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# THE VALUE OF PROTON MR-SPECTROSCOPY IN THE DIFFERENTIATION OF BRAIN TUMOURS FROM NON-NEOPLASTIC BRAIN LESIONS

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***Purpose:*** **Our aim was to evaluate the efficacy of Proton-MR Spectroscopy for the differentiation of cranial *masses from non-neoplastic brain disorders.***
***Material and method:*** **33 patients with intracranial mass lesions, 29 patients with non-neoplastic brain lesions: Ischemic-demyelinating-metabolic-benign cystic mass group; As a whole 62 patients: 30 males and 32 females were included in this study.**
***Results:*** **In brain tumours, average Cho/NAA ratio 2.84-NAA/Cr ratio was 0.97, Cho/Cr ratio 2.42 and Cho/MI ratio was 3.51. In non-neoplastic group; NAA/Cr ratio was extremely higher than tumour group, the other ratios were far lower than cranial mass lesions. Average Cho/NAA ratio: 0.50 ± 0.15, Cho/Cr ratio: 1.05 ± 0.14, Cho/MI ratio: 1.07 ± 0.73.**
***Conclusion:*** **Higher Cho/NAA and Cho/MI ratios with lower NAA/Cr ratio were most likely to be malignant. Additional lipid and lactate peaks were generally seen in malignant group.**

**Key-words: Brain, diseases – Brain neoplasms, MR – Magnetic resonance (MR), spectroscopy.**

Non-invasive and accurate differentiation between neoplastic and non-neoplastic brain lesions is important for determining the correct treatment plan and in some cases, may avoid the necessity of biopsy (1-3). Conventional MR imaging is a useful tool in the evaluation of tumoral and non-tumoral brain lesions but not really sufficient for diagnosing all conditions (2-4). Proton magnetic resonance spectroscopy [H-MRS]; A non-invasive technique, has been helpful in understanding the pathophysiology of different pathologic processes (1-6). It has been used to observe metabolite changes for different intracranial abnormalities such as tumours, stroke, tuberculomas, multiple sclerosis (MS) and metabolic-inherited brain disorders, epilepsy and traumatic injuries (1-3, 6). H-MRS provides biochemical information from tissues by reflecting the alterations of metabolites in the spectra, has proved to be useful for evaluating brain lesions especially the differentiation of tumours and non-neoplastic lesions (1, 2, 4). Several types of non-neoplastic brain disorders (infectious-demyelinating lesions etc.) can be potentially misdiagnosed as brain tumours, MR- Spectroscopy may improve the diagnosis of unknown brain lesions (2-4, 7). H-MRS provides information related to the neuronal integrity, cell proliferation or degradation, energy metabolism and necrotic transformation of brain or neoplastic tissues (5, 6, 8, 9). Particularly H-MRS is added to the routine brain MRI in order to solve diagnostic problems such as differentiation of neoplastic and non-neoplastic lesions, low and high grade tumours, ischemia from low grade gliomas or discriminating the metastases from primary brain tumours and abcesses (3, 5, 6, 9). Various spectroscopic methods have been used to study tumour biology, grade gliomas, plan treatment and etc (3, 5, 6, 8).

In this study, we aimed to test the strength of H-MRS in the discrimination of tumoral masses from non-neoplastic brain lesions. Furthermore, we also wanted to check if MRS can distinguish among the types of cerebral neoplasms.

## Material and method

33 patients with intracranial mass lesions confirmed by cranial MRI were selected for proton-MR-Spectroscopy; 17 males-16 females, age range from 9 to 85, mean age 49 ± 2, patients for non-neoplastic brain lesions suggested by cranial MRI were selected for H-MRS; 13 males-16 females with age range 17-80, mean age 48 ± 2. Totally 62 patients; 30 males and 32 females were included in this retrospective study. Informed consent was obtained from all the patients before the study.

The stratification of patients into tumoral or non-neoplastic group depends upon the following brain MRI items; For neoplastic group, Centrally or peripherally strong enhancing mass lesions with surrounding discrete vasogenic edema in cerebral or cerebellar hemispheres. For the non-neoplastic group; Plaque or nodular lesions mostly situated at pericallosal-periventricular white matter-thalamus and basal ganglia, non-enhanced lesions without obvious mass effect with restricted diffusion, extra-axial non-enhancing cystic masses with or without restriction in the Diffusion Weighted MRI and focal nodular or conglomerated white matter lesions. We have variety of non-neoplastic brain disorders that include ischemic-demyelinating-metabolic (Wilson's disease) and benign mass lesions. Ischemic group consisted of acute and subacute enfarcts , chronic ischemic areas or encephalomalasic regions were excluded. The demyelinating lesions were; MS and Acute disseminated ensephalomyelitis (ADEM), all the active or inactive plaques whether new or old, were included in this research. Diagnosis of all non-neoplastic brain disorders were confirmed by brain MRI, clinical and laboratoy findings. We had intracranial tumours that include high grade glial tumours (multiform glioblastoma-anaplastic astrocytomas), low-grade glial tumours (gliomatosis serebri-serebelli, gangliogliomas), meningiomas and metastasis. Except for a metastasis case and two menengiomas, diagnosis of all brain neoplasms

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were confirmed pathologically either by biopsy or open-surgery. Patient with cranial metastases was still suffering from a known primary neoplasm and has also metastatic infiltrations in his lungs and liver so biopsy was not needed. The diagnosis of extra-axial menengiomas was based upon the MRI and clinical findings as the patients refused the biopsy. All the MRI and Multi-voxel spectroscopic analysis were carried out with an 8-channel 1.5 T MR scanner (Philips Achieva, Philips Medical systems-Netherlands) by using a standart head and neck array coil. Multivoxel spectroscopic technique (MVS) was taken into account for all lesions in the study; in contrary we didn't perform single-voxel spectroscopy in this research.

The MRS was performed by using point-resolved spectroscopy (PRESS) with a volume of interest (VOI), 1*1*0.5 $cm^3$ standard voxel sizes for the MVS and presaturation bands placed around the VOI. Depending upon the tumour and the lesion size, approximately 5-10 $cm^3$ tumor area on the multivoxel imaging was harbored with the volume made up of such Standard voxels. We have positioned the possible voxel within the solid tumoural or lesional area avoiding areas of cysts, normal appearing brain parenchyma, scalp or skull base contamination (6-8). Automatic shimming of the linear x,y,z channels was used to optimize field homogeneity, water resonance and water suppression pulses were optimized for the consistent water saturation.

