INFORMATION BRIEF (RAPID REVIEW)

TUMOR-TREATING ELECTRIC FIELD FOR TREATMENT OF CANCER

Malaysian Health Technology Assessment Section (MaHTAS)
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TITLE: TUMOR-TREATING ELECTRIC FIELD FOR TREATMENT OF CANCER

PURPOSE

To provide brief information on the effectiveness, safety and cost-effectiveness of tumor-treating electric field for treatment of cancer based on request from the Office of Minister of Health Malaysia.

BACKGROUND

Cancer is a genetic disease, which means that it is caused by abnormalities in the genes that control how our cells behave, particularly how they grow and divide. Cancer-causing genetic alterations can occur as a result of; various mistakes that occur while cells divide, the damage to deoxyribonucleic acid (DNA) caused by toxic compounds in the environment (such as the toxins in cigarette smoke and ultraviolet rays from the sun and they were also inherited from our parents). Normally, the body kills cells with damaged DNA before they become malignant. However, as we age, our bodies' ability to do so declines. This contributes to the increased risk of cancer later in life. Each person's cancer has its own set of genetic alterations. Additional alterations will occur as the malignancy progresses.[1]

According to the World Health Organization (WHO), cancer is the world's largest cause of mortality, accounting for roughly 10 million deaths in 2020. In terms of new cancer cases in 2020, the most common were breast, lung and colorectal cancer. Moreover, every year approximately 400,000 children develop cancer. The most common cancers vary between countries. Cervical cancer is the most common in 23 countries.[2]

In Malaysia, there were 48,639 new cancer cases reported in 2020 and the cancer incidence in Malaysia is predicted to double by 2040. The most common cancers in Malaysia are lung cancer (for men) and breast cancer (for women), followed by colorectal cancer.[3]

Based on the retrievable evidence, the review will focus on brain cancer (glioblastoma), lung cancer and various cancers which are related to the tumor-treating electric field (TTEF) therapy.

Glioblastoma, commonly known as a grade IV astrocytoma is a rapidly developing and severe type of brain cancer. It invades neighbouring brain tissue but does not usually spread to distant organs. Glioblastoma can form from scratch in the brain or develop from a lower-grade astrocytoma. The disease is most common in adults in the cerebral hemispheres, particularly the frontal and temporal lobes. It is a deadly brain cancer that if left untreated, can result in death in six months or less; therefore, it is critical to seek specialist neuro-oncological and neurosurgical care as soon as possible since this can impact overall survival.[4] Glioblastoma has an incidence ranging from 0.59 to 5 per 100,000 people and is on the rise in several countries.[5] Surgery is the mainstay of glioblastoma treatment. The fundamental goal of surgery is to remove as much of the tumour as feasible while preserving the normal brain tissue required for optimal neurological function. Radiation therapy can begin after surgery, once the wound has healed. The purpose of radiation therapy is to eliminate the residual tumour cells that have penetrated the normal brain tissue around them. Each treatment harms both healthy and normal tissue. Chemotherapy patients are given medications that are specifically designed to kill tumour cells.[6] The current standard of care for glioblastoma is chemotherapy with the medication temozolomide which became available for newly diagnosed patients in 2005.[7] The medicine is usually given every day during radiation therapy

and then every six cycles afterward during the maintenance phase. However, the recurrent disease options remain limited. Bevacizumab received accelerated approval in 2009 and United States Food and Administration (USFDA) final approval in December 2017 for previously treated, symptomatic glioblastoma patients with progressing illness.[7] A therapy called as TTEF is a new method that is introduced during the maintenance phase of treatment. It generates alternating electrical fields, which inhibit cancer cell growth and division.[6]

