Correlation between Magnetic Resonance Spectroscopy and Perfusion at Non-enhancing Edematous Area and Tumor Recurrence in High-grade Gliomas after Maximal Safe Resection

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Background: *On neuroimaging in patients with high-grade glioma, the non-enhancing edematous area (NEA) is usually wider than the enhancing edematous area (EA).*
Objective: *To study the correlation between magnetic resonance spectrometry (MRS), perfusion MRI (MRP) parameters in the NEA and recurrent time of high-grade gliomas.*
Material and Method: *Sixty-two patients with high-grade gliomas underwent MRS and MRP before maximal safe resection. Choline (Cho), creatine (Cr), N-acetyl-aspartate (NAA), lactate, lipid (Lip), ratio of Cho/Cr and Cho/NAA and relative cerebral blood volume (rCBV) were collected from the NEA. Progression free survival and recurrent time after appropriate therapy were correlated with metabolic profiles and perfusion study.*
Results: *The majority of patients (93.5%) had peritumoral edema with various degree of edema. Mean recurrent time of glioblastoma was 5.9 months. To compare three parameters of MRS (Cho/NAA, Cho/Cr, rCBV) of the EA and NEA, there was statistical difference, but Cho/NAA and rCBV were not statistically significant for predicting recurrent time of the tumors.*
Conclusion: *Recurrent time depends on the presence of peritumoral edema resulting from infiltrative area of tumor in NEA demonstrated by high Cho/NAA, Cho/Cr and rCBV. The metabolic parameter (Cho/NAA) and perfusion MRI (rCBV) was not beneficial to determine recurrent time in patients with high-grade glioma.*

Keywords: *High-grade glioma, Non-enhancing edematous area, Proton magnetic resonance spectroscopy, Magnetic resonance perfusion*

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High-grade gliomas are the most common primary malignant brain tumors. According to 2007 World Health Organization (WHO) classification of tumor of the nervous system, these tumors were classified into grade III (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocy toma, anaplastic ependymoma, gliomatosis cerebri) and grade IV (glioblastoma and gliosarcoma)[1-3].

Fundamentally, these malignant tumors have poor prognosis, even with optimal treatment, such as maximal safe resection, radiotherapy or chemotherapy. Median survival time for patient with glioblastoma is less than 2 years and for anaplastic glioma is 2 to 5 years due to high infiltration and destruction of adjacent brain tissues[4-8].

Many studies reported the extent of tumor cells that was wider than demonstrated by conventional T1W with contrast study[9-15]. They considered using T2-weighted images (T2WI) or fluid attenuation inversion recovery (FLAIR) images (referred to the "non-enhancing edematous area" or NEA) for the extent of high-grade gliomas (Fig. 1). Accordingly, this area of tumor invasion would demonstrate a wider area than the area of enhancement on T1-weighted images with

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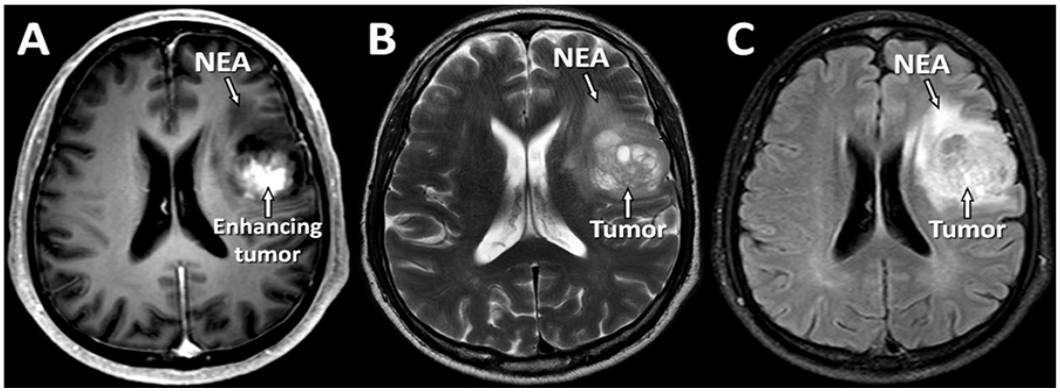

Fig.1 MRI of the brain in a patient with high-grade glioma; (A) Gd-T1WI shows enhancing tumor with NEA; (B) T2WI and (C) FLAIR image show area of the tumor and NEA.

gadolium (Gd-T1WI)[13,15].

The proton magnetic resonance spectroscopy (MRS) can be used to diagnose abnormal biochemical activity or metabolism of the lesion in brain tissue, such as choline (Cho), creatine (Cr), N-acetyl-aspartate (NAA), lactate (Lac), lipid (Lip)[16,17]. The magnitude of each biochemical spectrum often overlaps between malignant and low-grade tumor. Therefore, the commonly used measurement is reported in the ratio, such as Cho/Cr, Cho/NAA[12-18].

