Advances in Radiation Oncology (2024) 9, 101316

advances in radiation oncology

www.advancesradonc.org

Critical Review

Body Fluids Modulate Propagation of Tumor Treating Fields

Eric T. Wong, MD, MA,* and Edwin Lok, MS

Division of Hematology/Oncology, Rhode Island Hospital & Lifespan Cancer Center, Warren Alpert Medical School of Brown University, Providence, Rhode Island

Received 17 April 2023; accepted 13 July 2023

Abstract

Tumor treating fields (TTFields) are nonionizing alternating electric fields that have anticancer properties. After the initial approval for use in patients with recurrent glioblastoma in 2011 and newly diagnosed glioblastomas in 2015, they are now being tested in those with advanced lung cancer, ovarian carcinoma, and pancreatic cancer. Unlike ionizing radiation therapy, TTFields have nonlinear propagation characteristics; therefore, it is difficult for clinicians to recognize intuitively the location where these fields have the most impact. However, finite element analysis offers a means of delineating TTFields in the human body. Our analyses in the brain, pelvis, and thorax revealed that cerebrospinal fluid, edema, urine, ascites, pleural fluid, and necrotic core within a tumor greatly influence their distribution within these body cavities. Our observations thus provided a unified framework on the role of these compartmentalized fluids in influencing the propagation of TTFields.

Introduction

Tumor treating fields (TTFields) are lower-intensity, intermediate-frequency (100-500 kHz), nonionizing, alternating electric fields that have anticancer properties. They are delivered by the NovoTTF-100A or NovoTTF-200A device (Optune, Novocure Ltd, Haifa, Israel) via insulated transducer arrays applied onto the scalp or body surface. These electric fields penetrate the brain, thorax, abdomen, or pelvis and inhibit the growth and proliferation of tumor cells by interfering with mitosis, triggering autophagy, disrupting cellular membranes, and/or activating antitumor immunity.[1-4] Results from a randomized phase 3 clinical trial revealed that patients with newly diagnosed glioblastoma treated with TTFields plus temozolomide had longer progression-free survival and overall survival compared with those treated with temozolomide alone when the treatment was applied after initial radiation therapy and concomitant temozolomide.[5] Toxicity from TTFields was acceptable and consisted primarily of scalp irritation.[5] More importantly, this positive survival benefit was the first validation of the observed preclinical anticancer effect, and it paved the way for the application of this technology to other malignancies.

There is still a large knowledge gap in our understanding of the dosimetry of TTFields. This is because TTFields have nonlinear propagation characteristics. Unlike high-energy ionizing radiation therapy in which dose to the target can be calculated volumetrically based on the beam output characteristics, beam collimation geometry, and distance from the radiation source, dosimetry of TTFields can only be approximated by finite element analysis. This is because the lower energy alternating electric fields can

Sources of support: This research is made possible by the Musella Foundation.

Research data may be shared upon request to the corresponding author.

*Corresponding author: Eric T. Wong, MD, MA; email: ewong1@lifespan.org

https://doi.org/10.1016/j.adro.2023.101316

be greatly affected—either attenuated or summated—by the local geometry at the interface between adjacent tissues and differences in their electric conductivities. As a result, propagation of TTFields from the emitting transducers on the scalp or body surface to the tumor target could be intensified or attenuated at the gross tumor volume (GTV) or clinical target volume (CTV). Furthermore, TTFields propagate at a much lower frequency than ionizing radiation, in the range of 100 to 500 $\times$ 10^3 versus 10^{19} Hz, respectively. The time component, which influences the amount of energy deposition at the target, has a greater impact on TTFields than ionizing radiation therapy.[6] Therefore, identifying factors that influence electric field propagation in the head or body can potentially improve the treatment efficacy of TTFields.

Highly Conductive Fluids Determine the Flow of Electric Fields

The electric conductivity of a tissue or organ is determined by its composition of fluid and solute, and this will determine the extent of electric field propagation. In the frequency range of TTFields, conductivity (the ability for a medium to pass charges) exerts a greater influence on electric field distribution than relative permittivity (the ability of a medium to retain charges in an electric field).[7] Since fluid-filled cavities such as the bladder, cerebral ventricles, edematous regions, and pleural cavities are highly conductive, they all have a potential to alter the distribution of electric fields. In contrast, cavities that contain nonconductive air have low conductivity; therefore, the electric fields in these regions are often stronger in magnitude. Examples of these regions include bronchi and certain regions of the lungs as well as gas-filled colon, esophagus, and stomach. Thus, knowing the conductivity of the tissue or organ of interest will help estimate the penetration of TTFields and the distribution of these fields in the adjacent tissue or organ. Although this cannot be done analytically, it can be approximated using finite element analysis.[8]

A tissue or organ and its adjacent parenchyma are anisotropic due to their differences in electric properties. This anisotropy will influence the propagation of the electric fields. For example, if a fluid containing cavity is located adjacent to tissues that are less conductive, the electric field lines will concentrate at the adjacent tissues leading to a higher field intensity. This was first observed by our research team when a modeled glioblastoma was located within the right parietal white matter between the transducer arrays on the scalp surface and the lateral ventricle.[9] High intensity TTFields were observed between the tumor and the right lateral ventricle (Fig. 1).[9] Similar phenomenon was also observed at the genu of the corpus callosum, which is situated above the lateral ventricles.[10]