**Data analysis**

Proton spectrum was recorded in axial plane with TR; 1500 ms,TE; 26 and 144 ms, FOV; 24 x 24 cm, 0.5 cm slice thickness, 256 x 256 matrix and 24 x 24 phase encoding. Duration of scan for both TE acquisitions was about 5 min. Time domain data were multiplied with a Gaussian function of 90 (Centre 0, halfwidth 256 ms), 2D Fourier transformed phase and base-line corrected, quantified by means of frequency domain curve fitting with the assumption of a Gaussian line shape, spectral analysis and all post-processing were carried out by using a software of Philips Achieva Netherland workshop. 0-4.35 ppm is analysed and metabolite signals and the data were processed as follows; N-Acetyl aspartate (NAA) at 2 ppm, creatine (Cr) at 3-3.1 ppm, Phosphocreatine (Cr2) at 3.8-3.9 ppm, Choline (Cho) at 3.2 ppm, lipids (Lip) at 0.9-1.3 ppm, lactate (Lac) at 1.3-1.4 ppm , glutamate and glutamine (Glx) at 2.45 ppm, glycine and or myo-inositol (Gly-MI) at 3.6-3.75 ppm (3, 4, 6, 7). Standard, optimum and sufficient base-line correction for metabolites were also performed. Two doublets inverted owing to phase modulation due to J coupling were defined, Lac at 1.4 ppm and alanine (Ala) at 1.5 ppm. At TE 144 ms, Lac can be differentiated from lipids with a narrow bandwidth comparable with the peaks of other metabolites and shows an inverted J-coupled double peak at 1.4 ppm (3, 4, 6). Tumour and lesion metabolite signal intensities were quantified, normalized by expressing the peak area intensities of the metabolites especially NAA-Cho-Cr as ratios of normal brain parenchymal values to intratumoral metabolites (NAA\Cr, NAA \ Cho), Lip and Lac which were not detectable in normal brain, were normalized using the contralateral reference spectrum as an internal standart (1, 3, 8). For instance, we compared the lesional NAA to the lesional Cr, had the lesional NAA\Cr ratio and this was identical for all metabolites and ratios. Contralateral reference voxel was placed just symmetric to the center of the original brain lesion, however for the midline lesions; The normal reference spectra and metabolite ratios were obtained from the healthy volunteers who had no cerebral or cerebellar abnormalities. 3 healthy volunteers were included in this study.

All analyses were performed by using a software program (SPSS for Windows, SPSS, Chicago-Illinois). Significance of differences between various cranial masses and non-neoplastic lesion groups (Ischemic-demyelinating-metabolic and benign cystic mass lesions) for brain metabolites and metabolite ratios were tested with one-tailed parametric variance analysis test, Pearson chi-square test and difference test among mass groups, the sensitivity and the specificity of H-MRS for all neoplastic and non-neoplastic group, were tested by chi-square cross table test, $p < 0.05$ were considered to be statistically significant differences.

**Results**

In both cranial neoplastic mass lesions (Glial tumours-metastasis-menengiomas) and non neoplastic brain disorders, including ischemic-demyelinating (MS-ADEM)-metabolic (Wilson syndrome), benign cystic mass group (arachnoid-epidermoid cysts-cavernoma); we have the age and the gender of patients, lesion localizations, NAA/Cr, Cho/NAA, Cho/Cr, Cho/MI ratios, biopsy results and other increased metabolite peaks (Table I). 30 patients with space-occupying brain masses underwent biopsy or open surgery, only the metastasis and meningiomas had no histopathologic confirmation. In one patient, there was no mass profile in MRSI but the histopathology was anaplastic astrocytoma, except for this case H-MRS proved all the mass lesions (32/33). The statistical analysis and measurement of metabolite peaks were performed in 32 patients. The diagnosis of other non-neoplastic lesions were proved by MRI, by clinical routes and by biochemical laboratory results. The spectra from the contralateral brain or from the healthy volunteers revealed a consistent pattern of the four major peaks of NAA, Cr, Cho and MI, no lactate or lipid resonances were visible in these cases. The average NAA/Cr, Cho/NAA, Cho/Cr, Cho/MI ratios were 1.46 ± 0.13, 0.56 ± -0.22, 0.80 ± -0.07, 0.41 ± 0.09. These ratios were assumed to be the cut-off values for the differentiation between malignant and non-neoplastic brain lesions. We performed two acquisitions in this research, TE: 26 msec and 144 msec. Cho/MI ratio was obtained at short TE acquisition, all the other ratios were calculated at long TE application. The metabolites or the ratios of them were assumed to be increased or decreased in a voxel, only if the measurements in the mentioned pixel had been normalized with reference to the contralateral normal appearing pixel, this was calculated for each metabolite with regard to the healthy opposite side reference point.

According to H-MRS; We had 9 low-grade (Grade 1-2) gliomas, all low grade gliomas showed increased Cho and reduced NAA resonances, as an average Cho/NAA ratio; 1.66 ± 0.35, all low-grade gliomas in this study showed increased Cho and moderately decreased Cr, as an average Cho/Cr ratio; 2.25 ± 0.63. Low-grade glial tumours also showed moderately increased MI, with an average Cho/MI ratio; 2.55 ± 0.86 which was precisely elevated (Table II, Fig. 1). According to Cho/Cr ratio by using one-tailed parametrical variance analysis test, there was a significant

