Tumor treating fields: narrative review of a promising treatment modality for cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: T Kutuk, E Atak; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Tumor treating fields (TTFields) therapy have emerged as a potentially effective treatment for various malignancies by delivering low-intensity, intermediate-frequency electrical fields that disrupt many processes inside cells, resulting in the interruption of cell division in cancer cells. Additionally, TTFields therapy has been found to be synergistic with existing therapeutic approaches. In this review, we provide an introduction and background to the primary mechanisms of TTFields and discuss the emerging preclinical and clinical outcomes of this novel cancer treatment technology.

Methods: We performed a literature search on PubMed, ClinicalTrials.Gov, and Google Scholar using the terms 'TTFields' and 'cancer'. We included studies, review articles, and editorials published in English from 1st January 2000 to 1st October 2023. All obtained publications were reviewed and their key references are cross-checked to ensure a balanced and high-quality review.

Key Content and Findings: Clinical studies reported to date have demonstrated the survival advantage of TTFields therapy in newly diagnosed glioblastoma (GBM), non-small cell lung cancer (NSCLC), and meaningful clinical activity in recurrent GBM (rGBM) and malignant pleural mesothelioma. Moreover, TTFields therapy has exhibited promising safety profiles across a diverse range of cancers including pancreatic cancer, hepatocellular carcinoma (HCC), ovarian cancer, NSCLC, and gastric cancer, when combined with cytotoxic chemotherapy and/or immunotherapy regimens, suggesting broad applicability as an added treatment modality.

Conclusions: Based on preclinical and clinical studies, TTFields therapy show promise as a potential treatment option for patients with a number of different malignancies, offering a favorable safety profile and the potential for significant clinical benefit. Further research is warranted to establish the optimal treatment parameters and identify specific patient subgroups that may derive the greatest advantage from this treatment modality.

Keywords: Tumor treating fields (TTFields); cancer; electric fields

Submitted Aug 05, 2023. Accepted for publication Oct 18, 2023. Published online Nov 02, 2023.
doi: 10.21037/cco-23-82
View this article at: https://dx.doi.org/10.21037/cco-23-82

Introduction

Tumor treating fields (TTFields) have emerged as a promising noninvasive treatment modality, utilizing continuous low-intensity (1–3 V/cm) and intermediate-frequency (100–300 kHz) alternating electric fields applied through skin electrodes positioned over localized tumor regions. TTFields target cancer cells through multiple mechanisms, resulting in the disruption of crucial processes and ultimately leading to cell death. Extensive evidence demonstrates that TTFields impede mitosis, disrupt the cell cycle, induce autophagy and apoptosis in cancer cells, hinder DNA repair mechanisms, augment anti-tumor immune response, increase membrane permeability, and impair cell migration, thereby effectively suppressing tumor growth and invasion (1-6). Synergy with radiotherapy (RT), several chemotherapy agents, and immune-check point blockade has been demonstrated.

TTFields therapy is administered in a noninvasive manner using a portable medical device comprised of a field generator and transducer arrays applied to the skin. The effectiveness of TTFields therapy relies on several factors, including the frequency, intensity, and duration of treatment, with a recommended minimum of 18 hours of daily treatment for optimal outcomes (7). By applying electric fields within the frequency range of 100 to 300 kHz, TTFields can selectively target cancer cells while minimizing the impact on normal tissue (8,9). The selective targeting of dividing cancer cells by TTFields, while sparing normal non-dividing cells, renders it a valuable addition to cancer treatment strategies (10). The optimal frequency of TTFields depends on the specific cancer type (11). For example, a frequency of 150 kHz has been found to be most effective for targeting non-small cell lung cancer (NSCLC) and pancreatic ductal adenocarcinoma (PDAC) cells, whereas a frequency of 200 kHz has been identified as optimal for ovarian cancer cells (12-14) (*Table 1*). Through *in vitro/vivo* studies and clinical trials, consistent inhibitory effects of TTFields on the growth of various tumor types, including glioblastoma (GBM), NSCLC, malignant pleural mesothelioma (MPM), liver cancer, ovarian cancer, and PDAC, have been demonstrated (15-21). In some clinical scenarios where effective systemic and local treatments are limited, TTFields therapy has emerged as a potentially safe and effective option. This review delves into the fundamental mechanisms of TTFields and provides a comprehensive overview of the latest preclinical and clinical findings, shedding light on this innovative technology's potential for integration into cancer care. We present this article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-82/rc).

Table 1 Cancer subtypes and tumor treating fields optimal frequencies used for each

Cancer type	Optimal frequency (kHz)
Glioblastoma	200
Non-small cell lung cancer	150
Malignant pleural mesothelioma	150
Hepatocellular cancer	150
Pancreatic ductal adenocarcinoma	150
Gastric cancer	150
Ovarian cancer	200

Methods

We utilized PubMed, Google Scholar, and ClinicalTrials.gov search engines to conduct this narrative literature search. The selection of articles was performed by consensus among all authors, with particular attention given to the potential benefits for clinical practice. *Table 2* provides detailed information on the search strategy employed.

