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# The Role of Magnetic Resonance Spectroscopy in Differentiating Between Primary & Secondary Brain Tumors Based on Peri-Tumoral Area Metabolites in Iraqi Population

**Zahraa Ayad Jaber [1*], Prof. Abdulameer A. Almosawi [2], Yaareb Riyadh al Sherifi [3], Eman Majid Mahmood [4]**

***Author's Information***
1. *M.B.Ch.B ,C.A.B.H.F (Radiology) Head of the department of Radiology in Middle Eluphorate Neuroradiology Center*
2. *M.B.Ch.B , FIBMS- Radiology, Professor of Diagnostic Radiology, Faculty of medicine, Kufa University*
3. *M.B.Ch.B ,C.A.B.H.F (Radiology), Specialist radiologist, Middle euphrates oncology center*
4. *M.B.Ch.B. Candidate of the Fellowship of Arab Board of Health Specialization in Radio-Diagnosis*

***Corresponding author:***
***Dr. Zahraa Ayad Jaber***
*zhraaaayad313@gmail.com*

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## ABSTRACT

***Background:*** *Magnetic Resonance spectroscopy (MRS) allows analysis of metabolites. and can help to differentiate the primary brain tumors from metastasis.*

***Objective:*** *To assess the value of magnetic resonance spectroscopy (MRS) in differentiating primary brain tumors from secondaries confirmed by histopathology studies based on peritumoral area metabolite.*

***Patient and method:*** *A cross-sectional study conducted at Middle Euphrates oncology hospital in AL Najaf City during the period January 2022 to January 2023 and included 122 patients with brain tumors and had histopathological confirmation. Patients assigned into two groups; group one included 66 patients with primary and groups II included 56 patients with secondary tumors*

***Result:*** *Patients with primary tumors had a significantly higher Cho/Cr ratio and Cho/NAA ratio, and lower Lipid/NAA ratio than those with secondary tumor group, (P < 0.001). NAA/Cr ratio was not significantly different between groups, (P. value > 0.05). Receiver operating characteristics (ROC) curve analysis revealed that Cho/Cr and Lipid/NAA had excellent performance, Cho/NAA ratio showed a fair performance while NAA/Cr ratio failed in differentiation between primary tumors and metastatic lesions*

***Conclusion:*** *Magnetic resonance spectroscopy shows high sensitivity, specificity, and accuracy in differentiating primary from a secondary brain tumors. This study shows Cho/Cr and Cho/NAA ratio was significantly higher in the primary tumor compared to the metastatic tumours. The newly used lipid/NAA ratio shows further higher differentiation between primary and secondary brain tumors as a new marker.*

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***Keywords:*** *Brain tumors, Magnetic Resonance Spectroscopy, Peri-Tumoral Area Metabolites*

## 1. INTRODUCTION

A brain tumor is an area or mass of abnormal cells in the brain that can become life-threatening because of its ability to invade neighboring tissues and also form metastases (1) when these tumors grow inside the brain increasing intracranial pressure, which can cause brain damage and may even be life-threatening (2). Tumors can be benign or malignant and can occur in different parts of the brain, and can be classified as primary or secondary, a primary tumor began in the brain as opposed to a metastatic tumor, which originated elsewhere in the body and then progressed to the brain (3). The incidence of metastatic tumors is approximately four times greater than primary tumors (4). Imaging modality of choice is gadolinium-enhanced magnetic resonance imaging (5). There is no specific pathognomonic feature on imaging that differentiates between primary brain tumors and metastatic or nonneoplastic disease, in cases of suspected or pathologically proven metastatic disease, chest, and abdomen computed tomography may be helpful, although determining the site of the primary tumor is often difficult, especially if there are no clinical clues from the history and physical examination. Primary brain tumors in adults. are rare. The incidence of a new brain tumor is 6.4 per 100,000 persons per year with an overall five-year survival rate of 33.4%. (5). Grading of central nervous system tumors commonly occurs on a 4-point scale ( I-IV) created by the World Health Organization, (6,7). From other point of view, diffuse gliomas classified by phenotype/genotype (8). Several imaging methods are employed for detection of Brain Tumors, such as magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), single photon emission computer tomography (SPECT) imaging, and cerebral angiography. (9,10). Localized proton MR spectroscopy (MRS) of the human brain, first reported more than 20 years ago (11) is an established technique that is applied in clinical settings for the evaluation of brain tumors worldwide (12). While there have been studies of human brain tumors using heteronuclear such as phosphorus (31P) and sodium (11Na) by far most spectroscopy studies use the proton (1H) nucleus, because of both its high sensitivity and ease of implementation on commercial MRI scanners (11). MRS measures the chemical and the shift of non-water molecules in a region of interest as a noninvasive marker of tumor metabolism. In the normal brain, the