Di Costanzo et al reported a study of using MRS in NEA to distinguish tumor invasion from purely vasogenic edema, and found that the NEA with high Cho/NAA ratio more than 1 showed infiltrated tumor cells (infiltrative tumor)[14]. This NEA was very important to determine the extent of high-grade brain tumor for surgical planning or radiation therapy and associated with predictors of survival after treatment.

Perfusion study with magnetic resonance (MRI) is also a potential method for detecting tumor infiltration in NEA[19]. Relative cerebral blood volume was also interesting in many studies. Weber et al reported 97% sensitivity for detecting malignant glioma on perfusion MRI[20]. Chawalparit et al also demonstrated the effectiveness of discrimination between low-grade and high-grade gliomas by using perfusion MRI[21].

In our institute, surgical treatment of high-grade gliomas is an essential primary treatment to achieve maximal safe resection and tissue for pathologic diagnosis. Universally, surgical resection area is based on Gd-T1W. The extent of the abnormalities in NEA may persist after surgery that may lead to regrowth of the tumor. Therefore, this study was conducted to determine the correlation between the metabolic profile of NEA from MRS and perfusion MRI and time of recurrence of high-grade gliomas in patients who treated with maximal safe resection.

Material and Method

During February 2009 to December 2014, sixty-two cases of high-grade brain gliomas were recruited for advanced MRI in brain tumor project in Siriraj Hospital. Patients with newly diagnosed, high-grade gliomas underwent conventional and advanced MRI studies, including MRS and perfusion MRI before maximal safe resection. The patients were excluded if they had been treated with other methods, such as biopsy, radiation or chemotherapy alone. Extent of resection was categorized into total resection (>90%), near-total resection (75 to 90%), and partial resection (<75%) demonstrated by immediate postoperative MRI (within 72 hours)[20,22-24]. The histopathological reports of all 62 patients confirmed high-grade glioma according to the current 2007 WHO classification of the nervous system tumors[1-3]. Radiation and chemotherapy were given as the appropriate treatment after maximal safe surgery.

The medical records were reviewed for demographic information and treatment characteristics. The patients' data were collected, including age, sex, date of pre-operative MRI and MRS, date of surgical resection, adjuvant treatment, date of follow-up imaging that defined as the first recurrence, and date of last follow-up.

Tumor recurrence was defined as the appearance of residual tumor growth on imaging studies compared with previous studies during treatment period[25].

Recurrent time was defined as the time from

date of maximal safe resection to the time that the first tumor recurrence (the time point at which the contrast-enhancing volume increased) on follow-up imaging studies (CT and/or MRI) as determined by neuroradiologist.

Degree of peritumoral edema was classified by percent of NEA size on tumor size. It included "no edema", "mild edema" (edematous area ≤50% of tumor size), "moderate edema" (edematous area 50 to 75% of tumor size) and "severe edema" (edematous area ≥75% of tumor size).

The multi-voxel proton chemical shift imaging was performed after administration of gadolinium with the turbo spin echo technique (TR, TE, and NEX of 2000, 288 ms, and 1, respectively)[26]. Single section with 15-mm section thickness was obtained in 4 minutes and 42 seconds on axial plane. The volume of interest (VOI) consisted of a 10x10 cm-region placed within a 23x19 cm field of view (FOV), with a voxel size of 1x1x1.5 cm^3. Single voxel MR spectroscopy was performed by using a point-resolved spectroscopy (PRESS) turbo spin echo with TR and TE of 2,000 and 35 ms or 128 ms, respectively. The voxel size varied from 1x1x1 to 2x2x2 cm^3 depending on tumor size. The selected slices were based on Gd-T1WI at the areas of lesion enhancement. If no enhancing area was demonstrated, FLAIR and T2W were used for selection region of interest (ROI) by a neuroradiologist on duty. The radiologist selected the areas that were the most compatible with solid part of the tumor. The metabolite peaks were assigned as follows: Cho at 3.22 ppm; Cr at 3.02 ppm, NAA at 2.02 ppm; Lip at 0.5-1.5 ppm; and Lac at 1.33 ppm (Table 1). The MRS data were processed on the commercial software (Spectro-tool, ViewForum, Philips, The Netherlands).

The region of interest (ROI) was placed to measure each metabolite at enhancing edematous area (EA), NEA, and contralateral normal white matter (Fig. 2-4). The highest values of area under the metabolic curves, including Cho, Cr, NAA, Lac, Lip, ratio of Cho/Cr and Cho/NAA were collected from the EA and NEA. The ratios of each metabolite from the lesion to normal white matter were calculated and defined as nCho, nCr and nNAA.

The relative cerebral blood volume (rCBV) was measured and compared between tumor and NEA. Due to histological heterogeneity within high-grade gliomas is common[22,23], then the maximal CBV was taken to be representative of the ROI in the EA and NEA (Fig. 5). The ratio of rCBV was defined as rCBV (lesion) divided by rCBV (contralateral white matter).

