Proton Magnetic Resonance Spectroscopic Imaging in Children With Recurrent Primary Brain Tumors

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Purpose: **Proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) is a noninvasive technique for spatial characterization of biochemical markers in tissues. We measured the relative tumor concentrations of these biochemical markers in children with recurrent brain tumors and evaluated their potential prognostic significance.**

Patients and Methods: **^{1}H-MRSI was performed on 27 children with recurrent primary brain tumors referred to our institution for investigational drug trials. Diagnoses included high-grade glioma (n = 10), brainstem glioma (n = 7), medulloblastoma/peripheral neuroectodermal tumor (n = 6), ependymoma (n = 3), and pineal germinoma (n = 1). ^{1}H-MRSI was performed on 1.5-T magnetic resonance imagers before treatment. The concentrations of choline (Cho) and *N*-acetyl-aspartate (NAA) in the tumor and normal brain were quantified using a multislice multivoxel method, and the maximum Cho:NAA ratio was determined for each patient's tumor.**

Results: **The maximum Cho:NAA ratio ranged from 1.1 to 13.2 (median, 4.5); the Cho:NAA ratio in areas of normal-appearing brain tissue was less than 1.0. The maximum Cho:NAA ratio for each histologic subtype varied considerably; approximately equal numbers of patients within each tumor type had maximum Cho:NAA ratios above and below the median. Patients with a maximum Cho:NAA ratio greater than 4.5 had a median survival of 22 weeks, and all 13 patients died by 63 weeks. Patients with a Cho:NAA ratio less than or equal to 4.5 had a projected survival of more than 50% at 63 weeks. The difference was statistically significant (*P* = .0067, log-rank test).**

Conclusion: **The maximum tumor Cho:NAA ratio seems to be predictive of outcome in children with recurrent primary brain tumors and should be evaluated as a prognostic indicator in newly diagnosed childhood brain tumors.**

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BRAIN TUMORS ARE the most common solid tumors of childhood, but they represent a diverse group of tumors. The overall 5-year survival rate for children diagnosed with a primary brain tumor between 1989 and 1994 was 64%, but survival rates range from greater than 90% in children with low-grade cystic cerebellar astrocytomas to less than 10% in children with high-grade, diffuse brainstem gliomas.[1] In addition to tumor histology and grade, other prognostic factors that are predictive of outcome for childhood brain tumors include tumor location within the brain, extent of disease (eg, the presence of leptomeningeal metastases), and extent of tumor resection.[2-6]

Identifying tumor characteristics at diagnosis that are predictive for outcome is a critical component of treatment planning for a patient and can provide a basis for stratifying patients on clinical research trials. Ideally, these prognostic indicators should be measured noninvasively and before definitive treatment. Tumor histology, grade, and extent of tumor resection are determined after surgical intervention, but the location and extent of tumor can be delineated by neuroimaging techniques.

Magnetic resonance (MR) imaging has become the standard neuroimaging technique for childhood brain tumors. MR images are based on detection of hydrogen nuclei (protons) primarily in water and lipids because these nuclei are present in highest concentrations in tissue.[7] Proton magnetic resonance spectroscopy (^{1}H-MRS), which is a technique that can be performed on a conventional MR imager, can quantify the relative concentration of nonwater, proton-containing metabolites from discreet tissue regions by suppressing the signals from water and lipids.[8-10] In the brain, the principal metabolite signals that can be measured by ^{1}H-MRS at long echo times are *N*-acetyl aspartate (NAA), creatine, and choline (Cho) (Fig 1). NAA is a neuronal marker present in normal functioning neurons; creatines, including creatine and phosphocreatine, are important in energy metabolism and vary little in normal brain tissue; and Cho-containing compounds are constituents of cell membranes. Lactate, which is a marker of anaerobic metabolism, is not usually detected in normal brain but may be present in some brain tumors or areas of ischemic

