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RESEARCH

Long-term survival, patterns of progression, and patterns of use for patients with newly diagnosed glioblastoma treated with or without Tumor Treating Fields (TTFields) in a real-world setting

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Abstract

Purpose Tumor Treating Fields therapy (TTFields) is an FDA-approved locoregional treatment for patients with newly diagnosed glioblastoma (ndGBM). Previous trial data showed the addition of TTFields to standard TMZ-based therapy to significantly improve overall survival (OS), but real-world data is lacking, particularly with long follow-up duration. Here, we report real-world survival, patterns of progression, and patterns of use for patients for patients with ndGBM treated with or without TTFields.

Methods Patients diagnosed with GBM and treated with standard of care therapy at the Medical College of Wisconsin between March 2015–March 2023 were included. Survival outcomes were assessed and compared across groups who received or did not receive TTFields therapy during maintenance treatment. Patients were followed through March 1, 2024.

Results A total of 208 patients (TTFields: $n=109$; No-TTFields: $n=99$) were included for analysis. Baseline characteristics were consistent across groups. Median OS and PFS were significantly improved for the TTFields group vs. No-TTFields group (median OS: 21.7 vs. 17.7 months, $p=0.029$; median PFS: 12.4 vs. 9.6 months, $p=0.047$). Patients treated with TTFields exhibited a higher rate of non-local progression vs. No-TTFields group. Median OS and PFS were each significantly longer for the ≥ 75% usage group compared with < 75% via matched analysis.

Conclusion The results of this study reveal an association between TTFields use and long-term survival benefit, consistent with pivotal trial findings. TTFields use is associated with a higher incidence of non-local patterns of progression, and TTFields device usage ≥ 75% is associated with increased progression-free and long-term survival.

Keywords Tumor Treating Fields · Glioblastoma · Progression · Usage

Introduction

Glioblastoma (GBM) is the most common malignant tumor of the central nervous system (CNS), making up over 50% of all malignant CNS tumors [1]. Despite significant improvements in the field of neuro-oncology, overall survival (OS) for GBM remains low at a median 14–16 months with standard therapy and ~5% 5-year OS rate [2–4]. Molecular markers such as *Methylguanine methyltransferase* (MGMT) gene methylation are useful for prognostication of GBM wherein positive MGMT methylation prolongs OS [2, 5, 6]. Standard of care (SOC) includes maximal safe resection followed by radiotherapy (RT) with concurrent daily temozolomide (TMZ), followed by maintenance TMZ for 6 to 12 months [4, 7, 8]. Since the approval of TMZ for treatment of newly-diagnosed GBM, few randomized controlled trials have succeeded in identifying a similarly efficacious treatment modality [9, 10].

In 2015, the Tumor Treating Fields (TTFields) device was approved by the Food and Drug Administration (FDA) for treatment of patients with newly diagnosed GBM (ndGBM) [11]. TTFields delivers alternating electric fields to mapped brain regions via a portable battery-powered device with arrays that are placed on the surface of the scalp [12–14]. The alternating electric fields disrupt mitosis via several

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mechanisms, including disruption of the mitotic spindle, to arrest tumor cell growth and ultimately trigger apoptosis [15–19]. The pivotal phase III trial (EF-14) by Stupp et al. demonstrated that TTFields paired with SOC TMZ significantly prolonged median OS to 20.9 months and median progression-free survival (PFS) to 6.7 months compared to 16 months OS and 4 months PFS with TMZ alone independent of other factors [20]. A meta-analysis study published in 2023 corroborated these results in the clinical practice setting, finding significantly improved median OS from 17.4 months with SOC alone to 22.6 months with SOC plus TTFields [21].

A dose effect from using the TTFields device has been suggested from studies examining higher levels of device usage by the patient, as well as higher field intensities delivered to the tumor bed by the arrays [20, 22–24]. Post-hoc analyses of the pivotal trials in both newly diagnosed and recurrent GBM have shown that using the device at least 75% of the time, or 18 h on average out of a 24-hour period, is correlated with improved OS [20, 21, 25, 26]. Following a separate analysis of the EF-14 trial showing a link between higher TTFields dose and improved survival [22], further analyses of the spatial patterns of disease progression revealed that patients treated with TTFields and TMZ experienced more distant patterns of progression than patients treated with TMZ alone, and for TTFields-treated patients, normal brain areas that did not exhibit tumor progression received a higher dose of TTFields [24]. However, these effects have yet to be corroborated outside of the clinical trial setting.

