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The Role of Magnetic Resonance Spectroscopy in Grading Brain Glioma

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Abstract

Background: conventional magnetic resonance (MR) imaging are helpful in characterizing tumor aggressiveness, but grading using conventional MR imaging alone is often unreliable. Proton MR Spectroscopy (MRS) is a well-established technique for quantifying the brain regional biochemistry by providing valuable information on the metabolic composition within an area of tissue and comparing the relative concentration of these metabolites. The aim of this study is to evaluate the contribution of short and intermediate TE MRS in differentiation of high and low grade gliomas.

Patients and Methods: a prospective cross sectional study conducted on selected patients with untreated gliomas whom were referred to the radiology department presenting with different neurological symptoms from April 2018 to February 2019. 1.5 Tesla MRI and MRS were performed before any interventional procedure. Histopathological diagnosis was obtained and all tumors enrolled were graded according to the current World Health Organization criteria. The main metabolites identified by MRS were N-acetyl-aspartate (NAA) at 2.02 ppm, creatine (Cr) at 3.0 ppm, choline containing compounds (Cho) at 3.2 ppm. The following metabolic ratios were calculated using standard commercial software: NAA/Cr, Cho/Cr, and Cho/NAA at both short and intermediate TE.

Results: a total of 22 patients; (12 male and 8 females, age ranged 18–70 years). At intermediate TE, the difference between high and low grade tumors was statistically significant in Cho metabolite related ratios (Cho/NAA and Cho/Cr), p-value 0.001 and 0.003 respectively. At short TE, the difference between high and low grade tumors was statistically significant in Cho metabolite related ratios (Cho/NAA and Cho/Cr), P <0.001 and 0.01 respectively. On other hand, NAA/Cr ratio was statistically insignificant in differentiating low and high grade tumors.
Conclusion: MRS is a non-invasive technique that provides an insight into the underlying biological structure of brain gliomas and in turn improves the diagnostic accuracy. Cho/Cr and Cho/NAA ratios were the most valuable indicators in assessing the tumor grade.

Key words: Magnetic Resonance Spectroscopy, Brain Glioma

Introduction : Brain tumors are major health problem that increases annually. Of all primary brain tumors, gliomas are the most common. Tumor grading is important for the determination of appropriate treatment strategies [(1)]. Gliomas are the most common primary neoplasms of the central nervous system, varying histologically from relatively benign primary brain tumors (e.g., astrocytomas) to more malignant grades (anaplastic astrocytomas, and glioblastomas) with a survival probability beyond 5 years to be lower than 5% [(2)]. Prospective grading of primary cerebral gliomas is a hazardous endeavor but with a significant benefit in planning therapeutic approaches, as well as assessing the prognosis and response to therapy [(3)]. The current standard criterion for tumor grading is based on histopathologic assessment, which has two major limitations: It is an invasive procedure, and it has an inherent sampling error, especially with stereotactic biopsy [(4)].

Conventional MRI with gadolinium-based contrast agents is an established tool for characterization of cerebral tumors, but the sensitivity and specificity with which this modality defines tumor type and grade is limited, this is partly attributable to the existence of Gadolinium-enhanced necrosis that may be mistaken for tumor and partly to the difficulty in distinguishing between tumor, edema, and nonspecific treatment effects in the region of hypointensity on T2-weighted images [(5)]. DWI and diffusion-tensor MR imaging, perfusion- weighted imaging, and MRS are relatively new techniques that provide additional microstructural, microvascular, and biochemical information, respectively, compared with standard MRI. These techniques have been used to assess glial neoplasms and define their histologic grade [(6)].

Recent studies have shown that MRS can substantially improve the non-invasive categorization of human brain tumors, especially for gliomas. The recent emphasis on the utilization of MRS (coupled to routine MRI techniques) in the evaluation of tumors has arisen because it provides greater information concerning tumor activity and characterization of the tumor tissue than is possible with standard MRI techniques alone [(7)]. Moreover, since standard neuroimaging methods cannot reliably distinguish radiation necrosis from tumor recurrence, MRS may prove to be a highly beneficial modality in the post-irradiation care of patients with brain gliomas. Hence, MRS can potentially resolve ambiguities remaining after conventional MRI concerning tumor grade and extent and could reduce unnecessary biopsy procedures [(8)].

