

Short-Echo Time Proton MR Spectroscopy in the Presence of Gadolinium

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Purpose: The purpose of this work was to quantify the impact of contrast agents on short-TE single-voxel ^1H MR spectroscopy (MRS) diagnosis of recurrent brain tumors.

Method: Short-TE ^1H MRS was performed in 49 patients with biopsy-proven brain tumors and 14 control subjects. Eight patients (nine paired exams) were examined before and after administration of Gd-DTPA (interval approximately 5–7 min).

Results: Tumor spectra showed increased choline/creatine ratio (Cho/Cr; $p < 0.009$) and Cho concentrations ($p < 0.02$). Receiver operator characteristic for Cho/Cr = 0.93 differentiated 100% of tumors from control in the absence or presence of contrast agent. Repeated ^1H MRS varied $<3\%$. Cho T2 was significantly longer than Cr T2 ($p < 0.02$).

Conclusion: Proton MRS with TE of 30 ms may safely be used in combined contrast-enhanced MRI/MRS protocols. Further study is required with long-TE MRS because of the prolonged T2 of Cho.

Index Terms: Magnetic resonance, spectroscopy—Gadolinium—Neoplasms.

Proton MR spectroscopy (^1H MRS) is a noninvasive biochemical assay that can be applied in routine MR scanners for the differential diagnosis of a number of disorders that are difficult to resolve with MRI alone (1). The presence of a high choline/creatine ratio (Cho/Cr), low *N*-acetylaspartate (NAA)/Cr, and excess lipid and lactate has proven valuable as a signature pattern of brain tumor in ^1H MRS (1–7). Based on these spectral characteristics, the radiologic literature supports the use of MRS to make a positive diagnosis of tumor, distinguish malignant tumor from other focal lesions (8–10), grade neoplasms (6), distinguish recurrent brain tumor from radiation necrosis (11,12), and monitor response to a range of therapies (13–17). The diagnostic peak ratios are themselves strongly influenced by TE, a factor in clinical MRS that is insufficiently recognized (18).

Clinical protocols routinely include the use of contrast agents as gadolinium (Gd) enhancement of brain regions in which the blood-brain barrier is incomplete is presumed to reflect the presence of tumor (19–21). Gd-DTPA can also significantly improve diagnosis with single-voxel MRS by defining the optimum voxel placement. The MR examination should therefore include

both Gd-DTPA-enhanced MRI and MRS for the greatest efficacy in determining evidence of tumor in the brain.

However, there is widespread concern that Gd-DTPA may alter the MRS peak ratios necessary to the diagnosis. In an important study (6), proving efficacy of combined MRI and MRS, the use of Gd-DTPA is not described. Sijens et al. (22–24), using chemical shift imaging (CSI) at long TEs (TE 135 ms), showed a 12–15% decrease in Cho/Cr after Gd-DTPA, whereas in vitro studies demonstrate even larger discrepancies, dependent on acquisition parameters (25,26). On the other hand, Taylor et al. (27), in a study reported only as an abstract, showed no effect of a contrast agent on MRS performed at short TE. This points to one possible source of error in MRS performed after contrast agent administration: The MRS diagnosis of primary brain tumor or recurrence is made most accurately from Cho/Cr (28) and the effects of Gd-DTPA on metabolite T2 have a significant effect on diagnosis. In normal brain, Cho, the metabolite with the greatest impact on distinguishing tumor from normal, has a T2 that is 60% longer than that of Cr (29). Similar relative T2 values are noted for brain tumor (30). T2 effects of Gd-DTPA in enhancing tumors would be to reduce the apparent intensity of Cho to a greater extent than that of Cr. It is thus highly likely that if Gd were to enter the cellular compartment, which contains Cho and Cr, significant differences in the measured Cho/Cr could result and the sensitivity of MRS to tumor would be reduced. In normal brain, Gd-DTPA is excluded by an

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TABLE 1. Patient demographics

	No. of patients	Age (yrs)	Sex (M/F)	Localization (STEAM/PRESS/both)	Treatment		No. of voxels examined (PRESS)
					Yes	No	
Mixed tumor	49	50.0 ± 12.5	26/23	45/4/3	45 ^a	4	69 (12)
Controls	14	50.0 ± 11.7	8/6	11/3/0	7	7 ^b	26 (12)

^a Treatments include radiotherapy (n = 6), gamma knife (n = 7), immuno- or gene therapy (n = 7), surgery and/or chemotherapy (n = 21), and multiple treatments (n = 5).

