



Application of tumor treating fields for newly diagnosed glioblastoma: understanding of nationwide practice patterns

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Abstract

Background Tumor treating fields (TTF) harness magnetic fields to induce apoptosis in targeted regions. A 2015 landmark randomized phase III trial of newly diagnosed glioblastoma (GBM) patients demonstrated TTF + temozolomide to be superior to temozolomide alone. Given these results, we sought to assess practice patterns of providers in TTF utilization for GBM.

Methods A survey was administered to practices in the United States self-identifying as specializing in radiation oncology, medical oncology, neuro-oncology, neurosurgery, and/or neurology. Responses were collected anonymously; analysis was performed using Fisher's exact test.

Results A total of 106 providers responded; a minority (36%) were in private practice. Regarding case volume, 82% treated at least six high-grade gliomas/year. The provider most commonly certified to offer TTF therapy to GBM patients was the neuro-oncologist (40%), followed by the radiation oncologist (34%); 31% reported no TTF-certified physician in their practice. TTF users were more likely to have high volume, and be aware of TTF inclusion in National Comprehensive Cancer Network (NCCN) guidelines ($p < 0.05$).

Conclusions More than 80% of TTF for GBM in the United States is performed by groups who treat at least six high-grade gliomas per year; unfortunately more than 30% were in practices bereft of anyone certified to offer TTF therapy. These results indicate that there remains fertile soil for TTF therapy nationwide to be introduced into practices for GBM treatment. Providers seeking to refer newly diagnosed GBM patients for TTF should seek out practices with TTF user-associated characteristics to ensure optimal access for their patients.

Keywords Glioblastoma · Tumor treating fields · Neuro-oncology · Radiation oncology · National comprehensive cancer network guidelines

Introduction

Tumor treating fields (TTF) are a low-intensity, intermediate-frequency, non-invasive and regional antimetabolic treatment that harnesses magnetic fields to induce apoptosis in targeted regions [1]. In recurrent glioblastoma (GBM), a phase III trial demonstrated TTF as superior to active chemotherapy with regard to toxicity/quality of life, and comparable with regard to overall survival; this finding led to the approval of TTF for recurrent GBM by the Food and Drug Administration (FDA) in 2011 [2, 3]. Less than 4 years later, interim analysis of a phase III trial of newly diagnosed GBM patients found TTF + temozolomide superior to temozolomide alone in both overall survival and progression-free survival, leading to FDA approval of TTF for newly diagnosed GBM as well as the adoption of TTF in the 2016 National

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Comprehensive Cancer Network (NCCN) guidelines [3, 4]. Given these findings, we sought to assess practice patterns and trends of providers in the utilization of TTF for GBM in the United States.

Methods

A survey designed through the Oregon Clinical and Translational Research Institute and approved by the Oregon Health and Science University Institutional Review Board was administered in 2017 to practices in the United States which self-identified as specializing in radiation oncology, medical oncology, neuro-oncology, neurosurgery, and/or neurology. The survey was designed and hosted by Research Electronic Data Capture (REDCap), and contained screening questions to ensure respondents were currently practicing and not in training [5]. 2483 physicians were contacted by email and invited to complete the survey.

Responses were collected anonymously; the survey was constructed to identify characteristics of each respondent's typical practice patterns and to assess responder knowledge of appropriate clinical scenarios for TTF, knowledge of TTF therapy status on current NCCN guidelines, and personal approaches for patients with recurrent GBM. Demographic questions included the practicing status of the physician, profession, description of practice setting, year of completed residency/fellowship training, number of physician-partners in immediate practice group/department, region of practice, number of high-grade gliomas treated per year, and the presence of a certified TTF therapy provider. Based on responses, participants were categorized as "users" or "nonusers" of TTF for newly diagnosed GBM. Utilization of TTF was correlated with practice patterns using Fisher's exact test.

Results

A total of 106 providers responded; 95% were practicing physicians, most commonly representing Missouri (8.9%), Massachusetts (7.9%), California (6.9%), Pennsylvania (5.9%), Oregon (5.9%), and Illinois (5.9%). The most common responders were radiation oncologists (75%) and neuro-oncologists (22%); medical oncologists (3%) and neurosurgeons (1%) comprised the remaining responders. The average number of physician-partners in a responder's practice group was 7.6; a minority (36%) were in private practice. 81% of responders were aware that TTF therapy is listed on current NCCN guidelines; the remaining responders were unaware.

