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The Associations Between Preoperative Conventional MRI Features and Genetic Biomarkers Status in Newly Diagnosed GBMs: A Clinical Summary and Prognostic Analysis

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ABSTRACT

AIM: To analyze certain magnetic resonance imaging (MRI) features as well as six major genetic biomarkers, investigated their associations, and evaluated their prognostic roles in glioblastomas (GBMs).

MATERIAL and METHODS: Strict criteria included newly diagnosed GBM with optimal treatments. Simple manual imaging characteristics (tumor side, location, enhancement, diameter, depth, radiographic necrosis, and edema) were obtained from preoperative conventional MRI. Furthermore, all the status of the MGMT promoter, Chromosome 1p and 19q, IDH, TERT, and BRAF in tumor tissues were detected.

RESULTS: Among 126 inpatients, 60 cases were selected and enrolled in the study. The status of the MGMT promoter was significantly associated with the grade of radiographic necrosis (p=0.033). The rate of 19q deletion was significantly higher in tumors with the ring-shaped peritumoral edema (PTE) (p=0.035) and in tumors with the ring-enhanced trait (p=0.023). Univariate analysis showed that a low PTE index and MGMT promoter methylation were both unfavorable prognostic factors. While the PTE index statistically dropped out, the status of the MGMT promoter and the depth of the tumor were observed to be independent prognostic factors in multivariate analysis.

CONCLUSION: Based on simple neuroimaging metrics, novel connections between features of preoperative conventional MRI and status of major genetic biomarkers were observed, especially for the MGMT promoter and 19q.

KEYWORDS: Biomarkers, Glioblastoma, MRI, Prognosis

ABBREVIATIONS: BRAF: B-Raf and v-Raf murine sarcoma viral oncogene homolog B, **GBM:** Glioblastoma, **GTR:** Gross total resection, **HR:** Hazard ratio, **HGG:** High grade glioma, **IDH:** Isocitrate dehydrogenase, **iMRI:** Intraoperative MRI, **MGMT:** O6-methylguanine-DNA methyltransferase, **mMGMT:** Methylated MGMT, **MTD:** Maximum tumor diameter, **OS:** Overall suvival, **PTE:** Peritumoral edema, **PET:** Positron emission tomography, **TERT:** Telomerase reverse transcriptase, **T1W:** T1 weighted, **T1+C:** Contrast T1 sequence, **T2W:** T2 weighted, **TTE:** The maximum width outside the tumor border of enhancement within peritumoral edema, **TTM:** The nearest distance between the brain midline and the tumor border of enhancement, **uMGMT:** Unmethylated MGMT

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INTRODUCTION

Glioblastoma (GBM), which accounts for 17% of intracranial tumors (37), is the most common and fatal primary malignant brain tumor. Although many trials have been done with reporting promising outcomes, GBM remains a significantly burdensome disease because of the grim mortalities and morbidities. In most prognostic studies, authors agree on a list of crucial factors, such as preoperative MRI features (39), the extent of tumor resection (5), the tumor genotype of various biomarkers (8), postoperative radiotherapy, and chemotherapy (48).

Conventional MRI is a routine and noninvasive method that quantitatively demonstrates many manifestations of GBMs. Furthermore, a larger number of genetic biomarkers have become especially interesting with the release of the 2016 World Health Organization Classification of Tumors of the Central Nervous System (38). Particularly, Isocitrate dehydrogenase 1/2 (IDH), Telomerase reverse transcriptase (TERT), B-Raf and v-Raf murine sarcoma viral oncogene homolog B (BRAF), O6-methylguanine-DNA methyltransferase (MGMT), and Chromosome 1p and 19q have been identified as famous glioma biomarkers that are able to provide information on prognosis. Nowadays, radiogenomics has recently tried to find the associations between MRI features and genomic alterations (10,30).

Although pixel-based analysis of image information is particularly popular among Radiologists, clinical surgeons remain to prefer to measure using handy tools during the operations. For tumors in functional areas, neurosurgeons have to carefully determine how conservative they should be. If neuroimaging were to contribute to forecasting genetic signatures, this information may be of great use for surgeons to weigh their aggressive decisions before making an extended resection. Therefore, to supplement current literatures, we summarized certain features in preoperative conventional MRI and the properties of six major genetic biomarkers that were mentioned above, investigated their potential associations, and evaluated their prognostic roles.