After nearly a decade of the use of TTFields for the treatment of ndGBM, questions related to long-term survival benefit, patterns of progression, and the impact of device usage on survival outcomes in the real-world setting remain. Retrospective studies investigating these phenomena have been limited by the lack of sufficiently large patient populations and suitable granularity of data. The patient cohort at the Medical College of Wisconsin and Froedtert Hospital (MCW-FH) is one of the largest, single-institution datasets of TTFields users in the United States, which makes it an ideal cohort to evaluate TTFields in the clinical setting. This study aims to investigate real-world survival, patterns of progression, and patterns of device use across a large cohort of patients with ndGBM treated with or without TTFields.

Methods

Patient characteristics and data collection

All patients included in this retrospective study were diagnosed and treated for GBM at MCW-FH. Data was collected in accordance with local IRB approval to ensure patient privacy and safety. Consecutive patients with supratentorial ndGBM who were treated with SOC therapy between March 2015 and March 2023 were included for analysis. SOC consisted of concurrent radiotherapy with TMZ followed by maintenance TMZ with or without the addition of TTFields therapy, which became part of the SOC regimen at our institution in 2015, following results of the EF-14 study. All patients were counseled about TTFields, and those that declined were included in the control group. Further criteria for cohort selection included completion of TMZ-based chemoradiotherapy and initiation of maintenance TMZ (minimum 1 cycle). A minimum 30 days of device use was required for the TTFields group. Grade 4 GBM diagnosis was confirmed histologically in all but four patients. Molecular criteria were met in three of these four patients, leaving one patient in the combined cohort (in TTFields group) with IDH-wildtype astrocytoma grade 3. Demographic, tumor, and treatment characteristics were collected for all patients and survival outcomes were assessed. Patients were followed through March 1, 2024.

Progression pattern assessment

Local and distal (non-local) patterns of tumor progression were identified from manual review of baseline and follow-up MRI scans at the time of first documented progression. Local progression was defined as contiguous enhancement with the baseline lesion or enhancement within the T2 FLAIR region of vasogenic edema associated with the baseline lesion. Non-local sites of progression were defined as regions of non-contiguous enhancement in distinct anatomic locations relative to the baseline lesion: distant lesion in same hemisphere, contralateral hemisphere, leptomeningeal disease, and posterior fossa. Location of progression was documented for all cases of radiographic progression in each treatment group.

Assessment of TTFields use patterns

TTFields device usage information was extracted from the device log files of each patient. For quantifying the average rate of usage over time, the time period between when a patient first turned the device on and when the device was last operated served as the source of usage data. Average usage for each treatment month was calculated across the cohort. For quantifying the level of device usage for each patient, the average monthly usage was calculated over the first 12 months of treatment, unless otherwise specified.

Statistical analysis

Overall survival was measured from the date of diagnosis to the date of patient death or last known contact. PFS was measured from the date of diagnosis to the date of disease progression or death, whichever occurred first, or last known contact. Medians and rates of survival were compared between groups using the Kaplan-Meier method with Cox proportional hazards model. P values were calculated and $P<0.05$ was considered statistically significant. Propensity score matching and multivariate Cox regression were utilized where indicated to control for confounders between groups. Differences in categorical variables at baseline were evaluated using chi-squared or Wilcoxon tests for proportions or continuous variables, respectively. Differences in the rates of non-local progression were conducted using a chi-squared test.