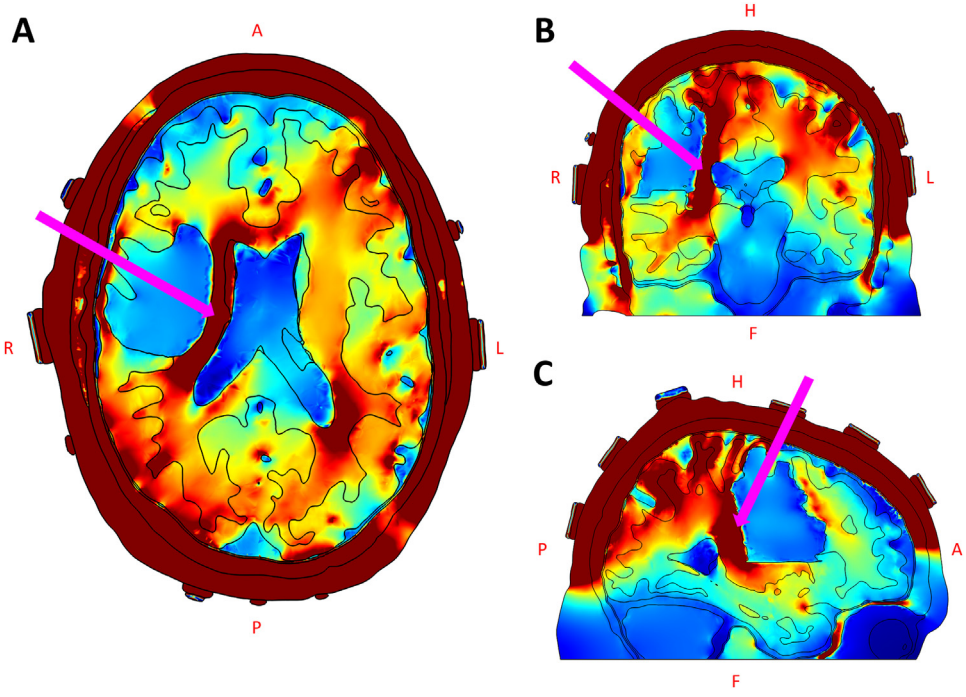

Figure 1 High intensity of tumor treating fields between the tumor and the lateral ventricle. High electric field strength is seen between the medial margin of the glioblastoma gross tumor volume and the right lateral ventricle in the (A) axial, (B) coronal, and (C) sagittal views. High intensity is also noted in the genu of the corpus callosum extending to the contralateral left frontal and left parietal white matter.

In contrast, the amount of cerebrospinal fluid within the subarachnoid space on the surface of the brain may attenuate the perpendicular penetration of TTFields into the brain from the scalp surface secondary to tangential dispersion. We performed a sensitivity analysis by altering the thickness of cerebrospinal fluid and found that a thicker fluid layer decreased TTFields at the GTV in the brain.[10] Additionally, the presence of necrosis within the glioblastoma may help to attract TTFields into the GTV due to higher conductivity in the necrotic fluid.[10] For example, in a patient with a solitary brain metastasis, it was shown that the presence of a necrotic core increased the electric field strength within the GTV by at least 37.5%.[11] Therefore, propagation of TTFields in the brain really depends on the aggregate effects of conductive fluids in the subarachnoid space, bilateral ventricles, edema around the tumor, and the necrotic core when present within the tumor (Fig. 1).

Current Density and Electric Fields Are Related Quantities in TTFields

Current density is the amount of charge flowing through a cross sectional area. The magnitude is proportional to both charge density and the applied electric field, whereas directionality is indicated by a vector denoting the direction of current flow.[12] Current density is an important measurable quantity in treatment planning because it can be influenced by a number of physical and biological components. First, human tissues can absorb electromagnetic fields and induce conduction and displacement currents. This interaction depends on a number of factors, including the frequency of electric fields, dielectric properties of the biologic tissue at a particular frequency, and tissue geometry.[13-16] Second, because current density is directly related to the electric field by electric conductivity according to Ohm's Law, the conductivity can influence the specific absorption rate (SAR) of biological tissues in the presence of a varying electric field.[17] For TTFields, SAR is the rate of energy absorbed by a mass of biological tissue when exposed to radiofrequency electromagnetic fields. Its measure is related to joule heating or stimulation of excitable biological tissues such as neurons and muscles by these radiofrequency fields.[17] Therefore, the electric conductivity is a critical parameter because it heavily influences the ability of TTFields penetrating a tumor target, which can be observed by the distribution of current density.

Our observations were corroborated by Korshoej et al in their modeling of TTFields.[18,19] Using magnetic resonance imaging data of a human head, they observed differences in electric field distribution when conductivity was modeled anisotropically versus isotropically, and this difference was significantly greater for the left-right array orientation compared with the anterior-posterior one.[18] The degree of fractional anisotropy can be quantified by the diffusion tensor of water, and they found that resection of a tumor actually increases the fractional anisotropy of the brain adjacent to the resection cavity by at least 37%.[19] They hypothesized that this is due to increased shunting of current from highly conductive cerebrospinal fluid in the resection cavity, which results in a higher electric field when the resection site is perpendicular to the applied TTFields. However, additional studies need to be performed to determine other contributory factors, such as array positioning, tumor geometry, and the radial distance of the tumor to the scalp surface.

The extent of anisotropy can be assessed or quantified by diffusion tensor on magnetic resonance imaging.[20] Tractography and connectome analysis, which exploits difference in water diffusion in the axial and radial directions of white matter tracts, are important tools for the preoperative planning of brain tumor resection.[21] The same algorithm can be used to quantify the extent of conductivity anisotropy in the brain. As shown previously, changes in fractional anisotropy could alter the distribution of TTFields at the GTV or CTV, and these changes cannot be solved analytically but can only be approximately by finite element analysis.[19]

Cerebral Edema Influences the Distribution of TTFields in the Brain

Our prior investigation in subjects with brain metastases revealed that increased electric conductivity of cerebral edema attenuates TTFields, SAR, and current density at the tumor target.[11] Specifically, the plan quality metrics increased linearly when the edema-to-GTV ratio decreased, whereas the plan quality metrics decreased vice versa when the edema-to-GTV ratio increased (Fig. 2).[11] However, cerebral edema may not have as much of an impact on glioblastoma compared with brain metastasis. Glas et al performed finite element analysis of patients with newly diagnosed glioblastoma enrolled in the EF-14 trial and showed that distant progression was more frequently observed among those treated with TTFields than the control group.[22] This finding suggests that TTFields exert local tumor control; therefore, distant progression is the predominant recurrence pattern in these patients. However, the extent of peritumoral edema was not analyzed. More than half of the enrolled subjects had gross total resection of their glioblastoma; therefore, they are expected to have a limited amount of cerebral edema.[22] Another possibility in causing the phenomenon of distant progression may be due to the invasive property of glioblastoma where edema and infiltrative tumor cells are intertwined along axonal or neuritic processes. Because the highly conductive edema is comingled with infiltrative tumor cells, the alternating

