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Tumor-Treating Fields for the treatment of glioblastoma: a systematic review and meta-analysis

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Abstract

Background. Tumor-Treating Fields (TTFields) is an emerging treatment modality for glioblastoma (GBM). Studies have shown a good safety profile alongside improved efficacy in newly diagnosed GBM (ndGBM), while a less clear effect was shown for recurrent GBM (rGBM). Despite regulatory support, sectors of the neuro-oncology community have been reluctant to accept it as part of the standard treatment protocol. To establish an objective understanding of TTFields' mechanism of action, safety, efficacy, and economical implications, we conducted a systematic literature review and meta-analysis.

Methods. A systematic search was conducted in PubMed, Scopus, and Cochrane databases. Twenty studies met the pre-defined inclusion criteria, incorporating 1636 patients (542 ndGBM and 1094 rGBM), and 11 558 patients (6403 ndGBM and 5155 rGBM) analyzed for the clinical outcomes and safety endpoints, respectively.

Results. This study demonstrated improved clinical efficacy and a good safety profile of TTFields. For ndGBM, pooled median overall survival (OS) and progression-free survival (PFS) were 21.7 (95%CI = 19.6-23.8) and 7.2 (95%CI = 6.1-8.2) months, respectively. For rGBM, pooled median OS and PFS were 10.3 (95%CI = 8.3-12.8) and 5.7 (95%CI = 2.8-10) months, respectively. Compliance of ≥75% was associated with an improved OS and the predominant adverse events were dermatologic, with a pooled prevalence of 38.4% (95%CI = 32.3-44.9). Preclinical studies demonstrated TTFields' diverse molecular mechanism of action, its potential synergistic efficacy, and suggest possible benefits for certain populations.

Conclusions. This study supports the use of TTFields for GBM, alongside the standard-of-care treatment protocol, and provides a practical summary, discussing the current clinical and preclinical aspects of the treatment and their implication on the disease course.

Keywords

alternating electric fields | glioblastoma | meta-analysis | systematic review | Tumor-Treating Fields

Glioblastoma (GBM) is the most common primary malignant brain tumor among adults, accounting for 46% of malignant CNS tumors, with an annual incidence rate of ~3.2 per 100 000.[1,2] In the last two decades, there has been some progress in understanding the pathophysiology and molecular background of the disease, however, modest advances were made in GBM treatment, and it remains an incurable and aggressive disease with a bleak prognosis. Current standard-of-care protocols for GBM combine three primary treatment modalities: resection, chemotherapy, and radiation. Patients with newly diagnosed GBM (ndGBM) are treated with maximal safe resection followed by radiotherapy (RT) plus concomitant

and maintenance of temozolomide (TMZ) based on the results of a phase III EORTC study.[3] The extent of tumor resection has been shown to affect prognosis significantly,[4] and the introduction of tumor fluorescence derived from 5-ALA (5-aminolevulinic acid) that enabled better resection, has led to further improvement in progression-free survival (PFS).[5] Chemotherapy regime includes TMZ as the first-line treatment and either bevacizumab or nitrosoureas, which serve as second-line therapy.[6,7] Since the establishment of the EORTC protocol, little progress has been made, and different trials have shown median overall survival (OS) and median PFS from diagnosis varying from 14.6-16.7 to 5.5-7.3 months, respectively.[8] Following disease recurrence, treatment options for GBM patients are limited. The OS from recurrence is commonly short and without effective therapy rarely exceeds 3-5 months, while with active treatment, the median survival is ~7 months (range 5-9.2 months) with 6-month PFS rates <20%.[9]

Besides the standard of care for GBM described above (surgery, radiation, and chemotherapy), a fourth treatment modality, Tumor-Treating Fields (TTFields; "Optune®"), was developed by Novocure Ltd., over the past two decades. Following preclinical studies *in vitro* and *in vivo*,[10–12] two large phase III multicenter clinical trials, EF-11[9] and EF-14[13] were conducted, showing a good safety profile, equivalence to chemotherapy in recurrent GBM (rGBM), and improved OS among ndGBM when added to standard protocol. Following these results, the FDA approved TTFields treatment for recurrent or refractory GBM in 2011,[14] and as adjuvant treatment for ndGBM patients after completing standard-of-care surgery and chemoradiation in 2015.[15] TTFields has also been recognized by the American Society of Clinical Oncology (ASCO),[16] and the National Comprehensive Cancer Network (NCCN) guidelines granted a "category 1" recommendation for ndGBM patients with good performance status, and a "category 2B" recommendation for rGBM.[17]

Nevertheless, skepticism and criticism have been directed at the studies' results. The studies were scrutinized for their unblinded design and lack of a sham device. Critics also noted that controls received less adjuvant chemotherapy than treatment group and noted the problematic time lag between diagnosis and randomization. Criticism was also directed at the unclear device mechanism of action, its high costs, and difficulty in use.[18–24] Finally, as with any proprietary treatment, TTFields literature may be influenced by financial ties, demonstrating a strong association between favorable views of TTFields and financial conflicts of interest with the device manufacturer.[23]

To address the controversy and establish an objective understanding of the device's mechanism of action and its efficacy for treating GBM, we conducted a systematic literature review and meta-analysis using accepted evidence-based techniques. The following systematic review summarizes the existing body of evidence concerning TTFields and uses quantitative meta-analytic methods to assess the treatment's clinical efficacy and safety profile. We also review the preclinical literature, presenting TTFields' molecular mechanism of action and discuss potential therapeutic clinical implications of combining it with other treatment methods to highlight the GBM patients' who may gain the most benefit from its' use, in addition to the current standard treatment paradigm. Finally, we aim to summarize the current data in an accessible manner for those who treat GBM patients regularly.

Materials and Methods

The meta-analysis presented below was conducted according to the PRISMA guidelines.[25] The PRISMA checklist for this meta-analysis is given in the supplementary materials section of this study.

Literature Search

A thorough literature search was performed in three main medical database engines: PubMed (Medline), Scopus (ELSEVIER), and Cochrane Central Register of Controlled Studies (CENTRAL). The search algorithm was generated as follows: *(glioblastoma OR GBM) AND ("tumor*treating field*" OR "tumor-treating field*" OR "alternating electric field*" OR "alternating-electric field*" OR ttfield* OR "novocure" OR optune OR NovoTTF-100A OR NovoTTF200A OR EF-14 OR EF-11).*

The most recent search was conducted on October 9, 2020.

Studies Selection

Studies meeting the following criteria were included in the quantitative analysis: (1) written in English; (2) original study (randomized controlled trials [RCT], cohort studies, observational studies, or case series); (3) patients treated for GBM; (4) patients ≥18; (5) report either clinical efficacy, daily compliance, or adverse events (AEs). When multiple studies analyzed the same population, we chose the study with a larger sample or most extended follow-up. The studies were categorized by patients' diagnosis: ndGBM or rGBM.

