Correlation of Magnetic Resonance Spectroscopy and Perfusion at Non-Enhancing Edematous Area in High-Grade Glioma for Tumor Recurrence After Maximal Safe Resection

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Background

Malignant glioma is the most common primary malignant brain tumors. These tumors were classified into WHO2007 grade III (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ependymoma, gliomatosis cerebri) and WHO grade IV (glioblastoma and gliosarcoma).[2,3]

These malignant tumors had 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 – 5 years[4-7] because of high infiltration and destruction of adjacent brain tissues.[8]

Many studies reported the extent of tumor cells that are wider than the demonstrations by conventional MRI T1W with contrast study.[9-15] They suggested that the consideration of extent of high-grade glioma by using MRI T2W images or T2-FLAIR images that demonstrated wider area than the imaging of T1W with contrast[13,15], which in this study are referred to the "non-enhancing edematous area" (NEA).

The Proton MR-spectroscopy (MRS) signal can be used to diagnose abnormal biochemical or metabolism of the lesion in brain tissue.[16,17]

The height of each biochemical spectrum often overlaps between malignant and low grade tumor. Therefore, The mainly useful measurement will be in the ratio[16-19], such as Cho/Cr, Cho/NAA

In addition, Alfonso et al.[14] reported the study about MRS in non-enhancing edematous area to distinguish non-enhancing edematous area from purely vasogenic edema area, the results of MRS with high Cho / NAA more than1 shows that the edema area will infiltrated with tumor cells (infiltrative tumor). These non-enhancing edematous area are very important to

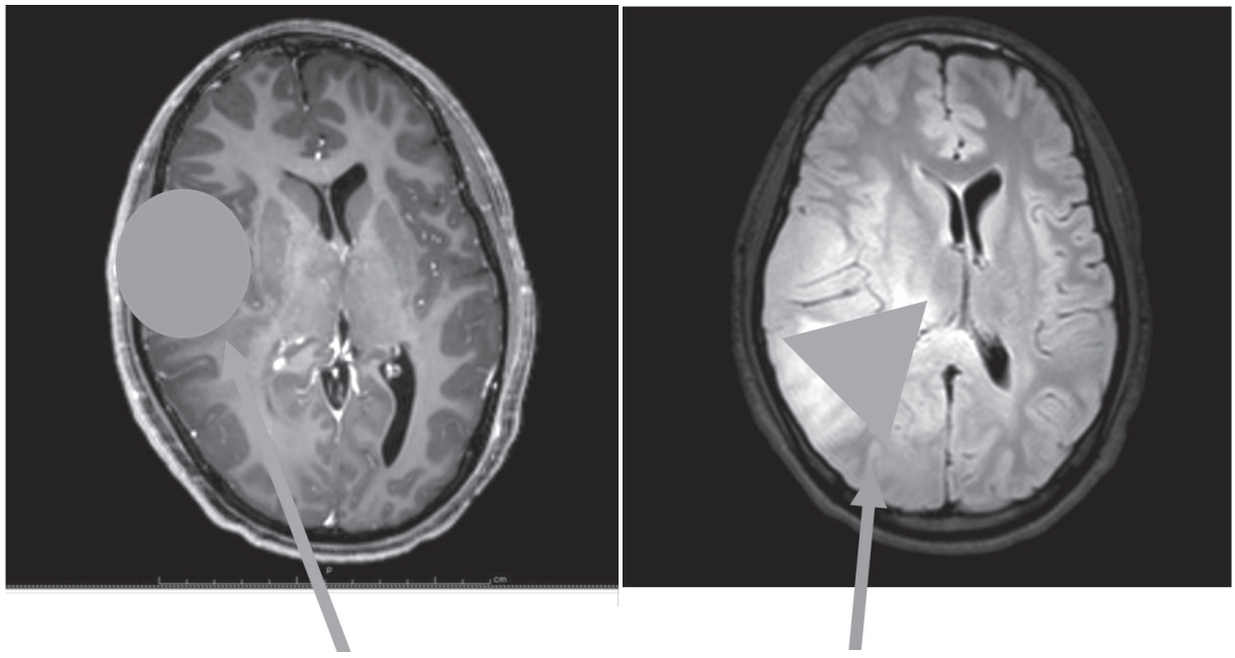

Figure 1 Demonstrate enhancing area (T1w gd) and Non-enhancing edematous area (NEA) (T2 FLAIR).

determine the extent of these high grade brain tumor for surgical planning or radiation therapy and associated with predictors of survival after treatment.[20]

Perfusion magnetic resonance imaging is potential methods for detecting tumor infiltration in NEA..Relative cerebral blood volume is also interested in many study.

