Chapter

Perspective Chapter: Theory and Application of Tumor Treating Fields in Brain Tumor Treatment

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Abstract

Glioblastoma (GBM) is the most common primary brain tumor in adults and continues to portend poor survival, despite multimodal treatment using surgery and chemoradiotherapy. The addition of Tumor Treating Fields (TTFields) to standard therapy has been shown to extend survival for patients, leading to the clinical approval of this approach by the FDA. TTFields represent a non-invasive anticancer modality consisting of low-intensity, intermediate-frequency alternating electric fields. It exhibits a broad mechanism of action by disrupting a multitude of biological processes, including cell proliferation, DNA repair, cell permeability, and immunological responses, to elicit therapeutic effects. This chapter describes advances in our current understanding of the mechanisms by which TTFields mediate anticancer effects. Additionally, we summarize the landscape of TTFields clinical trials across brain tumors and consider how emerging data might inform future clinical applications for TTFields.

Keywords: glioblastoma, GBM, tumor treating fields, TTFields, brain tumor, clinical trials

1. Introduction

GBM is the most common and aggressive type of primary brain tumor. It is responsible for most of the roughly 200,000 deaths worldwide from central nervous system tumors each year [1]. Even with maximum surgical removal of the tumor followed by radiation therapy and chemotherapy with temozolomide (TMZ), the average survival time is about 15 months [2]. This situation has not improved significantly in recent decades, highlighting the urgent need for more effective treatments for this devastating disease.

TTFields, with the market name of Optune Gio by Novocure, are a new non-invasive cancer treatment that uses low-intensity (1–3 V/cm), intermediate-frequency (100–300 kHz) alternating electric fields. These electric fields apply physical forces on charged and polar molecules in the body. The effectiveness of TTFields therapy depends on the duration of treatment, with evidence showing that using TTFields for more than 18 hours a day improves survival [3]. The frequency of the electric field

also matters and varies by cancer type. For glioma cells, TTFields are most effective at an optimal frequency of 200 kHz [4].

Two key clinical trials, EF-11 and EF-14, have been instrumental in the FDA's approval of TTFields for treating recurrent and newly diagnosed GBM (ndGBM) [5, 6]. The EF-11 trial showed that TTFields are effective for patients with recurrent GBM, while the EF-14 trial demonstrated that adding TTFields to the standard TMZ treatment significantly increased the median overall survival (mOS) by 4.9 months and median progression-free survival (mPFS) by 2.7 months in patients with ndGBM, without adding significant side effects. These results led to the FDA's approval of TTFields for ndGBM in 2015, marking a significant advancement in GBM treatment.

TTFields work by affecting several critical processes within cancer cells, such as cell division, DNA repair, autophagy, immune responses, and cell membrane permeability. Early data suggest that combining TTFields with other treatments, like radiotherapy, chemotherapy, and immunotherapy, may improve their effectiveness. Ongoing research and clinical trials are exploring its use in brain metastases and various extracranial tumors.

In summary, TTFields represent a significant advance in the treatment of GBM and potentially other brain tumors. Ongoing research into mechanisms of action and optimization of clinical use holds great promise for improving outcomes for patients facing these challenging diagnoses.

2. Mechanism of action using TTFields to treat brain tumors

2.1 TTFields disrupt mitotic processes

Mitosis disruption is one of the first anti-tumoral mechanisms identified. Studies have shown that the proliferation rate of the cells is more sensitive to TTFields-induced cell death [7]. Specifically, TTFields interact with key components involved in cell division, particularly proteins with high dipole moments such as tubulin and septin, disrupting critical stages of mitosis.

During metaphase, tubulin dimers in cancer cells align to form microtubules, essential for the mitotic spindle. TTFields cause these tubulin molecules to oscillate and spin due to the alternating electric fields, leading to instability in microtubule polymerization. This results in errors in spindle assembly and abnormal geometric shapes, causing delays in mitosis and the formation of cells with incorrect numbers of chromosomes (aneuploidy) [7, 8]. As mitosis progresses to anaphase, TTFields continue their disruptive action. Septin proteins, which help form the contractile ring necessary for cell division, are affected by the electric fields. TTFields interfere with the proper localization and function of septin, causing disorganized contraction of the cell membrane. This leads to membrane blebbing (bubbling) and ultimately disrupts cell division, leading to cell death [9].

