

# Evaluation of diagnostic accuracy of the approved tumor mapping protocol in grading of glial tumors

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(Submitted: 07 August 2020 – Revised version received: 23 August 2020 – Accepted: 10 September 2020 – Published online: 30 October 2020)

## Abstract

**Objective:** Current methods of grading glioma have inherent limitations. The current grading reference standard can be inaccurate when the biopsy specimen is not taken from the most malignant area of the tumor or when the tumor is not completely removed. This is a specific problem in glioma due to the spread of tumor penetration. Therefore, the aim of this study was to evaluate the diagnostic accuracy of the approved tumor mapping protocol in the grading of glial tumors.

**Methods:** This descriptive cross-sectional study was performed on patients aged 2–82 years with glial tumor. Patients were referred to the hospital for tumor mapping and underwent imaging with simultaneous methods of MRS & magnetic resonance (MR) perfusion and conventional MRI under the supervision of NIAG group. Then, the results of the second evaluation, including the ratios of the desired metabolites and the amount of blood flow, permeability of the target area were compared with the results of pathology. The results were analyzed by SPSS software version 24.

**Results:** In this study, 30 patients were included. Sensitivity, specificity, positive and negative predictive value for the determination of high-grade glioma with peripheral/internal relative cerebral blood volume (rCBV) were 100/100%, 100/93%, 93/100% and 100.100%, respectively. Sensitivity, specificity, positive and negative predictive value for the diagnosis of glioma by using peripheral/internal rCBV and thresholds of 2.65 and 1.06 were 100/100%, 93/100%, 93/100% and 100/100%, respectively. Sensitivity, specificity, positive predictive value and negative predictive value were determined for diagnosis of high-grade glioma tumor using Ch + Cr / NAA Cho / Cr and Cho / NAA ratios with detection threshold of 2.97 (93.3%), 3.5 (78.9%, 100%, 100%, and 73.3%), and 2.1 (100%). Threshold values of 3.5, 2.1 and 2.97 were obtained using Cho / Cr, Ch + Cr / NAA and Cho / NAA, respectively, for the detection of high-grade gliomas. The combination of rCBV, Cho / Cr, Ch + Cr / NAA and Cho / NAA had sensitivity, specificity, positive and negative predictive value of 67.7%, 80%, 77% and 70.5%, respectively. Significant differences in rCBV and Cho / Cr, Cho / NAA and NAA / Cr ratios were observed between low- and high-grade gliomas ( $P < 0.0001$ ).

**Conclusion:** Pre-operative grading of glioma based on routine MR imaging is often unreliable. As a result, measuring rCBV and Cho / Cr and Cho / NAA ratios independently and somewhat together can significantly improve the sensitivity and predictive values of pre-operative glioma grading.

**Keyword:** Brain tumor, Glial tumor, Tumor mapping protocol, Tumor grading.

## Introduction

There are two main groups of cells in the mammalian central nervous system, including neurons and glial (neuroepithelial) cells. Glial cells cover 90% of the cells of the central nervous system and play a role in protecting and supporting neurons. In addition, these cells are responsible for providing nutrients, oxygen to the nerves and myelin production, and also play a role in maintaining the homeostasis of the nervous system by destroying pathogens and eliminating dead nerve tissue. Glial cells include astrocytes, oligodendrocytes, microglia, and ependymas, which are morphologically distinct from each other.<sup>1</sup> Primary brain tumors are named based on the tissue from which they originate. Pathologically, tumors of glial origin are the most common primary neoplasms of the brain. These brain tumors constitute 45% of intracranial tumors.<sup>2</sup> According to the WHO classification, brain tumors are given low-grade (grade 1 and grade 2) or high grade (grade 3 and 4) depending on the cellular activity and the degree of invasiveness of the tumor. People with glioma eventually have surgery. After

surgery, other treatments such as radiation and chemotherapy may be appropriate, depending on the degree of the tumor and other aspects. The standard treatment for grade 4 tumors is radiation therapy and anti-cancer drugs (Temozolomide). In patients with slow-growing tumors, magnetic resonance imaging (MRI) scans are usually done at regular intervals to check tumor growth before treatment.<sup>3,4</sup> Technological advances in MRI imaging have led to the availability of new techniques for characterizing CNS tumors. For example, Diffusion Weight Imaging (DWI), Perfusion Weight Imaging (PWI) and MR Spectroscopy (MRS) are relatively new methods that are capable of combining morphological and structural information with physiological and biochemical data. These techniques have recently been used to evaluate glial neoplasms, especially in determining their histological grade.<sup>5-8</sup> With the current developments, the metabolic information of the study area can be obtained by brief changes in the method of frequency domain versus time domain analysis by MRS.<sup>9</sup>

