Using pattern analysis of in vivo proton MRSI data to improve the diagnosis and surgical management of patients with brain tumors

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Received 31 July 1997; revised 12 February 1998; accepted 12 February 1998

ABSTRACT: We have used pattern analysis of proton magnetic resonance spectroscopic imaging (1H MRSI) data in a variety of situations related to the clinical management of patients with brain tumors and other cerebral space-occupying lesions (SOLs). Here, we review how ‘leave-one-out’ linear discriminant analyses (LDAs) of in vivo 1H MRSI spectral patterns have enabled us to quickly, accurately, and non-invasively: (1) discriminate amongst tissue arising from the five most common types of supratentorial tumors found in adults, and (2) use the metabolic heterogeneity of cerebral SOLs to predict certain pathological characteristics that are useful in guiding stereotaxic biopsy and selective tumor resection. These findings suggest that pattern analysis of 1H MRSI data can significantly improve the diagnostic specificity and surgical management of patients with certain cerebral SOLs. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: brain neoplasm; diagnosis; image-guided neurosurgery; magnetic resonance spectroscopy; pattern recognition

INTRODUCTION

In this paper we review our recent efforts aimed at using pattern analysis of in vivo proton magnetic resonance spectroscopic imaging (1H MRSI) data in the clinical management of patients with brain tumors or other cerebral space-occupying lesions (SOLs). We will, in turn, discuss how ‘leave-one-out’ linear discriminant analyses (LDAs) of 1H MRSI spectral data have allowed us to quickly, accurately, and non-invasively: (1) discriminate amongst tissue arising from the five most common types of supratentorial tumors found in adults, and (2) use the metabolic heterogeneity of brain tumors to predict certain regional pathological characteristics (i.e. hypercellularity, pleomorphism and necrosis), that are useful in guiding stereotaxic biopsy or in the selection of tissue for resection. Based on these findings, we believe that our approach can significantly improve the diagnosis and surgical management of patients with brain tumors or other cerebral SOLs, while reducing some of the associated morbidity.

IMPROVING THE NON-INVASIVE DIAGNOSIS OF CEREBRAL SPACE-OCCUPYING LESIONS

Introduction

The prognosis and therapy of patients with brain tumors and other cerebral SOLs is determined largely by their histopathology: thus, accurate diagnosis is very important. Compared with X-ray computerized tomography (CT), conventional proton magnetic resonance imaging (MRI) has greatly increased our ability to detect brain tumors. It has not, however, brought about a similar gain in the specificity of diagnosis. Indeed, diagnostic classification of brain tumors, as well as that of other cerebral SOLs that need to be distinguished from brain tumors, is still based on histological examination of tissue samples obtained via biopsy or excision. Unfortunately, there may be significant problems associated with invasive biopsies. For example, this approach has serious limitations when it comes to tumors located in the eloquent cortex, or in the depths of the brain.
the development of non-invasive methods for the accurate characterization and classification of cerebral SOLs would provide distinct advantages for the patient and clinician.

$^1$H MRSI can provide a non-invasive biochemical assay of tissue in selected regions of the brain. $^{25-32}$ As shown in Plate 1, we can observe and quantify six major chemical resonances in the in vivo $T_2$-weighted spectra of normal human brain tissue and tumors: (1) tetramethyl amines, mostly choline-containing phospholipids (Cho) that participate in membrane synthesis and degradation; $^{33-36}$ (2) creatine and phosphocreatine (Cr), which play an important role in energy metabolism; $^{33,37}$ (3) $N$-acetyl groups, which consist mostly of the neuronal marker $N$-acetylaspartate (NA); $^{33,38,39}$ (4) alanine (Ala), a metabolite of intermediary metabolism; (5) lactate (LA), an indirect marker of abnormal glycolysis; $^{40-42}$ and (6) lipids (Lip) $^{33,43-45}$ and other macromolecules $^{46}$ which become visible on $^1$H MRSI following cell membrane breakdown.