In telophase, TTFields generate concentrated electric fields at the cleavage furrow, where the cell division is set to occur. This creates a dielectrophoretic effect, pushing charged macromolecules and organelles toward the narrowest part of the dividing cell. The increased pressure and disrupted organization lead to cell rupture and death [10]. Beyond these direct effects on mitotic structures, TTFields also influence the broader cellular environment. They reduce the stability and expression of CDK2-associated RNA (CDK2-AS1), which is crucial for cell cycle progression, leading to cell cycle arrest in the G1 phase and further preventing tumor cell proliferation [11].

2.2 TTFields impair DNA damage repair

Impaired DNA damage repair is another hallmark of TTFields. DNA repair is a crucial process that allows cells to fix damage caused by various factors, including radiation and chemotherapy. By interfering with this process, TTFields enhance the susceptibility of cancer cells to these treatments, leading to increased cell death and improved treatment outcomes.

One of the primary ways TTFields impair DNA repair is by inducing replication stress. The electric fields generated by TTFields create physical forces that interfere with the normal progression of DNA replication, leading to the formation of R-loops. These R-loops, which are RNA-DNA hybrid structures, act as markers of replication stress and hinder the proper repair of DNA double-strand breaks. This disruption of DNA replication increases the accumulation of DNA damage in cancer cells, making them more vulnerable to additional stressors [12].

Moreover, TTFields downregulate the expression of crucial DNA repair genes, such as BRCA1 and BRCA2 [13]. These genes play an essential role in homologous recombination, a process that accurately repairs DNA double-strand breaks. The reduction in BRCA1 and BRCA2 expression compromises the ability of cancer cells to repair damaged DNA effectively. This impairment is particularly significant because it makes cancer cells more sensitive to treatments that induce DNA damage, such as radiation therapy and certain chemotherapeutic agents like temozolomide [14, 15]. Poly ADP-ribose polymerase (PARP) is a protein involved in single-strand DNA break repair. While TTFields robustly activate PARP-mediated DNA repair in glioma stem cells (GSCs), concomitant exposure to PARP inhibitors leads to the accumulation of DNA damage and ultimately cell death, especially in cells already deficient in other DNA repair pathways [16].

Studies have shown that cancer cells treated with TTFields exhibit more significant and prolonged DNA damage when combined with ionizing radiation [17, 18]. This combination results in a higher number of γH2AX foci, markers of DNA double-strand breaks, indicating increased DNA damage. Preliminary data suggest that applying TTFields prior to or concurrently with radiotherapy shows increased sensitivity compared to TTFields administered after radiation therapy *in vitro* [13]. Whether this holds true clinically is currently undergoing validation.

2.3 TTFields increase permeability of cell membranes

TTFields create mechanical stresses and forces on the cell membrane, causing disruptions in its integrity. The electric fields can alter the arrangement and function of membrane proteins and lipids, leading to the formation of transient pores. These pores increase the permeability of the cell membrane, allowing for greater influx of multiple agents such as Dextran-FITC, ethidium D, or 5-aminolevulinic acid (5-ALA) by measuring increased bioluminescence or scanning augmented number (53.5 ± 19.1 vs. 23.9 ± 11.0) and size (240.6 ± 91.7 nm^2 vs. 129.8 ± 31.9 nm^2) of holes on the cellular membrane [19]. Additionally, there is a significant increase in the uptake of membrane-associating reagents with a size of 20 kDa, and no larger than 50 kDa, into glioma cells with TTFields. These changes are reversible and return to normal within 24 h of ceasing TTFields treatment [19].

One significant effect of increased cell membrane permeability is the enhanced uptake of chemotherapeutic drugs. Cancer cells exposed to TTFields show higher intracellular concentrations of drugs like Withaferin A. This increased drug

concentration within the cancer cells enhances the efficacy of chemotherapy, leading to synergistic treatment outcomes [20].

Additionally, TTFields can also affect the transport of ions and other small molecules across the cell membrane. The electric fields can modulate the activity of ion channels and transporters, altering the intracellular ionic environment. This disruption can lead to changes in cell signaling pathways, further sensitizing cancer cells to therapeutic interventions. For example, increased calcium influx due to TTFields can activate Ca_v 1.2 channels that promote GBM cell death providing the rationale to combine TTFields therapy with Ca^{2+} antagonists that are already in clinical use [21].