^b Controls indicated refer to contralateral, normal-appearing brain in a patient suspected of tumor or recurrence. STEAM, stimulated echo mode; PRESS, point-resolved spectroscopy.

intact blood-brain barrier; in tumors, enhancement indicates an incomplete blood-brain barrier.

To quantify the possible negative impact of Gd-DTPA on the ability of ¹H MRS to diagnose brain tumor, we (a) examined a consecutive series of 49 patients with biopsy-proven brain tumors and control subjects using single-voxel short-TE MRS and established diagnostic criteria, specificity and sensitivity for tumor versus normal, in terms of a receiver operator characteristic (ROC) for Cho/Cr; (b) performed repeated ¹H MRS examinations, before and after contrast material was administered, in nine pairs of MRS exams in eight patients (seven treated and one untreated); and (c) used the ROC established in (a) to determine the frequency with which Gd-DTPA affected the ¹H MRS diagnosis. The results indicate that single-voxel short-TE ¹H MRS is not adversely impacted by prior use of the contrast agent Gd-DTPA.

METHODS

Patients and Control Subjects

MRI and quantitative single-voxel ¹H MRS was performed on consecutive patients, using the following inclusion criteria: clinical and neurologic symptoms of brain tumor, evidence of focal mass on prior CT or on MRI performed with or without contrast agent, or history of treated brain tumor with visible anatomic abnormality on current MRI or CT. Patients with surgical clips or other metallic implants were excluded, as were patients undergoing local brachytherapy. All patients had undergone stereotactic or open biopsy and had histologically proven brain tumor but were not further divided on the basis of tumor type or grade.

Forty-nine consecutive patients (45 treated, 4 untreated) with malignant brain tumor and 14 control subjects were recruited to this study. Eight patients served as their own controls, in that a ¹H MR spectrum was acquired in a symmetrical region of the contralateral hemisphere not obviously involved by tumor. Of these eight, seven had received treatment. An additional six control subjects were patients without brain tumor on clinical or on MR examinations and subsequently had no treatment. The details of patients and control subjects before treatments and the MRS localization method used are shown in Table 1. A further four age- and gender-matched normal subjects were each examined twice to confirm the

stability and reproducibility of quantitative ¹H MRS, as part of the trial of Gd-DTPA (not included in Table 1).

Impact of the Contrast Agent Gd-DTPA on MRS

In eight of the tumor patients (nine examinations), T1-weighted MRI and quantitative short-TE single-voxel MRS were repeated immediately after the administration of Gd-DTPA (0.1 mmol/kg body wt, 15–20 ml/patient; Magnevist, Berlex, NJ, U.S.A.). This required bringing the bed out of the magnet bore for the placement of an intravenous catheter and injection of contrast agent and then using computer landmarking to reposition the patient and resume the MR examination. Approximately 1 min later, T1-weighted MRI and ¹H MRS were repeated. The total time interval between the end of first MRS exam and the start of the second MRS exam was approximately 5–7 min. The previously prescribed voxel was reexamined with identical MRS parameters, updating shimming to that within ±1 Hz achieved before contrast medium and water suppression. To determine the stability of repeated MRS, four normal subjects were each examined twice, bringing the patient bed out of the magnet bore. To ensure accurate duplication of the prescribed MRS voxels, patients and control subjects were immobilized during the examination and the MR images acquired before and after Gd-DTPA were co-registered to check that the patient position had not changed.