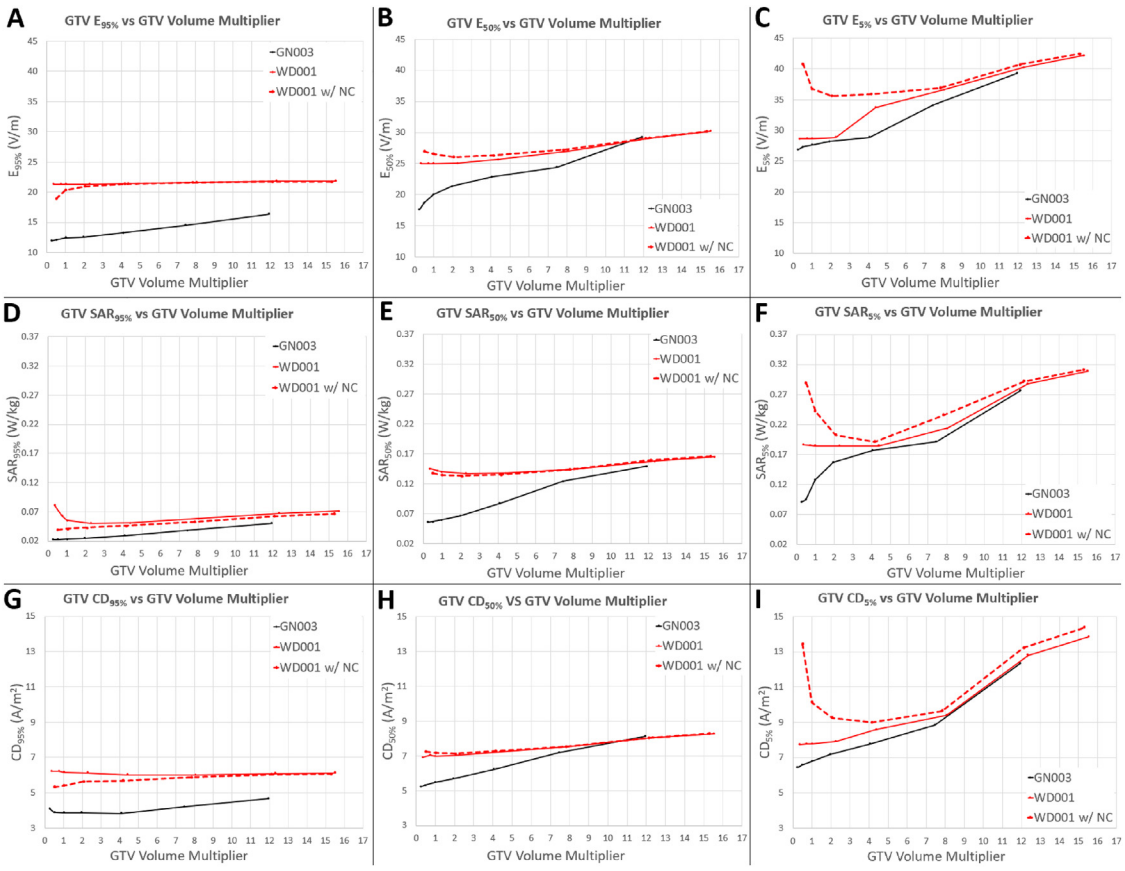

Figure 2 Plan quality metrics for GTV as a function of GTV-to-edema volume. The relationship for GN003, WD001 without necrotic core, and WD001 with necrotic core for (A-C) $E_{95\%}$, $E_{50\%}$, and $E_{5\%}$; (D-F) $SAR_{95\%}$, $SAR_{50\%}$, and $SAR_{5\%}$; and (G-I) $CD_{95\%}$, $CD_{50\%}$, and $CD_{5\%}$ (previously published in Lok et al).[29] *Abbreviations:* CD = current density; E = electric field; GTV = gross tumor volume; NC = necrotic core; SAR = specific absorption rate.

electric fields attracted to the edematous regions probably increases local field absorption, which could disrupt tumor cells as they undergo mitoses resulting in impaired cytokinesis and eventual cell death.[2]

There are at least 4 types of cerebral edema including vasogenic, cytotoxic, interstitial, and osmotic edemas.[23] First, vasogenic edema is most commonly associated with tumors in the brain due to the hyperpermeable cerebral vasculatures.[24] As a result, solutes and osmolytes from serum leak into the brain parenchyma, which secondarily draws fluids into the same area, resulting in cerebral edema, mass effect, or both.[24] The downstream neuronal dysfunctions include localized seizure, vascular compression, weakness, language impairment, and/or vision loss as well as generalized multifocal seizures, syndrome of inappropriate secretion of antidiuretic hormone, neurocognitive deficits involving multiple cognitive domains, or a combination of these deficits. Second, cytotoxic edema is a disorder of bioenergetics, and this is associated with loss of ATPase function resulting in cellular edema due to inability of the cell to maintain electrolyte balance;[25] cellular swelling is the principal consequence. Vascular compromise is the leading cause of cytotoxic cerebral edema.[26] Third, interstitial edema is associated with blockage of cerebrospinal outflow as in obstructive hydrocephalus. The cerebrospinal fluid therefore permeates via interstitial spaces within the brain parenchyma into the glymphatics system, cerebral veins, or both.[27] Lastly, hyperosmolality or hyposmolality in the brain, as in hypernatremia or hyponatremia, can secondarily change the fluid dynamics.[28] Because water is freely permeable inside the brain, an increase or decrease in osmolality secondary to alterations in osmolyte composition will either draw or remove fluid from the brain parenchyma, affecting both neuronal and axonal functions. Collectively, any one of these well-known mechanisms can change the fluid content in the brain and these changes may affect TTFields propagation in patients with brain tumors.

TTFields have different propagation characteristics depending on the type of cerebral edema in the brain. First, interstitial and osmotic edemas most likely have the highest conductivity and are therefore modeled with a conductivity value similar to cerebrospinal fluid. This is appropriate because these types of edemas predominantly have high fluid content. In contrast, cytotoxic edema is a result of cellular expansion and therefore this pushes out

fluid from the interstitial space. Therefore, this type of edema has a conductivity value more akin to gray matter. Lastly, vasogenic edema is due to leakage of solutes and electrolytes from hyperpermeable tumor vasculature. This type of edema is similar to blood and therefore has a conductivity value between cytotoxic edema and interstitial/osmotic edema. Using these parameters, our modeling study revealed that the electric field more than doubled when the edema type was changed from vasogenic to cytotoxic edema, whereas it decreased by more than half when the edema type was changed from vasogenic to interstitial edema.[11] In glioblastoma or other types of malignant gliomas in the brain, there is probably a mixture of different types of cerebral edema, and identifying the range of variance in a population is important.

