

MRI Predictors of Survival in Patients with Glioblastomas

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ABSTRACT

Objective: To evaluate predictive value of MRI findings in overall survival of glioblastoma patients.

Methods: A retrospective study was performed in 11 consecutive adult glioblastoma patients who underwent primary surgery, radiation and chemotherapy. The Kaplan-Meier curve was used to estimate overall survival probabilities. Fisher's exact test or Mann-Whitney U Test was used to explore the association between clinical and imaging factors and 2-year survival.

Results: The median survival for glioblastoma patients in this study was 963 days. Patients with tumor necrosis less than 50%, presence of pre-operative non-enhancing tumor (nCET), perilesional edema less than tumor volume, presence of cystic portion, absence of multifocality, extent of resection more than 50% involving noneloquent location, and the mass effect more than 5 mm had positive trends of longer survival (more than 2 years) implying better prognosis. However, no statistical significance was demonstrated.

Conclusion: MR imaging features were useful predictors for survival in glioblastoma patients.

Keywords: MRI, glioblastoma, survival, predictor

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INTRODUCTION

Glioblastomas is the most common primary malignant brain tumor in adults with a poor prognosis. Despite advances in adjuvant therapy, the median survival rate remains at 12-15 months.¹

Clinical data and pre-operative imaging features were reported to be correlated with survival of GBM. The two most common reported significant predictors were age and Karnofsky Performance Status (KPS). Extensive surgical resection was also reported as a good predictor of

survival in many studies,^{1,2} through some found no correlation.^{3,4,5}

In routine clinical practice, imaging studies especially MRI is used for pre-operative planning, post-operative management and follow up of GBM patients. Studying the relationship of pre-operative MRI features and survival are important for predicting outcome of the treatment regimens. In this study, we analyzed imaging features usually interpreted in clinical service by radiologists to determine any usefulness as a predictor for survival.

MATERIALS AND METHODS

Patients

The study was approved by the authors' Institutional Review Board (SIRB). The data for

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this retrospective study were retrieved from the database of all brain tumors with histologically verified glioblastomas and carried out at Siriraj Hospital during 2008 to 2010. All patients were treated by surgery, radiation therapy and concurrent chemotherapy. Radiation therapy was administered with a total dose varying from 56 to 68 Gy in 2-Gy fractions. Only one patient was administered with a total dose of 30 Gy in 3-Gy fractions for palliative treatment. Chemotherapy (Temozolomide) was also given in every patient.

Patients were excluded if no pre-operative cranial MRI and post-operative MRI or CT scan were available for review. Patients who did not receive either; surgery, radiation therapy or Temozolomide were also excluded from this study. Survival assessment was last performed in October, 2013 with the last patient at 29 months after complete treatment.

All images were reviewed by a neuro-radiologist (O.C, with 25-years' experience in neuroradiology), who was blinded to patient outcome. Post-operative images either CT or MRI prior to radiation therapy and chemotherapy were analyzed to determine the percentage of surgical resection. The MRI findings of tumor were characterized according to predetermined criteria (Table 1). The demographic data was also recorded (age, sex, mental status and perioperative KPS).

Imaging analysis

MRI scans were acquired from either 1.5 T or 3 T scanners between December 2007 and January 2011. In most cases, MR imaging sequences included pre- and post- contrast T1-weighted (T1W), T2-weighted fast spin-echo (T2W), and T2-fluid attenuated inversion recovery (T2-FLAIR). Diffusion-weighted images (DWI) were acquired with the apparent diffusion coefficient (ADC maps).

Post-operative MRI or post contrast CT scans were performed before radiation and chemotherapy and used for evaluating the extent of resection and any residual tumor by visual assessment. The extent of resection was defined as biopsy (< 10% resection), partial (10-50%), subtotal (51-90%), near-total (> 90%), or total (100%) resection.⁶

Positive residual tumors were marked if the patients demonstrated any amount of enhancing, solid tissue. (Fig 1) The solid-nonenhancing portion (nCET) on the pre-operative MRI was determined as positive when the neuroradiologist evaluated every pulse sequence together and concluded not edematous portion. The extent of resection was evaluated by comparing images before and after surgery. (Fig 1, 2)

TABLE 1. Imaging characteristics.

