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The Role Of Magnetic Resonance Spectroscopy To Improve The Accuracy Of Brain Tumor Diagnosis

Eko Arisetijono[1*], Satwika Pradhana[2], Yuyun Yueniwati[2]

[1] Department of Neurology, Faculty of Medicine, Universitas Brawijaya Malang.
[2] Department of Radiology, Faculty of Medicine, Universitas Brawijaya Malang.

**Corresponding author*
Email: drekoarisetijono.fk@ub.ac.id

Keyword :
Cho/Cr, Cho/NAA,lipid lactate, degree of malignancy of primary brain tumor, histopathology, MRSpectroscopy.

A b s t r a c t

Background: In Indonesia, primary brain tumor incidence reaches 7 per 100,000, with a mortality rate of 4.25 per 100,000 people per year. Histopathology is the gold standard for determining tumor type and degree of aggressiveness. Non-invasive approaches and precision in determining brain tumor grading are essential for management, avoiding less necessary surgical procedures and challenging cases, one of which is MR Spectroscopy. **Purpose:** To analyze the relationship between Cho/Cr and Cho/NAA's suitability ratio in MRS and the degree of malignancy in histopathology and investigate the influence of differences in Cho/Cr, Cho/NAA ratio, and lactate lipid peaks in MRS on the degree of malignancy in histopathology in primary brain tumors. **Methods:** We retrospectively reviewed 17 patients with high and low-grade brain tumors using an observational study with a cross-sectional study design. We measured the Cho/Cr and Cho/NAA ratios and identified the Lipid Lactate peak on the homogenous contrast enhancement area with the highest Cho area. We conducted data analysis using McNemar's test and independent t-test. **Result:** Statistical analysis showed no significant difference in the ratio of Cho/Cr, Cho/NAA, and lactate lipids ($p>0.05$), and this study obtained the suitability of the MRS indicator with histopathological results in Cho/NAA with $p = 0.219$ ($p > 0.05$) with an accuracy of 65%. **Conclusion:** The Cho/NAA ratio's conformity in determining the degree of brain tumor compared to histopathological results with an accuracy of 65%. Further research with a larger sample is necessary for the results to be more optimal.

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INTRODUCTION

Primary brain tumors are a heterogeneous group consisting of benign and malignant tumors derived from the brain's parenchyma and the surrounding structures. This group of tumors is a significant cause of morbidity and mortality in adults and children, and it is often the cause of severe disability and becomes a heavy burden on both the family and the health system [1,2,3]. In 2016, there were 330,000 incidents of malignancy in the Central Nervous System globally, with an average incidence of 4.63 per 100,000 people per year, with a 17.3% increase in cases over 26 years between 1990 and 2016. As of 2016, malignancy in the CNS was the cause of 227,000 deaths globally [2,4,5]. The incidence of primary brain tumors reached 17.6–22 per 100,000 populations in the Americas and Europe. In Indonesia, primary brain tumor incidence reaches 7 per 100,000 with a mortality rate of 4.25 per 100,000 people per year [3].

Radiologists have an essential role in determining the diagnosis and management of primary brain tumors. They must keep up with scientific developments to improve the quality of service. The World Health Organization (WHO) in 2016 has released an update to the primary brain tumor classification system that includes significant changes [4,6,7]. From 2010 to 2020, MR spectroscopy (MRS) research continues to be developed, both for clinical application and research development. MRS is mainly applied to brain tissue, which can detect localization, staging, evaluation of tumor aggressiveness or degree of malignancy, and tumor response to therapy in breast, prostate, liver, and other organ malignancy [5,8,9]. Hasan et al. examined that in intermediate Time to Echo (TE), choline metabolic rate cut-off values can be used to distinguish between high-grade and low-grade brain tumors by using Choline/N-acetyl aspartate (Cho/NAA) ratio (>1.8)and Choline/Creatinine (Cho/Cr) ratio (> 1.7) [6,]

MR spectroscopy can be used to determine the type and aggressiveness of a tumor and differentiate between tumor recurrence and radiation necrosis, which cannot be done with conventional MRI. Research on the use of MRS as a diagnostic test for primary brain tumors in Indonesia still needs to be completed. Therefore, it is necessary to evaluate and prove the suitability of the MRS results for determining the degree of malignancy by using MRI 3 Tesla with histopathological results to distinguish low and high-grade primary brain tumors[10].

