

Current usage of tumor treating fields for glioblastoma

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Abstract

Background. Tumor Treating Fields (TTF) have entered clinical practice for newly diagnosed and recurrent glioblastoma (GBM). However, controversies remain unresolved with regard to appropriate usage. We sought to determine TTF usage in major academic neuro-oncology programs in New York City, USA and Heidelberg, Germany and understand current attitudes toward TTF usage among providers.

Methods. We retrospectively determined TTF usage among patients with GBM, before and since the publication of key clinical trial results and regulatory approvals. We also surveyed attendees of an educational session related to TTF during the 2019 American Society of Clinical Oncology annual meeting.

Results. TTF usage remains infrequent (3–12% of patients with newly diagnosed GBM, and 0–16% of patients with recurrent disease) in our practices, although it has increased over time. Among 30 survey respondents (77% of whom self-identified as neuro- or medical oncologists), 60% were convinced that TTF prolongs survival for newly diagnosed GBM despite published phase III data and regulatory approval, and only 30% viewed TTF as definitively part of the standard of care treatment. A majority (87%) opposed mandating TTF incorporation into the design of clinical trials.

Conclusions. Providers continue to view TTF with some level of skepticism, with a lack of additional supportive data and logistical concerns representing continued barriers to uptake.

Key Points

- Tumor treating fields remain controversial as a glioblastoma therapy.
- Uptake is increasing but remains limited.

The use of “Tumor Treating Fields” (TTF, now Optune) is a new approach to anticancer therapy with studies completed or ongoing for brain, lung, and other solid tumors. The treatment involves a device worn on the skin above the involved organ that is designed to create alternating electric fields in tumor tissue which disrupt mitosis and leads to cancer cell death. For glioblastoma (GBM), the fields are emitted by a device worn on the shaven scalp. In 2011, the Food and Drug Administration (FDA) of the United States approved TTF for treatment of recurrent

GBM based on results of an open-label randomized (1:1) clinical trial (EF-11), in which the device was compared against “Best Physician Choice” (BPC) among 237 patients, presented first at the 2010 annual meeting of the American Society of Clinical Oncology (ASCO)¹ and then published in 2012.² The authors noted that BPC included bevacizumab in 31% of patients and nitrosourea containing regimens in 38%, which are commonly used treatments in second or later lines of therapy, and thus interpreted the results as demonstrating the device was as

Importance of the Study

Uptake of Tumor Treating Fields in the treatment of glioblastoma remains limited although it has increased over time. Surveyed academic

providers continue to view the benefit of the device with uncertainty.

effective as available other treatments with the added benefit of avoiding drug-induced toxicities.² However, several commentators pointed out that trial was neither designed nor powered to detect statistical non-inferiority.³ Subsequently, a randomized study in newly diagnosed disease (EF-14) was conducted among 695 patients, with interim results presented first at the 2014 Society for Neuro-Oncology⁴ and 2015 ASCO⁵ annual meetings, then published formally in *JAMA*.⁶ To the surprise of many including us, the interim and final results demonstrated longer survival with TTF (combined with radiotherapy and temozolomide) than without it (median 20.9 vs 16.0 months; hazard ratio 0.63, 95% confidence interval [CI] 0.53–0.76, $P < .001$).⁷ Lending further credence to the positive interpretation of results, the amount of benefit correlated “field intensity,”⁸ “dose density,”⁶ as well as the duration of daily device usage (ie, time on device),⁹ and it was reported that a survival benefit was maintained at various landmarks (eg, 5-year overall survival rate 13% with TTF, 95% CI 9–18%; vs 5% without TTF, 95% CI 2–11%).⁷ The FDA approved TTF for newly diagnosed GBM in 2015. Milestones in Europe are focused at the national level, as there is no mechanism at the European Medicines Agency. The device is allowed for use in several countries, and in Germany, a reimbursement mechanism has been in place since March 2020. Nonetheless, skepticism persists, with no shortage of opinion papers written by us^{3,10} and others.^{11,12}

