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Grading of Brain Tumors using MR Spectroscopy: Diagnostic value at Short and Long TE

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Abstract:
Objectives: To evaluate the usefulness of MR spectroscopy (MRS) in grading of brain tumors as well to evaluate which metabolite values/ratios could provide better classification/grading of brain tumors when using, short or long TE.
Methods: MRS was performed in 128 patients with brain tumors. Metabolite *NAA,Cho,Cr* lactates and lipids and metabolite ratios of Choline *(Cho)/N*-acetylaspartate *(NAA),* Cho/Creatine *(Cr), /NAA/ Cr* were calculated at short and long echo time (TEs). Tumors were subdivided into grades on the basis of radiologist results and the standard WHO values. Characteristic analysis of metabolites was performed to find the values in each tumor. The correlations between the metabolite values and grading were calculated.
Long TE as (1500/144ms) where the signal from most metabolites in the brain is lost except that of choline (Cho), creatine (Cr), *N*-acetyl aspartate (NAA), and lactate,and short TEs of (2000/35ms) that allow for identification of many other metabolites Lipids, lactate, ala, myoinositol, glutamate, and glutamine were applied.
Results: NAA, Cho, Cr, NAA/ Cr, Lactate and Lipids metabolic values showed no significant relation between the values to be increased or decreased according to grading therefore the dependency of grading should be based upon the Cho/ NAA and Cho/ Cr .From this account and metabolic ratios; the study suggested to diagnose, differentiate and grade gliomas after evaluating the Cho/ NAA and Cho/ Cr.
Conclusion :MRS metabolic ratios (Cho/Cr and Cho/NAA) can be used to grade and differentiate gliomas. Ratios less than 1.5 were suggested to be considered as normal values, ratios from 1.5 to 2 were suggested to subsist as low grade glioma and ratios higher than 2 were suggested to be high grade glioma or metastasis. Meningioma can be diagnosed by conventional MRI images. MRS should be added to routine MR imaging studies as it provides greater information concerning tissue characterization than what is possible with MR imaging studies alone.
Keywords - *Brain Tumors, MRS, MRI, Gliomas*

I. INTRODUCTION

Brain tumors are considered the essential cause of death and are often refractory to management. The grading of brain tumor has an important implication in clinical administration [1].The gold standard of tumor grading is histopathologic diagnosis requiring a biopsy with open neurosurgical procedure [2].

Differentiating brain lesions by CT or MR imaging can be difficult. These difficulties in the diagnosis of intracranial lesion are mainly due to the combination of non specific clinical results and similarities in the morphologic imaging appearance such as gliomas, metastases, and brain abscesses .[3]

Findings from several studies have suggested that MRS can noninvasively contribute to the establishment of the differential diagnosis between brain tumors and other brain lesions [4-8]
Despite expectations of noninvasive tumor characterization by clinical magnetic resonance (MR) spectroscopy, previous studies have capitulated unsatisfactory results [9]. On the other hand Initial studies indicated that MR spectroscopy might be able to aid in the diagnosis of various types or malignancy of brain tumors [10,11]. Studies also showed the ability of MR spectroscopy to give information on the basic metabolic processes in tumors [12,13 However, these studies concluded that there was no reliable indicator for discriminating among tumor types or malignancy. Conversely other studies have mentioned that the metabolic imaging is emerging as a promising diagnostic tool for the evaluation of cerebral gliomas [14],and the (MRS) has important role in evaluating and grading brain tumors [2].Studies have mentioned that MRS technique provides metabolic in sequence regarding the tissue being studied that harmonize the anatomic information obtained with MR imaging and have mentioned that the significant Imaging parameters to optimize the MR spectroscopy data acquisition, the appearance of the spectrum and the information that can be extracted is the TE .

TE is used in invivo MR spectroscopy by range between 18 and 288. In this respect, spectra are divided into short and long TE, ranging most short TE between 18 and 45 and long TE between 120 and 288. [16]Frequently inquired issue was whether or not MRS could help to diagnose tumor type and grade non-invasively, since this would have an influence on treatment and prognosis [17]

To the best of our knowledge there are no enough studies concerning the relevance of MRS metabolic ratios in the staging of brain glioma ,as well no study was obtained using short and long TE spectral metabolite values in clinical classification of brain tumors. Therefore, our purpose was to evaluate which metabolite values/ratios could provide better classification/grading of brain tumors when using, short or long TE, in patients with brain tumors found in clinical practice in order to avoid unnecessary biopsies.

