



## MAGNETIC RESONANCE IMAGING AND PROTON MR SPECTROSCOPY IN THE DIFFERENTIAL DIAGNOSIS OF INTRACRANIAL BRAIN TUMORS

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### Abstract.

**Background.** Magnetic resonance imaging (MRI) is the primary modality for structural assessment of intracranial tumors; however, conventional MRI sequences do not always allow reliable differentiation between neoplastic and non-neoplastic lesions or accurate grading of tumor malignancy. Proton magnetic resonance spectroscopy ( $^1\text{H}$ -MRS) provides additional metabolic information that significantly enhances diagnostic accuracy.

**Objective.** To analyze the diagnostic value of conventional MRI combined with proton MR spectroscopy in the differentiation of intracranial tumors and non-tumor brain lesions, as well as in the assessment of tumor histological type and malignancy grade.

**Materials and Methods.** A narrative review of international and regional literature focusing on MRI pulse sequences, technical aspects of single-voxel and multivoxel  $^1\text{H}$ -MRS, metabolite profiles, and metabolite ratio analysis in intracranial tumors.

**Results.** Characteristic metabolic patterns of intracranial tumors include decreased N-acetylaspartate (NAA), increased choline (Cho), reduced creatinine (Cr), and elevated lactate and lipid peaks depending on tumor malignancy.  $^1\text{H}$ -MRS demonstrates high sensitivity and specificity in differentiating tumors from non-tumor lesions and provides valuable information for distinguishing gliomas, metastases, meningiomas, abscesses, and lymphomas.

**Conclusion.** The integration of proton MR spectroscopy with conventional MRI significantly improves the accuracy of differential diagnosis of intracranial lesions and plays an important role in preoperative planning and treatment strategy selection.

**Key words:** Magnetic resonance imaging; Proton MR spectroscopy; Brain tumors; Differential diagnosis; Metabolite ratios; Glioma.

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## МАГНИТНО-РЕЗОНАНСНАЯ ТОМОГРАФИЯ И ПРОТОННАЯ МР-СПЕКТРОСКОПИЯ В ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКЕ ВНУТРИЧЕРЕПНЫХ ОПУХОЛЕЙ ГОЛОВНОГО МОЗГА

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### Аннотация.

**Актуальность.** Магнитно-резонансная томография является ведущим методом диагностики опухолей головного мозга, однако стандартные МР-последовательности не всегда позволяют достоверно дифференцировать опухолевые и неопухолевые процессы, а также определить степень злокачественности новообразований. Протонная МР-спектроскопия предоставляет дополнительную информацию о метаболическом состоянии тканей.

**Цель.** Оценить диагностическую значимость сочетанного применения МРТ и протонной МР-спектроскопии при дифференциальной диагностике внутричерепных опухолей и неопухолевых поражений головного мозга.

**Материалы и методы.** Проведен обзор современных отечественных и зарубежных публикаций, посвященных методикам МРТ и  $^1\text{H}$ -МРС, анализу метаболитов и их соотношений при различных внутричерепных поражениях.

**Результаты.** Для опухолей характерны снижение NAA, повышение Cho, уменьшение Cr, а также появление пиков лактата и липидов.  $^1\text{H}$ -МРС позволяет с высокой точностью дифференцировать опухолевые и неопухолевые процессы и уточнять гистологическую природу опухолей.

**Заключение.** Комплексное применение МРТ и протонной МР-спектроскопии повышает диагностическую точность и способствует оптимизации тактики лечения пациентов с опухолями головного мозга.

**Ключевые слова:** Магнитно-резонансная томография; Протонная МР-спектроскопия; Опухоли головного мозга; Дифференциальная диагностика; Метаболиты; Глиомы.

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## BOSH MIYA ICHKI O'SMALARINI DIFFERENSIAL DIAGNOSTIKA QILISHDA MAGNIT-REZONANS TOMOGRAFIYA VA PROTON MR-SPEKTROSKOPIYA

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### Annotatsiya.

**Dolzarbli.** Magnit-rezonans tomografiya bosh miya o'smalarini aniqlashda asosiy usul hisoblanadi, biroq standart MRT tasvirlari har doim ham o'sma va noo'sma jarayonlarni aniq farqlash imkonini bermaydi. Proton MR-spektroskopiya miya to'qimalarining metabolik holatini baholash imkonini beradi.

