Original article

Folia Neuropathologica

Spectral changes in postoperative MRS in high-grade gliomas and their effect on patient prognosis

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Folia Neuropathol 2009; 47 (1): 43-49

Abstract

The aim of the study was to find differences in magnetic resonance spectroscopy (MRS) which might facilitate differential diagnosis between tumour regrowth and a remnant tumour with present postradiation changes or postradiation necrosis in the vicinity of the postoperative bed, based on the assessment of the dynamics between two MRS, i.e. preoperative and postoperative scanning, performed at 6 months after surgery. Therefore, in 9 patients with high-grade gliomas, MRS spectra were obtained. Subsequently, a partial tumour resection was done in 5 patients, and 4 subjects underwent a gross total resection. On the second MRS the voxel was placed on an observed contrast enhancement area. The tumour regrowth onset was established by comparing the results of control MRI with postoperative CT scans, and also on the basis of changes in clinical condition as well as a further follow-up, including MRI studies. In patients with tumour regrowth Cho/NAA and Lac/Cr ratios increased and the NAA/Cr ratio decreased between the two MRS studies; in the patients without regrowth, the ratio changes were inverse. In both groups, a decrease in Cho/Cr ratio was observed. In a univariate analysis the presence of tumour regrowth and an increase in Cho/NAA ratio between the two MRS were correlated with a shorter further survival time; a tendency to shorter further survival time was noted with decrease in NAA/Cr ratio. In conclusion, MRS is a diagnostic tool which, on the basis of direction of changes in the value of metabolite ratios, helps additionally confirm the diagnosis of glioma regrowth. In the case of a visible contrast enhancement area on the postoperative MRI with observed concomitant increase in Cho/NAA ratio and decrease in NAA/Cr ratio between pre- and postoperative MRS examinations, preliminary suspicion should be that of glioma regrowth rather than of remnant tumour after surgery or postradiation lesions.

Key words: *single-voxel proton magnetic resonance spectroscopy, brain gliomas, tumour regrowth.*

Introduction

Treatment failure in the majority of neoplastic diseases is due to cancer dissemination and the patient's death resulting from metastases. High-grade brain gliomas exhibit a totally different behaviour, and death is caused by tumour regrowth. Cases of glioma metastases, observed mainly to the lungs, are highly sporadic [15]. Therefore, a crucial issue in the complex management of patients with high-grade gliomas is that of a visible contrast area enhancement on a control postoperative MRI study; the

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question is whether the enhancement is consistent with tumour regrowth, or with postradiation necrosis in the remnant tumour or with cerebral necrosis in the irradiation field [3,5,12,17,18]. To approach these questions magnetic resonance spectroscopy may be useful, as its clinical significance at the onset of the disease, when aid in differentiating brain gliomas from other pathological conditions has already been proved [1,9].

To find the MRS studies helpful also on suspicion of glioma regrowth, it seems crucial to determine the direction of changes of metabolite ratios between preoperative and postoperative MRS studies, and correlate these changes with the clinical information about the disease course. Maybe, due to that, spectroscopy will be, in the future, a reliable tool used to differentiate between tumour regrowth and other conditions not requiring reoperation or other treatment regimens [3,12,17,18].

In order to find differences in behaviour of metabolite ratios between glioma regrowth and a stable postoperative remnant tumour with postradiation necrosis or cerebral necrosis in the irradiation field, we performed two spectroscopic investigations in our patients: one prior to surgery, and the other at six months following the operation; observed alterations between two MRS were correlated with clinical data with respect to the presence of tumour regrowth, and also those resulting from further follow-up assessment, including imaging studies.

Material and Methods

Over the years 2002–2003, in nine patients (seven men, two women; aged 23–67 years) MRS studies were performed before and at six months after surgery by means of a one-dimensional voxel spectroscopy with a Philips 1.5 T Gyroscan ACS-NT scanner, equipped with a head coil with a quadrate signal detection. PRESS sequences were used (TE=136 ms, TR=2000 ms, acquisition number 128; single scan time – 4 min. 20 sec., voxel size was lesion dependent, not exceeding 20 mm × 20 mm × 20 mm). Analysis of the obtained spectra was done using standard software. After surgery, all the patients underwent early control biphasic computed tomography (CT), which helped provide objective assessment of the extent of resection, and localize a presumed remnant tumour. All the patients underwent postoperative radiation therapy. On a subsequent MRI study, at six months after surgery, the voxel was obtained from visible pathological contrast enhancement at the tumour resection site. The patients were followed up monthly at the Outpatient Clinic; a planned control MRI study was done every three months, and routinely at the onset of new symptoms. January, 2007 was the date of the last follow-up examination. The results were analysed using standard descriptive statistical methods and survival analysis (Kaplan-Meier curves, F-Cox test).

