



Tumor Treating Fields Therapy

Effective: January 1, 2026

Next Review: February 2026

Last Review: December 2025

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Tumor treating fields therapy is a noninvasive technology that is intended to treat glioblastoma using alternating electric fields.

MEDICAL POLICY CRITERIA

- I. Tumor treating fields (TTF), including the use of mapping software for optimizing TTF therapy, may be considered **medically necessary** when all of the following (A.- F.) are met:
 - A. To treat newly diagnosed glioblastoma; and
 - B. Patient is 18 years of age or older; and
 - C. Location of the tumor is in the supratentorial region of the brain; and
 - D. Tumor is a histologically-confirmed glioblastoma. (Note: Glioblastoma includes grade IV astrocytoma and grade IV glioma, and glioblastoma subtypes are gliosarcoma and giant cell glioblastoma); and
 - E. Following radiation and chemotherapy; and
 - F. TTF is given concurrently with temozolomide (TMZ) therapy.
- II. The use of TTF and/or TTF-associated mapping software is considered

investigational when Criterion I. is not met and for all other indications, including but not limited to recurrent glioblastoma.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Documentation of histologically-confirmed glioblastoma demonstrating tumor is in the supratentorial region of the brain
- Radiation and chemotherapy history
- Documentation of Temozolomide (TMZ) maintenance treatment and response

CROSS REFERENCES

None

BACKGROUND

Glioblastomas, also referred to as glioblastoma multiforme (GBM), are the most common and deadly type of malignant brain tumor. Glioblastomas are grade IV astrocytomas, a rapidly progressing glial cell tumor that carries a poor prognosis.^[1] The peak incidence for glioblastomas occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to 1 year, and the 5-year survival rate was around 6%.^[2]

The primary treatment for glioblastoma is surgery followed by concurrent radiation therapy and daily temozolomide (TMZ) chemotherapy. Six cycles of adjuvant temozolomide follows the completion of concurrent chemoradiation.^[1] After primary treatment magnetic resonance imaging (MRI) surveillance is initiated. Disease recurrence is treated with debulking surgery if possible. Systemic therapy and radiation therapy are also used to treat recurrent glioblastoma. Palliative/supportive care is recommended for recurrent glioblastoma if performance status is poor.^[2]

TUMOR TREATING FIELDS THERAPY

Tumor Treating fields (TTF) therapy are proposed as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM. TTF is a noninvasive technology that is intended to treat glioblastomas on an outpatient basis using electrical fields.^[3-5] TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis.

The Optune™, formerly known as NovoTTF-100A™ System, (Novocure Inc.) has been approved by the U.S. Food and Drug Administration (FDA) to deliver TTF therapy. TTF

therapy via the Optune™ is delivered by a battery-powered, portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the tumor.^[3 4] The device is used by the patient at home on a continuous basis (20-24 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.^[3 4]

NOVOTAL™ SYSTEM

The NovoTAL™ (Transducer Array Layout) System (Novocure Inc.) is a proprietary software tool that produces a custom transducer array layout to optimize Optune therapy for each patient. The software accomplishes this by maximizing the intensity of Tumor Treating Fields (TTFields) based on MRI measurements of the head, tumor size and location(s) and optimizing TTFields distribution.

REGULATORY STATUS

Optune™, (assigned the generic name of TTF) was approved by Food & Drug Administration (FDA) in April 2011 through the premarket approval (PMA) process for treatment of adult patients (22 years of age and older) with histologically-confirmed recurrent glioblastoma multiforme (GBM).^[6]

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.^[7]

In October 2015, FDA expanded the indication for Optune in combination with temozolomide to include newly diagnosed GBM.^[8] The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune device, called the Optune System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

In May 2019, the FDA approved a modified version of the Optune System (NovoTTF-100A System), which is now called the Optune Lua™ System (NovoTTF™-100L System), for "treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy. The indication was modified from that granted for the Humanitarian Device Exemption designation to more clearly identify the patient population the device is intended to treat and in which the safety and probable benefit of the device is supported by the available clinical data."^[9]