### Previous attempts and associated problems with tumor spectra classification

Previous $^1$H MRSI studies have attempted to use information about the aforementioned metabolites in order to discriminate amongst various types of human brain tumors. For example, in vitro $^1$H MRS analyses of surgically removed astrocytoma specimens have generally found increases in Cho levels and decreases in NA levels; $^{33,47,48}$ two trends which are supposed to be associated with increases in tumor malignancy. $^1$H MRSI studies of human astrocytomas have also found similar relationships in vivo between these metabolic features and a tumor’s histopathological grade. $^{1,34,49-53}$ Furthermore, LA is more likely to be present in malignant tumors than in low-grade astrocytomas, $^{1,26,53-56}$ whereas Lip is more likely to occur in tumors of higher histopathological grade. $^{1,45,53}$ Indeed, the presence of Lip in intact surgical specimens has been found to correlate with the amount of cellular necrosis seen under the microscope. $^{43,44}$ Despite the above, basically true, generalizations, studies of individual $^1$H MRSI metabolite intensities have found a great deal of variation within similar types of brain tumors, as well as substantial overlap between different types of brain tumors. Such results would seem to preclude the use of $^1$H MRSI in the diagnosis of brain tumors.

A number of factors may, however, account for the limited specificity in previous studies. Firstly, other tumors of neuroepithelial origin (e.g. ependymomas, oligodendrogliomas and mixed astrocytic-oligodendroglomas) have sometimes been mixed in with astrocytomas. Secondly, glial tumors and atypical meningiomas commonly show regional metabolic heterogeneities which are ignored in studies that sample one, or only a few, voxels. Thirdly, studies frequently include non-SOL tissues (e.g. cyst, ventricle, or edema) in the region of interest (ROI), which results in mixing metabolites from within the SOLs with those of the surrounding tissue. Finally, the analysis of $^1$H MRSI signal intensities has, for the most part, been too simplistic in trying to find one peak alone that correlates with tumor type or the grade of malignancy. Thus far, different cerebral SOLs have not been reliably distinguished by characteristic changes in any one particular resonance in the $^1$H MRSI spectrum. Nevertheless, several recent studies have suggested that it is possible to differentiate amongst common intracranial tumors based on their spectral patterns. $^{1,57,58}$

### Non-invasive classification of the five most common adult intracranial tumors based on $^1$H MRSI spectral pattern analysis

We recently performed a preliminary pattern analysis study in which we attempted to overcome some of the aforementioned problems associated with past $^1$H MRSI studies. $^1$ We used in vivo $^1$H MRSI to non-invasively measure the amounts of Cho, Cr, NA, Ala, LA, and Lip, in the healthy brain tissue of 14 normal control (NC) subjects, as well as in the tumor tissue of 91 patients who had one of the following SOLs: (1) a low-grade astrocytoma (LGA, $n = 20$); (2) an anaplastic astrocytoma (AA, $n = 22$); (3) a glioblastoma multiforme, (GbM, $n = 24$); (4) a meningioma (Men, $n = 9$); or (5) a metastasis from lung or breast cancer (Met, $n = 16$). These five tumors represent the most common types of supratentorial tumors found in the adult human, and the numbers in each group are consistent with their incidence in other large clinical studies of brain tumors.

Each tumor was histopathologically verified by a neuropathologist, based on tissue samples obtained from at least three different biopsy sites or from tissue resected during a craniotomy. Astrocytomas were graded using the World Health Organization (WHO) histopathological system. $^5-7$ All patients were untreated except for steroids. Patients were examined sequentially and were only included in this study if: (1) their tumor was at least 1.5 cm in the cranio-caudal dimension, (2) their tumor was situated in an area known to produce an adequate signal (e.g. not associated with the base of the cranium), (3) the patient could give informed consent, and (4) there were no technical problems with their $^1$H MRSI scan.

Unlike previous studies which only studied single voxels, our $^1$H MRSI methodology allowed us to define large ROIs that included the tumor as well as either contralateral, or remote, brain tissue that appeared normal on conventional MRI (see Fig. 1). Furthermore, we included in our analysis only those voxels that were completely filled with tumor tissue and that were
uncontaminated by the surrounding edema, normal tissue, ventricular fluid, cyst fluid, or hemorrhage.

\[ \text{1H MRSI acquisition and post-processing} \]

