

# T2/FLAIR Abnormality Could Be the Early Sign of Glioblastoma Dissemination

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## Research Article

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# Abstract

## Purpose

Newly emerged or constantly enlarged contrast-enhancing (CE) instead of T2/FLAIR lesions were the necessary sign for the diagnosis of glioblastoma (GBM) progression. This study aimed to investigate whether the T2/FLAIR abnormal transformation could predict and assess progression for GBMs, especially for dissemination.

## Methods

A consecutive cohort of 246 *de novo* GBM with regular follow-up and sufficient radiological data were included in this study. The series of T2/FLAIR, T1CE images were retrospectively reviewed. The patients were separated into T2/FLAIR and T1CE discordant and accordant subgroups based on the initial progression images.

## Results

A total of 170 qualified patients were finally analyzed. The incidence of discordant T2/FLAIR and T1CE images was 25.9% (44/170). The median time of T2/FLAIR indicated tumor progression was 119.5 days (ranging from 57 days-unreached) prior to T1CE. Nearly half of patients (20/44, 45.5%) in discordant subgroup suffered from tumor dissemination, substantially higher than accordant patients (23/126, 20.6%,  $P < 0.001$ ). The median time to progression (TTP), post-progression survival (PPS), and overall survival (OS) were not statistically different (all  $P > 0.05$ ) between discordant and accordant patients.

## Conclusions

T2/FLAIR abnormality could be the early sign of GBM progression, especially for newly emerged lesions disseminated from the primary cavity. Physicians should cast more attention on the dynamic change of T2/FLAIR images for progression assessment and subsequent clinical decision-making.

## Introduction

The *de novo* glioblastoma is one of the most lethal malignancies and harbors profoundly intratumoral and intertumoral heterogeneity<sup>1-3</sup>. This heterogeneity encompasses substantially molecular and spatial-temporal distinction and could be reflected on imaging<sup>4</sup>. Though glioblastoma typically presents as contrast-enhancing tumors (CET) on MRI, components beyond contrast-enhancing margins, regarded as non-contrast-enhancing tumors (nCET), could also progress rapidly and evolve to CET that severely threaten survival<sup>5</sup>. Recently, dozens of studies focusing on the nCET proposed the innovative surgical strategy that nCET should be considered to be removed, which might be helpful to improve prognosis<sup>6,7</sup>. This informed us that more attention should be attached to the nCET.

Multicentric and multifocal GBM, consisting of 1-35% newly diagnosed GBM, tends to portend a worse prognosis than unifocal<sup>8</sup>. In contrast to multicentric GBM, multifocal GBM presents obvious communication on T2/FLAIR imaging. However, both the definition of multicentric and multifocal GBM require CE rather than the non-contrast-enhancing (nCE) lesions as one of the centers or focuses<sup>9</sup>. Till now, few researchers reported GBMs with nCE lesions as multi-focal or multicentric GBMs. Lasocki et al. firstly reported nine of 151 (6%) *de novo* GBM patients had isolated nCE lesions and further proved glioblastoma, which warned us to pay more attention to this phenomenon<sup>10</sup>.

Multifocal or multicentric lesions could not only be diagnosed for primary GBM but in tumor recurrence or progression. Though local recurrence dominates the patterns of progression, non-local progression, including distant intracranial metastasis, subependymal spread, and leptomeningeal dissemination, as well as extracranial visceral metastasis, occurs in 2-34.5% GBM patients<sup>11</sup>. The RANO and modified RANO criteria require new emerged or significantly enlarged CE lesions as the necessary evidence to consider tumor progression<sup>12-14</sup>, nevertheless, non-local recurrence could be similar to nCE multifocal or multicentric GBMs. They might not be visible on T1CE images but T2/FLAIR. Till now, no studies focused on this issue. Thus, we performed a retrospective study to explore whether T2/FLAIR could be more sensitive in distinguishing early progression than T1CE images, especially for non-local progressed GBM.

## Methods And Materials

### Patients

A cohort of 246 consecutive adult patients from 1st March 2013 to 31st August 2020, surgically treated and pathologically defined as *de novo* supratentorial IDH wild-type GBM based on 2021 WHO classification of brain tumors were included in this retrospectively study<sup>15</sup>. All tissue sections were meticulously reviewed by 3 senior neuropathologists to generate a consensus diagnosis. Patients with inadequate follow-up, and comorbidity or other malignancies were excluded. Clinical, radiological, and pathological information was recorded.

