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Imaging of Brain Tumors: MR Spectroscopy and Metabolic Imaging

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Introduction

Localized proton MR spectroscopy (MRS) of the human brain, first reported more than 20 years ago,(1–3) is a mature methodology that is used clinically in many medical centers worldwide for the evaluation of brain tumors.(4) While there have been studies of human brain tumors using heteronuclei such as phosphorus (³¹P) and sodium (²³Na),(5,6) by far the most spectroscopy studies use the proton (¹H) nucleus, because of both its high sensitivity and ease of implementation on commercial MRI scanners. This review will therefore focus on proton MRS in human brain tumors.

There are two classes of spatial localization techniques for MR spectroscopy; single-voxel (SV) techniques (commonly used methods includes ‘PRESS’(7) and ‘STEAM’(8)) which record spectra from one region of the brain at a time, or multi-voxel techniques (‘MR spectroscopic imaging’ (MRSI), also called ‘Chemical Shift Imaging’ (CSI)(9)) which simultaneously record spectra from multiple regions and thereby map out the spatial distribution of metabolites within the brain. MRSI is typically performed in 2- or 3-dimensions, but does not usually include full brain coverage. While SV-MRS and MRSI each have their own advantages and disadvantages (e.g. in terms of spectral quality, scan time, spatial resolution, spatial coverage, and ease of use/interpretation), a key consideration for brain tumors is their metabolic inhomogeneity. For instance, the spectrum from the necrotic core of a high-grade brain tumor is quite different from a spectrum from the actively growing rim, while peri-tumoral edema is different from tumor invasion into surrounding brain tissue; for these reasons and others, high-resolution MRSI is often favored for evaluating brain tumor metabolism. For a detailed discussion of the relative merits of SV-MRS and MRSI, please see reference.(10)

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Early in the development of human brain proton MRS, it was realized that brain tumors exhibited markedly different spectra from normal brain tissue.(4,11) It was found that nearly all brain tumors have decreased N-acetyl aspartate (NAA) signals, and often also have increased levels of Choline (Cho), leading to increased Cho/NAA ratios. The decrease in NAA is widely interpreted as the loss, dysfunction or displacement of normal neuronal tissue since NAA is believed to be primarily of neuronal and axonal origin.(12) The 'Cho' signal actually contains contributions from several different choline-containing compounds, which are involved in membrane synthesis and degradation; it has been suggested that it is increased in brain tumors due to increased membrane turnover. *In vitro* studies have indicated that the elevated Cho signal in brain tumors is due to increased levels of phosphocholine (PCho). Cho has also been found to correlate well with the cellular density of the tumor,(13) and the degree of tumor infiltration into brain tissue.(14) The use of MRSI to map Cho levels has therefore been suggested as a method for defining tumor boundaries in treatment planning (see section 5 below).

Other relatively common metabolic changes in human brain tumors are elevated signals in the lactate and lipid region of the spectrum,(15) and also sometime increased levels of *myo*-inositol (mI) in short echo time (TE) spectra.(16,17) The increase in lactate is most likely the result of anaerobic glycolysis,(5,15,18) although it could also be due to insufficient blood flow leading to ischemia, or possibly also due to necrosis. The observation of elevated lipid levels is believed to be associated with necrosis and membrane breakdown.(19–21) Increased levels of mI are believed to reflect increased numbers of glial cells, which have been reported to contain high levels of mI, and in particular have been reported to be high in grade II gliomas.(16) It has also been reported that patients with gliomatosis cerebri may exhibit elevated inositol levels, even in the absence of increased Cho.(22) Examples of brain tumor spectra are given in Figures 1 and 2.

Tumor classification

Early in the development of MRS of brain tumors, a commonly asked question was whether or not MRS could help to diagnose tumor type and grade non-invasively, since this would have an influence on management decisions and prognosis. While MRI is without doubt the most sensitive modality available for the detection of brain tumors, its specificity is low, and several different tumor types (as well as lesions of other etiologies) may share a similar MRI appearance. Two particularly important imaging diagnoses are the differentiation between high-grade and low-grade tumors, or between neoplastic and non-neoplastic lesions (see section 3), respectively. High-grade brain tumors are usually treated more aggressively than low-grade tumors, and so preoperative diagnosis of tumor grade is important for this reason.

