Review Article

Emerging potential of tumor treating fields as a treatment modality for pancreatic cancer: a narrative review of therapeutic evolution

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

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Background and Objective: Pancreatic ductal adenocarcinoma (PDAC) is poorly responsive to conventional treatment and therefore is among the deadliest cancers. Tumor treating fields (TTFields) delivers low-intensity electrical fields that alternate in direction and frequency to disrupt cell division in cancer cells and has emerged as a potentially effective therapy for PDAC. In this narrative review, we discuss the primary mechanisms of TTFields as well as emerging preclinical and clinical outcomes of this novel technology for PDAC.

Methods: We performed a literature search on PubMed, Clinicaltrials.gov and Google Scholar using the terms "tumor treating fields" and "pancreatic ductal adenocarcinoma". We included studies, review articles and editorials published in English between 1st January 2000 and 5th January 2023. All papers reviewed and their key references are cross-checked to maintain a balanced and high-quality literature review on the subjects.

Key Content and Findings: Preclinical studies have demonstrated anti-mitotic effects of TTFields on PDAC cell lines, and the safety of TTFields has been demonstrated in a phase II study. An ongoing phase III trial of chemotherapy +/– TTFields will hopefully provide valuable insights into whether TTFields should become a standard of care (SOC) for locally advanced unresectable pancreatic cancer. Thus, TTFields could represent a major breakthrough in the treatment of this highly malignant disease.

Conclusions: Preliminary clinical findings suggest that TTFields could be a promising treatment option for patients with PDAC, given its favorable safety profile and potential for significant clinical benefit. However, further research is needed to determine the optimal treatment parameters and patient subgroups that may benefit the most from this therapy.

Keywords: Tumor treating fields (TTFields); pancreatic ductal adenocarcinoma (PDAC); pancreas cancer

Received: 29 April 2023; Accepted: 25 September 2023; Published online: 02 November 2023.
doi: 10.21037/dmr-23-20
View this article at: https://dx.doi.org/10.21037/dmr-23-20

Introduction

Pancreatic cancer is the seventh most common cause of cancer-related deaths in both men and women worldwide and the fourth leading cause of cancer-related death in the United States (1,2). In 2023, it is estimated that there will be 64,050 new diagnoses of pancreatic cancer in the United States, and more than 50,550 people will die from the disease (1). Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic malignancy, accounting for about 85% of cases. While the overall survival (OS) rates of some cancer types have improved significantly in recent years, the expected survival from PDAC has remained consistently poor (3). According to projections by Ferlay *et al.*, PDAC may surpass breast cancer as the leading cause of cancer-related deaths in Europe by 2025 due to the lack of effective treatment options available (4). These findings highlight the urgent need for further research and development of innovative treatments for PDAC.

The management of PDAC is challenging and requires a multidisciplinary approach, with the involvement of radiation oncologists, medical oncologists, surgeons, and palliative care specialists. Due to its symptoms can be vague at early stage, most cases of PDAC are diagnosed at the locally advanced or metastatic stage, which makes them unsuitable for primary surgery (5). Surgery is the preferred first-line treatment if the cancer is localized and resectable. However, perioperative chemotherapy is often necessary to achieve improved outcomes. While surgical resection with negative margins is considered the only potentially curative treatment for PDAC, less than 20% of patients have resectable disease at the time of diagnosis (5). Even among those who undergo successful surgery with negative margins, the 5-year OS rate is only around 20% due to the high incidence of local and/or distant disease progression in spite of removal of all visible tumor tissue (6-8). Most patients harbor occult micrometastatic disease in regional and/or distant sites, which eventually progresses despite aggressive systemic therapy (9). For patients diagnosed with locally advanced, inoperable PDAC, typically due to extensive vascular involvement, long-term survival rates are especially poor, even with the use of multi-agent chemotherapy and/or radiation therapy (10). Overall, the effective management of PDAC requires a comprehensive approach that integrates various treatment modalities and provides patients with the best possible care. In this narrative review, we meticulously examine the fundamental mechanisms of tumor treating fields (TTFields), which is a novel therapy that targets cancer cells through multiple mechanisms, and evaluate the latest preclinical and clinical findings concerning the potential of this innovative technology to treat PDAC. We present this article in accordance with the Narrative Review reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-23-20/rc).