Conventional MRI scans, as well as two-dimensional (2D) \(^1\text{H} \) MRSI scans, were acquired using a 1.5 T imaging/spectroscopy system (Gyrosan ACS II/III Philips Medical Systems, Best, The Netherlands). MRI was performed using standard proton density, T1- and T2-weighted sequences. A large ROI which included the tumor as well as contralateral or remote ‘normal-appearing’ brain tissue was defined for selective excitation. ROIs ranged in size from 70–120 mm antero-posterior, 75–120 mm medial-lateral and 14–24 mm rostro-caudal. \(^1\text{H} \) MRSI ROIs were aligned parallel to the transverse MRI scout slices, and spectra were obtained using a 90°–180°–180° (PRESS) pulse sequence for volume selection. ROIs in the normal controls were varied in position and encompassed the range of locations found in the patients. Water was suppressed by selective excitation. The following acquisition parameters were used: an interpulse delay \((\text{TR})\) of 2000 ms; a spin-echo refocusing time \((\text{TE})\) of 272 ms; a field of view \((\text{FOV})\) of 250 \(\times\) 250 mm\(^2\); 32 \(\times\) 32 phase encoding steps; and one signal average per phase-encoding step. The water-suppressed \(^1\text{H} \) MRSI image was followed by a non-water-suppressed image obtained using a \(\text{TR}\) of 850 ms, a \(\text{TE}\) of 272 ms, a \(\text{FOV}\) of 250 \(\times\) 250 mm\(^2\) and 16 \(\times\) 16 phase encoding steps. To correct for artifacts arising from magnetic field inhomogeneities, the water-suppressed \(^1\text{H} \) MRSI was divided by the unsuppressed \(^1\text{H} \) MRSI after zero-filling the latter to 32 \(\times\) 32 profiles. This yielded a nominal voxel size of 0.78 ml. Total imaging time, including ROI definition, shimming, gradient tuning and \(^1\text{H} \) MRSI acquisition, ranged from 55 to 85 min; acquisition of the \(^1\text{H} \) MRSI itself took 41 min.

Post-processing of data included a mild Gaussian filter and an inverse 2D Fourier transform to both the water-suppressed and unsuppressed \(^1\text{H} \) MRSIs. Water was further suppressed by left shifting the time domain data and subtracting it from itself. This procedure modulates the amplitude of the spectrum and increases the ratio of NA to Cr, but by an amount that is proportional to the true NA to Cr ratio in each voxel. This post-processing was performed using XUNSPECl software (Philips Medical Systems, Best, The Netherlands) running on a Sun SPARC station.

\[ \text{Pattern analysis of } ^1\text{H MRSI metabolite ratios} \]

For each tumor, peak heights of resonances from individual voxels in the \(^1\text{H} \) MRSI region that were entirely filled with tumor tissue were quantified, and then averaged to determine the mean peak height for each of the six metabolite resonances mentioned above. We used each individual’s ‘normal’ brain tissue Cr intensity as an internal standard, against which to compare the relative changes in the other metabolites’ intensities.\(^{31,37}\) Thus, for each individual brain tissue sample, metabolite values were expressed as ratios relative to Cr values measured in remote, normal-appearing brain tissue.

In order to see if patterns across these six metabolite ratios were able to classify individual tissue samples, we used a form of cross-validated linear discriminant analysis. Lachenbruch’s ‘leave-one-out’ method was used, in order to be sure that only the true predictive power of the metabolite intensity ratios was considered.\(^{59,60}\) In this procedure each individual (the ‘test’ individual) is, in turn, classified using a set of linear discriminant functions derived from the other \(n-1\) individuals (the ‘training set’). For the \(^1\text{H} \) MRSI metabolites, a set of linear discriminant functions that best discriminated between the groups of interest were derived from the ‘training-set’ samples, Cho, Cr, NA, Ala, LA and Lip metabolite intensity ratios. These functions were then used to classify the test sample’s profile, and the associated posterior probability was taken as an indication of that prediction’s degree of certainty. This process was repeated for each individual sample’s metabolic profile. The overall success at predicting the presence and type of tumor was evaluated with Cohen’s \(\kappa\) statistic.

\[ \text{Our findings} \]

As can be seen in Fig. 1 resonance profiles across the six metabolite ratios were similar for individual samples of similar tissue type, and quite distinct across the different types of tissue. Indeed, ‘leave-one-out’ linear discriminant analyses based on the patterns across the six metabolite resonances, correctly predicted the histopathological findings in 104 out of the 105 samples (Cohen’s \(\kappa = 0.988\), asymptotic standard error = 0.012), including 90 out of 91 brain tumors (Cohen’s \(\kappa = 0.986\), asymptotic standard error = 0.014). This represents a significant improvement over the primary preoperative clinical diagnosis of the same patients using all the available clinical information (i.e. X-ray CT, conventional MRI and angiography), which achieved a success rate of only 78% (71 out of 91).