In astrocytomas, several studies, but not all, have suggested an association between tumor grade and Cho levels, with the higher grade tumors having greater Cho concentrations.(10,23,24) This would appear consistent with the more aggressive tumors having higher membrane turnover and cellular density. However, some studies have found high-grade tumors (e.g. grade IV glioblastoma multiforme (GBM)) to have lower levels of Cho than grade II or grade III astrocytoma.(19) This may be due to the presence of necrosis in high-grade tumors, particularly those with necrotic cores, since necrosis is associated with low levels of all metabolites.(25) Since tumors are commonly heterogenous, with necrotic cores, proliferative rims and invasion of surrounding brain tissue, the spectrum may vary greatly depending on the region that is sampled by MRS (see Figure 3).(26) Hence, the region-of-interest chosen for analysis will have a large influence on the results, and, as stated above, MRSI is generally considered preferable since it allows metabolic heterogeneity to be evaluated, and the voxel with the maximum Cho signal to be chosen for analysis.(27) One recent MRSI study used MR perfusion imaging (arterial spin labeling) to guide the spectral

measurement location; in regions with elevated flow, Cho (as well as glutamate plus glutamine (Glx), and lactate plus lipid) was found to be higher in high-grade compared to low-grade gliomas.(28) No metabolic differences between high-grade and low-grade gliomas were found in normal or hypoperfused tumor regions.

Using sophisticated analysis schemes and/or pattern recognition techniques, several groups have been able to use proton MRS or MRSI to accurately diagnose different types of neoplasia (29–32). However, because of lesion variability, heterogeneity, overlap between different tumor types, and also dependence on data collection and analysis techniques, these results have proven difficult to replicate in general clinical practice. In most cases, therefore, it is very difficult for a clinician to use MRS alone to diagnose a brain lesion with high confidence. Rather, MRS should perhaps be seen as an adjunct technique that may contribute to differential diagnoses that are being considered on the basis of MRI, clinical and other information. For instance, as depicted in figures 1 and 2, high Cho levels are typically seen in non-necrotic high-grade brain tumors (for instance anaplastic astrocytoma, GBM, primary CNS lymphoma), while necrotic GBM and metastases are characterized by low levels of all metabolites and increased lipids). Meningiomas are usually readily diagnosed based on conventional imaging features, but the diagnosis may be additionally confirmed by the presence of a signal from alanine (a doublet centered on ~1.47 ppm), which has been reported to be elevated in many meningiomas.(33)

For discriminating solitary metastases from primary brain tumors, it has been suggested that investigation of peri-enhancing tumor regions may be useful; whereas gliomas are often invasive lesions which show elevated Cho in surrounding tissue, metastatic lesions tend to be more encapsulated and do not typically show high Cho signals or other abnormalities outside the region of enhancement.(34,35) Metastatic lesions and glioblastomas nearly always show elevated lipid peaks; thus, if the lesion does not exhibit mobile lipid signals, anaplastic glioma is more likely.(36)

Tumors vs. non-neoplastic lesions

If a lesion can be confidently diagnosed as non-neoplastic, an invasive brain biopsy procedure may be avoided and a different treatment course, depending on the lesion etiology, may be considered. Examples of non-neoplastic lesions that may mimic brain tumors on conventional imaging are infectious (including abscess) or ischemic lesions, or demyelinating lesions (e.g. tumefactive demyelination). Differentiation between tumors and non-neoplastic lesions using conventional MRI may be challenging. While MRI is a sensitive technique for detection of brain lesions, the specificity and capability of conventional MRI for distinguishing between benign and malignant lesions is limited. Low-grade gliomas and many non-neoplastic lesions, such as early stage lesions or diffusely infiltrating lesions, may not exhibit a mass effect. Low-grade gliomas may present as small T₂ hyperintense lesions, that may be difficult to differentiate from focal cortical dysplasias or other pathologies. (37) The use of a contrast agent may also not increase diagnostic specificity, since various non-neoplastic processes are often associated with disruption of the blood-brain barrier, and not all tumors enhance.(38)

Since tumors typically exhibit elevated Cho and decreased NAA, the greatest benefit of adding MRS to a clinical examination may be in including (or excluding) diagnoses with markedly different spectroscopic patterns, e.g. strokes, or focal cortical dysplasias, neither of which are expected to have increased Cho. Conversely, differentiation between tumors and acute demyelinating lesions based on MRS alone, may be difficult as both entities typically present with elevated Cho and decreased NAA, and well as often increased lactate.(39) A

combination of conventional MRI with modern techniques of physiological imaging, in particular, perfusion MRI, can therefore improve the classification.

