Research Square

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Continuation of TTFields after recurrence in patients with glioblastoma may be associated with prolonged post-recurrence survival

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Abstract

Purpose

The efficacy of tumor-treating fields (TTFields) in newly diagnosed glioblastoma is established, but the benefit of continuing treatment after first recurrence remains unclear. This study evaluated the association between TTFields continuation and survival after recurrence.

Methods

This single-center retrospective cohort study included consecutive patients with newly diagnosed supratentorial glioblastoma who received TTFields between April 2018 and December 2025. TTFields were initiated with maintenance temozolomide after standard chemoradiation. At first radiographic progression, patients chose whether to continue or discontinue TTFields. Post-recurrence survival and overall survival from surgery were analyzed using the Kaplan–Meier method and Cox proportional hazards models. TTFields adherence (≥ 75% vs. <75%) was also evaluated.

Results

Of 39 TTFields-treated patients, three without recurrence and one with missing usage data were excluded, leaving 35 for analysis: 15 continued treatment after recurrence and 20 discontinued it. Baseline characteristics did not differ significantly between groups. Overall survival from surgery did not differ significantly (median, 35 vs. 20 months; $p = 0.104$), whereas post-recurrence survival was longer in the continuation group (median, 11 vs. 9 months; $p = 0.0434$). Survival did not differ significantly by adherence (≥ 75% vs. <75%). In multivariable Cox proportional hazards analysis adjusted for age, sex, and adherence, continued TTFields use remained associated with longer post-recurrence survival (adjusted hazard ratio, 0.376; 95% confidence interval, 0.150–0.943; $p = 0.0370$).

Conclusion

Continuing TTFields after first recurrence was associated with longer post-recurrence survival. This association persisted after adjustment for age, sex, and adherence, although the retrospective design and small sample size limit causal interpretation.

Introduction

As the most common primary malignant brain tumor, glioblastoma accounts for approximately half of these tumors [1]. Several new therapies, including immunotherapy and oncolytic virotherapy, have been investigated [2–4]. Nevertheless, prognosis remains poor, with median overall survival (OS) of only 15–18 months [1, 4, 5]. Standard treatment comprises maximal safe surgical resection followed by

radiotherapy with concurrent and adjuvant temozolomide (TMZ) [6]. Tumor-treating fields (TTFields) offer an additional treatment option during maintenance TMZ therapy.

In 2015, a pivotal phase III trial (EF-14) reported the efficacy of TTFields in newly diagnosed glioblastoma [7]. The interim and final analyses of EF-14 showed that adding TTFields to standard-of-care TMZ significantly prolonged survival [7, 8]. The survival benefit was independent of other prognostic factors. However, a multicenter retrospective cohort study in Japan found no significant improvement in progression-free survival or OS associated with TTFields use among patients with newly diagnosed glioblastoma [9]. Thus, the survival benefit of TTFields among patients with glioblastoma in Japan remains uncertain.

The efficacy of TTFields in recurrent glioblastoma was also evaluated in a pivotal phase III trial [10]. A trend toward longer survival was observed, although the OS difference was not statistically significant. A post hoc analysis of EF-14 suggested a possible survival benefit when TTFields were combined with second-line chemotherapy after first recurrence [11].

In Japan, TTFields are approved for newly diagnosed and recurrent glioblastoma. However, initiating TTFields at recurrence is not covered by public health insurance, whereas continuation after recurrence is permitted for patients who began TTFields for newly diagnosed glioblastoma. Nevertheless, the clinical significance of continuing TTFields after recurrence remains uncertain.

Therefore, we conducted a single-center retrospective pilot cohort study of patients with newly diagnosed glioblastoma who received TTFields to evaluate the association between treatment continuation after recurrence and post-recurrence survival.

Methods

Study design

This single-center retrospective observational study included all consecutive patients who initiated TTFields for newly diagnosed glioblastoma at our institution between April 2018 and December 2025. TTFields were administered in accordance with guidelines for adult patients with supratentorial glioblastoma who underwent maximal safe resection followed by radiotherapy with concomitant TMZ [12]. TTFields were initiated at the start of maintenance TMZ therapy. The study was approved by the Institutional Review Board of Kyoto University Hospital (No. R2088), which waived the requirement for informed consent because of the retrospective design.

