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# Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma

## A Secondary Analysis of a Randomized Clinical Trial

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**IMPORTANCE** Tumor-treating fields (TTFields) therapy improves both progression-free and overall survival in patients with glioblastoma. There is a need to assess the influence of TTFields on patients' health-related quality of life (HRQoL).

**OBJECTIVE** To examine the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma.

**DESIGN, SETTING, AND PARTICIPANTS** This secondary analysis of EF-14, a phase 3 randomized clinical trial, compares TTFields and temozolomide or temozolomide alone in 695 patients with glioblastoma after completion of radiochemotherapy. Patients with glioblastoma were randomized 2:1 to combined treatment with TTFields and temozolomide or temozolomide alone. The study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

**INTERVENTIONS** Temozolomide, 150 to 200 mg/m$^2$/d, was given for 5 days during each 28-day cycle. TTFields were delivered continuously via 4 transducer arrays placed on the shaved scalp of patients and were connected to a portable medical device.

**MAIN OUTCOMES AND MEASURES** Primary study end point was progression-free survival; HRQoL was a predefined secondary end point, measured with questionnaires at baseline and every 3 months thereafter. Mean changes from baseline scores were evaluated, as well as scores over time. Deterioration-free survival and time to deterioration were assessed for each of 9 preselected scales and items.

**RESULTS** Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months; $P < .01$); physical (5.1 vs 3.7 months; $P < .01$) and emotional functioning (5.3 vs 3.9 months; $P < .01$); pain (5.6 vs 3.6 months; $P < .01$); and leg weakness (5.6 vs 3.9 months; $P < .01$), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months; $P < .001$) and pain (TTFields improved; 13.4 vs 12.1 months; $P < .01$). Role, social, and physical functioning were not affected by TTFields.

**CONCLUSIONS AND RELEVANCE** The addition of TTFields to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00916409

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Invited Commentary
page 504

Supplemental content

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Glioblastoma has a poor prognosis,[1,2] and, as tumors grow, patients often experience a progressive decline in neurologic function and health-related quality of life (HRQoL).[3-7] The current standard of care is not curative but results in prolongation of life. However, extension of survival is meaningful only if patients' functioning and well-being can be retained or improved.[8-11] Therefore, it is important to determine the net clinical benefit of each new treatment or treatment modality introduced; possible benefits of a new treatment, in terms of prolonged survival, have to be carefully weighed against potential negative effects of the treatment on the patients' quality of life.

The current standard of care for patients with newly diagnosed glioblastoma comprises surgical resection to the extent safely feasible followed by radiotherapy with concomitant and maintenance chemotherapy with temozolomide.[12] Tumor-treating fields (TTFields) (Optune; Novocure Ltd) is an antimitotic physical treatment modality[13,14] delivered by a home use medical device with wired transducer arrays placed on the patients' scalp. When added to standard maintenance temozolomide chemotherapy, TTFields has been demonstrated to improve both progression-free survival and overall survival in a randomized clinical trial (NCT00916409).[15]

Treatment with TTFields involves the patient carrying a mobile electrical device for more than 18 hours per day and having 4 arrays of transducers continuously fixed to the shaved scalp. Concerns regarding the influence of wearing the device on patients' HRQoL have therefore been raised.[16,17] The incidence of adverse events was not increased by the addition of TTFields to temozolomide therapy except for an expected mild to moderate skin irritation beneath the electrodes in 52% of patients (severe in 2%). Herein, we report on the influence of treatment with TTFields on the patients' HRQoL, which was a predefined secondary objective of the randomized clinical trial. The present study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

### Key Points

**Question** What is the influence of adding tumor-treating fields to the standard treatment on health-related quality of life in patients with glioblastoma?

**Findings** In this secondary analysis of the EF-14 randomized clinical trial, the addition of tumor-treating fields did not negatively influence health-related quality of life except for itchy skin, an expected consequence from the transducer arrays.

**Meaning** Tumor-treating field therapy has previously been shown to prolong both progression-free and overall survival. When considering the net clinical benefit, improved survival without a negative influence on health-related quality of life supports the addition of tumor-treating fields to standard treatment in patients with glioblastoma.

## Methods

### Study Population

Patients eligible for this study were aged 18 years or older, had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma), were progression free after undergoing maximal safe debulking surgery or biopsy, and had completed standard radiotherapy with concomitant temozolomide. Patients were required to have a Karnofsky Performance Status score of at least 70 at the time of enrollment, corresponding to at least being able to perform self-care. Further details on the study population are available elsewhere.[15] All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centers and the relevant competent authorities (eAppendix 1 in Supplement 1); the participants did not receive financial compensation.

### Study Design and Treatment

This prospective, multicenter, open-label, randomized clinical phase 3 trial recruited 695 patients at 90 medical centers in North America, Europe, the Republic of Korea, and Israel. The trial protocol is available in Supplement 2. The trial was designed to test the efficacy of TTFields in combination with the best standard of care in the treatment of newly diagnosed glioblastoma (ie, radiotherapy with concomitant and adjuvant temozolomide). The primary end point was progression-free survival, with overall survival as a powered secondary end point. Health-related quality of life was a secondary end point. Patients who were progression free after completion of radiochemotherapy were randomized within 4 to 7 weeks at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150-200 mg/m$^2$ for 5 days every 28 days for 6 cycles) with or without the addition of TTFields. If tolerated well, TTField therapy was to be continued until the second progression or up to 2 years.