Several studies have evaluated the utility of ^1H MRS to differentiate between tumors and non-neoplastic lesions (40–44) or compared spectroscopic characteristics of specific groups of neoplastic and nonneoplastic lesions.(45–47) Two recent retrospective studies evaluated the value of MRSI (38) and single voxel MRS (48) to differentiate between brain tumors and non-neoplastic lesions. In the ^1H MRSI study performed at a TE of 280ms, 84% of 69 brain lesions (36 tumors) were correctly classified using the ratios NAA/Cho, NAA/Cr, and Cho and NAA signal areas normalized to signal areas in a control region.(38) There were 5 cases of tumors misclassified as nonneoplastic lesions (anaplastic astrocytoma WHO grade II, infiltrating astrocytoma WHO grade III, gliomatosis cerebri WHO grade II, oligodendroglioma WHO grade II, ganglioglioma WHO grade II) and 6 non-neoplastic lesions classified as tumors (the diagnoses included demyelination, radiation necrosis, postsurgical gliosis, and stable lesions not confirmed on pathologic examination). In a subgroup of 32 lesions, perfusion MRI also showed significant differences between high-grade and low-grade tumors, and also between high-grade tumors and non-neoplastic lesions. By combining both MRSI and perfusion MRI, a sensitivity of 72.2% and specificity of 91.7% in differentiating tumors from nonneoplastic lesions was achieved with cutoff points of NAA/Cho ≤ 0.61 and rCBV ≥ 1.50 corresponding to tumor diagnosis.(38) Examples of benign and malignant lesions from this study are shown in figures 4 and 5. In a single voxel MRS study of 84 solid brain masses performed at a short TE (30 ms) and long TE (136 ms), presence of tumor was indicated when mI/NAA ratio (obtained at short TE) was greater than 0.9 and when Cho/NAA ratio (obtained at the long TE) was greater than 1.9.(48) In this study, the group of tumors was represented by gliomas of WHO grade II and III. (48) In a retrospective study of 32 children with primary brain lesions (19 tumors, 13 benign lesions), 78% of originally grouped cases could be correctly classified based on the Cho/Cr ratio.(10)

Typical imaging features of the most common intracranial masses in adults - primary neoplasms (high-grade and low-grade), secondary (metastatic) neoplasms, lymphoma, tumefactive demyelinating lesions, abscesses, and encephalitis on perfusion MRI, diffusion MRI, and proton MR spectroscopy and examples of individual cases were summarized in a recent review.(49) The role of commonly used advanced imaging techniques in differentiation among intracranial masses in adults was retrospectively evaluated (49,50) and the accuracy of MRI-based strategy to differentiate among histologically-confirmed lesions was assessed.(50) A practical MRI-based algorithm including results from post-contrast MRI, diffusion-weighted MRI, perfusion MRI, and ^1H MRSI was proposed to improve the diagnosis and classification of these lesions (50) (Figure 6). The diagnostic strategy was evaluated based on 40 patients who had complete data from all included imaging modalities; to differentiate between tumors and non-neoplastic lesions, the accuracy, sensitivity, and specificity of the classification strategy was 90%, 97%, and 67%.(49,50) These results suggest that integration of advanced imaging techniques with conventional MRI may help to improve the reliability of the diagnosis and classification of brain lesions.(51)

Generally, spectra from brain abscesses are quite different from those of high-grade neoplasia – they usually have low Cho signals, as well as decreased NAA and Cr, and often also exhibit increased signals from amino acids that are not typically seen in neoplasia, e.g. alanine, acetate, acetoacetate, succinate, in variable amounts depending on the source of the primary infectious process.(52,53) Therefore, the distinction between abscess and neoplasm should be straightforward using MRS, which may add confidence to the diagnosis made by other techniques (e.g. diffusion-weighted imaging (54)).

Prediction of survival

Long-term prognosis for patients with high-grade gliomas is poor despite aggressive treatment strategies. Nevertheless, survival time can be quite variable, and is important information for patients and their families. The ability of MRS to predict survival has been evaluated in both adult and pediatric brain tumor populations. A series of papers have evaluated the role of ^1H MRSI in prediction of survival of GBM patients.(55–58) In a recent study, conventional MRI, ^1H MRSI, diffusion and perfusion MRI were used in a group of grade IV glioma patients (examined before surgery and treatment); Kaplan–Meier survival curves were generated and Cox proportional hazards model was applied to evaluate the utility of selected parameters on patients' survival.(56) Survival was relatively poor in patients with lesions exhibiting large areas of contrast enhancement, abnormal metabolism or restricted diffusion. Specifically, of the parameters involving tissue volumes, high relative volumes (in the T_2 hyperintense lesion) of a) combined contrast enhancement and necrosis areas, b) the region with abnormal (elevated) Cho/NAA index, and c) the region with ADC less than 1.5 times of the ADC in normal appearing white matter were negatively associated with survival. Survival time was also negatively associated with high lactate and lipid levels, and the ADC within the enhancing volume. None of the evaluated perfusion parameters was predictive of survival.(56) In another study, ^1H MRSI was applied with MRSI, as well as conventional, diffusion, and perfusion MRI in 68 GBM patients with a median age of 58 years, examined after surgery, but before administration of adjuvant radiation treatment and chemotherapy.(55) All evaluated MRI measures, in this case, including volume of increased CBV on perfusion MRI, were related to survival. As in the previous study, high Cho/NAA ratios and the combined lactate and lipid signal were associated with a higher risk of poor outcome.(55)