Table 1 Patient, tumor, and treatment characteristics by cohort

Characteristic	TTFields ($n=109$)	No TTFields ($n=99$)
Age, y		
Median (range)	60 (27–86)	64 (28–88)
Sex		
Men	62 (57)	56 (57)
Women	47 (43)	43 (43)
Tumor grade/histology		
Grade 4	108 (99)	99 (100)
Tumor presentation		
Multifocal disease	6 (6)	3 (3)
Frontal	35 (32)	32 (32)
Occipital	6 (6)	4 (4)
Parietal	20 (18)	20 (20)
Temporal	26 (24)	31 (31)
Frontoparietal	5 (5)	2 (2)
Frontotemporal	3 (3)	0 (0)
Temporal-occipital	2 (2)	1 (1)
Temporal-parietal	3 (3)	4 (4)
Parieto-occipital	3 (3)	2 (2)
IDH1 Status		
Mutated	6 (6)	3 (3)
Wildtype	102 (94)	92 (93)
Unknown	1 (1)	4 (4)
MGMT promoter methylation status		
Methylated	37 (34)	31 (31)
Unmethylated	44 (40)	47 (47)
Unknown	28 (26)	21 (21)
Resection status		
Gross total resection	46 (42)	34 (34)
Sub-total resection	51 (47)	59 (60)
Biopsy	12 (11)	6 (6)
Maintenance TMZ		
Median cycles (range)	7 (1–65)	5 (1–27)
TTFields therapy duration		
Median (range), months	6.8 (1–94)	-

Results

Patient and treatment characteristics

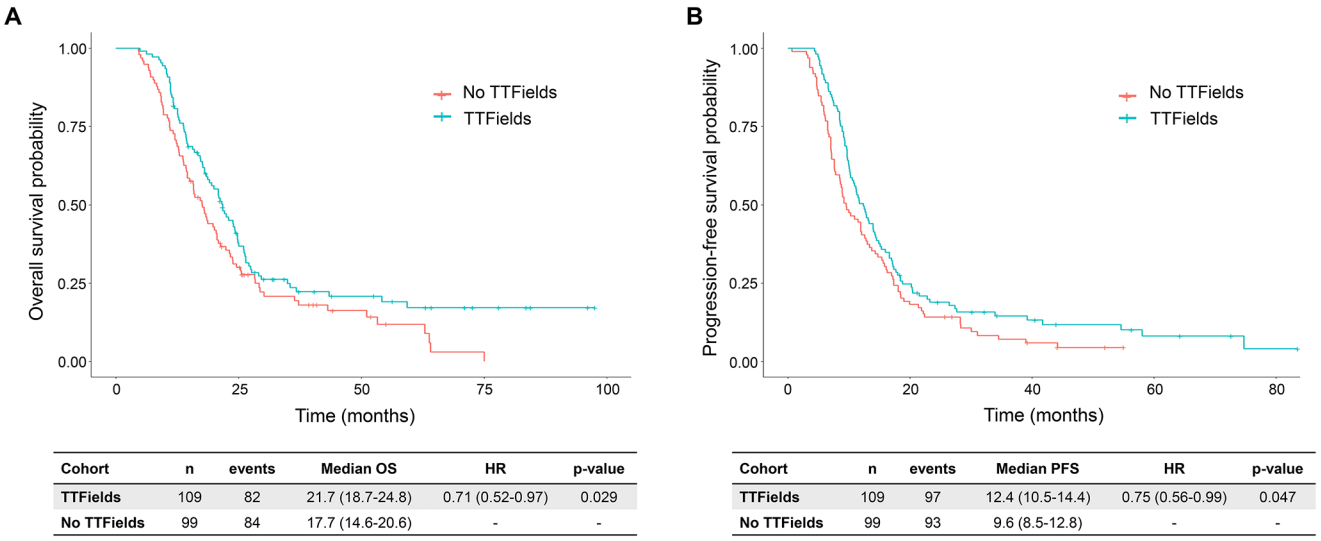
Between March 2015 and March 2023, 231 patients were diagnosed at our institution and treated for GBM. Of those patients, 214 patients completed concurrent radiotherapy with TMZ and initiated maintenance TMZ treatment with or without TTFields therapy. The TTFields group comprised patients who received TTFields for a minimum of 30 days ($n=109$), whereas the non-TTFields group comprised patients who did not receive TTFields at all in their first-line treatment ($n=99$).

Patient demographics, tumor, and treatment characteristics for the TTFields and non-TTFields groups are shown in Table 1. Baseline characteristics were balanced between groups, not accounting for subgroups with missing MGMT promoter methylation or isocitrate dehydrogenase (IDH) mutational status. The median age for the TTFields group was 60 and for the non-TTFields group was 64. The male to female ratio was equal between groups. The proportions of patients having gross total resection and biopsy were slightly higher in the TTFields group. The median number of TMZ cycles was 7 in the TTFields group and 5 in the non-TTFields group.