Dynamic Susceptibility Contrast, and MRI are the most commonly used techniques for measuring tumor perfusion, that typically measured by the relative cerebral blood volume (rCBV). The lack of recurrent blood flow and the deposition of contrast material can be evaluated by measuring rCBV, which is violated in high-grade tumors with leakage pattern.<sup>10,11</sup>

In clinical studies, 95%–100% sensitivity of differentiating high glioma from low glioma grade has been determined by the threshold of 5.1 rCBV or 75.1. Although in similar studies, the specificity was relatively low (5.75%–69%),<sup>12</sup> part of which could be due to spatial tumor heterogeneity or potential histological sampling bias.<sup>13</sup> In addition, a significant increase in rCBV was found in low-grade glioma (Transforming) up to 12 months before the new enhancement, suggesting that rCBV could predict malignancy. Perfusion quantitative parameters can also be obtained without the use of corrective methods, including Percentage Signal Recovery (PSR) and Peak Height (PH) that are known as independent parameters in differentiating glioma from metastasis and recurrent metastatic disease from radiation necrosis.<sup>14</sup> Therefore, the aim of this study was to evaluate the diagnostic accuracy of Tumor Mapping protocol in grading of glial tumors.

## Materials and Methods

This descriptive cross-sectional study was performed on patients with brain glioma tumors who were referred to Imam Khomeini Hospital in Tehran-Iran. Data were collected using a checklist in which information such as brain metabolites, ratios, perfusion parameters, and histopathological response were recorded.

Inclusion criteria were:

1. Age between 2 and 82 years
2. Approval by neurologists and neurosurgeons.

Exclusion criteria were:

1. Having a history of any brain surgery

The sample size was calculated according to the sensitivity and specificity of Cho / Cr and rCBV parameters. To do this, a formula appropriate to the diagnostic accuracy in a community has been used. Considering the specificity of 96%, error 0.15 and prevalence 3.0, the minimum sample size was calculated as 24.

$$\text{sample size (n) based on specificity} = \frac{Z^2 \frac{1-a/2 \times s_p \times (1-s_p)}{L^2 \times (1-\text{Prevalence})}}$$

Za <sup>2</sup>	3/84
Sp	0.96
1-sp	0.04
Prev	0.3
1-Prev	0.7
L <sup>2</sup>	0.02074
N	24

## Procedure

In this study, 30 patients were selected in the initial evaluation by neurological colleagues and diagnosed as glial tumors among patients with brain tumors. Patients were referred to

Imam Khomeini Hospital for Tumor Mapping and underwent conventional imaging and simultaneous (MR perfusion techniques and MR spectroscopy (MRS) under the supervision of NIAG in addition to Conventional.

MRS imaging was performed by SVS and MRSI methods with short and medium TEs (20–35 milliseconds and 135–144 milliseconds) from at least three points from the active site of the tumor, peripheral parts and surrounding edema. Then, integration of Cho, Cr, MI, Lactate, Lipid, NAA metabolites was performed from the bottom of the diagram. Cho / Cr, Ch / NAA ratios of NAA / Cr, LL / Cr, MI / Cr and Cho + Cr / NAA (in tumors with severe heterogeneity) were extracted by data analysis software. Patients were also subjected to perfusion imaging (PW) with dynamic susceptibility contrast (DSC) method obtained from T2 \* W images according to the protocol.

After performing technical correction methods, detailed analysis of the obtained data was performed to extract rCBV, PSR, PH parameters. Preliminary data were collected in the database so that patients were divided into four subgroups (1, 2, 3, 4) from low-grade astrocytoma to glioblastoma, respectively, after surgery based on the results of resected tissue pathology and WHO criteria. Then the patients were divided into two main groups: Low grade and High grade equally (15 low-grade tumors and 15 high-grade tumors).