In other studies, an inverse relationship between Cho/Cr ratio and survival time was detected in seven patients with gliomatosis cerebri, examined before treatment.(59) A prospective longitudinal study examined 14 patients with high-grade gliomas prior to radiation treatment, at week 4 of radiation treatment, and 2 months post-treatment.(60) Several spectroscopic indices were associated with unfavorable survival (including Lac/NAA at week 4 and the change in normalized Cho/Cr between baseline and the first follow-up); the most significant was a more than 40% decrease in normalized Cho between the first and second follow-up visits in the contrast-enhancing region.(60) However, no spectra were presented in this paper, making it difficult to judge the quality of the primary data that these conclusions were based on. In a retrospective ^1H MRSI study (performed at long TE, data collected before treatment) of 51 histopathologically verified cases of supratentorial gliomas, four MRSI indices (maximum value of Cho/Cr, maximum value of Lac/Cr, total number of voxels with NAA/Cr values less than two thirds of the mean value from the normal appearing contralateral region, and the number of voxels with Lac/Cr ratios ≥ 1) measured in the area of abnormal MRI signal were significant predictors of survival.(61) Multivariate analysis of spectra of 21 patients with brain metastases differentiated between patients surviving 5 months and patients with a shorter survival.(62)

However, not all studies have found associations between metabolic indices and prognosis; for instance, in 16 patients with a B-cell lymphoma, presence of Lac and lipids in the spectra collected before treatment was not associated with overall survival.(63) In another prospective ^1H MRS study, 50 patients with newly diagnosed low-grade gliomas (WHO grade II) evaluated prior to surgery showed no relationship between Cho and Cr levels in the tumor and survival.(64)

Several studies have also examined the prognostic value of spectroscopy in pediatric brain tumors. In a ^1H MRSI study of 76 children with brain tumors, a low value (< 1.8) of an

index including choline and lactate+lipid levels, normalized to contralateral Cr, was found to be a strong predictor of survival.(65) In another study of children with recurrent gliomas, a high Cho/NAA ratio was associated with decreased survival.(66)

Treatment planning

Accurate, non-invasive diagnosis in glioma patients is important, as the prognosis and therapeutic plan (including surgery, if any) is often based on the histopathological grade of the tumor.(67,68) Proton MRSI and other physiological imaging techniques may assist the surgeon in obtaining representative samples of the tumor tissue for histology and surgical resection, by identifying regions of active tumor. As described above, MRSI provides information on tumor heterogeneity, including distinguishing normal tissue, infiltrating tumor and vasogenic edema.(68) This information is also of great potential value in planning targeted radiotherapy, as well as to help to differentiate residual or recurrent tumor from radiation necrosis on follow-up (see section 6). Multi-modality MRI including MRSI may potentially provide information that may aid in stratifying patients into high- or low-risk groups for clinical trials, and in selecting optimal treatment for individual patients.(56)

MRSI integration in multimodality imaging

Proton MRSI may be readily integrated into a multi-modality MRI examination for presurgical evaluation of patients with gliomas.(68,69) In one study of 143 newly diagnosed glioma patients, MRSI, and conventional, perfusion and diffusion MRI were performed before any treatment had begun.(69) Analysis of the results suggested that this multi-modality approach, with appropriate analysis techniques, could accurately identify tumors of different grade, and hence be used to guide treatment choices.(69)

In another study, multi-modality 3T MRI (including long TE MRSI) was performed in 31 patients with either high- or low-grade glioma.(68) Using linear discriminant analysis, patterns associated with tumor tissue, edema, and tumor-infiltrated edema in perienhancing regions with abnormal signal on conventional MRI, and a pattern of infiltration in perienhancing tissue with normal MRI appearance were presented. To differentiate among the patterns in perienhancing regions of high-grade gliomas, the best discrimination was achieved when all MRI parameters were used (i.e., normalized Cho and NAA, ADC, and rCBV). The regions presumed to be a tumor, had normalized Cho >1.3 and Cho/NAA ratio >1, and lower ADC and higher rCBV than vasogenic edema. Presumed vasogenic edema had normal Cho/NAA ratio (<1). Presumed tumor-infiltrated edema had Cho levels similar to or lower than normal values, with abnormal Cho/NAA ratio, higher ADC and lower rCBV than regions defined as tumors, and lower ADC and higher rCBV than vasogenic edema regions. Peri-enhancing regions with normal appearance were classified as presumed tumor-infiltrated regions (with normalized Cho >1.3 and/or Cho/NAA ratio >1) or presumably normal regions (with close to normal metabolite levels). Low and high-grade tumors could be separated based on all examined MR parameters, except ADC. In low-grade tumors, normalized Cho was significantly lower in the tumor margins, normalized NAA higher in the tumor mass and the margins, normalized Cr higher in the tumor mass, and rCBV lower both in the mass and tumor margins. In contrast to high-grade gliomas, spectra of low-grade gliomas did not show an elevated lactate/lipid signal. High- and low-grade tumors and their margins could be differentiated based on the lactate/lipid signal and rCBV. The classification was based only on MRI-related parameters as no histological correlations were performed in the study.(68)