Statistical analysis

Statistical analysis was performed by using SPSS version 18. Descriptive statistics, inferential statistics for general data, Kaplan-Meier survival analysis, and Cox-regression analysis with recurrent time as the dependent variables were analyzed. The two-sample t-test was used to compare the average metabolic ratio for NEA and EA. Time to recurrence was censored if the patient had progression free at the time of analysis.

This study was ethically approved by Siriraj Institutional Review Board (SIRB), Mahidol University.

Results

Sixty-two patients with clinical symptoms and neuroimaging compatible with high-grade gliomas (HGG) underwent conventional and advanced MRI. All of them underwent maximal safe resection and histopathology showed high-grade gliomas (HGG). The pathologic diagnosis was based on the 2007 WHO classification of tumors of the nervous system. Demographic data, final diagnosis, tumor size, tumor location, grade of tumor edema and extent of maximal safe resection were summarized in Table 2.

Of 62 patients**,** there were 35 male (56.5%) and 27 female (43.5%) with median age of 46.5 years. Almost of tumor located in subcortical areas, including parietal lobe (21 out of 62), frontal lobe (19 out of 62) and

Table 1. The spectrum of specific metabolites, locations and properties of substances often used in the MRS study[16,17]

Metabolite	Location (ppm)	Property
Lipids (Lip)	0.9-1.4	Products of brain destruction
Lactate	1.3	Product of anaerobic glycolysis
N-acetyl-aspartate (NAA)	2.0	Neuronal marker
Creatine (Cr)	3.0	Energy metabolism
Choline (Cho)	3.2	Cell membrane marker

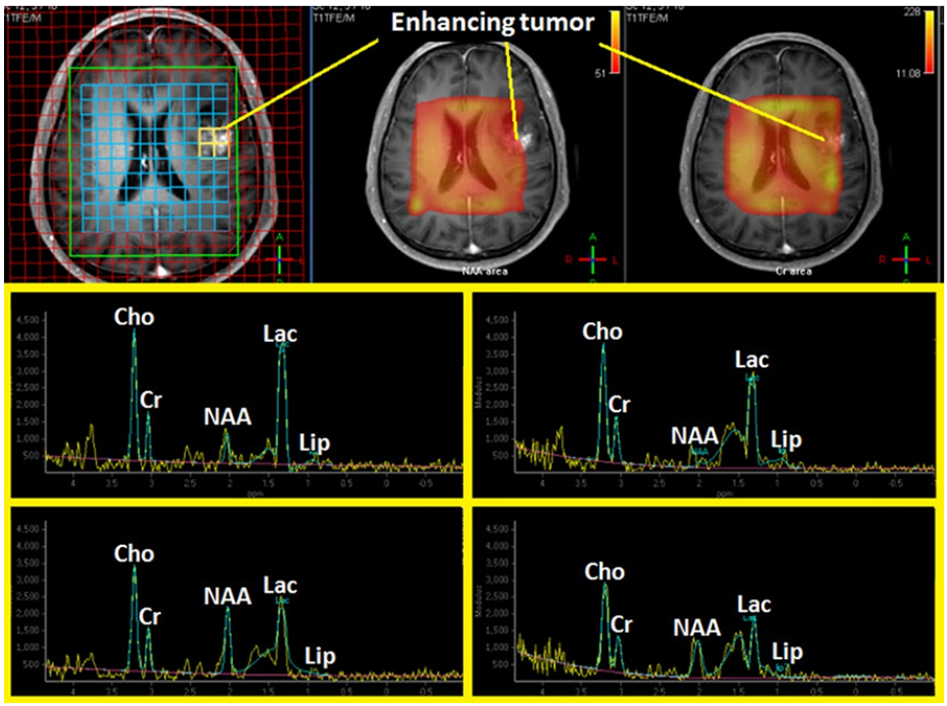

Fig. 2 MRS of the brain at area of enhancing tumor showing high Cho/Cr and Cho/NAA ratios.