II. MATERIALS AND METHODS

MRI cases with brain tumors were reviewed, and performed descriptive analytical (case-control) study on patients (study group) presented to neuro-surgery & Oncology departments. All of the selected patients submitted their comprehensive clinical history and clinical examination report. Moreover, MRI of brain tumors was discussed and evaluated by the radiologist, oncologist, neuro-surgeons. One hundred twenty eight participants were selected for the purpose of investigation. 89(69.5%) were males individuals and 39(30.5%) were females individuals were selected who were suffering from different types of brain tumors. The participants were mean age was 47.08 ±18.1 ranged from 3-86years. No participant had undergone radiotherapy or chemotherapy.

World Health Organization has categorized the malignancy of glioma into four grades from 1 to 4. Grade 1 brain tumors are known as gliomas [18]. Grade 2 brain tumors are known as anaplastic astrocytomas, Grade 3 brain tumors are mostly known as anaplastic oligodedrogiomas Grade 4 brain tumors are known as anaplastic gangliogliomas and anaplastic ependymomas. [19].The malignancy of glioma was graded from 1 to 4 according to the World Health Organization (*WHO*) grading was as follows Grade I: Small subset, Grade II: low-grade astrocytoma ,Grade III: Anaplastic astrocytoma,Grade IV: Glioblastoma,multiform(GBM) ,Were (Grade I: Small subset) = 0.5 to 1.5,Grade II: low-grade astrocytoma = 1.6 to 2.5,Grade III: Anaplastic astrocytoma= 2.6 to 3,Grade IV: Glioblastoma multiform(GBM) > 3. And consider the mean values for normal Cho/Cr, and NAA/Cho ratios were 0.66 and 2.20 respectively [20]. We have utilized a 1.5 Tesla superconducting syngo MRI system with 25mT/m maximum gradient potential and standard head coil.The study used two different techniques for spectroscopy examination with syngo MRI system, which include single voxel spectroscopy (SVS) SVS and chemical shift imaging (CSI). Both of these methods differ in their localization properties.

Imaging protocol sequence in MRS was obtained as: Phase-encoding gradients were used to encode spatial information after the RF pulses and the gradient of slice selection. MRS is acquired using only slice selection and phase encoding gradients, besides the spoiler gradients. Spectroscopic study was carried out using (CSI) and acquiring a localized scan at the lesion's equator,as well was used as the lesions were localized in areas where multi-voxel acquisition had proved difficult (cerebellum, brainstem or in supratentorial cortico-subcortical site),the spectroscopic voxel was placed over an enhancing region of the tumor, avoiding areas of necrosis, hemorrhage, calcification, and cysts. Each patient was examined by both short TE (2000/35) (TR/TE) and long TE (1500/144) sequences.Spectroscopy imaging quantitative data was analyzed blindly by experienced neuroradiologist using a dedicated post-processing workstation. With reference to spectroscopy, the maximum Cho/NAA ratio of a voxel selected in the solid tumor area was calculated. In addition, the presence of lactate peak was also taken into account.

III. FIGURES AND TABLES

The ***Table No (1): Descriptive Statistics of classification of lesions according to WHO grading, MRS metabolite and Radiologist MR imaging features of brain tumors.***

Descriptive Statistics					
	N	Minimum Metabolite Value	Maximum Metabolite Value	Mean Metabolite Value	Std. Deviation
Benign (G1)	35	0.25	2.88	1.1591	.36675
Benign (GII)	13	1.50	2.25	1.8346	.24333
Malignant (GIII)	39	2.17	2.97	2.7997	.19250
Malignant (GIV)	39	2.88	6.38	3.7905	.98943

Table No (2) Distribution of study sample according to radiologist diagnosis.

