Adult Brain Tumors
Clinical Applications of Magnetic Resonance Spectroscopy

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KEYWORDS
- Proton magnetic resonance spectroscopy (H-MRS) • Adult brain tumors • Tumor histology
- Tumor grade • Tumor extension • Tumor progression • Therapeutic response
- Differential diagnosis

KEY POINTS
- Proton magnetic resonance spectroscopy (H-MRS) may be helpful in suggesting tumor histology and tumor grade and may better define tumor extension and the ideal site for biopsy compared with conventional magnetic resonance imaging.
- Combining H-MRS with other advanced imaging techniques such as diffusion-weighted imaging, perfusion-weighted imaging, and permeability maps improves diagnostic accuracy for intraaxial brain tumors.
- Short echo time allows for recognition of more metabolites than long echo time, which is important for differential diagnosis of brain masses and grading tumors.
- Higher choline (Cho) levels and lower myoinositol (Myo)/creatine (Cr) ratio are seen in more malignant tumors compared with lower-grade tumors.
- Lactate is directly related to tumor grade in adult brain tumors. However, lactate is found in essentially all pediatric brain tumors regardless of histologic grade.
- Gliomas are often invasive and show increased Cho levels in surrounding tissues, which may be used to distinguish these lesions from metastases.
- When lipids and lactate are found in a solid lesion, lymphoma should be suggested.
- A prominent lipid peak is seen in lymphomatosis cerebri, whereas a significant increase in Myo is characteristic of gliomatosis cerebri.
- A significant increase in the Cho peak and the presence of lipids and lactate are commonly seen in pilocytic astrocytoma, a grade I tumor.
- Typically, higher levels of Cho occur in grade III gliomas; whereas, in glioblastoma multiforme, the Cho levels may be much lower as a result of necrosis.
- If the Cho/N-acetylaspartate ratio is increased outside the area of enhancement, tumor infiltration can be diagnosed.
- An increase in Cho-containing compounds after radiation therapy may be seen in radiation necrosis misclassified as tumors.
- H-MRS in specific cases improves the accuracy and level of confidence in differentiating neoplastic from nonneoplastic masses.

Funding Sources: None.
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http://dx.doi.org/10.1016/j.nic.2013.03.002
1052-5149/13/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
INTRODUCTION

Localized proton magnetic resonance spectroscopy (H-MRS) of the human brain, first reported more than 20 years ago,1–3 is a mature methodology used clinically worldwide for evaluation of brain tumors.4 H-MRS may help with differential diagnosis, histologic grading, degree of infiltration, tumor recurrence, and response to treatment mainly when radiation necrosis develops and is indistinguishable from tumor by conventional magnetic resonance (MR) imaging.5 Combining H-MRS with other advanced imaging techniques such as diffusion-weighted (DW) imaging, perfusion-weighted (PW) imaging, and permeability maps improves diagnostic accuracy for intraaxial brain tumors.6–8

TECHNIQUE

Short Echo Time Versus Long Echo Time

Different H-MRS parameters may be optimized and 1 of the most relevant is echo time (TE).9 Short TE allows for recognition of more metabolites than long TE, which is important for differential diagnosis of brain masses and grading tumors. For example, myoinositol (Myo), a marker for low-grade gliomas, is only seen on short TE acquisitions.5

Multivoxel MRS Versus Single-Voxel MRS

A key consideration for brain tumor evaluations is their metabolic inhomogeneity. Multivoxel (MV) techniques, also called chemical shift imaging (CSI),10 simultaneously record spectra from multiple regions and therefore map the spatial distribution of metabolites.11 MV H-MRS provides smaller volumes of interest compared with single-voxel (SV), avoiding sampling error. For these reasons, high-resolution MV MRS such as MRS imaging is often favored for evaluating brain tumors.5,12 Nevertheless, SV H-MRS has some advantages compared with MV techniques.13 SV H-MRS is quicker and easier to obtain in standard clinical settings, providing the opportunity to obtain more than 1 spectrum (ie, spectra at 2 different TEs) in a reasonable amount of time. Evaluating spectra at both short and long TE improves the level of accuracy in differentiating focal brain lesions.13 SV H-MRS provides better quality spectra compared with MRS imaging. The authors recommend that both techniques be used in the evaluation of brain masses (Fig. 1).

SPECTRAL PATTERN OF TUMORS

The spectral pattern of intracranial tumors may vary according to histology and malignancy grade and is discussed here.14–18

Reduction in N-Acetylaspartate Levels and in N-Acetylaspartate/Creatine Ratio

Reduction in N-acetylaspartate (NAA) levels and NAA/creatine (Cr) ratio is observed in tumors, indicating decreased viability and number of neurons (see Fig. 1; Fig. 2). The reader should bear in mind that in low-grade gliomas, the spectral pattern might be similar to that of normal brain (Fig. 3).19 Absence of NAA in an intraaxial tumor generally implies an origin outside the central nervous system (metastasis) (Fig. 4) or a highly malignant tumor that has destroyed all neurons in that location (Fig. 5).5

Decreased Cr Levels

Decrease in Cr may occur, representing energy failure in aggressive malignant neoplasms (see Figs. 1 and 2).

Increase in Choline Levels and in Choline/NAA and Choline/Cr Ratios

An increase in choline (Cho) levels is shown by an increase in the Cho/NAA or Cho/Cr ratio, rather than its absolute concentration. Increased Cho is associated with higher turnover in the cell membrane and higher cell density resulting from proliferation of tumor cells (see Figs. 1 and 2).20,21 In tumors, Cho levels correlate with the degree of malignancy and are linearly correlated with cell density (the inverse of what is seen with the apparent diffusion coefficient [ADC]) instead of the proliferative index. Higher Cho levels are seen in more malignant tumors (see Figs. 1 and 2) and lower levels in lower-grade tumors (see Fig. 3). Cho is usually higher in the center of a solid mass and decreases peripherally. Cho is consistently low in necrotic areas (see Fig. 5).5

Myo

Myo is a glial marker because it is primarily synthesized in glial cells, almost only in astrocytes. The Myo/Cr ratio is usually higher in lower-grade (see Fig. 3) than in higher-grade tumors (see Fig. 2).22

Lactate Peak

Increased lactate levels are likely the result of anaerobic glycolysis, although they can also be due to insufficient blood flow leading to ischemia or necrosis.23,24 Lactate is directly related to tumor grade in adult brain tumors, with higher peaks seen in higher-grade tumors (see Fig. 2). However, lactate is found in essentially all pediatric brain tumors regardless of histologic grade.
Increased levels of lipids are believed to be caused by necrosis and membrane breakdown and are observed in metastasis (see Fig. 4),

aggressive high-grade primary brain tumors such as glioblastoma multiforme (GBM) (see Figs. 1, 2, and 5) and lymphoma (Fig. 6), and in nonneoplastic

**Lipids**

Increased levels of lipids are believed to be caused by necrosis and membrane breakdown and are
lesions such as inflammatory processes and abscesses. A prominent lipid peak is also characteristic for radiation necrosis.