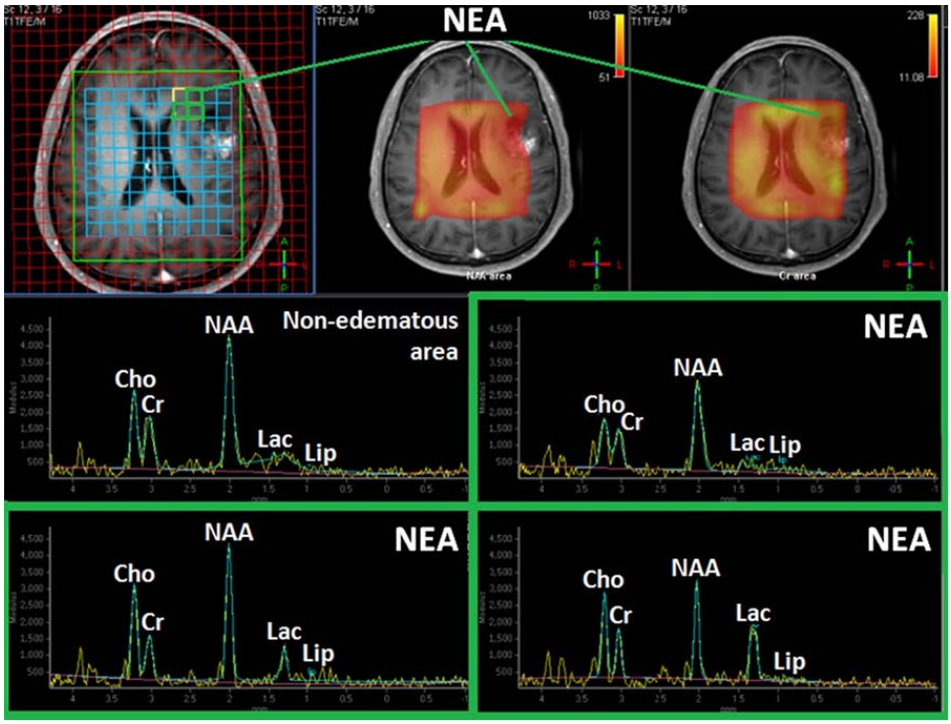

Fig. 3 MRS of the brain at the non-enhancing edematous area (NEA) showing high Cho/Cr ratio.

temporal lobe (14 out of 62). The vast majority of the patients had edema (93.5%) on pre-operative MRI with difference in degree of edema (mild, moderate and severe). Forty-four out of 62 patients (71%) had

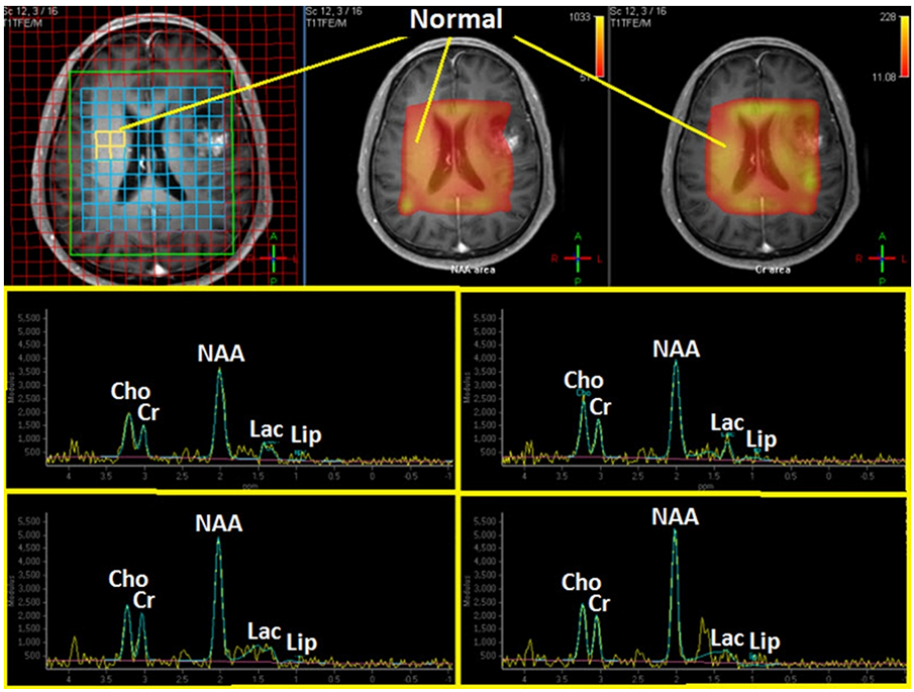

Fig. 4 MRS of the brain at area of normal brain showing normal metabolic profiles.

