Single-center retrospective study of factors associated with early discontinuation of tumor-treating fields therapy in glioblastoma

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Abstract. Glioblastoma (GBM) is the most aggressive primary malignant tumor of the adult central nervous system with poor survival outcomes despite multimodal standard treatment. Tumor-treating fields (TTFields) therapy prolongs survival in patients with newly diagnosed GBM; however, sustained adherence is essential to achieve therapeutic benefits. The risk factors for early discontinuation of TTFields remain poorly understood, as patients with treatment durations of <2-3 months have been typically excluded from previous analyses. In the present single-center retrospective study, the clinical and molecular factors associated with early discontinuation of TTFields were investigated in 16 consecutive adult patients with supratentorial GBM treated between September 2019 and February 2025. Early discontinuation was defined as the cessation of treatment within 90 days without resumption. Clinical variables, activities of daily living, neurocognitive assessments and molecular profiles were evaluated. Early discontinuation occurred in five patients (31.3%). Comparative analysis revealed that hemiparesis at treatment initiation (P=0.018), attentional impairment (P=0.036), lower baseline Karnofsky performance status (P=0.005) and Barthel Index (P=0.013) were significantly more frequent in the early discontinuation group than in the continuation group. Furthermore, overall survival was significantly shorter in the early discontinuation group (hazard ratio 8.857, 95% confidence interval 1.56-50.29, P=0.004), and progression-free survival showed a non-significant trend toward a shorter duration. No significant differences were found in the other neurocognitive test scores or molecular alterations. These findings indicated that specific neurological deficits and functional impairments may hinder treatment persistence. Therefore, early identification of at-risk patients and implementation of supportive strategies, including enhanced caregiver involvement and welfare support, may improve adherence and optimize the clinical benefits of TTFields in GBM.

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Introduction

Glioblastoma (GBM) is the most aggressive primary malignant tumor of the adult central nervous system and has a poor prognosis. Despite comprehensive standard-of-care treatment-including maximal safe surgical resection, followed by radiotherapy with concomitant temozolomide (TMZ), and subsequent maintenance TMZ-progression-free survival (PFS) typically ranges from 6.2 to 7.5 months, and overall survival (OS) remains limited to 14.6-16.7 months (1).

Tumor-treating fields (TTFields) are non-invasive antimitotic therapies that use low-intensity, intermediate-frequency alternating electric fields to disrupt mitosis and induce apoptosis in dividing cancer cells (2). In an initial phase III randomized controlled trial involving 237 patients with recurrent GBM, TTFields did not significantly improve PFS or OS compared to physician-choice chemotherapy (3). Nevertheless, TTFields were associated with a preserved quality of life, minimal systemic adverse effects, and high patient acceptability, leading to Food and Drug Administration approval in 2011 for use after recurrence following standard chemoradiotherapy.

Subsequent evidence from the EF-14 trial established the efficacy of TTFields combined with maintenance TMZ in newly diagnosed GBM and demonstrated a significant survival benefit over TMZ alone (4). This finding supports the adoption of TTFields as a standard adjunctive therapy worldwide, including insurance approval in Japan in 2019.

The optimal therapeutic benefits of TTFields are achieved by high adherence. Post-hoc analyses from the EF-14 showed that patients with device usage rates of at least 75% and daily usage of ≥18 h exhibited significantly improved PFS and OS (5). Moreover, a longer treatment duration correlated with better outcomes; patients treated for at least 6 months, 9 months, or longer achieved superior OS and higher 2-year survival rates than those treated for shorter durations. In addition, real-world data indicate that patients who continued TTFields for ≥12 months experienced a median OS improvement of >10 months compared to those who received standard treatment alone (6).

Conversely, patients with treatment durations <2-3 months are commonly excluded from analyses because therapeutic efficacy is difficult to evaluate in such cases. Therefore, the risk factors associated with early discontinuation of TTFields remain poorly understood.

This study identified the clinical and demographic factors associated with early discontinuation of TTFields therapy in adult patients with GBM, based on a retrospective analysis conducted at a single institution.

Patients and methods

Aim. This retrospective cohort study was conducted at a single institution to identify the clinical and molecular factors associated with early discontinuation of TTFields therapy in patients with GBM.

