

DISTINCTION BETWEEN RECURRENT GLIOMA AND RADIATION INJURY USING MAGNETIC RESONANCE SPECTROSCOPY IN COMBINATION WITH DIFFUSION-WEIGHTED IMAGING

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Purpose: The aim of this study was to explore the diagnostic effectiveness of magnetic resonance (MR) spectroscopy with diffusion-weighted imaging on the evaluation of the recurrent contrast-enhancing areas at the site of treated gliomas.

Methods and Materials: In 55 patients who had new contrast-enhancing lesions in the vicinity of the previously resected and irradiated high-grade gliomas, two-dimensional MR spectroscopy and diffusion-weighted imaging were performed. Spectral data for *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), lipid (Lip), and lactate (Lac) were analyzed in conjunction with the apparent diffusion coefficient (ADC) in all patients. Diagnosis of these lesions was assigned by means of follow-up or histopathology.

Results: The Cho/NAA and Cho/Cr ratios were significantly higher in recurrent tumor than in regions of radiation injury ($p < 0.01$). The ADC value and ADC ratios (ADC of contrast-enhancing lesion to matching structure in the contralateral hemisphere) were significantly higher in radiation injury regions than in recurrent tumor ($p < 0.01$). With MR spectroscopic data, two variables (Cho/NAA and Cho/Cr ratios) were shown to differentiate recurrent glioma from radiation injury, and 85.5% of total subjects were correctly classified into groups. However, with discriminant analysis of MR spectroscopy imaging plus diffusion-weighted imaging, three variables (Cho/NAA, Cho/Cr, and ADC ratio) were identified and 96.4% of total subjects were correctly classified. There was a significant difference between the diagnostic accuracy of the two discriminant analyses (Chi-square = 3.96, $p = 0.046$).

Conclusion: Using discriminant analysis, this study found that MR spectroscopy in combination with ADC ratio, rather than ADC value, can improve the ability to differentiate recurrent glioma and radiation injury.
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Magnetic resonance imaging, Magnetic resonance spectroscopy, Glioma, Radiotherapy, Neoplasm recurrence.

INTRODUCTION

In subjects with previously resected and irradiated high-grade glioma, differentiation of recurrent tumor from radiation injury on routine follow-up magnetic resonance (MR) images is problematic, despite the fact that both types of lesions can be associated with more specific characteristics: for example, corpus callosum involvement or multiple enhancing lesions in the former case (1), and “soap bubble” or “Swiss cheese” pattern of enhancement in the latter (2). Use of MR spectroscopy and diffusion-weighted (DW) imaging (3–6), which are noninvasive functional imaging methods that provide information complementary to that furnished by anatomic imaging, have been proposed as alternative modalities for differentiating the two entities.

Although MR spectroscopy has been applied to the diagnosis of recurrent glioma, single-voxel MR spectroscopy

used in earlier investigations resulted in interpretative difficulties, with overlapping metabolic ratios as a result of partial volume contamination in these histologically heterogeneous lesions (6, 7). Multivoxel MR spectroscopy—either two-dimensional (2D) (5, 8) or three-dimensional (9)—enables coverage of a larger volume and investigation of multiple regions of the lesion. However, multivoxel MR spectroscopy cannot correctly classify lesions in about 18% of cases by detecting altered levels of biochemical tissue compounds (7, 10).

Use of DW imaging has been considered a means to characterize and differentiate morphologic features such as edema, necrosis, and tumor tissue by measuring differences in the apparent diffusion coefficient (ADC) (11). This technique has been applied to determining glioma grade (12) and evaluating necrotic brain tissue in the temporal lobe

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Table 1. Means (\pm SD) of selected magnetic resonance spectroscopy ratios in various lesions types

Lesion type	Cho/Cr	Cho/NAA	Lac/Cr	Lip/Cr	NAA/Cr
Tumor ($n = 32$)	2.82 ± 0.65	3.52 ± 0.98	1.28 ± 1.60	0.14 ± 0.20	0.84 ± 0.23
Radiation injury ($n = 23$)	1.61 ± 0.34	1.55 ± 0.54	0.45 ± 0.72	0.54 ± 0.71	1.10 ± 0.26

Abbreviations: Cho = choline-containing compounds; Cr = (phospho-) creatine; Lac = lactate; Lip = lipid-containing compounds; NAA = *N*-acetyl-aspartate; SD = standard deviation.

after radiotherapy for nasopharyngeal carcinoma (13). Recently it was verified that assessment of ADCs of enhancing regions was useful in differentiating between recurrent glioma and radiation injury (3, 4).

Both 2D MR spectroscopy and DW imaging can be carried out in our MR scanner. Therefore, both MR techniques were performed on 55 patients in an attempt to distinguish recurrent glioma from radiation injury. The aim of this investigation was to explore whether the addition of DW imaging to MR spectroscopy would improve our ability to discriminate between the two entities.