Critiques can be grouped mainly as (1) inadequacy of trial design lacking a “sham” device, with the finding of statistical significance potentially representing a false-positive result; (2) a mechanism of action that remains incompletely elucidated despite repeated explanation; (3)

lack of a biomarker predicting the subpopulation most likely to benefit; (4) high cost to the health care system estimated as between \$150 000 and \$615 000 per life-year gained,^{13,14} regardless of the payer; (5) a “hassle” factor associated with its usage,¹⁵ notwithstanding secondary analyses demonstrating no obvious reduction in overall health-related quality of life¹⁶; and (6) inescapable breach of privacy regarding the diagnosis of a brain tumor during device usage in public, an issue partially addressed through the covering of the device by clothing when treating cancers arising outside the brain, such as mesothelioma.¹⁷ Cumulatively, these factors result in the overarching concern that the perceived benefit may be low relative to other therapies and patient inconvenience (Table 1) and reinforce our concern that the EF-14 trial participants were highly selected and motivated patients who consented to participate,¹⁰ and may accordingly not represent the broader population of patients with GBM. Uptake in the field remains far from universal.

Into that cauldron of controversy, in 2019, we (A.B.L. and W.W.) were invited as faculty experts to discuss these and related topics as part of the educational curriculum offered by the ASCO during its annual meeting. The Ticketed Session was formally entitled by ASCO as “Clinical Controversies: Do We Need More Data on Tumor Treatment Fields for GBMs?” We were each assigned the responsibility to support either the view that “No, Tumor treatment fields are ready for primetime in the community” (A.B.L.) or “Yes: We need more data” (W.W.). Between the invitation in October 2019 and the formal session on June 2, 2019, we each

Table 1. Comparative Differences in Survival Among Positive Phase III Trials in Newly Diagnosed Glioblastoma

Treatment	N	Median survival (months)	Absolute increase (months)	Relative increase (%)	2-year survival rate (%)	Absolute increase (%)	Relative increase (%)
RT ¹⁸	286	12.1			11		
RT +TMZ (TMZ) ¹⁸	287	14.6	2.5	21	27	16	~150
RT +TMZ ⁷	216	16.0			31		
RT +TMZ +TTF ⁷	456	20.9	4.9	31	43	12	39
RT ¹⁹	106	11.4			7		
RT + wafer ¹⁹	101	13.1	1.7	15	12	5	71

Absolute improvement in median survival is 4.9 months from TTF compared to 2.5 months from the addition of temozolomide (combining all *MGMT* subgroups). However, the relative improvement in 2-year survival is 42% from TTF whereas a dramatic ~150% relative increase is achieved with temozolomide. Therefore, the improvement is modest depending on one’s perspective, particularly when viewed in the context of other positive phase III trials. RT, radiotherapy; TMZ, temozolomide; TTF, Tumor Treating Fields; wafer, carmustine-eluting wafers implanted into the operative cavity at the time of tumor resection.

conducted an independent literature search and overlaid our own views to support the assigned positions, although neither of us necessarily agreed with our binary roles. We discussed our remarks in advance in order to reduce the potential for repetition between our discussions, and we each prepared a presentation lasting approximately 15 min. Finally, recognizing that many questions surrounding the use of TTF remain unanswered and without uniformity of approach by providers, we also used the session as an opportunity to analyze the frequency of TTF usage in clinical practice at an academic medical center and referral site for patients with GBM. We took advantage of the attendance by interested participants in the subject matter to engage attendees through a survey on attitudes toward TTF (see [Supplementary Data](#)). Here, we summarize the results of the retrospective analysis of TTF usage and the survey on attitudes toward TTF.

Methods

We retrospectively determined the frequency of TTF usage among patients in our institutions. Before FDA approval in 2011, usage was unavailable on- or off-label except as part of a clinical trial. Therefore, we assessed usage since 2011. We also determined usage before and since 2015 when the FDA approved TTF for the newly diagnosed disease. We intended only to demonstrate the frequency of usage in routine care; therefore, we did not attempt to determine nor did we capture duration of use, compliance with the device, or concurrently administered therapies.