Ethical approval. The study protocol was approved by the Ethics Committee of the University of Occupational and Environmental Health (UOEH; Kitakyushu, Japan; approval no. CR24-117). The GBM-specific next-generation sequencing (NGS) panel data used in the present study were obtained from a multicenter collaborative project approved by the Ethics Committee of Kagoshima University (approval no. 180104-Eki; Kagoshima, Japan) and were additionally approved by the Ethics Committee of UOEH for participation as a collaborating site (approval no. UOEHCRB20-100). All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients, in accordance with the approval of the institutional ethics committee.

Patient data. This study included 16 consecutive adult patients (≥18-years-old) newly diagnosed with supratentorial GBM between September 2019 and February 2025, who initiated TTFields therapy at the University Hospital of Occupational and Environmental Health. Clinical and treatment-related data were retrospectively collected from medical records. The assessed variables included age, sex, medical history, family history, presenting symptoms, activities of daily living (ADL), neurocognitive assessment results at TTFields initiation, histopathological findings, extent of resection, adjunctive therapies, pre- and post-treatment imaging findings, average TTFields adherence rate, treatment duration, travel distance to the hospital, and availability and type of caregivers. All patients were diagnosed with GBM according to the World Health Organization (WHO) classification criteria at the time of diagnosis. All patients were treated according to the standard of care, which included maximal safe resection followed by radiotherapy (RT) with concurrent daily TMZ and maintenance TMZ for 6-12 months.

ADL and neurocognitive function were assessed at the initiation of TTFields therapy. Based on a previous study (7), early discontinuation was defined as the cessation of TTFields therapy within <3 months without subsequent resumption.

Molecular data. Tumors were classified according to the 5th edition of the WHO Classification of Tumors of the Central Nervous System. The molecular profiling required for integrated diagnosis was conducted using a GBM-specific NGS panel as previously described (8). Our institution participated as a collaborating center in this molecular study and obtained ethical approval from both the central review board and the coordinating institution (approval number: UOEHCRB20-100).

Statistical analysis. All statistical analyses were performed using EZR version 1.54 (2020), a graphical interface for R (9). $P<0.05$ was considered to indicate a statistically significant difference. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. The Shapiro-Wilk test was used to assess normality for continuous variables, with $P\geq0.05$ indicating a normal distribution. Unpaired Student's t-test was applied to normally distributed variables, while the Mann-Whitney U test was used for non-normally distributed variables. Kaplan-Meier survival analysis with the log-rank test was used to estimate PFS and OS. Hazard ratios (HRs) were calculated using the Cox proportional hazard model. Outlier analysis for continuous variables was performed using the Smirnov-Grubbs test. To evaluate robustness without case exclusion after outlier screening, Welch's t-test was used for between-group comparisons of continuous variables. In addition, the treatment duration and distance from the patient's residence to the hospital were analyzed using both parametric and non-parametric tests after normality assessment. Outlier analysis identified two extreme values in treatment duration and one extreme value in distance from the patient's residence to the hospital. These cases were retained in the primary analyses and were excluded only in sensitivity analyses, with results compared with those of the full dataset to confirm robustness. All statistical analyses were univariate. Multivariate analyses were not performed because of the limited sample size and risk of model overfitting.

Results

Patient and treatment characteristics. Overall, our analyses included 16 patients newly diagnosed with supratentorial GBM, who were initiated on TTFields therapy (Table I). The mean age was 57.4±14.6 years (range: 19-80), with nine males and seven females. The Smirnov-Grubbs test was performed to identify outliers; however, no outliers were detected. Therefore, all cases were included in the analysis. The presenting symptoms included hemiparesis in three patients (18.8%), symptomatic epilepsy in three patients (18.8%), and motor aphasia in three patients (18.8%). The surgical resection status included seven cases of gross total resection (43.8%), five cases of subtotal resection (31.3%), and four biopsies (25.0%). The primary caregiver was a spouse in 11 cases

Table I. Patient and treatment characteristics (n=16).

