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Tumour-treating fields in addition to current standard therapy for glioblastoma as first-line treatment[1]

Extract

[1] Translation of Chapters 1 to 6 of the rapid report N18-02 *Tumortherapiefelder zusätzlich zur derzeitigen Standardbehandlung beim Glioblastom als Erstlinientherapie* (Version 1.1; Status: 12 July 2019 [German original], 18 October 2019 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Key statement

Research question

The objective of this investigation is to

- assess the benefit of TTF therapy as an add-on to current standard therapy as first-line treatment in comparison with standard therapy alone

in patients with glioblastoma in terms of patient-relevant outcomes.

Conclusion

The benefit assessment included 1 study in patients with newly diagnosed glioblastoma who had already undergone resection (or biopsy) and completed radiochemotherapy.

In this study, TTF therapy was started as part of maintenance therapy as first-line treatment, and it was possible to continue it even after tumour progression.

From this study, results on mortality (overall survival), morbidity (including symptoms, cognitive performance, activities of daily living, and [serious] adverse events), and health-related quality of life were used.

For the outcome of overall survival, there was an indication of greater benefit of TTF therapy as an add-on to the current standard treatment with temozolomide in comparison with temozolomide monotherapy.

For morbidity, there was a hint of greater benefit of TTF therapy as an add-on to the current standard therapy for the outcomes of cognitive functioning and activities of daily living. For 1 out of the 3 examined symptoms (itchy skin), based on an early analysis time point, there was a hint of greater harm of TTF therapy as an add-on to the current standard therapy.

For all other outcomes, i.e. health-related quality of life, (serious) adverse events as well as the two other examined symptoms (pain and leg weakness), there was no hint of greater benefit or harm of TTF therapy as an add-on to the current standard treatment in comparison with temozolomide monotherapy.

No other planned or ongoing studies were found that would be able to verify this result within a foreseeable period.

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List of abbreviations

Abbreviation	Meaning
AE	Adverse events
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organization for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MD	Mean difference
MGMT promoter status	Promoter methylization status of the O6 methylguanine DNA methyltransferase gene
MMRM	Mixed model for repeated measurements
QLQ-BN20	Quality of Life Questionnaire Brain cancer module 20
QLQ-C30	Quality of Life Questionnaire Core module 30
RCT	Randomized controlled trial
SAE	Serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
TTF	Tumour-treating fields
WHO	World Health Organization

1 Background

In accordance with the WHO Classification of Tumours of the Central Nervous System, glioblastomas are considered the highest grade, IV. Their incidence rate is approximately 3 to 4 per 100 000 population [1]. They most commonly affect people between 55 and 74 years of age [2]. The 2-year and 5-year survival rates were 13.6 % and 4.7 %, respectively [3].

Depending on its size and location, the symptoms of glioblastoma include various neurological symptoms, such as neurocognitive deficits, focal deficits, and the initial onset of epileptic seizures. Additional characteristic signs include signs of intracranial space-occupying lesions, including headache, nausea, and vomiting as well as altered states of consciousness [4, 5]. The primary diagnostic tool is typically magnetic resonance imaging [1].

First-line therapy (primary therapy) usually consists of the sequence of 1) resection or biopsy, 2) radiochemotherapy, and 3) adjuvant chemotherapy [1]. The standard of care further includes psycho-oncological support and palliative care [1, 5].

Surgical resection aims to remove the tumour as completely as possible while preserving function [4]. During subsequent radiochemotherapy, patients are to receive a total dose of up to 60 Gray of radiation over approximately 6 weeks with concomitant temozolomide, an alkylating chemotherapeutic agent [4]. According to the current state of knowledge, the effectiveness of temozolomide depends particularly on the promoter methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) gene. Guidelines therefore fully endorse temozolomide particularly for patients with methylated MGMT promoter, while treatment, especially of older patients without methylation, should be more carefully weighed [4]. For adjuvant chemotherapy, temozolomide is used as well for a duration of approximately 6 months [5]. This assessment does not cover relapse treatment.

