1-H MR Spectroscopy in Grading of Cerebral Gliomas Using Short and Intermediate Echo Time Sequences

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Abstract

Purpose: The aim of this study was to determine the diagnostic value of short and intermediate TEs in determining the grade of cerebral glioma with reference to operative and histopathological results whenever possible.

Material and Methods: Thirty-one patients (21 males and 10 females), ranging in age from 15-63 years (mean 34.4 years) were prospectively recruited for this study. All had a brain tumor recently diagnosed by MRI and had received no previous treatment, except for steroids. They were referred for MRS examination before surgical biopsy and/or resection or radiotherapy. MI level and MI/Cr ratio were obtained for each lesion and compared with the grade of the lesion.

Results: The levels of MI/Cr were higher (1.89 ± 1.27) in patients with low-grade astrocytoma, and lower in patients with anaplastic astrocytoma (0.35 ± 0.11) and GBM (0.04 ± 0.07). Thirty out of the thirty-one patients were correctly classified using MI/Cr ratio; one patient was misdiagnosed as high-grade glioma and the biopsy revealed grade II glioma. The diagnostic accuracy, sensitivity and specificity of MI/Cr ratio for the grading of glioma was 96.7%, 100%, and 95%, respectively.

Conclusion: MRS has proven to be an important complementary tool in diagnosing and grading gliomas, saving the patient from unnecessary biopsy taking when it is conclusive thus altering the treatment planning. This study had demonstrated that MI level, MI/Cr ratio as well as, lipid lactate peaks are important in presurgical grading of brain tumors.

Key Words: Grading – Gliomas – Short TE – Intermediate TE.

Introduction

The role of conventional magnetic resonance imaging (MRI) with gadolinium-based contrast agent (GBCA) is well established in the characterization of different cerebral tumors and is considered in some instances a reference standard in preoperative evaluation, however, it is still not considered effective or specific in differentiation of the tumorous types and their grading [1].

Brain glial tumors are classified into low grade (grade I & II, benign) and high grade (grade III & IV) according to the WHO classification system dated [2].

Surgical biopsy/resection and histopathological assessment are the current “gold standard” for the determination of glioma grading. However, biopsies may experience several errors [3,4]; the most significant one is the limitation of the number of samples. Thus, a high-grade tumor might be diagnosed as a low-grade one because samples were taken from a less malignant region. Thus, non-invasive or minimally invasive imaging technologies are being used alternatively in evaluating the malignancy of brain tumors [5].

Owing to the great advances during the last decades regarding the newly developed magnetic resonance (MR) imaging techniques, the efficacy of such non-invasive diagnostic tools is increasing. However, diagnosis and grading of gliomas by conventional MR imaging is sometimes doubtful as the sensitivity of glioma grading is ranging from 55% to 83% [6].

Non-invasive pre-operative prediction of grading of cerebral glioma grading is important in treatment planning and prognosis anticipation [7].

The changes in metabolism of tumor cells represented in changes of the concentration of particular metabolites in the tumor tissue are related to malignant transformation [8]. This is leading to a growing interest in MR spectroscopy increasing the sensitivity of the routinely used diagnostic imaging [9].

Nowadays, the optimal pulse sequence parameters of MRS for characterizing tumors are controversial. TE is one of the parameters that can largely influence the spectrum in TE [10]. Different criteria
have been argued in favor and against every option in the evaluation of the brain tumors at both short and intermediate echo time (TE) sequences [10].

It is more preferable to use combined short and intermediate TEs even though either TE alone showed no significant difference in the diagnostic accuracy of grading cerebral gliomas [7].

Short TE is required for better assessment of some metabolites (e.g. lipids, myo-inositol, glutamine, and glutamate). It affects their intensity, as well as, the presence of peaks depending on the differing T2 relaxation of metabolites [6,11,12,13].

One of the most abundant metabolites seen in 1H-MRS at short TE (30ms) is Myo-inositol (MI). It can be recognized as a multiplet of peaks with its main components located at 3.5 ppm of the spectrum [9]. The MI concentration is significantly increased in various cerebral diseases [14,15] including brain tumors [16]. It is involved in the activation of protein C kinase, which leads to production of protyolotic enzymes often found in malignant and aggressive primary tumors. Therefore, the level of MI detected in MRS may be helpful in predicting the histologic grade of brain tumors [16].

The peak of lactate is at 1.32 ppm. It has a configuration of two closely spaced resonant peaks called a “doublet”. The other peak is seen at 4.1 ppm. It is generally suppressed as it is very close to that of water. The presence of lactate is an indication that the normal cellular oxidative respiration mechanism is not effective and that the carbohydrate catabolism took over (as in hypoxia). It can be confirmed that a peak at 1.32 ppm is lactate by altering TE. At long TE = 272 ms, lactate projects above the baseline and is inverted below it at the intermediate TE = 136 ms [17,18].

