OptimalTTF-1: Enhancing tumor treating fields therapy with skull remodeling surgery. A clinical phase 1 trial in adult recurrent glioblastoma.

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Abstract

**Background:** Preclinical studies suggest that skull remodeling surgery (SR-surgery) increases the dose of tumor treating fields (TTFields) in glioblastoma (GBM) and prevents wasteful current shunting through the skin. SR-surgery introduces minor skull defects to focus the cancer-inhibiting currents towards the tumor and increase the treatment dose. This study aimed to test the safety and feasibility of this concept in a phase 1 setting.

**Methods:** 15 adult patients with first recurrence of GBM were treated with personalized SR-surgery, TTFields and physician’s choice oncological therapy. The primary endpoint was toxicity and secondary endpoints included standard efficacy outcomes.

**Results:** SR-surgery resulted in a mean skull defect area of 10.6 cm² producing a median TTFields enhancement of 32% (range 25-59%). The median TTFields treatment duration was 6.8 months and the median compliance rate 90%. Patients received either bevacizumab, bevacizumab/irinotecan, or temozolomide rechallenge. We observed 71 adverse events (AEs) of grades 1 (52%), 2 (35%), and 3 (13%). There were no grade 4 or 5 AEs or intervention-related serious AEs. Six patients experienced minor TTFields-induced skin rash. The median progression-free survival (PFS) was 4.6 months and the PFS rate at 6 months was 36%. The median overall survival (OS) was 15.5 months and the OS rate at 12 months was 55%.

**Conclusions:** TTFields therapy combined with SR-surgery and medical oncological treatment is safe and non-toxic and holds potential to improve the outcome for GBM patients through focal dose enhancement in the tumor.

**Keywords**

Glioblastoma, neuro-oncology, tumor treating fields, neurosurgery, craniectomy
Key points

- Craniectomy and small burr holes in the skull focally enhance the dose of TTFields.
- Craniectomy is safe in combination with TTFields and not a contraindication.
- TTFields in combination with craniectomy or small burrholes is safe and likely effective.

Importance of the study

We present phase 1 data for a new, rational, and innovative intervention combining tumor treating fields (TTFields) with targeted skull-remodeling surgery to enhance the field dose and clinical efficacy against recurrent glioblastoma. The concept builds on preclinical dosimetry studies and recent clinical evidence that the field dose correlates with overall survival. Our study is the first to successfully achieve a significant and personalized TTFields dose accumulation focally in the tumor and we have used dosimetry methods to illustrate the concept and its impact. The treatment is easy to understand and implement, and potentially extends to all intracranial applications of TTFields. Our data suggest that the treatment is safe and effective (median overall survival 15.5 months and progression-free survival rate at six months 36%). Based on these results, we have initiated a subsequent prospective randomized phase 2 clinical trial scheduled to begin recruitment in summer 2020 (NCT04223999).
Introduction

Glioblastoma (GBM) is the most prevalent and severe primary adult brain cancer. Despite maximum safe resection, radiotherapy, and chemotherapy the prognosis is dismal with a median overall survival (OS) of approximately one year for newly diagnosed cases (1-4). Recently, tumor treating fields (TTFields, Optune®) were included as a Category 1 recommendation for patients with newly diagnosed GBM by the National Comprehensive Cancer Network in the United States (5). TTFields are low-intensity (1-3 V/m) and intermediate frequency (200 kHz) alternating fields that disrupt mitosis and inhibit tumor growth (6). A recent randomized controlled phase III trial (EF-14) established that TTFields result in a sustained overall survival benefit (OS = 20.9 vs. 16.0 months, p<0.001) and prolonged progression-free survival (PFS = 6.7 vs. 4.0 months, p<0.001) for newly diagnosed GBM when added to temozolomide maintenance therapy (7). Although efficacy benefits have been less profound for recurrent GBM (rGBM), a randomized controlled phase III trial (EF-11) has demonstrated superior toxicity for TTFields monotherapy compared to best practice medical oncological therapy alone (8). Subsequent retrospective studies and a meta-analysis has since indicated a significant survival benefit for both recurrent and newly diagnosed GBM (9, 10).

TTFields dosimetry and dose enhancement with skull-remodeling surgery

Different methods have been implemented to quantify the dose distribution of TTFields in the brain and provide strategies for treatment planning and response prediction. Although the efficacy of TTFields is influenced by multiple factors, such as frequency and spatial correlation of the fields (6,11,12), the field intensity distribution is commonly accepted as a surrogate measure of treatment dose. The field intensity correlates positively with the tumor kill rate \textit{in vitro} (6) and the overall survival, i.e. high field intensities in the tumor lead to longer OS (13). The field distribution can be estimated using finite element methods (14-17) based on personalized computational models constructed from MRI data, see Korshoej et
al., 2019 (18), and Wenger et al., 2018 (17), for further details on TTFields dosimetry and its clinical implications.