METHODS AND MATERIALS

Patients

A total of 55 patients (30 male and 25 female; mean age, 43.67 ± 11.91 years, range 23–67 years) who had undergone surgical resection with pathologically proven high-grade gliomas (primary histology according to the classification schemes of the World Health Organization: grade III, $n = 36$; grade IV $n = 19$) were enrolled in the study. All subjects had undergone a full course of conventional fractionated radiotherapy after surgery, and all had development of new contrast-enhancing lesions in the vicinity of the original treated tumors visualized on scheduled follow-up MR images. Written informed consent was obtained from all patients after the nature of the examination had been fully explained. The study was approved by the institutional review board, and the Declaration of Helsinki principles were followed in all aspects of the study.

Follow-up MR imaging examinations were performed 6 weeks after completion of radiotherapy and at 2-month intervals during the first year. During years 2 and 3, follow-up MR images were obtained at 3- or 4-month intervals, depending on the clinical course. If clinical deterioration occurred, MR images were obtained as needed. The MR spectroscopy and DW imaging examinations were performed after initial identification of the recurrent contrast-enhancing lesion on follow-up MR images.

Histopathologic examination and follow-up MR imaging after MR spectroscopy were used to establish the identity of the con-

trast-enhancing lesion. Lesions were considered as tumor recurrence if they met either of the following criteria: later histopathologic evidence of active tumor by biopsy or surgical resection; or follow-up MR image showing mass effect and steady growth of enhancement. Lesions classified as radiation injury met either of the following criteria: later histopathologic verification of radiation injury without tumor, by biopsy or surgical resection; or stable-appearing or resolving regions of enhancement on subsequent MR image.

Histopathologic examinations of 39 tissue specimens, 10 by means of stereotactic biopsy and 29 by means of surgical resection, were performed by a board-certified neuropathologist. Of the specimens, 13 were classified as radiation injury and 26 as tumor recurrence.

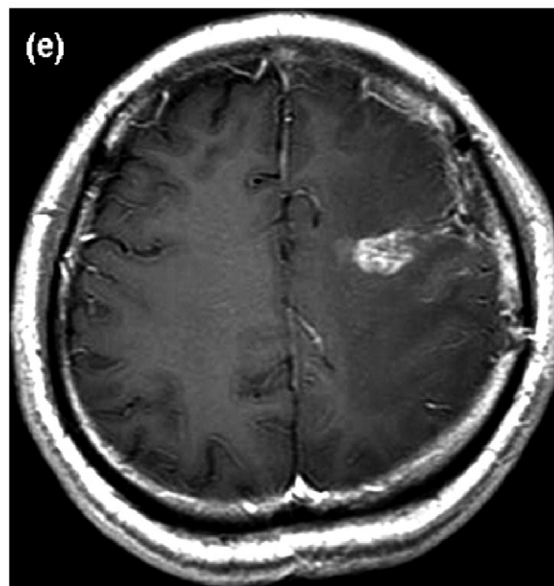
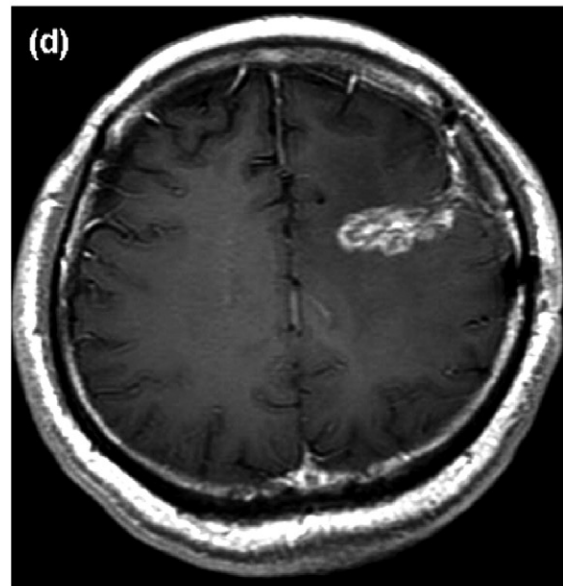
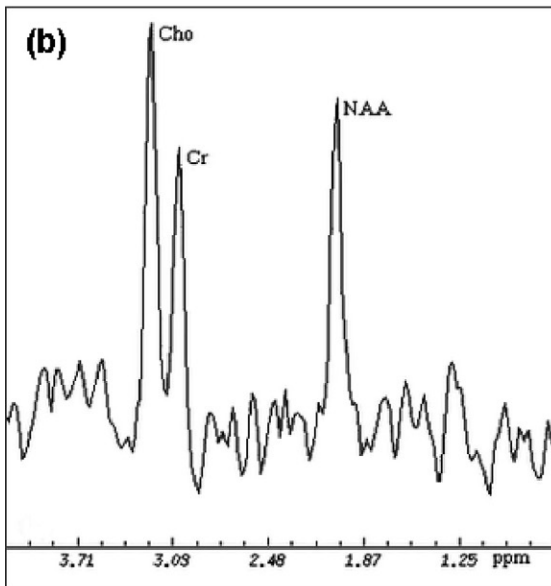
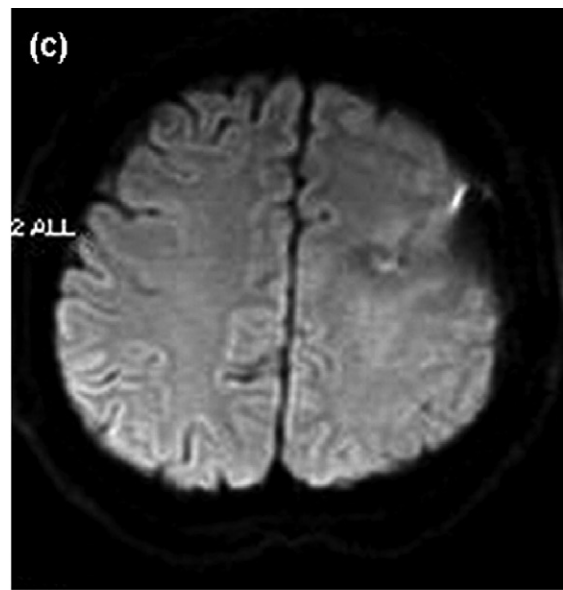
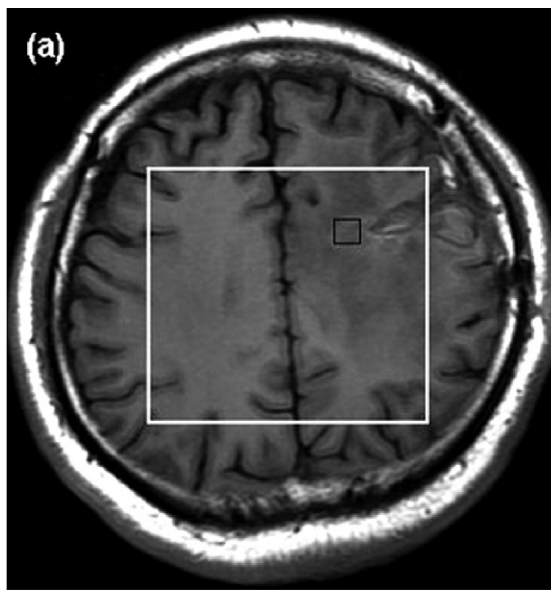
Apart from histopathologic examination to determine the nature of lesions, 16 patients underwent additional follow-up. The follow-up time of the patients after the MR spectroscopy examination was 14.71 months (range, 10–20 months) in 6 patients whose lesions were classified as tumor recurrence and was 17.7 months (13–22 months) in 10 patients classified as radiation injury.