The lipids’ protons produce peaks at 0.8, 1.2, 1.5, and 6.0 ppm. Methyl, methylene, allelic, and vinyl protons of unsaturated fatty acids form these peaks respectively. These metabolites are increased in high-grade astrocytoma reflecting a necrotic process. Lipids in the brain are frequently not observed unless a short TE is used as they have very short relaxation times [17].

The aim of this study was to determine the diagnostic value of short and intermediate TEs in determining the grade of cerebral glioma with reference to operative and histopathological results whenever possible.

Patients and Methods

Thirty-one patients (21 males and 10 females), ranging in age from 15-63 years (mean 34.4 years) were prospectively recruited for this study during a period from January 2013 to December 2014. They all had a brain tumor recently diagnosed by MRI and received no previous treatment, except for steroids. They were referred for MRS examination before surgical biopsy and/or resection or radiotherapy.

This study was performed after the approval of the scientific and ethics committee of the hospital.

The study was performed on a 1.5-T MR scanner (Gyroscan Intera, Philips medical systems) using standard imaging head coil. Images were acquired with the patient in a supine position with a placed head support pillow to minimize the patient’s movement and the procedure was explained carefully to the patients. They were asked to relax and stay still during the examination.

Initially, each patient was subjected to routine spin echo (SE) sequences. The volume of interest (VOI) from the lesion was selected on SE-T2-weighted images for single voxel (SVS). The voxel was centered on the region which was previously noted to correspond to maximum contrast enhancement and if contrast enhancement was subtle or not present, the area of maximal T2 abnormality and mass effect was sampled. The size of the voxel ranged from 1 x 1 x 1cm to 2 x 2 x 2cm according to the size of the lesion. The former used size of the voxel lead to a more lengthy examination compared to the latter one. So, the time of the whole MRS examination using the single voxel technique ranged from 40 to 50min.

The three TE sequences (long, short and intermediate TEs) were done. SVS studies were performed with Point Resolved Spectroscopy sequence (PRESS). Multi-voxel study was performed for one patient.

MRS technique: First: Axial, sagittal and coronal planes of the brain were done in T2WI: TE=100, TR=3658, Field of view (FOV) 18 x 24cm and Matrix 192 x 256. Then, MRS in long TE=288, short TE=31 and intermediate TE=144 with TR=2000 and spectral bw=1000.

Interpretation:

The important metabolites and ratios to be commented upon are:

In the long TE: The Cho (at 3.2 ppm), NAA (at 2.0 ppm), Cr (3.02 ppm) and sometimes the MI
Chemical shift pps

Results

The tumor grades detected using MRS were compared with those found by histopathology/follow-up by conventional MRI after radiotherapy. Twenty-five cases were confirmed histologically via either surgical biopsy and/or resections, and six cases were treated by radiotherapy. Follow-up by conventional MRI was done in all cases.

According to the classification of the WHO criteria, 19 patients were classified as low-grade gliomas, including WHO grade II [astrocytoma (n=18), oligodendroglioma (n=1)], whereas in 12 patients the tumors were classified as high-grade gliomas, including 4 with WHO grade III (anaplastic astrocytoma) and 8 with WHO grade IV (glioblastomas). The levels of MI/Cr were higher (1.89±1.27) in patients with low-grade astrocytoma, and lower in patients with anaplastic astrocytoma (0.35±0.11) and GBM (0.04±0.07) (Figs. 1-3 Table 1). Of the 31 patients with verified gliomas, 30 were correctly classified, with one false-positive case who was misdiagnosed as high-grade glioma using MI/Cr ratio and the biopsy revealed grade II glioma. The diagnostic accuracy, sensitivity and specificity of MI/Cr ratio for the grading of glioma was 96.7%, 100%, 95%, respectively.
Fig. (2-A,B): Thirty five years old male patient with left temporo-parietal intermediate grade glioma (Astrocytoma grade II) large lesion. A single voxel (1x1x1 cm) was placed on the lesion. (A) MRS obtained at long TE (288) showing elevated Cho, depressed NAA, with estimated Cho/NAA: 16.8, Cho/Cr: 6 and NAA/Cr: 0.36. (B) MRS obtained at short TE (31) showing moderately elevated MI peak and MI/Cr: 0.5.

