Apparent diffusion coefficient and Magnetic resonance spectroscopy in grading of malignant brain neoplasms

Mahmoud Abd Elaziz Dawoud 1, Mohamed Fouad Sherif 2, Mohamed Adel Eltomey *

Radiology & Imaging Department, Faculty of Medicine, Tanta University, Elbahr Street, Tanta 31111, Egypt

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KEYWORDS
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Abstract
Aim: This work aims to study the role of combined apparent diffusion coefficient (ADC) and Magnetic resonance spectroscopy (MRS) in grading malignant brain neoplasms.

Methods: A prospective study included 40 patients who were evaluated by standard contrast enhanced MRI, diffusion weighted imaging and multivoxel spectroscopy.

Results: Statistically significant difference was found between tumoral ADC values in low grade versus high grade tumors and metastasis and also between the peritumoral ADC values in metastasis versus low and high grade tumors. Statistically significant difference is noticed between tumoral Cho/Cr ratio values in low grade versus high grade tumors and metastasis, and also peritumoral Cho/Cr ratio values in low grade and metastasis versus high grade tumors. Statistically significant difference between tumoral Cho/NAA ratio in low grade versus high grade tumors and metastasis and lastly between peritumoral Cho/NAA ratio in low grade and metastasis versus high grade tumors was found. Lipid and lactate peaks were found frequently in high grade tumors and metastasis.

Conclusion: The combination of calculated ADC values and MR spectroscopy is useful in grading of malignant brain tumors and were more useful together than each on its own.

1. Introduction
Intracranial tumor management and treatment depends on proper grading. High grade gliomas are frequently treated by resection followed by radiotherapy and chemotherapy, while surgery alone is usually sufficient for treating low grade gliomas (1–3).
Imaging plays an integral role in intracranial tumor management. Magnetic resonance (MR) imaging in particular has emerged as the imaging modality most frequently used to evaluate intracranial tumors (4).

Diffusion-weighted imaging (DWI) provides image contrast which is dependent on the molecular motion of water (5). The use of ADC values within the enhancing tumor tissue and the peri-tumor area provides quantitative information on tumor cellularity and characterization of tumor-related edema that is not readily discernible on conventional MRI (6).

Magnetic resonance spectroscopy is generally known as an analytical method in chemistry to identify molecules and to determine their biophysical characteristics. Magnetic resonance spectroscopic imaging (MRSI) is a non-invasive imaging technique that provides metabolic information on brain tumor (7).

2. Aim of the work

This work aims to study the role of the combined application of apparent diffusion coefficient (ADC) values and Magnetic resonance spectroscopy (MRS) in grading of malignant brain neoplasms.

3. Patients and methods

Between March 2013 and March 2014, 40 patients (29 males and 11 females) known to have intracranial space occupying lesions by CT were included in this study. Their ages ranged from 9 years to 67 years (mean 41.4 ± 16.4).

3.1. MRI examination of brain

All the cases were evaluated using the standard brain MRI protocol at our institution using 1.5T MRI machine (GE Signa 1.5T, GEMSOW), the protocol includes a 3 plane localizer, Axial & Sagittal T1WI, Axial T2 WI, Axial fluid attenuation inversion recovery (FLAIR). Post contrast T1WI in axial, coronal and sagittal planes using Gadolinium-DTPA (0.2 mg/kg). A slice thickness of 5 mm and 4 mm spacing was used.

Diffusion weighted imaging (DW) with apparent diffusion coefficient calculation of brain lesions for all patients: DW images were obtained using an axial echo-planar Spin Echo sequence, on average 5-mm section thickness. DW images and ADC maps were acquired by using b-values of 0 and 1000 s/mm² applied in the X, Y and Z directions. Post processing of ADC maps was performed using software provided on the machine console. Regions of Interest (ROIs) for ADC calculation were placed manually in the solid enhancing parts of the tumor, preferably avoiding cystic or necrotic areas, and in the peritumoral regions. Standard mean ADC values were calculated automatically and expressed in 10⁻³ mm²/s.