## Data Analysis

Frequency and percentage were used to describe qualitative data and mean and standard deviation were used for quantitative data. ROC curve was used to calculate the sensitivity and specificity. To compare the methods, the area under the ROC curve (AUC) was examined using Medcalc software. SPSS software version 24 was used for data analysis and the significance level in all tests was 0.05.

## Ethical Considerations

After obtaining the consent of the University Ethics Committee, all information was collected and kept confidential. The participants in the project adhered to the declaration of Helsinki. A complete description of the research objectives and working methods was provided to the officials of the centers and all research units in written and oral form. Written consent was obtained from patients to perform this plan.

## Results

In this study, 30 patients with inclusion criteria were included in the study. In the high-grade glioma group, 15 patients included 9 patients (30%) with glioblastoma multiforme (GBM), 4 patients (13.3%) with anaplastic astrocytoma and 2 patients (6.6%) with anaplastic oligodendroglioma. There were 15 patients in the low-grade glioma group, including 10 patients (33%) with astrocytoma and 5 patients (17%) with oligoastrocytoma.

Table 1 shows the metabolic levels of MRS, and PWI (PSR and RCBV) in both high- and low-grade glioma groups. Among patients, peripheral rCBV levels, internal RCBC, Cho

Table 1. **Metabolic levels of MRS, PWI (PSR and RCBV) in two groups of high- and low-grade glioma.**

Variable	Group	N	Mean	Std. Deviation	P-Value
PSR	low grade	15	93.700	2.3513	<0.001
	high grade	15	85.033	2.9488	<0.001
RCBV Peripheral	low grade	15	0.7253	0.20832	<0.001
	high grade	15	1.4780	0.28138	<0.001
RCBV Internal	low grade	15	1.8300	0.30131	<0.001
	high grade	15	3.4093	0.27408	<0.001
CH/CR	low grade	15	2.5547	0.49129	<0.001
	high grade	15	3.5213	0.81321	<0.001
CH/NAA	low grade	15	1.5513	0.32443	<0.001
	high grade	15	2.8060	0.33749	<0.001
CH+CR/NAA	low grade	15	2.3853	0.38338	<0.001
	high grade	15	3.8600	0.44029	<0.001
MI/CR	low grade	15	0.6760	0.16084	<0.001
	high grade	15	0.2873	0.11585	<0.001
LL/CR	low grade	15	0.7167	0.32778	<0.001
	high grade	15	2.6093	0.78733	<0.001

/ Cr, Ch / NAA and Cho + Cr / NAA, LL / CR was significantly higher in the group with high-grade glioma than in the low-grade glioma ( $P < 0.05$ ).

Also, PSR, MI / Cr levels were significantly lower in the group with high-grade glioma than in the low-grade glioma ( $P < 0.05$ ).

In the current study, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the diagnosis of high-grade glioma tumor using peripheral rCBV with a diagnostic threshold of 1.06 were 100, 93.3, 93.8 and 100%, respectively.

Sensitivity, specificity, PPV and NPV for the diagnosis of high-grade glioma tumor using internal rCBV with a detection threshold of 2.65 were also determined as 100%.

Additionally, sensitivity, specificity, PPV and NPV for the diagnosis of high-grade glioma tumors using the Ch / Cr ratio with a detection threshold of 3.5 were 73.3, 100, 100, and 78.9%, respectively.

Our results revealed that sensitivity, specificity, PPV and NPV for the diagnosis of high-grade glioma tumors using the CH / NAA ratio with a detection threshold of 2.1 were 100%. Furthermore, sensitivity, specificity, PPV and NPV for the diagnosis of high-grade glioma tumors using the Ch + Cr / NAA ratio with a detection threshold of 2.97 were 93.3%. sensitivity, specificity, PPV and NPV for the diagnosis of high-grade glioma tumors using MI / CR ratio with a detection threshold of 0.5 were also found to be 6.7%. Sensitivity, specificity, PPV and NPV for the diagnosis of high-grade glioma tumors using LL / CR ratio with a detection threshold of 1.5 were 100, 88.2, 88.2, and 100%, respectively. The diagnostic accuracy of PSR in differentiating high-grade tumor from low glioma was found to be 0 and lack of sensitivity, specificity, PPV and NPV value was also revealed. The diagnostic thresholds of the combination of metabolic level and rCBV for differentiating high-grade from low-grade glioma had sensitivity, specificity, PPV, and NPV of 67, 80, 77, and 70.5%, respectively.

