Differentiation between Oligodendroglioma Genotypes Using Dynamic Susceptibility Contrast Perfusion-Weighted Imaging and Proton MR Spectroscopy

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ABSTRACT

BACKGROUND AND PURPOSE: Oligodendrogliomas with 1p/19q chromosome LOH are more sensitive to chemoradiation therapy than those with intact alleles. The usefulness of dynamic susceptibility contrast–PWI-guided 1H-MRS in differentiating these 2 genotypes was tested in this study.

MATERIALS AND METHODS: Forty patients with oligodendrogliomas, 1p/19q LOH (n = 23) and intact alleles (n = 17), underwent MR imaging and 2D-1H-MRS. 1H-MRS VOI was overlaid on FLAIR images to encompass the hyperintense abnormality on the largest cross-section of the neoplasm and then overlaid on CBV maps to coregister CBV maps with 1H-MRS VOI. rCBVmax values were obtained by measuring the CBV from each of the selected 1H-MRS voxels in the neoplasm and were normalized with respect to contralateral white matter. Metabolite ratios with respect to ipsilateral Cr were computed from the voxel corresponding to the rCBVmax value. Logistic regression and receiver operating characteristic analyses were performed to ascertain the best model to discriminate the 2 genotypes of oligodendrogliomas. Qualitative evaluation of conventional MR imaging characteristics (patterns of tumor border, signal intensity, contrast enhancement, and paramagnetic susceptibility effect) was also performed to distinguish the 2 groups of oligodendrogliomas.

RESULTS: The incorporation of rCBVmax value and metabolite ratios (NAA/Cr, Cho/Cr, Glx/Cr, myo-inositol/Cr, and lipid + lactate/Cr) into the multivariate logistic regression model provided the best discriminatory classification with sensitivity (82.6%), specificity (64.7%), and accuracy (72%) in distinguishing 2 oligodendroglioma genotypes. Oligodendrogliomas with 1p/19q LOH were also more associated with paramagnetic susceptibility effect (P < .05).

CONCLUSIONS: Our preliminary results indicate the potential of combining PWI and 1H-MRS to distinguish oligodendroglial genotypes.

ABBREVIATIONS: Glx = glutamate + glutamine; LOH = loss of heterozygosity; rCBV = relative cerebral blood volume; rCBVmax = maximum rCBV; WHO = World Health Organization
ing results were reported in the differentiation of LOH in grade II oligodendrogliomas, there was a substantial overlap in patients with grade III oligodendrogliomas.\textsuperscript{11,12} Using \textit{1}H-MR spectroscopy, Jenkinson et al\textsuperscript{13} reported a higher Cho/Cr ratio in oligodendrogliomas with 1p/19q deletion than in those with intact alleles; however, the difference was not significant.

Combined use of PWI and \textit{1}H-MR spectroscopy may improve the overall reliability of these advanced MR techniques in preoperative genetic profiling of oligodendrogliomas. Some investigators have used both PWI and \textit{1}H-MR spectroscopy to grade oligodendrogliomas.\textsuperscript{13} However, the accuracy of differentiation was poor because the selection of the \textit{1}H-MR spectroscopy voxel was random, regardless of underlining rCBV values. High rCBV is a surrogate marker of neoangiogenesis and is associated with increased mitotic activity.\textsuperscript{14,15} Thus, we hypothesize that \textit{1}H-MR spectroscopy sampling of the “islands” of high rCBV, within the neoplasm, might aid in the selection of the optimal \textit{1}H-MR spectroscopy voxel, which in turn might improve the discriminative performance of \textit{1}H-MR spectroscopy. In accordance with this hypothesis, Chawla et al\textsuperscript{16} reported significantly higher Cho/Cr and lipid + lactate/Cr from high-grade oligodendrogliomas than in low-grade neoplasms when \textit{1}H-MR spectroscopy voxels were sampled from regions of high cerebral blood flow. Thus in our current study, we investigated whether \textit{1}H-MR spectroscopy voxels guided by dynamic susceptibility contrast–PWI will also be useful in discriminating oligodendrogliomas with 1p/19q LOH from oligodendrogliomas with intact alleles.

