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# Clinical Efficacy of Tumor Treating Fields for Newly Diagnosed Glioblastoma

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**Abstract.** *Background/Aim: Whether adding tumor treating fields (TTF) to the Stupp protocol increases survival for glioblastoma (GBM) patients in routine clinical care remains unknown. Patients and Methods: We retrospectively identified adult patients with newly diagnosed GBM (n=104) treated with the Stupp protocol or TTF at our Institution. Results: Thirty-six percent (37/104) of patients received TTF in conjunction with the Stupp protocol and these patients had increased 6-month (p=0.006) and 1-year (p=0.170), but not 2-year survival rates compared to the 67-patients who received Stupp alone. The improvement of survival rate at 6-month was further confirmed by a modified Poisson model (p=0.010). However, we did not observe any improvement in overall survival (OS) with a Cox model. Conclusion: While adding TTF to the Stupp protocol appeared to benefit patients with newly diagnosed GBM, this effect was mild and may be largely due to selection bias.*

Glioblastoma (GBM) is the most common and highest grade of malignant glioma with very poor survival, estimated to be 36.5% at 1 year and 5% at 5 years (1). GBM has an incidence rate of approximately 4 per 100,000 population in the US (1, 2) and has significantly increased over the past decade (2). Additionally, the number of patients with GBM will likely continue to rise as the US population ages and with improved diagnostic imaging (3, 4).

Thus, effective management of malignant glioma is critical. Currently, maximal safe resection followed by post-operative radiotherapy and temozolomide chemotherapy is the standard of care (the Stupp Protocol) for malignant glioma patients. More recently, tumor treating fields (TTF) therapy delivered by Optune® has been approved as a novel therapeutic approach to GBM, initially investigated in a phase 3 trial (EF-11) for recurrent GBM (5). TTF treatment selectively inhibits proliferating tumor cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields *via* four transducer arrays which are applied to the shaved patient's scalp (6-9). A more recent clinical trial (EF-14) of TTF as adjuvant therapy for newly diagnosed GBM showed a significant survival advantage with TTF (10, 11). Subsequently, TTF therapy has been included in the National Comprehensive Cancer Network as part of standard-of-care treatment paradigm. However, the results of these studies are not necessarily translatable into a general population as the study selection criteria were relatively narrow. Often survival advantages demonstrated in clinical trials are somewhat more muted when the treatment strategy is applied to a more varied real-world patient population. For example, while the widespread adoption of temozolomide following the Stupp trials in 2005 led to increased overall survival (OS) for GBM patients in the National Cancer Database after 2005 compared to prior cohorts, the OS of the population treated with temozolomide has always remained less than that of patients enrolled in the clinical trials (12).

Notable limitations of both EF-11 and EF-14 are the lack of a true placebo control (5, 10, 11, 13) and the incremental benefit observed in these studies (14). As such, the EF-11 and EF-14 studies were met with controversy and skepticism (14, 15) and relatively few patients choose to wear the device in real clinical practice (14, 16). The post-marketing

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clinical efficacy of adding TTF to the Stupp protocol for GBM remains largely under-studied. No data, to our knowledge, are currently available for TTF efficacy for newly diagnosed GBM in the real-world clinical setting. In this report, we retrospectively studied clinical efficacy of adding TTF to the Stupp protocol for patients with newly diagnosed GBM treated at our Institution.

## Patients and Methods

*Study population*. The present study was approved by the University of Rochester's Research Subjects Review Board. We received a waiver of informed consent from patients since this retrospective study involved only review of medical records, and the majority of our patient cohort is deceased. Patients with newly diagnosed GBM (age ≥18 years) who met the following inclusion criteria were included in the present study: 1) those who completed the Stupp protocol treatment or added TTF to the Stupp protocol (hereinafter TTF) at the University of Rochester Medical Center from January 1, 2014 to July 31, 2017; 2) those who have known survival information. In order to study 2-year survival time for all patients, we set a cut-off date for follow-up on July 31, 2019. All patient information was collected from the University of Rochester Wilmot Cancer Institute Tumor Registry and electronic health record.