Moreover, the increased permeability of the cell membrane caused by TTFields may enhance the delivery of other therapeutic agents, such as targeted drugs and nanoparticles [22]. The ability of TTFields to create transient pores in the cell membrane can facilitate the entry of these agents into the cancer cells, improving their therapeutic efficacy. This has significant implications for the development of combination therapies that utilize TTFields to enhance the delivery and effectiveness of novel anticancer agents.

2.4 TTFields disrupt the blood brain barrier (BBB)

The BBB is a selective barrier that protects the brain from harmful substances in the bloodstream while allowing essential nutrients to pass through. However, this protective function can also hinder the delivery of therapeutic agents to brain tumors, posing a challenge for effective treatment [23]. TTFields have been shown to disrupt the integrity of the BBB in several ways, thereby enhancing the delivery of chemotherapeutic drugs and other therapeutic agents to the central nerve system (CNS).

The concept was first tested by a group using low-voltage pulses (5–100 V) to an external human BBB model. Although the exact mechanism was unclear, the paracellular pathway was affected, leading to a brief breach of the BBB [24]. Salvador et al. explored the effects of TTFields on the BBB and found that TTFields resulted in a reversible opening of the BBB. In their *in vitro* experiments using mouse cerebellar microvascular endothelial cells, immunofluorescence analysis showed that the tight junction (TJ) protein claudin-5 delocalized from the cell membrane to the cytoplasm when treated with TTFields. This relocation was mediated through the activation of the Rho/Rho kinase pathway, which phosphorylates claudin-5, disrupting its binding to other TJ-anchored proteins and increasing BBB permeability. Further *in vivo* experiments demonstrated that TTFields allowed paclitaxel, a chemotherapeutic agent normally restricted by the BBB, to exert its effects, reducing both tumor volume and tumor cell proliferation in rats [25].

Additionally, an *in vitro* 3D coculture model of the human BBB, constructed using human brain microvascular endothelial cells (HBMVECs) and immortalized human pericytes, showed that TTFields increased BBB permeability by altering the location of intracellular TJ proteins in HBMVECs [26]. However, in both pre-clinical studies, only the 100 kHz frequency has been proven to affect the BBB, which is not the approved frequency for clinical GBM treatment. A future strategy that involves combining two TTFields frequencies (i.e., 100 and 200 kHz) might be worth exploring for GBM and other brain tumor treatments. The lower 100 kHz frequency could be used to open the BBB for enhanced drug delivery, followed by a switch to 200 kHz to target the proliferating GBM cells.

2.5 TTFields and anti-tumoral immunity

Over the past decade, the field of cancer immunotherapy has witnessed remarkable advancements, prompting a reevaluation of traditional cancer treatments like radiotherapy, chemotherapy, and surgical therapy. The critical question is whether these methods are immunogenic and can be effectively combined with immunotherapy. As a relatively recent entrant in this domain, TTFields also need to establish their value. Fortunately, an increasing body of evidence suggests that TTFields can effectively activate the immune system through unique mechanisms, making them a promising candidate within the current immunotherapy landscape.

TTFields are believed to cause tumor cell death by disrupting the mitotic spindle, resulting in chromosome missegregation and eventually apoptosis. This process triggers immunogenic cell death (ICD), where tumor cell death generates an endoplasmic reticulum stress response, producing reactive oxygen species and releasing immune signaling molecules. These events increase the immunogenicity of tumor cells and enhance the immune functions of dendritic cells (DCs) [27].

In vitro studies have shown that TTFields-treated cells exhibit increased secretion of high-mobility group box 1 (HMGB1) protein, a key ICD marker. Additionally, TTFields treatment leads to the translocation of calreticulin (CRT) to the cell surface, signaling DCs to engulf the dying cells. These ICD markers were also observed in mouse models, where TTFields treatment resulted in significant elevations of circulating HMGB1 and phosphorylated eukaryotic translation initiation factor 2 (p-eIF2), reinforcing the idea that TTFields induce ICD [28].

Furthermore, TTFields activate innate immunity through the release of large micronuclei clusters and nuclear protrusions, which are often not encapsulated by the nuclear envelope. This disruption activates DNA sensors like cyclic GMP-AMP synthase (cGAS) and absent in melanoma 2 (AIM2), leading to the formation of inflammasomes. The cGAS-STING pathway, predominant in many cell types, activates proinflammatory cytokines and type 1 interferons (T1IFNs), while the AIM2 pathway activates inflammasomes leading to cell death. These pathways collectively enhance the immune response against tumors [29].