### Molecular information

The 1p/19q codeletion, 7+/10-, EGFR amplification status were determined by fluorescence in situ hybridization (FISH). IDH1 R132 and IDH2 R172 mutation, TERT promoter C228T/C250T mutation was tested by Sanger sequencing<sup>16,17</sup>. The status of MGMT promoter was determined by pyrosequencing and patients were divided into methylated and unmethylated by the average methylation level of 12%<sup>18</sup>. BRAF V600E, FGFR1, and H3K27M mutations were evaluated by Sanger sequencing for exclusion when required.

### Collection of radiological data

All MRI studies were performed on 3.0-T clinical scanners (Siemens Trio Tim, or GE, USA) in the routine clinical workup. The protocol included axial T1-weighted (TR 1750-2250 ms, TE 9.4-19.8 ms, matrix

256×198, slice thickness 5 mm), T2-weighted fast spin-echo (TR 4900-6711 ms, TE 97-116.6 ms, FA=150°, matrix 256×320, slice thickness 5 mm, spacing 1mm, FOV=220×220mm, NEX=3), T2 FLAIR (TR=7000-8000 msec, TE 91-152.0 msec, TI 2340ms, matrix 256×186; slice thickness 5mm, spacing 1mm, FOV=220×220mm, NEX=3), and axial and coronal contrast-enhanced T1-weighted images (CE-T1WI; TR 1779.2-2110 ms, TE 9.4-19.8 ms, matrix: 320×288, FA=15°, FOV=240×188mm, slice thickness 5 mm, spacing 1 mm, NEX=1) with the administration of gadopentetate dimeglumine (0.2 mmol/kg).

MRI examinations were independently analyzed by 2 investigators (X.H.R., a neurosurgical oncologist with 15 years of experience and H.Y.C., a radiologist with 25 years of experience). Both were blinded to clinical history, molecular status, and histopathologic diagnosis. Reassessment was performed when discordant results were acquired. If the disagreement persisted, a third reviewer (X.Z.C, a radiologist in brain imaging with 25 years of experience), joined the discussion for final consensus.

## Treatment and follow-up

All enrolled patients were surgically treated. After the operation and a waiting period of about 3-5 weeks, the Stupp's protocol, radiation with guideline-recommended dose concurrent daily TMZ (75 mg/m<sup>2</sup>/d), was finished, and following cycles of maintenance TMZ (150 to 200 mg/m<sup>2</sup> for 5 days every 28 days) adjuvant chemotherapy was administered.

CE-MRI was meticulously followed within 4 weeks after CCRT and regularly surveilled with an interval of 8-12 weeks or if necessary. The patterns of tumor progression were classified as local or in situ (obvious connection with the primary resection cavity), distant intracranial metastasis (newly emerged parenchyma lesions without a clear connection with the original tumor on T2/FLAIR images), subependymal spread (lesions disseminated along with the subependymal zone) and leptomeningeal dissemination (diffuse leptomeningeal enhancement around the contours of the gyri and sulci with/without multiple nodular deposited in the subarachnoid space) based on the initial MR images with progression<sup>11</sup>. We also employed the principles of RANO for low-grade glioma to evaluate the dynamic change of T2/FLAIR of this GBM cohort<sup>19</sup>. MR spectrum (MRS), Perfusion-weighted MRI (PWI) by dynamic susceptibility contrast (DSC) and <sup>18</sup>F-FDG-PET MRI were available to some but not all patients during the follow-up to provide valuable information to distinguish treatment response (pseudoprogression and radiation necrosis) from true progression.

Time to progression (TTP) was defined as the duration from the initial surgery to the time of true tumor progression, and overall survival (OS) was termed as the duration between the initial surgery and the death, or date of the last follow-up<sup>17,20</sup>. Post-progression survival (the time span between tumor progression and death) was also calculated and documented for further analysis.

## Statistical analysis

The student's t-test was used for continuous variables, and the Mann-Whitney U-test was applied for nonparametric data. The Chi-square test or Fisher's exact test was used to compare the categorical

variables. Graphpad Prism (Version 8.0.1, GraphPad Software, USA) was used for statistical analysis. The survival rate of patients was estimated with the Kaplan-Meier plot, and differences between curves were compared by the log-rank test. Probability values were obtained using 2-sided tests with statistical significance defined as  $P < 0.05$ .