Identification of active tumor and tumor invasion

The primary therapeutic goal in neuro-oncology is complete removal of the tumor; therefore, it is essential to know the exact tumor borders.(70) However, in high-grade gliomas, the tumor boundaries and the degree of infiltration are difficult to define due to their diffuse growth pattern. By evaluating metabolic abnormalities, proton MRS can also enhance the diagnostic yield of stereotactic brain biopsy, which is usually performed based on anatomic appearance of the lesion or enhancement characteristics.(71) Brain biopsy carries multiple risks, such as bleeding or infection. In high-grade heterogeneous tumors, there is a possibility that an 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.(72) The role of proton MRS in biopsy guidance is to recognize regions of high metabolic activity: regions of elevated Cho levels (and low NAA levels) indicative of tumor tissue, represent a good target for biopsy. (12,67,71,73–75) Regions with low Cho and NAA levels may indicate radiation necrosis, astrogliosis, macrophage infiltration or mixed tissue.(73)

In one study, biopsy samples were obtained in 26 patients from the target tissue identified on MRSI and the utility of MRSI in guiding biopsy was evaluated.(71) In 17 out of 21 patients, who had confirmed neoplasm, Cho was elevated; however, low Cho levels (similar to those observed in necrotic regions) were observed in 4 patients with tumors. In all patients with necrosis, Cho levels were low.(71) In nine patients with T₂-hyperintense lesions without contrast enhancement suggestive of low-grade glioma on conventional MRI, ¹H MRSI was performed presurgically and the area of the highest Cho intensity (or, if not apparent, area from the center of the lesion) was chosen as a biopsy target using a frameless stereotactic system.(67) MRSI correctly classified all 4 histologically confirmed gliomas WHO grade III and 4 out of 5 WHO grade II gliomas.

To assess the degree of tumor infiltration, MRSI data obtained in 7 patients with untreated supratentorial gliomas (WHO grades II and III) were fused with 3D-MRI data sets and integrated into a frameless stereotactic system for image-guided surgery, in an interactive manner.(76) Tissue samples were obtained from three regions, defined individually in each patient based on the Cho/NAA ratio: 1. spectroscopically normal region, 2. transitional region, and 3. region with maximum spectroscopical abnormality. The biopsy coordinates were labeled in the 3D-MRI dataset and metabolic maps for later correlations to histopathology. In all cases, the highest Cho/NAA ratios were obtained in the tumor center, and intermediate values in the regions of low tumor invasion. However, in four subjects, biopsies sampled in regions with normal Cho/NAA ratio showed tumor infiltration. One of the reasons may be low resolution of MRSI with respect to glioma borders.(76) A retrospective study performed in 10 glioma patients, examined the relationship between metabolite levels and histopathologic parameters in the border zone of gliomas.(77) 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.(77)

As mentioned above, improvement in tissue classification and visualization of tumor spread may be achieved by using methods of pattern recognition.(78–80) A recent MRSI study in patients with gliomas applied independent component analyses to segment the tumor core (cystic and necrotic tissue), infiltrative growth, and normal brain tissue.(80) Diffusion indices (fractional anisotropy and mean diffusivity) were also computed and compared for MRSI voxels in the three evaluated tissue groups. It was concluded that both MRSI and DTI can provide markers of infiltrative tumor growth and that the combination of these two techniques may improve delineation of tumor invasion.

Delineation of the target volume for radiation therapy

Radiation therapy was the first adjuvant treatment for brain tumors.(81) The aim of localized radiation therapy is to maximize the therapeutic dose to the tumor while delivering minimal doses to surrounding normal tissue.(81) Radiation therapy planning for management of gliomas requires optimization of the radiation doses, time of radiation and choice of treatment technique, depending on the characteristics of different glioma subtypes.(82) Patients with high-grade gliomas receive high dose to the areas of active tumor (gross total volume, defined based on MRI- or CT-contrast enhancement) while the regions suspicious for tumor infiltration (clinical target volumes) are treated with lower doses.(83,84) However, MRI metrics such as contrast enhancement and/or T2-hyperintensity may not reliably identify regions of active tumor or the extent of the tumor.(85) In fact, in many cases they may be associated with necrosis or edema, not active tumor. Therefore, there is a strong rationale for incorporating other modalities, such as ^1H MRSI, into the planning process, which may provide more specific information about the location of active tumor growth.(84)

The potential of ^1H MRSI to improve the accuracy of target volumes definition based on metabolic information was evaluated in 34 patients with WHO grade II-IV gliomas.(83) Comparison of the extent (and location) of active tumor as defined by MRI and MRSI demonstrated differences between the two techniques.(83) This report and later studies documented that the area of metabolic abnormality as defined by MRSI may exceed the area of abnormal T₂-weighted signal.(76,83,86) Furthermore, a study in 26 patients with WHO grade IV gliomas treated with gamma knife surgery showed that patients in who the volume of metabolically active lesion defined by ^1H MRSI was mostly within the radiosurgically treated volume had a longer survival time than patients with a lesser overlap.(58)