In September 2021, the FDA granted breakthrough designation to the NovoTTF-200T System for use together with atezolizumab and bevacizumab for first-line treatment of patients with unresectable or metastatic liver cancer.^[10]

PRIMARY GLIOBLASTOMA

Systematic Reviews

Ballo (2023) published a systematic review and meta-analysis of the impact of TTF on overall survival (OS) from glioblastoma.^[11] Nine studies from the past decade involving 1430 patients were included. OS was longer in patients with newly diagnosed GBM receiving TTF therapy with standard of care compared to standard of care alone (HR: 0.63; 95% CI 0.53-0.75; $p < 0.001$). A subset of post-approval studies also found longer OS with TTF in addition to standard chemoradiotherapy (HR: 0.66; 95% CI 0.54-0.82; $p < 0.001$).

Regev (2021) conducted a systematic review of studies describing the use of TTF therapy for the treatment of GBM.^[12] The authors included a total of 20 studies of patients with newly diagnosed GBM and recurrent GBM. For newly diagnosed GBM ($n=542$), only one randomized controlled trial (RCT) was identified (Stupp, 2017), which is described in further detail in the section below. The remainder of the data for newly diagnosed GBM was observational. The pooled median overall survival (OS) and progression free survival (PFS) in newly diagnosed patients was 21.7 months (95% confidence interval [CI], 19.6 to 23.8) and 7.2 months (95% CI, 6.1 to 8.2) months, respectively. The pooled rate of OS at 1, 2, and 3 years was 73.5%, 45.1%, and 29.3%, respectively. The pooled rate of PFS at 6, 12, and 18 months was 55.9%, 32.4%, and 21.7%, respectively. Statistical comparisons to other treatment modalities were not provided.

Randomized Controlled Trials

In 2015, Stupp published interim results of the EF-14 study, an RCT regarding the safety and efficacy of TTF used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with GBM.^[13] Patients were randomized in a 2:1 fashion to receive maintenance treatment with TTF and TMZ ($n=466$) or TMZ only ($n=229$). Study eligibility required patients to be 18 years or older, have a histologically confirmed supratentorial glioblastoma, be progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and have completed standard concomitant chemoradiotherapy with TMZ. The median time from diagnosis to randomization was 3.8 months in both groups and patients were not blinded due to ethical concerns. TTF was delivered continuously (> 18 hours/day) via 4 transducers placed on the shaved scalp and TMZ (150-200 mg/m²/d) was given for 5 days of each 28-day cycle. Transducer array layouts were determined using the NovoTAL™ mapping software system for TTFIELDS to optimize field intensity within the treated tumor. A planned interim analysis was to be conducted on the first 315 patients at 18 months follow-up. The primary study endpoint was progression-free survival (PFS) in the intent-to-treat populations (with a significance threshold of .01) with overall survival (OS) in the per-protocol population ($n = 280$) as a powered secondary end point (significance threshold of .006). A total of 695 patients were enrolled across 83 centers; however, the trial was terminated as it met its efficacy endpoints at interim analysis (median 38 months, 315 patients).

The interim analysis included the planned 315 subjects, with 210 in the TTF/TMZ group and 105 in the TMZ only group. The analysis was conducted at a median 38 months follow-up (range, 18-60 months). Prespecified per-protocol median PFS in the TTF/TMZ group was 7.1 months (95% CI, 5.9-8.2 months) compared to 4 months (95% CI, 3.3-5.2 months) in the TMZ

only group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). The median OS in the per-protocol population was statistically improved in the TTF/TMZ group (20.5 months; 95% CI, 16.7-25.0 months) compared to the TMZ only group (15.6 months; 95% CI, 13.3-19.1 months; HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004). An additional analysis of the intention-to-treat population demonstrated and OS of 19.6 months (95% CI, 16.6-24.4 months) in the TTF/TMZ group compared to 16.6 months (95%CI, 13.6-19.2months) in the TMZ only group (HR,0.74 [95% CI,0.56-0.98]; stratified log-rank p = .03). Forty-three percent of patients in the TTF/TMZ group were alive at 2-year follow-up, compared to 29% in the TMZ only group (p = .006).