Data Acquisition

MRI and quantitative ¹H MRS were performed on a 1.5 T GE Signa Clinical MR scanner with 5X software

TABLE 2. Metabolite ratios and tissue concentrations (mmol/kg) determined in patients with primary or recurrent brain tumors

	Brain tumor	n	Normal tissue	n	t test (p)
NAA/Cr	1.00 ± 0.32	57	1.09 ± 0.19	14	> 0.05
Cho/Cr	1.51 ± 0.36	57	0.77 ± 0.17	14	< 0.005
mI/Cr	0.73 ± 0.27	57	0.54 ± 0.27	14	< 0.05
[NAA]	6.83 ± 2.40	49	9.24 ± 2.33	12	< 0.005
[Cr]	5.35 ± 1.89	49	7.11 ± 1.43	12	< 0.005
[Cho]	2.37 ± 0.76	49	1.43 ± 0.60	12	< 0.005
[mI]	7.37 ± 3.32	49	8.26 ± 5.35	12	> 0.05

NAA, N-acetylaspartate; Cr, creatine; Cho, choline; mI, myo-inositol.

(GEMS, Waukesha, WI, U.S.A.). Axial T2-weighted, proton-weighted, and T1-weighted images were obtained in each patient. When available, previous Gd-enhanced MR images were used for localization. Otherwise, locations were made based on suspicious areas on T2-weighted MRI. Voxel sizes were chosen to maximize the partial volume of tumor in each single-volume study. A total of 69 MR spectra were acquired in the 49 patients with brain tumor and 26 in the 14 control subjects. Metabolite T2 relaxation times for NAA, Cr, Cho, and myoinositol (mI) were determined in a single patient with brain tumor and in 10 control subjects, as previously described (29). Stimulated echo mode (STEAM), TE of 30 ms, and TR of 1,500 ms were used throughout, as already described in detail (29,31). In a small number of exceptions shown in Table 1, an alternative localization sequence, point-resolved spectroscopy (PRESS), with TE of 30 ms and TR of 2,000 ms was used to improve signal/noise ratio acquired from voxels of $<5 \text{ cm}^3$ vol-

ume. Details of this procedure have been given (32).

Postprocessing of the spectra was performed with SA/GE software (GEMS). Peak heights and peak areas of NAA, Cho, mI, and Cr (creatine plus phosphocreatine) were calculated for all spectra and expressed as ratios to Cr (33). Lipid and/or lactate peaks were defined and reported as either present in excess or absent. Absolute concentrations of NAA, Cr, Cho, and mI as well as glutamine plus glutamate (Glx) were corrected for coil loading using an external reference, CSF, and brain dry matter, and expressed in millimoles per liter of brain water, as previously described (29). Metabolite ratios were tabulated for both STEAM and PRESS studies and concentrations in millimoles per liter of brain water for STEAM. Difference spectra were constructed for comparison of pre- and postcontrast spectra and for repeated examinations of normal subjects by scaling individual spectra to the Cr amplitude, as described previously (34) and shown in Figure 2.