METHODS

This research is an analytical observational study with a cross-sectional research design in which the data was taken retrospectively. Data was collected from 2015 to 2020 after being declared passing the ethics review by the Health Research Ethics Committee of Saiful Anwar General Hospital, Malang, based on letter no. 400/203/K.3/302/2020.

Populations and Samples

The subjects eligible for this study were patients with high- and low-grade primary brain tumors at Saiful Anwar Malang Hospital who have met the established inclusion and exclusion criteria. This study's inclusion criteria were high- and low-grade primary brain tumor patients who performed MRI examinations at the Radiology Installation from 2015 to 2020. The exclusion criteria of this study are that the DICOM (Digital Imaging and Communications) MRI files cannot be reviewed, there are histopathological results, but the slides and blocks are not representative to be reread. The results of the histopathological examination samples do not contain representative tumor tissue.

Research Methods

This study used secondary data from brain tumor patients who had MRI examinations from 2015 to 2020.

Then, the data obtained will be searched for the results of the anatomical pathology examination from the Anatomical Pathology Installation of RSUD Dr. Saiful Anwar Malang. MRS data and histopathology were re-reviewed by consultants from Neuroradiology and Anatomical Pathology.

MRI data was obtained from MRI 3T (Philips Ingenia) standard 24-channel phased array RF coil and receiver. This study also used T1WI with automatic shimming.

Multi-voxel PARAMETER MRS measurement used the 2D-MRSI, i.e., TR/TE: 1500/135 ms, (FOV): 120 x 120 mm, thickness: 10 mm, and a total scan time of 7 minutes. The Single-voxel parameter uses 1500/35 ms (TR/TE) with a voxel size of about 1.5 cm^3. The total scan time is 3.14 minutes. This study utilized MR spectroscopy with single and multiple voxels and images in the DICOM format, and the metabolic ratio was recorded using Phillips MRI software.