Results

The patients were treated surgically; in five subjects resection was partial (>80%) with a residual tumour infiltrating towards the midline structures; four patients underwent a gross total resection. The extent of resection was based on recognition of the operating surgeon and a control postoperative CT imaging study. Histopathology showed four anaplastic astrocytomas, two glioblastomas multiforme, two gliosarcomas, and one anaplastic oligodendroglioma. At six months following the surgery, MRI with MRS was performed. In all the patients pathological contrast enhancement was noted at the resection site, or the adjacent area. Based on comparison of these MR images with the preoperative MRI scans and with postoperative CT images and based on clinical assessment as well as further follow-up of patients, including subsequent MRI studies, five cases of tumour regrowth were noted (two cases of WHO grade III gliomas and three cases of WHO grade IV gliomas); there was no regrowth in four patients. In view of the tumour regrowth infiltrating towards the midline structures, the patients were not reoperated on except for one person with a regrowth in the surgical bed, who underwent a gross total resection again and in whom histopathological diagnosis was the same, i.e. glioblastoma multiforme (case 4). The group of patients without glioma regrowth included those with stable residual tumour, with likely postradiation changes, and one patient after a gross total resection, which was confirmed on postoperative CT, and the further follow-up showed that at that time the diagnosis of an absence of tumour regrowth was correct. Therefore, it may be concluded that the contrast enhancement visible in that patient (case 7) was most probably consistent with postradiation necrosis (Table I).

The majority of patients with recognised tumour regrowth died within a short period of time; cases

Table I. Patient data: age, sex, histopathology, WHO grade, extent of surgical resection, presence of tumour regrowth after six months

Case	Age	Sex	Histopathology	WHO grade	EOR*	Regrowth after 6 m.
1.	42	M	Anaplastic astrocytoma	III	>80%	absent
2.	27	M	Gliosarcoma	IV	GTR	present
3.	62	M	Anaplastic astrocytoma	III	>80%	present
4.	67	W	Glioblastoma multiforme	IV	GTR	present
5.	66	M	Gliosarcoma	IV	>80%	absent
6.	23	W	Anaplastic oligodendroglioma	III	>80%	absent
7.	32	M	Anaplastic astrocytoma	III	GTR	absent
8.	42	M	Glioblastoma multiforme	IV	GTR	present
9.	48	M	Anaplastic astrocytoma	III	>80%	present

** EOR – extent of resection (extent of surgical resection).*

2 and 3 (massive tumour regrowth) one month later; case 8 – after eight months; case 9 (additionally chemotherapy was given – 3 temozolomide courses) – after 11 months. A female patient (case 4) who was reoperated on, and to whom subsequently 2 courses of temozolomide were given, died 9.5 months later.

Patients without tumour regrowth at six months after surgery ultimately developed a regrowth. One of them was reoperated on (case 1); histopathological findings were the same, i.e. anaplastic astrocytoma; the patient received in addition six courses of temozolomide, and died eight months after the reoperation (24.5 months after a postoperative MRS examination). Another patient (case 5) with gliosarcoma was not reoperated on because of tumour regrowth penetrating towards the midline structures; there was no additional therapy; the patient died at 12 months after surgery (6 months after a postoperative MRS study). In the female patient with anaplastic oligodendroglioma regrowth was found at 26 months after surgery; she was not reoperated on because of multifocal tumour regrowth; chemotherapy courses were given according to the PCV protocol, followed later by temozolomide; the patient died ten months later (29.5 months after a postoperative MRS). The last patient with tumour regrowth after 22.5 months post operation was alive on completion of follow-up, which was continued for 41 months from the date of the operation. He had not been reoperated on for tumour regrowth but chemotherapy had been given (CCNU, next temozolomide).

