DOI: 10.7860/JCDR/2026/85338.23954

Review Article

Oncology Section

Tumour Treating Fields in Solid Tumours: Integrating Physics with Cancer Treatment

RAM PUKAR BHARAT[1], RAVI KANODIA[2], AMOL SHANKAR DONGRE[3]

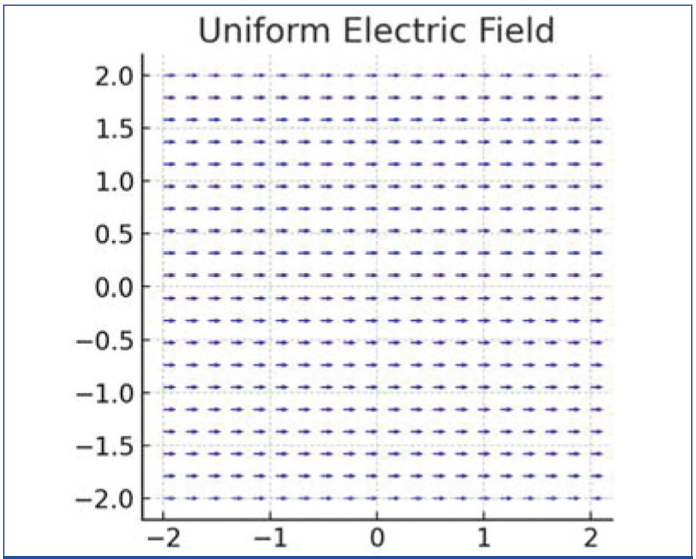
ABSTRACT

Tumour Treating Fields (TTFields) are non-invasive cancer treatment modality. They disrupt mitotic spindle formation and cytokinesis, inducing mitotic arrest and apoptosis, while also affecting Deoxyribonucleic Acid (DNA) repair, membrane permeability, and anti-tumour immunity. TTFields are clinically approved for the treatment of Glioblastoma Multiforme (GBM) and Malignant Pleural Mesothelioma (MPM). When combined with standard therapies, TTFields have been shown to significantly improve Progression-Free Survival (PFS) and Overall Survival (OS). Ongoing clinical trials are evaluating their efficacy in advanced ovarian cancer, Pancreatic Adenocarcinoma (PAC), and Non-Small Cell Lung Cancer (NSCLC) in combination with systemic therapies. Treatment is generally well tolerated, with mild, localised skin reactions being the most common adverse effect, supporting TTFields as a safe and effective adjunctive therapy for aggressive tumours.

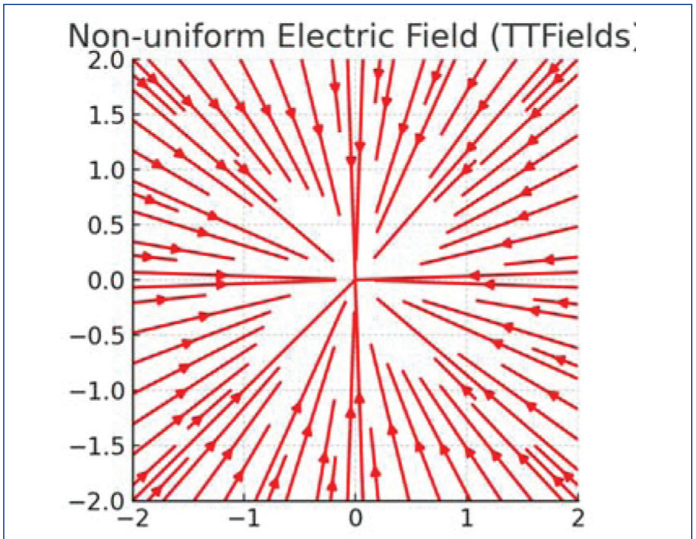
Keywords: Alternating electric fields, Apoptosis, Glioblastoma, Non-invasive cancer treatment

INTRODUCTION

The TTFields are an emerging cancer therapy delivering low-intensity (1-3 V/cm), intermediate-frequency (100-300 kHz) alternating electric fields to tumours through non invasive transcutaneous arrays. TTFields selectively disrupt dividing tumour cells by interfering with dipolar macromolecules, including tubulin and septins, causing mitotic spindle disruption, chromosomal missegregation, cytokinesis failure, and dielectrophoretic effects, while sparing normal tissues [1,2]. Initially, established in GBM, the EF-14 trial demonstrated significant improvements in PFS and OS with TTFields plus temozolomide (TMZ), leading to FDA approval [1]. Benefits were also observed in recurrent GBM (rGBM) [3,4]. Ongoing trials evaluate TTFields in solid tumours, including Non-Small Cell Lung Cancer (NSCLC) (LUNAR, METIS), pancreatic (PANOVA-3), and ovarian cancers (INNOVATE), often in combination with chemotherapy or immunotherapy [5-9]. Preclinical studies suggest synergistic effects with Immune Checkpoint Inhibitors (ICIs), supporting ongoing combination trials. TTFields represent a physics-based, non-toxic adjunctive therapy, and phase III studies are evaluating their broader role in solid tumours [10].



[Table/Fig-1a]: Uniform electric field distribution produced by a parallel-plate capacitor.



[Table/Fig-1b]: Non-uniform alternating electric field distribution produced by TTFields. TTFields generate non-uniform alternating electric fields that disrupt the dynamics of dipolar proteins such as tubulin and septins, resulting in impaired polymerisation, metaphase arrest, and subsequent cancer cell death [2,13].

Development of TTFields: Physics and Mathematical Principles

The TTFields are based on electromagnetic principles and mathematical models describing electric fields, forces, and dielectric polarisation. The following core equations and concepts are central to TTFields.

a. **Gauss's law:** Gauss's law states that the electric flux through a closed surface equals the enclosed charge divided by the permittivity of free space [11].

$$\oint E \bullet dA = Q/\varepsilon_0$$

where E is the electric field, dA represents the differential area element, Q is the enclosed charge, and ε_0 denotes the permittivity of free space. This principle governs field distribution in TTFields systems.

b. **Electric field in a parallel plate capacitor:** For a parallel-plate capacitor [2,12], the electric field is expressed as:

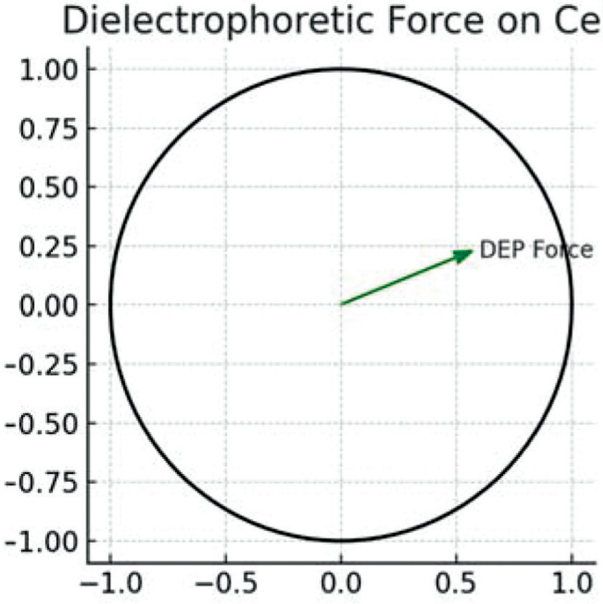
$$E = V/d$$

where V represents the applied potential difference and d denotes the plate separation. In contrast, TTFields generate non-uniform electric fields because of alternating frequencies and electrode geometry. [Table/Fig-1a,b] illustrate the difference between a uniform electric

field generated by a parallel-plate capacitor and the non-uniform electric field distribution produced by TTFields [2,13].

c. **Dielectrophoretic (DEP) force:** Non-uniform electric fields in TTFields give rise to dielectrophoretic forces [14]. $F_{DEP} = 2\pi r^3 \varepsilon m \, Re \{K(\omega)\} \nabla |E|^2$

where r denotes the particle radius, ε_m represents the medium's permittivity, $K(\omega)$ is the Clausius-Mossotti factor, and $\nabla|E|^2$ is represents the gradient of the squared electric field magnitude. [Table/Fig-2] illustrates dielectrophoretic forces acting on a dividing cell during telophase.



[Table/Fig-2]: Dielectrophoretic forces acting on a dividing cell under TTFields.

During telophase, this force displaces polar structures such as the septins complex, leading to the mislocalisation of contractile proteins, abnormal cytokinesis, and impaired chromosomal segregation. The final outcomes are the formation of cytoplasmic blebs, aneuploidy, and apoptosis.

d. **Frequency, power dissipation and tissue safety:** At high frequencies, tissues experience dielectric losses and heating [15].

$$P=\sigma |E|^2$$

where σ denotes tissue conductivity, and |E| represents the electric field magnitude. TTFields operate at 100-300 kHz, thereby avoiding left depolarisation of excitable tissues (<1 kHz) and dielectric heating (>1 MHz) while effectively inhibiting mitosis.

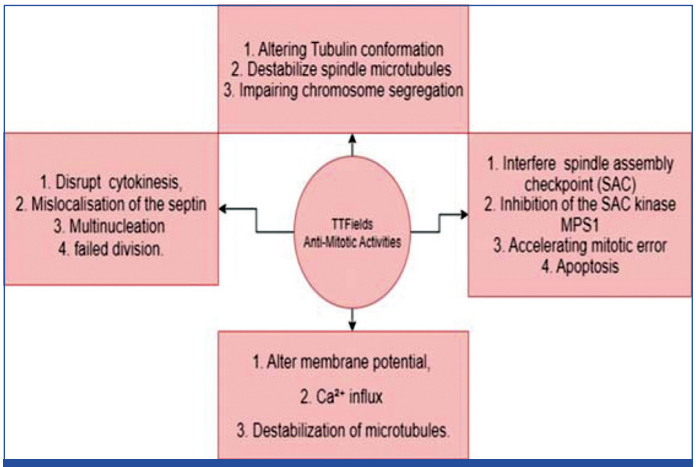
TTFields Electronic Delivery System

1. **Transducer arrays:** Flexible ceramic electrode arrays are applied to the scalp or thoraco-abdominal regions, delivering alternating electric fields to tumour tissue [16]. TTFields are administered through non-invasive transducer arrays connected to a portable device and are typically applied for at least 18 hours per day [1,4,16].
2. **Field generation unit**: A portable device (1.2-1.5 kg) generates fields at 100-300 kHz, with adjustable frequency and intensity [16].
3. **Power supply and control:** Rechargeable batteries enable continuous use (>18 h/day), with compliance monitoring and stable delivery [1,4,16].
4. **Field distribution:** Orthogonal array placement maximises tumour coverage; computational models account for conductivity, anisotropy, and patient anatomy [16].
5. **Safety features:** Insulated arrays reduce the risk of heating; mild, localised skin irritation remains the most common adverse effect [1,16].

Cell-Type Specificity of TTFields: Linking Biophysics to Tumour Biology

The antitumour efficacy of TTFields is inherently cell-type specific, reflecting fundamental biophysical differences between normal and malignant cell division and heterogeneity across tumour lineages. TTFields do not act uniformly on all dividing cells but preferentially exploit vulnerabilities characteristic of mitosis in cancer cells [16].

Normal somatic cells undergo tightly regulated mitosis with short mitotic duration, symmetric spindle geometry, intact spindle assembly checkpoints, and rapid cytokinesis, limiting exposure to alternating electric fields and reducing susceptibility to dielectrophoretic forces. In contrast, cancer cells frequently exhibit prolonged metaphase, abnormal spindle architecture, chromosomal instability, and impaired checkpoint control, increasing the window during which polar macromolecules such as tubulin and septins are vulnerable to TTFields-induced disruption [17]. Altered membrane properties, cytoskeletal disorganisation, and increased cellular anisotropy in cancer cells further amplify non-uniform field gradients during cytokinesis, promoting septins mislocalisation, cytokinetic failure, and mitotic catastrophe, effects that are largely absent in non-dividing normal tissues [Table/Fig-3].



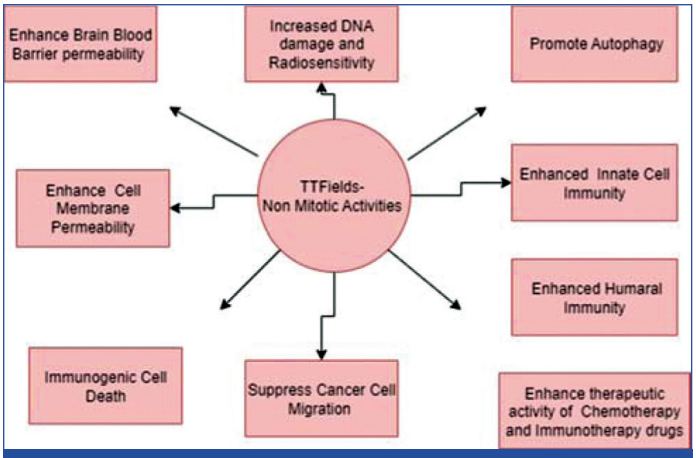
[Table/Fig-3]: Schematic representation of the antimitotic mechanisms of TTFields.