Survival outcomes

Overall survival for patients in the TTFields group was significantly improved over patients in the non-TTFields group (HR: 0.71 (0.52–0.97), $p=0.029$; Fig. 1a). Median OS was 21.7 months (95% CI 18.7–24.8) for the TTFields group and 17.7 months (14.6–20.6) for the Non-TTFields group, with 5-year OS rates of 17% (95% CI 11–28) and 12% (95% CI 6–23), respectively. Multivariate analysis showed treatment with TTFields to have a significant effect on OS when adjusting for known prognostic factors including age, gender, IDH mutational status, MGMT methylation status, and extent of resection ($p=0.017$). PFS was also significantly improved for the TTFields group compared with the non-TTFields group ($p=0.047$; Fig. 1b), but the difference was not found to be significant when adjusting for known prognostic factors ($p=0.069$). Median PFS was 12.4 months (95% CI 10.5–14.4) for the TTFields group and 9.6 months (95% CI 8.5–12.8) for the non-TTFields group.

To understand the profile of patients surviving ≥2 years and assess factors predisposing patients to living longer, we examined patient characteristics for the two treatment groups (Table 2). As expected, median age was lower and IDH-mutant status, MGMT-methylation status, and gross total resection were higher for both treatment groups. No significant differences were noted between TTFields-treated



Cohort	n	events	Median OS	HR	p-value
TTFields	109	82	21.7 (18.7-24.8)	0.71 (0.52-0.97)	0.029
No TTFields	99	84	17.7 (14.6-20.6)	-	-

Cohort	n	events	Median PFS	HR	p-value
TTFields	109	97	12.4 (10.5-14.4)	0.75 (0.56-0.99)	0.047
No TTFields	99	93	9.6 (8.5-12.8)	-	-

Fig. 1 Overall (**A**) and progression-free survival (**B**) for patients by TTFields therapy cohort

Table 2 Patient characteristics and survival among subgroup surviving 2 years or longer

	TTFields ($n=40$)	No TTFields ($n=28$)
Patient and treatment characteristics among 2-year survivors		
Age, y		
Median (range)	57 (29–75)	56 (28–83)
Sex		
Men	23 (58)	14 (50)
Women	17 (43)	14 (50)
Multifocal disease	2 (5)	0 (0)
IDH1 Status		
Mutated	6 (15)	3 (11)
Wildtype	34 (85)	24 (86)
Unknown	0 (0)	1 (4)
MGMT promoter methylation status		
Methylated	19 (48)	13 (46)
Unmethylated	13 (33)	12 (43)
Unknown	8 (20)	3 (11)
Resection status		
Gross total resection	17 (43)	15 (54)
Sub-total resection	20 (50)	13 (46)
Biopsy	3 (8)	0 (0)
Maintenance TMZ		
Median cycles (range)	12 (1–65)	12 (1–27)
≥6 cycles	36 (90)	21 (75)
TTFields therapy duration		
Median (range), months	13.1 (1.6–93.8)	-
≥6 months	34 (85)	-
Survival outcomes for patients surviving≥2 years		
Death events, n	20	17
OS, additional 2 years, % (CI)	51 (36–70)	52 (35–78)
OS, additional 3 years, % (CI)	42 (27–64)	38 (21–69)
OS, additional 4 years, % (CI)	42 (27–64)	9 (2–57)

and non-TTFields-treated patients across factors we evaluated. Survival curves are shown in Supp. Figure 1. For the TTFields-treated patients surviving > 5 years ($n=9$), 4 were still on treatment at the time of data cutoff and 6 had IDH-wildtype tumors.

Patterns of progression

Spatial patterns of tumor progression were radiologically assessed for each treatment group. The rate of non-local progression was significantly higher for the TTFields group compared with the non-TTFields group (28% vs. 14%, $p=0.028$), and the difference was significant on multivariate analysis when adjusting for other prognostic factors ($p=0.031$) (Fig. 2a). Progression in the contralateral hemisphere was the most frequent type of non-local progression for TTFields patients, followed by distal progression within the same hemisphere (Fig. 2b). Rates of non-local progression subtypes were numerically higher for TTFields-treated patients across categories, but samples were too small to compare statistically. Examples of non-local, intraparenchymal patterns within the TTFields cohort are shown in Fig. 2c.