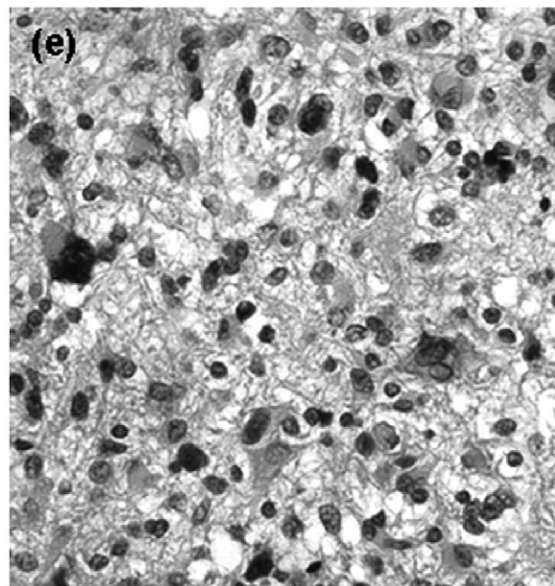
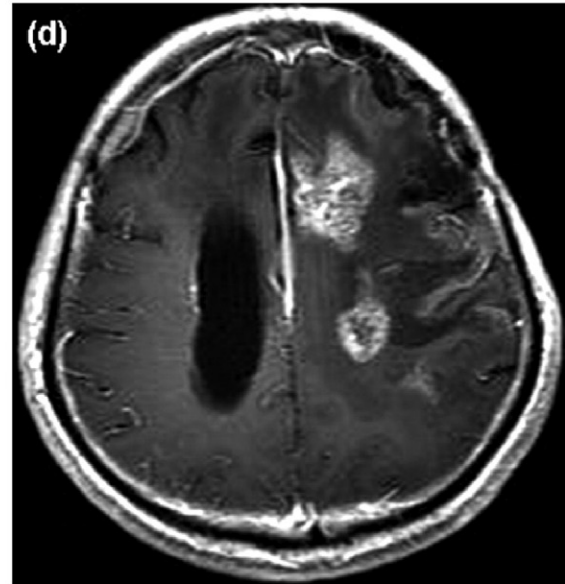
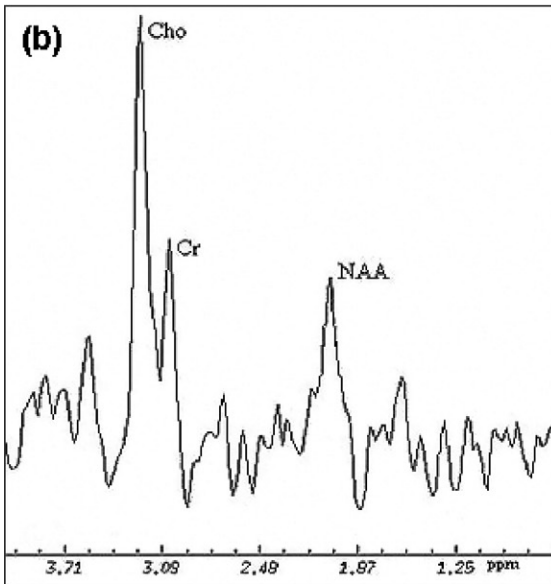
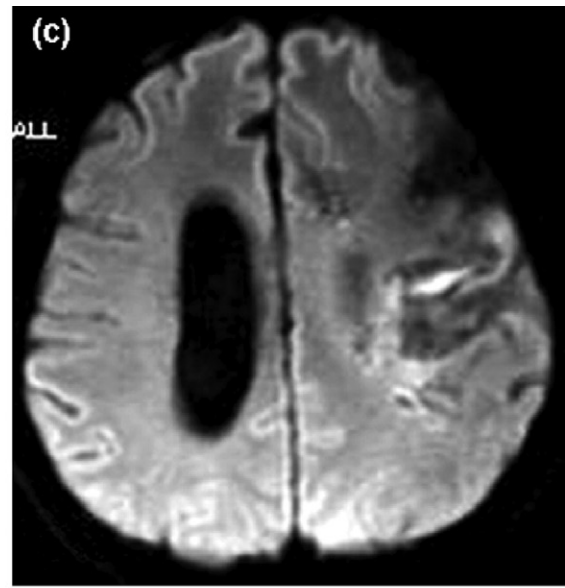
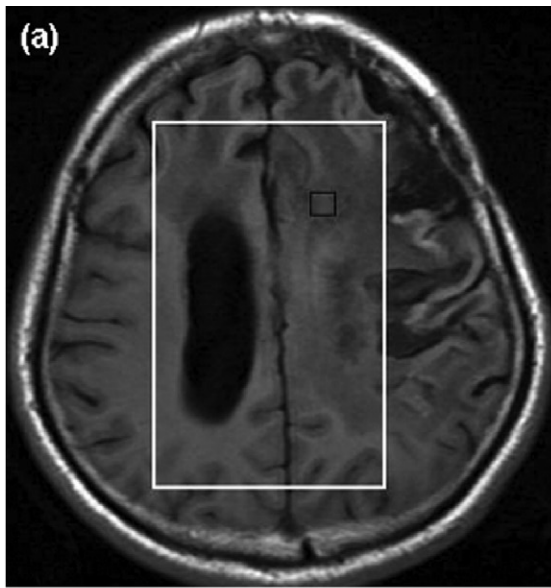
MR and DW imaging