Diagnosis	Frequency	Percentages (%)
Astrocytoma (Pilocystic, Anaplastic and Diffused)	58	45.3
Gliomatosis Cerebri/ Glioblastic Multiform/ (GBM)/ Oligodendroglioma	44	34.4
Meningioma	8	6.3
Metastatic	3	2.3
Lymphoma	2	1.6
Ependymal tumors	13	10.1
Total	128	100.0 (%)

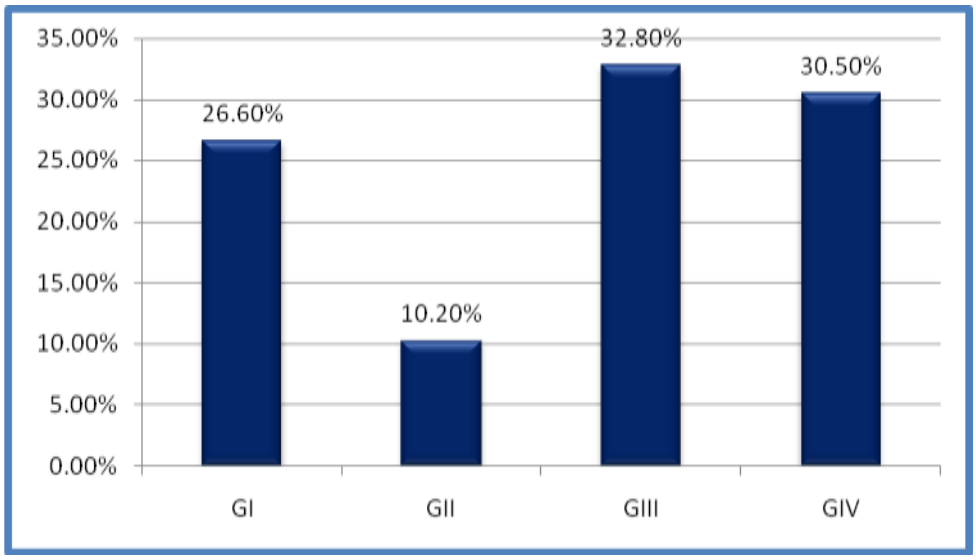

Figure No (1) Distribution of study sample according to Participant's tumors Grading

Table No (3) Mean age, gender distribution, metabolite ratio values, diagnosis-category of grading tumors {mean values} and radiologist diagnosis according to the standard criteria of Pilocystic, Anaplastic and Diffused Astrocytoma.

Mean age /Gender	Metabolite Values		Diagnosis-category Grading tumors*				Diagnosis
			Benign		Malignant		
	Cho/ NAA	Cho/ Cr	GI	GII	GIII	GIV	
41.82±16.14 ***M=9,F=8***	1.12 ±0.17	1.38 ±0.39	1.17 ±0.14	-	-	-	Pilocystic Astrocytoma
53.0±14.98 **M=9,F=6**	1.85 ±0.80	2.68 ±0.43	-	-	2.79 ±0.10	3.01 ±0.0	Anaplastic Astrocytoma
43.34±15.57 **M=21, F=5**	2.19 ±1.26	2.87 ±0.57	-	-	2.75 ±0.0	3.51 ±0.32	Diffused Astrocytoma

**Site of brain tumors were as follows : Both frontal lobes ,Insular cortex , Basal ganglia , Occipital lobe, ,RT frontal ,LT frontal ,RT temporal, LT temporal, Intra- axial , RT. Parietal-occipital, Fronto-temporal , Left cerebral hemisphere, Splenium of corpus callosum, Hypothalamus, left cerebellar hemisphere , vermis and Thalamus*

Table No (4) Mean age, gender distribution, Metabolite ratio Values, diagnosis-category of Grading tumors {mean values} and radiologist diagnosis according to the standard criteria of ependimal Tumors

Mean age /Gender	**Metabolite Values**		**Diagnosis-category of Grading tumors**				**Diagnosis**
			Benign		**Malignant**		
	Cho/ NAA	**Cho/ Cr**	**GI**	**GII**	**GIII**	**GIV**	
56±15.44 **F □ M**	0.94	2.05	0.89	-	2.8	1.67	*Ependymal Giant Cell Astrocytoma
58.57±16.81 **M □ F**	1.20 ±0.25	1.31 ±0.27	1.07 ±0.02	1.76 ±0.0	-	-	**Sub Ependymal Giant Cell Astrocytoma