Following initiation of maintenance TMZ therapy and TTFields, patients underwent magnetic resonance imaging (MRI) every several months to monitor for recurrence. Recurrence was defined using Response Assessment in Neuro-Oncology (RANO) criteria. At recurrence, patients could choose whether to continue or discontinue TTFields. Post-recurrence TTFields use was defined as continued treatment for

at least 1 month after recurrence. Among patients who continued TTFields, treatment was maintained until a second radiographic progression or clinical deterioration.

Evaluation of parameters

Baseline characteristics and initial treatment data were extracted from electronic medical records. Variables assessed at initial treatment included extent of resection, carmustine wafer placement, photodynamic therapy, and continuous steroid use. IDH mutation status and MGMT promoter methylation status were assessed using immunohistochemistry, followed by DNA sequencing and methylation analyses. At recurrence, assessments included Karnofsky Performance Status (KPS), salvage surgery, habitual steroid use, continuation of maintenance TMZ, re-irradiation, and treatment with bevacizumab or three-drug combination chemotherapy with ifosfamide, cisplatin, and etoposide (ICE therapy).

TTFields adherence data were extracted from each patient's device logs. Records spanning initial device activation to the last recorded use were analyzed to determine average usage over time. Mean monthly usage was calculated for the entire cohort. Electronic medical records were also reviewed for TTFields-related adverse events, including skin irritation, seizures, leukoencephalopathy, and wound dehiscence.

Statistical analysis

Patient characteristics in the continuation and discontinuation groups were summarized as median (range) or mean ± standard deviation for continuous variables, as appropriate, and counts for categorical variables. OS was defined as the time from initial surgery to death from any cause. Progression-free survival (PFS) was defined as the time from initial surgery to first MRI-confirmed radiographic progression or death from any cause, whichever occurred first. Post-recurrence survival was defined as the time from first MRI-confirmed radiographic progression to death from any cause. For OS and post-recurrence survival, patients without documented deaths were censored at the last date known to be alive. For PFS, patients without progression or death were censored at the last evaluable MRI. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test.

Normally distributed continuous variables were compared between groups using *t*-tests. Age and TTFields treatment duration were compared using the Mann–Whitney *U* test because their distributions were non-normal. KPS scores were compared using the Mann–Whitney *U* test because they are ordinal. Categorical variables were compared using Fisher's exact test. Multivariable Cox proportional hazards regression assessed the association between TTFields continuation after recurrence and post-recurrence survival, adjusting for age, sex, and TTFields adherence (≥ 75% vs. <75%).

All statistical tests were two-sided, with $p \leq 0.05$ considered statistically significant. Analyses were performed using R software for Windows (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

TTFields were administered to 39 patients with newly diagnosed glioblastoma. After excluding three patients without recurrence and one with missing TTFields usage data, 35 patients were included in the final analysis (Fig. 1). Of these, 15 continued TTFields after first progression, whereas 20 discontinued treatment. No deaths occurred within 1 month after recurrence in either group. Patient characteristics are presented in Table 1. Median age was lower in the continuation group (52 years; range, 28–74 years) than in the discontinuation group (64 years; range, 42–79 years), although the difference was not statistically significant (p = 0.137).

Table 1
Baseline characteristics of the study population

Total patients, n	**Continuation (n = 15)**	**Discontinuation (n = 20)**	***p* value**
	15	**20**	
Sex			0.312
Male	11	11	
Female	4	9	
Age, years, median (range)	52 (28–74)	64 (42–79)	0.137
Primary treatment			
GTR or STR	11	15	1.00
Carmustine wafer implantation	3	7	0.458
PDT	2	1	0.565
Steroid use	0	0	–
Tumor pathology			
IDH wildtype	15	20	–
MGMT promoter methylation	3	8	0.281
Tumor recurrence in eloquent area	6	5	0.467
Treatment after recurrence			
KPS, median (range)	80 (40–100)	80 (50–100)	0.476
Salvage surgery	5	4	0.451
TMZ	3	4	1.00
RT	11	17	0.430
BEV	14	18	1.00
ICE	12	16	1.00