All examinations were performed on a 3.0T MR scanner (Signa EXCITE II; GE Medical Systems, Milwaukee, WI). The conventional MR images consisted of axial T1-weighted (500/8 ms [TR/TE]) spin-echo (SE), T2-weighted (4500/102 ms) fast SE, and fluid-attenuated inversion-recovery (FLAIR) (9000/120/2250 ms [TR/TE/TI]) images obtained by using 6-mm section thickness, 240-mm field of view (FOV), and 320×224 matrix. The DW images were obtained by using an axial echo-planar SE sequence (5000/64.9 ms [TR/TE]; one average; 6-mm section thickness; diffusion gradient encoding in three orthogonal directions; $b = 1000$ s/mm²; 240-mm FOV; 160×192 matrix) in 1 min. Contrast-enhanced T1-weighted SE images were then obtained in axial, coronal, and sagittal planes after intravenous administration of gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) at a dose of 0.1 mmol/kg of body weight.

Postprocessing of ADC maps was performed by using standard software on a workstation (Functool 3.1 software; Sun, GE Health-

Fig. 1. Radiation injury in a 46-year-old man who underwent surgery, radiotherapy, and chemotherapy for a left frontal lobe glioblastoma multiforme. (a) Axial T1-weighted image, over which volume of interest of magnetic resonance (MR) spectroscopy is placed. (b) Two-dimensional MR spectroscopic image that shows pathologic spectra with increased choline (Cho)/*N*-acetylaspartate (NAA) and Cho/creatinine (Cr) ratio (1.30 and 1.53, respectively), and a decrease in the NAA/Cr ratio (1.18). (c) Diffusion-weighted image ($b = 1000$ s/mm²) that exhibits an apparent diffusion coefficient (ADC) in the contrast-enhancing lesion of 1.35×10^{-3} mm²/s and a normalized ADC ratio of the contrast-enhancing region of 1.66. (d) Contrast-enhanced T1-weighted image that shows the initial contrast-enhancing region. (e) Contrast-enhanced T1-weighted image at 12-month follow-up after MR spectroscopy examination that reveals marked regression of enhancement area.





care), which had been used in a recently published study (3). In brief, regions of interest (ROIs) were drawn manually onto the obtained ADC maps in the region corresponding to the enhancing area on contrast-enhanced T1-weighted images. The ADC value was calculated automatically by the Functool 3.1 software. For normalizing ADC levels, an ADC ratio was calculated as the quotient of the ADC values of the enhancing region and the matching structure of same-size ROIs in the contralateral hemisphere.