## Results

### **Descriptive Characteristics and the incidence of different patterns of progression**

A total of 246 patients were initially included in this study. Patients with no recurrence, ambiguous diagnosis of progression or follow-up interval longer than three months were excluded for subsequent analysis (Fig. 1). In 170 qualified GBM patients with assessable progression patterns, 25.3% (43/170) demonstrated non-local progression, including distant intracranial metastasis (17/170, 10.0%), subependymal spread (20/170, 11.8%), and leptomeningeal dissemination (6/170, 3.5%), while local or diffuse recurrence was present in the other 127 (74.7%) patients (Table 1).

Table 1  
Clinical, demographic and radiological characteristics of patients with/without discordant T2/FLAIR T1CE images.

Characteristics	Discordant	Accordant	P-value
Number of patients	44 (25.9%)	126 (74.1%)	-
Age at diagnosis (years)			
Mean	46.3±12.8	49.6±12.1	0.130
Median	50.0	51.0	0.847
Gender			
Male	30 (68.2%)	85 (67.5%)	0.930
Female	14 (31.8%)	41 (32.5%)	
Preoperative KPS			
>70	36 (81.8%)	81 (64.3%)	<b>0.031</b>
≤70	8 (18.2%)	45 (35.7%)	
Extent of resection			
GTR	32 (72.7%)	64 (50.8%)	<b>0.012</b>
Non-GTR	12 (27.3%)	62 (49.2%)	
Tumor volume (cm <sup>3</sup> )			
Mean	34.1±33.3	44.5±51.9	0.215
Median	26.6	37.8	0.116
Ventricle infringement			
Yes	23 (52.3%)	79 (62.7%)	0.224
No	21 (47.7%)	47 (37.3%)	
MGMT promoter			
Methylated	19 (43.2%)	44 (35.8%)	0.384
Unmethylated	25 (56.8%)	79 (64.2%)	
Tumor location			
Frontal	13 (29.5%)	41 (32.5%)	0.926
Temporal	16 (36.4%)	40 (31.7%)	

Abbreviations: T1CE, T1 weighted contrast-enhancing images; KPS, Karnofsky Performance Status score; GTR, gross total removal of tumor; MGMT, O-6-methylguanine DNA methyltransferase.

Characteristics	Discordant	Accordant	P-value
Insular	9 (20.5%)	22 (17.5%)	
Parietal	4 (9.1%)	16 (12.7%)	
Occipital	2 (4.5%)	7 (5.6%)	
TERT promoter			
Mutant	11 (37.5%)	49 (42.3%)	0.080
Wild	17 (62.5%)	35 (57.7%)	
Patterns of progression			
Local recurrence	24 (54.5%)	103 (81.7%)	<b>0.003</b>
Distant metastasis	9 (20.5%)	8 (6.3%)	
Subependymal spread	9 (20.5%)	11 (8.7%)	
Leptomeningeal dissemination	2 (4.5%)	4 (3.2%)	
Abbreviations: T1CE, T1 weighted contrast-enhancing images; KPS, Karnofsky Performance Status score; GTR, gross total removal of tumor; MGMT, O-6-methylguanine DNA methyltransferase.			

## The incidence of discordant T2/FLAIR and T1CE images for GBM

We observed the dynamic change discordance between T2/FLAIR and T1CE in a small subgroup of GBM patients (44/170, 25.9%). The abnormal finding of T2/FLAIR was prior to T1CE in most cases (37/44, 84.1%), and the four of remaining patients received re-operation before the new or constantly enlarged T1CE lesions emerged, and the other three patients were only found T2/FLAIR abnormal space-occupying lesions without enhancement till the last follow-up.

The median time-span between T2/FLAIR and T1CE indicated progression was 119.5 days (ranging 57 days -unreached). In the discordant patients, two developed leptomeningeal dissemination (2/44, 4.5%), nine presented subependymal spread (9/44, 20.5%), nine showed distant intracranial metastases (9/44, 20.5%), and the remanent twenty-four patients suffered *in situ* recurrences (54.5%). Generally speaking, nearly half of discordant patients were observed with non-local tumor progression (20/44, 45.5%), while in accordant subgroup, only 18.3% of patients suffered non-local progression (23/126,  $P<0.001$ ) (Table 1). Therefore, newly emerged non-contrast-enhancing lesions, especially for these distant from the primary tumor cavity, should be cast more attention because T2/FLAIR abnormal lesions could still be the sign of GBM progression.