We calculated overall survival (OS) time from the end of concurrent radiochemotherapy to the date of death for any reason, or the date the patient was last known to be alive, which is the same method used in the EF-14 trial (10, 11). We implemented TTF in our clinic in 2014, the same year the interim favorable results of EF-14 trial were presented at the Society for Neuro-Oncology annual meeting (17). All eligible patients have been offered TTF as a treatment option in our center since 2014. Once a patient opted for participation, they started TTF treatment as described in the EF-14 clinical trial (10, 11). We sought to determine if patients treated with TTF had longer survival compared to patients treated with Stupp alone.

*Statistical analysis*. Statistical analysis of survival status at 6, 12 and 24 months from the end of radiochemotherapy included unadjusted group comparisons by Chi-square tests and adjusted group comparisons using modified Poisson regression models (18). Treatment groups were defined at each time point by whether or not the subject had started TTF therapy. Without the benefit of randomization, multivariable regression models attempt to control for the imbalance of other prognostic variables in the treatment groups. The modified Poisson regression models allowed the estimation of the relative risk of being alive for those receiving TTF compared to those who did not, after adjusting for other prognostic factors associated with survival status. Similarly, the association between TTF and survival from the end of radiochemotherapy was evaluated using Cox's proportional hazards regression after adjusting for other prognostic factors. TTF treatment was modeled as a time-dependent covariate since the TTF exposure was defined during the follow-up period (19). Estimated survival curves were plotted with the Simon and Makuch method (20) to account for TTF as a time-varying covariate. All statistical analyses were conducted with SAS (version 9.4) with the exception of the Simon – Makuch plots which were produced in R.

Table I. *Demographic and clinical characteristics for the study cohort*.

| | TTF (37) | The Stupp protocol (67) |
|---|---|---|
| Gender, No. (%) | | |
| Male | 23 (62.2) | 38 (56.7) |
| Female | 14 (37.8) | 29 (43.3) |
| Age | | |
| Median (range) | 61 (28, 81) | 65 (28, 83) |
| ≥65 (%) | 35.1* | 55.2 |
| <65 (%) | 64.9 | 45.8 |
| Race, No. (%) | | |
| White | 37 (100.0) | 65 (97.0) |
| Non-white | 0 (0.0) | 2 (3.0) |
| Unknown | 0 (0.0) | 0 (0.0) |
| Resection, No. (%) | | |
| Biopsy | 6 (16.2) | 8 (11.9) |
| Subtotal | 10 (27.0) | 28 (41.8) |
| Gross total | 21 (56.8) | 31 (46.3) |
| MGMT, No. (%) | | |
| Methylated | 6 (16.2)* | 24 (35.8) |
| Unmethylated | 23 (62.2) | 24 (35.8) |
| Unknown | 8 (21.6) | 19 (28.4) |
| IDH, No. (%) | | |
| Mutant | 3 (8.1) | 3 (4.5) |
| Wide type | 33 (89.2) | 55 (82.1) |
| Unknown | 1 (2.7) | 9 (13.4) |
| KPS | | |
| Median (range) | 90 (70, 100) | 90 (50, 100) |
| >80 (%) | 78.4 | 59.7 |
| ≤80 (%) | 21.6* | 40.3 |
| Vital status (%) | | |
| Dead | 34 (91.9) | 62 (92.5) |
| Alive | 3 (8.1) | 5 (7.5) |

TTF: Tumor treating fields; *indicates statistical difference between Stupp and TTF cohorts by chi-square test ($p \leq 0.05$); MGMT: $O^6$-methylguanine-DNA methyltransferase; IDH: isocitrate dehydrogenase; KPS: Karnofsky performance scale.