Point resolved spectroscopy (PRESS) technique was applied using long and short TE (144 & 35 ms), respectively. Sampling analysis was performed by Multivoxel MR spectroscopic technique (MVS), 2 or 3 were positioned in the solid parts of the lesions guided by enhancement in post contrast T1WIs avoiding areas that showed signs of hemorrhage or necrosis, also avoiding contamination from nearby bone or CSF spaces, the voxels size ranged from 1 x 1 x 1 cm³ to 2 x 2 x 2 cm³, other similar voxels (2 or 3) were placed in peri-lesion edema. A voxel was positioned in the contralateral normal brain white matter to obtain a reference spectrum. Choline/Creatine and Choline/N-Acetyl Aspartate ratios were calculated for the tumor and peritumoral edema. Lipid and lactate peaks were read at 1.3 ppm on long and short TE sequences as present or absent.

Surgical resection was performed in 28 patients and stereotactic biopsy in 12 patients, the resected specimens were evaluated by Histopathology.

The study was approved by the local ethics committee at our institution, patient consent was obtained from all study subjects and their data were kept in a secure electronic file in an anonymous manner to insure patient confidentiality.

Statistical analysis was performed using Mann–Whitney U test to compare the ADC values and MRS ratios, Chi-square test was performed on the lipid peak in long and short TE, p value of <0.05 was considered statistically significant. Software used was Minitab V.17 (Minitab Inc. USA).

4. Results

The final histopathological results of the 40 patients revealed 28 cases of primary tumors divided into 11 cases of low grade glioma (WHO I–II) (27.5%), 17 cases of high grade glioma (42.5%) including 5 cases of anaplastic astrocytoma (12.5%), 12 cases of glioblastoma multiformis (30%), while metastasis was found in 12 cases (30%) (Table 1, Figs. 4A, 5A, 6A).

ADC values of the tumoral area were higher in low grade tumors (1.216 ± 0.059 x 10⁻³ mm²/s) than high grade (0.95 + 0.12 x 10⁻³ mm²/s) and metastatic tumors (0.99 + 0.153 x 10⁻³ mm²/s). A statistically significant difference was seen between tumoral ADC values in low grade versus high grade tumors and metastasis with p < 0.0001 and p = 0.0026, respectively. No statistically significant difference of the tumoral ADC values between high grade tumors and metastasis was found p = 0.5208 (Table 2, Figs. 1A, 4B, 5B, 6B).

Peritumoral ADC values calculated were higher in metastases (1.66 ± 0.068) than high grade primary tumors (1.22 ± 0.065) (Table 3). ADC values of the peritumoral area were higher in metastatic tumors (1.66 ± 0.068 x 10⁻³ mm²/s) than low grade (1.59 + 0.052 x 10⁻³ mm²/s) and high grade tumors (1.22 ± 0.065 x 10⁻³ mm²/s). A statistically significant difference was seen between the peritumoral ADC values in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Showing histological diagnosis of the 40 cases included in the study.</th>
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<tbody>
<tr>
<td></td>
<td>Primary low grade (WHO I–II)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>11 (27.5%)</td>
</tr>
<tr>
<td>GBM = glioblastoma multiformis; AA = anaplastic astrocytoma.</td>
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</table>
metastasis versus low and high grade with \( p = 0.0210 \) and \( p = 0.0102 \), respectively. No statistically significant difference of the peritumoral ADC values between Low and high grade tumors was found \( p = 0.832 \) (Table 2, Figs. 1B, 4B, 5B, 6B).

Cho/Cr ratio values of the tumoral area were lower in low grade tumors (2.23 ± 0.512) than high grade (4.48 ± 2.09) and metastatic tumors (4.23 ± 2.02) (Table 3). A statistically significant difference was seen between Cho/Cr ratio values in low grade versus high grade tumors and metastasis with \( p = 0.0003 \) and \( p = 0.0019 \), respectively. No statistically significant difference of the Cho/Cr ratio values between high grade tumors and metastasis was found \( p = 0.6419 \) (Table 3, Figs. 2A, 4C, 5C, 6C).