MR spectroscopy

In each case MR spectroscopy was performed as an additional sequence within 24 to 48 h after contrast-enhanced MR imaging to minimize the influence of gadolinium on MR spectroscopy and to ensure voxel placement over the area of contrast enhancement.

The following parameters were used for 2D MR spectroscopy: a point-resolved spectroscopy sequence (PRESS), which included water and outer volume saturation pulses; 1500/144 ms [TR/TE]; 16-cm FOV; 16 × 16 matrix; 10-mm slice thickness; acquisition, 1 average; scanning time, 4 min 20 s. The volume of interest (VOI) was placed on axial T1-weighted images corresponding to the contrast-enhancing area on contrast-enhanced axial T1-weighted images. Automatic prescanning was performed before each spectroscopic scan to ensure adequate water suppression. The full-width half-maximum was kept at less than 15 Hz and water saturation between 95% and 99%.

Details of the postprocessing procedure used for MR spectroscopy have been reported previously (5). Within the obtained VOI, separate 1 cm × 1 cm × 1 cm voxels were individually placed in the area of enhancement corresponding to contrast-enhanced axial T1-weighted image. Metabolite peaks used were as follows: *N*-acetylaspartate (NAA) at 2.02-ppm, choline-containing compounds (Cho) at 3.22-ppm, (phospho-) creatine (Cr) at 3.01-ppm, lipid-containing compounds (Lip) in the range of 0.9–1.3 ppm, and lactate (Lac) at 1.35-ppm (an inverted β-methyl doublet). Metabolite values were calculated automatically from the area under each metabolite peak by the Functool 3.1 software. Metabolite ratios (NAA/Cr, Cho/Cr, Lip/Cr, Lac/Cr, and Cho/NAA) were manually calculated.

Statistical analysis

Statistical analysis was performed with SPSS for Windows software, release 11.5 (SPSS Inc., Chicago, IL). Metabolite ratios and ADC parameters (ADC value and ADC ratio) between the recurrent tumor group ($n = 32$) and radiation injury group ($n = 23$) were compared using the unpaired, two-tailed Student *t* test. A forward stepwise discriminant analysis was undertaken to assess the power of metabolite ratios and ADC parameters to distinguish tumor recurrence and radiation injury. Diagnostic accuracy was then compared between metabolite ratios and metabolite ratios

plus ADC parameters for discriminating the two entities by using the Chi-square test. The level of significance was set at $p < 0.05$.

RESULTS

Findings of MR spectroscopy

The Cho/Cr, Cho/NAA, and Lac/Cr ratios of the contrast-enhancing lesions in the recurrent tumor group were significantly higher than those in the radiation injury group ($p < 0.01$, $p < 0.01$, and $p = 0.01$, respectively), whereas the NAA/Cr and Lip/Cr ratios of the contrast-enhancing lesions in the recurrent tumor group were significantly lower than those in the radiation injury group ($p < 0.01$ and $p = 0.01$, respectively). The mean values of the metabolite ratios in respective lesions are summarized in Table 1. Representative MR images and MR spectroscopy are shown in Figures 1 and 2.

Findings of DW imaging

The recurrent tumor group showed significantly lower ADC value ($1.20 \pm 0.08 \times 10^{-3} \text{ mm}^2/\text{s}$, mean \pm SD) compared with the radiation injury group ($1.39 \pm 0.09 \times 10^{-3} \text{ mm}^2/\text{s}$). Significance was set at the level of $p < 0.01$.

We subsequently obtained data normalized by creating the ratio of ADC of the enhancing lesion to ADC of matching structure in the contralateral hemisphere (*i.e.*, ADC ratio). The ADC ratio was significantly lower in the recurrent tumor group (1.42 ± 0.10) compared with that in the radiation injury group (1.69 ± 0.08 ; $p < 0.01$). A box-and-whisker diagram of the ADC values and ADC ratio is used to illustrate these results in Figures 3 and 4. Representative MR images and DW image are shown in Figures 1 and 2.

Findings of MR spectroscopy in conjunction with DW imaging

To analyze the power of correct classification, two discriminant analyses were carried out separately for metabolite ratios alone and for metabolite ratios in conjunction with ADC parameters. In the first analysis, which focused only on the available metabolite ratios, NAA/Cr, Cho/Cr, Lip/Cr, Lac/Cr, and Cho/NAA were used as independent variables. In the second analysis, all variables (metabolite ratios and ADC parameters) were used as independent variables. For both analyses, the findings of follow-up or histopathology served as the group variable.

In the first analysis, two variables were shown to be significant. The Cho/NAA value emerged as the first vari-

Fig. 2. Tumor recurrence in a 35-year-old woman who underwent surgery and radiotherapy for a left frontal lobe anaplastic astrocytoma. (a) Axial T1-weighted image, over which volume of interest of magnetic resonance (MR) spectroscopy is placed. (b) Two-dimensional MR spectroscopic image that shows pathologic spectra with increased choline (Cho)/*N*-acetylaspartate (NAA) and Cho/creatinine (Cr) ratio (2.99 and 2.54, respectively), and a decrease in the NAA/Cr ratio (0.85). (c) Diffusion-weighted image ($b = 1000 \text{ s/mm}^2$) that exhibits an apparent diffusion coefficient (ADC) in the contrast-enhancing lesion of $1.16 \times 10^{-3} \text{ mm}^2/\text{s}$ and a normalized ADC ratio of the contrast-enhancing region of 1.46. (d) Contrast-enhanced T1-weighted image that shows the initial contrast-enhancing region. (e) Photomicrograph (hematoxylin-and-eosin stain; original magnification, ×400) showing a hypercellular astrocytic neoplasm with areas of radiation changes.