**Maqsad.** Bosh miya ichki o'smalarini differensial diagnostika qilishda MRT va proton MR-spektroskopiyaning diagnostik ahamiyatini baholash.

**Material va usullar.** Zamonaviy ilmiy adabiyotlar asosida MRT va  $^1\text{H}$ -MRS metodlari, metabolit spektrlari va ularning diagnostik mezonlari tahlil qilindi.

**Natijalar.** O'smalarda NAA kamayishi, Cho oshishi, Cr pasayishi hamda laktat va lipid piklarining paydo bo'lishi aniqlanadi.  $^1\text{H}$ -MRS yordamida o'smalar va noo'sma jarayonlarni yuqori aniqlikda farqlash mumkin.

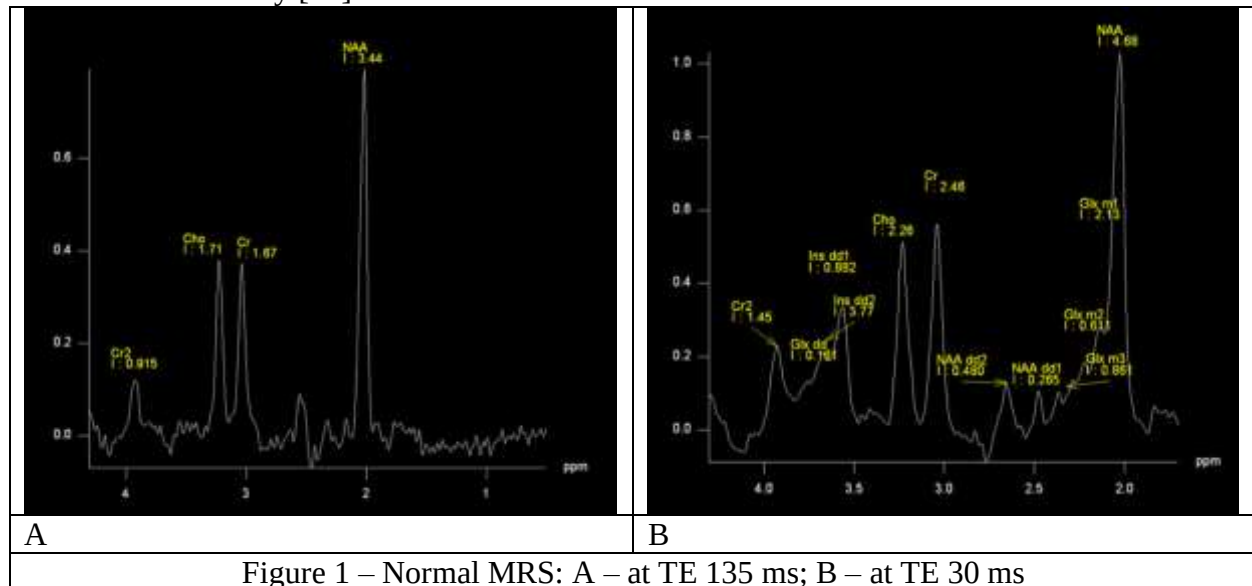
**Xulosa.** MRT va proton MR-spektroskopiya birgalikda qo'llash bosh miya o'smalarini diagnostika qilishda muhim ahamiyatga ega.

**Kalit so'zlar:** Magnit-rezonans tomografiya; Proton MR-spektroskopiya; Bosh miya o'smalari; Differensial diagnostika; Metabolitlar; Glioma