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 1* provides detailed information on the search strategy employed.

TTFields mechanism of action

An electric field is a field of electric forces that surrounds a source charge, whether positively or negatively charged, or if it is a dipole (11). In a constant and uniform electric field, a charged particle moves towards the opposite polarity. However, in an alternating electric field, charges oscillate back and forth, and dipoles rotate. This fundamental principle is harnessed in TTFields which alter the normal movement of charged particles and/or dipoles (11,12). In a non-uniform electric field with converging lines of force, the electric field intensity concentrates into a higher intensity at the smaller electrode. This creates a phenomenon known as dielectrophoresis, whereby polar cellular components are pushed towards the areas of the highest field intensity. During cell division, the non-uniform electric field created by the dividing cell can result in the polar components being pushed towards the cleavage furrow of the two daughter cells. If the non-uniform electric field is too strong, the cells may not be able to divide properly (12).

TTFields is a novel therapy that targets cancer cells through multiple mechanisms, resulting in the disruption of crucial processes and ultimately leading to cell death (13). Within the cell, highly polarized tubulin subunits are forced to align with the direction of the alternating electric fields generated by TTFields. This disruptive effect can interfere with the formation of microtubule spindles during cell division, leading to delayed mitosis and potentially apoptosis. Additionally, this therapy induces an anti-mitotic effect by disturbing mitotic spindle formation

Table 1 The search strategy summary

Items	Specification
Date of search	January 5, 2023
Databases and other sources searched	PubMed, Google Scholar, Clinicaltrials.gov
Search terms used	Tumor treating fields (TTFields), pancreatic cancer, pancreas cancer, pancreatic ductal adenocarcinoma (PDAC)
Timeframe	January 1, 2000–January 5, 2023
Exclusion criteria	Studies that were not written in English and those lacking available full text were excluded from our analysis
Selection process	All authors participated in the selection process together, reaching a consensus based on the potential benefits to clinical practice

and septin arrangement, causing cytoplasmic membrane blebbing and asymmetric chromosome segregation (14,15). A recent research has proposed that this effect may be due to changes in the membrane potential of tumor cells, leading to abnormal spindle formation (16). This disruption also leads to the formation of radial protrusions of peripheral actin filaments and focal adhesions, causing a loss of cytoskeletal directionality and cellular polarity (17). TTFields also downregulates genes important for DNA repair and promote the formation of DNA double-strand breaks and chromatid aberrations, further contributing to cell death. Moreover, this therapy enhances antitumor immune responses by promoting immunogenic cell death, upregulating autophagy, and increasing infiltration of activated tumor leukocytes (18,19). Preclinical studies have shown that TTFields in combination with immunotherapies result in an augmented antitumor effect, reduced tumor volumes, and increased infiltration of tumor leukocytes (20,21). Importantly, TTFields treatment does not impair T-cell cytotoxicity. Furthermore, TTFields disrupt the nuclear envelope and activate STING and AIM2 inflammasomes, inducing downstream adaptive immunity (22). Overall, TTFields present a promising therapeutic option for cancer treatment with a multi-faceted approach targeting both tumor cells and immune responses (22,23).

TTFields is delivered in a noninvasive manner using a portable medical device that includes skin arrays and a field generator. The efficacy of TTFields depends on factors such as frequency, intensity, and duration of treatment, with at least 18 hours of daily treatment recommended for maximal benefits (24). TTFields can target cancer cells without significantly affecting normal tissue by applying electric fields at frequencies ranging from 100 to 500 kHz (24,25). The frequency of TTFields can be tailored to the type of cancer being treated (26). For instance, 150 kHz is optimal for non-small cell lung cancer (NSCLC) and PDAC cells, while 200 kHz is optimal for ovarian cancer cells (27-29). TTFields selectively target cancer cells based on their unique characteristics, such as morphology and division rate, leaving healthy cells largely unaffected (30,31).