Changes in metabolite ratio values between two MRS examinations, i.e. prior to and at six months following surgery, were compared. Comparison showed differences between the group with tumour regrowth and that without tumour regrowth (stable remnant tumour with presumed postradiation changes or postradiation necrosis around site of tumour removal) (Table II). The Cho/NAA ratio increased in patients with recognized tumour regrowth and decreased in patients without regrowth. The Cho/Cr ratio decreased in both groups; however, in terms of percentage, its decrease was higher in patients without tumour regrowth (52% vs. 42%). The NAA/Cr ratio fell in patients with tumour regrowth and rose in patients without tumour regrowth. In the group of five patients with tumour regrowth, increase in Lac/Cr ratio was observed in three cases; in one patient Lac/Cr ratio decreased; and in one patient lactates, which were not observed in the preoperative MRS study, appeared in the postoperative MRS examination. In two out of four patients without tumour regrowth, who had exhibited lactates on the preoperative MRS, the Lac/Cr ratio decreased from 5.28 to 0.5 in one case and from 0.27 to 0.03 in the other case; but in one patient lactates, which were absent on the initial MRS study, were found on a subsequent one performed at six months following the surgery.

Further survival time assessed using the Kaplan-Meier curves was significantly different between patients with glioma regrowth and those without regrowth (F-Cox test, p=0.026) (Figure 1). Evaluation was also done to see if the direction of alterations in the metabolite ratio values between the two investigations might exert any effect on prognosis. It was found that the further survival time differed betwe-

Table II. Mean metabolite ratios in patients with and without tumour regrowth on two MRS examinations, i.e. prior to and at six months following surgery

	Mean ± Standard Error of Mean			
	Cho/Cr Before operation	Cho/Cr 6 months after oper.	Cho/NAA Before operation	Cho/NAA 6 months after oper.
Regrowth of tumour	5.23 ± 1.55	3.02 ± 0.9	4.49 ± 1.2	22.35 ± 19.42
Without regrowth	4.25 ± 0.99	2.04 ± 0.15	18.81 ± 5.78	4.28 ± 1.37
	NAA/Cr Before operation	NAA/Cr 6 months after oper.	Lac/Cr Before operation	Lac/Cr 6 months after oper.
Regrowth of tumour	0.92 ± 0.38	0.56 ± 0.51	6.42 ± 4.91 n = 4 cases	26.12 ± 23.87 n = 5 cases
Without regrowth	0.38 ± 0.15	0.57 ± 0.18	2.77 ± 2.5 n = 2 cases	0.3 ± 0.26 n = 3 cases

en the patients in whom the Cho/NAA ratio had increased or decreased between the two MRS imaging studies, indicating its significance for patient prognosis (F-Cox test, p=0.042) (Figure 2). The Cho/NAA ratio had increased in three patients with tumour regrowth, and in none without tumour regrowth; whereas it had decreased in two patients with regrowth and in all patients without regrowth. Increase in the NAA/Cr ratio between MRS studies tended to show a longer further survival time (F-Cox test, p=0.082). Alterations in the Cho/Cr and Lac/Cr ratios had no correlation with the further survival time.

Discussion

Contrast enhancement area found on control magnetic resonance imaging studies after glioma operation raises two questions. Firstly, do we deal with tumour regrowth? And secondly, is the visible regrowth highly malignant, with a high proliferative rate? Contrast enhancement may also be due to remnant tumour, left during the operation, with postradiation changes at this moment, or may be due to cerebral necrosis in the irradiation field around the postoperative bed. The need to find a method of high sensitivity and specificity, discriminating betwe-