*Table I. — List of patients.*

| Name-age-gender | Lesion localization | MRS RESULTS | Biopsi Results | | Name-age-gender | Lesion localization | MRS RESULTS |
|---|---|---|---|---|---|---|---|
| T.K. 34 M | Right Frontal | Highgrade Glial tm | Low grade Glial tm | 35- | E.E 80 F | Left temporal | İschemia |
| E.B 43 F | Corpus Callozum | Highgrade Glial tm | GBM | 36- | K.Y. 37 M | Right Fronto-parietal | İschemia |
| Y.Y 43 F | Left Frontal | Highgrade Glial tm | Highgrade Glial tm | 37- | N.A. 44 F | Left occipital | Ischemia |
| E.K. 22 M | 4. Ventricule | Highgrade Glial tm | Low grade Glial tm | 38- | F.Y. 24 F | Left Thalamus | İschemia |
| L.S 40 M | Cerebellum | Low grade Glial tm | Low grade Glial tm | 39- | M.E. 52 F | Left parieto-occipital | İschemia |
| B.U. 9 M | Left Parietal | Low grade Glial tm | Low grade Glial tm | 40- | S.A. 36 F | Right fronto-parietal | İschemia |
| M.P.48 F | Cerebellar Vermis | Highgrade Glial tm | Low grade Glial tm | 41- | C. . 29 M | Right Occipital | İschemia |
| H.C. 50 F | Left Occipito-Parietal | GBM | GBM | 42- | S.A. 60 M | Right Occipito-temporal | İschemia |
| H.B. 43 M | Bil.Centrumsemiovale | Highgrade Glial tm | Highgrade Glial tm | 43- | M.Ö. 31 M | Bilat.periventricular | İschemia |
| C.A. 44 M | Right Post. Parietal | Menengioma Extra- | axial, no biopsy | 44- | S. 58 F | Right Temporo-occipital | İschemia |
| İ.K. 78 M | Left Frontoparieta | Highgrade Glial tm | GBM | 45- | H.B. 53 F | Right Occipital | İschemia |
| A.D. 69 M | Right Temporal | Highgrade Glial tm | GBM | 46- | M.K. 56 M | Right Occipito-temporal | İschemia |
| A.D. 34 F | Right Cerebellar | Highgrade Glial tm | Highgrade Glial tm | 47- | M.D 17 M | Left Temporo-occipital | İschemia |
| D.D. 38 F | Left Occipito-Temporal | Low grade Glial tm | GBM | 48- | H.U 23 F | Left Fronto-parietal | İschemia |
| G.D. 64 F | Left Temporal | Low grade Glial tm | Highgrade Glial tm | 49- | A 50 F | Right Parietal | İschemia |
| H.C. 46 M | Right Medial Temporal | Low grade Glial tm | Low grade Glial tm | 50- | B.D. 44M | Left Frontal | İschemia |
| M.B. 58 M | Left Frontotemporal | Highgrade Glial tm | GBM | 51- | Z.T.67 F | Right thalamus,basal ganglia. | İschemia |
| M.S. 50 F | Right Frontotemporal | Low grade Glial tm | Highgrade Glial tm | 52- | A 36y,M | Right occipital | İschemia |
| M.H 42 F | Left Frontoparietal | Low grade Glial tm | Highgrade Glial tm | 53- | S.T 53 F | Bilat.periventricular | Demyelinating lesions |
| S.K. 36 M | Left Occipitotemporal | Highgrade Glial tm | Anaplastik Astrositom | 54- | E.B 32 F | Bilat.periventricular | Demyelinating lesions. |
| S.K. 39 F | Left Pontobulbar | Highgrade Glial tm | Metastasis | 55- | H.G 38 M | Bilat.periventricular | Demyelinating lesions. |
| B.T. 42 M | Right Mezencephalon | GBM | GBM | 56- | H.B 30 M | Bilat.periventricular | Demyelinating lesions. |
| R.Ö 43 M | Left Frontoparietal | Highgrade Glial tm | Highgrade Glial tm | 57- | V.T 31 M | Bilat.periventricular | Demyelinating lesions |
| I.Ş.24 M | Right Temporal | Highgrade Glial tm | Low grade Glial tm | 58- | R.Ö 32 M | Thalamus-Midbrain | Metabolic disease |
| V.K. 52 M | Corpus Callozum | Highgrade Glial tm | Highgrade Glial tm | 59- | G.N 47 F | Right post. parietal | Arachnoid cyst, MRS negative. |
| S.T 81 F | Right Temporal | GBM | GBM | 60- | M.D 45 F | Right paramedian | epidermoid cyst |
| N.Y. 28 F | Right Frontoparietal | Menengioma | Extra-axial, no biopsy. | 61- | C.Ö 65 F | Cerebellum | Cavernoma. |
| M.G. 43 M | Left Frontoparietal | Highgrade Glial tm | GBM | 62- | C.E 72 M | Right Frontal | Arachnoid cyst, MRS negative. |
| A.A. 60 M | Corpus Callozum | No mass effect. | Highgrade Glial tm | 63- | H.Ö. 30 F | Right Occipital | Neuroepithelial cyst, MRS negative |
| A.Ö. 33 F | Left Pontobulbar | Low grade Glial tm | Low grade Glial tm | | | | |
| H.B. 85 F | Left Temporo-oksipital | GBM | GBM | | | | |
| Ö.D. 38 F | Left Temporo-oksipital | GBM | GBM | | | | |
| Ş.Ü. 52 F | Left Frontal Low grade | Glial tm | Low grade Glial tm | | | | |
| **NEOPLASTIC MASS GROUP** | | | | | **NON-NEOPLASTIC MASS GROUP.** | | |

*Table II. — Ratios in different brain lesions.*

| Measurement | Mass groups | Patient | Mean value | Standart deviation | F | P |
|---|---|---|---|---|---|---|
| Cho/MI Ratio | Low grade glial tm | 9 | 2,55 | 0.86 | 0.873 | 0,512 |
| | High grade glial tm | 15 | 3,46 | 3,19 | | |
| | GBM | 5 | 6,12 | 5,37 | | |
| | Menengioma | 2 | 3,46 | 2,59 | | |
| | Metastasis | 1 | 3,96 | | | |
| | Sum | 32 | 3,61 | 3,20 | | |

| NAA/Cr ratio | Patient | Mean value | Standart deviation | F | P |
|---|---|---|---|---|---|
| Low grade glial tm | 9 | 1,24 | 0,43 | 1,066 | 0,401 |
| High grade glial tm | 15 | 0,88 | 0,42 | | |
| GBM | 5 | 1,08 | 0,43 | | |
| Menengioma | 2 | 0,74 | 0,33 | | |
| Metastasis | 1 | 0,84 | . | | |
| Sum | 32 | 1,00 | 0,40 | | |

| Measurement | Mass groups | Patient | Mean value | Standart deviation | F | P |
|---|---|---|---|---|---|---|
| Cho/NAA ratio | Low grade glial tm | 9 | 1,66 | 0,35 | 1,126 | 0,372 |
| | High grade glial tm | 15 | 3,31 | 3,04 | | |
| | GBM | 5 | 4,39 | 1,54 | | |
| | Menengioma | 2 | 1,96 | 0,33 | | |
| | Metastasis | 1 | 2,88 | - | | |
| | Sum | 32 | 2,91 | 2,04 | | |

| Measurement | Mass groups | Patient | Mean value | Standart deviation | F | P |
|---|---|---|---|---|---|---|
| Cho/Cre Ratio | Low grade glial tm | 9 | 2.25 | 0,86 | 4.810 | 0.003* |
| | High grade glial tm | 15 | 2,24 | 0,99 | | |
| | GBM | 5 | 4,39 | 1,58 | | |
| | Menengioma | 2 | 1,39 | 0,41 | | |
| | Metastasis | 1 | 2,42 | . | | |
| | Sum | 32 | 2,46 | 0.96 | | |

statistically difference between low-grade tumours and the other cranial mass groups ($p < 0.05$). With parametrical variance analysis test for Cho/NAA and Cho/MI ratios, there was no statistical difference between low-grade tumours and the other brain neoplasms ($p > 0.05$). In low-grade group, the average NAA/Cr ratio was about $1.24 \pm 0.43$ and by using difference test among mass groups, there wasn't any statistical difference between low-grade tumours and the other brain neoplasms ($p > 0.05$) (Table II).