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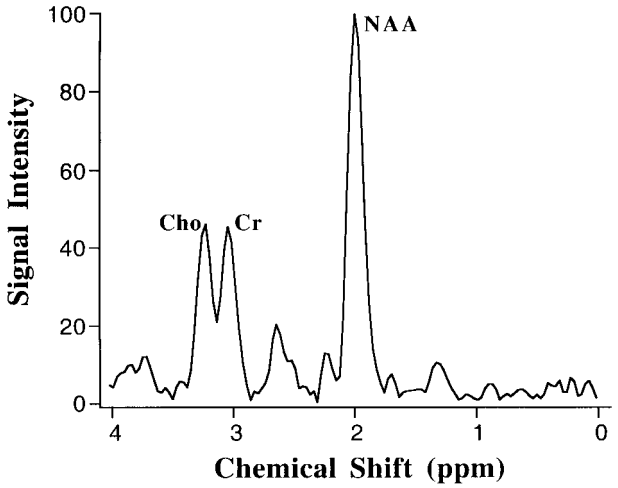

Fig 1. ^{1}H-MRS of normal brain tissue. The relative concentration of primary metabolites is proportional to signal intensity (y-axis). The frequency at which the hydrogen nuclei from each metabolite resonate is influenced by the chemical environment. This chemical shift (x-axis) allows MR to differentiate between chemical species.

injury.[11,12] ^{1}H-MRS has been used to study the metabolic profiles of various CNS diseases, including ischemia, metabolic diseases, demyelination, and brain tumors.[11,13-19]

The MR spectra from primary brain tumors are substantially different than the spectra from normal brain tissue. In tumors, the relative concentration of NAA is decreased, and Cho concentration is increased.[18] Lactate may also be detected in some brain tumors, depending on the extent of anaerobic glycolysis. Tumor spectra have been used to noninvasively diagnose the most common types of supratentorial brain tumors in adults using pattern recognition analysis.[20] In addition, serial monitoring of ^{1}H-MRS in adults with gliomas seems to be capable of detecting malignant degeneration and disease progression.[21]

A low-resolution metabolite map that reflects the spatial distribution of each of the metabolites over multiple slices in the brain can be generated by collecting MR spectroscopic data from multiple contiguous discreet regions (voxels) of the brain. This technique is called ^{1}H-MRSI.[22] The ^{1}H-MRSI metabolite maps can be superimposed onto conventional MR images to correlate structural changes with metabolite distribution (Fig 2). We performed a pilot study in pediatric patients with recurrent brain tumors to determine whether tumor biochemical profiles measured by ^{1}H-MRSI are predictive of disease outcome.

PATIENTS AND METHODS

We studied 27 children with recurrent primary brain tumors who were referred to the Pediatric Oncology Branch of the National Cancer Institute for investigational drug treatment trials (Table 1). All patients were studied under a protocol approved by the National Cancer