**Alanine**

Alanine is an amino acid that has a doublet centered at 1.48 ppm. This peak is located above the baseline in spectra obtained with short or long TE and inverts below the baseline on acquisition using TE of 135 to 144 milliseconds.\(^5\) In tumors, an increased level of alanine is considered specific for meningioma (Fig. 7).

**Glutamine and Glutamate**

Glutamine and glutamate (Glx) and Myo are metabolites better assessed with a TE of 30 milliseconds.\(^2^9\) Except for meningiomas, in which an increased Glx peak may be seen (see Fig. 7), a significant increase in Glx levels should suggest non-neoplastic lesions.\(^1^9\)

**MAIN CLINICAL APPLICATIONS**

**Suggest Histology**

Although conventional MR imaging is a sensitive modality available for detection of brain tumors,
its specificity is low, and several tumor types may share a similar MR imaging appearance. On the other hand, some tumors may present with a typical spectral pattern that may help to suggest the histology.

**GBM**
The spectral pattern of GBM is typical. There is a significant increase in Cho along with reduction of NAA, Cr, and Myo peaks. Increase of lipids and lactate is also common (see Figs. 1 and 2). When there is extensive necrosis, no increase in the Cho peak is seen. In this situation, prominent lipid and lactate peaks may be the only spectral abnormality (see Fig. 5). An overlap may be seen between the spectral pattern of GBM and metastasis. Although the absence of NAA in an intraxial tumor generally implies an origin outside the central nervous system (metastasis) (see Fig. 4), a highly malignant tumor that has destroyed all neurons in that location may also demonstrate absence of NAA (see Fig. 5). On the other hand, NAA may be present in the spectra of a metastatic lesion if there is a partial volume effect with the adjacent parenchyma. For discriminating solitary metastases from primary high-grade tumors, it has been suggested that investigation of peritumoral regions is useful. Metastases are encapsulated and do not show high Cho levels outside the region of enhancement, whereas gliomas are often invasive and show increased Cho in surrounding tissues. However, if tumor infiltration is not significant, no increase in Cho is seen in the peritumoral area surrounding a GBM (Fig. 8).

**Meningioma**
Meningiomas are readily diagnosed based on conventional imaging features, but the diagnosis may be confirmed by the presence of alanine, which has been reported in many meningiomas. A significant increase in Cho along with some increase in the Glx peak and the presence of alanine are common spectral findings (see Fig. 7).
Increase in Cho is characteristic and should not suggest malignancy. Meningiomas induced by radiation therapy tend to occur in younger patients, with equal frequency in males and females (sometimes more common in males), and present more atypia and higher nuclear/cytoplasm ratios. In these cases, a large lipid peak along with reduction of all other metabolites including Cho may be seen. Their spectral pattern is similar to that of dural-based metastasis.

**Lymphoma**

Lymphomas may present as a solitary or multifocal solid lesion with no macroscopic evidence of necrosis in immunocompetent patients. On DW imaging, lymphoma shows hyperintensity with low ADC reflecting a higher nuclear/cytoplasm ratio. The relative cerebral blood volume (rCBV) of lymphomas may be normal to slightly increased compared with the rCBV of high-grade gliomas. The spectral pattern of lymphomas is similar to that of other malignant tumors and is characterized by increase in Cho, reduction in Myo, and prominent lipids. When lipids and lactate are found in a solid lesion, lymphoma should be suggested. The spectral pattern described for solitary and multifocal lymphomas is similar to that seen in lymphomatosis cerebri.

**Gliomatosis cerebri**

Gliomatosis cerebri is a distinct entity of glial tumors characterized by diffuse infiltration of the glial cell neoplasm throughout the brain. The WHO classification denotes grades II, III and IV gliomatosis cerebri. Therefore, patients with this tumor have a variable prognosis. The most common finding in spectroscopy is reduction of NAA. Increase in Myo is characteristic of gliomatosis...
grade II, especially if there is no increase in Cho (Fig. 11). Marked increases in Myo and Cr have been found in gliomatosis cerebri and may be attributed to glial activation rather than to glial proliferation because the Cho level is only moderately increased suggesting low glial cell density. Sometimes Cho is reduced (see Fig. 11). A prominent lipid peak is seen in lymphomatosis cerebri (see Fig. 10), whereas a significant increase in Myo is characteristic of gliomatosis cerebri (see Fig. 11). In patients diagnosed with gliomatosis grade III, the Myo peak will be reduced and elevation of the Cho peak will be demonstrated (Fig. 12).
Medulloblastoma

Medulloblastomas are more common in the pediatric population, although they may also present in adults aged 30 to 35 years. They are aggressive tumors (WHO grade IV) with a high propensity to disseminate throughout the cerebral fluid space. Their spectral pattern is characterized by a significant increase in Cho along with a reduction in the NAA and Myo peaks. Some lipids and lactate may be seen. Spectra with short TE show increased taurine at 3.3 ppm in patients.\textsuperscript{50–55} Altering the TE can confirm that a peak at 3.3 ppm corresponds to taurine. At a TE of 30 milliseconds, taurine projects above the baseline, whereas at a TE of 144 milliseconds, the taurine peak is below the baseline.\textsuperscript{50} It has been speculated that increased taurine is associated with increased cellular proliferation and tumoral aggressiveness.\textsuperscript{50–52,55,56}

Ependymoma

Ependymomas are more common in the pediatric population, although they may also present around the age of 30 to 35 years. They typically

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**Fig. 9.** Multifocal lymphoma. Multifocal solid enhancing nodules (A) are demonstrated in the frontal lobes and the cingulate gyri. Spectroscopy (B) shows a prominent lipid-lactate peak (arrow), increase in Cho, and reduction of Myo. Cho, choline; Cr, creatine; Ins, myo-inositol; Myo, myo-inositol; NAA, N-acetyl-aspartate.