We had 15 high-grade glial neoplasms (Grade 3 astrocytomas and anaplastic astrocytomas ); They presented increased Cho and highly reduced NAA resonances, as an average Cho/NAA ratio; $3.31 \pm 1.04$ (Table II), increased Cho, moderately decreased Cr and decreased MI, as an average Cho/Cr ratio; $2.24 \pm 0.99$ and Cho/MI ratio; $3.46 \pm 1.19$ (Table II – Fig. 2). According to Cho/NAA and Cho/MI ratios; There was no statistical differences between high grade glial tumours and the other brain tumour groups ($p > 0.05$). According to Cho/Cr ratio by using parametrical variance analysis test; There was a significant statistically difference between high grade astrocytomas and the other cranial space occupying mass lesions ($p < 0.05$).

In high-grade gliomas, the average NAA/Cr ratio was about $0.88 \pm 0.48$ and by using difference test among mass groups, there was no statistically difference between high grade glial tumours and the other brain neoplasms ($p > 0.05$) (Table II).

We had in this report 5 glioblastome multiforme (GBM) cases (Grade 4 ). Although they were also high-grade neoplasms, we had organized them in a private group as the GBM masses due to their extremely high metabolite ratios; They presented precisely increased Cho and reduced NAA, MI and Cr resonances , as an average Cho/NAA ratio; $4.39 \pm 1.54$, Cho/Cr ratio; $4.39 \pm 1.58$, Cho/MI ratio; $6.12 \pm 3.37$ (Table II, Fig. 3). According to Cho/NAA and Cho/MI ratios, there wasn't any statistical difference between GBM group and the other cranial brain tumour groups ($p > 0.05$), according to Cho/Cr ratio by using a tailed parametrical variance analysis test, there was a significant statistically differences between GBM and the other cranial neoplasm groups ($p < 0.05$). In GBM group;The average NAA/Cr ratio was about $1.08 \pm 0.43$ and by using difference test among mass groups, there was no statistical differences between GBM and the other brain neoplasms ($p > 0.05$) (Table II).

