Tumor Treatment Fields Therapy*

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DESCRIPTION

Tumor treating fields (TTF) therapy is a noninvasive technology intended to treat glioblastoma on an outpatient basis and at home using electrical fields. Glioblastoma is the most common form of malignant primary brain tumor in adults. Glioblastomas are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors. The peak incidence for GBM 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; the 5-year survival rate and average length of survival is estimated at 6.8 % and 12 to 18 months, respectively.

Due to its multiple forms, it is also termed Glioblastoma multiforme (GBM). The term "multiforme" is no longer part of the World Health Organization (WHO) designation, though glioblastoma is still often abbreviated "GBM."

The types of glioblastomas collectively referenced as glioblastoma are differentiated below:

- Glioblastoma, IDH-wildtype
  - Giant cell glioblastoma
  - Gliosarcoma
  - Epithelioid glioblastoma
- Glioblastoma, IDH-mutant
- Glioblastoma, NOS (not otherwise specified)

Currently there is no known cure, but treatments are available. Tumor treatment fields (TTF) (e.g., Optune® device) is one such treatment that aims to prolong progression-free survival (PFS) and overall survival (OS).

The mechanism of action as described by the manufacturer: Tumor treating fields (TTF) /Electric tumor treatment fields is a locally or regionally delivered treatment that produces electric fields within the human body to disrupt the rapid cell division exhibited by cancer cells. TTF therapy works by creating alternating, "wave-like" electric fields that travel across their region of usage in different directions. Because structures within dividing cells have an electric charge, they interact with these electric fields.

Newly Diagnosed Glioblastoma (GBM)
The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy (RT), chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation (see 2.04.113 on MGMT promotor methylation for malignant gliomas).

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section). For patients with good performance status, the most aggressive treatment (standard RT plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur in essentially all patients.

Recurrent Glioblastoma (GBM)
When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam RT are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (e.g., lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.4, There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

Clinical studies are ongoing to determine the safety and efficacy of TTF therapy as part of combination therapy for treating recurrent GBM. TTF therapy is under investigation as a combination therapy with chemotherapy plus bevacizumab and as a combination therapy with chemotherapy after irradiation therapy for treating recurrent GBM.

Treatment Outside of Glioblastoma
Malignant pleural mesothelioma (MPM) is an aggressive tumor that is associated with significant morbidity and mortality. It is associated with asbestos exposure and has a latency period of about 40 years after asbestos exposure. Recommendations for treatment are mainly chemotherapy as first line with pemetrexed plus platinum. Surgical cytoreduction is also recommended in selected patients with early-stage disease. Adjuvant radiation can be offered for patients who have resection of intervention tracts found to be histologically positive or for palliation of symptomatic patients.

Tumor treating fields technology (TTF) is also being studied as a treatment for malignant pleural mesothelioma and other solid tumors (e.g., melanoma, pancreatic adenocarcinoma, and non-small cell lung cancer). However, there is a lack of published evidence from randomized controlled trials examining the long-term safety and effectiveness of TTF as a treatment of these cancers at this time.

Tumor Treating Fields Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed Glioblastoma Multiforme

Clinical Context and Therapy Purpose
The purpose of TTF therapy, also referred to as alternating electrical field therapy, is to provide a treatment option that is an alternative to or an improvement on existing therapies for patients with newly diagnosed GBM. Tumor treating fields therapy has been

investigated 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.

The questions addressed in this evidence review is: Does the use of TTF therapy as an adjunct to standard maintenance therapy improve the net health outcome in patients with newly diagnosed GBM?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are patients who have newly diagnosed GBM and good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions
Tumor treating fields therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields. Tumor treating fields therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. Tumor treating fields therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase. Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune branded products (formerly NovoTTF-100A System) are the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators
The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

Tumor treating fields therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months.

Outcomes
The general outcomes of interest are whether TTF improves survival or quality of life during treatment and the time to tumor recurrence because most GBMs recur. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment, such as side effects of chemotherapy and the possibility of seizures, need to be assessed.

Due to the rapid progression of GBM, the time of interest for both progression-free survival (PFS) and overall survival (OS) is months.

Study Selection Criteria
To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
Studies with duplicative or overlapping populations were excluded.