**Fig. 10.** Lymphomatosis cerebri. A 40-year-old man presenting with focal seizures, progressing to status epilepticus. There is a nonenhancing lesion compromising most of the left hemisphere (A), crossing the midline, and presenting with high signal intensity on the fluid attenuated inversion recovery (FLAIR) sequence (B). Spectroscopy (B, C) demonstrates a prominent lipid peak, increase in the Cho peak, and reduction of Myo. Cho, choline; Cr, creatine; ml, myo-inositol; Myo, myo-inositol; NAA, N-acetyl-aspartate. (Courtesy of Dr Leonardo Avanza, Espirito Santo, Brazil.)
occur within the fourth ventricle. A most important imaging finding to identify ependymomas is extension of the tumor through the fourth ventricular outflow foramina (Fig. 13). On computed tomography, the tumor reveals mixed density with punctate calcification in 50% of cases, with variable enhancement. These tumors are heterogeneous on MR imaging, reflecting a combination of

Fig. 11. Gliomatosis cerebri. A 49-year-old woman presenting with a nonenhancing infiltrative lesion (A) with high signal intensity on T2 (B, C) compromising the frontal and parietal lobes bilaterally. Spectroscopy (C, D) demonstrates increased Myo along with a reduction in the Cho and NAA peaks. Cr is also increased. Cho, choline; Cr, creatine; Myo, myo-inositol; NAA, N-acetyl-aspartate.

Fig. 12. Gliomatosis cerebri. There is an extensive infiltrating lesion compromising the frontal and parietal lobes, presenting with some tiny areas of discrete irregular enhancement (A) and high signal intensity on T2 (B). Spectroscopy (B, C) demonstrates prominent Cho and reduction in the Myo, Cr, and NAA peaks; a spectral pattern different from that shown in Fig. 11. Cho, choline; Cr, creatine; ml, myo-inositol; Myo, myo-inositol; NAA, N-acetyl-aspartate.
solid component, cyst, calcification, necrosis, edema, or hemorrhage. When performed, perfusion MR imaging of ependymoma generally shows markedly increased rCBV and, unlike many other glial neoplasms, poor return to baseline, which may be attributable to fenestrated blood vessels and an incomplete blood-brain barrier (see Fig. 13C, D). MRS shows considerable heterogeneity. In general, ependymomas have low NAA and moderately increased Cho and Cr. Harris and colleagues stated that the presence of high Myo strongly suggests a diagnosis of ependymoma when short TE (30 milliseconds) is used at 1.5 T (see Fig. 13E–F). Another study also demonstrated that high Myo and glycine are found in ependymomas, more significant at short TE. According to these findings, when a mass is found in the fourth ventricle, high Myo and glycine suggest ependymoma, whereas high Cho supports primitive neuroendocrine tumor. Sometimes, no increase in Cho is seen in ependymomas (see Fig. 13F).

**Suggest Tumor Grade**

Differentiation between high-grade and low-grade tumors is important for therapeutic planning and estimating prognosis. H-MRS may indicate the tumor grade with more accuracy than a blind biopsy, because it assesses a larger amount of tissue than what is usually excised at biopsy. Tumors are commonly heterogeneous, and their spectra may vary depending on the region sampled by MRS. Hence, the region of interest chosen for analysis has a large influence on the results, and, as stated earlier, MRS imaging is generally considered preferable because it allows metabolic heterogeneity to be evaluated. One recent MRS imaging study used MR perfusion imaging (arterial spin labeling) to guide the spectral measurement location; in regions with increased flow, Cho was found to be higher in high-grade gliomas compared with low-grade gliomas. No metabolic differences between high-grade and
low-grade gliomas were found in normal or hypoperfused tumor regions.

H-MRS is considered 96% accurate in differentiating low-grade versus high-grade gliomas.68 H-MRS may be readily integrated into a multimodality MR imaging examination for presurgical evaluation of patients with gliomas.69–72

**Useful metabolites for suggesting tumor grade**

**Cho** Increased Cho correlates with cellular proliferation and density. There is a high correlation between the in vivo concentration of Cho in brain tumors and in vitro tumor proliferation markers. Statistically significant higher Cho/Cr, Cho/NAA, and rCBV values in high-grade gliomas than in low-grade gliomas have been reported,45 although threshold values of metabolite ratios for grading of gliomas are not well established. Cho/Cr is the most frequently used ratio. Some institutions use a threshold value of 2.0 for Cho/Cr to differentiate low-grade from high-grade gliomas; others use a cutoff value of 2.5. Although increased Cho is related to tumor grade (higher Cho is found in higher-grade tumors than in lower-grade tumors), some studies have found grade IV GBM to have lower levels of Cho (see Fig. 1C) than grade II or grade III (Fig. 14) gliomas.26 This may be due to the presence of necrosis in high-grade tumors, because necrosis is associated with a prominent lipid peak along with reduction of all other metabolites (see Fig. 5).73

**Lipids and lactate** The presence of lipids and lactate correlates with necrosis in high-grade gliomas (see Figs. 1, 2, and 5). Di Constanzo and colleagues69 evaluated 31 patients with either high-grade or low-grade tumors through multimodality 3-T MR imaging (including long TE MRS

![Fig. 14. Grade III glioma. There is a solid mass compromising the left frontal and temporal lobes with tiny foci of enhancement (A), isointense on T2 (B) suggesting high cell density. SV-MRS (B, C) demonstrates a significant increase in Cho along with a reduction in NAA and Cr. MV MRS (D, E) demonstrates the same findings. Cho, choline; Cr, creatine; ml, myo-inositol; NAA, N-acetyl-aspartate.](image-url)
imaging). They concluded that high-grade and low-grade tumors and their margins could be differentiated based on the lactate/lipid signal and rCBV. Lipids are also the main spectral finding in metastasis (see Fig. 4). When lipids are demonstrated in solid lesions, lymphoma should also be considered (see Fig. 9).