Meanwhile, the **lung cancer** can spread to lymph nodes or other organs, including the brain. Cancer from other organs can travel to the lungs as well and metastases occur when cancer cells travel from one organ to another.[8] The chemotherapy treatment is different for small and non-small lung cancer. A combination of chemotherapy drugs (cisplatin or carboplatin) is commonly used in limited disease, and extensively combined with immunotherapy drug (such as atezolizumab or durvalumab) for extensive disease.[9] The WHO (2020) reported that, there were 5,139 new cases and 4,509 deaths associated with lung cancer in Malaysia.[3] One of the early study of TTEF on lung cancer conducted *in vitro* experimental set up was found in 2004. This impact, which had been proved to be non-thermal, affected dividing cells while leaving quiescent cells alone. These fields had two effects; they stopped cell proliferation and they destroyed cells as they divided.[10]

Tumor-treating electric field mechanisms of action

Tumor-treating electric field is a non-biochemical and non-ablative device. The mechanism of the technology is based on frequency-specific, low-intensity alternating electric fields to destroy structures within cancer cells during mitosis, resulting in apoptosis. The TTEF takes advantage of the unique traits, geometric shape and rate of developing cancer cells that make them susceptible to the impacts of TTEF. At an intermediate frequency (100 to 300 kHz), TTEF affects the tumour cell polarity. The frequency utilised for TTEF is determined by the target cell type. This technology has been demonstrated to disrupt normal microtubule spindle assembly by imposing directed stresses on polar intracellular components such macromolecules and organelles. These mechanisms cause physical cell disruption **(See Figure 1)**.[11] **Figure 2** showed the example diagrams of patients with TTEF.[13] The technology was approved by FDA in 2011 for recurrent or progressive glioblastoma based on the pivotal EF-11 clinical cancer. However, there was no statement and approval by FDA for lung cancer.[12] The National Comprehensive Cancer Network Clinical Practise Guidelines in Oncology for central nervous system tumours included TTEF therapy in 2015, urging that clinicians consider it for patients with glioblastoma who progress or return after first treatment.[14]

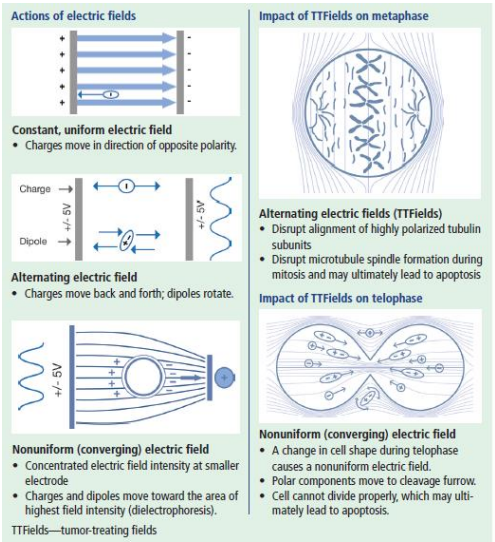

Figure 1: Actions of electric fields and impacts on metaphase and telophase.[11]

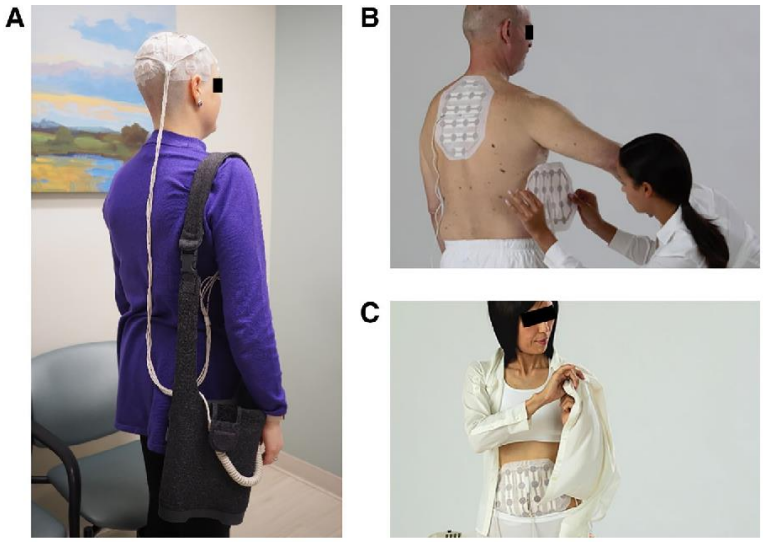

Figure 2: A) patient with the transducer arrays on shaved scalp and the portable battery in a shoulder bag. B) Transducer arrays are placed on a patient's back for mesothelioma or lung cancer. C) Transducer arrays are placed on abdomen or pelvis for ovarian cancer.[13]

