Modulation of Tumor-Treating Fields by Cerebral Edema from Brain Tumors

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Abstract

Purpose: Cerebral edema is an important component of brain metastasis, and its presence may alter the distribution of tumor-treating fields (TTFields). We therefore performed a computational study to model the extent of this alteration according to various edema conditions associated with the metastasis.

Methods and Materials: Postacquisition magnetic resonance imaging data sets were obtained from 2 patients with solitary brain metastases from non-small cell lung cancer. After delineation of various anatomies, a 3-dimensional finite element mesh model was generated and then solved for the distribution of applied electric fields, rate of energy deposition, and current density at the gross tumor volume (GTV), edema, and other cranial structures. Electric field–volume histograms, specific absorption rate–volume histograms, and current density–volume histograms were generated, by which plan quality metrics were derived from and used to evaluate relative differences in field coverage between models under various conditions.

Results: Changes in the conductivity of cerebral edema altered the electric fields, rate of energy deposition, and current density at the GTV region. At the cerebral edema region, increasing electric conductivity of the edema only decreased the electric fields and rate of energy deposition while the current density increased. The ratio of edema-to-tumor is also important because the plan quality metrics increased linearly when the edema-to-GTV ratio decreased, and increased vice versa. Furthermore, a conductive necrotic core additionally altered the distribution of TTFields according to the plan quality metrics.

Conclusions: Our modeling study demonstrated that cerebral edema alters the distribution of applied TTFields in patients. Personalized treatment planning will need to take into account the modulating effects of cerebral edema on TTFields as well as additional effects from a necrotic core inside the GTV.

Introduction

Non-small lung cancer (NSCLC) accounts for about 85% of lung malignancies, and approximately 20% to 40% of patients will develop brain metastasis during the course of their disease.1 Current treatment for these patients includes a combination of initial surgical resection if indicated, radiation (stereotactic or whole brain radiation therapy), drug treatment (chemotherapy, target therapy or immunotherapy), or any combination of these.
modalities. However, there is yet no strategy to prevent the occurrence of brain metastasis. TTFields have a multitude of effects on dividing and migrating cancer cells, including mitosis disruption, immunogenic cell death and anti-invasion properties. Studies have shown in preclinical animal models that TTFields can prevent the development of metastases using melanoma cell lines, and they are being tested in a randomized phase 3 trial to delay brain metastasis development in patients with advanced non-small cell lung cancer (NCT02831959). In fact, TTFields have clinically proven anticancer efficacy and this treatment has been approved by the United States FDA for recurrent and newly diagnosed glioblastoma.

Treatment planning is currently performed by using NovoTAL (Novocure Ltd). Therefore, TTFields hold promise as a potential preventive strategy and/or treatment modality for brain metastasis.

Cerebral edema is an important constituent associated with NSCLC brain metastasis. It is a result of hyperpermeable tumor microvasculatures that allow the leakage of plasma across vessel walls into the brain parenchyma. This vasogenic edema may be an important factor to account for differences in the distribution of TTFields within the brain. Therefore, using the magnetic resonance imaging (MRI) data set from 2 patients with solitary brain metastasis from NSCLC, we modeled in silico the distribution of TTFields according to various edema conditions associated with the metastasis. By incorporating the GTV into a prediagnosis head MRI, we found that edema significantly altered the intensity of TTFields at the white matter, gray matter and other brain structures including the gross tumor volume (GTV). But the intensity also fluctuated significantly depending on the size of edema and the presence or absence of a necrotic core. Furthermore, compared with vasogenic edema, cytotoxic edema increased TTFields at the GTV while interstitial edema reduced them.

Methods and Materials

Two patients, GN003 and WD001, with brain metastasis from non-small cell lung cancer surrounded by cerebral edema were identified for analysis. Details of their respective treatment histories are described in Appendix E1. We sought to determine the effects on TTFields coverage on intracranial structures due to the presence of brain tumor as well as cerebral edema.