TTFields mechanism of action

Understanding the exact mechanism of action of TTFields requires a brief review of electromagnetic properties. An electric field, encompassing electric forces originating from a charged source or dipole, plays a crucial role in determining the motion of charged particles. In the context of TTFields, this principle is leveraged to disrupt the normal movement of charged particles and dipoles. TTFields generate alternating electric fields that cause charges to oscillate and dipoles to rotate. Notably, in non-uniform electric fields characterized by converging lines of force, the intensity of the electric field becomes amplified. This phenomenon, known as dielectrophoresis, drives the movement of polar cellular components towards regions of higher field intensity. During cell division, the non-uniform electric field produced inside the cells can influence the localization of polar components towards the cleavage furrow between the two daughter cells. However, excessive strength of the non-uniform electric field may hinder proper

Table 2 The search strategy summary

Items	Specification
Date of search	Oct 01, 2023
Databases	PubMed, Google Scholar, ClinicalTrials.Gov
Search terms	Tumor treating fields or TTFields or TTF and glioblastoma, non-small cell lung cancer, malignant pleural mesothelioma, mesothelioma, brain metastasis, brain metastases, pancreatic cancer, pancreatic ductal adenocarcinoma, hepatocellular cancer, gastric cancer, ovarian cancer, liver metastasis, solid tumors, malignant melanoma, breast cancer, colorectal cancer
Timeframe	Jan 01, 2000–Oct 01, 2023
Inclusion and exclusion criteria	Studies that were written in any language other than English excluded
Selection process	All authors conducted the selection together. Consensus obtained in accordance with possible benefits to the clinical practice

TTFields/TTF, tumor treating fields.

cell division (22,23). Dipole alignment and dielectrophoresis are two crucial concepts that significantly influence the cellular effects of TTFields. This understanding of electric field dynamics forms the basis for exploring the therapeutic potential of TTFields in scientific research.

The effects of TTFields are attributed to various mechanisms, as elucidated by several studies, which shed light on distinct aspects of cellular processes. These investigations have highlighted multiple underlying cellular effects, such as the disruption of microtubule assembly, modulation of permeability in cell and organelle membranes, immune regulation, and activation of molecular pathways leading to DNA damage, autophagy and apoptosis (24).

Induction of apoptosis and autophagy

TTFields-induced cellular stress can elicit autophagy as a survival response, while simultaneously, under specific conditions, promoting apoptosis and cell death. TTFields, either administered alone or in combination with hyperthermia or certain drugs such as paclitaxel, sorafenib, and MPS1-IN-3 (a spindle assembly checkpoint inhibitor), have demonstrated the ability to enhance apoptosis in glioma cells (25,26). The extent of apoptosis induction varies among different cell lines and is positively correlated with the intensity of TTFields (27). Nevertheless, in their study, Chang *et al.* have suggested that at higher field intensities and optimal inhibition frequencies, TTFields may not significantly increase apoptosis (28). Inhibition of autophagy, on the other hand, leads to a heightened level of apoptosis and cell death (29).

Autophagy, an important cellular process that involves the degradation of cellular components, has been identified as a key pathway of cell death in various cancer cell lines in response to abnormal mitosis induced by TTFields (29). A study conducted by Lei *et al.* examined the mechanisms underlying cell death induced by TTFields, revealing that it does not involve caspase activation. Instead, their findings suggested that autophagy serves as the primary mechanism driving cell death. The study further demonstrated cell cycle arrest and the formation of abnormal nuclear figures in cells exposed to alternating electric fields (10).

Changes in membrane permeability [nuclear membrane, cell membrane, blood-brain barrier (BBB)]

TTFields have been observed to impact the permeability of membranes in cancer cells, although the precise underlying mechanisms leading to this effect are still being investigated. In a pivotal experiment conducted by Chang *et al.*, it was conclusively demonstrated that TTFields induce specific and reversible induction of membrane pores. This study specifically revealed an increase in both the number and size of pores in the cell membranes of U87-MG cancer cells, while no discernible difference was observed in healthy human fibroblast cultures. This specific effect plays a crucial role in facilitating improved penetration of chemotherapeutic agents into malignant cells while preserving the integrity of healthy tissues (28). Moreover, TTFields have been shown to reversibly weaken the BBB in both *in vivo* (rat models) and *in vitro* [murine cerebellar microvascular endothelial cells (cerebEND)] as well as in a three-dimensional (3D) co-culture model of the BBB. The

mechanism underlying this effect involves the mobilization of tight junction proteins, particularly claudin-5, from the cell membrane to the cytoplasm, resulting in increased permeability of the BBB. This finding, as demonstrated by Salvador *et al.*, highlights the potential of TTFields to modulate the BBB and allow for enhanced drug delivery strategies in glial tumor treatment (30).

TTFields have also been observed to induce local rupture and perforation of the nuclear envelope, processes that are closely linked to the cell cycle. It has been demonstrated that entry into the S phase is a prerequisite for TTFields to trigger nuclear envelope disruption and the subsequent formation of micronuclei (31,32). Additionally, following TTFields exposure, nuclear membrane disruption, micronuclei formation, and the release of fragmented DNA can activate Caspase1, leading to the cleavage of gasdermin D. This cleavage event, in turn, induces pyroptosis and membrane disruption, thereby amplifying the effects of TTFields on cellular processes.

Immune regulation

While the primary focus of research on TTFields has been their direct anti-tumor effects, recent studies have also unveiled their potential impact on the immune system (1,31,32). TTFields can engage with the immune system through various mechanisms, including the modulation of immune cell polarization and activation, the influence on cytokine production, and the modulation of the tumor microenvironment. Notably, TTFields have been found to promote dendritic cell activation and maturation *in vitro*, as observed in LLC-1, CT-26, MOSE-L, HEPG2, and H520 cell lines. Moreover, *in vivo* studies have demonstrated the enhanced ability of TTFields to attract leukocytes, further emphasizing its immunomodulatory effects (1). TTFields have demonstrated the remarkable ability to activate the STING pathway, leading to increased levels of dendritic cells within regional lymph nodes. Chen *et al.* elucidated this crucial pathway, highlighting how TTFields disrupt the nuclear membrane in tumor cells, resulting in the formation of cytosolic micronuclei clusters. These clusters, in turn, trigger AIM2/caspase 1 and cGAS/STING inflammasomes, thereby activating potent antitumor immunity against GBM cells (31).