### Table 2  
Showing ADC values in tumoral and peritumoral regions of the cases.

<table>
<thead>
<tr>
<th></th>
<th>Primary low grade (WHO I–II)</th>
<th>Primary high grade (WHO III–IV)</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC tumoral ( (\times 10^{-3} \text{mm}^2/\text{s}) )</td>
<td>1.216 ± 0.059</td>
<td>0.953 ± 0.12</td>
<td>0.997 ± 0.153</td>
</tr>
<tr>
<td>ADC peritumoral ( (\times 10^{-3} \text{mm}^2/\text{s}) )</td>
<td>1.59 ± 0.052</td>
<td>1.22 ± 0.065</td>
<td>1.66 ± 0.068</td>
</tr>
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</table>

Fig. 1  
(A) Box and whisker plot of the ADC values in the tumor. (B) Box and whisker plot of the ADC values in the peritumoral region.

Fig. 2  
(A) Box and whisker plot of the Cho/Cr ratio in the tumor. (B) Box and whisker plot of the Cho/Cr ratio in the peritumoral region.

Fig. 3  
(A) Box and whisker plot of the Cho/NAA ratio in the tumor. (B) Box and whisker plot of the Cho/NAA ratio in the peritumoral region.
Cho/Cr ratio values of the peritumoral area were lower in low grade tumors (1.25 ± 0.344) and metastasis (1.28 ± 0.523) than high grade tumors (2.071 ± 0.95). A statistically significant difference was seen between Cho/Cr ratio values in low grade and metastasis versus high grade tumors with $p = 0.0225$ and $p = 0.0139$, respectively. No statistically significant difference of the peritumoral Cho/Cr ratio values between low grade tumors and metastasis was found $p = 0.926$ (Table 3, Figs. 2B, 4E, 5E, 6E).

Cho/NAA ratio values of the tumoral area were lower in low grade tumors (1.99 ± 0.86) than high grade tumors (7.81 ± 1.72) and metastatic tumors (7.49 ± 2.03). A statistically significant difference was seen between Cho/NAA ratio values in low grade and metastasis versus high grade tumors with $p < 0.0001$ and $p = 0.0001$, respectively. No statistically significant difference of the peritumoral Cho/NAA ratio values between low grade tumors and metastasis was found $p = 0.5799$ (Table 3, Figs. 3A, 4C, 5C, 6C).

Cho/NAA ratio values of the peritumoral area were lower in low grade tumors (1.1 ± 0.2) and metastasis (1.14 ± 0.207) than high grade tumors (2.8 ± 1.07). A statistically significant difference was seen between Cho/NAA ratio values in low grade and metastasis versus high grade tumors with $p < 0.0001$. No statistically significant difference of the peritumoral Cho/NAA ratio values between low grade tumors and metastasis was found $p = 0.6223$ (Table 3, Figs. 3B, 4E, 5E, 6E).

Both long and short TE (144 and 35 ms), respectively were used to evaluate the presence of lactate and lipid. The lactate peak was well demonstrated on the long TE while the lipid peak was much more evident on the short TE.

Chi square test showed a statistically significant difference between the presence of lipid peak in metastatic and high grade tumors on both long and short TE $p = 0.02$ & $p = 0.47$, respectively.

Low grade primary tumors showed absent lactate and lipid on both long and short TE sequences.

Lactate peak on long TE was seen in 5 cases of GBM, 4 cases of AA and 2 cases of metastatic tumors. It was less evident on short TE being seen in only 4 cases of AA (Tables 4 and 5).

Lipid peak was most frequently seen in metastatic tumors on both long and short TE, 8 & 10 cases, respectively. GBM also showed lipid peak on both long and short TE, in 4 & 8 cases, respectively (Tables 4 and 5, Figs. 4D, 5D, 6D).