TTFields temporarily reduce the integrity of the tight junctions among endothelial cells in the brain vasculature, making it easier for anticancer drugs to pass through the blood-brain barrier and increase drug concentrations (32). *In vitro* studies using glioblastoma multiforme (GBM) cell lines have demonstrated that TTFields can also temporarily enhance the sensitivity of cancer cells to treatments by modifying the structure of their cell membranes and inducing the formation of pores to enhance permeability (30,33-35). Importantly, this effect is reversible and only lasts for 24 hours after the discontinuation of TTFields therapy. Overall, TTFields presents a promising approach to enhancing drug delivery and increasing cancer cell susceptibility to therapeutics (33).

TTFields for GBM

The efficacy and safety of TTFields were first demonstrated for GBM, which is a disease with a poor prognosis despite aggressive multi-modality therapy. In a phase I/II pilot clinical trial with 20 patients with GBM, 10 patients with recurrent disease received TTFields as monotherapy, while 10 patients with primary disease were treated with TTFields in combination with adjuvant temozolomide (TMZ) after completing concurrent radiation and TMZ (26). The trial

reported no device-related adverse effects (AEs) other than mild to moderate contact dermatitis beneath the electrodes delivering the treatment, and progression-free survival (PFS) and OS were improved compared to historical controls. With longer follow-up in the study, four patients, including two with primary disease and two with recurrent disease, remained alive and without relapse 12 years after initiating TTFields treatment (36). Interestingly, two of the surviving patients experienced early radiological evidence of progression, however continued TTFields monotherapy and ultimately experienced tumor regression after a median of four months. These results provided encouraging evidence for the clinical efficacy and long-term survival outcomes of TTFields in patients with recurrent GBM.

A phase III prospective trial called EF-11 was conducted on patients with recurrent GBM after receiving chemotherapy and after surgical and radiation options had been exhausted. The aim of the study was to evaluate the safety and efficacy of TTFields as monotherapy compared to physician's best choice of chemotherapy which was determined based on the historical assessment of effective recurrent GBM therapies and included bevacizumab (37). The trial involved 28 institutions from seven countries randomizing 237 patients, with 120 patients receiving TTFields monotherapy and 117 patients receiving chemotherapy. The primary endpoint was OS. Secondary endpoints were PFS, radiological response rate, quality of life, and safety. The results showed that TTFields monotherapy had similar efficacy as chemotherapy, with comparable median OS of 6.6 *vs.* 6.0 months and a 1-year OS rate of 20% *vs.* 20%. TTFields treatment also had fewer severe AEs (6% *vs.* 16%; P=0.02), and patients reported better quality of life (36). Further analysis demonstrated that patients with TTFields adherence of at least 75% (at least 18 hours/day) had higher median OS (7.7 *vs.* 4.5 months; P=0.04) (38). The median PFS was found to be 2.2 months in the group receiving TTFields monotherapy and 2.1 months in the group receiving the physician's choice of chemotherapy, with a hazard ratio of 0.81 (P=0.16). Because of the noninvasive, regional delivery of TTFields, the typical systemic side effects associated with chemotherapy were not observed in the patients treated with TTFields. Sixteen percent of patients had a grade 1/2 medical device site reaction, which was mild to moderate dermatitis underneath the transducer arrays. None of these cases were assessed as severe by the investigator.