Review of Evidence
(2021) Regev et al. conducted a systematic review of studies describing the use of TTF therapy for the treatment of GBM. The authors included a total of 20 studies of patients with newly diagnosed GBM and recurrent GBM. For newly diagnosed GBM (n=542), only 1 RCT was identified (Stupp et al, 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 OS and 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.

(2017) Kesari et al. conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence. Some patients in the temozolomide alone group crossed over to receive tumor treatment field (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=.043).

(2017) Stupp et al published results of the EF-14 multicenter, open-label phase three randomized control trial (RCT) that evaluated maintenance therapy with tumor treating fields (TTF) for **newly diagnosed GBM**. The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by radiotherapy and chemotherapy. A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to tumor treating fields (TTF) plus maintenance temozolomide or maintenance temozolomide alone. All patients were seen monthly for follow-up. Quality of life was assessed every three months, and magnetic resonance imaging (MRI) was performed every two months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was progression-free survival (PFS), and the secondary outcome was overall survival (OS). The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to tumor treating fields (TTF) following the planned interim analysis. An independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The U.S. Food and Drug Administration approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the U.S. Food and Drug Administration considered for the 2015 expanded approval of Optune, was published by Stupp et al (2015). At the time of the interim analysis, data were available for 210 patients randomized to tumor treating fields (TTF) plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

Results of the final analysis of the EF-14 trial were similar to the interim analysis. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (i.e., temozolomide). Progression free survival increased by 2.7 months ($p<.001$) and OS increased by 4.9 months ($p<.001$) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy ($p<.01$).

There was a similar percentage of dropouts at the final analysis with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In a secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life

with TTF compared with temozolomide alone aside from "itchy skin". Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at three months and 41.7% of the 473 patients alive at 12 months).

A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis. notable limitations identified in this trial; the major limitation is the lack of patient blinding to treatment assignment. However, progression-free survival (PFS) was assessed by investigators who were blinded to treatment, and placebo effects on OS were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment. However, PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers.

(2017) Kesari et al conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the **first recurrence**. Some patients in the temozolomide alone group crossed over to receive tumor treatment field (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=.043).

Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective

RCT is needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

(2014) A registry study published Mrugala et al. assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting. Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 months) was reported as superior to that attained in the EF-11 pivotal trial (6.6 months, p<.001) (see Table 10). More patients in the PRiDe registry were treated **for first recurrence** (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

(2012) The 2011 U.S. Food and Drug Administration approval of the NovoTTF-100A System (now called Optune) was based on a phase three multinational randomized control trial (RCT) (EF-11), results of which were published by Stupp et al (2012). This trial compared tumor treating fields (TTF) therapy alone with physician's choice medical therapy in 237 adults who had **relapsed or progressive glioblastoma**. Patients had failed conventional treatment with radiotherapy, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the two groups.

Participants were followed monthly, which included laboratory tests. Magnetic resonance images were evaluated at two, four, and six months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. Quality of life questionnaires were completed every three months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included progression-free survival (PFS), the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, quality of life, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy. With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at one, two, and three years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF

patients. Severe (grades 3 to 4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal quality of life data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive, and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had several limitations, that included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal quality of life could be analyzed only for 27% of patients who remained on study therapy for three months. The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

ECRI Institute: Optune Treatment Kit (Novocure, Ltd.) for Treating Newly Diagnosed Glioblastoma:
(2019) Conclusions: Evidence from one high-quality randomized controlled trial (RCT) indicates TTF plus TMZ increases overall survival and progression-free survival in patients with newly diagnosed glioblastoma compared to TMZ alone. Quality of life (QOL) and systemic adverse events (AEs) did not differ statistically between the two groups. Independent RCTs comparing TTF plus TMZ with TMZ alone would be informative to confirm these findings. Ongoing TTF trials are addressing other issues.