MATERIAL and METHODS

Populations

This retrospective study included patients who were diagnosed with GBM and underwent tumor resection in the General Hospital of People's Liberation Army of China from December 2016 to May 2019. The inclusion criteria were as follows: 1) recently confirmed pathologically, 2) had complete imaging of both preoperative and postoperative MRI, 3) received gross total resection (GTR), 4) possessed valid data of genetic biomarkers, and 5) received palliative treatment after tumor recurrence instead of re-resection. The exclusion criteria were as follows: 1) any history of other intracranial tumor or surgery, 2) any sign of multiple lesions, 3) any treatment of radiotherapy or chemotherapy before the initial surgery, and 4) either an incomplete postoperative radiochemotherapy or chemotherapy. Our institutional review board approved this study, and informed consent was obtained from all patients.

MRI Acquisition and Features Measurement

All MR scans were performed with a 1.5 Tesla equipment (Siemens Espree, Erlangen, Germany). The serial parameters were previously reported, including 3D- T1 weighted (T1W), T2 weighted (T2W), and Contrast T1 sequence (T1+C) (49). Neurosurgeons finished all the measurements by Syngo Fastview Software (Siemens, Germany).

Tumor enhancement judgment was marked as positive for hyperintense regions on T1+C imaging after Gd-DTPA administration. Tumors with an extent of resection greater than 95% were defined as GTR upon volume comparison between the preoperative T1+C imaging and contrast enhancement on intraoperative MRI (iMRI) or postoperative MRI within 72 hours.

Manual measurements of tumoral and peripheral features are illustrated in Figure 1, including the maximum tumor diameter (MTD), the nearest distance between the brain midline and the tumor border of enhancement (TTM), and the maximum width outside the tumor border of enhancement within peritumoral edema (TTE) that represented tumor size, tumor depth, and peritumoral edema (PTE) width, respectively. PTE index was a ratio of TTE to MTD. For the evaluation of a tumor and PTE's morphology on MRI, a ringlike pattern referred to a lesion with a near-circular margin versus others with an irregular margin.

Radiographic necrosis was identified as an area showing hypointense on T1 imaging, hyperintense on T2 imaging, and heterogeneous hypointense within the tumor on T1+C imaging. The degree of necrosis was evaluated using the Hammoud method as follows: Grade I = amount of necrosis is less than 25% of the sectional area of the tumor, Grade II = amount of necrosis is between 25% and 50%, Grade III = amount of necrosis is greater than 50% (16, 21).

Detection of Genetic Biomarkers and Pathology

Two pieces of tumor tissue within the enhanced region were harvested during surgical resection of each patient. One piece was assigned for pathological diagnosis and was presented to two independent senior neuropathologists who were blinded to clinical and radiological information. About 100 mg of the other piece was delivered for genetic analysis. The properties of the MGMT promoter and Chromosome 1p and 19q were determined by pyrosequencing and capillary electrophoresis. The genotype of IDH (R132 / R172), TERT (C228T / C250T), and BRAF were detected as either mutant or wild type by high-throughput sequencing.

Surgery, Treatment, and Follow-up

Surgical resection was completed with the aid of neuronavigation. Immediate administration of concurrent temozolomide chemotherapy (Standard Stupp regimen) and Tumor-Treating Fields after clinical discharge was highly recommended. Follow-up information was updated either via phone call or outpatient feedback. The interval between the date of surgery and death was assigned as overall survival (OS) time, which was censored for a surviving patient at last follow-up.

