Human cerebral neoplasms studied using MR spectroscopy: a review

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Abstract: Of primary central nervous system tumors treated each year, the majority are glioma, followed by meningioma and then pituitary adenoma. While the use of magnetic resonance (MR) and computed tomographic imaging is well established in the diagnosis and management of such tumors, these techniques have a limited role in determining the metabolic state, either prior to or following therapy. Multinuclear MR spectroscopy, on the other hand, provides information on tumor metabolism and the effect of therapy on tumor viability. This paper reviews MR spectroscopic studies performed on patients with central nervous system tumors and discusses the impact that such studies have had on tumor diagnosis and management.

Key words: CNS neoplasia, MR spectroscopy, metabolism.

Introduction

Using recent population surveys, the incidence rates for primary intracranial neoplasms have been estimated to range from 10.5 to 12.3 per 100 000 of the population (Fogelholm et al. 1984; Sutherland et al. 1987). The average annual incidence rates for all intracranial neoplasms by age and sex are shown in Fig. 1. The incidence curves show two peaks for both sexes, one in the 0–4 year age group and the other in the 60–69 year age group. On the basis of population data from Manitoba, Canada, the frequency of various intracranial neoplasms is shown in Fig. 2. In that study, as in others, glioma is by far the most common intracranial neoplasm, followed by meningioma and then pituitary adenoma (Sutherland et al. 1987; Walker et al. 1985). Patients with primary intracranial neoplasm present with a constellation of symptoms and signs reflecting either the intra- or extra-cerebral location of the neoplasm and its effect on adjacent brain tissue, cranial nerves, cerebrospinal pathways, and to a lesser degree, cranium. The more common symptoms include personality change, headache, confusion, focal weakness, and seizures, while paresis and confusion are the most frequently found signs (Tatter et al. 1996).

Traditionally, the premanagement evaluation of intracranial tumors has been based on computed tomographic (CT) and magnetic resonance (MR) imaging properties such as an intra- or extra-axial location, contrast-aided assessment of blood–brain barrier integrity, and abnormal tumor morphology augmented with radiological evaluation of the vascular anatomy. Despite tremendous advances in neuroimaging, radiation therapy, and understanding of the genetic and immunologic influences governing tumor biology, central nervous system (CNS) neoplasia, in particular glioma, continues to represent a considerable and frustrating challenge to both clinicians and scientists. This has been characterized by only a modest improvement in treatment outcome and prognosis, despite decades of research and clinical experience. Major
reasons for this difficulty relate to the intracerebral location of these lesions together with their biological heterogeneity.

The heterogeneity of primary CNS neoplasia is exemplified by the histologic diversity and the number of different and modified classification systems that have been proposed (Daumas-Duport et al. 1988; Kepes 1990; Kernohan et al. 1949; Ringertz 1950; Zulch 1979). The 1990 modification to the World Health Organization classification of CNS tumors by Kepes (1990) describes nine subcategories and over 35 individual types of tumors of neuroepithelial tissue alone. This diversity further applies to intratumoral characteristics. In lesions of astrocytic lineage, comprising the majority of primary brain tumors, various proposed grading systems attempt to integrate tumor histology with prognosis. The relative inadequacy of these traditional systems is in part inherent in the polyclonal character and diversity of intratumor histology. Features such as cellularity, anaplasia, mitoses, endothelial cell proliferation, and necrosis may differ widely in different regions within a single tumor (Brooks 1990). Consequently, a high variability of metabolism exists within a tumor as well as in comparison to adjacent normal brain.

In recent years, MR spectroscopy has become established as a method to study the chemical composition and metabolism of the brain and the effect of disease on these parameters (Arnold et al. 1992; Peeling and Sutherland 1992, 1993). Measurement of metabolite concentrations and MR spectroscopic patterns can potentially be used to characterize and differentiate neoplasms. Dynamic properties such as dedifferentiation or the effect of treatment might be identified using serial MR spectroscopic studies. The histologic and metabolic heterogeneity of brain tumors has been shown to correlate with biochemical variability as determined by MR spectroscopy.