The study of Weber MA et.al. on Perfusion MRI with sensitivity to detecting malignant glioma was 97%.In Siriraj hospital, Piyapittayanan S.,10 also demonstrated the effectiveness of discrimination between low grade and high grade glioma by using perfusion MRI.

In our institution, surgical treatment of brain high-grade glioma is an essential primary treatment in order to achieve maximal safe resection and tissue for pathologic diagnosis. As usual, surgical area will be resected based on T1W with contrast MRI but the extent of the abnormalities in brain tissue called "non-enhancing edematous area" may remain after surgery, these may have opportunities to regrowth of the tumor. Hence, this study aimed to determine the correlation between recurrent time of the high-grade brain glioma patients who treated with standard treatment and the metabolic effects of magnetic resonance spectroscopy and perfusion MRI in non-enhancing edematous area.

Objective

To study between the correlation of magnetic resonance spectrometry parameter and perfusion MRI and the recurrent time of malignant glioma after maximal safe resection. Progression free survival and recurrent time after adjuvant therapy were analyzed.

Materials and Methods

During February 2009 to December 2014, 62 cases with clinically suspicious of malignant glioma were collected for advanced MRI project in Siriraj hospital. Included patients with newly diagnosed with a group of high-grade brain glioma, the diagnostic MRI

and advanced MRI including MR-spectroscopy and perfusion MRI were performed before maximal safe resection. The patients were excluded for analysis if they treated with other methods such as biopsy, radiation or chemotherapy alone without maximal safe tumor resection. All of these patient underwent maximal safe resection met the inclusion criteria. Extent of resection was categorized to total resection (GTR> 90%), near-total resection (NTR 75-90%), partial resection (<75%)[20-23] and confirm with immediate post op MRI (within 72 hours).

The histopathology reports of all 62 patients confirmed high-grade glioma according to the current World Health Organization (WHO) classification 2007[1,2]. Radiation and neuro-oncologists were consulted for appropriated radiation chemotherapy.

We reviewed the medical records to obtain information of the patients and treatment characteristics. The patients age, sex, date of preoperative MRI and MRS, date of maximal safe resection, adjuvant treatment, date of follow up imaging that defined as 1st recurrence, and date of last follow up.

Tumor recurrence was also defined by the appearance of residual tumor growth on imaging studies compared with previous imaging studies during treatment period[24].

Recurrent time was defined by the time from date of maximal safe resection to the time that 1st tumor recurrence (the time point at which the contrast-enhancing volume increased) was found on follow-up imaging studies (CT and/or MRI) as determine by neuro-radiologist.

Degree of edema was classified by percent of NEA size on tumor size.

Mild edema = <50% tumor size

Moderate edema = 50-75% tumor size

Severe edema = > 75 % tumor size

The Multi-voxel MRS was performed after administration of gadolinium[25]. Multi-voxel proton chemical shift imaging or spectroscopic imaging used the turbo spin echo technique with TR, TE, and NEX of 2000, 288 ms, and 1 respectively. 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 used a point-resolved spectroscopy (PRESS) turbo spin echo with TR and TE of 2000 and 35 ms or 128 ms, respectively. The voxel size varied from 1x1x1 to 2x2x2 cm^3 depending on tumor size. The metabolite peaks were assigned as follows: Cho, 3.22 ppm; Cr, 3.02 ppm, NAA, 2.02 ppm; metabolite lipids, 0.5-1.5 ppm; Lactate, 1.33 ppm. The MRS data was sent for processing on the commercial software (Spectro-tool, ViewForum, Philips, the Netherlands). The selected slices were based on Gd-T1WI at the areas of lesion enhancement. If no enhancing area was demonstrated, FLAIR and T2WI were used for selection region of interest (ROI) by a neuroradiologist. The radiologist se-