**LT temporal, LT anterior horn of lateral ventricle, Occipital lobe. **RT Parietal, RT Frontal, Bi- frontal, LT orbital apex LT temporal and Thalamus.*

Table No (5) Mean age, gender distribution, Metabolite Values, diagnosis-category of Grading tumors {mean values} and radiologist diagnosis according to the standard criteria of Glioblastic Multiform (GBM) Gliomatosis Cerebri and Oligodendroglioma

Mean age /Gender	**Metabolite Values**		**Diagnosis-Category Grading Tumors**				**Diagnosis**
			Benign		**Malignant**		
	Cho/NAA	**Cho/ Cr**	**GI**	**GII**	**GIII**	**GIV**	
42.72±15.14 **F= 11,M =13**	2.72 ±1.76	3.14 ±1.23	1.23	1.98	2.88	4.07 ±1.26	Glioblastic Multiform(GBM)
41.91±14.16 **F=3 ,M=6**	1.70 ±0.11	2.13 ±0.53	-	1.89 ±0.22	2.8	2.13 ±0.34	Gliomatosis Cerebri
47.62±12.11 **F=4, M=7**	1.74 ±0.82	3.19 ±0.26	-	-	2.88 ±0.02	3.93 ±0.00	Oligodendroglioma

Table No (6) Mean age, gender distribution, Metabolite Values, diagnosis-category of Grading tumors {mean values} and radiologist diagnosis according to the standard criteria of Meningioma , Lymphoma

Mean age /Gender	**Metabolite Values**		**Diagnosis-Category Grading Tumors**				**Diagnosis/site**
			Benign		**Malignant**		
	Cho/ NAA	**Cho/ Cr**	**GI**	**GII**	**GIII**	**GIV**	
M=4, F=4 49.63±15.98	1.26±0.33	2.08±0.88	1.09	1.5	2.87	3.21	**Meningioma** Extra-Axial, Under Flax
M=5 52.0±14.00		1.39 ±0.22	**1.08 ±0.18**		**1.23 ±0.19**		**Lymphoma** RT. Parietal-Occipital

***Table No (7) Mean age, gender distribution, Metabolite ratio Values, diagnosis-category of Grading tumors {mean values} and radiologist diagnosis according to the standard criteria of* Metastases**

Mean age /Gender	**Metabolite Values**		**Diagnosis-Category Grading Tumors**				**Diagnosis/site**
			Benign		**Malignant**		
	Cho/ NAA	**Cho/ Cr**	**GI**	**GII**	**GIII**	**GIV**	
M =3 47±17.38	2.04 ±0.41	2.88 ±1.04		**2.13**	**2.5**	**2.97**	**Metastases** Intra- Axial

Table No (8) Metabolite Values, diagnosis-category of Grading tumors {mean values} and p- value

Grading	***NAA***	***Cho***	***Cr***	***Cho/ NAA***	***Cho/ Cr***	***NAA/ Cr***	***Lactate***	***Lipids***
GI	1.29 ±1.484	1.32 ±1.51	1.45 ±1.65	1.07 ±.224	1.43 ±.554	1.13 ±.262	1.70 ±.632	.94 ±.056
GII	0.77 ±.278	0.92 ±.340	1.00 ±.80	1.60 ±.292	2.07 ±.613	1.34 ±.697	1.23 ±.234	1.12 ±.311
GIII	0.96 ±.578	1.36 ±1.12	1.28 ±.988	1.78 ±.956	2.69 ±.498	1.40 ±.885	1.34 ±.258	.84 ±.110
GIV	0.64	1.18	1.31	2.61	3.19	1.22	1.21	1.06

	±.421	±1.14	±1.18	±1.670	±.935	±.649	±.285	±.573
P-value	***.016***	***.696***	***.733***	***.000***	***.000***	***.509***	***.182***	***.801***

IV. DISCUSSION

In our clinical practice we used for MRS : Long TE (1500/144ms) where the signal from most metabolites in the brain is lost except that of choline (Cho), creatine (Cr), *N*-acetyl aspartate (NAA), and lactate and conversely, short TEs (2000/35ms) that allow for identification of many other metabolites Lipids, lactate, ala, myoinositol, glutamate, and glutamine were obtained. There are no enough studies available concerning the application of Cho/Cr, and Cho/NAA ratios in studying the brain tumors with pathology related radiologist findings. This study provided a comparative evaluation of Cho/Cr, Cho/NAA ratios and pathological grade in the evaluation of brain tumors. Metabolite concentrations were detected and quantitatively analyzed by MRS.