Characteristic	Value
Age, years	
Mean ± SD (range)	57.4±14.6 (19-80)
Sex, n (%)	
Men	9 (56.3)
Women	7 (43.8)
Clinical symptom, n (%)	
Hemiparesis	3 (18.8)
Motor aphasia	3 (18.8)
Epilepsy	3 (18.8)
Higher brain dysfunction, n (%)	7 (43.8)
Attention impairment, n (%)	6 (37.5)
Resection status, n (%)	
GTR	7 (43.8)
STR	5 (31.3)
Biopsy	4 (25.0)
Caregiver, n (%)	
Spouse	11 (68.8)
Parent	2 (12.5)
Child	4 (25.0)
Sibling	1 (6.3)
Distance to the medical facility, km	
Mean ± SD (range)	20.4±17.0 (1.2-65.0)
TTFields treatment status	
Duration of TTFields, days,	
Mean ± SD (range)	199.5±206.5 (1-800)
Mean ± SD adherence rate, % (range)	58.5±26.5 (3-96.96)
Mean ± SD survival outcome, days (range)	
OS	484.9±234.1 (187-958)
PFS	397.0±203.9 (143-800)
ADL	
Mean ± SD KPS (range)	85.6±16.7 (50-100)
Mean ± SD Barthel Index (range)	88.9±22.5 (39-100)
≥85[a], n (%)	13 (81.3)

[a]A Barthel Index score of ≥85, which is generally considered the threshold for independence in ADL, was used as the cutoff value. The Smirnov-Grubbs test identified no outliers in the age distribution; therefore, all cases were included in the analysis. In two cases, the patients had multiple primary caregivers (spouse and child). Each caregiver type was counted separately, resulting in a total exceeding the number of participants. SD, standard deviation; GTR, gross total removal; STR, subtotal removal; TTFields, tumor-treating fields; OS, overall survival; PFS, progression-free survival; ADL, activities of daily living; KPS, Karnofsky performance status.

(68.8%), a parent in 2 cases (12.5%), child in 4 cases (25.0%), and sibling in 1 case (6.3%). In two cases, multiple primary caregivers were present (spouse and child); thus, each caregiver type was counted separately. The mean distance from the patient's residence to the hospital was 20.4±17.0 km (range: 1.2-65.0 km). The mean duration of TTFields therapy was 199.5±206.5 days. Early discontinuation, defined as cessation within 90 days without resumption, occurred in five patients (31.3%). The primary reason for early discontinuation was the preference of patients and their families. The mean adherence rate during treatment was 58.5±26.5% (range: 3-96.96), while the mean OS and PFS were 484.9±234.1 days and 397.0±203.9 days, respectively.

The molecular profiles obtained using a GBM-specific NGS panel were available for 12 of the 16 patients (75%). Among these, isocitrate dehydrogenase (IDH) 1/2 mutations were found in two cases, TP53 mutations in five cases, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α mutations in three cases, epithelial growth factor receptor amplification in two cases, and telomerase reverse transcriptase promoter mutations in six cases (C228T: four cases; C250T: two cases). According to the 2021 edition of the

WHO classification, the integrated diagnoses were as follows: 10 cases of GBM, IDH wild-type; 2 cases of astrocytoma, IDH mutant, grade 4; and 4 cases of GBM, not otherwise specified.

All ADL assessments were performed by a multidisciplinary team of rehabilitation professionals including physicians, physical therapists, occupational therapists, and speech-language pathologists. At the initiation of TTFields therapy, the mean Karnofsky performance status (KPS) was 85.6±16.7 (range: 50-100) and mean the Berthel index (BI) was 88.9±22.5 (range: 39-100). Thirteen patients (81.3%) had BI scores >85, which is generally considered indicative of ADL independence.

Neurocognitive function was evaluated by a multidisciplinary team including rehabilitation specialists (Table II). All patients underwent at least one assessment. The reasons for missing or incomplete examinations included patient refusal, inability to continue the assessment because of reduced endurance, and the examiner's judgment that the test was inappropriate. In some cases, the examiner determined that alternative higher-order cognitive assessments would be more suitable. However, these were not included in the current analysis because of sample size limitations. The tests included the Mini-Mental State Examination (MMSE) in 13 patients (81.3%), Frontal Assessment Battery (FAB) in 10 patients (62.5%), Trail Making Test (TMT) in 8 patients (50.0%), including 1 patient with only part A; and the Rey-Osterrieth Complex Figure Test (ROCFT) in 3 patients (18.8%). Mean scores (± standard deviation) were as follows: MMSE, 26.8±3.6; FAB, 14.6±4.2; TMT-A, 83.0±96.7 sec (four patients below age-based cutoff); TMT-B, 80.4±46.6 sec (two patients below cutoff); ROCFT copy score, 34.3±1.5; and memory score, 24.2±9.3. Therefore, seven patients (43.8%) were judged to have neurocognitive dysfunction, and six (37.5%) were considered to have attention impairment.