Table 1 Show the spectrum of specific metabolites. Locations (ppm) and properties of substances that were often used in the MRS study[16,17]

ppm	Metabolite	Properties
0.9-1.4	Lipids	Products of brain destruction
1.3	Lactate	Product of anaerobic glycolysis
2.0	NAA	Neuronal marker
3.0	Creatine	Energy metabolism
3.2	Choline	Cell membrane marker

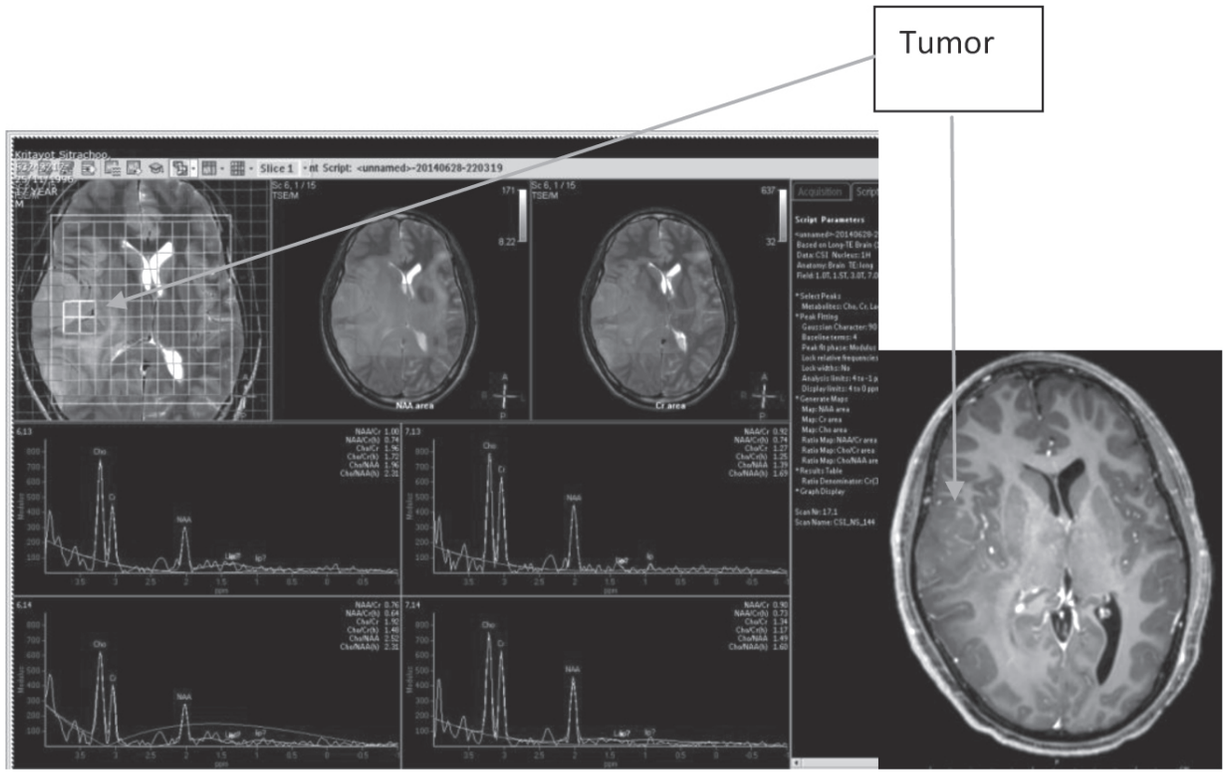

Figure 2 Region of interest was placed in tumor (cluster of yellow square). The spectrum of each metabolite was measure,the vertical axis is the height of peak of the metabolite; the horizontal axis is the specific ppm (location) of each specific metabolite.