**Introduction.** Magnetic resonance imaging (MRI) is a highly informative imaging technique for brain tumors. An MRI examination consists of a series of pulse sequences (image series) in the transverse, sagittal, and coronal planes. The following pulse sequences are typically used for brain tumor imaging. T2-weighted images in the transverse plane with a slice thickness of 3 mm allow for good anatomical detail visualization of the tumor, its necrosis, and perifocal edema, as well as assessment of the condition (compression or dilation) of the ventricles and subarachnoid spaces. T2-weighted images in the coronal (frontal) plane with a slice thickness of 3 mm provide a better understanding of the displacement of midline structures in the event of mass effect, as well as the relationship of the tumor to the basal ganglia and corpus callosum, which is important for surgical planning. T1-weighted images in the transverse plane with a slice thickness of 5 mm supplement the obtained information on the tissue characteristics of the tumor and allow detection of hemorrhagic components. However, their primary value lies in subsequent comparison with post-

contrast T1-weighted images. In this case, the pre-contrast T1 series is copied unchanged (with the same slice positions and thicknesses) for examination with a contrast agent. This subsequently allows for simultaneous viewing of both series and reliably assessing the presence of even minimal contrast enhancement in the pathological lesion. We also perform post-contrast T1-weighted images in the coronal and sagittal planes, which allows for a three-dimensional assessment of the tumor's relationship with surrounding structures. In some cases, the pre-contrast examination may be supplemented with sagittal T2 and/or T1-weighted images, as well as a FLAIR series. The latter is particularly sensitive to areas of edema and leukoaraiosis. The described pulse sequences provide an excellent idea of the anatomical features of the brain and a fairly complete picture of the tumor structure. At the same time, information on the metabolic and functional activity of the brain, which can be obtained, for example, using positron emission tomography, is becoming increasingly important. New MRI techniques (functional, diffusion, perfusion MRI, MR spectroscopy) also largely fill this gap. The method of MR spectroscopy (MRS) has long been used to determine the chemical composition of fluids in vitro, tissue samples and cellular systems of animals and humans outside the body. In 1989, Frahm J. et al. published the first results of in vivo magnetic resonance spectroscopy, describing the methodology for detecting and measuring metabolite concentrations in the human brain [1,2]. The first publications on the use of MRS in brain tumors date back to the same period [3,4]. Currently, MRS is considered as an adjunct to structural MR imaging. By comparing the relative concentrations of metabolites in the studied areas of the brain, it is possible to assess the viability and energy metabolism of nervous tissue, proliferation and destruction of cell membranes, necrotic transformation of the brain and tumors. The main attention is paid to proton MRS ( $^1\text{H}$ -MRS), since hydrogen is the most abundant element in the human body, and its nucleus emits a strong radiofrequency signal in an external magnetic field. Less commonly used is MRS based on the nuclei of carbon  $^{13}\text{C}$  and phosphorus  $^{31}\text{P}$ , which are characterized by lower magnetic sensitivity, and the  $^{13}\text{C}$  nucleus is also less abundant. This leads to insufficient spatial resolution of MRS based on  $^{13}\text{C}$  and  $^{31}\text{P}$  in focal lesions in the brain [5]. Instead of the usual "anatomical" MR images, an MR spectrogram is a graph of peaks corresponding to individual metabolites. The conditions for detecting metabolites in the  $^1\text{H}$  spectrum are: the presence of hydrogen protons in their composition; the concentration of the metabolite must exceed a certain minimum level ( $\geq 0.5$  mmol/L); metabolites must resonate at different frequencies (the so-called chemical shift phenomenon); effective suppression of the signal from water [6]. The specific position of the signal from the metabolite on the horizontal axis is a constant value inherent to a given metabolite. It is determined by its chemical shift and is characterized by the value of "parts per million" (ppm). This implies that the hydrogen protons are in a specific environment within the metabolite, leading to a change in the local magnetic field and, consequently, the frequency at which these protons resonate in the external magnetic field  $B_0$ . This is essentially the phenomenon of chemical shift. The change in the local magnetic field is very small (amounting to parts per million) relative to  $B_0$  [7]. 5 mmol/L); metabolites must resonate at different frequencies (the so-called chemical shift phenomenon); effective suppression of the signal from water [6]. The specific position of the signal from the metabolite on the horizontal axis is a constant value inherent to a given metabolite. It is determined by its chemical shift and is characterized by the value of "parts per million" (ppm). This implies that hydrogen protons are in a specific environment within the metabolite, leading to a change in the local magnetic field and, consequently, the frequency at which these protons resonate in the external magnetic field  $B_0$ . This is essentially the phenomenon of chemical shift. The change in the local magnetic field is very small (amounting to parts per million) relative to  $B_0$  [7].