In this review, the application of MR spectroscopy to human CNS tumors is discussed under the headings of $^1$H, $^{31}$P, and other nucleus MR spectroscopy.

$^1$H MR spectroscopy

Significant metabolic perturbations found in association with human glial tumors are presented in Table 1. They are discussed under the headings plasma samples, brain tumor samples: in vitro, brain tumor samples: ex vivo, and brain tumor samples: in vivo.

Plasma samples

Intracranial neoplasia is associated with systemic lipid abnormalities (Peeling et al. 1988). The $^1$H MR spectra of plasma obtained from patients with CNS tumors have shown a difference in the methyl and methylene $^1$H MR linewidths between the plasma from patients with benign (meningioma, schwannoma) and malignant (high-grade astrocytoma) tumors. Narrow linewidths (<25 Hz) were suggestive of malignancy, while a wide linewidth (>30 Hz) suggested a benign tumor. There was also the suggestion that among patients with astrocytoma, the linewidth inversely correlated with the degree of anaplasia. $^{13}$C MR spectroscopy was consistent with higher plasma levels of monounsaturated and polyunsaturated fatty acids in patients with the malignant tumors, which would account for the narrower linewidths. Subsequent studies showed that such linewidth changes are present in other disease states, such as trauma, even that associated with surgical intervention, thereby greatly decreasing the diagnostic potential of $^1$H MR spectroscopy in patients with CNS neoplasia (Sutherland and Peeling 1989).

Brain tumor samples: in vitro

The MR spectroscopic study of human tissue sampled at surgery has a number of advantages over in vivo methods. The use of excised tissue removes any uncertainty regarding the volume being observed and facilitates correlation with histological data. Spectra of extracts are of significantly higher resolution than in vivo spectra, both because the effects of tissue heterogeneity on spectral linewidths are removed and because extracts can be studied at higher field strengths, giving greater spectral dispersion. As illustrated in Fig. 3, $^1$H MR spectroscopy of extracts from normal and neoplastic brain tissue reveals measurable levels of alanine, $N$-acetylaspartate (NAA), $\gamma$-aminobutyric acid (GABA), glutamate, glutamine, aspartate, glycine, taurine, succinate, creatine (Cr), cholines (Cho), and myo-inositol (Peeling and Sutherland 1992). Despite the large number of metabolites, the three major peaks observed in these spectra are associated with NAA; the choline-containing compounds (choline,
phosphorylcholine, glycerophosphorylcholine), arising from membrane degradation and synthesis; and Cr (Cr, phosphocreatine), an important compound in energy metabolism.

It is well established that NAA is neuronal in distribution (Nadler and Cooper 1972; Simmons et al. 1991) and decreases in NAA levels have been observed in association with CNS neoplasms (Gill et al. 1990; Kinoshita et al. 1994; Keusel et al. 1994a, 1994b; Peeling and Sutherland 1992). NAA is absent in malignant astrocytoma, where neurons are rare or absent, and decreased in infiltrating low-grade astrocytoma and oligodendrogloma, where neurons while significantly reduced in number are still present (Kinoshita et al. 1994; Peeling and Sutherland 1992).

The correlation of Cho-containing compounds with high-grade astrocytoma has been suggested (Fulham et al. 1992; Kinoshita et al. 1994). Several studies, however, have shown no difference between Cho concentration in healthy brain and high- or low-grade astrocytoma. Kinoshita et al. (1994) found the Cho peak to be the highest in grade III or anaplastic astrocytoma, pituitary adenoma, and metastatic pulmonary adenocarcinoma whereas levels in normal brain tissue and low-grade astrocytoma were identical. Similar results were found in the study by Useni et al. (1994) where no significant difference in the Cho peak was observed between normal and malignant glioma and the highest peak was found in grade III astrocytoma.