Urine in Bladder Changes the Distribution of TTFields Within the Pelvis

The pelvis has a number of fluid-filled spaces that influence the propagation of TTFields. These include the bladder and the peritoneal cavity. Our modeling study has shown a number of important observations. First, urine in the bladder is highly conductive, and this medium alters the directionality of field vectors (Fig. 3). Our prior modeling analysis revealed that the bladder had the highest current density and the lowest electric field strength compared with other organs within the abdomen or pelvis.[29] This finding is corroborated by Voloshin et al who also show lower electric field strength in the bladder compared with other pelvic organs.[30] When the electric conductivity of the bladder was altered in a sensitivity analysis, large changes in electric field strength within the tumor target were observed, suggesting that the fluid content within the bladder modulates the electric field lines traversing the pelvis.[29] However, it is still unclear how the aggregate effect, based on the relative positions of the transducer electrodes, bladder, and tumor, influences TTFields at the tumor volume. For example, if the tumor is situated in the path of TTFields from the emitting electrodes on the body surface and the centrally located bladder, will the tumor volume encounter an increase in electric field? Or, if the tumor is located behind the bladder, will the electric field at the tumor volume be attenuated? Further modeling investigations will need to be done in order to address these questions. Second, the peritoneal cavity is a potential space that can be filled with body fluid. The consistency of this fluid can be a transudate or a denser exudate with higher protein and cellular content from peritoneal carcinomatosis, and this transudate or exudate may influence the propagation of TTFields depending on their respective electric conductivities. Therefore, in our patient with malignant ascites, we delineated the entire pelvic cavity as the CTV and observed that current density permeated the entire cavity

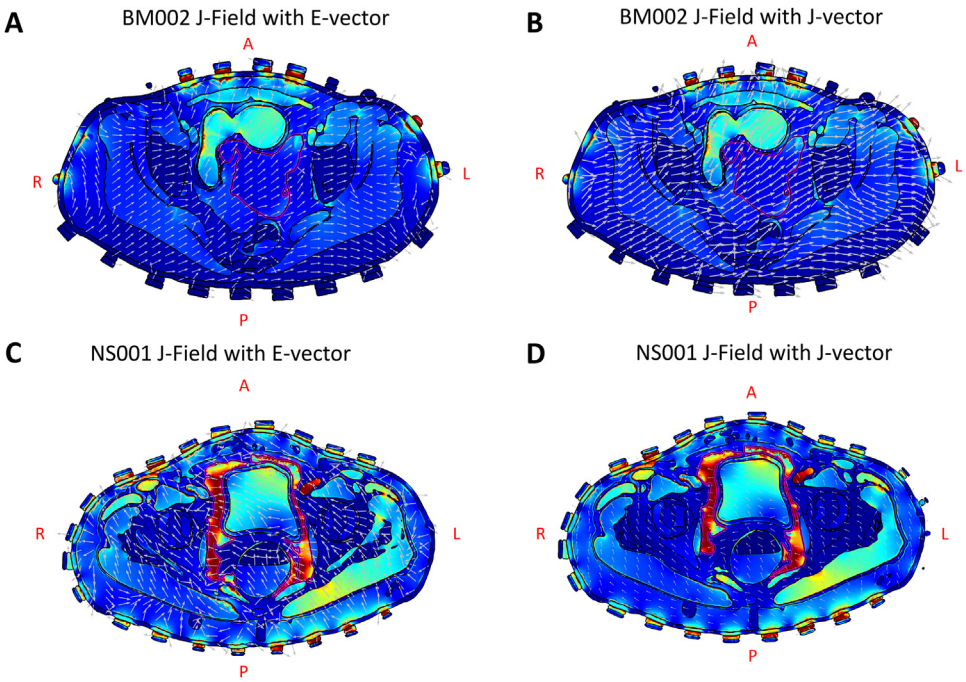

Figure 3 Current density map of 2 patients with ovarian carcinoma as influenced by the bladder in the pelvis. Finite element modeling of a patient with bilateral ovarian carcinomas reveals (A) electric field and (B) current density vectors pointing toward the bladder. Finite element modeling of another patient with malignant ascites from ovarian carcinoma also shows high intensity (C) electric field and (D) current density vectors pointing toward the bladder. *Abbreviations:* A = anterior; L = left; P = posterior; R = right.

while SAR at the peritoneal wall was high.[29] Collectively, these fluids in the bladder and peritoneal cavity determine the flow of electric fields and the subsequent energy deposition in the CTV.

Additionally, bladder volume may account for potentially drastic changes in TTFields distribution throughout the day as the patient voids or retains urine. For example, in patients with pelvic cancer, bladder volume differences between an empty and full one may vary between 20 cc and 650 cc according to several studies on bladder volume effects on radiation dose to various critical structures in the pelvis.[31-33] This volume is important for daily fractionated beam delivery to keep the dose tolerance of bladder, bowel, and other organs at risk within acceptable criteria. Therefore, it may also be valid to question: to what extent does bladder volume affects the directionality and magnitude of TTFields?

The relative location of the tumor target and transducer electrodes is relevant for treatment planning. If the CTV is located away from the centroid of the abdominal or pelvic cavity, then rotating the array positions on the body surface may improve TTFields delivery. For example, in our analysis, rotating the arrays from 0° to 50° clockwise from the surface increased the electric field, SAR, and current density to an eccentrically positioned lymph node by >75%, >200%, and >100%, respectively.[29]

Pleural Fluid Alters the Penetration of TTFields Into the Thorax

In the thorax, the pleura is a fluid-filled cavity that can potentially modulate the propagation of TTFields. In our thoracic modeling study, tumors that were not attached to the pleura had significantly reduced TTFields.[34] Furthermore, successive volume expansion of the GTV increased TTFields intensity, particularly when the expanded volume makes partial contact with the pleura.[34] High field intensity emanating from the surface electrodes on the chest, traversing the pleura and the lung parenchyma, and penetrating the GTV and CTV were also noted by Bomzon et al.[35] Together, these findings indicate that lung tumors that are flushed against the pleura can potentially receive a higher dose of TTFields. In addition, we performed a sensitivity analysis by changing the conductivity of the margin around the GTV, or the difference between CTV and GTV, and noted that the electric property of this margin can alter the amount of energy deposited at the target. Similar to our observation in the abdomen and pelvis, SAR in the GTV, CTV, and the margin between the GTV and CTV also increased up to a maximum and then attenuated as the conductivity increased further.[29,34] Therefore, the conductivity between the thoracic target and the pleura is an important determinant of TTFields intensity.