Also, we distributed a survey to Ticketed Session attendees in order to ascertain their attitudes toward TTF usage, with completed surveys collected at the conclusion of our presentations and following informed consent by participants (see [Supplementary Data](#)). ASCO charged attendees a ticket fee to enter the session, and survey participation was voluntary. Neither of us (A.B.L. and W.W.) was compensated for preparing or delivering our presentations, although we received in-kind support from ASCO in the form of a waived registration fee to the annual meeting. ASCO did kindly assent to conduct of the survey independently during the session. However, ASCO staff were not involved in the creation or distribution of the survey to attendees, the collection of the completed surveys at the conclusion of the Ticketed Session, nor in an analysis of results, and the results and conclusions drawn are entirely those of the authors of this manuscript, not of ASCO. The survey was performed after approval by a local Human Investigations Committee which also approved the contents of the anonymous paper survey that embedded the following statement: "This survey is considered research by the Institutional Review Board/Human Research Protection Program of Columbia University which has approved it as exempt from further review. There are no correct answers. Answering anonymously will allow confidentiality, and you may decline, or withdraw from participating. The risks are inconvenience

whereas potential benefits include contributing to the understanding of how the community of brain cancer specialists currently thinks about Tumor Treating Fields (TTF) for GBM. Thank you."

Results

TTF Usage in Clinical Practice

Before 2011, no patients at Columbia University Irving Medical Center incorporated TTF into treatment in routine practice as the device was not available for either on- or off-label usage. From 2011 to 2014, the period when TTF was FDA-approved for recurrent GBM but not for newly diagnosed disease, there were 200 patients with recurrent GBM with sufficient data in the medical record to determine usage of TTF. Among these, 4% ($n = 7$) used the device as part of a second or greater lines of therapy ([Supplementary Table S1](#)). During the same period, 0% (0/207) used the device as part of the treatment for the newly diagnosed disease. Since 2015 (through 2019) when the FDA-approved TTF for newly diagnosed GBM, 16% (49/297) and 12% (36/310) of patients used the device for recurrent disease and newly diagnosed disease, respectively ([Figure 1](#); [Supplementary Table S1](#)).

In Heidelberg, Germany, at the earlier time period, treatment was only available as part of a clinical trial. Uptake started in 2015 with single patients using the device at recurrence, but no use in newly diagnosed patients. In the past 4 years, since the first presentations of the data in newly diagnosed GBM,^{4,5} the use in recurrence has basically stopped, but between 3% and 7% of patients with newly diagnosed GBM per year use the treatment and 25 records have been assessed. We did not capture whether TTF was used alone or in combination with other therapies.

Survey

Respondents ($n = 30$) self-identified most frequently as neuro-oncologists (60%) or medical oncologists (17%), with 70% practicing in the United States, 70% in an urban setting, and 77% at an academic or university medical center ([Table 2](#)). Only 60% were convinced that TTF prolongs survival for newly diagnosed GBM with 30% unsure and 7% not convinced. Among those not convinced by the EF-14 data, 67% were concerned by the lack of a sham device in the trial design or the potential that results were spurious. Substantial barriers to use were expressed by 43%, particularly patient choice for convenience, compliance, or other (40%). Only 30% expressed that TTF is definitively the standard of care for newly diagnosed GBM. Mandating TTF as part of the design of clinical trials for newly diagnosed GBM, with the exclusion of patients who refuse, was suggested in only 13%. Positive data from other trials in brain or other cancers were viewed as the most likely factor (43%) to increase TTF usage for GBM.