Table II. Neurocognitive test scores of patients treated with TTFields.

Neurocognitive test (n)	Score, mean ± SD (range)
MMSE (13)	26.8±3.6 (19-30)
FAB (10)	14.6±4.2 (5-18)
TMT	
Part-A (8)	83.0±96.7 (21.8-317)
Part-B (7)	80.4±46.6 (37.5-151)
ROCFT	
Copy (3)	34.3±1.5 (33-36)
Memory (3)	24.2±9.3 (13.5-30)

The reasons for missing or incomplete examinations included patient refusal, reduced endurance, and the examiner's judgment that the test was inappropriate. Some patients underwent alternative assessments; however, these were not included in the present analysis. MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; TMT, Trail Making Test; ROCFT, Rey-Osterrieth Complex Figure Test.

Comparative characteristics by cohort. A comparative analysis was conducted between the early discontinuation (n=5) and continuation (n=11) groups, focusing on clinical characteristics, TTFields treatment status, survival outcomes, and ADL (Table III). The mean duration of TTFields use was significantly shorter in the early discontinuation group than in the continuation group (46±29.7 days vs. 269.3±210.5 days; Mann-Whitney U test, P<0.001). Welch's t-test yielded consistent results (P=0.007). Outlier analysis identified two extreme values; however, when these cases were excluded (n=14), the difference remained statistically significant (t-test, P<0.001), confirming the robustness of our finding. No significant differences were observed in age, sex, or baseline characteristics between groups. Regarding the distance from the patient's residence to the hospital, Welch's t-test using the full dataset showed no significant differences between the groups (P=0.177). An outlier analysis identified one extreme value; however, when this case was excluded, the Mann-Whitney U test also indicated no significant difference (P=0.892), confirming that the presence of this outlier did not alter the interpretation. However, hemiparesis at TTFields therapy initiation (P=0.018) and attention impairment (P=0.036) was significantly more frequent in the early discontinuation group than in the continuation group. Regarding ADL, the early discontinuation group had significantly lower baseline KPS scores (P=0.005), with a trend similar trend to that observed for BI scores (P=0.013). No significant differences were observed in the overall neurocognitive test scores between the two groups. Regarding survival outcomes, OS was significantly shorter in the early discontinuation group [HR: 8.857, 95% confidence interval (CI): 1.56-50.29, P=0.004; Fig. 1A] than in the continuation group. Although the difference was not significant, PFS also tended to be shorter in the early discontinuation group (HR: 3.35, 95% CI: 0.83-13.59, P=0.073; Fig. 1B) than in the continuation group. Regarding molecular status, TP53 mutations tended to be more frequent in the treatment continuation group than in the early discontinuation group; however, this difference was not statistically significant (P=0.061). No differences were observed in the molecular profiles between the two groups (Table IV).

Discussion

This single-institution retrospective study identified hemiparesis, low baseline KPS, and attentional impairment as significant factors associated with the early discontinuation of TTFields therapy in patients with GBM. To the best of our knowledge, few studies have directly examined the predictors of early treatment termination, as most pivotal trials, including the EF-14 trial, have excluded patients who discontinued therapy within the first 2-3 months (5,6). Identifying factors that may predict early withdrawal after treatment initiation is essential to enable more appropriate patient selection and predict the need for treatment support interventions. Our findings provide novel insights into clinical characteristics that may hinder treatment persistence in real-world settings.

Previous studies have established that high adherence and prolonged TTFields use are strongly correlated with improved survival outcomes (5,6). In this study, the TTFields continuation group demonstrated a significantly prolonged OS and

Table III. Comparison of patient characteristics between cohorts.