A total of 96 patients achieved GTR, and in the discordant subgroups, the GTR rate was higher than accordant patients (32/44, 72.7% for discordant and 64/126, 50.8% for accordant, respectively,  $P=0.012$ ).

And the preoperative status was better in discordant than accordant (preoperative KPS>70: 36/44 (81.8%) for discordant and 81/126 (64.3%) for accordant,  $P=0.031$ ). The phenomenon informed us that the discordant subgroup achieved better local tumor control and resulted in a lower incidence of local progression (Table 1).

## **Radiological and Pathological finding**

Distinguishing treatment-induced response, including pseudoprogression and radionecrosis, from true progression is of utmost importance for subsequent clinical decision-making and prognosis assessment. In the whole discordant subgroup, eleven performed advanced imaging checks, including MRS, PWI, PET, or combined. Significantly increased Cho/NAA ratio, rCBV, and high glucose uptake was observed in these nine patients (9/11, 81.8%) while the other two showed mild to moderate perfusion and metabolic transformation.

Eleven patients in discordant subgroup (three of them performed advanced imaging check, and seven of them were local recurrence) accepted reoperation, and eight of them were reported with glioblastoma (all accepted re-operation till the tumor evolved into contrast-enhancing). The other three without enhancement were histologically confirmed astrocytoma with anaplastic characteristics (no obvious microvascular proliferation or necrosis were observed though this diagnosis should be refined as glioblastoma based on the 2021 WHO brain tumor classification), and all of them were distant metastasis. Therefore, highly aggressive glioblastoma could transform into astrocytoma with histologically indicated gentle tumor behavior. This phenomenon was rare and has a close relationship with the distant non-CE lesion. Though most non-CE lesions evolved to CE lesions eventually, physicians should be aware that non-CE lesions might be the early sign of tumor progression for GBM, especially for distant lesions.

## **Similar prognosis between discordant and accordant patients**

For the whole cohort, the median TTP, OS and PPS were 6.0, 19.0 and 11.0 months, respectively. The comparison of TTP, OS, and PPS between discordant and accordant patients was not significant (discordant vs. accordant, median TTP: 8.0 vs. 5.0 months,  $P=0.222$ , Fig. 3A; median OS: 21.0 vs. 19.0 months,  $P=0.164$ , Fig. 3B; median PPS: 11.5 vs. 10.5 months,  $P=0.171$ , Fig. 3C). The results demonstrated that though discordant subgroup initially presented less aggressive tumor behavior with non-CE lesions, they progressed as fast as the CE lesions in accordant patients and harbored a lethal prognosis.

More discordant patients suffered from non-local tumor progression, thus simple comparison between discordant and accordant subgroups might overlook some critical information. Survival comparison demonstrated that the prognosis of non-local progression patients in discordant subgroup was superior to accordant patients (median TTP: 7.1 vs. 5.0 months,  $P=0.083$ , Fig. 3D; median OS: 18.25 vs. 12.5 months, Fig. 3E; median PPS: 10.7 vs. 6.0 months, Fig. 3F). This result implied that the occurrence of

tumor dissemination for discordant patients might be later due to better local tumor control, and disseminated nCE tumor cells might harbor a relatively gentle tumor behavior in discordant patients.

## Discussion

The IDH wild-type *de novo* GBM is one of the most lethal malignancies that embraces highly molecular, temporospatial, and radiological intratumoral and intertumoral heterogeneity<sup>9</sup>. The RANO and modified RANO criteria for GBM request newly emerged or constantly enlarged contrast-enhancing lesions as the basic prerequisite to defining progression, regardless of T2/FLAIR<sup>12-14</sup>. Our longitudinal observation demonstrated that extra attention should be paid to the dynamic change of T2/FLAIR, which might be the early sign of progression, especially for non-local progression GBMs.