main metabolite peaks are choline at 3.2 parts per million(ppm), creatine at 3.0 ppm, and N-acetyl aspartate at 2.0 ppm, which form an upward slope from left to right(i.e, Hunter's angle)Cho/Cr ratio >2 is suggestive of a high-grade tumor (13). N-Acetylaspartate (NAA) is a compound found only in neurons and therefore a marker of neuronal density, Its peak is the most prominent peak in normal adult brain proton MRS which resonates at 2.0 ppm (8). Creatine (Cr) is a measure of energy metabolism that is predominantly produced from amino acids in the kidneys and liver and delivered to peripheral organs by blood. 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 (14). 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 Choline (Cho) is a metabolic indicator of cellular growth and cell membrane stability, the Choline peak is seen at 3.2 ppm and is the most important metabolic peak for the diagnosis of glioma (15). Choline may be considered a tumor marker. If an intracranial mass is indeterminate with respect to etiology, the elevation of the choline-to-creatine ratio may help to distinguish radiation necrosis from a recurrent tumor or infection (15). Myoinositol (Myo) is a simple sugar with a 3.56 ppm assigned. It is regarded as a glial marker since it is almost exclusively produced by astrocytes, which are glial cells. Moreover, it is the most significant osmolyte in astrocytes. The presence of brain disorders that have obvious gliosis can be seen in the elevation in Myo that was discovered, a higher Myo/Cr ratio is seen in low-grade glioma (8). 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 a direct correlation between Lac level and glioma grade. The level of Lip detected by MRS appears to reflect the severity of tissue damage (15). Glutamate (Glu)-glutamine (Gln) and gamma-aminobutyric acid Glx is a complex peak from glutamate (Glu), glutamine (Gln), and gamma-aminobutyric acid (GABA) assigned at 2.05–2.50 ppm. 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. An elevated concentration of Gln is found in a few conditions such as hepatic encephalopathy (16). Alanine (Ala) is an amino acid , has a doublet peak ascribed to it at 1.48 ppm. In spectra with short or long TE. Ala has an unknown function, however, it is involved in the citric acid cycle. The lactate peak may block out the alanine peak. Insufficiencies in oxidative metabolism may result in an elevated concentration of Ala. A higher amount of Ala in tumors is thought to be particularly for meningiomas. 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 (15). Early in the development of human brain proton MRS, it was realized that brain tumors exhibited markedly different spectra from normal brain tissue ,it was found that nearly all brain tumors have decreased N-acetyl aspartate (NAA) signals, and often also have increased levels of Choline (Cho), which lead to increased Cho/NAA ratio. The decrease in NAA is widely interpreted as the loss, dysfunction, or displacement of normal neuronal tissue. Cho elevated in brain tumors due to an increase in membrane damage(17). Other relatively common metabolic changes in human brain tumors are elevated signals in the lactate and lipid region of the spectrum and also increased levels of Myo-inositol (mI) in short echo time (TE) spectra The increase in the level of lactate is most likely the result of anaerobic glycolysis (18). Increased levels of mI are believed to be due to an increase in the number of glial cells, in particular, have been reported to be high in grade II gliomas (19). MRS have shown to be play an important role in differentiation of primary brain tumor and metastasis in peritumoral area. It is a useful tool to distinguish whether a brain mass is neoplastic or nonneoplastic but has not been shown to reliably distinguish metastasis from high-grade primary glial neoplasm such as glioblastoma . Spectra from contrast-enhancing tumor tissues and peritumoral edema can be compared in order to evaluate the presence or absence of peritumoral white matter infiltration by non-enhancing tumors (15). The enhancing components of both brain metastases and high-grade gliomas demonstrate increased choline/ creatine peak ratios compared with normal brains. However, studies are inconsistent aboutwhether the choline/ creatine ratio is higher or lower in metastases compared with high-grade glial neoplasms lipid and lactate may be elevated in brain tumors due to necrosis (15). While brain metastases have been reported to