Patients in the TTFields plus temozolomide group received continuous TTFields combined with maintenance temozolomide. TTFields were delivered through a portable device in an outpatient setting. Patients receiving TTFields had 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain. Although uninterrupted treatment was recommended, the patient could take short breaks if needed; patients were advised to continue treatment for at least 18 hours a day. More details on the study design and treatment are published elsewhere.[15]

### HRQoL Assessment

The evaluation of HRQoL was performed using the validated European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) and brain module (QLQ-BN20).[18-20] Questionnaires were completed on paper at baseline (prior to randomization) and subsequently every 3 months for up to 12 months. Nine scales and items were preselected as important based on relevance for patients with glioblastoma and hypothesized effects of the TTFields delivery device on patients' HRQoL: global health status; physical, cognitive, role, social, and emotional functioning; itchy skin; pain; and weakness of legs. We hypothesized that any burden of carrying the device (on physical functioning and itchy skin) or detriment to social and role functioning due to the visibility of the therapy may be balanced by patients' feeling of well-being (global health status and emotional functioning)

related to active participation of both the patient and the caregiver in the fight against cancer and increasing patient empowerment. Moreover, we hypothesized that treatment with TTFields would not have an influence on cognitive functioning, pain, and weakness of legs.

## Statistical Analysis

### Calculation of HRQoL Scores

The items on both questionnaires were scaled and scored using the recommended EORTC procedures.[21] Raw scores were transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms. The results of this study are presented in accordance with guidelines for reporting HRQoL in cancer clinical trials and methods.[22-24] Differences of at least 10 points (on a 0-100 scale) were classified as the minimum clinically meaningful change in any HRQoL scale/item.[24]

### Descriptive Statistics

Descriptive statistics were used to report HRQoL scores as well as the sociodemographic and clinical variables for the population of patients who completed at least 1 HRQoL scale at baseline separately for both treatment groups. Means and SDs or medians and ranges were calculated for continuous variables depending on the distribution of the variable. Frequencies and percentages were calculated for nominal variables. Differences between arms were tested using a 2-sided $\chi^2$ test or an independent 2-tailed, unpaired *t* test or Mann-Whitney test at an α value of .05 for each variable.

Adherence to HRQoL assessments was calculated as the number of forms received divided by the number of forms expected at every assessment. Patients who completed the assessments at the time of progression were included in this analysis.

### HRQoL Scores Over Time

Mean HRQoL scores over time were calculated as well as the mean changes from baseline. A stable HRQoL score was defined as a change of less than 10 points, and a change of 10 or more points indicated a deterioration or improvement depending on the scale or item. Mean change from baseline was plotted to evaluate the longitudinal course of patients' experience of disease and treatment, and a linear mixed-model repeated-measures analysis was used to estimate the treatment effect over time. A sensitivity analysis of complete cases using multiple imputations with a predictive mean matching regression model was used to check the robustness of the treatment effect over time. An additional sensitivity analysis used a repeated-measures model that assumes there is random variation among participants that is related to the time of dropout.

### Stable or Improved HRQoL During the Progression-Free Period

The percentage of patients with stable (<10-point change) or improved (≥10-point change) HRQoL during the progression-free period, thus excluding the HRQoL assessment at progression, was determined separately for both treatment arms. This calculation was based on the total number of patients with a valid baseline HRQoL assessment and at least 1 additional follow-up assessment. Moreover, the area under the curve of stable or improved HRQoL for the entire duration of stability or improvement was determined, and differences between arms were assessed with the trapezoidal method (eAppendix 2 in Supplement 1).

### Deterioration-Free Survival and Time to Deterioration

Deterioration-free survival was defined as the time to a greater than 10-point deterioration in scores from baseline without a subsequent 10-point or more improvement in scores compared with baseline, progressive disease, or death in the absence of a previous definitive deterioration before the next assessment. Disease progression was included as a surrogate measure. Data were censored at the last HRQoL assessment date for patients with a change of less than 10 points, patients who did not progress, or patients who died after 9 weeks since the last assessment. Data for patients with missing baseline scores were not included, and patients missing all postbaseline HRQoL assessments were censored at randomization. Time to deterioration (TTD) was defined similarly to deterioration-free survival, with the exception that progressive disease was excluded as an event (ie, nonmissing HRQoL data beyond progression were included). Kaplan-Meier methodology was used to estimate deterioration-free survival and TTD distributions and median times, and 95% CIs were computed using the Greenwood formula. The difference between treatment arms was compared using a 2-sided stratified log-rank test. Hazard ratios were estimated using a stratified (for extent of resection and *MGMT* status) Cox proportional hazards regression model.

SAS, version 9.4 (SAS Institute) was used for all statistical analyses, and comparisons between groups were based on the intent-to-treat principle. *P* values <.05 were considered to be statistically significant. The Hochberg procedure was used to adjust for the multiplicity of treatment comparisons in the preselected HRQoL scales analyses.