EVIDENCE SUMMARY

A total of 16,737 titles were retrieved from the scientific databases such the Ovid interface; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to 24 May 2023, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to May 24, 2023, Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations 1946 to May 24, 2023, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 2017 to May 24, 2023, Ovid MEDLINE(R) 1946 to May Week 3 2023, Ovid MEDLINE(R) 1996 to May Week 3 2023, Ovid MEDLINE(R) Epub Ahead of Print May 24, 2023, Ovid MEDLINE(R) Daily Update May 24, 2023 and Ovid MEDLINE(R) 2017 to May Week 3 2023. Searches were also run in PubMed, INAHTA, Cochrane Library and US Food and Drug Administration. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 25 May 2023. Eleven articles were found to be relevant and included in this review which comprised of one systematic review, five randomised controlled trials (RCTs), one clinical trial, one prospective study and three cost-effectiveness study.

EFFECTIVENESS

There were six studies reported on the effectiveness of TTEF for treatment of glioblastoma, one study on lung cancer and one study on various types of cancer.

A systematic review consisted of two pilot clinical trials, two randomised controlled trials (RCTs) and five retrospective studies **was performed by Shah PP et al. (2020)** to evaluate the efficacy and safety of TTEF in 1,191 adult patients (≥ 18 years old) with high-grade gliomas. In the studies of newly diagnosed glioblastoma, TTEF was applied alongside maintenance temozolomide for patients who had completed concomitant radiotherapy and temozolomide. A 10-patients study demonstrated a median progression-free survival (PFS) of 155 weeks and OS >39 months for TTEF with maintenance temozolomide, which was superior to a PFS of 31 weeks in concurrent controls and an OS of 14.7 months in historical control

patients who received temozolomide alone. A phase III RCT showed TTEF plus maintenance temozolomide demonstrated significantly prolonged survival with median PFS 6.7 months versus 4.0 months, p<0.001 and median OS 20.9 months versus 16.0 months, p<0.001 compared to temozolomide alone.[15, level I]

In the studies of recurrent glioblastoma, a pivotal clinical trial of TTEF demonstrated a median time to progression of 26.1 weeks and median OS of 62.2 weeks, which was markedly superior when compared to reported aggregate historical controls for recurrent glioblastoma patients with average time to progression 9.5 ± 1.6 weeks, average OS 29.3 ± 6 weeks. This provided the basis for EF-11, a phase III clinical trial comparing TTEF therapy versus 'physician's best choice' chemotherapy for recurrent glioblastoma. The best choice chemotherapy was chosen for the control arm due to lack of an established standard of care for recurrent glioblastoma. The OS was not superior in the TTEF arm compared to chemotherapy (median 6.6 months versus 6.0 months, p=0.27).[15, level I]

In assessing the quality of life, for EF-11 (recurrent glioblastoma) clinical study, the QoL was assessed using EORTC Core Quality of Life (EORTC QLQ-C30) questionnaire to measure the effects of TTEF on QoL at baseline and every three months thereafter. The study showed no meaningful differences between TTEF and control arms in global health and social functioning. The global health status or QoL might not be improved due to other burdens associated with TEFF use. For EF-14 (newly diagnosed glioblastoma) studies that utilised EORTC QLQ-C30 and QLQ-BN20 (brain tumor module) survey, the analysis demonstrated that there was no change from baseline in any QoL metrics for either the TTEF plus temozolomide or the temozolomide monotherapy arm. These results suggested that TTEF prolonged survival without negatively impacting QoL for newly diagnosed patients.[15, level I]