demonstrate elevated lipid and lactate peaks, these peaks have not been found reliable in distinguishing brain metastases from high-grade gliomas, which may also be. necrotic. High-grade gliomas tend to have elevated. myoinositol peaks and this has not been reported in brain metastases (20). Both tumor types may have depressed NAA, while no clear means of differentiating metastases from high-grade gliomas by spectroscopy of the enhancing component of the tumor has become evident, evaluation of the non-enhancing T2WI surrounding enhancing brain metastases represents pure vasogenic edema, while in glial tumors, this often represents a combination of vasogenic edema and infiltrative neoplastic cells, which significantly causes elevated choline/creatine ratios compared with metastases, this peritumoral area around the enhancing mass has shown promise for differentiating. primary glial tumors from metastases (21).

## 2. METHODOLOGY

**Study design and setting:**

This was a prospective cross-sectional study conducted at the Middle Euphrates Oncology hospital in AL Najaf City during the period between January 2022 to January 2023.

**Study Population and eligibility :**

The study included 122 participants with brain space-occupying lesions (51 females and 71 males), aged 7 –83 year. Patients with brain tumors had histopathological confirmation. Patients were categorized as group I (66 patients with primary brain tumors and Group II (56patient with brain metastasis).

In all patients, MRS metabolites used in the peritumoral area to differentiate primary brain tumors from secondaries, and confirmed by histopathology, all patients.

**Inclusion Criteria:**

All Patients with brain tumors and confirmed by histopathology and had MR spectroscopy of both genders.

**Exclusion Criteria:**

1. MR spectroscopy with the artifact, baseline noise, and patient-done single voxel MRI.
2. Patient was also excluded if he/she
    a. Received radiation

b. Not been operated on

c. Had a history of head trauma or ischemia.

**Material:** The participants underwent MRI sequences T1W SE Axial and Sagittal, T2 Axial and Coronal, Coronal T2 FLAIR and T1 post-contrast (Gadolinium 0.1 mmol/kg body weight). All examinations will be performed using a 1.5 T MR Unit (SIGNA Horizon, General Electric Medical System, Milwaukee, WI) using a head coil. Multi-voxel MR spectroscopy was performed using a spin-echo mode 144 - TE sequence. We used Multivoxel MR spectroscopy (H+) with PRESS sequence ( point Resolved Spectroscopic Sequence ) using (2 x 2 x 2) = 8 cm3 voxel in GE 1.5 T machine. The spectra were obtained with a long echo time. Metabolites peaks; N-Acetylaspartate (NAA) at 2.0 ppm, Choline (Cho) at 3.2 ppm, Creatine (Cr) at 3.0 ppm, Lactate (Lac) at 1.3 ppm, were analyzed as well as the ratios between them. For the spectra analysis, used by evaluation of the peritumoral area in T2WI surrounding brain tumor, and take zone of interest (15mm)the highest peak of each studied metabolite was considered and the relations among them were calculated. The findings in both MRI and Multivoxel MRS were analyzed by two experienced radiologists who were unaware of the histopathological results. These data were matched with the pathologic findings of lesions obtained by stereotactic biopsy or surgery

**Statistical Analysis:** Data of the patients were analyzed using the statistical package for social sciences (SPSS) version 27. Descriptive statistics presented as mean, standard deviation, frequencies and percentages. Appropriate statistical tests, analysis and procedures were performed accordingly. Receiver operating characteristics (ROC) curve used to assess the validity of metabolic ratios in differentiation between primary tumors and secondary brain lesions. All statistical tests were applied at a level of significance of ≤ 0.05.