These interim results demonstrate an approximate three-month improvement of PFS and five-month improvement of OS when TTF therapy is used concurrently with TMZ in patients with newly diagnosed GBM.

In 2017, Stupp published final results from this trial, including all 695 subjects.^[14] From the time of randomization, median progression-free survival was 6.7 months in the TTF/TMZ group, and 4.0 months in the TMZ only group (HR, 0.63; 95% CI, 0.52-0.76; P < .001). Median overall survival was 20.9 months in the TTF/TMZ group as compared to 16.0 months in the TMZ only group (HR, 0.63; 95% CI, 0.53-0.76; P < .001). The application of TTF therapy in addition to TMZ treatment compared to TMZ treatment alone was not associated with an increase in adverse events (48% vs 44%, P = 0.58). Mild to moderate skin irritation was observed in 52% of patients who received TTF/TMZ treatment.

In 2021, Glas published a follow-up study of the E-14 trial that analyzed surveillance magnetic resonance imaging (MRI) data to assess tumor progression patterns and correlate the sites of tumor progression with patient outcomes.^[15] The study found no significant difference in the incidence of distant progression between the participants who had TTF therapy and those that did not (p=0.17), but the location of the lesions that developed with progressive disease was different. The difference in the median distance between the primary and distant progressions was larger in the TTF therapy group (p=0.03). Patients who had TTF therapy and distant progression had a longer time to progression than patients who had TTF therapy and had local progression (p=0.015). The TMZ only (control) group did not have a difference in time to progression related to the location of the new tumor (p=0.27). While the difference in progression free survival suggests TTF may prevent recurrence of the primary tumor, the difference in overall survival was not significant (p=0.085).

RECURRENT GLIOBLASTOMA

Systematic Reviews

Li (2022) published a systematic review and meta-analysis evaluating the safety and efficacy of TTF for recurrent glioblastoma.^[16] Nine studies were included in which 1048 participants were treated with TTF. Two of the studies were RCTs. Regarding efficacy, pooled analysis of five studies that reported HR for OS found that OS was longer in the TTF-treated group than in controls (HR 0.75 [95% CI 0.63-0.89]; p=0.001). The pooled one-year survival was 0.47 (95% CI 0.29-0.67). The authors noted the one-year survival rate for glioblastoma by race in the U.S. (2000-2014) was 0.414, and previous studies have found higher performance status scores are associated with OS in recurrent GBM. Heterogeneity in the meta-analysis was noted to be high ($I^2=91%$, p<0.01), and did not decrease with subgroup analysis based on patient age, compliance, or performance status (KPS score). The most common adverse event was local scalp dermatitis, with an incidence of 0.48 (95% CI 0.22-0.75). The authors

concluded that while OS was longer in people with recurrent glioblastoma receiving TTF, further study is needed to confirm the benefit of TTF and address the degree of heterogeneity in the current available evidence.

Randomized Controlled Trials

The use of TTF and the corresponding effects on living tissue have been studied in clinical settings.^[17-19] For example, in 2007, Kirson, reported the findings of a case study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent GBM.^[17] Median time to progression (TTP) in these patients was 26.1 weeks and median overall survival (OS) was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related adverse event observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was the use of historical controls, since the patients included may not be comparable on major clinical and prognostic features.^[17]

These preliminary findings served as a basis for a 2012 prospective Phase III multinational RCT by Stupp (EF-11), which was sponsored and funded by the manufacturer of the device (NovoCure). This study compared TTF therapy (delivered by the NovoTTF-100A™ System) to the best standard of care chemotherapy (active control).^[3] Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive GBM, despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky performance status (KPS) of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens (\geq second recurrence), and 20% had failed bevacizumab prior to study enrollment.^[3]

Two hundred thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only (n=120) or active control (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers.^[3] Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosoureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per day, for personal needs (e.g., shower). In addition, patients assigned to the TTF group were allowed to take 2 to 3 days off treatment at the end of each of 4-week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with TTF was considered 1 full treatment course.^[3]

The primary study end point in this RCT was OS.^[3] Secondary end points included progression-free survival (PFS) at 6 months, total time to progression (TTP), 1-year survival rate, quality of life (QOL), and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment, with subsequent MRIs done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.^[3]