# Results

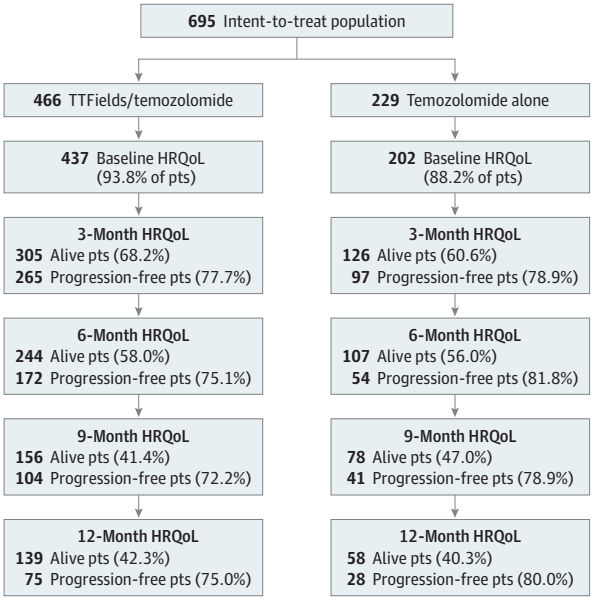
## Patients

A total of 695 patients were randomly assigned in a 2:1 ratio to TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229). A total of 639 (91.9%) patients completed at least 1 HRQoL scale at baseline: 437 (93.8%) of those in the TTFields plus temozolomide arm and 202 (88.2%) patients in temozolomide-alone arm (**Figure 1**). The baseline demographics of the patients who provided HRQoL data were comparable to those of the intention-to-treat population[15] and were well balanced between treatment arms in this subpopulation (**Table 1**).

## HRQoL Completion Rates and Baseline Scores

Adherence to HRQoL assessments decreased from 91.9% at baseline to 65.8% (431 of 655 patients alive) at 3 months and dropped to 41.7% (197 of 473 patients alive) at 12 months of follow-up (Figure 1). Mean and median baseline HRQoL scores

Figure 1. CONSORT Diagram




Data are the number and percentage of patients in the categories (baseline, alive, and progression-free) who completed the health-related quality-of-life (HRQoL) questionnaire at the indicated times. pts indicates patients; TTFields, tumor-treating fields.

were comparable between arms for all preselected scales/items (eTable 1 in Supplement 1), as well as the exploratory scales and items. Reference values of HRQoL scores of a healthy general population[25] were available for 7 of 9 predefined scales and items (except itchy skin and weakness of legs). Patients with glioblastoma after completion of radiochemotherapy showed clinically relevant worse functioning or more symptoms compared with the general population on all scales except pain, which was similar.[25]

### Mean Changes in HRQoL From Baseline and the Repeated-Measures Mixed-Effect Model

Mean changes in HRQoL over time for the global health status is presented in **Figure 2**A and for all 9 predefined HRQoL scales in the eFigure in Supplement 1. Throughout the 12-month assessment period, mean changes from baseline were stable (<10-point change from baseline) for all 9 predefined HRQoL scales in both treatment arms (eFigure in Supplement 1) with the exception of itchy skin (Figure 2B). For itchy skin, a clinically relevant deterioration (ie, an increase in itchy skin) compared with baseline was seen at the month 3 evaluation in the TTFields plus temozolomide arm (mean [SD] increase, 10.4 [30.1] points vs an improvement of 2.3 [24.4] points in the temozolomide arm). For differences between treatment arms, patients treated with TTFields plus temozolomide had significantly and clinically relevant worse itchy skin at 3, 6, and 9 months than patients treated with temozolomide alone, but not at 12 months (mean [SD] increase of 10.4 [30.1] in the TTFields plus temozolomide arm vs a decrease of 2.3 [24.4] in the temozolomide-alone arm, $P = .005$; increase of 8.1 [31.6] in the TTFields plus temozolomide arm vs a decrease of 4.2 [31.4] in the temozolomide-alone arm, $P = .008$; increase of 5.3 [28.0] in the TTFields plus temozolomide arm vs a decrease of 5.2 [29.6] in the temozolomide-alone arm, $P = .04$; increase of 4.6 [32.8] in the TTFields plus temozolomide arm vs a decrease of 1.9 [36.9] in the temozolomide-alone arm, $P = .66$, respectively). For all other scales, there were no statistically significant or clinically relevant differences between treatment arms.

The repeated-measures mixed-effect model supported this finding, with no statistically significant difference between treatment arms in HRQoL scores over time in any predefined scale or item except for itchy skin ($P < .001$), which was worse in the TTFields plus temozolomide arm (eTable 2 in Supplement 1). The sensitivity analyses showed that the results of the linear mixed model were robust.