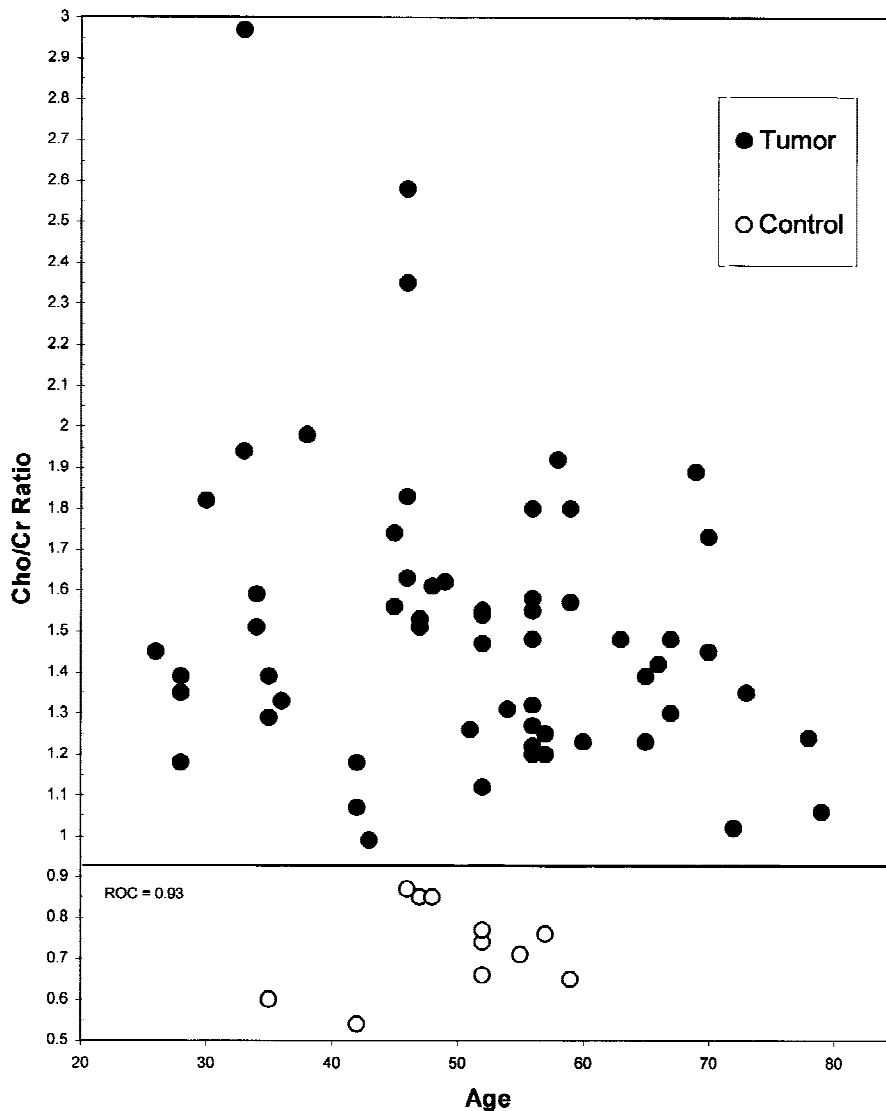
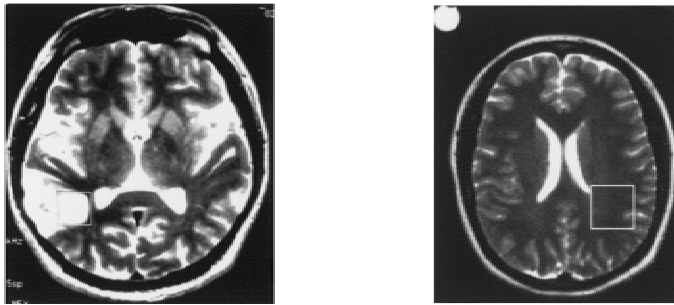
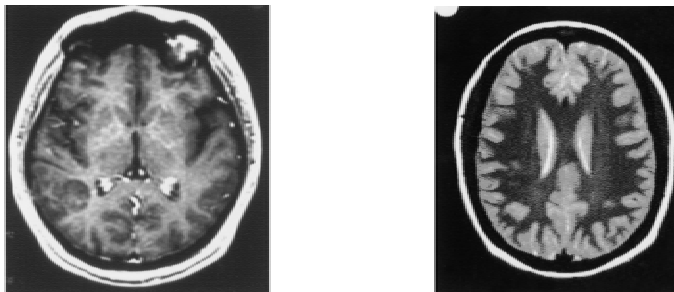


FIG. 1. Proton MRS-determined choline/creatine ratio (Cho/Cr) receiver operator characteristic (ROC) of tumor versus control: Cho/Cr values for tumor and control data from 49 consecutive patients and 14 control subjects (number of voxels, $n = 59$ for tumor, $n = 14$ for control). ROC of Cho/Cr = 0.93, determined as described in Methods, separated the groups without overlap.