Variable	Imaging features				
Necrosis	☐ none	☐ <25%	☐ 25-50%	☐ >50%	of total tumor volume
Enhancement	☐ none	☐ low-to-medium enhanced		☐ medium-to-high enhanced	
Enhancing margin	☐ well-defined		☐ none or poorly defined		
Pre-operative	☐ no	☐ yes			
Non-enhancing tumor (Evaluated on all sequences together)					
Edema	☐ none	☐ < tumor volume	☐ >= tumor volume		
Mass effect	☐ none	☐ deformity of ventricle, no midline shift			
		☐ moderate, < 5mm midline shift		☐ significant, > 5mm midline shift	
Cyst (thin wall, not in the center)	☐ no	☐ yes			
Multifocal lesions	☐ no	☐ yes			
Extent of resection	☐ total resection	☐ >90%	☐ 51-90%	☐ 10-50%	☐ <10%
Functional location	☐ noneloquent		☐ near-eloquent		☐ eloquent
Site	☐ superficial (only cortical)				
	☐ deep (insula, thalamus, basal ganglia, posterior fossa)				

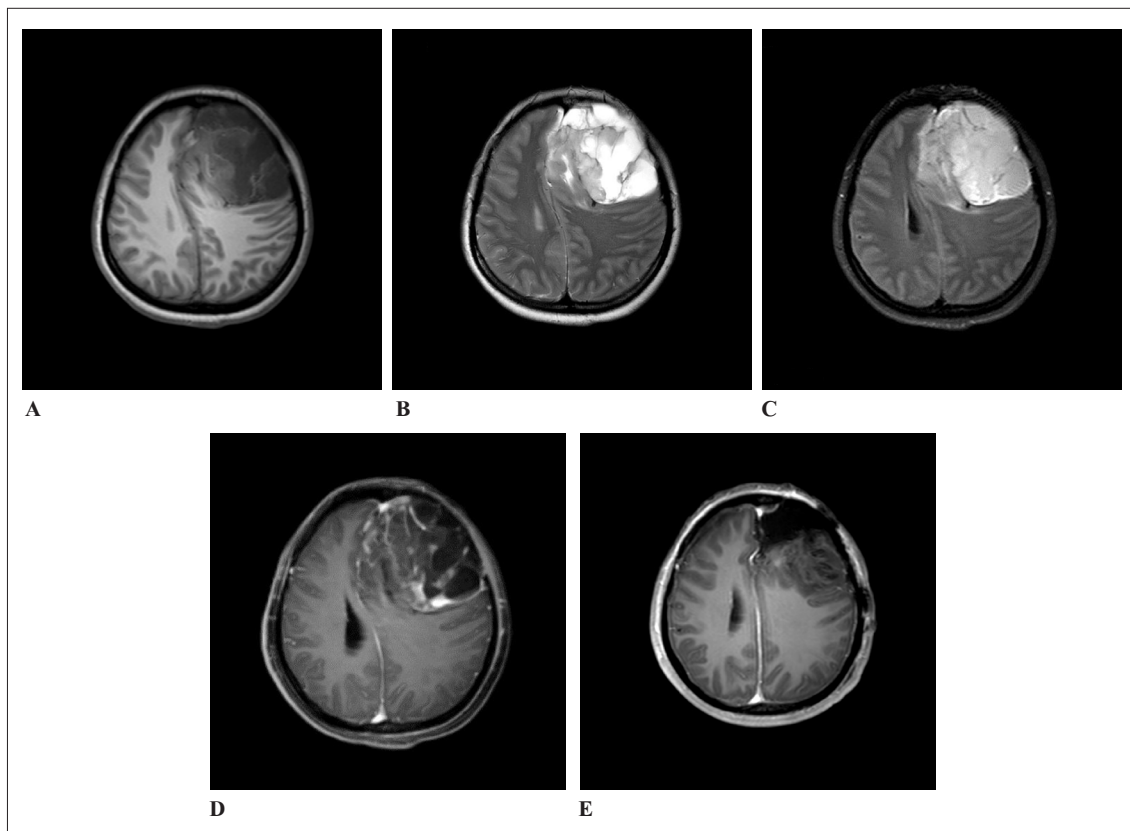


Fig 1. MR imaging of a patient with glioblastoma: axial T1W (A), axial T2W (B), axial T2-FLAIR (C), post contrast T1W (D and E). A-D were pre-operative images, E was post-operative image. There was a heterogeneous mass at left frontal region (superficial location) with irregular enhancing tumor at medial aspect of the tumor and cystic portion at lateral aspect. The significant mass effect (more than 5 mm midline shifting) was demonstrated. Post-operative MR image showed no residual enhancing portion, suggested total resection of tumor.