Monitoring of therapy and post-therapy evaluation

Radiation therapy

In 3 to 24% of glioma patients receiving adjuvant radiotherapy, radiation necrosis, a focal reaction to radiation, is identified. Typical MRI appearance of radiation necrosis is a T₂-hyperintense signal and T₁-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).(87) In glioma patients, clinical MRI is typically performed at predetermined intervals, for instance every 3 months after completion of chemotherapy, or 6 weeks, 3 months, 6 months, and 12 months after radio- and/or chemotherapy in high-grade gliomas. However, early evaluation and prediction of tumor response based on physiological and functional tumor parameters may be a more beneficial strategy. Availability of surrogate markers that could differentiate between therapy-related necrosis and tumor recurrence would help to decide early in the course of therapy whether the treatment scheme should be continued, adapted, or changed completely.(70) The role of MRSI in assessment of the effect of radiation on the tumor and normal appearing brain tissue was reviewed recently.(88)

Proton MRS has been applied to differentiate between radiation-induced tissue injury and tumor recurrence in adult and pediatric brain tumor patients post-radiation, after gamma knife radiosurgery, and brachytherapy. Increased Cho signal (evaluated as Cho levels relative to Cho signal in normal-appearing tissue, Cho/Cr or Cho/NAA ratios) are suggestive of recurrence, while significantly reduced Cho (and Cr) levels are suggestive of radiation necrosis.(25,89–91) Figure 7 shows an example of MRSI in a patient with a large right hemisphere astrocytoma treated with radiation. For the most part, the spectra exhibit low metabolite signals consistent with necrosis; however, spread of the tumor (high Cho) is also apparent through the splenium of the corpus callosum into the contralateral hemisphere. Necrotic regions may also show elevated lipid and lactate signals.(92–94) A recent

retrospective MRSI study in 31 patients with a previous diagnosis of an intracranial tumor reported a sensitivity of 85%, a specificity of 69% to differentiate between recurrent tumor and radiation necrosis using the Cho/NAA ratio.(95) Comparison with biopsy specimens revealed that MRSI cannot reliably differentiate between tissue containing mixed tumor/radiation necrosis and either tumor or radiation necrosis, although it did achieve good separation between pure necrosis and pure tumor.(92)

Adding ADC values to MRSI parameters did not improve differentiation between mixed tissue and pure tumor or pure necrosis (96) but did improve differentiation between pure tumor and radiation necrosis (which exhibits higher ADC values than tumors).(96,97) The diagnostic accuracy of MRS in differentiating between radiation necrosis may be improved if spectra of both the abnormal and normal tissue are available pre- and post-treatment.(93) If the spectrum is indeterminate (i.e. indicating presence of both residual tumor and radiation change), repeated examination is suggested after an interval of 6–8 weeks.(93)

On conventional MRI, the evaluation of treatment response and the categorization as stable disease, responder (partial remission) and non-responder (progression) are usually based predominantly on changes in tumor volumes.(70) Potentially, MRSI may be able to distinguish metabolic changes in the tumor prior to any change in volume. Following radiotherapy or gamma knife radiosurgery, reduction in Cho may indicate partial remission, while no change or increase in Cho is suggestive of progression.(84,98,99) In a longitudinal study evaluating glioma patients before radiation treatment and up to 2–3 months post-radiation, shrinkage of tumor in 6 out of 11 patients was accompanied by a decrease in Cho signal in four patients and increase in Cho in two patients.(100) Disappearance of lactate in three patients was associated with decrease in Cho and in tumor diameter; no changes in NAA were observed.(100) MRSI was able to differentiate patients with stable disease and patients with disease progression (malignant degeneration of a low-grade tumor or tumor recurrence) in a group of 27 patients with grade I-IV gliomas treated with combinations of surgery, chemotherapy and radiation therapy.(101) The patients were examined at least twice, with a between-studies interval of 8.3 ± 5.1 months, at 49 ± 41 months after time of disease onset. In patients with stable disease (assessed as unchanged clinical status since previous examination), the changes in normalized Cho intensity were smaller than a critical value of 35% (range 33% to 28%). In patients with progressive disease, the between-studies changes in normalized Cho were larger than 45% (range 46% to 104%). MRSI categorization also demonstrated an excellent agreement with survival data.(101)

MRSI has also been applied to predict onset of new contrast enhancement on MRI after therapy. A prospective clinical trial including patients with GBM sought to compare locations of MRSI abnormality (Cho/NAA ≥ 2 , at TR/TE=1000/135 ms) at baseline with location of new contrast enhancement and abnormal MRSI after treatment with radiation and chemotherapy.(102) At relapse, 82% of the 17 voxels with Cho/NAA ≥ 2 at baseline exhibited either continuing or new contrast enhancement (as compared to 15% of 323 voxels with normal Cho/NAA ratio). The study also showed that combining MRSI and post-contrast T₁ and T₂-weighted MRI may better predict regions of relapse after treatment than MRI alone.(102)