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed one cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device.^[3] For each TTF treatment month, the median compliance was 86% (range, 41%-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except one individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.^[3]

This RCT did not reach its primary end point of improved survival compared to active chemotherapy.^[3] With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared to 6.0 months in the active control group (HR, 0.86; 95% confidence interval [CI], 0.66 to 1.12; $p=0.27$). For both groups, 1-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at 6 months was 21.4% in the TTF group, compared to 15.1% in the active control group ($p=0.13$). Objective radiological responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI, 7.9% to 22.4%) compared to 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized; severe (grades 3 and 4) toxicity was observed in 3% of participants.^[3]

Longitudinal QOL data were available in 63 participants (27%).^[3] There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group.

In summary, this RCT failed to demonstrate the primary end point of improved survival with TTF therapy in comparison to chemotherapy.^[3 20] Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of one or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or of TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy.

A further limitation was high dropout rates in both groups. For example, over 20% of participants in the active control group were lost at follow-up, and this may have underestimated the toxicity evaluation in this group. Similarly, over 20% of participants in the TTF arm discontinued treatment within a few days due to noncompliance or inability to handle

the device. This implies that compliance might be an issue with TTF, as it requires the patient to continuously wear transducers on the shaved head. Finally, the number of patients who completed the QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators may have been subject to bias due to the lack of blinding.^[3 6] Therefore, due to the numerous methodologic limitations, evidence from this trial is not sufficient to demonstrate that TTF therapy results in improved health outcomes for patients with recurrent GBM.

Post hoc subgroup analyses of these trial data have been published in abstract form comparing outcomes of patients between both groups who had failed bevacizumab prior to study enrollment.^[21 22] For example, Wong et al., published a subgroup analysis of the previously described RCT to determine characteristics of responders and non-responders in the treatment and active control groups.^[23] Tumor response was assessed by the Macdonald criteria. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months, $p < 0.001$), and there was a strong correlation (Pearson's r) between response and OS in the TTF arm ($p < 0.001$) but not in chemotherapy arm ($p = 0.29$). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

Nonrandomized Studies

In 2017, Kesari conducted a post hoc analysis of the EF-14 trial to evaluate the efficacy of TTF in patients who had the first recurrence.^[24] Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM. Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months. In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months ($p = 0.043$).

A study published in late 2014 included OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in 91 centers.^[25] The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF pivotal trial (9.6 months vs 6.6 months; HR=0.66, 95% CI, 0.05 to 0.86; $p < 0.001$). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the pivotal RCT (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the pivotal RCT. These results, although promising, are limited by a lack of randomized comparison group with which to isolate the direct effect of TTF therapy upon symptom improvement and overall outcomes.

In addition, two very small case series have also been published of long-term survival (>6 years) with TTF therapy.^[26 27] Since the approval of the NovoTTF device, additional case reports and very small case series ($n = 3-5$) have been reported.^[28-30]

NON-SMALL CELL LUNG CANCER

Leal (2023) published a randomized open-label phase 3 trial comparing TTF therapy with standard systemic therapy to standard systemic therapy alone in adults with metastatic non-small cell lung cancer (NSCLC).^[31] The primary endpoint was overall survival (OS). A total of 276 people were enrolled and randomized 1:1 to TTF therapy with standard therapy (n=137) or standard therapy alone (n=139). After median follow-up of 10.6 months in the TTF arm and 9.5 months in the control arm, OS was significantly longer in the TTF therapy arm (median 13.2 months [95% CI 10.3-15.5] vs. 9.9 months [8.1-11.5]; hazard ratio [HR] 0.74 [95% CI 0.56-0.98]; p=0.035). Serious adverse events were reported in 53% of subjects in the TTF therapy arm and 38% of controls. TTF-related adverse events were reported in 71% of the TTF group, and were primarily grade 1-2 skin and subcutaneous effects. Three deaths were attributed to standard therapy and no deaths were due to TTF treatment.

