

REVIEW

COMMENTS AND CONTROVERSIES

Magnetic resonance spectroscopy and gliomas

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Abstract

In vivo proton magnetic resonance spectroscopy (1HMRS) can substantially improve the non-invasive categorization of human brain tumors, especially for gliomas. It provides greater information concerning tumor activity and characterization of the tumor tissue than is possible with MRI techniques alone. Moreover, 1HMRS may ultimately prove to be a highly beneficial modality in the post-irradiation care of patients with brain gliomas. This paper reviews the current status of 1HMRS with the emphasis on its clinical utility in the diagnosis of active tumor processes of gliomas, and its use in planning surgical and radiation therapy interventions and monitoring tumor treatment paradigms.

Keywords: Proton; magnetic resonance spectroscopy; gliomas; grade; treatment.

Introduction

Morphological studies using CT and MR imaging and physiological imaging using PET and SPECT scanning have played a pivotal role in defining landmarks used to manage primary brain tumors clinically. However, many questions regarding the care of patients with cerebral gliomas remain unanswered. Recent studies have shown that proton magnetic resonance spectroscopy (1HMRS) can substantially improve the non-invasive categorization of human brain tumors, especially for gliomas. The recent emphasis on the utilization of 1HMRS (coupled to routine MRI techniques) in the evaluation of tumors has arisen because it provides greater information concerning tumor activity and characterization of the tumor tissue than is possible with standard MRI techniques alone. Moreover, since standard neuroimaging methods cannot reliably distinguish radiation necrosis from tumor recurrence, 1HMRS may prove to be a highly beneficial modality in the post-irradiation care of patients with brain gliomas. This paper will review the current status of proton MR

spectroscopy with emphasis on its clinical utility in the diagnosis of active tumor processes of gliomas and its use in planning surgical and radiation therapy interventions and in monitoring tumor treatment.

1HMRS techniques and interpretation

There are two types of spectroscopic imaging, namely, single-voxel and multivoxel MR spectroscopy. Single-voxel imaging involves the sampling of only one region of tissue. PRESS (point-resolved spectroscopy) and STEAM (stimulated echo acquisition mode) are the two types of sequences used for single-voxel spectroscopy. Multiple volume MR spectroscopy is also referred to as either chemical shift imaging (CSI) or spectroscopic imaging. It is a method for obtaining spectroscopic information from multiple adjacent volumes over a large volume of interest. It is essentially similar to single-voxel spectroscopy except that the defined volume is normally a large slab. Spectroscopic imaging combines features of both MR imaging and MR spectroscopy.

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Spectral patterns or specific metabolite intensities can be overlaid onto gray-scale MR images either to compare changes in spectra from adjacent voxels or to obtain a distribution pattern of a particular metabolite within the tissue examined. For instance, in the case of focal lesions, spectra from a tumorous lesion can be compared with spectra from normal tissue, then specific metabolite distributions over the region can be obtained.

Metabolites which can be identified on a standard brain proton MR spectroscopy include *N*-acetyl aspartate (NAA), choline (Cho), creatine (Cr), *myo*-inositol (MI), glutamate and glutamine compounds (Glu-n). NAA is a marker for neuronal density and viability and therefore is decreased in all disease processes in which there is death of the neurons or replacement of neurons by other cells. The NAA peak is assigned at 2.0 ppm and is the largest peak. The second largest peak is creatine. This peak is composed of resonances from Cr with contributions from creatine phosphate, gamma-aminobutyric acid, lysine and glutathione. The peak is assigned at 3.03 ppm and serves as a marker for energy-dependent systems in the brain cells. The Cho peak is assigned at 3.2 ppm and contains contributions from glycerophosphocholine, phosphocholine and phosphatidylcholine. It reflects the metabolism of cellular membrane turnover and therefore is increased in all processes leading to hypercellularity. Glu-n peak, resonating at 2.3–2.5 ppm, is detected in more tumors than controls, and a rise of Glu-n peak may relate to a role of glutamate as an excitotoxin in accelerated cell proliferation of malignant brain tumors. An abnormal peak of lactate is normally not found in the brain. It is assigned at 1.32 ppm and when detected indicates the presence of anaerobic or nonoxidative metabolism, e.g. in abscess or necrosis.

1HMRS in the preoperative grading and outcome prediction of gliomas

Prospective grading of primary cerebral gliomas is a hazardous endeavor but with significant clinical benefit. The treatment and prognosis of different grades of tumors are different and can potentially affect the clinical outcome. Conventional MR imaging provides important information regarding contrast material enhancement, perienhancement edema, distant tumor foci, hemorrhage, necrosis, mass effect, and so on, which are all helpful in characterizing tumor aggressiveness and hence tumor grade. However, often a high-grade glioma may be mistaken for a low-grade glioma when it demonstrates minimal edema, no contrast material enhancement, no necrosis, and no mass effect. Moreover, large cerebral gliomas are often histopathologically heterogeneous and may have components of varying grades of malignancy within them^[1]. Therefore, accurate preoperative grading of gliomas and planning of adequate treatment strategies are often difficult with conventional MR imaging alone. In addition, conventional MR imaging does not provide

reliable information on tumor physiology such as metabolism, micronecrosis, or cellularity, all of which are also important in determining tumor grade.

The addition of complementary biochemical information, as provided by 1HMRS imaging, could lead to further advances in the determination of the tumor grade of gliomas. Specifically, an elevation in Cho with depression of NAA is a reliable indicator of tumor. There is extensive literature demonstrating the metabolite ratios of Cho/Cr, NAA/Cr, and MI/Cr and the presence of lipids and lactate to be useful in grading tumors and predicting tumor malignancy. The recent finding of a direct correlation between Cho and cellular proliferative activity provides objective confirmation of the potential of MR spectroscopy in predicting tumor grade^[2].