A phase III randomized trial, EF-14, was conducted by Stupp and colleagues to evaluate the efficacy and safety of TTFields in combination with standard treatment for newly diagnosed GBM (39,40). The trial involved 695 patients who completed standard concurrent chemoradiation and were stratified by O6-methylguanine-DNA methyltransferase (MGMT) methylation and resection status before being randomized to receive maintenance treatment with either TTFields plus TMZ or TMZ monotherapy. The primary endpoints were PFS and OS, with a preplanned interim analysis evaluating the outcomes for the first 315 patients with at least 18 months of follow-up. The interim analysis demonstrated superior outcomes in the TTFields plus TMZ arm compared to the TMZ alone arm, with a median PFS of 7.1 *vs.* 4.0 months (P=0.001) and a median OS of 19.6 *vs.* 16.6 months (P=0.034) which resulting in Food and Drug Administration (FDA) approval for TTFields in primary GBM. The updated result of EF-14 also demonstrated that the addition of TTFields to TMZ resulted in significantly improved 5-year OS, and the improvement was seen across all patient subgroups. The median PFS was 6.7 months in the TTFields + TMZ arm compared with 4.0 months in the TMZ-alone arm (P<0.001). The median OS in the TTFields + TMZ arm was 20.9 months compared with 16.0 months in the TMZ-alone arm (P<0.001). The degree of adherence and higher electric field intensity to the tumor bed were predictive of outcome (41). Consequently, the National Comprehensive Cancer Network (NCCN) guidelines for central nervous system cancers currently include TTFields in combination with TMZ following standard chemoradiotherapy as a suggested postoperative adjuvant treatment choice for patients with newly diagnosed GBM (42).

TTFields for pancreas cancer

The clinical benefits achieved for GBM patients subsequently prompted exploration of TTFields for other cancers including PDAC. TTFields treatment is being tested in PDAC for several reasons. Firstly, PDAC tends to spread locally within the abdominal region to the liver and peritoneum, making it a good candidate for TTFields which is applied to the entire abdominal cavity (43). Secondly, there has been promising activity in *in vitro* and orthotopic tumor models (28,44). Finally, preclinical studies have shown that combining TTFields with chemotherapy drugs such as gemcitabine and taxanes may provide additional efficacy benefit (30). Together, these factors suggest that TTFields has the potential to be a valuable addition to the treatment options for PDAC patients.

A preclinical study conducted by Jo *et al.* demonstrated that the combination of TTFields and radiation therapy was more effective in delaying PDAC cell growth compared to monotherapy with either treatment in CFPAC-I and HPAF-II pancreatic cancer cell lines (45). Moreover, the combination therapy enhanced apoptosis, indicating potential for a synergistic effect between the two treatments. Giladi *et al.* conducted a study to evaluate the antimitotic properties of TTFields on pancreatic cancer cells *in vitro* and *in vivo* (14). The study demonstrated the effectiveness of TTFields (150 kHz) on hamster PDAC (PC-1.0) cells, as well as on human PDAC (AsPC-1 and BxPC-3) cells. *In vitro* application of TTFields resulted in a substantial reduction in cell count, an increase in cell size, and diminished clonogenicity. Further analysis revealed a significant increase in the quantity of abnormal mitotic figures, along with a decrease in the G2-M cell population. In *in vivo* application, TTFields significantly reduced tumor volume, accompanied by an increased frequency of abnormal mitotic events. When combined with chemotherapy, the efficacy of TTFields was enhanced *in vitro* and *in vivo* studies. In addition, the study demonstrated that increasing treatment time up to 48 hours can enhance treatment efficacy, resulting in a higher number of cells undergoing mitosis. In another study involving TTFields and human pancreatic cancer cell lines, it was found that a combination of mild hyperthermia (38.5 ℃) with TTFields (150 kHz) had a synergistic effect on reducing colony formation, inducing autophagy, and inhibiting cell viability in those cell lines (46).