Increase in the lipid peak is inversely correlated to survival.74

Lipids and lactate, although usually related to high-grade primary brain tumors and metastasis, may also be demonstrated in pilocytic astrocytomas.

Myo Useful information on tumor grade may be acquired by using a short TE (30–35 milliseconds) to assess Myo.22 In low-grade tumors, the Myo/Cr ratio is typically higher (see Fig. 3) than in high-grade tumors (see Figs. 1 and 2).24,26 This may be due to a low mitotic index in low-grade gliomas and, thus, lack of phosphatidylinositol metabolism activation, which results in Myo accumulation. Howe and colleagues26 concluded that high Myo was characteristic of grade II astrocytomas. Increased levels of Myo have been reported to be useful for identifying low-grade astrocytomas in which the Cho/Cr ratio was not altered.75,76

NAA and Cr The greatest reductions in NAA and Cr levels occur in higher-grade tumors (compare Figs. 1 and 2 with Fig. 3).

Glucose Short TE spectra may allow the evaluation of a peak around 3.67 ppm (probably glucose), which is directly related to survival. Tumors with more metabolic activity show low glucose levels in the spectra.74

Typical spectral findings in grade II, III, and IV gliomas

Grade II gliomas H-MRS in low-grade gliomas may look similar to normal spectra, demonstrating a discrete reduction in the NAA peak, along with a discrete increase in the Cho peak.26,50,77 An increase in Myo can be the only finding in the spectra of a grade II astrocytoma (see Fig. 3).13

No lipids or lactate are usually demonstrated.

Low-grade glioma was studied in vivo at 4 T in 11 patients using H-MRS (incorporating the direct measurement of macromolecules in the spectrum) and 23Na imaging. The results showed that absolute levels of glutamate and NAA were significantly decreased, whereas levels of Myo and 23Na were significantly increased in low-grade glioma tissue.78 The observation of decreased NAA levels is consistent with previous studies.26,50,77–79 The observed decrease in glutamate contradicts a previous study75 performed at 1.5 T that suggested that increased Glx maybe characteristic of low-grade gliomas. The discrepancy may be due to the removal of the macromolecule baseline signal intensity in the current study before quantification. The observed increase in Myo is consistent with previous studies.24,26

Grade III gliomas In grade III gliomas, there is a significant increase in the Cho peak, which correlates well with high cell density in these tumors.80

The NAA, Cr, and Myo peaks are reduced (see Fig. 14). Metastases and glioblastomas nearly always show increased lipid peaks; thus, if the lesion does not exhibit mobile lipid signals, anaplastic gliaoma is more likely.81 In the authors’ experience, however, some increase in lipids and lactate may be seen in grade III gliomas (Fig. 15A, B).

Grade IV gliomas The spectral pattern of grade IV gliomas is characterized by severe reduction of the NAA, Cr, and Myo peaks. Cho is increased (see Fig. 1C), although not as much as in a grade III glioma (see Fig. 14C), because a lot of necrosis is usually present in grade IV gliomas, which results in a significant increase in the lipid peak (see Fig. 1C). Typically, higher levels of Cho occur in grade III gliomas, whereas, in GBM, the Cho levels may be much lower as a result of necrosis.82 When the voxel is placed within the necrotic area of a GBM, no Cho is detected and a prominent lipid-lactate peak is the only spectral abnormality (see Fig. 5).82

Special things to remember

Some overlap in the spectral pattern may be seen between grade II and grade III gliomas (see Fig. 15A–D). Evaluation of the spectra along with the information obtained from the other functional studies such as DW imaging, PW imaging, and permeability maps enhance the diagnostic capacity of brain tumors (see Fig. 15E–J). Some aggressive tumors, such as metastases, GBM, and gliomatosis cerebri may present with no increase in Cho (see Figs. 4, 5, and 11). The Cho peak and the Cho/Cr and Cho/NAA ratios may be higher in grade III (see Fig. 14C) than in grade IV gliomas (see Fig. 1C). Some benign tumors such as meningiomas present with a significant increase in the Cho peak (see Fig. 7). Pilocytic astrocytomas usually present with a significant increase in the Cho peak. Some lipids and lactate are also usually seen in these tumors.

Oligodendroglioma This tumor is divided into 2 groups according to the WHO classification: grades II and III.83 It originates from oligodendrocytes but often contains a mixed population of cells, particularly astrocytes. On dynamic
contrast-enhanced MR perfusion, low-grade oligodendrogliomas may demonstrate high rCBV because they contain a dense network of branching capillaries.\textsuperscript{34,85} Thus, many oligodendrogliomas can be misinterpreted as high-grade tumors because of their high rCBV.

One study showed that rCBV was not significantly different between low-grade and
high-grade oligodendrogliomas.\textsuperscript{66} In contrast, another study\textsuperscript{86} showed that rCBV was significantly different between low-grade and high-grade oligodendrogliomas. The results of H-MRS studies in oligodendrogliomas are more consistent than those of MR perfusion studies. Similar to astrocytomas, H-MRS of oligodendrogliomas demonstrates significantly higher Cho, Cho/Cr ratio, and a higher incidence of lactate and lipids in high-grade tumors than in low-grade tumors.\textsuperscript{79,86,87} Nevertheless, low-grade oligodendrogliomas may show highly increased Cho (see Fig. 15C, D), mimicking high-grade tumors (see Fig. 15A, B), because these low-grade tumors can have high cellular density but absent endothelial proliferation and necrosis.\textsuperscript{86} Apart from higher rCBV, the level of Glx is significantly higher in low-grade oligodendrogliomas than in low-grade astrocytomas and may help to distinguish these tumors from each other.\textsuperscript{79}

**Assess Tumor Extension**

In infiltrative lesions, tumor activity can be demonstrated by H-MRS beyond the enhanced area identified on gadolinium-enhanced conventional MR imaging (Figs. 16 and 17). Comparison of the extent (and location) of active tumor as defined by MR imaging and MRS imaging demonstrates the differences between the 2 techniques.\textsuperscript{87} The area of metabolic abnormality as defined by MRS imaging may exceed the area of the abnormal T2-weighted signal.\textsuperscript{87–90} H-MRS may better define tumor extension than conventional MR imaging.\textsuperscript{91}