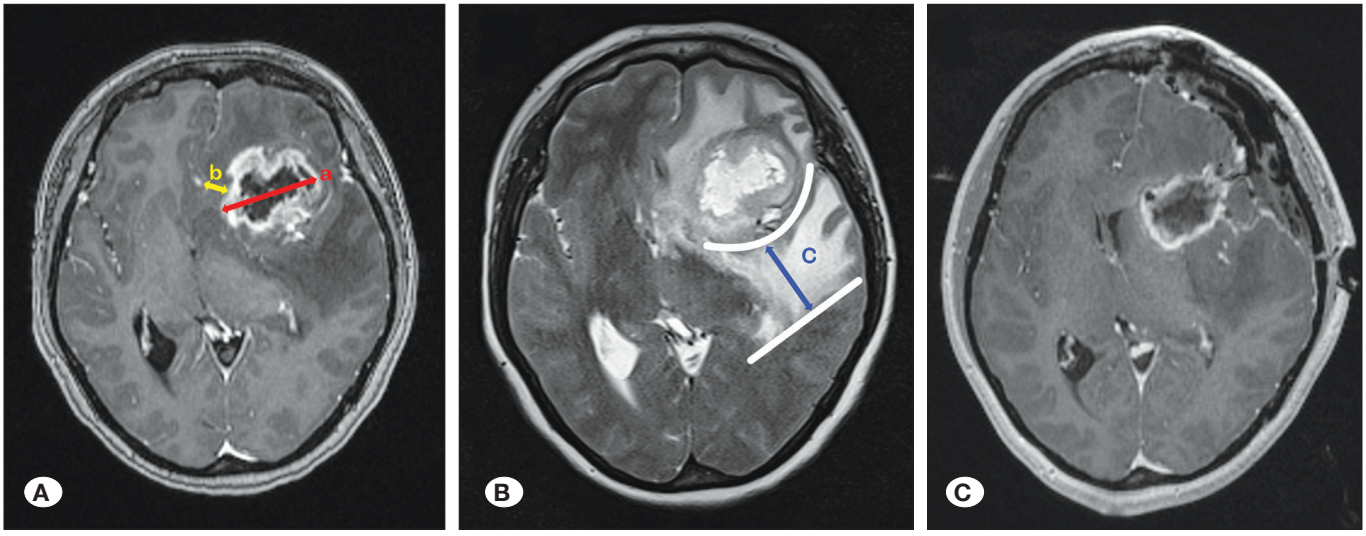

Figure 1: Illustration case. A 47-year-old female patient presented with intermittent headaches. **A)** Conventional MRI revealed a tumor in the left frontal lobe. A cross section displaying MTD was identified in an axial view. The tumor was heterogeneously enhanced with irregular shape on the postcontrast imaging. The red line **(a)** (MTD, 40.5mm) represented the tumor size, the yellow line **(b)** (TTM, 11.6mm) represented the tumor depth. The area of hypointense region on T1+C imaging within the tumor was larger than 50%, which indicated a Grade III of radiographic necrosis. **B)** The tumor border on this section of T1+C imaging was cast on T2W imaging. The PTE referred to the area of hyperintense region beyond the tumor border on T2W imaging. The margin of hyperintense region out of the tumor on T2W imaging, similar to the outline of tumor border, was delineated as PTE edge. The blue line **(c)** (TTE, 30.1mm) represented the width of PTE edge. The PTE index was 74.3% by a ratio of TTE to MTD. **C)** A GTR was eventually performed according to the postcontrast imaging of iMRI. Although received optimal treatment, she suffered from tumor recurrence (seven months) and passed away (fourteen months) after her operation. **GTR:** Gross total resection, **MTD:** Maximum tumor diameter, **TTE:** The maximum width outside the tumor border of enhancement within PTE, **TTM:** The nearest distance between the brain midline and the tumor border of enhancement, **PTE:** Peritumoral edema.

Statistical Analysis

Chi-square test (or Fisher's exact test) was used to analyze genetic biomarker status and MRI features. The median (MTD, TTM, TTE, PTE index) served as the cut-off values for dichotomous grouping in the prognostic study. Log-rank analysis of Kaplan–Meier survival curve was used to compare OS time. Multivariate analysis was used to determine the prognostic effect using Cox proportional hazards model. A p-value of less than 0.05 was considered as statistically significant. SPSS (IBM version 18) performed all statistical calculations.

RESULTS

Populations

A total of 126 GBMs was obtained from medical electronic records. Of these, 60 cases were enrolled after the selection workflow (Figure 2). The median age was 54 years with a range from 19 to 73. The gender ratio was 34/26 (male versus female).

