Minireview

Multivoxel Magnetic Resonance Spectroscopy of Brain Tumors

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Abstract
Magnetic resonance spectroscopy (MRS) is becoming more widely available for clinical applications and is able to provide information about the metabolic properties of regions of normal and abnormal tissue morphology. A critical question for the clinical management of patients with brain tumors is whether multivoxel MRS is able to add new information to the high-quality anatomical data provided by conventional MR imaging techniques and whether this information is relevant for the diagnosis and clinical management of such patients. In this article, the state of the art for acquiring and analyzing multivoxel MRS data is reviewed and placed in context relative to imaging findings for metastatic and primary brain tumors. The MRS data are seen to provide unique information that when combined with high-quality anatomical MR images has implications for defining tumor type and grade, directing biopsy or surgical resection, planning focal radiation or biological therapies, and understanding the mechanisms of success and failure of new treatments.

Introduction
Although patients with brain tumors typically have a relatively poor prognosis, the time to progression and median survival can be mediated for selected subpopulations of patients by applying aggressive therapy (1–7). Selecting the treatment that is most appropriate for a specific patient and directing that therapy to the region of active tumor is crucial for achieving the best possible outcome. Critical factors in evaluating prognosis are tumor type, grade, and volume (1, 5, 8, 9). Despite the excellent soft tissue contrast provided by MRI3, the sensitivity and specificity with which this modality defines tumor type and grade is limited. This is partly attributable to the existence of Gadolinium-enhanced necrosis that may be mistaken for tumor and partly to the difficulty in distinguishing between tumor, edema, and nonspecific treatment effects in the region of hypointensity on T2-weighted images (10, 11).

Overcoming these problems requires the development of new imaging modalities that highlight functional or metabolic properties of the tumor. Although there have been studies that have investigated positron emission tomography and single photon emission tomography as candidates for such analysis (12–15), there would be a considerable savings in cost and patient discomfort if similar information could be defined using an MR methodology. Two new imaging methods that have been considered for this application are perfusion-weighted and diffusion-weighted MRI (16–23). These make use of echo planar pulse sequences to examine the tissue architecture and microvasculature in the lesion and surrounding brain parenchyma. Although they do provide information about physiological properties of the tumor that have been linked to cellularity, structural integrity, andangiogenesis, they are not yet used routinely for clinical management of patients.

Single voxel proton MR spectroscopy has been applied for characterizing the metabolic signatures of brain tumors for some time (24–32). There is strong evidence for a reduction in N-acetylaspartate and increase in choline containing compounds in tumor relative to normal brain parenchyma (28, 29). Also, for some metastatic lesions and for high-grade gliomas, typically, there are resonances corresponding to lactate or lipids (26, 27). Initial reports concerning the potential for single voxel MRS in tumor grading gave varied results with a large variability in data quality between institutions (30). With the introduction of automated packages for performing single voxel proton MRI on clinical scanners, the quality and reproducibility of the data have been improved. Multivariate statistical analysis procedures have also been applied in an attempt to identify patterns that characterize specific tumor types and grades (31, 32). More recent studies have also included the acquisition of spectra with both short and long echo times so that levels of myo-inositol, glutamine, and glutamate can be included in the analysis and provide the potential for improved discrimination between different types of lesions (33, 34).

Although single voxel proton MRS is a relatively rapid method for obtaining information about the metabolism in a 4–8-cc region within the lesion, it does not address spatial heterogeneity and is unable to contribute to defining the spatial extent of the lesion. These factors are particularly important for planning focal treatments such as radiation and surgical resection and for following response to therapy. To address these issues, it is necessary to consider multivoxel proton MRSI (1-H). In this article, we examine the limitations of conventional MRSI for metastatic and primary brain tumors,

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3 The abbreviations used are: MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MRSI, magnetic resonance spectroscopic imaging; CNI, choline to N-acetylaspartate index; PRESS, point resolved acquisition mode.
discuss techniques for obtaining 1-H MRSI of brain tumors, and present examples of situations in which the information that is obtained differs from conventional MRI. The objective will be to highlight situations where the 1-H MRSI has the potential for changing the clinical management of the patient and thereby make a significant contribution to improving the outcome. We will focus on the application to adult brain tumors as the types of lesions that occur in pediatric patients and prognosis are quite different.