Generation of finite element models

Workflow for finite element analysis of TTFields is available in our prior publication. Briefly, intracranial gross anatomy was first segmented using a combination of 3-dimensional Magnetization-Prepared Rapid Gradient-Echo (MP-RAGE) and Fluid-Attenuated Inversion Recovery (FLAIR) image sequences. MP-RAGE was used due to its high-resolution features and FLAIR was critical for delineating cerebral edema. A finalized mesh was then imported into COMSOL Multiphysics 5.5 (COMSOL, Burlington, MA), where appropriate material properties and boundary conditions were defined with values similar to those used by Lok et al (Table E1). Electric field distribution was then solved using frequency domain analyses in the AC/DC module where magnetic fields were assumed to be negligible. Electric field—volume histograms, specific absorption rate—volume histograms, and current density—volume histograms were generated using derived values from model solutions and a set of plan quality metrics (PQM) was also generated comparing changes in the distribution of TTFields between models. PQM in this study included the 95% coverage metrics or magnitude of fields encompassing 95% of a particular structure’s volume (E95%, SAR95%, and CD95%), the median percentage coverage (E50%, SAR50% and CD50%) or magnitude of fields encompassing 50% of a particular structure’s volume, and hotspots defined by the 5% coverage or magnitude of fields encompassing 5% of a particular structure’s volume (E5%, SAR5% and CD5%).

Baseline analysis

The first analysis comprised of delineating neuroanatomy without the presence of tumor or cerebral edema using prediagnosis MP-RAGE sequences. The objective is to establish quantifiable differences of TTFields within normal intracranial structures, without the presence of tumor or edema, and that serves as a basis for comparison later in the study.

Analysis of TTFields on GTV without edema

The second analysis used the same MRI data set used in the baseline study for electric field mapping. However, the GTV was imported from each patient’s initial diagnostic MP-RAGE imaging study where the gross tumor was first identified. The tumor was then virtually placed and coregistered in the corresponding patient’s prediagnostic image set.

Types of cerebral edema and distribution of TTFields

The primary analysis required the assignment of different electric conductivity values to compare differences in the strength of TTFields affected by 3 different types of cerebral edema. These assigned values were similar to (1) gray matter (0.14 S/m) for cytotoxic edema, (2) blood plasma (0.71 S/m) for vasogenic edema, and (3)
cerebrospinal fluid (2.0 S/m) for interstitial edema. Therefore, 3 subsequent models were made for each patient, GN003 and WD001, to determine the effects of change in electric conductivity on TTFields. Because GN003 does not have necrosis within the GTV, the contribution from necrotic core was analyzed in WD001 by removing it and the space filled in with GTV-like material properties for consistency based on physician’s discretion. By observing these differences, an accurate conductivity value could be determined and used for the secondary analysis.

Volumetric changes and the distribution of TTFields

The secondary analysis was designed to identify potential correlation between TTFields coverage on the GTV and the volume of the surrounding cerebral edema. A series of expansion models were generated by dilating the GTV until it is outside the boundary of edema but without penetrating the dura or skull. Therefore, GN003 was expanded 2, 4, 8, or 12 times, while WD001 was expanded up to 15 times after the same expansion iterations. Absolute volumes were used to gauge whether the dilations were performed to meet the desired expansion effect. Similarly, contraction models were generated by shrinking the GTV until the volume was half or one-quarter of the original volume. All models with an edematous region were computed using the initial diagnosis scan. For WD001, the accompanying necrotic core was removed and filled in with GTV-like material properties for consistency. However, additional models were generated with the necrotic core and GTV expanded for WD001. For each model, the edema region was assigned the conductivity of vasogenic edema for computation, according to methodologies used in the primary analysis. These models were then generated and the distribution of TTFields was computed for GTV and various intracranial structures.