The potential association between TTFields and the adaptive immune system is becoming evident through DC activation. TTFields-prepared cells enhance phagocytosis by bone marrow-derived DCs (BMDCs) and stimulate BMDC maturation [27]. *In vivo* models have demonstrated that TTFields enhance cytotoxic T cells recruitment within mouse GBM tumors [29]. Clinical settings further affirm these findings, with some patients showing substantial T cell influx and signs of T cell activation toward memory development after TTFields therapy [29, 30].

Additionally, TTFields do not hinder the maturation or functionality of T cells. Studies have shown that T cells retain their pivotal anti-tumoral functions, including IFN-γ secretion and cytotoxic degranulation, under TTFields exposure [30]. This indicates that TTFields can be combined with immunotherapies like immune checkpoint inhibitors (ICIs) or CAR-T cell therapy to enhance therapeutic efficacy.

2.6 Other cancer biology functions impaired by TTFields

Studies have shown that TTFields significantly decrease the migration and invasion capabilities of various glioma cell lines, including U87, U373, A172, LN18, and LN229, as well as glioma stem cells T325 and ZH161 [31, 32]. TTFields can destroy

primary cilia, which are abundant on the surface of glioma cell membranes, by disrupting SHH pathway activity and interfering with glioma cell invasion and migration ability [33].

TTFields have also been shown to inhibit vascular endothelial cell growth [32], downregulate the expression of HIF1α, VEGF, and MMP2/9, and inhibit both neovascularization and epithelial-mesenchymal transition (EMT). These effects are mediated through the downregulation of the PI3K/AKT/NF-κB signaling pathway [34].

TTFields reduce the expression of the glycolytic biomarker pyruvate kinase M2 (PKM2) in human GBM. This reduction can be non-invasively detected using a novel radiotracer, [^{18}F] DASA-23 [35]. Additionally, TTFields, when combined with the CUSP9v3 drug repurposing approach (which includes nine repurposed drugs plus metronomic temozolomide), induce metabolic reprogramming and exhibit synergistic anti-glioblastoma activity *in vitro* [36].

2.7 Resistant mechanism of TTFields

Although TTFields significantly impact tumor cell behavior in many aspects and lead to prolonged survival in ndGBM patients, resistance to TTFields eventually develops, leading to treatment failure and disease progression. Autophagy is a hallmark of TTFields treatment effects and is believed to be linked with the resistance mechanism of glioma cells. Specifically, depletion of AMP-activated protein kinase (AMPK) or autophagy-related protein 7 (ATG7) inhibited the upregulation of autophagy in response to TTFields, as well as sensitized cells to the treatment, suggesting that cancer cells utilize autophagy as a resistance mechanism to TTFields [37].

Utilizing a machine learning algorithm combined with rigorous experimental validation, prostaglandin E2 receptor 3 (PTGER3) has been identified as another key mediator responsible for the resistance mechanism by regulating the stemness of GBM cells [38]. This resistance mechanism mediated by PTGER3 is particularly linked to long-term resistance, in contrast to the more immediate effects of autophagy.

3. Current and future use of TTFields for brain tumors

3.1 Current GBM regimen with TTFields

Prior to the EF-14 trial, the standard treatment for GBM involved maximum surgical resection followed by radiation and chemotherapy. The EF-14 trial introduced TTFields to this regimen, significantly improving patient outcomes. The median PFS increased from 4.0 months to 6.7 months, while the mOS improved from 16.0 months to 20.9 months [5].

Further subgroup analysis revealed a more pronounced benefit in the Asian population, with mOS increasing from 15.2 to 27.2 months [39]. Elderly patients with ndGBM typically have a poorer prognosis than younger patients, but the addition of TTFields to the treatment regimen was well tolerated in elderly patients. This new regimen increased PFS from 3.9 months to 6.5 months and OS from 13.7 months to 17.4 months in this cohort [40].

Moreover, patients with high compliance to TTFields treatment (daily usage of more than 22 hours) experienced a greater survival benefit: HR = 0.78; p = 0.031; OS at compliance ≥75% vs. < 75% [3]. Thus, the current recommendation is to use the device for at least 18 hours a day.

Based on previous validation, several directions are currently being explored to further enhance the efficacy of TTFields in treating GBM with ongoing trials summarized in **Table 1**.