Using dosimetry methods, we previously showed that skull-remodeling surgery (SR-surgery), including burr holes and minor craniectomies placed above the tumor region, provide a substantial (~70%) and highly focused enhancement of TTFields in the tumor without affecting the dose in the healthy tissues, Fig. 1G (14). The skull defects serve as low-resistance pathways that facilitate current flow into the tumor region (Fig. 1D) and prevent wasteful shunting of currents through the skin between the arrays, caused by shielding effects of the high-impedance skull (Fig. 1C&E).

Here, we present the results of a proof-of-concept phase 1 clinical trial testing SR-surgery as a rational, innovative, and dose-enhancing method to improve TTFields therapy against rGBM.

**Methods**

The trial was a prospective, open-label, single-center phase 1 trial investigating safety, feasibility, and preliminary efficacy of SR-surgery in combination with TTFields and best choice chemotherapy for rGBM (clinicaltrials.gov id NCT02893137). The study was performed at Aarhus University Hospital, Denmark, in the period Oct 1st 2016 to May 31st 2019. All study procedures were in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association (19) and followed guidelines for Good Clinical Practice (ICH-GCP), ISO-14155 standards, and relevant Danish regulations, see Supplementary Material S1 for further protocol details).
Eligibility and enrollment

Inclusion criteria

1) Age ≥18 years, 2) histopathological primary diagnosis of GBM using WHO 2016 classification (21), 3) estimated survival ≥ 3 months, 4) supratentorial tumor location, 5) not a candidate for further radiotherapy, 6) first disease progression according to RANO criteria (20) based on MRI performed no later than 4 weeks prior to enrollment, 7) Karnofsky performance score (KPS) ≥ 70, 8) ability to comply with TTFields, 9) significant expected benefit from feasible SR-surgery combined with TTFields, i.e. (a) focal disease and (b) at least some part of the tumor or resection cavity had to be closer than 2 cm from the brain surface, and 10) signed written consent form.

Exclusion criteria

1) Pregnancy or nursing, 2) less than four weeks since radiation therapy, 3) infratentorial tumor, 4) implanted pacemaker, 5) programmable shunts, 6) deep brain stimulator, 7) refractory symptomatic epilepsy, 8) contraindications for SR-surgery, e.g. bleeding diathesis or severe infection, 9) significant comorbidities, i.e. significant liver function impairment, significant renal impairment, coagulopathy, thrombocytopenia, neutropenia, anaemia, and 10) active participation in another therapeutic interventional clinical trial.

Patients were also excluded, if rGBM could not be confirmed on histopathological examination of resected tissue after inclusion.
Treatment plan

All patients were treated with SR-surgery, TTFields and physician’s choice medical oncological therapy.

SR-surgery and resection

The objective of the SR-surgery was to maximize the field intensity (i.e. dose) in the residual tumor or the region surrounding the resection cavity. The SR-surgery configuration was optimized for each individual (see Fig. 2 for examples) by calculating the personalized field distributions before and after different virtual SR-configurations (e.g. size, shape and position). Configurations were explored on a trial-and-error basis. In general, the skull holes were clustered in a relatively small region directly above the resection cavity, to ensure that the TTFields were focused toward the underlying tumor. Due to the complexity of field estimation, with many individual factors influencing the results, it was not feasible to implement a specific dose-escalation regimen (Supplementary Material S2 and (25)). Instead, we required the chosen SR-configuration to induce >25% enhancement of the average field dose in the tumor to justify any potential risk imposed on the patient due to the SR-surgery. Furthermore, we generally required the total skull defect area to be below 30 cm² as a safety limitation for mechanical brain protection. This area limit was exceeded at the request of two patients, as a larger defect induced greater field enhancement in these cases. The SR-surgery design was conducted prior to surgery and implemented with neuronavigation.

Maximum safe resection was performed for all patients, although this was not an inclusion criterion. Surgeries resulting in measurable residual disease on the postoperative MRI (<72 hours) according to the RANO criteria were classified as partial resections, whereas surgeries resulting in no residual disease or non-measurable residual disease were categorized as gross total resections.
TTFields therapy

TTFields therapy was initiated four weeks from surgery. Array layouts were planned to maximize the TTFields dose in the tumor (16). In a normal clinical setting, the TTFields array layout is planned using the CE marked and FDA approved NovoTAL® (Novocure™) software, which uses individual morphometric measures of the head size and tumor size/position to determine a suitable personalized layout. However, this approach was not appropriate for the present trial, because SR-surgery causes a redistribution of the electric field (Fig. 2D), which is not accounted for by NovoTAL®. We therefore planned the layouts using more general principles for layout personalization (16,34) and TTFields dosimetry (15,35). Basically, we positioned the arrays such that a row of edge electrodes from one array in each pair overlaid the burr holes and tumor region (Fig. 2B). This was done for both pairs so that one array from each pair overlapped the remodeled skull region. The rationale for the approach is that stronger fields are induced at the periphery of the arrays due to the “edge effect”, see (16) and Supplementary Material S3). Therefore, it was not desirable to place holes underneath the central parts of the arrays or far away from the array. The other array in the same pair was placed on the opposite side of the skull so that the line between the paired arrays passed through the target regions of interest. This ensured that both array pairs contributed current flow through the skull holes, inducing high fields in the tumor throughout the entire duty cycle. Given the perpendicular orientation of the two array pairs relative to each other, they covered different areas of the underlying tumor and brain region as previously described by Korshoej et al. (34). The virtual placement of electrodes was performed using the SimNIBS GUI and a custom Matlab script (Mathworks, Inc.).
Adjuvant medical treatment