Aim: To evaluate the contribution of short and intermediate TE MRS in differentiation of high and low grade glioma.

Patients and Methods : This study is a prospective cross sectional study carried out in MRI unit of Radiology Department in Al-Imamein Al-Kadhimein Medical city/ Baghdad/ Iraq during the period from 1st of April, 2018 to 1st of February, 2019. The study was approved by the local scientific committee of the Arab board of Medical specialization, and an oral informed consent was taken from all patients.

The number of patients were 22 (14 male and 8 females (age range: 18–70) with untreated gliomas whom were referred to the radiology department presenting with different neurological symptoms. For each patient, demographic information were stated along with brief clinical history. MRI and 1HMRS were performed before any interventional procedure.

Histopathological diagnosis was obtained via either biopsy or resection and all tumors enrolled were graded according to the current World Health Organization (WHO) criteria.
Exclusion criteria: pediatric brain tumors, histopathology not given, general contraindication for MRI, allergy to contrast media and disturbed renal function.

Conventional MRI Protocol: 1.5Tesla MRI scanner (Magnetom Aera, Siemens, Erlangen, Germany). All the cases were examined in supine position with standard circularly polarized head coil using the following sequences. Axial and Sagittal T1WI (362/4.7 ms) TR/TE spin echo. Coronal T2WI (4900/88 ms) TR/TE spin echo. Axial FLAIR (5500/79 ms) TR/TE spin echo, 5 mm section thickness, 207 x 207 Field of view (FOV) and 240x 240 matrix size. After IV administration of Gadolinium-DTPA, contrast enhanced T1WI in axial, sagittal and coronal planes was obtained.

MRS protocol: 2 localization methods have been performed, each has a different TE. Data were acquired using Point RE Solved Spectroscopy (PRESS) pulse sequence and spectroscopic localization has been performed on post contrast T1WI with automatic shimming. Measurement parameters were TR/TE: 1500/135 ms, FOV 120x 120 mm, section thickness 10 mm. The Region of interest (ROI) was carefully placed to avoid strong interference from subcutaneous fat and lipids of the skull. Measurement parameters used in SVS scans were 1500/35 ms (TR/TE) and voxel size was 1.5 cm3. The total scan time was 20 min.

Spectra Evaluation: main metabolites identified by 1HMRS are N-acetyl-aspartate (NAA) at 2.02 ppm, creatine (Cr) at 3.0 ppm, choline containing compounds (Cho) at 3.2 ppm. The following metabolic ratios were calculated using standard commercial software: NAA/Cr, Cho/Cr, and Cho/NAA at both short and intermediate TE.
Histopathological diagnosis obtained either by biopsy or by surgical resection and the specimens were graded according to the WHO grading system.

Statistical analysis: data analysis was performed using the statistical software package SPSS. (Version 22.0) for windows. Nonparametric Mann–Whitney U tests were used to evaluate the significance in the metabolites and metabolic ratio differences between high and low grade tumors in both groups. P values less than 0.05 were considered statistically significant. In order to identify the optimal cut-off values of the most discriminative metabolic ratios, receiver-operating characteristic (ROC) curve analysis was performed. The efficacies of the significant parameters were assessed in terms of sensitivity, specificity, and the accuracy.

Results : Twenty two patients were included in this study, the age ranging between 18 and 70 years. Depending on MRS results, the tumors were divided into high grade in 15 patients (68.2%) and low grade in 7 patients (31.8%). On histopathological diagnosis, the tumors subdivided into high grade (grade IV) in 15 patients (68.2%) and low grade (I, II) 7 (31.8%), no lesion was graded III by histopathological report. The mean age for the patient with low grade glioma (LGG) was 33.4±11.35, ranging from (18-46 years) and for those with high grade glioma

(HGG) was 51.9±11.6 (30-70 years), but the difference between the two groups was not significant with P-value 0.06.

On short TE: the mean ratios of NAA/Cr, Cho/Cr and Cho/NAA were (1.62, 1.4 and 0.78 respectively) for LGG which were lower than the mean ratios for HGG (2.91, 3.4, and 1.74 respectively). The results were statistically significant for both Cho/Cr and Cho/NAA ratios where P-value was (<0.001 and 0.01 respectively), for NAA/Cr ratio the result was not statistically significant (p-value =0.08) as shown in table (1).