3.2 Adjusted treatment regimen under exploration

The current regimen based on the EF-14 clinical trial applies TTFields post-concomitant radiation and chemotherapy. The concept of initiating TTFields prior to and concurrently with radiation was first tested in pre-clinical models [13]. Following the confirmation of safety in a phase I study [41], subsequent trials, such as PriCoTTF and EF-32, have been conducted to investigate this approach further.

The PriCoTTF is a phase I/II study that enrolled 33 patients with ndGBM. In this study, TTFields were initiated immediately after surgery and continued concurrently with chemoradiation and adjuvant chemotherapy for a total of approximately 9 months. Radiation therapy was conducted with the TTFields arrays present on the patients' scalps and TTFields rechallenge was permitted upon GBM recurrence. As of the 2023 ASCO Annual Meeting, the mOS had not yet been reached (48% of events had occurred). Multivariable Cox regression analysis found that OS was independently associated with the number of days patients received more than 23 hours of TTFields therapy (HR 0.96, 95% CI 0.93–0.99, P = 0.008) [42].

The randomized, prospective, open-label phase III trial (TRIDENT, EF-32, NCT04471844) aims to evaluate whether the concurrent initiation of TTFields and postoperative radiation therapy improves clinical outcomes compared to the standard treatment regimen. This trial is set to enroll 950 patients at 129 sites worldwide, with the primary endpoint being patient OS. The estimated primary completion date for this study is August 2024 [43].

3.3 TTFields leverage immune therapies

Previous phase III trials that added only ICIs to standard therapy failed to improve survival in GBM patients, likely because ICIs require pre-existing infiltration of immune cells within tumors [44, 45]. A growing body of evidence suggests that TTFields can effectively induce ICD, stimulate innate immunity, and drive immune cell infiltration, thereby "heating up" immunologically cold tumors, making TTFields a good candidate combining with ICIs.

The 2-THE-TOP trial (NCT03405792) is a phase II prospective single-arm open-label clinical trial in which 26 ndGBM patients were treated with pembrolizumab, TTFields, and TMZ after completing concurrent chemoradiotherapy. The triple therapy was well tolerated by the patients. The final analysis showed that patients in the 2-THE-TOP study had a median PFS of 12.0 months compared to 5.8 months for the historical EF-14 cohort. The mOS was 24.8 months versus 14.6 months, respectively [46]. This promising pilot study has led to the announcement of a phase III trial (EF-41/Keynote D58) to further confirm the therapeutic benefits of this combination.

TTFields could also enhance DC activation and antigen uptake, improving the efficacy of cancer vaccines. One approach being explored is personalized neoantigen vaccines (PNVs), as in the NCT03223103 trial for GBM. The combined treatment is well tolerated with the induction of robust epitope-specific T cell responses [47]. Other immunotherapy approaches that could benefit from combining with TTFields include CAR-T cell therapy. TTFields may create a more favorable tumor microenvironment to attract CAR-T cells and enhance their cytotoxicity.

Trial number	ND/R	Phase	Arm(s)	Enrollment	Primary outcome measures	Current status
NCT06353360	ND	II	Experimental: TTFields + TMZ + Tislelizumab	30	Progression-Free Survival	Not Yet Recruiting
NCT06222138	ND	N/A	TTFields	80	Overall Survival, Time to Progression	Not Yet Recruiting
NCT06136611	ND	I	Experimental: TTFields Before/After Surgery No Intervention: Routine GBM Care	42	Incidence of Treatment-Emergent Adverse Events	Not Yet Recruiting
NCT06017063	ND	N/A	Experimental: Intervention Arm - TTFields + Psychological intervention No Intervention: Control Arm - TTFields alone	275	Efficacy of Intervention	Not Yet Recruiting
NCT05973903	R	I/II	Pembrolizumab + Lenvatinib + TTFields	47	Progression-Free Survival (6 months)	Not Yet Recruiting
NCT05086497	ND	N/A	Arm 1: TTFields + "standard array mapping" Arm 2: TTFields + "Alternative (more precise) array mapping"	155	Time to progression	Recruiting
NCT04902586	ND	II	Experimental: Chemoradiotherapy + TMZ + TTFields + RT No Intervention: Chemoradiotherapy + TMZ + RT	30	Disease-Free Survival	Unknown
NCT04717739	ND	N/A	TTFields	500	Time of TTFields Usage, TTFields Adverse Events, Lifestyle Changes, Changes in Sleep Quality et al.	Recruiting
NCT04689087	R	N/A	Experimental: TTFields + BPC chemotherapy used after relapse surgery	40	Overall Survival at 6 Months	Unknown
NCT04671459	Both	II	SRS + TTFields	40	One-Year Survival Rate	Active, Not Recruiting
NCT04492163	R	II	TTFields	25	Progression-Free Survival	Unknown