Table 2. Survey Results

	n (of 30)	%
Q1. I understand the mechanism of action for Tumor Treating Fields (TTF)		
A. Yes	12	40
B. Sort of	17	56.7
C. No	1	3.3
Q2. I understand the mechanism of action for TTF as well as I understand the mechanism of action for temozolomide, lomustine, bevacizumab, or other treatments in use/trials for glioblastoma		
A. Yes	12	40
B. No	17	56.7
No answer	1	3.3
Q3. Patients in my practice are able to obtain TTF without going to a provider in another practice or institution		
A. Yes	19	63.3
B. No	9	30
C. Not sure	1	3.3
No answer	1	3.3
Q4. I perform NovoTAL (field planning) for TTF		
A. Yes	8	26.6
B. No	20	66.6
C. Not sure	1	3.3
No answer	1	3.3
Q5. Barriers to prescribing TTF in my practice are substantial, and an impediment to its use		
A. Yes	13	43.3
B. No	14	46.6
C. Not sure	2	6.7
No answer	1	3.3
Q6. The cost to the patient/health care system is too high for the potential benefit of TTF		
A. Yes	10	33.3
B. No	10	33.3
C. Not sure	9	30
No answer	1	3.3
Q7. Concerns about quality of life while using TTF are a barrier for me to recommend it or for patients to use it		
A. Yes	7	23.3
B. No	16	53.3
C. Not sure	6	20
No answer	1	3.3
Q8. Use of TTF		
A. Is part of <i>the</i> standard of care for newly diagnosed glioblastoma	9	30
B. Is part of <i>a</i> standard of care for newly diagnosed glioblastoma, but necessarily the standard of care	12	40
C. Not sure	8	26.6
No answer	1	3.3
Q9. Use of carmustine-eluting wafers (Gliadel)		
A. Is part of <i>the</i> standard of care for newly diagnosed glioblastoma	2	6.7
B. Is part of <i>a</i> standard of care for newly diagnosed glioblastoma, but necessarily the standard of care	13	43.3
C. Not sure	11	36.7
Responders added new answer: not standard of care	3	10
No answer	1	3.3
Q10. When discussing TTF with my patients with newly diagnosed glioblastoma		
A. I recommend TTF strongly	6	20

Table 2. Continued

	n (of 30)	%
B. I recommend TTF but not necessarily strongly	7	23.3
C. I give information about it but do not recommend for or against it	9	30
D. I recommend against TTF	0	0
E. Other	7	23.3
No answer	1	3.3
Q11. The most important barrier for me to TTF use among my patients is		
A. I do not understand the mechanism	1	3.3
B. The clinical data is not adequate to justify a strong recommendation	5	16.7
C. Patient choice for convenience, compliance, or other	12	40
D. Cost/lack of insurance coverage	7	23.3
E. Administrative barrier within my practice (other than related to cost or insurance)	2	6.7
F. Precluded as part of a clinical trial	3	10
G. Lack of a biomarker to identify patients most likely to benefit	2	6.7
H. Other	4	13.3
No answer	1	3.3
Q12. When designing a clinical trial		
A. TTF use must be part of the design, either included in the treatment arm or in a control arm, or both. Patients who do not want to use it are excluded.	4	13.3
B. TTF must not be mandated in a clinical trial, either included in the treatment arm or in a control arm, or both. Patients who want to use it are excluded.	7	23.3
C. Stratification by intent to use TTF is the best way to address TTF in trial design.	18	60
D. Other	0	0
No answer	1	3.3
Q13. Which of the following would most likely increase uptake of TTF for glioblastoma?		
A. Other positive trials in different types of brain tumors/other cancers	13	43.3
B. Improved understanding of the mechanism of action	7	23.3
C. A predictor of individual benefit	8	26.6
D. More reliable reimbursement for NovoTAL	4	13.3
E. Reduced administrative barriers (not related to reimbursement for NovoTAL or treatment)	2	6.7
F. Other	5	16.7
No answer	2	6.7
Q14. The published data has convinced me that TTF prolong survival for newly diagnosed glioblastoma when added to radiotherapy and temozolomide		
A. Yes	18	60
B. No	2	6.7
C. Not sure	9	30
No answer	1	3.3
Q15. If the published data has NOT convinced me that TTF prolong survival for newly diagnosed glioblastoma when added to radiotherapy and temozolomide, I am not convinced because		
A. Not applicable (the data has convinced me)	9	30
B. There was no "sham" device in the phase 3 trial	10	33.3
C. The improvement in observed survival with TTF was because of a "placebo" effect	3	10
D. The improvement in observed survival with TTF was because of adherence, selection, or other bias	8	26.6
E. The data was fabricated or otherwise misinterpreted	0	0
F. Other	1	3.3
No answer	8	26.6
Q16. I am a		
A. Neuro-oncologist	18	60