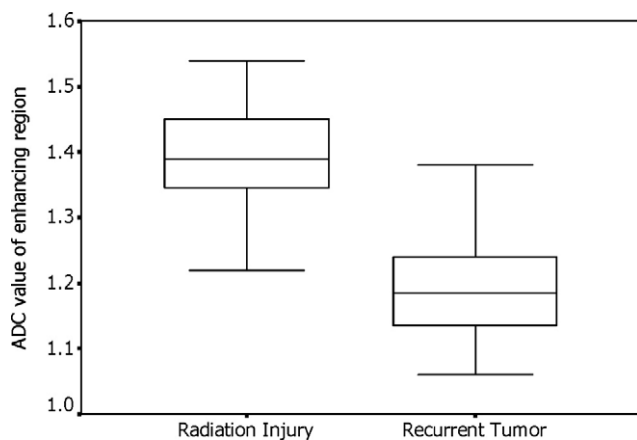


Fig. 3. Comparison of apparent diffusion coefficient values ($\times 10^{-3}$ mm²/s) between the radiation injury and recurrent tumor groups. Line indicates the range of data; boxes represent the distance between the first and third quartiles, with the median between them.

able to differentiate tumor recurrence from radiation injury. To determine the classification ability of other variables, Cho/NAA was removed as a candidate, and Cho/Cr emerged as the second variable. When Cho/Cr was forced out, other variables did not contribute significantly. When both variables (Cho/NAA and Cho/Cr) were grouped together for classification, 85.5% of total subjects were classified correctly according to radiation injury (91.3%) vs. tumor recurrence (81.3%) (Table 2).

In the second analysis, three significant variables were identified. The first variable correlated highly with Cho/NAA, the second with ADC ratio, and the third with Cho/Cr. The ADC value did not contribute significantly to differentiate tumor recurrence from radiation injury. When all the three variables (Cho/Cr, Cho/NAA, and ADC ratio) were subjected together for classification, 96.4% of total subjects were classified into correct groups (radiation injury, 100%; tumor recurrence, 93.8%; Table 2). Compared

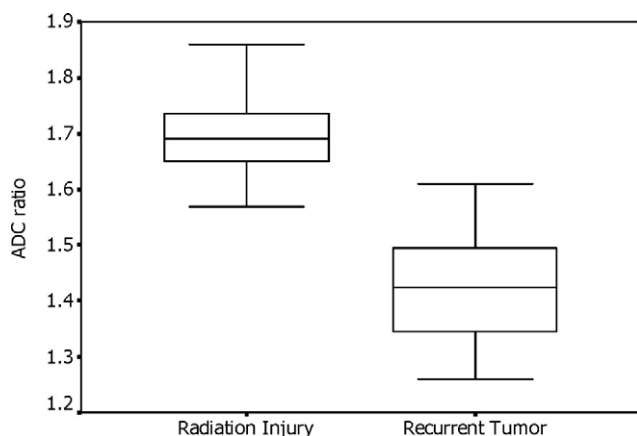


Fig. 4. Comparison of apparent diffusion coefficient ratio between the radiation injury and recurrent tumor groups. Line indicates the range of data; boxes represent the distance between the first and third quartiles, with the median between them.

Table 2. Results of stepwise discriminant analysis*

Variable	Function		Classification	
	Tumor recurrence	Radiation injury	Group	Classified (%)
Stepwise discriminant analysis of metabolite ratios				
Cho/NAA	2.77	0.67	Tumor recurrence	81.3
Cho/Cr	7.50	4.98	Radiation injury	91.3
Constant	-16.13	-5.22	Total	85.5
Stepwise discriminant analysis of combination of metabolite ratios and ADC parameters				
Cho/NAA	6.43	4.87	Tumor recurrence	93.8
ADC ratio	180.16	206.60	Radiation injury	100
Cho/Cr	8.24	5.83	Total	96.4
Constant	-151.87	-183.73		

Abbreviations: ADC ratios = quotient of apparent diffusion coefficient of contrast-enhancing lesion and matching structure in contralateral hemisphere; Cho = choline-containing compounds; Cr = (phospho-) creatine; Lac = lactate; Lip = lipid-containing compounds; NAA = *N*-acetyl-aspartate.