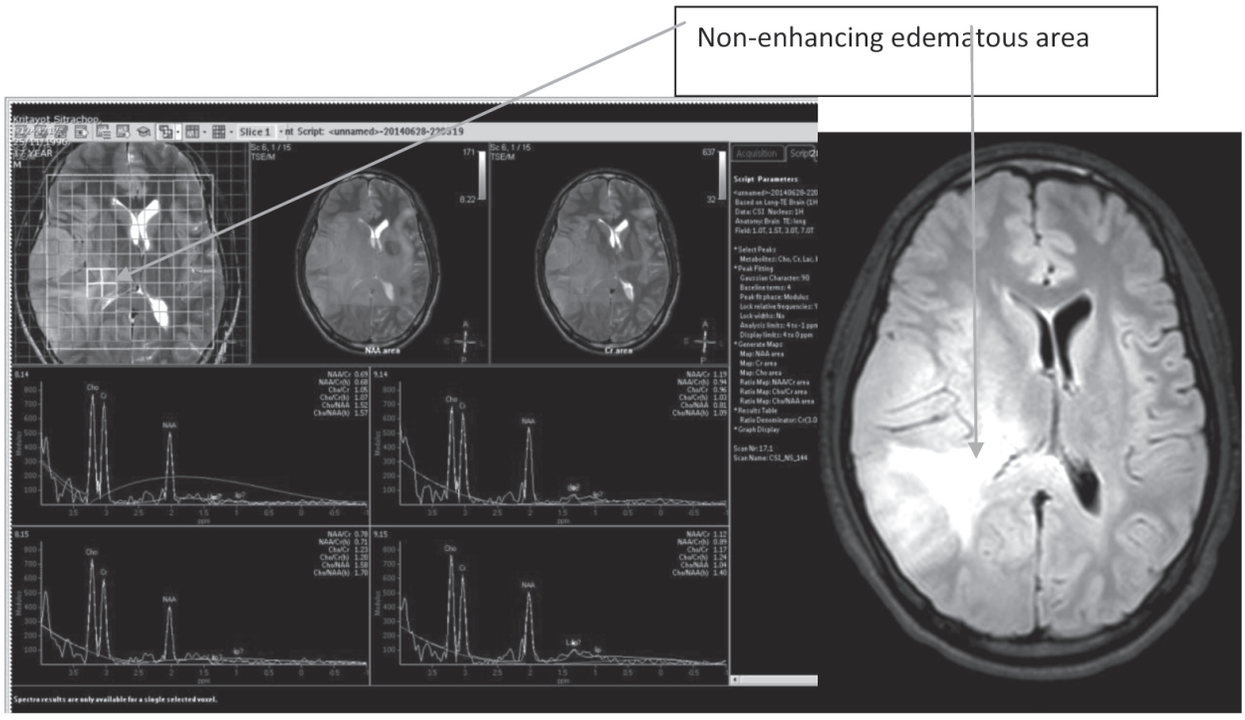

Figure 3 Region of interest was placed in NEA (cluster of yellow square). The spectrum of each metabolite was measure, the vertical axis is the height of peak of the metabolite; the horizontal axis is the specific ppm (location) of each specific metabolite.

lected the areas which was the most compatible with solid part of the tumor.

The region of interest was placed for measuring each metabolite at enhancing area (EA), Non-enhancing edematous area (NEA), and contralateral normal white matter. The metabolites displayed on the monitor were collected from the highest values of areas including lesion choline (Cho), creatine (Cr), N-acetyl-aspartate (NAA), lactate (Lac), lipid (Lip), ratio of Cho/Cr and Cho/NAA. Calculation of ratio of lesion Cho to normal Cho(nCho), nCr(Cr lesion/Cr normal) and nNAA (NAA lesion/NAA normal) was also performed.

The relative cerebral blood volume was measure and compare between tumor and NEA (rCBV ratio = rCBV[tumor]/rCBV[contralateral white matter a] because histological heterogeneity within malignant gliomas is common, rCBV maps of high-grade tumors are often heterogeneous, containing both high and low rCBV foci.We focus on maximal CBV is taken to be representative of the region of interest,enhancing area and NEA[30,31]. Stephan G et.al. studied on best method to measure CBV,and suggest to use maximal CBV.

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 is used to compare the average metabolic ratio for non-enhancing edematous area and the enhancing area.