The PANOVA-2 multi-center, non-randomized, open-label phase II study (EF-20, NCT01971281) investigated the efficacy and safety of using TTFields in combination with chemotherapy in the management of PDAC (47). This study enrolled 40 patients with unresectable, locally advanced, or metastatic PDAC who had not previously received chemotherapy or radiation therapy. Patients were treated with either TTFields and gemcitabine, or TTFields, gemcitabine, and nab-paclitaxel. The primary endpoint was the safety of TTFields, while secondary endpoints were TTFields compliance, PFS, and OS. Most patients in both treatment arms had an Eastern Cooperative Oncology Group (ECOG) score of 1, and 60% of them had distant metastases. The study required TTFields to be used for at least 18 hours daily, and while the compliance rate was 78% (14 hours/day) in the gemcitabine alone arm, it was 68% (12.2 hours/day) in the nab-paclitaxel arm. AEs were minimal, with no systemic toxicity related to TTFields observed. Specifically, 85% of patients in each cohort reported at least one grade ≥3 AEs. In the TTFields + gemcitabine cohort, the most common AEs reported were neutropenia (20%), diarrhea (10%), constipation (10%), dermatitis (10%) and fatigue (10%). In comparison, the most common AEs reported in the TTFields + gemcitabine + nab-paclitaxel cohort were neutropenia (35%), nonspecified skin lesion (20%), thrombocytopenia (15%), abdominal pain (15%), and fatigue (15%). Despite the occurrence of these AEs, no increase in serious AEs was observed when compared to the anticipated incidence with systemic chemotherapy alone. Dermatitis was seen skin under the arrays, with grades 1–2 and 3–5 reported in 15% and 10% of patients, respectively and all resolved after temporarily reducing the daily TTFields usage. Regarding efficacy, the combination therapy of TTFields and chemotherapy was found to be safe and tolerable for PDAC patients. The PFS at six months was 56% in the TTFields + gemcitabine arm and 65% in the TTFields + gemcitabine + nab-paclitaxel arm. The 1-year OS rate was 55% in the TTFields + gemcitabine arm and 72% in the TTFields + gemcitabine + nab-paclitaxel arm. The median PFS was 9.3 months in metastatic disease and has not been reached in locally advanced populations. Overall, the PANOVA-2 phase II trial highlights the potential of TTFields in combination with chemotherapy as a safe and effective treatment option for PDAC patients.

Optimizing TTFields therapy for the PDAC is notably challenging because of differences in body habitus and positioning of internal organs, as compared to the cranium and thoracic region. Recent preclinical studies have indicated that the effectiveness of TTFields is related to the intensity of the electric field, and that a therapeutic threshold of 1 V/cm exists (48,49). However, the distribution of the electric field in the body can be altered depending on the placement of the arrays. Currently, it is common practice to position arrays on the scalp to achieve maximum field intensity in the targeted tumor when treating GBM. Unfortunately, little research has been conducted to examine the placement of arrays on the abdomen in order to optimize the distribution of the electric field in this region (50). In the PANOVA-2 study, a generic layout was utilized. A study conducted by Naveh *et al.* aimed to investigate the effects of altering the transducer array layout on the mid-body and its impact on the field distribution within the abdomen and pancreas by using computer simulations (50,51). Three realistic computerized models were employed to mimic the

application of TTFields to the abdominal area, representing a male, a female, and an obese male. In each model, different setups were tested, using combinations of arrays with either 13 or 20 disks per array, resulting in 6–8 unique layouts for each model. Arrays were positioned on the upper portions of the six typical abdominopelvic regions, and the distribution of field intensity within these areas was assessed. A matrix for selecting between eight individual array layouts was generated and a clinical practical guideline was formulated based on the results.

After the successful demonstration of the safety of combination therapy in the PANOVA-2 study, a phase III trial, PANOVA-3 (EF-27, NCT03377491), was initiated to further investigate its efficacy (52). This trial is a prospective, randomized, open-label, pivotal study where the patients were randomized in two groups to receive combination therapy of TTFields with gemcitabine and nab-paclitaxel or TTFields and gemcitabine as a front-line treatment for locally advanced PDAC. This ongoing trial is currently recruiting locally advanced PDAC patients who will receive the same treatment as in the PANOVA-2 trial, and the primary endpoint will be OS. In the event of local disease progression, patients will be closely monitored for survival on a monthly basis. Secondary endpoints include PFS, objective response rate, resectability rate, quality of life, and toxicity.