The total Cr content is typically lower in all types of tu-
mors than in normal brain tissue (Lowry et al. 1977; Gill et al. 1990). Cr levels are diminished by as much as 35% in malignant astrocytomas (Usenius et al. 1994) and diminished even more in meningiomas (Peeling and Sutherland 1992). Neuroectodermal tumors tend to have a higher concentration of Cr than non-neuroectodermal tumors, introducing the possibility that Cr levels may differentiate between metastatic and primary CNS tumors (Kinoshita et al. 1994). Together these data are in keeping with a large fraction of tumor cells in the G0 or resting stage.

Glycine levels are significantly higher in glial tumors (Kinoshita et al. 1994). In glioblastoma and malignant astrocytoma, glycine concentrations are elevated by more than 500% over those in normal brain. Glycine levels were even higher in one ependymoma and one medulloblastoma, and low in metastatic tumors, further suggesting that it is possible to differentiate metastatic tumors from those of neuroectodermal origin (Kinoshita et al. 1994).

Despite these differences in absolute metabolite concentrations, tumor spectra are commonly described by ratios of metabolites to allow comparison with in vivo data. In comparison to normal white matter, the Cho/Cr ratio is progressively elevated in astrocytoma with increasing tumor grade, whereas the NAA/Cr ratio reciprocally diminishes (Gill et al. 1990). Another study also found a higher Cho/Cr ratio in glioblastoma multiforme (Carpinelli et al. 1996). Alanine levels are significantly elevated in most tumors in comparison to brain tissue controls (Peeling and Sutherland 1992; Gill et al. 1990). This might be due to a decoupling of glycolysis and the tricarboxylic acid cycle resulting in buildup of pyruvate and its metabolites (i.e., lactate and alanine). The alanine/Cr ratio is particularly elevated in meningioma, and this ratio has been proposed to be of diagnostic value in the differentiation of astrocytomas and meningiomas (Gill et al. 1990).

Brain tumor samples: ex vivo

The ex vivo identification and evaluation of mobile lipids, reflecting intratumoral necrosis in various CNS tumors (Keusel et al. 1994a, 1994b), aids in the interpretation of in vivo spectra. Mobile lipid resonances are present in variable amounts in CNS neoplasms, from being barely detectable in meningioma to progressively increasing levels with increasing histologic grade of astrocytoma and schwannoma (Keusel et al. 1994a). Correlation of ex vivo MR spectroscopy with
histopathology reveals that the accumulation of mobile lipids increases with the extent of necrosis (Fig. 4). Interestingly, the majority of high-grade astrocytomas contain higher levels of mobile lipids even though no evidence of necrosis may be present on preoperative MR imaging (Keusel et al. 1994b). This is important as histological necrosis in astrocytoma correlates with a poor prognosis. Speculatively, patients with low-grade astrocytoma in whom ex vivo MR spectroscopy shows high levels of mobile lipids may be at risk for tumor dedifferentiation and hence early recurrence.

The concentration of Cr was reported to be significantly lower in both low- and high-grade astrocytoma than normal grey and white matter (Keusel et al. 1994b); however, Cr levels could not differentiate the different grades of astrocytoma. Cho was also found to be lower in glioma tissue than in grey matter but not white matter (Keusel et al. 1994b).

**Brain tumor samples: in vivo**

Several investigators have attempted to characterize CNS tumors using in vivo 1H MR spectroscopy at various magnetic field strengths, from 0.5 to 4.0 T (Bruhn et al. 1989; Demaerel et al. 1991; Kugel et al. 1992; Langkowski et al. 1989; Poptani et al. 1995; Prost et al. 1997; Ott et al. 1993; Sutton et al. 1992, 1997; Tedeschi et al. 1997). One multicenter study prospectively examined glial tumors (Negendank et al. 1996). Although pathognomonic spectral patterns for individual tumor types are yet to be described, similarities between spectra of various tumors do exist. In vivo 1H MR spectroscopy may aid in differentiating recurrent tumor tissue from tissue affected by radiotherapy where MRI, CT, and PET may fail (Preul et al. 1998).