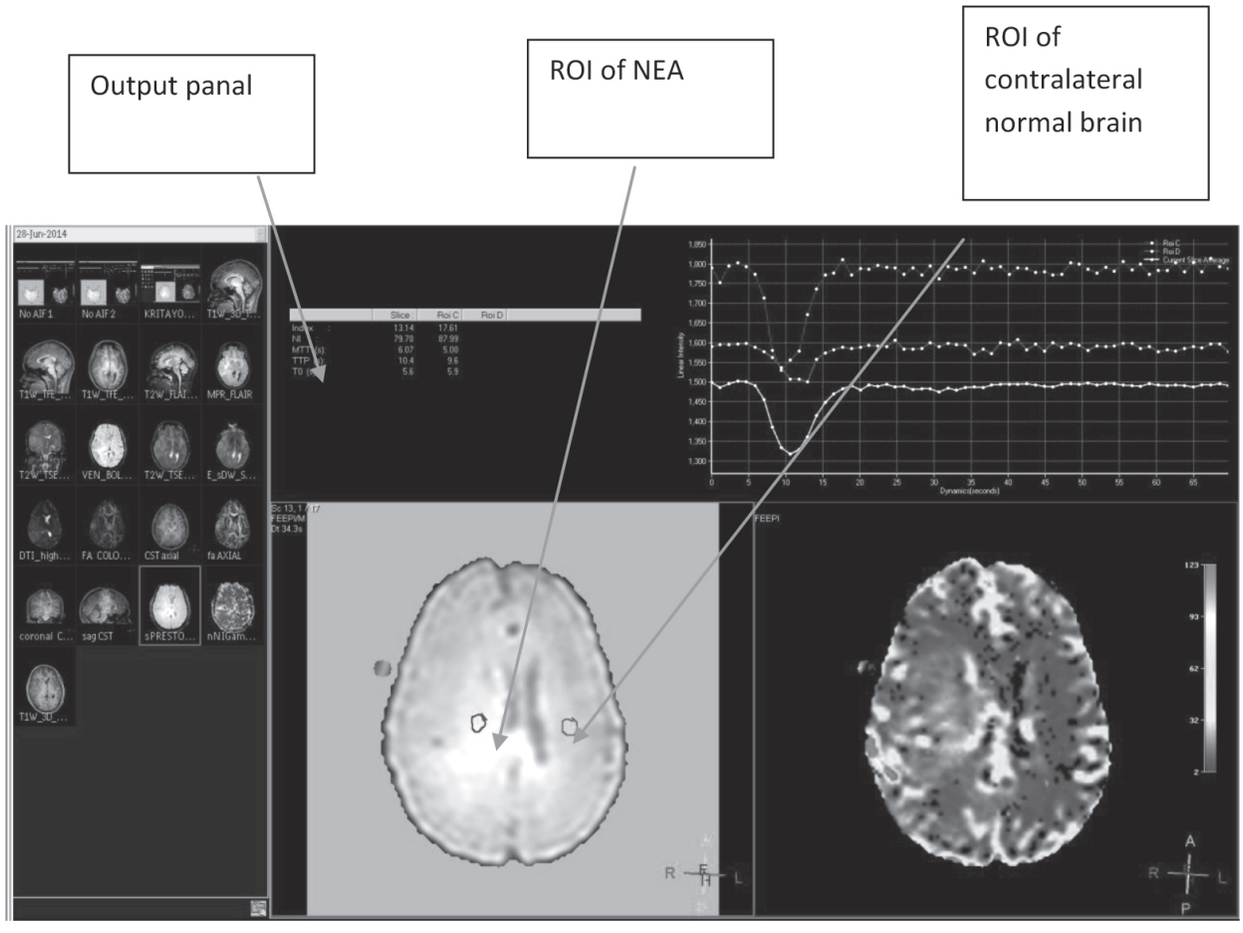

Figure 4 Show work station window to measure region of interest by pick up highest CBV foci in each ROI.