Typically, GBM is highly aggressive, infiltrative and invasive brain malignancy with prominent blood-brain barrier disruption<sup>9</sup>. The canonical manifestation on radiology is pronounced contrast-enhancing lesions with surrounding T2/FLAIR abnormality areas<sup>21</sup>. However, the inherently high heterogeneity renders neither all GBMs nor the whole body of GBMs is aggressive and destructive enough that could be reflected by CE MRI. Not only a minority of GBMs were non-contrast-enhancing but the ratio of nCE/CE in the GBMs varied significantly<sup>22, 23</sup>. Both the CE and T2/FLAIR abnormal regions are enriched with malignant tumor cells that could reproduce and propagate rapidly<sup>7, 24</sup>. Contemporarily, no assessment criterion focusing on GBM was established according to radiological alteration of T2/FLAIR, neither treatment effect assessment for Bevacizumab-naïve patients nor progression surveillance. The extent of resection (EOR) of GBM is based on the percentage of contrast-enhancing tumors removed or the accurate resident volume of enhancement, regardless of T2/FLAIR. Complete response, partial response, stable disease, or progression after treatment for GBM of RANO was defined by dynamic alteration CE lesions for patients who did not receive antiangiogenic therapy<sup>12, 25, 26</sup>. Studies reported the sensitivity of FLAIR signal increase prior to enhancement indicated *in situ* progression ranged from 34-75%<sup>27-31</sup>, higher than ours, which might be accountable due to the difference in inclusion criteria, GTR and ventricle infringement rate in our study. Our study firstly reported the incidence of T2-FLAIR discordance in dissemination monitoring and revealed its poor clinical outcome.

Traditionally, multifocal or multicentric GBM refers to the concept that synchronous multiple lesions at diagnosis, and the former was defined as multiple CE lesions embedded in a relatively large area with abnormal T2/FLAIR weighted signal while the latter usually invading different hemisphere or lobe devoid of connection. Furthermore, multiple GBMs occurred at a distinct time without connection on MRI were also viewed as multicentric GBM<sup>2, 32</sup>. However, these definitions were established based on the CE lesions with/without well-demarcated margins. Lasocki et al. firstly reported the incidence of multicentric nCE lesions of GBM was 6% (9/151) at preoperative diagnosis, and the survival was much worse than patients without multicentric non-enhancement lesions. In four patients with follow-up MRIs, all developed enhancement and necrosis within 1 year<sup>10</sup>. This phenomenon informed us that nCE lesions distant from the dominant lesion could be the reason for disease progression and treatment failure, and

much more attention should be attached to the nCE lesions because they could not only be multicentric GBMs at diagnosis but at recurrence. Future response assessment criteria should incorporate the dynamic change of T2/FLAIR especially distant signal alteration to monitor GBM *in situ* recurrence or intracranial dissemination.

Local recurrence dominates the patterns of GBM progression (ranging from 60-85%)<sup>11</sup>. The standard care of GBM demands radiotherapy to eliminate the residual tumor cells and postpone tumor recurrence. Demyelination caused by radiation in target volume could lead to evident T2/FLAIR abnormality<sup>14</sup>. At the very early stage of progression, tumor-related edema or infiltration effect was quite obscure and totally covered by demyelination on T2/FLAIR images, but even tiny CE lesion on MRI could be extraordinarily conspicuous on T1CE images. Thus, for local recurrence and leptomeningeal dissemination monitoring, the newly emerged or constantly enlarged CE lesions could be more sensitive for recurrence predicting. Tumor cells could also migrate into areas out of beam target or the low dose of the target where demyelination was less pronounced. Tumor cells from nCE areas of initially dominant bulk could form new non-CE lesions out of the original target zone, or at the very early stage of new lesion forming, the transformation of T2/FLAIR was prior to T1CE images. Our results showed that 25.9% of patients could be found with a nCE lesion that eventually developed into CE lesions with necrosis, and three of them were pathologically confirmed as nCE GBM. Berzero et al. reported that histological grading was important for IDH wild-type glioma prognosis assessment<sup>33</sup>, and our result confirmed this result in non-local progressed discordant patients. Thus, T2/FLAIR should be added to determine dissemination and predict prognosis for GBM, especially in the very early stage.

Currently, the concept of supratotal maximal resection (SMR), which is termed as total removal of both CE and T2/FLAIR abnormal regions for eligible patients, has raised great interest in neurosurgeons for GBM treatment. Some retrospective studies demonstrated that GBM patients might derive a survival benefit from supratotal maximal resection while some were not<sup>34-42</sup>. GBMs appropriate for supratotal maximal resection commonly located on the prefrontal lobe, where a high percentage of GBMs were G-CIMP subtype and MGMT promoter methylated<sup>43,44</sup>. The evidence level of SMR for GBM could never be equal to a multicenter, prospective trial due to the impractical nature of exploring the impact of EOR on survival. Though some results were contradictory, we still could not entirely deny the benefit yielded from SMR. This is the initial concern for T2/FLAIR abnormality for GBM, and we believe this would be inspirable and enlightened.