Data Extraction

A standardized electronic tool named *State of the Art through Systematic Review* (*StArt*) was used to systematize the data extraction and examination.[26] Studies were screened by title and abstract; relevant studies were then screened by full text for final inclusion. For each eligible study, we extracted the following data: authors, year of publication, study type, intervention, GBM status, number of patients, gender, age, Karnofsky Performance Status (KPS), treatment compliance, and number of recurrences. Also, we extracted clinical endpoints: median OS, median PFS, PFS at 6 months, survival at 1, 2, and 3 years, AEs, and Kaplan-Meier (KM) curves.

Assessment of Methodological Quality and Risk of Bias

To evaluate the quality and risk of bias in the included studies' methodological design, we used the Oxford Centre

for Evidence-Based Medicine guidelines,[27] the Newcastle-Ottawa Quality Assessment tool for non-RCT studies,[28] and the RoB 2 for RCTs[29] (Table 1 and Supplementary Tables 1 and 2). A quantitative analysis of publication bias was not conducted due to the small number of comparative studies.

Statistical Analysis

To generate a pooled distribution-free KM survival curves, we used the method proposed by Combescure et al.[30] Published survival curves were digitalized using *DigitizeIt* software, and survival probabilities were extracted at fixed intervals. Corresponding numbers of at-risk patients in each interval were collected when available or estimated using the method proposed by Tierney et al.[31,32] Pooled KM curve, median OS, median PFS, and survival rates with 95%CI were calculated using the R *MetaSurv* package.[30] Also, as a sensitivity analysis, for all studies reporting median OS and PFS, we estimated pooled median OS and PFS using the R *MetaMedian* package[33] (Supplementary Figure 1). The pooled prevalence of AEs was calculated using the *MetaProp* package in R.

The Cochrane Q chi-square test and I^2 statistic were used to examine the heterogeneity across studies. The fixed-effects model was used for pooled results with low heterogeneity ($I^2 \leq 50\%$); otherwise, the random-effects model was used for analysis. All analyses were performed using the R software.

Results

Studies Identification and Selection

Of the initial 645 papers identified; 20 studies met the predefined inclusion criteria (Figure 1(. The studies consisted of: 2 RCTs (EF-11[9] and EF-14[34]), 5 prospective single-arm clinical trials,[10,12,35–37] 1 prospective observational study,[38] 2 registry-based studies (PRiDe on US patients,[39] and a global post-marketing registry[40]), 3 retrospective studies,[41–43] 1 case series,[44] and 3 post hoc analyses (2 of EF-14[45,46] and 1 of EF-11[47]).[45–47] Also, we included 3 conference presentations that have not yet been published in peer-reviewed journals due to the importance of their findings.[48–50] Seven studies included ndGBM, 13 included rGBM, and 2 included both. The studies include 1636 (542 ndGBM and 1094 rGBM) patients analyzed for the clinical outcomes' endpoints, and 11 558 (6403 ndGBM and 5155 rGBM) patients analyzed for the safety endpoints (Tables 1–4).

Clinical Efficacy

In ndGBM, the EF-14 RCT demonstrated significantly prolonged survival in patients treated with TTFields compared to controls, with a median OS of 20.9 vs 16.0 months, and a median PFS of 6.7 vs 4.0 months, respectively. Several smaller studies have investigated the efficacy of combined therapy in addition to TTFields + TMZ and the use of

TTFields during the RT stage to increase its efficacy (Tables 1 and 2). To better assess the efficacy of TTFields, we constructed pooled KM survival plots. Four studies had OS KM curves[12,34,41,42] and five had PFS KM curves,[12,34,36,41,42] summing to 512 and 522 patients, respectively. The pooled OS and PFS survival curves with 95%CI compared to EF-14 and historical controls are shown in Figure 2A, B. The pooled median OS was 21.7 months (95%CI = 19.6-23.8). The 1-, 2-, and 3-year pooled OS rates were 73.5% (95%CI = 69.5-77.6), 45.1% (95%CI = 40.6-50), and 29.3% (95%CI = 24.8-34.7), respectively. The pooled median PFS was 7.2 months (95%CI = 6.1-8.2). The 6-, 12-, and 18-month pooled PFS rates were 55.9% (95%CI = 50.9-61.4), 32.4% (95%CI = 27.9-37.5), and 21.7% (95%CI = 17.9-26.2), respectively.

In rGBM, TTFields efficacy remained vague, with contradicting results between EF-11 and later non-RCT studies. EF-11 reported median OS was not significantly superior in the TTFields arm than controls (6.6 vs 6 months, respectively). However, patients in the control group had a slightly better recurrence rate, which may have affected clinical outcomes.[9] Several follow-up studies re-evaluated the efficacy of TTFields for rGBM patients, showing significantly improved outcomes compared to EF-11 controls. The Patient Registry Dataset (PriDe), a large post-marketing registry, reported a median OS of 9.6 months among TTFields patients, significantly higher than the 6 months among EF-11 controls.[39] However, here too, the improved survival was suggested to be due to an earlier stage of disease course follow-up as compared to the EF-11 controls.[39] Preliminary results from the EF-19, a new prospective study, demonstrated a median OS of 7.4 and 8.1 months in the intention-to-treat and per-protocol patients, respectively.[50] A post hoc analysis of EF-14 RCT found that TTFields + TMZ vs TMZ alone after first recurrence significantly prolonged median OS (11.8 vs 9.2 months).[45] Several smaller studies investigated the efficacy of combined therapy in addition to TTFields, and one suggested a skull-remodeling surgery to increase TTFields dose in the tumor (Tables 1 and 2).

To better assess the efficacy of TTFields among rGBM, and to clarify the contradicting results from the different studies concerning TTFields efficacy among rGBM patients, we constructed pooled KM survival plots of the relevant studies. Seven studies had OS KM curves,[9,10,39,41,45,49,50] and four had PFS KM curves[9,10,41,49] summing to 984 and 201 patients, respectively (Tables 1 and 2). The pooled OS and PFS survival curves with 95%CI compared to EF-11 controls are shown in Figure 2C, D. The pooled median OS was 10.3 months (95%CI = 8.3-12.8). The 1-, 2-, and 3-year pooled OS rates were 43.7% (95%CI = 34.4-55.4), 21.3% (95%CI = 14-32.3), and 14% (95%CI = 8.7-22.6), respectively. The pooled median PFS was 5.7 months (95%CI = 2.8-10). The 6-, 12-, and 18-month pooled PFS rates were 47.8% (95%CI = 29-78.7), 29.3% (95%CI = 18.4-46.7), and 19.7% (95%CI = 10.3-37.6), respectively.