Summarizing the Influence of Body Fluids on Propagation of TTFields

The electric conductivity of a tumor is also an important determinant of energy deposition by TTFields. Our sensitivity analyses in the brain, thorax as well as abdomen and pelvis revealed that as the conductivity of the CTV increases, the electric field strength and current density behaved in an inverse manner.[11,29,34] For example, increased conductivity leads to an attenuation in electric field strength and a surge in current density, or vice versa, indicating that as the conductivity of the CTV increases, TTFields will incur an increase in tangential vector component of the field and decrease in normal vector component, at the surface boundary of the tumor (Figs. 4-6). However, it should be noted that this phenomenon is highly dependent on not only the electric conductivity of the region of interest (ROI) but also on its surrounding tissue or space. It can be observed in Figs. 5 and 6 that when both the intermediate region surrounding the circular ROI have the same conductivities, the field strength is relatively uniform in magnitude over the entire region between the energized electrodes above and below. Additionally, the direction of the streamlines representing the electric field lines and current density field lines, respectively, are also relatively uniform in direction. However, when the conductivity of the circular ROI is below that of its surrounding, the vector fields tend to bow inwards toward the midline of the circular region between both electrodes. Conversely, when the conductivity of the circular ROI is greater than its surrounding, the vector field tends to bow outwards, away from the midline. In fact, the current density field lines tend to have a much higher tangential component due to an increase in charge flow along the surface of the circular ROI. This is consistent with Gauss' Law, which describes the electric field at the center of a perfectly conducting sphere is 0. This can also be expressed in Ohm's law:

$$\vec{J} = \sigma\vec{E} \text{ or } \vec{E} = \frac{\vec{J}}{\sigma}$$

where $\vec{J}$ is the current density, σ is the electric conductivity, and $\vec{E}$ is the electric field. A perfectly conducting material indicates that $\sigma \to \infty$, and the limit then becomes $\vec{E} = \lim_{\sigma \to \infty} \frac{1}{\sigma}\vec{J} = 0$. Conservation of energy shall be preserved, where $\vec{J}$ should be bounded in order for the limit to be true.

In contrast, the rate of energy deposited at the CTV behaved differently. SAR increased up to a maximum and then attenuated as the conductivity increased further. Although the precise mechanism is unclear due to the plethora of tissue heterogeneities in terms of shape, dimensions, and physical characteristics, this phenomenon may be a result of loss of resistivity in the CTV, the relative difference in conductivity between the CTV and the adjacent tissues, or both. In either case, TTFields may

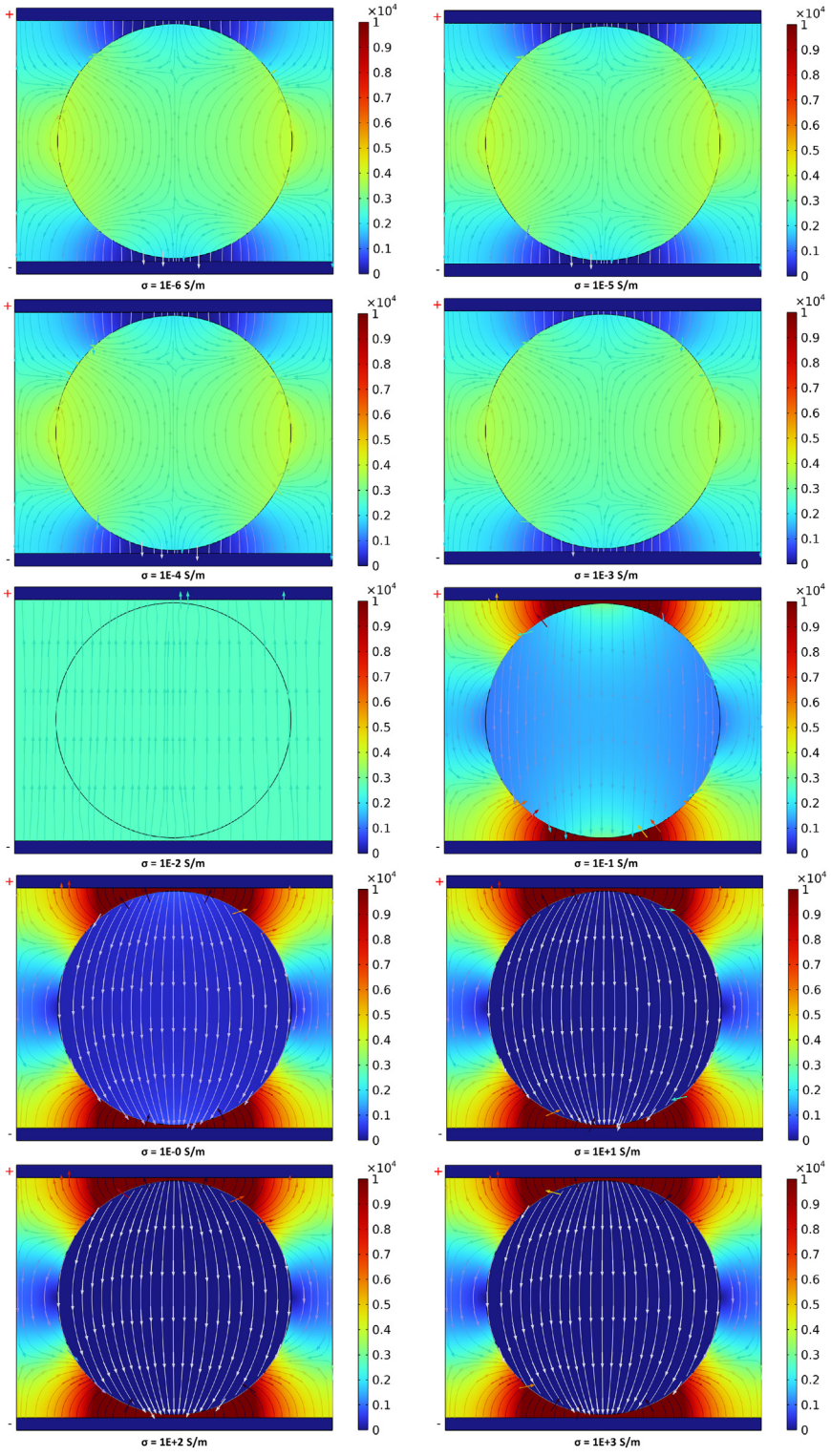

Figure 4 Electric field with electric field vector field analysis of a representative circular cross section of a spherical tumor. The tumor sphere is embedded within an environment with a conductivity value of 0.01 S/m. By varying the conductivity of the tumor sphere at lower conductivity values from 0.000001 S/m to 0.00001 S/m, 0.0001 S/m, and 0.001 S/m, the electric field vectors are seen flowing into and out of the sphere at various points. However, when the conductivity values are near the value in the surrounding environment at 0.01 S/m, there is no net flow of electric field vectors in or out of the sphere. Further increasing the conductivity of the sphere from 0.1 S/m to 1 S/m, 10 S/m, 100 S/m, and 1000 S/m resulted in a more intense electric field vector flow from cathode to anode.