Finally, radiotherapy planning involves a careful balance between maximizing dose to the tumor while limiting radiotoxicity to surrounding normal brain tissue. Radiation injury may be acute, short term or long term. Long term injury is particularly an issue in radiotherapy of children, where radiation may have long term deleterious effects on the developing brain (88). MRS has been shown to be able to detect effects of radiation on normal brain, and may have some role in monitoring injury to normal brain tissue. The most commonly reported changes following radiation are decreases in NAA (103), which can be detected one to 4

months after radiation in non-tumoral regions receiving between 20–50 Gy (104) and decreases in Cho levels.(88)

Chemotherapy

In patients with gliomas, chemotherapy is often used as the initial treatment after histological diagnosis in combination with radiation therapy, or at recurrence after surgery and radiation therapy.(105) In patients treated with chemotherapy, proton MRS may provide data on functional response on tumor chemosensitivity to potentially allow for early treatment modification and to avoid unnecessary toxicity.(106) In malignant glioma patients, survival time is short in the absence of effective treatment; therefore, the ability to evaluate chemosensitivity early in the course of treatment would represent a significant advancement in chemotherapy planning.(107)

In an early study of MRSI monitoring of chemotherapy, sixteen patients treated with high-dose tamoxifen for recurrent malignant glioma were evaluated with proton MRSI both before and during treatment. Starting at week 4 into the tamoxifen therapy, responders had a significantly lower tumor volume and higher Karnofsky score. Using linear discriminant analyses, responders (7 patients) and non-responders could be differentiated based on five metabolite ratios (Cho, Cr, NAA, lactate, lipids in the tumor - relative to contralateral Cr) obtained before treatment, and at two and four weeks into treatment. No time-related differences in Cho, Cr, and NAA ratios were detected between responders and non-responders; however, lactate and lipid ratios decreased over time in responders (Figure 8). (107) In another study, patients with oligodendroglial tumors and anaplastic astrocytomas, increases in the lactate/Cr ratio (in the contrast-enhancing region) and in Cho/Cr ratio (in regions adjacent to non-enhancing tumor) during treatment, and low baseline NAA/Cr ratio in regions adjacent to non-enhancing tumor, correlated with decreases in progression-free survival time.(108) Fourteen patients included in this retrospective pilot MRSI study were treated with Procarbazine, CCNU, and Vincristine (the follow-up intervals were 42–146 days); ten patients also had a previous radiotherapy.(108)

Single voxel spectroscopy has also been applied to assess response to temozolomide treatment in 12 patients with low grade gliomas.(109) The patients were examined before treatment, and at 3, 6, 9, and 12 months follow-up intervals. Over the course of the treatment, the decrease in Cho signal (normalized to water) paralleled the decrease in tumor volume (i.e. metabolite changes did not precede volumetric changes).(109) Reduction in tumor volume and in Cho/Cr ratio (and normalized Cho intensity) was also reported in a WHO grade II astrocytoma patient with tumor recurrence, 3 months after chemotherapy. (110) A preliminary longitudinal study in three patients with GBM also suggested that MRSI is a feasible technique to detect metabolic response in individual patients to treatment with BCNU chemotherapy wafers.(111) Collectively these papers indicate the potential for MRSI to monitor the effects of chemotherapy on brain tumors, although individually they are all small studies. They also highlight the importance (as with MRI) of performing serial MRSI scans to monitor changes in metabolite levels over time, rather than looking at a single time point in order to judge treatment response.

Conclusions

In using MRS for application to brain tumors, the limited spatial resolution (usually 1 cm³ or less for MRSI and ~4 to 8 cm³ for single voxel MRS) and partial volume effects should be kept in mind. For example, in treatment planning, MRSI pixel whose ‘point-spread function’ overlaps both tumor and normal tissue has the potential to be mis-classified as tumor invasion into surrounding brain if this issue is neglected. For this reason, use of high as possible spatial resolution is recommended (76). High resolution MRSI with good signal-to-

noise ratios is best performed using high magnetic field strengths and multi-channel phased-array coils, and efficient pulse sequences. Multi-slice or 3D MRSI techniques which provide full lesion coverage, as well as including surrounding and contralateral brain regions, are also very important (112). Unfortunately, many previous human brain tumor MRSI studies have used PRESS-based techniques, which do not always fulfill these criteria.

While the utility of MRS in diagnosis and evaluation of treatment response of brain tumors has been widely documented, MRS has not been widely accepted as a routine clinical tool. Robust and automated procedures are needed to collect the data, analyze the spectra and display the results in a timely fashion. Standardization across sites and different vendors of acquisition and analysis techniques is also important. Finally, carefully designed, multi-center trials complying with criteria of evidence-based medicine have not yet been completed, and as a result MRS is only relatively occasionally used for tumor evaluation outside of major academic medical centers.(113)

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Figure 1.