**MATERIALS AND METHODS**

**Patients**

The study was approved by the Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act. Histopathologically confirmed oligodendrogliomas or mixed oligoastrocytomas, according to the WHO classification system,
\textsuperscript{2} were included in the study. Because mixed oligoastrocytomas have a prominent composition of oligodendroglial cells, they were included in the oligodendroglioma group. Only treatment-näive patients were included, and patients with prior biopsy or surgery were excluded. Histopathologic diagnosis was obtained in all patients by surgical resection or biopsy after the imaging study. Cytogenic profile was obtained either by fluorescent in situ hybridization on fresh tumor specimens or polymerase chain reaction on paraffin-embedded specimens. Fifty patients with oligodendroglioma were recruited from July 2006 to September 2010. Six patients who did not have a cytogenic profile were excluded from the study. In addition, 4 patients were excluded from the analysis because of suboptimal PWI or \textit{1}H-MR spectroscopy data quality. Data analysis was performed on the remaining 40 patients [average age, 45.24 ± 14.04 years; 22 men and 18 women]. These patients were classified into 2 groups: patients with 1p or 1p and 19q LOH (\textit{n} = 23), and patients with intact alleles (\textit{n} = 17). Thirteen of 23 patients with 1p/19q LOH oligodendrogliomas had low-grade tumors (WHO grade II), and 10 had high-grade tumors (WHO grade III). Among the 17 oligodendrogliomas with intact alleles, 9 were of low grade and 8 were of high grade.

**Fluorescence In Situ Hybridization**

Surgical specimens were dissociated in tissue culture medium and directly processed for interphase fluorescent in situ hybridization analysis. The probes for 1p36 (PAX7) and 19q13.4 (CTC284K17) were labeled by nick translation with ChromoTide AlexaFluor 594-dUTP (Molecular Probes, Carlsbad, California). The BAC clone for 1q31 (CTC224L21) was labeled by nick translation with ChromoTide fluorescein-12-dUTP (Molecular Probes). The probe for 19pter (D19S353E) was labeled with SpectrumGreen-dUTP (Vysis, Des Plaines, Illinois). The probes were applied to tumor cell suspension slides and codenatured at 75°C on an isolight 125D heat block (Fisher Scientific, Pittsburgh, Pennsylvania). Slides were incubated overnight at 37°C in a moist slide moat (Boekel Scientific, Feasterville, Pennsylvania) and were washed in 0.4 × standard saline citrate solution at 73°C for 2 minutes followed by a 1-minute wash in 2 × standard saline citrate/0.1% NP-40, and counterstained with 4,6-diamidino-2-phenylindole (Sigma Chemical, St. Louis, Missouri). Fluorescent signals from 100 cells were evaluated at 100 × with a Axioplan fluorescent microscope (Carl Zeiss Microscopy, Jena, Germany) equipped with the proper filter sets. An Applied Imaging System device (Applied Imaging, San Jose, California) was used to record images of stained cells.

**Polymerase Chain Reaction**

The allelic status of 1p or 19q was assessed by LOH assays in constitutional/tumor DNA pairs by use of microsatellite markers on 1p36 (D1S1608, D1S1161, and D1S1597) and 19q13 (D19S431, D19S559, and D19S601), as described previously.
\textsuperscript{17} Tumor DNA was extracted from microdissected, formalin-fixed, paraffin-embedded sections and constitutional DNA from blood leukocytes or paraffin sections of the adjacent uninvolved brain.

**MR Imaging**

MR imaging and multivoxel 2D \textit{1}H-MRS studies were performed on a 3T Tim Trio MR scanner (Siemens, Erlangen, Germany) by use of a 12-channel phased array head coil. The imaging protocol included a 3-plane scout localizer, axial T1-weighted magnetization-prepared rapid acquisition of gradient echo (TR, 1620 ms; TE, 3.9 ms; TI, 950 ms; matrix size, 192 × 256; section thickness, 1 mm; sections per slab, 192; flip angle, 15°; NEX, 1; bandwidth, 150 Hz/pixel), an axial FLAIR image (TR, 9420 ms; TE, 141 ms; TI, 2500 ms; section thickness, 3 mm; number of sections, 60; flip angle, 170°; NEX, 1; bandwidth, 287 Hz/pixel), and an axial T2-weighted image (TR, 2260 ms; TE, 91 ms; section thickness, 3 mm; number of sections, 60). Contrast-enhanced T1-weighted magnetization–prepared rapid acquisition of gradient echo images were acquired after administration of a standard dose (0.1 mmol/kg) of gadodiamide contrast agent (Omniscan; GE Healthcare, Oslo, Norway).