Table 1 Summarizes the clinical characteristics, tumor characteristics and surgical resections of all 62 patients. (GBM=glioblastoma multiform, AA=anaplastic astrocytoma, AO=Anaplastic oligodendroglioma, AE=anaplastic ependymoma, RT=Radiotherapy, CMT=Chemotherapy)

Characteristic		All patient n=62	GBM n=50	AA n=5	AO n=6	AE n=1
Mean age in years (SD)		46.48 (13.87)	47.26 (14.5)	41.40 (13.77)	42.33(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)
Size (cm), (SD)		4.11 (1.71)	4.22 (1.65)	3.22 (1.76)	4.16 (2.28)	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
Lobe	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
	Cerebella (%)	1 (1.6)	1 (2)	0	0	0
Edema	Absence (%)	4 (6.5)	2 (4)	0	2 (33.3)	0
	Presence (%)	58 (93.5)	48 (96)	5	4 (66.6)	1 (100)
	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
Deficit	Absence (%)	46 (74.2)	40 (80)	3 (60)	6 (100)	1 (100)
	Presence (%)	12 (19.4)	10 (20)	2 (40)	0	0
Adjuvant	Therapy					
	Radiotherapy (%)	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

Time to recurrence was censored if the patient had progression free at the time of analysis.

Approval for this study was obtained from the Siriraj Institutional Review Board, Mahidol University.

Result

62 patients with suspicious clinical symptoms and initial imaging of gliomas underwent conventional and advanced MRI for brain tumor. All of the 62 patients underwent maximal safe resection and histopathologic results of high-grade glioma were selected for evaluation.The pathologic diagnosis was based on WHO 2007 included. Demographic data, diagnosis, tumor size, tumor location, grade of tumor edema and extent of maximal safe resection were summarized in Table 2

In this study, there were 35 male and 27 female with median age of 46.5 years. Almost of tumor located in subcortical area, parietal (21 out of 62), frontal (19 out of 62) and temporal (14 out of 62) respectively. Most of the patient has edema (93.5%) on preoperative MRI with no significant different in degree of edema. Forty four out of 62 patients (71%) accomplished gross total resection. Forty six from 62 had no immediate post op deficit (74.2%.). The vast majority of pathologic result was glioblastoma (WHO 2007 grade IV), anaplastic oligodendroglioma (WHO 2007 grade III) and anaplastic astrocytoma (WHO 2007 grade III) respectively. Adjuvant therapy in our study mainly is radiotherapy, and concurrence radiotherapy and chemotherapy based on evidence based support. Recurrent time was calculated and present in

Table 2 Time to recurrence depend on presence of edema (months)

edema	Mean	SD
no edema	8.50	7.77
edema	6.69	6.16
Total	6.82	6.14

Table 3 Time to recurrence depend on degree of edema (months).

Pathology	Total (n=26)	Mild (SD)	Moderate (SD)	Severe (SD)
GBM	5.9 (21)	4.1 (2.8)	6.0 (8.4)	7.5 (4.2)
AA	18 (2)	24 (-)	12 (-)	-
AO	4.5 (2)	4.5 (4.9)		
AE	4 (1)			
All pathology (SD)	6.7 (6.2)	6.0 (6.5)	6.8 (8.0)	7.5 (4.2)

Table 4 Compare mean of radiologic factor and difference between enhancing area (EA) and Non-enhancing edematous area.

Radiologic parameter	Mean (SD)		p-value
	EA	NEA	
Choline/NAA	2.96 (3.10)	1.11 (2.38)	0.001
Choline/Creatin	3.14 (6.70)	1.24 (0.62)	0.041
rCBV	5.36 (5.94)	2.16 (1.94)	0.01

"months". Median recurrent time was 4.7 months and slightly decrease in GBM, while patients with grade III WHO2007 has tendency to recurrence after 1 years

Mean recurrent time in patients with peri-tumoral edema and those without peri-tumoral edema was show in Table 2. Overall recurrent time was 6.82 months with much more longer recurrent time in patients without peri-tumoral edema 8.50 months compare with 6.69 months in group of peri-tumoral edema.

The degree of edema was compare based on pathologic result, there is no statictic significant between degree of edema and recurrent time based on pathologic feature.

There was statistic significant in all three parameter (Choline/NAA,Choline/Creatin,rCBV) to differentiate enhancing edematous area and non-enhancing edematous area (Table 4).

Univariate analysis of predictor of recurrent time (Table5) in ours study revealed no statistic significant in variable of general parameter and ratio of metabolite in lesion and NEA. Relative cerebral blood volume was not significant different in lower and more than 1. There was no statistic significant 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 tend to progress later (anaplastic astrocytoma and anaplastic oligodendroglioma). The degree of edema and recurrent time was analyzed. (Figure 3)

Table 5 Univariate predictorof TTR, cox propportional Hazard.