Trial number	ND/R	Phase	Arm(s)	Enrollment	Primary outcome measures	Current status
NCT04474353	ND	I	Gadolinium, TMZ, Stereotactic Radiosurgery (SRS), TTFields	12	Dose-Limiting Toxicity (DLT)	Active
NCT04471844	ND	III	Arm 1: TMZ + RT + TTFields Arm 2: TMZ + RT + TTFields (after 6 weeks)	950	Overall Survival	Active
NCT04469075	Both	II	Topical Clindamycin Phosphate and Triamcinolone Acetonide, TTFields	58	Grade 2 or Higher Skin Toxicity	Recruiting
NCT04397679	ND	I	RT + TMZ + Chloroquine + TTFields	2	Rate of Grade 3 or Higher Dermatitis	Active
NCT04223999	R	II	Experimental: Intervention Skull remodeling Surgery + TTFields + Best Practice Treatment Active Comparator: TTFields + Best Practice Treatment	70	Overall Survival (12 months)	Recruiting
NCT04221503	R	II	Experimental (Cohort A): Niraparib + TTFields Active Comparator (Cohort B): Surgical Resection + Niraparib + TTFields	30	Disease Control: Complete Response, Partial Response, Stable Disease	Active, Not Recruiting
NCT03780569	ND	N/A	RT + TMZ + TTFields	10	Safety of Combined Radiotherapy/TMZ and TTFields	Unknown
NCT03687034	N/A	I	BRCX014 + TMZ + TTFields	21	Number of Treatment-Related Adverse Events	Unknown
NCT03405792	ND	II	Experimental: TMZ + TTFields + Pembrolizumab Control: TMZ + TTFields	40	Progression-Free Survival	Active, Not Recruiting
NCT03258021	ND	N/A	TTFields	710	Overall Survival, TTFields-Related Serious Adverse Events, TTFields Treatment Compliance, Time to First GBM Progression, Changes in Quality of Life et al.	Unknown
NCT03194971	Both	II	TTFields	20	Pathological Assessment	Recruiting
NCT03223103	ND	I	MTA-Vaccine: Mutation-derived tumor vaccine (Peptides. + Poly-ICLC + TTFields)	13	Dose-Limiting Toxicity (DLT)	Active

Trial number	ND/R	Phase	Arm(s)	Enrollment	Primary outcome measures	Current status
NCT05030298	ND	I/II A	TMZ, TTFields Arm 1: Stereotactic Biopsy, Radiosurgery, Surgery Arm 2: Surgery, Radiation Therapy, Chemotherapy	40	Adverse Events	Recruiting
NCT03642080	Both	N/A	TTFields	48	Progression of Disease	Unknown

ND: newly diagnosed GBM, R: recurrent GBM, TMZ: temozolomide, RT: radiotherapy, SRS: Stereotactic radiosurgery.

Table 1.
Current clinical trials exploring the efficacy of TTFields in treating glioblastoma.

NCT number	Disease	Phase	Arm(s)	Enrollment	Primary outcome measures	Current status
NCT05746325	Leptomeningeal Metastases Within the Spine	I	MRI + Lumbar Puncture + TTFields	5	Incidence of Significant Toxicity of TTFields, Feasibility of TTFields to complete 30-day trial	Recruiting
NCT05310448	Glioma with at least partial involvement of the thalamus, cerebral peduncles, midbrain, pons, or medulla	I	RT + TTFields	10	Incidence of Adverse Events	Recruiting
NCT05341349	Melanoma Brain Metastases	I	Arm 1: SRS + Pembrolizumab + TTFields Arm 2: SRS + Nivolumab and Ipilimumab + TTFields	10	Percentage of Patients Developing Grade 3 CNS Toxicity	Recruiting
NCT04967027	Brain Metastases	I	Resistant to Drug/RT TTFields Treatment	5	Adverse Events, Time to Progression, Overall Survival Rate	Unknown
NCT03033992	Supratentorial High-Grade Glioma (HGG) Ependymoma (Stratum 1) Newly Diagnosed Diffuse Intrinsic Pontine Glioma (Stratum 2)	N/A	Arm 1: TTFields Arm 2: RT + TTFields	80	Pediatric Device Usage Compliance, Pediatric Device-Related Toxicity, Feasibility of Concurrent TTFields/RT, Device-Limiting Toxicities, Overall Survival	Recruiting
NCT02831959	NSCLC Brain Metastases	III	Arm 1: SRS + TTFields Treatment Arm 2: SRS + Best Standard of Care	270	Time to Intracranial Progression	Active, not recruiting
NCT01755624	NSCLC Brain Metastases	II	Arm 1: TTFields Arm 2: Best Standard of Care	18	Time to Local/Distant Progression in Brain	Unknown