Characteristic	Early discontinuation group (n=5)	Continued use group (n=11)	P-value
Age, years			
Mean ± SD (range)	60.6±11.3 (42-73)	56.0±15.5 (19-80)	0.607
Sex, n (%)			>0.999
Men	3 (60.0)	6 (54.5)	
Women	2 (40.0)	5 (45.5)	
Clinical symptom, n (%)			
Hemiparesis	3 (60.0)	0 (0.0)	0.018[a]
Motor aphasia	2 (40.0)	1 (9.1)	0.214
Epilepsy	1 (20.0)	2 (18.2)	>0.999
Higher brain dysfunction, n (%)	4 (80.0)	3 (27.3)	0.106
Attention impairment, n (%)	4 (80.0)	2 (18.2)	0.036[a]
Resection status, n (%)			
GTR	1 (20.0)	6 (56.3)	0.308
STR	2 (40.0)	3 (56.3)	>0.999
Biopsy	2 (40.0)	2 (56.3)	0.547
Caregiver, n (%)			
Spouse	5 (100)	6 (54.5)	0.119
Parent	0 (0.0)	2 (18.2)	>0.999
Child	1 (20.0)	3 (27.3)	>0.999
Other	0 (0.0)	1 (9.1)	0.509
Distance to the medical facility, km			
Mean ± SD (range)	21.2±10.9 (13-41)	20.1±19.3 (1.2-65)	0.335
TTFields treatment status			
Duration of TTFields, days,			
Mean ± SD (range)	46±29.7 (1-89)	269.3±210.5 (102-800)	<0.001[b]
Mean ± SD adherence rate, % (range)	55.5±33.8 (17-96.96)	59.6±25.5 (3-86.7)	0.800
Mean ± SD survival outcome, days (range)			
OS	303.2±93.9 (187-429)	567.5±227.4 (265-958)	0.004[a]
PFS	268.8±97.7 (143-381)	455.3±210.3 (265-800)	0.073
ADL			
Mean ± SD KPS (range)	66.0±15.1 (50-90)	94.5±6.9 (80-100)	0.005[b]
Mean ± SD Barthel Index (range)	65.8±30.7 (39-100)	99.5±1.3 (96-100)	0.013[a]
≥85[c], n (%)	2 (40.0)	11 (100)	0.018[a]

[a]P<0.05; [b]P<0.01; [c]A Barthel Index score of ≥85, which is generally considered the threshold for independence in ADL, was used as the cutoff value. SD, standard deviation; GTR, gross total removal; STR, subtotal removal; TTFields, tumor-treating fields; OS, overall survival; PFS, progression-free survival; ADL, activities of daily living; KPS, Karnofsky performance status.

favorable PFS. However, determinants of poor adherence and early treatment discontinuation remain largely unknown.

In this cohort, the presence of hemiparesis at the start of treatment may have contributed to treatment difficulties due to challenges in maintaining balance during movement and cognitive-motor interference when operating the device while walking. Previous studies examining the transport ability of patients with hemiparesis after stroke have reported a prolonged unloading phase and difficulties in maintaining posture during the transition from lifting to placing objects (10). Furthermore, in another study involving patients with chronic stroke, even those capable of walking short distance without assistive devices exhibited significant reductions in walking speed when performing simple cognitive and motor tasks, such as carrying water in a cup without a handle or walking while performing serial subtraction, likely due to cognitive-motor interference (11).

Similarly, impaired attention has been associated with difficulties in continuing TTFields treatment. Such deficits may reduce a patient's ability to comply with the complex routines required for effective TTFields. This observation aligns with previous reports showing that attention deficits are associated with reduced treatment adherence in patients with higher brain function disorders. Conditions characterized by attention deficit and executive dysfunction, such as attention-deficit hyperactivity disorder, are associated with impaired diabetes management and low treatment

