Efficacy of TTFields in high-grade gliomas: a protocol for systematic review and meta-analysis

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ABSTRACT

INTRODUCTION

Even though gliomas, which are brain tumours of glial cell origin, account for a relatively small proportion (28%) of all primary brain tumours, they comprise ~80% of all malignant primary brain tumours in adults.1 Recently reported molecular-based data suggest that some gliomas have growth patterns and molecular features of high-grade gliomas (HGGs). Gliomas with WHO grade III and grade IV are considered HGGs, and these gliomas present a malignant growth pattern and are associated with extremely poor overall survival (OS).2 Anaplastic astrocytoma is the most common WHO grade III glioma. The OS of patients having anaplastic astrocytoma after diagnosis is typically 2–3 years. Conversely, glioblastoma multiforme (GBM) is the most common WHO grade IV glioma.1 In adults, HGGs such as GBM typically have dismal prognoses owing to frequent recurrence and treatment resistance even after all standard of care (SOC) treatments.3 Patients with GBM have a median survival period of ~20 months and 1-year and 5-year survival rates of 35.0% and 4.7%, respectively,4 indicating dismal prognoses.

The SOC for HGGs is maximally safe surgical resection followed by 6-week treatment with concurrent temozolomide (TMZ) and radiation therapy and then 6-month treatment with adjuvant TMZ.5 In addition to TMZ, one device (tumour treatment fields, TTFields) and four drugs (bevacizumab, carmustine wafer implants, intravenous carmustine and lumostine) have received FDA approval for the treatment of HGGs.6–8 However, for newly diagnosed HGGs, only carmustine, TTFields, TMZ and wafer implants have been approved by the FDA.9

In addition, new research therapies, which

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ No relevant reports were seen (a meta-analysis comparing tumour treatment fields efficacy on a standard of care basis).
⇒ The quality of the included literature and final outcomes, even adverse events, will be evaluated.
⇒ In the case of neurological symptoms in the adverse events, each study difference may be relatively large, and we can only make data statistics based on the data they provide.
⇒ Restriction of publication language to English only is a limitation of this study.


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include immunotherapies such as checkpoint suppression, oncolytic viruses and vaccine therapy,\textsuperscript{16} have not received FDA approval.

TTFields, a novel cancer therapeutic modality, exert their effect based on the principle that alternating electric fields applied at specific frequencies have the ability to interrupt cancer cell division and cause cancer cell death.\textsuperscript{11} In 2015, TTFields received FDA approval for use in cases with newly diagnosed GBM(ndGBM).\textsuperscript{6} These fields are applied via a portable device and pulsed through the shaved scalp. The device is used for over 18 hours daily for at least 4 weeks. This device delivers intermediate frequency (200 kHz), low intensity (1–3 V/cm) alternating electric fields that selectively disrupt mitosis in tumour cells.\textsuperscript{12} Skin disorders (36%), general disorders/application site conditions (31%) and nervous system disorders (27%) were the most commonly reported adverse events (AEs) among all patients, the incidence rate varied little among age groups. Treatment-related skin responses were significantly less pronounced in recurrent GBM(rGBM) (29%) than in ndGBM (28%). Other AEs associated with TTFields included electric sensation (ie, underarray tingling, 11%) and heat sensation (ie, underarray warmth, 10%). These AEs belong to general disorders.\textsuperscript{13} In addition, headaches and seizures were also considered as adverse effects belonging to neurological symptoms. However, because of the brain tumour and the SOC treatment, these headaches and seizures may be related to the tumour and other treatments, and it was thus difficult to determine if they were related to the primary disease. Skin reactions are the most concerning and have very high incidence. They represent the most common AEs, and although there are still some other AEs, their incidence is very low. A randomised controlled trial (RCT) comparing the effects of TTFields+TMZ versus TMZ alone on the survival of GBM patients reported that the former showed significantly improved progression-free survival (PFS, 7.1 vs 4.2 months) and OS (20.5 vs 15.6 months).\textsuperscript{12} Several subsequent experiments since then have confirmed these improvements in the PFS.\textsuperscript{14,15}

Currently, the clinical effect of simultaneous or sequential use of TTFields with the current SOC has been reported by few studies. Using this review protocol, we aim to identify the efficacy of TTFields in HGGs when administered concurrently with the standard treatment; furthermore, we aim to determine whether the enhanced effect, if any, justifies the remarkable increase in medical expenses. Taken together, we aim to uncover and showcase medical evidence to determine if TTFields should be an integral part of the SOC for HGG.

**MATERIALS AND METHODS**

**Study registration**

We registered this review protocol with the PROSPERO network (registration number: CRD42023398972). The protocol will follow the statement guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses.\textsuperscript{16} Given that this is not a prospective study, ethical approval will not be required.