Tumour-treating fields (TTF) therapy is a potential new treatment method for patients with glioblastoma [6]. It is a non-invasive method intended to inhibit tumour growth with the aid of alternating electrical fields at a frequency of 100 to 200 kHz [7]. The TTFs are applied using ceramic gel pads (arrays) affixed to the skull. The scalp has to be shaved to allow for direct skin contact. A portable field generator ensures the power supply [7]. TTF therapy is used in an outpatient setting as an add-on to standard therapy and intended to be self-administered by patients, optimally for 18 hours daily [7].

The use of TTF is the subject of debate: On the one hand, the treatment method is described as a “new and positively evaluated treatment option” [1], on the other, there are doubts as to the validity of the underlying study results [8, 9].

2 Research question

The objective of this investigation is to

- assess the benefit of TTF therapy as an add-on to current standard therapy as first-line treatment in comparison with standard therapy alone

in patients with glioblastoma in terms of patient-relevant outcomes.

3 Methods

Patients with newly diagnosed glioblastoma (WHO grade IV) were the target population of the benefit assessment. The experimental intervention was TTF therapy as an add-on to current standard first-line therapy (see Chapter 1). The comparator intervention was current standard therapy alone.

The investigation considered the following patient-relevant outcomes:

- Mortality (e.g. overall survival)
- Morbidity (e.g. seizures or altered states of consciousness)
- Health-related quality of life
- (Serious) Adverse events

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration.

A systematic literature search for studies was conducted in the databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews, and HTA Database.

The following sources of information and search techniques were additionally used: study registries, manufacturer queries, documents supplied by the Federal Joint Committee (G-BA), viewing of reference lists, and author queries.

Relevant studies were selected by 3 reviewers independently from one another. The results of the selection were summarized after the full text assessment. Data were extracted into standardized tables. To assess the qualitative certainty of results, the risk of bias at study and outcome levels was assessed and rated as high or low. The results of the individual studies were organized according to outcomes and described.

To the extent that the studies were comparable in terms of the research question and relevant characteristics, and no meaningful heterogeneity was observed, the individual results were to be quantitatively pooled in meta-analyses.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of these 3 scenarios. The latter was the case if no data were available or the available data did not permit classification into one of the 3 other categories. In that case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

4 Results

4.1 Results of the comprehensive information retrieval

The information retrieval found 1 randomized controlled study to be relevant for the research question of this benefit assessment. No planned or ongoing studies were found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 7 January 2019.

Table 1: Study pool of the benefit assessment

Study	**Available documents**		
	Full publication (in professional journals)	**Registry entry / results report from the study registries**	**Clinical study report from manufacturer documents (not publicly accessible)**
EF-14	Yes [10-16]	Yes [17] / no	Yes [18]

4.2 Characteristics of the studies included in the evaluation

The identified study EF-14 [12, 14, 18] is a multicentre, randomized study performed in 83 centres in North America, Europe, South Korea, and Israel. The study included 695 patients with newly diagnosed glioblastoma. At the start of first-line therapy, all patients underwent maximum safe resection or biopsy and received subsequent radiotherapy plus concomitant temozolomide. Before the subsequent maintenance phase, patients were randomized in a 2:1 ratio to either 6 cycles of adjuvant temozolomide chemotherapy in combination with TTF – hereinafter temozolomide + TTF – (n = 466) or 6 cycles of temozolomide monotherapy – hereinafter temozolomide – (n = 229).

The two groups were named based on the start of first-line therapy with temozolomide; in case of disease progression, a switch to relapse treatment was possible in both groups and is reflected in the group naming.

It was possible to continue TTF therapy up to a second tumour progression or at most for 24 months. TTF therapy was administered in the residential setting by the (trained) patients themselves, with 4 ceramic gel pads (transducer arrays) being placed onto the shaved scalp; the intended application period was18 hours daily, and the ceramic gel pads were regularly replaced (twice weekly).

It was possible to continue temozolomide treatment beyond the 6 planned cycles in accordance with the standards of care of the participating centres. In both groups, in case of tumour progression, temozolomide treatment was replaced by relapse treatment in accordance with the highest standard of care; the options listed in the study protocol include renewed surgery, local radiotherapy, further chemotherapy, or a combination of these options.