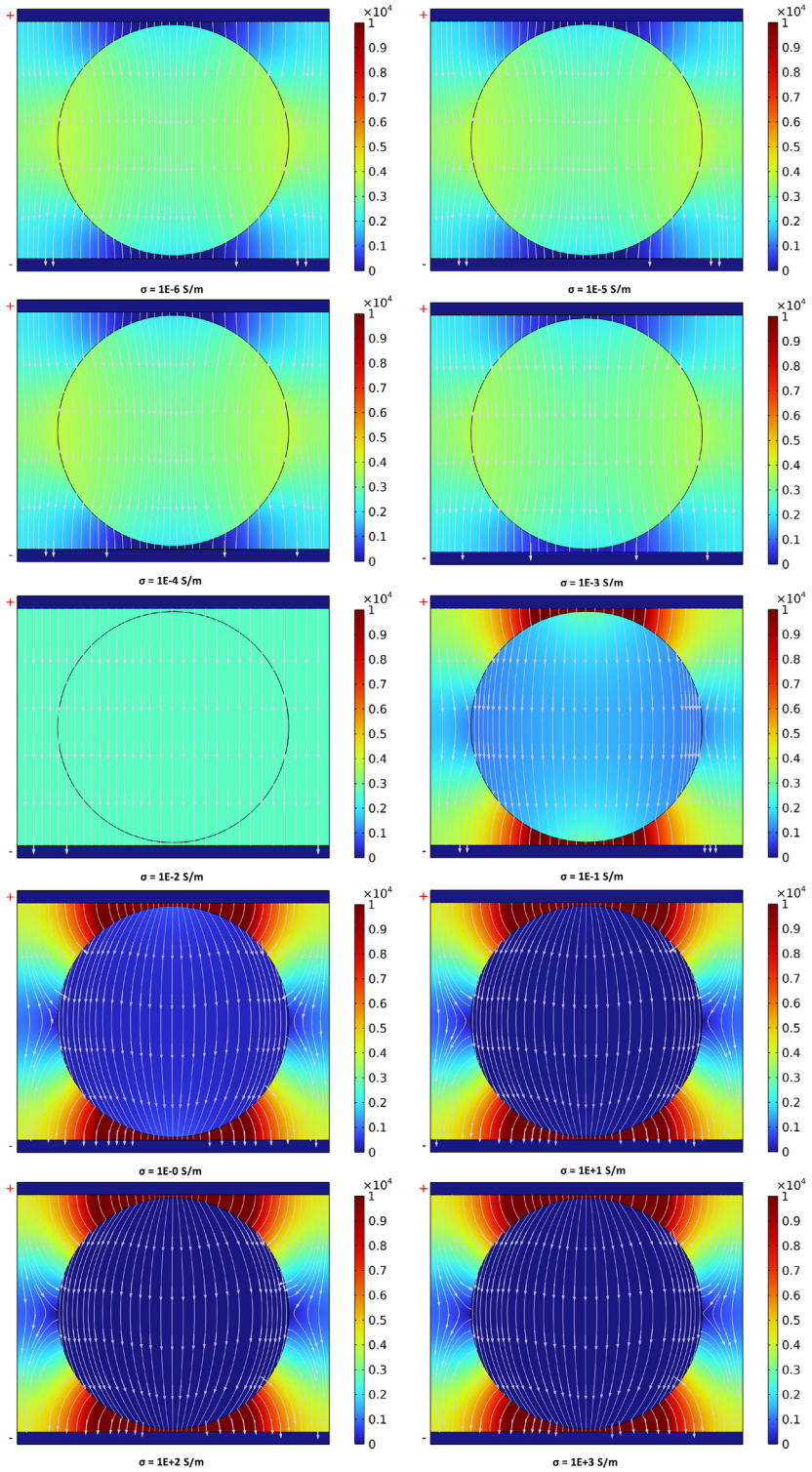

Figure 5 Electric field with current density vector field analysis of a representative circular cross section of a spherical tumor. The tumor sphere is embedded within an environment with a conductivity value of 0.01 S/m. By varying the conductivity of the tumor sphere at lower conductivity values from 0.000001 S/m to 0.00001 S/m, 0.0001 S/m, and 0.001 S/m, the current density vectors are seen flowing pass the sphere from cathode to anode with field lines bowing less inwards as the conductivity increases. However, when the conductivity value is set above the value to the surrounding environment at 0.1 S/m, increasing the conductivity from 0.1 S/m to 1 S/m, 10 S/m, 100 S/m, and 1000 S/m revealed that increased electric field magnitude is now seen at the junction between the sphere and the cathode or anode while the electric field within the circular cross section of the tumor exhibits little to no magnitude with field lines bowing outwards.