Compliance as a Prognostic Factor

Given its mechanism of action, and in contrast to systemic therapies, TTFields has no half-life; therefore, continuous application and optimal device compliance are required for therapeutic efficacy. It has been shown that a minimum of 4

Table 1. Summary of Clinical and Socio-Demographic Characteristics of Studies

Source	Study Design	Quality of Evidence[a]	Risk of Bias[b]	Intervention	Patients, No.	Age, y Median (Range)	KPS, Median (Range)	Male, n (%)	Recurrence Number	Daily Compliance, %(range)
Newly diagnosed GBM										
Kirson et al. 2009	P	3	6 Stars	TTF +TMZ	10	50 (32-70)	90 (80-100)	8 (80)		
				TMZ	32[c]					
Stupp et al. 2017 (EF-14)	RCT	2	Some Concern	TTF +TMZ	466	56 (19-83)	90 (60-100)	316 (68)		75% of pt. ≥18 h/d
				TMZ	229	57 (19-80)	90 (70-100)	157 (69)		
Lu et al. 2019	R	3	7 Stars	TTF +TBI	8					
				TTF + BBC	12					
Lazaridis et al. 2020	R	3		TTF + CCNU + TMZ	16	50 (27-70)	90 (60-100)	9 (66)		83 (45-99)
Song et al. 2020	P	3		TTF +TMZ + RT	10	61 (49-73)	90 (70-90)	8 (80)		Concurrent phase 83.5 (49-93) Maintenance phase 77 (15-94)
Bokstein et al. 2020	P	3		TTF +TMZ + RT	10	60.2 (42-72)	90 (80-100)	8 (80)		RT: 79.3 (SD 8.36) First 3 months: 77.0 (SD 10.56)
Shi et al. 2020	R	3	6 Stars	TTF[d]	5887	<18: 0.3% 18-64: 69% ≥65: 30.7%		3849 (65.4)		
Recurrent GBM										
Kirson et al. 2007	P	3	6 Stars	TTF	10	53 (28-68)	90 (70-100)	7 (70)		Mean 18h/d
Stupp et al. 2012 (EF-11)	RCT	2	Some Concern	TTF	120	54 (24-80)	80 (50-100)	92 (77)	1st: 9% 2nd: 48% ≥3rd: 43%	86 (41-98)
				BSC	117	54 (29-74)	80 (50-100)	73 (62)	1st: 15% 2nd: 46% ≥3rd: 39%	
Mrugala et al. 2014 (PRiDe)	R	3	6 Stars	TTF[d]	457	55 (18-86)	80 (10-100)	310 (67.6)	1st: 33.3% 2nd: 26.9% ≥3rd: 27.4% Unknown: 12.5%	70 (12-99)
				BSC	117	54 (29-74)	80 (50-100)	73 (62)	1st: 15% 2nd: 46% ≥3rd: 39%	
Wong et al. 2015	R	3	6 Stars	TTF + BEV	34	57 (30-77)	70 (50-90)	21 (62)	1st: 17.6% 2nd: 26.5% ≥3rd: 55.9%	83.5
				TTF + BEV +TCCC	3	56 (51-56)	70 (60-70)	2 (66)	1st: 0% 2nd: 66.6% ≥3rd: 33.3%	66.7
Mahadevan et al. 2015	R	3	6 Stars	TTF ± SRS	40	57 (47-79)		24 (60)		
Ansstas et al. 2016	R	4		TTF	8	51 (35-62)		5 (62.5)	3rd: 87.5% 4th: 12.5%	74.2 (48.2-92.9)
Kesari et al. 2017 (EF-14)	RCT-PH	2	Some Concern	TTF +TMZ	144	57 (29-83)	90 (60-100)	108 (75)	1st: 100%	
				TMZ	60	58 (22-75)	90 (70-100)	45 (75)	1st: 100%	
Lu et al. 2019	R	3	7 Stars	TTF +TBI	18	57.8 (11.6)e		12 (66.7)		
				TTF + BBC	30	52.3 (9.9)[e]		19 (63.3)		

Table 1. Continued

Source	Study Design	Quality of Evidence[a]	Risk of Bias[b]	Intervention	Patients, No.	Age, y Median (Range)	KPS, Median (Range)	Male, n (%)	Recurrence Number	Daily Compliance, %(range)
Korshoej et al. 2019	P	3		TTF + SR Surgery	15	57 (39-67)	≥70	11 (73)	1st: 100%	90 (48-98)
Onken et al. 2019	O	3	6 Stars	TTF + BSC	30	52 (36-64)		20 (67)	ndGBM:47% 1st: 53%	1st month: 83 (40-97) 2nd month: 85 (56-97)
				BSC	27	47[e]		19 (70)	ndGBM: 100%	
Zhu et al. 2020 (EF-19)	P	3	6 Stars	TTF	192	80 (9.83)[e]	55.9 (12.2)[e]	125 (65)		
				BSC	117	80 (11.01)[e]	53 (10.77)[e]	73 (62)	1st: 15% 2nd: 46% ≥3rd: 39%	
Fallah et al. 2020	P	3	7 Stars	TTF + BEV	23	60 (17-78)		18 (78)		
Shi et al. 2020	R	3	6 Stars	TTFd	4345	<18: 0.5% 18-64: 76.8% ≥65: 22.7%		2921 (67.2)		

Abbreviations: P, prospective; R, retrospective; RCT, randomized controlled trial; RCT-PH, post hoc analysis of RCT; O, observational study; TTF, Tumor-Treating Fields; TMZ, temozolomide; BSC, best standard of care; BEV, bevacizumab; TCCC, 6-thioguanine + lomustine + capecitabine + celecoxib; BBC, bevacizumab ± irinotecan or lomustine; TBI, temozolomide + bevacizumab + irinotecan; RT, radiotherapy; SR Surgery, skull-remodeling surgery; SRS, stereotactic radiosurgery.
[a]Level of evidence according to Oxford Centre for Evidence-Based Medicine guidelines.
[b]RCTs: according to RoB 2 scale; non-RCTs: according to Newcastle-Ottawa Quality Assessment tool.
[c]Historical control, matched on KPS and age.
[d]Patients may have received combination therapy in addition to TTFields.
[e]Mean (SD).

weeks of continuous treatment is necessary for tumor stasis or shrinkage.[51] Several studies examined the effect of compliance on patients' prognosis, both in rGBM patients[39,47,50,51] and ndGBM.[46,52] The studies showed a significant increase in median OS and PFS, and in 1-year survival rate for patients with ≥75% daily compliance rate, as well as a stepwise increase in prognosis as the compliance rate increased (Table 3). Moreover, the studies showed compliance to be associated with improved outcomes independently of other prognostic factors such as performance status, age, and methylguanine-DNA-methyltransferase (MGMT) methylation status.[46]

We examined the pooled effect of compliance on rGBM patients' survival who used TTFields ≥75% of the day vs those who used the device for <75% of the day, summing to 262 and 286 patients, respectively. The pooled OS survival curves with 95%CI for both patient groups are shown in Figure 3. For patients with daily compliance of ≥75%, the pooled median OS was 10.3 months (95%CI = 8.6-12.3). The 6-, 9-, and 12-month pooled OS rates were 73.5% (95%CI = 67.5-80), 54.3% (95%CI = 47.7-61.9), and 44.4% (95%CI = 37.9-51.9), respectively. In contrast, for patients with daily compliance of <75%, the pooled median OS was 5.7 months (95%CI = 4.8-8.1). The 6-, 9-, and 12-month pooled OS rates were 48% (95%CI = 41-56.2), 40.6% (95%CI = 33.7-49), and 32.5% (95%CI = 25.8-40.9), respectively.