Multiple recurrences in GBM indicated a more aggressive and invasive tumor behavior and portended inferior prognosis without exception. There still lacks efficient and effective treatment modalities for GBM dissemination control. Some polite studies revealed stereotactic radiosurgery (SRS) might be helpful for a single, small lesion with satisfactory disease control<sup>17,45</sup>. For eligible patients, SRS might be an ideal choice to alleviate suffering and prolong survival.

Limitations do exist due to the nature of retrospective studies within a single institute. Acquisition of consecutive MRI data every 2-3 months in a large cohort of patients was quite difficult. Different medical

centers for follow-up, poor compliance and financial problems might be the major reasons that impede us from sufficient data. Till now, this is nevertheless one of the largest cohorts of studies with series of MRI to dynamic monitor treatment response. Another limitation lies in that pathology confirmation was only achieved in a small part of patients. These limitations could not cover up the meaningful finding of this study, and neuro-oncologist should shed more light on the dynamic image change during follow-up, not only T1WI CE but T2/FLAIR images.

## Conclusion

T2/FLAIR abnormality could be the early sign of GBM progression, especially for newly emerged lesions distant from the primary tumor cavity. The subsequent modified GBM assessment criterion should incorporate the T2/FLAIR information for disease monitoring, and physicians should cast more attention on the dynamic change of T2/FLAIR images for progression evaluation and subsequent clinical decision-making.

## Abbreviations

GBM, glioblastoma; IDH, isocitrate dehydrogenase; MGMT, O<sup>6</sup>-methylguanine-DNA methyltransferase; KPS, Karnofsky Performance Status score; GTR, gross total removal of tumor; SMR, supratotal maximal resection; TTP, time to progression; OS, overall survival; PPS, post-progression survival.

## Declarations

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### Compliance with ethical standards