PLEURAL MESOTHELIOMA

TTF therapy has been investigated as an adjunct to pemetrexed and platinum-based chemotherapy for the treatment of unresectable, locally advanced, or metastatic pleural mesothelioma (MPM).

Ceresoli (2019) reported on the STELLAR study, which enrolled 80 patients with inoperable, previously untreated MPM.^[32] Participants were treated with cisplatin or carboplatin in combination with TTF therapy delivered by the NovoTTF-100L System at 12 sites outside the U.S. The primary outcome was OS as measured from start of study treatment until date of death. Secondary outcomes were PFS based on investigator assessment of computed tomography (CT) scan imaging, radiological response rate, one and two-year survival rates, and safety. In STELLAR the median OS was 18.2 months and median PFS was 7.6 months. Seventy-two of the 80 patients enrolled had at least one follow-up CT scan. Of those, 40% had a partial response, 57% had stable disease, and 3% progressed. The only adverse event associated with TTF treatment was skin reaction; this adverse event was mild to moderate for the majority of patients who experienced it (66%). Because there was no control group, it is not possible to draw conclusions about the effectiveness of TTF therapy compared to standard medical care alone. Additional limitations include the small sample size and no reporting of symptoms or quality of life outcomes.

Kutuk (2022) published a single-arm retrospective study of five patients with unresectable MPM who received TTF therapy from 2019 to 2021 at a single center in the US.^[33] The median follow-up was 5.4 months (range, 1.1 to 20.9). All patients were also treated with pemetrexed plus platinum-based chemotherapy. The median number of four-week TTF cycles was five (range, 2 to 7) and the median TTF device usage in the first three months was 12.5 hours per day (range, 5 to 16.8). Treatment-related dermatitis was the only side effect associated with TTF and was reported as grade 1-2 in all patients. There were no grade 3 device-related toxicities. The authors note that this was the first publication of real-world implementation of TTF for MPM.

HEPATOCELLULAR CARCINOMA

Gkika (2022) published results of the HEPANOVA study, a prospective, open-label, phase II, single arm trial to test the efficacy and safety of TTF concomitant with sorafenib in adults with advanced hepatocellular cancer (HCC).^[34] Twenty-seven patients were enrolled. They were treated with TTF and sorafenib and followed until disease progression with computed

tomography (CT) or magnetic resonance imaging (MRI) every 12 weeks. After disease progression, TTF was discontinued, and follow-up phone calls occurred every eight weeks. The primary endpoint was overall response rate (ORR) compared to historical controls. The ORR was higher than historical controls but not statistically significant ($p=0.24$). Nearly all participants experienced at least one adverse event (AE). The most common AE was skin reaction in the TTF field (70%), followed by diarrhea (56%), asthenia (41%), decreased appetite (30%) and ascites (22%). Sixteen participants had severe (grade 3-4) AEs. No patient deaths were attributed to TTF. The study was limited by the small patient population; only eleven participants completed 12 weeks of TTF therapy. Other limitations include its single arm, non-randomized design. Further research with larger populations is needed to determine if the trend toward higher ORR seen in the HEPANOVA study can be replicated with adequately powered trials.

OVARIAN CANCER

Vergote (2025) published a RCT that compared TTF with paclitaxel (PTX) to PTX alone in the treatment of platinum-resistant epithelial ovarian cancer.^[35] The study randomized 558 patients with a history of between one and four prior lines of therapy following platinum resistance. After a median follow-up of 10.7 months for patients in the TTF+PTX group and 9.9 months for the PTX only group, there was no difference in OS (12.2 months vs. 11.9 months; HR, 1.01; 95% CI, 0.83-1.24; $p=0.89$). An exploratory post-hoc analyses found that a subgroup of 201 pegylated liposomal doxorubicin (PLD)-naïve patients had longer OS with TTF+PTX (16.0 months vs. 11.7 months; HR [95% CI], 0.67 [0.49-0.94]; $p=0.03$). The authors concluded that PLD-naïve patients with platinum-resistant ovarian cancer may benefit from TTF therapy, but further study is needed.