Fig. (3-A,B): Twenty eight years old male patient with a left temporo-parietal para-sylvian low grade glioma (Astrocytoma grade II) mainly cystic lesion. A single voxel (1x1x1 cm) was placed within the solid part of the lesion. (A) MRS obtained at long TE (288) showing significantly elevated Cho, depressed NAA, with estimated Cho/NAA: 3.1, Cho/Cr: 3.4 and NAA/Cr: 1 (B). MRS obtained at short TE (31) showing elevated MI & lipid/lactate peaks with estimated MI/Cr: 1.
Table (1): Results of MI/Cr ratios derived from magnetic resonance spectroscopy (MRS) with low-grade, intermediate-grade, and high-grade gliomas

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Low-grade glioma</th>
<th>Anaplastic astrocytoma</th>
<th>GBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM/Ch</td>
<td>1.89±1.27</td>
<td>0.35±0.11</td>
<td>0.04±0.07</td>
</tr>
<tr>
<td>Cho/NAA</td>
<td>9.8±7.8</td>
<td>10.9±8.3</td>
<td>33.34±66</td>
</tr>
</tbody>
</table>

Discussion

It is considered a challenge to grade gliomas through a non-invasive method inspite of its significant role in prognosis and management planning of patients having brain neoplasms [19].

Using conventional MR imaging in preoperative grading of gliomas is often unreliable [20]. The sensitivity of radiologic grading of gliomas using conventional MR ranges from 55 to 83% [9,21].

The degree of contrast enhancement, extent of mass effect and cyst formation are the characteristic findings seen in conventional MR imaging that help in differentiating the low and high-grade gliomas as they are more pronounced in the latter [22].

Many high-grade tumors do not show contrast enhancement, the thing that may yield a false-negative diagnosis [23,24]. This has led to the studies and trials in the advanced new MR imaging techniques that can be used in grading gliomas [20].

It is important to understand that MRS is very sensitive to abnormal metabolic changes, but the specificity is relatively low [25]. The sensitivity, specificity, and accuracy of MRS in differentiating between high and low-grade neoplasms are 100%, 86%, and 96%, respectively [26]. Thus, the clinical utility of proton MRS in glioma grading is still being investigated [25].

The different metabolites and methods seen and used in MRS result in a wide variation regarding the grading of gliomas using MRS [27].

Previous studies have shown the potential of MRS to differentiate low from high-grade gliomas [21]. They used Cho/Cr, Cho/NAA ratios in the determination of the glioma grade. They had observed higher Cho/Cr and Cho/NAA in high-grade compared to low-grade tumors, though threshold values of metabolite ratios for grading of gliomas are not well established. In this study, we did not rely on Cho/Cr or Cho/NAA ratio for the grading of gliomas. We found a high level of Cho in high-grade tumors, however high levels for Cho with high Cho/Cr and high Cho/NAA ratios were noted in some low-grade gliomas. This was similar to previous results by Law et al. [21] who reported high Cho level in low-grade glioma. On the other hand, Hall et al., 2001 reported low Cho level ratios in some GBM [28]. This may be attributed to extensive necrosis, which increases the false-positive rates and false negative rates in predicting low and high-grade gliomas respectively [29].

In this study, we confirmed the diagnosis of glioma versus other disorders like cortical dysplasia and encephalitis in four cases based on the Cho/NAA, Cho/Cr and MI/Cr ratios. MI can also be used to differentiate low and high-grade gliomas [30,31].

Low-grade gliomas show higher levels of MI compared with high-grade ones. This may be due to the lack of activation of phosphatidylinositol metabolism resulting in the accumulation of MI [29]. Only few publications have evaluated the diagnostic potential of MI/Cr ratio in glioma grading. In this study, tumoral grading was done based on the MI/Cr ratio. The results of Castillo et al., were considered as a base line for grading, showing a threshold value of 0.82±0.25, 0.33±0.16, and 0.15±0.12 for MI/Cr ratio in predicting low, anaplastic and high-grade tumors respectively [16].

We were able to differentiate between low-grade (II) and high-grade (III+IV) gliomas using the MI/Cr ratio. The levels of MI/Cr were higher (1.89±1.27) in patients with low-grade astrocytoma, and lower in patients with anaplastic astrocytoma (0.35±0.11) and GBM (0.04±0.07).

Such findings were in concordance with Majos and his colleague who reported that MI at short TE provided some differences between low-grade astrocytoma and anaplastic astrocytoma. It also showed a significant difference between tumor groups that are difficult to differentiate (low-grade astrocytoma versus GMB-metastases, and anaplastic astrocytoma versus GBM-metastases) [10].