Similar to standard MR pulse sequences, the amount of information obtained in MRS depends on the repetition time (TR) and echo time (TE), since each metabolite has its own T1 and T2 relaxation times. TE can vary from 18 to 288 ms. With long TEs (120-288 ms), fewer metabolites can be isolated, but their peaks are more clearly defined, namely: N-acetyl aspartate (NAA), creatinine (Cr), choline (Cho), lactate (Lac) (Figure 1A). With short TEs (18-45 ms), additional metabolites can be isolated – glutamine and glutamate (Glx), myo-inositol (ml), the lipid peak (lip) is more pronounced (Figure 1B) [8,9]. Since short TEs release more metabolites, peak overlap is more likely, which can complicate spectral interpretation. Long TEs are more commonly used in brain tumors. According to a "Systematic Review of the Literature on the Use of MR Spectroscopy for Brain Tumor Characterization" published in August 2006, long TEs were used in 15 of 22 studies, short TEs were used in 4 studies, both long and short TEs were used in 2 studies, and a nonstandard TE of 65 ms was used in one study [10].



H-MRC can be implemented in two versions: single-voxel and multi-voxel spectroscopy. Single-voxel spectroscopy (SVS) is the most common. It obtains a spectrum from a cubic region (voxel) of brain or tumor tissue measuring 2x2x2 cm (8 cm<sup>3</sup>), which takes 3 to 5 min. In some cases, it is desirable to reduce the voxel size so that the measurement is performed specifically in the tumor without including surrounding tissue. An undesirable consequence of this is a decrease in the signal-noise ratio. The advantage of single-voxel spectroscopy is obtaining higher-quality spectra with fewer post-processing steps. The main disadvantage is the limited study area, which is why correct voxel placement is critical. Blood and its products, air, cerebrospinal fluid, fat, necrosis, bone, calcifications, and metal should not be included in the study area. All these media lead to inhomogeneity of the local magnetic field and the formation of non-diagnostic spectra [6]. The voxel position should correspond to the most viable areas of the tumor, which, in contrast to necrosis, usually accumulate contrast agent (except for grade I and II gliomas). Ricci PE et. al. [11] draw attention to the importance of voxel placement on the periphery of the contrast-enhanced zone. Multivoxel spectroscopy, also called chemical shift imaging (CSI) or spectroscopic imaging, allows for the placement of multiple voxels in the area of interest and can be implemented in two-dimensional and three-dimensional space. Multivoxel spectroscopy is the preferred method for examining intracranial tumors. Its advantage over single-voxel spectroscopy is the superposition of color maps of metabolites or their ratios over a sufficiently large area of the brain, including not only the tumor area but also the opposite hemisphere, which enables direct comparison of the tumor and unaltered areas of the brain. The technical implementation of multivoxel spectroscopy is more complex, since it requires maintaining magnetic field homogeneity over a much larger area. In the posterior cranial fossa, due to its reduced volume and proximity to bone structures, it is often easier to obtain high-quality spectra using single-voxel spectroscopy [6]. Due to the complexity of shimming (equalizing the magnetic field homogeneity), long acquisition time (from 8 to 19 min), and a multi-step information processing process, multivoxel spectroscopy was until recently

available only in specialized centers [11]. Multivoxel spectroscopy was used in only five of 22 studies published in 2002-2004 [10].