Cho has been found to correlate well with the cellular density of the tumor\textsuperscript{80} and the degree of

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**Fig. 16.** Tumor extension. A 48-year-old woman diagnosed with GBM. There is a large infiltrative lesion in the right frontal lobe crossing the midline with heterogeneous signal intensity on T2 (A) and areas of contrast enhancement (B). MV MRS (C, D) demonstrates significant increase in Cho and the Cho/Cr and Cho/NAA ratios in the corpus callosum along with the presence of lactate compatible with tumor infiltration beyond the areas of enhancement. There is also an increase in blood volume in the same area (E, rCBV map). Cho, choline; lac, lactate; MV MRS, multivoxel magnetic resonance spectroscopy; NAA, N-acetyl-aspartate; rCBV map, relative cerebral blood volume map.
The use of MRS imaging to map Cho levels has been suggested as a method for defining tumor boundaries. To assess the degree of tumor infiltration, MRS imaging data obtained from 7 patients with untreated supratentorial gliomas (WHO grades II and III) were fused with three-dimensional MR imaging data sets and integrated into a frameless stereotactic system for image-guided surgery in an interactive manner. Tissue samples were obtained from 3 regions, defined individually in each patient based on the Cho/NAA ratio: (1) a spectroscopically normal region, (2) a transitional region, and (3) a region with maximum spectroscopic abnormality. In all cases, the highest Cho/NAA ratios were obtained in the tumor center, and intermediate values in the regions of low tumor invasion. In 4 patients, however, biopsies sampled in regions with normal Cho/NAA ratio showed tumor infiltration. One of the reasons may be the low resolution of MRS imaging with respect to glioma borders. Based on this observation, it can be concluded that if the Cho/NAA ratio is increased outside the area of enhancement, tumor infiltration can be diagnosed. On the other hand, if no increase in the Cho/NAA ratio is demonstrated, tumor infiltration cannot be ruled out. The reason for this is probably the fact that increases in the Cho/Cr and Cho/NAA ratios are related to the number of neoplastic cells that have infiltrated outside the enhancing lesion. A retrospective study performed on 10 gliomas examined the relationship...
between metabolite levels and histopathologic parameters in the border zone of gliomas. A strong negative correlation was detected between NAA concentration and both absolute and relative measures of tumor infiltration; no correlation for Cho was detected. The study concluded that NAA concentration is the most significant parameter for the detection of low levels of tumor cell infiltration. MRS may demonstrate tumor infiltration not only in the area of vasogenic edema but also in the normal-appearing white matter (NAWM) contralateral to the affected hemisphere. Kallenberg and colleagues have shown that, in patients with histopathologically confirmed primary GBM, H-MRS of the NAWM contralateral to the affected hemisphere revealed an increase in the concentrations of Myo and glutamine but otherwise normal metabolite levels. These results indicate increased density of cells of astrocytic origin in the NAWM of patients with GBM in the presence of still normal neuroaxonal tissue, as indicated by the absence of changes in the major metabolites. This observation may, in turn, be taken as a potential indicator of the presence of tumor cells in NAWM, representing an early sign of neoplastic infiltration, suggesting a new role for H-MRS in the treatment of patients with brain tumors.

The results from this study are in agreement with findings observed in previous reports on H-MRS and conventional MR imaging of glioma infiltration in inconspicuous brain parenchyma remote from the tumor.

Fig. 18. Ideal site for biopsy. A 47-year-old man after surgical resection of a right frontal lesion 3 months previously; pathology was negative. The area that enhances (circle A) presents with low capillary density seen as low perfusion (B, rCBV map) and thus is not the ideal site for biopsy. Surrounding the area of enhancement posteriorly, there is an area of high capillary density (B, red circle) seen as high perfusion and high cell density (C, D) presenting with high Cho and high Cho/Cr and Cho/NAA ratios. This area is the best site for biopsy. Cho, choline; Cho/Cr, choline/creatine; Cho/NAA, choline/N-acetyl-aspartate; Cr, creatine; NAA, N-acetyl-aspartate; rCBV map, relative cerebral blood volume map.
Indicate the Ideal Site for Biopsy

Biopsy is not always performed in the area of the tumor with greatest cellularity so it may underestimate the pathology of the lesion. By evaluating metabolic abnormalities, H-MRS may better define the ideal site for biopsy than conventional MR imaging. Stereotactic brain biopsy is usually performed based on the anatomic appearance of the lesion or enhancement characteristics. The area of enhancement does not necessarily represent the area of greater tumor activity. In high-grade heterogeneous tumors, there is a possibility that unspecific or lower-grade tumor tissue is sampled or that important functional tracts are damaged. Ideally, regions of increased angiogenesis, vascular permeability, and high metabolic activity should be sampled. The role of H-MRS in biopsy guidance is to recognize regions of high metabolic activity: regions of increased Cho levels (and low NAA levels) indicating tumor tissue are a good target for biopsy (Fig. 18). Regions with low Cho and NAA levels may indicate radiation necrosis, astrogliosis, macrophage infiltration, or mixed tissue.

Follow Tumor Progression

Serial H-MRS examinations may be used to follow the progression of gliomas. Anaplastic degeneration can be demonstrated early with H-MRS and perfusion mapping compared with conventional MR imaging. Tumor progression is characterized by increased Cho levels in serial examinations (Fig. 19). Tedeschi and colleagues demonstrated that interval percentage changes in Cho intensity in stable gliomas and progressive gliomas (malignant degeneration or recurrent disease) is less than 35 and more than 45, respectively. Interval increased Cho/Cr or Cho/NAA is suggestive of malignant progression.