Inhibition of cellular structures

TTFields have been shown to effect on the assembly of microtubules in cancer cells, which play essential roles in cellular processes such as cell division, intracellular transport, and maintenance of cellular shape (33). A study by Gera *et al.* showed that TTFields disrupt the localization of septin during anaphase, particularly when cells are attaching and spreading on fibronectin, impeding its association with microtubules. This disruption leads to abnormal metaphase exit, ultimately resulting in distorted nuclear architecture, cellular stress, reduced cell proliferation, and apoptosis. Notably, the impact of p53 mutational status significantly influences this process, emphasizing the intricate relationship between TTFields and the cell cycle (34). In addition to the effects on cell division, TTFields have been shown to influence the distortion of polarity generation and motility in cancer cells, thereby impacting metastasis. A study conducted by Voloshin *et al.* revealed that TTFields interfere with the directionality and robustness of cancer cell migration, activating the GEF-H1/RhoA/ROCK signaling pathway. This activation leads to the formation of focal adhesions and alterations in the architecture of the actin cytoskeleton, ultimately modulating cancer cell migration patterns. These molecular events not only provide insights into the mechanism of action of TTFields but also highlight their potential in attenuating metastatic potential (2).

DNA damage signaling pathways

TTFields have been found to enhance the efficacy of RT when applied simultaneously. Giladi *et al.* demonstrated that TTFields not only induce DNA damage on their own but also stabilize the DNA damage induced by RT. This synergistic effect leads to improved outcomes and increased effectiveness of irradiation (35). Karanam *et al.* revealed that exposure to TTFields leads to the downregulation of the BRCA1 signaling pathway, which plays a key role in repairing DNA double-strand breaks. In addition to slowing down the pace of DNA damage repair, the observed accumulation of γ-H2AX foci, colocalized γ-H2AX/53BP1 foci, and increased occurrence of chromatid-type aberrations supported the idea that TTFields also induce replication stress (36). Moreover, TTFields potentially lead to DNA damage through a reduction in the expression of crucial replication genes (*MCM10* and *MCM6*). The study also highlights the impact of TTFields on R-loops, which are unique nucleic acid structures formed during transcription, playing a role in gene expression regulation. TTFields exposure amplifies

Table 3 Completed clinical trials of tumor treating fields

Study name	Trial number	Condition	N	Phase	Arms	Intervention	Results
EF-11	NCT00379470	rGBM	237	III	2	TTFields *vs.* chemotherapy	OS: 6.6 *vs.* 6.0 mo; AEs: 6% *vs.* 16%
EF-14	NCT00916409	ndGBM	695	III	2	TMZ + TTFields *vs.* TMZ	OS: 11.8 *vs.* 9.2 mo; PFS: 6.7 *vs.* 4.0 mo
–	NCT01894061	rGBM	25	II	1	Bevacizumab + TTFields	OS: 10.5 mo; PFS: 4.1 mo
COMET	NCT01755624	Brain metastasis (from NSCLC)	60	II	2	TTFields *vs.* BSC	AEs: no safety concerns
STELLAR	NCT02397928	Mesothelioma	80	II	1	Pemetrexed + platinum + TTFields	OS: 18.2 mo; PFS: 7.6 mo; 1-year OS: 62.2%
EF-15	NCT00749346	NSCLC (stage IIIB–IV)	42	II	1	Pemetrexed + TTFields	PR: 14.6%; SD: 48.8%; OS: 13.8 mo; time to in-field progression: 28 weeks
LUNAR (EF-24)	NCT02973789	NSCLC	276	III	2	ICI or DTX + TTFields *vs.* ICI or DTX alone	OS: 13.2 *vs.* 9.9 mo
HEPANOVA	NCT03606590	HCC	25	II	1	Sorafenib + TTFields	ORR: 18%; DCR: 76%; AEs: no safety concerns
PANOVA-2	NCT01971281	PDAC	17	II	2	Gemcitabine + TTFields *vs.* gemcitabine + nab-paclitaxel + TTFields	PFS: 8.3 mo, OS: 14.9 mo *vs.* PFS: 12.7 mo, OS: not reached yet
EF-31	NCT04281576	Gastric cancer	28	II	1	XELOX + TTFields	PFS: 7.8 mo; OS: 12.2 mo; DCR: 81%; ORR: 50%
INNOVATE	NCT02244502	Ovarian cancer	31	II	1	Paclitaxel + TTFields	OSR (1-year): 61%; PFS: 8.9 mo; PFS rate: 57%

rGBM, recurrent GBM; GBM, Glioblastoma; TTFields, tumor treating fields; OS, overall survival; mo, months; AEs, adverse events; ndGBM, newly diagnosed GBM; TMZ, temozolomide; PFS, progression free survival; NSCLC, non-small cell lung cancer; BSC, best standard care; PR, partial response; SD, stabile disease; ICI, immune checkpoint inhibitors; DTX, docetaxel; HCC, hepatocellular carcinoma; ORR, objective response rate; DCR, disease control rate; XELOX, capecitabine/oxaliplatin; PDAC, pancreatic ductal adenocarcinoma; OSR, overall survival rate.

R-loop formation, and the persistence of R-loops leads to DNA damage. BRCA1 and BRCA2 play vital roles in resolving these R-loops, and their depletion amplifies DNA damage (37).

Clinical outcomes with TTFields therapy

The initial clinical successful studies in recurrent GBM (rGBM) paved the way for further exploration of TTFields therapy in several malignancies (15,17,20,38,39). *Table 3* presents a comprehensive summary of clinical trials that have been completed and *Table 4* presents details about currently ongoing studies. The table encompasses essential details such as the patient group, sample size, additional interventions, and results.