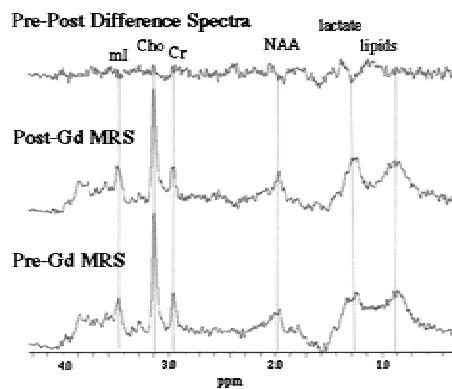
A. Pre-Gd T2-weighted MRI of Tumor B. T2-weighted MRI Prior to First Acq



C. Post Gd T1-weighted MRI of Tumor D. T1-weighted MRI Prior to 2nd Acq



E. MRS of Pre-Post Gd



F. MRS of Sequential Exams in Control

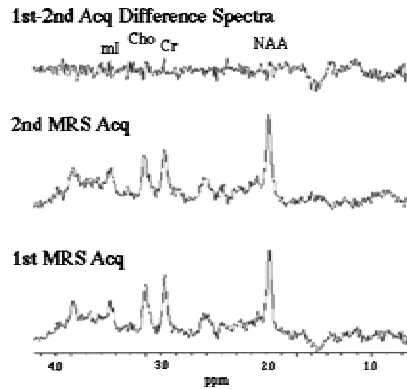


FIG. 2. Effects of Gd-DPTA on MRI and ^1H MRS of untreated brain tumor. Representative MR spectra and difference spectra from an untreated brain tumor and a control are illustrated. MR images acquired before (**A and B**) and after (**C and D**) intravenous administration of contrast agent are shown. Tumor spectra (**E**) are clearly abnormal when compared with control (**F**) but were highly reproducible in the presence or absence of contrast agent (difference spectra, **E and F**).

Statistical Analysis

To distinguish patients from control subjects, means and SD for each metabolite were compared in unpaired Student *t* tests using a modified Bonferroni correction ($p < 0.05$ was accepted as significant). For the principal determinant, which was Cho/Cr, an ROC was defined graphically (35). Power tests were conducted based on the ROC and standard difference of Cho/Cr in control subjects (35). Tissue metabolites assayed in each patient before and after Gd-DTPA were compared in paired Student *t* tests (35). In addition, the difference spectrum prepared for each patient by subtracting pre- and post-Gd-DTPA spectra scaled to Cr was expanded times four

and inspected for increased (negative) or decreased (positive) peak areas. The amount of Gd-DTPA in the voxel area was estimated from the number of pixels of enhancement divided by the voxel volume calculated using GE Signa image analysis software.

RESULTS

Diagnostic Accuracy of Single-Voxel Short-TE ^1H MRS for Brain Tumor

MRI confirmed the locations of the tumor in each patient. Spectra from tumors all included characteristic

patterns of reduced NAA/Cr, increased Cho/Cr, and additional peaks for lipid and lactate. Numerical values for metabolite ratios (Table 2) as well as the concentrations of NAA, Cho, Cr, and Glx were significantly different from control values. Results of PRESS MRS expressed as metabolite ratios (not included in Table 2) showed comparable discrimination between tumor and controls as well (Cho/Cr 1.32 ± 0.29 vs. 0.91 ± 0.13 ; $p < 0.005$). Significant differences between [Cho] (increased) and [Cr] (decreased) indicated that the increase in the Cho/Cr is the result of significant alterations in opposite directions of the two constituents.

Complete discrimination between tumor and control was achieved on the basis of Cho/Cr (Fig. 1), using an ROC of 0.93. When applied to the same data, Cho/Cr alone shows a specificity and sensitivity of 100% in distinguishing tumor from normal. This is comparable with the sensitivity and specificity achieved by long-TE CSI using linear correlation of NAA, Cho, and Cr ratios and lipid/lactate reported by others (6). Power tests showed that a sample of eight tumors would be sufficient to define an impact of Gd-DTPA on diagnosis with $p < 0.01$ at the 99% level.

Metabolite T2 Values in Brain Tumor

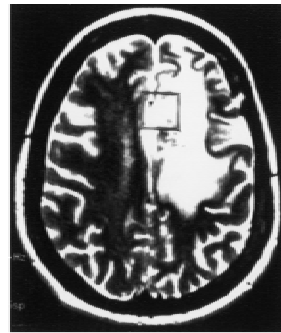
In normal brain, the T2 of Cho is significantly longer than the T2 of Cr, explaining why Cho/Cr depends so heavily on the TE of the measuring MRS sequence. The T2 relaxation time of Cho determined in one patient with tumor was clearly longer than that of Cr and within the range reported for brain tumors (30). However, T2 Cho and T2 Cr in the tumor did not differ significantly from those measured in this laboratory in normal adult brain ($p > 0.05$) (29). When results were pooled, T2 Cho (0.372 ± 0.12 s) was significantly longer (+80%) than T2 Cr (0.206 ± 0.03 s) ($p < 0.05$).