## 3. RESULTS

The study included 122 patients with a mean age of 51.4 ± 14.5 (range: 7 – 83 years. Males were dominant and contributed to 58.2% of the studied group (71 males and 51 females). Headache was the more frequent symptom, contributed for 45.1% followed by fit (34.4%). combined headache and fit (15.6%) and the least frequent symptom was weakness in 4.9% of the patients. Among the patients, 32% experienced their symptoms at almost daily, 50% at least, weekly, and 18% at least monthly (**Table1**). Primary tumors were reported in 66 out

of the 122 patients, (54.1%), while secondary metastasis in the remaining 56 patients (45.9%), (**Figure 1**). High-grade grade gliomas were the most reported primary tumor, (95.5%), while Lung metastasis was the more frequent secondary tumor, (57.1%), (**Table 2**). All primary tumors showed hypointensity on T1WI compared to 82.1% of secondary tumors. Also, all primary tumors showed Hyperintensity on T2WI compared to 92.9% of secondary metastasis lesions. On FLAIR all of the primary and secondary metastasis showed hyperintensity. Among the primary tumors, mild enhancement was more frequent than that in secondary metastasis, 47% vs. 37.5%, respectively, so as for heterogeneous enhancement, while avid was less frequent with primary tumors than in secondary metastasis, 25.8% vs. 57.1%, respectively, these and other findings are shown in (**Table 3**). Patients with primary tumors had a significantly higher Cho/Cr ratio of 2.79 compared to 1.25 in the secondary metastasis group, (P. value < 0.001), The mean Cho/NAA ratio was significantly higher in the primary tumors compared to the secondary metastasis group, 1.84 vs. 1.21, respectively, (P. value = 0.027). No significant difference was found in the mean values of the NAA/Cr ratio between both subgroups, (P. value > 0.05). Lipid/NAA ratio was significantly lower in primary tumor group than secondary metastasis group, the mean value was 0.53 compared to 2.04, respectively (**Table 4**). Receiver operating characteristics (ROC) curve analysis for the validity of different ratios in differentiation between primary and secondary tumors revealed that Cho/Cr at an optimal cutoff point of 1.75 showed excellent performance with an area under the ROC curve (AUC) of 0.953, the sensitivity, specificity, and accuracy were high; 98.5%, 85.7%, and 91.8%, respectively. For Cho/NAA ratio, it showed a fair performance with an AUC of 0.697 at an optimal cutoff point of 1.25, it produced a sensitivity of 65.2%, specificity of 80.4% and accuracy of 72.5%. The lipid/NAA ratio. was the stronger predictor, at an optimal cutoff point of 0.950, the AUC was 0.994, sensitivity was 98.8%), specificity 93.9% and accuracy was 96.1%. The NAA/Cr ratio failed to differentiate between primary tumors and secondary metastasis where the AUC was 0.503 at a cutoff point of 2.35, Sensitivity was only 28.6%, specificity 84.8% while accuracy was 56.4%, Results of Pearson's, Spearman's and Kendall's tau tests showed that none of the patient's characteristics including age, gender, smoking, BMI, or comorbidities had a significant correlation with each of the metabolic ratios, (P. value > 0.05), (**Figure 2 and Table 5**).

Table 1. Descriptive characteristics of the studied group (N=122)

| Variable | | Value |
|---|---|---|
| Age (mean ± SD years) | | 51.4 (14.5) |
| Gender n (%) | Male | 71 (58.2) |
| | Female | 51 (41.8) |
| Comorbidities n (%) | Hypertension | 64 (52.5) |
| | Diabetes mellitus | 44 (36.1) |
| Symptoms | Headache | 55 (45.1) |
| | Fit | 42 (34.4) |
| | Headache and Fit | 19 (15.6) |
| | Weakness | 6 (4.9) |
| Frequency of symptoms | Daily | 39 (32.0) |
| | At least weekly | 61 (50.0) |
| | At least Monthly | 22 (18.0) |
| Weight (mean ± SD kg) | | 80.6 ± 9.8 |
| Height (mean ± SD cm) | | 163.0 ± 5.1 |
| BMI (mean ± SD kg/m²) | | 30.3 ± 3.6 |