Patterns of device use with TTFields therapy

To better understand how patients in the TTFields group complied with using their device, a temporal analysis of device usage rate was conducted. A total of 108 patients treated with TTFields had device usage data available for analysis. Across the cohort, the average rate of device usage was maintained over time and did not diminish with prolonged use (Fig. 3a). Instances of usage rate declines were transient in nature. A period of sustained usage decline was

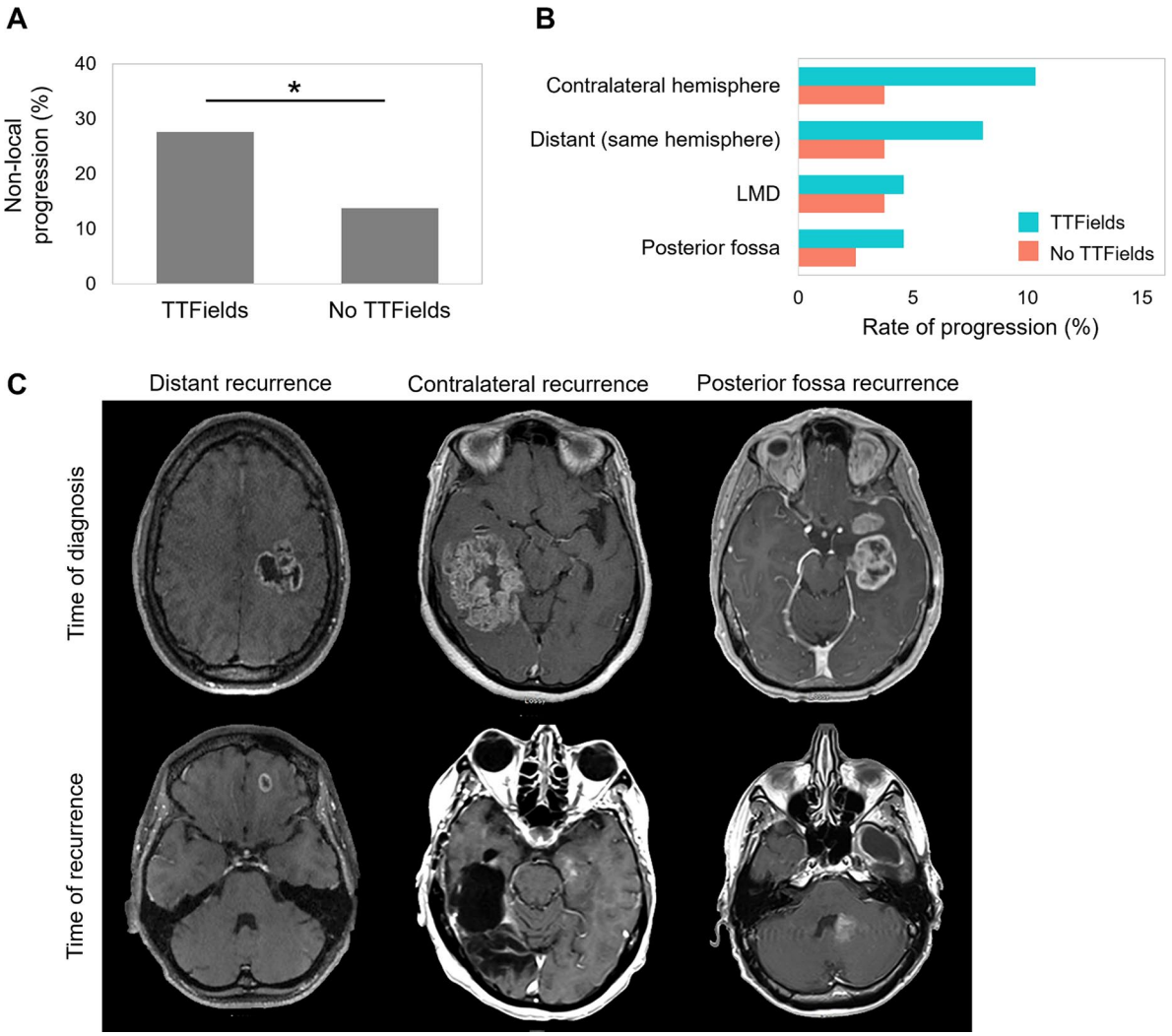


Fig. 2 Spatial pattern of progression for patients by TTFields therapy cohort. Rate of non-local progression overall (**A**) and by anatomic location (**B**), with example patterns shown for TTFields-treated cohort (**C**)