Effect of Gd-DTPA on ^1H MRS

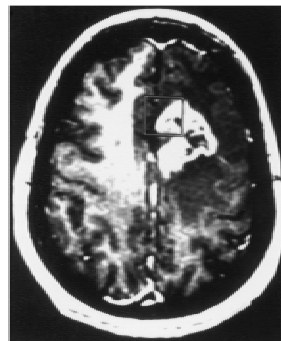
In contrast to earlier reports of work at long TE (135 or 270 ms), Gd-DTPA had no obvious effect on the spectra of an untreated (Fig. 2) or treated (Fig. 3) brain tumor. Difference spectra of tumors with little enhancement were not distinguishable from those with brisk enhancement (Fig. 3). Broadening of the Cho peak, a decrease in peak height with increased peak width, reported by others (24) was observed in only two of nine examinations. However, the peak area remained the same between pre- and post-Gd-DTPA, and the line broadening was insufficient to affect the difference spectra. No correlation between the degree of enhancement and Cho peak width was found ($R^2 > 0.5$).

Repeated MRS acquisitions in control subjects showed <2% variation of the principal metabolite ratios and <3% variation in measured metabolite concentrations (Table 3). The differences between pairs of MRS

A. Pre-Gd T2-weighted MRI



B. Post-Gd T1-weighted MRI



C. MRS of Pre-Post Gd

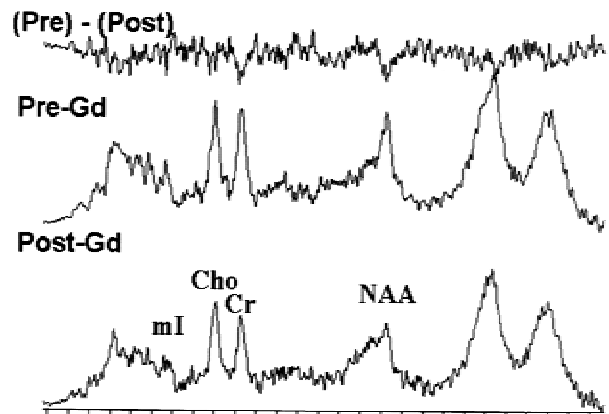


FIG. 3. Effects of Gd-DTPA in a treated brain tumor. In a patient with a briskly enhancing tumor (A and B), MRS (C) showed excess lipid (lactate), reduced *N*-acetylaspartate/creatine ratio (NAA/Cr), and choline (Cho)/Cr exceeding 0.93 (middle). Several minutes after Gd-DTPA administration, another well-resolved spectrum was acquired in which subtle differences in line-width of all metabolite peaks can be identified, which also are distinguishable in the difference spectrum (top).

measurements acquired in tumor were <2% except for mI/Cr and [mI]. This is explained by the proximity of mI (3.56 ppm) to the variable water resonance (4.7 ppm) and is most likely due to water suppression. There was no correlation between degree of enhancement and the quantitative differences in the metabolite ratios ($R^2 < 0.5$)

TABLE 3. Reproducibility of ^1H MRS in control subjects and in patients with brain tumor examined before and after contrast agent