SD: standard deviation

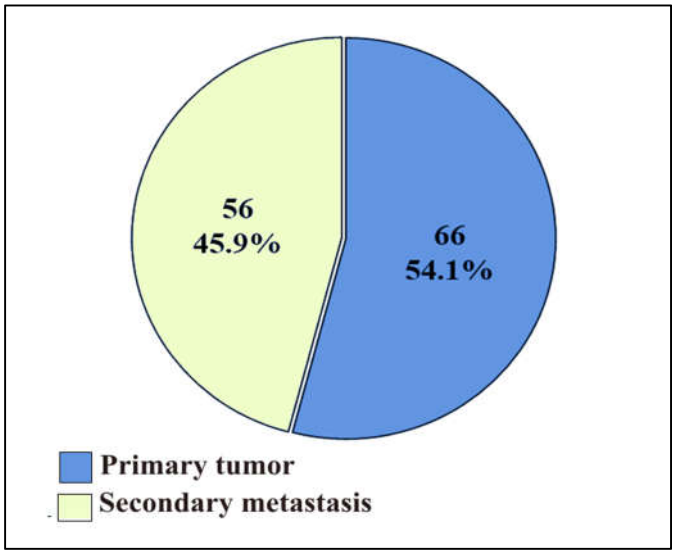


Figure 1. Distribution of the studied groups according to the type of tumor

Table 2. Distribution of Types of primary and secondary tumors (N=122)

| Type of tumors | | No. | % |
|---|---|---|---|
| Primary | High-grade glioma | 63 | 95.5 |
| | Low-grade glioma | 2 | 3.0 |
| | High-grade medulloblastoma | 1 | 1.5 |
| | Total | 66 | 100.0 |
| Secondary | Lung metastasis | 32 | 57.2 |
| | Breast metastasis | 18 | 32.1 |
| | Pancreatic metastasis | 4 | 7.1 |
| | Lymphoma metastasis | 2 | 3.6 |
| | Total | 56 | 100.0 |

Table 3. Distribution of the MRS findings of the studied groups according to the type of tumor

| Finding | | Primary (n=66) | | Secondary (n=56) | | P. value |
|---|---|---|---|---|---|---|
| | | No. | % | No. | % | |
| T1WI | Hyper-intensity | 0 | 0.0 | 10 | 17.9 | <0.001sig |
| | Hypo-intensity | 66 | 100.0 | 46 | 82.1 | |
| T2WI | Hyper-intensity | 66 | 100.0 | 52 | 92.9 | 0.027 sig |
| | Hypo-intensity | 0 | 0.0 | 4 | 7.1 | |
| FLAIR | Hyper-intensity | 66 | 100.0 | 56 | 100.0 | NA |
| | Hypo-intensity | 0 | 0.0 | 0 | 0.0 | |
| Enhancement | Mild | 31 | 47.0 | 21 | 37.5 | <0.001sig |
| | avid | 17 | 25.8 | 32 | 57.1 | |
| | Heterogeneous | 18 | 27.3 | 3 | 5.4 | |
| DWI | Non-restricted | 60 | 90.9 | 50 | 89.3 | 0.047 sig |
| | Restricted | 2 | 3.0 | 6 | 10.7 | |
| | Partial restricted | 4 | 6.1 | 0 | 0.0 | |
| Oedema | Grade I | 26 | 39.4 | 41 | 73.2 | <0.001sig |
| | Grade II | 28 | 42.4 | 15 | 26.8 | |
| | Grade III | 12 | 18.2 | 0 | 0.0 | |
| Site of lesion | Frontal lobe | 12 | 18.2 | 25 | 44.6 | 0.008 sig |
| | Parietal lobe | 29 | 43.9 | 19 | 33.9 | |
| | Fronto- Parietal | 8 | 12.1 | 6 | 10.7 | |
| | Temporal | 11 | 16.7 | 6 | 10.7 | |
| | Cerebellum | 6 | 9.1 | 0 | 0.0 | |

sig: significant

Table 4. Comparison of metabolic ratio values of patients according to the type of tumors

| Parameter | Primary tumor (n=66) | | Secondary metastasis (n=56) | | P. value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Cho/Cr | 2.79 | 0.87 | 1.25 | 0.68 | <0.001sig |
| Cho/NAA | 1.84 | 0.71 | 1.21 | 0.42 | 0.001sig |
| NAA/Cr | 1.76 | 0.64 | 1.70 | 0.73 | 0.625 ns |
| Lipid/NAA | 0.53 | 0.30 | 2.04 | 0.69 | <0.001sig |