Values are presented as median (range) for continuous variables and as number of patients for categorical variables. Range indicates the minimum and maximum values

*Statistically significant ($p < 0.05$)

BEV, bevacizumab; GTR, gross total resection; ICE, ifosfamide, cisplatin, and etoposide; IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Status; MGMT, O^6-methylguanine-DNA methyltransferase; PDT, photodynamic therapy; RT, re-irradiation; STR, subtotal resection; TMZ, continuation of maintenance temozolomide; TTFields, tumor-treating fields

Total patients, n	Continuation (n = 15)	Discontinuation (n = 20)	*p* value
	15	**20**	
Continuous steroid use	2	3	1.00
Duration of TTFields, months, median (range)	14 (6–41)	5.5 (0–73)	< 0.001*
TTFields adherence ≥ 75%	8	6	0.187
Adverse events during TTFields treatment			
Skin-related adverse events	8	9	0.738
Seizures	2	4	0.680
Leukoencephalopathy	0	1	1.00
Wound dehiscence	0	0	–
Values are presented as median (range) for continuous variables and as number of patients for categorical variables. Range indicates the minimum and maximum values			
*Statistically significant ($p < 0.05$)			
BEV, bevacizumab; GTR, gross total resection; ICE, ifosfamide, cisplatin, and etoposide; IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Status; MGMT, O^6-methylguanine-DNA methyltransferase; PDT, photodynamic therapy; RT, re-irradiation; STR, subtotal resection; TMZ, continuation of maintenance temozolomide; TTFields, tumor-treating fields			

At first recurrence, median KPS was 80 (range, 40–100) in the continuation group and 80 (range, 50–100) in the discontinuation group, with no significant between-group difference. Table 1 summarizes post-recurrence treatments by group. Use of re-irradiation, bevacizumab, and ICE therapy did not differ significantly between groups. Median total TTFields treatment duration was significantly longer in the continuation group than in the discontinuation group (14 vs. 5.5 months; $p < 0.001$).

Survival analysis

OS from initial surgery did not differ significantly between the continuation and discontinuation groups ($p = 0.104$; Fig. 2a), with median values of 35 and 20 months, respectively. In contrast, post-recurrence survival was significantly longer in the continuation group ($p = 0.0434$; Fig. 2b), with median values of 11 and 9 months, respectively. The median PFS was 15.0 months in the continuation group and 10.5 months in the discontinuation group ($p = 0.427$; Online Resource 1). A TTFields adherence rate of ≥ 75% has been reported as independently associated with improved OS in patients with glioblastoma [13, 14]. In our cohort, neither OS nor post-recurrence survival differed significantly by adherence (Fig. 2c, d). In Cox proportional hazards analysis adjusted for age, sex, and TTFields adherence (≥ 75% vs. <75%), continued TTFields use after recurrence remained significantly associated with longer post-recurrence

survival (Table 2). The adjusted hazard ratio was 0.376 (95% confidence interval, 0.150–0.943; p = 0.0370).

Table 2
Multivariable Cox proportional hazards regression analysis of post-recurrence survival

Variable	Category	Adjusted HR (95% CI)	*p* value
Sex			
Female	Reference	1	
Male		0.969 (0.442–2.12)	0.937
Age	Per 1-year increase	0.977 (0.947–1.01)	0.146
TTFields adherence	≥ 75% vs. <75%	1.05 (0.480–2.30)	0.904
TTFields after recurrence	Continuation vs. discontinuation	0.376 (0.150–0.943)	0.0370*
*Statistically significant (p < 0.05)			
CI, confidence interval; HR, hazard ratio; TTFields, tumor-treating fields			

Adverse events

Among 35 patients, skin-related adverse events requiring medication were recorded in 17 (49%). Seizures and leukoencephalopathy were recorded in six patients (17%) and one patient (2.9%), respectively. No wound dehiscence was observed.