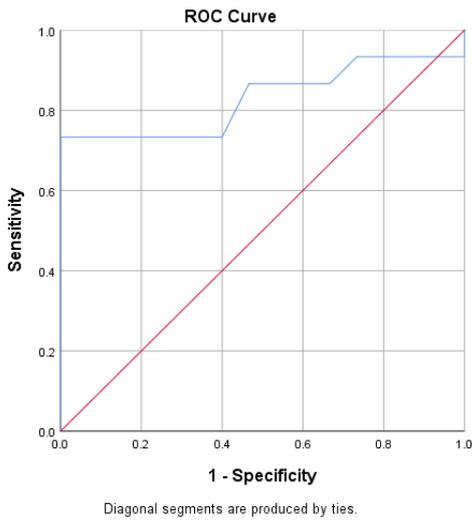


Fig. 1. ROC curve for the sensitivity and specificity of choline to creatine ratio in the diagnosis of high-grade glioma.

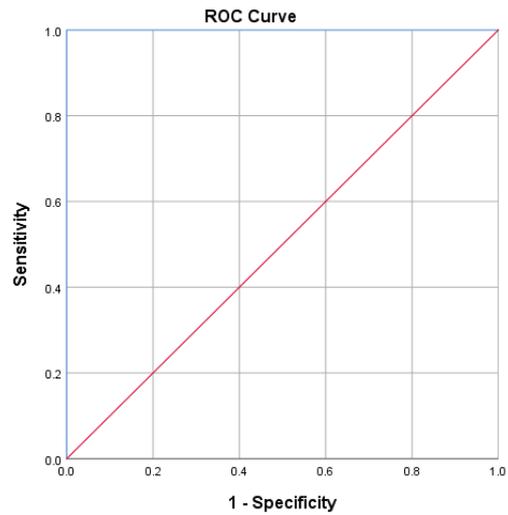


Fig. 2. ROC curve for the sensitivity and specificity of the CH / NAA ratio in the diagnosis of high-grade glioma.

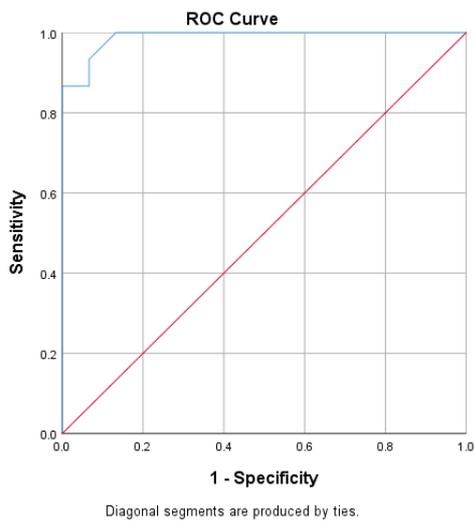


Fig. 3. ROC curve for the sensitivity and specificity of the Ch + Cr / NAA ratio in the diagnosis of high-grade glioma.

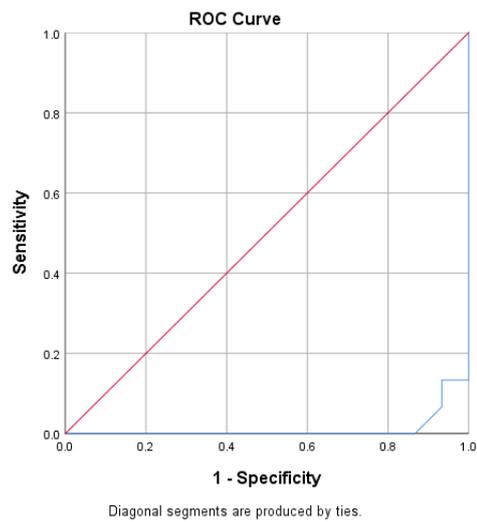


Fig. 4. ROC curve for the sensitivity and specificity of the MI / CR ratio in the diagnosis of high-grade glioma.