NOVOTAL™ SYSTEM

Nonrandomized Studies

In 2016, Connelly published a small feasibility study using the NovoTAL™ System with nonstandard non-contrast enhancement and advanced imaging.^[36] All patients presented with gliomas (grades 2-4) and had previously received standard therapy prior to initiation of TTFIELDS. A standard pre- and postcontrast MRI scan was acquired and used for TTFIELDS treatment planning, in conjunction with other imaging modalities. Eight patients were reported on in this series: three underwent T2 imaging, one underwent FLAIR, one used diffusion weighted imaging, and one used MR-perfusion imaging. This case series demonstrates that treatment planning beyond the extent of contrast enhanced MRI is clinically feasible but it must be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

In 2015, Chaudhry evaluated physician performance in conducting transducer array layout mapping using the NovoTAL™ System compared with mapping performed by the Novocure in-house clinical team.^[37] Fourteen physicians (seven neuro-oncologists, four medical oncologists, and three neurosurgeons) evaluated five blinded cases of recurrent glioblastoma. Concordance for each physician versus Novocure on 20 MRI measurements was 0.96 (standard deviation, $SD \pm 0.03$, range 0.90-1.00), indicating very high agreement between the two groups, indicating that physicians prescribing TTFIELDS, when trained on the NovoTAL™ System, can independently perform transducer array layout mapping required for the initiation and maintenance of patients on TTFIELDS therapy. This study did not address clinical utility.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on central nervous systems tumors (v.4.2024) recommend TTF therapy as adjuvant therapy in conjunction with standard brain radiation therapy and concurrent/adjuvant TMZ for patients with glioblastoma or WHO grade 4 IDH-mutant astrocytoma, supratentorial disease and good performance status.^[2] This is a category 1 recommendation.

The guidelines recommend consideration of TTF for recurrent glioblastoma that is not surgically resectable (category 2B recommendation). In the guidelines discussion section, it is noted that due to a lack of clear efficacy data for TTF in the Stupp RCT, the panel is divided about recommending it for the treatment of recurrent glioblastoma.^[2]

The NCCN guidelines on treatment for non-small cell lung cancer (v.3.2025), pleural mesothelioma (v.2.2025), hepatocellular carcinoma (v.4.2024), and ovarian cancer (v1.2025) do not address TTF.^[38-40]

SUMMARY

The research on the safety and efficacy of tumor treating fields (TTF) therapy, and the associated optimizing software for patients with glioblastoma has some limitations. However, the small number of studies published do show that TTF therapy improves progression-free and overall survival in select adult patients with newly diagnosed glioblastoma who are receiving concurrent temozolomide (TMZ) treatment. Therefore, TTF therapy and TTF-associated mapping software may be considered medically necessary when criteria are met.

There is not enough research to show that tumor treating fields (TTF) therapy and TTF-associated mapping software for indications other than those specified in criteria improves overall health outcomes. More research is needed. Due to a lack of evidence and clinical practice guidelines based on research, the use of TTF and TTF-associated mapping software is considered investigational when criteria are not met.

REFERENCES

1. National Cancer Institute (NCI) - Adult Brain Tumors Treatment (PDQ®). . Secondary National Cancer Institute (NCI) - Adult Brain Tumors Treatment (PDQ®). 2/12/2025 [cited 03/10/2025]. 'Available from:' <http://www.cancer.gov/cancertopics/pdq/treatment/adultbrain/HealthProfessional>.
2. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Central Nervous System Cancers. V.142024. Secondary National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Central Nervous System Cancers. V.142024 [cited 3/10/2025]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.