Kim CY et al. (2020) conducted an RCT to evaluate the efficacy and safety of TTEF used in combination with temozolomide maintenance treatment after chemo-radiation therapy for patients with glioblastoma. A total of 39 Korean patients were enrolled (24 in the TTEF plus temozolomide treatment group, one of whom never started treatment, and 15 enrolled in the temozolomide alone group). The study showed that the median PFS in the TTEF plus temozolomide group was 6.2 months (95% CI: 4.2, 12.2) versus 4.2 months (95% CI: 1.9, 11.2) in the temozolomide alone group. Meanwhile, the median OS for the patients was 27.2 months (95% CI: 21, not available data) in the TTEF plus temozolomide group, which was significantly higher than the temozolomide alone group, 15.2 months (95% CI: 7.5, 24.1); hazard ratio (HR) 0.27 (0.098, 0.750; p=0.01). The one- and two- year survival rates in the EF-14 population were higher in the TTEF plus temozolomide group compared to the temozolomide alone group (p=0.033 in one-year survival rate, p=0.041 in two-years survival rate. Furthermore, a greater percentage of patients in the TTEF plus temozolomide group (67.0% versus 57.0%) showed stable diseases as measured by radiological progression.[16, level I]

Another **RCT with similar objective as Kim CY et al. (2020) was conducted by Stupp R et al. (2015)**. After completion of chemo-radiotherapy, patients with glioblastoma were randomised to receive maintenance treatment with either TTEF plus temozolomide (n=466) or temozolomide alone (n=229) between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel and South Korea. Treatment with TTEF was delivered continuously (>18 hours/day) via four transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150 to 200 mg/m^2/d) was given for five days of each 28-day cycle. The interim analysis included 210 patients randomised to TTEF plus temozolomide and 105 randomised to temozolomide alone. After a median follow-up of 38-months (range 18 to 60 months), the reported median PFS in the intent-to-treat population was 7.1 months (95% CI: 5.9, 8.2) in the TTEF plus temozolomide group and 4.0 months (95% CI: 3.3, 5.2) in the temozolomide alone group; HR 0.62 (98% CI: 0.43, 0.89); p=0.001. The median OS was reported at 19.6 months (95% CI: 16.6, 24.4) in the TTEF plus temozolomide

group compared with 16.6 months (95% CI: 13.6, 19.2) in the temozolomide alone group, HR 0.74 (99.4% CI: 0.56, 0.98); stratified log ranked p=0.03. The percentage of patients alive at two years following enrolment was 43.0% in the TTEF plus temozolomide group and 29.0% in the temozolomide alone group. Meanwhile, in the per-protocol population, the median OS was 20.5 months (95% CI: 16.7, 25.0) in the TTEF plus temozolomide group (n=196) compared with 15.6 months (95% CI: 13.3, 19.1) in the temozolomide alone group (n=84); HR 0.64 (99.4% CI: 0.42, 0.98); p=0.004.[17, level I]

Kesari S et al. (2017) in an RCT evaluated the efficacy and safety of TTEF when added to second-line treatment according to physician's best choice after first disease recurrence among patients enrolled in the EF-14 phase III trial. Following temozolomide discontinuation due to toxicity or radiologic disease progression, the second-line therapy (including re-operation, radiosurgery, chemotherapy, bevacizumab or combination therapy) was offered and continued until second progression for a maximum of 24 months. Therefore, 60 patients were treated with second-line chemotherapy alone and 144 patients with TTEF plus second-line chemotherapy after first disease progression. After a median follow-up of 12.6 months, the median OS in patients who received TTEF plus temozolomide after first recurrence was 11.8 months, compared with 9.2 months in patients who received temozolomide alone, HR 0.70 (95% CI: 0.48, 1.00); p=0.049. As bevacizumab was the most frequent second-line treatment of physician's choice (either as monotherapy or in combination with cytotoxic chemotherapy), the evaluated median OS from first disease recurrence with TTEF plus bevacizumab was 11.8 months, compared with 9.0 months in patients who received bevacizumab alone, HR 0.61 (95% CI: 0.37, 0.99); p=0.043.[18, level I]