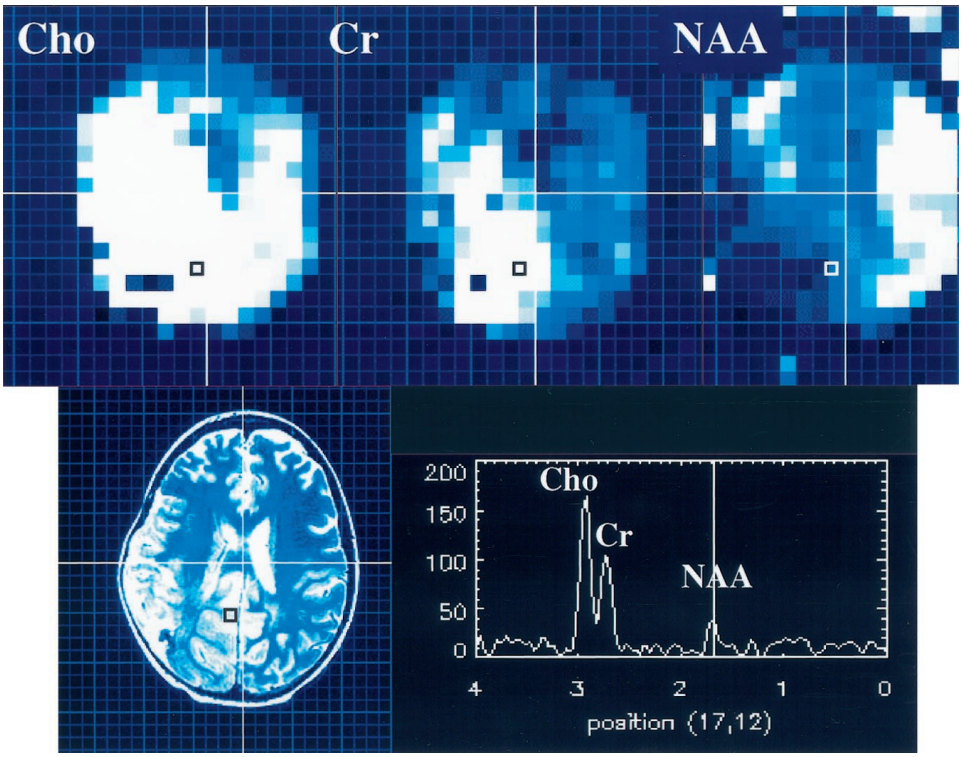

Fig 2. Axial metabolite images for Cho, creatine (Cr), and NAA from a patient with high-grade glioma and gliomatosis cerebrii and an axial T2-weighted MR image for the same section. Cho levels are elevated and NAA levels are decreased in the region of tumor.

Table 1. Patient Characteristics at the Time of Study Entry

Patient No.	Diagnosis	Recurrences (No.)	Radiation (Gy/Site)	Surgery (No.)	Chemotherapy Regimens (No.)	Other Prior Therapy	Maximum Cho:NAA Ratio	Survival (weeks)
1	BSG	1	70.40/L	0	0	None	6.7	17.3
2	EP	3	55.00/CS	3	3	None	1.6	136+
3	GBM	1	54.00/L	2	1	None	11.3	15.9
4	GBM or HGG	4	50.00/L	4	1	Gene therapy	4.4	41
5	PNET	1	72.00/CS	1	1	None	6.2	21.1
6	GBM	3	54.00/L	3	1	None	7.7	11.7
7	MBL	2	55.00/CS	1	2	Phase I	4.9	63.7
8	GBM	1	60.00/L	1	1	None	1.9	116.7+
9	MBL	4	72.00/CS	2	4	BMT	5.8	29.7
10	HGG	1	54.00/L	1	0	None	9.2	23.6
11	GBM	1	72.00/L	0	1	None	1.4	8.7
12	AA	1	54.00/L	1	2	None	3.5	90.7+
13	MBL	3	56.00/CS	1	3	BMT IT thiotepa	1.2	58.7+
14	GBM	2	60.00/L	1	1	None	9.2	42.1
15	HGG	4	55.80/L	1	3	None	13.2	26.3
16	MBL	5	54.00/CS	2	2	BMT IT melphalan	10.2	19.9
17	HGG	1	60.00/CS	1	1	None	2.1	42.7+
18	EP	5	54.00/CS	4	1	BMT	1.1	45.7+
19	EP	3	54.00/CS	1	2	None	4.5	22.7
20	MBL	3	55.80/CS	1	1	BMT	2.1	38.9+
21	BSG	1	57.30/L	0	2	None	2.9	15.1
22	BSG	2	59.40/L	0	1	None	6.6	14.0
23	BSG	1	60.00/L	0	1	None	11.1	1.0
24	BSG	1	70.00/L	0	0	None	2.3	7.3
25	Pineal germinoma	4	50.00/L	1	2	None	3.4	36.6
26	BSG	1	55.80/L	0	0	None	1.2	21.8+
27	BSG	1	Unknown/L	0	1	None	5.1	15.4

Abbreviations: BSG, brainstem glioma; EP, ependymoma; GBM, glioblastoma multiforme; HGG, high-grade glioma; PNET; primitive neuroectodermal tumor; MBL, medulloblastoma; AA, anaplastic astrocytoma; L, local; CS, craniospinal; BMT, bone marrow transplant; Phase I, phase I investigational agents; IT, intrathecal.

Institute's Institutional Review Board, and informed consent was obtained from all patients or their legal guardians. Each patient had ^{1}H-MRSI performed at the time of presentation, before the initiation of treatment at our institution. The median age of the patient population was 14 years (range, 5 to 20 years). The patients had a median of two prior tumor recurrences (range, one to five recurrences), and had received a median of one prior chemotherapy regimen (range, zero to five regimens). All patients had previously received radiation treatment, including 17 patients who received local radiation to the tumor and 10 patients who received craniospinal radiation. Diagnoses included high-grade glioma (n = 10), brainstem glioma (n = 7), medulloblastoma/peripheral neuroectodermal tumor (n = 6), ependymoma (n = 3), and pineal germinoma (n = 1).