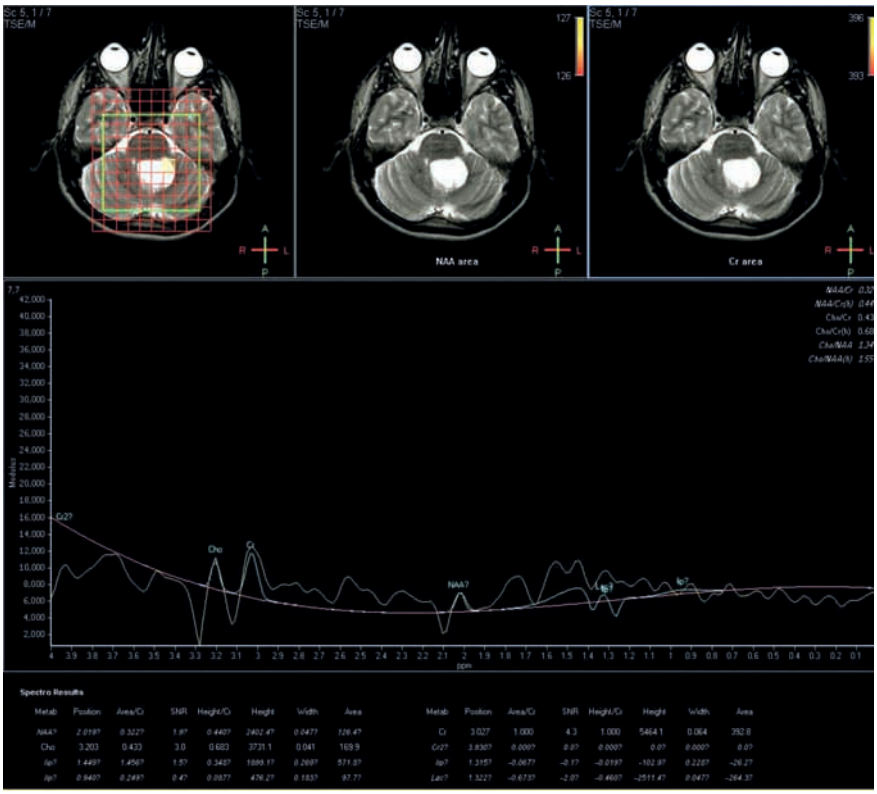


*Fig. 1.* — Metabolite peaks in low grade glial tumour

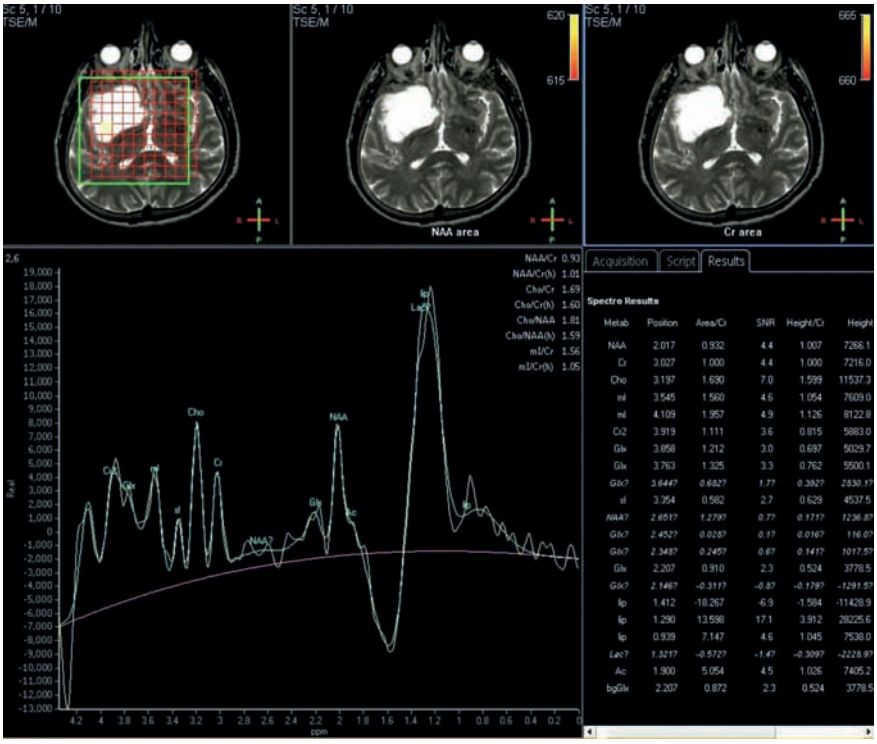


*Fig. 2.* — Metabolite peaks in high grade glial tumour

Menengiomas represented increased Cho, slightly decreased Cr, reduced NAA and MI resonances; As an average Cho/NAA ratio 1.39 ± 0.41, Cho/Cr ratio; 1.66 ± 0.33, Cho/MI ratio; 3.46 ± 1.59 (Table II). According to Cho/NAA and Cho/MI ratios; There was no statistical difference between meningiomas and the other brain mass lesions ($p > 0.05$), According to Cho/Cr ratio by using parametrical variance analysis test, there was a significant statistical difference between meningiomas and all the other cranial mass groups ($p < 0.05$). For meningiomas, average NAA/Cr ratio was about 0.74 ± 0.38 and by using difference test among mass groups, there was no statistical difference between meningiomas and the other brain neoplasms ($p > 0.05$) (Table II).

For metastasis; Increased Cho, decreased Cr, highly reduced NAA and MI resonances, Cho/NAA ratio; 2.88, Cho/Cr ratio; 2.42, Cho/MI ratio; 3.96 were taken (Table II). According to Cho/NAA and Cho/MI ratios. There was no statistical difference between metastasis and the other brain tumour groups ($p > 0.05$), according to Cho/Cr ratio by using parametrical variance analysis test, there was a significant statistically difference between metastasis and the other brain neoplasms ($p < 0.05$). In this group, the average NAA/Cr ratio was about 0.84 and by using difference test among mass groups, there was no statistical difference between metastasis and the other brain neoplasms ($p > 0.05$) (Table II).

As a whole for 33 brain mass lesions; Average Cho/NAA ratio was 2.84 ± 2.35, NAA/Cr ratio was 0.97 ± 0.42, Cho/Cr ratio was 2.42 ± 1.28 and Cho/MI ratio about 3.51 ± 3.21 (Table III). The sensitivity of MRSI was 97% and the specificity of H-MRS was 87.9%, calculated by chi-square cross table test.

We had 18 cases in ischemic group; Average NAA/Cr ratio was 1.96 ± 0.80 , average Cho/NAA ratio was; 0.40 ± 0.23, average Cho/Cr ratio; 0.58 ± 0.37 and the average Cho / MI ratio was about 1.37 ± 1.23 (Fig. 4), 5 cases in demyelinating group; Average NAA/Cr ratio was 2.72 ± 0.92, Cho/NAA ratio ; 0.59 ± 0.17, Cho/Cr ratio; 1.75 ± 1.05 and the average Cho / MI ratio was about 0.78 ± 0.30 (Fig. 5), one case for metabolic disease group ; Average NAA/Cr ratio was 2.23, Cho/NAA ratio; 0.89, Cho/Cr ratio; 0.68 and the average Cho/ MI ratio was about 1.05, 5 cases in benign cystic mass group; The average NAA/Cr ratio was 2.69 ± 1.51, Cho/NAA ratio; 0.34 ± -0.15, Cho/Cr ratio; 1.04 ± 0.51 and the average Cho/MI ratio was about 1.10 ± 0.76 (Table IV). With variance analysis test for Cho/Cr and Cho/NAA ratios; There was a significant statistical difference through the all non-neoplastic brain disorder

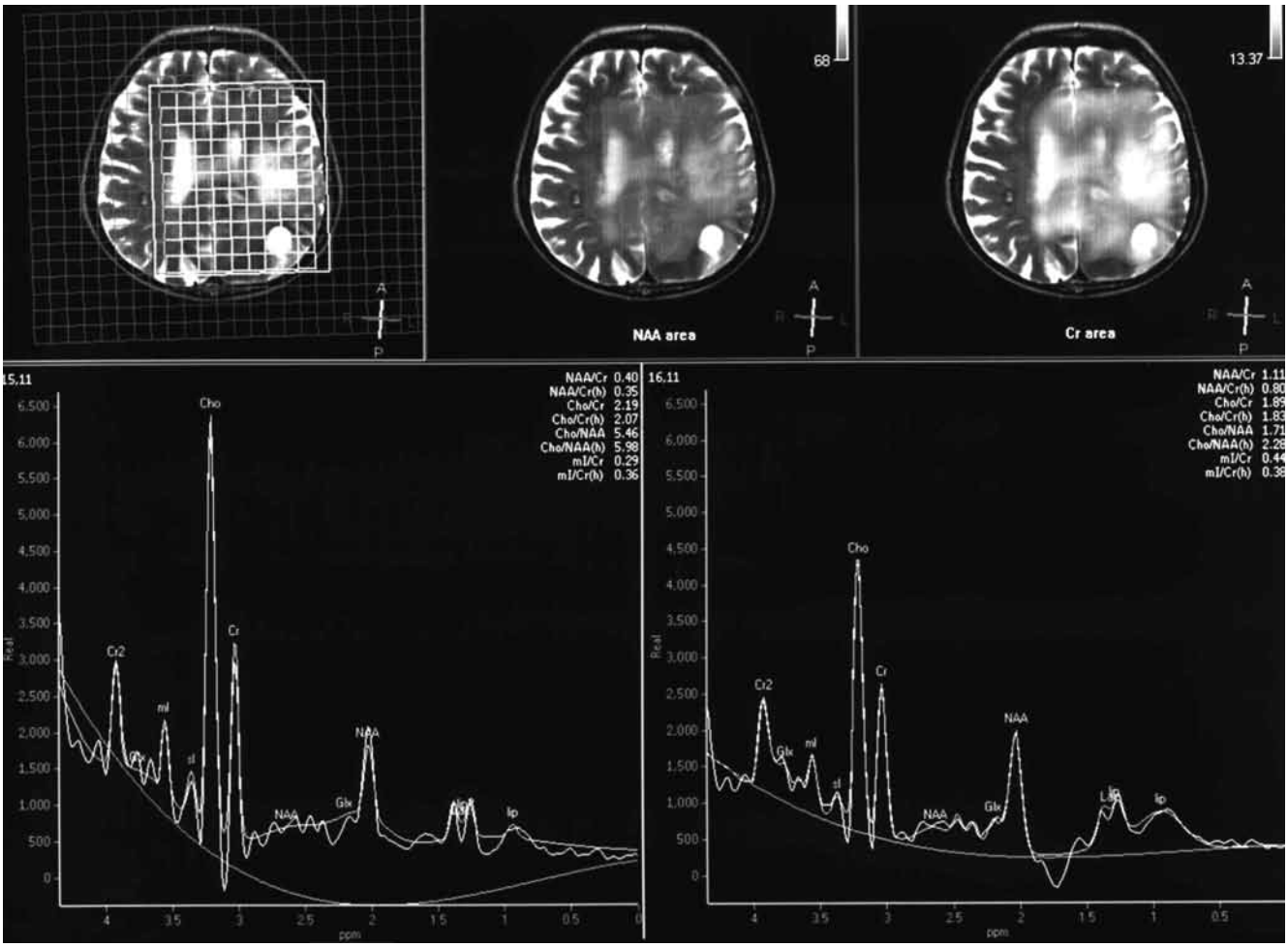


*Fig. 3.* — Metabolite peaks in GBM.