Medical oncological treatment was initiated two to four weeks after surgery and included bevacizumab (10 mg/kg every two weeks, three administrations per cycle) alone or in combination with either lomustine (90 mg/m² every six weeks, one administrations per cycle) or irinotecan (125 mg/m² every 4 weeks) (22). Temozolomide rechallenge (200 mg/m²) was preferred for patients with MGMT methylated tumors who had initially completed six cycles adjuvant temozolomide therapy. We did not impose restrictions on supportive care. Corticosteroid administration was reduced to the minimum effective dose (23,24).

Endpoint assessment

The primary endpoint was the severity and frequency of AEs evaluated by the investigators using CTCAEv4.0 (27).

Secondary endpoints were median OS, PFS at six months (PFS6), median PFS, overall survival rate at twelve months (OS12), objective response rate (ORR), QoL score (EORTC QLQ-C30 and QLQ–BN20 questionnaires) (26), cumulative corticosteroid dosage, and KPS decline. Treatment response was evaluated by trained neuroradiologists and neuro-oncologists using the immunotherapy response assessment in neuro-oncology (iRANO) criteria (29), to allow for the potential delayed response previously demonstrated for TTFields (24).

Patient follow-up and monitoring

Clinical examination, including quality of life (QoL) and toxicity assessment, was conducted 1) at baseline, 2) postoperatively during admission, 3) before TTFields and medical oncological therapy, and 4) regularly during adjuvant treatment. MRI, clinical examination and lab tests were conducted every twelve weeks during follow-up, while QoL and toxicity was assessed every six weeks. Additional examinations were conducted upon suspected or validated progression.
**Treatment discontinuation, patient exclusion, and trial termination.**

TTFFields therapy was discontinued upon 1) disease recurrence, i.e. second overall disease recurrence, 2) grade 3-5 serious AE (SAE) caused by the intervention, or 3) unacceptable AEs regardless of grade. Upon active request from the patient, TTFFields therapy beyond progression was allowed on a compassionate use basis or in connection with continued medical treatment. Patients were excluded in the events of 1) death, 2) trial completion, 3) loss to follow-up, 4) withdrawal of consent, or 5) safety prohibiting further participation. The trial was terminated when the final patient was excluded and the necessary data had been acquired. Furthermore, the trial was set to stop in the occurrence of more than eight SAEs attributed to the intervention.

**Statistical methods**

The trial was exploratory and descriptive so we did not perform sample size calculations nor risk stratification (See Supplementary Material S1). AEs were reported as the number and frequencies of patients experiencing a particular AE at least once at any grade. For ongoing AEs with variable grade over time, e.g. variable intensity of headache, we reported the AE as a single event with the highest grade observed. Time-to-event data (e.g. OS and PFS) were calculated from the date of inclusion until the date of the event and censored in the case of patient exclusion. The resulting data were reported using the Kaplan-Meier method with median estimates and 95% confidence intervals. Binomial data, such as PFS6 and OS12, were reported incl. 95% confidence intervals using the exact binomial distribution. TTFFields compliance rates were calculated as the relative device on-time (%) in the total treatment period. KPS decline was calculated as the absolute difference between the KPS at progression and the KPS at TTFFields initiation. The cumulative corticosteroid dose was calculated as a weighted average over the entire inclusion period and expressed in methylprednisolone equivalents. QoL was expressed as the global, functional, and symptom scores according to the EORTC QLQ-C30 and –BN20 guidelines.
Electrical field estimates were calculated and reported as described previously in the paper. The relative field enhancement caused by SR-surgery was calculated for each patient, as the increase in predicted field intensity after SR-surgery relative to the field intensity before SR-surgery, i.e. \( \frac{E_{\text{after}} - E_{\text{before}}}{E_{\text{before}}} \).

**Results**

**Patient flow**

Twenty patients were screened for participation in the period Dec 12th 2016 to Apr 25th 2018. Fifteen were enrolled and followed until May 31st 2019, Fig. 3. Of those not enrolled, three had declined participation, while two were excluded due to KPS < 70. Of the fifteen enrolled patients, four were excluded prior to TTFields therapy due to radionecrosis/non-recurrence, postoperative infection, neurodeficit (Gerstmann Syndrome), and withdrawal of consent, respectively. The remaining eleven patients completed the trial with active TTFields therapy. Baseline data and treatment outline is given in Table 1. The median follow-up period was 14.8 months (range 5.8 to 25.2 months). All patients were followed until exclusion and none were lost to follow-up.