**Perfusion-Weighted Imaging**

Dynamic susceptibility contrast–PWI was performed 5 minutes after a 3-mL preloading dose of intravenous gadodiamide contrast agent. The preloading injection was performed to reduce the effect of contrast leakage. For PWI, T2*-weighted gradient-echo EPI was performed during the first pass of a standard dose (0.1
mmol/kg, 5 mL/s) of intravenous contrast agent. FLAIR images were used to plan twenty 3-mm-thick axial sections covering the neoplasm (field of view, 22 × 22 cm²; matrix size, 128 × 128; in-plane resolution, 1.72 × 1.72 × 3 mm³; TR, 2000 ms; TE, 45 ms; bandwidth, 1346 Hz/pixel; flip angle, 90°; EPI factor, 128; echo spacing, 0.83). Forty-five sequential measurements were acquired for each section, with a temporal resolution of 2.1 s.

**Proton MR Spectroscopy**

We performed single-section 2D multi-voxel ¹H-MRS by using a point-resolved spectroscopy sequence after acquisition of PWI and postcontrast T₁-weighted images. Sequence parameters included a TR of 1700 ms; TE, 30 ms; NEX, 3; field of view, 16 × 16 cm²–20 × 20 cm²; section thickness, 15–20 mm; bandwidth, 1200 Hz; matrix size, 16 × 16; and vector size, 1024. The size of the ¹H-MRS voxel varied from 10 × 10 × 15 mm³ (volume, 1.5 cm³) to 10 × 12.5 × 20 mm³ (volume, 2.5 cm³), depending on the dimensions of the neoplasm. The VOI was selected based on FLAIR images to include the largest cross-section of neoplasm and contralateral normal brain parenchyma in the same plane. Areas of scalp, skull base, and sinuses were avoided in the selection of the VOI. In addition, 8 outer volume saturation slabs (30-mm thick) were placed outside of the VOI to suppress lipid signals from the bone and scalp. The dataset was acquired by use of elliptic k-space sampling with weighted-phase encoding to reduce the acquisition time. Manual shimming was performed to achieve an optimal value of full width at half maximum of the water signal. In all cases, a shimming of <20 Hz was achieved on the magnitude signal of the water resonance. Both water-suppressed and unsuppressed ¹H-MRS spectra were acquired, and the unsuppressed water signal was used to compute metabolite concentrations.

**Data Analysis**

We constructed CBV maps on a Leonardo workstation (Siemens, Erlangen Germany) using a PWI task card (Massachusetts General Hospital, Boston, Massachusetts), as described previously.¹⁹ We initially overlaid ¹H-MR spectroscopy VOI on the FLAIR images to select the voxels of interest encompassing the hyperintense abnormality on a Leonardo workstation by using the syngo software (Siemens). The ¹H-MR spectroscopy VOI was then overlaid on the CBV maps to coregister the CBV maps and ¹H-MR spectroscopy VOI. This method allowed us to sample CBV values only from the regions that corresponded to the ¹H-MR spectroscopy voxels. We obtained CBV values by drawing regions of interest from each selected voxel based on the FLAIR image hyperintensity in each neoplasm. The size of the regions of interest was similar to the ¹H-MR spectroscopy voxel dimensions. The regions of interest were drawn by the primary author, who has more than 10 years of experience with clinical spectroscopy, and verified by an experienced neuroradiologist (>10 years of experience). Care was taken to avoid the cerebral blood vessels and hemorrhagic and cystic regions. CBV values were normalized with respect to contralateral normal-appearing white matter.

All ¹H-MR spectroscopy data were analyzed by using a user-independent spectral fit program (LCModel; Stephen Provencher, Oakville, Ontario, Canada).²⁰ The following metabolites were evaluated: NAA, Cr, Cho, Glx, and myo-inositol. The resonance at 1.3 ppm was assigned to a combination of lactate and lipid metabolites with Cramer-Rao lower bounds greater than 20% SD were excluded.²⁰ Metabolite concentrations were normalized with respect to the ipsilateral Cr for each voxel.