Results

Baseline modeling of TTFields distribution with and without GTV or GTV plus necrotic core

To investigate the effects of GTV on TTFields distribution, we first compared the PQM of electric field, SAR, and CD in various normal brain structures using the prediagnosis models (derived from the head MRI data set before diagnosis of brain metastasis), with and without the incorporation of GTV in GN003 as well as the incorporation of GTV with necrotic core in WD001. Changes were minimal in both cases. In GN003, the largest percent difference out of the 3 metrics quantified was +6.7% in the SAR₉₅% hotspot within the orbits, while the rest of the structures had <5% change (Table 1; Fig. 1, first 2 columns in upper panel). Similarly, in WD001, the largest percent differences between the models were +10.1% and +8.2% for SAR₉₅% and median coverage SAR₅₀%, respectively, at the bilateral ventricles, as well as +5.1% for median coverage SAR₅₀% at the scalp (Table 1; Fig. 1, first 2 columns in lower panel). Therefore, the GTV or GTV plus necrotic core does not significantly alter TTFields distribution in the brain.

We next investigated the effect of introducing edema in the models and compared the PQM of electric field, SAR, and CD in various intracranial structures between the prediagnosis model and the initial diagnosis model containing both cerebral edema and the GTV. In GN003, changes were noted by as much as +55.1% in the SAR₅₀% of gray matter and −45.5% in SAR₅₀% of dura mater (Table 1; Fig. 1, third column in upper panel). In WD001, who had less edema (volume = 200.3 cm³) compared with GN003 (volume = 277.6 cm³), significantly greater changes were also identified by as much as +275.9% in SAR₅₀% of bilateral ventricles and −28.5% in SAR₅₀% of dura mater (Table 1; Fig. 1, third column in lower panel). These changes strongly indicate that edema alters TTFields distribution in the brain, and the extent of alteration correlates with the size of edema.

Change in the conductivity of cerebral edema alters electric field, SAR, and CD at the GTV

We next sought to evaluate the effects of increasing electric conductivity of the cerebral edema, from cytotoxic to vasogenic and then to interstitial edema, on TTFields coverage at the GTV and the edema itself. As expected, when conductivity of the edema increased from cytotoxic to vasogenic and then to interstitial type, all of the metrics for electric field, SAR, and current density decreased and increased vice versa (Table 2, Fig. 2).

Using vasogenic edema as reference, E₉₅% at the GTV of GN003 nearly doubled (or +99.5% increase) when the edema type was changed from vasogenic to cytotoxic (more to less conductive), and almost halved (or −44.9% decrease) when the edema type was changed from vasogenic to interstitial (less to more conductive) (Fig. 2A). Similar increases and decreases in E₅₀% or median electric field coverage and E₅% or hotspot were noted when the edema type was changed from vasogenic to cytotoxic and from vasogenic to interstitial, respectively. Because specific absorption rate is proportional to the electric field squared, the SAR₉₅% at the GTV also increased by +435.0% or more than 4-fold when the edema type was...
### Table 1 Percentage change in PQM for electric fields, SAR, and CD*