Predict Prognosis and Survival

Histopathology remains the gold standard for prognostic assessment, providing insights into

Fig. 19. Tumor progression. A 27-year-old man presenting with seizures. First examination demonstrates a left frontal lesion with high signal intensity on the FLAIR sequence (A). Spectroscopy demonstrates that the NAA peak is higher than the Cho peak (B). Biopsy results were compatible with a grade II glioma (C). Nine months later, (D, E) Cho is higher than NAA indicating higher cell density and suggesting anaplastic transformation. The lesion was resected and pathology demonstrated a high cell density and highly vascular lesion, compatible with grade III glioma (F), as suggested by the MRS study. Cho, choline; MRS, magnetic resonance spectroscopy; NAA, N-acetyl-aspartate. (C, E) Courtesy of Dr Leila Chimelli, Rio de Janeiro, Brazil.)
the morphologic cytostructure of the tumor. However, histopathology has limitations in providing prognostic value.\textsuperscript{74} DW imaging, PW imaging, and H-MRS yield structural and metabolic information that may provide better insight into tumor functionality and improve the prognostic stratification of brain tumors.\textsuperscript{74}

A pretreatment H-MRS study of 187 patients with high-grade astrocytomas produced 180 spectra at short TE (30 milliseconds) and 182 at long TE (136 milliseconds).\textsuperscript{74} The study demonstrated that a high-intensity value of the peaks at 0.98 and 1.25 ppm, attributed to lipids, correlated with tumoral necrosis and with low survival. More interesting was the finding that another region of the short TE spectrum, around 3.67 ppm, showed a direct correlation with patient survival. This peak probably represents glucose. High metabolic activity and consequently poor prognosis correlate with depletion of glucose in the extracellular compartment and, accordingly, with low intensity of the resonances that represent this compound in the spectra, centered at 3.67 ppm. The investigators found that H-MRS could be used to stratify prognostic groups in high-grade gliomas and that this prognostic assessment could be made by evaluating the intensity values of 2 points on the spectrum at short TE (0.98 and 3.67 ppm) and another 2 at long TE (0.98 and 1.25 ppm). Short TE H-MRS may be considered somewhat superior to long TE H-MRS for prognostic assessment of high-grade gliomas. Nevertheless, spectra at both TEs may provide relevant information.\textsuperscript{74}

Oh and colleagues\textsuperscript{107} found a significantly shorter median survival time for patients with a large volume of metabolic abnormality, measured by H-MRS. Additional studies have evaluated some particular resonances of the spectrum such as Cho-containing compounds, NAA, Cr, lipids, and lactate, and have found them to be useful for predicting patient outcome in gliomas.\textsuperscript{108,109} A series of articles have evaluated the role of MRS imaging in predicting survival of patients with GBM.\textsuperscript{108,110–113} In a recent study, conventional MR imaging, MRS imaging, DW imaging, and perfusion MR imaging were used in a group of grade IV gliomas (examined before surgery and treatment). Survival was relatively poor in patients with lesions exhibiting large areas of contrast enhancement, abnormal metabolism, or restricted diffusion. Specifically, of the H-MRS parameters, high relative volumes of regions with increased Cho/NAA index were negatively associated with survival. Survival time was also negatively associated with high lactate and lipid levels (see Fig. 1) and the ADC within the enhancing volume.

Not all studies have found associations between metabolic indices and prognosis; for instance, in 16 patients with a B-cell lymphoma, the presence of lactate and lipids in the spectra collected before treatment was not associated with overall survival.\textsuperscript{114} In another prospective H-MRS study, 50 patients with newly diagnosed low-grade gliomas (WHO grade II) evaluated before surgery showed no relationship between Cho and Cr levels in the tumor and survival.\textsuperscript{115} Despite the few studies mentioned here,\textsuperscript{114,115} most of the studies published in the literature agree that H-MRS is helpful for predicting the prognosis of brain tumors.

### Assess Therapeutic Response

An important issue about postradiation therapy in patients with brain tumors is differentiation between recurrent brain tumor and radiation injury/change, particularly when new contrast-enhancing lesions are seen in previously operated and/or irradiated regions.\textsuperscript{116–120} Typical conventional MR imaging appearance of radiation necrosis is a T2 hyperintense signal and enhancement after contrast administration, which is difficult to distinguish from tumor progression or pseudoprogression (a transient increase in edema, mass effect, and contrast enhancement that resolves over time).\textsuperscript{115} Differentiating residual or recurrent tumors from treatment-related changes is limited on conventional MR imaging as well as on histologic examination; areas

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**Fig. 20.** Radiation necrosis versus tumor recurrence. A 24-year-old woman diagnosed with GBM after surgical resection, radiation therapy, chemotherapy, and steroids. A surgical cavity is seen in the right parietal lobe (A) with some irregular enhancement in the surrounding parenchyma (B). MV MRS (C, D) demonstrates a significant reduction in the NAA, Cho, and Cr peaks along with a prominent lipid peak consistent with radiation necrosis. Perfusion is reduced in the surgical bed (E; rCBV map) and there is no increase in permeability (F; G) also indicating therapeutic response rather than tumor. Four months later, H-MRS shows an increase in Cho and the Cho/NAA ratio indicating tumor cell proliferation (H). A perfusion study (I) demonstrates high capillary density and there is increased permeability (J, K) in the same area. Results from H-MRS, perfusion, and permeability studies are compatible with tumor recurrence. Cho, choline; Cho/NAA, choline/N-acetyl-aspartate; Cr, creatine; H-MRS, proton magnetic resonance spectroscopy; lip, lipids; MV MRS, multivoxel magnetic resonance spectroscopy; NAA, N-acetyl-aspartate; rCBV map, relative cerebral blood volume map.
of T1 contrast enhancement after radiation treat-
ment often contain both residual and recurrent
tumor and tissue affected by therapy-related
changes. In addition, the heterogeneity of gliomas
before and after therapy and the inaccuracy of
biopsy sampling pose another challenge in the his-
tologic differentiation of tumors from necrosis.121
On conventional MR imaging, the evaluation of
treatment response and categorization as stable
disease, responder (partial remission), and nonre-
responder (progression) are based predominantly
on changes in tumor volumes.122 MRS imaging
does distinguish metabolic changes in the tumor
before any change in volume. H-MRS has been
applied to differentiate between radiation-induced
tissue injury and tumor recurrence in adult and
pediatric patients with brain tumors after radiation,
gamma knife radiosurgery, and brachytherapy.123
Significantly reduced Cho and Cr levels suggest ra-
diation necrosis.73,75,124–129 Necrotic regions may
also show increased lipid and lactate signals
(Fig. 20A–G).75,130,131 On the other hand, increased
Cho (evaluated as Cho levels relative to the Cho
signal in normal-appearing tissue, Cho/Cr, or Cho/
NAA ratios) suggests recurrence (see Fig. 20H–
K).112,129,128,129 Many studies have found that
Cho/Cr and/or Cho/NAA ratios are significantly
higher in recurrent tumor (or predominantly tumor)
than in radiation injury.117–120 In a retrospective
MRS imaging study of 33 tumors using an interme-
diate TE of 144 milliseconds, Smith and col-
leagues18 demonstrated that higher Cho/Cre or
Cho/NAA ratios and a lower NAA/Cr ratio suggest
recurrence compared with radiation change. Ac-
cording to this study, the Cho/NAA ratio demon-
strated the best confidence interval to distinguish
between tumor recurrence and radiation change.
The distinction between recurrent tumor and radia-
tion necrosis using the Cho/NAA ratio could be
made with 85% sensitivity and 69% specificity.118
According to Elias and colleagues,132 the Cho/
NAA and NAA/Cr ratios best differentiated recurrent
brain tumor from radiation injury using H-MRS in
previously treated patients diagnosed with primary
intracranial neoplasm. Comparison with biopsy
specimens revealed that MRS imaging cannot reli-
ably differentiate between tissue containing mixed
tumor/radiation necrosis and either tumor or radia-
tion necrosis, although it did achieve good separa-
tion between pure necrosis and pure tumor.75