In vivo 1H MR spectroscopy requires several technical considerations in comparison to ex vivo or in vitro methods. In particular, accurate localization of the region of interest (ROI) with attention to voxel size is necessary to avoid contamination of spectra by signals from adjacent anatomic regions such as cerebrospinal fluid, white matter, grey matter, and capillary volumes. Since tissue water, so useful in MR imaging, occurs at a concentration of ca. 45 M and the compounds of interest are present in the millimolar range, care must be taken in suppressing the water resonance. Quantification of metabolites by in vivo 1H MR spectroscopy suffers from a lack of an internal concentration standard, with concentrations often expressed as ratios to an assumed static peak such as Cho.

These technical challenges have been managed in several ways. The use of image-guided voxel localization has made accurate ROI placement relatively simple. Several methods of MR image-guided spectroscopy are available, but two of these are of primary importance: STEAM (Frahm et al. 1989) and PRESS (Bottomley 1984). Both are single shot, where all information necessary to define the ROI is contained within a single pulse sequence, as opposed to methods such as ISIS, which require manipulation of spectra obtained from a number of slices to produce the spectrum from the ROI. Significant water signal suppression can be obtained using one or more chemical-shift selective (CHESS) pulses followed by crusher magnetic field gradients to destroy the resulting magnetization. Metabolite concentrations can now be determined by fitting a library of concentration-calibrated model spectra of compounds to the in vivo spectrum (Michaelis et al. 1993). Using this method, even concentrations of metabolites with overlapping resonances can be determined as long as additional 1H resonances exist at other frequencies.

Studies of normal brain reveal correlation of in vivo and in vitro measurements of metabolite concentrations. The in vivo concentrations of NAA (7.8 mmol/kg), Cho (1.6 mmol/kg), and Cr (5.3 mmol/kg) (Michaelis et al. 1993) compare well with the 5.2, 1.1, and 6.9 mmol/mg values measured in in vitro samples, respectively (Peeling and Sutherland 1992). The calculated in vivo ratios for Cho/NAA, Cho/Cr, and NAA/Cr are 0.21, 0.30, and 1.5, respectively (Michaelis et al. 1993). These values are comparable with several other in vivo studies: 0.55, 0.82, and 1.48 (Poptani et al. 1995), 0.59, 0.97, and 1.78 (Negendank et al. 1996), and 0.75, 1.08, and 1.49 (Sutton et al. 1992) for Cho/NAA, Cho/Cr, and NAA/Cr, respectively.

The in vivo spectra of normal brain and of intracranial tumors, shown in Fig. 5, commonly contain four sharp peaks from NAA, Cr (2), and Cho, with myo-inositol, glutamate, glutamine, and N-acetylaspartylglutamate resonances also.
observable. Lactate is reported inconsistently in tumors, being present in only 12–44% of glial tumors (Fulham et al. 1992; Kugel et al. 1992; Negendank et al. 1996; Ott et al. 1993). One reason for this inconsistency may be that the lactate resonance at 1.33 ppm is often difficult to distinguish from the acyl group of lipids. The most consistent finding in brain tumors is the decrease in the NAA signal in tumors of all types (Bruhn et al. 1989; Demaerel et al. 1991; Kugel et al. 1992; Langkowski et al. 1989; Ott et al. 1993; Poptani et al. 1995; Prost et al. 1997; Sutton et al. 1992, 1997; Tedeschi et al. 1997).

In agreement with in vitro studies, the Cho/NAA ratio increases in brain tumors (Kugel et al. 1992; Negendank et al. 1996; Ott et al. 1993; Poptani et al. 1995; Prost et al. 1997; Sutton et al. 1992, 1997). This increase is highest in astrocytic tumors where the Cho/NAA ratio has been shown to correlate to tumor grade. This has been interpreted to be secondary to decreases in neuronal cell number and subsequently NAA, in combination with increases in Cho residues from membrane lipids. Although one study did observe a significant difference in Cho/NAA between low-grade and high-grade glioma (Poptani et al. 1995), Negendank et al. (1996), in their multicenter study examining 86 tumors of various histological types including low-grade astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, oligodendroglioma, and ependymoma, did not. In that study, the tumors did show a significantly elevated Cho/NAA ratio compared with normal brain.