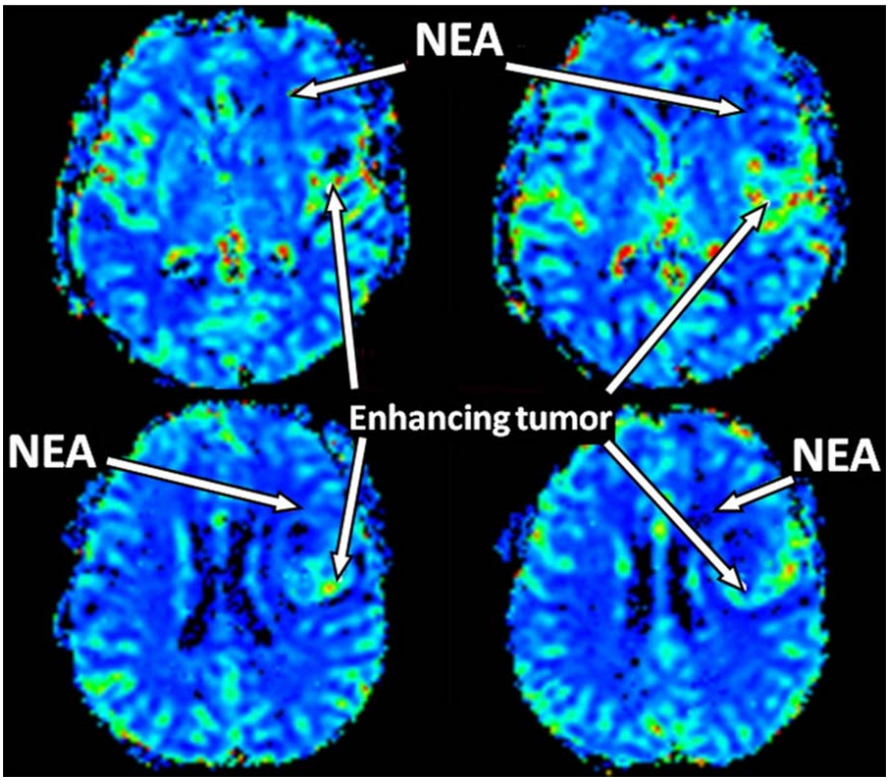

Fig. 5 MRP of the brain showing area of enhancing tumor and NEA.

Table 2. Demographic characteristics and treatments

	All patient	GBM	AA	AO	AE
n	62	50	5	6	1
Mean age in years (SD)	46.5 (13.9)	47.3 (14.5)	41.4 (13.8)	42.3(6.6)	58
Sex					
Male (%)	35 (56.5)	28 (56)	4 (80)	3 (50)	0
Female (%)	27 (43.5)	22 (44)	1 (20)	3 (50)	1 (100)
Tumor size (cm) (SD)	4.1 (1.7)	4.22 (1.7)	3.22 (1.8)	4.16 (2.3)	2.6
Side					
Left (%)	31 (50)	24 (48)	4 (80)	2 (33.3)	1 (100)
Right (%)	30 (48.4)	25 (50)	1 (20)	4 (66.6)	0
Bilateral (%)	1 (1.6)	1 (2)	0	0	0
Location					
Parietal (%)	21 (33.9)	16 (32)	4 (80)	1 (16.6)	0
Frontal (%)	19 (30.6)	15 (30)	0	4 (66.6)	0
Temporal (%)	14 (22.6)	12 (24)	1 (20)	1 (16.6)	0
Insular (%)	4 (6.5)	4 (8)	0	0	0
Occipital (%)	2 (3.2)	1 (2)	0	0	1 (100)
Brain stem (%)	1 (1.6)	1 (2)	0	0	0
Cerebellum (%)	1 (1.6)	1 (2)	0	0	0
Edema					
Absent (%)	4 (6.5)	2 (4)	0	2 (33.3)	0
Mild (%)	20 (32.3)	15 (30)	1 (20)	3 (50)	1 (100)
Moderate (%)	18 (29.0)	16 (32)	1 (20)	1 (20)	0
Severe (%)	20 (32.3)	17 (34)	3 (60)	0	0
Resection					
Gross total (%)	44 (71.0)	36 (72)	3 (60)	4 (66.6)	1 (100)
Near total (%)	17 (27.4)	13 (26)	2 (40)	2 (33.3)	0
Partial (%)	1 (1.6)	1 (2)	0	0	0
Neurological deficit					
Absent (%)	46 (74.2)	40 (80)	3 (60)	6 (100)	1 (100)
Present (%)	12 (19.4)	10 (20)	2 (40)	0	0
Adjuvant therapy					
RT (%)	28 (45.2)	22 (44)	2 (40)	3 (50)	1 (100)
CMT + RT (%)	21 (33.9)	18 (36)	1 (20)	2 (33.3)	0
None (%)	13 (21.0)	10 (20)	2 (40)	1 (16.6)	0
Median time to recurrence in months (n = 44)	4.7	4.5	14.2	15.1	4.2

AA = anaplastic astrocytoma; AE = anaplastic Ependymoma; AO = anaplastic oligodendroglioma; CMT = chemotherapy; GBM = Glioblastoma; RT = radiation therapy

been accomplished gross total resection. Forty-six out of 62 (74.2%) had no immediate postoperative neurologic deficit. Main pathology (50 out of 62) was glioblastoma (WHO 2007 grade IV). The minority were anaplastic oligodendroglioma (WHO 2007 grade III) and anaplastic astrocytoma (WHO 2007 grade III), respectively. Adjuvant therapy was mainly radiotherapy, and concurrent radiotherapy and chemotherapy based on evidence based support. Median recurrent time was 4.7 months and decreased slightly in the glioblastoma group, while patients with WHO 2007 grade III had tendency to recurrence after 1 year.