Three different untreated, primary brain tumors recorded using MRSI at long echo time (TE 280 msec, 0.8 cm³ voxel size, 1.5T). (A) Glioblastoma multiforme (GBM) involving the left side of the corpus callosum has a large increase in Cho and decrease in NAA compared to the contralateral side. (B) Left frontal WHO grade II oligodendroglioma shows reduced NAA compared to the contralateral side and minimal increase in Cho. (C) Left parietal primary central nervous system lymphoma shows increased Cho and decreased NAA compared to the contralateral hemisphere.

Figure 2.

Group average spectra from normal parietal white matter (n=6), astrocytoma grade II (n=5), meningioma (n=8), anaplastic astrocytoma (grade III) (n=7), metastases (n=6), and GBM (grade IV, n=13) recorded at 1.5T using single voxel spectroscopy (STEAM, TE = 30 ms, 4–8 cm³ voxel size). All lesions have reduced NAA and also lower Cr than normal white matter. Spectra from the necrotic core of metastases and GBM show reduced levels of all metabolites and elevated lipids (in contrast to the GBM spectrum in figure 1 which was non-necrotic). Grade II and III astrocytomas show elevated Cho and lactate signals; grade II astrocytomas also have a prominent *myo*-inositol (mI) signal. A signal from alanine (Ala) is assigned in the meningioma spectra. Reproduced with permission from reference (19).

Figure 3.

MRSI (PRESS: TR/TE=1200/135 ms; 24×24 matrix; FOV=200×200×15 mm³) and conventional MRI in a 56-year-old man who had chemotherapy after partial surgical resection of a GBM in the left temporal and inferior parietal lobe. The enhancing rim of the lesion is characterized by a high Cho signal (regions 2 and 4), while the central necrotic core (region 3) has elevated lipids and reduced levels of other metabolites. NAA is reduced in all T2-hyperintense regions, including the core and enhancing rim. The bright rim outside the brain in the Lip and NAA images arises from lipid signals in the scalp. Arrows in the Cr and Cho images metal point to field-inhomogeneity artifact due to surgical staples. Region 1 shows the normal spectrum from the right hemisphere. Data provided courtesy of Dr Alberto Bizzi, Istituto Neurologica Carlo Besta, Milan, Italy.

Figure 4.

Example of MRI (FLAIR, and T1-weighted post-Gd), MRSI (Cho, Cr and NAA, 1.5T, TE 280 msec) and MR perfusion imaging (rCBV) in a 38 year old female with left parietal primary CNS lymphoma. This malignant, contrast-enhancing lesion shows both elevated rCBV and Cho, as well as reduced NAA. Adapted with permission from (38).

Figure 5.

Example of MRI (FLAIR, and T1-weighted post-Gd), MRSI (Cho, Cr and NAA, 1.5T, TE 280 msec) and MR perfusion imaging (rCBV) in a 27-year old female with left frontal meningoencephalitis. This non-neoplastic, contrast-enhancing lesion shows decreased levels of all metabolites (Cho, Cr and NAA) suggestive of loss of cellularity and edema. Lesion rCBV is decreased cortically but appears mildly increased in the sub-cortical white matter. Adapted with permission from (38).

Figure 6.

A flow-chart for determining brain lesion type based on conventional contrast-enhanced MRI, diffusion-weighted MRI, MR spectroscopy and MR perfusion imaging. Abbreviations: $1.1/100\text{MM}^2/\text{ADC} = 1.1 \times 10^{-3} \text{ mm}^2/\text{sec}$, ADC = apparent diffusion coefficient, CE = contrast material enhanced, Cho = choline, NAA = N-acetylaspartate, rCBV = relative cerebral blood volume, TDL = tumefactive demyelinating lesion. Reproduced with permission from reference (50).

Figure 7.

MRI (FLAIR, T1 post Gd) and MRSI (Cho, NAA) in a 53 year old female with a right frontal anaplastic astrocytoma previously treated with surgery and radiation. The T2 hyperintense large right hemisphere lesion is characterized by reduced levels of all metabolites (A), consistent with radiation necrosis, while high Cho is observed in the splenium of the corpus callosum crossing into the left hemisphere, consistent with tumor growth (B). A spectrum from a normal appearing region in the left hemisphere is shown in (C) for comparison. Note that the lipids seen in (A–C) most likely artifacts resulting from head motion during the scan, and also affect the reconstructed NAA image. Small nodules of contrast enhancement are seen in the right hemisphere and the left side of the corpus callosum. The MRSI results were in good accordance with an FDG-PET scan performed contemporaneously.

Figure 8.

T2-weighted MRI and MRSI in two different cases with recurrent glioma before and after response to tamoxifen (TMX) therapy. Case (A), a recurrent astrocytoma, shows a large decrease in lactate in the lesion at one month, which corresponded to a clinical improvement in the patient, while other metabolites (Cho, Cr, NAA) are largely unchanged. (B) Case B, a recurrent GBM, did not respond the therapy and had symptom progression. The spectrum after 4 weeks of TMX is similar (in particular unchanged lactate levels) to that pretreatment. Adapted with permission from (107).