After completion of radiochemotherapy, i.e. from the start of the maintenance phase, all patients were to be followed up for at least 24 months. A pre-scheduled interim analysis was conducted after 315 patients had been followed up for at least 18 months; therefore, 2 data cut-offs were available for mortality. Following the interim analysis, patients in the comparator group were free to switch into the intervention group – temozolomide + TTF.

4.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 1 study. Table 2 presents an overview of the available data on patient-relevant outcomes from the included study.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes					
	Mortality	Morbidity				QoL
	Overall survival	Symptoms[a]	Cognitive functioning[b]	Activities of daily living[c]	(Serious) Adverse events[d]	Health-related quality of life[e]
EF-14	●	●	●	●	●	●

● Data were reported and were usable.

a: This includes the symptoms of pain, itching of the skin, and weakness of the legs, each surveyed using the corresponding symptom scale of the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire Brain Cancer Module 20 (QLQ-BN20).

b: Surveyed using the Mini-Mental-Status-Test (MMST).

c: Surveyed with the Karnofsky index (Karnofsky performance status scale).

d: This includes serious adverse events (SAEs), discontinuation due to adverse events (AEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3); the selection was made on the basis of incidence and relevance for the clinical picture.

e: This includes general health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning, each surveyed by means of the corresponding functional scale of the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; MMST: Mini-Mental Status Test; QLQ-BN20: Quality of Life Questionnaire Brain Cancer Module-20; QLQ-C30: Quality of Life Questionnaire Core 30; QoL: health-related quality of life; SAE: serious adverse event

4.4 Assessment of the risk of bias of results

At the study level, the risk of bias regarding the results of the final analysis after 24 months was rated as high. This was due to the fact that, after the pre-scheduled interim analysis, a large percentage of patients switched treatment, which may generally affect the results of all

outcomes. Furthermore, patients were not blinded, which may particularly affect the outcomes on symptoms and health-related quality of life.

Consequently, the qualitative certainty of results for each outcome – except for the outcome of overall survival – was seen as moderate. The qualitative certainty of results for the outcome of overall survival was rated as high since the results of the final analysis were confirmed by the results available for this outcome from a pre-scheduled interim analysis available for this outcome (before treatment switchers became an issue) confirm the results of the final analysis. The interim analysis provided no evaluations on the remaining outcomes.

4.5 Results on patient-relevant outcomes

Table 3 below provides an overview of the results for all patient-relevant outcomes in the comparison of temozolomide + TTF versus temozolomide. Mean differences (MDs) for symptoms and health-related quality of life from the mixed model repeated measures analysis are presented for the time points 3 months and 12 months after the start of maintenance therapy, i.e. for an early time point at the start of the intervention and a late time point (excluding the intermediate time points at 6 and 9 months). Data from subgroup analyses were available for overall survival (see Section 4.5.1), but not for the other outcomes.

Table 3: Overview of the results of patient-relevant outcomes

Patient-relevant outcome	**Results**
Mortality	
Overall survival	Interim analysis after 18 months: HR = 0.76, 95% CI [0.59; 0.96]; p = 0.023 Final analysis after 24 months: HR = 0.63, 95% CI [0.53; 0.76]; p < 0.001
Morbidity	
Pain	MMRM 3 months: MD −3.20, 95% CI [−7.19; 0.79]; p = 0.116 MMRM 12 months: MD 1.30, 95% CI [–4.16; 6.76]; p = 0.639
Itchy skin	MMRM 3 months: MD 8.00, 95% CI [2.25; 13.75]; p = 0.007; Hedges' g: 0.29, 95% CI [0.08; 0.50] MMRM 12 months: MD 1.70, 95% CI [–6.23; 9.63]; p = 0.673
Weakness of legs	MMRM 3 months: MD –2.20, 95% CI [–7.38; 2.98]; p = 0.404 MMRM 12 months: MD –1.40, 95% CI [–8.57; 5.77]; p = 0.701
Cognitive functioning	Time until definitive deterioration: HR = 0.81, 95% CI [0.68; 0.97]; p < 0.012
Activities of daily living	Time until definitive deterioration: HR = 0.84, 95% CI [0.71; 0.99]; p < 0.009

(continued)

Table 3: Overview of the results of patient-relevant outcomes (continued)