### Stable or Improved HRQoL During Progression-Free Time

Compared with baseline, more patients in the TTFields plus temozolomide arm compared with the temozolomide-alone arm reported stable or improved scores for global health status (53.5% vs 38.0%, respectively, $P = .001$), physical functioning (54.0% vs 37.0%, respectively; $P = .001$), pain (56.8% vs 35.9%, respectively; $P < .001$), and weakness of legs (58.7% vs 42.0%, respectively; $P = .001$) but not in any of the other HRQoL scales and items. However, the duration of stable or improved HRQoL was shorter in the TTFields plus temozolomide arm, although not significantly different from the temozolomide arm for any of the HRQoL scales and items. Overall, with a combination of these measures, the area under the curve analysis showed no significant differences between treatment arms for any of the HRQoL scales and items, indicating a similar HRQoL between treatment arms while patients did not experience tumor progression (**Table 2**).

### Deterioration-Free Survival and TTD

The addition of TTFields to standard temozolomide chemotherapy resulted in statistically significant longer deterioration-free survival in global health status, physical and emotional functioning, pain, and weakness of legs (**Figure 3**A and eTable 2 in Supplement 1); the significant difference remained after correction for multiple testing. When progression was removed as a deterioration event (TTD), there was no negative influence of TTFields plus temozolomide treatment on the TTD of HRQoL (Figure 3B) except for itchy skin, which was worse in the TTFields plus temozolomide arm (8.2 vs 14.4 months). In contrast, the addition of TTFields to temozolomide resulted in a statistically significant prolongation until deterioration for pain (13.4 vs 12.1 months, $P < .01$). There were no other significant differences in TTD between arms (Figure 3B).

## Discussion

In our detailed analysis of HRQoL during therapy with TTFields in addition to temozolomide, no significant difference was found between the groups in patients' HRQoL over time except for the skin reaction. As expected, itchy skin was

Table 1. Baseline Demographic and Disease Characteristics

| Characteristic | TTFields Plus Temozolomide (n = 437) | Temozolomide (n = 202) | All Patients (N = 639) | *P* Value |
|---|---|---|---|---|
| Age, y | | | | |
| Mean (SD) | 54.6 (11.4) | 55.2 (11.6) | 54.8 (11.5) | .50 |
| Median (range) | 56.0 (19-83) | 57.0 (19-80) | 56.0 (19-83) | |
| Sex, No. (%) | | | | |
| Male | 297 (68.0) | 140 (69.3) | 437 (68.4) | .73 |
| Female | 140 (32.0) | 62 (30.7) | 202 (31.6) | |
| Antiepileptic medication at baseline, No. (%) | 174 (39.8) | 79 (39.1) | 253 (39.6) | .87 |
| Corticosteroid therapy at baseline, No. (%) | 129 (29.5) | 60 (29.7) | 189 (29.6) | .96 |
| Region, No. (%) | | | | |
| United States | 203 (46.5) | 97 (48.0) | 300 (46.9) | .71 |
| Canada, Europe, Israel, and Korea | 234 (53.5) | 105 (52.0) | 339 (53.1) | |
| Extent of resection, No. (%) | | | | |
| Biopsy | 55 (12.6) | 24 (11.9) | 79 (12.4) | .97 |
| Partial resection | 149 (34.1) | 70 (34.7) | 219 (34.3) | |
| Gross total resection | 233 (53.3) | 108 (53.5) | 341 (53.4) | |
| Tumor position, No. (%)[a] | | | | |
| Corpus callosum | 23 (5.3) | 12 (5.9) | 35 (5.5) | .66 |
| Frontal lobe | 177 (40.5) | 74 (36.6) | 251 (39.3) | |
| Occipital lobe | 55 (12.6) | 24 (11.9) | 79 (12.4) | |
| Parietal lobe | 138 (31.6) | 78 (38.6) | 216 (33.8) | |
| Temporal lobe | 179 (41.0) | 81 (40.1) | 260 (40.7) | |
| Missing | 2 (<1) | 2 (1.0) | 4 (0.6) | |
| Tumor location, No. (%)[a] | | | | |
| Left | 202 (46.2) | 84 (41.6) | 286 (44.8) | .65 |
| Right | 234 (53.5) | 116 (57.4) | 350 (54.8) | |
| Both | 4 (0.9) | 2 (1.0) | 6 (0.9) | |
| Corpus callosum | 14 (3.2) | 9 (4.5) | 23 (3.6) | |
| Completed radiotherapy, No. (%) | | | | |
| <57 Gy | 20 (4.6) | 10 (5.0) | 30 (4.7) | .38 |
| 60 Gy (standard; ±5%) | 399 (91.3) | 188 (93.1) | 587 (91.9) | |
| >63 Gy | 15 (3.4) | 3 (1.5) | 18 (2.8) | |
| Missing | 3 (0.7) | 1 (0.5) | 4 (0.6) | |
| Karnofsky performance score | | | | |
| Median (range) | 90 (60-100) | 90 (70-100) | 90 (60-100) | .26 |
| Baseline Mini-Mental State Examination score available, No. (%) | 429 (98.2) | 194 (96.0) | 623 (97.5) | |
| ≤26 | 81 (18.9) | 43 (22.2) | 124 (19.9) | .34 |
| 27-30 | 348 (81.1) | 151 (77.8) | 499 (80.1) | |
| Cycles (months) of treatment with TTFields | | NA | NA | NA |
| No. | 425 | | | |
| Mean (SD) | 12.5 (11.8) | | | |
| Median (range) | 8.3 (0-82) | | | |
| Cycles of treatment with temozolomide | | | | |
| No. | 430 | 192 | 622 | |
| Mean (SD) | 8.9 (8.3) | 7.5 (6.2) | 8.5 (7.8) | .02 |
| Median (range) | 6.2 (0-51) | 5.5 (0-33) | 5.9 (0-51) | |
| Adherence to TTFields therapy [b] | 327 (74.8) | NA | NA | NA |