^{1}H-MRSI was performed on a 1.5-T whole-body imager (Signa; GE Medical Systems, Milwaukee, WI) equipped with self-shielded gradients and a standard quadrature head coil. Spectroscopy data was acquired using a multislice, multivoxel technique that simultaneously collects spectra from multiple voxels, each with a nominal volume of 0.84 mL, over approximately 20 minutes.[22] Phase encoding was used to obtain a 32 × 32 matrix of 1,024 spectra for each of four axial 15-mm thick slices. After ^{1}H-MRSI acquisition was complete, T2-weighted MR images using the same field of view and angulation were obtained to allow the MR images to be coregistered with the ^{1}H-MRSI. Spectroscopy data was analyzed on a Sun Workstation (Sun Microsystems, Mountain View, CA) with a customized software package developed at the NIH using Interactive Data Language (Research Systems, Inc, Boulder, CO) data processing language.[21,22] Quantitative analysis of metabolites was performed for each voxel to yield relative concentrations. The relative concentration of each metabolite in a voxel was derived by integrating the area under the signal intensity peak for that metabolite,[23] and the concentrations for each metabolite in all voxels were displayed in two-dimensional metabolite maps (Fig 2). The relative concentrations of metabolites were normalized by expressing them as ratios. For our study the Cho:NAA ratio was derived from each voxel, and the maximum Cho:NAA ratio for each patient's tumor was used in the survival analysis.

The 27 patients were split into two groups according to whether their maximum tumor Cho:NAA ratio was greater than the median value for the entire group or less than or equal to this median value. The duration of survival was derived from the date that the spectroscopy was performed to the date of death or the date of last follow-up for surviving patients. The survival of each group was analyzed graphically

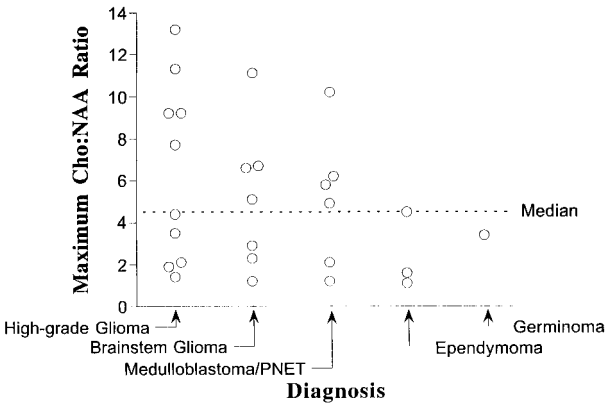

Fig 3. Scattergram of the maximum Cho:NAA ratio for each patient's tumor according to the histologic diagnosis.

using the Kaplan-Meier method, and the significance of the difference in survival between the two groups was assessed by the log-rank test for censored survival data.[24]

RESULTS

In all patients, the maximum Cho:NAA ratio occurred within the tumor, which was identified from the T2-weighted MR image, or in the brain immediately surrounding the tumor. The maximum Cho:NAA ratio for each patient's tumor according to the histologic diagnosis is shown in Fig 3. The median Cho:NAA ratio for the entire population of 27 patients was 4.5 (range, 1.1 to 13.2). There was a wide range of values within each histologic subtype of brain tumor and considerable overlap in the values across tumor types. The median Cho:NAA ratio in the patients with recurrent high-grade gliomas was 6.0, the median metabolite ratio in patients with brainstem gliomas was 5.1, and the median ratio in patients with medulloblastoma or peripheral neuroectodermal tumor was 5.4.

Approximately equal numbers of each histologic subtype of brain tumor fell above and below the median Cho:NAA ratio for the entire group (Fig 3); therefore, the population was split into two groups based on the median Cho:NAA ratio for the entire group, which resulted in approximately equal representation of each tumor type in the two groups. In addition, the two groups had a similar age profile. The median age for the group with a Cho:NAA ratio equal to 4.5 was 15 years (range, 5 to 20 years). For the group with a Cho:NAA ratio greater than 4.5, the median age was 12 years (range, 5 to 18 years). Six of 14 patients with a low Cho:NAA ratio had previously received craniospinal radiation compared with four of 13 patients with a high Cho:NAA ratio. The number of prior recurrences and the number of prior chemotherapy regimens were also similar in the two groups (Fig 4).