- One RCT reported median overall survival was longer in the TTF plus TMZ group than in the TMZ-only group (20.9 months [95% confidence interval [CI]: 19.3 to 22.7] versus 16.0 months [95% CI: 14.0 to 18.4] p <0.001). Progression-free survival was also longer for patients in the TTF plus TMZ group (6.7 months [95% CI: 6.1 to 8.1] versus 4.0 months [95% CI: 3.8 to 4.4, p <0.001]). At two-year follow-up, mortality was 57% in the TMZ plus TTF group and 69% in the TMZ-only group (p <0.001). Incidence, distribution, and severity of systemic AEs did not differ statistically between groups. Mild skin toxicity occurred in 52% of patients, and severe skin toxicity occurred in 2% of patients in the TTF plus TMZ group; no instances of skin toxicity occurred in the TMZ-only group.
- Health-related QOL (i.e., EORTC QLQ-C30 [European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30], EORTC QLQ-BN20) did not differ statistically between groups at 12-month follow-up, but assessment of this outcome may have a risk of bias due to high attrition. (Accessed September 2021)

ECRI: Optune Treatment Kit (Novocure, Ltd.) for Treating Recurrent Glioblastoma

- (2019) Conclusions: Moderate-strength evidence indicates TTF results in fewer adverse events (AEs) than chemotherapy (i.e., serious hematologic AEs, diarrhea,

nausea, infection, anorexia, muscle weakness). However, moderate-strength evidence shows no difference in median overall survival between TTF and best standard care (BSC) chemotherapy. Low-strength evidence indicates TTF results in more skin-site reactions and falls than BSC. Studies comparing TTF with BSC reported on too few patients to permit conclusions for quality of life. None of the 6 small ongoing trials will address key evidence gaps.

- ECRI Institute's 2016 Emerging Technology Evidence Report, Tumor Treating Fields Therapy (Optune) for Recurrent Glioblastoma, found differing strengths of evidence (ranging from very low to moderate) for different outcomes; some outcomes had inconclusive evidence. Whether TTF has clinical value for a given patient with recurrent glioblastoma may depend on which outcomes are most important to the patient and clinician. Given that median overall survival did not differ between chemotherapy and TTF, the decision may rest on whether a patient wishes to avoid chemotherapy-related AEs.
- One publication, at high risk of bias, published since ECRI Institute's 2016 Emerging Technology Evidence Report provided no evidence to confirm or change the report's conclusions. The publication reports median overall survival is 11.8 months in the TTF plus chemotherapy group compared with 9.2 months in the chemotherapy-alone group (HR = 0.70; 95% CI: 0.48 to 1, p = 0.049). Authors reported serious AEs in 49% of patients in the TTF plus chemotherapy group and in 33% of patients in the chemotherapy-alone group. (Accessed September 2021)

UpToDate: Initial Treatment and Prognosis of IDH-Wildtype Glioblastoma in Adults

(2021) In addition to radiation and temozolomide, we discuss the option of low intensity alternating electric field therapy (TTFields), which has been shown to improve survival in a large, randomized trial. Use of the device is encouraged in interested patients, although the requirement to carry a device and maintain a shaved scalp for the duration of treatment presents a potential burden that is not acceptable to all patients. (*Accessed September 2022*)

Section Summary: Tumor Treating Fields Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed Glioblastoma Multiforme

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment. However, PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers. In a systematic review that included the EF-14 trial along with other observational studies, the pooled median OS and PFS in newly diagnosed patients who received TTF therapy was 21.7 months and 7.2 months, respectively

Tumor Treating Fields Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent Glioblastoma Multiforme

Clinical Context and Therapy Purpose

The purpose of TTF therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for patients with progressive or recurrent GBM.

Tumor treating fields therapy has been investigated as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

The questions addressed in this evidence review is: Does the use of TTF therapy as an adjunct or alternative to standard medical therapy improve the net health outcome in patients with progressive or recurrent GBM?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients who have recurrent GBM with good performance status.

Interventions

The therapy being considered is TTF therapy as an adjunct or alternative to standard medical therapy.

Comparators

The following practice is currently being used to make decisions about progressive or recurrent GBM: standard medical therapy (e.g., bevacizumab, nitrosoureas, temozolomide rechallenge).

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and the time to tumor recurrence because most GBMs recur. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment, such as side effects of chemotherapy and the possibility of seizures, need to be assessed.

Due to the rapid progression of GBM, the time of interest for both PFS and OS is months.

Study Selection Criteria

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.

Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews
(2021) A systematic review by Regev et al. is introduced above. For patients with recurrent GBM (n=1094), only 2 RCTs were identified (Stupp et al. [2012] and post hoc analysis of Kesari et al. [2017]), which are described in further detail in the section below. The remainder of the data for recurrent GBM was observational. For patients with recurrent GBM, the pooled median OS and PFS were 10.3 months (95% CI, 8.3 to 12.8) and 5.7 (95% CI, 2.8 to 10) months, respectively. The pooled rate of OS at 1, 2, and 3 years was 43.7%, 21.3%, and 14%, respectively. The pooled rate of PFS at 6, 12, and 18 months was 47.8%, 29.3%, and 19.7%, respectively. As previously noted, statistical comparisons to other treatment modalities were not provided.

Randomized Controlled Trials
The 2011 U.S. FDA approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al (2012). This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see the Table below). Patients had failed conventional treatment with RT, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma

Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
					Active	***Comparator***
Stupp et al (2012); EF-11	U.S., E.U., Israel	28	1987-2013	• 237 adults with relapsed or progressive supratentorial	120 patients treated with TTF alone, 93 (78%)	117 patients treated with physician's

				glioblastoma • KPS score ≥70%	completed 1 cycle	choice of medical therapy

E.U.: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields. Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (i.e., carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, which included laboratory tests. Magnetic resonance images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. Quality of life questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, quality of life, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see the Table below). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3 to 4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal quality of life data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

The trial had a number of limitations (see the Tables below), which included lack of blinding and high loss to follow-up. Discontinuation of TTF therapy occurred in 22% of patients due to noncompliance or inability to handle the device, usually within the first few days. In the control group, 21 (18%) patients did not return to the treatment site, and details on disease progression and toxicity were not available. Longitudinal quality of life could be analyzed only for 27% of patients who remained on study therapy for 3 months.

The trial was designed as a superiority trial and did not provide adequate evidence of noninferiority.

Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma

Study; Trial	LTFU, n (%)	Median OS, mo	PFS		OS (95% CI), %		
			Median, mo	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al (2012); EF-11							
TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
HR (95% CI)		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				
P value		.27	.16	.13			

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; OS: overall survival; PCC: physician's choice chemotherapy; PFS: progression-free survival; TTF: tumor treating fields.

Study Relevance Limitations

Study	Population	Intervention	Comparator	Outcomes	Follow-Up[e]
Stupp et al (2012); EF-11			2. Physician's choice chemotherapy		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Study Design and Conduct Limitations

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Stupp et al (2012); EF-11		1. Not blinded to treatment assignment		1. 78% of TTF group completed only 1 cycle of therapy, 18% of control group lost to follow-up; longitudinal QOL data were available for 27% of patients		1. Not designed as a noninferiority trial

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
QOL: quality of life; TTF: tumor treating fields.
[a] *Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.*
[b] *Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.*
[c] *Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.*
[d] *Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).*
[e] *Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.*
[f] *Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.*

Nonrandomized Comparative Studies

(2017) Kesari et al. conducted a post hoc analysis of the EF-14 trial (see Stupp et al [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence. 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 (see the Table below). 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 (see Table 10). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months (p=.043).

A registry study published Mrugala et al. (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 9).

Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 months) was reported as superior to that attained in the EF-11 pivotal trial (6.6 months, p<.001) (see the Table below). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Characteristics of Key Nonrandomized Trial Results

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
Kesari et al (2017)	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 months
Mrugala et al (2014)	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	NR

E.U.: European Union; FU: follow-up; GBM: glioblastoma; NR: not reported; TTF: tumor treating fields.

Summary of Key Nonrandomized Trial Results

Study	Median OS, months	Additional OS outcomes	
Kesari et al (2017); EF-14	Median OS without bevacizumab, months	Median OS with bevacizumab, months	
TTF plus chemotherapy	11.8	11.8	
Chemotherapy alone	9.2	9.0	
HR (95% CI)	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)	
P value	.049	.043	
Mrugala et al (2014)	Median OS with TTF	1-Year OS, %	2-Year OS, %
PRiDe Registry	9.6	44	30
EF-11	6.6	20	9
HR (95% CI)	0.66 (0.05 to 0.86)	NR	NR
P value	<.001	NR	NR

CI: confidence interval; HR: hazard ratio; NR: not reported; OS: overall survival, TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control. They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al. (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy. The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group (p=.009). These post hoc analyses are considered to be hypothesis-generating.