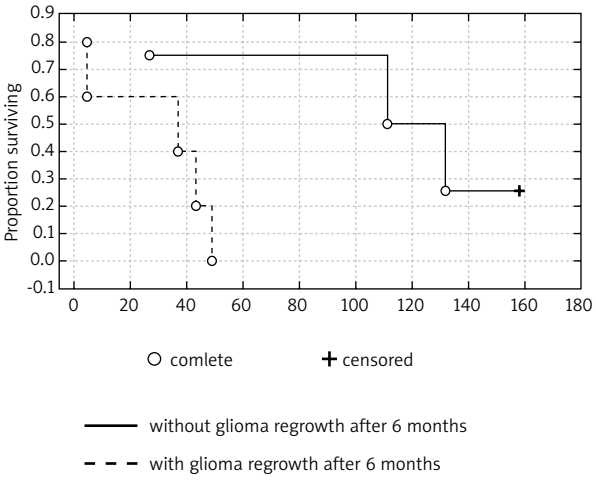

Fig. 1. Further survival time in patients with and without glioma regrowth

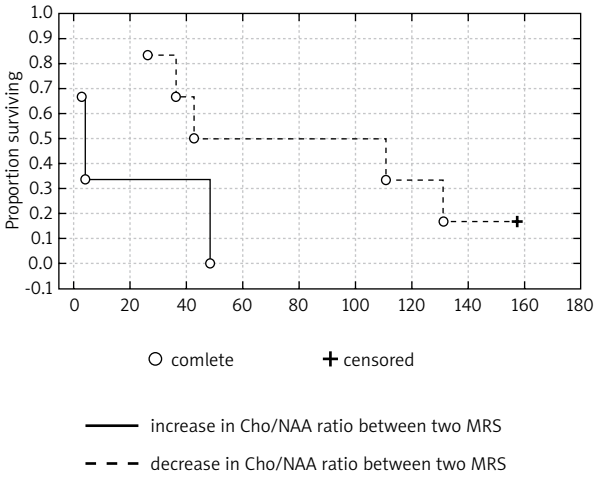

Fig. 2. Further survival time in relation to direction of changes in Cho/NAA ratio

en glioma regrowth and other conditions producing contrast enhancement, requires an urgent solution at the time of increasingly growing possibilities of using chemotherapy in the complex management of these tumours. The most appropriate approach to solve the issue would be to use a widely available, cheap technique, which might be additionally used during the control imaging studies. A solution to the problem may be to employ proton magnetic resonance spectroscopy [3,5,11,12,17,18].

Our goal was to find differences on MR spectroscopy which might allow discrimination between tumour regrowth and other conditions producing contrast enhancement on control MRI, i.e. residual tumour with postradiation changes or postradiation cerebral necrosis in the vicinity of the postsurgical bed. Hence, we compared values of metabolite ratios between two examinations: prior to and following surgery, on which contrast enhancement was visible. Changes in the metabolite ratios were compared in two groups of patients: with and without tumour regrowth. This management, including not absolute ratio values on control examination but the direction of changes in ratio values between the two MRS studies, seems to be the most appropriate regarding substantial differences in ratio values among tumours on preoperative MRS study [3,17,18].

In our material, tumour regrowth was found in five patients; in four cases there was no regrowth. In the group without glioma regrowth three patients had stable, residual tumour, with present postradiation changes, and one patient had necrotic postradiation lesions in the vicinity of the postsurgical bed, which was confirmed by a further follow-up.

An increased Cho level has been observed in cell proliferation and also may result from cell membrane remodelling [2,16-20]. Hence, increased metabolite ratio values for Cho/NAA and Cho/Cr have been found in cases of tumour recurrence or further progression of malignancy [3,5,13,18]. It has been shown that the Cho/NAA and Cho/Cr ratio values are significantly correlated with grades of malignancy assessed according to the proliferation activity index, i.e. with the percentage of cells at the division phase, identified by means of antibodies against Ki-67 (cariokinetic spindle antigen) [14,16]. In our material, Cho/NAA showed a substantial rise in patients with tumour regrowth, most likely due to cell proliferation on the one hand, and an NAA signal reduction on the other hand (resulting from decreased number of neurons inside the tumour) [3,8,13,19,20]. In numerous reports, the Cho/NAA ratio is the main metabolite ratio associated with tumour malignancy [8,19], correlated with the survival time [17,20]. Graves et al. [3] also reported an increase in Cho/NAA ratio in the vicinity of the postsurgical bed, preceding at that site the presence of contrast enhancement and tumour regrowth, visible later on subsequent control MRI studies.

In the case of stable remnant tumour, we found a reverse reaction, i.e. a decrease in Cho/NAA ratio, which is consistent with reports on the good response of tumour tissue to radiation therapy [3,6,19]. Many authors [6,12,13] emphasize the significance of the Cho/Cr ratio for the patient prognosis. In our study the ratio showed an unexpected fall in both groups of patients, with and without regrowth. It may be explained by the following: in patients without tumour regrowth, reduction in the Cho/Cr ratio may result from a decreased Cho level since that group of patients also showed a decrease in Cho/NAA ratio; while in the group of patients with glioma regrowth, a decrease in Cho/Cr ratio might have rather been caused by a higher increase in Cr value due to increased metabolism than an increase in Cho level resulting from cell membrane remodelling. The increase in Cho value in cases of tumour regrowths may be relatively low because of focal necrosis found in high-grade gliomas [3].