Discussion

Although the EF-14 post hoc analysis suggested a potential survival benefit from continuing TTFields with second-line therapy after first progression, evidence supporting treatment beyond progression remains limited. European Association of Neuro-Oncology (EANO) guidelines recommend against continuing ineffective treatment after confirmed progression because clinical benefits have not been established [15]. Nevertheless, continuing TTFields beyond progression is not uncommon in clinical practice. In a Japanese multicenter cohort, 53 of 162 patients with recurrence (32.7%) continued TTFields for more than 2 months after recurrence [9]. Jelgersma et al. reported that 55% of patients with high-grade glioma continued TTFields beyond first recurrence in a real-world cohort, although their study focused on treatment use rather than survival benefits from continuation [16]. Dono et al. retrospectively evaluated 149 patients with IDH-wildtype recurrent glioblastoma, of whom 29 received TTFields at first recurrence [17]. Post-progression survival was numerically longer in patients receiving TTFields than in those who did not (13.9 vs. 10.9 months), but the difference was not statistically significant (p = 0.068). A significant association with survival was observed in the subgroup with PTEN-mutant tumors, suggesting that the benefit of TTFields in recurrent glioblastoma may vary with tumor biology. Together,

these real-world studies indicate that TTFields are frequently used at or beyond recurrence, although the survival benefit of continuation after progression remains uncertain.

In our cohort, continued TTFields use after first recurrence was significantly associated with longer post-recurrence survival, suggesting potential clinical benefit from treatment continuation despite tumor recurrence.

The prognosis of glioblastoma remains poor. Maximal safe surgical resection followed by the Stupp regimen of radiotherapy with concomitant and adjuvant temozolomide has remained standard care for nearly two decades. Over the past decade, TTFields have demonstrated survival benefits in patients with newly diagnosed glioblastoma. TTFields deliver alternating electric fields that disrupt mitosis and inhibit tumor cell proliferation [18–20].

In the pivotal phase III trial of TTFields in newly diagnosed glioblastoma (EF-14), median overall survival was 20.9 months with TTFields plus temozolomide versus 16.0 months with temozolomide alone [7, 8]. Survival benefits have also been reported in several studies, including meta-analyses, supporting the growing recognition of TTFields as a treatment for newly diagnosed glioblastoma [9, 21–25]. However, its efficacy in recurrent glioblastoma remains uncertain. In the first pivotal phase III trial (EF-11), TTFields did not significantly improve overall survival [10].

Nevertheless, some registry studies have suggested a potential survival benefit [13, 14, 26]. Although evidence remains limited, findings suggesting a benefit of TTFields in recurrent glioblastoma continue to emerge.

However, whether TTFields should be continued after first recurrence in patients with newly diagnosed glioblastoma remains unclear. In EF-14, patients could continue TTFields after first progression until second progression or for up to 24 months [7, 8]. A post hoc analysis of EF-14 suggested a potential survival benefit from continued TTFields use after recurrence [11]. Nevertheless, evidence remains limited. Continuation after first progression was permitted because TTFields may be associated with transient tumor enlargement before clinical benefit emerges [7, 8, 27]. A previous study of response patterns during TTFields therapy reported initial tumor enlargement followed by regression in some tumors [28]. These observations suggest a clinical rationale for continuing TTFields after first recurrence to allow for a delayed treatment response, although any survival benefit remains uncertain.

In our study, patients chose whether to continue or discontinue TTFields at first recurrence. TTFields could be continued until second progression without a predefined maximum duration, allowing assessment of outcomes associated with treatment continuation. We therefore examined the associations of TTFields continuation and other previously reported TTFields-related factors with survival.

Previous studies have reported an independent association between TTFields adherence and survival, with adherence ≥ 75% linked to significantly longer survival. In our cohort, patients were stratified by

adherence (≥ 75% vs. <75%) and TTFields continuation after recurrence. OS from surgery and post-recurrence survival were compared between groups. Cox proportional hazards regression showed that continuation remained significantly associated with longer post-recurrence survival after adjustment for age, sex, and adherence, whereas adherence itself was not significantly associated with survival. Thus, the association between continuation and post-recurrence survival persisted after statistical adjustment for adherence. The nonsignificant adherence-related survival findings may reflect the relatively low proportion of patients achieving ≥ 75% adherence in our cohort (40%) compared with previously reported rates of 44%–77% [8, 9, 14, 25, 26]. The small number of highly adherent patients may have reduced statistical power to detect a difference.