**Reasons for discontinuation of treatment**

TTFields was discontinued for eight out of the eleven patients. All cases of permanent TTFields discontinuation occurred due to disease progression. AEs did not result in discontinuation for any patient. Four patients continued TTFields therapy beyond progression. Two of these were on a compassionate use basis, while the other two also continued active medical treatment with temozolomide and bevacizumab, respectively. Three patients were still on active TTFields at the end of the trial period.
Baseline data and treatment exposure

We included eleven male patients and four female patients. All patients had IDH-wildtype tumors. Baseline characteristics of patients treated with TTFields are presented in Table 1 along with the general treatment outline.

SR-surgery and tumor resection

For the fifteen enrolled participants, the median time from inclusion to SR-surgery and resection was 6 days (range 0-14 days). Fig. 2 shows examples of three different configurations of SR-surgery of varying extensiveness, including a visualization of the field enhancing effects induced by the most commonly employed configuration (4x15 mm diameter). Field enhancement >25% could be obtained for all patients (Fig. 2E). The SR-surgeries were technically feasible, easy to perform and added less than 15 minutes of additional surgery time. Tumor resection was performed in all cases (see Table 1 for extent of resection).

Of the 11 patients receiving TTFields, three had 4 burr holes of 15 mm diameter, one had 5 holes of 15 mm diameter, four had 6 holes of 15 mm diameter, one had five peripheral 15 mm holes and one central 25 mm hole, one had seven holes of 15mm diameter, and one had an elliptic craniectomy (semi-axis diameters 85x65 mm).

Of the four patients excluded before TTFields therapy two had five 15 mm holes, one had eight 20 mm holes, and one had a total craniectomy (60x50 mm). Two of these patients had gross total resection and two had non-measurable residual tumors.

The relationship between the SR-surgery configuration, e.g. the size, arrangement and number of burr holes, and the induced relative field enhancement was highly complex (Fig. 2E). Although a complete review of this relationship was beyond the scope of this study, we generally observed that identical configurations had different efficacy for different patients, e.g 6x15 mm burr holes, 10.6 cm², induced field enhancements in the wide range of 25-60%). The field enhancement appeared to plateau around 55-60% when...
the total area of the skull holes was >15-20 cm². There was no linear correlation between the relative field enhancement and the skull hole area \((r^2=0.55)\). Similarly, we observed no correlation between the absolute field intensity in the tumor after SR-surgery and the increase absolute field intensity in the tumor after SR-surgery \((r^2=0.49\) and \(r^2=0.094\), respectively). As a part of the scheduled preparation, dosimetry calculations were performed for all patients included in the trial (Fig. 2E), i.e. also the four patients who did not proceed to TTFIELDS therapy. Since all 15 included patients contribute information about the expected field enhancement and the potential correlation with SR-size and configuration, we included all patients in the correlation analysis.

**TTFIELDS therapy and adjuvant medical treatment**

Details of the TTFIELDS treatment and adjuvant therapy are given in Table 1. Of all patients receiving TTFIELDS, eight were treated with bevacizumab monotherapy (median no. of cycles = 5, range 2 to 16). One patient received bevacizumab/irinotecan combination treatment (2 cycles), while two patients were treated with temozolomide rechallenge (3 and 4 cycles, respectively). Of the four patients not treated with TTFIELDS, one received supportive care only, two bevacizumab monotherapy (6 and 9 cycles, respectively), and one bevacizumab/lomustine combination treatment (7 cycles).

Of those experiencing progression during TTFIELDS (i.e. second total recurrence), two patients were re-operated, five discontinued all treatment, one continued bevacizumab with addition of irinotecan (3 cycles), one received temozolomide rechallenge (6 cycles), one continued bevacizumab in combination with lomustine (2 cycles), and one continued bevacizumab monotherapy (8 cycles). Of the four patients not receiving TTFIELDS, three discontinued all treatment at progression in the trial (i.e. second recurrence) and one received two cycles of temozolomide before discontinuation.
Outcomes

Adverse events

The observed AEs are presented in Table 2, Supplementary Table 4 (grading) and Supplementary Table S5 (causality).

In total, we observed 71 AEs of which most were mild to moderate (grades 1 or 2). Considering all patients, 52%, 95% CI [40%; 64%], of all AEs were strictly mild with a maximum grade of 1, while 35%, 95% CI [24%; 48%], were moderate or below with a maximum grade of 2. We recorded 11 grade 3 SAEs (13%, 95% CI [7; 23%]), all unrelated to the intervention, and no grade 4 or 5 SAEs. Most SAEs were neurological (N=5): Three were seizures, which required admission and occurred at progression in patients with prior seizures, one experienced severe headache, while two had progressive focal deficits in connection with disease progression. Systemic SAEs were fatigue, deep vein thrombosis, and diarrhea all unrelated to the intervention.