### Conflict of interest

No potential conflicts of interest were disclosed.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the Capital Medical University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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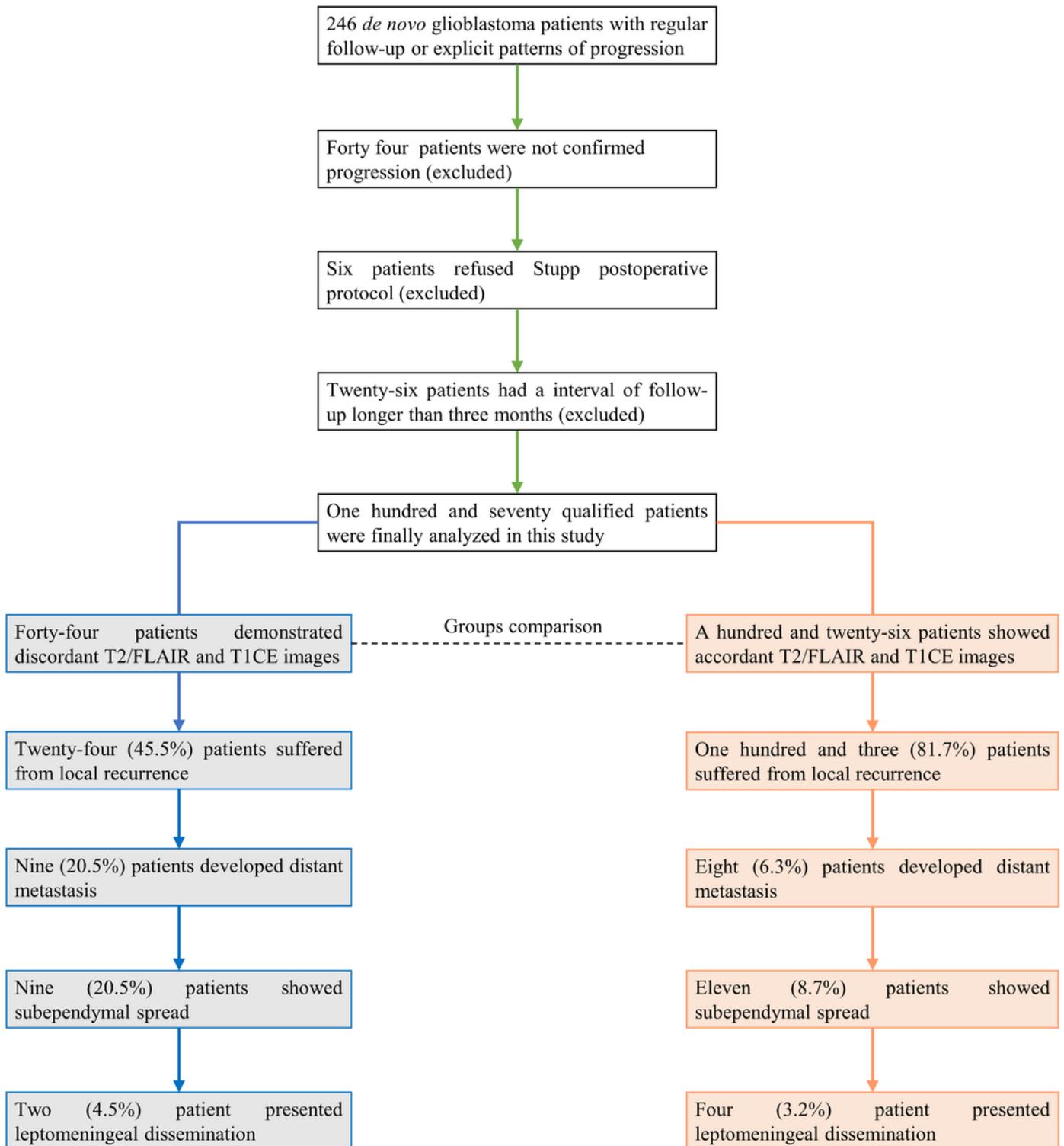
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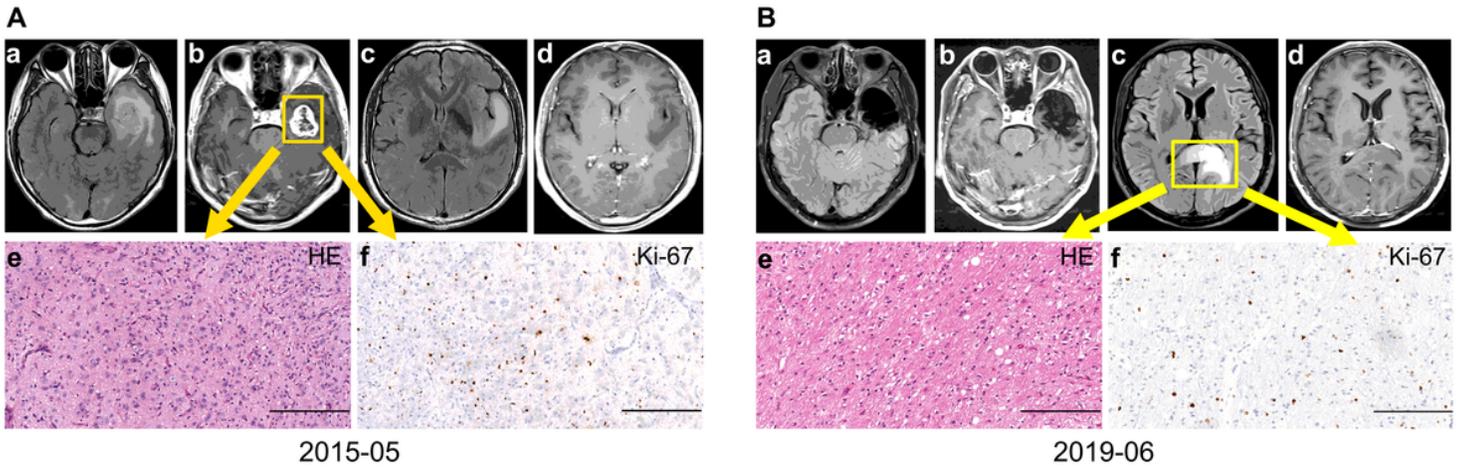
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# Figures