**MAIN METABOLITES. IN 1 H-MR SPECTROSCOPY** [6,9] N-Acetyl aspartate (NAA) is a neuronal marker. It is present in neuronal cell bodies and axons and indicates their viability. Under physiological conditions, NAA gradually increases in newborns and decreases in the elderly. In pathological conditions, decreased NAA levels indicate neuronal loss, which occurs in gliomas, ischemia, and degenerative brain diseases. NAA peaks are located at 2.02 ppm, 2.5 ppm, and 2.6 ppm. Creatinine (Cr) is a marker of aerobic metabolism of brain cells. The concentration is higher in gray matter than in white matter. It has the most constant peak, independent of oxygenation and perfusion levels, and is therefore used as an "internal standard" for calculating metabolite concentration ratios. It decreases in tumors, infections, hypoxia, and stroke. Peaks are at 3.02 ppm and 3.94 ppm. Choline (Cho) is a component of phospholipid metabolism and a marker of cell membranes, reflecting cell proliferation. An increase in Cho levels is associated with increased membrane synthesis and cell proliferation (brain tumors). Decreases with abscesses and necrosis. Peak at 3.22 ppm. Lactate (Lac) is the end product of anaerobic glycolysis and a hypoxia marker. In healthy volunteers, lactate concentrations are at the detection limit of the method, meaning they are usually undetectable in the spectra. They increase with ischemia and tumors. The double lactate peak is at 1.33 ppm, with an inverted peak (out of phase) at TE 135 ms and an upward peak (in phase) at TE 30 ms. Lipids (lip) are an indicator of necrosis and destruction of myelin sheaths. They are usually undetectable in healthy volunteers and increase with tumors, necrosis, abscesses, and demyelination. Peaks at 0.8 ppm and 1.3 ppm. The signal from lipids is best detected at low TE values (less than 35 ms) and decreases at higher values. Since Lac and lip resonate at the same frequency (1.3 ppm), their peaks may be indistinguishable if both metabolites are present in the region of interest. To isolate the Lac peak, it is recommended to pay attention to the following points: Lac has a double peak; at TE of about 135 ms, the Lac peak is inverted; when using high TE values (270 ms), the signal from lip is suppressed and only the signal from Lac remains [6]. Myo-inositol (ml) is a myelin degradation product. It increases in multiple sclerosis and decreases in tumors. Peaks are at 3.56 ppm and 4.06 ppm. Glutamine and glutamate (Glx) are an astrocyte marker and a neurotoxin, respectively. They increase in encephalopathy. Peaks are at 2.1 ppm and 2.55 ppm. Alanine has a double peak at 1.48 ppm. Similar to lactate, the alanine peak is inverted at TE 135 msec and upward at TE 30 msec. To interpret MR spectra, it is necessary to quantify the metabolites and compare the obtained values with normal values. For quantitative characterization, the height (amplitude) of the peaks and the area under them (integral) can be measured. The integral is more commonly used, since the area under individual peaks is proportional to the concentration of each metabolite. Furthermore, the integral is independent of magnetic field inhomogeneity and is less sensitive to noise. The magnitude of the MR signal is not expressed in absolute values, as it is influenced by many local and external conditions. Therefore, in MRS, it is common to calculate the ratios of peak integrals to each other. Specifically, in a multicentric study conducted by Siemens, the ratios of metabolite integrals in the occipital lobe of 156 healthy volunteers were: NAA/Cho  $2.73 \pm 0.59$ , NAA/Cr  $2.20 \pm 0.41$ , Cho/Cr  $0.82 \pm 0.16$  (manufacturer's information). In practice, with single-voxel spectroscopy, after measuring the spectrum in a tumor, it is advisable to obtain a spectrum from a symmetrical region of the opposite hemisphere of the same patient and compare the two spectra.

**DIFFERENTIATION OF TUMOR AND NON-TUMOR DISEASES.** In non-oncological practice, 1 H-MRC was used in diagnostics and prognosis of ischemic (Figure 2) [12] and traumatic [13] brain lesions, abscesses [14], demyelinating diseases, including multiple sclerosis [15], focal lesions in the brain in AIDS [16], in the diagnosis of dementia [17], epilepsy [18], neonatal encephalopathy [19], and hepatic encephalopathy [20].