An RCT was conducted by Stupp R et al. (2012) to study the efficacy and safety of the entire novel treatment and modality compared to widely accepted active chemotherapies for the treatment of recurrent glioblastoma patients. From September 2006 until May 2009, a total of 237 patients from 28 institutions in seven countries were randomly assigned to receive phase III trial of chemotherapy treatment of TTEF (n=120) or active control chemotherapy (n=117) in the treatment of patients with recurrent glioblastoma. The study reported there was no statistical difference detected between the two groups. Median survival was 6.6 versus 6.0 months, HR 0.86 (95% CI: 0.66, 1.12); p=0.27. Median PFS (TTEF: 2.2 months, control: 2.1 months; HR 0.81 [95% CI: 0.60, 1.09]; log rank p =0.16). In terms of QoL, there were no meaningful differences in the domains of global health and social functioning between two groups, however, cognitive, role and emotional function favoured TTEF. In contrast, physical function might be slightly worse with TTEF. The study reported that the EF-11 trial failed to demonstrate the significant superiority of TTEF alone over chemotherapy in recurrent glioblastoma.[19, level I]

Taphoorn MJB et al. (2018) conducted an RCT to examine the association of TTEF therapy with PFS and HRQoL among patients with glioblastoma. This secondary analysis of EF-14 compared TTEF plus temozolomide with temozolomide alone in 695 patients with glioblastoma after completion of radio-chemotherapy. However, adherence to HRQoL assessments decreased from 91.9% at baseline to 41.7% (197 of 695 patients alive) at 12 months of follow-up. Compared with baseline, more patients in the TTEF plus temozolomide group reported stable or improved scores compared to temozolomide alone group; global health status (56.5% versus 38.0%, p=0.001), physical function (54.0% versus 37.0%, p=0.001), pain (56.8% versus 35.9%, p<0.001) and weakness of leg (58.7% versus 42.0%, p=0.001). The deterioration-free survival was significantly longer with TTEF for global health (4.8 versus 3.3 months, p<0.01), physical (5.1 versus 3.7 months, p<0.01), emotional function (5.3 versus 3.9 months, p<0.01), pain (5.6 versus 3.6 months, p<0.01) and weakness of leg (5.6 versus 3.9 months, p<0.01), likely to improved PFS.[20, level I]

For lung cancer, Pless M et al. (2013) conducted a clinical trial phase I/II to investigate further the feasibility of TTEF in lung cancer. There were 42 patients in four centres in

Switzerland recruited from May 2008 until September 2009. The patients enrolled had stage IIIB (with pleural effusion) or stage IV non-small cell lung cancer and had failed at least one (and up to five) lines of prior chemotherapy. Patients received an average of 6.1 cycles of pemetrexed (range one to 33) and an average of 18 weeks of TTEF therapy (range one to 32) for a cumulative duration in all patients over 720 weeks. The length of the average daily use of all patients was 11.2 hours and the median follow-up time was 9.5 months. The study reported that the median OS was 13.8 months and one-year survival rate was 57.0%. There were dynamic changes in lesion size in a patient who suffered from adenocarcinoma confined to the effective region of TTEF therapy. All the primary lesions (right inferior and superior lobe, para-aortal and right hilar) decreased in size more than 30 weeks after initiating the treatment and already after the development of the out-of-field disease.[21, level II-2]

A prospective study was conducted by Salzberg M et al. (2008) to evaluate the safety and tolerability profile of TTEF therapy and the tumor response in patients with locally advanced and/or metastatic solid tumor. Six patients with a median age of 66 years (range 24 to 76) and suffering from various cancers were recruited. All patients were previously treated with several lines of therapy and no additional standard treatment option was available to them. Four of the patients suffered from skin lesions, one had glioblastoma and one had metastases from a mesothelioma in the retroperitoneal cavity. Therapy was initiated in the outpatient clinic of the Basel University Hospital under medical supervision for the first six hours of treatment and the patients were released to continue treatment on an ambulatory basis. The tumor size was assessed by digital photography in the four patients with skin lesions as the measureable lesion and the other two patients by computed tomography scans. An arrest of tumor growth during treatment was reported in three patients with skin lesions. The tumors were flattened and the appearance of healthy looking granulation tissue at the tumor margins were recorded. The reduction in tumor size was 20.0% after six weeks of TTEF treatment. However, another patient was reported to experience progressive disease. Moreover, in the mesothelioma patient, some tumor regression was seen in the area which was exposed to TTEF, while the other portions of the tumor were stable and progressive. Meanwhile, the glioblastoma patient (who was resistant to temozolomide and carmustine) did not respond to the four weeks of treatment with TTEF.[22]