TTFields sensitivity is therefore determined by several interrelated parameters, including cell size and geometry, mitotic duration and proliferative fraction, cytoskeletal organisation, and tumour location and surrounding tissue conductivity. Larger, elongated, and highly proliferative cells experience stronger dielectrophoretic forces and greater mitotic disruption, whereas slow-cycling or quiescent tumour cell populations show attenuated responses. Differences in tissue dielectric properties further contribute to organ-specific variability in effective field distribution.

Collectively, these principles explain the consistent clinical benefit of TTFields in rapidly proliferating solid tumours such as GBM and mesothelioma, while accounting for variable efficacy in slower-growing malignancies [17]. This cell-type specificity underpins the favourable therapeutic index of TTFields and supports rational patient selection and biomarker-guided optimisation across tumour types [Table/Fig-4].

Resistance Mechanisms to TTFields

Although TTFields are mutation-agnostic, relative resistance may arise through adaptive, non-genetic mechanisms rather than stable mutational escape and is typically dynamic and potentially reversible. Reduced mitotic duration limits the time window for TTFields-mediated disruption of spindle assembly and cytokinesis, while cytoskeletal remodelling, including altered microtubule dynamics and septin organisation may decrease susceptibility to dielectrophoretic forces. Changes in cellular dielectric properties, driven by variations in membrane composition, cell size, or shape, can further attenuate effective field gradients [18].



[Table/Fig-4]: Schematic illustration of the non-antimitotic mechanisms of TTFields.

Cancer cells may also activate compensatory survival pathways, particularly PI3K/AKT signalling and autophagy, thereby enhancing stress tolerance under TTFields exposure. Importantly, available preclinical and clinical data suggest that these adaptations do not confer permanent resistance and may be mitigated by combination strategies, optimised field delivery, or treatment scheduling. Overall, TTFields resistance is predominantly adaptive rather than mutational, supporting rational combination approaches and biomarker-guided optimisation [18].

a. **TTFields with antimitotic activity:** TTFields inhibit tumour cell proliferation by disrupting mitosis through biophysical and biological mechanisms. During metaphase, uniform alternating electric fields align polar molecules, including tubulin dimers, impairing polymerisation and spindle formation. TTFields prevent cleavage furrow formation by disrupting septin 2/6/7 GDP-binding protein complex during anaphase. During cytokinesis, non-uniform fields concentrate at the furrow, producing dielectrophoretic forces that displace polar structures, causing abnormal chromosome segregation, multinucleation, and cell death [17,18]. Unlike conventional chemotherapy or radiotherapy, TTFields primarily target the metaphase-to-anaphase transition, inducing membrane blebbing, spindle dysfunction, and apoptosis, effects that may be modulated by p53 status. By affecting spindle integrity, checkpoint regulation, cytokinesis, and ionic balance, TTFields provoke mitotic catastrophe and programmed cell death [18]. This multimodal mechanism offers selective cytotoxicity in dividing cells while sparing non-dividing tissues, highlighting TTFields as a non-invasive, physics-based adjunctive therapy for aggressive solid tumours, with the potential to enhance standard treatments and improve clinical outcomes [17-19].

b. **TTFields with DNA damage and radiosensitivity:** The TTFields sensitise tumour cells to radiotherapy and DNA-damaging agents by inducing DNA damage and blocking repair. Preclinical studies show that TTFields applied before irradiation delay repair of double-strand breaks, increase mitotic catastrophe, and reduce survival in glioma and NSCLC cells. The TTFields inhibit homologous recombination repair by downregulating Homologous Recombination Repair (HRR)- and Fanconi pathway-related genes (BRCA1, ATRIP, MLH1, MRE11A, FANCM, FANCD2) and promoting persistent γH2AX and RAD51 foci. They also destabilise replication forks by increasing RPA foci, R-loops, and reducing DNA fibre length. TTFields enhance sensitivity to chemotherapy and PARP inhibitors, supporting combination with DNA-targeted therapies [20,21].

c. **TTFields with autophagy:** TTFields induce context-dependent autophagy. Preclinical studies have shown that early or moderate autophagy acts as a cytoprotective stress response, mediated through AMPK activation and inhibition of the PI3K/Akt/mTOR pathway, potentially supporting short-term tumour cell survival and resistance [22]. However, with sustained TTFields exposure, autophagy occurs in conjunction with mitotic catastrophe, ATP depletion, and defective DNA damage repair, thereby shifting toward autophagy-associated, non-apoptotic cell death rather than durable survival [23,24]. Importantly, clinical trial data consistently demonstrate net therapeutic benefit with TTFields, indicating that autophagy does not function as a dominant resistance mechanism in vivo. Survival improvements observed in EF-14, STELLAR, and PANOVA trials further support the concept that, particularly when combined with chemotherapy or radiotherapy, cumulative cellular stress overrides any early cytoprotective autophagy response [3,7,8,25].

d. **TTFields with innate immunity:** TTFields consistently induce immunogenic cell death, enhance antigen presentation, and increase $CD8^+$ T-cell infiltration, indicating a robust acute immune-activating effect. However, available preclinical and early clinical data suggest that TTFields alone are unlikely to generate durable immune memory. TTFields primarily function as an immune priming modality, reshaping the tumour microenvironment rather than inducing long-lasting adaptive immunity [26]. In particular, macrophages, which constitute approximately 30-40% of the GBM microenvironment play a central role in this response [27]. TTFields promote M1-like macrophage polarisation, increasing TNF-α, IL-6, IL-1β, nitric oxide, and Reactive Oxygen Species (ROS), with downstream activation of NF-κB and MAPK signalling, thereby amplifying pro-inflammatory and anti-tumour transcriptional programs [27,28]. Conditioned media from TTFields-treated macrophages reduce cancer cell viability, supporting a functional innate immune effect. Sustained anti-tumour immunity likely requires combination strategies, particularly with ICIs that TTFields synergise with PD-1/PD-L1 blockade to prolong immune activation and systemic tumour control, whereas TTFields monotherapy does not appear sufficient to establish durable immune surveillance or memory T-cell responses [28,29].

e. **TTFields with abscopal effect and antitumour immunity:** TTFields modulate both innate and adaptive immunity. They stimulate macrophages to produce ROS, nitric oxide, and proinflammatory cytokines, thereby promoting a pro-immunogenic tumour microenvironment. TTFields trigger immunogenic cell death through calreticulin exposure and ATP/high-mobility group box 1 (HMGB1) release, enhancing dendritic cell recruitment, maturation, and T-cell activation [30]. This is accompanied by increased infiltration of $CD4^+$ and $CD8^+$ T cells and systemic antitumour effects, including decreased metastasis. TTFields synergise with PD-1 checkpoint inhibitors in preclinical lung and colon cancer models. These findings support combining TTFields with immunotherapy to enhance antitumour efficacy [30,31].