## Results

A total of 104 patients with newly diagnosed GBM who met the inclusion criteria were included in the present study. Table I shows the demographic and clinical characteristics for these patients. Most of these patients were male, white and have died (all causes) during the follow-up interval. Median age at the time of diagnosis was 62 years (range=28-84 years). Median follow-up time was 42 months (range=29-58 months). Among them, 35.6% (37/104) of patients received TTF treatment. The proportion of patients older than 65 years was significantly lower in the TTF group compared to that in the Stupp group (35.1% *vs*. 55.2%, $p=0.050$). Additionally, the proportion of patients with worse KPS (≤80) was significantly lower in the TTF group compared to the Stupp group (21.6% *vs*. 40.3%, $p=0.054$). At 6 months from the end of radiochemotherapy, 34 subjects had started TTF therapy. A

Table II. *Multivariable Poisson regression model for GBM survival.*

| | Unadjusted | | Adjusted* | |
|---|---|---|---|---|
| Time (month) | RR (95% CI) | *p*-Value | RR (95% CI) | *p*-Value |
| 6 | 1.28 (1.11, 1.48) | 0.006 | 1.25 (1.05, 1.49) | 0.010 |
| 12 | 1.26 (0.92, 1.72) | 0.170 | 1.15 (0.85, 1.54) | 0.367 |
| 24 | 0.76 (0.31, 1.54) | 0.493 | 0.79 (0.37, 1.69) | 0.548 |

*Model adjusts relative risk of survival at each time for those variables shown in Table III; RR: Relative risk; CI: confidence interval.

total of 18 subjects had died before this time point. There was a significantly higher proportion alive among subjects who had started TTF compared to those who had not (97.1% *vs.* 75.7%, Chi-square test $p=0.006$). The improvement for survival at 6-month was further demonstrated by a modified Poisson regression model adjusting for prognostic factors including sex, age, KPS, extent of resection and MGMT methylation status (relative risk (RR): 1.25, 95% CI=1.05-1.49, $p=0.010$). At 1 year from the end of radiochemotherapy, 37 subjects had started TTF therapy. A total of 43 deaths were observed prior to this time point. Although the unadjusted survival rate was qualitatively higher for the TTF group, it did not reach statistical significance (67.6% *vs.* 53.7%, Chi-square test $p=0.170$). After adjusting for other patient characteristics in the modified Poisson regression model, TTF treatment was not associated with the probability of being alive at this time (RR: 1.15, 95% CI=0.85-1.54, $p=0.367$). Similarly, at 2 years from the end of radiochemotherapy, patients treated with TTF did not see survival improvement (RR: 0.79, 95% CI=0.37-1.69, $p=0.548$) (Table II).

In order to study survival duration for patients treated with TTF, we used Cox proportion hazard model to adjust for those abovementioned prognostic factors. In our TTF patient cohort, patients varied widely regarding when they started TTF after the end of radiochemotherapy (median=7.1 weeks, range=3.3-41.7 weeks). To mitigate such "immortal time bias" (19), TTF treatment was modeled as a time-varying covariate. The model showed no significant survival benefits for patients treated with TTF when compared to those treated with the Stupp protocol only (HR=0.93, 95% CI=0.58-1.47, $p=0.741$) (Table III). Age at diagnosis <65 ($p=0.041$) and methylation status ($p=0.021$) were both independently associated with longer survival. The Simon-Makuch plot (Figure 1) illustrates the unadjusted survival probability over time for risk sets that are redefined at each failure time, allowing a single subject to provide information on both curves depending on if and when they begin TTF therapy. Qualitatively, TTF therapy has better survival in early time period.

Table III. *Cox proportion hazards model for the study cohort.*

| Covariate | HR | 95% CI lower | 95% CI upper | *p*-Value |
|---|---|---|---|---|
| Gender | | | | |
| Male (ref) | | | | |
| Female | 1.01 | 0.63 | 1.60 | 0.980 |
| Age | | | | |
| <65 (ref) | | | | |
| ≥65 | 1.64 | 1.02 | 2.64 | 0.041 |
| KPS | | | | |
| 90-100 (ref) | | | | |
| ≤80 | 1.19 | 0.74 | 1.92 | 0.481 |
| Resection | | | | |
| Subtotal (ref) | | | | |
| Biopsy | 1.39 | 0.70 | 2.75 | 0.352 |
| Gross total | 0.80 | 0.51 | 1.26 | 0.333 |
| MGMT | | | | |
| Unmethylated (ref) | | | | |
| Methylated | 0.52 | 0.30 | 0.91 | 0.021 |
| Unknown | 0.99 | 0.58 | 1.68 | 0.965 |
| TTF | | | | |
| No (ref) | | | | |
| Yes | 0.93 | 0.58 | 1.47 | 0.741 |

HR: Hazard ratio; ref: reference.

