Neuro-Oncology Advances

5(1), 1–3, 2023 | https://doi.org/10.1093/noajnl/vdad100 | Advance Access date 19 August 2023

Intracranial stimulation for brain cancer—The case for implantable, intracranial tumor treating fields

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Among the many therapies, procedures, and tools developed to combat cancer, tumor treating fields (TTF) stands out as a unique technology and the only device approved for the treatment of glioblastoma (GBM).[1] Despite successful trials demonstrating prolongation of survival, this therapy has faced limited adoption among neuro-oncologists and patients due to a combination of skepticism by some providers and patient concerns such as frequent head shaving.[2] In contrast to the approved noninvasive device, an invasive, implantable method for the delivery of TTF may substantially improve therapeutic efficacy while addressing some of the challenges that appear to have limited the widespread use of this promising therapy.[3]

Currently approved TTF therapy is a form of noninvasive electric field modulation applied to the scalp. Electrode pads applied to shaved skin emit a continuous alternating electric field that exerts a dose-dependent inhibition of tumor growth, with initial results in cell culture and animal models demonstrating field-strength-dependent efficacy in both GBM and melanoma.[4–7] Initially believed to exert an antimitotic effect by disrupting microtubule spindle formation, TTF therapy likely also exerts anticancer effects by impacting DNA repair, autophagy, immunogenicity, migration, and cell permeability.[8]

The Optune TTF device, developed by Novocure, is FDA approved for both recurrent and newly diagnosed supratentorial GBM.[9] While some have criticized the trial design, particularly the lack of a sham device in this trial and the possibility of adherence bias,[10] TTF remains one of a small number of therapies to consistently demonstrate a survival advantage in a large number of GBM patients.

The Optune device delivers large amounts of current (0.9 amperes (A) peak amplitude) at 200 kHz, with treatment recommended for over 18 hours per day.[11,12] Delivery of energy in this frequency range is too fast to result in noticeable effects on action potential generation in peripheral nerves, muscle, or the CNS, while simultaneously low enough to avoid the more significant tissue heating seen at higher frequencies.[6] Multiple lines of evidence are converging to suggest that higher TTF doses, which can be considered a combination of field strength and stimulation time, result in more effective inhibition of tumor growth and improvements in overall survival in GBM.[4,6,7,11] If increased field strength and increased stimulation time do increase TTF efficacy, developing solutions to achieve these endpoints should be of high priority. Due to its low conductivity, the skull attenuates electric fields delivered from scalp electrodes, and bypassing the skull is a logical solution to achieving higher field strengths. Consistent with this hypothesis, Korshoej et al. explored the use of targeted craniectomy in conjunction with transcranial TTF to achieve stronger field strengths at target, which demonstrated promising preliminary results in a small phase 1 trial.[13] While this method offers an exciting advance and may provide substantially higher field strengths in hemispheric tumors, the authors suggest that this technique is unlikely to reach therapeutic field strengths in deep brain targets.[14] Furthermore, this approach does not address patient concerns regarding head shaving, visibility, and privacy, which likely play a meaningful role in slowing adoption of noninvasive TTF therapy,[2] and remains limited in stimulation time, as patients generally only