This study has some limitations. First, the retrospective design is susceptible to treatment selection bias and residual confounding. Defining TTFields continuation as treatment for at least 1 month after recurrence also raises the possibility of immortal time bias. Although no deaths occurred within 1 month after recurrence in either group, reducing concerns about bias from early deaths, patients with slower disease progression, better functional status, or greater treatment motivation may have been more likely to continue TTFields. Second, the small sample size limited statistical power and the number of covariates included in the multivariable analysis. Although patients in the continuation group were younger and age was included in the Cox model, adjustment for age, sex, and TTFields adherence could not exclude confounding by other prognostic factors, including MGMT promoter methylation status, performance status at recurrence, and subsequent treatments. Third, adherence was calculated over the entire treatment period, including post-recurrence use in the continuation group. Differences in adherence measurement periods and progression-related changes in adherence may complicate its use as an adjustment variable. Finally, this was a single-center study, and only 40% of patients achieved TTFields adherence ≥ 75%. Consequently, the findings may reflect institutional treatment patterns and may not generalize to other settings. Thus, our results suggest an association between TTFields continuation after first recurrence and longer post-recurrence survival but do not establish a causal treatment effect. Prospective studies are warranted to clarify the clinical benefits of continuing TTFields after first recurrence.

Conclusion

Continuing TTFields after first recurrence was associated with longer post-recurrence survival. This association remained statistically significant after adjustment for age, sex, and TTFields adherence. Given the retrospective, single-center design and small sample size, prospective studies are warranted to determine whether continuing TTFields after recurrence improves survival.

Declarations

Funding

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Competing interests

Yoshiki Arakawa reports grants from Philips, Otsuka, Chugai, Nihon Medi-Physics, Daiichi Sankyo, Stryker, Eisai, Japan Blood Products Organization, Ono Pharmaceutical, Taiho Pharma, Sumitomo Dainippon Pharma, Astellas Pharma, Incyte Biosciences, and Servier, and personal fees from Nippon Kayaku, Novocure, UCB Japan, Ono Pharmaceutical, Brainlab, Merck, Chugai, Eisai, Daiichi Sankyo, Carl Zeiss, Nihon Medi-Physics, and Stryker. The other authors have no relevant financial or non-financial interests to disclose.

Author contributions

STO and NS: protocol/project development, data collection, data analysis, manuscript writing. TM, EH-Y, HI, STA, MT and YM: data collection, manuscript editing. YA: project supervision, manuscript editing. All authors read and approved the final manuscript.

Data availability

The datasets generated and analyzed during the current study are not publicly available because of patient privacy but are available from the corresponding author on reasonable request.

Ethics approval

This study was approved by the Institutional Review Board of Kyoto University Hospital (No. R2088) and was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Consent to participate

The requirement for informed consent was waived by the Institutional Review Board of Kyoto University Hospital because of the retrospective nature of the study.

Consent to publish

Not applicable. This article does not contain any identifiable individual data or images.

Clinical trial number

Not applicable.

Acknowledgments

This study was presented as a poster at the 43rd Annual Meeting of the Japan Society for Neuro-Oncology, Yamagata, Japan.