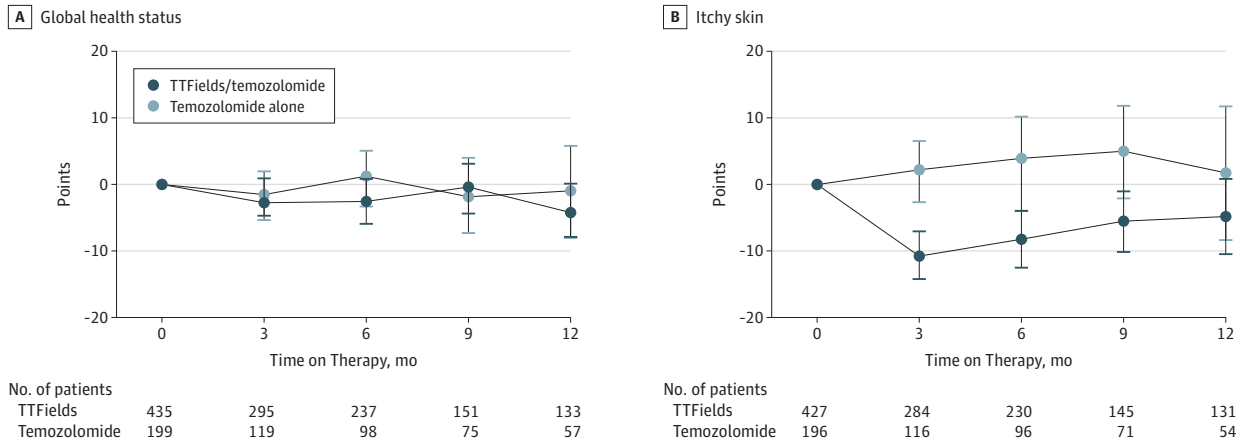
Abbreviations: Gy, gray; NA, not applicable; TTFields, tumor-treating fields.

[a] Multiple locations possible.

[b] Defined as use of the device 75% or more of the time during the first 3 months of treatment.

reported more frequently in patients treated with TTFields because of the transducer arrays that have to be placed on the scalp of the patient. Consistently, over half of the patients also reported skin irritation as an adverse event. We had hypothesized that patients treated with TTFields may have better HRQoL in some domains as a result of active participation in

Figure 2. Changes in Global Health Status and Itchy Skin




Mean changes in points on health-related quality of life scales from baseline in global health status (A) and itchy skin with (B) with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. No change, between 0 and 10 points; improvement and deterioration, changes of 10 points or more. Error bars indicate SD.

the fight against cancer and the frequent interactions between patients and caregivers and device technicians regarding the device. However, on a group level, global health status and emotional functioning were not significantly different between treatment arms. Likewise, our hypotheses that the addition of TTFields would result in worse role and social functioning (due to the visibility of the device) and worse physical functioning were not confirmed. In line with our hypotheses, cognitive functioning, pain, and weakness of legs were not negatively affected by the addition of TTFields to temozolomide treatment. Most relevant for patients, HRQoL was maintained (in 8 of 9 of the predefined scales/items) over time. Combining the results of the survival and HRQoL analyses suggests that the addition of TTFields to adjuvant temozolomide is of value to patients with glioblastoma.

Patients who received TTFields had significantly longer deterioration-free survival compared with those in the temozolomide-alone arm for global health status (4.8 vs 3.3 months; $P < .01$), physical (5.1 vs 3.7 months; $P < .01$) and emotional functioning (5.3 vs 3.9 months; $P < .01$), pain (5.6 vs 3.6 months; $P < .01$), and weakness of legs (5.6 vs 3.9 months; $P < .01$). For the other scales and items, there was no significant difference in deterioration-free survival between the 2 treatment arms. The prolonged deterioration-free survival for these scales is explained by the extended progression-free survival for patients in the combined TTFields plus temozolomide arm, as progressive disease is included as an event in this analysis. Therefore, TTD analyses, excluding progressive disease as an event, is important to illustrate the influence of a treatment on HRQoL: TTD was not significantly different across any HRQoL scale or item in TTFields-treated patients except for pain and itchy skin, indicating that treatment with TTFields had an influence only on the level of pain and itchy skin. In patients treated with TTFields, TTD was significantly longer for pain (13.4 vs 12.1 months; $P < .01$) and significantly shorter for itchy skin (8.2 vs 14.4 months; $P < .001$). The difference between deterioration-free survival and TTD indicates the importance of disease progression (rather than treatment) as a key event driving HRQoL decline, as suggested by previous studies.[26,27] Moreover, in only 1% of patients, regardless of treatment arm, was a clinically relevant improvement in HRQoL seen after initial deterioration, supporting this observation. Taken together, the results of the deterioration-free survival and TTD analyses support the results of the longitudinal analysis by showing that the addition of TTFields to the standard of care did not adversely affect HRQoL. In fact, the delay in TTD for pain seen in TTFields-treated patients may reflect a delay in the occurrence of tumor-related headaches (although not significant, patients in the TTFields plus temozolomide arm had a longer TTD compared with patients in the temozolomide-alone arm for headaches: hazard ratio, 0.77; 95% CI, 0.54-1.10; $P = .16$). Future studies are needed to better understand this finding, as the median TTD values for pain were longer than the median progression-free survival for both arms.