Fig. 4 Forty year old male complaining of headache. Operative resection biopsy revealed low grade glioma (WHO grade I). (A) Axial post contrast T1WI showed a well defined rounded focal lesion in the left parietal region showing thin faint marginal enhancement, no peritumoral edema was seen. (B) ADC map of the lesion, the intratumoral ADC value was $1.15 \times 10^{-3} \text{mm}^2/\text{s}$, peritumoral ADC value was $1.62 \times 10^{-3} \text{mm}^2/\text{s}$. (C) Multivoxel Long TE (144 ms) spectroscopy in the tumor showed Cho/Cr = 3.25, Cho/NAA = 1.91. (D) Multivoxel Short TE (35 ms) in the tumor showed absence of lipid and lactate peaks. (E) Multivoxel Long TE (144 ms) spectroscopy in the peritumoral region showed Cho/Cr = 1.78 and Cho/NAA = 2.06.
5. Discussion

The low accuracy of differentiation of primary intracranial tumors and metastasis on convention MR imaging leads to the need of more advanced MR techniques including diffusion weighted imaging and MRS (8).

Our results showed that tumoral ADC values were higher in low grade tumors than high grade tumors and metastasis with a statistically significant difference between primary low grade tumors and primary high grade and metastatic brain tumors, however ADC values failed to differentiate primary high grade tumors from metastatic brain tumors, our results matched those of Server et al. (3), Murakami et al. (9) and Lee et al. (10). These findings could be attributed to the fact that the higher the grade of malignancy the cellularity of the tumor increases thus restricting water diffusion. On the other hand several studies failed to differentiate between primary low and high grades tumors. Including those of Pavlisa et al. (11) and Rollin et al. (12).

In this study it was found that ADC values in peritumoral area were significantly higher in metastatic tumors than those of low and high grade primary tumors and that there was no statistically significant difference in the peritumoral ADC value between low and high grade tumors. These results matched those of Lee et al. (10) and Server et al. (3). Lee et al. (10) explained this finding by the increased cellularity in the peritumoral region in primary tumors as a result of infiltration, while in metastatic tumors there is vasogenic edema with no infiltration. It is noted that the Guzman et al. (13) reported the ability of peritumoral ADC values to differentiate low from high grade tumors, contradicting our results. This contradiction could be attributed to the limitation of having a small population in this study.

Choline/Creatine (Cho/Cr) ratio in the tumoral area was significantly lower in primary low grade tumors than in primary high grade tumors and metastasis. No significant difference was seen between primary high grade tumors and metastasis. This agreed with the result of Martinez-Bisbal et al. (14), Chen et al. (15) & Shokry (16) that increase in Cho/Cr ratio in lesion could only differentiate low grade primary tumors from high grade primary tumors. The increase in Cho/Cr ratio in high grade tumors was reported to correlate

Fig. 5  Fifty-six year old female complaining of headache. Stereotactic biopsy revealed GBM (WHO grade III). (A) Axial post contrast T1WI showed a well defined irregular shaped intra axial space occupying lesion in the right parieto-temporal region showing uneven peripheral strong marginal enhancement, moderate peritumoral edema was seen with mass effect. (B) ADC map of the lesion, the intratumoral ADC value was $0.95 \times 10^{-3} \text{mm}^2/\text{s}$, peritumoral ADC value was $1.42 \times 10^{-3} \text{mm}^2/\text{s}$. (C) Multivoxel Long TE (144 ms) spectroscopy in the tumor showed Cho/Cr = 4.45, Cho/NAA = 6.125. (D) Multivoxel Short TE (35 ms) spectroscopy in the tumor showed a high lipid peak. (E) Multivoxel Long TE (144 ms) spectroscopy in the peritumoral region showed Cho/Cr = 2.23 and Cho/ NAA = 2.07.
significantly with expression of proliferating cells by Chen et al. (15).