It should be noted that the 104 ‘correct’ predictions were associated with a high degree of certainty, as demonstrated by a minimum associated posterior probability of 0.922 (mean = 0.999, standard deviation = 0.008). On the other hand, in the one ‘incorrect’ prediction (a GBM being mistaken for an AA) the posterior probability of being an AA was 0.506, and the posterior probability of being a GBM was 0.496. Thus, in this case, the data were still able to predict that the tissue came from a high grade of glioma, and a reasonable...
threshold for posterior probability would have avoided the misclassification and left this tumor as unclassified.

**Discussion**

These results suggest that pattern analysis of the biochemical information obtained from $^1$H MRSI may allow for the noninvasive diagnosis of the five most prevalent types of brain tumors with more specificity than is possible with current non-invasive techniques. This approach could be particularly useful for tumors in deep or eloquent areas of the brain.

We do not yet know how well this approach would work if we were to include other types of cerebral SOLs. For example, various cell types of neuroepithelial origin have been reliably distinguished using in vitro preparations, but these and other tumors might be indistinguishable based on spectra obtained in vivo. In such cases, stereotaxic biopsies would still be necessary.

$^1$H MRSI data could still be useful in such situations. It could, for example, guide the surgeon’s choice of biopsy location to regions of the tumor that are histopathologically most informative. Currently, there is little information regarding the relationship between the chemical profiles obtained with in vivo and in vitro $^1$H MRSI and tissue histopathological characteristics. In order to study this, we recently related stereotaxically localized $^1$H MRSI data and histologically determined regional cellular composition in a series of brain tumors. These findings are presented in the next section.

**IMPROVING THE SELECTION OF STEREOTAXIC BIOPSY SITES AND SELECTIVE RESECTION OF BRAIN TUMOR TISSUE**

**Introduction**

Typical neuroimaging features for adult supratentorial astrocytomas are usually considered to include: (1) a low-attenuation mass lesion on X-ray CT; (2) a lack of contrast enhancement on X-ray CT; (3) a low signal intensity on $T_1$-weighted MRI, with high signal intensity on $T_2$-weighted MRI; and (iv) an absence of enhancement with MRI paramagnetic contrast agents.
Unfortunately, based on several reports, as well as the clinical misclassification rate of ~21% that we have observed in our institute, it is clear that these standard neuroimaging features do not consistently predict the histological diagnosis and clinical behavior of many gliomas. Moreover, in contrast to the often-used criteria above, gliomas are often heterogeneous in their imaging appearance, and 31% or more of anaplastic astrocytomas do not show contrast enhancement on X-ray CT or MRI.15,18,65 Furthermore, tumors originally diagnosed as astrocytomas often turn out to be anaplastic glial tumors, which require more aggressive management.

Conventional neuroimaging methods not only lack specificity, but in some cases they lack sensitivity as well. For example, the limits of contrast enhancement do not correlate with the boundaries of infiltrating tumors, such as gliomas, but may incorporate areas of edema or necrosis. X-ray CT and MRI are unable to differentiate non-enhancing solid tumor tissue from parenchyma infiltrated by isolated tumor cells. Prior surgery or other treatment may also alter the imaging characteristics of tumors. In the absence of better non-invasive methods of investigation, stereotaxic biopsy has been advocated in all patients who present with imaging features that suggest a brain tumor.15,19,22,23,66,67

**Stereotaxic biopsy of cerebral space-occupying lesions**

Diagnosis and grading of intracranial tumors located in non-eloquent regions of the brain, can be established relatively safely by means of resection or stereotaxic biopsy, which remains the ‘gold standard’ for: (1) establishing a histological diagnosis; (2) determining the histological boundaries of a lesion; and (3) establishing whether the lesion comprises solid tumor tissue, isolated tumor cells within the parenchyma, or some other growth pattern. Moreover, for deep-seated SOLs located in periventricular areas, the basal ganglia, or the thalamus—removal of which is now made possible, in some cases, by the recent refinements of stereotaxic devices adapted for the surgical microscope—a preliminary stereotaxic biopsy is often performed, so that regional histological information can be used in planning the resection procedure.19,22,23,66,67

In our institution, the targeting for stereotaxic biopsies is planned using software incorporating conventional CT or MR images, acquired within a stereotaxic frame or with fiducial markers placed on the patient’s head. Biopsy sites are defined on the images by means of their stereotaxic coordinates, and tissue is obtained by passing a probe through a 3 mm diameter cranial twist drill hole, which retrieves cylindrical samples 1.0 cm in length and 1.5 mm in diameter.