Subject	n	Gd	NAA/Cr	Cho/Cr	mI/Cr	[NAA] (mmol/kg)	[Cr] (mmol/kg)	[Cho] (mmol/kg)	[mI] (mmol/kg)
Tumor									
Mean \pm SD	9	-	1.11 \pm 0.31	1.36 \pm 0.50	0.71 \pm 0.19	6.74 \pm 1.92	5.13 \pm 0.70	2.25 \pm 0.75	7.21 \pm 3.33
Mean \pm SD	9	+	1.09 \pm 0.23	1.34 \pm 0.56	0.80 \pm 0.25	6.61 \pm 1.63	5.11 \pm 0.98	2.21 \pm 0.73	7.85 \pm 4.03
Δ			-0.02 (2%)	-0.02 (1.5%)	+0.09 (12%)	-0.13 (2%)	-0.02 (0.3%)	-0.04 (2%)	+0.64 (9%)
p (paired <i>t</i>)			>0.01	>0.4	<0.04	>0.5	>0.5	>0.5	>0.5
Control									
Δ	4	-	+0.03 (2%)	+0.02 (2%)	0.00 (0%)	+0.29 (3%)	+0.09 (1%)	-0.00 (0%)	0.14 (2%)
p (paired <i>t</i>)			>0.2	>0.2	>0.3	>0.4	>0.4	>0.4	>0.3

NAA, N-acetylaspartate; Cr, creatine; Cho, choline; mI, myoinositol.

Effect of Gd-DTPA on Diagnosis

With use of ROC Cho/Cr = 0.93, the nine pairs of studies in which ^1H MRS was repeated after contrast agent are plotted in Fig. 4 and show that nine of nine diagnoses (100%) remained the same after Gd-DTPA. In each case, the change in apparent Cho/Cr after Gd-DTPA was negligible, being within the limits of variation observed in repeated examinations in control subjects. In Patient 4 with an untreated low-grade glioma, in whom Cho/Cr increased from 2.6 to 2.8 (+7%), there was no

impact on diagnosis by Gd. In four of nine patients, the changes were opposite in direction to that predicted by T2 alone (24) and may represent true variability of MRS. By using the $\Delta\text{Cho/Cr}$ (-0.02, 1.5%; from Table 3) and applying it to the Cho/Cr of all 49 tumor spectra indicated in Fig. 1, it is clear that this small change would not cause a change in diagnosis (indicated by a crossover of the ROC of 0.93) in any of the cases. This demonstrates quantitative evidence that the MRS diagnosis would have been affected by Gd-DTPA administration prior to MRS acquisition. This is especially noteworthy as there are several low-grade tumors (Fig. 1) where a larger