MRI of Metastatic Lesions
For these lesions, the volume of Gadolinium enhancement on T1-weighted spin echo or gradient echo images is thought to encompass all of the active tumor. In many cases, there are also central regions of hypointensity within the enhancing lesion that correspond to necrosis. The region of hypointensity on the T1-weighted image and corresponding hyperintensity on T2-weighted images that typically surrounds the enhancing volume is thought to correspond to edema or nonspecific treatment effects rather than to infiltrative tumor. Detection of small lesions and improved visualization of larger enhancing lesions is possible using double or triple doses of Gadolinium (35). The number and size of metastatic lesions within the brain influences the decision as to whether the most appropriate treatment is surgery, radiosurgery, or whole brain radiation therapy (5–7). Other factors taken into account are the status of the primary lesion and metastases in other organs.

Fig. 1 gives three examples of Gadolinium-enhanced T1-weighted and T2-weighted images from patients with brain metastases. The first patient had a metastasis from melanoma. Even at this time, the lesion had a small central region of hyperintensity corresponding to necrosis. It grew rapidly and survival was only for an additional 2 months. The second patient had a large region of central necrosis at the time of presentation for this scan. The primary lesion was from lung and was stable at this time. Despite treatment with gamma knife radiosurgery, the lesion did not respond, and the patient survived an additional 3 months. The third patient also had a primary lung lesion and had received prior radiation therapy for the metastasis on the left side of the brain. The enhancing lesion in the vermis was seen as a new lesion on a follow-up imaging study. Treatment at this time was by gamma knife radiosurgery to both the original and the new lesion. After radiosurgery, there was a significant reduction in the size of the newer lesion.
lesion and the patient survived an additional 33 months with no additional treatment.

**MRI of Primary Brain Tumors**

Gadolinium-enhanced T1-weighted MR images from 12 patients with gliomas are seen in Fig. 2. These are the most common types of primary brain tumor in adults and are extremely heterogeneous in terms of imaging appearance and in their response to therapy. They are infiltrative lesions with poorly defined margins on both T1- and T2-weighted images (36–39). The prognosis varies significantly with tumor grade, ranging from a median survival of 7–10 years for grade 2 lesions, 2–4 years for grade 3 lesions, and < 1 year for grade 4 lesions (1, 2). Definition of grade is based upon histological analysis of tissue samples obtained by biopsy or during surgical resection (8, 9). Because it is common for there to be regions of different tumor grade within the same lesion, directing the surgeon to the region that is likely to be of highest grade is critical to obtain representative samples for histological analysis. Although a tumor is known to be outside the lesion as well, the enhancing lesion is widely used as the target for surgery resection or for planning radiation therapy (11).

As can be seen in Fig. 2, grade 2 gliomas are typically nonenhancing after injection of Gadolinium. They are identified as a region of hypointensity on T1-weighted images and hyperintensity on T2-weighted images. Grade 3 gliomas have large regions of hypointensity on T1-weighted images but may also have regions in which the blood brain barrier is compromised and which therefore appear bright on postcontrast T1-weighted images. Although grade 4 gliomas may also be nonenhancing, it is more common for them to have substantial regions of Gadolinium enhancement with a central area of hypointensity that corresponds to necrosis. Higher doses of Gadolinium do improve the visibility of the enhancing lesion and heavily T2-weighted fluid attenuated inversion recovery images contribute to distinguishing regions of edema and nonenhancing tumor from cerebrospinal fluid and cysts (36–39). Despite the widespread use of MRI for assessment of gliomas, there are many circumstances where the data are ambiguous in terms of defining tumor margins and in distinguishing treatment-induced necrosis from recurrent tumor. It is with these difficulties in mind that 1-H MRSI has been proposed as a technique that can add to the evaluation and characterization of these lesions (40–51).
Methods for Obtaining Multivoxel 1-H MRSI