## Limitations

A common problem in many cancer clinical trials, as in this study, is missing HRQoL data. This absence is especially apparent during the follow-up period, hampering longitudinal data analysis. Patients with better prognostic factors and a good treatment response will be overrepresented at later stages.[28,29] However, our mixed-model analyses, accounting for missing data, confirmed the results found in the mean change from baseline analyses. Another limitation of clinical trials is generalizability of results—patients in clinical trials may not be representative of a general glioblastoma population. Patients in this trial were included only if they successfully completed the combined radiochemotherapy. In addition, it may be that not all patients are prepared to accept wearing the TTFields device. Nevertheless,

Table 2. Stable or Improved Health-Related Quality of Life During Progression-Free Time

| Characteristic | TTFields Plus Temozolomide (n = 361) | Temozolomide (n = 142) | *P* Value | α Value |
|---|---|---|---|---|
| Pain | | | | |
| Stable/improved from baseline, No./No. (%) | 205/361 (56.8) | 51/142 (35.9) | <.001 | .05 |
| Median duration (95% CI), mo | 6.2 (5.9 to 7.0) | 6.3 (5.6 to 9.1) | .88 | |
| Median CFB AUC until last stable/improved status (95% CI) | 0 (0 to 0) | 0 (0 to 0) | .80 | |
| Global health status | | | | |
| Stable/improved from baseline, No./No. (%) | 192/359 (53.5) | 53/141 (37.6) | .001 | .025 |
| Median duration (95% CI), mo | 6.3 (5.9 to 7.4) | 7.9 (5.9 to 9.8) | .24 | |
| Median CFB AUC until last stable/improved status (95% CI) | 24.4 (11.9 to 35.0) | 65.9 (13.1 to 121.3) | .13 | |
| Physical functioning | | | | |
| Stable/improved from baseline, No./No. (%) | 195/361 (54.0) | 54/142 (38.0) | .001 | .017 |
| Median duration (95% CI), mo | 6.2 (5.9 to 8.2) | 9.1 (5.9 to 9.8) | .21 | |
| Median CFB AUC until last stable/improved status (95% CI) | 0 (0 to 18.7) | 0 (0 to 30.0) | .53 | |
| Weakness of legs | | | | |
| Stable/improved from baseline, No./No. (%) | 206/351 (58.7) | 58/138 (42.0) | .001 | .013 |
| Median duration (95% CI), mo | 6.3 (6.0 to 8.3) | 9.1 (5.9 to 9.8) | .08 | |
| Median CFB AUC until last stable/improved status (95% CI) | 0 (0 to 0) | 0 (0 to 0) | .51 | |
| Cognitive functioning | | | | |
| Stable/improved from baseline, No./No. (%) | 181/359 (50.4) | 55/142 (38.7) | .02 | .01 |
| Median duration (95% CI), mo | 6.0 (4.9 to 6.5) | 6.2 (5.7 to 9.6) | .65 | |
| Median CFB AUC until last stable/improved status (95% CI) | 26.3 (0 to 48.6) | 0 (0 to 93.3) | .37 | |
| Emotional functioning | | | | |
| Stable/improved from baseline, No./No. (%) | 196/359 (54.6) | 62/142 (43.7) | .03 | .008 |
| Median duration (95% CI), mo | 6.3 (6.0 to 8.3) | 7.7 (5.8 to 9.4) | .38 | |
| Median CFB AUC until last stable/improved status (95% CI) | 22.6 (5.8 to 35.0) | 25.2 (0 to 54.4) | .73 | |
| Social functioning | | | | |
| Stable/improved from baseline, No./No. (%) | 173/359 (48.2) | 58/142 (40.8) | .14 | .007 |
| Median duration (95% CI), mo | 6.2 (5.9 to 7.1) | 6.7 (5.9 to 9.6) | .40 | |
| Median CFB AUC until last stable/improved status (95% CI) | 16.5 (0 to 47.2) | 0 (0 to 54.4) | .90 | |
| Role functioning | | | | |
| Stable/improved from baseline, No./No. (%) | 173/361 (47.9) | 58/141 (41.1) | .17 | .006 |
| Median duration (95% CI), mo | 5.9 (4.4 to 6.3) | 7.3 (5.7 to 9.3) | .27 | |
| Median CFB AUC until last stable/improved status (95% CI) | 0 (0 to 25.0) | 46.7 (0 to 75.8) | .34 | |
| Itchy skin | | | | |
| Stable/improved from baseline, No./No. (%) | 148/349 (42.4) | 64/137 (46.7) | .39 | .0056 |
| Median duration (95% CI), mo | 6.0 (4.7 to 6.3) | 6.7 (5.6 to 9.4) | .37 | |
| Median CFB AUC until last stable/improved status (95% CI) | 0 (0 to 0) | 0 (−102.2 to 0) | .19 | |