3. Stupp R, Wong ET, Kanner AA, 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;48:2192-202. PMID: 22608262
4. Davies AM, Weinberg U, Palti Y. Tumor treating fields: a new frontier in cancer therapy. *Annals of the New York Academy of Sciences*. 2013;1291:86-95. PMID: 23659608
5. Pless M, Weinberg U. Tumor treating fields: concept, evidence and future. *Expert opinion on investigational drugs*. 2011;20(8):1099-106. PMID: 21548832
6. U.S. Food and Drug Administration (FDA). Tumor treatment fields. NovoTTF-10A System. Summary of safety and effectiveness data (SSED). Premarket Approval Application (PMA) No. P100034. Premarket Notification Database. Rockville, MD: FDA; April 8, 2011. Secondary U.S. Food and Drug Administration (FDA). Tumor treatment fields. NovoTTF-10A System. Summary of safety and effectiveness data (SSED). Premarket Approval Application (PMA) No. P100034. Premarket Notification Database. Rockville, MD: FDA; April 8, 2011 [cited 3/10/2025]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034b.pdf.
7. (FDA) USFaDA. Supplemental application for device name change. Secondary Supplemental application for device name change 09/28/2014 [cited 3/10/2025]. 'Available from:' https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p100034s010.
8. U.S. Food and Drug Administration (FDA). Tumor treatment fields. Summary of Safety and Effectiveness Sata (SSED) October 5, 2015. Secondary U.S. Food and Drug Administration (FDA). Tumor treatment fields. Summary of Safety and Effectiveness Sata (SSED) October 5, 2015. [cited 3/10/2025]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf10/p100034s013b.pdf.
9. (FDA) USFaDA. NovoTTF 100L System: Summary of Safety and Probable Benefit. Secondary NovoTTF 100L System: Summary of Safety and Probable Benefit 05/23/2019 [cited 3/10/2025]. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/pdf18/H180002B.pdf.
10. FDA Grants Breakthrough Device Designation to the NovoTTF-200T System for Advanced Liver Cancer. Secondary FDA Grants Breakthrough Device Designation to the NovoTTF-200T System for Advanced Liver Cancer 09/09/2021 [cited 3/10/2025]. 'Available from:' <https://www.novocure.com/fda-grants-breakthrough-device-designation-to-the-novottf-200t-system-for-advanced-liver-cancer>.
11. Ballo MT, Conlon P, Lavy-Shahaf G, et al. Association of Tumor Treating Fields (TTFields) therapy with survival in newly diagnosed glioblastoma: a systematic review and meta-analysis. *J Neurooncol*. 2023;164(1):1-9. PMID: 37493865
12. Regev O, Merkin V, Blumenthal DT, et al. Tumor-Treating Fields for the treatment of glioblastoma: a systematic review and meta-analysis. *Neurooncol Pract*. 2021;8(4):426-40. PMID: 34277021
13. Stupp R, Taillibert S, Kanner AA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. *Jama*. 2015;314(23):2535-43. PMID: 26670971
14. Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-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. PMID: 29260225