sig: significant, ns: not significant

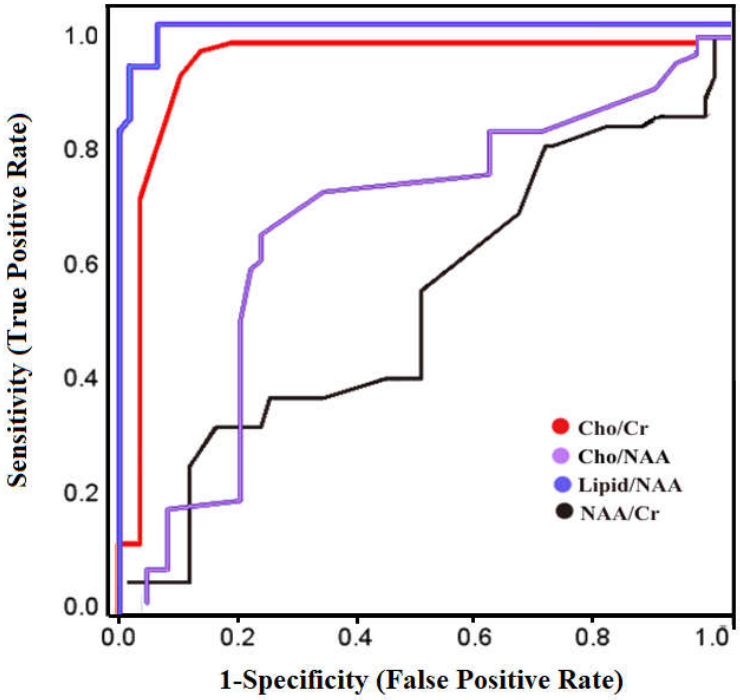


Figure 2. Receiver operating characteristics (ROC) curve analysis for the validity of Cho/Cr (AUC = 0.953) , Cho/NAA (AUC= 0.697), NAA/Cr (AUC = 0.503) and Lipid/NAA (AUC = 0.994), in differentiation between primary tumor and secondary metastasis.

Table 5. Summary of validity parameters of all brain metabolites in differentiation between primary and secondary brain tumor

| parameter | Cutoff value | AUC | sensitivity | specificity | accuracy | PPV | NPN |
|---|---|---|---|---|---|---|---|
| Cho/Cr | 1.75 | 0.953 | 98.5% | 85.7% | 91.8% | 87.3% | 98.1% |
| Cho/NAA | 1.25 | 0.69 | 65.2% | 80.4% | 72.5% | 76.8% | 69.6% |
| NAA/Cr | 2.35 | 0.50 | 28.6% | 84.8% | 56.4% | 65.3% | 54.1% |
| Lipid/NAA | 0.95 | 0.99 | 98.8% | 93.9% | 96.1% | 94.2% | 98.6% |

Table 6 Results of bivariate Correlation between Metabolic ratios and patients characteristics

| Variable | *Statistics* | Cho/Cr | Cho/NAA | NAA/Cr | Lipid/NAA |
|---|---|---|---|---|---|
| Age | R | 0.151 | 0.124 | 0.078 | 0.118 |
| | P. value | 0.173 | 0.221 | 0.391 | 0.123 |
| Gender | R | 0.001 | 0.038 | 0.101 | 0.009 |
| | P. value | 0.990 | 0.677 | 0.270 | 0.920 |
| Smoking | R | 0.017 | 0.022 | 0.035 | 0.112 |
| | P. value | 0.852 | 0.810 | 0.705 | 0.220 |
| BMI | R | 0.063 | 0.071 | 0.182 | 0.055 |
| | P. value | 0.490 | 0.435 | 0.045 | 0.548 |
| Hypertension | R | 0.107 | 0.018 | 0.146 | 0.108 |
| | P. value | 0.239 | 0.846 | 0.213 | 0.235 |
| DM | R | 0.038 | 0.101 | 0.161 | 0.057 |
| | P. value | 0.678 | 0.266 | 0.147 | 0.531 |

## 4. DISCUSSION

Magnetic resonance spectroscopy (MRS) is a rapidly developing field of neuroimaging that allows noninvasive. vivo analysis of metabolites of any brain lesion. Our results indicate that visual assessment of peritumoral non-enhancing lesions can help to differentiate the primary brain. tumors from metastasis. The key to doing that lies in the peritumoral non-enhancing lesion beyond the enhancing margin of the tumor (22). Our study included 122 patients primary tumors were reported in 66 out of the 122 patients, (54.1%), while secondary metastasis in the remaining 56 patients (45.9%), High-grade grade gliomas were the most