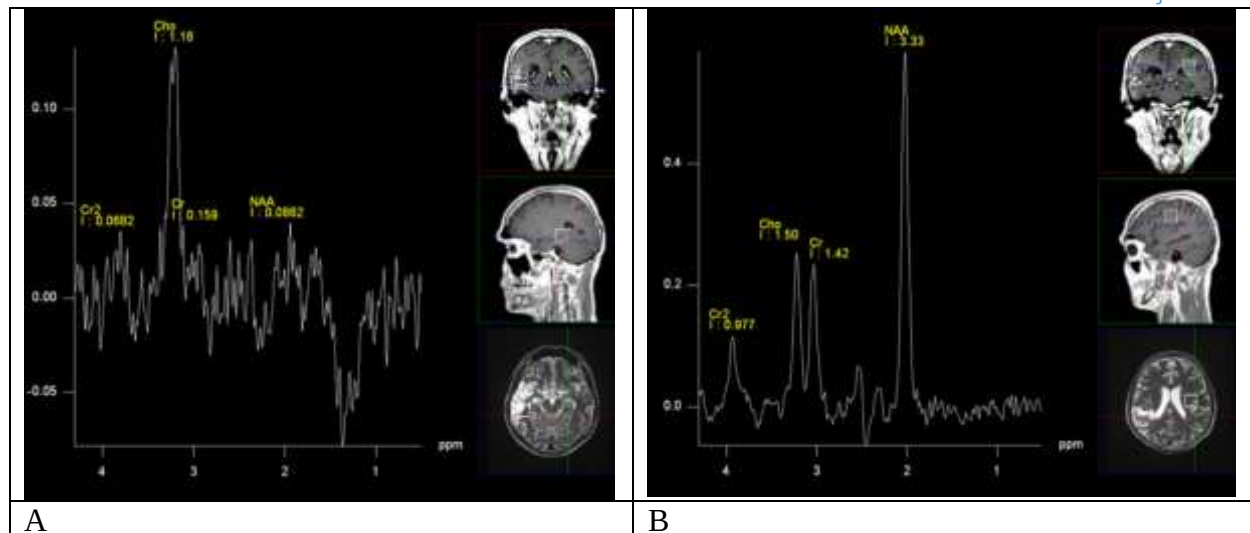


Figure 2 – MRS in ischemic stroke: A – in the infarction zone, Cho is slightly reduced, Cr (a marker of energy metabolism) and NNA (a neuronal marker) are sharply reduced, Lac (a marker of hypoxia) is significantly increased; B – a spectrum from the opposite hemisphere for comparison

MRS allows differentiating tumor and non-tumor formations in the brain, which have the same visualization features in a standard MR examination, with an accuracy of 95-100%. MR spectra of tumors depend on their histological nature and degree of malignancy. Characteristic signs of intracranial tumors are [5,6]:

- A decrease in the NAA peak and the NAA/Cr ratio, which reflects a decrease in the number of neurons. With a normal NAA value, data for a tumor are questionable. Exceptions are low-grade gliomas, for which the spectrum may be close to that of normal brain matter, as well as cases where the formation is significantly smaller than the voxel size and NAA is artificially increased due to the inclusion of surrounding areas of the brain.
- A decrease in the Cr peak due to the increased energy requirements of the tumor.
- An increase in the Cho peak and the Cho/NAA, Cho/Cr ratios. Choline is the main metabolite of interest in tumors. An increase in its level reflects the increased cell density as a consequence of their proliferation. An increase in the Cho level is characteristic of gliomas of grades II and III malignancy and may be less high in glioblastomas due to the prevalence of necrosis in them.
- The Lac peak is higher, the higher the degree of tumor malignancy. At the same time, Lac is found in almost all tumors in children.
- The presence of a lip peak is a sign of necrosis in tumors, but is also determined in abscesses and demyelinating diseases (a sign of destruction of the sheaths of myelin fibers).

Rand et al. [21] determined the diagnostic capabilities of single-voxel  $^1\text{H}$ -MRS in 53 patients with 42 tumors and 13 non-neoplastic processes in the brain. When studying only MR spectrograms, the sensitivity, specificity and accuracy of the method for dividing formations into tumor and non-tumor were 85%, 74% and 83%, respectively. When clinical information and imaging results were available at the time of studying the MR spectra, the sensitivity, specificity, and accuracy reached 95%, 100%, and 96%. Butzen J et al. [22] used a Cho/NAA ratio of more than 1 as a criterion for separating tumor and non-tumor diseases of the brain. The sensitivity and specificity when studying 99 spectra were 79% and 77%, respectively. Moller-Hartmann W. et al. [23] analyzed the MR spectra of 164 patients who were subsequently verified to have low-grade astrocytoma (23 patients), anaplastic astrocytoma (28), glioblastoma (39), PNET or medulloblastoma (4), metastases (18), meningioma (9), neurinoma (9), abscess (25), and cerebral infarction (9). In non-neoplastic diseases (abscess, infarction), decreased peaks of three major metabolites (Cho, Cr, and NAA) were observed, while in tumors, an increase in Cho and a decrease in Cr and NAA were observed. In gliomas, a significant increase in Cho was observed, as well as the appearance of lipids with increasing grade of malignancy. Cho was elevated in metastases, as was the case in anaplastic astrocytomas. However, metastases could be differentiated from high-grade gliomas by a higher lipid level. Extra-axial tumors (meningiomas and neurinomas) were characterized by the almost complete disappearance of the neuronal marker NAA. Additional information obtained by MRS increased the rate of correct