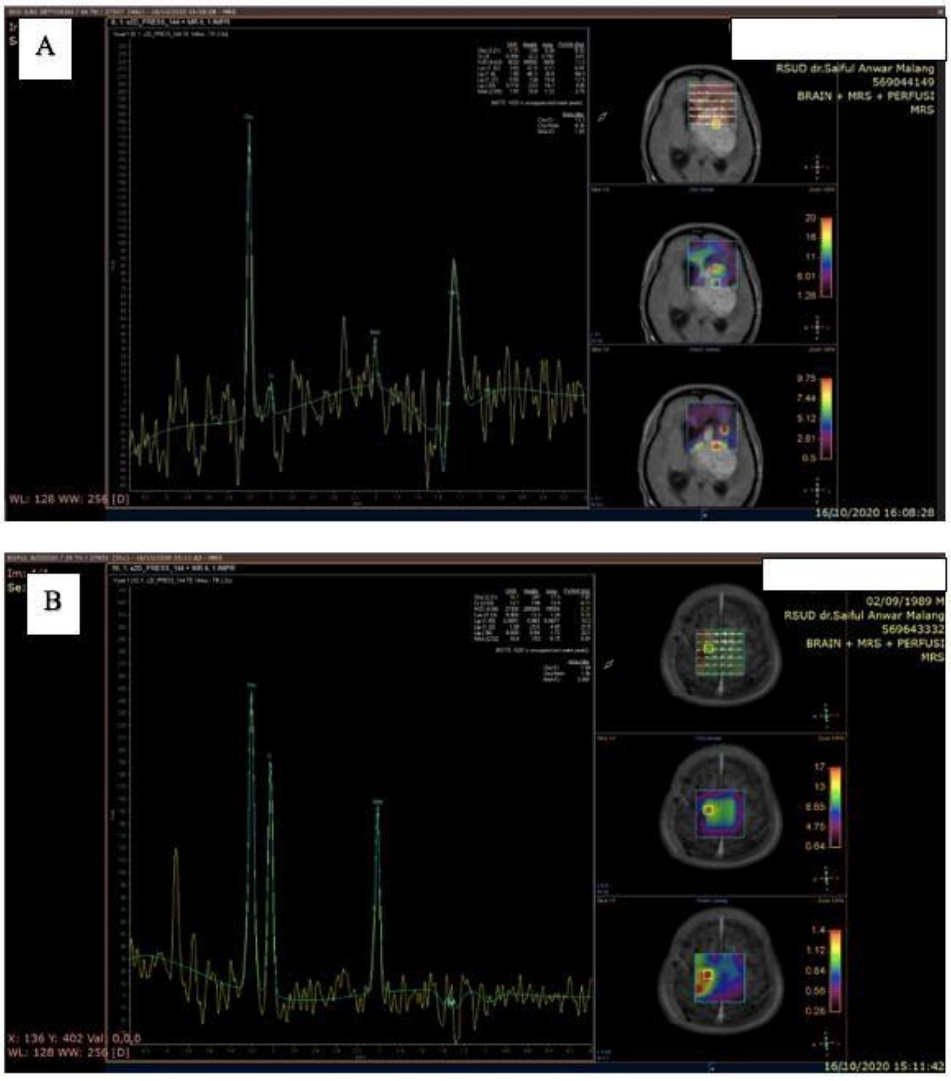

Figure 1. The placement of voxels on the T1WI sequencing with contrast in the tumor area. The voxel was placed in an area with the most homogeneous weighting pattern, followed by the placement of voxels in the highest choline area (with red area code). This ensured the most homogeneous baseline, noted the ratio value of Cho/Creatine, Cho/NAA, and the presence of peak lipid lactate compared to histopathology as the gold standard.
In Figure A, the ratio of Cho/Cr is 13.3, and Cho/NAA is 8.30 with a positive lactate lipid peak. In Figure B, the ratio of Cho/Cr is 1.64, and Cho/NAA is 1.86 with adverse lactate lipid [7].

The MRS method determines some coverage locations in solid parts with the most substantial enhancement, peritumoral, and healthy brain tissue around the tumor. On the T1WI sequencing with contrast, voxels are placed on the tumor area. Then, an area with the most homogeneous weighting pattern is selected, followed by the placement of voxels in the highest choline area (with red area code), ensuring the most homogeneous baseline, and the ratio value of Cho/Cr, Cho/NAA, and the presence of lipid lactate peak.

Statistical analysis

The independent variables in this study are Cho/Cr, Cho/NAA ratio, and the presence of lactate lipids in MRS. The dependent variable is the degree of a primary brain tumor in histopathology (high-grade and low-grade). The data was analyzed using SPSS software version 25. Descriptive data are presented as a table to measure central tendency (average, standard deviation, median, minimum value, and maximum). The suitability between MRS and histopathological diagnosis was tested using McNemar's test. All of them used a degree of confidence of 95%, alpha = 0.05. Significance is achieved when $p < 0.05$. Meanwhile, the differences in the ratio of Cho/Cr and Cho/NAA based on the degree of primary brain tumors on the MRS test were tested using an independent t-test in the event of normal data distribution.

RESULTS

This research sample consists of 17 subjects from retrospective data in the Saiful Anwar Hospital, confirmed with histopathological results from the Anatomical Pathology installation of RSSA from 2015 to 2020. Out of a total of 17 subjects, 5 of whom (29%) experienced high-grade primary brain tumors, and the remaining 12 (71%) had a histopathology result of low-grade primary brain tumors. Based on gender, 10 (58%) subjects were female, and 7 (41%) were male. In both high- and low-grade primary brain tumor subjects, women were more than men, with 3 (60%) and 7 (58.8%), respectively. The average age of subjects with high-grade primary brain tumors was 52.00 ± 17.66 years, while subjects with low-grade brain tumors were 37.00 ± 14.35 years. (Table 1). We used The Shapiro–Wilk test to evaluate the normality test for age, Cho/Cr, and Cho/NAA ratio data in the subject group of high-grade and low-grade primary brain tumors with a sample count 17. Normality test results in age group, Cho/Cr ratio, and Cho/NAA display normal distribution with $p>0.05$, while the Cho/NAA low-grade group has abnormal distribution ($p < 0.05$).