Because a region with rCBVmax is generally thought to reflect tumor aggressiveness,²¹ NAA/Cr, Cho/Cr, Glx/Cr, myo-inositol/ Cr, and lipid + lactate/Cr ratios were computed from the voxel that also exhibited the rCBVmax value from the tumor region that was encompassed within the VOI of ¹H-MR spectroscopy.

As conventional MR imaging parameters have also been used for genotyping of oligodendrogliomas,²²,²³ the following imaging characteristics were also evaluated qualitatively: 1) sharp vs indistinct tumor border on T2-weighted images, 2) homogeneous vs heterogeneous tumor signal intensity on T2-weighted and T1-weighted images, 3) presence or absence of a paramagnetic susceptibility effect on T2-weighted and T2*-weighted gradient-echo EPI images, and 4) presence or absence of contrast enhancement.

**Statistical Analysis**

Kolmogorov-Smirnov tests were used to determine data distributions. As the data did not depart from Gaussian distribution, independent-sample t tests were performed to look for differences in rCBVmax and metabolite ratios between the 2 groups of oligodendrogliomas. Logistic regression analyses were performed to determine the significant independent predictor and to evaluate the association between rCBVmax values and metabolite ratios to ascertain the best model to distinguish the 2 genotypes. To estimate the goodness of fit of the best logistic regression model, we performed the Hosmer-Lemeshow test. A P value was computed from the χ² distribution with 8 df to test the fit of the logistic model. If the P value was >.05, the model fit was considered acceptable. Receiver operating characteristic analyses were also used to ascertain the accuracy of the discriminatory models, and the area under the receiver operating characteristic curve at a 95% confidence interval determined the accuracy. A Bonferroni correction was applied for analysis of the multivariate data involving 6 parameters (rCBVmax NAA/Cr, Cho/Cr, Glx/Cr, myo-inositol/ Cr, and lipid + lactate/Cr). To evaluate the robustness of multivariate logistic regression models, we also applied leave-one-out cross-validation tests.

Fisher exact χ² tests were performed to evaluate the conventional MR imaging characteristics in distinguishing the 2 groups. All data analyses were performed with a statistical tool (SPSS for Windows, version 15.0; SPSS, Chicago, Illinois).

**RESULTS**

Representative images displaying the ¹H-MR spectroscopy voxel corresponding to the rCBVmax region and spectra from patients with oligodendrogliomas harboring 1p/19q LOH and intact alleles are presented in Figs 1 and 2, respectively. rCBVmax values and metabolite ratios between 2 genotypes of oligodendrogliomas are shown as box-and-whisker plots in Fig 3. Significant differences in Cho/Cr (P = .046) between oligodendrogliomas with 1p/19q LOH and intact alleles were observed by use of the independent-sample t test. No significant differences in rCBVmax values and other ¹H-MRS indices were observed between the 2 groups (P > .05).
When univariate logistic regression models were used to classify the genotypes, no single variable demonstrated significant contribution. However, among all of the variables tested in the univariate logistic regression model, the Cho/Cr ratio had the best predictive value. Receiver operating characteristic analysis demonstrated moderate accuracy (area under the receiver operating characteristic curve, 0.68) of the Cho/Cr ratio (cutoff value, 0.41), with a sensitivity of 69.6% and a specificity of 64.2% (Fig 4). Among all bivariate logistic regression models, the Cho/Cr ratio, together with the rCBV_max value, provided the best discriminatory classification with an accuracy (area under the receiver operating characteristic curve, 0.69), a sensitivity of 69.7%, and a specificity of 70.6% (Fig 4). Accuracies for the bivariate models involving rCBV_max and other metabolite ratios (NAA/Cr, myo-inositol/Cr, Glx/Cr, and lipid/lactate/Cr) were inferior to that of a model involving rCBV_max and Cho/Cr (data not shown). It is interesting to note that after incorporation of all of the metabolite ratios (NAA/Cr, Cho/Cr, Glx/Cr, myo-inositol/Cr, and lipid/lactate/Cr) and the CBV_max value in the multivariate logistic regression model, a significant improvement in the performance of the model was observed ($P < 0.018$). A higher discriminative accuracy (area under the receiver operating characteristic curve, 0.72), sensitivity (82.6%), and moderate specificity (64.7%) were observed in distinguishing 2 groups of oligodendrogliomas (Fig 4). A $\chi^2$ value of 8.04 and a $P$ value of .429 were obtained from the Hosmer-Lemeshow test, reflecting an acceptable fit for the multivariate logistic regression model. Leave-one-out cross-validation tests revealed that 70% of oligodendrogliomas were correctly classified into 1p/19q LOH and intact alleles by the multivariate logistic regression model.