On intermediate TE: the ratios of NAA/Cr, Cho/Cr and Cho/NAA were (1.48, 1.72 and 1.52 respectively) for LGG and (1.0, 3.5 and 4.2 respectively) for HGG. The results were significantly higher for Cho/Cr and Cho/NAA ratios with p- value was (0.003 and 0.001 respectively). The NAA/Cr ratio again was not significant (p-value =0.08). As shown in table (1)

Table (1): The mean±SD of metabolites ratios between HGG and LGG on short and intermediate TE.

		Short TE			Intermediate TE		
		NAA/Cr	Cho/Cr	Cho/NAA	NAA/Cr	Cho/Cr	Cho/NAA
LGG	Mean±SD	1.62±0.67	1.4±0.84	0.78±0.64	1.48±0.9	1.72±1.01	1.52±1.16
	Minimum	0.60	0.67	0.14	0.02	0.94	0.56
	Maximum	2.85	2.92	1.70	2.92	3.86	3.73
HGG	Mean±SD	2.91±1.85	3.4±0.69	1.74±0.77	1.07±0.86	3.5±0.8	4.2±1.30
	Minimum	0.47	2.40	0.64	0.38	1.80	1.40
	Maximum	7.49	4.52	3.20	3.92	5.10	7.09
P-Value		0.08	<0.001*	0.01*	0.32	0.003*	0.001*

This result shows that there is high sensitivity (85.7%) and high specificity (93.3%) of the MRS to differentiate between LGG and HGG. The accuracy was 90.9%, sensitivity was 85.7%, specificity was 93.3%, PPV was 85.7%, NPV was 93.3%.

At short TE: the cut off value of the NAA/Cr ratio was>2.85 and this was not significant (P-value = 0.08), with low sensitivity (60%) and specificity of (85.1%). The cutoff value of the Cho/Cr ratio was >2.2, and this was statistically significant (P-value <0.001), the sensitivity was (100%) and specificity (85.7%). The cutoff value of Cho/NA-A ratio >0.92, it was statistically significant (P-value 0.014), the sensitivity was (86.7%) and specificity was (71.4%).

At intermediate TE: the cut off value of the NAA/Cr ratio was ≤0.97, and the result was not significant (P-value = 0.19), with low sensitivity (65%) and specificity (61.4%). The cut off value of the Cho/Cr ratio was >1.86, which was statistically significant (P-value =0.003), the sensitivity was (93.3%) and specificity was (85.7%). The cutoff value of Cho/NAA ratio >2.04 and it was statistically significant at (P-value 0.001), the sensitivity was (93%) and specificity was (85.7%).

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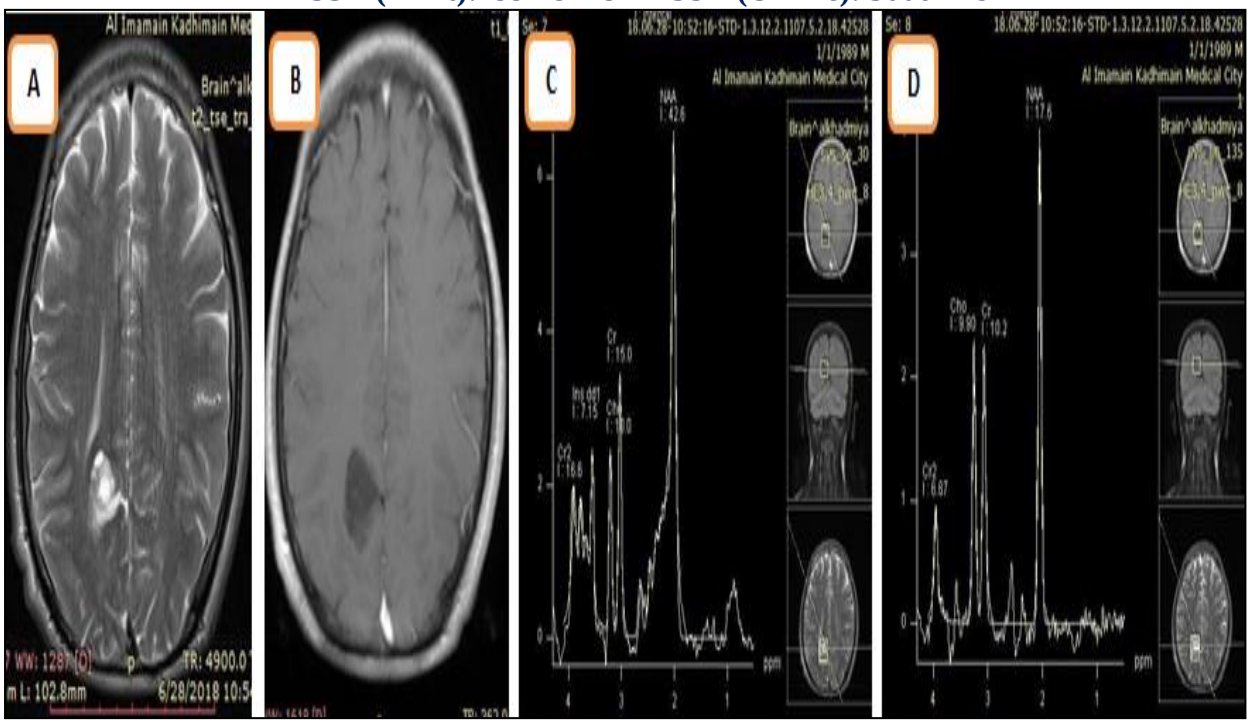