H-MRS is a promising, noninvasive tool for pre-
dicting and monitoring the clinical response to te-
mozolamide in patients with low-grade gliomas.133
In these patients, the H-MRS profile changes more
widely and rapidly than tumor volume during
relapse and represents an early predictive factor
of outcome over 14 months of follow-up.

Tumor recurrence may be detected by H-MRS
in a site remote from the irradiated area. In some
cases, the development of a spectral abnormality
may precede a coincident increase in contrast
enhancement by 1 to 2 months.126,134

Some overlap may be seen in the H-MRS of tu-
mors and radiation change. An increase in Cho-
containing compounds after radiation therapy as
a result of cell damage and astrogliosis may be
seen in radiation necrosis misclassified as tu-
mors.135 In addition, both tumors and necrotic tis-

ue have low levels of NAA, consistent with
neuronal damage. Also, residual tumor may be
present along with some radiation changes in the
same patient. If the spectrum is indeterminate (ie,
indicating the presence of both residual tumor
and radiation change), repeated examination is
suggested after an interval of 6 to 8 weeks.130 If
the increase in Cho is related to radiation change,
it will normalize with time. Additional information
from the perfusion and permeability studies may
also help to correctly differentiate between tumors
and radiation necrosis. Recurrent tumors have a
higher CBV (see Fig. 20I) and higher permeability
(see Fig. 20J, K) compared with radiation necrosis
(see Fig. 20E–G).10,94

A discrete and isolated increase in Cho in se-
rial examinations should not be considered evi-
dence of tumor recurrence. Interval increased
Cho/Cr or Cho/NAA is suggestive of malignant
progression/tumor recurrence if the percentage
change in Cho is more than 45% and/or is as-
associated with increased blood volume and per-
meability indicating vascular proliferation and
significant compromise of the blood-brain bar-
rier, respectively.

H-MRS is able to detect the effects of radiation
on normal brain. The most commonly reported
changes after radiation are decreases in NAA,136
which can be detected 1 to 4 months after ra-
diation in nontumoral regions receiving between
20 and 50 Gy137 and decreases in Cho levels.123
Radiation therapies may result in a decrease in
whole-brain NAA with no corresponding changes
in the mental status.

DIFFERENTIAL DIAGNOSIS BETWEEN LESIONS
THAT LOOK ALIKE

In many cases, reliable differentiation of neoplastic
from nonneoplastic brain masses is difficult or even
impossible with conventional MR imaging.137–147
Use of contrast agent may also not increase diag-
nostic specificity because various nonneoplastic
processes are often associated with disruption
of the blood-brain barrier and not all tumors
enhance.135 Studies have shown that the use of
H-MRS in specific cases improves the accuracy and level of confidence in differentiating neoplastic from nonneoplastic masses.\textsuperscript{13,15,135,138,148–150} The differential diagnosis of a brain mass varies depending on its solid or necrotic aspect.\textsuperscript{13} When a necrotic mass is encountered in the brain, the main diagnoses include aggressive brain tumors, abscess, tuberculoma, parasitic infection, or radiation necrosis. On the other hand, when the lesion is solid, the main diagnoses include tumors without necrosis, lymphoma, and pseudotumoral demyelinating disease. Hourani and colleagues,\textsuperscript{135} using cutoff points of NAA/Cho equal to or less than 0.61 and rCBV equal to or greater than 1.50 (corresponding to diagnosis of the tumors), achieved a sensitivity of 72.2% and specificity of 91.7% in differentiating tumors from non-neoplastic lesions. Although studies have shown that perfusion MR imaging and the combination of H-MRS imaging and perfusion MR imaging had were comparable with MRS imaging alone in differentiating tumors from nonneoplastic lesions, in the authors’ experience, a multifunctional approach with DW imaging, PW imaging, permeability mapping, and H-MRS is the most accurate way to make a precise diagnosis.

**Tumor Versus Stroke**

Differentiation between a glioma and a vascular lesion may be difficult or impossible using conventional MR imaging. In these cases, increased Cho makes the diagnosis of neoplasm more likely, whereas no increase in Cho makes the diagnosis of tumor less likely. Increased lipids along with reduction of all other metabolites is characteristic of infarcts but these findings may also be present in tumors with extensive necrosis (see Fig. 5). On the other hand, increased Cho may be seen in infarction especially in the subacute stage, mimicking tumor (Fig. 21). In this situation, the clinical history and a multifunctional approach with DW imaging and perfusion mapping help in making the correct diagnosis.