diagnoses from 55% to 71%, decreased the rate of incorrect diagnoses from 15% to 9%, and decreased the rate of unclear diagnoses from 30% to 14%. Differentiating abscesses from cystic and necrotic tumors can be difficult due to vague clinical symptoms and similar imaging patterns. At the same time, the  $^1\text{H}$ -MR spectra of tumors and abscesses differ significantly. Abscesses are characterized by the presence of peaks of amino acids (valine, leucine, isoleucine) at 0.9 ppm, lactate at 1.3 ppm, alanine at 1.5 ppm, acetate at 1.9 ppm, succinate at 2.4 ppm, which are the end products of microorganism metabolism. In cystic and necrotic tumors (metastases, glioblastoma), only peaks of lactate and lipids are detected [24].

**DIFFERENTIATION OF HISTOLOGICAL TYPES OF TUMORS.** The largest number of published works on  $^1\text{H}$ -MRS are devoted to the differentiation of histological types of tumors and the degrees of malignancy of gliomas. Differential diagnosis of primary tumors and metastases in the brain is important, since in case of metastases it is necessary to search for the primary tumor first, and the treatment of primary and metastatic tumors in the brain has a number of significant differences. Metastases are characterized by the absence or almost complete absence of NAA and Cr (not neuronal tumors). The study of MR spectra from areas of peritumoral edema helps in differential diagnosis: the Cho/NAA ratio  $> 1$  and an increase in the Cho/Cr ratio are characteristic of highly malignant gliomas. This probably reflects tumor infiltration beyond its visible borders, as opposed to vasogenic edema in metastases [6,25]. The values of the NAA and Cr peaks in meningiomas and neurinomas are practically zero. Meningioma is characterized by a significant increase in Cho, as well as an increase in the alanine peak (Figure 3) [26]. In cystic and necrotic tumors (metastases, glioblastoma), only lactate and lipid peaks are detected [24].

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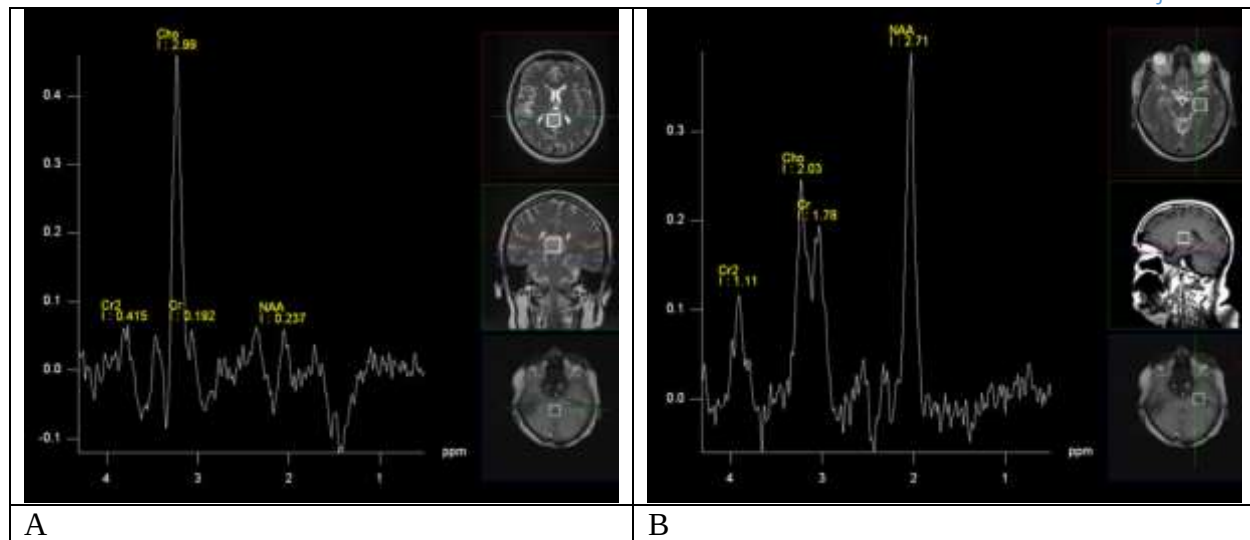