## Discussion

The current standard of care for GBM is the Stupp protocol. A recent clinical trial (EF-14) demonstrated a survival benefit for adding TTF to the Stupp protocol for GBM patients (10, 11). This trial has generated controversy because of the limited clinical impact of the device despite its high cost. Post-market analysis of its effectiveness in clinical practice is critical to either establishing or refuting its utility.

In this report, we focused on the impact of TTF on survival for newly diagnosed GBM. To this end, we identified one hundred four newly diagnosed GBM patients who have completed the Stupp protocol and received all aspects of care (surgery, chemotherapy, radiation therapy) in a standardized fashion within our Institution. In our practice, 35.6% of our GBM patients from 2014 to 2017 received TTF, a rate identical to a recent report (36%) surveying frequency of TTF usage (16). During the time period in question, TTF was offered as a treatment option to all eligible patients in our Center. Given the complexities of complying with TTF therapy as well as its steep financial cost, we feel that 36% of all patients probably represents near the ceiling of GBM patients who can realistically be treated with this device. It is important to recognize that there may be biases in how patients are offered TTF and which patients choose to initiate therapy. These biases may be related to age, socioeconomic status, education level, availability of caregiver support and insurance status. For

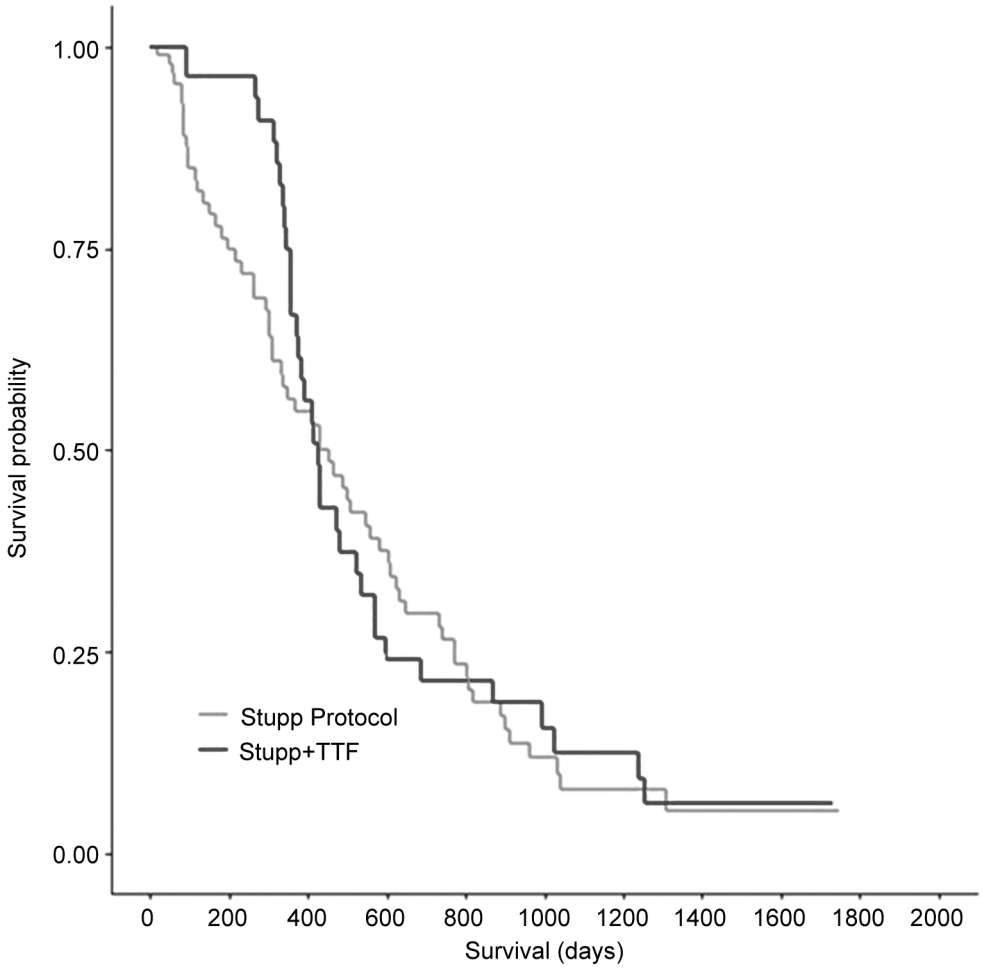


Figure 1. *Estimated survival curves (the Simon and Makuch method) for patients with GBM who received the Stupp protocol only or combination of the Stupp protocol with TTF. TTF: Tumor treating fields. Overall survival time was calculated as described in the Methods.*

example, TTF treatment involves significant patient costs which may be variably reimbursed under different insurance plans and it requires significant care giver involvement which may not be available to all candidates. Therefore, we can't eliminate the possibility that significant patient selection bias may be involved in the study results.

When we compared survival for patients treated with TTF with those patients treated with the Stupp protocol, we found that patients treated with TTF and the Stupp protocol appeared to initially have better survival when compared to those treated with the Stupp protocol only (Figure 1). The effect appeared most pronounced at 6-months where use of TTF was the only prognostic variable to correlate with survival (Table II) even after accounting for age, KPS and MGMT methylation status. Using a Cox proportional hazard model to evaluate the effect of TTF over the entire study period, no benefit was found (Table III). These data indicate