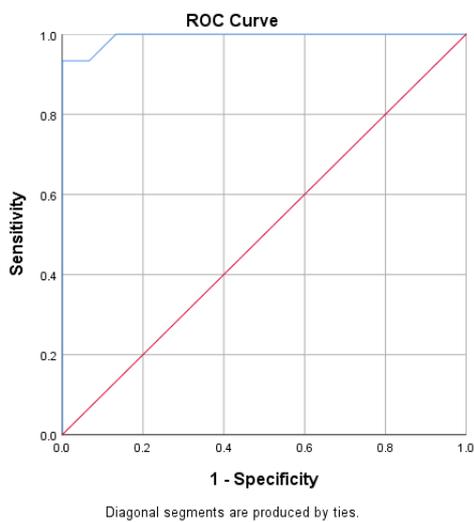


Fig. 5. ROC curve for the sensitivity and specificity of the LL / CR ratio in the diagnosis of high-grade glioma.

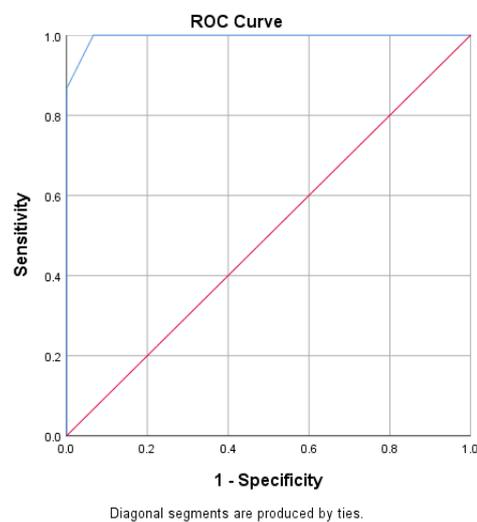


Fig. 6. ROC curve for sensitivity and specificity of RCBV Peripheral ratio in the diagnosis of high-grade glioma.

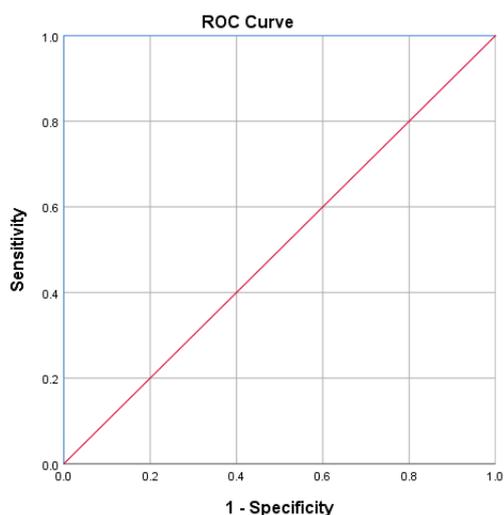


Fig. 7. ROC curve for the sensitivity and specificity of the RCBV Internal ratio in the diagnosis of high-grade glioma.

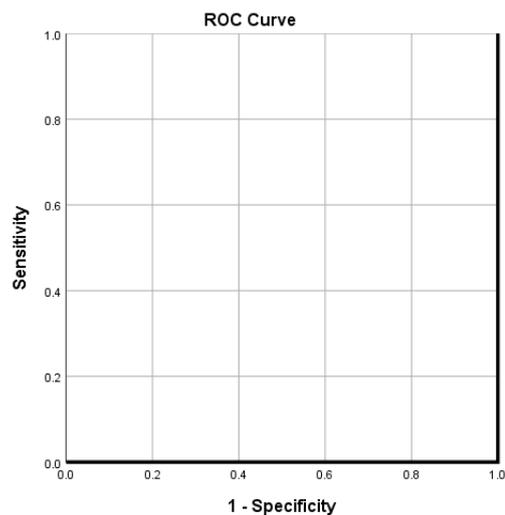


Fig. 8. ROC curve for sensitivity and specificity of PSR ratio in the diagnosis of high-grade glioma.

## Discussion

Current methods of grading glioma have inherent limitations. The current grading reference standard can be inaccurate when the biopsy specimen is not taken from the most malignant area of the tumor or when the tumor is not completely removed. This particular problem in glioma is due to the spread of tumor infiltration, so the aim of this study was to evaluate the diagnostic accuracy of the approved tumor mapping protocol in the grading of glial tumors.<sup>15</sup> To date, few systematic attempts have been made to compare the sensitivity, specificity, PPV and NPV of MR perfusion and MR spectroscopy with conventional MR imaging in glioma grading.