Figure (1): SOL seen at Rt. posterior parietal lobe, A: predominantly hyperintense in T2, B: minimal or no enhancement in T1 post contrast, C: at short TE Cho/Cr ratio was 0.67 and Cho/NAA was 0.17, D: at intermediate TE Cho/Cr ratio was 0.97 and Cho/NAA was 0.56, these findings were suggestive of LGG, subsequent histopathological result confirm LGG.

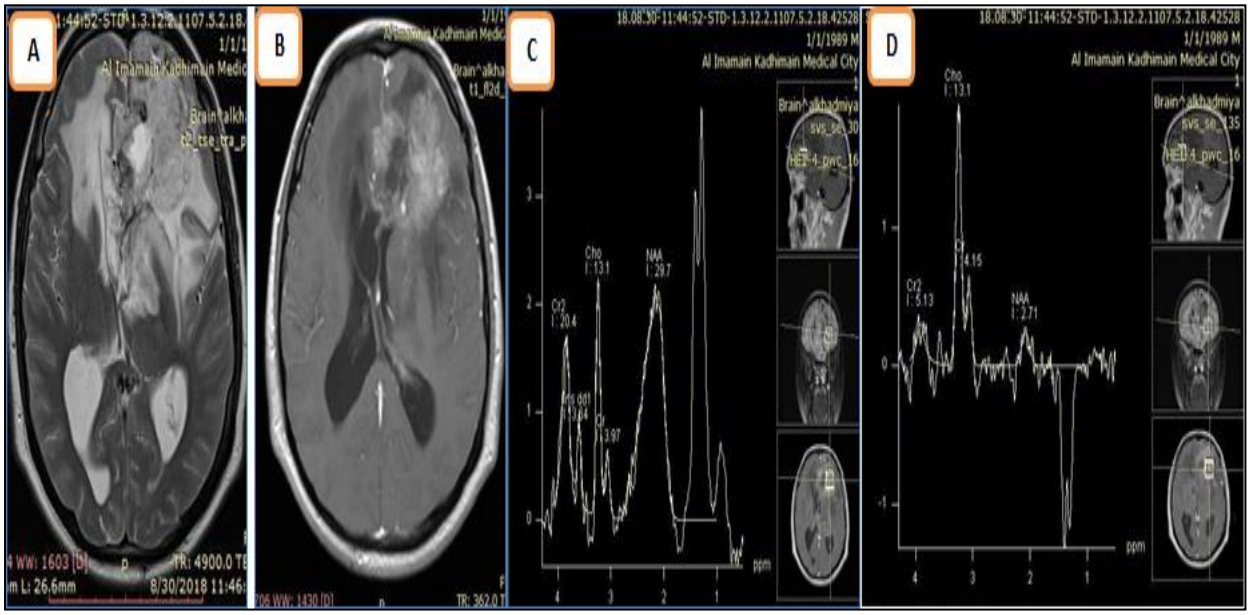

Figure (2): A: T2 WI show large mass of solid and necrotic component at anterior left frontal lobe with surrounding edema, exerting mass effect, crossing the midline and invading the corpus callosum, B: there is enhancement of solid portion at T1 post contrast, C: at short TE Cho/Cr ratio was 3.35 and Cho/NAA was 2.12, D: at intermediate TE Cho/Cr ratio was 3.17 and Cho/NAA was 4.85, (D) these findings were in favor of HGG, subsequent histopathological result confirm HGG.