**Searching strategy**

This study will use the following databases: China National Knowledge Infrastructure, Embase, Cochrane Library, Wanfang Database, China Science and Technology Journal Database, China Biomedical Literature Database, Web of Science, Allied and Complementary Medicine Database and PubMed. Literature retrieval will not be limited to a time period but is limited to English and Chinese papers. The following keywords will be used for the literature search: “Tumor treating fields,” “Tumortreating fields,” “TTFields,” and “alternating electric fields” related to the keywords “glioblastoma,” “glioma,” “high-grade glioma,” “HGG,” “malignant glioma,” and “GBM” using the Boolean operator “AND.” The Chinese database search will be conducted using the keywords “电场,” “电场治疗” and “肿瘤治疗电场” related to the keywords “胶质母细胞瘤,” “胶质瘤,” “高级别胶质瘤,” “恶性胶质瘤,” and “IV级胶质瘤” using the Boolean operator “AND.” The detailed searching strategy is included in online supplemental file 1.

**Eligibility criteria**

Studies meeting the following criteria will be included in our analyses.

1. RCTs.
2. Patients aged more than 18 years with a new and definitive diagnosis of HGGs.
3. The intervention and control groups received the SOC+TTFields and only the SOC, respectively.
4. The studies reported findings for one or more of the following aspects: clinical efficacy, AEs, the Karnofsky performance status, OS and PFS. Besides the OS, outcome measures may differ among different literatures, such as 1-year or 2-year survival. We here aim to collect this information and conduct statistical analysis according to the actual situation. If we identify multiple studies that have analysed the same population, we will include the study with the largest sample or the longest follow-up.

Studies will be excluded if their full texts cannot be accessed, they are found to have a poor quality score as per the stated criteria, or they are duplicate citations.

**Data selection**

First, to select eligible studies, two investigators will use EndNote V.9 software to perform a preliminary assessment of the title and abstract of all published papers as per the established criteria for study inclusion. Full texts of the studies selected in the preliminary assessment will be evaluated, and studies with inconsistent evaluation criteria or similar data and studies that did not use controls or randomisation will be excluded. Finally, the studies selected for inclusion after applying all criteria will be exchanged and cross-checked by researchers. Any disagreements between the two researchers on the
eventual inclusion of a study will be resolved by consulta-
tion with the third author.

Data extraction
Two researchers will perform data extraction and will collect data on the following parameters: disease diag-
nosis, age, sample size, outcomes, AEs, interventions and
details about the control group and follow-up. The third
author will be approached to resolve any disagreement
with respect to data collection. Studies with unclear,
missing, difficult-to-extract or poorly presented data will
be excluded.

Risk of bias assessment
Using the Cochrane risk of bias assessment tool, two inves-
tigators will independently assess the risk of bias associated
with the included studies. Each study will be primarily
evaluated on the following seven parameters: incomplete
outcome data, blinding of outcome assessment, selective
outcome reporting, random sequence generation, allocation
hiding, blinding of participants and personnel, and
other biases. Finally, the level of bias for each study will be
rated as ‘low’, ‘high’ or ‘ambiguous’. All these parameters
will be independently reviewed by two reviewers, and any
discrepancies or disagreements will be resolved by a third
reviewer.

Statistical analysis
We will perform all statistical analyses using the Review
Manager software (V.5.3), and the threshold for statistical
significance will be set at a p<0.05. Risk ratios or ORs with
95% CIs will be used to analyse dichotomous data. Continuous
variables measured on the same scale will be analysed
using weighted mean differences and expressed as a
mean±SD. Heterogeneity among studies will be assessed
using the I² test and χ² test statistic (Q). The Q-statistic test
will be used to identify heterogeneity, and the I² test will
be used to estimate the percentage of variation caused by
the heterogeneity. A Q value of >0.05 will be considered
to indicate that the outcome variable is statistically signif-
cant, and if the p value is >0.1 and I² value is <50%, the
fixed-effects model will be selected. Conversely, if I² value
is ≥50% and the p value is <0.1, the random-effects model
will be selected.

Patient and public involvement
No patient involved.

Research time
The study is scheduled to begin in April 2023 and end in
June 2024. The period may be extended as appropriate in
the light of the documentation.

DISCUSSION
The purpose of this study is to propose an objective and
transparent method to conduct a systematic review and
meta-analysis aimed at investigating the effectiveness of
TTFields based on the SOC.