Table 2. Continued

	n (of 30)	%
B. Medical oncologist	5	16.7
C. Radiation oncologist	1	3.3
D. Neurosurgeon	3	10
E. Neuro-psychologist	0	0
F. Neuro-pathologist	0	0
G. Nurse practitioner	0	0
H. Patient or patient advocate	1	3.3
I. Other	2	6.7
No answer	1	3.3
Q17. I identify as a		
A. Man	19	63.3
B. Woman	9	30
C. Prefer not to answer	2	6.7
Q18. My age is		
A. <30 years: 0 (0%)	0	0
B. 31–40: 8 (26.6%)	8	26.6
C. 41–50: 8 (26.6%)	8	26.6
D. 51–60: 6 (20%)	6	20
E. >60: 6 (20%)	6	20
F. Prefer not to answer	1	3.3
Q19. My practice is located in		
A. USA	21	70
B. Canada	3	10
C. Mexico	0	0
D. Central America, Country	0	0
E. South America, Country	1	3.3
F. Europe, Country	1	3.3
G. Asia, Country	1	3.3
H. Australia	1	3.3
I. New Zealand	0	0
J. Other	1	3.3
No answer	1	3.3
Q20. My practice is		
A. Urban	21	70
B. Suburban	4	13.3
C. Rural	2	6.7
No answer	2	6.7
Responder added NA	1	3.3
Q21. My practice is part of		
A. Academic Medical Center/University	23	76.7
B. Small private practice (1–4 physicians)	0	0
C. Medium private practice (5–10 physicians)	2	6.7
D. Large private practice (>10 physicians)	3	10
E. Other	0	0
No answer	2	6.7
Responder added NA	1	3.3