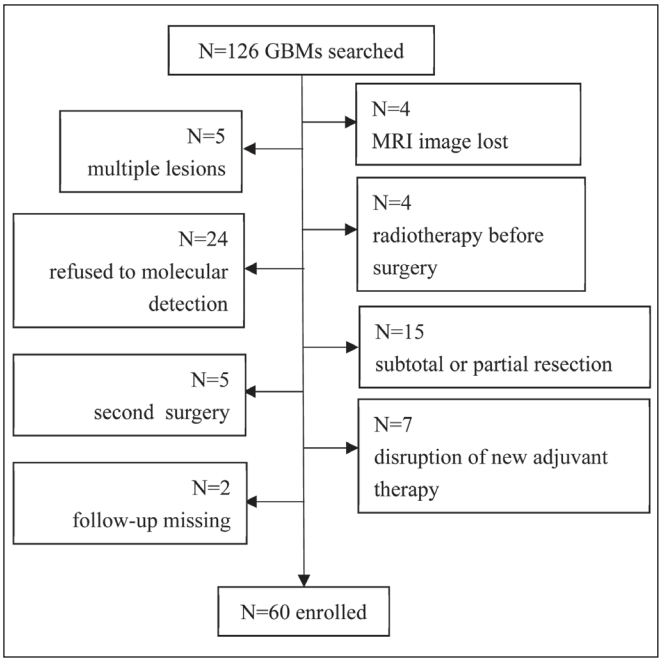

Figure 2: Workflow of Patients Selection.

Association of Image Features and Genetic Biomarkers

Tumor characteristics (Table I) indicated that the main body of a lesion was mostly located in the frontal lobe, and less frequently in the insular lobe or thalamus. TERT promoter mutation occurred in 37 patients (62%), and C225T type

Table I: Tumor Characteristics

Characteristics	Categories	n
MRI features		
Tumor side	Left / right	27 / 33
Tumor location	Frontal / temporal Parietal / occipital Insular, thalamus, and etc	29 / 13 7 / 5 6
Tumor enhancement	Ring / irregular	23 / 37
Tumor diameter, MTD	Median (range) (mm)	47 (18~82)
Tumor depth, TTM	Median (range) (mm)	10 (-28~38)
PTE width, TTE	Median (range) (mm)	23 (3-50)
PTE index	Median (range) (ratio)	58% (6%-132%)
PTE shape	Ring / irregular	37 / 23
Necrosis	Grade I / II / III	8 / 17 / 35
Biomarkers		
MGMT	Unmeth / meth	36 / 24
Chromosome 1p	Intact / deletion	53 / 7
Chromosome 19q	Intact / deletion	46 / 14
IDH1	Mutant / wild	5 / 55
TERT	Mutant / wild	37 / 23
BRAF	Mutant / wild	1 / 59

was seen in 68% of mutant tumors. Only five patients were reported to have the IDH1 mutation (IDH2 mutation, none). The 1p deletion and BRAF mutation was observed in only seven and one patients, respectively.

The metrics of MTD, TTM, and TTE were normally distributed. There were significant associations between genetic biomarkers status and MRI features (Table II). In terms of radiographic necrosis grade on MRI, the rate of methylated MGMT promoter (mMGMT) in the severe necrosis group (Grade III) was higher than that in the moderate necrosis group (Grade I+II) (51% versus 24%). Concerning tumor enhancement, the rate of 19q deletion in the ring-enhanced group was greater than that in the irregular group (39% versus 14%). With respect to the PTE shape, the rate of 19q deletion in the ring group was also higher than that in the irregular group (32% versus 8%). However, this study yielded nothing despite our attempts to reveal any additional associations among age, gender, simple anatomical information, the rest of the MRI features, and the rest of genetic biomarkers (p-value not shown).

Survival Analysis

Nine patients died, whereas 28 patients survived one year after their operation. Another 12 patients died in the following year. The median follow-up period was 13 months (95% CI, 10.7–15.3 months), and the median OS time was 17 months (95% CI, 14.9–19.1 months). No patients received Tumor-Treating Fields therapy.

Table II: Significant Associations between MRI Features and Biomarkers Status

MRI Features	Biomarkers Status	p
Necrosis	MGMT (Unmeth / meth)	0.033†
Moderate	19 / 6	
Severe	17 / 18	
Tumor enhancement	Chromosome 19q (Intact / deletion)	0.023†
Ring	14 / 9	
Irregular	32 / 5	
PTE shape	Chromosome 19q (Intact / deletion)	0.035†
Ring	25 / 12	
Irregular	21 / 2	

†p value <0.05.