TTFields therapy for GBM

The initial demonstration of the efficacy and safety of TTFields in the treatment of GBM has provided promising results for this aggressive disease with a historically poor prognosis despite intensive multimodality therapies. In a phase I/II pilot clinical trial with 20 patients, ten patients with recurrent malignant glioma received TTFields as monotherapy, while ten patients with newly diagnosed disease were treated with TTFields in combination with adjuvant temozolomide (TMZ) after completing concurrent RT and TMZ (40). Notably, the trial reported minimal device-related adverse effects, primarily mild to moderate contact dermatitis beneath the arrays. Moreover, although a small pilot study, it demonstrated improved progression-free survival (PFS) and overall survival (OS) compared to

Table 4 Summary of selected ongoing clinical trials of tumor treating fields

Study name	Trial number	Condition	N	Phase	Arms	Interventions
TRIDENT (EF-32)	NCT04471844	ndGBM	950	III	2	RT + TMZ + TTFields *vs.* RT + TMZ
	NCT05310448	Brainstem gliomas	10	Pilot	1	TTFields
Keynote B36 (EF-36)	NCT04892472	NSCLC	100	II	1	Pembrolizumab + TTFields
METIS (EF-25)	NCT02831959	Brain metastasis (from NSCLC)	270	III	2	SRS + TTFields *vs.* SRS + BSC
	NCT05341349	Brain metastasis (from melanoma)	10	I	1	Pembrolizumab + SRS + TTFields
	NCT05746325	Leptomeningeal metastasis (from breast cancer)	5	Pilot	1	TTFields
INNOVATE-3	NCT03940196	Ovarian cancer	540	III	1	Paclitaxel + TTFields
PANOVA-3	NCT03377491	PDAC	556	III	2	Gemcitabine + TTFields *vs.* gemcitabine + nab-paclitaxel + TTFields
	NCT05679674	PDAC	48	II	1	SABR + TTFields
	NCT04605913	PDAC	40	I	1	mGCN +TTFields
	NCT03203525	Liver metastasis	52	I	2	FOLFOX6 + bevacizumab + TTFields *vs.* DAT + TTFields
	NCT05092373	Advances solid tumors	36	I	2	Cabozantinib + TTFields or nab-paclitaxel *vs.* atezolizumab + TTFields
	NCT05004025	Uveal melanoma	10	I	1	Nivolumab + ipilimumab + TTFields

ndGBM, newly diagnosed GBM; GBM, glioblastoma; RT, radiotherapy; TMZ, temozolomide; TTFields, tumor treating fields; NSCLC, non-small cell lung cancer; SRS, stereotactic radiosurgery; BSC, best standard care; PDAC, pancreatic ductal adenocarcinoma; SABR, stereotactic ablative body radiation; mGCN, modified nab-paclitaxel, cisplatin and gemcitabine; DAT, liposomal doxorubicin, bevacizumab, temsirolimus.

historical controls. Encouragingly, with a longer follow-up, four patients, including two with primary disease and two with recurrent disease, exhibited long-term remission and remained alive without relapse even 12 years after initiating TTFields therapy (41). Two of the surviving patients experienced early signs of radiological progression but continued TTFields monotherapy, ultimately resulting in tumor regression after a median duration of four months. These findings provide preliminary evidence for the clinical efficacy and long-term survival benefits of TTFields therapy in patients with GBM.

In a phase III prospective trial (EF-11), the efficacy and safety of TTFields were evaluated as monotherapy compared to the physician's best choice of chemotherapy in patients with rGBM who had exhausted other treatment options (18). The study, conducted across 28 institutions in 7 countries, randomized 237 patients, with 120 patients receiving TTFields monotherapy and 117 patients receiving chemotherapy selected based on the historical assessment of effective rGBM therapies. The primary endpoint was OS, while secondary endpoints included PFS, radiological response rate, quality of life (QoL), and safety. The results demonstrated that TTFields monotherapy showed comparable efficacy to chemotherapy, with a similar median OS of 6.6 *vs.* 6.0 months and a 1-year OS rate of 20% in both groups (18). TTFields therapy exhibited a lower incidence of severe adverse events (6% *vs.* 16%; P=0.02) and was associated with improved QoL (18). Further analysis revealed that patients with high compliance with TTFields therapy (at least 75% of the time, equivalent to at least 18 hours per day) exhibited a higher median OS (7.7 *vs.* 4.5 months; P=0.04) (19). Notably, the localized delivery of TTFields therapy resulted in a reduced occurrence of the typical systemic side effects associated with chemotherapy, but a grade 1/2 medical device site reaction, characterized as mild to moderate skin irritation beneath the transducer

arrays, was experienced by 16% of patients, with no severe cases. These findings highlight the comparable efficacy, improved safety profile, and favorable QoL associated with TTFields monotherapy in rGBM patients, supporting its potential as an alternative therapeutic option. The PRiDe study, encompassing a cohort of 457 patients, provided real-world data that exhibited even more promising outcomes. Notably, the median treatment duration with TTFields extended to 4.1 months, compared to 2.3 months in the EF-11 study's TTFields arm. The 1- and 2-year OS survival rates were 44% and 30%, respectively, compared to 20% and 9% observed in the TTFields arm of the EF-11 trial. This study also unveiled the patients with a Karnofsky Performance Scale (KPS) ≥90, those experiencing their initial recurrence, and those who are naive to bevacizumab demonstrated better OS rates (42).