Safety

Twelve studies reported the frequency of AEs among patients treated with TTFields, summing 11 558 patients (Table 4). Overall, TTFields have a good safety profile with no known systemic toxicity, a finding attributed to the device's localized mechanism of action. Moreover, studies showed significantly fewer severe AEs and either a lower or same overall incidence of AEs in patients treated with TTFields alone as compared to controls.[9,34,40,50] Across all studies, the most predominant AEs associated with the use of TTFields are array-associated dermatologic AEs (dAEs), which include allergic and irritant dermatitis, mechanical lesions, ulcers, and skin infection.[53] Most dAEs were mild to moderate, with a pooled prevalence of 38.4% (95%CI = 32.3-44.9) among TTFields patients (Supplementary Figure 2). Only two studies reported severe dAEs (≥ grade 3 AE); in EF-14, 2% of TTFields patients reported a grade 3 AE,[34] and in the global post-marketing safety surveillance, less than 1% of patients experienced severe device-related dAEs (Table 4).[40] The occurrence of these dAEs is most probably related to chronic skin exposure to irritants in transducer arrays, which are applied noninvasively to deliver TTFields through the skin to the tumor bed.[53,54] Prophylactic strategies for dAEs include proper shaving and cleansing of the scalp, array relocation, and topical therapies.[53] A recent preclinical study investigated the safety profile of topical treatments use with TTFields *in vivo*, reporting that all petroleum-based ointments tested led to an increase in electrical impedance, which lead to temperature increase beneath the arrays, and thus, are not recommended.[55]

During their disease course, GBM patients may require shunt placement. Since TTFields may interfere with ventricular shunts' adjustable valves as well as with patients' cardiac pacemakers or defibrillators, it is important to confirm

Figure 1. Flowchart of studies included in this study.
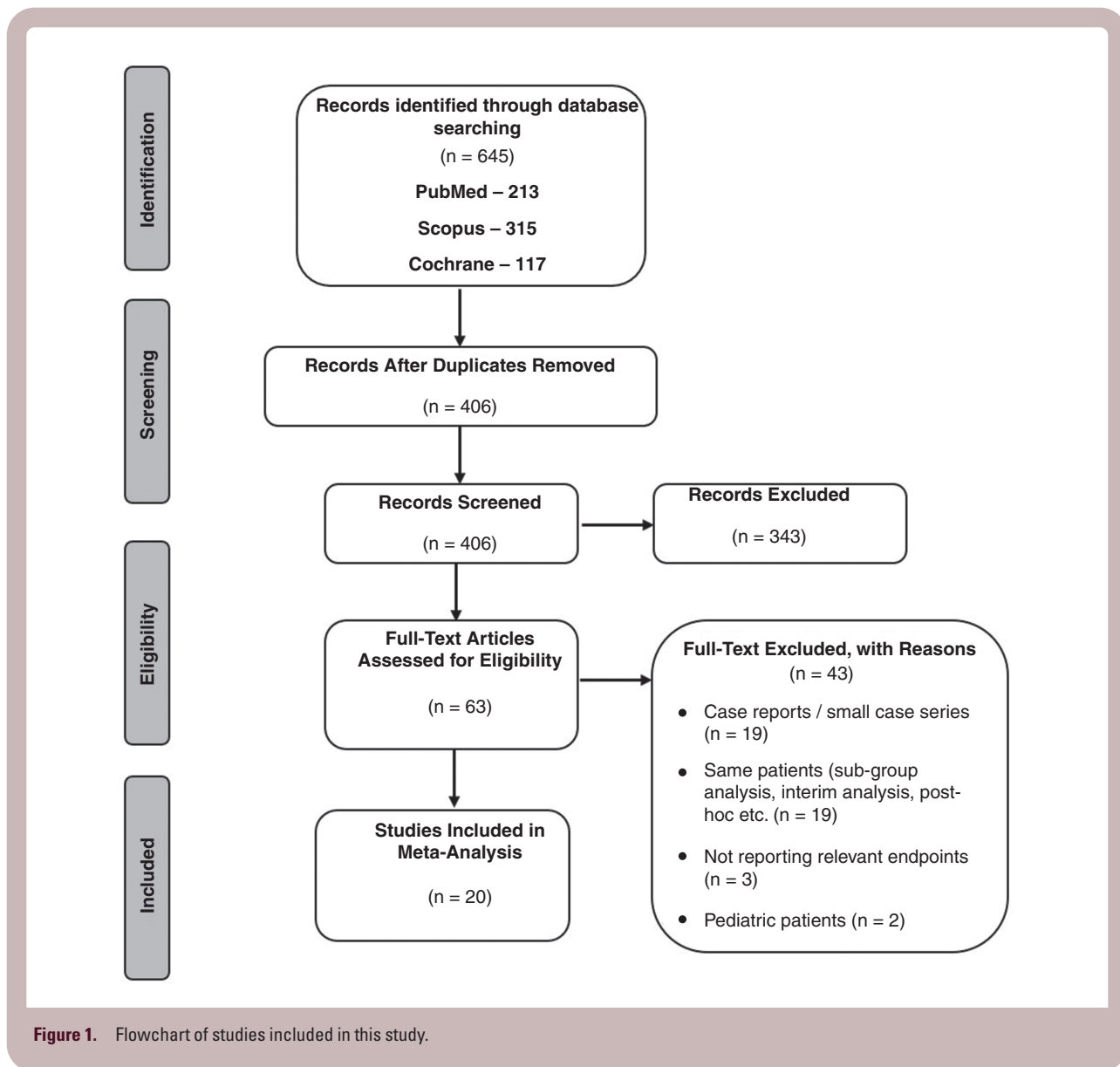
the safety of concomitant use of TTFields with these implanted devices. A post-marketing surveillance study reported 104 patients treated with TTFields with a concurrent implanted device (79 non-adjustable shunts, 11 with adjustable shunts, and 14 with pacemakers/defibrillators). The study reported no unexpected safety issues on the concomitant use of TTFields with implanted devices.[56] Case reports of patients treated with TTFields with either shunts or cardiac pacemakers, also reported no unexpected safety issues.[57–59]

Quality of Life

Due to the impact of GBM on patients' progressive decline in neurologic function and health-related quality of life (HRQoL), it is crucial to address the effect of TTFields not only on prolongation of life but also on the patient's well-being.