UpToDate: Management of Recurrent High-Grade Gliomas
(2021) A portable medical device that generates low intensity alternating electric fields (tumor treating fields [TTFields]) is also available for treatment of recurrent glioblastoma. Clinicians must be trained and certified to prescribe the device. The device is applied to a shaved scalp, with four transducer arrays connected to a portable battery or power supply operated device; continuous treatment is recommended. The device is an alternative to other salvage therapies for interested patients.

Approval in the United States, Europe, and elsewhere was based on results of a clinical trial that randomly assigned 237 patients with recurrent glioblastoma to TTFields or clinician's choice chemotherapy. The majority of patients were enrolled at the time of second or greater recurrence and approximately 20 percent had received prior bevacizumab. Median progression-free and overall survival were similar in those treated with TTFields versus chemotherapy (2.2 versus 2.1 months and 6.6 versus 6 months, respectively). The objective response rate was nonsignificantly higher in patients treated with TTFields compared with chemotherapy (14 versus 10 percent). Quality-of-life data available in only 27 percent of patients were similar between groups. Mild to moderate scalp dermatitis related to transducer arrays was the most common device-related side effect (16 percent). Hematologic and gastrointestinal adverse events, primarily mild or moderate, occurred in 20 percent of those treated with chemotherapy and less than 3 percent of device-treated patients.

A subsequent open-label randomized trial in patients with newly diagnosed glioblastoma showed prolonged progression-free and overall survival in the group assigned to TTFields when used in combination with postradiation temozolomide.

Consensus-based guidelines published by the National Comprehensive Cancer Network (NCCN) include alternating electric field therapy as a treatment option for patients with recurrent glioblastoma based on the trial data reviewed above as well as post marketing analysis of > 450 patients treated commercially in the United States. (*Accessed September 2022*)

Section Summary: Tumor Treating Fields Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent Glioblastoma Multiforme
The single RCT for TTF as an alternative to chemotherapy reported that outcomes following TTF therapy were similar to outcomes following standard chemotherapy. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. The noninferiority of TTF compared with chemotherapy might be considered a sufficient health benefit, if TTF reduced treatment toxicity. However, because the trial was not designed as a noninferiority trial no inferences of noninferiority compared with chemotherapy can be made. Physician's choice therapy during the trial was heterogeneous, although analysis indicated that survival was not affected by choice of chemotherapy. More patients in the TTF group than in the control group did not complete the treatment course. The number of patients who contributed quality of life data was approximately one-quarter of total enrollment, and the self-reported quality of life indicators might have been subject to bias due to the lack of blinding. A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed. In a systematic review that included the RCT and post hoc analysis of the EF-14 trial, along with other observational studies, the pooled median OS and PFS in patients with recurrent GBM who received TTF therapy was 10.3 months and 5.7 months, respectively

Summary of Evidence: Glioblastoma
For individuals who have **newly diagnosed GBM** on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an randomized controlled trial (RCT) and a systematic review. Relevant outcomes include OS, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, PFS was assessed by blinded evaluators, and the placebo effects on the objective measure of OS are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have **progressive or recurrent GBM** who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (OS) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that

treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial showing a life span increased from 9.2 to 11.8 months. A high-quality, prospective RCT is needed. While the evidence may not permit conclusions regarding TTF therapy for progressive or recurrent GBM, the FDA approval brings an additional treatment option for these patients with few other options which trial show an additional 2.6 months of life. Also, whether TTF has clinical value for a given patient with recurrent glioblastoma may depend on which outcomes are most important to the patient and clinician. Given that median overall survival did not differ between chemotherapy and TTF, the decision may rest on whether a patient wishes to avoid chemotherapy-related AEs and improved quality of life.

Malignant Pleural Mesothelioma (MPM)
(2019) Ceresoli et al. reported tumor treatment fields therapy for patients with metastatic, MPM has been evaluated in one prospective, single-arm study (STELLAR). The STELLAR study enrolled 80 patients with inoperable, previously untreated MPM. Patients 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, 1- and 2-year survival rates, and safety.

Median OS was 18.2 months and median PFS was 7.6 months. 72 of the 80 patients enrolled had at least 1 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.