In a phase III randomized trial (EF-14), conducted by Stupp and colleagues, the safety and efficacy of TTFields therapy in combination with standard treatment were assessed in patients with newly diagnosed GBM (ndGBM) (43,44). The trial enrolled 695 patients who underwent standard concurrent chemoradiation and were stratified based on O6-Methylguanine-DNA Methyltransferase (MGMT) methylation and resection status. The patients were then randomly assigned to receive maintenance treatment with either TTFields plus TMZ or TMZ alone. The primary endpoints of the study were PFS and OS, with an interim analysis conducted for the first 315 patients with a minimum follow-up of 18 months (44). The results demonstrated that the addition of TTFields therapy to TMZ significantly improved both PFS and OS compared to TMZ alone, leading to the approval of TTFields by the Food and Drug Administration (FDA) for ndGBM. The updated findings of the EF-14 trial further revealed a significant improvement in 5-year survival rate with the addition of TTFields to TMZ, with consistent benefits observed across all patient subgroups (13% *vs.* 5%; P=0.004). In the TTFields + TMZ arm, the median PFS was 6.7 months compared to 4.0 months in the TMZ-alone arm (P<0.001), and the median OS was 20.9 months compared to 16.0 months (P<0.001) (43). This study also included a survey to evaluate the QoL, conducted every 3 months, and the results revealed no worsening in both the short and long term (45). Similar to the EF-11 trial, subsequent analysis of the EF-14 trial revealed that compliance levels of 50% or higher led to a notable enhancement in both PFS and OS. Even more, when the compliance rate exceeds 90% the median OS reaches to 24.9 months, accompanied by an encouraging 5-year survival rate of 29.3% (7). The degree of treatment adherence and higher electric field intensity applied to the tumor bed were identified as predictive factors for treatment outcome (46). Furthermore, Kesari *et al.* published the *post-hoc* analysis of the EF-14 trial, including 204 patients experiencing recurrence. Findings demonstrated that combining TTFields with chemotherapy after the first recurrence significantly extended the median OS to 11.8 months, compared to 9.2 months with chemotherapy alone [hazard ratio (HR): 0.70; P=0.049] (47). As a result, the National Comprehensive Cancer Network (NCCN) guidelines (v1.2023) currently recommend the use of TTFields therapy in combination with TMZ and RT as a preferred regimen for postoperative adjuvant treatment option for patients with ndGBM as a category 1 recommendation (48,49), yet its utilization is variable across institutions and geographic regions (3). Recent data from a meta-analysis, drawing from nine different studies involving 1,430 ndGBM patients, provides real-world data demonstrating improved OS with TTFields alongside standard care compared to standard care alone. Moreover, consistent device usage of more than 75% is associated with prolonged survival, highlighting the therapy's effectiveness when used diligently (50).

Following these two influential studies, additional supporting clinical data have been published. A retrospective multi-center study conducted in Germany aimed to assess the safety and efficacy of the CCNU (lomustine) plus TMZ regimen in combination with TTFields therapy in newly diagnosed isocitrate dehydrogenase (IDH) wild-type GBM patients with MGMT promoter methylation. A key finding of this study was that patients who used TTFields for a duration longer than 8 weeks demonstrated improved OS compared to those who used it for a shorter duration (21.5 *vs.* 11.2 months; P=0.01) (51). These results highlight the feasibility and safety of combining TTFields with CCNU and TMZ in the treatment of newly diagnosed MGMT promoter methylated, IDH wild-type GBM patients (51). Two other studies from Germany, the TIGER study (NCT03258021) and the TIGER PRO-Active Study (NCT04717739), have evaluated TTFields with respect to QoL. According to the presented results of the TIGER study, TTFields did not negatively impact QoL, with the exception of a higher incidence of skin itchiness. Results from the TIGER PRO-Active study are expected in 2024 (52,53). An open-labeled phase II study (NCT01894061) was designed to investigate the feasibility and safety of combination therapy of TTFields with bevacizumab for

the treatment of rGBM and demonstrated promising results, with a median PFS of 4.1 months and median OS of 10.5 months (54).

These successful outcomes have also sparked interest in exploring the use of TTFields therapy in the context of rare brain tumors, such as brainstem glioma. A phase 1 study (NCT05310448) has been initiated and is currently recruiting patients to evaluate the safety and potential efficacy of TTFields therapy in this patient population. Furthermore, the TRIDENT study (NCT04471844) is planned to enroll 950 ndGBM patients and randomize them into two cohorts: one receiving RT with TMZ plus TTFields therapy, and the other receiving RT with TMZ alone. The study aims to compare the OS, PFS, and QoL outcomes between these two groups (38).

Three studies have conducted cost estimations regarding the integration of TTFields into the standard-of-care therapy for GBM using data from the EF-14 trial (55-57). Bernard-Arnoux *et al.* and Connock *et al.* based their assumptions on a French National Health Insurance perspective in their economic modeling, whereas Guzauskas *et al.* conducted their analyses from the United States healthcare perspective. In the study conducted by Guzauskas *et al.*, the analysis revealed that the addition of TTFields to TMZ resulted in an undiscounted increase in mean survival of 1.8 life years compared to TMZ alone. The incremental cost-effectiveness ratio was calculated to be $150,452 per life year gained and $197,336 per quality-adjusted life year gained (57). Based on these results, the authors concluded that treatment with TTFields can be deemed cost-effective within the reported range of willingness-to-pay thresholds in the United States.