In EF-11, HRQoL was assessed using the EORTC QLQ-C30 questioner at baseline and every 3 months. Longitudinal data were available only for 27% of the patients. Assessing the change between baseline and 3 months, the study reported no meaningful differences between TTFields and controls in global health and social functioning domains. Cognitive, emotional, and role functioning favored TTFields, while physical functioning was slightly worse with TTFields.[9]

In EF-14, HRQoL was assessed using both EORTC QLQ-C30 and QLQ-BN20 questioners. The number of patients filling the HRQoL questioners decreased from 91.9% at baseline to 65.8% at 3 months and 41.7% at 12 months. HRQoL was maintained from baseline in 8 of 9 scales, except for itchy skin, which worsened in TTFields patients. TTFields cases had significantly better deterioration-free survival for physical and emotional functioning, global health, pain, and leg weakness, likely due to improved

Table 2.   Clinical Efficacy of TTFields

Source	Intervention	Patients, No.	Median OS (95% CI)	Median PFS (95% CI)	PFS 6 Months,%	OS 1 Year,%	OS 2 Years,%	OS 3 Years,%
Newly diagnosed GBM								
Kirson et al. 2009	TTF +TMZ	10	>39	38.8				
	TMZ	32	14.7	7.8				
Stupp et al. 2017 (EF-14)	TTF +TMZ	466	20.9 (19.3-22.7)	6.7 (6.1-8.1)	56%	73%	43%	26%
	TMZ	229	16.0 (14.0-18.4)	4.0 (3.8-4.4)	37%	65%	31%	16%
Lu et al. 2019	TTF +TBI	8	32.5 (17.0-49.0)	6.6 (3.7-9.2)				
	TTF + BBC	12	17.8 (13.3-19.9)	5.1 (3.3-6.1)				
Lazaridis et al. 2020	TTF + CCNU +TMZ	16		20[a]				
Song et al. 2020	TTF +TMZ + RT	10		6.9				
Bokstein et al. 2020	TTF +TMZ + RT	10		8.9 (2.1-12.9)	58.30%			
Recurrent GBM								
Kirson et al. 2007	TTF	10	15.6 (5.1-31)	6.5 (0.75-31)	50%	67.50%		
Stupp et al. 2012 (EF-11)	TTF	120	6.6	2.2	21.40%	20%	8%	5%
	BSC	117	6	2.1	15.10%	20%	4%	1%
Mrugala et al. 2014 (PRiDe)	TTF	457	9.6			44%	30%	
	BSC	117	6			20%	7%	
Wong et al. 2015	TTF + BEV	34	4.1 (0.3-22.7)	2.8 (0.1-20.7)				
	TTF + BEV +TCCC	3	10.3 (7.7-13.6)	8.1 (6.4-13.2)				
Mahadevan et al. 2015	TTF ± SRS	40	8 (12 SRS vs 4 no SRS)					
Ansstas et al. 2016	TTF	8	7.9	2.7				
Kesari et al. 2017 (EF-14 post hoc)	TTF +TMZ	144	11.8					
	TMZ	60	9.2					
Lu et al. 2019	TTF +TBI	18	18.9 (10.7-25.3)	10.7 (6.7-20.8)				
	TTF + BBC	30	11.8 (8.6-15.8)	4.7 (3.6-6.3)				
Korshoej et al. 2019	TTF + SR Surgery	15	15 (9.6-16.2)	8.8 (6.2-13.2)	64%	64%		
Zhu et al. 2020 (EF-19)	TTF	192	7.4 (PP 8.1)			42%		
	BSC	117	6.4			23.40%		
Fallah et al. 2020	TTF + BEV	23	10.5 (8.2-14.9) Male: 9.9 Female: 16	4.1 (3.6-9.5) Male: 3.9 Female: 13	33%	46%		

Abbreviations: P, prospective; R, retrospective; RCT, randomized controlled trial; RCT-PH, post hoc analysis of RCT; TTF, Tumor-Treating Fields; TMZ, temozolomide; BSC, best standard of care; BEV, bevacizumab; TCCC, 6-thioguanine + lomustine + capecitabine + celecoxib; BBC, bevacizumab ± irinotecan or lomustine; TBI, temozolomide + bevacizumab + irinotecan; RT, radiotherapy; SR Surgery, skull-remodeling surgery; SRS, stereotactic radiosurgery; PP, per-protocol population.
[a]Median PFS from diagnosis. TTFields was initiated after a median interval of 19 weeks (range 12-33 weeks).

PFS. Social, role, and physical functioning were not affected.[60] Finally, the study showed a significantly longer time to sustained 6- and 10-point decline in the Mini-Mental State Examination and KPS, respectively.[34]

A small two-center study examined 30 high-grade glioma patients treated with TTFields and 27 controls.[38] The study assessed HRQoL using a device-specific questionnaire (DSQ), several modules of the EORTC questioner (QLQ-30, QLQ-BN20, QLQ-FA13), and the SSUK-8 (social support) questioner. Two months after treatment initiation, the surveys were completed by 91% of enrolled patients. The study showed that TTFields patients had significantly better emotional function, and reported significantly lower incidence of insomnia, pain, dyspnea, loss of appetite, nausea, and vomiting. Also, TTFields users had better emotional, physical, and cognitive functions than social and role functioning. The study showed TTFields frequently affected multiple aspects of the patients' daily lives; nevertheless, 70% would recommend TTFields to others, and 67% would reuse the device.