* Based on the analysis, the discriminant equation is as follows:

For metabolite ratios: $D(\text{tumor recurrence}) = 2.77(\text{Cho/NAA}) + 7.50(\text{Cho/Cr}) - 16.13$

$D(\text{radiation injury}) = 0.67(\text{Cho/NAA}) + 4.98(\text{Cho/Cr}) - 5.22$

For combination of metabolite ratios and ADC parameters:

$D(\text{tumor recurrence}) = 6.43(\text{Cho/NAA}) + 8.24(\text{Cho/Cr}) + 180.16(\text{ADC ratio}) - 151.87$

$D(\text{radiation injury}) = 4.87(\text{Cho/NAA}) + 5.83(\text{Cho/Cr}) + 206.60(\text{ADC ratio}) - 183.73$

with the first analysis, the second analysis could further increase the accuracy of discriminant analysis for the assessment of the recurrent enhancing lesion (Chi-square = 3.96, $p = 0.046$).

On the basis of discriminant analysis, two different equations were derived (Table 2). If $D(\text{tumor recurrence})$ was more than $D(\text{radiation injury})$, the lesion was classified as tumor recurrence. If $D(\text{radiation injury})$ was more than $D(\text{tumor recurrence})$, the lesion was classified as radiation injury.

DISCUSSION

Complete surgical ablation of tumor as a primary therapy is a goal for patients with high-grade gliomas, but in many cases the extent of excision is limited by the involvement of neoplasm in vital or functional anatomic parts of the brain (14). For this reason postsurgical external-beam radiotherapy is a generally accepted and common procedure for the management of glioma (15). Nevertheless, the sequential MR images obtained in these patients have demonstrated a variety of radiation-induced brain injury. When a patient with an irradiation-treated high-grade glioma develops a contrast-enhancing lesion, the clinical question is referred as "recurrent tumor vs. radiation injury". Because of shared MR imaging characteristics such as areas of abnormal enhancement with surrounding edema that are located in or

near the primary site of glioma and within the irradiated volume, recurrent glioma and radiation injury are difficult to distinguish (1). Thus, in the follow-up of these patients, classifying newly manifested, contrast-enhancing lesions is one of the key goals in neuro-oncologic imaging (1, 2). Furthermore, any sequential therapeutic measures depend on the correct classification.

Either MR spectroscopy or DW imaging has been used to distinguish glioma relapse from radiation injury (3–6, 16). In our clinical practice, these two imaging modalities have been used in the follow-up of patients treated with radiation for high-grade gliomas in an attempt to distinguish the two entities. The major findings of this study were as follows. (1) Significant differences in Cho/Cr, Cho/NAA and ADC ratios were found between tumor recurrence and radiation injury in patients with irradiation-treated glioma, respectively. (2) With discriminant analysis, Cho/Cr, Cho/NAA, and ADC ratios were the key factors to discriminate recurrent tumor from radiation injury, and the addition of ADC ratios to MR spectroscopy could improve the power of differentiation for the two entities.

A discriminant analysis is a statistical procedure that is highly apt to detect subtle differences in populations by weighting the influence of dependent variables to maximize the distance between groups. To reach this goal, the dependent variables are combined into different classification vectors according to their intercorrelations to distinguish between the previously defined investigation groups. In the first discriminant analysis, the first classification vector we found correlated highly with Cho/NAA. The second classification vector concerned mainly Cho/Cr. According to the classification vectors we used in our study to differentiate between the two groups of radiation injury and tumor recurrence, 85.5% of total subjects were classified into correct groups, which was consistent with previous reports (7, 10). In a similar population examined with 2D MR spectroscopy, Cho/Cr, and Cho/NAA ratios allowed a correct retrospective classification in more than 80% of the cases (10).

The ADC values of biologic tissue reflect the Brownian movement of water molecules, thereby potentially revealing histopathologic characteristics of cellular structure (3). For brain tumors after therapy, cellularity is one of the important factors that influences the ADC. Higher cellularity in recurrent neoplasm would contribute to lower ADC values, as previously reported (17). Thus, recurrent growth of tumor cells determines in part the tissue ADC within the contrast-enhancing region in the recurrence group, which might explain the differences in ADC value between the two

groups in our study. However, the function of discriminant analysis was correlated highly with Cho/Cr, Cho/NAA, and ADC ratio in the second analysis. The ADC value did not contribute through discriminant analysis to further differentiate tumor recurrence and radiation injury, a result that is in excellent agreement with a previous study (18). Using metabolite ratios and ADC values, Rock *et al.* analyzed 18 patients with malignant glioma previously treated with surgery and radiotherapy. The author concluded that metabolite ratio analysis might allow for the clinical discrimination between specimens of tumor and necrosis, but the direct addition of ADC value to MR spectroscopy did not add to the value of MR spectroscopy in distinguishing the two entities. After the normalization procedure used in our methods, a highly significant difference of the ADC ratio between the two entities was observed. In addition, DW imaging could estimate entire contrast-enhancing regions (19), which may make up for the shortcoming of 2D MR spectroscopy that only captures a limited region size. For these reasons, when the three variables (Cho/Cr, Cho/NAA, and ADC ratio) were considered together for classification in the second discriminant analysis, 96.4% of the total subjects were correctly classified.