TTFields therapy for NSCLC

For patients with metastatic NSCLC, treatment in the second-line setting can include cytotoxic chemotherapy or single agent immune checkpoint inhibitor (ICI) therapy, however, response rates remain low across all treatment options (58). To address this need, clinical trials have been designed to investigate the combination of TTFields with various chemotherapy regimens. One such trial (EF-15, NCT00749346) focused on combining pemetrexed with daily TTFields therapy in 42 patients with inoperable stage IIIB and IV NSCLC who had experienced tumor progression. Patients were followed until disease progression, with the primary endpoint being the time to in-field progression. The results showed a median time to systemic progression of 22 weeks and a median time to in-field progression of 28 weeks. Six patients (14.6%) achieved partial remission, and 20 patients had stable disease (48.8%). Additionally, after 30 weeks of initiating the protocol, all primary lesions demonstrated a decrease in size. The one-year survival rate was 57%, and the median OS was 13.8 months. Importantly, the combination of pemetrexed with TTFields did not result in any significant adverse events (59). This study exhibited that pemetrexed with TTFields therapy was tolerable with high compliance rates and favorable efficacy compared to historical rates with pemetrexed alone. Further insights came from the LUNAR trial (NCT02973789), a phase III randomized study focusing on stage IV NSCLC patients together with standard therapies following progression while on or after treatment with platinum-based therapy. This trial compares TTFields plus standard of care (SOC) [docetaxel (DTX) or ICIs] to SOC alone, with OS as the primary endpoint. Secondary endpoints include PFS, overall response rate, QoL, and safety (17). The study included 276 patients, and its recently published findings revealed a significant improvement in median OS when TTFields were added to the SOC (13.2 *vs.* 9.9 months; P=0.035; HR: 0.74). Moreover, in the subgroup of patients who received a combination therapy of ICI and TTFields, a more pronounced increase in OS was observed when compared to those receiving ICI alone (18.5 *vs.* 10.8 months; P=0.030; HR: 0.63). In the subgroup of patients who received DTX, the addition of TTFields to the treatment regimen resulted in a slight increase in OS (11.1 *vs.* 8.7 months; P=0.28; HR: 0.81). These results suggested that the addition of TTFields to the standard treatment regimen significantly improves OS, especially when combined with ICI. This trial provided valuable information on the efficacy of combining TTFields with standard therapies in stage IV NSCLC patient population (60). Given the intriguing survival benefit in the patients treated with single agent ICI therapy, the ongoing EF-36/Keynote B36 trial (NCT04892472) aims to specifically evaluate the safety and efficacy of TTFields therapy (150 kHz) in combination with pembrolizumab as a first-line treatment for advanced NSCLC. This multicenter, randomized, phase II open-label study is still recruiting patients and focuses on advanced or metastatic intrathoracic, programmed death-ligand 1 (PD-L1) positive, treatment-naïve NSCLC patients (61). The results of this study are highly anticipated as they will shed light on the potential of TTFields therapy as a first-line treatment option in advanced NSCLC.

TTFields therapy for malignant pleural mesothelioma

MPM is a rare and poor prognosis condition with limited treatment options, resulting in a median survival rate of less than 2 years, even in stage I disease (62,63). Given the paucity of effective therapies for MPM, the phase II clinical trial STELLAR (NCT02397928) evaluated the efficacy of TTFields (150 kHz) in combination with systemic chemotherapy (pemetrexed and platinum) for patients with unresectable MPM (16). The STELLAR trial, which enrolled 80 patients, yielded promising outcomes, demonstrating a median OS of 18.2 months. Notably, only four patients experienced grade 3 skin toxicity attributed to the TTFields therapy. After the STELLAR study, the FDA approved TTFields in combination with pemetrexed and a platinum-based chemotherapy via the Human Device Exemption (HDE) pathway for patients with unresectable, locally-advanced or metastatic MPM in 2019. The findings of STELLAR study have been recently supported by real-world data, which confirmed the efficacy of TTFields in MPM treatment without significant high-grade TTFields-related side effects (64). The encouraging evidence generated by these studies has led to the approval of TTFields as a treatment option for MPM, making it the second malignancy to receive FDA indication for TTFields. The combination of TTFields with systemic chemotherapy shows potential in improving survival outcomes for patients with unresectable MPM, while demonstrating a favorable safety profile. However, a recent analysis evaluating device usage rates and patterns of use for TTFields in patients with MPM across 14 institutions in the United States reported that the real-world usage level, at 12 hours per day and 50%, was lower than the suggested daily usage of 18 hours per day and 75% (65). It is essential to develop further initiatives and guidelines to assess the impact of this finding on tumor control.

TTFields therapy for brain metastasis

The management of limited brain metastasis has undergone significant changes over the years, with stereotactic radiosurgery (SRS) replacing whole-brain radiotherapy (WBRT) (66), however, patients treated with focal therapy alone remain at increased risk of local and distant intracranial failure (67). Consequently, the application of TTFields therapy for brain metastasis has also been explored in clinical trials to help provide control of microscopic intracranial disease. Initially, the phase II COMET trial (NCT01755624) demonstrated the safety of TTFields therapy in 17 patients with brain metastasis from NSCLC without severe adverse effects (68). Building on these findings, the METIS trial (EF-25, NCT02831959) randomized 270 NSCLC patients with 1–10 brain metastases into two groups: one receiving SRS alone and the other receiving a combination of SRS and TTFields. The primary endpoint of the study was the time to first intracranial progression, with secondary endpoints including OS, time to neurocognitive failure, radiological response rate, and QoL. The results of the METIS trial are eagerly awaited as they will provide valuable insights into the use of TTFields in combination with SRS for brain metastasis (39).

While our current understanding of TTFields therapy in the context of brain metastasis is primarily limited to NSCLC, ongoing clinical trials aim to explore the potential benefits in other cancer types. A phase I trial (NCT05341349) is investigating the use of TTFields combined with SRS and ICIs for brain metastases from melanoma. Furthermore, a pilot study (NCT05746325) including five patients is currently underway to assess the safety and feasibility of TTFields therapy for leptomeningeal metastases from breast cancer. This study will provide insights into central nervous system metastasis beyond the brain.