For glial tumors which do not enhance, biopsy sites are selected on images within what appears as the mass, while in tumors which enhance, including in the case of recurrence or progression of tumors following treatment (e.g. radiotherapy), biopsy targets are selected within the enhancing areas. However, because glial tumors are spatially heterogeneous in histopathology, and because of the aforementioned unreliability of conventional neuro-diagnostic imaging to characterize the underlying heterogeneous tissue components of many brain tumors, targeting on the basis of appearance on images that primarily show structure, may not be the most efficacious method of acquiring tissue which is most meaningful for a diagnosis. The surgeon tries to acquire a biopsy specimen that demonstrates the presence of one or all of the following features: (1) non-pleomorphic tumor cells; (2) pleomorphic tumor cells; and/or (3) necrosis.4–9,11,68–71 The presence of tumor cells in the biopsy specimen is, of course, important for making a histological diagnosis. Moreover, the presence or absence of pleomorphism in these tumor cells is a key feature in distinguishing less aggressive, from more aggressive gliomas.5–7,11,12 Furthermore, necrosis is a sign of malignancy seen in glioblastomas and metastases, and is also seen in abscesses. Indeed, these three histological features are crucial for the accurate histological diagnosis of brain tumors.

In actual clinical practice, however, it is almost impossible to completely define a tumor histologically by means of needle biopsy specimens.19,20,23,24,67 The probe is rarely passed through the tumor more than three times and, if blood is acquired, the procedure may be abbreviated, or curtailed altogether. Indeed, multiple passes of the probe through high-grade gliomas pose a significant risk of hemorrhage because of the abnormal blood vessels. Moreover, since tumors located in eloquent brain are not resected unless careful cortical mapping techniques can establish that the involved parenchyma is ‘silent’, there may be large portions of such tumors that cannot be adequately examined histologically. For these reasons, a priori knowledge of subregions of the SOL that demonstrate the aforementioned histological features would facilitate the planning of biopsy, resection or adjuvant therapy. Indeed, if 1H MRSI spectral patterns could be used to predict regional histopathological characteristics, such findings might be able to guide the surgeon’s choice of biopsy location so as to provide the most diagnostic utility.

**Non-invasive histopathological predictions based on 1H MRSI spectral pattern analysis**

Recently, ex vivo 1H MRS studies have shown that histopathological characteristics of primary brain tumors are related to their regional metabolic heterogeneity.43,44,47 In order to examine this approach in vivo, we correlated stereotaxically localized 1H MRSI data with histologically determined regional cellular composition,
in 25 patients who underwent stereotaxic biopsy or resection of their SOLs.\(^2,^3\) Using these data and the same sort of ‘leave-one-out’ linear discriminant analyses described in the first section, we have been able to non-invasively predict individual samples’ histopathological compositions, based on their \(^1\)H MRSI spectral patterns.

### Comparing \(^1\)H MRSI with neurosurgical image-directed tissue biopsies

In 15 of the 25 cases, stereotaxic biopsy was acquired using standard CT or MR images, and the biopsy sites were visually related to the MR images used to define the \(^1\)H MRSI ROI, and to the metabolic images. In the other 10 cases, \(^1\)H MRSI was integrated into a frameless stereotaxic image-guided neurosurgical navigation system [Visual Integration Platform for Enhanced Reality (VIPER), NeuroImaging Laboratory, Montreal Neurological Institute, McGill University, Montreal, Canada], which supports integrated multimodal imaging data sets (e.g. MRI, fMRI, FDG PET, fPET, \(^1\)H MRSI, CT). We co-registered \(^1\)H MRS images (acquired and processed according to the methods described in the first section) with standard transverse MR images, which were obtained in the same plane and with a standard \(T_1\)-weighted high-resolution (1 mm\(^3\)) 3D gradient-echo global volume of the head.\(^32,73,74\)

Using the tracked probe of our neurosurgical guidance system (Viewing Wand, ISG Technologies, Mississauga, Ontario, Canada) for localization, specimens were biopsied or resected from various regions of the patients’ tumors, with the knowledge of the exact stereotaxic coordinates on all imaging modalities. These samples were examined under the microscope by a neuropathologist for the presence of: (1) tumor cells without pleomorphic features; (2) tumor cells with pleomorphic features; and/or (3) necrosis. These histopathological findings could then be compared with the \(^1\)H MRSI data which were acquired from the voxel(s) corresponding to the exact location from which the pathologic specimens were obtained (see Plates 2 and 3).