With regard to case volume, only 18% treated 0–5 high-grade gliomas per year, while 24% treated 6–10 annually,

and 58% treated at least 10 high-grade gliomas annually. The provider most commonly reported as certified to offer TTF therapy to GBM patients was the neuro-oncologist (40%), followed by the radiation oncologist (34%); 31% reported no physician in their practice being certified to administer TTF therapy (Fig. 1).

Users of TTF were more likely to have greater high-grade glioma volume (> 10 GBM patients/year; $p=0.024$; relative risk 1.5), be knowledgeable of TTF inclusion on the 2016 NCCN guidelines ($p<0.0001$; odds ratio = 10.4; relative risk = 3.0), and specialize in radiation oncology or neuro-oncology ($p=0.016$) (Table 1). There was no difference in years of practice, location of training, geographic location of practice, number of physician-partners in immediate practice, or academic versus private practice setting between users and nonusers of TTF.

Discussion

With the most recent evidence firmly in support of TTF plus temozolomide increasing median overall survival in newly diagnosed GBM by 4.9 months over temozolomide alone (more than a 30% increase in life span), it is becoming more imperative for TTF to be made available to GBM patients [6]. We sought to assess the nationwide trends and practice patterns of TTF application in the United States.

Our results indicate that TTF for newly diagnosed GBM in the United States is administered by providers who are knowledgeable of its inclusion in the 2016 NCCN guidelines, have elevated high-grade glioma volume, and specialize in radiation oncology or neuro-oncology. Knowledge of TTF inclusion in the 2016 NCCN guidelines roughly tripled the likelihood of TTF utilization for newly diagnosed GBM, and GBM volume of at least 10 patients/year increased the

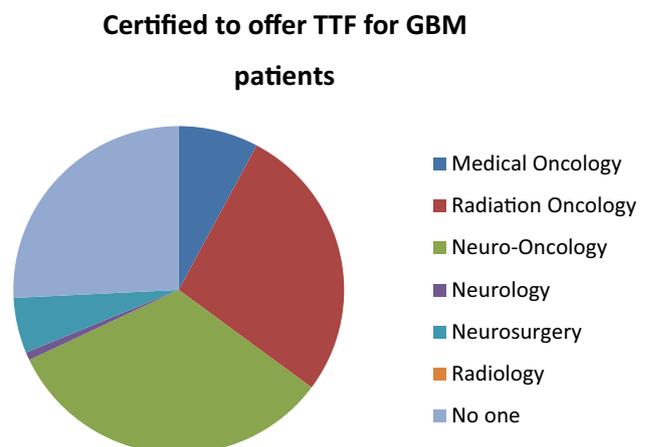


Fig. 1 Depiction of subspecialties certified to offer tumor treating fields (TTF) for glioblastoma (GBM)

Table 1 Association between clinical practice variables and use versus non-use of tumor treating fields (TTF) for newly diagnosed glioblastoma (GBM)

Clinical demographic	Clinical practice variable	TTF nonuser	TTF user	P value
Practice setting	Academic	18 (58.1%)	46 (65.7%)	0.462
	Private practice	13 (41.9%)	24 (34.3%)	
GBM patients treated yearly	Fewer than 10	19 (61.3%)	23 (32.9%)	0.024
	10 or more patients	12 (38.7%)	47 (67.1%)	
Number of physician-partners in immediate practice	0–4	16 (51.6%)	26 (37.1%)	0.484
	5–9	8 (25.8%)	23 (32.9%)	
	10+	7 (22.6%)	18 (25.7%)	
Subspecialty	Radiation oncology	27 (87.1%)	48 (68.6%)	0.016
	Medical oncology	2 (6.5%)	1 (1.4%)	
	Neuro-oncology	2 (6.5%)	20 (28.6%)	
	Neurological surgery	0 (0%)	1 (1.4%)	
Years of independent practice	0–4	3 (9.7%)	12 (17.1%)	0.112
	5–9	4 (12.9%)	16 (22.9%)	
	10–19	7 (22.6%)	22 (31.4%)	
	20+	17 (54.8%)	20 (28.6%)	
Awareness of TTF therapy on National Comprehensive Cancer Network (NCCN) guidelines	Yes	17 (54.8%)	65 (92.9%)	< 0.001
	No	14 (45.2%)	5 (7.1%)	

likelihood of TTF utilization by roughly 50%. Despite widespread implementation of TTF, there remains a substantial portion of medical practices (31%) unable to offer TTF as a treatment modality to GBM patients, and 1/5 of providers remain unaware of the inclusion of TTF in the NCCN guidelines for newly diagnosed GBM. Furthermore, because more than 80% of TTF is performed by groups who treat at least six high-grade gliomas per year (with nearly 60% performed by groups treating more than 10 high-grade gliomas/year), it becomes increasingly imperative for GBM patients to be referred towards high-volume centers to optimize their likelihood of being offered TTF as a treatment modality. This becomes problematic when examining the racial and socioeconomic realities of brain tumor patients, as poor and nonwhite patients are the least likely to be referred to high-volume centers for neuro-oncologic care [7, 8].