TTFields therapy for pancreatic cancer

PDAC carries a grim prognosis, with most patients being diagnosed at an advanced stage and long-term OS of less than 10% (69). As traditional treatment options have shown limited effectiveness, researchers have turned their attention to alternative approaches such as TTFields therapy. Promising *in vivo* and *in vitro* studies prompted the initiation of the first multi-center, non-randomized, open-label phase II clinical trial, known as PANOVA-2 (EF-20, NCT01971281), which aimed to evaluate the safety and efficacy of TTFields therapy in PDAC (13,70,71). The PANOVA-2 study enrolled 40 treatment-naïve patients with locally advanced, unresectable, or metastatic PDAC. All eligible patients received TTFields therapy in combination with gemcitabine, while patients in one arm also received nab-paclitaxel. The primary endpoint was the safety and compliance of TTFields therapy, with PFS and OS as secondary endpoints. Adverse events observed were comparable to historical studies, with dermatitis being the main side effect attributed to TTFields therapy, reported by 21 patients, of which seven experienced grade

3 dermatitis. The compliance rate was 68% (14 hours/day) in the nab-paclitaxel cohort and higher at 78% (12.2 hours/day) in the gemcitabine alone cohort. Median OS and PFS were 14.9 and 8.3 months, respectively (72). These encouraging results led to the initiation of a phase III trial, PANOVA-3 (NCT03377491), which commenced patient recruitment in February 2018. The trial aims to enroll 556 patients with unresectable locally advanced PDAC, with OS as the primary endpoint, and PFS, response rate, resectability rate, adverse events, and QoL as secondary endpoints (15). Additionally, an ongoing phase I/Ib study (NCT04605913) is examining the role of TTFields therapy in metastatic PDAC, where the primary objective is to assess the safety of protein-bound paclitaxel, cisplatin, and gemcitabine combined with TTFields, while secondary endpoints encompass OS, PFS, and overall response rate. At the Miami Cancer Institute, an ongoing phase II clinical trial (NCT05679674) is also being conducted to assess the synergistic potential of combining the application of TTFields therapy directed at the abdomen with induction chemotherapy and ablative magnetic resonance-guided radiation therapy. The primary objective is to determine whether this therapeutic approach can significantly prolong PFS in comparison to the results observed in a historical control cohort of patients diagnosed with locally advanced PDAC treated with RT alone.

TTFields therapy for liver cancer

Hepatocellular carcinoma (HCC), characterized by limited treatment options especially due to the frequent presence of background liver cirrhosis, has motivated the investigation of TTFields as a potential therapeutic modality. The HEPANOVA trial (NCT03606590) is a phase II open-label, prospective, single-arm study designed to evaluate the efficacy and safety of TTFields therapy for HCC. Twenty-seven patients who were deemed unsuitable for surgery or local non-surgical treatment were enrolled and all patients received sorafenib in combination with TTFields (150 kHz) that was recommended to be applied for at least 18 hours a day. The primary endpoint of the trial was objective response rate (ORR), with secondary endpoints including OS, PFS, distant metastasis-free survival, and disease control rate. The interim analysis indicated no toxicity associated with TTFields (73). The ORR was higher but not statistically significant with TTFields therapy compared to historical results of sorafenib monotherapy (9.5% *vs.* 4.5%, P=0.24). Sixteen patients reported grade 3/4 adverse events (59%). The most frequently observed event was decrease in appetite, only one patient experienced TTFields-related grade 3 skin erosion beneath the arrays. Notably, no serious side effects were attributed to TTFields (21). These findings not only offer encouraging evidence supporting the utilization of TTFields in the treatment of HCC without significant safety concerns but also establish a foundation for further exploration of TTFields' potential in managing liver metastasis. A phase I study (NCT03203525) is currently ongoing to assess the use of TTFields in combination with bevacizumab and different chemotherapies for liver metastasis. The primary outcome of this study is the incidence of adverse effects, while the secondary outcome focuses on treatment response.

TTFields therapy for gastric and gastro-esophageal junction (GEJ) cancer

Surgery is the cornerstone of gastric and GEJ cancer management although may not be pursued for patients with advanced disease. In a recent phase II, single-arm, multi-center, open-label trial (EF-31/ZL-8301-001, NCT04281576), 28 patients with unresectable gastric or GEJ adenocarcinoma, who had not received prior treatment, were enrolled to assess the efficacy and safety of combining TTFields and XELOX (capecitabine/oxaliplatin). The results demonstrated favorable outcomes compared to historical controls, with a higher ORR (50% *vs.* 45% for TTFields plus XELOX *vs.* historical controls, respectively) (74). Additionally, the median duration of response was reported to be 10.3 months, and the disease control rate reached 81%. The trial further revealed a median OS of 12.2 months and a median PFS of 7.8 months. Importantly, adverse effects attributed to TTFields were limited to mild to moderate skin-related events, indicating a favorable safety profile (74). These promising findings suggest that the combination of TTFields and XELOX could be a potential therapeutic option for unresectable gastric or GEJ cancer patients.

TTFields therapy for ovarian cancer

The application of TTFields has provided a new treatment opportunity for patients with recurrent platinum-resistant ovarian cancer. In the phase II, single-arm clinical trial INNOVATE (EF-22, NCT02244502), TTFields were administered in combination with paclitaxel to evaluate both safety and efficacy for recurrent platinum-resistant ovarian cancer. Thirty-one patients were enrolled, and all received

weekly paclitaxel alongside TTFields at a frequency of 200 kHz. The primary endpoint focused on safety, while secondary endpoints included OS, PFS, and response rate. The results revealed a median PFS of 8.9 months, with OS not yet reached, while noteworthy 6-month and 1-year OS rates of 90% and 61%, respectively, were observed, demonstrating encouraging outcomes. The treatment-related adverse events were predominantly limited to mild to moderate skin toxicity, such as localized rash or irritation, which were observed in 28 patients (90%), with only two patients (6%) experiencing grade 3 skin toxicities (75). These promising findings have paved the way for a phase III trial, INNOVATE-3 (NCT03940196), further validating the potential of TTFields in the treatment of recurrent platinum-resistant ovarian cancer (20).