Mean recurrent time in patients with peritumoral edema and those without peritumoral edema was show in Table 3. Overall, recurrent time was 6.82 months. The recurrent time in patients without peritumoral edema of 8.50 months was longer than 6.69 months in the group with peritumoral edema. The degree of edema based on pathologic result had no statistical significance in recurrent time. Interestingly,

Table 3. Peri-tumoral edema and recurrent time (months)

Peri-tumoral edema	Mean recurrent time in months (SD)
Absence of peri-tumoral edema	8.5 (7.7)
Presence of peri-tumoral edema	6.7 (6.2)
Total	6.8 (6.1)

Table 4. Pathology, degree of brain edema and recurrence time (months)

Pathology		Mean recurrent time in months (SD)		
	Total	Mild edema	Moderate edema	Severe edema
GBM (50 cases)	5.9 (21)	4.1 (2.8)	6.0 (8.4)	7.5 (4.2)
AA (5 cases)	18 (2)	24 (0)	12 (0)	-
AO (6 cases)	4.5 (2)	4.5 (4.9)	-	-
AE (1 case)	4 (1)	-	-	-
All pathology (SD)	6.7 (6.2)	6.0 (6.5)	6.8 (8.0)	7.5 (4.2)

AA = anaplastic astrocytoma; AE = anaplastic ependymoma; AO = anaplastic oligodendroglioma; GBM = Glioblastoma

Table 5. Comparison of radiologic parameters between the EA and NEA

Parameter	Mean (SD)		*p*-value
	EA	NEA	
Chol/NAA	2.96 (3.10)	1.11 (2.38)	0.001
Chol/Cr	3.14 (6.70)	1.24 (0.62)	0.041
rCBV	5.36 (5.94)	2.16 (1.94)	0.010

severe peritumoral edema in GBM group had longer recurrent time than moderate and mild edema (Table 4).

There was statistically different in all three parameters of MRS (Cho/NAA, Cho/Cr) and MR perfusion using rCBV to differentiate EA and NEA (Table 5). The ratio of Cho/NAA in EA (2.96) was significant higher than in NEA (1.11) as well as the ratio of Cho/Cr in EA (3.14) and NEA (1.24). Accordingly, the rCBV in EA (5.36) was also higher than NEA (2.16) that means NEA was the infiltrative tumor area in high-grade gliomas.

Univariate analysis of predictors of recurrent time (Table 6) revealed no statistical significance in all parameters, including ratio of metabolite **(**Cho/NAA, Cho/Cr) of lesion and NEA. To identify the difference of MR metabolic spectrum and perfusion study in NEA, we compared hazard ratio of below and equal to higher than 1 in these parameters, there was no statistically significance to predict recurrent time. There was no statistic difference in recurrent time in quality of resection. Adjuvant treatment with concurrence chemotherapy and radiation had longer time recurrent when compare to radiotherapy alone.

GBM had tendency to progress earlier, while WHO grade III (anaplastic astrocytoma and anaplastic oligodendroglioma) tended to progress later (Fig. 6) Interestingly, moderate edema had the shortest progression time when compared with mild and severe edema (Fig. 7).

Discussion

There were many reports about the variable that there was significant to improved outcome of high-grade gliomas treatment such as age, extent of surgical

Table 6. Univariate analysis for predictor of recurrence time

Variable	Median recurrent time (months)	Hazard ratio	95% CI	*p*-value
Age (years)				
<60	5.2	1		
≥60	3.8	1.01	0.46 to 2.2	0.972
Sex				
Male	4.8	1		
Female	4.4	0.72	0.39 to 1.33	0.298
Degree of brain edema				
Mild	6.0	1		
Moderate	6.8	1.28	0.57 to 2.84	0.541
Severe	7.5	0.70	0.33 to 1.49	0.260
Resection				
Total	4.7	1		
Near total	3.0	0.99	0.46 to 2.97	0.989
Partial	1.9	5.03	0.64 to 39.3	0.120
Adjuvant therapy				
RT	4.6	1		
RT + CMT	3.6	1.02	0.5 to 2.09	0.949
Cho/NAA				
<1	4.6	1		
≥1	5.2	0.48	0.18 to 1.26	0.138
Cho/NAA of NEA				
<1	4.6	1		
≥1	5.1	0.95	0.41 to 2.18	0.899
rCBV of NEA				
<1	5.9	1		
≥1	4.2	0.67	0.24 to 1.86	0.442