Table No (1) showed descriptive statistics of classification of lesions according to WHO grading of, MRS metabolite and radiologist MR imaging features of brain tumors. Its ranges were 1.2±.37, 1.8±0.24, 2.8±0.19 and 3.8±0.99 for GI,GII,GIII, and GIV respectively where GIII and GIV were the most frequent in our sample as seen in figure (1)We classified the astrocytoma to as classified into (Pilocystic, Anaplastic and Diffused) and all were constituting 58 out of 128 cases ,Gliomatosis Cerebri/ Glioblastic Multiform/(GBM)/ Oligodendroglioma constituting 44 cases. Meningioms were 8, lymphoma were 2 ,Ependymal tumors were 13 and metastases were3cases out of 128as presented in table (2).Pilocystic Astrocytomas were diagnosed as GI which is low grade tumor demonstrated marked reduction of Cho/Cr comparing with anaplastic which were diagnosed as grade III and IV(3.01) ,and higher levels were found in diffused astrocytoma Grade III(3.51±0.32) as presented in table (3).Studies showed that MRS can distinguishes normal brain tissues from astrocytomas [21]. However, it may not be able to distinguish between different histologic grades of malignancy in astrocytomas [22].

The typical MRS characteristics of astrocytomas include a significant reduction in NAA, a moderate reduction in Cr, and an elevation of Cho and Cho/ Cr (table8)making the Anaplastic Astrocytoma and diffused Astrocytoma to be categorized as malignant with GIII and GIV .Reduction of NAA probably indicates a loss of normal neuronal elements as they are destroyed and/or substituted by malignant cells,this was similarly what was mentioned by previous studies[23] .Reduction of Cr is probably related to an altered metabolism, and elevation of Cho may reflect increased membrane synthesis and cellularity both of which are present in tumors [23].Elevation of lactate may reflect tumor hypoxia.[24]Pilocystic Astrocytoma was found to be related to gradeI.

Ependimal tumors were classified into ependymal giant cell astrocytoma which were classified in most of the cases to be grade I,III and IV and Sub Ependymal Giant Cell Astrocytoma were classified as GI and GII ,they affected both genders with similar age groups ,however in the literature it was mentioned that Ependymoma are common in children and Subependymoma affected the older patients ,however we found in our sample that the most affected ages were 56.0 for females and 58.5 years for malesand ependimoma were more in females and the sub ependymoma were present more in males similarly it was mentioned that Subependymoma which is asymptomatic fourth ventricular tumor found in elderly males [25] 66% arise in the fourth ventricle; 33% in lateral ventricles, unlikely our current study found that it can affected any site within the brain including the left temporal, left anterior horn of lateral ventricle, Occipital lobe. Right Parietal, Right Frontal, Bi- frontal, left orbital apex ,left temporal and Thalamus.Cho/ Cr showed higher values than subependimoma(table 4)

Glioblastic Multiform (GBM) showed increased in Cho/NAA and Cho/ Cr as presented table(5)and considered as high grade tumors GIV followed by Oligodendroglioma then Gliomatosis Cerebri, as well all of these tumors have an increasing in lactate values as presented in table(8) .Similarly some investigators have proposed that the presence of lactate are correlated with a higher degree of malignancy and that it is commonly observed in glioblastoma multiforme [26].Meningiomas were found Extra-Axial and Under Flax,with high values of Cho/ Cr and were considered to be as gradeI.II,III and IV. The diagnosis of a meningioma was done with clear-cut from the MR images. Meningiomas do not contain NAA because it arises outside the central nervous system [11]. The signal of Cho is markedly increased and the Lactate and alanine are also elevated similar findings were observed in the previous studies [11,22]There is no clear explanation for the increase in alanine in meningiomas[22].Some meningiomas, which invade the brain, show resonances in the location of NAA, which made the differentiations from astrocytomas difficult. Therefore the biopsy is important in those cases .Lymphoma was presented In 5 male patients at the right Parietal-Occipital region, and was classified as grade I and III tumors. In the presence of a lesion, differentiating between primary and secondary brain tumors is important but not frequently achievable. As well MRS findings are also unclear in this situation where it was diagnosed as GII, GIII, and GIV with high Cho/ Cr and Cho/ NAA similar results have been mentioned in previous studies [27, 13].