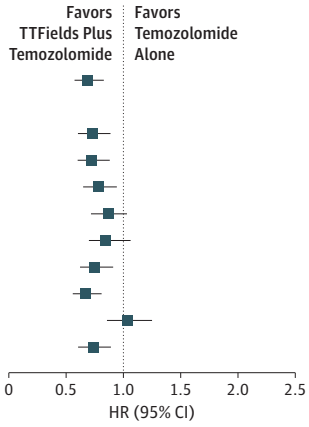
Abbreviations: AUC, area under the curve; CFB, change from baseline; TTFields, tumor-treating fields.

patients participating in this trial were similar with respect to clinical characteristics to those participating in the EORTC 26981 study[12] comparing radiotherapy alone with radiotherapy plus temozolomide. Lastly, many factors may affect HRQoL, such as age, comorbidity, tumor characteristics, previous antitumor treatment (eg, radiation dose), and supportive treatment. However, it is unlikely that these factors influenced our conclusion, as the objective of this study was to compare HRQoL results between 2 treatment arms in which patients were similar due to randomization.

Figure 3. Deterioration-Free Survival and Time to Deterioration

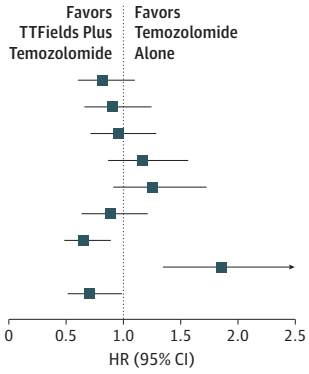
A Deterioration-free survival

| Source | Median, mo: TTFields Plus Temozolomide | Median, mo: Temozolomide Alone | HR (95% CI) |
|---|---|---|---|
| Progression-free survival | 6.7 | 4.0 | 0.69 (0.57-0.83) |
| Deterioration-free survival | | | |
| Global health status | 4.8 | 3.3 | 0.73 (0.60-0.88) |
| Physical functioning | 5.1 | 3.7 | 0.73 (0.60-0.88) |
| Cognitive functioning | 4.4 | 3.6 | 0.78 (0.64-0.94) |
| Role functioning | 4.3 | 3.8 | 0.86 (0.71-1.02) |
| Social functioning | 4.5 | 3.9 | 0.84 (0.70-1.06) |
| Emotional functioning | 5.3 | 3.9 | 0.75 (0.62-0.91) |
| Pain | 5.6 | 3.6 | 0.67 (0.56-0.81) |
| Itchy skin | 3.9 | 4.0 | 1.03 (0.85-1.25) |
| Weakness of legs | 5.6 | 3.9 | 0.74 (0.61-0.89) |




B Time to deterioration

| Source | Median, mo: TTFields Plus Temozolomide | Median, mo: Temozolomide Alone | HR (95% CI) |
|---|---|---|---|
| Global health status | 14.130 | 9.63 | 0.81 (0.60-1.10) |
| Physical functioning | 14.170 | 13.97 | 0.90 (0.66-1.24) |
| Cognitive functioning | 10.270 | 13.97 | 0.95 (0.71-1.28) |
| Role functioning | 9.20 | 13.97 | 1.16 (0.86-1.56) |
| Social functioning | 10.60 | 13.97 | 1.25 (0.91-1.72) |
| Emotional functioning | 13.430 | 14.03 | 0.88 (0.64-1.21) |
| Pain | 13.370 | 12.13 | 0.65 (0.48-0.89) |
| Itchy skin | 8.167 | 14.40 | 1.85 (1.33-2.57) |
| Weakness of legs | 14.170 | 14.03 | 0.71 (0.51-0.99) |




Deterioration-free survival (A) and time to deterioration (B) for health-related quality-of-life domains in patients who received tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone. HR indicates hazard ratio.

## Conclusions

Use of TTFields prolongs progression-free and overall survival in patients with glioblastoma. The addition of this novel device-delivered treatment neither negatively affects nor improves functioning and well-being of the patient, including critical HRQOL issues, such as role, social, and physical functioning. Patients reported more itchy skin, which is a direct and expected consequence of the placement of transducer arrays on the patients' scalp. Considering the net clinical benefit, our HRQoL data support the addition of TTFields to standard therapy in patients with glioblastoma.

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**Author Contributions:** Drs Taphoorn and Dirven contributed equally to the study. Drs Stupp and Kirson had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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*Drafting of the manuscript:* Taphoorn, Dirven, Lavy-Shahaf, Bruna, Kirson, Stupp.
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*Study supervision:* Bruna, Roth, Desai, Villano, Kirson, Ram, Stupp.