Choline/Creatine (Cho/Cr) ratio in the peritumoral area was significantly lower in primary low grade tumors and metastasis than in primary high grade tumors, no significant difference was seen between primary low grade tumors and metastasis. These findings agreed with those of Chiang et al. (17), Matteo Bendini et al. (18) and Faria et al. (19). The findings were explained on the bases that primary high grade tumors have been reported to have peritumoral infiltrating neoplastic cells. So perilesional edema areas show spectroscopic malignant changes in the form of higher CHO/Cr ratio in primary tumors than metastatic.

Choline/N-acetyl aspartate (Cho/NAA) ratio in the tumoral area were significantly lower in primary low grade tumors than primary high grade tumors and metastasis and no significant difference was seen between primary high grade and metastatic tumors. These results matched those reported by LIU et al. (20) and Server et al. (21).

Choline/N-acetyl aspartate (Cho/NAA) ratio in the peritumoral area was significantly lower in primary low grade tumors and metastatic than primary high grade tumors with

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Showing MRS ratios in tumoral and peritumoral regions of the cases on long TE (144 ms).</th>
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<tbody>
<tr>
<td></td>
<td>Primary low grade (WHO I–II)</td>
</tr>
<tr>
<td>Cho/Cr tumoral</td>
<td>2.23 ± 0.512</td>
</tr>
<tr>
<td>Cho/Cr peritumoral</td>
<td>1.255 ± 0.334</td>
</tr>
<tr>
<td>Cho/NAA tumoral</td>
<td>1.99 ± 0.86</td>
</tr>
<tr>
<td>Cho/NAA peritumoral</td>
<td>1.1 ± 0.2</td>
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Fig. 6  Thirty-seven year old female with known history of breast cancer. (A) Axial post contrast T1WI showed a well defined irregular focal lesion in the left parietal region showing strong heterogeneous enhancement, mild peritumoral edema was seen. (B) ADC map of the lesion, the intratumoral ADC value was $1.05 \times 10^{-3}$ mm²/s, peritumoral ADC value was $1.76 \times 10^{-3}$ mm²/s. (C) Multivoxel Long TE (144 ms) spectroscopy in the tumor showed Cho/Cr = 3.87, Cho/NAA = 3.44. (D) Multivoxel Short TE (35 ms) in the tumor showed a lipid peak. (E) Multivoxel Long TE (144 ms) spectroscopy in the peritumoral region showed Cho/Cr = 1.18 and Cho/NAA = 0.09. Stereotactic biopsy revealed metastatic lesion.
no significant difference seen between primary high grade and metastatic tumors. These results matched those of Server et al. (3) and Server et al. (21).

Lipid peaks were seen in High grade tumors and metastasis on both long TE (144 ms) and short TE (35 ms) sequences however the peaks were higher on short TE sequences. A statistically significant difference between the presence of a Lipid peak was seen between high grade tumors and metastasis on both short and Long TE sequences. This agreed with Shokry (16), Opstad et al. (22) and van der Graaf (23) who gave a possible explanation for the elevated lipids in metastatic lesions as the cancer cells of different origin, contain mobile spectroscopically detectable lipids in their cell membrane, while cell cultures of tumors which do not lead to metastases do not exhibit these mobile lipids.

Lactate peak was seen on long TE sequences in High grade tumors and metastasis. Law et al. (24) reported presence of lipids and lactate peaks in high grade primary tumors. Lipid and lactate presence do correlate with necrosis in high-grade glioma and may also be used as an adjunct tool for differentiating glioma grades (24).

In conclusion, the diagnosis and grading of primary and secondary brain tumors and differentiating them from other focal intra-cranial lesions based on imaging procedures alone are still a challenging problem, based on the findings in this study it can be concluded that the combination of MRS and ADC calculation provides additive valuable information, rather than using each parameter on its own, helping in grading of intra-cranial tumors leading to improved diagnosis and hence management and prognosis.

**Conflict of interest**

None declared.

**References**