groups ($p < 0.05$), according to NAA/Cr and Cho / MI ratios; There was no statistical differences between non-neoplastic brain lesions ($p > 0.05$) (Table IV).

In ischemic and demyelinating group; There was no NAA depression and no Cho peak rise, Cr peak was almost normal in ischemic group and decreased in demyelinating group. In only one case of ischemia, we had increased MI and Glx. In metabolic group; There was no NAA depression, slightly increased Cho peak and the Cr peak was slightly decreased, MI was also increased. In benign cystic mass group, we had reliably increased Lip peaks but in 3 cases, H-MRS was inaccurate for showing the details of these lesions, didn't provide adequate information for the diagnosis. The sensitivity of H-MRS was about 40% and 27% specificity for this group.

When we make a comparison between cranial masses and all the other non-neoplastic brain disorders; Cho/Cr- Cho / MI and Cho/NAA ratios were far more higher in brain masses than the other non-neoplastic groups but at the same time, NAA/Cr ratio was lower in brain tumours, higher in demyelinating group (Table III). With variance parametrical analysis test, there was a significant statistical difference between brain masses and the other non-neoplastic brain disorders for all ratios ($p < 0.05$).

When we briefly looked at the other metabolites for all neoplastic and non-neoplastic groups; Dominant metabolite for ischemic lesions, was the Lac and also highly seen in high-grade glial tumours and GBM group. Lip was seen in all brain masses except for the low-grade gliomas and might be the dominant metabolite in the high-grade glial tumour group, was also consistent in the ischemic lesions. According to Lac and Lip peaks by using chi-square test; There was a significant statistical differences between ischemic lesions, high grade glial tumours and the GBM group ($p < 0.05$). The others presented non significant statistical differences under $p > 0.05$. In demyelinating and the low-grade group; We had reliably increased MI peaks, low-grade tumours and the metabolic disease group showed a high Glx peak. According to MI and Glx peaks by using chi-square test, there was a significant statistical differences between demyelinating lesions, low-grade tumours and the metabolic disease group ($p < 0.05$). The other groups in this research presented non-significant statistical differences for MI and Glx peaks ($p > 0.05$).

## Discussion

H-MRS has a potential for definite diagnosis without surgical tissue sampling, also serves a significant role before neurosurgical planning, it has the non-invasive potential to

*Table III. — Metabolite ratios in brain lesions.*

| | | N | Mean | Std. deviation | F | p |
|---|---|---|---|---|---|---|
| Cho/NAA Ratio | Brain Masses | 33 | 2,84 | 2,35 | 7,132 | 0,000* |
| | Demyelinating | 5 | 0,59 | 0,17 | | |
| | Ischemia | 18 | 0,40 | 0,23 | | |
| | Methabolic | 1 | 0,89 | . | | |
| | Benign cystic masses | 5 | 0,34 | 0,15 | | |
| Cho/Cre Ratio | Brain Masses | 33 | 2,42 | 1,28 | 10,227 | 0,000* |
| | Demyelinating | 5 | 1,75 | 1,05 | | |
| | Ischemia | 18 | 0,58 | 0,37 | | |
| | Methabolic | 1 | 0,68 | . | | |
| | Benign cystic masses | 5 | 1,04 | 0,51 | | |
| Cho/MI Ratio | Brain Masses | 33 | 3,51 | 3,21 | 3,312 | 0,017* |
| | Demyelinating | 5 | 0,78 | 0,30 | | |
| | Ischemia | 18 | 1,37 | 1,23 | | |
| | Methabolic | 1 | 1,05 | . | | |
| | Benign cystic masses | 5 | 1,10 | 0,76 | | |
| NAA/Cr Ratio | Brain Masses | 33 | 0,97 | 0,42 | 13,518 | 0,000* |
| | Demyelinating | 5 | 2,72 | 0,91 | | |
| | Ischemia | 18 | 1,96 | 0,80 | | |
| | Methabolic | 1 | 2,23 | . | | |
| | Benign cystic masses | 5 | 2,69 | 1,51 | | |

*p < 0.05.

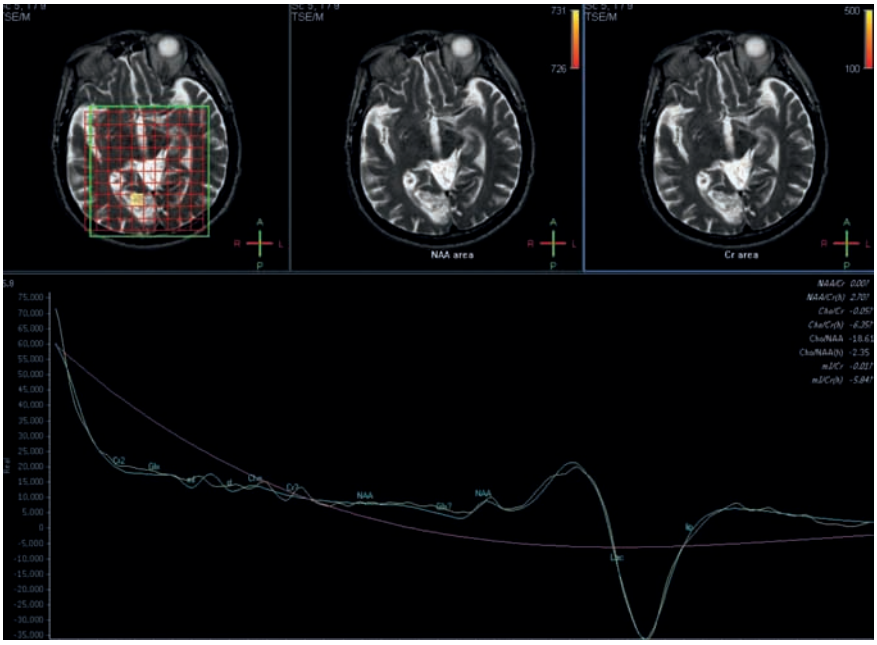


*Fig. 4.* — Metabolite peaks in ischemic brain lesion.