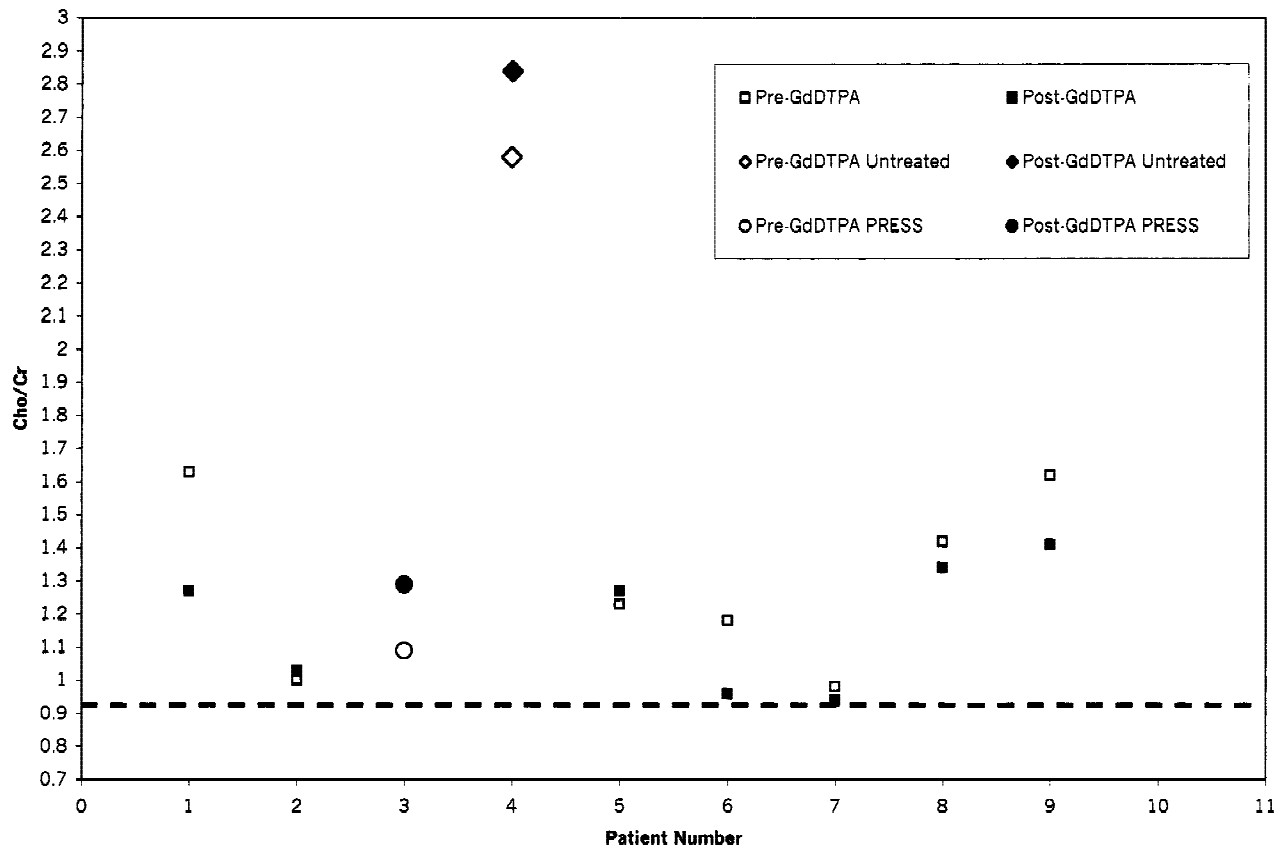


FIG. 4. Impact of contrast agent on MRS diagnosis. The receiver operator characteristic [choline/creatine ratio (Cho/Cr)] used to define the MRS diagnosis is shown. The Cho/Cr value determined in nine subjects before and after contrast agent is plotted. Differences were small and did not alter MRS diagnosis in any patient.

change of ≥ 0.06 in Cho/Cr would have caused the measurement to fall below the ROC, altering the "diagnosis."

DISCUSSION

Based on the relative T2 relaxation times of Cho and Cr, Gd-DTPA could have a negative impact on tumor diagnosis by decreasing the Cho/Cr observed. However, when MRS was performed at TE of 30 ms, the Gd-DTPA effect on the measured [Cho], [Cr], or Cho/Cr in eight tumors was within the limits of error in reproducing MRS in normal control subjects. Difference spectroscopy is probably the most sensitive means of identifying such a change. Cho/Cr, which can be measured with $\pm 2\%$ precision as determined from control subjects, also failed to show significant effect of Gd-DTPA when compared in Student *t* tests.

As so elegantly demonstrated previously (25), at a TE of 135 or 270 ms, Gd-DTPA (0.5 mM, the probable local concentration in the brain) alters the amplitude of Cho by almost 100%. It is generally assumed that the Gd-DTPA remains extracellular. Sijens et al. (24) therefore advanced the alternative hypothesis that an extracellular component of choline exists in brain tumors that is affected by the local concentration of the contrast agent.

Although some authors view these effects of Gd-DTPA as clinically unimportant (18,36), Sijens et al. (22) suggest that diagnostic MRS examinations should not be performed immediately after contrast agent. Their conclusion, which was heavily influenced by the use of a long-T2 MRS sequence, was in turn dictated by the choice of a multivoxel MRS technique (CSI) also used in the work by Preul et al. (6). At TEs of ≤ 30 ms, the differential T2 effect of Gd-DTPA on Cho proves to be undetectable. This would represent a considerable advantage for single-voxel MRS, which at shorter TEs is more reliable than CSI (33).

CONCLUSION

We conclude that Gd-DTPA did not significantly alter ^1H MRS metabolite ratios of the key tumor markers NAA, Cr, and Cho in short-TE single-voxel ^1H MRS and hence did not alter diagnosis. The number of patients studied is small. However, so robust is the definition of brain tumor by ^1H MRS based on the clear segregation in 49 patients by ROC that the power calculation indicates that this number suffices to identify a statistically significant negative diagnostic impact of contrast agent injection.

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