Glioma, particularly HGG, is the most common type of
cancer in the central nervous system, and it is currently
considered incurable. The prognosis of HGG patients
remains unfavourable despite multiple therapies and
combination treatments involving surgery, radiotherapy
and molecular targeting. The median survival time for
GBM patients is approximately 12–15 months. Owing
to the low quality of life and poor prognosis of patients
with HGGs, various treatment approaches have been
implemented; however, none of them have yielded satis-
factory final results. Even now, various treatment methods
are being experimentally studied by the researchers. The
development of TTFields was done by Novocure over the
past two decades. This technique has achieved good
results in clinical trials and in vitro and in vivo experi-
ments, and based on these results, the FDA approved the
use of TTFields for recurrent or refractory GBM in 2011
and as adjuvant treatment for newly diagnosed GBM after
the completion of the SOC surgery and chemoradiation
in 2015.

To our knowledge, no meta-analysis has compared the
efficacy of TTFields on an SOC basis. Therefore, the
biggest asset of this study is its novelty. Previous meta-
analyses on TTFields incorporated too many RCTs with
different treatment regimens. Although their sample
sizes are large, their comparison outcomes are relatively
biased.

This study has some potential limitations. Publication
bias and information bias are points of concern as we
only covered papers in Chinese and English. In addition,
since English papers may come from different regions,
differing medical conditions in these regions can also
lead to biases.

TTFields have not been added to the SOC because the
technique is highly cost-intensive and causes increased
inconvenience to the patients. However, we believe that
it is important to study the extent of benefits it has when
used alongside the SOC.

Contributors YP and GY designed the study and were the main coordinators of the
study. YP was the principal investigator and guarantor. JW gave statistical support.
XL wrote the article. All authors reviewed and approved the final version of the
manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in
the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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REFERENCES
Additional file
Detailed search strategies for databases

1. Search strategy for PubMed
#1 Glioma [Mesh Terms]
#2 (“glioma” OR “glioblastoma” OR “high-grade glioma” OR “HGG” OR “GBM” OR “malignant glioma”) [Title/Abstract]
#3 #1 OR #2
#4 Tumor treating fields [Mesh Terms]
#5 (“tumor treating fields” OR “tumor-treating fields” OR “TTFields” OR “alternating electric fields” OR “TTF”) [Title/Abstract]
#6 #4 OR #5
#7 Randomized Controlled Trial [Publication Type]
#8 (Randomized Controlled Trials OR Clinical Trials, Randomized OR Trials, Randomized Clinical OR Randomized) [Title/Abstract]
#9 #7 OR #8
#10 Humans [filter]
#11 Animals [filter]
#12 Case reports [filter]
#13 Editorial [filter]
#14 #9 OR #10 OR #11
#15 #3 AND #6 AND #9 AND #10 NOT #14

2. Search strategy for the Cochrane Library
#1 [Glioma] explode all trees
#2 (“glioma”):ab OR (“glioblastoma”):ab OR (“high-grade glioma”):ab OR (“HGG”):ab OR (“GBM”):ab OR (“malignant glioma”):ab
#3 #1 OR #2
#4 [Tumor treating fields] explode all trees
#5 (“tumor treating fields”):ab OR (“tumor-treating fields”):ab OR (“TTFields”):ab OR (“alternating electric fields”):ab OR (“TTF”):ab
#6 #4 OR #5
#7 (“Randomized Controlled Trial”):pt
#8 Humans [mh]
#9 Animals [mh]
#10 Case reports [mh]
#11 Editorial [mh]
#12 #9 OR #10 OR #11
#13 #3 AND #6 AND #7 AND #8 NOT #12

3. Search strategy for the EMBASE
#1 Glioma /exp
#2 (“glioma” ‘glioblastoma’ OR ‘high-grade glioma’ OR ‘HGG’ OR ‘GBM’ OR ‘malignant glioma’):ti,ab,kw
#3 1-2/OR
Tumor treating fields/exp OR tumor treating fields OR TTFIELDS OR alternating electric fields OR TTF), :ti,ab,kw
randomized controlled trial/epx
trial. ti,ab,kw
(exp animal/ or exp animal experiment/ or exp case reports/ or exp editorial)
#3 AND #6 AND #10 NOT #11

Tumor treating fields OR Tumor-treating fields OR TTFields OR alternating electric fields OR TTF
randomly. ti,ab,kw
trial. ti,ab,kw
randomly.

Refinement was performed by checking English and Chinese in the language options and by checking Thesis and Clinical Trial in the literature type.

Search strategy for China National Knowledge Infrastructure (CNKI)

Search strategy for Chinese Biomedical Literatures database (CBM)

Search strategy for WANFANG data

Search strategy for VIP database
“任意字段=胶质瘤 or 胶质母细胞瘤 or 恶性胶质瘤 or 高级别胶质瘤 or IV级胶质瘤 or III级胶质瘤 or 神经胶质瘤 and 电场 or 电场治疗 or 肿瘤治疗电场”