The role of necrosis in glioma grading is important. The presence of necrosis is one important distinction between anaplastic astrocytomas (Grade III) and glioblastoma multiforme (Grade IV). This agrees with the histopathological finding that malignant brain tumors contained mobile lipids. The lipid peak arises predominantly from fatty acyl moieties that are relatively mobile and probably no longer confined to membrane phospholipids. Presence of high lipid peaks may suggest macroscopic necrosis due to membrane breakdown. Therefore, lipids do correlate with necrosis in high-grade glioma and so may also be useful in differentiating glioma grades. Meanwhile, it has been confirmed by previous studies that the relative increase in choline present in most high-grade gliomas is due to the increase in membrane synthesis and accelerated cell proliferation. However, high Cho peak in a tumoral region is characteristic of rapidly growing tumors rather than unique for gliomas^[3]. The rise of MI peak in tumoral region is possibly related to gliosis and poor myelination because MI has been labeled as a breakdown product of myelin. Theoretically, increased MI levels in the tumoral region are more likely to be present in high-grade gliomas though this is still controversial and needs further consideration^[4]. In addition, Glu-n peak, resonating at 2.3–2.5 ppm, may be detected in more high-grade tumors than low-grade ones, and this has been confirmed by recent studies. This may relate to a possible role of glutamate as an excitotoxin in accelerated cell proliferation of malignant brain tumors. Therefore, excessive accumulation of glutamate in a tumoral region may be an indicator of poor prognosis for malignant gliomas, though Glu-n peak alone cannot differentiate between high-grade and low-grade gliomas. However, accurate detection is difficult due to the proximity of the Glu-n peak to the dominant NAA resonance in this region^[3].

Recently, several 1HMRS studies have been published looking at the peritumoral region of gliomas. The determination of the peritumoral region is critically important for the proper planning of treatment and enables the physician to anticipate the course of the disease^[5]. The peritumoral region (the so-called uncertain zone) is

peritumoral tissue that appeared morphologically normal on routine MR images but may be infiltrated by tumor as determined by histologic analysis. It is assumed that malignant gliomas are not strictly focal lesions but rather are characterized by intracerebral dissemination of malignant glial cells along the myelinated axons and blood vessels or through the subarachnoid space. The presence of peritumoral region is a characteristic of high-grade glioma owing to its remarkable invasiveness. Therefore, both high Cho and Glu-n peaks in peritumoral regions are more valuable indicators for high-grade gliomas with a poor prognosis compared with those in tumoral regions, although its clinical utility warrants further investigation in a larger study. In addition, using only conventional MR images, overestimation or underestimation of tumor size occurs in at least 40% of cases; while 1HMRS study of the peritumoral region of gliomas may be used to map tumor margins and extension, and provide an insight as to the location most likely to yield the most representative tumor specimen.

1HMRS and tumor treatment effect

Distinguishing radiation necrosis from tumor recurrence is a key aspect of post-radiation follow-up in patients with malignant gliomas. Radiation necrosis occurs 3–12 months following radiation treatment and can be associated with exuberant gliosis. On CT scan or MRI, contrast enhancement can be seen in both radiation necrosis and recurrent tumor due to disruption of the blood–brain barrier. Therefore, radiation necrosis may be indistinguishable from recurrent or residual tumor by imaging alone; it is difficult to use these imaging methods to evaluate the viability or the proliferation activity of a tumor.

The results of various 1HMRS studies of tumor treatment effects indicated a decrease in NAA in both tumor and radiation necrosis consistent with the loss of functioning neurons in both pathologies; however, an increase in choline in tumor recurrence (reflecting the increased cellularity of malignant tissues) compares to the decreased choline associated with necrosis. Higher glucose utilization rates for lesions in which lactate is detected usually indicate high-grade gliomas. The various biochemical components provided strong evidence for the presence of tumor since increased choline and a lactate peak would not be expected in necrotic tissue^[6].

Cho is the most important metabolite for the distinction between tumor and radiation damage, particularly if a pre-treatment choline value is obtained. A persistent or newly arisen distinct choline accumulation indicates residual or recurrent tumor after radiation therapy. 1HMRS is able to diagnose tumor recurrence early and unambiguously in cases where focal choline accumulation is detected. Meanwhile, Cho concentration is thought to be a useful marker for the evaluation of

both early and late post-radiation response. Delayed cerebral necrosis (DN) is a significant risk for brain tumor patients treated with high-dose irradiation. The primary diagnostic information for differentiating DN from tumor lay in the normalized MRS peak areas for Cho and Cr: a marked depression of the intracellular metabolite peaks from Cho, Cr, and NAA indicates DN, and median to high Cho with easily visible Cr metabolite peaks is labeled progressive/recurrent tumor^[7].

Proton MR spectroscopic imaging also provides diagnostic and monitoring information after radiosurgery^[8]. Radiation response is usually observed as a reduction of Cho and Cr levels and an increase in lipid levels, typically within 6 months of treatment. Lipids are also detected probably as a result of cellular breakdown products. Complete necrosis is manifested spectroscopically as an absence of all metabolites; increases in Cho correlated with poor radiologic response and suggested tumor recurrence. Most therapy-induced damage occurs in combination with zones of viable tumor. Multivoxel spectroscopy and spectroscopic imaging delineate areas of tumor, radiation-induced changes and viable brain. Successful therapy is heralded by a progressive decrease in level of choline and modest increases in NAA.

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