Patient-relevant outcome	Results
(Serious) Adverse events	**SAEs:** **Total rate**: OR = 1.16, 95% CI [0.82; 1.64]; p < 0.425 **Common SAEs (≥ 5% in at least 1 study arm):** Infections: OR = 2.09, 95% CI [1.03; 4.25]; p < 0.038 For all others, there were no statistically significant differences.
	Specific SAEs (vomiting, balance disorders, seizures, headaches, visual field defects, status epilepticus, psychiatric disorders): No statistically significant difference
	AEs of CTCAE grade ≥ 3: Total rate: OR = 1.19, 95% CI [0.86; 1.65]; p < 0.312 No statistically significant differences for common AEs of CTCAE grade **≥ 3** (≥ 5% in at least 1 study arm)
	Discontinuation due to AEs: None
Health-related quality of life	
Global health status	MMRM 3 months: MD 0.70, 95% CI [–3.69; 5.09]; p = 0.754 MMRM 12 months: MD 0.50, 95% CI [–5.57; 6.57]; p = 0.871
Physical functioning	MMRM 3 months: MD –0.40, 95% CI [–4.78; 3.98]; p = 0.858 MMRM 12 months: MD –0.90, 95% CI [–6.66; 4.86]; p = 0.758
Role functioning	MMRM 3 months: MD –5.90, 95% CI [–12.06; 0.26]; p = 0.061 MMRM 12 months: MD 5.50, 95% CI [–2.75; 13.75]; p = 0.190
Emotional functioning	MMRM 3 months: MD 2.00, 95% CI [–2.38; 6.38]; p = 0.370 MMRM 12 months: MD 0.10, 95% CI [–4.31; 4.51]; p = 0.964
Cognitive functioning	MMRM 3 months: MD 0.90, 95% CI [–4.14; 5.94]; p = 0.726 MMRM 12 months: MD −3.20, 95% CI [–9.67; 3.27]; p = 0.331
Social functioning	MMRM 3 months: MD –5.70, 95% CI [–11.52; 0.12]; p = 0.055 MMRM 12 months: MD –3.30, 95% CI [–10.89; 4.29]; p = 0.392
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; MD: mean difference; MMRM: mixed-effect model repeated measurement; OR: odds ratio; SAE: serious adverse event	

4.5.1 Results on mortality

For the outcome of overall survival, a statistically significant difference in favour of temozolomide + TTF in comparison with temozolomide was found at the end of the study: HR = 0.63, 95% CI [0.53; 0.76]. While median survival in this group was 20.9 months (95% CI [19.1; 22.6]), it was only 16.0 months (95% CI [13.9; 18.2]) in the comparator group. This effect was confirmed by a pre-scheduled interim analysis after the first 315 patients had been followed up for at least 18 months.

For mortality, this results in an indication of greater benefit of add-on TTF therapy in comparison with the current standard treatment with temozolomide.

The graphic presentation of results for the subgroup characteristics of age and sex as well as promoter methylation status of the O6-methylguanine-DNA methyltransferase gene shown in the study report suggests that there is no effect modification for this outcome.

4.5.2 Results on symptoms

For the symptoms of pain, itching of skin, and weakness of the legs, the mean values at months 3 and 12 were examined (mixed model repeated measurements [MMRM] analysis). For the outcomes of pain and weakness of the legs – as measured by the respective symptom scales of EORTC QLQ-C30 and EORTC QLQ-BN20 – no statistically significant difference between treatment groups was found.

For the outcome of itching of the skin – as measured by the EORTC QLQ-BN-20 symptom scale – a statistically significant difference was found to the disadvantage of temozolomide + TTF in comparison with temozolomide for the time point 3 months, but not for the time point 12 months. The relevance assessment by means of Hedges' g showed that this difference is clinically relevant (0.29, 95% CI [0.08; 0.50]).

Consequently, for the outcomes of pain and weakness of the legs, there is overall no hint of greater benefit or harm of temozolomide + TFF in comparison with temozolomide. For the outcome of itching of the skin, there is a hint of greater harm of temozolomide + TTF in comparison with temozolomide; this hint is based on data from the early analysis time point.