| Structure                          | Pre-Diagnosis vs. Pre-Diagnosis with GTV (% Difference) | Pre-Diagnosis Initial Diagnosis with GTV (% Difference) | Pre-Diagnosis with GTV vs. Initial Diagnosis with GTV (% Difference) |
|------------------------------------|--------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------|
| **GN003**                          |                                                        |                                                        |                                                                  |
| Bilateral Ventrices                | 0.3 [-1.2 -0.4 -1.0 -2.2 -1.0 0.2 -1.6 -0.6]         | 31.2 [10.2 -16.5 22.8 20.8 -16.1 32.7 17.2 -15.0]        |                                                                  |
| Brainstem                          | 1.3 [4.4 0.0 1.8 3.2 0.0 2.0 2.3 0.2]                 | 13.3 [22.2 5.7 24.2 44.8 8.7 11.5 8.8 4.9]               |                                                                  |
| Cerebellum                         | 1.4 [4.0 1.1 2.4 4.1 1.9 1.1 1.2 1.1]                 | 3.3 [9.2 -2.8 11.2 18.8 -4.1 0.4 2.5 -3.9]               |                                                                  |
| CSF                                | 0.8 [-0.5 -0.4 1.5 1.4 -1.0 0.4 0.4 -0.4]             | 5.2 [5.8 7.6 10.7 15.8 16.1 7.1 5.3 7.7]                 |                                                                  |
| Dura Matter                        | -0.2 [-1.0 -0.9 0.7 -2.2 -1.6 0.4 0.8 -1.0]           | -0.3 [-0.3 1.2 -1.8 -0.2 2.2 -0.3 -0.1 1.1]             |                                                                  |
| Grey Matter                        | -0.3 [-1.1 5.6 -45.5 -2.2 11.7 -27.5 -3.7 6.0]        | 2.0 [1.4 1.5 0.7 1.2 6.7 -1.6 1.3 2.8]                   |                                                                  |
| Orbits                             | 2.0 [-0.3 0.0 -0.1 -0.6 -0.1 0.0 -0.2 0.0]            | 4.0 [-3.3 3.3 -1.1 1.7 7.9 -22.0 -1.5 5.9]              |                                                                  |
| Scalp                              | 0.6 [-0.3 0.1 4.4 -0.5 0.8 1.5 -0.2 0.1]              | -21.7 [-3.3 3.3 -1.1 1.7 7.9 -22.0 -1.5 5.9]             |                                                                  |
| Skull                              | 0.6 [0.7 -0.1 2.0 1.6 -0.2 0.3 1.0 0.2]               | -10.8 [-9.3 34.5 -9.4 -16.7 44.0 3.2 8.9 13.3]           |                                                                  |
| White Matter                       |                                                        |                                                        |                                                                  |
| **WD001**                          |                                                        |                                                        |                                                                  |
| Bilateral Ventrices                | 2.9 [3.6 0.0 10.1 8.2 0.0 3.3 2.3 -0.1]               | 35.1 [31.5 29.2 43.5 29.5 26.0 60.9 59.6 45.4]            |                                                                  |
| Brainstem                          | -0.1 [-0.4 1.1 -0.7 -1.0 2.2 -0.5 -0.5 1.7]           | -1.6 [-2.0 -1.0 -2.0 -3.9 -2.0 -1.4 -0.4 -1.4]           |                                                                  |
| Cerebellum                         | -1.4 [-0.8 -0.8 -2.4 -2.0 -1.5 -1.2 -1.0 -0.8]        | -0.7 [-0.5 -0.7 -3.4 -1.1 -1.6 -1.2 -0.7 -0.6]           |                                                                  |
| CSF                                | -1.2 [-0.6 -0.6 -1.5 -0.4 -1.2 -0.7 -0.1 -0.6]        | -1.2 [-1.0 0.0 0.2 0.3 0.2 -1.5 -0.8 0.3]                |                                                                  |
| Dura Matter                        | -1.9 [-1.9 -0.4 -1.0 -5.1 -0.4 -1.7 -2.0 -0.4]        | -2.2 [-1.0 -0.2 -3.0 -2.1 -0.8 -2.4 -1.2 -0.3]           |                                                                  |
| Grey Matter                        | -0.9 [-0.4 -0.1 -4.1 -0.6 -0.2 0.2 -0.2 -0.2]         |                                                        |                                                                  |
| **Abbreviations**: CD = current density; CSF = cerebrospinal fluid; E = electric field; GTV = gross tumor volume; NC = necrotic core; PQM = plan quality metrics; SAR = specific absorption rate. Red denotes increased values and blue denotes decreased values.