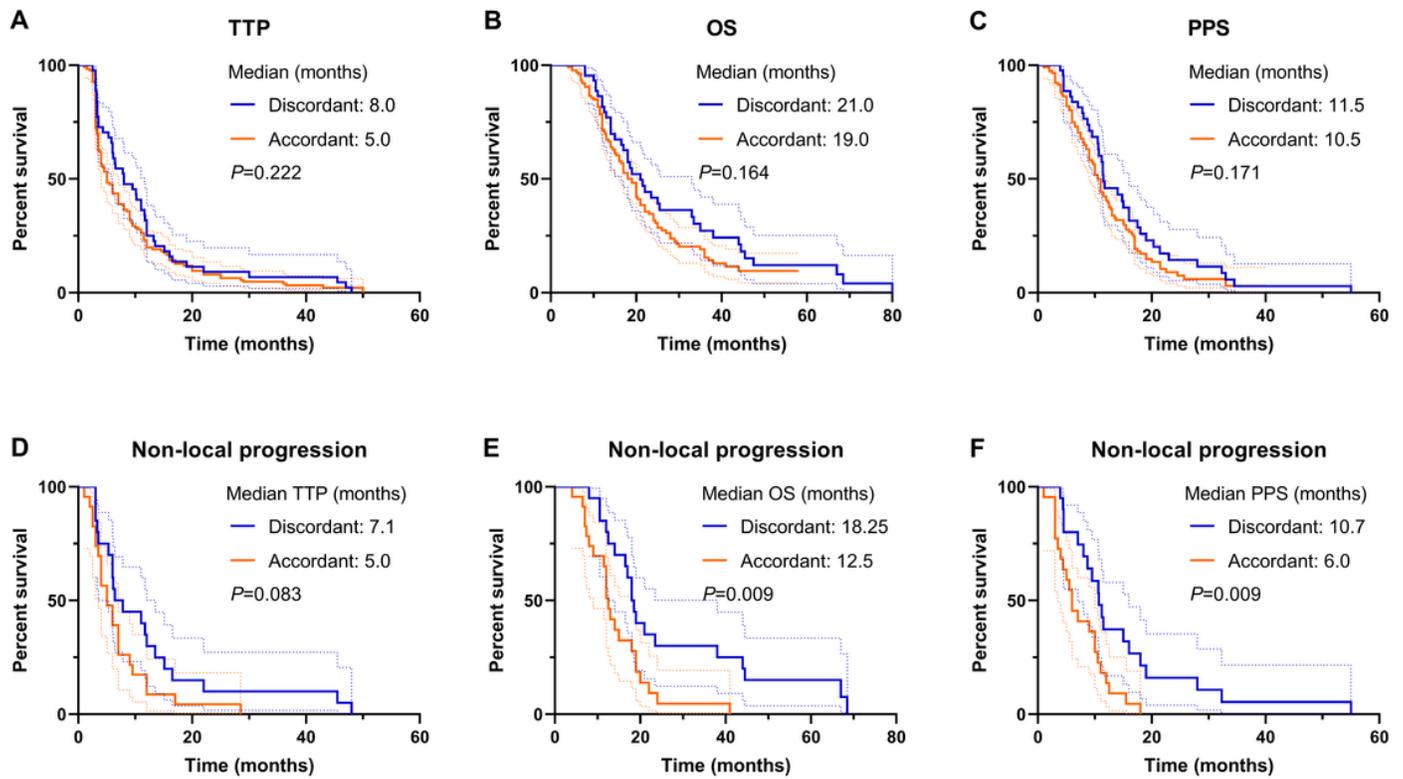
**Figure 1**

Patients included in this study. The final analysis showed that 25.9% of patients (44/170) presented discordant results between T2/FLAIR and T1CE images.



**Figure 2**

A representative case for the discordant subgroup with distant intracranial metastasis. A, the patient presented unbearable headache with contrast-enhancing (CE) lesion on left temporal (a-d). Craniotomy was performed and the tumor was totally removed. The final diagnosis was primary GBM, IDH wild-type, WHO grade 4 (e-f). B, forty-nine months after the operation, a non-CE lesion on the splenium of the corpus callosum with space-occupying effect (a-d) was suspected tumor progression. The final pathology diagnosis was GBM, IDH wild-type, WHO grade 4 (e-f) based on the WHO 2021 brain tumor classification system (Bars, 200 $\mu$ m).



**Figure 3**

Prognosis comparison between T2/FLAIR and T1CE discordant and accordant patients. A-C, the TTP, OS, and PPS were not different between the two subgroups. D-E, for non-local progression patients, the OS and PPS in discordant subgroup were favorable than accordant subgroup, but not for the TTP.