**Conventional MR Imaging Characteristics**

Paramagnetic susceptibility effect was higher in patients with 1p/19q LOH oligodendrogliomas compared with those with intact alleles ($P = .04$). Of the 23 patients with 1p/19q LOH, 18 patients demonstrated a susceptibility effect, whereas only 8 of 17 patients with intact alleles had a susceptibility effect. In addition, more patients with 1p/19q LOH oligodendrogliomas ($n = 19/23$) had an indistinct border on T2-weighted images than those with intact
alleles \( (n = 12/17) \), with a trend toward significance \( (P = .07) \). However, contrast enhancement and signal intensity on T2- and T1-weighted images did not differ between the 2 groups of oligodendrogliomas \( (P > .05) \).

**DISCUSSION**

Our study demonstrates that the integration of rCBV\(_{\text{max}}\) and \(^1\)H-MRS indices may aid in the discrimination of oligodendrogliomas with 1p/19q LOH from those with intact alleles. The prevalence of 1p/19q LOH in oligodendrogliomas is 50%–80%, which is consistent with a 60%–70% response rate to procarbazine, vincristine, lomustine (PCV),\(^{24}\) whereas 50%–60% of patients respond to temozolomide.\(^{25}\) Although most anaplastic oligodendrogliomas are chemosensitive, the responsiveness of low-grade oligodendrogliomas and the most appropriate timing for therapy are unclear and debatable.\(^{26-28}\) On the contrary, some studies\(^{8,9}\) have demonstrated that oligodendrogliomas harboring 1p/19q LOH, irrespective of histologic grade, present a favorable outcome to PCV chemotherapy, thus corroborating the need for a genetic profile to guide clinical management in such patients.

Previous studies have reported that both dynamic susceptibility contrast–PWI and arterial spin-labeling PWI can distinguish histologic grades of gliomas.\(^{29,30}\) However, PWI had limited usefulness in the differentiation of subgroups of oligodendrogliomas with considerable overlap in rCBV\(_{\text{max}}\) and maximal cerebral blood flow between low and high grades.\(^{21,29,31}\) One study reported specific genotypic differences in oligodendrogliomas by use of dynamic susceptibility contrast–PWI,\(^{11}\) with significantly higher rCBV\(_{\text{max}}\) in only low-grade oligodendrogliomas with 1p/19q LOH.\(^{11}\)

![](https://example.com/fig3.png)

**FIG 3.** Box-and-whisker plots demonstrating the range of distribution of metabolite ratios from a voxel with rCBV\(_{\text{max}}\) in patients with 1p/19q LOH (shaded) and intact alleles (white). Boxes represent the median, the 25th percentile, and the 75th percentile. Outlying values are marked with open circles. Cho/Cr was significantly different between the 2 genotypes of oligodendrogliomas.

![](https://example.com/fig4.png)

**FIG 4.** Receiver operating characteristic curves for Cho/Cr ratio measured from rCBV\(_{\text{max}}\) voxel exhibit an area under the receiver operating characteristic curve of 0.68 (broken line). The Cho/Cr ratio, together with the rCBV\(_{\text{max}}\) value in the multivariate logistic regression model, the area under the receiver operating characteristic curve is 0.72 (solid line). The multivariate logistic regression analysis provided the best model to distinguish the 2 groups of oligodendrogliomas, with a sensitivity of 82.6% and a specificity of 64.7%. Leave-one-out cross-validation tests revealed that 70% of oligodendrogliomas were correctly classified.