* The percentage change in $E_{95\%}, E_{50\%}, E_{5\%}, S A R_{95\%}, S A R_{50\%}, S A R_{5\%}, C D_{95\%}, C D_{50\%},$ and $C D_{5\%}$ from the model containing GN003 GTV in the pre-diagnosis and initial diagnosis scans were calculated. The percentage change in $E_{95\%}, E_{50\%}, E_{5\%}, S A R_{95\%}, S A R_{50\%}, S A R_{5\%}, C D_{95\%}, C D_{50\%},$ and $C D_{5\%}$ from the model containing WD001 GTV and necrotic core in the pre-diagnosis and initial diagnosis scans were calculated. In both GN003 and WD001, the variance was significantly higher when the initial diagnosis scan was compared with the pre-diagnosis scan.
Fig. 1  Heat maps for GN003 (A) and WD001 (B) models. GN003 models using the prediagnosis scan without GTV or edema, prediagnosis scan with GTV but without edema, and initial diagnosis scan with GTV and edema (upper panel). The heatmaps are also arranged for electric fields (A-C), SAR (D-F), and CD (G-I). WD001 models using the prediagnosis scan without GTV or edema, prediagnosis scan with GTV but without edema, and initial diagnosis scan with GTV and edema (lower panel). The heatmaps are also arranged for electric fields (J-L), SAR (M-O), and CD (P-R). Abbreviations: CD = current density; GTV = gross tumor volume; SAR = specific absorption rate.
changed from vasogenic to cytotoxic, and decreased by $-82.6\%$ when the edema type was changed from vasogenic to interstitial (Fig. 2E). Similarly, $\text{CD}_{95\%}$ at the GTV increased by $+87.6\%$ when the edema type was changed from vasogenic to cytotoxic and decreased by $-55.7\%$ when the edema type was changed from vasogenic to interstitial (Fig. 2I).

For WD001, $\text{E}_{95\%}$ at the edema site increased by $+14.5\%$ when the edema type was changed from vasogenic to cytotoxic, and decreased by $-48.5\%$ when the edema type was changed from vasogenic to interstitial (Fig. 2C). Similar increases and decreases in $\text{E}_{50\%}$ and $\text{E}_{5\%}$ at the GTV were noted when the edema type was changed from vasogenic to cytotoxic and from vasogenic to interstitial, respectively. $\text{SAR}_{95\%}$ at the GTV increased by $+121.8\%$ when the edema type was changed from vasogenic to cytotoxic and decreased by $-59.7\%$ when the edema type was changed from vasogenic to interstitial (Fig. 2G). $\text{CD}_{95\%}$ at the GTV increased by $+1.6\%$ when the edema type was changed from vasogenic to cytotoxic and decreased by $-50.5\%$ when the edema type was changed from vasogenic to interstitial (Fig. 2K).

### Change in the conductivity of cerebral edema alters electric field, SAR, and CD at the edema site

The conductivity of cerebral edema also influences the electric field, SAR, and CD within the region of edema. In general, when the conductivity of the edema increases, both the electric field and energy absorption metrics at the edema site decrease, but the metric for current density increases (Table 2, Fig. 2).

For GN003, the $\text{E}_{95\%}$ at the edema site nearly tripled (or $+197.6\%$ increase) when the edema type was changed from vasogenic to cytotoxic, and decreased by $-59.4\%$ when the edema type was changed from vasogenic to interstitial (Fig. 2B). Similar increases and decreases in $\text{E}_{50\%}$ or median coverage and $\text{E}_{5\%}$ or hotspot at the edema were also noted when the edema type was changed respectively from vasogenic to cytotoxic and from vasogenic to interstitial. $\text{SAR}_{95\%}$ at the edema site increased by $+61.3\%$ when the edema type was changed from vasogenic to cytotoxic, and decreased by $-44.7\%$ when the edema type was changed from vasogenic to interstitial (Fig. 2F). However, $\text{CD}_{95\%}$ at the edema site decreased by $-40.5\%$ when the edema type was changed from vasogenic to cytotoxic, and increased slightly by $+11.7\%$ when the edema type was changed from vasogenic to interstitial (Fig. 2J).