reported primary tumor, (95.5%), while Lung metastasis was frequently frequent reported secondary tumor, (57.1%). Our study agrees with the same finding as Jung, et al. (2021). Differentiation between glioblastoma and solitary metastasis which exhibits an aggressive and infiltrative pattern of growth, peritumoral areas demonstrate altered not only interstitial water but also scattered neoplastic cell infiltration (23). Indeed, neoplastic cells have been found in the non-enhancing-T2 hyperintense regions surrounding the primary tumor histopathology. Therefore, a peritumoral non-enhancing lesion of glioblastoma consists of 'vasogenic' plus 'neoplastic cell infiltrative' edema. However, in metastases, peritumoral areas contain no infiltrating neoplastic cells (20). The First finding in our study shows that the patients with primary tumors had a significantly higher Cho/Cr ratio of 2.79 compared to 1.25 in the secondary metastasis. group, (P. value < 0.001). On the other hand, the mean Cho/NAA ratio was acceptable in the primary tumor compared to the secondary metastasis group, 1.84 vs. 1.21, respectively, (P. value = 0.027). The study of Tsougos, et al and Fountas, et al(2012). also found that Cho/Cr and Cho/NAA ratios in the peritumoral area of glioblastomas were significantly higher than those of metastases is consistent with previous observations (22). The second finding in our study there was no significant difference found in the mean values of the NAA/Cr ratio between both subgroups, (P. value > 0.05). As mentioned in Chiang et al. and Law et al.(2004) reported that there was no significant difference in peritumoral NAA/Cr. between the high-grade gliomas and metastases (24). Creatine (Cr) is a measure of energy metabolism and contain in normal neurons and glial cells so is decreased in any tumor cell because of the destruction of the glial cell (15). The third finding was Lipid/NAA ratio was significantly lower in the primary tumor group than in the secondary metastasis group, the mean value was 0.53 compared to 2.04, respectively. Lipid/NAA ratio was the strongest predictor among the four parameters, at an optimal cutoff point of 0.950, the AUC was 0.994, sensitivity (was 98.8%), specificity (93.9%) and accuracy was (96.1%). The presence of lactate and lipid peaks are usually consistent with aggressive tumors, reflecting increased anaerobic metabolism and cellular necrosis, respectively. Tsougos et al(2012) have reported that. the presence of lipids in glioblastomas and metastases is due to areas of necrosis, in glioblastomas and metastases lipid signal arises from different origins such as pure tumor necrosis for.infiltrative tumor cells and there is less

necrosis combined with lipid membrane structure for migratory tumor cells, which might be a possible explanation for the lower peritumoral NAA/Cr on GBMs (22). In comparison with the study of Jung et al.(2021) peritumoral edema in high-grade gliomas is a combination of vasogenic edema. and neoplastic cell infiltration due to their infiltrative nature.. On the other hand, peritumoral edema of intracranial metastases is purely vasogenic because of increased. extracellular water from the leakage of plasma fluid from altered tumor capillaries, but no tumor cells are present (25). The same idea of our study done by Server et al(2010). compared metabolite ratios between 53 high-grade gliomas and 20 metastases (26) (62) This study compared metabolic peak area ratios obtained using a multivoxel, two-dimensional chemical shift imaging (2D CSI) technique at an echo time of 135 on a 1.5 Tesla magnet. With this technique, spectroscopic evaluation of the peritumoral area was the most accurate method for distinguishing metastasis from high-grade glial neoplasms by The receiver-operator curve analysis utilizing cut-off values of choline/creatine ratios of 1.24 in the peritumoral region and choline/NAA ratios of 1.11 was the most accurate way using this methodology for separating metastasis from high-grade glial neoplasms (27). However, there are certain limitations to the present study where there is a lack of availability of MRS in our centers and the difficulty in referral the patient to another hospital to do MRS , additionally, difficulty in the follow up for the histopathology study of the patients moreover, the new application of WHO classification of tumors according to gene mutation is not widely used in our hospitals.

## 5. CONCLUSIONS

Magnetic resonance spectroscopy showed high sensitivity, specificity, and accuracy in differentiating primary from a secondary brain tumors. This study showed that Cho/Cr and Cho/NAA ratio was significantly higher in the primary tumor compared to the metastatic tumors. The newly used lipid/NAA ratio showed further higher differentiation between primary and secondary brain tumours as a new marker. Hence, we recommend using MRS as a routine sequence and complementary to conventional MRI studies, especially in differentiation between primary brain tumor and solitary brain metastasis.

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