provide additional metabolic information to improve pre-surgical diagnosis, disease extension and direct anatomical replacement of surgical biopsy if needed (2, 4, 10). MRSI can also help to identify the tumour type and grade, grading of brain tumour and histopathologic classification of brain lesions which has important implications for clinical management (9, 11, 12). In our study, we find out that MRSI can be used for differentiation of malignant brain masses from the non-neoplastic ones. It can be acquired as an additional pulse sequence and contribute to a multimodality research of morphological and metabolic information, MVS also provides wider anatomical coverage and better spatial resolution, for the assessment of lesion heterogeneity (1, 2, 7, 10). In MRSI; Resonances of brain metabolites as mentioned above, are briefly analysed for correct diagnosis of brain disorders especially for tumours and non-neoplastic lesions. NAA is a marker of functional neurons and decreases in all kinds of brain damages whether infiltrative, degenerative or destructive processes (3, 5, 8, 11-13). Cho resonances increase in all brain tumours, acute MS plaques and tuberculous abcesses due to increased cell membrane synthesis and turnover, reflect the abnormal processes like proliferating tumoral cells and active demyelinating plaques (1-3, 7, 11, 13). Cr-PhosphoCr are ubiquitous metabolites of ATP/ADP cycle, therefore Cr is considered to be an indicator of energy metabolism, generally increased in chronic MS plaques, decreased in acute MS and in glial tumours, brain tumours generally show decreased Cr levels (1-3, 6-8, 11-14). Lac is produced in anaerobic glycolysis; is more prominent in high grade tumours, ischemic diseases and acute infarction, Lip usually correlates to the extent of tissue necrosis, only observed in short TE acquisition because of its short relaxation time, generally seen in high-grade neoplasms, metastasis,

*Table IV. — Metabolite ratios in non malignant brain lesions.*

| Measurement | Groups | N | Mean | Std.deviation | F | Sig. |
|---|---|---|---|---|---|---|
| NAA/Crea | Ischemia | 16 | 1,89 | 0,81 | 1,423 | 0,262 |
| | Demyelinating | 5 | 2,72 | 0,92 | | |
| | Metabolic | 1 | 2,23 | . | | |
| | Benign cystic masses | 5 | 2,69 | 1,51 | | |
| | Sum | 27 | 2,20 | 1,01 | | |
| Cho/NAA | Ischemia | 16 | 0,41 | 0,22 | 3,239 | 0,041* |
| | Demyelinating | 5 | 0,59 | 0,17 | | |
| | Metabolic | 1 | 0,89 | . | | |
| | Benign cystic masses | 5 | 0,34 | 0,15 | | |
| | Sum | 27 | 0,45 | 0,22 | | |
| Cho/Crea | Ischemia | 16 | 0,54 | 0,37 | 5,924 | 0,004* |
| | Demyelinating | 5 | 1,75 | 1,05 | | |
| | Metabolic | 1 | 0,68 | . | | |
| | Benign cystic masses | 5 | 1,04 | 0,51 | | |
| | Sum | 27 | 0,86 | 0,71 | | |
| CHO/MI | Ischemia | 18 | 1,37 | 1,23 | 0,419 | 0,741 |
| | Demyelinating | 5 | 0,78 | 0,30 | | |
| | Metabolic | 1 | 1,05 | . | | |
| | Benign cystic masses | 5 | 1,10 | 0,76 | | |
| | Sum | 29 | 1,21 | 1,03 | | |

*p < 0.05.

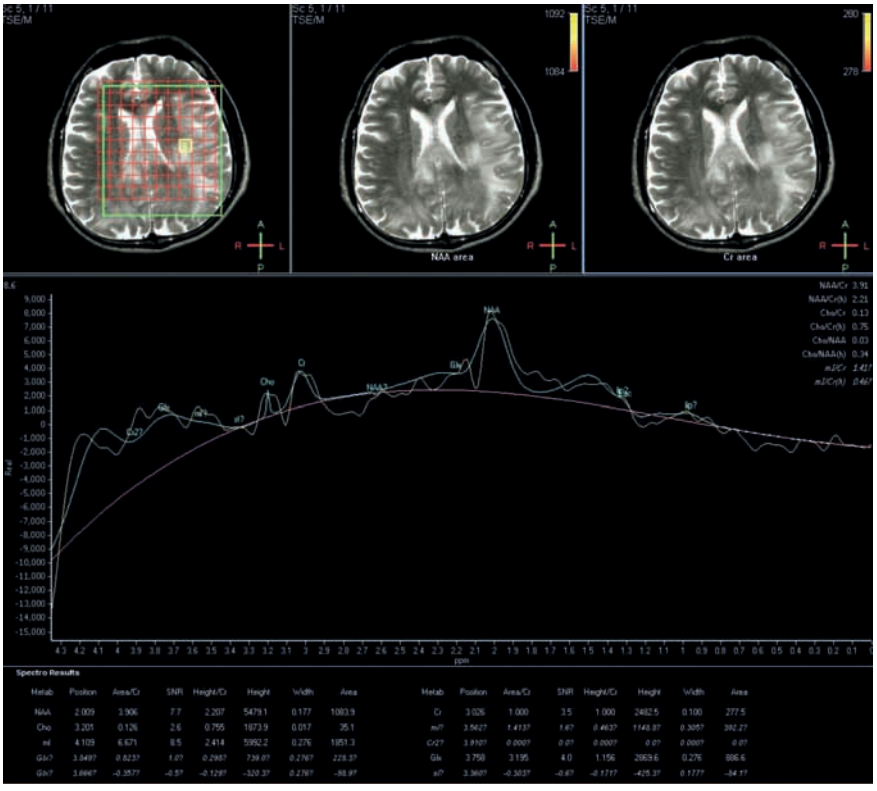


*Fig. 5.* — Metabolite peaks in demyelinating disorders (MS).

acute MS plaques and brain abscesses, Lip-Lac metabolites routinely were undetectable in healthy brain (1-3, 7 , 10, 12-14). Glx is a neurotransmitter, generally increased in Wilson disease, Ala peak is generally shown in meningiomas and involves in partial oxidation (8, 13), but in our cases; we had no precise Ala peaks. With the further advancement of MRI technology; new commercial or free software packages may improve the quality of MRS data by increasing the absolute quantification of metabolites or quantification by fitting against the metabolite data bases.