Patients excluded prior to TTFields therapy, i.e. within 4 weeks from inclusion, accounted for 19.0%, 95% CI [11%; 30%], of AEs. These were mainly neurological deficits attributed to the disease itself or resection surgery, although one patient did experience a grade 3 postoperative infection, which led to exclusion and required surgical revision. None of the surgical AEs could be directly attributed to the SR-surgery per se but rather to the general concept of open surgery, e.g. infection, or to tumor resection, e.g. postoperative deficits.

Neurological AEs accounted for 37%, 95% CI [26%; 49%], of all AEs regardless of grade. The most common neurological AEs were headache (N=9), seizures (N=5) and focal deficits (N=7). Headache was the most frequently observed AE overall, occurring in 60%, 95% CI (32; 84%), of all patients and exclusively in those treated with TTFields. A causal relationship between headache and TTFields was found in three cases, while one was related to surgery and five had unknown causes although unrelated to the intervention. Focal neurological deficits were caused by the disease or resection surgery and
all seizures were attributed to disease and progression.

Systemic AEs accounted for 39% (95% CI [28%; 52%]), and were generally associated with chemotherapy, GBM or unknown causes. The most common systemic AEs were fatigue (40% of patients, 95% CI [16%; 68%]), nausea (40% of patients, 95% CI [16%; 68%]) and fever (33% of patients, 95% CI [12%; 62%]). Causality could not be firmly established in 15 out of the 29 observed systemic AEs, although these were likely attributed to medical oncological treatment or GBM (e.g. fever, nausea, fatigue). No systemic AE was related to TTFields, six were caused by medical oncological treatment (nausea, abdominal pain, diarrhea), four were caused by surgery (postoperative fatigue, nausea, fever), while three AEs had other causes, such as opiate administration or corticosteroid withdrawal.

Regional AEs accounted for 24% (95% CI [15%; 36%]), of all cases and mainly comprised grade 1 and 2 skin rash (55% of TTFields treated patients, 95% CI [23; 83]) and minor scalp ulcerations (18%, 95% CI [2.3; 52]). These manifestations only occurred in patients treated with TTFields and were observed with caution and easily managed with topical corticosteroids and short pauses (1-3 days) in TTFields. One patient had a poor compliance rate of 48% on average due to recurring scalp ulcers. The patient had previously been treated repeatedly with antibiotics for pustulous acne and hidrosadenitis. The ulcers occurred with unchanged frequency and severity and also at distant locations unaffected by TTFields, e.g. in the axillary and perineal regions. One patient had a minor post-operative wound rupture with localized infection, which was successfully treated with minor wound revision in local anesthesia and oral antibiotics. This resulted in a two-week delay of TTFields initiation but did not affect the remaining treatment. One patients in the TTFields group had minor wound rupture shortly after surgery, which was successfully treated with a single suture. There were no signs of infection and the complications did not affect the medical oncological treatment or TTField.

No surgery inflicted AEs could be associated with the skull-remodeling procedure per se, but rather represented common neurosurgical complications, e.g. due to...
resection or complicated wound healing. Within the investigated range of SR-surgery, encompassing minor burr holes and large craniectomies, we did not observe particular toxicity limitations or reach an apparent maximum tolerated dose neither for the induced field intensity, nor for the introduced skull-defects.

**Efficacy outcomes**

Survival estimates and efficacy outcomes are presented in Table 3. In general, the results were promising with longer OS (median OS = 15.5 months, 95CI% [9.4; NA]) and PFS (PFS6 = 36%, 95%CI [8; 64]) estimates compared to historical data although the study was not powered for direct statistical comparison. Kaplan-Meier curves for OS and PFS are shown in Supplementary Figure S6.

**Corticosteroid use, KPS and Quality of Life**

The median daily methylprednisolone dose was 14.3 mg (range 0-50 mg) over the course of the trial. The mean total decline in steroid dose during the trial, i.e. the presurgical dose at inclusion minus the dose at the time of progression, was considerable (11.8 ±19.4 mg) with the most significant reduction occurring after surgery. Accordingly, the presurgical dose at inclusion, was reduced by 10.4 mg ±14.3 mg at the time of initiation of TTFIELDS and oncological treatment, and further by 1.45 ± 12.0 mg at the time of disease progression, see Table 3. Three out of the 11 patients treated TTFIELDS received a high-dose corticosteroid treatment on average (i.e. > 21.3 mg methylprednisolone daily corresponding to >4 mg of dexamethasone daily), which has previously been show to correlated with poor response to TTFIELDS therapy (23, 24). Two of these patients experienced progression before 6 months, and two died before one year of follow-up. The samples size was too low to analyze this correlation.