4.5.3 Results on the outcome of cognitive functioning

For the outcome of cognitive functioning, as measured by time until definitive deterioration by at least 6 points compared to the baseline value in the Mini-Mental Status Test (MMST), a statistically significant difference in favour of temozolomide + TTF in comparison with temozolomide was found: HR = 0.81, 95% CI [0.68; 0.97]. The median time until definitive deterioration was 16.7 months for temozolomide + TTF compared to 14.2 months for temozolomide. For cognitive functioning, this results in a hint of greater benefit of temozolomide + TTF in comparison with temozolomide.

4.5.4 Results on the outcome of activities of daily living

For the outcome of activities of daily living, as measured by the time until definitive deterioration by at least 10 points compared to the baseline value in the Karnofsky index, a statistically significant difference in favour of temozolomide + TTF in comparison with temozolomide was found: HR = 0.84, 95% CI [0.71; 0.99]. The median time until definitive deterioration was 5.5 months for temozolomide + TTF compared to 3.9 months for temozolomide. For the outcome of activities of daily living, this results in a hint of greater benefit of temozolomide + TTF in comparison with temozolomide.

4.5.5 Results on (serious) adverse events

This includes serious adverse events (SAEs), discontinuation due to adverse events (AEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). For each of the outcomes of SAEs, severe AEs, and discontinuation due to AEs, the total rates exhibit no statistically significant difference between treatment groups (see Table 3).

The individual SAE analysis for infections showed a statistically significant difference to the disadvantage of temozolomide + TTF in comparison with temozolomide (OR = 2.09, 95% CI [1.03; 4.25]).

For each of the examined specific SAEs of vomiting, balance disorders, seizures, headaches, visual field defects, status epilepticus, and psychiatric disorders, there is no statistically significant difference between treatment groups. It should, however, be noted that, with the exception of the outcome of seizures, the evidence was insufficient.

Overall, this results in no hint of greater harm of temozolomide + TTF in comparison with temozolomide.

4.5.6 Results on health-related quality of life

For the outcome of health-related quality of life, as measured by the mean values at months 3 and 12 from the MMRM analysis of the functional scales of EORTC QLQ-C30, no statistically significant difference between treatment groups is found for either of the scales of global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. For each of these scales, this results in no hint of greater benefit or harm of temozolomide + TTF in comparison with temozolomide.

4.6 Evidence map

Table 4 shows the evidence map regarding patient-relevant outcomes.

Table 4: Evidence map regarding patient-relevant outcomes

Study	Outcomes														
	Mortality	Morbidity								Health-related quality of life and psychosocial aspects					
	Overall survival	Pain	Itchy skin	Weakness of legs	Cognitive performance	Activities of daily living	SAEs	Severe AEs (CTCAE grade 3–4)	Discontinuation due to AEs	General health status	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning
EF-14	⇑[a]	⇔	⇘[b]	⇔	⇗	⇗	⇔	⇔	⇔	⇔	⇔	⇔	⇔	⇔	⇔

a: The indication of greater benefit of TTF + temozolomide results from the qualitative certainty of results for mortality being rated as high, despite the high risk of bias in the final analysis (see Section A3.3.1 of the full report).

b: Based on data at the early analysis time point (after 3 months).

⇑: Indication of greater benefit of TTF + temozolomide in comparison with temozolomide.

⇗: Hint of greater benefit of TTF + temozolomide in comparison with temozolomide.

⇘: Hint of greater harm of TTF + temozolomide in comparison with temozolomide.

⇔: No hint, indication, or proof; homogeneous result.

5 Classification of the assessment result

Several potentially results-influencing characteristics of the included EF-14 study as well as aspects of the use of TTF therapy in routine care are discussed below.

Timing of TTF therapy

In this study, TTF therapy of patients with newly diagnosed glioblastoma was started in first-line therapy as part of the maintenance phase; in case of tumour progression, it was possible to continue TTF therapy even after temozolomide had been replaced by different treatments as part of relapse therapy.