Several other clinical trials are currently underway to investigate the use of TTFields in combination with various other treatments for PDAC. The first clinical trial mentioned is a Phase III randomized open label study from Fudan University, Shanghai, China (NCT05653453, P100-LAPC1), which aims to evaluate the safety and effectiveness of a combination of TTFields, gemcitabine, and nab-paclitaxel for the treatment of locally advanced PDAC in the first line treatment. This trial involves a comparison between TTFields combined with gemcitabine and nab-paclitaxel and gemcitabine plus nab-paclitaxel alone and will help determine whether this combination therapy can improve patient outcomes compared to standard treatments. A single arm phase II trial at Miami Cancer Institute (NCT05679674) is evaluating whether using induction chemotherapy followed by ablative magnetic resonance-guided radiation therapy and TTFields applied to the entire abdominal cavity will prolong PFS compared to historical control for locally advanced PDAC. The rationale for this trial is that distant progression, especially in the liver and peritoneum, is the most common cause of death among patients who have induction chemotherapy followed by ablative radiation therapy. Another single arm phase II trial from The Ohio State University (NCT05624918, BTCRC GI21-500) will test the use of peri-operative TTFields in combination with gemcitabine and nab-paclitaxel for resectable PDAC. This trial aims to determine the rate of resection rate following the neoadjuvant treatment with TTFields in combination with chemotherapy compared to standard neoadjuvant chemotherapy. Finally, a phase I/Ib pilot trial from Mayo Clinic (G200217, NCT04605913) will investigate a combination of nab-paclitaxel, cisplatin, and gemcitabine with TTFields for patients with metastatic and/or recurrent PDAC. The trial aims to evaluate the safety and effectiveness of this combination therapy by measuring grade 4 treatment-related AEs. *Table 2* provides an overview of ongoing and completed clinical trials using TTFields in pancreatic cancer patients, including the trial status, patient group, sample size, phase, device, other interventions, primary and secondary endpoints, and completion dates.

TTFields for other malignancies

A study found that TTFields combined with sorafenib at 150 kHz showed the best effectiveness in various hepatocellular cancer (HCC) cell lines and murine models (53). To further investigate this, a phase II single-arm study called the HEPANOVA trial was conducted with 27 HCC patients who received both sorafenib and TTFields (54). The preliminary safety data for the initial nine patients were presented and once again indicated the absence of any unforeseen severe toxicities linked to the combinations. The preliminary safety data for the initial nine patients were presented and once again indicated the absence of any unforeseen severe toxicities linked to the combinations. Recently, the authors reported the final results, which indicated that the combination of TTFields therapy and sorafenib treatment resulted in a two-fold increase in response rates (9.5% *vs.* 4.5%, P=0.24) compared to historical data with sorafenib monotherapy (55). Additionally, no new safety concerns or systemic toxicity were observed with the addition of TTFields. The response rate was even more improved in patients who received TTFields concomitant with sorafenib for at least 12 weeks. These findings suggested that the use of TTFields therapy in combination with sorafenib may be an effective treatment option for patients with advanced HCC.

Optimal efficacy of TTFields on ovarian cancer cell lines has been demonstrated in preclinical studies at a

Table 2 Clinical trials of tumor treating fields in pancreatic cancer: study characteristics and outcomes

Trial	Status	Patient group	Sample size	Phase	Device	Other interventions	Primary endpoints	Secondary endpoints	Completion date
NCT01971281 (PANOVA-2)	Completed	Unresectable locally advanced or metastatic pancreatic adenocarcinoma	17	Phase 2	NovoTTF-100L	Nab-paclitaxel, gemcitabine	AE Compliance rate	PFS OS OS rate (1 year) PFS rate (6 months) ORR	December 2017
NCT03377491 (PANOVA-3)	Recruiting	Locally advanced pancreatic adenocarcinoma	556	Phase 3	NovoTTF-200T	Nab-paclitaxel, gemcitabine	OS (4 years)	PFS LPFS QOL OS rate (1 year) Pain-free survival Rate of resection AEs	September 2024
NCT04605913	Recruiting	Metastatic pancreatic adenocarcinoma	40	Phase 1, Phase 2	NovoTTF-100L(P)	Nab-paclitaxel, cisplatin, and gemcitabine	Safety	PFS ORR OS	April 2025
NCT05624918	Not yet recruiting	Resectable pancreatic adenocarcinoma	38	Phase 2	NovoTTF-200T	Nab-paclitaxel, gemcitabine	OS (2 years), rate of resection	AEs ORR DFS Patterns of recurrence TLR TDM Compliance rate	February 2025
NCT05679674	Recruiting	Locally advanced pancreatic adenocarcinoma	48	Phase 2	NovoTTF-100L	Stereotactic ablative body radiation 50 Gy/5 Fr	Median PFS (2 years)	LC DMFS OS QOL AEs Location of recurrence CFI	March 2027
NCT05653453	Not yet recruiting	Locally advanced pancreatic adenocarcinoma	512	Phase 3	Not specified	Nab-paclitaxel, gemcitabine	OS (1 year)	AEs PFS (30 months) PFS (6 months)	September 2027

