71 vs 5.02 ± 3.66 [$p > 0.05$]) and NAA/Cr (1.17 ± 0.98 vs 0.92 ± 0.52 [$p > 0.05$]) ratio in low-grade glioma had no obvious difference before and after the image quality assessment (Table 2). Cho/Cr (5.85 ± 4.45 vs 7.90 ± 5.64 [$p > 0.05$]), Cho/NAA (6.21 ± 5.27 vs 6.39 ± 3.66 [$p > 0.05$]) and NAA/Cr (1.03 ± 0.87 vs 1.00 ± 0.62 [$p > 0.05$]) ratio in high-grade glioma had no statistically significant difference before and after the image quality assessment (Table 3).

Table 1. Metabolite ratios in different grade gliomas ($\overline{X} \pm S$).

Ratio	Low-grade (n = 48)	High-grade (n = 50)	T Value	p
Cho/Cr	3.81 ± 2.40	5.85 ± 4.45	2.840	0.006
Cho/NAA	4.70 ± 3.71	6.21 ± 5.27	1.643	0.104
NAA/Cr	1.17 ± 0.98	1.03 ± 0.87	−0.751	0.455

Table 2. Metabolite ratio in low-grade glioma before and after image quality assessment (QA).

Ratio	Before QA (n = 48)	After QA (n = 16)	T Value	p
Cho/Cr	3.81 ± 2.40	2.76 ± 0.80	2.609	0.011
Cho/NAA	4.70 ± 3.71	5.02 ± 3.66	−0.306	0.761
NAA/Cr	1.17 ± 0.98	0.92 ± 0.52	0.975	0.333

Table 3. Metabolite ratio in high-grade glioma before and after image quality assessment (QA).

Ratio	Before QA (n = 50)	After QA (n = 18)	T Value	p
Cho/Cr	5.85 ± 4.45	7.90 ± 5.64	−1.563	0.123
Cho/NAA	6.21 ± 5.27	6.39 ± 3.66	−0.128	0.899
NAA/Cr	1.03 ± 0.87	1.00 ± 0.62	0.119	0.905

ROC analysis findings before and after MRS image quality assessment

The results showed that the area under the curve (AUC) of the Cho/Cr ratio was 0.671 before the MRS image quality assessment. However, the area under the curve (AUC) of the Cho/Cr ratio after the MRS image quality assessment was 0.854.

The accuracy rate of glioma grading before the image quality assessment

Before the MRS image quality assessment, the Cho/Cr ratio with high sensitivity and high specificity is the best index of glioma grading. The cutoff point of Cho/Cr was 3.63. According to the threshold of 3.63, MRS diagnosed 50 cases of low-grade glioma and 48 cases of high-grade glioma. According to the pathology grading results, 48 cases of low-grade glioma were diagnosed by pathology, 34 cases were diagnosed correctly by MRS and 14 cases were misdiagnosed. The grading accuracy rate was 71%. 50 cases of high-grade glioma were diagnosed by pathology, 34 cases were diagnosed correctly by MRS and 16 cases were misdiagnosed. The grading accuracy rate was 68%. The accuracy rate of glioma MRS grading was 69%.

The accuracy rate of glioma grading after the image quality assessment

After the MRS image quality assessment, the Cho/Cr ratio with high sensitivity and high specificity is the best index of glioma grading. The cutoff point of Cho/Cr was 3.72. According to the threshold of 3.72, MRS diagnosed 18 cases of low-grade glioma and 16 cases of high-grade glioma. According to the pathological grading results, 16 cases of low-grade glioma were diagnosed by pathology, 15 cases were diagnosed correctly by MRS, and 1 case was misdiagnosed. The grading accuracy rate was 92%. 18 cases of high-grade glioma were diagnosed by pathology, 15 cases were diagnosed correctly by MRS and 3 cases were misdiagnosed. The grading accuracy rate was 83%. The accuracy rate of glioma MRS grading was 88%.