Discussion

The study presented here provides a practical summary of TTFields modality for clinicians who treat
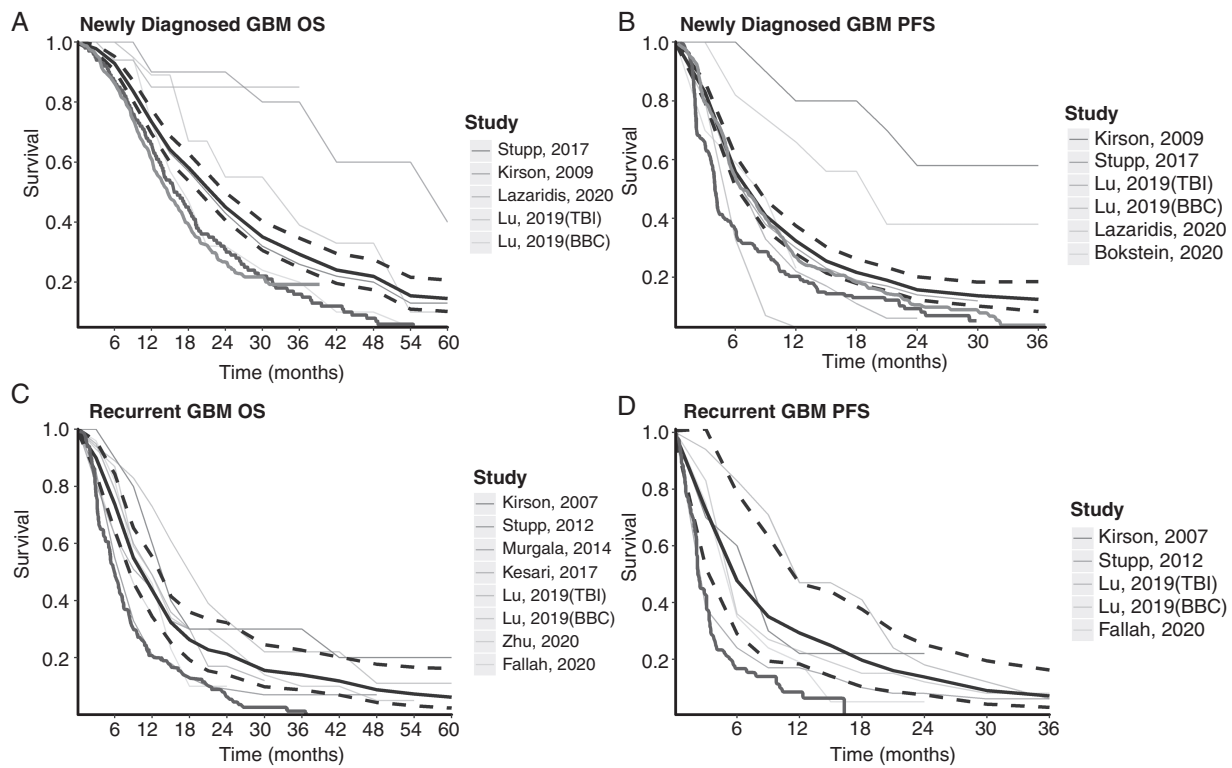
Figure 2. Pooled Kaplan-Meier (KM) survival curves of patients treated with TTFields for GBM. Pooled KM survival curves of OS (A and C) and PFS (B and D). The gray-scale thin lines represent the survival in each individual study. The thick black line represents the summarized survival curve with the 95%CI (dashed black lines). The thick dark gray line represents the original survival curve of controls according to EF11 (rGBM: best standard-of-care treatment) and EF14 (ndGBM: RT + TMZ). The thick bright gray line represents the original survival curve of ndGBM patients treated with RT + TMZ in the historic study by Stupp et al.[3] which established the current standard of care for ndGBM (EORTC protocol). (A) OS survival curve for ndGBM (512 patients), (B) PFS survival curve for ndGBM (522 patients), (C) OS survival curve for rGBM (984 patients), (D) PFS survival curve for rGBM (201 patients). Abbreviations: GBM, glioblastoma; ndGBM, newly diagnosed GBM; OS, overall survival; PFS, progression-free survival; rGBM, recurrent GBM; RT + TMZ, radiotherapy + temozolomide; TTFields, Tumor-Treating Fields.

GBM patients. It has some advantages over previous systematic TTFields reviews.[61,62] It includes more clinical studies and uses both qualitative and quantitative analysis, thus, allowing for an extensive examination of the literature. The study also used several innovative statistical tools, creating pooled survival curves and allowing assessment of single-arm studies that are currently the majority of trials in TTFields literature. Lastly, it reviews the preclinical alongside clinical literature, promoting future research and therapeutic channels for the device.

Clinical Findings

The findings presented in this study support TTFields' clinical efficacy for ndGBM and suggest it for rGBM. In ndGBM patients, TTFields use alongside the EORTC protocol, as established by both EF-14 RCT and later clinical studies, enhanced GBM patients' survival to 21.7 months. In rGBM patients, TTFields use improved survival to 10.3 months,

and therefore, it may be considered either as a single treatment or alongside other salvage therapies. Nevertheless, more studies are needed to better establish the clinical efficacy in rGBM cases.

This study also demonstrated that despite its restrictive effect on daily life, TTFields had an overall good impact on patients' HRQoL. Particularly, patients' cognitive and emotional well-being, as well as functional status, were favorably affected by TTFields. Subsequently, 70% of patients would recommend TTFields to others, and 67% would reuse it.[38] However, these findings should be further assessed in larger cohorts.

TTFields treatment's safety was also evaluated and showed no known systemic toxicity so far; a finding attributed to the device's localized effect, which main AE was mild to moderate dermatitis in 38.4% of the patients. Also, no unexpected safety issues on the concomitant use of ventricular shunts or implanted cardiac devices were shown, although this trend should be cautiously considered until further validation of existing evidence is performed.

Table 3. Effect of Compliance on Efficacy of TTFields Treatment

Source	Diagnosis	Compliance	Patients, No.	Median OS
Mrugala et al. 2014 (PRiDe)	rGBM	≥75%	127	13.5
		<75%	160	4
Kanner et al. 2014 (EF-11)	rGBM	≥75%	92	7.7
		<75%	28	4.5
		<60%	10	5.8
		60-79%	33	6
		≥80%	77	7.7
Zhu et al. 2020 (EF-19)	rGBM	≥75%	82	9.83
		<75%	102	6.67
Toms et al. 2019 (EF-14)	ndGBM	>90%	43	24.9
		80-90%	166	21.5
		70-80%	91	21.7
		60-70%	46	19.9
		50-60%	42	18
		30-50%	40	17.9
		<30%	22	18.2