TTFields therapy for other malignancies

Other malignancies with dismal prognosis have also been a field of interest for the use of TTFields therapy. Uveal melanoma often leads to metastatic disease and prognosis remains poor; thus, a clinical trial investigating the efficacy of TTFields with nivolumab and ipilimumab in uveal melanoma is registered under the identifier NCT05004025. Furthermore, a phase Ib trial (NCT05092373) aims to evaluate the safety profile, adverse reactions, and optimal dosing of TTFields therapy when combined with either cabozantinib or nab-paclitaxel and atezolizumab for the management of patients with metastatic solid tumors in the abdominal or thoracic regions. The study aims to include patients with different pathological subtypes such as renal cell cancer, breast cancer, fallopian tube cancer, and uterine cancer. Only one ongoing clinical trial (NCT03203525) includes colorectal cancer patients so far which is a pilot study investigating safety profile of TTFields when used in combination with chemotherapy and bevacizumab for liver metastasis.

Dermatological adverse events

The main adverse events associated with TTFields predominantly manifest as dermatologic issues, particularly in areas where the skin directly interfaces with the arrays. These events encompass a broad spectrum, ranging from mild dermatitis to skin ulcers and secondary soft tissue infections (76). Extra caution should be exercised when employing combination therapies. For instance, bevacizumab may delay wound healing, while neutropenia and thrombocytopenia resulting from TMZ can make the skin more prone to secondary infections and bleeding (77). The type of adverse event and the severity of its manifestations define the appropriate intervention. On the other hand, maintaining clean and dry skin under the arrays is fundamental as a prophylactic approach (78).

Future directions

TTFields have been recognized as a fourth therapeutic modality in the treatment of malignancies with unfavorable prognoses and ongoing and upcoming clinical studies are contributing to the accumulation of strong evidence to support this inclusion. The potential of TTFields treatment in various cancer types, such as colorectal, renal, and breast cancer, is supported by preclinical data and emerging evidence, emphasizing the need for conducting clinical trials to broaden the eligible patient population for this therapy (79-84). Furthermore, preclinical studies conducted on head and neck squamous cell cancer and liposarcoma cell lines indicate the combination treatments with TTFields may offer promising results (85,86). Additionally, in order to address unexplored cancers in the context of TTFields, ongoing clinical trials play a crucial role in evaluating the efficacy of combining TTFields therapy with existing anticancer agents across diverse cancer types. These efforts aim to establish the feasibility of making TTFields therapy more widely available across different cancer types in the future. As attention shifts towards cancers in various anatomical regions, potential adaptations in transducer array design may be necessary to ensure optimal delivery of TTFields therapy while maintaining patients' QoL. Through continued research and innovation, the field of TTFields therapy holds promise for improving outcomes across a broader spectrum of cancers, paving the way for enhanced treatment options in the years to come.

Preclinical studies have shown that combining programmed cell death 1 (PD-1) inhibitors with TTFields can promote antitumor immune responses (1). The combination of TTFields with olaparib, a PARP1 inhibitor, shows promise as preclinical data indicate synergistic effects in enhancing cell killing, and ongoing trials, like the study combining niraparib and TTFields in GBM (NCT04221503), hold significant potential (37). Active investigations are underway to explore the combination of TTFields with other DNA-damage response processes, particularly focusing on targeting the Fanconi anemia pathway, which has implications in therapeutic resistance

to TMZ and also exhibits lethality with BRCA loss (87,88). Continued research in these areas will provide valuable insights into optimizing TTFields-based combination therapies, opening new avenues for improving treatment outcomes in cancer patients.

Conclusions

The preclinical and clinical studies discussed in this review underscore the significant clinical benefit of TTFields therapy demonstrated across multiple randomized clinical trials for several cancer types, and the emerging evidence indicating that indications for TTFields therapy may expand in the near future for other cancers. Advancing our understanding of the molecular mechanisms underlying TTFields-induced cellular toxicity, as well as its tumor specificity and therapeutic index, is crucial. Such knowledge will facilitate the wider acceptance and integration of TTFields as a novel modality within existing and innovative treatment approaches. Combining TTFields therapy with other local and systemic therapies may result in synergy, and this should be explored in future clinical trials. Lastly, attention should be directed at identifying patient subgroups most likely to benefit from TTFields therapy in addition to treatment-related factors associated with more favorable outcomes.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-82/rc

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-82/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-82/coif). TK and ALR report receiving travel stipend from GammaTile. RK reports receiving honoraria from Accuray Inc., Elekta AB, ViewRay Inc., Novocure Inc., Elsevier Inc., Brainlab, Kazia Therapeutics, Castle Biosciences, and Ion Beam Applications; institutional research funding from Medtronic Inc., Blue Earth Diagnostics Ltd., Novocure Inc., GT Medical Technologies, AstraZeneca, Exelixis, ViewRay Inc., Brainlab, Cantex Pharmaceuticals, Kazia Therapeutics, and Ion Beam Applications. MM is the Consultant of Kazia, Novocure, Zap, Xoft, Karyopharm and Sapience; MPM is on the advisory board of Mevion Technological, is board of directors of Oncoceutics and owns stocks of Chimerix. MDC reports receiving honoraria from ViewRay Inc. and Sirtex; research funding from ViewRay Inc, Novocure Inc. and StratPharma. MDC is on the advisory board of ViewRay Inc. EA has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Kutuk T, Atak E, La Rosa A, Kotecha R, Mehta MP, Chuong MD. Tumor treating fields: narrative review of a promising treatment modality for cancer. Chin Clin Oncol 2023. doi: 10.21037/cco-23-82