Statistic methods

The Kaplan-Meier curve was used to analyze overall survival probabilities. The end point of the study was patient alive, taken from the date of diagnosis (date of pathological report) until death or until last available follow-up in October, 2013. Fisher's exact test or Mann-Whitney U Test was used to explore the association between factors and 2-year survival. For all analyses, a p value of <0.05 was considered as statistically significant. (SPSS v.18)

RESULTS

This study included 87 consecutive patients who underwent primary surgery for glioblastomas in the time period of January 2008 - December 2010. Seventy-nine patients were excluded due to unavailable pre-operative MR imaging (N=50), unavailable post-operative imaging (N=11),

incomplete treatment (N=13), and unavailable treatment record (post-operative treatment in other hospital) (N=2). The remaining eleven patients were included in the analysis. A summary of the patient characteristics has been given in Table 2.

At the time of analysis (November 2013), 5 of 11 patients (45%) died within 2 years of diagnosis. There were 6 (55%) patients who still survived. We divided the patients into two groups; those who died within 2 years of diagnosis and who had a survival more than 2 years. No significant difference of age and KPS between these two groups was shown. The 2- and 3 year probabilities of survival were 54.5 % and 43.6 %, respectively. The median survival was 963 days (95% CI 78.8 – 1,847.1). The survival curve has been shown on Fig 3.

No imaging feature was found statistically significantly correlated with any patient's survival. However, the following imaging features

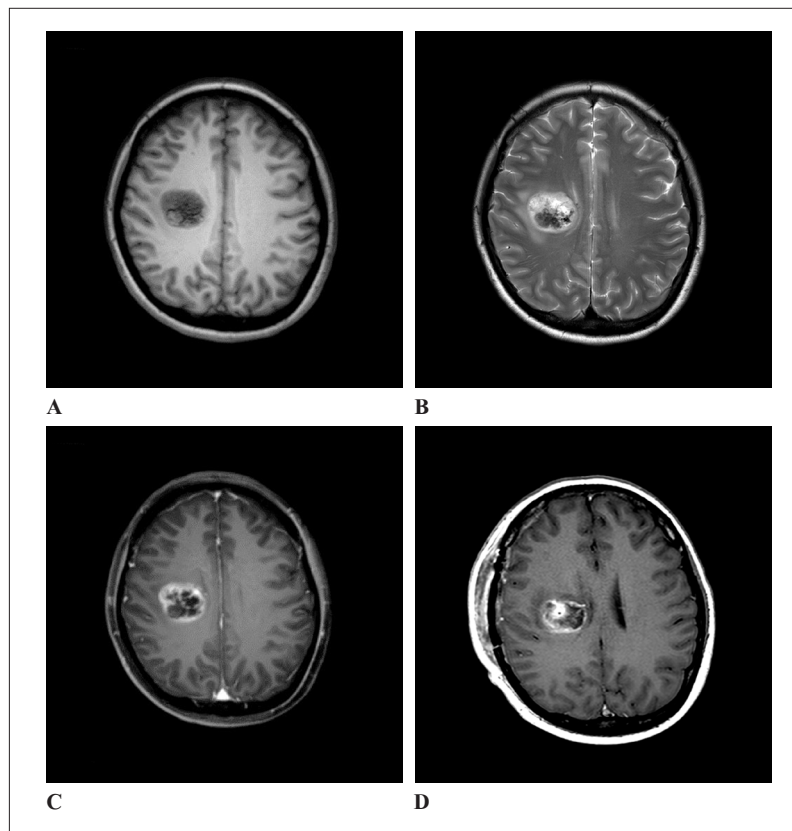


Fig 2. MR imaging of a patient with glioblastoma: axial T1W (A), axial T2W (B), post contrast T1W (C and D). A-C were pre-operative images, D was post-operative image. There was a well-defined heterogeneous mass at right periventricular region (deep location) with internal hemorrhage and necrotic portion, minimal mass effect and minimal perilesional edema (less than tumor volume). Post-operative MR image showed residual enhancing portion, suggestive partial resection (extent of resection less than 50%).