Limitations of this study include its low response rate, given that only 106 of the 2483 physicians contacted chose to participate (4.3% response rate); this is unfortunately similar to low response rates reported in studies involving other subspecialties [9]. Because responses were in the format of multiple choice, the full range of opinions may not have been adequately captured. Third, survey fatigue can result in responses that are not genuine; we sought to curb this by not offering an incentive (financial or otherwise) to complete the survey that we hope maximized the rate of legitimate responses. Finally, an important consideration is the lack of granularity in addressing the socioeconomic and racial demographic of patients, the latter of which may impact the applicability of randomized controlled trials comprised of

inadequately low nonwhite patient participation, as has been recently noted in localized prostate cancer [10, 11].

In conclusion, the vast majority of TTF for GBM in the United States is administered by neuro-oncologists and radiation oncologists, usually in an academic setting involving 7–8 physician-partners. However, one-fifth of providers were unaware of TTF therapy being listed on current NCCN guidelines for GBM treatment, and more than 30% were in practices bereft of anyone certified to offer TTF therapy. These results indicate that opportunities exist for TTF therapy nationwide to be introduced into practices for GBM treatment. Given the continued promising results of TTF for newly diagnosed and recurrent GBM in clinical trials thus far, this opportunity should be seized energetically [6, 12]. Providers seeking to refer newly diagnosed GBM patients for TTF should seek out practices with multiple characteristics (i.e. high volume, NCCN guideline inclusion knowledge, radiation oncologist or neuro-oncologist, etc.) to ensure optimal TTF access for their patients.

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Compliance with ethical standards

Conflict of interest Dr. Mitin receives research funding from Novocure. No other author has any conflicts of interest.

Ethical approval All studies involving human participants were in accordance with the ethical standards of the institutional research committee.

References

1. Davies AM, Weinberg U, Palti Y (2013) Tumor treating fields: a new frontier in cancer therapy. *Ann NY Acad Sci* 1291:86–95
2. Stupp R, Wong ET, Kanner AA et al (2012) NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomized phase III trial of a novel treatment modality. *Eur J Cancer* 48:2192–2202
3. U.S. Food and Drug Administration (2015) FDA approves expanded indication for medical device to treat a form of brain cancer (FDA Press Announcement No. 4658744). Retrieved from U.S. Food and Drug Administration website: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465744.htm>. Accessed 13 Jan 2018
4. Stupp R, Taillibert S, Kanner AA et al (2015) Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. *JAMA* 314:2535–2543
5. Harris PA, Taylor R, Thielke R et al (2009) Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 42:377–381
6. Stupp R, Taillibert S, Kanner A et al (2017) Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients With glioblastoma: a randomized clinical trial. *JAMA* 318:2306–2316
7. Mukherjee D, Zaidi HA, Kosztowski T et al (2010) Disparities in access to neuro-oncologic care in the United States. *Arch Surg* 145:247–253
8. Sherwood PR, Dahman BA, Donovan HS, Mintz A, Given CW, Bradley CJ (2011) Treatment disparities following the diagnosis of an astrocytoma. *J Neurooncol* 101:67–74
9. Pines JM, Penninti P, Alfaraj S et al (2017) Measurement under the microscope: high variability and limited construct validity in emergency department patient-experience scores. *Ann Emerg Med*. <https://doi.org/10.1016/j.annemergmed.2017.11.011>
10. U.S. Census Bureau (2011) The Black Population: 2010. <https://www.census.gov/prod/cen2010/briefs/c2010br-06.pdf>. Accessed 30 Sept 2017
11. McClelland S 3rd, Mitin TM (2018) The danger of applying the ProtecT trial to minority populations. *JAMA Oncol* 4:291
12. Kesari S, Ram Z (2017) EF-14 Trial Investigators. Tumor-treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: a post hoc analysis of the EF-14 trial. *CNS Oncol* 6:185–193