CMT = chemotherapy; RT = radiation therapy

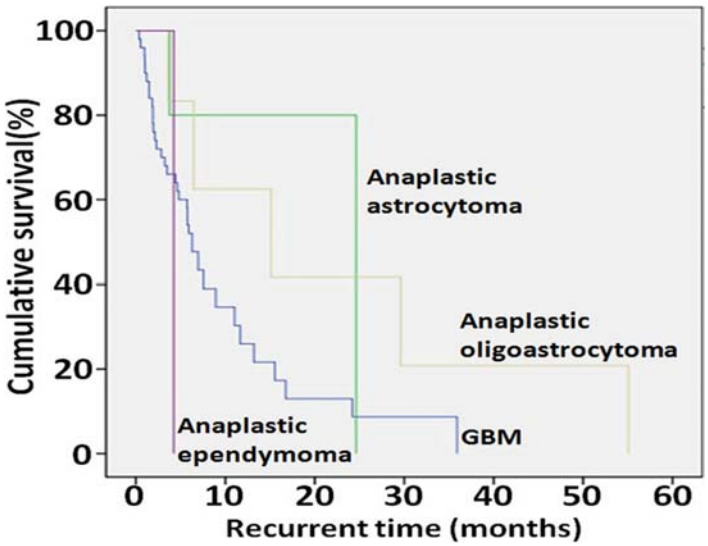

Fig. 6 Kaplan-Meier plot showing recurrent time in different types of high-grade glioma.

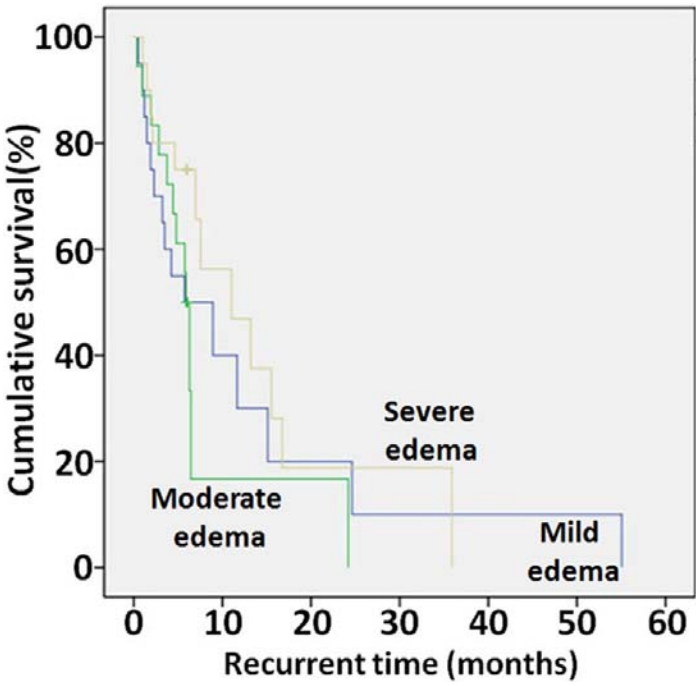

Fig. 7 Kaplan-Meier plot showing recurrent time in different degrees of peritumoral edema.

resection and chemo-radiation treatment[24-33]. There was no statistic difference in recurrent time in quality of resection. Adjuvant treatment with concurrence chemotherapy and radiation had longer time recurrent when compare to radiotherapy alone.

Wu CX et al studied in 87 patients and found significant correlation between the presence of peritumoral edema and tumor necrosis on survival of malignant gliomas[34]. Our study has also demonstrated that the absence of peritumoral edema was significantly longer than the presence of peritumoral edema, and even higher degrees of edema had longer time to recurrence. The null hypothesis of this study, if the high-grade glioma patients with high ratio of Cho/NAA and high rCBV in NEA, had shorter time to recurrence than those patients with normal metabolic ratio of MRS and normal rCBV in this area. Even though this study shows significant difference in MRS parameters of Cho/NAA, Cho/Cr, rCBV on EA and NEA, our results were statistically insignificant in correlation with MR-spectroscopy at NEA in high-grade-gliomas for tumor recurrence after maximal safe resection.

Conclusion

High-grade glioma patients without peritumoral edema had significant longer recurrent time after maximal safe resection. The beneficial treatment after maximal safe resection of high-grade gliomas is concurrent chemo-radiation. The ratio of Cho/NAA, Cho/Cr and rCBV in NEA are significantly different from EA. To predict tumor recurrent time, these radiologic parameters may not be beneficial.

Limitation of this study is the difference of aggressiveness of each type of high-grade gliomas. Basically, glioblastoma has worse prognosis than anaplastic astrocytoma that are newly classified as 2016 World Health Organization (WHO) classification of tumor of the nervous system[35].

What is already known on this topic?

Contrast enhancing MRI, MR spectroscopy and perfusion MRI are useful for determining extent of high-grade glioma. Survival of patients with high-grade glioma is associated with peritumoral edema and tumor necrosis.

What this study adds?

High-grade glioma with peritumoral edema has significantly shorter recurrent time than that without the edema. Significant differences of Cho/NAA, Cho/Cr and rCBV between NEA and EA were found.