**Tumor Versus Demyelination**

Differentiation between high-grade gliomas and some acute demyelinating lesions based on H-MRS alone may be difficult because of histopathologic similarities, which include hypercellularity, reactive astrocytes, mitotic figures, and areas of necrosis.\textsuperscript{121,125,138,149} Both entities typically present with increased Cho and decreased NAA, and lactate and lipids are often increased (Fig. 22).\textsuperscript{148–153}

In the acute stage of a demyelinating disease, increased lactate reflects the metabolism of inflammatory cells.\textsuperscript{148–150}

Majós and colleagues\textsuperscript{13} found that the increase in Cho and decrease in NAA at long TE are even higher in tumors and that these metabolites can discriminate between tumors and pseudotumoral lesions. However, in the authors’ experience, a significant increase in Cho along with significant reduction of NAA may be demonstrated in acute demyelinating plaques (see Fig. 22). According to Cianfoni and colleagues,\textsuperscript{150} increase in Glx helps differentiate demyelinating tumefactive lesions from neoplastic masses, avoiding unnecessary biopsy and potentially harmful surgery, as well as providing a more specific diagnosis during the initial MR examination, allowing the earlier institution of appropriate therapy.

**Fig. 21.** Infarct with high Cho in the spectrum. A significant increase in the Cho peak is demonstrated in the spectrum from a left thalamic infarct. The spectral pattern resembles that of a brain tumor. Cho, choline.
Tumor Versus Focal Cortical Dysplasia

In some cases of focal cortical dysplasia, Cho may be moderately increased probably as a result of intrinsic epileptic ictal activity.\(^{154}\)

Tumor Versus Abscess

The differential diagnosis between brain abscess and neoplasms (primary and secondary) is a challenge. Both appear as cystic lesions with rim enhancement on conventional MR imaging. Pyogenic abscesses have high signal intensity on DW imaging, which is usually not seen in tumors. Nevertheless, some neoplasms may occasionally have restricted diffusion and biopsy is inevitable. \(^{155}\) H-MRS may help to establish a diagnosis. In the case of a rim-enhancing lesion, to differentiate between a necrotic tumor and an abscess, the voxel should be placed within the cystic-necrotic area.\(^{155}\) Abscesses and tumors both demonstrate high lactate peaks. Nonetheless, the presence of acetate, succinate, and amino acids such as valine, alanine, and leucine in the core of the lesion has high sensitivity for pyogenic abscess (Fig. 23).\(^{82,155,156}\) To demonstrate the typical spectral abnormalities in the abscess cavity, an intermediate (144 milliseconds) or high (270 milliseconds) TE should be used.\(^{155}\)

Typical spectra of anaerobic bacterial abscesses (acetate, succinate, and amino acids) do not exist in abscesses caused by \textit{Staphylococcal aureus}, which are aerobic bacterial abscesses.\(^{156}\) In this situation, lipids and lactate may be the only spectral findings and the spectrum is similar to that of a necrotic brain lesion.\(^{155}\) Also, the resonances of acetate, succinate, and amino acids may disappear with effective antibiotic therapy. A high Cho peak and high Cho/NAA and Cho/Cr ratios may be seen in infection and should not be considered as evidence of tumor.

Tumor Versus Encephalitis

Among the encephalitis, herpes simplex encephalitis has a typical distribution of brain involvement at the hippocampus and cortex of the temporal, frontobasal, and insular lobes.\(^{157}\) H-MRS shows marked reduction of NAA and the NAA/Cr ratio, and increase in Cho and the Cho/Cr ratio at the involved region, which reflect neuronal loss and gliosis and correlate with histopathologic findings. H-MRS findings may resemble those of brain tumors. However, increase in the Glx peak should favor encephalitis over tumor.

A practical MRI-based algorithm, including the results from postcontrast MR imaging, DW imaging, perfusion MR imaging, and MRS imaging, allowed the classification of tumors and nonneoplastic lesions with accuracy, sensitivity, and specificity of 90\%, 97\%, and 67\%, respectively.\(^{7,8}\)

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**Fig. 22.** Tumor versus demyelination. A 61-year-old man presenting with blurred vision. There is a left frontal lesion hyperintense on FLAIR (A) that shows a significant increase in Cho and the Cho/NAA and Cho/Cr ratios along with a reduction in NAA (B). A diagnosis of tumor was suggested and a stereotactic biopsy showed findings consistent with demyelination. A close inspection of the spectrum shows a high Glx peak (B, arrows), more consistent with demyelination than high-grade glioma. Cho, choline; Cho/Cr, choline/creatine; Cho/NAA, choline/N-acetyl-aspartate; Cr, creatine; Glx, glutamine and glutamate; Ins, myo-inositol; NAA, N-acetyl-aspartate.
Fig. 23. Tumor versus abscess. A 39-year-old man, HIV positive, presenting with a ring-enhancing lesion in the right frontal lobe (A). There is restricted diffusion (high signal intensity on DW imaging (B) and low signal intensity on the ADC map (C)), compatible with the diagnosis of pyogenic abscess. Spectra from the abscess cavity performed with intermediate TE (144 milliseconds) (D, E) demonstrates lipids and lactate, which can also be seen in the necrotic core of a GBM (F, G) in the study obtained with low TE (30 milliseconds). However, amino acids (0.9 ppm), acetate (1.9 ppm), and succinate (2.4 ppm) are also seen in the abscess cavity (E). These findings have high sensitivity for the diagnosis of pyogenic abscesses and are not demonstrated within the necrotic core of a GBM. AAS, aminoacids; Ac, acetate; ADC, apparent diffusion coefficient; DW, diffusion weighted; GBM, glioblastoma multiforme; lac, lactate; lip, lipids; Suc, succinate; TE, echo time.
These results suggest that integration of advanced imaging techniques with conventional MR imaging may help to improve the reliability of the diagnosis and classification of brain lesions.158

SUMMARY

H-MRS may be helpful in suggesting tumor histology and tumor grade and may better define tumor extension and the ideal site for biopsy compared with conventional MR imaging. A multifunctional approach with DW imaging, PW imaging and permeability mapping, along with H-MRS, may enhance the accuracy of the diagnosis and characterization of brain tumors and estimation of therapeutic response. Also, integration of advanced imaging techniques with conventional MR imaging and the clinical history helps to improve the accuracy, sensitivity, and specificity in differentiating between tumors and nonneoplastic lesions.

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