SAFETY

There were eight studies reported on the safety of TTEF for treatment of cancer.

The studies reported skin irritation,[14, 15,16,19, level I, 21, level II-2] skin toxicities due to medical device site reaction beneath the transducer arrays,[14, 16,17,19, level I] scalp dermatitis,[14, 17,20, level I] anxiety with confusion, insomnia, headache and seizure,[16,19, level I] systemic toxic,[16, level I] thrombocytopaenia, convulsion, hemiparesis and epilepsy[19, level I].

In terms of adverse events, none of the serious adverse events reported during the phase III trial was considered TTEF-related.[21, level II-2] Two studies showed that the severity of adverse events were similar in patients in both groups.[15-16, level I] Two studies revealed patients treated with TTEF experienced a list of grade one to four adverse events compared to the control groups.[17,19, level I]

In a systematic review, one study reported that, the >4.1 mg per day dexamethasone might interfere with TTEF. Another study compared TTEF plus a triple-drug regimen (tomozolomide, bevacizumab and irinotecan) with TTEF plus bevacizumab-based chemotherapies for recurrent glioblastoma patients. There was no significant difference in OS from time of recurrence.[15, level I]

Tumor-treating electric field was primarily approved by the United States of Food and Administration for the treatment of recurrent glioblastoma in 2011, then the indication was expanded to treat patients with newly-diagnosed glioblastoma in 2015.[12]

COST-EFFECTIVENESS

There were three studies reported on cost-effectiveness of TTEF for treatment of glioblastoma.

Bernard-Arnoux F et al. (2016) in a cost-effectiveness study determined the cost-effectiveness of TTEF for the treatment of newly diagnosed patients with glioblastoma. A Markov model was constructed to measure and compare the medical cost and health outcomes for the two following strategies; standard of care alone with radio-chemotherapy and addition of TTEF therapy to standard of care. The Markov decision model included three mutually exclusive health states; stable disease, progressive disease and death. The target population was a hypothetical cohort of 1,000 people with the same characteristics as those in the EF-14 trial (main inclusion criteria: newly diagnosed grade IV astrocytoma, Karnofsky Performance status score ≥ 70). The analysis was conducted from the perspective of the French Health Insurance hypothesising a full reimbursement of expenses associated with TTEF. The incremental cost-effectiveness ratio (ICER) expressed as monetary costs per life-years gained (LYG). A 4.0% annual discount rate to costs and outcomes was applied according to French national guidelines. The study estimated 0.34 LYG from the addition of TTEF to maintenance of temozolomide, with an added cost of €184,476. The estimated ICER was reported to be €549,909. A one-way sensitivity analysis on the ICER showed that the parameters with the most influence on the ICER were the cost of TTEF therapy, followed by OS and PFS in both arms. The probabilistic sensitivity analysis showed at a threshold of €100,000/LYG, the probability of TTEF therapy being cost-effectiveness was 0.0%.[23]

The previous cost-effectiveness analysis[23] was based on the EF-14 preliminary data.[17, level I] **Connock M et al. (2019) in a cost-effectiveness study** had updated the cost-effectiveness evaluation using the more flexible potential of the partitioned survival model design and used the latest effectiveness data. The analysis showed, the base case model generated incremental benefit of 0.604 LY at a cost of €453,848 which, after 4.0% annual discounting of benefits and costs, yielded an ICER of €510,273/LYG. Using sensitivity analyses and bootstrapping methods results were found to be relatively robust and were only sensitive to TTEF device costs and the modelling of OS. In order to achieve an ICER below €100,000/LYG, it would require a reduction in TTEF device cost of approximately 85.0%.[24]