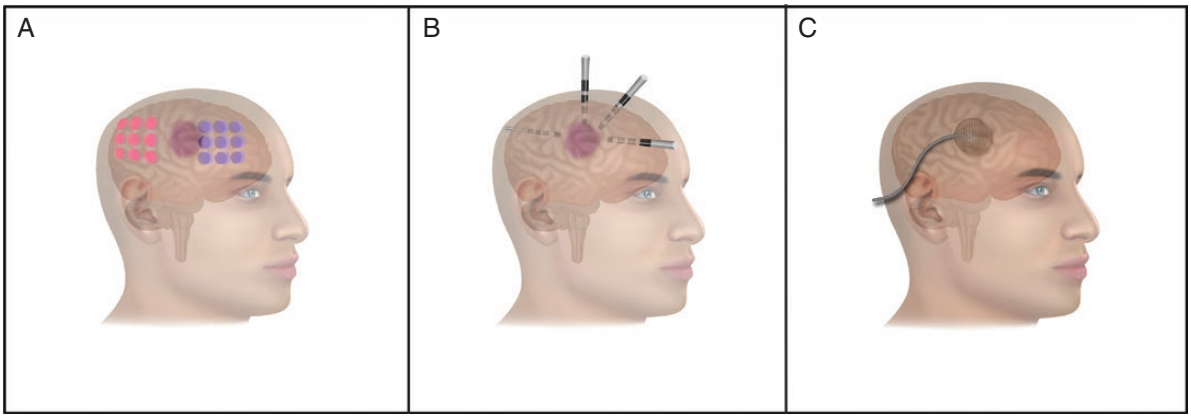

Figure 1. Possible intracranial tumor treating fields electrode configurations could include brain surface arrays (A), intraparenchymal depth electrodes (B), intra-cavitary electrode arrays (C), or a combination of these techniques, to obtain maximally efficient coverage of tumor volumes.

wear the device while awake and may not wear the electrodes consistently, limiting the overall dose density.

To augment field strength, increase the hours in the day available for stimulation, and eliminate the need for head shaving and visible electrode application, we recently proposed that a surgically implanted stimulation system might provide substantial improvements in the treatment of high-grade glioma and other brain tumors.[3] Intracranial TTF (iTTF) may be of even more dramatic benefit in certain challenging cases by enabling high field strengths to reach tumors in deep-seated locations including the brainstem or thalamus, such as diffuse midline gliomas. While less common, tumors in these locations are difficult or impossible to treat with existing transcranial methods.

To assess the impact of the skull on TTF field delivery, we compared in silico, finite element models of transcranial TTF and iTTF stimulation on the brain surface.[3] Unsurprisingly, we found that substantially higher field strengths may be achieved within a tumor volume, reaching field strengths that have been associated in cell cultures with complete tumor growth arrest. By bypassing the skull, these higher field strengths were achievable with significantly less current than the existing FDA-approved device. While chemotherapy, radiation, and TTF are not initiated immediately after surgery in part to allow for wound healing, an implanted therapy might provide the opportunity for immediate activation upon placement, enabling delivery of a therapy significantly earlier than the current standard of care. In combination with clinical and in vitro data, these data strongly support the development and testing of an iTTF device with the theoretical potential to strongly improve the efficacy of electric field modulation therapy for patients with GBM and ultimately other cancers.

As highlighted previously, several clear obstacles exist in developing an iTTF device; upper limits for this form of energy delivery directly to the brain are unknown, tissue heating will require monitoring, and implantable battery capacity may restrict the upper limit of feasible energy delivery. Similar to existing MRI conditional deep brain stimulation systems, implantable devices for cancer treatment would need to be developed to facilitate safe and effective serial MR imaging.

We describe a system using brain surface electrodes (Figure 1A) to assess the effect of the skull on TTF stimulation parameters, but alternative approaches, such as placing depth electrodes around a tumor volume (Figure 1B) or placing arrays within and surrounding a tumor cavity (Figure 1C) may further increase field strengths within a tumor and reduce power requirements by shortening the proximity between the treatment volume and electrode contacts. These targeted solutions may obviate some of the challenges associated with limited battery capacity when employed in conjunction with the improving rechargeable battery technology used for deep brain stimulation. Additional finite element modeling will be important for optimizing the design of a clinically useful system and for assessing the risk posed by energy delivery and heating. Should energy requirements continue to exceed available implantable solutions, an implanted electrode array could be powered by an external generator. This technique, while clearly increasing infection risk, has been effectively pioneered for use in other life-saving technologies such as left ventricular assist devices.[15] The introduction of intracranial electrode-based devices also opens the door to further advances in the growing field of cancer neuroscience, creating a platform that could ultimately be used to explore neurophysiologic properties affecting brain tumor growth, and potentially study new forms of therapeutic stimulation.[16] An implantable iTTF system will require substantial technology development and safety testing en route to eventual human clinical trials, with the goal of demonstrating safety and a survival benefit in the treatment of GBM and hopefully other intracranial neoplasms. While only human clinical data can ultimately prove the efficacy of this treatment modality, the potential to add another powerful tool to the arsenal of treatments for GBM should provide adequate motivation to spur the development and testing of such a system.

Conflict(s) of interest statement

The authors declare no potential conflicts of interest.

Disclosures statement

The authors declare no relevant disclosures. No third party had input or gave support to the writing of this editorial. All authors have been involved in the writing and editing of the manuscript and have read and approved the final version.

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