Discussion

In this retrospective cross-sectional study, we proved the application value of image quality assessment in the accurate grading of glioma by comparing MRS performance in different-grade gliomas before and after MRS image quality assessment. The clear advantage of 3D 1H-MRS is an increase of spatial coverage in the three-dimensional space.[9,10,19]

The results of our study showed that the levels of Cho, NAA, and Cr metabolites and the Cho/Cr, Cho/NAA, and NAA/Cr ratios were different for different grades of

gliomas, which can be distinguished between low-grade and high-grade glioma. The ratio of Cho/Cr and Cho/NAA in high-grade glioma was higher than that in low-grade glioma, while NAA/Cr ratio was lower than that of low-grade glioma. The ratio of Cho/Cr and Cho/NAA in glioma grading was greater than the NAA/Cr ratio. These changes were consistent with those reported in previous studies.[5,6,9,28]

Our study mentioned an important point that metabolite ratio in the glioma is different before and after MRS image quality assessment. After the MRS image quality assessment, the Cho/Cr ratio obviously decreased in the low-grade glioma group, and the difference was remarkably significant. This indicates that MRS image quality affects the ratio of glioma metabolites, which affects the outcome of glioma grading. MRS with poor image quality can significantly affect the metabolite ratio especially the Cho/Cr ratio, resulting in some low-grade gliomas misdiagnosed as high-grade gliomas. After the MRS image quality assessment, the glioma metabolite ratio decreased, reducing the incidence of a misdiagnosis. This also proves to some extent that the MRS image quality assessment flow chart in this study is effective and feasible. Of course, there are some other reasons for glioma grading errors. It is well known that the pathological grade is the gold standard for glioma grading. However, due to intraoperative pathology sampling and uncontrollable selection of the sampling position, the results are easily reproducible with regards to sampling error. The tumor resection part may not represent the true level or the highest level of the tumor. This is unavoidable. A previous study has the same view point.[29]

By comparing the results of the two ROC curves before and after MRS image quality assessment, we concluded that the Cho/Cr ratio with the highest sensitivity and specificity is the most stable and reliable glioma grading index. The sensitivity and specificity of the Cho/Cr ratio for glioma grading were observably improved after the MRS image quality evaluation. In addition, the cutoff value of the Cho/Cr ratio increased after the MRS image quality evaluation (3.63 vs 3.72). The results also showed that there was no exaggeration of the glioma metabolite ratios before the MRS image quality assessment, and spectral image quality was closely related to glioma metabolite ratios.

Another important finding in this study was that the accuracy rate of glioma grading was remarkably improved after the MRS image quality assessment. The accuracy rate of glioma grading before the MRS image quality assessment was 69%, while the accuracy rate of glioma grading after MRS image quality assessment was 88%. It was found that the MRS image quality affected the glioma grading results; on the other hand, the results showed that the MRS image quality assessment flow chart was effective and could improve the diagnostic efficiency of glioma MRS grading.

Our study still has a number of limitations. First, the current MRS image quality assessment flow chart is based on the GE machine as a model. In the future, we need to take the differences between MRI machines into account in order to further improve and optimize the image quality assessment to achieve universality. Second, due to strict quality assessment standards, our study was performed only on a small cohort of 34 glioma patients after the MRS image quality assessment. In order to obtain more accurate objective data, it is necessary to expand the sample size to do more in-depth and accurate research.

In conclusion, this study indicated that MRS image quality can significantly affect the metabolic ratio of glioma and grading diagnosis results. Poor quality of MRS images may exaggerate the metabolite indicators, resulting in glioma grading errors, which can be corrected through image quality assessment. After the MRS image quality assessment, the Cho/Cr ratio with 83.3% sensitivity and 93.7% specificity is the most stable and reliable indicator of preoperative glioma scaling. Combining the MRS image quality assessment, physicians can significantly improve the accuracy and stability of MRS glioma grading. In future, image quality assessment will play a more important role in medical imaging.

Declaration of conflicting interests

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