The most straightforward method for generalizing single voxel MR spectroscopy is to select a larger volume of interest and then apply phase encoding to obtain localization to a one-, two-, or three-dimensional array of voxels (52). PRESS or stimulated echo acquisition mode (STEAM) are the two most common methods used for volume selection, with PRESS being preferred when the echo time allows because of its intrinsically higher signal to noise ratio. An advantage of this approach is that the volume can be selected to eliminate as much of the s.c. lipids as possible and to avoid regions likely to cause large variations in susceptibility such as the sinuses. This permits improved shimming and provides spectra with narrower peaks and higher signal to noise (46–51). The advantage of obtaining a two-dimensional or three-dimensional array of spectra is that it is possible to observe not only heterogeneity within the lesion but to examine surrounding tissue that may appear normal on MRI. This provides a reference for comparing metabolite levels in the tumor and makes it possible to identify regions of abnormal metabolism outside the morphological lesion (47–50). For treatment planning and long-term follow-up, it is necessary to evaluate tumor progression, and it is critical to obtain three-dimensional coverage of a large volume of interest.

Most of the studies that have been performed to date have used echo times of 144 or 270 ms, which provide spectra dominated by five different metabolite peaks: choline; creatine; N-acetylaspartate; lactate; and lipid (46, 47). The choline peak includes a number of different choline-containing compounds and reflects membrane synthesis and turnover. Creatine is important in cellular energetics, whereas N-acetylaspartate is a neuronal marker. Lactate reflects anaerobic metabolism, and lipids are observed in regions of cellular breakdown caused by necrosis. Fig. 3 shows examples of spectra from normal brain tissue, necrosis, and regions from different types of brain tumors. The normal brain has N-acetylaspartate that is approximately twice the intensity of choline and creatine. Tumor generally has decreased N-acetylaspartate and increased choline and variable levels of creatine. Peaks corresponding to lactate and lipid may be present in regions of necrosis for both metastatic and primary brain tumors (47). Because the nominal voxel size for a volume head coil at 1.5 T is 1 cc, individual voxels may contain a mixture of tumor, necrosis, and normal brain tissue.

Although it is possible to obtain three-dimensional 1-H MRSI data with chemical shift selective water suppression and conventional volume selection radiofrequency pulses, there are many circumstances where the water and lipid suppression are inadequate and compromise the quality of the data obtained. This is especially true for patients who have had surgical resection and can be a severe problem for patients that are treated by brachytherapy using permanent radioactive seeds. To improve the quality of water suppression, it is possible to implement alternative radiofrequency pulses that are able to provide improved spatial and frequency selection (53, 54). Another critical tool for obtaining full coverage of the lesion and for sharpening the edges of the selected volume has been the implementation of very spatially selective saturation bands (55). These have a very sharp transition band and can be applied parallel to the edges of the selective volume to make it more cubic in shape or at an oblique orientation to conform the volume to the anatomy.

Other approaches for obtaining volumetric coverage of the lesion are to use multislice and multiple echo time techniques for providing spatial localization in a time effective fashion (56–58). In this case, lipid suppression has typically been provided by spatial and frequency selective pulses, inversion recovery, and spatial saturation pulses. These techniques have the advantage of obtaining complete in plane coverage but may be limited close to the sinuses or surgery cavities because of susceptibility artifacts. For multislice acquisitions, it is necessary to have a slice gap to avoid cross-talk, and two acquisitions are required to provide complete coverage of the lesion. Another strategy for obtaining volumetric coverage of the brain with a reasonable acquisition time is to use echo planar spectroscopic imaging with either oscillating...
gradients in one spatial dimension or spiral sampling within a given plane (59–61). This has been shown to provide good data quality for normal volunteers and patients with neurodegenerative diseases but may be limited for patients with brain tumors once they have undergone surgical resection. Future studies are expected to use a hybrid PRESS-echo planar spectroscopic imaging technique with spatially selective saturation bands that allow greater k-space coverage but eliminate signals from regions that are likely to cause susceptibility artifacts.