Discussion : Gliomas are the most common primary brain neoplasms and have histological findings that vary from low to high grade. Glioma grading is fundamental for guiding treatment plan and suggesting prognosis. The principle risk for inaccurate grading is the use of an unfitting therapy which can result in inappropriate exposure of patient to either the risks directly associated with surgery or the risks caused by delaying it [4].

Conventional MR imaging affords significant information regarding the presence of contrast material enhancement, perifocal edema, multicentricity and/or multifocality, mass effect, hemorrhage and necrosis, which are all helpful in characterizing tumor aggressiveness. Nonetheless, there still be an overlap in MR imaging features between high and low grade gliomas, that made grading using conventional MR imaging alone is often unreliable, with a sensitivity ranging from 55% to 83% [9].

MRS is a non-invasive method that can substantially improve categorization of brain tumors especially gliomas by providing additional information on the biochemical profile within an area of tissue, and by evaluating the relative concentration of certain metabolites, therefore the additional information provided by MRS are useful to reinforce a clinical suspicion, or to specify a wide differential diagnosis [10]. MRS is a multi-parameter diagnostic tool and modification of each parameter results in spectrum morphology changes. In particular, changing the echo time (TE) represents a useful tool to highlight different diagnostic elements, but also has a significant impact on the spectrum morphology. Diagnostic errors can result if the role of TE is not properly considered [11].

In this study we trying to investigate the impact of short and intermediate TE MRS in differentiating high from low grade gliomas. At intermediate TE, we established that the difference was statistically significant in Cho metabolite related ratios (Cho/NAA, and Cho/Cr), between high and low grade tumors . In concordance with our results, Naser et al [12] revealed that Cho/NAA and Cho/Cr ratios have the higher diagnostic value in predicting glioma grade. Additionally, another study performed in 2008 to appreciate the value of MRS in grading gliomas, investigators demonstrated that Cho and Cho related ratios (Cho/Cr and Cho/NAA) are the most valuable indices for grading glioma in comparison with other metabolite ratios [13]. On the other hand some studies showed that differences were insignificant between high and low grade tumors in either Cho/Cr or Cho/NAA ratios, authors attributed these variations to the different techniques with various spectral acquisitions, and to the inherent histological heterogeneity of each type and grade of glioma [14].

AT short TE, and in respect to Cho metabolite, the Cho/Cr and Cho/NAA ratios were significant in ranking gliomas into low and high grade. This results was in agreement with previously reported studies which investigated the role of short TE in tumor grading [12, 15].

The current study revealed that NAA/Cr ratio was statistically insignificant in differentiating low and high grade tumors, this results was in agreement with previously reported studies [12, 14, 15]. Other studies established that NAA/Cr ratio was useful in determining the tumor grade; nonetheless, it was of low accuracy in comparison to Cho/NAA and Cho/Cr ratios [16, 17].

In this study by using ROC curve analysis, valuable cutoff values for Cho metabolite related ratios at both short and intermediate TE were obtained to differentiate low -grade from high -grade tumors, these results show variation in comparison with that of previously reported studies [5, 12, 18]. The likely explanation of these variations could be attributed to the MRS imaging

methods, including field strength, voxel size and location, acquisition parameters. Another possible explanation could be the difference in patients number and tumors heterogeneity.

A study done by Kousi et al [18] investigated the role of both TEs in grading glioma at 3T MRI, they measured the metabolite ratio at both intratumoral and peritumoral regions and they found out that intra-tumoral Cho/Cr at short TE is of higher sensitivity compared to those of intra-tumoral Cho/Cr and Cho/NAA at intermediate TE.

Conclusions: MRS is a non-invasive technique that provide an insight into the underlying biological structure of brain gliomas and in turn improve the diagnostic accuracy. Cho/Cr and Cho/NAA ratios were the most valuable indicators in assessing the tumor grade. Acquiring spectra at both short and intermediate TE provide higher sensitivity and specificity than each one separately.