Potential conflicts of interest

None.

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ความสัมพันธ์ระหว่างการตรวจวิเคราะห์สารด้วยแม่เหล็กไฟฟ้าและการตรวจปริมาณเลือดที่ไปเลี้ยงสมองด้วยแม่เหล็กไฟฟ้าที่บริเวณสมองบวมซึ่งไม่มีการเปลี่ยนแปลงหลังการฉีดสารทึบรังสีกับการกลับเป็นซ้ำของในมะเร็งสมองชนิดไกลโอมาหลังการผ่าตัด

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ภูมิหลัง: ในการตรวจภาพของสมองในผู้ป่วยมะเร็งสมองชนิดไกลโอมาบริเวณสมองบวมซึ่งไม่มีการเปลี่ยนแปลงหลังการฉีดสารทึบรังสีมักจะกว้างกว่าบริเวณสมองบวมที่มีการเปลี่ยนแปลงหลังการฉีดสารทึบรังสี

วัตถุประสงค์: เพื่อศึกษาความสัมพันธ์ระหว่างการตรวจวิเคราะห์สารด้วยแม่เหล็กไฟฟ้าและการตรวจปริมาณเลือดที่ไปเลี้ยงสมองด้วยแม่เหล็กไฟฟ้าที่บริเวณสมองบวมซึ่งไม่มีการเปลี่ยนแปลงหลังการฉีดสารทึบรังสีกับระยะเวลากลับเป็นซ้ำของมะเร็งสมองชนิดไกลโอมา

วัสดุและวิธีการ: ผู้ป่วยมะเร็งสมองชนิดไกลโอมา 62 ราย ได้รับการตรวจวิเคราะห์สารด้วยแม่เหล็กไฟฟ้าและการตรวจปริมาณเลือดที่ไปเลี้ยงสมองด้วยแม่เหล็กไฟฟ้าก่อนได้รับการผ่าตัดเพื่อวิเคราะห์สารโคลีน ครีเอติน เอนอะซิติลแอสพาเตท แลคเตท ไขมัน อัตราส่วนระหว่างโคลีนต่อครีเอติน อัตราส่วนระหว่างโคลีนต่อเอนอะซิติล แอสพาเตท และปริมาณเลือดที่ไปเลี้ยงสมองในบริเวณสมองบวม ซึ่งไม่มีการเปลี่ยนแปลงหลังการฉีดสารทึบรังสี จากนั้นจึงทำการวิเคราะห์หาความสัมพันธ์ระหว่างอัตราการรอดชีวิตและระยะเวลากลับเป็นซ้ำของเนื้องอก หลังการผ่าตัดกับการตรวจวิเคราะห์สารและการตรวจปริมาณเลือดที่ไปเลี้ยงสมองดังกล่าว

ผลการศึกษา: ผู้ป่วยร้อยละ 93.5 มีสมองบวมรอบเนื้องอก ซึ่งมีระดับความรุนแรงของการบวมต่างกันออกไป ระยะเวลากลับเป็นซ้ำเฉลี่ยของมะเร็งสมองไกลโอบลาสโตมาเท่ากับ 5.9 เดือน พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของอัตราส่วนระหว่างโคลีนต่อเอนอะซิติลแอสพาเตท อัตราส่วนระหว่างโคลีนและครีเอตินและปริมาณเลือดที่ไปเลี้ยงสมองระหว่างบริเวณสมองบวม ซึ่งไม่มีการเปลี่ยนแปลงหลังการฉีดสารทึบรังสีกับบริเวณสมองบวม ซึ่งมีการเปลี่ยนแปลงหลังการฉีดสารทึบรังสี แต่ไม่พบความสัมพันธ์ระหว่างการตรวจวิเคราะห์สารดังกล่าวกับระยะเวลากลับเป็นซ้ำของเนื้องอก

สรุป: ระยะเวลากลับเป็นซ้ำของเนื้องอกขึ้นกับการบวมของสมองรอบเนื้องอก ซึ่งเกิดจากการที่มีเนื้องอกแทรกอยู่ในบริเวณสมองบวมซึ่งไม่มีการเปลี่ยนแปลงหลังการฉีดสารทึบรังสี โดยบริเวณดังกล่าวจะตรวจพบการเพิ่มขึ้น ของอัตราส่วนระหว่างโซลีนต่อเอนอะซิติลแอสพาเตท อัตราส่วนระหว่างโคลีนและครีเอตินและปริมาณเลือดที่ไปเลี้ยงสมอง อย่างไรก็ตามการตรวจวิเคราะห์สารดังกล่าวและการตรวจปริมาณเลือดที่ไปเลี้ยงสมองไม่สามารถใช้ในการบอกระยะเวลากลับเป็นซ้ำของเนื้องอกในผู้ป่วยมะเร็งสมองชนิดไกลโอมาได้