Between-group comparability of treatments

The distribution of relapse therapies in the as-treated population shows that bevacizumab or other chemotherapies were primarily used, or tumour resection was performed. Percentages did not differ between groups. Forgoing relapse therapy was also an option, but it was chosen only in the intervention group TTF + temozolomide: 26% of patients in this group chose TTF monotherapy after tumour progression. This distribution supports the assumption that the observed effects cannot be explained by differences in relapse therapy.

No statistically significant difference between the two groups was found for the number of temozolomide cycles received. Patients in the intervention group received a maximum of 28 cycles, while those in the comparator groups had a maximum of 24 cycles. According to the study authors, this difference is due to the fact that tumour progression was observed later in the intervention group, and therefore, the switch to relapse therapy occurred later.

Characteristics of the study population

The inclusion and exclusion criteria as well as the characterization of the study population show that, given the severity of disease, the patients from this study are functioning at a comparatively high level: The inclusion criteria call for a Karnofsky index of 70 or higher, and the characterization of the study population shows a median Karnofsky score as high as 90. The inclusion criteria required a life expectancy above 3 months, and radiochemotherapy with temozolomide had to have already been completed, i.e. tolerance to temozolomide had already been established. Consequently, it cannot be reasonably assumed that the results, particularly on overall survival (extension by nearly 5 months), can be expected to the same extent in patients under different conditions who receive care outside of clinical studies.

Compliance in the intervention group has been rated as good. Of the participating patients, 75% applied TTF therapy for 18 hours daily (as surveyed in the first 3 months). This is notable because handling the TTF treatment system may in itself represent a further burden when compared to other therapies: The electrodes for TTF application must be affixed to the shaved scalp for quite a long period, 18 hours daily; this means that patients have to wear a visually noticeable wired cap connected on their heads as well as a bag or backpack to hold the associated device.

Outcome selection

For incurable and life-limiting illnesses such as glioblastoma, 2 general treatment goals must be distinguished: on the one hand, prolonging life and, on the other, raising or optimally preserving the quality of life, including appropriate symptom control [19, 20]. As a result, it is necessary to collect and report data on the effects on patient-reported outcomes and the adverse events profile of treatment.

Both were done in this study, and the results suggest that the prolongation of life associated with treatment with temozolomide + TTF in comparison with temozolomide is not achieved at the expense of other patient-relevant outcomes: while, in the category of common SAEs, TTF therapy is associated with a higher incidence rate for infections, and the study data show that itchy skin is initially more common under TTF therapy, there is simultaneously a hint of greater benefit of TTF + temozolomide in comparison with temozolomide for the outcomes of cognitive functioning and activities of daily living. For all outcomes of health-related quality of life, there is no hint of greater benefit or harm of TTF + temozolomide in comparison with temozolomide.

Nevertheless, TTF therapy may represent a burden for patients insofar as they are supposed to wear a wired cap on their shaved heads for at least 18 hours daily. Particularly given the life-limiting nature of the illness, this aspect must not be neglected when considering treatment goals and treatment decisions.

Publication bias

The available information does not suggest publication bias.

6 Conclusion

The benefit assessment included 1 study in patients with newly diagnosed glioblastoma who had already undergone resection (or biopsy) and completed radiochemotherapy.

In this study, TTF therapy was started as part of maintenance therapy as first-line treatment, and it was possible to continue it even after tumour progression.

From this study, results on mortality (overall survival), morbidity (including symptoms, cognitive performance, activities of daily living, and [serious] adverse events), and health-related quality of life were used.

For the outcome of overall survival, there was an indication of greater benefit of TTF therapy as an add-on to the current standard treatment with temozolomide in comparison with temozolomide monotherapy.

For morbidity, there was a hint of greater benefit of TTF therapy as an add-on to the current standard therapy for the outcomes of cognitive functioning and activities of daily living. For 1 out of the 3 examined symptoms (itchy skin), based on an early analysis time point, there was a hint of greater harm of TTF therapy as an add-on to the current standard therapy.

For all other outcomes, i.e. health-related quality of life, (serious) adverse events as well as the two other examined symptoms (pain and leg weakness), there was no hint of greater benefit or harm of TTF therapy as an add-on to the current standard treatment in comparison with temozolomide monotherapy.

No other planned or ongoing studies were found that would be able to verify this result within a foreseeable period.

7 References for English extract

Please see full rapid report for full reference list.