observed during the immediate 4 months following treatment start but recovered thereafter. Usage rates were similarly found to be maintained over time for both long- and short-term users of the device (Fig. 3b), with the average rate of usage higher for the ≥2-year users compared with the <2-year group. Transient drop-offs in usage were more pronounced at month 13 and month 19 in the <2-year and ≥2-year groups, respectively. When examining the association of usage and duration more closely, the duration of treatment with TTFields was found to increase in a graded manner with higher rates of usage (Supp. Figure 2).

To further examine the impact of device usage on patient outcomes in a real-world setting, survival was evaluated across high and low usage groups. A usage threshold of 75% (average use of 18 h per day) was applied as it is a common usage target for patients and was evaluated in previous trial settings [20, 25]. Approximately half the patients in the TTFields cohort had an average usage level of 75%. Due to the high usage rates observed among patients with IDH-mutant tumors in our cohort, usage groups were restricted to IDH-wildtype patients to avoid bias in the analysis of survival. Upon initial inspection, OS and PFS did not significantly differ between patients in the ≥75% and <75% groups (Fig. 3c and Supp Fig. 3a), with only a trend of increased OS and PFS for the high usage patients. However, baseline characteristics were not balanced between the cohorts and missingness in MGMT methylation status remained (Supp Table 2). With propensity score matching applied to match the usage cohorts on known prognostic factors, OS and PFS were each significantly longer for the ≥75% group compared with the <75% group (HR(OS): 0.46 (0.26–0.82), $p=0.008$; HR(PFS): 0.51 (0.30–0.85); $p=0.011$) (Fig. 3d and Supp Fig. 3b). The effect remained significant on multivariate analysis when adjusting for the same covariates used for matching.