Eight of the 11 patients treated with TTFIELDS had stable KPS from inclusion until progression (73%, 95%CI [39;94%]). Three experienced a KPS decline of 10-20 points after resection surgery (27%, 95%CI [6.0; 61]). In two of these patients, KPS remained
stable from surgery until progression (18%, 95%CI [2.3;52%]), while the final patient experienced a KPS recovery of 10 points during TTFields therapy (9.1%, 95%CI [0.2;41%]).

Quality of life scores were comparable to previous observations (7), Supplementary Table S7. The majority of the patients had high and constant global (median = 141-167) and functional (median = 80-89) QoL scores throughout the trial. Symptom scores were generally low (median = 8.5-11).

Discussion

In this study, we have evaluated the safety, feasibility and preliminary efficacy of TTFields in combination with targeted SR-surgery against recurrent GBM. The intervention introduces skull holes in the vicinity of the tumor to facilitate the current flow into the region of interest and thereby enhance the TTFields efficacy.

The intervention was well tolerated and we observed no SAEs directly attributed to the intervention. SAEs were all grade 3 and included fever, fatigue, diarrhea, deep vein thrombosis as well as seizures occurring at progression in patients with previously known tumor-induced epilepsy.

Overall, the most prevalent AE was headache (60% of patients), whereas minor skin rash of grades 1 and 2 was the most common AE in patients treated with TTFields (55%). These observations correspond well with previously reported rates (10) and AEs were generally easily managed. The majority of the AEs were systemic (39%, Table 2 and Supplementary Tables S4&5) and caused by the disease or the medical oncological treatment.

With regards to efficacy, we observed positive preliminary signals justifying further investigations. The median OS was 15.5 months, CI95% = [9.4;NA], which is a considerable improvement compared to the 9 months commonly reported for patients receiving comparable second line oncological treatment alone (31,32). Furthermore, this survival benefit was larger than the expected effects caused by addition of TTFields alone,
although our study was not powered for comparison with historical data. The sole effects of TTFields in first recurrence of GBM were recently investigated in a post-hoc analysis of the randomized EF-14 trial data (NCT00916409), Kesari et al. 2017 (33). The study compared the efficacy of TTFields plus physician’s choice chemotherapy with chemotherapy alone after the first recurrence. TTFields prolonged the median OS by approximately two months (11.8 months vs. 9.2 months, p=0.049) compared to chemotherapy alone and the authors concluded that the addition of TTFields to medical oncological treatment at first disease recurrence is likely beneficial. This corresponds with observations from the retrospective PRiDe study investigating real-world application of TTFields therapy in recurrent GBM in the United States (9). In the PRiDe cohort, approximately 1/3 of patients received TTFields after the first recurrence and the median OS was 20 months. Collectively, these studies indicate that part of our observations could possibly be explained by TTFields alone and further randomized studies are therefore needed to clarify the potential effects of using SR-surgery to enhance the dose of TTFields. With regards to disease progression, our cohorte had a median PFS of 4.6 months and a PFS6 rate of 36%, which is comparable to previous reports of patients treated with comparable second-line medical treatment (median PFS = 3-4.2 months and PFS6 = 16-41%, (31,32)).

Limitations

Despite promising outcomes, our study was subject to important caveats to be considered. Given the small sample size, it was not powered for conclusive estimation, confounder adjustment or direct comparison with historical data. Furthermore, our cohort was subject to selection bias in the sense that 1) the male/female = 9/2 ratio was higher than expected, 2) the clinical performance was relatively high (median KPS = 90, range 70-100), 3) the rate of gross total resection among TTFields treated patients was high (9/11), and 4) the median TTFields compliance rate was high (90%, range 48-98), of which the latter three are known favorable outcome predictors (9,30). Therefore, our cohort was expected to perform better than the average population of recurrent GBM patients. Furthermore, two
non-responders to TTFields in our cohort were treated with high doses of corticosteroids, which may have potentially reduced the efficacy of TTFields (23, 24).

Also, it should be noted that array placement was based on edge effect considerations and general rules of thumb and not the standard practice NovoTAL approach. Although this approach may have impacted the TTFields efficacy on its own, previous studies indicate that such effects would likely be considerably less compared to those induced by the SR-surgery (16).

Future perspectives

We consider the tested intervention suitable for further investigation, and a randomized controlled phase 2 trial (NCT04223999) is scheduled to begin recruitment in the fall of 2020. The trial includes TTFields in both treatment arms and patients are randomized 1:1 to receive SR-surgery or not. The trial was designed to test the potential for clinical implementation of SR-surgery with TTFields and further to shed additional light on the TTFields dose-response relationship.