Multiple studies have shown that the Cho/Cr ratio increases in brain tumors (Kugel et al. 1992; Negendank et al. 1996; Ott et al. 1993; Poptani et al. 1995; Prost et al. 1997) with all types of glial tumors (astrocytoma, oligodendroglioma, ependymoma, etc). These differences are statistically significant in comparison to normal brain (Negendank et al. 1996). Furthermore, in two studies a significant difference was demonstrated in the Cho/Cr ratio between low-grade and high-grade astrocytoma (Poptani et al. 1995) and between low-grade and grade III astrocytoma (Negendank et al. 1996).

In glial tumors, the NAA/Cr ratio typically decreases in comparison to normal brain (Kugel et al. 1992; Negendank et al. 1996; Ott et al. 1993; Poptani et al. 1995; Prost et al. 1997; Sutton et al. 1992, 1997). This decrease was significant for glial tumors, with ratios of 0.78 (low-grade astrocytoma), 0.99 (grade III astrocytoma), 0.89 (glioblastoma multiforme), 1.03 (oligodendroglioma), and 0.98 (ependymoma) versus 1.78 (normal brain) (Negendank et al. 1996). These values do not allow differentiation between various tumor types.

Mobile lipids show a weak correlation to histologic grade. Lipid occurring at 1.3 ppm was found in 16% of low-grade astrocytomas, 36% of anaplastic astrocytomas, and 44% of glioblastoma multiforme (Negendank et al. 1996). The ratio of lipid/Cho showed a near significant difference between glioblastoma (3.2), anaplastic astrocytoma (1.8), and low-grade astrocytoma (0.5). Mobile lipids relate to necrosis and cell breakdown (Negendank et al. 1996), reflecting regions of poorly perfused tumor (Keusel et al. 1994a, 1994b). Similar to ex vivo studies, it is evident that mobile lipids, or necrosis, may be present in a significant proportion of low-grade and anaplastic astrocytoma. This is of particular relevance in considering that the correlation of histopathologic grade and prognosis using current systems is imperfect and may be a result of unrecognized foci of necrosis in a select population of these tumors.

31P MR spectroscopy

Brain tumor: in vitro

One study correlating spectral profile and tumor type has been performed using extracts of excised tumors. The narrower linewidths of the resonances in extracts allow differentiation of a number of phosphorus-bearing compounds in the phosphodiester (PDE) and phosphomonoester (PME) regions of the spectrum (Seijo et al. 1994). A number of intertumor relationships in the levels of phospholipids were observed. Among these, neural sheath tumors, neurilemmoma, neurofibroma, and fibrosarcoma demonstrated significantly increased levels of sphingomyelin relative to glial tumors, while glioblastoma showed a decreased phosphatic acid concentration relative to that in neurilemmoma and a decreased phosphatidylethanolamine concentration relative to that in meningioma. Glioblastoma multiforme contained higher levels of lysophosphatidylcholine and choline phospholipid relative to meningioma.

Brain tumor: in vivo

Figure 6 and Table 2 show that the energy state of brain tumors may be evaluated using 31P MR spectroscopy. The spectra provide information on tissue pH, ATP, phosphocreatine (PCr), and inorganic phosphate (Pi). These are compounds and markers of energy utilization and transfer within the cell, and levels are affected by intratumoral and intracellular energy balance. PDE- and PME-containing compounds are also resolved by in vivo 31P MR spectroscopy. These signals arise from compounds participating in cell membrane degradation and biosynthesis and the levels may indicate relative rates of cell turnover.