AE, adverse event; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; LPFS, local PFS; QOL, quality of life; DFS, disease-free survival; TLR, time to local recurrence; TDM, time to distant metastasis; LC, local control; DMFS, distant metastasis-free survival; CFI, chemotherapy-free interval.

frequency of 200 kHz (27). In a phase II trial (INNOVATE) of 31 heavily pretreated recurrent platinum-resistant ovarian cancer patients, TTFields were administered in combination with weekly paclitaxel (56,57). Patients had received an average of four prior lines of therapy, and almost all had previously received taxane-containing regimens. No significant adverse events were linked to TTFields, although a few patients experienced mild to moderate skin irritation. The median PFS was 8.9 months, and the median OS was not reached. These results were considered encouraging and paved the way for a large pivotal phase III randomized trial. In this upcoming trial, 540 patients with recurrent platinum-resistant ovarian cancer will be randomized to receive either weekly paclitaxel or the same treatment combined with TTFields. *Table 3* shows the AEs related to the use of TTFields in patients with abdominopelvic malignancies in three different clinical trials: PANOVA-2, HEPANOVA, and INNOVATE.

The effectiveness of TTFields delivered to the thorax in combination with systemic chemotherapy for patients with unresectable malignant pleural mesothelioma (MPM) was evaluated in the phase II clinical STELLAR (NCT02397928) trial and the application of TTFields to the thorax along with pemetrexed and platinum chemotherapy is considered a safe and effective treatment option for patients with unresectable MPM (58). Recently, a retrospective case series was published to report the real-world implementation of TTFields in combination with pemetrexed and platinum-based chemotherapy for MPM treatment (59). The authors reported that there were no significant device-related major toxicities, indicating the safety of the treatment. These results provide additional evidence to support the potential use of TTFields in combination with chemotherapy for MPM treatment. After a preclinical experiment on NSCLC cells showed that combining TTFields and paclitaxel resulted in reduced cell proliferation and clonogenicity, a pilot clinical trial was conducted on 42 advanced NSCLC patients who received pemetrexed concurrently with TTFields (60). The combination showed no increased toxicities and demonstrated a median PFS of 28 weeks and OS of 13.8 months. A large phase III randomized (LUNAR) trial was then initiated to test the efficacy of TTFields in combination with standard therapies in the second-line therapy. Due to changes in the SOC for NSCLC, the trial combined TTFields with immune checkpoint inhibitors [programmed cell death-1 (PD-1) inhibitors nivolumab or pembrolizumab], docetaxel *vs.* immune checkpoint inhibitors, or docetaxel alone in patients with stage 4 NSCLC (61). After an interim analysis involving 210 patients showed no increased systemic toxicity, the recent results of the LUNAR trial were presented at American Society of Clinical Oncology (ASCO) 2023. In the analysis, which included 267 patients, the median OS increased with the addition of TTFields to SOC [immune checkpoint inhibitor (ICI) or docetaxel] (13.2 *vs.* 9.9 months, P=0.035). Additionally, a more substantial increase was observed in patients receiving combination therapy compared to those receiving ICI alone (18.5 and 10.8 months, P=0.03). The trial offers valuable insights into the effectiveness of adding TTFields to standard therapies in stage IV NSCLC patients, particularly in combination with ICI (62).