In the literature, there were several former studies trying to analyze the efficacy of MRSI in brain tumours and most of the authors used Cho/NAA, Cho/Cr ratios to differentiate brain tumours from non-neoplastic disorders (2-4, 9, 12). There was a general concordance in previous studies that Cho was the best index for grading cerebral gliomas and its peak reliably increased from low-grade to GBM group (2-4, 9, 12, 15). In this research, we had also similar results. For GBM group, the Cho peak was extremely high. The second best discriminator between low-grade glial tumours and malignant gliomas was the amount of lipids while changes of Cr and NAA peaks were less helpful for the analysis of potential malignancy of cerebral tumours (2-4, 12). In addition to high-grade gliomas, metastases were also assumed to have extremely increased Cho, significantly reduced NAA and Cr (2-4, 9, 15). Besides the similar results to the literature, our metastases group had high lip peak.

In the benign cystic cranial masses of non-neoplastic group, we had also strong lipid resonances.

MR-Spectroscopy has also an important diagnostic role, especially when it reveals reduced NAA without increased Cho, in these instances MRS findings may spare the patient from biopsy (4, 16, 17). Cho/NAA, Cho/Cr ratios were the valuable tools for determining the malignancy of cranial neoplasms, used by most of the authors (3-5, 9-12, 15). In most of the former studies, both ratios increased from low-grade to high-grade gliomas, also extremely higher in metastases and Primitive neuroectodermal tumours (PNET) (3, 5, 8, 9, 11, 15). In this research, Cho/Cr ratio more than 2.5 was presented as malignant ($p < 0.05$) . We had no PNET type tumour but both ratios were similarly increased in low-high grade glial tumours and in metastases. In our study, the lowest Cho/Cr ratio among the other brain masses was presented in meningiomas. In this group, we had strong elevation of Cho resonance but contrary to literature, there was no precise Cr decrease and Cho/Cr ratio was the lowest in meningiomas, we didn't see any Ala resonance for both meningiomas.

We tried to make another variation by using Cho/MI ratio in order to categorize tumours according to their potential malignancy and tried to differentiate malignant cranial masses from non-neoplastic disorders which were not frequently seen in the past former studies. Among these masses; Cho/MI ratio was the highest in GBM and lowest in Low-grade glial tumours. It was also extremely high in higher-grade gliomas and metastasis groups. In cranial mass groups; We had an average Cho/MI ratio about 3.51, therefore we could easily conclude that increased ratio was strongly related with malignancy of the tumours. In non-neoplastic group; The highest Cho/MI ratio was in ischemic group, about 1.37. With these datas, one could easily conclude that Cho/MI ratio more than 3 was most likely to be malignant rather than benign ($p < 0.05$). In our research, Cho/MI ratio was really a diagnostic tool for grading gliomas, categorizing the tumours according to their malignancy rates and differentiation from non-neoplastic lesions.

The primary results of our study presented that MR-Spectroscopy had a good sensitivity and specificity among the non-neoplastic brain disorders except for the cystic cranial masses, Perfusion MR and Diffusion Weighted MR imaging could also be added to MRS findings in order to get more beneficial results (2, 4, 7, 10, 16). When we look at the literature; Elevated Cho levels and reduced NAA levels had been reported in acute MS plaques and had been explained by reactive astrogliosis, inflammation and early axonal degeneration, MI at short TE was also a discriminating metabolite for the acute MS and also increased in cases of glial activation or gliosis, represented dominancy in low-grade astrocytomas related to abnormal astrocyte proliferation, nevertheless might also be seen in Encephalitis, Dementia, Epilepsy and SSPE-PML like brain disorders (1, 7, 10, 13, 14), but in high grade gliomas, metastases and more malignant tumours, its peak sharply declined (1, 2, 4, 15, 17). In our study, we had also elevated MI peaks in non-neoplastic demyelinating group. According to previous studies, there was no significant difference in the level of Cr among the non-neoplastic brain lesions (1, 4, 17). In our series, Cr peak was strongly decreased in demyelinating group. Infarctions as mentioned in the literature show increased Lac, progressive Cho reduction in the chronic phase and also increased NAA peak especially in acute and subacute phases (1, 7, 10). In our ischemic group, Lac was also the dominant metabolite. Glx peak was the highest in the metabolic group. In the non-neoplastic group, Cho peak was highest in metabolic group and Cr was strongly decreased at the demyelinating group. NAA/Cr ratio was also higher in demyelinating group. In the differentiation of low-grade group from the non-neoplastic disorders; Most of the authors considered the Cho peak and Cho/NAA, Cho/Cr ratios as the reference standards, they mostly made the discrimination by the elevated Cho/NAA, Cho/Cr ratios and high Cho peak in the selected voxels (2-4, 9, 12, 13). In our paper with correspondence to these ratios, low-grade group had significantly higher results than the non-neoplastic brain lesions as seen in the former studies, at the same time we also used the Cho/MI ratio for the differentiation of both groups and although this ratio was lowest in low-grade group through the other neoplastic mass groups, was certainly higher than the non-neoplastic group.

In the previous researches, evaluation of non-neoplastic brain disorders and differentiation of them from the brain tumours based on the NAA/Cr, Cho/ NAA ratios (1, 2, 4, 7, 10). NAA/Cr ratio more than 2 was presented as non-malignant ($p < 0.05$) and elevated NAA/Cr ratio was highly specific for the demyelinating diseases (2, 4, 7, 17). In our experience; NAA/Cr ratio was the highest in demyelinating group and the lowest in brain masses. Cho/NAA ratio above 1.5 was assumed to be malignant in the previous former studies (2-6, 13, 15). In our paper, the non-neoplastic group had precisely lower Cho/NAA ratio than the cranial mass groups. To our belief, Cho/NAA ratio above 2 mostly focused to malignancy ($p < 0.05$). Some cases of demyelinating lesions were presented as mimicking high-grade gliomas because of histopathologic similarities which include hypercellularity-reactive astrocytes-mitotic and necrotic areas (1, 4, 17), we didn't have such misclassified cases in our report. As a whole; This study provided that increased Cho/NAA, Cho/MI and Cho/Cr ratios with decreased NAA/Cr ratio should easily be used in the differentiation of malignant ones from the non-neoplastic brain lesions and could aid to the relevant literature with this aspect.

## Conclusion

As a summary, a brain lesion with higher Cho/NAA, Cho/Cr and Cho/MI ratio plus lower NAA/Cr ratio was most likely to be malignant. Additionally, lip and lac peaks were also frequently seen in more malignant lesions. A higher MI peak generally presented low-grade malignancy or a non-neoplastic disorder especially demyelinating lesions.

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