We examined 25 tumors in this way: six astrocytomas (four low-grade, two anaplastic); seven oligodendrogliomas (two of which were recurrences); eight glioblastomas (two of which were recurrences); two primary central nervous system lymphomas; and two metastatic carcinomas. Between one and three voxels were sampled in each tumor. We used ‘leave-one-out’ linear discriminant analyses (as described in Section one) of the six \(^1\)H MRSI metabolite ratios, in order to predict which individual voxels contained tissue that was: (1) hypercellular without pleomorphism; (2) hypercellular with pleomorphism; and/or (3) necrotic. In order to maintain a reasonable degree of certainty in our predictions, we only considered those classifications which were associated with a posterior probability of greater than 0.80.

### Results

As shown in Table 1, we were able to predict which voxels contained concentrated areas of tumor cells, as opposed to necrotic tissue, with a high degree of specificity—but with a relatively lower degree of sensitivity. For example, predictions regarding the presence of tumor cells without pleomorphism could be made in 11 of the 25 tumors (44%) that showed this feature under the microscope: out of these 11 tumors, however, 13 of the 14 voxels (93%) that were predicted to show this feature did, in fact, do so. Predictions regarding the presence of tumor cells with pleomorphism could be made in 13 of the 22 tumors (59%) that showed this feature under the microscope: out of these 13 tumors, 17 of the 18 (94%) voxels that were predicted to show this feature did so. We were able to predict which voxels contained necrotic tissue with both a high degree of specificity and sensitivity. Indeed, necrosis was predicted in eight of the 10 tumors (80%) that showed this feature under the microscope and, out of these eight tumors, all of the 14 voxels (100%) that were predicted to show this feature did so.

### Discussion

Our preliminary results show that, in a significant proportion of cases, our approach can be useful in localizing those regions of an SOL that are most likely to be histologically informative and, thus, that may provide

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NMR IN BIOMEDICINE, VOL. 11, 192–200 (1998)
the surgeon with an in vivo biochemical basis for better selecting targets for stereotaxic biopsy or resection during craniotomy.

There were too few samples included in this study to draw any strong conclusions about the sensitivity of this technique. It may be the case that our potential ability to predict histological characteristics of SOL subregions based on the 1H MRSI data was attenuated because of a lack of power associated with our low sample size. If so, then increasing the size of our training set might increase our discriminative ability. On the other hand, it may be the case that the 1H MRSI data set which we examined was insufficiently discriminative, in and of itself, to provide strong predictions more frequently than we observed in this preliminary study. Regardless, our results suggest that this strategy can prove useful—even if strong predictions cannot be made in all cases.

In the future, such 1H MRSI findings can be incorporated with findings from other imaging modalities (e.g. conventional MRI, PET and fMRI) into an image-guided neurosurgical planning system, that can supply the neurosurgeon with on-line visual information regarding the anatomy, in vivo biochemistry and physiological function of the patient’s brain tumor and surrounding tissue. Using such strategies, it should be possible to improve the success of characterization and resection of tumors over that which is possible in current neurosurgical practice.

CONCLUSIONS

In this paper we have reviewed our recent findings regarding the use of pattern analysis of in vivo 1H MRSI data in the clinical management of patients with brain tumors or other cerebral SOLs. We have shown how the ‘leave-one-out’ linear discriminant analysis of 1H MRSI spectral data has allowed us to quickly, accurately and non-invasively discriminate amongst tissues arising from the five most common types of supratentorial tumors found in adults, and how it has allowed us to use the metabolic heterogeneity of brain tumors to predict certain regional pathological characteristics which are useful in guiding the surgery of brain tumors. We believe that, in these and other ways, pattern analysis can significantly improve the diagnosis and treatment of patients with cerebral SOLs, while reducing some of the associated morbidity. Furthermore, although our work has focused on pattern analysis based on the ‘leave-one-out’ linear discriminant analysis, similarly cross-validated nonlinear methods of pattern analysis (e.g. nonlinear cluster analysis or cross-correlation neural network modeling) may prove to be even more powerful. The potential for improved non-invasive diagnosis of cerebral SOL that are associated with this approach, should offer many benefits for a patient with a brain tumor or other cerebral SOL: including lowered costs, reduced suffering and improved quality of life.