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tissue compartments because of partial volume averaging. This of the neoplasm, it is possible that metabolite levels from a large with patients with intact alleles. Given the heterogeneous nature Cho/Cr ratio in oligodendrogliomas with 1p/19q LOH compared from high-grade oligodendrogliomas compared with low-grade types.33,34 Recently, 1H-MR spectroscopy has also rCBVmax between 2 genotypes among high-grade oligodendro- gliomas. These studies exemplify the limitation of rCBV alone because a priori knowledge of WHO grading (via biopsy or sur- gical samples) would defeat the purpose of a noninvasive diagnos- tic imaging technique. Therefore, it is essential to explore the use- fulness of other imaging biomarkers or a combination of biomarkers that can identify oligodendrogliarial genotypes before commencement of any treatment.

Numerous studies have shown the potential of 1H-MR spectroscopy in the evaluation of tumor grade33,34 and differentiation of tumor types.33,34 Recently, 1H-MR spectroscopy has also shown promise in determining the genotype profile of brain tu- mors.35 Nafe et al36 reported a significant correlation between Cho/Cr and the degree of epidermal growth factor receptor in astrocytic tumors, suggesting that molecular analysis by 1H-MR spectroscopy may provide better characterization of brain tu- mors. Jenkinson et al39 observed a nonsignificant, but higher Cho/Cr ratio in oligodendrogliomas with 1p/19q LOH compared with patients with intact alleles. Given the heterogeneous nature of the neoplasm, it is possible that metabolite levels from a large single voxel (used in that study) might have included multiple tissue compartments because of partial volume averaging. This belief is also supported by a considerable overlap of 1H-MR spectroscopy indices between 2 grades of oligodendroglio- mas.37 To address the tumor heterogeneity, Chawla et al36 used cerebral blood flow–guided analysis of 1H-MR spectroscopy and observed significantly higher Cho/Cr and lipid + lactate/Cr from high-grade oligodendrogliomas compared with low-grade oligodendrogliomas.

Because the rCBVmax region corresponds to greatest malignancy,21 we evaluated the Cho/Cr ratios from the voxel with the rCBVmax region and observed significantly different ratios be- tween the 2 genotypes of oligodendrogliomas. However, no sig- nificant contribution of any single variable was observed in the univariate logistic regression models in distinguishing the 2 geno- types. This may be the result of tumor heterogeneity, which is prevalent in oligodendrogliomas. To the best of our knowledge, our study is the first that explores the usefulness of combining PWI-directed 1H-MR spectroscopy and PWI to distinguish 1p/ 19q LOH oligodendrogliomas from those with intact alleles. Be- cause we focus on areas of high perfusion only, we believe that the differences (though small, but significant) are real and are not related to intratumoral heterogeneity. As ours is a single-institu- tion study on a limited number of patients, future studies on larger cohorts may be necessary to evaluate the true clinical poten- tial of our work.

When rCBVmax and Cho/Cr values were incorporated in a bivariate logistic regression analysis, a moderate sensitivity, spec- ificity, and accuracy was observed. However, incorporating rCBVmax value and corresponding 1H-MRS indices as interaction components in a multivariate regression analysis provided the best accuracy. A relatively high sensitivity of 82.6% for this model indicates a high positive rate in discriminating the 2 groups of oligodendrogliomas. Given the inherently different physiologic and biochemical information that rCBVmax and 1H-MRS indices provide, we believe that these parameters may be complementary in tumor diagnosis. Multiparametric data analysis allows us to exploit the unique strengths of the different imaging techniques. As a combination of PWI and 1H-MR spectroscopy improves the diagnostic accuracy of gliomas,38 we used a similar approach to obtain greater discrimination of genotypes of oligodendroglio- mas and showed that it was more sensitive than any single PWI/ 1H-MR spectroscopy parameter.

Cho-containing compounds (choline, phosphocholine, and glycerophosphocholine) are part of the normal phospholipid pathways that maintain cell membrane integrity. Higher Cho lev- els in tumors indicate increased membrane turnover because of cell proliferation or high cell density.39 Tumor vasculature plays a critical role in supplying nutrients and oxygen to cancer cells, providing a favorable environment for the cells to grow. This argument is supported by the fact that high rCBV correlates with increased Cho levels in gliomas.40 Histopathologic analysis shows that oligodendrogliomas with 1p/19q LOH grow as compact and hypercellular lesions,41 corroborating our observation of elevated levels of Cho/Cr in these oligodendrogliomas. Higher prolifera- tion of neoplastic cells and elevated metabolic rate lead to hypoxic regions; this cycle ultimately leads to energy failure and cell death that results in necrosis. We believe that elevated levels of lipid and lactate in the 1p/19q LOH oligodendrogliomas in our study is possibly attributed to a combined process of hypoxia, micro- scopic cellular necrosis, and cell proliferation in rCBVmax regions of the neoplasms. Both myo-inositol and Glx play important roles in the growth of oligodendrogliomas through multiple mecha- nisms.33,42 We believe that increased mitotic activity of neoplastic cells in the rCBVmax regions of 1p/19q LOH oligodendrogliomas may account for the increased myo-inositol and Glx levels.