showed positive trends in the group of longer survival (more than 2 years): necrosis less than 50% (83.3%), perilesional edema less than tumor volume (100%), presence of cystic portion (75%), absence of multifocality (55.6%), extent of resection more than 50% (55.6%), and the tumor involving noneloquent location (66.7%).

Furthermore, the poorly defined enhancing margin, the mass effect more than 5 mm, and the deep location of tumor were also found more in the longer survival group than the shorter one. The imaging features and survival have been shown in Table 3.

TABLE 2. Baseline characteristic of all study subjects.

	Total (N=11)	<2 yr survival (N=5, 45%)	>2 yr survival (N=6, 55%)	p value
Age (years)				0.537
Median	53	53	59.5	
Minimum	31	34	31	
Maximum	74	66	74	
KPS				0.931
Median	80	80	85	
Minimum	60	70	60	
Maximum	90	90	90	

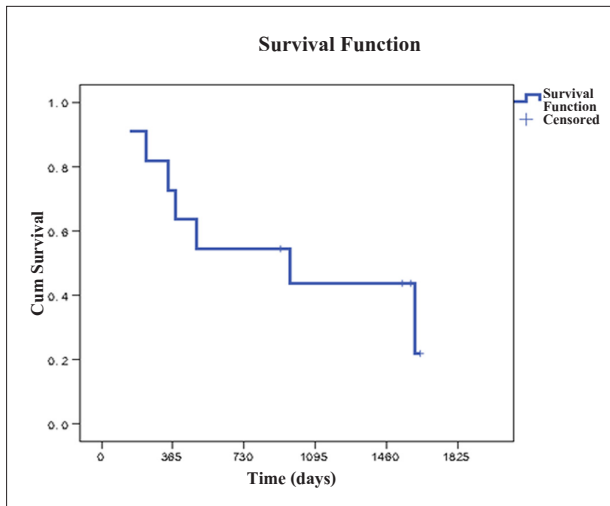


Fig 3. Survival curve for glioblastomas.

DISCUSSION

In the present study, we evaluated 10 imaging features of eleven patients with glioblastomas including necrosis, enhancing margin, pre-operative non-enhancing tumor (nCET), edema, mass effect, cystic component, multifocality, extent of resection, and location of tumor. These imaging features were analyzed to determine which would be the most useful prognostic factors. The selected MRI features are routinely reported by the radiologists from the conventional techniques. Determini-

TABLE 3. Fisher's exact test of imaging features and survival.

Imaging features	Total (N)	<2 yrs. survival (N)	>2 yrs. survival (N)	p value
Necrosis				0.08
25-50%	6	1 (16.7%)	5 (83.3%)	
>50%	5	4 (80%)	1 (20%)	
Enhancing margin				0.45
Well-defined	9	5 (55.6%)	4 (44.4%)	
None or poorly defined	2	0 (0%)	2 (100%)	
Non-enhancing tumor (nCET)				1.00
No	8	4 (50%)	4 (50%)	
Yes	3	1 (33.3%)	2 (66.7%)	
Edema				0.45
area < tumor volume	2	0 (0%)	2 (100%)	
area ≥ tumor volume	9	5 (55.6%)	4 (44.4%)	
Mass effect				1.00
Midline shift <5 mm	8	4 (50%)	4 (50%)	
Midline shift >5 mm	3	1 (33.3%)	2 (66.7%)	
Cyst				0.54
No	7	4 (57.1%)	3 (42.9%)	
Yes	4	1 (25%)	3 (75%)	
Multifocal				1.00
No	9	4 (44.4%)	5 (55.6%)	
Yes	2	1 (50%)	1 (50%)	
Extent of resection				1.00
≤ 50%	2	1 (50%)	1 (50%)	
>50%	9	4 (44.4%)	5 (55.6%)	
Functional location				0.56
Noneloquent	6	2 (33.3%)	4 (66.7%)	
Eloquent	5	3 (60%)	2 (40%)	
Site				0.63
Superficial	8	4 (50%)	4 (50%)	
Deep	3	1 (33.3%)	2 (66.7%)	

nation of prognosis from routine imaging studies would promptly influence treatment decisions.