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Figures

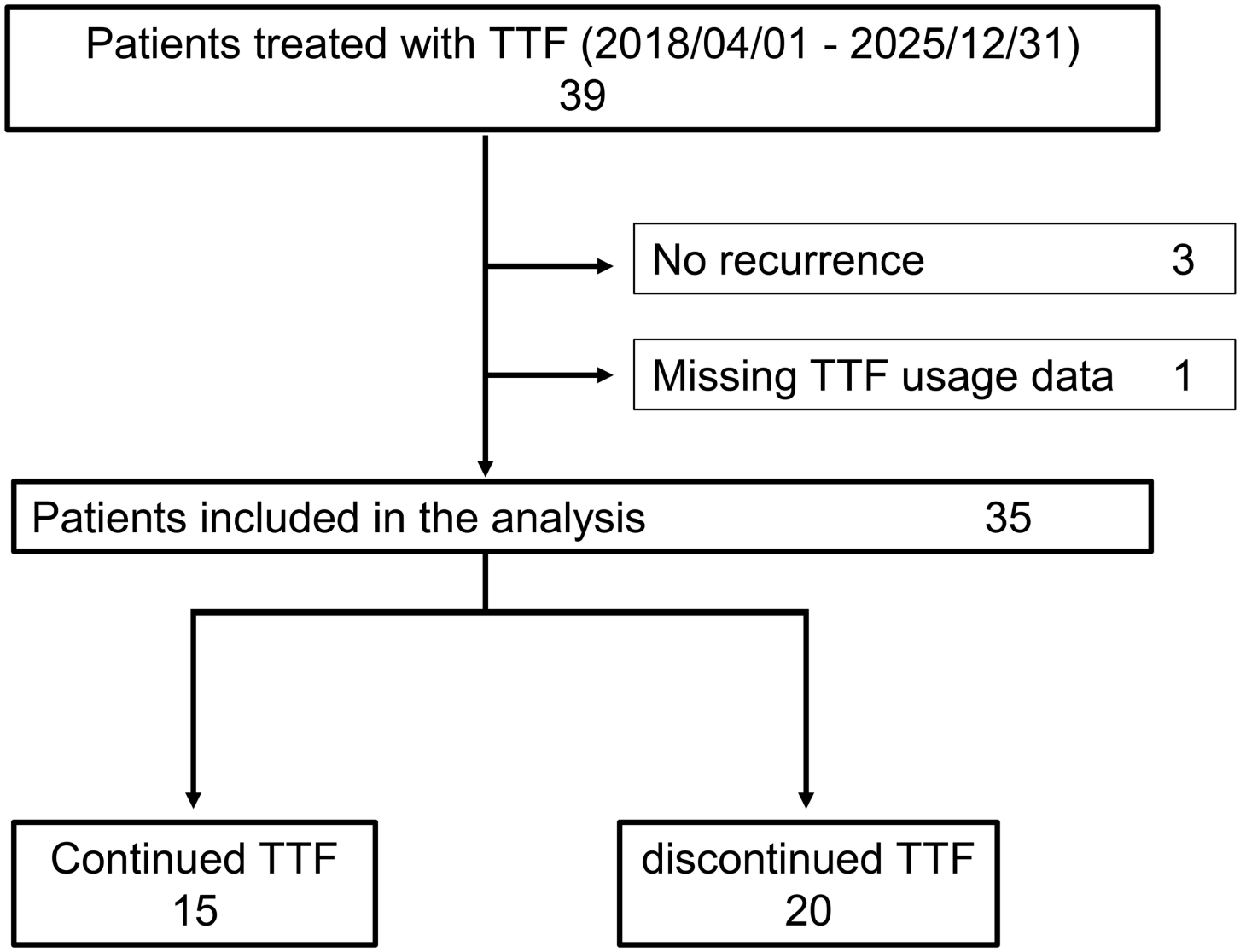


Figure 1

Flow diagram of patient selection. TTF, tumor-treating fields (TTFields)