Reconstruction and Postprocessing of 1-H MRSI Data

The reconstruction of 1-H MRSI data and analysis of the resulting arrays of spectra combines fourier transforms and apodization with automated methods of spectral processing to provide data that can be interpreted by visual inspection or quantified to generate maps of the spatial distribution of different metabolites (62). The first step is to apply an apodization function to the k-space-free induction decays and perform a fourier transform to produce k-space spectra. The next step is to reconstruct the spatial dependence of the data. For spiral or irregular k-space sampling, the approach is to first re-grid the k-space data onto a rectangular array (59–61). For conventional phase encoding, this step is unnecessary. To center the data at the most appropriate spatial location, it is possible to phase-weight the k-space array with the appropriate voxel shift. This is followed by applying any required spatial apodization and then performing the spatial fourier transformations. The resulting array of spectra will typically have spatially dependent frequency and phase errors that need to be corrected, as well as baseline variations because of residual water.

Numerous methods for estimating frequency, phase, and baseline corrections for spectral data have been reported in the literature (63–69). Characteristics of the 1-H MRSI data that guide the choice of methodology are the larger number of spectra that need to be considered, and the need for whatever method is chosen to be robust to differences in signal to noise and peak configurations corresponding to different tissue types. One approach is to acquire a separate dataset with no water suppression (64). This is time consuming, but the high signal to noise of the water resonance allows for an accurate estimate of frequency and phase parameters. Provided that the data acquisition window is timed correctly, there should be no need for frequency-dependent phase correction, and the phase of the water in each voxel should be the same as for the other metabolites.

An alternative to acquiring a separate water reference dataset is to deliberately limit the water suppression to leave behind a relatively large water peak in the spectrum. The accuracy of this approach depends upon the quality of the volume selection and out of voxel suppression because incomplete suppression of water outside the excited volume may cause spurious peaks with different frequency and phase to be folded into the selected volume. Another strategy is to make use of prior knowledge of possible peak locations (69), obtain estimates of corrections from metabolite peaks in voxels that have sufficient signal to noise, and then apply spatial interpolation to fill in corrections for voxels with low signal to noise (62). This provides arrays of phased and frequency referenced spectra for visual correlation with the anatomy as shown in Figs. 4–7.

More quantitative analysis of the data requires the estimation of peak locations, heights, and areas. Prior knowledge of relative peak locations is valuable for performing this analysis and provides the basis for a robust method that identifies statistically significant peaks, determines peak heights, and calculates peak areas by integration within a defined range of frequencies for each metabolite. Additionally, more sophisticated fitting algorithms can be applied to spectra that have sufficient signal to noise for the optimization routines to be reliable (e.g., 69). The output of the analysis is a number of spatial maps of metabolite parameters that can be applied to identify regions of normal and abnormal metabolism. As indicated in a previous publication (62), additional corrections for spatial variations in intensity caused by the data acquisition procedures may also be required if comparing relative intensities of metabolites such as choline, creatine, N-acetylaspartate, lactate, and lipid.

Our studies have indicated that the relative increase in choline and decrease in N-acetylaspartate is critical for defining the spatial extent of the metabolic abnormality corresponding to active tumor. We have developed an index for clinical applications, termed the CNI, that describes this quantity and can be derived automatically from a given 1-H MRSI dataset without reference to the anatomical images (70). The CNI is a statistical quantity that is normalized by the range of metabolite levels in normal tissue and can be used to infer the probability of each voxel that is abnormal. Note that this analysis cannot guarantee that the abnormality is attributable to tumor in a randomly selected population because other pathologies may also result in increased choline and decreased N-acetylaspartate. However, it does provide an objective method for highlighting regions that have spectral characteristics consistent with tumor. The differences in CNI with tumor grade and correlation with histology are summarized in recent publications (70–73). Similar indices can be defined to represent the regions with abnormal choline relative to creatine and abnormal creatine relative to N-acetylaspartate.

Differences in MRI and Metabolic Lesions

A critical question for using 1-H MRSI for evaluation of brain tumors is whether the spatial extent of the metabolic lesion is different from the Gadolinium-enhancing region and hyperintensity on T2-weighted images (47). If there is no distinction between these lesions, there may be no added value for the 1-H MRSI data over and above conventional MR images. For metastases, the focus is on whether it is possible to distinguish between regions of tumor and enhancing necrosis. In practice, it is difficult to get definitive evidence because it is rare for such lesions to be biopsied. Evaluation