f. **TTFields in Blood Brain Barrier (BBB) modulation and tumour cell dynamics:** TTFields temporarily disrupt the BBB via Rho kinase-mediated claudin-5 phosphorylation, enhancing CNS drug delivery, as evidenced by improved paclitaxel efficacy in tumour-bearing rats [32]. TTFields also inhibit cancer cell migration and invasion, including glioma-initiating cells, by suppressing NF-κB, MAPK, and PI3K/AKT signalling pathways, thereby reducing MMP2/MMP9, VEGF, and HIF-1α expression. This permeability range is sufficient to enhance intracellular delivery of small-molecule chemotherapeutics (e.g., TMZ, paclitaxel, cisplatin, and gemcitabine), radiosensitisers, and selected biologic fragments or nucleic-acid-based agents such as siRNA, antisense oligonucleotides, and small plasmid constructs. Importantly, this effect does not permit entry of full-length monoclonal antibodies (~150 kDa), but may facilitate

uptake of antibody fragments, nanoparticles, and drug-carrier conjugates within this molecular weight range. Thus, TTFields-induced membrane permeabilisation provides a mechanistic rationale for synergy with cytotoxic chemotherapy and emerging nucleic-acid or nanocarrier-based therapeutics, rather than with intact antibody therapies as supported by the superior survival observed in the EF-14 trial with TTFields plus TMZ [33].

Clinical Applications

TTFields represent a non-invasive cancer therapy that has been evaluated in preclinical models and clinical trials, administered either as monotherapy or in combination with standard treatments for solid tumours. [Table/Fig-5] provides details of individual malignancies in which TTFields have shown potential application [1,4-9,25,34-39].

a. **Recurrent Glioblastoma (GBM):** TTFields are a safe and effective therapeutic option for rGBM. Early phase II and pilot studies in highly selected patients with newly diagnosed GBM treated with TTFields in combination with radiotherapy and TMZ reported prolonged survival exceeding 39 months [4]; however, these findings are not directly comparable to the EF-11 trial, which evaluated TTFields in rGBM and demonstrated a median Overall Survival (mOS) of 6.6 months with fewer severe adverse events and better quality of life (QOL), leading to FDA approval. Ongoing phase II trials are evaluating TTFields with ICIs (nivolumab ± ipilimumab, NCT03430791) [40] and the PARP inhibitor niraparib (NCT04221503) [41] to enhance efficacy and guide biomarker-driven strategies in rGBM.

b. **Newly Diagnosed Glioblastoma (GBM):** The phase III EF-14 trial investigated TTFields in combination with adjuvant TMZ in 695 patients with newly diagnosed GBM. The addition of TTFields to TMZ significantly improved PFS (6.7-7.1 vs. 4.0 months) and OS (20.5-20.9 vs. 15.6-16.0 months), with two-year survival rate 43% compared with 29% (p<0.001) [1]. The therapy was well tolerated, with mild-to-moderate skin irritation reported in 52% of patients, leading to FDA approval and inclusion in NCCN guidelines [42]. Ongoing trials including 2-THE-TOP II [43], NCT03705351 [44], NCT03477110 [45], and TIGER [46] are assessing TTFields with TMZ, radiation, and pembrolizumab, demonstrating safety, immune activation, and promising survival outcomes.

c. **Malignant Pleural Mesothelioma (MPM):** MPM is a highly aggressive malignancy associated with limited therapeutic options. The phase II STELLAR trial (NCT02397928) assessed TTFields (150 kHz) combined with pemetrexed and platinum-based chemotherapy in 80 patients with unresectable MPM. Median overall survival reached 18.2 months compared with the historical value of 12.1 months, with a PFS of 7.6 months and a 12-month survival rate of 79.7%. The regimen was well tolerated, with only mild-to-moderate dermatitis reported and no increase in systemic toxicity. Based on these findings, the FDA approved TTFields for first-line MPM, supporting further investigation [25].

d. **Non-Small Cell Lung Cancer (NSCLC):** TTFields have demonstrated therapeutic potential in NSCLC. The LUNAR trial showed favourable tolerability, with predominantly mild skin toxicity, and reported 1- and 2-year survival rates of 53% and 27%, respectively [5]. In the EF-15 trial (NCT00749346), TTFields combined with pemetrexed improved mOS to 13.8 months compared with 8.3 months in historical controls [47]. Preclinical data further confirmed synergistic effects of TTFields

Cancer	TTFields frequency	Study name	Treatment	Results	References
Glioblastoma (GBM)	200 kHz	EF-14	Temozolomide (TMZ) vs. Temozolomide (TMZ) with TTFields	-mPFS (6.7-7.1 vs. 4.0 mo), -mOS (20.5-20.9 vs. 15.6–16.0 mo -2 year survival increased to 43% compared to 29% with TMZ alone	[1]
GBM , Recurrent	200k Hz	EF-11	TTF versus physician's choice chemotherapy	-1-year survival rate: 20% in both groups. -QOL: Better with TTFields. - mOS: 6.6 mo with TTFields vs. 6.0 mo with physician's choice chemotherapy.	[4]
NSCLC	150 kHz	LUNAR	Arm 1- TTFields (150 kHz) + physician's choice of Immune Checkpoint Inhibitor (ICI: anti-PD-1/ PD-L1) or docetaxel Arm 2- ICI or docetaxel alone	-mOS- 13.2 mo (TTFields + SoC) vs. 9.9 mo (SoC alone). -24-mo survival rate-18% vs. 7%. -Benefit stronger with ICIs- mOS 18.5 mo with TTFields + ICI vs. 10.8 mo with ICI alone	[5]
Brain metastasis from NSCLC	150 kHz	COMET	TTFields vs. supportive care for 1-5 brain metastases	Final Result awaited Safety profile data. 1/6 patient had mild dermatitis event. No serious adverse events	[34,35]
Brain metastasis from NSCLC	150 kHz	METIS	Radiosurgery With or Without TTFields for 1-10 brain metastases	Time to intracranial progression - Median 21.9 mo with TTFields plus BSC vs. 11.3 mo with BSC alone. QoL: TTFields group achieved a longer QoL deterioration-free survival. No cognitive decline noted Safety: mild-to-moderate skin reactions	[6,36]
Brain metastasis secondary SCLC	150 kHz	NCT03995667, NCT03488472	TTFields for brain Metastases	Result awaited	[37,38]
Malignant mesothelioma	150 kHz	STELLAR	Single arm study	-mOS increased by 6 months. PFS - 7.6 months. TTFields (150 kHz, ≥18 h/day) +Standard chemotherapy (Pemetrexed + cisplatin/carboplatin	[25]
Hepatocellular Carcinoma (HCC)	150 kHz	HEPANOVA	Single arm. -TTFields (150 kHz) applied to the liver with sorafenib (standard dose).	ORR was higher (9.5 % vs. 4.5 %), but not statistically significant (p = 0.24). 18% in patients treated ≥12 weeks. Disease control rate: 76% overall; 91% in patients treated ≥12 weeks. mPFS: 5.8 months	[39]
Pancreatic cancer	150 kHz	PANOVA	Arm A: TTFields (150 kHz, ≥18 h/day) + gemcitabine. Arm B: TTFields + gemcitabine + nab-paclitaxel.	Arm A (TTFields + gemcitabine): mPFS = 8.3 mo, mOS = 14.9 mo. Arm B (TTFields + gemcitabine + nab-paclitaxel): mPFS = 12.7 mo, mOS not reached	[7,8]
Ovarian cancer	200 kHz	INNOVATE	Tumour Treating Fields (TTFields, 200 kHz) with weekly paclitaxel	PFS of 8.9 mo. Clinical benefit rate: 71%. Partial response rate: 25%. One-year survival rate: 61%	[9]

