Neuro-Oncology Advances
6(1), 1–3, 2024 | https://doi.org/10.1093/noajnl/vdad170 | Advance Access date 3 January 2024

Tumor treating fields (TTFields) for spinal metastasis—The case for bone removal and spinal implants as waveguides to enhance field strength at the target

Claudio E. Tatsui, Kristen W. Carlson, and Chirag B. Patel

Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA (C.E.T.); Carlson Research, Boston, Massachusetts, USA (K.W.C.); Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA (C.B.P.)

Corresponding Author: Claudio E. Tatsui, MD, Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Room FC7.2000, 1515 Holcombe Blvd., Unit 442, Houston, TX 77030, USA (cetatsui@mdanderson.org).

It is estimated that 5%–14% of cancer patients will develop symptomatic metastatic epidural spinal cord compression (ie, spinal metastasis) during the course of their disease, which can lead to devastating complications such as vertebral body fractures, intractable pain, loss of bowel and bladder function, and paralysis.[1] Treatment of spinal metastases is complex. Here, we describe a novel approach employing tumor treating fields (TTFields), the "fourth modality" of cancer treatment.[2]

TTFields is an alternating electric fields therapy FDA-approved as a therapeutic modality in glioblastoma and malignant pleural mesothelioma.[3] Its mechanism of action relates to the disruption of the mitotic spindle in rapidly dividing cancer cells through the dielectrophoretic effect.[4] Simulations of the distribution of TTFields strength in the intracranial,[5] thoracic,[6] abdominal,[7] and pelvic[8] compartments using finite element models that assign tissue-specific electric properties (ie, conductivity, permittivity) to the different tissue layers overlying the tumor. TTFields strength, and therefore efficacy, is inversely proportional to the tissue conductivity in the intervening tissues.[9] This has important implications for the effectiveness of tumor control, as the TTFields dose is proportional to the square of the TTFields strength (eg, 1 V/cm), multiplied by the duration of usage, and a higher dose corresponds to prolonged survival, akin to specific absorption rate in radiotherapy (eg, 1.1 mW/cm^3).[5,10] If the tumor is surrounded by tissues of lower conductivity (the skull in the case of glioblastoma), then the TTFields strength reaching the tumor is attenuated.[5] Conversely, if the lesion is surrounded by a more conductive layer (cerebrospinal fluid in the case of glioblastoma), then electric current can be shunted, and a greater TTFields strength is achieved in the tumor.[5] Taken together, it is possible that significant variability in tumor location, skull thickness, and the amount of cerebrospinal fluid (CSF) in the subarachnoid space may diminish the TTFields strength that can be achieved in a significant subset of patients with glioblastoma.

Spinal metastasis represents just one location of diffuse cancer involvement; therefore, therapeutic decision-making for local treatment depends on multiple factors including the presence of neurological deterioration, pain, comorbidities, surgical risks, convalescence, tissue healing, the need for interruption in chemotherapy, and expected patient survival. Complex anatomical relations between the vertebral column, spinal cord, nerves, vascular structures, and internal organs hinder surgery for spinal metastasis, often precluding complete resection with clean margins. It is demonstrated that surgery followed by radiation therapy provides superior functional and survival outcomes compared to radiation therapy alone.[1] The spinal cord radiation constraint is the most significant limiting factor for the application of this therapeutic modality. Multiple regimens of radiotherapy hypofractionation rely on exposing the tumor to different doses and fractions of radiation, ultimately respecting the spinal cord radiation tolerance. Once this threshold value has been reached, no further radiation therapy can be given due to the prohibitive risk of radiation-induced spinal cord necrosis. In such cases, further surgery usually provides a short-term benefit at the expense of lengthy recovery, postoperative decline in functional performance, and a significant subset of patients failing to thrive and not go on to receive further systemic treatment after surgery. Unlike radiotherapy, TTFields has no demonstrated tolerance limit.

The goal of surgery in the setting of metastatic epidural spinal cord compression is to decompress and stabilize the spine. Tumor involvement occurs as cancer grows in the epidural space, decreases the diameter of the spinal canal, distorts the dura mater, obliterates the CSF column, and ultimately compresses the spinal cord, thereby creating a vascular injury leading to loss of neurological function. The most common surgical approach to spinal metastasis consists of a laminectomy to access the spinal canal and expose the tumor. Complete tumor resection to decompress the spinal cord requires additional bone removal including the facet joints and pedicles, which disrupts the spinal stability and necessitates reconstruction with titanium pedicle screw constructs that are highly electrically conductive, that typically span two vertebral levels above and below the tumor site (Figure 1A, B). Thus,

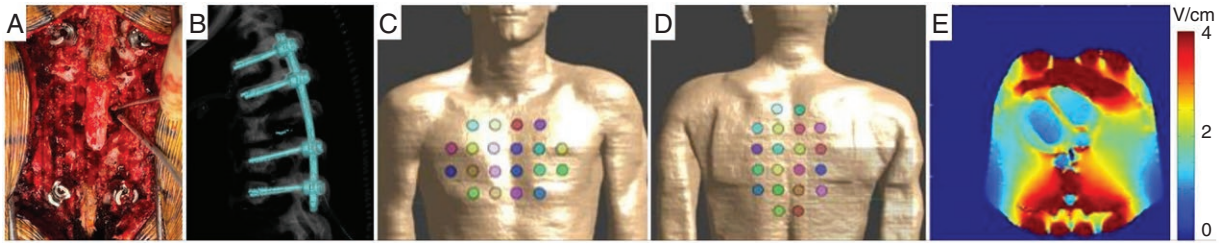

Figure 1. (A) Typical bony resection (laminectomy, facetectomy, and pediculectomy) used to decompress the spinal cord prior to resection of spinal metastasis. (B) Electrically conductive titanium hardware used to stabilize the spine postresection of the metastatic cancer. Computational modeling of tumor treating fields (TTFields) for the treatment of thoracic cancers using electrode transducer array placement on the (C) chest and (D) back. (E) The predicted electric field intensity in an axial slice through the lungs demonstrates that a high TTFields strength (>3 V/cm) can be achieved in the bone and paraspinal region. Figure 1C–E reproduced with permission from Figure 2A–C, respectively, of Bomzon et al.[6]

surgical disruption of the spinal anatomy in combination with the use of spinal implants would create a therapeutic opportunity for the use of TTFields, especially in the setting of radiation-refractory spinal metastasis.