For WD001, $\text{E}_{95\%}$ at the edema site increased by almost 3-fold (or $+194.4\%$ increase) when the edema type was changed from vasogenic to cytotoxic, and more than halved (or $-59.6\%$ decrease) when the edema type was changed from vasogenic to interstitial. Similar increases and decreases in $\text{E}_{50\%}$ and $\text{E}_{5\%}$ at the edema site were noted when the edema type was changed respectively from vasogenic to cytotoxic and from vasogenic to interstitial (Fig. 2D). $\text{SAR}_{95\%}$ at the edema site increased by $+50.8\%$ when the edema type was changed from vasogenic to cytotoxic, and increased slightly by $+11.7\%$ when the edema type was changed from vasogenic to interstitial (Fig. 2H). Similar to GN003, WD001’s $\text{CD}_{95\%}$ at the edema site had a decrease by $-44.4\%$ when the edema type was changed from vasogenic to cytotoxic, and

### Table 2 Plan quality metrics for the GTV volume in electric field—volume histogram, specific absorption rate—volume histogram, and current density—volume histogram in the presence of cytotoxic, vasogenic, and interstitial cerebral edema

| Case ID | Structure | Edema Δ | $\text{E}_{95\%}$ | $\text{E}_{50\%}$ | $\text{E}_{5\%}$ | $\text{SAR}_{95\%}$ | $\text{SAR}_{50\%}$ | $\text{SAR}_{5\%}$ | $\text{CD}_{95\%}$ | $\text{CD}_{50\%}$ | $\text{CD}_{5\%}$ |
|---------|-----------|---------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| GN003   | GTV       | Vasogenic to interstitial | -44.9% | -52.8% | -41.6% | -82.6% | -32.3% | -34.5% | -55.7% | -53.7% | -49.1% |
|         | Edema     | Vasogenic to interstitial | 99.5% | 81.1% | 71.2% | 435.0% | 295.0% | 196.6% | 87.6% | 81.7% | 148.4% |
| WD001   | GTV       | Vasogenic to interstitial | -48.5% | -40.7% | -35.2% | -59.7% | -60.6% | -52.3% | -50.5% | -49.6% | -47.8% |
|         | Edema     | Vasogenic to interstitial | 14.5% | 45.6% | 77.7% | 121.8% | 69.4% | 147.0% | 16.1% | 42.0% | 117.1% |

Abbreviations: $\text{CD}$ = current density; $\text{E}$ = electric field; GTV = gross tumor volume; SAR = specific absorption rate. Red denotes increased values and blue denotes decreased values.
Presence of cerebral edema alters TTFields coverage according to edema-to-tumor volume ratio

Because TTFields coverage of GTV is altered by the surrounding cerebral edema, we asked whether the volume of edema would correlate with TTFields coverage. Multiple models were generated by expanding the volume of GTV within the edema using prespecified volume multipliers. For GN003, the $E_{95\%}$ coverage increased linearly as a function of increasing volume of GTV inside the surrounding edema (Fig. 3A). Other PQM metrics such as $E_{50\%}$ or median coverage and $E_{5\%}$ or hotspot also generally increased in a linear fashion (Fig. 3B, 3C). Similarly, SAR also increased relatively as a function of increasing GTV within the edema (Fig. 3D, 3E). Although SAR$_{95\%}$ did not follow a linear relationship, a positive correlation was still apparent with increasing GTV volume multipliers (Fig. 3F). CD$_{95\%}$ also increased relatively linearly (Fig. 3H, 3I). For WD001 without the presence of a necrotic core, similar patterns were observed across all the PQM metrics. Interestingly, while most of the metrics were relatively linear as a function of varying GTV volume within the edema, the SAR$_{95\%}$ coverage deviated from linearity, where the distributions appear to diverge when the GTV volume was less than or greater than 2 times baseline (Fig. 3D). Likewise, the SAR$_{5\%}$ coverage deviated even more dramatically when the GTV volume was less than or greater than 4 times baseline (Fig. 3F).