[Table/Fig-5]: Summary of clinical trials evaluating TTFields in solid tumours [1,4-9,25,34-39].
Abbreviation: mOS: median Overall survival; mPFS: median Progression free survival; mo: month; QOL: Quality of Life; PFS: Progression free survival; SoC: Standard of care

with pemetrexed, cisplatin, or paclitaxel. The ongoing phase III LUNAR-2 trial (NCT06216301) is investigating TTFields in combination with docetaxel or PD-1 inhibitors to improve survival outcomes [48].

e. **TTFields for NSCLC and SCLC brain metastases:** TTFields are being investigated for brain metastases arising from NSCLC and SCLC. The METIS phase III trial (NCT02831959) [6,36] is enrolling 270 NSCLC patients with 1-10 brain metastases following radiosurgery, randomised to receive TTFields plus supportive care or supportive care alone, with endpoints including cerebral progression, survival, neurocognitive outcomes, and Quality of Life (QoL). The COMET trial [34,35] evaluates TTFields with or without radiosurgery in patients with unresectable NSCLC metastases. Additional studies including NCT03995667 [37] and NCT03488472 [38], are assessing TTFields in SCLC brain metastases, either alone or following stereotactic radiosurgery. Preliminary data indicate favourable tolerability, supporting TTFields as a safe, non-invasive adjunctive therapy for brain metastases.

f. **Hepatocellular Carcinoma (HCC):** TTFields (150 kHz) show potent anti-tumour activity in HCC, reducing cell viability and clonogenicity while inducing apoptosis and autophagy. The phase II HEPANOVA trial investigated TTFields in combination with sorafenib in 27 patients with advanced HCC, demonstrating an objective response rate of 9.5% and a disease control rate of 76%, which increased to 18% and 91%, respectively, in patients treated for ≥12 weeks. These findings support TTFields as a potential adjunctive therapy for advanced HCC [39].

g. **Pancreatic Adenocarcinoma (PAC):** PAC remains a highly lethal malignancy with limited treatment options. TTFields at 150 kHz reduce proliferation and clonogenicity, induce abnormal mitosis, suppressing tumour growth. The phase I/II PANOVA trial evaluated TTFields with gemcitabine, reporting median PFS of 8.3 months and a median OS of 14.9 months. The combination of TTFields with gemcitabine and nab-paclitaxel improved PFS to 12.7 months and one-year survival to 72%. The most common adverse event was mild-to-moderate skin dermatitis [49]. In the phase III PANOVA-3 trial (NCT03377491), TTFields plus chemotherapy improved OS (16.2 vs. 14.2 months), pain-free survival (15.2 vs. 9.1 months), and distant PFS (13.9 vs. 11.5 months) in locally advanced pancreatic cancer [7].

h. **Ovarian cancer:** Advanced ovarian cancer is typically treated with surgery, platinum-based chemotherapy, and maintenance therapy. Preclinical studies demonstrated that TTFields (200 kHz), combined with paclitaxel suppressed cell viability and tumour growth in experimental models. The phase II INNOVATE trial (NCT02244502) [9] in 31 platinum-resistant patients reported a median PFS of 8.9 months, a partial responses in 25%, and clinical benefit in 71%. The phase III ENGOT-ov50/INNOVATE-3 trial (NCT03940196) showed no OS benefit with TTFields plus paclitaxel; the therapy was well tolerated, and final results awaited [50].

Limitations and Challenges

Despite encouraging clinical outcomes, several limitations and unresolved challenges of TTFields warrant critical discussion.

a. **Patient selection:** Not all patients derive equal benefit from TTFields. Current evidence suggests maximal benefit in tumours characterised by a high mitotic index, such as GBM, MPM, PAC, and selected lung cancers. Clinical benefit is also closely linked to patient-related factors, including good performance status and the ability to maintain high treatment adherence (≥18 hours/day). Real-world data indicate that reduced compliance significantly attenuates the survival benefit, emphasising the importance of careful patient selection, counselling, and supportive care to ensure sustained device use.

b. **Comparison with standard therapies:** TTFields are not intended to replace established treatment modalities such as chemotherapy or radiotherapy. Instead, they function as an adjunctive therapy, providing additive survival benefit without overlapping systemic toxicity. Unlike cytotoxic agents, TTFields do not induce myelosuppression, neuropathy, or organ-specific toxicity, allowing their safe integration into multimodal treatment regimens. However, survival gains with TTFields are generally incremental rather than transformative, underscoring their role as an adjunct to standard-of-care rather than a standalone alternative.

c. **TTFields versus other emerging therapies:** Compared with targeted therapies, Antibody-Drug Conjugates (ADCs), PARP inhibitors, and ICIs, TTFields possess several distinguishing features. They are mutation-agnostic, avoiding dependence on specific genomic alterations; non-systemic, minimising off-target toxicity; and potentially resistance-sparing, as they act through biophysical rather than biochemical mechanisms. Nonetheless, unlike molecularly targeted agents or immunotherapies, TTFields lack predictive genomic biomarkers and require continuous device-based delivery, which may limit acceptance and accessibility in some patient populations.

d. **Preclinical-clinical correlation:** A key limitation is the imperfect translation of robust preclinical synergy into consistent clinical benefit. While in vitro and in vivo studies demonstrate enhanced cytotoxicity and radio-sensitisation when TTFields are combined with chemotherapy, PARP inhibitors, or immunotherapy, these effects do not uniformly translate into OS improvement. This discrepancy is highlighted by the phase III INNOVATE-3 trial in ovarian cancer, where a strong preclinical rationale did not result in an OS benefit. These findings underscore the influence of tumour biology, treatment timing, disease burden, and clinical context on TTFields efficacy.

e. **Biomarkers for response:** At present, validated predictive biomarkers of TTFields response are lacking, representing a major unmet need. Emerging candidates include tumour mitotic index, cellular size and anisotropy (which influence dielectrophoretic forces), DNA repair status, particularly Homologous Recombination Deficiency (HRD), and immune microenvironment features such as macrophage polarisation and T-cell infiltration. However, these markers remain exploratory, and prospective biomarker-driven trials are required before clinical implementation.