Increase in Cho/Cr ratio and decrease in NAA/Cr ratio are typical of tumour regrowth [5,6,13]. Rock et al. [13] showed that NAA/Cr was significantly lower in the regrowth group as compared with the controls (a healthy cerebral hemisphere in patients with newly diagnosed gliomas) and also significantly lower in relation to the tumour part where histopathology had revealed necrosis and the tumour cells did not exceed more than 20%. In our study the NAA/Cr ratio has decreased in patients with tumour regrowth and has increased in cases without regrowth, which was also confirmed by other authors [16].

Helpful in distinguishing tumour regrowth from postradiation lesions may be the Lac/Cr ratio, whose rise, with a simultaneous decrease in Cho/Cr ratio, was found in postradiation necrosis [4].

An answer to the question of how metabolite ratios change in patients with tumour regrowth in relation to other conditions (postsurgical remnant tumour, postradiation cerebral necrosis) may help to monitor the efficacy of glioma response to the

treatment offered, e.g. radiation therapy, or chemotherapy [6,17]. Assessment of changes in metabolite ratios in tumours which have regrown perhaps will give us some more information. MRS may also provide prompts to determine whether the residual tumour visible on MRI scans after radiation therapy is active, with a high proliferative ratio, and therefore requiring aggressive, adjuvant treatment, or it is a remnant tumour with a low ratio of cell divisions [13,17]. The treatment method of the residual tumour is not neutral for the patient's health and his quality of life, particularly when a decision has to be made about the necessity to administer further courses of chemotherapy, and its resulting toxic effects, or in the case when the decision is to reoperate [10,21].

Further survival time in our study after the subsequent MRI examination was significantly correlated, fairly obviously, not only with the fact of recognizing tumour regrowth as compared to a stable residual tumour or postradiation cerebral necrosis, but also with the direction of changes in the value of the Cho/NAA ratio between two MRS examinations. An increase in Cho/NAA ratio was correlated with a shorter further survival time [7]. It should also be noted that the increase in Cho/NAA occurred only in patients with tumour regrowth, and its decrease was found mainly in cases of residual tumour or postradiation cerebral necrosis [3,5,6,12,18,19]. There was a statistical trend towards a longer further survival time when the NAA/Cr ratio increased [7]. In all the cases without tumour regrowth an increase in NAA/Cr ratio was found between both MRS examinations, while in patients with regrowths decreases in NAA/Cr ratios were predominant [5,6,13,16].

Assessment of the two above-mentioned metabolite ratios may be particularly crucial when there is no early postoperative imaging control and therefore there is no objective assessment of the completeness of the resection and a long-term follow-up imaging study visualizes a contrast enhancement. Assessment of the Cho/NAA and NAA/Cr alterations in those cases may allow clinicians to manage the patients as well as determine their prognosis [3,5,7].

Conclusions

Magnetic resonance spectroscopy is a diagnostic method which, from the direction of changes in the value of metabolite ratios, may additionally help confirm the diagnosis of glioma regrowth. In the case of a visible contrast enhancement area on a control MRI as well as an increase in Cho/NAA ratio and decrease in NAA/Cr ratio, the initial diagnosis should favour glioma regrowth rather than residual tumour post surgery or postradiation cerebral necrosis.