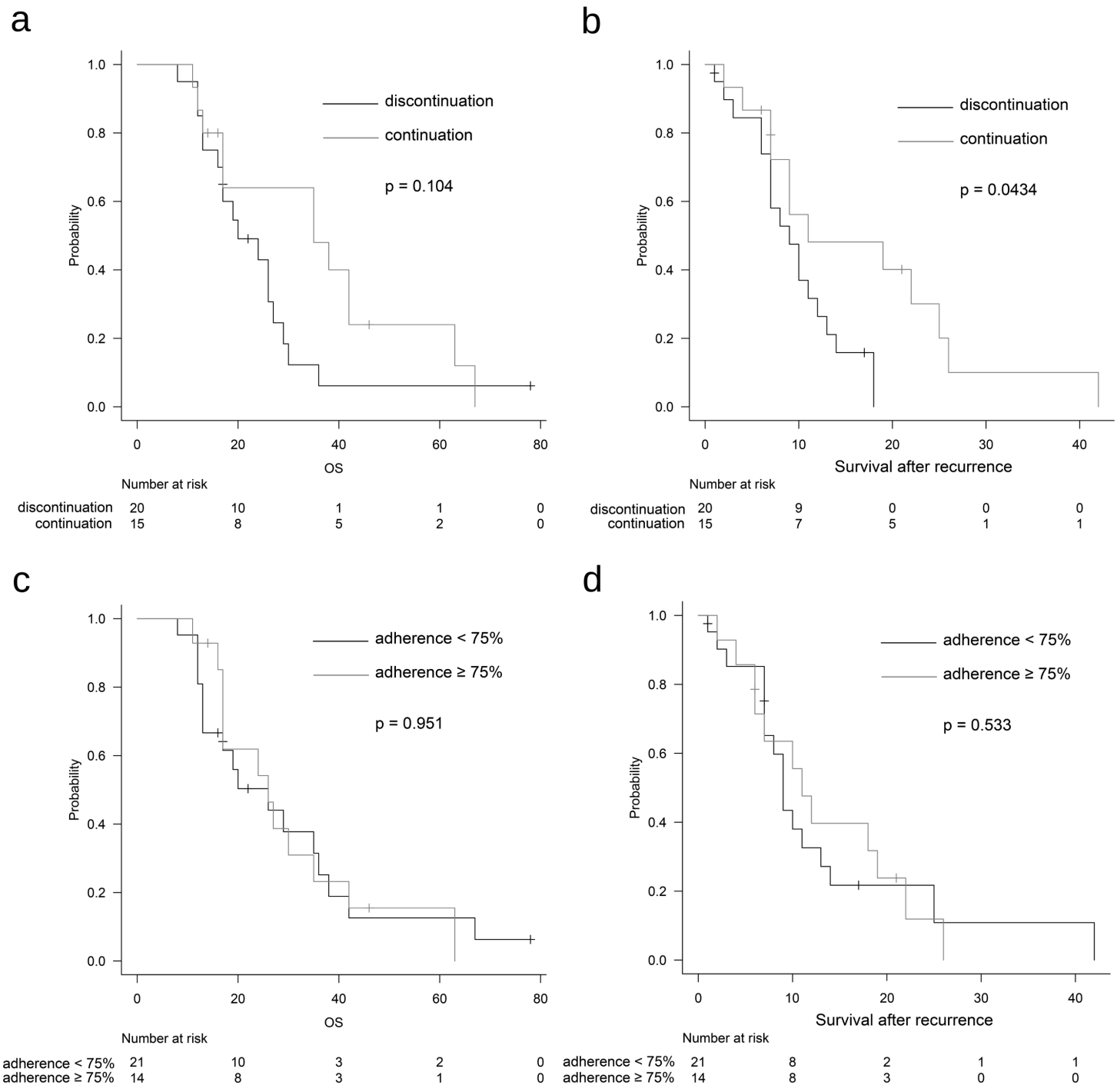


Figure 2

Kaplan–Meier survival curves for patients included in the final analysis. **a**Overall survival from initial surgery by tumor-treating fields (TTFields) continuation status. Median survival was 35 months in the continuation group and 20 months in the discontinuation group (p= 0.104). **b** Post-recurrence survival by TTFields continuation status. Median survival was 11 months in the continuation group and 9 months in the discontinuation group (p = 0.0434). **c** Overall survival from initial surgery by TTFields adherence (≥75% vs. <75%). Median survival was 26 months in both groups (p = 0.951). **d** Post-recurrence survival by TTFields adherence (≥75% vs. <75%). Median survival was 11 months in the ≥75% group and 9

months in the <75% group (p = 0.533). Time is shown in months; tick marks indicate censored observations; p values were calculated using the log-rank test. OS, overall survival

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ESM1.pdf