that there is a reasonable chance that the apparent unadjusted survival improvement we are seeing in Figure 1 is due, in part, to patient selection bias. We may be merely selecting patients for TTF or patients with younger age, better KPS, and excellent support networks tended to accept the TTF regimen when offered, although the adjusted analysis of survival status at 6 months still indicates an advantage for TTF therapy.

Our study has limitations, but in many ways, they highlight the very problems associated with TTF treatment. First, we were not able to collect compliance data, due to much of it being absent from the patients' medical records and the manufacturer was unable to retrospectively provide this data to us. Our study is not intended to shed light on the biological impact of TTF and compliance as others have previously demonstrated (21, 22). It is important to note that in real-world clinical experience, we are dependent on how

a patient complies with a therapy at home and too often, physicians do not have a true measure of that and this remains the case for oral chemotherapy regimens as well. Second, while the number of patients (n=37) treated with TTF at our Center was relatively small, our relative percent of patients treated during the study interval was high and in line with other published report (16). The lack of resultant statistically improved survival indicates that larger numbers will be required to see any meaningful benefit if it exists. This raises questions regarding the cost effectiveness of the treatment, if the number needed to treat to demonstrate a clinically meaningful result is economically unfeasible.

In conclusion, our real-world clinical experience showed that adding TTF to the Stupp protocol appeared to provide a small survival benefit and short-term 6-month intervals to a subset of patients with GBM, however, these favorable benefits may be due partly to selection bias. Healthcare costs for malignant gliomas are substantial and higher than other forms of cancers (23, 24) and such costs are expected to continue to rise (25). In the era of value-driven cancer care, the cost and value consideration of novel additional therapies is of particular importance for clinical management of cancers like GBM. We are currently studying the cost-effectiveness of TTF in the real-world setting.

## Conflicts of Interest

Jennifer Serventi is a member of Novocure speaker's bureau and sits on their medical advisory board. All other Authors have no conflicts of interest to declare.

## Authors' Contributions

Conceived and designed the study: YL, KAW. Analyzed the data: MSS, YL. Assisted with data collection: YL, KTW, MR, JNS. Contributed to the writing of the manuscript: YL, MSS, JNS, NAM, MTM, KAW.

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