Finally, there is a need for further characterization of the effects of different SR configurations, including the number, size, and arrangement of burr holes. We are currently investigating these aspects with focus on identifying optimal configurations with minimal SR size. Our aim is to establish a feasible SR-surgery approach based on simple rules of thumb and standard operating procedures with priority on clinical utility. These guidelines should also address the aspect of optimal array positioning when using SR-surgery, which differs from the conventional NovoTAL approach, as discussed above.

Conclusion

In conclusion, SR-surgery offers a rational approach to enhance the TTFields intensity for patients with rGBM and potentially other brain tumors with TTFields sensitivity. The combination of TTFields and SR-surgery is safe and non-toxic and potentially provides individual benefit with prolonged overall survival. The trial is the first to prospectively modulate the “dose” of TTFields and investigate its impact on safety and clinical outcome.
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Captions

**Fig. 1. Distributions of current density and field intensity before and after SR-surgery.** Panel A shows the position of one array pair on the surface of the patients head, while the craniectomy and underlying regions of interest (tumor – yellow; peritumoral borderzone – blue) are shown in panel B. Craniectomy reduced the amount of current shunted through the skin between the arrays (panel C vs. E) and redirects the current through the hole in the skull (panel D vs. F) and towards the tumor. Panel G shows the change in field intensity induced on the surface of the brain. Craniectomy enhances the field intensity by approximately 300 V/m in the region of interest, while the dose in the surrounding brain tissue remains unaffected.

**Fig. 2. Examples of SR-surgery.** Panel A shows three examples of SR-surgery configurations illustrated with 3D reconstructions of the skull surface based on CT scans. Four burr holes of 15 mm diameter were used in the leftmost example, seven burr holes of 18 mm diameter in the middle example, and a total elliptic craniectomy of 85x65mm semi-axes in the rightmost example, respectively. In all cases, the skull defects were distributed above the resection cavity and its surrounding borders, as shown in panel B for the leftmost case in Panel A. The representation in Panel B generally shows the skull and tumor outline in the computational model for the (courtesy of Novocure, Ltd.) with the skull surface shown in purple, the craniotomy bone flap in red (primary surgery) and dark red (repeated surgery), the craniotomy line in pink, the underlying tumor in blue, and the resection cavity in green. The transducer array layout is shown in the rightmost illustration in panel B with orange markings on the A/P pair. Panel C shows surface reconstructions of the field distribution before (left) and after (right) SR-surgery for the same patient. Parts of the figure are reproduced from Korshoej *et al.* 2019 (25). Panel D shows the difference in current density distribution before and after SR-surgery equivalent the case in panel A (left), B and C. Results are shown for the skin (left) and CSF (middle) surfaces, respectively, and for the L/R
array pair only. It is evident, that a significant amount of current is shunted though the burr holes. The rightmost illustration in panel D shows the equivalent absolute difference in field distribution in the underlying brain. Finally, panel E shows the relationship between the total area of the skull defect for the individual SR-surgery configurations (cm²) and the corresponding relative field enhancement (%). Patients treated with TTFields (N=11) are shown in blue and patients excluded prior to TTFields (N=4) are shown in red.

Fig. 3. Patient flow diagram.

Table 1. Baseline characteristics and treatment outline.

Table 2. Frequency of adverse events. The table shows the numbers and frequencies of patients experiencing the observed AEs. A patient is registered as having an AE, if the AE occurred at least once, regardless of severity. All observed AEs were grades 1-3. Patients are separated into those treated with TTFields (left column) and those not treated with TTFields (middle column). The right column shows results for all patients collectively. Supplementary Tables 4 and 5 lists a breakdown of the AE data into grades and causalities, respectively.

Table 3. Survival and efficacy outcomes.
Table 1. Patient characteristics and treatment outline.

| Basic characteristics                        | Estimate            |
|----------------------------------------------|---------------------|
| Age in years, median (range)                 | 57 (39-67)          |
| Male/female (N)                              | 9/2                 |
| Preoperative KPS, median (range)             | 90 (70-100)         |
| MGMT methylation (N)                         | 4                   |
| Tumor location (N)                           |                     |
| Frontal                                      | 2                   |
| Parietal                                     | 2                   |
| Temporal                                     | 5                   |
| Parieto-occipital                            | 2                   |

| SR-surgery and TTFFields                     | Median (range)      |
|----------------------------------------------|---------------------|
| Skull defect area (cm²)                      | 10.5 (7-48)         |
| Field intensity in the tumor (V/m)           | 173 (111-210)       |
| Relative field enhancement (%)              | 32 (25-59)          |
| Absolute field enhancement (V/m)             | 40 (28-69)          |
| TTFFields compliance rate (%)               | 90 (48-98)          |
| TTFFields duration (months)                  | 7.6 (2.3-24.0)      |

| Extent of resection                         | Number (N)          |
|---------------------------------------------|---------------------|
| No residual tumor                           | 4                   |
Non-measurable residual tumor | 5  
Measurable residual tumor | 2  