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Plate 1. Comparison of $^1$H MRSI spectra from two patients with tumors that appear similar on conventional MRI. Both patients had MRI with gadolinium (not shown) that showed marked heterogeneous enhancement. At the top left is a scout spin-echo MRI for $^1$H MRSI localization in a 67-year-old woman, with a history of a previous resection of a low-grade astrocytoma from the same area as the current tumor. She had a 3 month history of headaches, seizures, poor co-ordination and a visual field deficit. The clinical diagnosis favored a malignant glioma. Numbered voxels correspond to similarly numbered spectra (top right). One of the spectra shows the presence of alanine (Ala). Owing to the presence of LA and Lip in the tumor, it was suspected that the tumor was also necrotic in some areas. Pattern recognition analysis of the spectra classified the tumor as a meningioma. A diagnosis of a necrotic meningioma was confirmed at surgery and by histological examination. The bottom left scout spin-echo MRI for $^1$H MRSI localization in a 58-year-old man with a 6 month history of a visual field deficit and disorientation. The clinical diagnosis favored a malignant glioma. Numbered voxels correspond to similarly numbered spectra (bottom right). Pattern recognition analysis of the spectra classified this tumor as a glioblastoma multiforme, and histological analysis of the tumor after biopsy (the patient refused craniotomy) confirmed that it was a glioblastoma. (Relevant peaks have been made bold for clarity.)
Plate 2. Imaging results in a 26-year-old man who presented with seizures. Conventional MRI showed a non-enhancing mass with scant surrounding edema in the temporal lobe. The clinical and radiological diagnosis favored a low-grade glioma. $^1$H MRSI disclosed an area of high LA within the mass and within the larger region of high Cho signal. This was interpreted as being indicative of a more aggressive tissue. Stereotaxic biopsies from the site corresponding to spectrum 1 showed hypercellular tissue without pleomorphism (indicative of a low-grade oligodendroglioma – see histology image 1), while biopsy from the site corresponding to spectrum 2 showed hypercellular tumor tissue with pleomorphism (indicative of anaplastic astrocytoma – see histology image 2). The patient underwent gross total resection of the tumor and received post-operative radiotherapy because of the aggressive nature of the tumor. The patterns of spectra 1 and 2 are typical for their reflection of hypercellularity without pleomorphism and pleomorphic hypercellularity, respectively. While tissue characterized by hypercellularity without pleomorphism shows high Cho and decreased NA, in addition to these, pleomorphic hypercellular tissue shows the presence of a robust LA peak. (Relevant peaks have been made bold for clarity.)

Plate 3. Imaging results in a 46-year-old woman who presented with speech difficulty. A left frontal low-grade oligodendroglioma had been sub-totally resected 4 years previously and had subsequently progressed. She was re-operated upon using our image-guided neurosurgical navigation system, integrating images from gadolinium-enhanced MRI, fPET, and $^1$H MRSI (LA and Cho images). Although the gadolinium MRI showed a large area of heterogeneous enhancement that was interpreted as reflecting malignant transformation of the tumor, the $^1$H MRSI did not show spectra that suggested a high-grade glioma: high Cho peaks were evident in the spectra from the tumor but LA was not prominent. Functional PET showed that the frontal language cortex was displaced by the tumor and resided at the very inferior edge of the tumor (seen best on sagittal and coronal images), perhaps being partially composed of tumorous tissue (seen as a faint signal on the axial image). The arrows mark the locations of four tissue samples and their respective spectra, with labels of tissue characteristics found at each site. While the anterior two thirds of the tumor was composed of a grade II oligodendroglioma, the posterior third of the tumor was largely cystic, and the tissue surrounding the cyst was composed of very densely packed grade II oligodendroglioma cells. The patient had a gross total removal of her tumor. Post-operatively, dysphasia worsened for 3 days. At discharge on day 7 post-op, however, her speech was near normal.