Summary of Evidence: Malignant Pleural Mesothelioma (MPM)
For individuals who have unresectable, locally advanced or metastatic, MPM who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes 1 single-arm observational study conducted in 80 patients. Relevant outcomes include OS, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. In patients who received TTF therapy in combination with pemetrexed and cisplatin or carboplatin, median overall survival was 18.2 months (95% CI 12.1 to 25.8 months). Because there was no comparison group, it is not possible to

make conclusions about the effectiveness of the intervention compared to medical therapy alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome

Follow Up/Monitoring Disease Progression
(2020) Jing et al. reported the following:

- Patients were routinely followed up using MR scans with an interval of 3 months, or 1 month if there was any proof indicated disease progression.
- Progression represented a ≥ 25% increase in the maximal cross-sectional tumor area, or the appearance of any new lesion, or significant increase in T2/FLAIR nonenhanced lesions. Overall survival (OS) was defined as the time period from the date of operation to the date of death or last follow-up.

Practice Guidelines and Position Statements

European Association of Neuro-Oncology (EANO)
(2020) Guideline on the Diagnosis and Treatment of Diffuse Gliomas of Adulthood: The use of TTF is not mentioned within the information provided in the treatment section for Glioblastoma. (*Accessed September 202*2)

National Cancer Institute (NIH)
(2022) Adult Central Nervous System Tumors Treatment (PDQ®)–Health Professional Version-Glioblastoma Treatment**:** For patients with glioblastoma (WHO grade IV), the cure rate is very low with standard local treatment.

Standard treatment options for patients with newly diagnosed glioblastoma include the following:

1. Surgery plus radiation therapy and chemotherapy.
2. Surgery plus radiation therapy.
3. Carmustine-impregnated polymer implanted during initial surgery.
4. Radiation therapy and concurrent chemotherapy.

The standard treatment for patients with newly diagnosed glioblastoma is surgery followed by concurrent radiation therapy and daily temozolomide, and then followed by six cycles of temozolomide. The addition of bevacizumab to radiation therapy and temozolomide did not improve overall survival (OS).

The use of TTF is not mentioned within the information provided in the treatment section for Glioblastoma. (*Accessed September 2022*)

The National Comprehensive Cancer Network (NCCN): Glioblastoma

- The Guidelines on Central Nervous Systems Cancers version 1.2022 recommends the following:

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Treatment	• Radiation therapy (RT) + concurrent and adjuvant Temozolomide (TMZ) + Tumor Treatment Fields (TTF)	• None	• RT + concurrent or adjuvant TMZ (for patients age ≤ 70). • RT with concurrent and adjuvant lomustine and TMZ (for patient with MGMT promoter - methylated tumors, and age < 70 years) (category 2B)
Recurrence Therapy	• Bevacizumab • TMZ • Lomustine or carmustine • PCV • Regorafenib	• Systemic therapy + bevacizumab: ○ Carmustine or lomustine + bevacizumab ○ TMZ + bevacizumab	• If failure or intolerance to the preferred or other regimens: ○ Etoposide (category 2B) ○ Platinum-based regimend (category 3) • NTRK gene fusion tumors ○ Larotrectinib ○ Entrectinib • BRAF V600E activation mutation ○ BRAF/MEK inhibitors ▪ Dabrafenib/trametinib ▪ Vemurafenib/cobimetinib

- **Therapy for Recurrence**

Alternating electric field therapy is also FDA approved for treating recurrent glioblastoma based on the safety results of this medical device from the EF-11 clinical trial. This phase III study randomized 237 patients with recurrent glioblastoma to alternating electric field therapy or the treating oncologist's choice of chemotherapy. The study did not meet its primary endpoint of demonstrating an improvement in survival in the cohort of patients treated with alternating electric field therapy. Although median OS was similar in both of the treatment arms (6.6 vs. 6 months), the study had not been powered for a non-inferiority determination. Due to lack of clear efficacy data for alternating electric field therapy in EF-11, the panel is divided about recommending it for the treatment of recurrent glioblastoma. *(Accessed September 2022)*

The National Comprehensive Cancer Network (NCCN): Malignant Pleural Mesothelioma

- The guideline (1.2022) does not address tumor treating fields (TTF) as a treatment option for malignant pleural mesothelioma. (*Accessed September 2022*)

National Institute for Health and Care Excellence (NICE)

(2018; Updated 2021) Guideline Brain Tumors (primary) and Brain Metastases in Adults
This guideline manages suspected and confirmed glioma, suspected, and confirmed meningioma, and suspected and confirmed brain metastases.