The presence of low PTE index and unmethylated MGMT promoter (uMGMT) were both poor factors of OS in univariate analysis (p=0.025, 0.024; HR=0.340, 0.313; Table III). Additionally, the gender, the tumor depth, the necrosis grade, and the PTE width grade showed borderline significance (p=0.076, 0.076, 0.067, 0.068, Table III). All six parameters were analyzed with multivariate analysis. MGMT promoter status and tumor depth value both turned out to be independent prognostic factors, while PTE index remained inconclusive (Table III, Figure 3).

DISCUSSION

MGMT and Necrosis

Based on previous reports showing that patients with mMGMT lived significantly longer than patients with uMGMT, MGMT has been considered to play an essential role in the therapeutic strategy (15,23,41,43). This article reaffirms the viewpoint that the status of promoter methylation probably stratifies outcomes in patients receiving temozolomide chemotherapy.

To our knowledge, necrosis has been reported to refer to three aspects: histopathological interpretation, tumor appearance impression on preoperative MRI, and radiotherapy consequence. In this study, the heterogeneous enhancement of pretreatment tumors on MRI is a point of interest, since a finding of radiographic necrosis is a typical sign of GBM. While previous studies mostly related this feature to a poor prognosis (11,16,18,21,25,26,34,45,46,50,55), our study failed to reveal any significant impact on survival, similar to other studies (12, 19, 36). Nevertheless, the relationship of the MGMT promoter

Table III: Survial Analysis of Clinical, Radiographic Data and Biomarkers

Variables Type	Univariate			Multivariate		
	Estimation of median OS (95% CI)	p	HR	HR	Cox regression 95% CI	p
Sex		0.076ǂ	-			
Male	16.0 (11.2~20.8)					
Female	22.0 (15.5~28.5)					
Tumor depth		0.076ǂ	-	0.380	0.150~0.966	0.042†
Deep-seated	16.0 (14.4~17.6)					
Superficial	22.0 (15.4~28.6)					
Necrosis		0.067ǂ	-			
Moderate	16.0 (12.2~19.8)					
Severe	16.0 (10.1~21.9)					
PTE width		0.068ǂ	-			
Narrow	16.0 (11.7~20.3)					
Wide	22.0 (14.7~29.3)					
PTE index		0.025†	0.340			
Low	16.0 (12.6~19.4)					
High	22.0 (13.9~30.1)					
MGMT		0.024†	0.313	0.272	0.091~0.815	0.020†
Unmeth	16.0 (11.0~21.0)					
Meth	18.0 (10.1~25.9)					

ǂ p value adjacent to 0.05, † p value <0.05.