The reported prognostic factors for survival are patient age, Karnofsky Performance Status (KPS), grade of resection, type of treatment, methylation status of the MGMT gene promoter^{7,8} and isocitrate dehydrogenase (IDHs) mutation. However, the survival benefit of tumor resection remains controversial.^{2,3} It was reported that resection of 98% of the tumor volume was associated with a significant survival rate.^{2,9} However, the negative result was reported from the study of Pope, et al.³

The extent of necrosis and amount of edema was also reported in many studies as negative predictors of survival.^{2,10} In this study, we found that glioblastoma patients with less tumor necrosis (25-50% necrosis) on pre-operative MRI survived longer than patients with greater amounts of necrosis (more than 50%). In addition, the edema more than tumor volume was associated with worse prognosis. The underline explanation may be that the aggressive tumor, tends to have larger tumor necrosis and more peritumoral edema.

The presence of pre-operative non-enhancing tumor (nCET) was also associated with better prognosis, which corresponded with the result of prior study by Pope, et al.³ We proposed that the nCET component might represent the less aggressive portion, which showed better prognosis.

About the mass effect, we found that patients who had >5mm mass effect showed longer survival time, which is the same as the result of Zacharaki, et al.⁹ Infiltrative tumors are believed to have less mass effect and incomplete resection.

From the study of Maldaun MV et al,¹¹ patients harboring a glioblastomas that contained a large cyst would survive longer and had a longer time to recurrence than those who lack such a cyst. Our study also found that the patients who presented with cystic portion of the tumor survived longer than the patients who had no cystic portion. The reason was possibly cystic glioblastomas showed comparatively little infiltration of the peritumoral brain parenchyma.¹²

Pope, et al,³ showed that multifocal lesions had significantly poorer prognosis. Our study showed no difference of the survival according

to this finding. However, patients in the group of single tumor tended to have longer survival time. Increased rates of p53 germ-line mutations were found related to multi-focal GBM.¹³ Study comparing the difference in gene expression between uni-focal and multi-focal GBM may clarify this imaging feature.

About the functional location of tumor, it was not a statistically significant prognostic indicator in previous studies.^{2,9} However, in this study we might imply that the functional location should be associated with survival advantage, in which the noneloquent location was associated with better surgical result and leading to good prognosis.

Location and size of tumors determine surgical resection result. Prediction beforehand will help clinicians to plan surgical procedures in these patients.¹⁴ However, the different result was found in patients with deep grey matter tumor who survived longer than in a lobar location.¹⁵ We also found that the deep located tumors tended to be in the longer survival group. Difference in genetic expression, again, may be the explanation of favorable location of each tumor subtype.

In our study we found that the well-defined tumors were associated with short survival time, but the poorly defined tumors, which should represent infiltrative tumor and worst prognosis, tended to be in the longer survival group. A larger study is needed to show the prognostic indicator of the enhancing margin of the tumor.

Genetic difference of the individual glioblastomas was intensively studied to explain variation of treatment response and survival. Many studies have evaluated the relationship of MRI findings to the genomic study in glioblastomas, leading to the new term of “radiogenomics”. These studies all together would disclose the underlying reasons for the MRI predictors of the prognosis.¹⁶⁻²³

A limitation of this study was the retrospective data analysis causing difficulty to control bias and confounders. There was likely to be a selection bias that favors good candidates for surgery, radiation therapy and Temozolomide treatment (good functional status). Furthermore, only a small number of available patients were

included in the study, so there was no statistical significance of clinical data and imaging features with the survival. A larger study is required.

CONCLUSION

Many MR imaging features in pre-operative glioblastomas are potentially useful predictors for overall survival, although there is no statistically significant supportive evidence. Careful evaluation of these findings should benefit patient management.

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