Abbreviations: rGBM, recurrent glioblastoma; ndGBM, newly diagnosed glioblastoma.
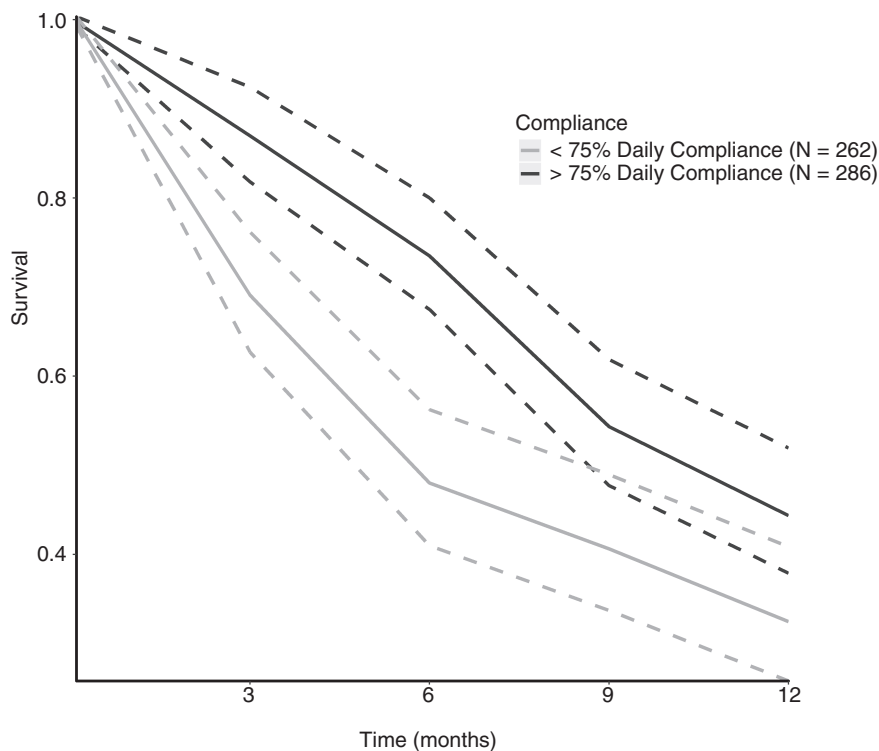
Figure 3. Pooled Kaplan-Meier (KM) survival curves of OS according to daily compliance for rGBM patients. Pooled KM survival curves of OS for rGBM patients. The dark gray lines represent the pooled survival curve (solid line) with the 95%CI (dashed lines) of patients who used TTFields for ≥75% of the day (>18 h/d). The bright gray lines represent the pooled survival curve (solid line) with the 95%CI (dashed lines) of patients who used TTFields <75% of the day (<18 h/d). Abbreviations: OS, overall survival; rGBM, recurrent GBM; TTFields, Tumor-Treating Fields.

Table 4. TTFields-Related Local Adverse Events

Source	Diagnosis	Patients, No.	Mild-Moderate dAEs	Severe dAEs	Headache	Heat Sensation	Electric Sensation
Kirson et al. 2007	rGBM	10	90%				
Kirson et al. 2009	ndGBM	10	100%		20%		
Stupp et al. 2012 (EF-11)	rGBM	120	16%				
Mrugala et al. 2014 (PRiDe)	rGBM	457	24.30%		5.70%	11.30%	7.70%
Stupp et al. 2017 (EF-14)	ndGBM	456	52%	2%			
Onken et al. 2019	ndGBM + rGBM	30	40%				3%
Korshoej et al. 2019	rGBM	15	47%		60%		
Lazaridis et al. 2020	ndGBM	16	37%				
Song et al. 2020	ndGBM	10	80%		30%		
Bokstein et al. 2020	ndGBM	10	80%				
Zhu et al. 2020 (EF-19)	rGBM	192	36%				
Shi et al. 2020	ndGBM	5887	40%	<1%	8%	11%	11%
	rGBM	4345	31%		7%	10%	9%

Abbreviations: dAEs, dermatologic adverse events; rGBM, recurrent glioblastoma; ndGBM, newly diagnosed glioblastoma.

Treatment compliance of ≥75% of the day has been shown to significantly affect GBM patient's survival, a finding that should be emphasized to both patients and their caregivers. It should be considered, though, that patient's compliance may be affected by both social and clinical factors and may pose certain difficulties on them and their caregivers. For example, some patients may be reluctant to comply with the head-shaving required at every array change, and some may feel self-conscious due to wearing the arrays on a shaved head, calling attention to their condition.[63] Also, since TTFields are administered in the home and outpatient setting, it places the burden of compliance on the patient and their caregivers. Thus, a good home support system is critical when considering therapy for a GBM patient.[46,63]

Cost-Effectiveness

The estimated monthly cost for TTFields in the United States is $21 000, leading to concerns regarding its cost-effectiveness.[21,64,65] Several studies examined the incremental cost-effectiveness ratio (ICER) for ndGBM patients based on EF-14, reporting contradicting results. Two studies reported an ICER ranging at €510 273-549 909 per life-year gained (LYG), claiming TTFields is not cost-effective.[66,67] A third study reported an ICER of $150 452/LYG, suggesting treatment can be considered cost-effective within the reported range of willingness-to-pay thresholds in the United States.[68] Due to their post hoc design, these studies had limited access to potential cost factors such as hospitalizations which are major sources of health care expenditures.[65] Also, the cost-effectiveness of TTFields vs salvage therapy has not been examined among rGBM. Notably, in Israel, 2020, TTFields became part of the standard-of-care treatment for GBM patients, given following the EORTC protocol and as maintenance therapy. It is, thus, subsidized by the Ministry of Health of Israel (The Ministry of Health of Israel website, in Hebrew). In summary, data are still scarce concerning the cost-effectiveness of TTFields in general and also regarding its use in specific subpopulations which may benefit most from it.[64] Future prospective trials are needed concerning both ndGBM and rGBM and may provide a more accurate estimate of the real-world cost-effectiveness.[65]

Mechanism of Action and Combinational Treatment Potential

Examination of both preclinical and clinical studies demonstrates TTFields' diverse mechanism of action and emphasizes its clinical potential to support and enhance treatment efficacy when combined with current treatment protocols and novel treatments, which may lead to improved patient outcomes. It disrupts DNA repair, cell mitosis[10,11,69–71] and angiogenesis[72]; suppress migration and invasion[71,72]; induces apoptosis,[69] autophagy,[71,73] and immunogenic cell death[71,74–76]; causes temporary BBB (blood-brain barrier) disruption and increase cell membrane permeability.[77,78]

MGMT status among ndGBM patients is known to influence the efficacy of TMZ. The EF-14 study demonstrated improved clinical efficacy in patients treated with TMZ + TTFields regardless of MGMT status.[34] A preclinical study investigating TTFields combination with TMZ, focusing on MGMT status and TMZ resistance reinforced these findings, demonstrating that TTFields efficacy was not dependent on MGMT status nor diminished in TMZ-resistant cell lines.[71] The effect of TTFields on angiogenesis[72] suggests possible synergistic potential with anti-angiogenetic agents such as bevacizumab. This combined treatment was examined in several preliminary studies, suggesting improved clinical efficacy with no additive side effects.[41,43,45,49] TTFields, therefore, may be attractive to ndGBM patients who are

unlikely to benefit from TMZ due to unmethylated MGMT promoter, and in addition to second-line treatment with bevacizumab.