A study by Aydin et al., tried to make another variation by using Cho/MI for the categorization of tumors according to their malignancy rate and to differentiate from non-neoplastic lesions. They demonstrated that the Cho/MI ratio is a good diagnostic tool in glioma grading, with the highest Cho/MI ratio found in GBM and lowest in the low-grade gliomas [32].

Our results did not match with the previous reports by Kousi and his colleagues who used 3T 1H-MRS in grading cerebral gliomas at short and
long TE in 71 patients with untreated glioma [33]. They reported increased MI in different glioma grades, the MI/Cr ratio was 0.85 ± 0.24 and 0.90 ± 0.35 for low and high-grade gliomas, respectively and hence that ratio did not significantly differentiate the two tumor groups.

Kim et al. [7] also used 3T MR-spectroscopy for the grading of glioma in 35 patients. They detected increased MI/Cr ratio with the grading of the tumor. MI/Cr ratio was 0.86 ± 0.19, 1.23 ± 0.37, 1.15 ± 0.52 for grade II, grade III, and grade IV tumors, respectively [7].

In this study, the accuracy of MI/Cr for predicting the glioma grade was high. One case was diagnosed as anaplastic glioma based on the MI/Cr ratio however the biopsy revealed grade II glioma, this may be due to that the biopsy was not necessarily taken from the area of the lesion with greatest cellularity, thus underestimating the tumor grade [34,35].

In our study, one case was diagnosed as low-grade astrocytoma, but follow-up MRI done after one year showed progressive increase in the size of the lesion, with a newly developed large cystic component. The pathology revealed mixed astrocytoma grades II and III. This may be either due to the increase of the tumor grading over this considerable period or due to the voxel site that was not at the same location of the biopsy site.

Previous studies by Castillo et al. and Smith et al., showed that there is of ten times levels of MI in oligodendroglioma and mixed oligoastrocytoma similar to high-grade astrocytoma [16,17]. In our study we have one case of oligodendroglioma, which showed in addition to the elevated Cho level, mildly elevated lipid/lactate peaks, the MI was elevated as well the MI/Cr ratio being 0.65.

Lipid and lactate elevation correlate with necrosis in high-grade gliomas and have shown to be useful in differentiating low and high-grade gliomas [36]. In this study, high lipid/lactate peak was observed in the eight cases of high-grade GBM.

The limitations of the study included the small sample size that may reduce or bias the power of the results. Also not all low-grade gliomas underwent biopsy however; they had follow-up studies after radiotherapy. Lastly, because only a single-voxel technique was used, the possibility of sampling errors in tumors of heterogeneous appearance cannot be excluded.

Conclusion:
MRS has proven to be an important complementary tool saving the patient from unnecessary biopsy procedures when it is conclusive thus altering the treatment planning. This study had demonstrated that the MI level, the MI/Cr ratio and the lipid lactate peaks are important in presurgical grading of brain tumors.

Conflict of interest:
The authors declare that there is no conflict of interest.

References


I-H MR Spectroscopy in Grading of Cerebral Gliomas Using Short

المملوک العربي

الهدف: الهدف من هذه الدراسة هو إظهار القيمة التشخيصية لوقت التردد القصير والمتوسط في تحديد درجة الورم الدماغي الديفي بالرجوع إلى نتائج العملية الجراحية والعينة النسيجية.

المواد والطريقة: شملت دراسة مريضين (21 ذكر و10 أنثى) تتراوح أعمارهم من 15-62 سنة (متوسط 42.47). تم تحويلهم مستقبلاً لهذه الدراسة. لم يتم تشخيصهم باعتبارهم مصابين بالعصب في الدماغ، وتم استخدام الورم الدماغي المغناطيسي. تم تحويلهم لمعمل قسم رنين مغناطيسي طيفي قبل أخذ العينة أو التدخل الجراحي والعلاج الإشعاعي. تم الحصول على مستويات Cr ومثبطات الورم لكل حالة ومقارنتها بدرجة الورم.

النتائج: نسبة MI/Cr كانت أعلى (1.89±0.25) في مرضى الورم الدماغي الأولي وأقل في مرضى الورم (الدائم). نسبة Cr (0.04±0.02) ونسبة Cr (0.07). 30 مريض من ال 31 المريض تم تشخيصهم بشكل صحيح دقة التشخيص وحساسية وخصوصية نسبة الـ MI/Cr في تحديد درجة الورم الدماغي الدقيق هو 97.7/0 و95.1% على التوالي.

الاستنتاج: أثبت الورم المغناطيسي الطيفي التعرض وحدة الورم الدماغي لعمليات جراحية أو أخذ عينة غير ضرورية في بعض الحالات.