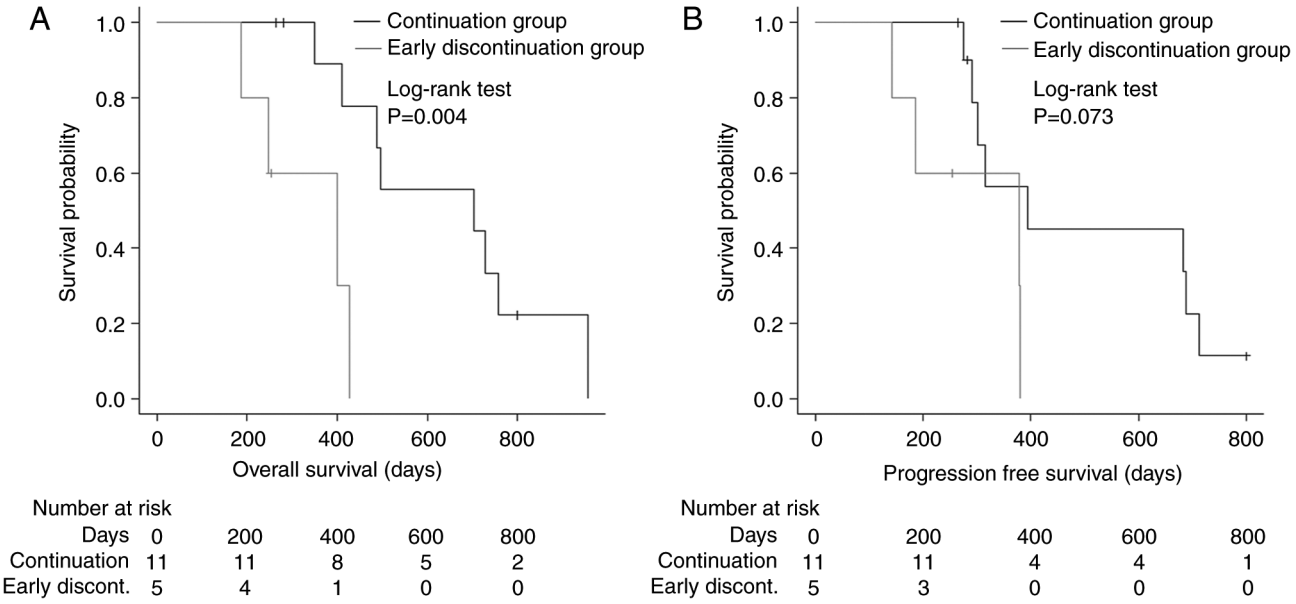

Figure 1. Kaplan-Meier curves comparing OS between early TTFields discontinuation and continuation groups. Kaplan-Meier survival curves comparing OS between patients who discontinued TTFields therapy early (early discontinuation group) and those who continued treatment (continuation group). The early discontinuation group included patients who discontinued TTFields within 90 days of initiation, whereas the continuation group included those who used TTFields beyond this period. Statistical differences between groups were assessed using the log-rank test. (A) The P-value for OS was P=0.004, (B) while that for PFS was P=0.073. Early discont., early discontinuation group; Continuation, continuation group; OS, overall survival; TTFields, tumor-treating fields.

adherence rates (12). Although the association between higher brain dysfunction and treatment adherence is well-established, evidence specific to wearable treatment devices remains limited. A review of continuous positive airway pressure, another wearable treatment device with results comparable to TTFields, reported that for patients with mild cognitive impairment and Alzheimer's disease, device setup and continued use require attention, memory, and executive function; moreover, support or caregiver involvement is important when adherence declines (13).

In this study, no significant differences were observed between the two groups in neurocognitive evaluation test score, which were associated with attention and executive function. This may be attributed to the small sample size, which prevented multivariate analysis from being performed. Therefore, our results should be interpreted with caution. In addition, the type of neuropsychological tests administered and the lack of data may have influenced our results. Nevertheless, these findings suggest that impaired attention may be an important factor that hinders the continuation of TTFields treatment.

In addition, molecular profiles were available for 12 of the 16 patients. A trend toward a higher frequency of TP53 mutations was observed in the continued use group, although the difference was not statistically significant. TP53 has been primarily investigated for its role in tumor proliferation, treatment responsiveness, and prognosis (14). To date, no direct association between TP53 mutations and functional indicators such as the KPS or the BI has been established. Moreover, reports on the prognostic significance of TP53 mutations in glioblastoma remain controversial (15). Given the limited sample size of our cohort, these findings should be interpreted with caution, and confirmation in large-scale studies is warranted.