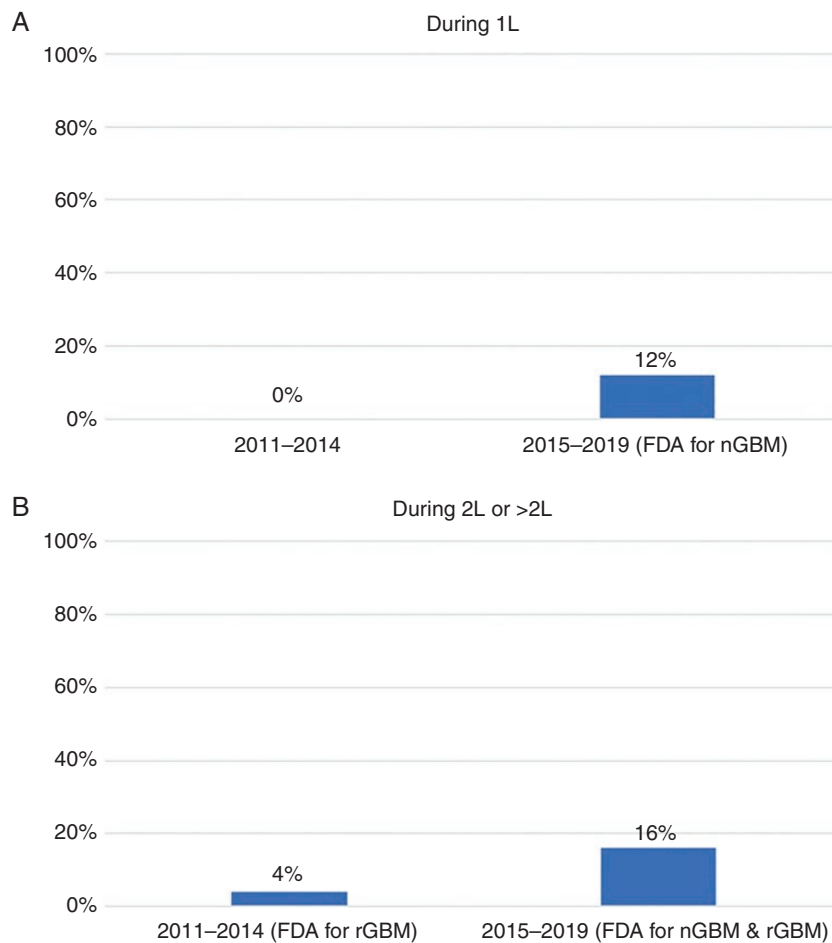


Figure 1. Usage of Tumor Treating Fields (TTF) during 1L (A) or later than 1L (B) treatment at Columbia University Irving Medical Center. 1L, first-line therapy as part of initial treatment regimen before progression of the disease; 2L, second-line therapy after recurrence/progression of the disease. GBM, glioblastoma; nGBM, newly diagnosed GBM; rGBM, recurrent/progressive GBM.

Discussion

Usage of TTF by patients with newly diagnosed or recurrent GBM remains low although it is increasing over time. This finding is consistent with increasing availability among providers. A previous survey demonstrated that 41% of respondents offered TTF,²⁰ whereas we found 63% have it available. Coverage by Medicare for newly diagnosed GBM, announced in July 2019 and effective September 2019,²¹ may reduce one barrier; although our survey was conducted among a small number of self-selected participating providers, the results nonetheless suggest that concerns about cost were perceived as the most important hurdle by only a minority (23%) of providers (Table 2). Declination by patients to wear the device, combined with continued difficulty with understanding the mechanism of action and doubt about the favorable outcome results of existing studies, continues to represent challenges to widespread uptake.

In addition, new therapeutic options will emerge only through clinical trials. At present, there is a lack of uniformity among investigators, industry partners, governmental agencies such as the NCI, and regulators regarding how to incorporate TTF into the design of trials, particularly for newly diagnosed GBM, if at all. Trials we recently led or are leading exclude its use altogether. For example, the randomized placebo-controlled phase III clinical trial of depatuxizumab mafodotin for EGFR-amplified newly diagnosed GBM excluded TTF usage from both the treatment and control arms.²² Similarly, the open-label multi-arm GBM-AGILE study (NCT03970447) also disallows TTF on all arms. The NOA-20 (N2M2) trial (NCT03158389, EudraCT 2015-002752-27)²³ also disallows TTF. Accrual does not suffer from this design, which to the contrary resulted mainly from concerns that mandating TTF usage would hinder the willingness of patients to participate, and if compliance differed between arms could create imbalance. Nonetheless, excluding TTF usage from clinical trials of new drugs represents another barrier to uptake, perhaps most particularly

at academic centers. However, others have raised ethical concerns about disallowing TTF usage, particularly among patients randomized to a control arm. One manner to address this concern is to stratify by intent to use TTF at the time of randomization, recognizing its imperfections and that actual use over time could diverge widely from initial intent. Stratification by intent to use was viewed as the best way to address TTF in trial design by 60% of our survey participants (Table 2).

What remains from the educational events, our survey, and the present development with TTF? There is still a need for data from an independent device-controlled trial, optimally in a non-overlapping patient population to EF-14. Options could be older patients or a neoadjuvant approach both at diagnosis or recurrence. The latter also has the potential to address mechanistic questions by obtaining tissue before and during TTF therapy, which may help to define optimally benefitting patients and therefore enhance the take-rate. One scientifically challenging concept involves the interference of TTF with the newly discovered glioma networks.^{24–26} The pragmatic approach to trials will be necessary to ensure ethically sound options and extension of experience with the device. All these may slowly increase the acceptance rate. To which level? This will undoubtedly continue to vary from site to site and depend as well on other options in trials and hopefully soon with more standard treatments to come.

Supplementary Data

Supplementary data are available at *Neuro-Oncology Advances* online.

Keywords

attitudes | barriers | glioblastoma | survey | tumor treating fields

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