Some studies22,23 have assessed the relationship between con- ventional MR imaging and genotypes of oligodendrogliomas. An indistinct tumor border, heterogeneous signal intensity, and paramagnetic susceptibility are associated with oligodendroglio- mas harboring 1p/19q LOH.22,23 We observed a significantly higher susceptibility effect in oligodendrogliomas with 1p/19q de- letions. Calcification and tumor-associated hemorrhage are com- monly seen in oligodendrogliomas,43 which may have contrib- uted to the susceptibility effect in our study.

Previous studies22,23 have also reported that oligodendroglio- mas harboring 1p/19q loss usually demonstrate an indistinct border, whereas a sharp border is a characteristic of those with intact 1p/19q alleles. We also observed an indistinct border more fre- quently in oligodendrogliomas with 1p/19q LOH compared with intact alleles; however, the difference was not significant. Furthermore, unlike previous reports,22 no significant difference in signal intensity of T2- and T1-weighted images was observed in our study between 2 groups of oligodendrogliomas. As morphologic imaging characteristics are usually evaluated qualitatively and are
observer-dependent, assessment of imaging features is subjective and may have considerable user bias. We believe that the discrepancy between our results and those published in the literature may be attributed to observer variability in assessing these imaging characteristics. These observations further imply that evaluation of conventional imaging features alone may not be a reliable approach in distinguishing genotypes of oligodendrogliomas. On the contrary, techniques such as PWI and $^1$H-MR spectroscopy are physiologically sensitive and quantitative and consequently may be more reliable.

Our study was limited by the relatively small sample size, as we had to exclude 10 patients because of unavailability of a cytogenetic profile and suboptimal PWI or $^1$H-MRS data. The second limitation of our study was a certain degree of heterogeneity in our patient population, as we also included patients with oligoastrocytomas. In general, oligoastrocytomas exhibit p53 deletions and 17p LOH that are associated with astrocytic biologic behavior. However, allelic loss on chromosomes 1p and 19q is also exhibited by oligoastrocytomas, suggesting a monoclonal origin of oligodendrogliomas and oligoastrocytomas. Similar to pure oligodendrogliomas, patients with oligoastrocytomas also exhibit favorable prognosis and clinical response to chemoradiation therapy. On the basis of similarities in genetic aberrations and clinical features, oligodendrogliomas and oligoastrocytomas are often grouped together as oligodendrogial tumors; thus, their inclusion in the current study is justifiable.

Another limitation of our study was limited tissue coverage, as we used a single-section $^1$H-MRS to coregister rCBV maps; thus, only a part of the tumor was analyzed. To cover the whole neoplasm, or at least the bulk of the tumor volume, it is desirable to use a 3D $^1$H-MRS sequence. However, such techniques lead to increased acquisition time that could be prohibitive in routine clinical settings. Parallel MRS with sensitivity encoding or generalized autocalibrated partially parallel acquisitions or echo-planar spectroscopic imaging techniques can overcome this problem.

 Leakage of the gadolinium-based contrast agents in neoplastic lesions from the vascular compartment to the interstitial space may lead to underestimation of rCBV values. To account for this error, a preloading dose of contrast agent was administered 3 minutes before the contrast bolus to acquire PWI data as has been reported previously. Although largely successful, the resulting signal might still be contaminated by a T1 effect that can be accounted for by mathematical modeling. Although we did not perform such corrections, we believe that this potential error would cancel out because the assumed underestimation of CBV would have affected both of the patient groups.

**CONCLUSIONS**

Our study demonstrates that integration of $^1$H-MRS indices from the rCBV$_{max}$ voxel may be helpful in distinguishing oligodendrogliomas with 1p/19q LOH from those with intact alleles. However, further studies in a larger patient population are required to confirm our findings.

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