- 1.2.26 Do not offer tumor-treating fields (TTF) as part of management of a newly diagnosed grade IV glioma (glioblastoma).
- 1.2.34 Do not offer tumor treating fields (TTF) as part of management of recurrent high-grade glioma.

Based on the available evidence, the committee recommended that certain treatments should not be offered. This included tumor treating fields (TTF) based on published health economic evidence that they are not an efficient use of NHS resources. They also agreed, based on their clinical experience, that it would be useful for healthcare professionals to tell people with glioma that no evidence had been found to suggest that certain treatments are beneficial. (*Accessed September 2022*)

Regulatory Status

Date	Description
September 2014	FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®. The FDA approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."
October 2015	FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM. 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.
July 2016	A smaller, lighter version of the Optune® device, called the Optune® System (NovoTTF-200A System), received FDA approval. The FDA labeled indication are as follows: Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically confirmed glioblastoma (GBM).

	Optune™ with temozolomide (TMZ) 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. For the treatment of recurrent GBM, Optune™ is indicated following histologically- or radiologically confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.
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.
March 2020	The manufacturer of Optune products announced a plan to include a suffix after the brand name for newly approved indications to further delineate specific indications for individual products (e.g., Tumor Treatment Fields).
September 2021	The FDA granted breakthrough designation to the NovoTTF-200T System for use together with atezolizumab and bevacizumab for the first-line treatment of patients with unresectable or metastatic liver cancer.

To date, all the existing tumor treating fields products fall under the brand name Optune®. In March 2020, the manufacturer of Optune products announced a plan to include a suffix after the brand name for newly approved indications to further delineate specific indications for individual products (eg, Optune Lua).

The subjects receive multiple one-month courses of continuous Optune treatment. Optune treatment was discontinued in the case of clinical disease progression, if a device-related serious adverse event occurred, or after 24 months or second progression whichever occurred first.

PRIOR APPROVAL

Prior approval is required.

POLICY

See Related Medical Policy

- 06.01.15 Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT)

- 10.01.14 Humanitarian Use Devices

Initial Review for Newly Diagnosed Glioblastoma (GBM)
Tumor treatment fields (TTF) therapy (e.g., Optune®) to treat **a newly diagnosed glioblastoma (GBM)** is considered **medically necessary** when **all of the** following conditions are met:

- The patient ≥ 18 years of age; **and**
- Histologically confirmed, new diagnosed glioblastoma; **and**
- The tumor is in the supratentorial region of the brain (cerebrum)**; and**
- The individual has completed initial treatment with **one of the** following:
    - Surgery (resection, debulking, or biopsy); **or**
    - Radiation therapy; **or**
    - Chemotherapy;

And the individual meets **all of the following**:

- Has a Karnofsky Performance Status (KPS) score ≥70%,
- Is receiving standard maintenance therapy with Temodar® (temozolomide); **and**
- Is willing to use the device according to the Food and Drug Administration (FDA) criteria including but not limited to **all of the following**:
    - Maintain a shaved head; **and**
    - Wear the device at least 18 hours daily.

Continuation for Newly Diagnosed Glioblastoma (GBM)
Tumor treatment field (TTF) therapy (e.g., Optune®) for continued use to treat a **newly diagnosed glioblastoma (GBM)** is considered **medically necessary** when **all of the** following conditions are met:

- The patient meets the initial review for newly diagnosed glioblastoma (GBM) medical review criteria above; **and**
- Magnetic Resonance Imaging (MRI) scan or related imaging has been performed within 90 days of the continuation request; **and**
- There is no evidence of disease progression as defined as **one** of the following:
    - A ≥ 25% increase in the maximal cross-sectional tumor area; **or**
    - The appearance of any new lesion**; or**
    - A significant increase in T2/FLAIR nonenhanced lesions; **and**
- Documentation the patient has been complaint using the device according to the FDA label including but not limited to **all** of the following:
    - Maintaining a shaved head; **and**
    - Wearing the device at least 18 hours daily; **and**
    - Tumor treating fields (TTF) therapy has been used 24 months or less.