Impact of TTFields on Quality of Life (QoL), Compliance, and Long-term Safety

a. **Impact on Quality of Life (QoL):** Beyond localised dermatologic toxicity, multiple trials have systematically evaluated health-related QoL with TTFields. In GBM (EF-11, EF-14) and brain metastasis studies (METIS), TTFields were associated with preservation or improvement of global QoL, cognitive functioning, and role functioning compared with chemotherapy or supportive care alone. Importantly, TTFields do not exacerbate fatigue, nausea, neuropathy, or haematologic toxicity, symptoms that frequently limit tolerance of systemic therapies. Thus, the overall QoL impact of TTFields is largely driven by device-related burden rather than physiological toxicity.

b. **Compliance challenges related to prolonged daily use:** A major limitation of TTFields is the requirement for prolonged daily application (≥18 hours/day) to achieve maximal efficacy. Clinical and real-world data demonstrate a strong exposure-response relationship, with reduced compliance correlating with inferior progression-free survival and OS. Factors contributing to non-adherence include device weight, heat sensation, skin irritation, battery management, and interference with daily routines. These

challenges necessitate careful patient selection, education, and multidisciplinary support to optimise adherence.

c. **Psychological and social impact of device use:** Wearing a visible, continuously operating medical device may impose psychological and social burdens. Patients have reported altered body image, self-consciousness in public settings, sleep disturbance, and restrictions in occupational or social activities. Conversely, some patients perceive TTFields as empowering, as they allow active participation in treatment outside hospital settings. Psychosocial support, counselling, and normalisation strategies are therefore essential components of long-term TTFields management.

d. **Long-term safety and comparison with standard therapies:** Long-term safety data extending beyond five years, particularly from the EF-14 follow-up cohorts, demonstrate no cumulative systemic toxicity, organ damage, secondary malignancies, or neurocognitive decline attributable to TTFields. This contrasts sharply with standard therapies such as chemotherapy and radiotherapy, which are associated with myelosuppression, neuropathy, cardiotoxicity, nephrotoxicity, endocrine dysfunction, and late radiation effects. The absence of systemic adverse effects positions TTFields as uniquely suitable for prolonged administration, especially in patients requiring long-term disease control.

e. **Comparative toxicity profile:** Compared with conventional systemic treatments, TTFields exhibit a favourable toxicity profile, limited primarily to manageable skin reactions. Unlike chemotherapy, targeted agents, or immunotherapy, TTFields do not cause immune-related adverse events, cumulative bone marrow suppression, or dose-limiting organ toxicity. However, this favourable biological safety profile must be balanced against the practical and psychosocial burden of continuous device use, which remains a key limitation.

CONCLUSION(S)

TTFields constitute a non-invasive cancer therapy that disrupts tumour cell growth through biophysical and immunological mechanisms. Approved for GBM and MPM, TTFields are under active clinical evaluation across multiple solid tumours, demonstrating safety and therapeutic potential. Clinical studies demonstrate improved efficacy when combined with chemotherapy, radiotherapy, or immunotherapy, with minimal systemic toxicity. Trials in ovarian and pancreatic cancers have shown promising improvements in PFS and OS. Despite commercial availability through Novocure, high monthly treatment costs (approximately US$20,000-US$40,000) limit accessibility, particularly in low- and middle-income countries. Ongoing research seeks to optimise delivery, expand indications, and improve affordability, establishing TTFields as a safe and effective adjunctive therapy across multiple solid tumours.

REFERENCES

[1] Stupp R, Taillibert S, Kanner A, Read W, Steinberg DM, Lhermitte B. et al. Effect of tumour-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. JAMA. 2017;318(23):2306-16. Doi: 10.1001/jama.2017.18718.

[2] Kirson ED, Gurvich Z, Schneiderman R, Dekel E, Itzhaki A, Wasserman Y, et al. Disruption of cancer cell replication by alternating electric fields. Cancer Res. 2004;64(9):3288-95. Doi: 10.1158/0008-5472.can-04-0083.

[3] Kesari S, Ram Z, EF-14 Trial Investigators. Tumour-treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: A post hoc analysis of the EF-14 trial. CNS Oncol. 2017;6(3):185-93. Doi: 10.2217/cns-2016-0049.

[4] Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. Eur J Cancer. 2012;48(14):2192-202. Doi: 10.1016/j.ejca.2012.04.011.

[5] Leal T, Kotecha R, Ramlau R, Zhang L, Milanowski J, Cobo M, et al. Tumour Treating Fields therapy with standard systemic therapy versus standard systemic therapy alone in metastatic non-small-cell lung cancer following progression on or after platinum-based therapy (LUNAR): A randomised, open-label, pivotal phase 3 study. Lancet Oncol. 2023;24(9):1002-17. Doi: 10.1016/S1470-2045(23)00344-3.

[6] Mehta M, Brown P, Gondi V, Ahluwalia M. CLRM-10 METIS (EF-25): A pivotal, randomized controlled study of tumour treating fields in patients with 1–10 brain metastases from non-small cell lung cancer. Neuro-Oncol Adv. 2022;4(Suppl 1):i8. Doi: 10.1093/noajnl/vdac078.030.

[7] Babiker HM, Picozzi V, Chandana SR, Melichar B, Kasi A, Gang J, et al. Tumour treating fields with gemcitabine and nab-paclitaxel for locally advanced pancreatic adenocarcinoma: Randomized, open-label, pivotal Phase III PANOVA-3 study. J Clin Oncol Off J Am Soc Clin Oncol. 2025;43(21):2350-60. Doi: 10.1200/JCO-25-00746.

[8] Weinberg U, Faber O, Giladi M, Bomzon Z, Kirson E. PANOVA-3: A phase 3 study of TTFields with gemcitabine and nab-paclitaxel for front-line treatment of locally-advanced pancreatic adenocarcinoma (LAPC). Ann Oncol. 2017;28:iii81. Doi: 10.1093/annonc/mdx261.228.

[9] Vergote I, von Moos R, Manso L, Van Nieuwenhuysen E, Concin N, Sessa C. Tumour Treating Fields in combination with paclitaxel in recurrent ovarian carcinoma: Results of the INNOVATE pilot study. Gynecol Oncol. 2018;150(3):471-77.

[10] Wang Y, Pandey M, Ballo MT. Integration of Tumour-Treating fields into the multidisciplinary management of patients with solid malignancies. The Oncologist. 2019;24(12):e1426-e1436. Doi: 10.1634/theoncologist.2017-0603.