Bomzon et al. described a computational model of the distribution of TTFields in a realistic human torso (Figure 1C–E).[6] Surgical management of thoracic spinal metastasis takes place within this region of the body. In this setting, the target is the dorsal bony surface of the vertebral body, where spinal metastasis growth must be suppressed to avoid postresection recurrence of the spinal cord compression. Given the low conductivity of bone and the fact that all layers overlying the residual vertebral body have lower impedance, we would anticipate a greater TTFields strength achieved in the spine. The simulation from reference[6] demonstrates that a TTFields strength of 3 V/cm can be achieved, which is more than 3-fold greater than what is achieved in the brain parenchyma in the context of TTFields therapy for glioblastoma. We theorize that astute placement of titanium hardware in the adjacent spinal levels postresection would have a profound shunting (or wave-guiding) effect on the electrical current from the surrounding muscle layer toward the vertebral bodies. This would in turn boost the TTFields strength achieved in the spinal levels adjacent to the resection cavity. We postulate that this could prevent the colonization of the adjacent vertebral bodies from tumors invading the Batson plexus or from hematogenous dissemination. At this stage, unpublished computational modeling that considers different degrees of bone removal and compares the utilization of electrically conductive titanium and relatively lower-conductivity carbon fiber—polyethyl-ether-ether-ketone spinal implants validates this concept.

The application of TTFields as an adjunct to surgery may offer a new therapeutic option for patients with radiation-refractory spinal metastasis who would otherwise not be considered surgical candidates due to the known short-interval recurrence after resection. In this context, TTFields could be used as a histology agnostic modality, given its effects being related to its frequency and the enhanced deposition of field strength in the resection cavity. We believe TTFields therapy could be initiated 2–3 weeks after postresection wound healing has been achieved. Under such a paradigm of postresection TTFields therapy, even frail patients who would not be able to tolerate chemotherapy in the early postoperative convalescence period could benefit from this noninvasive modality.

Keywords

spinal metastasis | tumor treating fields (TTFields) | waveguides

Funding

Funding for this work was provided by the American Association for Cancer Research (AACR)-Novocure Tumor Treating Fields (TTFields) Research Grant to C.E.T. and the AACR-Novocure Career Development Award for TTFields Research to C.B.P. C.B.P. is a McNair Scholar through the McNair Medical Institute at The Robert and Janice McNair Foundation.

Conflict of interest statement

C.E.T., K.W.C., and C.B.P. received consulting fees from Novocure, Ltd. CET receives research support from the American Association for Cancer Research (AACR)-Novocure Tumor Treating Fields (TTFields) Research Grant. C.B.P. receives research support from the AACR-Novocure Career Development Award for TTFields Research. K.W.C. and C.B.P. are co-inventors on patents with Novocure, Ltd. K.W.C. owns stocks in Novocure, Ltd.

Authorship statement

C.E.T., K.W.C., and C.B.P. were responsible for study conception, data collection, data analysis, interpretation of the results, and manuscript writing.

References

1. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet*. 2005;366(9486):643–648.
2. Arvind R, Chandana SR, Borad MJ, et al. Tumor-treating fields: a fourth modality in cancer treatment, new practice updates. *Crit Rev Oncol Hematol*. 2021;168:103535.
3. Shams S, Patel CB. Anti-cancer mechanisms of action of therapeutic alternating electric fields (tumor treating fields [TTFields]). *J Mol Cell Biol*. 2022;14(8):1–16.
4. Pohling C, Nguyen H, Chang E, et al. Current status of the preclinical evaluation of alternating electric fields as a form of cancer therapy. *Bioelectrochemistry*. 2023;149:108287.
5. Ballo MT, Urman N, Lavy-Shahaf G, et al. Correlation of tumor treating fields dosimetry to survival outcomes in newly diagnosed glioblastoma: a large-scale numerical simulation-based analysis of data from the phase 3 EF-14 randomized trial. *Int J Radiat Oncol Biol Phys*. 2019;104(5):1106–1113.
6. Bomzon Z, Urman N, Wenger C, et al. Modelling tumor treating fields for the treatment of lung-based tumors. *Annu Int Conf IEEE Eng Med Biol Soc*. 2015;2015:6888–6891.
7. Hershkovich HS, Urman N, Yesharim O, Naveh A, Bomzon Z'ev. The dielectric properties of skin and their influence on the delivery of tumor treating fields to the torso: a study combining in vivo measurements with numerical simulations. *Phys Med Biol*. 2019;64(18):185014.
8. Lok E, San P, White V, et al. Tumor treating fields for ovarian carcinoma: a modeling study. *Adv Radiat Oncol*. 2021;6(4):100716.
9. Nguyen H, Schubert KE, Chang E, et al. Electric field distributions in realistic 3D rat head models during alternating electric field (AEF) therapy: a computational study. *Phys Med Biol*. 2023;68(20):1–14.
10. Moser JC, Salvador E, Deniz K, et al. The mechanisms of action of tumor treating fields. *Cancer Res*. 2022;82(20):3650–3658.