The low-grade Cho/NAA ratio data is abnormally distributed (Shapiro Wilk $p=0.001$ test), so we could not use a parametric test. We transformed the data using inverse square root (T_CHNAA_LG), and the eventual normality test results showed $p=0.494$ (normally distributed). Furthermore, the transformed data were analyzed using an independent t-test. Based on the above results, statistical analysis of age data, Cho/Cr, and Cho/NAA ratios can be performed using parametric tests (Table 2).

Astrocytoma consists of subtypes: Diffuse astrocytoma, Anaplastic astrocytoma, and Glioblastoma. This study obtained diffuse astrocytoma, included in the WHO degree II, characterized by the proliferation of astrocytic cells with atypia and mild-moderate pleiomorphism arranged in a fibrillary matrix (Figure 2).

In this study, a picture of Glioblastoma multiforme was also obtained, included in the WHO degree IV, which is marked with a description area showing palisading necrosis with tumor cells arranged at the edge of necrosis and proliferation of endothelial cells are visible, forming glomeruloids. (Figure 3)

Table 1. Research sample characteristics

Characteristics of the patient	High-grade brain tumor (n=5)	Low- Grade Brain Tumor (n=12)	p
Age (years) (average ± sd)	52 ± 17.66	37 ± 14.35	0.45[a]
Gender			
• Male	2	5	
• Female	3	7	1[b]
Biomarker			
• Cho/Crratio	10.2 ± 7.09	5.67 ± 5.67	0.181[a]
• Cho/NAA ratio	8.66 ± 5.64	2.16 ± 1.74**	0.061[a]
• Lipid Lactate			
○ Present	5	7	0.245[b]
○ Not Present	0	5	

a = independent t-test, b = Fisher's exact test, *significant if p < 0.05, ** inverse square roottransformation

Table 2. Normality test results

Grup	P value
Age	0.177*
High Cho/Cr	0.983*
High Cho/NAA	0.957*
Low Cho/Cr	0.472*
Low Cho/ NAA	0.001→0.494* (transformasi inverse square root)

Data has normal distribution if p > 0.05

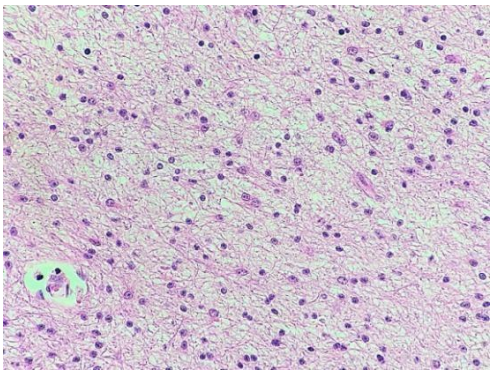

Figure 2. Diffuse astrocytoma (WHO grade II). Tumors with the proliferation of astrocytic cells with mild-moderate atypia and pleomorphism, arranged in a fibrillary matrix

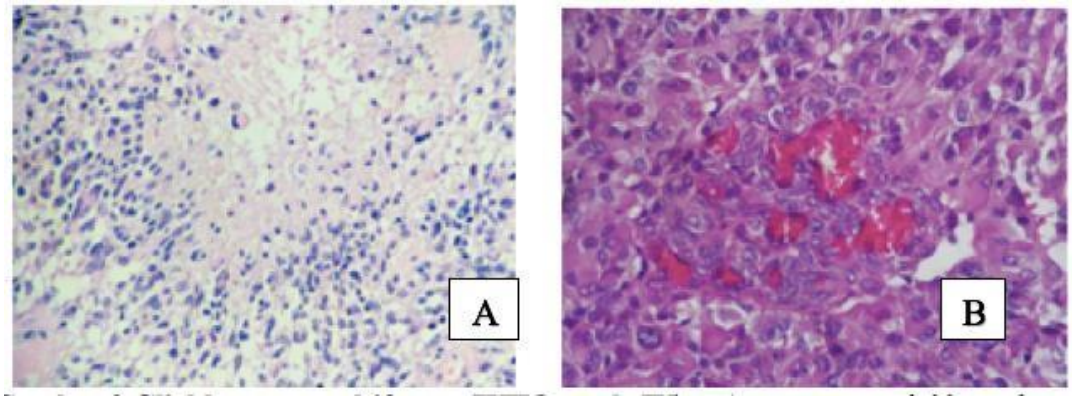

Figure 3. Glioblastoma (WHO grade IV) a. The area that indicates palisading necrosis with tumor cells arranged at the necrosis edge; B. Visible vascular proliferation (endothelial cell cells) forms a glomeruloid feature.