In a study conducted in 2013, 56 patients with a primary diagnosis of glioma underwent MRP, DWI and MRS, where CBV individually showed a sensitivity and specificity of 100% and 88%, respectively, according to a threshold value of 3.34. In the conclusion of this study, rCBV measurement had the most diagnostic performance in grading glioma tumors, but combining all of the imaging parameters play a more accurate role in classification of glioma tumors.<sup>11</sup> In line with mentioned study, rCBV was able to detect high-grade glioma tumors with a diagnostic threshold of 1.06 where sensitivity, specificity, PPV, and NPV were determined to be 100, 93.3, 93.8, 100, respectively.

Internal rCBV showed high sensitivity, specificity, PPV and NPV for the diagnosis of high-grade glioma tumor with a detection threshold of 2.65 (100%). Another study was performed in 2010 on 40 patients with an initial diagnosis of glioma. After obtaining the parameters of two modalities of perfusion MRI and spectroscopy, they came to the conclusion that the combination of rCBV, Cho / Cr, Cho / NAA and MI / Cr was associated with specificity of 68%, sensitivity of 95%, PPV of 76% and NPV of 86.7% for grading of glioma tumors that was in line with our study.<sup>9</sup>

In a 2003 study by Zidan on 160 patients with an initial diagnosis of glioma, rCBV was obtained from the region with the highest perfusion and MRS parameters with moderate and short TE. Their results showed that the combination of Cho / NAA, Cho / Cr, rCBV had sensitivity, specificity, NPV and PPV of 3.93%, 60%, 87% and 75% in glioma tumor grading,

respectively. Contrary to our study, this means that the combination of rCBV with cerebral metabolic parameters is more valuable than conventional MRI and each of the above methods alone. Furthermore, rCBV is of greater diagnostic value in tumor grading among the parameters measured in this study that was in agreement with our findings.<sup>16</sup>

A meta-analysis of 83 articles in the NCBI Database between 2000 and 2013 showed that LGG had clearly less Cho / NAA, Cho / Cr, rCBV than MTS and HGG, but no significant difference was observed in ADC where the best differentiation and grading between HGG and LGG are formed by combining the parameters of Cho / NAA, Cho / Cr, and rCBV, but these criteria cannot accurately differentiate between HGG and metastasis.<sup>10</sup>

In our study, levels of peripheral rCBV, internal rCBV, Cho / Cr, Cho / NAA, and LL / CR were significantly higher in the group with high-grade glioma than in those with low-grade glioma, and PSR, MI / Cr levels were significantly lower in the high-grade glioma than low-grade glioma.

Perfusion parameters and spectroscopic concentration ratios in 55 consecutive patients with histopathologically proved lymphomas, glioblastomas, and metastases have been previously evaluated by Vallee et al.<sup>17</sup> By obtaining rCBV and PSR (percentage signal intensity recovery) parameters and brain metabolites and the corresponding ratios of both modalities, it was concluded that PSR, Cho / Cr, Cho / NAA have 95% sensitivity and 97% specificity in the diagnosis of glioblastoma from metastasis and lymphoma.<sup>17</sup> In line with mentioned study, the Cho / Cr ratio showed a sensitivity, specificity, PPV, and NPVs of 78.9, 100, 100, and 73.3, respectively, for the diagnosis of high-grade glioma tumors with a detection threshold of 3.5. Cho / NAA ratio showed sensitivity, specificity, PPV and NPV of 100% for the diagnosis of high-grade glioma tumors with a detection threshold of 2.1. In contrast, the PSR lacked diagnostic accuracy.

Finally, in addition to vascular proliferation, cellularity, mitotic activity, nuclear pleomorphism, and necrosis are important criteria in grading glioma tissue. Ki-67 labeling index is used in histological examination as a marker for cell proliferation. Higher levels of Ki-67-positive cells correspond to more malignancies in gliomas. Metabolite ratios, especially

Cho levels, are correlated with Ki-67 levels in gliomas,<sup>18</sup> so MR spectroscopy of Cho / Cr and Cho / NAA ratios is useful in grading gliomas.

## Conclusion

Pre-operative grading of gliomas based on routine MR imaging is often unreliable. As a result, measuring rCBV and Cho / Cr and Cho / NAA ratios independently and to some extent together can significantly improve the sensitivity and predictive values of pre-operative glioma grading.

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