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Appendix A – Search strategies

A.1 – Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to December Week 4 2018
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 03, 2019
- Ovid MEDLINE(R) Daily Update January 03, 2019
- Ovid MEDLINE(R) Epub Ahead of Print January 03, 2019

The following filters were adopted:

- Systematic review: Wong [21] – High specificity strategy
- RCT: Lefebvre [22] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	**Searches**
1	Glioblastoma/
2	(glioblastoma* or gbm).ti,ab.
3	1 or 2
4	Electric Stimulation Therapy/
5	(novottf* or optune* or ttfields*).ti,ab.
6	((electric* or (tumo?r* adj1 treat*)) adj3 fields*).ti,ab.
7	or/4-6
8	randomized controlled trial.pt.
9	controlled clinical trial.pt.
10	(randomized or placebo or randomly or trial or groups).ab.
11	drug therapy.fs.
12	or/8-11
13	exp animals/ not humans.sh.
14	12 not 13
15	Cochrane database of systematic reviews.jn.
16	meta analysis.pt.
17	(search or MEDLINE or systematic review).tw.
18	or/15-17
19	14 or 18
20	and/3,7,19

#	Searches
21	20 not (comment or editorial).pt.

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search glioblastoma* [TIAB] OR gbm* [TIAB]
#2	Search (novottf* [TIAB] OR optune* [TIAB] OR ttfields* [TIAB])
#3	Search ((electric* [TIAB] OR ((tumor [TIAB] OR tumour [TIAB]) AND (treating* [TIAB] OR treatment* [TIAB]))) AND fields* [TIAB])
#4	Search (#2 OR #3)
#5	Search (clinical trial*[TIAB] OR random*[TIAB] OR placebo[TIAB] OR trial[TI])
#6	Search (search[TIAB] OR meta analysis[TIAB] OR MEDLINE[TIAB] OR systematic review[TIAB])
#7	Search (#5 OR #6)
#8	Search (#1 AND #4 AND #7)
#9	Search (#8 NOT Medline [SB])

3. Embase

Search interface: Ovid

- Embase 1974 to 2019 January 03

The following filters were adopted:

- Systematic review: Wong [21] – High specificity strategy
- RCT: Wong [21] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	glioblastoma/
2	(glioblastoma* or gbm).ti,ab.
3	1 or 2

#	Searches
4	(novottf* or optune* or ttfields*).ti,ab.
5	((electric* or (tumo?r* adj1 treat*)) adj3 fields*).ti,ab.
6	4 or 5
7	(random* or double-blind*).tw.
8	placebo*.mp.
9	or/7-8
10	(meta analysis or systematic review or MEDLINE).tw.
11	9 or 10
12	and/3,6,11
13	12 not medline.cr.
14	13 not (exp animal/ not exp human/)
15	14 not (Conference Abstract or Conference Review or Editorial).pt.

4. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 1 of 12, January 2019
- Cochrane Central Register of Controlled Trials: Issue 1 of 12, January 2019

ID	Search
#1	[mh ^"glioblastoma"]
#2	(glioblastoma* or gbm*):ti,ab
#3	#1 or #2
#4	[mh ^"Electric Stimulation Therapy"]
#5	(novottf* or optune* or ttfields*):ti,ab
#6	((electric* or (tumo*r* near/1 treat*)) near/3 fields*):ti,ab
#7	#4 or #5 or #6
#8	#3 and #7 in Cochrane Reviews, Cochrane Protocols
#9	#3 and #7 in Trials

5. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR glioblastoma
2	(glioblastoma* or gbm*)

Line	Search
3	#1 OR #2
4	MeSH DESCRIPTOR Electric Stimulation Therapy
5	(novottf* or optune* or ttfields*)
6	((electric* OR (tumo*r* AND treat*)) AND fields*)
7	#4 OR #5 OR #6
8	#3 AND #7
9	(#8) IN HTA

A.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
(novottf OR optune OR ttfields OR tumor treating fields OR tumour treating fields OR electric fields) AND (glioblastoma OR GBM)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategy
novottf OR novo-ttf OR novo ttf OR optune OR ttfields OR tumor treating fields OR tumour treating fields OR electric fields