**Conflict of Interest Disclosures:** Dr Taphoorn has performed paid consultancy for Hoffmann-La Roche. Dr Lavy-Shahaf is an employee of and received personal fees from Novocure during the conduct of the study. Drs Weinberg and Kirson are employees of and own minority stock in Novocure. Dr Taillibert received fees from Centre-de-Recherche-en-Neuro-Oncologie for enrolling patients at Salpêtrière University Hospital during the conduct of the study. Dr Idbaih received research support from Foundation ARC, IntselChimos, Beta-Innov, and Carthera and travel support from Carthera and Hoffmann-La Roche and served as a paid member of the advisory boards of BMS, Hoffmann-La Roche, and Lettre du Cancérologue. Dr Hottinger received research support from Novocure and served on advisory boards of Servier and BMS (fees paid to the institution). Dr Roth served as a paid member of the advisory boards of Roche and MSD and received personal fees for lectures on behalf of BMS and Novocure. Dr Ram received grants and personal fees from and owns minority stock in Novocure. Dr Stupp received nonfinancial support from Novocure, and his institution received fees from Celgene, Novartis, AbbVie, Merck KGaA (Darmstadt), and MSD-Merck & Co. Dr Stupp's spouse is a full-time employee of Celgene. No other conflicts were reported.

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Invited Commentary

# Tumor-Treating Fields
## Answering the Concern About Quality of Life

Lia M. Halasz, MD; Timur Mitin, MD, PhD

**Since the 2005 publication** of the randomized European Organization for Research and Treatment of Cancer/National Cancer Institute of Cancer trial that established concurrent radiotherapy (RT) and temozolomide for upfront treatment of glioblastoma (GBM),[1] little progress has been made. Thus, it was remarkable when the interim results for the EF-14 trial were published, documenting a 4.9-month increase in median overall survival with the addition of tumor-treating fields (TTFields) to standard therapy with combined RT and temozolomide.[2] These findings were strengthened by presentation of the mature analysis at the Society for Neuro-oncology Meeting in 2016, which confirmed that the median survival improved from 16 months after randomization to RT plus temozolomide to 21 months with the addition of TTFields to RT plus temozolomide.[3] The survival advantage continued at later times, such as the 2-year survival rate of 30% vs 42.5% ($P$ = .001).

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Since its introduction, many physicians have remained skeptical about including TTFields as standard of care,[4] in part due to the novelty of the mechanism of action. The device generates low-intensity, intermediate-frequency (200 kHz) alternating electric fields that interfere with mitosis and disrupt the division of cells. Since its initial use for treatment of GBM, TTFields is now being tested for other cancer types, including metastatic non-small cell lung cancer,[5] and as an alternative to prophylactic cranial irradiation in small cell lung cancer (Oregon Health Sciences University/University of Washington trial, starting accrual in early 2018). Furthermore, physicians and patients have been concerned about the quality-of-life implications of wearing a mobile electrical device with 4 arrays of transducers continuously fixed to a shaved scalp for at least 18 hours a day. The battery pack for the device is large and heavy enough that it could interfere with daily activities. Quality of life remains a priority for many of our patients since clinical trials have shown incremental improvement in overall survival, but not cure.

An interim analysis of the EF-14 trial focusing on health-related quality of life (HRQoL), published by Zhu and colleagues,[6] suggested initial improvement in global HRQoL with TTFields in the first 6 months. Skin toxic effects concerns were higher among patients randomized to the combined TTFields, RT, temozolomide arm. The final analysis of these data, published by Taphoorn and colleagues[7] in this issue of *JAMA Oncology*, presents important data for evaluating the overall effect of TTFields on our patients. In contrast to the interim report, the investigators found no significant difference in HRQoL between the 2 treatment arms, except for itchy skin, which was worse with TTFields.

The finding of worsening itchy skin was not surprising given the known dermatologic adverse effects of the treatment. In the EF-14 trial, where TTFields was used with concurrent temozolomide shortly after RT, the rate of grade 1 and 2 skin toxic effects was 43%.[3] Because TTFields therapy is frequently being combined in the real-world setting with other agents, such as bevacizumab, the resultant skin toxic effects are not well studied and the incidence may be even higher. Hence, evaluation and appropriate and rapid management of skin toxic effects are critical to avoid significant treatment interruptions—and even discontinuation—to maximize TTFields therapy adherence and the resulting survival benefit.

One of the difficulties of this study,[7] which is common to many evaluations of HRQoL, is the low adherence to HRQoL assessments. Although 91.9% of patients had HRQoL assessments at baseline (before randomization), only 65.8% had assessments at 3 months and 41.7% at 12 months of follow-up. However, the authors performed sensitivity analyses with mixed-model analyses to account for missing data, which confirm their findings.

It is comforting to learn that the burden of carrying the device was not detrimental to patients' physical, social, or emotional functioning; however, overall it is important to remember that the trial participants were a highly selective group of patients. These individuals elected to take part in the trial, and thus represent a group of patients who are already open to wearing a device on their scalp daily for an indefinite time. In our experience, there are many social and cultural reasons that patients have for declining TTFields despite the data of improved survival. Many do not want the physical and visual cues that may remind them of their life-altering, life-limiting diagnosis. This factor may echo studies finding that patients with breast cancer rate alopecia as one of the most distressing treatment-related adverse effects because it can result in anxiety, depression, negative body image, lowered self-esteem, and reduced sense of well-being.[8]

With societal changes and the greater acceptability of wearable devices, ranging from fitness trackers to assistive