Preclinical studies also demonstrated TTFields' utility in reducing DNA repair mechanisms' effectiveness within GBM cells following RT. Studies showed a synergistic effect of TTFields and RT when given either before or following RT, inducing DNA damage, inhibiting DNA repair and mitotic activity, and suppressing cell migration and invasion.[79–82] Therefore, ndGBM patients may benefit not just from adjuvant treatment as conducted in EF-14, but also concurrent TTFields alongside RT. This notion was recently examined by two phase I studies, demonstrating preliminary efficacy results with no significant safety issues.[35,36]

GBM microenvironment is known to be highly immunosuppressive,[83] making TTFields immunogenic effect of interest. Preclinical studies showed TTFields induces apoptosis,[69] increases autophagy,[71,73] promotes tumor cell immunogenicity and immunogenic cell death, drives increased immune recognition and tumor rejection,[74–76] and improves the infiltrative capacity of CD4 and CD8 T cells in animal models.[84] Moreover, early during TTFields treatment, a transient stage of increased peritumoral edema is often observed, followed by an objective radiographic response, suggesting that a major component of therapeutic efficacy by TTFields may be due to an immune-mediated process.[76] This highlights the potential of combining TTFields with different immunotherapies.[76] One example is anti-PD-1, which showed enhanced antitumor immunity when combined with TTFields in preclinical studies alongside improved clinical outcomes in a preliminary clinical study.[85] Also, TTFields potential influence on T cells[84] suggests potential synergistic effect with novel immunotherapies such as dendritic cell vaccines.[75,86]

In this context, dexamethasone used to control symptomatic cerebral edema, can induce immunosuppression and interfere with the patient's antitumor immunity, impairing TTFields activity.[43,87] Preliminary examination of dexamethasone use among TTFields patients revealed patients who used doses <4.1 mg per day had a significant increase in OS.[87] Moreover, patients who showed tumor response to treatment had a significantly lower dexamethasone burden.[88] Yet, this association should be further assessed since it may be affected by the fact that more severe GBM patients receive higher doses of dexamethasone and have a worse prognosis. The use of bevacizumab can aid in controlling vasogenic cerebral edema, thus partially replacing dexamethasone, which may increase TTFields efficacy.[43,87,88]

Preclinical studies demonstrated a dose-dependent induction of cell death *in vitro*,[10,11,71] while computational models showed field intensity depends on tumor position alongside the surrounding tissue conductivity.[89] Post hoc analyses of EF-14 showed higher dose density was associated with significantly longer OS and PFS and improved quality of life.[90] Also, tumor progression has been shown to occur more frequently outside the field, where electric intensity is lower, requiring the device's repositioning to control progression.[91,92] A skull-remodeling surgery was proposed recently to reduce the skull's high resistivity, which leads to a reduction of current intensity. The surgery comprises either skull-thinning, formation of burr holes, or craniotomy over the tumor, allowing direct TTFields current

to the tumor and a minimum increase of 25% of TTFields intensity.[93] A preliminary phase I trial validated the surgery safety and feasibility, also reporting prolongation in OS.[37]

TTFields' effect on GBM membrane permeability and BBB disruption[77,78] suggests a potential new application, assisting in delivering non-permeable pharmacological agents through the BBB, enhancing drug accessibility to GBM cells and potentially, improving the extent of tumor resection. For example, increased 5-ALA uptake was shown in GBM cells in preclinical studies.[78]

TTFields' diverse mechanism of action and lack of significant side effects emphasizes its synergistic potential when combined with other treatments, leading to improved patient outcomes. It may improve the extent of tumor resection, enhance RT efficacy, provide benefit to specific populations such as patients with unmethylated MGMT, enhance immunotherapies, and support second-line treatment with bevacizumab or nitrosourea.

Limitations

Limitations of the studies included in the meta-analysis.—The literature concerning TTFields has several limitations. Both EF-11 and EF-14 were criticized for their unblinded design and lack of a placebo or sham device. It was suggested that the survival benefit might reflect a strong placebo effect, an adherence bias, or perhaps be due to higher palliative care received from TTFields supporting team.[18,20,24] It was also noted that in the EF-14 trial, the control patients group received less adjuvant chemotherapy than treatment group,[24] and noted the problematic time lag between diagnosis and randomization, which impacts the generalizability of the present data.[21] Nevertheless, it was claimed that a placebo effect would not be associated with a dose-response and cannot entirely explain the magnitude of the effect,[18,20,94] and that using a sham device, requesting patients to shave their hair and spend most of their day carrying a heavy device, may be unethical.[18] In addition to concerns regarding the studies' design, physicians note the uncertain exact mechanism of action, the device's high cost, and difficulty in use.[20,21,64,94] A limitation in both EF-11 and EF-14 studies, common in other cancer clinical trials, is the high rates of missing longitudinal HRQoL data, which may influence the results reported in both studies since patients with better prognostic factors and good treatment response will be overrepresented at later stages. However, it should be noted that the EF-14 addressed this limitation using sensitivity analyses, which confirmed their findings.[60]

Limitations of the meta-analysis itself. —Notably, this study has its own limitations. Given the characteristics of the studies published to date, which included only two RCTs alongside single-arm studies, we could not conduct a comparative meta-analysis but only to investigate the efficacy and safety of TTFields treatment by itself. The findings concerning TTFields efficacy in rGBM should be treated with caution since except for the EF-11 study and a post hoc analysis of EF-14, all other studies concerning rGBM were single-arm studies that may be affected by selection bias. Finally, and as in any meta-analysis, the presented

results should be treated with caution due to differences in study methodology and quality, the difference in sample size, and the relatively small number of studies published to date. These limitations reflect the current literature limitations concerning TTFields and underlie the importance of further clinical research, ideally blinded RCTs.

Conclusions and Future Directions

According to this study results, further research is needed to establish the different aspects of TTFields' influence on GBM disease. For example, it will be essential to determine which GBM patients may benefit the most from the therapy, according to their specific prognostic factors classification (ie, their hemoglobin level,[95] IDH1/2 mutation, and MGMT methylation status, other molecular and genetic tumor features).

Also, examining TTFields effect when added to common treatment modalities, ie, a phase II RCT study examining RT with concurrent and maintenance TMZ + TTFields (experimental arm) vs RT with concurrent TMZ alone followed by maintenance TMZ + TTFields (control arm) is closing accrual; or limitation of dexamethasone use to maximize TTFields immunogenic efficacy, are essential.[96] As noted above, combined TTFields treatment and bevacizumab was examined in several preliminary studies, suggesting improved clinical efficacy with no additive side effects, though further research is again, needed.[41,43,45,49] Future studies should also consider using TTFields before 5-ALA administration, possibly resulting in better demonstration of the infiltrative tumor margin, thus, improving the extent of resection[4] and creating an additive effect on patients' survival.

These preliminary findings and investigation suggestions based on them, emphasize the necessity for further in-depth research, both in the lab and clinical settings, enabling the realization of the potential inherent in TTFields.

To conclude, this study systematically assessed the current literature concerning TTFields, allowing a better, unbiased, and practical understanding of it, and its findings further support the clinical benefit, safety, and potential therapeutic synergism of its use by GBM patients.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

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