References

1. Nelson SJ. Multivoxel magnetic resonance spectroscopy of brain Tumors1. Molecular cancer therapeutics. 2003 May 1;2(5):497-507.
2. Law M, Yang S, Wang H, Babb JS, Johnson G, Cha S, Knopp EA, Zagzag D. Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. American Journal of Neuroradiology. 2003 Nov 1;24(10):1989-98.
3. Inoue T, Ogasra K, Beppu T, Ogawa A, Kabasawa H. Diffusion tensor imaging for preoperative evaluation of tumor grade in gliomas. Clinical neurology and neurosurgery. 2005 Apr 1;107(3):174-80.
4. Barker P, Gillard J, Waldman A. Fundamentals of MR spectroscopy. Clinical MR Neuroimaging, Diffusion, Perfusion and Spectroscopy. Journal of Neuroradiology. 2005;34:4553.
5. Fan G. Magnetic resonance spectroscopy and gliomas. Cancer Imaging. 2006;6(1):113.
6. Kim JH, Chang KH, Na DG, Song IC, Kwon BJ, Han MH, Kim K. 3T 1H-MR spectroscopy in grading of cerebral gliomas: comparison of short and intermediate echo time sequences. American journal of neuroradiology. 2006 Aug 1;27(7):1412-8.
7. Zonari P, Baraldi P, Crisi G. Multimodal MRI in the characterization of glial neoplasms: the combined role of single-voxel MR spectroscopy, diffusion imaging and echo-planar perfusion imaging. Neuroradiology. 2007 Oct 1;49(10):795-803.
8. Toyooka M, Kimura H, Uematsu H, Kawamura Y, Takeuchi H, Itoh H. Tissue characterization of glioma by proton magnetic resonance spectroscopy and perfusion-weighted magnetic resonance imaging: glioma grading and histological correlation. Clinical imaging. 2008 Jul 1;32(4):251-8.
9. Di Costanzo A, Scarabino T, Trojsi F, Popolizio T, Catapano D, Giannatempo GM, et al. Proton MR spectroscopy of cerebral gliomas at 3 T: spatial heterogeneity, and tumour grade and extent. European radiology. 2008 Aug 1;18(8):1727-35.

10. Arvinda HR, Kesavadas C, Sarma PS, et al. Glioma grading: sensitivity, specificity, positive and negative predictive values of diffusion and perfusion imaging. J of Neurooncol. 2009;94(1):87–96.
11. Soares DP, Law M. Magnetic resonance spectroscopy of the brain: review of metabolites and clinical applications. *Clinical Radiology*. 2009;64(1):12–21.
12. Zou QG, Xu HB, Liu F, Guo W, Kong XC, Wu Y. The assessment of supratentorial glioma grade: the combined role of multivoxel proton MR spectroscopy and diffusion tensor imaging. Clinical radiology. 2011 Oct 1;66(10):953-60.
13. Cianfoni A, Law M, Re TJ, Dubowitz DJ, Rumboldt Z, Imbesi SG. Clinical pitfalls related to short and long echo times in cerebral MR spectroscopy. Journal of Neuroradiology. 2011 May 1;38(2):69-75.
14. Liu ZL, Zhou Q, Zeng QS, Li CF, Zhang K. Noninvasive evaluation of cerebral glioma grade by using diffusion-weighted imaging-guided single-voxel proton magnetic resonance spectroscopy. Journal of International Medical Research. 2012 Feb;40(1):76-84.
15. Kousi E, Tsougos I, Tsolaki E, Fountas KN, Theodorou K, Fezoulidis I, Kapsalaki E, Kappas C. Spectroscopic evaluation of glioma grading at 3T: the combined role of short and long TE. The Scientific World Journal. 2012;20:12-9.
16. Verma N, Cowperthwaite MC, Burnett MG, Markey MK. Differentiating tumor recurrence from treatment necrosis: a review of neuro-oncologic imaging strategies. Neuro-oncology. 2013 Jan 16;15(5):515-34.
17. Caulo M, Panara V, Tortora D, Mattei PA, Briganti C, Pravatà E, Salice S, Cotroneo AR, Tartaro A. Data-driven grading of brain gliomas: a multiparametric MR imaging study. Radiology. 2014 Mar 22;272(2):494-503.
18. Naser RK, Hassan AA, Shabana AM, Omar NN. Role of magnetic resonance spectroscopy in grading of primary brain tumors. The Egyptian Journal of Radiology and Nuclear Medicine. 2016 Jun 1;47(2):577-84.