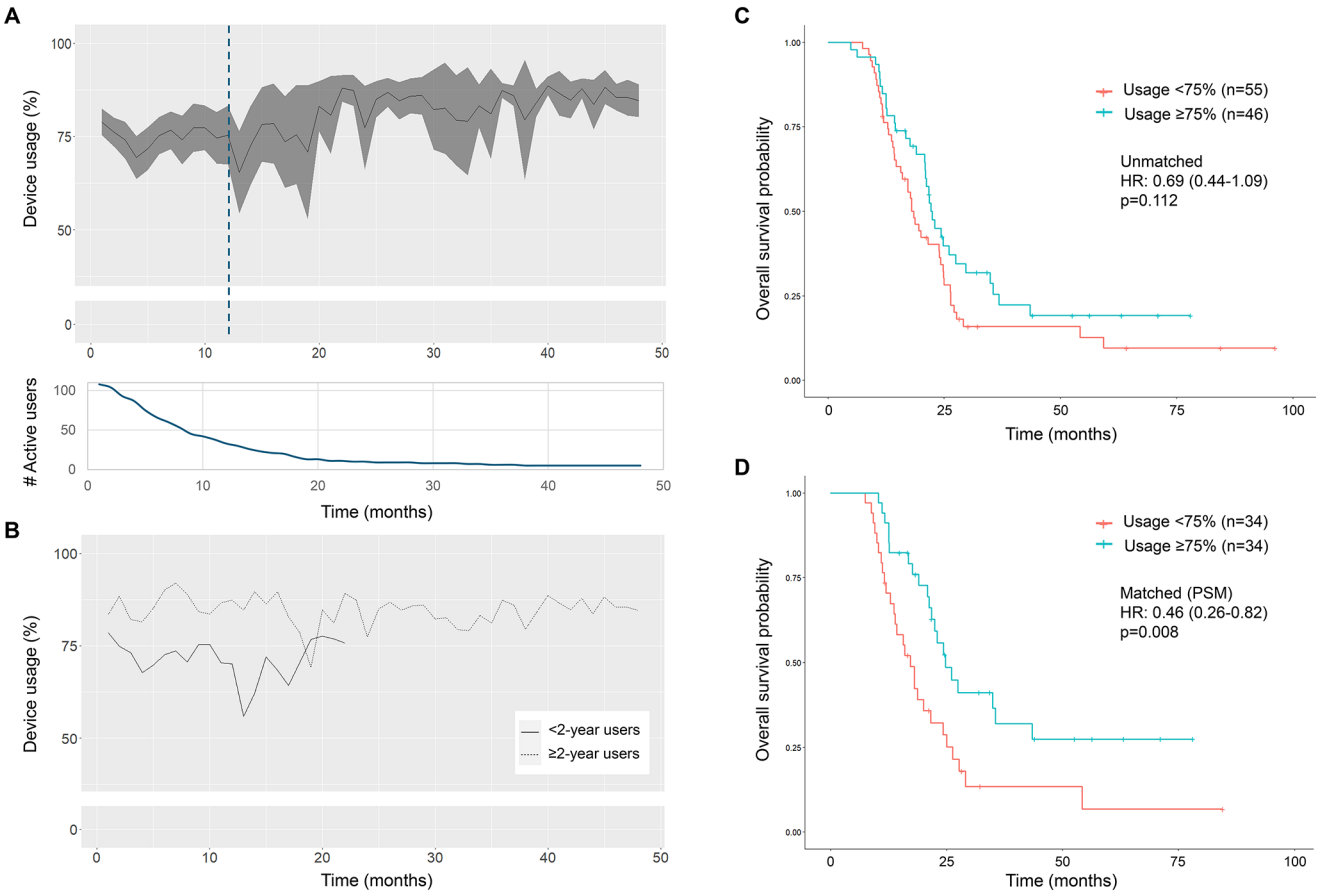


Fig. 3 Patterns of TTFields device usage and correlation with overall survival. Device usage rate overall (**A**) and by length of TTFields therapy use (**B**). Overall survival for IDH-wt patients by usage level from unmatched (**C**) and propensity-score matched (**D**) cohort analysis

Discussion

As experience with TTFields therapy for ndGBM has increased over the past decade, understanding the real-world treatment patterns and outcomes associated with using this device are necessary for informed treatment decision-making. From retrospective analysis of a large real-world cohort of patients with GBM, this study provided complementary evidence to the pivotal trial results of Stupp et al., in which the addition of TTFields therapy to SOC led to increased OS and PFS over SOC alone [11]. In our study, treatment with TTFields was found to significantly improve OS for patients with ndGBM compared to treatment with SOC alone, with durable long-term survival benefit that did not appear to depend on known GBM prognostic factors. Additionally, this study revealed correlations between higher usage and prolonged OS and PFS, as well as an association of more distal patterns of disease recurrence with TTFields treatment, the first time being demonstrated in a real-world GBM population.

As a loco-regional modality, a higher degree of tumor control might be expected with use of the device. Indeed, results of this study are consistent with post-hoc analysis of the EF-14 trial showing a reduced incidence of local failure among patients receiving treatment with vs. without TTFields. However, regional differences among types of non-local recurrence have been less clear, such as differentiating between same-hemisphere recurrence versus contralateral hemisphere recurrence versus recurrence in the posterior fossa [24]. In our study, we show that patients treated with TTFields and SOC are significantly more likely to experience non-local progression, with incidence higher across all region categories and measurable increases in contralateral and distal progressions within the same hemisphere. Interestingly, while some studies have suggested a potential relationship with OS and more distal forms of progression [24, 27], we did not observe a difference in survival between patterns of progression. This lack of observed difference may be due to sample size limitations and/or the presence of additional confounding factors, although in general more work is needed to further understand the relationship between patient outcomes and spatial-temporal patterns of disease progression within the brain.