A low baseline functional status, as reflected by KPS, likely compounded these difficulties, making sustained treatment less feasible. These findings are consistent with the inclusion criteria of the EF-14 trial, which required a KPS ≥70, and with the National comprehensive network guidelines, which recommend adjuvant treatment for patients with good performance status, defined as KPS ≥60 (16).

Our cohort did not include patients with sensory aphasia, as they have been reported to contribute to TTFields discontinuation. However, motor aphasia was not identified as a contributing factor in this study (17). These results may have been influenced by the limited sample size and should, therefore, be interpreted with caution.

These observations underscore the importance of early identification of patients at high risk of treatment discontinuation. In such cases, proactive interventions, including enhanced caregiver involvement, structured educational programs, and frequent follow-up visits to monitor device usage, are warranted. Moreover, comprehensive welfare support such as the provision of in-home nursing services, assistive devices, and transportation assistance may alleviate both physical and logistical barriers to treatment continuity. Integrating these supportive measures into standard clinical practice potentially improves adherence and thereby enhances therapeutic benefits, particularly in patients with neurological deficits or cognitive impairment.

This study had several limitations. The small sample size and single-center design limited the generalizability of our findings. The small cohort also reduced the statistical power of the analysis and may have resulted in unstable estimates of effect sizes. Therefore, our results should be interpreted as exploratory rather than confirmatory. The retrospective nature of this study may have introduced selection and information biases, and unmeasured confounding factors cannot be excluded. Neurocognitive assessments were not performed uniformly across all patients, and molecular profiling data were unavailable for a cohort subset. Furthermore, treatment

Table IV. Comparison of tumor molecular profiles between cohorts.

Molecular profile	Early discontinuation group (n=4)	Continued use group (n=8)	P-value
IDH1/2 mutation	0	2	0.515
TP53 mutation	0	6	0.061
PI3KCA mutation	0	3	0.491
EGFR amplification	2	1	0.236
TERT promoter mutation	3	3	0.545
C228T	2	2	0.547
C250T	1	1	>0.999

IDH, isocitrate dehydrogenase; PI3KCA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; EGFR, epidermal growth factor receptor; TERT, telomerase reverse transcriptase.

adherence and discontinuation may have been influenced by unmeasured psychosocial or socioeconomic factors that were not captured in this analysis. Despite these limitations, the consistency of the associations observed between functional deficits and early discontinuation suggests that these factors warrant further investigation. Future research should focus on validating these findings through larger, prospective, multicenter studies that incorporate standardized neurocognitive testing, comprehensive molecular profiling, and detailed psychosocial assessments to better elucidate the determinants of treatment persistence.

In conclusion, our findings highlight specific clinical features, including hemiparesis, attentional impairment, and reduced KPS status, which may predispose patients with GBM to early discontinuation of TTFields therapy. Addressing these challenges through targeted clinical and welfare support strategies may improve treatment persistence and maximize the survival benefits of TTFields. Future studies should explore the effects of these interventions on patient adherence and long-term outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author. The GBM-specific NGS panel data generated in the present study are not publicly available due to institutional and ethical restrictions imposed by the governance policy of the multicenter consortium but may be requested from the corresponding author.

Authors' contributions

KSu designed the study, collected and analyzed the clinical data, and drafted the manuscript. KSu, SN and JY confirm the authenticity of all the raw data. KSa, SN, RM, TS, YN and JY contributed to the study design, acquisition and analysis of clinical data, and critically reviewed the manuscript for important intellectual content. NH, TA, AT and RH were responsible for the acquisition and analysis of molecular data, and contributed to data interpretation. All authors read and approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the University of Occupational and Environmental Health (UOEH) (approval number: CR24-117). The glioblastoma-specific next-generation sequencing panel data used in the present study were obtained from a multicenter collaborative project approved by the Ethics Committee of Kagoshima University (approval no. 180104-Eki) and were additionally approved by the Ethics Committee of UOEH for participation as a collaborating site (approval no. UOEHCRB20-100). All procedures were performed in accordance with the ethical standards of the Institutional Research Committee and the 1964 Declaration of Helsinki and its later amendments. Patient participation consent was obtained through an opt-out procedure approved by the institutional ethics committee.

Patient consent for publication

Not applicable, as this study did not include any individual patient images or identifiable data requiring consent for publication.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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