To evaluate the concordance between the ratio of Cho/Cr, Cho/NAA, and lipid lactate with the degree of malignancy of primary brain tumors based on the results of histopathology, McNemar's test was conducted. Cho/Cr p=0.039 with a conformity accuracy of 47%; Cho/NAA shows the result of p=0.219 with a conformity accuracy of 65%; and lipid lactate shows a consequence of p=0.016 with a conformity accuracy of 58%. (Table 3)

To evaluate the influence of gender differences and lactic lipids' presence on tumor histopathological degrees, this study used Fisher's exact test as a non-parametric statistical test. This test obtained a p-value = 1.0 for gender and p = 0.245 for lactate lipids. A value is considered significant if $p < 0.05$.

To evaluate whether age, Cho/Cr, Cho/NAA, and tumor grade are influenced, we used a parametric statistical test, the independent t-test. This test, p = 0.45 was obtained for age, p = 0.181 for Cho/Cr, andp = 0.061 for Cho/NAA. A value is considered significant if $p < 0.05$. (Table 4)

DISCUSSION

Among 17 samples, 5 (29%) had a high- grade primary brain tumor and 12 (70.58%) with a low-grade primary brain tumor. The result shows that those with low-grade primary tumors dominated the samples in this study. Because the sampling technique used was total sampling with histopathological data and MRS result datataken retrospectively with a total sample of 17, this cannot represent the epidemiology in general. Primary brain tumors have a slight incidence rate, ranging from 1.4% of the total overall malignancy, and have 17.6 to 22 per 100,000 populations in the Americas and Europe. In Indonesia, the incidence is 7 per 100,000 people and has amortality rate of 4.25 per 100,000 people in1 year [3].

Based on gender, 10 (58.82%) subjects were women, and 7 (41.17%) were male. In both high- and low-grade primary brain tumor subjects, more were women, with 3 (60%) and 7 (58.8%), respectively. The average age of subjects with a high-grade primary brain tumor was 52.00 ± 17.66, while the average of subjects with a low-grade brain tumor was 37.00 ± 14.35. According to Yang et al., several studies distinguish Glioblastoma by gender at the molecular level, allowing differences in targets at the molecular level. In the United States, epidemiological data showed a ratio

of men to women to be 1.6:1. Recent research explains that this gender difference may be related to the influence of cancer's biological properties and clinical response. One of the ways this is influenced is by the loss of intrinsic cell response in the function of the p53 gene in male astrocytes, which causes astrocyte cells to be susceptible to malignant transformation compared to astrocytes in females [8,11,12]. In our study, many female samples were obtained due to the possibility of insufficient sample limitations to represent a population. In the age group, the average age of subjects with a high-grade primary brain tumor was 52 ± 17.66, while that of subjects with a low-grade brain tumor was 37.00 ± 14.35. There were no significant differencesbased on age in high-grade and low-grade brain tumors compared to histopathological results with a value of p = 0.45 (p > 0.05) in different tests. According to Diwanji et al., CNS tumors are less common in the 15–39 age range compared to the older age groups. The annual incidence of low-grade glioma in pediatrics is 1.3–2.1 per 100,000 inhabitants in the United States. In adults, low-grade glioma is more common, with an estimated incidence rate of 9.1–12.5 cases per 100,000 [9,13,14,15].