Our results for device usage are also in alignment with previous studies [20, 21, 25, 26]. Usage ≥ 75% significantly prolonged OS and PFS after propensity score matching was applied to match the usage cohorts on known prognostic factors. Furthermore, the temporal trends in device usage we observed suggest subjective user experiences with the device that affect percent daily usage and likelihood of continuation. Overall, we did not observe a decline in the average usage rate over time; rather, the average device usage rate was sustained, and generally correlated with treatment duration. The period of sustained decline during the immediate 4 months following treatment start may partly reflect patients who discontinued TTFields early in their treatment course, as reduced levels of device usage can often precede discontinuation. Tumor response to TTFields develops slowly; patients who terminated TTFields use after a short period of time may not have experienced an OS benefit [28], although the minimum duration of TTFields treatment to achieve clinical benefit remains unknown. The transient drop-offs in usage at month 13 and month 19 in the < 2-year and ≥ 2-year groups may be associated with clinical decline or patient preference associated with disease recurrence.

In the subgroup of patients surviving > 5 years, all 9 patients had a device usage rate > 50%, with 5 patients > 75%. Six of these patients were progression-free for > 4 years. Previous results from EF-14 showed OS to be incrementally improved with higher rates of usage, with maximal survival benefit observed for patients with average usage rates > 90% [23]. Further analysis could compare these patients to others with similar long-term survival, though this analysis would likely be limited by a small cohort. This leaves the potential for a multi-institution retrospective analysis of long-term survivors on TTFields.

There remains a need to understand the clinical limitations to TTFields. Treatment with TTFields does not increase toxicities associated with other cancer treatments [29] or significantly impair quality of life [30]. There are few complications caused by TTFields other than mild-to-moderate skin irritation at the site of array placement [11, 20], yet some patients report low usage rates or will discontinue device usage within a year of starting therapy. Since the approval of TTFields, multiple studies have helped clarify treatment planning and skin management best practices [31–33]. Despite these efforts, barriers to effective use of the device continue to exist, and may include convenience, mobility issues, subjective discomfort, and limitation of daily activities (i.e., swimming). These barriers may share commonality with patient-reported reasons for declining treatment with TTFields [34]. To better understand the sources of usage variability, future studies can consider collecting objective measurement of device usage fluctuations in relationship to routine interventions (i.e., clinic visits, MRIs), clinical condition, or subjective patient data on reasons for < 75% usage and/or device termination.

This study is not without limitations. Generally, prospective studies with randomized designs yield stronger results than retrospective cohort studies. To limit the potential for patient selection biases across comparative groups, we utilized multivariate regression and propensity score matching to help control for confounding variables. Also, while our cohort represents the largest single institution analysis of TTFields to date [35], a larger cohort size may have permitted more in-depth analyses of progression pattern subtypes, particularly for the rarer leptomeningeal disease and posterior fossa recurrence, as well as analysis of outcomes across multiple usage thresholds and dose metrics. Finally, while our study followed patients between March 2015 to March 2023, there still remains a subset of patients who have yet to experience recurrence, particularly patients whose disease was diagnosed within a year of the end of analysis. Longer follow-up would provide additional insight both into long-term patterns of disease recurrence > 10 years and allow for additional data on patterns of recurrence in recently-diagnosed patients.

Conclusion

Analysis of patients from a large single institutional dataset reveals an association between TTFields use and long-term survival benefit, consistent with pivotal trial findings. TTFields use is associated with a higher incidence of non-local patterns of progression. TTFields device usage ≥ 75% is associated with increased progression-free and long-term survival when controlled for prognostic factors between cohorts. Future studies can consider further analyzing subtypes of non-local progression and subjective patient experiences that lead to < 75% device usage or early discontinuation.

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Author contributions DCR led writing of main manuscript text and was jointly accountable for acquisition of data. BLB was jointly accountable for acquisition of data. PC contributed to writing of main manuscript text, was jointly accountable for analysis of data, and prepared figures. GC was jointly accountable for analysis of data and prepared figures. JMC was primary investigator and oversaw all elements of the study. All authors reviewed the manuscript.

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Data availability Data is provided within the manuscript or supplementary information files.

Declarations

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Institutional Review Board (IRB) approval was granted by the Ethics Committee of the Medical College of Wisconsin (11/11/2019, PRO00036224).

Consent to participate and publish Participant consent was waived per IRB. De-identified data was used for analysis and all participants remain de-identified in the body of the manuscript and figures.

Competing interests Authors Patrick Conlon and Gordon Chavez are current employees of Novocure Inc. Jennifer M. Connelly recently served on a Physician Advisory Panel for Novocure. Devon C. Riegel, and Britta L. Bureau declare they have no financial interests.

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