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of whether a lesion corresponds to active tumor is typically based on whether it subsequently gets larger on Gadolinium-enhanced MRI. Another complication is that as the lesion gets larger, it forms central necrosis and, with a voxel size of 1–2 cc, it is difficult to obtain spectra free from partial volume effects of tumor and necrosis. In a study of 18 patients with brain metastases that were treated with gamma knife radiosurgery, we found that all but two of the lesions had decreased N-acetylaspartate, as well as a peak corresponding to lactate or lipid. Of the lesions that were followed after treatment, all lesions that showed decreases in the volume of the enhancing lesion also showed reduction in lactate, lipid, and choline peaks. There were also three lesions that showed reduced metabolism but had stable or slightly increasing volume. Lesions that showed increased enhancement on long-term follow-up also had a corresponding increase in choline and lactate or lipid peaks (47). From this study, it appears that the MRSI can provide additional confidence in as to whether lesions are responding to therapy and in some cases may give information that is not present in anatomical images.

The situation is more complex for patients with gliomas as there is the need to separate tumor from necrosis and to distinguish nonenhancing tumor from edema and treatment effects. To evaluate the feasibility of using 1-H MRSI in this manner, we have looked at the differences in anatomical and metabolic lesions in patients with newly diagnosed gliomas who had been scanned before surgical resection (50, 51, 71–73). The goal was to determine how many of these lesions were enhancing and had the voxel with most abnormal metabolic signature (maximum CNI) outside the enhancing volume. Of 46 grade 2 lesions, 13% were enhancing and 95% had their maximum CNI in the nonenhancing region of the T2 lesion. The mean and the median of the maximum CNI were both 6.9. It was much more common for the grade 3 lesions to be enhancing than for the grade 2 lesions, with 23% considered as weakly enhancing and 38% fully enhancing. The location of the maximum CNI was in nonenhancing tissue for 83% of the lesions, the median maximum CNI was 7.1 and the mean maximum CNI was 8.0. For the 31 grade 4 patients that were studied, 75% had visible regions of macroscopic necrosis and all of them had enhancing regions. There was a large variation in the maximum CNI within each lesion and, although the median value was 6.9, there were some lesions with very high CNIs so that the mean value was 9.4. Fig. 5 shows examples of grades 2, 3 and 4 gliomas with regions having abnormal CNI highlighted. It is clear from these types of studies that the Gadolinium enhancement does not usually correspond to the region with highest choline. Another interesting finding was that the region...
Potential for Tumor Grading

Given the differences in spatial extent of metabolic and anatomical lesions, the question arises as to whether the metabolic data are able to contribute to defining tumor type and grade. In a study that used two-dimensional 1-H MRSI, Preul et al. (34) found an excellent classification of patients using a multivariate pattern recognition analysis of peaks corresponding to choline, creatine, \(N\)-acetylaspartate, lactate, lipid, and alanine. From looking at the metabolite levels in each class, it was clear that meningiomas were distinguished as they were the only lesions that had alanine. Grade 2 gliomas tended to have low lactate and lipid, some \(N\)-acetylaspartate, and some creatine. Grade 3 gliomas tended to have low lactate and lipid, less \(N\)-acetylaspartate and creatine, with higher choline. Grade 4 gliomas tended toward high lactate and lipid, with very low \(N\)-acetylaspartate. Although these results were very promising, there has not yet been a prospective study using the statistical classification that these authors derived.

One of the complications in analyzing data obtained with a multivoxel data acquisition technique is in determining which spectrum to consider for each lesion. Suggestions that have been made include using the most abnormal voxel and the average of all voxels within the lesion. Both of these approaches involve a subjective decision that takes the anatomical appearance of the lesion into account. For example, does the lesion include the entire T2 abnormality or is it restricted to the enhancing volume. As seen in Fig. 5, the spectral characteristics of these regions may be quite different (72). The same issue is present with single voxel analysis, but in that case, the decision is made implicitly at the time of data acquisition by the choice of the selected volume. Our studies have suggested that although it may be possible to detect mean differences between populations of gliomas with different grades based upon metabolite levels, there is considerable overlap, both for mean metabolite levels or for the most abnormal voxels within the T2 lesion (72). Because there are such large variations in anatomical appearance, it