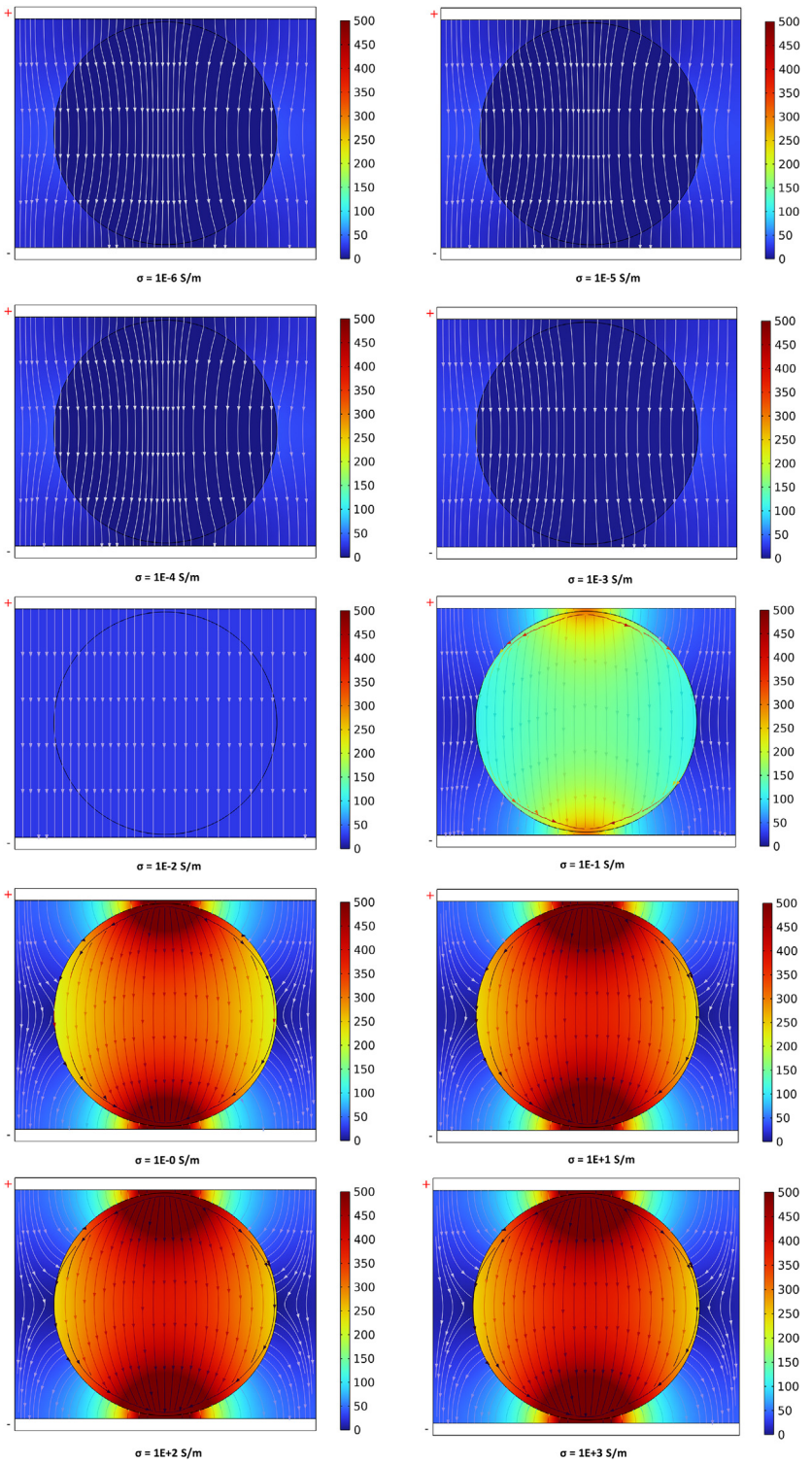

Figure 6 Current density with current density vector field analysis of a representative circular cross section of a spherical tumor. The tumor sphere is embedded within an environment with a conductivity value of 0.01 S/m. By varying the conductivity of the tumor sphere at lower conductivity values from 0.000001 S/m to 0.00001 S/m, 0.0001 S/m, 0.001 S/m, and 0.01 S/m, the current density vectors are seen essentially flowing past the sphere from cathode to anode. However, when the conductivity value is set above the value to the surrounding environment at 0.1 S/m, tangential current vectors first appear on the surface of the sphere. Further increasing the conductivity of the sphere from 1 S/m to 10 S/m, 100 S/m, and 1000 S/m resulted in a more intense tangential current density vector flow on the surface of the tumor sphere as well as magnitude within the circular region of interest.

begin to travel more along the surface of the CTV rather than through it, leaving much less energy deposited within. Therefore, TTFields at the CTV or GTV depends not only on the electric conductivity of the tumor but also its surroundings, particularly when the surrounding has highly conductive fluids.

Conclusion

TTFields have nonlinear propagation characteristics, and their presence or absence within a patient's body cavity are difficult to recognize intuitively. Finite element modeling offers clinicians a means of visualizing the conditions where TTFields have the most impact. Our past analyses of the brain, pelvis, and thorax revealed that fluids within these cavities greatly influence their propagation characteristics. Specifically, the cerebrospinal fluid within the ventricles draws in TTFields radially toward the center of brain whereas the cerebrospinal fluid on the surface disperses them tangentially. The liquid consistency of the necrotic core helps to attract TTFields toward the glioblastoma GTV. In the pelvis, urine in the bladder and fluid within the peritoneal cavity can determine the flow of electric fields and current density and consequently influence the intensity of TTFields delivered to the ovarian carcinoma CTV. Furthermore, pleural fluid on the surface of the thorax can help guide the transmittal of TTFields into the lungs, particularly when the lung cancer CTV is located flush against the pleura. Our observations provide a unified framework on the role of these fluids in influencing the propagation of TTFields within the human body.

Disclosures

Eric T. Wong received research fundings from AstraZeneca, Five Prime Therapeutics, Immunocellular Therapeutics, Merck, Northwest Biotherapeutics, Novocure, Oblato, Orbus, Pfizer, and Vascular Biogenics. Eric T. Wong also served as consultant and advisory board member for Gtree, Novocure, Orbus, Sumitomo Dainippon Pharma Oncology, and ZaiLab. Eric T. Wong participated on a data safety monitoring board for Turning Point Therapeutics (now Bristol Myers Squibb), and OptimalTTF phase 2 trial (investigator initiated). Eric T. Wong and Edwin Lok have United States patent application No. 16/335,920 "System and Methods For Cancer Treatment Using Alternating Electric Fields." Edwin Lok received payment to perform clinical duties at US Oncology.