15. Glas M, Ballo MT, Bomzon Z, et al. The Impact of Tumor Treating Fields on Glioblastoma Progression Patterns. *Int J Radiat Oncol Biol Phys.* 2022;112(5):1269-78. PMID: 34963556
16. Li X, Jia Z, Yan Y. Efficacy and safety of tumor-treating fields in recurrent glioblastoma: a systematic review and meta-analysis. *Acta Neurochir (Wien).* 2022;164(8):1985-93. PMID: 35397674
17. Kirson ED, Dbaly V, Tovarys F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A.* 2007;104:10152-7. PMID: 17551011
18. Kirson ED, Schneiderman RS, Dbaly V, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). *BMC Med Phys.* 2009;9:1. PMID: 19133110
19. Salzberg M, Kirson E, Palti Y, et al. A pilot study with very low-intensity, intermediate-frequency electric fields in patients with locally advanced and/or metastatic solid tumors. *Onkologie.* 2008;31:362-5. PMID: 18596382
20. De Bonis P, Doglietto F, Anile C, et al. Electric fields for the treatment of glioblastoma. *Expert review of neurotherapeutics.* 2012;12(10):1181-4. PMID: 23082733
21. Ram Z, Gutin PH. Subgroup and quality of life analyses of the phase III clinical trial of NovoTTF-100A versus best standard chemotherapy for recurrent glioblastoma. *Neuro-Oncology.* 2010;12:iv48-iv49. PMID: No PMID Entry
22. Ram Z, Wong ET, Gutin PH. Comparing the effect of novotf to bevacizumab in recurrent GBM: A post-HOC sub-analysis of the phase III trial data. *Neuro-Oncology.* 2011;13:iii52. PMID: No PMID Entry
23. Wong ET, Lok E, Swanson KD, et al. Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. *Cancer medicine.* 2014;3(3):592-602. PMID: 24574359
24. Kesari S, Ram Z. Tumor-treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: a post hoc analysis of the EF-14 trial. *CNS oncology.* 2017;6(3):185-93. PMID: 28399638
25. Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A system for glioblastoma: The Patient Registry Dataset (PRiDe). *Seminars in oncology.* 2014;41 Suppl 6:S4-S13. PMID: 25213869
26. Rulseh AM, Keller J, Klener J, et al. Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields. *World J Surg Oncol.* 2012;10:220. PMID: 23095807
27. Villano JL, Williams LE, Watson KS, et al. Delayed response and survival from NovoTTF-100A in recurrent GBM. *Med Oncol.* 2013;30(1):338. PMID: 23307238
28. Turner SG, Gergel T, Wu H, et al. The effect of field strength on glioblastoma multiforme response in patients treated with the NovoTTF-100A system. *World J Surg Oncol.* 2014;12:162. PMID: 24884522
29. Elzinga G, Wong ET. Resolution of cystic enhancement to add-on tumor treating electric fields for recurrent glioblastoma after incomplete response to bevacizumab. *Case Rep Neurol.* 2014;6:109-15. PMID: 24847254
30. Ansstas G, Tran DD. Treatment with Tumor-Treating Fields Therapy and Pulse Dose Bevacizumab in Patients with Bevacizumab-Refractory Recurrent Glioblastoma: A Case Series. *Case Rep Neurol.* 2016;8:1-9. PMID: 26889149
31. Leal T, Kotecha R, Ramlau R, et al. Tumor 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. PMID: 37657460
32. Ceresoli GL, Aerts JG, Dziadziuszko R, 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. PMID: 31628016
 33. Kutuk T, Appel H, Avendano MC, et al. Feasibility of Tumor Treating Fields with Pemetrexed and Platinum-Based Chemotherapy for Unresectable Malignant Pleural Mesothelioma: Single-Center, Real-World Data. *Cancers (Basel).* 2022;14(8). PMID: 35454925
 34. Gkika E, Grosu AL, Macarulla Mercade T, et al. Tumor Treating Fields Concomitant with Sorafenib in Advanced Hepatocellular Cancer: Results of the HEPANOVA Phase II Study. *Cancers (Basel).* 2022;14(6). PMID: 35326718
 35. Vergote I, Copeland LJ, Van Gorp T, et al. Tumor 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.* 2025;219:115306. PMID: 40010134
 36. Connelly J, Hormigo A, Mohilie N, et al. Planning TTFIELDS treatment using the NovoTAL system-clinical case series beyond the use of MRI contrast enhancement. *BMC Cancer.* 2016;16:842. PMID: 27809808
 37. Chaudhry A, Benson L, Varshaver M, et al. NovoTTF-100A System (Tumor Treating Fields) transducer array layout planning for glioblastoma: a NovoTAL system user study. *World J Surg Oncol.* 2015;13:316. PMID: 26558989
 38. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Mesothelioma: Pleural. V2.2025. Secondary National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Mesothelioma: Pleural. V2.2025 [cited 3/10/2025]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf.
 39. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hepatocellular Carcinoma. v4.2024. Secondary National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hepatocellular Carcinoma. v4.2024 [cited 3/10/2025]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf.
 40. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer v3.2025. Secondary National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer v3.2025 [cited 3/10/2025]. 'Available from:' https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

CODES

NOTE: There is no specific code for the NovoTAL™ System software program. While some may submit using CPT code 77261, the appropriate CPT code for this service is unlisted code 77299.

Codes	Number	Description
CPT	1025T	Alternating electric fields dosimetry and delivery-simulation modeling, creation and selection of patient-specific array layouts, and placement verification
	77261	Therapeutic radiology treatment planning; simple
	77299	Unlisted procedure, therapeutic radiology clinical treatment planning
HCPCS	A4555	Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only

Codes	Number	Description
	E0766	Electrical stimulation device, used for cancer treatment, includes all accessories, any type

Date of Origin: April 2023