| Medical treatment                              | Estimate                  |
|-----------------------------------------------|---------------------------|
| Bevacizumab monotherapy (N)                   | 8                         |
| Bevacizumab/irinotecan (N)                    | 1                         |
| Temozolomide rechallenge (N)                  | 2                         |
| Daily methylprednisolone dose in mg, median (range) | 14.3 (0-50)               |
Table 2. Frequency of adverse events

| Type of AE                  | TTF (N=11) | No TTF (N=4) | Total (N=15) |
|-----------------------------|------------|--------------|--------------|
|                             | N % 95%CI  | N % 95%CI    | N % 95%CI    |
| **Neurological**            |            |              |              |
| Headache                    | 9 81.8 (48; 98) | 0            | 9 60.0 (32; 84) |
| Speech disturbances         | 3 27.3 (6.0; 61) | 1 25.0 (0.6; 81) | 4 26.7 (7.8; 55) |
| Seizure                     | 5 45.5 (17; 77) | 0            | 5 33.3 (12; 62) |
| Paresis                     | 1 9.1 (0.2;41) | 3 75.0 (19; 99) | 4 26.7 (7.8; 55) |
| Visual disturbances         | 2 18.2 (2.3; 52) | 0            | 2 13.3 (1.7; 41) |
| Neglect                     | 1 9.1 (0.2;41) | 0            | 1 6.7 (0.2; 32) |
| Memory disturbances         | 1 9.1 (0.2;41) | 0            | 1 6.7 (0.2; 32) |
| **Regional**                |            |              |              |
| Skin rash                   | 6 54.5 (23; 83) | 0            | 6 40.0 (16; 68) |
| Scalp ulceration            | 2 18.2 (2.3; 52) | 0            | 2 13.3 (1.7; 41) |
| Surgical wound infection    | 1 9.1 (2.3; 52) | 1 25.0 (0.6; 81) | 2 13.3 (1.7; 41) |
| Surgical wound rupture      | 2 18.2 (6.0; 61) | 1 25.0 (0.6; 81) | 3 20.0 (4.3; 48) |
| Shoulder pain               | 2 18.2 (2.3; 52) | 1 25.0 (0.6; 81) | 3 20.0 (4.3; 48) |
| Axillary abscess            | 1 9.1 (0.2;41) | 0            | 1 6.7 (0.2; 32) |
| **Systemic**                |            |              |              |
| Fatigue                     | 4 36.4 (11; 69) | 2 50.0 (6.8; 93) | 6 40.0 (16; 68) |
| Nausea                      | 3 27.3 (6.0; 61) | 3 75.0 (19; 99) | 6 40.0 (16; 68) |
| Fever                       | 3 27.3 (6.0; 61) | 2 50.0 (6.8; 93) | 5 33.3 (12; 62) |
| Diarrhea                    | 3 27.3 (6.0; 61) | 0            | 3 20.0 (4.3; 48) |
| Constipation                | 2 18.2 (2.3; 52) | 0            | 2 13.3 (1.7; 41) |
| Condition                                | Count | Percentage (95% CI) |
|------------------------------------------|-------|---------------------|
| Abdominal pain                           | 2     | 18.2 (2.3; 52)      |
| Dehydration                              | 1     | 9.1 (0.2; 41)       |
| DVT                                      | 1     | 9.1 (0.2; 41)       |
| Corticosteroid withdrawal syndrome       | 1     | 9.1 (0.2; 41)       |
| Abnormal ECG                             | 1     | 9.1 (0.2; 41)       |
Table 3. Efficacy outcome estimates.

| Outcome                                      | Estimate                          |
|----------------------------------------------|-----------------------------------|
| Median OS, months                            | 15.5 months, 95%CI [9.4; NA]      |
| OS at 12 months, %                           | 55%, 95%CI [25; 84]               |
| Median PFS, months                           | 4.6 months, 95%CI [4.1;NA]       |
| Progression-free survival rate at 6 months, %| 36%, 95%CI [8; 64]                |
| Objective response rate, %                   | ORR = 9.1%, 95%CI [0.2; 41.3]    |
| Methylprednisolone dose decline, mg          |                                   |
| Total, i.e. from inclusion until progression | 11.8 ± 19.4 mg                    |
| Post-surgery, i.e. from inclusion until TTFields initiation | 10.4 ± 14.3 mg |
| TTFields, i.e. from TTFields initiation until progression | 1.45 ± 12.0 mg |
Figure 1

[Diagram showing brain models with and without craniectomy]
Figure 3

Screened: 20

Excluded: 5
• KPS < 70: 2
• Declined: 3

SR-surgery: 15 (4F/11M)

Received TTFIELDS: 11 (2F/9M)

Did not receive TTFIELDS: 4
• Withdrawal of consent: 1
• Post-op infection: 1
• Post-op cognitive dysfunction: 1
• Non-recurrence: 1

Follow-up: 15
Analysed for safety: 15
Analysed for efficacy: 11