Variable	Hazard ratio	95% CI	P value	TTR in months (median)
Age <60	1			5.2
Age>,=60	1.01	0.46-2.20	0.972	3.8
Male	1			4.8
Female	0.72	0.39-1.33	0.298	4.4
Degree of edema				
Mild	1			6.0
Moderate	1.28	0.57-2.84	0.541	6.8
Severe	0.70	0.33-1.49	0.260	7.5
Resection				
GTR	1			4.7
NTR	0.99	0.46-2.97	0.989	3.0
STR	5.03	0.64-39.30	0.120	1.9
Adjuvant				
RT	1			4.6
RT+CMT	1.02	0.50-2.09	0.949	3.6
Chol/NAA<1	1			4.6
Chol/NAA>,=1	0.48	0.18-1.26	0.138	5.2
Chol/NAA peri<1	1			4.6
Chol/NAAperi >,=1	0.95	0.41-2.18	0.899	5.1
rCBVPeri<1	1			5.9
rCBVPeri>,=1	0.67	0.24-1.86	0.442	4.2

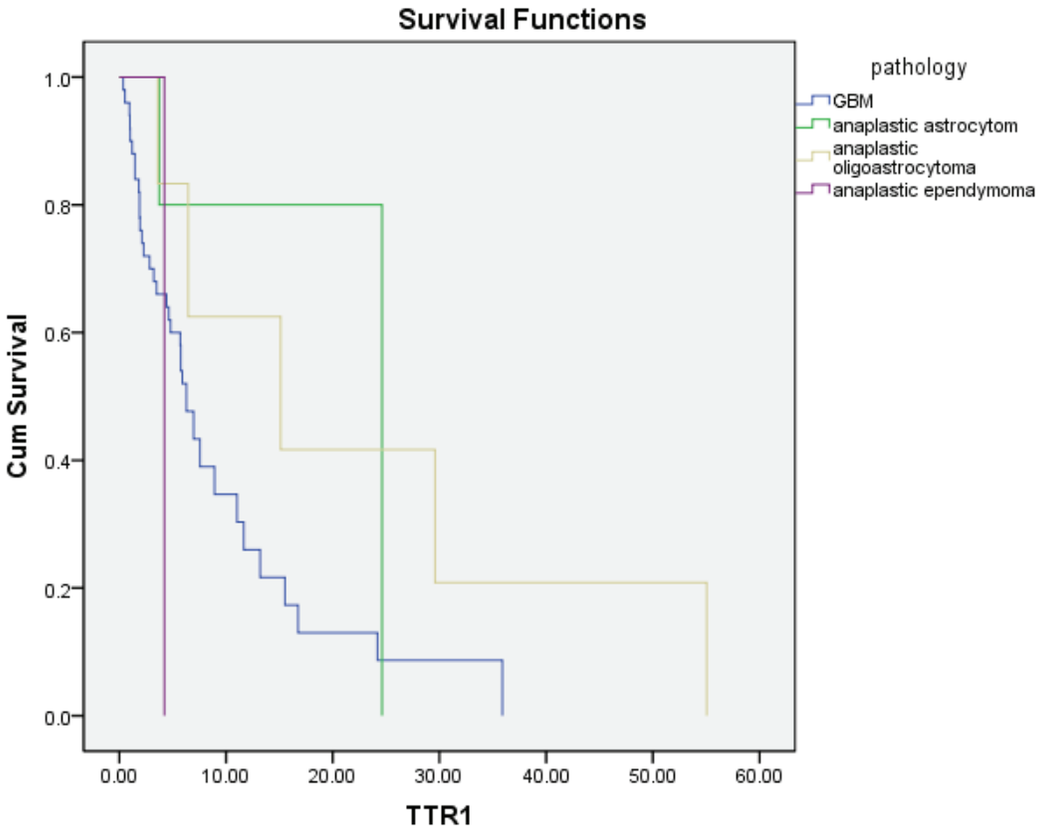

Figure 2 Kaplan–Meier plot: time to recurrence in high grade glioma patients.