Metastases show reduction of NAA, a decreased Cr signal, and elevated Cho these features are similar to astrocytomas we have justified the difficulties in diagnosis the metastases is that some metastases may also contain lipids [28] and the Lipid is present in high-grade astrocytomas ,therefore metastases to the brain become as difficult burden to the radiologists in the differentiation between metastases and astrcytoma. The mean values for normal NAA/Cr, Cho/Cr, and NAA/Cho ratios were 1.44, 0.66 and 2.20 respectively. [20]

In tumors, Cho levels increase from GII and GIII because of increased membrane synthesis and proliferation, while NAA levels fall from 0.96±.578 in grade III to grade IV (0.64±.42) because neurons and axons are impaired and destroyed ,the same justification was mentioned in previous study done by[29].There is also a fall in Cr levels in tumors in GI and GII ,GIII and IV because of energy exhaustion and rise in lipids from necrosis as mentioned by [30].The presence of lipid or lactate resonances in the MR spectra was not predictive for tumor growth with no significant relation between the grading and the values of lactate and lipids (p= 0.182 and 0.801) as presented in table (8) the justification is that necrosis can resulted from tumor progression and therefore they could not be used for the differentiation of lesions, similarly previous studies have mentioned that concern [30,31,32,33].Results of this study showed that grade IV tumor had mean Cho/NAA and Cho/Cr ratios higher than gradeIII and ratios were two times higher than ratios of grade I or II. This were significantly correlated in tumor grading at p=0.000 and 0.000 respectively.

The predictable metabolite concentrations accounted in this study were, in agreement with the prior literature values [29,30,31].In grade IV, the mean Cho/NAA and Cho/Cr ratios in this study were 2.61±1.670 and 3.19±.935 respectively. In grade III tumors, ratios were 1.78 ±.956and 2.69 ±.498 respectively, while in grade II tumors, the ratios were 1.60 ±.292and 2.07 ±.613respectively. In grade I astrocytoma, ratios were 1.07±.224 and 1.43±.554 respectively, so grade IV tumors had the highest ratios and the grade I astrocytoma had the lowest and was proved to be correlated significantly at *p*= 0.000 and 0.000 (table8).Ratios higher than 1.5 for either Cho/Cr or Cho/NAA were used for diagnosis of tumor and ratios higher than 2 were suggestive of high grade glioma. This agrees with Weybright et al. 2005[34].NAA, Cho, Cr, NAA/ Cr, Lactate and Lipids metabolic values alone showed no significant relation between the values to be increased or decreased according to grading therefore the dependency of grading should be based upon the Cho/ NAA and Cho/ Cr .From this account and metabolic ratios it was suggested to diagnose, differentiate and grade gliomas after evaluating the Cho/ NAA and Cho/ Cr.

V. CONCLUSION

Long TE of (1500/144ms) where the signal from most metabolites in the brain is lost except that of choline (Cho), creatine (Cr), *N*-acetyl aspartate (NAA), and lactate and short TEs of (2000/35ms) those allow for identification of many other metabolites Lipids, lactate, ala, myoinositol, glutamate, and glutamine were used. MRS metabolic ratios (Cho/Cr and Cho/NAA) can be used to grade and differentiate gliomas. Ratios less than 1.5 were suggested to be in necrotic or normal brain tissue; ratios from 1.5 to 2 were suggested to be as low grade glioma and ratios higher than 2 were suggested to be high grade glioma or metastasis. Metastases were similar to high grade glioma in its readings .Meningioma can be diagnosed by MRI images. MRS should added to routine MR imaging studies as it provides greater information concerning tissue characterization than what is possible with MR imaging studies alone

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