A limitation of this study is the lack of histopathologic confirmation in all cases, such that imaging follow-up data had to be used as surrogate markers for tissue identification in contrast-enhancing lesions. Although histopathologic confirmation may be desirable in all patients, it is not always clinically practicable because of a high risk of morbidity and approximately 10% sampling error in biopsy cases (20). The prolonged follow-up of these lesions after MR spectroscopy should minimize the possibility of misclassification. Another limitation is that ROIs on FLAIR images, in areas corresponding to T2 prolongation outside the contrast-enhancing region, were not studied. Therefore, the usefulness of FLAIR MR data to improve ability to differentiate tumor recurrence and radiation injury requires further investigation.

CONCLUSION

In conclusion, our results suggest MR spectroscopy allows the noninvasive differentiation of recurrent glioma from radiation injury in patients presenting with suspicious findings on routine follow-up MR images. Adding the ADC ratio to MR spectroscopy, however, substantially improves the ability to differentiate the two entities. The accuracy of differential diagnosis of MR spectroscopy in conjunction with ADC ratio is higher than that of MR spectroscopy.

REFERENCES

1. Mullins ME, Barest GD, Schaefer PW, *et al.* Radiation necrosis versus glioma recurrence: Conventional MR imaging clues to diagnosis. *Am J Neuroradiol* 2005;26:1967–1972.
2. Kumar AJ, Leeds NE, Fuller GN, *et al.* Malignant gliomas: MR imaging spectrum of radiation therapy- and chemotherapy-induced necrosis of the brain after treatment. *Radiology* 2000; 217:377–384.
3. Hein PA, Eskey CJ, Dunn JF, *et al.* Diffusion-weighted imaging in the follow-up of treated high-grade gliomas: Tumor recurrence versus radiation injury. *Am J Neuroradiol* 2004; 25:201–209.
4. Asao C, Korogi Y, Kitajima M, *et al.* Diffusion-weighted imaging of radiation-induced brain injury for differentiation from tumor recurrence. *Am J Neuroradiol* 2005;26:1455–1460.

5. Weybright P, Sundgren PC, Maly P, *et al.* Differentiation between brain tumor recurrence and radiation injury using MR spectroscopy. *Am J Roentgenol* 2005;185:1471–1476.
6. Schlemmer HP, Bachert P, Henze M, *et al.* Differentiation of radiation necrosis from tumor progression using proton magnetic resonance spectroscopy. *Neuroradiology* 2002;44:216–222.
7. Schlemmer HP, Bachert P, Herfarth K, *et al.* Proton MR spectroscopic evaluation of suspicious brain lesions after stereotactic radiotherapy. *Am J Neuroradiol* 2001;22:1316–1324.
8. Rabinov JD, Lee PL, Barker FG, *et al.* In vivo 3-T MR spectroscopy in the distinction of recurrent glioma versus radiation effects: Initial experience. *Radiology* 2002;225:871–879.
9. McKnight TR, von dem Bussche MH, Vigneron DB, *et al.* Histopathological validation of a three-dimensional magnetic resonance spectroscopy index as a predictor of tumor presence. *J Neurosurg* 2002;97:794–802.
10. Lichy MP, Plathow C, Schulz-Ertner D, *et al.* Follow-up gliomas after radiotherapy: 1H MR spectroscopic imaging for increasing diagnostic accuracy. *Neuroradiology* 2005;47:826–834.
11. Castillo M, Smith JK, Kwock L, *et al.* Apparent diffusion coefficients in the evaluation of high-grade cerebral gliomas. *Am J Neuroradiol* 2001;22:60–64.
12. Lam WW, Poon WS, Metreweli C. Diffusion MR imaging in glioma: Does it have any role in the pre-operation determination of grading of glioma? *Clin Radiol* 2002;57:219–225.
13. Tsui EY, Chan JH, Ramsey RG, *et al.* Late temporal lobe necrosis in patients with nasopharyngeal carcinoma: Evaluation with combined multi-section diffusion weighted and perfusion weighted MR imaging. *Eur J Radiol* 2001;39:133–138.
14. Kreth FW, Berlis A, Spiropoulou V, *et al.* The role of tumor resection in the treatment of glioblastoma multiforme in adults. *Cancer* 1999;86:2117–2123.
15. Herfarth KK, Gutwein S, Debus J. Postoperative radiotherapy of astrocytomas. *Semin Surg Oncol* 2001;20:13–23.
16. Kallen K, Burtscher IM, Holtas S, *et al.* 201Thallium SPECT and 1H-MRS compared with MRI in chemotherapy monitoring of high-grade malignant astrocytomas. *J Neurooncol* 2000;46:173–185.
17. Kono K, Inoue Y, Nakayama K, *et al.* The role of diffusion-weighted imaging in patients with brain tumors. *Am J Neuroradiol* 2001;22:1081–1088.
18. Rock JP, Scarpace L, Hearshen D, *et al.* Associations among magnetic resonance spectroscopy, apparent diffusion coefficients, and image-guided histopathology with special attention to radiation necrosis. *Neurosurgery* 2004;54:1111–1117.
19. Bammer R. Basic principles of diffusion-weighted imaging. *Eur J Radiol* 2003;45:169–184.
20. McGirt MJ, Woodworth GF, Coon AL, *et al.* Independent predictors of morbidity after image-guided stereotactic brain biopsy: A risk assessment of 270 cases. *J Neurosurg* 2005;102:897–901.