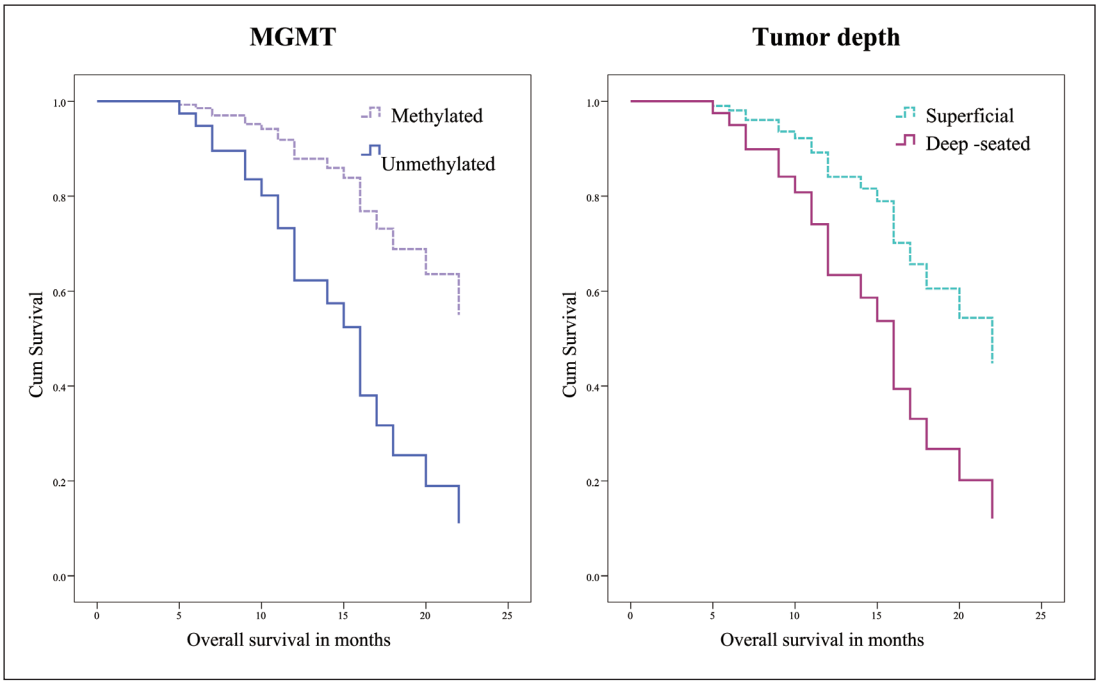

Figure 3: Survival analysis of MGMT promoter and tumor depth.

status and radiographic necrosis can be seen as similar to previous results (17,22,29,30). This may be theoretically supported by the suppression effect of promoter methylation on downstream molecular expressions, since previous studies reported that MGMT protein shortage caused DNA impairment which may lead to histopathological necrosis inside the tumor (2,13). Moreover, although we did not adopt advanced or special MRI sequences, positron emission tomography (PET) has been advocated as an effective way for differentiating treatment-induced necrosis from tumor recurrence by more reports (24,27,28,53). Furthermore, Kong et al. recently reported that a signature of ^{18}F-FDG-PET-based radiomics may predict the status of MGMT promoter methylation in a glioma (31). Combined with the results from our study, this technique may also strengthen the link of preoperative imaging features and MGMT promoter methylation.

Chromosome 19q

Frequently, the chromosomes are lost in solid tumors (14). In terms of oligodendrogliomas, the 1p and 19q co-deletion of has been significantly validated and widely predicted through imaging by numerous studies (3,7,9,33,53). In high-grade glioma (HGG), relevant studies also reported that co-deletion appeared to be a prognostic marker (1,20,40). However, studies on solitary 19q deletion are relatively rare, therefore the finding that 19q deletion was associated with certain MRI features in our study is interesting.

In HGGs, GBMs were observed to exhibit 19q deletion at more than random frequency (33,42). Some researchers also found that 19q deletion was positively correlated with a longer OS in HGG (4,6,17). In GBMs, the presence of 19q gain was also significantly associated with the prognosis (32,51). However, no survival benefits from 19q deletion were found in our study, which is inconsistent with other studies (35,44,54). Although several genes on chromosome 19q have been reported as potential tumor suppressors, the underlying molecular mechanisms of the biological effect induced by 19q deletion remains unknown (47,52). In addition, it is well known that blood-brain-barrier breakdown causes contrast enhancement due to malignant tumor behavior. Our finding that 19q deletion was related to ring enhancement hints on the role of chromosome 19 and its relative genes in tumorigenesis. Moreover, we described a high rate of 19q deletion in tumors with the ring-shaped PTE, which points to a new direction in the predictions for 19q.

Limitations

Several limitations exist in this study. Bias may be present due to the fact that the patients were retrospectively selected from a single institution. Furthermore, this study had to deal with a small sample size and insufficient data on mutant IDH and BRAF tumors after our rigorous screening. Future prospective and large-scale study may provide more concrete results.

CONCLUSION

For newly diagnosed GBMs, the deletion of 1p and the mutation of IDH or BRAF happened infrequently. Simple manual metrics of preoperative MRI were observed to be associated with properties of major genetic biomarkers. The status of the MGMT promoter was significantly associated to the grade of radiographic necrosis. The rate of 19q deletion was significantly higher in tumors with the ring-shaped PTE and in tumors with the ring-enhanced trait. In the prognostic analysis, although the effect of PTE on survival required further investigation, the status of the MGMT promoter and the depth of a tumor were both independent factors of OS.

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