Table 2.
Ongoing clinical trials utilizing TTFields for the treatment of non-GBM brain tumors.

3.4 Combination therapies with specific targets

Several other trials are exploring different aspects of TTFields therapy based on preliminary studies. One direction involves combining TTFields with the PARP inhibitor niraparib. A phase II study (NCT04221503) is investigating this combination in patients with recurrent high-grade glioma (HGG). Although the combination therapy has been found to be safe, it has not yet demonstrated a significant signal of efficacy [48].

Another focus is on overcoming the resistance mechanisms associated with TTFields. Since autophagy is linked to cancer cell survival under TTFields treatment, chloroquine, an autophagy inhibitor, is being tested in combination with TTFields in a clinical trial (NCT04397679) to determine its potential to enhance treatment efficacy. Additionally, a retrospective study evaluated the effect of celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, when combined with TTFields. The study found that patients not receiving celecoxib (n = 14) had a mOS of 8.1 months, while those receiving celecoxib (n = 28) had a mOS of 12.9 months (chi-square 5.42, p = 0.002, HR = 2.1, 95% CI = 1.19–5.59) [49]. Since COX-2 is upstream of PTGER3, another potential target to overcome TTFields resistance, it may be worthwhile to conduct a prospective clinical trial to confirm the benefits of combining celecoxib with TTFields.

3.5 Clinical trials to treat other brain tumors

Since TTFields treatment to the brain has been shown to be safe and to extend OS in GBM patients, there is an acute need to test its efficacy in brain metastases, which are more common than GBM, or lower-grade gliomas (**Table 2**). In the recently completed phase III trial (METIS, EF-25, NCT02831959), 298 mutation-negative non-small cell lung cancer (NSCLC) patients with 1–10 brain metastases were enrolled and randomized to receive either TTFields therapy with supportive care or supportive care alone following stereotactic radiosurgery (SRS). The primary endpoint, time to intracranial progression from SRS, was significantly prolonged in the group receiving SRS followed by TTFields therapy with best supportive care (BSC) compared to the group receiving SRS plus BSC alone (median of 21.9 vs. 11.3 months; HR = 0.67 [0.48–0.93], p = 0.02) [50]. In addition to NSCLC, another ongoing phase I trial (NCT05341349) is studying the combination of SRS, ICIs, and TTFields for the treatment of melanoma brain metastases.

4. Conclusion

TTFields have emerged as a revolutionary non-invasive treatment modality, offering new hope for patients with GBM and potentially other challenging brain malignancies. By leveraging low-intensity, intermediate-frequency alternating electric fields, TTFields disrupt crucial cellular processes, including mitosis, DNA repair, cell membrane permeability, and immune responses, thereby exerting multifaceted anticancer effects. Pilot studies such as 2-THE-TOP have raised hope to further improvements in patient survival.

As research advances, the potential of TTFields continues to expand. Ongoing studies are exploring the efficacy of TTFields in combination with ICIs, PARP inhibitors, autophagy inhibitors, and other novel therapies to enhance therapeutic outcomes and overcome resistance mechanisms. Furthermore, the promising results from trials investigating TTFields in brain metastases highlight the versatility and

broad applicability of this treatment. By continuing to unravel the underlying mechanisms and optimizing clinical protocols, TTFields may become a revolutionize cancer care, especially for brain tumors that have very limited treatment options with traditional methods.

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Conflict of interest

Dongjiang Chen has received personal honoraria from Novocure for consultant work. The book chapter preparation was performed by the authors independently of Novocure. Dongjiang Chen is the inventor of three patent applications related to the work reported in this book chapter. However, royalty-free commercialization rights were transferred to Novocure per the funding agreement. Other co-authors declare no conflict of interest.

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