References

1. Rominiyi O, Vanderlinden A, Clenton SJ, Bridgewater C, Al-Tamimi Y, Collis SJ. Tumour treating fields therapy for glioblastoma: current advances and future directions. *Br J Cancer*. 2021;124:697-709.
2. Gera N, Yang A, Holtzman TS, Lee SX, Wong ET, Swanson KD. Tumor treating fields perturb the localization of septins and cause aberrant mitotic exit. *PLoS One*. 2015;10: e0125269.
3. Chen D, Le SB, Hutchinson TE, et al. Tumor treating fields dually activate STING and AIM2 inflammasomes to induce adjuvant immunity in glioblastoma. *J Clin Invest*. 2022;132: e149258.
4. Jones TH, Song JW, Abushahin L. Tumor treating fields: An emerging treatment modality for thoracic and abdominal cavity cancers. *Transl Oncol*. 2022;15: 101296.
5. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide versus maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. *JAMA*. 2017;318:2306-2316.
6. Breckenkamp J, Berg G, Blettner M. Biological effects on human health due to radiofrequency/microwave exposure: A synopsis of cohort studies. *Radiat Environ Biophys*. 2003;42:141-154.
7. Lok E, Swanson KD, Wong ET. Tumor treating fields therapy device for glioblastoma: Physics and clinical practice considerations. *Expert Rev Med Devices*. 2015;12:717-726.
8. Timmons JJ, Lok E, San P, Bui K, Wong ET. End-to-end workflow for finite element analysis of tumor treating fields in glioblastomas. *Phys Med Biol*. 2017;62:8264-8282.
9. Lok E, Hua V, Wong ET. Computed modeling of alternating electric fields therapy for recurrent glioblastoma. *Cancer Med*. 2015;4:1697-1699.
10. Lok E, San P, Hua V, Phung M, Wong ET. Analysis of physical characteristics of tumor treating fields for human glioblastoma. *Cancer Med*. 2017;6:1286-1300.
11. Lok E, Clark M, Liang O, Malik T, Koo S, Wong ET. Modulation of tumor-treating fields by cerebral edema from brain tumors. *Adv Radiat Oncol*. 2022;8: 101046.
12. Shrivastava BD, Barde R, Mishra A, Phadke S. Interaction of electromagnetic fields and biological tissues. *J Phys Conf Ser*. 2014;534: 012062.
13. Gabriel C, Gabriel S, Corthout E. The dielectric properties of biological tissues: I. Literature survey. *Phys Med Biol*. 1996;41:2231-2249.
14. Gabriel C, Peyman A, Grant EH. Electrical conductivity of tissue at frequencies below 1 MHz. *Phys Med Biol*. 2009;54:4863-4878.
15. Michaelson SM, Lin JC. *Biological effects and health implications of radiofrequency radiation*. New York, NY: Springer Science & Business Media; 1987.
16. Singh S, Tyagi A, Vidhani B. Physics of absorption and generation of electromagnetic radiation. In: Wang L, ed. *Electromagnetic wave propagation for industry and biomedical applications*. London, UK: IntechOpen; 2022:81-108.
17. Osaigbovo IA, Isabona J. Current density and SAR analysis of biological tissues due to radiant electromagnetic waves from base station antennas. *Int J Adv Res Phys Sci*. 2018;5:15-23.
18. Korshoej AR, Hansen FL, Thielscher A, von Oettingen GB, Sørensen JCH. Impact of tumor position, conductivity distribution and tissue homogeneity on the distribution of tumor treating fields in a human brain: A computer modeling study. *PLoS One*. 2017;12: e0179214.
19. Korshoej AR, Thielscher A. Estimating the intensity and anisotropy of tumor treating fields using singular value decomposition. Towards a more comprehensive estimation of anti-tumor efficacy. *Paper presented at: 40th Annual International Conference of the IEEE Engineering in Medicine and Biological Society*. Honolulu, HI; July 17-21, 2018.
20. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson*. 2011;213:560-570.
21. Henderson F, Abdullah KG, Verma R, Brem S. Tractography and the connectome in neurosurgical treatment of gliomas: The premise, the progress, and the potential. *Neurosurg Focus*. 2020;48:E6.

22. Glas M, Ballo MT, Bomzon Z, et al. The impact of tumor treating fields on glioblastoma progression patterns. *Int J Radiat Oncol Biol Phys*. 2022;112:1269-1278.
23. Dalby T, Wohl E, Dinsmore M, Unger Z, Chowdhury T, Venkatraghavan L. Pathophysiology of cerebral edema - A comprehensive review. *J Neuroanaesth Crit Care*. 2021;8:163-172.
24. Kaal EC, Vecht CJ. The management of brain edema in brain tumors. *Curr Opin Oncol*. 2004;16:593-600.
25. Yang GY, Chen SF, Kinouchi H, Chan PH, Weinstein PR. Edema, cation content, and ATPase activity after middle cerebral artery occlusion in rats. *Stroke*. 1992;23:1331-1336.
26. Liebeskind DS, Jüttler E, Shapovalov Y, Yegin A, Landen J, Jauch EC. Cerebral edema associated with large hemispheric infarction. *Stroke*. 2019;50:2619-2625.
27. Brinker T, Stopa E, Morrison J, Klinge P. A new look at cerebrospinal fluid circulation. *Fluid Barriers CNS*. 2014;11:10.
28. Verbalis JG. Brain volume regulation in response to changes in osmolality. *Neuroscience*. 2010;168:862-870.
29. Lok E, San P, White V, et al. Tumor treating fields for ovarian carcinoma: A modeling study. *Adv Radiat Oncol*. 2021;6: 100716.
30. Voloshin T, Munster M, Blatt R, et al. Alternating electric fields (TTFields) in combination with paclitaxel are therapeutically effective against ovarian cancer cells in vitro and in vivo. *Int J Cancer*. 2016;139:2850-2858.
31. Chen VE, Gillespie EF, Manger RP, et al. The impact of daily bladder filling on small bowel dose for intensity modulated radiation therapy for cervical cancer. *Med Dosim*. 2019;44:102-106.
32. Moiseenko V, Liu M, Kristensen S, Gelowitz G, Berthelet E. Effect of bladder filling on doses to prostate and organs at risk: A treatment planning study. *J Appl Clin Med Phys*. 2006;8:55-68.
33. Pinkawa M, Asadpour B, Siluschek J, et al. Bladder extension variability during pelvic external beam radiotherapy with a full or empty bladder. *Radiother Oncol*. 2007;83:163-167.
34. Lok E, Liang O, Malik T, Wong ET. Computational analysis of tumor treating fields for non-small cell lung cancer in full thoracic models. *Adv Radiat Oncol*. 2023;8: 101203.
35. Bomzon Z, Urman N, Wenger C, et al. Modelling tumor treating fields for the treatment of lung-based tumors. *Paper presented at: 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. Milan, Italy; August 25-29, 2015.