Table 3. Conformity test results using

Parameter	P value	Precision
Cho/ Cr	0.039	47%
Cho/ NAA	0.219*	65%
Lipid Laktat	0.016	58%

*Significant if p> 0.05

Table 4. Difference test result

Grup	Test	P value
Sex	Fisher exact test	1.0
Lipid laktat	Fisher exact test	0.245
Age	Independent t test	0.45
Cho/Cr	Independent t test	0.181
Cho/NAA	Independent t test	0.061

To evaluate the concordance between the ratio of Cho/Cr with the degree of malignancy of primary brain tumors based on histopathology results, we conducted McNemar's test with the result of p = 0.039 (p < 0.05). As a result, we conclude that there is no conformity between the ratio of Cho/Cr with the degree of malignancy of primary brain tumor with histopathological results with an accuracy of 47 %. Baker et al. propose that cholesterol increases are an essential marker of tumor development and response to therapy, as well as increased cell membrane synthesis, catabolism, and abnormal metabolic changes. Experimental data shows that if there is an increase in choline, it is closely related to the degree of malignancy. Meanwhile, a decline is associated with the cessation of growth [15,16,17,18]. These differences can occur due to differences in imaging methods, including magnetic field strength, acquisition parameters, voxel size, tumor location, tumor heterogeneity, sample count, and sample distribution [17,19,20,21].

The study results obtained conformity between the ratio of Cho/NAA with the degree of malignancy of primary brain tumors with the result of $p = 1.0$ ($p > 0.05$). Consequently, we concluded that there is a conformity between the ratio of Cho/NAA and the degree of malignancy of primary brain tumors with histopathological results, with an accuracy of 65%. Hamsini et al. mentioned a conformity between histopathological results and an increase in the ratio of Cho/NAA. NAA is a neuronal marker, and it decreases in almost all high-grade brain tumors due to damage to neurons replaced by malignant cells [17,22,23].

The study results obtained discrepancies between the presence of lactic lipids and the degree of malignancy of primary brain tumors based on histopathology results; we conducted McNemar's Test with the result of $p = 0.016$ ($p < 0.05$). Therefore, we concluded that there is no conformity between lactic lipids' presence and the degree of malignancy of primary brain tumors with histopathological results with a precision of 58%. Necrotic components cause a noticeable increase in lipids in high-grade brain tumors. Other studies have also shown that high-grade tumors areheterogeneous with solid tumors, necrosis, and bleeding [17,24]. These differences can occur due to different imaging methods, including magnetic field forces, acquisition parameters, voxel size, tumor location, tumor heterogenity, sample count, and sample distribution [17,23]. This study showed no significant difference in Cho/Cr ratio between high- and low-degree primary brain tumors with a $p = 0.181$ ($p > 0.05$). This result contrasts with a study by Naser et al. (2016), which found a significant difference in Cho/Cr ratio in the high-grade brain tumor group compared to the low-grade brain tumor group [10,24]. These differences are most likely due to heterogeneity in tumor tissue, including cysts, necrosis, and bleeding [11,17]. Creatin and phosphocreatine experienced an increase before and after birth. Unlike other metabolite components, creatine and phosphocreatine's signal intensity is almost always stable after the first year of life. The spectra concentration can be seen at 3.0 ppm and used as an internal reference [12]. Creatine is used as a reference molecule because its stability and concentration in various brain areas are well-documented. Creatine is not produced in the brain, so impaired liver or kidney function may lower the spectra of creatine peak. In addition, local causes of creatine decline can occur in tumors that have high metabolic activity, such as high-degree glioma [13].

In this study, there was no significant difference in Cho/NAA ratio between the high-degree primary brain tumor group and the low-grade primary brain tumor group with $p = 0.219$ ($p > 0.05$). A study by Zeng et al. (2011) explained that the Cho/NAA ratio performed well in predicting the degree of malignancy of brain tumors. NAA shows neuron density and viability if there is a decrease in the loss of neuron function [14]. These differences in results are most likely caused by heterogeneity in tumor tissue, including cysts, necrosis, and bleeding [11].

CONCLUSION

In this study, we analyzed the conformity between the Cho/NAA ratio in MRS and the degree of malignancy in primary brain tumors based on histopathology results. The ratio of Cho/Cr, Cho/NAA, and lipid lactate peaks in MRS did not differ from the degree of histopathological malignancy in primary brain tumors.

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