Fig. 5. Arrays of spectra from grade 2 (left), grade 3 (middle), and grade 4 (right) gliomas. The acquisition parameters were as in Fig. 4. Note the heterogeneity of the spectral patterns in these lesions. Spectra that have metabolic abnormalities are shaded, and those with peaks corresponding to lactate or lipid are marked with a "*".
seems likely that both anatomical and metabolic patterns are relevant for classification and that whichever procedure is considered should ensure that the influence of both types of data are explicitly considered in the analysis. Information such as relative cerebral blood volume or apparent diffusion coefficient may also help in grading tumors and in distinguishing between tumors and other types of mass lesions.4

Potential for Evaluating Response to Therapy

Another potentially important clinical role for 1-H MRSI is the ability to make an early evaluation of whether a lesion has responded to therapy. If this were possible, it would allow tailoring therapy to each individual patient and modifying an ineffective treatment strategy before the lesion shows a large increase in volume. It would also be possible to avoid giving unnecessary treatment in the case that an increase in enhancing volume is attributable to formation of treatment-induced necrosis as opposed to recurrent or residual tumor. For 1-H MRSI to be included in the clinical management of the patient in this manner, it is important to map out both the temporal and spatial distribution of metabolite changes in response to the therapy of interest. This requires the use of three-dimensional 1-H MRSI and is most easily achieved for the case of focal therapies such as surgery or radiation (74). Registration of the MR images and 1-H MRSI data are critical for correlating data from such sequential examinations.

We have already presented some of our results for gamma knife radiosurgery of metastatic lesions. To study this application for gliomas requires a consideration of whether the treatment volume covered the metabolic lesion, as well as how the lesion responded to therapy. It is clear from our analysis of data from 36 patients with recurrent gliomas that the Gadolinium-enhancing lesion is not an adequate target for gamma knife radiosurgery in at least 50% of the recurrent grade 3 and grade 4 lesions that were considered (48, 49). Patients for whom the metabolic lesion extended outside the gamma knife target had a larger increase in enhancing volume 6 months after therapy, shorter time to additional treatment and worse survival than patients with either no metabolic lesion or a metabolic lesion contained within the target (48). Fig. 6 shows an example of the time course of response to gamma knife radiosurgery for a patient who had a relatively small initial lesion that was inside the target. The anatomical and metabolic lesion shrunk by the first follow-up scan at 2 months after therapy and shrunk additionally by 8 months after treatment. The changes in the metabolic lesion were a reduction in choline and increase in N-acetylaspartate. The latter was interpreted as being because of the return of normal brain tissue into the voxel as the tumor shrunk.

Fig. 7 shows an example of a patient who had a much larger metabolic than anatomical lesion before radiosurgery.
The target addressed only a few abnormal voxels in the center of the metabolic lesion. Two months after therapy, the choline had not changed significantly inside the target, but there was an increase in a resonance corresponding to lactate or lipid. The voxels outside the irradiated region did not change. Three months after therapy, the choline had decreased inside the target and the lactate/lipid had increased additionally. The Gadolinium-enhancing region increased in volume at both time points, and hence, the treatment was considered to have failed. If we had used the metabolite levels as indicators of response, the treatment would have been classified as having some effect within the target region. Similar findings were observed in patients being treated with brachytherapy (46). For fractionated radiation therapy, where the treated volume is much larger and the dose distribution more variable, it is necessary to take into account changes in the normal appearing brain tissue caused by intermediate doses of radiation, as well as the changes within the tumor (74).

**Conclusions**

From the studies that have been performed thus far, it is clear that 1-H MRSI is an important adjunct to anatomical imaging for evaluation of tumor type and grade, as well as for targeting and evaluating response to therapy. Although the prognostic value of this technique is still under investigation, there is every reason to expect that it will provide information that will be relevant for choosing the most appropriate therapy for individual patients and for understanding the mechanisms of success and failure of new treatments. This is particularly critical for screening therapies based upon the biological properties of the tumor, where it is important to know whether the lack of response was because of the agent being unable to access the tumor or to the lesion being insensitive to that particular approach. Possibilities for improving the sensitivity and specificity of the 1-H MRSI data include the use of shorter echo times, the application of radiofrequency coils with improved signal to noise and of magnets with higher field strength.

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**References**

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