[11] Carrieri FA, Smack C, Siddiqui I, Kleinberg LR, Tran PT. Tumour treating fields: At the crossroads between physics and biology for cancer treatment. Front Oncol. 2020;10. Doi: 10.3389/fonc.2020.575992.

[12] Wenger C, Miranda PC, Salvador R, Thielscher A, Bomzon Z, Giladi M, et al. A review on Tumour-Treating Fields (TTFields): Clinical implications inferred from computational modeling. IEEE Rev Biomed Eng. 2018;11:195-207. Doi: 10.1109/RBME.2017.2765282.

[13] Rominiyi O, Vanderlinden A, Clenton SJ, Bridgewater C, Al-Tamimi Y, Collis SJ. Tumour treating fields therapy for glioblastoma: Current advances and future directions. Br J Cancer. 2021;124(4):697-709. Doi: 10.1038/s41416-020-01136-5.

[14] Tuszynski JA, Wenger C, Friesen DE, Preto J. An overview of sub-cellular mechanisms involved in the action of TTFields. Int J Environ Res Public Health. 2016;13(11):1128. Doi: 10.3390/ijerph13111128.

[15] Moser JC, Salvador E, Deniz K, Swanson K, Tuszynski J, Carlson KW, et al. The mechanisms of action of tumour treating fields. Cancer Res. 2022;82(20):3650-58. Doi: 10.1158/0008-5472.CAN-22-0887.

[16] "nvcr-10k_20151231.htm." Accessed: Aug. 24, 2025. [Online]. Available: https://www.sec.gov/Archives/edgar/data/1645113/000156459016013777/nvcr-10k_20151231.htm?utm_source=chatgpt.com.

[17] Gera N, Yang A, Holtzman TS, Lee SX, Wong ET, Swanson KD. Tumour treating fields perturb the localization of septins and cause aberrant mitotic exit. PLoS ONE. 2015;10(5):e0125269. Doi: 10.1371/journal.pone.0125269.

[18] Giladi M, Schneiderman RS, Voloshin T, Porat Y, Munster M, Blat R, et al. Mitotic spindle disruption by alternating electric fields leads to improper chromosome segregation and mitotic catastrophe in cancer cells. Sci Rep. 2015;5(1):18046. Doi: 10.1038/srep18046.

[19] Nishikawa R, Yamasaki F, Arakawa Y, Muragaki Y, Narita Y, Tanaka S, et al. Safety and efficacy of tumour-treating fields (TTFields) therapy for newly diagnosed glioblastoma in Japanese patients using the Novo-TTF System: A prospective post-approval study. Jpn J Clin Oncol. 2023;53(5):371-77. Doi: 10.1093/jjco/hyad001.

[20] Karanam NK, Srinivasan K, Ding L, Sishc B, Saha D, Story MD. Tumour-treating fields elicit a conditional vulnerability to ionizing radiation via the downregulation of BRCA1 signaling and reduced DNA double-strand break repair capacity in non-small cell lung cancer cell lines. Cell Death Dis. 2017;8(3):e2711. Doi: 10.1038/cddis.2017.136.

[21] Mumblat H, Martinez-Conde A, Braten O, Munster M, Dor-On E, Schneiderman R, et al. FP07.04 Effect of Tumour Treating Fields (TTFields) on DNA damage and The FA-BRCA DNA repair pathway in mesothelioma. J Thorac Oncol. 2021;16(10):S956-S957.

[22] Silginer M, Weller M, Stupp R, Roth P. Biological activity of tumour-treating fields in preclinical glioma models. Cell Death Dis. 2017;8(4):e2753. Doi: 10.1038/cddis.2017.171.

[23] Tanida I, Ueno T, Kominami E. LC3 and autophagy. Methods Mol Biol Clifton NJ. 2008;445:77-88. Doi: 10.1007/978-1-59745-157-4_4.

[24] Shteingauz A, Porat Y, Voloshin T, Schneiderman RS, Munster M, Zeevi E, et al. AMPK-dependent autophagy upregulation serves as a survival mechanism in response to Tumour Treating Fields (TTFields). Cell Death Dis. 2018;9(11):1074. Doi: 10.1038/s41419-018-1085-9.

[25] Ceresoli GL, Aerts JG, Dziadziuszko R, Ramlau R, Cedres S, van Meerbeeck JP, et al. Tumour Treating Fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): A multicentre, single-arm phase 2 trial. Lancet Oncol. 2019;20(12):1702-09. Doi: 10.1016/S1470-2045(19)30532-7.

[26] Kim EH, Jo Y, Sai S, Park M-J, Kim J-Y, Kim JS, et al. Tumour-treating fields induce autophagy by blocking the Akt2/miR29b axis in glioblastoma cells. Oncogene. 2019;38(39):6630-46. Doi: 10.1038/s41388-019-0882-7.

[27] Martinez-Lage M, Lynch TM, Bi Y, Cocito C, Way GP, Pal S, et al. Immune landscapes associated with different glioblastoma molecular subtypes. Acta Neuropathol. Commun. 2019;7(1):203. Doi: 10.1186/s40478-019-0803-6.

[28] Wang N, Liang H, Zen K. Molecular mechanisms that influence the macrophage M1-M2 polarization balance. Front Immunol. 2014;5:614. Doi: 10.3389/fimmu.2014.00614.

[29] Arango Duque G, Descoteaux A. Macrophage cytokines: Involvement in immunity and infectious diseases. Front Immunol. 2014;5:491. Doi: 10.3389/fimmu.2014.00491.