The postspectroscopy treatment was also comparable in the two groups. Twenty-six of the 27 patients were treated on one or more phase I investigational treatment protocols after their spectroscopy was performed. Twenty-two patients initially received a carboplatin-based investigational treatment regimen, and, of these 22 patients, 13 had a maximum Cho:NAA less than or equal to 4.5 and the remaining nine patients had a ratio greater than the median. Four of 22 patients treated on this regimen had objective responses, including one complete and two partial responses in the patients with Cho:NAA greater than 4.5 and one

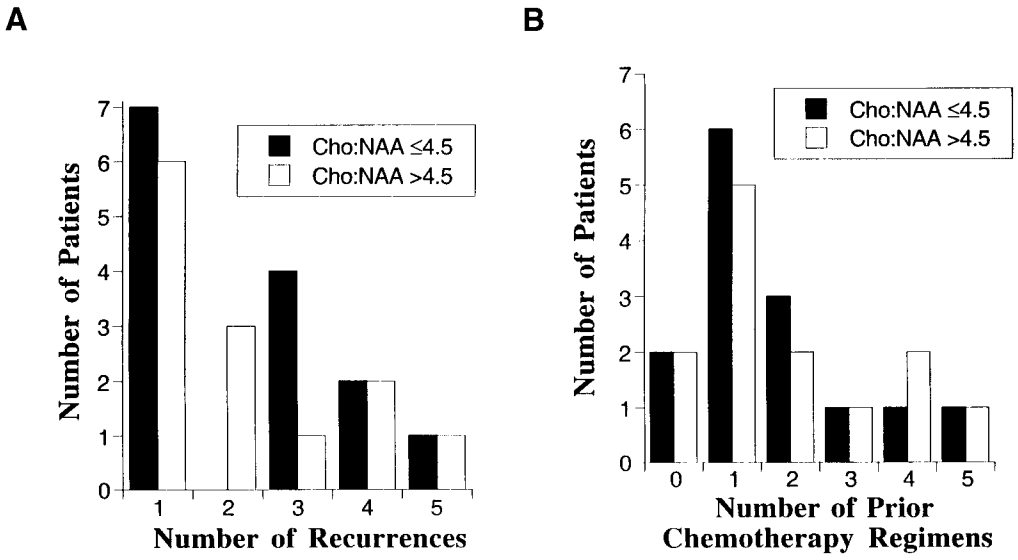

Fig 4. Frequency distribution of the number of prior recurrences (A) and the number of prior chemotherapy regimens (B) for patients in the low Cho:NAA ratio group (■) and the high Cho:NAA ratio group (□).

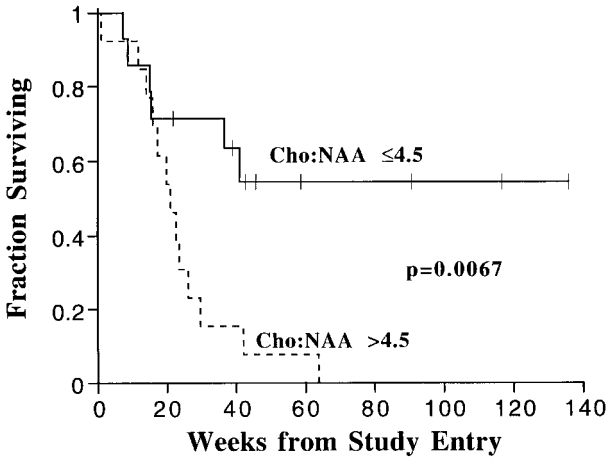

Fig 5. Kaplan-Meier estimated cumulative survival for children with recurrent primary brain tumors grouped by maximum tumor Cho:NAA ratio above the median (dashed line) or equal to or below the median (solid line). Using the log-rank test the difference between the two curves was statistically significant ($P = .0067$).

partial response in a patient with a Cho:NAA less than or equal to 4.5. Four of the remaining five patients were treated on other phase I trials, and one patient received no further treatment.

The Kaplan-Meier estimated cumulative survival of children with recurrent primary brain tumors that were split into two groups based on the maximum tumor Cho:NAA ratio is shown in Fig 5. Patients with a Cho:NAA ratio greater than 4.5 had a median post^{1}H-MRSI survival time of 22 weeks, and all 13 patients had died by 63 weeks. In the patients with a Cho:NAA ratio less than or equal to 4.5, the projected survival rate at 63 weeks exceeds 50%. Eight of the 14 patients are alive 22 to 136 weeks after ^{1}H-MRSI. Using the log-rank test, the survival of patients with a Cho:NAA ratio below the median was significantly greater than the survival in the patients with a high Cho:NAA ratio ($P = .0067$).