The seven main peaks of the 31P spectrum of normal brain correspond to PME, P, PDE, PCr, and α, β, and γ-ATP. The PME, P, and PCr (defined to be 0 ppm) peaks are clustered between 0 and 8.0 ppm and the γ, α, and β-ATP peaks are found at approximately −5, −10.5, and −17.5 ppm. The PCr peak is typically the most prominent, being about twice the intensity of the adjacent γ-ATP peak, and the peaks of PDE, P, and PME are progressively smaller with increasing chemical shift (Arnold et al. 1991; Heindel et al. 1988; Thomsen et al. 1988). Products of membrane breakdown, glycerophosphorylcholine and glycerophosphorylcholine resonances comprise the PDE peak while the PME peak is composed of the resonances of membrane synthesis compounds: phosphorylcholine, ribose-5-phosphate, and phosphorylcholamine (Glonek et al. 1982). Relative changes in these two peaks might represent the growth state of the tumor.

The intracellular pH, calculated from the shift of the Pi peak relative to the PCr peak, is fairly consistent in 31P MR spectroscopy studies. In these studies, pH of normal brain varies from 6.95 to 7.03 (Arnold et al. 1991; Cadoux-Hudson et al. 1989; Heindel et al. 1988; Hubesch et al. © 1998 NRC Canada

Alterations in parameters of the energy state of gliomas in

**Table 2.** Human glial tumors: metabolite changes detected using $^{31}$P MR spectroscopy.

<table>
<thead>
<tr>
<th>MR sample type</th>
<th>Metabolite</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td>Lysophosphatidylcholine</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Choline phospholipid</td>
<td>Increased</td>
</tr>
<tr>
<td>In vivo</td>
<td>pH</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>$P_i$</td>
<td>Unchanged</td>
</tr>
<tr>
<td></td>
<td>PCr</td>
<td>Decreased, unchanged</td>
</tr>
<tr>
<td></td>
<td>$P_i$/ATP</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>PCr/ATP</td>
<td>Decreased, increased, unchanged</td>
</tr>
<tr>
<td></td>
<td>$P_i$/PCr/ATP</td>
<td>Decreased</td>
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<tr>
<td></td>
<td>PDE</td>
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<td></td>
<td>PDE/ATP</td>
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**Note:** $P_i$, inorganic phosphate; PCr, phosphocreatine, ATP, adenosine triphosphate.

Fig. 6. In vivo $^{31}$P MR spectra from (a) normal brain tissue, (b) a patient with glioblastoma, (c) a patient with grade II astrocytoma, and (d) a patient with meningioma. Reprinted from Arnold et al. (1991) with permission.
comparison to normal brain are both inconsistent and inconclusive. Arnold (1991) found that both low- and high-grade gliomas exhibited no difference in $P_i$ or PCr concentrations whereas others found that PCr was significantly decreased (Hubesch et al. 1990). One group reported an increase in the $P_i$/ATP ratio for gliomas (Rutter et al. 1995), whereas others found the PCr/ATP ratio to be decreased, unchanged, or increased (Arnold et al. 1991; Cadoux-Hudson et al. 1989; Rutter et al. 1995; Segebarth et al. 1989; Oberhaensli et al. 1986). A significant decrease in the PCr/$P_i$ ratio has been observed in astrocytomas (Hubesch et al. 1990) as well as in some pediatric tumors of various malignant histological types (Sutton et al. 1990).

In all gliomas, PDE is reportedly decreased in comparison to normal brain while appearing to be relatively higher in glioblastoma than in lower grade tumors (Arnold et al. 1991; Hubesch et al. 1990). Glioblastoma multiforme has also shown significantly elevated $PME$ levels (Arnold et al. 1991; Cadoux-Hudson et al. 1989; Heindel et al. 1988; Oberhaensli et al. 1986; Segebarth et al. 1989). The $PME$/ATP and PDE/ATP ratios have been reported to be elevated in glial tumors (Cadoux-Hudson et al. 1989; Rutter et al. 1995) and in particular glioblastomas (Rutter et al. 1995). In higher grade tumors, a relatively elevated $PME$ peak and a relatively decreased PDE peak may reflect a higher rate of cellular turnover.