While the two studies above adapted from the perspective of the French Health Insurance, **Guzaukas GF et al. (2019) conducted the same protocols in the United States healthcare system perspective**. The outcomes for the newly-diagnosed glioblastoma patients were estimated over a lifetime horizon using an area under the curve model with three health states as the studies above. A 3.0% discount rate was applied to future costs and outcomes. The study showed, the addition of TTEF to maintenance temozolomide increased survival and quality-adjusted life year (QALY) with additional incremental costs. Mean lifetime survival of patients treated with TTEF plus temozolomide was 3.34 years, an incremental 1.25 LYG compared with treatment with temozolomide alone. The average patient treated with TTEF plus temozolomide achieved 2.57 QALYs, an increase of 0.96 QALYs compared to patients treated with temozolomide alone. For the average costs per patient, the incremental costs were $188,637 (95% credibile range [CR]: $145,324, $225,330) for patients treated with TTEF. The ICER was $150,452 (95% CR: $105,135, $214,318) per LYG and $197,336 (95% CR: 134,839, $287,249) per QALY **(see Table 1)**. The addition of TTEF to maintenance temozolomide was 57.0% and 98.0% likely to be cost-effective at willingness-to-pay thresholds per QALY of $200,000 and $300,000 respectively. The ICER was lower than the other two studies because this study integrated EF-14 data with external glioblastoma

epidemiology data and United States life expectancy data to estimate long-term conditional survival.[25]

Table 1: Model results[25]

	TTFields + TMZ		TMZ Monotherapy		Incremental	
	Base case	95% credible range	Base case	95% credible range	Base case	95% credible range
Total cost	$231,620	($188,250–$270,180)	$42,983	($35,081–$52,579)	$188,637	($145,324–$225,330)
Treatment acquisition costs	$194,485	($152,469–$232,496)	$19,886	($14,193–$28,512)	$174,599	($131,651–$211,421)
Adverse events and supportive care in SD state	$5,192	($4,605–$5,872)	$4,115	($3,635–$4,538)	$1,077	($694–$1,582)
Supportive care in PD state	$31,943	($23,522–$40,195)	$18,982	($14,033–$23,615)	$12,961	($7,094–$19,212)
Life years	3.34	(2.93–3.69)	2.09	(1.85–2.25)	1.25	(0.89–1.67)
Cost/LY gained	—	—	—	—	$150,452	($105,135–$214,318)
QALYs	2.57	(2.07–3.00)	1.61	(1.30–1.84)	0.96	(0.67–1.30)
Cost/QALY gained (ICER)	—	—	—	—	$197,336	($134,839–$287,249)

Adapted from Guzaukas GF, Pollom EL, Stieber VW et al. Tumor Treating Fields and Maintenance Temozolomide for Newly-diagnosed Glioblastoma: A Cost-effectiveness Study. Journal of Medical Economics. 2019; 22(10): 1006-1013.

A total monthly cost TTEF therapy was around $21,000 (subject to discounts negotiated by healthcare providers/ payers).[26] This cost included the TTEF delivery system, transducer arrays, array layout planning, patient/ physician training, and 24-hour technical support. Additional costs connected with TTEF implementation may include additional staff and training, as well as costs associated with treating treatment-related morbidities.[27]

CONCLUSION

There was substantial, high level of evidence on TTEF for treatment of glioblastoma and limited evidence on lung cancer and other types of cancer. The evidence showed that in newly diagnosed glioblastoma, the addition of TTEF therapy to the temozolomide monotherapy improved the PFS and OS of patients. However, the impact on quality of life was inconclusive.

There were no severe adverse events reported and no difference in safety when compared to standard treatment. The TTEF therapy had been approved by the United States of Food and Drug Administration since 2011.

Addition of TTEF to standard treatment incurred high cost and was shown to be not cost-effective in France and United States.

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