Figure 3 – MRS in meningioma: A – the tumor has an elevated Cho and alanine peak; B – a spectrum from an unchanged area of the brain for comparison

Increased lip in a solid tumor may indicate lymphoma (Figure 4), while increased lip in the necrotic portion of the tumor is characteristic of glioblastoma.

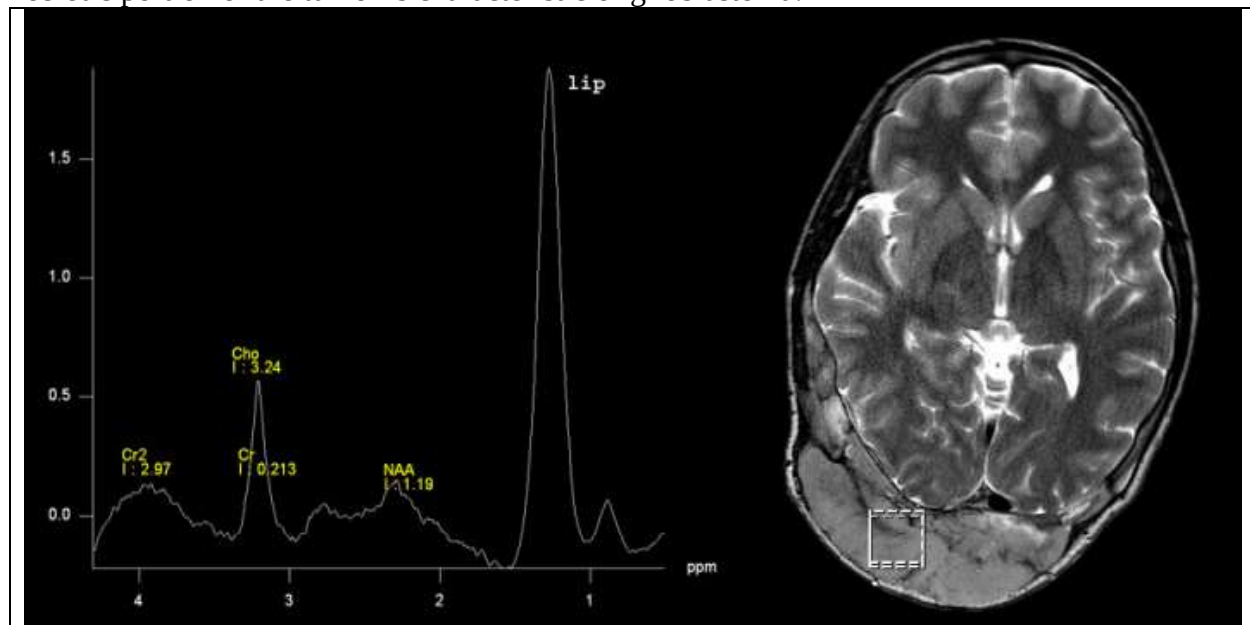


Figure 4 – MRI scan of non-Hodgkin's lymphoma with occipital bone involvement. The tumor has a significantly elevated lipid peak. The MRI image on the right shows the data collection site.

**Conclusion.** Proton magnetic resonance spectroscopy significantly complements conventional MRI by providing metabolic and biochemical information that cannot be obtained from anatomical imaging alone. The characteristic alterations in NAA, choline, creatinine, lactate, and lipid peaks enable reliable differentiation between neoplastic and non-neoplastic intracranial lesions, assessment of tumor malignancy grade, and identification of histological tumor types. The combined use of MRI and  $^1\text{H}$ -MRS enhances diagnostic confidence, supports optimal surgical planning, and contributes to personalized treatment strategies in patients with intracranial brain tumors.

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