References

1. Czernicki Z, Horsztyński D, Jankowski W, Grieb P, Walecki J. Malignancy of brain tumors evaluated by proton magnetic resonance spectroscopy (1H-MRS) in vitro. Acta Neurochir Suppl 2000; 76: 17-20.
2. Esteve F, Rubin C, Grand S, Kolodié H, Le Bas JF. Transient metabolic changes observed with proton MR spectroscopy in normal human brain after radiation therapy. Int J Radiat Oncol Biol Phys 1998; 40: 279-286.
3. Graves EE, Nelson SJ, Vigneron DB, Verhey L, McDermott M, Larson D, Chang S, Prados MD, Dillon WP. Serial proton MR spectroscopic imaging of recurrent malignant gliomas after gamma knife radiosurgery. Am J Neuroradiol 2001; 22: 613-624.
4. Kamada K, Houkin K, Abe H, Sawamura Y, Kashiwaba T. Differentiation of cerebral radiation necrosis from tumor recurrence by proton magnetic resonance spectroscopy. Neurol Med Chir (Tokyo) 1997; 37: 250-256.
5. Kinoshita K, Tada E, Matsumoto K, Asari S, Ohmoto T, Itoh T. Proton MR spectroscopy of delayed cerebral radiation in monkeys and humans after brachytherapy. Am J Neuroradiol 1997; 18: 1753-1761.
6. Leclerc X, Huisman TA, Sorensen AG. The potential of proton magnetic resonance spectroscopy (H-MRS) in the diagnosis and management of patients with brain tumors. Curr Opin Oncol 2002; 14: 292-298.
7. Li X, Jin H, Lu Y, Oh J, Chang S, Nelson SJ. Identification of MRI and 1H MRSI parameters that may predict survival for patients with malignant gliomas. NMR Biomed 2004; 17: 10-20.
8. McKnight TR, von dem Bussche MH, Vigneron DB, Lu Y, Berger MS, McDermott MW, Dillon WP, Graves EE, Pirzkall A, Nelson SJ. Histopathological validation of three-dimensional magnetic resonance spectroscopy index as a predictor of tumor presence. J Neurosurg 2002; 97: 794-802.
9. Moller-Hartmann W, Herminghaus S, Krings T, Krings T, Marquardt G, Lanfermann H, Pilatus U, Zanella FE. Clinical application of proton magnetic resonance spectroscopy in the diagnosis of intracranial mass lesions. Neuroradiology 2002; 44: 371-381.
10. Nieder C, Grosu AL, Molls M. A comparison of treatment results for recurrent malignant gliomas. Cancer Treat Rev 2000; 26: 397-409.
11. Palumbo B, Lupattelli M, Pelliccioli GP, Chiarini P, Moschini TO, Palumbo I, Siepi D, Buoncristiani P, Nardi M, Giovenali P, Palumbo R. Association of ^{99}Tc-MIBI brain SPECT and proton magnetic resonance spectroscopy (1H-MRS) to assess glioma recurrence after radiotherapy. Q J Nucl Med Mol Imaging 2006; 50: 88-93.
12. Rabinov JD, Lee PL, Barker FG, Louis DN, Harsh GR, Cosgrove GR, Chiocca EA, Thornton AF, Loeffler JS, Henson JW, Gonzalez RG. In vivo 3-T MR spectroscopy in the distinction of recurrent glioma versus radiation effects: initial experience. Radiology 2002; 225: 871-879.

13. Rock JP, Hearshen D, Scarpace L, Croteau D, Gutierrez J, Fisher JL, Rosenblum ML, Mikkelsen T. Correlation between magnetic resonance spectroscopy and image-guided histopathology with special attention to radiation necrosis. Neurosurgery 2002; 51: 912-920.
14. Shimizu H, Kumabe T, Shirane R, Yoshimoto T. Correlation between choline level measured by proton MR spectroscopy and Ki-67 labeling index in gliomas. Am J Neuroradiol 2000; 21: 659-665.
15. Smith DR, Hardman JM, Earle KM. Metastasizing neuroectodermal tumors of the central nervous system. J Neurosurg 1969; 31: 50-58.
16. Tamiya T, Kinoshita K, Ono Y, Matsumoto K, Furuta T, Ohmoto T. Proton magnetic resonance spectroscopy reflects cellular proliferative activity in astrocytomas. Neuroradiology 2000; 42: 333-338.
17. Tedeschi G, Lundbom N, Raman R, Bonavita S, Duyn JH, Alger JR, Di Chiro G. Increased choline signal coinciding with malignant degeneration of cerebral gliomas: a serial proton magnetic resonance spectroscopy imaging study. J Neurosurg 1997; 87: 516-524.
18. Wald LL, Nelson SJ, Day MR, Noworolski SE, Henry RG, Huhn SL, Chang S, Prados MD, Sneed PK, Larson DA, Wara WM, McDermott M, Dillon WP, Gutin PH, Vigneron DB. Serial proton magnetic resonance spectroscopy imaging of glioblastoma multiforme after brachytherapy. J Neurosurg 1997; 87: 525-534.
19. Walecki J, Sokół M, Pieniążek P, Maciejewski B, Tarnawski R, Krupska T, Wydmański J, Grieb P. Zastosowanie spektroskopii protonowej MR o krótkim czasie TE w monitorowaniu wczesnych zmian popromiennych. Rez Magn Med 1999; 7: 5-11.
20. Warren KE, Frank JA, Black JL, Hill RS, Duyn JH, Aikin AA, Lewis BK, Adamson PC, Balis FM. Proton magnetic resonance spectroscopic imaging in children with recurrent primary brain tumors. J Clin Oncol 2000; 18: 1020-1026.
21. Wong ET, Hess KR, Gleason MJ, Jaeckle KA, Kyritsis AP, Prados MD, Levin VA, Yung WK. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. J Clin Oncol 1999; 17: 2572-2578.