[30] Jiang X, Wang J, Deng X, Xiong F, Ge J, Xiang B, et al. Role of the tumour microenvironment in PD-L1/PD-1-mediated tumour immune escape. Mol Cancer. 2019;18(1):10. Doi: 10.1186/s12943-018-0928-4.
[31] Voloshin T, Kaynan N, Davidi S, Porat Y, Shteingauz A, Schneiderman RS, et al. Tumour-treating fields (TTFields) induce immunogenic cell death resulting in enhanced antitumour efficacy when combined with anti-PD-1 therapy. Cancer Immunol Immunother. 2020;69(7):1191-204. Doi: 10.1007/s00262-020-02534-7.
[32] Salvador E, Kessler AF, Domröse D, Hörmann J, Schaeffer C, Giniunaite A, et al. Tumour Treating Fields (TTFields) reversibly permeabilize the blood–brain barrier in vitro and in-vivo. Biomolecules. 2022;12(10):1348. Doi: 10.3390/biom12101348.
[33] Giladi M Schneiderman RS, Voloshin T, Porat Y, Munster M, Blat R, et al. Mitotic spindle disruption by alternating electric fields leads to improper chromosome segregation and mitotic catastrophe in cancer cells. Sci Rep. 2015;5(1):18046. Doi: 10.1038/srep18046.
[34] NovoCure Ltd. A Phase II randomized study of TTField Therapy (150 kHz) versus supportive care in non-small cell lung cancer patients with 1-5 brain metastases following optimal standard local treatment. clinicaltrials.gov, Clinical trial registration NCT01755624. Sept. 2016. Accessed: Aug. 24, 2025. [Online]. Available: https://clinicaltrials.gov/study/NCT01755624.
[35] Brozova H, Lucas A, Salmaggi A, Vymazal J. BMET-06COMET: A Phase II randomized study of ttfields versus supportive care in non-small cell lung cancer patients with 1-5 brain metastases - initial safety results. Neuro-Oncol. 2015;17(5):v46. Doi: 10.1093/neuonc/nov208.06.
[36] NovoCure Ltd. METIS Phase 3 clinical trial met primary endpoint significantly delaying time to intracranial progression with improved quality of life deterioration-free survival | Novocure.com. Accessed: Aug. 24, 2025. [Online]. Available: https://www.novocure.com/metis-phase-3-clinical-trial-met-primary-endpoint-significantly-delaying-time-intracranial?utm_source=chatgpt.com.
[37] Mitin T. Prophylactic tumour treating fields in management of patients with small cell lung cancer. clinicaltrials.gov, Clinical trial registration NCT03995667. 2023. Accessed: Aug. 24, 2025. [Online]. Available: https://clinicaltrials.gov/study/NCT03995667.
[38] Boggs DH. A pilot and feasibility trial to determine the rate of the brain relapse in Small Cell Lung Cancer (SCLC) patients with brain metastases treated with Stereotactic Radiosurgery (SRS) followed by Tumour Treating Fields (TTF). clinicaltrials.gov, Clinical trial registration NCT03488472, May 2023. Accessed: Aug. 25, 2025. [Online]. Available: https://clinicaltrials.gov/study/NCT03488472.
[39] Gkika E, Grosu AL, Macarulla Mercade T, Cubillo Gracián A, Brunner TB, Schultheiß M, et al. Tumour Treating Fields Concomitant with Sorafenib in Advanced Hepatocellular Cancer: Results of the HEPANOVA Phase II Study. Cancers. 2022;14(6):1568. Doi: 10.3390/cancers14061568.
[40] Baptist Health South Florida. Trial of Combination Tumour Treating Fields (TTF; Optune), Nivolumab Plus/Minus Ipilimumab for Recurrent Glioblastoma. ctv.veeva.com. Accessed: Aug. 24, 2025. [Online].
[41] Clinical Trial: NCT04221503 - My Cancer Genome. Accessed: Aug. 24, 2025. [Online]. Available: https://www.mycancergenome.org/content/clinical_trials/NCT04221503/?utm_source=chatgpt.com.
[42] Central G. New Guidelines from ASCO, NCCN, ESMO, NICE & More Published Early 2025 - Oncology guidelines rundown. Guideline Central. Accessed: Aug. 24, 2025. [Online]. Available: https://www.guidelinecentral.com/insights/early-2025-oncology-guidelines-rundown/.
[43] Tran DD, Ghiaseddin AP, Chen DD, Le SB. Final analysis of 2-THE-TOP: A phase 2 study of TTFields (Optune) plus pembrolizumab plus maintenance temozolomide (TMZ) in patients with newly diagnosed glioblastoma. J Clin Oncol. 2023;41(16_suppl):2024-24. Doi: 10.1200/JCO.2023.41.16_suppl.2024.
[44] Providence Health & Services. Safety and Tolerability of Tumour Treating Fields (TTFields) combined with chemoradiation in newly diagnosed glioblastoma (Unity). clinicaltrials.gov, Clinical trial registration NCT03705351, Aug. 2023. Accessed: Aug. 24, 2025. [Online]. Available: https://clinicaltrials.gov/study/NCT03705351.
[45] Miller R, Song A, Ali A, Niazi M, Bar-Ad V, Martinez N, et al. Scalp-Sparing Radiation With Concurrent Temozolomide and Tumour Treating Fields (SPARE) for patients with newly diagnosed glioblastoma. Front Oncol. 2022;12:896246. Doi: 10.3389/fonc.2022.896246.
[46] Bähr O, Tabatabai G, Fietkau R, Goldbrunner R, Glas M. Tumour treating fields (TTFields) therapy in patients with glioblastoma: Long-term survival results from TTFields in Germany in routine clinical care (TIGER) study. J Clin Oncol. 2024;42(16_suppl):2036-36. Doi: 10.1200/JCO.2024.42.16_suppl.2036.
[47] Pless M, Droege C, von Moos R, Salzberg M, Betticher D. A phase I/II trial of Tumour Treating Fields (TTFields) therapy in combination with pemetrexed for advanced non-small cell lung cancer. Lung Cancer Amst Neth. 2013;81(3):445-50. Doi: 10.1016/j.lungcan.2013.06.025.
[48] Eaton MS-S, Cobo M, Zhang L, Hochmair M, Langer CJ. LUNAR-2: Pivotal, randomized, open-label study of tumour treating fields (TTFields, 150 kHz) concomitant with pembrolizumab and platinum based chemotherapy for the treatment of metastatic non-small cell lung cancer. J Clin Oncol. 2024;42(16_suppl):TPS8665-TPS8665. Doi: 10.1200/JCO.2024.42.16_suppl.TPS8665.
[49] Rivera F, Benavides M, Gallego J, Guillen-Ponce C, Lopez-Martin J, Küng M. Tumour treating fields in combination with gemcitabine or gemcitabine plus nab-paclitaxel in pancreatic cancer: Results of the PANOVA phase 2 study. Pancreatol Off J Int Assoc Pancreatol. IAP Al. 2019;19(1):64-72. Doi: 10.1016/j.pan.2018.10.004.
[50] Vergote I, Copeland LJ, Gorp TV, Laenen A, Scambia G, Thaker PH, et al. Tumour Treating Fields therapy in platinum-resistant ovarian cancer: Results of the ENGOT-ov50/GOG-3029/INNOVATE-3 pivotal phase 3 randomized study. Eur J Cancer Oxf Engl. 1990;219:115306. Doi: 10.1016/j.ejca.2025.115306.

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Medical Oncology, Jawaharlal Nehru Medical College/Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
2. Senior Resident, Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi, Delhi, India.
3. Professor, Department of Medical Oncology, Jawaharlal Nehru Medical College/Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Ram Pukar Bharat,
Senior Resident, Department of Medical Oncology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research,
Wardha-442107, Maharashtra, India.
E-mail: rampukarbharat@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Nov 18, 2025
- Manual Googling: Mar 02, 2026
- iThenticate Software: Mar 05, 2026 (1%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Nov 12, 2025**
Date of Peer Review: **Dec 14, 2025**
Date of Acceptance: **Mar 07, 2026**
Date of Publishing: **Aug 01, 2026**