DISCUSSION

In a heterogeneous population of children with recurrent primary brain tumors, our study demonstrated that ^{1}H-MRSI, specifically the maximum tumor Cho:NAA ratio, seems to be predictive of outcome. A high Cho:NAA ratio within the tumor was associated with a shorter duration of survival. Although the small size of this study precluded a multivariate analysis assessing the independence of the Cho:NAA ratio as a prognostic factor, the two groups, which were split based on the median Cho:NAA ratio for the entire population, were balanced for histologic diagnosis, age, number of recurrences, prior therapy (radiation and chemotherapy), and the type of treatment administered after ^{1}H-MRSI.

The multislice, multivoxel technique used in this study measures the relative concentrations of Cho, creatine, and NAA in four axial slices of the brain. Calculating ratios of these metabolites normalizes the relative concentrations and allows for comparisons across patients and between groups. Absolute quantification of metabolite concentration requires the use of external standards and specific acquisition and postprocessing procedures, which would substantially prolong the scan time.[25] An alternative to using ratios of metabolites within the same voxel is comparing individual metabolite levels within the tumor with metabolite levels in the contralateral normal brain or with metabolite levels in a selected area of the brain, such as the centrum semiovale. In our patient population, the effects of prior therapy, such as craniospinal radiation, on metabolite levels in the brain are not well studied, and this method would not be applicable to midline lesions, such as brainstem gliomas.

Cho and NAA are known to fluctuate with age in normal brain tissue. Cho is the highest peak in normal newborns and gradually decreases until 2 to 3 years of life. NAA increases steadily until adolescence and is the major normal metabolite peak after 4 months of age.[26] To avoid these potentially confounding developmental changes, we excluded children less than 3 years of age from our study.

The Cho:NAA ratio accentuates the differences between brain tumors and normal brain tissue because brain tumors typically have higher Cho concentrations and lower NAA concentrations than normal brain.[11,15,16] Cho:NAA ratios in normal brain tissue are less than 1.0.[27,28] In our study, the maximum tumor Cho:NAA ratio was greater than 1.0 in all patients. The maximum Cho:NAA ratio was selected for this analysis because a prior study in pediatric patients with low-grade astrocytomas demonstrated considerable heterogeneity in Cho:NAA ratios within a single brain tumor.[29] The concept of worst voxel analysis has been used in a previous study, in which the highest tumor Cho level correlated with malignant degeneration of cerebral gliomas.[21]

The relationship between high Cho:NAA ratio and short duration of survival may have a biologic basis. The Cho signal is derived from choline, phosphocholine, and glycerophosphocholine, which are the constituents of phospholipid metabolism and components of cell membranes. Increased choline has been associated with an increased number of cells, a greater rate of membrane synthesis, and increased cell turnover.[21,30] NAA is found only in neurons and axons.[31] Neoplasms are thought to replace or destroy the NAA-containing cells, thereby accounting for the decreased NAA.[18]

The majority of prior MR spectroscopy studies have used single voxel techniques in which metabolite concentration is measured in a single preselected volume of interest that incorporates the tumor volume.[32-35] These single voxel techniques are more widely available, use short acquisition times, and provide absolute quantification of metabolite concentrations. However, single voxel techniques require preselection of a defined region of interest (ROI) from which spectroscopic data is obtained. The volume of the ROI is usually large (8 mL), and areas of surrounding normal brain tissue or CSF may be included in the ROI. The voxel size of the multislice, multivoxel technique is 0.84 mL, which lowers the chance for partial volume effects.

The range of Cho:NAA ratios for different histologic subtypes of recurrent childhood brain tumors from our study overlapped considerably. Therefore, this ratio does not seem to be useful for providing a noninvasive method for determining tumor histology in childhood brain tumors.

The potential value of ^{1}H-MRSI as a clinical tool has been enhanced by advances in technology that enable patients to be scanned in a reasonable time period and allow for more efficient data analysis. Conventional MR imaging hardware that is found in most medical centers can be used to perform this ^{1}H-MRSI technique with only additional software requirements. Our study suggests that the biochemical profile obtained from ^{1}H-MRSI can complement the anatomic images from MR imaging scans and may be predictive of the clinical behavior of childhood brain tumors. Based on the results of this pilot study, ^{1}H-MRSI should be prospectively evaluated as a prognostic tool in newly diagnosed childhood brain tumors.

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