$^{31}$P MR spectroscopy has been used to examine the response of low-grade astrocytoma to radiation therapy (Segebarth et al. 1987). In one patient increases in PME and $P_i$ levels were found. Interestingly, similar changes were not found in irradiated normal brain (Szegry et al. 1993).

In a manner similar to that for the calculation of tissue pH, the intracellular free Mg$^{2+}$ concentration can be determined from the chemical shift differences of the three ATP phosphorus resonances. The one published example of this application showed that the intracellular free Mg$^{2+}$ concentration was increased in tumors relative to normal brain (Taylor et al. 1991).

$^{13}$C, $^{23}$Na, and $^{19}$F MR spectroscopy

Other nuclei have been considered in the study of brain tumor metabolism. These include the application of $^{19}$F MR spectroscopy to study intracellular Ca$^{2+}$ by using fluorinated calcium chelating agents and the use of $^{23}$Na MR spectroscopy to indirectly study differences in sodium homeostasis. The $^{23}$Na signal appears to be higher in glioma than in meningioma and may have some utility in assessing peritumoral edema (Hashimoto et al. 1991). $^{19}$F MR spectroscopy may also have some role in tumor assessment by identifying tumor hypoxia using fluorinated probes (Gill et al. 1994; Maxwell et al. 1989).

The application of $^{13}$C MR spectroscopy to the study of tumor metabolism in humans has been limited, since the information available can also be obtained using $^1$H MR spectroscopy. A number of factors, including the low natural abundance and sensitivity of $^{13}$C, make $^1$H MR spectroscopy a more attractive technique. However, the application of $^{13}$C MR spectroscopic methods along with labeled substrates would increase our understanding of tumor metabolism. For instance, $^1$H-observe $^{13}$C-edit MR spectroscopic techniques following administration of [1-$^{13}$C]glucose have been used to estimate tricarboxylic acid cycle flux in human brain by following the time dependence of label incorporation into glutamate (Rothman et al. 1992). Application of these techniques to CNS neoplasia would yield novel and potentially important biochemical information.

**Conclusions**

While MR spectroscopy has provided significant contributions to the characterization of brain tumor neurochemistry and energy state, the clinical utility and application are yet to be demonstrated and determined. Despite the numerous studies attempting to find characteristic differences amongst tumors of various histological types and grades, consistent MR spectroscopic differences thus far do not exist.

Attempts have been made to correlate $^1$H MR spectral profiles to clinical diagnosis of tumors. Changes in Cho, lipid, and lactate content of metastatic tumors might be used to categorize metastatic tumors into early, intermediate, and late stage (Sijens et al. 1996). More sophisticated methods involving artificial neural networks have been applied to both in vivo and ex vivo $^1$H MR spectra of brain tumors (Somorjai et al. 1996). Using in vivo spectra, gliomas could be classified into either malignant or low-grade groups with an accuracy of about 82% (Usenius et al. 1996). Histological confirmation using excised tissue samples from patients with meningioma, astrocytoma, and epilepsy, accurate classification of pathology was obtained with 92% confidence. Using the pattern of several compounds present on the in vivo $^1$H MR spectra of various tumor types, including grades II–IV astrocytoma, meningioma, and lung or breast cancer metastases, accurate diagnosis of these particular tumors was superior to that of conventional diagnostic practice (Preul et al. 1996). Of 91 cases, MR spectroscopy misdiagnosed only 1 tumor, whereas 20 were misclassified using conventional methods. Although this study suggests improved diagnostic accuracy with MR spectroscopy, the results need to be substantiated through a multicentre trial prior to widespread clinical application.

Current MR imaging provides images of high-quality resolution from which treatment options are readily determined. It is unlikely, therefore, that the additional data provided by MR spectroscopy would significantly change initial clinical management. MR spectroscopy provides, however, the noninvasive assessment of tumor metabolism, the manipulation of which might optimize adjuvant therapy. Many MR spectroscopic techniques directed toward this have been applied in experimental studies of intracranial tumors, but their application to human subjects has been limited.

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