After the successful results of the use of TTFields in the treatment of GBM, there has been a growing interest in its potential application for the treatment of solid cancer brain metastasis. However, the blood-brain barrier and blood-tumor barrier present significant challenges for the delivery of therapeutic agents to intracranial tumors due to their cellular, molecular, and physical characteristics (63). Preclinical evidence of TTFields activity NSCLC cell lines led to a pilot trial targeting patients with NSCLC brain metastasis, which demonstrated the safety of TTFields without severe toxicities (64). Building on these results, a large pivotal randomized controlled trial (EF-25, NCT02831959) was initiated in 2016 to evaluate the efficacy of TTFields in patients with 1–10 newly diagnosed brain metastases from NSCLC and the trial is still ongoing (65).

Conclusions

Early clinical data suggest that TTFields may offer significant clinical benefit for PDAC patients. The therapeutic ratio of TTFields for PDAC may be especially attractive because of its favorable safety profile, given non-invasiveness and potential efficacy. However, future studies will need to determine the optimal treatment duration, frequency, and intensity of TTFields therapy, as well as identify the patient subgroups that may benefit the most from this treatment approach. Additionally, the use of TTFields in combination with other treatment modalities, such as immunotherapy or targeted therapy, is an area of active investigation.

Table 3 Adverse effects related with tumor treating fields in patients with abdominopelvic malignancies

Factors	PANOVA-2 (47)		HEPANOVA (55)		INNOVATE (57)	
	Grades 1–2	Grades 3–5	Grades 1–2	Grades 3–5	Grades 1–2	Grades 3–5
Primary tumor	Pancreatic cancer (n=40)		Hepatocellular cancer (n=27)		Ovarian cancer (n=31)	
Chemotherapy	Nab-paclitaxel + gemcitabine		Sorafenib		Paclitaxel	
Hematological						
Anemia	12 [30]	2 [5]	3 [11]	0	4 [13]	4 [13]
Leukopenia	6 [15]	1 [3]	–	–	1 [3]	1 [3]
Neutropenia	4 [10]	11 [28]	–	–	1 [3]	3 [10]
Thrombocytopenia	8 [20]	3 [8]	–	–	–	–
Dermatological						
Dermatitis	3 [8]	3 [8]	5 [19]	0	26 [84]	2 [6]
Erythema	4 [10]	0	4 [15]	0	–	–
Gastrointestinal						
Abdominal pain	17 [43]	4 [10]	–	–	13 [42]	0
Constipation	12 [30]	2 [5]	3 [11]	0	8 [26]	0
Diarrhea	10 [25]	3 [8]	13 [48]	2 [7]	15 [48]	2 [6]
Nausea	23 [58]	0	3 [11]	0	13 [42]	0
Vomiting	12 [30]	1 [3]	–	–	7 [23]	0
Loss of appetite	18 [45]	1 [3]	5 [19]	3 [11]	5 [16]	0
Pulmonary						
Cough	4 [10]	0	–	–	–	–
Dyspnea	3 [8]	3 [8]	3 [11]	2 [7]	–	–
Cardiovascular						
Hypertension	2 [5]	1 [3]	1 [4]	2 [7]	–	–
Peripheral edema	11 [28]	1 [3]	3 [11]	2 [7]	14 [45]	0
General						
Pyrexia	12 [30]	0	0	0	5 [16]	0
Fatigue	6 [15]	5 [13]	–	–	10 [32]	0
Asthenia	–	–	9 [33]	2 [7]	5 [16]	0

Data are presented as n [%].

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Digestive Medicine Research* for the series "Novel Therapies for Pancreas Cancer". The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dmr.amegroups.com/article/view/10.21037/dmr-23-20/coif). The series "Novel Therapies for Pancreas Cancer" was commissioned by the editorial office without any funding or sponsorship. MDC served as the unpaid Guest Editor of the series, and serves as an unpaid editorial board member of *Digestive Medicine Research* from March 2019 to March 2025. TK reported that he receives travel stipend from Gammatile. MDC reported that he receives Honoraria from ViewRay, Sirtex, and research funding from ViewRay, Novocure, StratPharma, and is in the Advisory board for ViewRay. The authors have no other 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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doi: 10.21037/dmr-23-20
Cite this article as: Kutuk T, Atak E, Kaiser A, Chuong MD. Emerging potential of tumor treating fields as a treatment modality for pancreatic cancer: a narrative review of therapeutic evolution. Dig Med Res 2023.