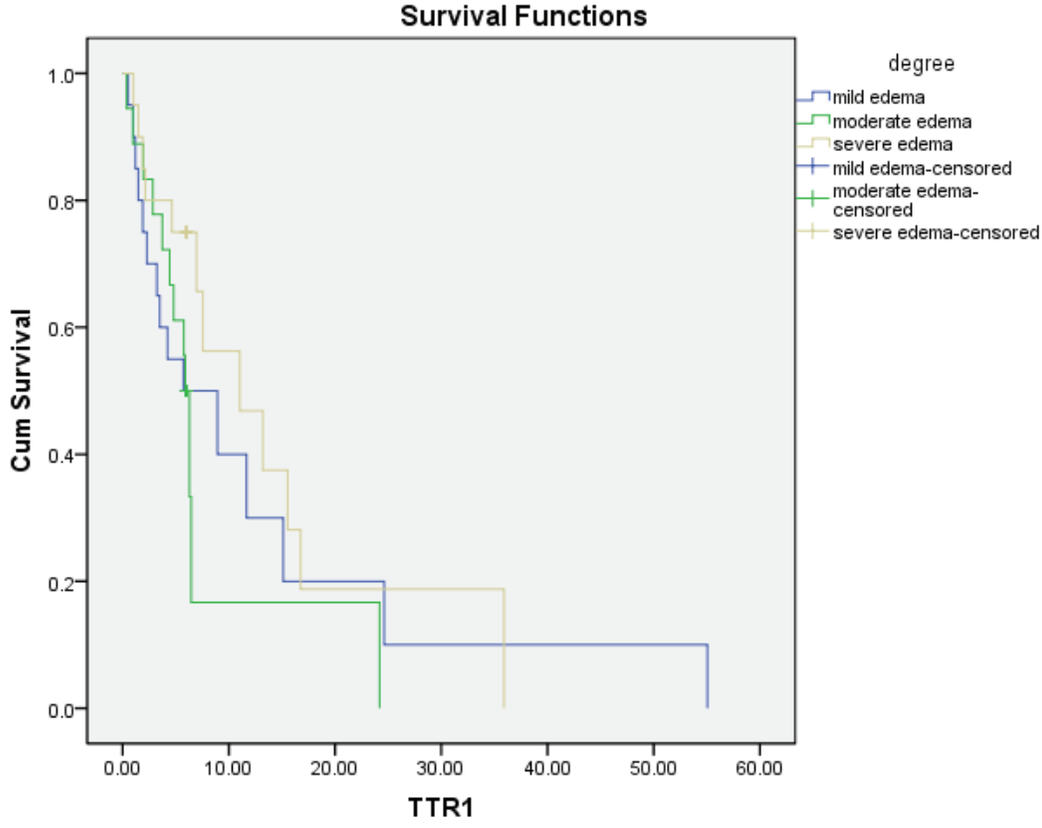

Figure 3 Kapplan–Meier plot, Times to recurrence with degree of edema.

Interestingly moderate edema had shortest progression time when compare with mild and severe edema.

Discussion

Previously paper from our center Wongpraphairot Suban[32] study on choline/NAA, Choline/Creatine parameter on recurrent time in high grade glioma and found statistic insignificant between these parameter (only age parameter that is significant correlation with recurrent time). Chen-Xing Wu et al.[34] study on 87 patient and found significant correlation between presence of peri-tumoral edema and tumor necrotic on survival of malignant glioma. In many study there were many significant variable on recurrent time (age, extent of surgical resection and chemo-radiation treatment)[20,26-29], but in our study there was statistic insignificant in these parameter

In our study from 62 patient we found significant different in MRI parameter Choline/NAA, Choline/Creatin, rCBV on enhancing and

non-enhancing edematous area.But when we compared hazard ratio of below and equal to higher than 1 in these parameter we found statistic insignificant to predict recurrent time. This insignificant may need more sample size and follow up time.

Conclusion

Relative cerebral blood volume (rCBV) and ratio of Choline/NAA in non-enhancing edematous area is different from enhancing area. To predict tumor recurrent time, these radiologic parameters may not useful.

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