Initial Review for Recurrent Glioblastoma (GBM)
Tumor treatment field (TTF) therapy (e.g., Optune®) therapy for the treatment of a **recurrent glioblastoma (GBM)** is considered **medically necessary** when **all** of the following conditions are met:

- Diagnosis of recurrent glioblastoma; **and**

- The tumor is in the supratentorial region of the brain (cerebrum)**; and**
- Previous treatment with standard therapeutic options, such as maximum safe debulking surgery and systemic chemotherapy and irradiation; **and**
- Will be used as monotherapy; **and**
- The patient is willing to use the device according to the Food and Drug Administration (FDA) label to include but not limited to **all** of the following:
    - Maintain a shaved head; **and**
    - Wear the device at least 18 hours daily.

Continuation Review for Recurrent Glioblastoma (GBM)
Tumor treating fields (TTF) therapy (e.g., Optune®) for continued used in the treatment of a **recurrent glioblastoma (GBM)** is considered medically necessary when **all** of the following conditions are met:

- The patient meets the initial review for recurrent glioblastoma (GBM) medical review criteria above; **and**
- Magnetic Resonance Imaging (MRI) scan or related imaging has been performed within 90 days of the continuation request; **and**
- There is no evidence of disease progression as defined as one of the following:
    - A ≥ 25% increase in the maximal cross-sectional tumor area; **or**
    - The appearance of any new lesion**; or**
    - A significant increase in T2/FLAIR nonenhanced lesions; **and**
- Will be used as monotherapy; **and**
- Documentation the patient has been complaint using the device according to the FDA label including but not limited to **all** of the following:
    - Maintaining a shaved head; **and**
    - Wearing the device at least 18 hours daily; **and**
    - Tumor treating fields (TTF) therapy has been used 24 months or less.

Tumor Treatment Field (TTF) Therapy: Not Medically Necessary
Tumor treatment field (TTF) therapy (e.g., Optune®) is **not medically necessary** for the treatment of patients who have been diagnosed glioblastoma (GBM) with any of the following:

- Defibrillators; **or**
- Deep brain stimulators; **or**
- Pacemakers; **or**
- Programmable shunts; **or**
- Skull defect (i.e., missing bone with no replacement); **or**
- Spinal cord stimulators; **or**
- Vagus nerve stimulators.

Tumor Treatment Field (TTF) Therapy: Investigational
Tumor treatment field (TTF) therapy is considered **investigational in all other conditions** including, but not limited to the following situations, because the evidence is insufficient in determining the technology results in improved net health outcomes:

- Not meeting the above criteria for **initial** and **recurrent** glioblastoma (GBM); **or**
- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for patients with **progressive** or **recurrent** glioblastoma (GBM); **or**
- As an adjunct to **maintenance therapy** other than temozolomide (Temodar®); **or**
- As an alternative to standard medical therapy for patients with **initial**, **progressive or recurrent** glioblastoma (GBM) **or**
- For brain metastases; **or**
- For cancer in other areas of the brain; **or**
- As an adjunct to standard medical therapy (pemetrexed and platinum-based chemotherapy) for members with malignant pleural mesothelioma.

Policy Guidelines

- **Progressive Disease:** Tumor growth greater than 25% compared to smallest measured tumor area or the appearance of one or more new glioblastoma (GBM) lesions in the brain.
- **Recurrent Disease**: Cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the original (primary) tumor or to another place in the body. Also called recurrence.
- **The Supratentorial Region:** The supratentorial region of the brain is the area located above the tentorium cerebelli and it contains the cerebrum. The area of the brain below the tentorium cerebelli is the infratentorial region and it contains the cerebellum. Tumor treatment field therapy is only recommended for those with supratentorial disease.
- **Karnofsky Performance Status**: The Karnofsky Performance Scale Index allows individuals to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.

Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- E0766 Electrical stimulation device, used for cancer treatment, includes all accessories, any type
- A4555 Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only

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POLICY HISTORY

Date	Reason	Action
October 2022	Annual Review	Policy Revised
March 2022	Interim Review	Policy Revision
October 2021	Annual Review	Policy Revision
November 2020	Annual Review	Policy Revision
March 2020	Interim Review	Policy Revision
November 2019	Annual Review	Policy Revision
June 2019	Interim Review	Policy Revision
October 2018	Annual Review	Policy Revision
October 2017	Annual Review	Policy Revision
October 2016	Annual Review	Policy Revision
October 2015	Annual Review	Policy Revision
November 2014		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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