Necrotic core influences edema’s effect on TTFields distribution

Metastatic brain tumors frequently have necrosis. Therefore, we questioned whether the presence of a necrotic core in addition to edema would alter the distribution of TTFields. To address this, we first used the pre-diagnosis head MRI as the modeling template and added the GTV with and without the necrotic core. Of the 2 patients, only WD001 has necrosis inside the tumor and $E_{95\%}$ of the GTV increased by as much as +37.5% in the model with necrotic core compared with the one without (Table 3). The corresponding SAR$_{95\%}$ and SAR$_{5\%}$ also increased by +33.5% and +34.8%, respectively, while the
CD95% and CD50% increased by a smaller extent of +21.8% and +2.3%, respectively (Table 3). Furthermore, to confirm our findings, we repeated our modeling using the head MRI from initial diagnosis as the modeling template. We also found that the SAR95% at the GTV increased by +35.7%, but there was a minimal increase of +4.7% in E95%, while the SAR5% and CD5% dropped by −23.8% and −23.2%, respectively (Table 3). The minimal change in E95% and E50% may be due to shift of brain tissue in the initial diagnosis MRI where cerebral edema displaced adjacent structures. Still, both modeling results from prediagnosis and initial diagnosis head MRIs consistently indicate that the necrotic core increased the 95% metrics for electric field, SAR, and CD of the GTV.

Discussion

In this study, we were able to determine the extent of TTFields coverage to GTV based on the amount of surrounding cerebral edema. Additionally, we were able to produce a side-by-side comparison of changes in field distribution within the head with and without a GTV. These changes were quantified by comparing each model’s PQM, namely, 95% coverage, 50% median coverage, and 5% hotspots for each of the electric field—volume histogram, specific absorption rate—volume histogram, and current density—volume histogram metrics. Specifically, varying the GTV volume relative to edema was associated with marked alterations in TTFields coverage and this finding has potential implication on patient treatment.

A proper rendition of TTFields distribution in the head without tumor-associated abnormalities is needed to evaluate the extent of alteration from edema. One approach involves virtually removing the edema associating the tumor from a head model derived from the initial diagnosis MRI. But this method can lead to large inaccuracies in predicting TTFields distribution due to either deformed spaces or missing radiologic data representing normal contours of native intracranial tissues. A better rendition of TTFields, free of influence from edema, involves the use of a prediagnosis MRI and compare the results to those derived from the initial diagnosis MRI where both tumor and edema are present. In both GN003 and WD001, prediagnosis head
MRI scans were available and, as predicted, we found that edema significantly altered the PQM at the GTV. This also raises a potential limitation of virtually inserting GTV(s) to a universal head model as a method of analyzing TTFields distribution.

We applied the conductivity value of vasogenic edema in our previous analysis and questioned to what extent do other types of cerebral edema would alter TTFields distribution. The models revealed drastic changes in electric field, SAR and current density when the edema type is modeled according to conductivities for cytotoxic, vasogenic, and interstitial edema. A dramatic increase in electric field strength and SAR was observed when the conductivity was switched from that of vasogenic to cytotoxic edema within the GTV and edema regions. In contrast, large decreases in field strengths to both GTV and edema were observed in electric field and SAR when it was modeled as interstitial edema. Therefore, our data indicate that applying the correct electric conductivity to the edema region during modeling is extremely important. Because vasogenic edema is predominantly associated with brain tumors, we therefore applied the value of vasogenic edema to the remaining model analyses.

Our analysis demonstrated that, in general, TTFields coverage at the GTV correlates with increasing GTV volume in the presence of edema. Lang et al have shown that cerebral edema surrounding glioblastoma affects electric field distribution heterogeneously but most significantly at the interface between edema and tumor with a maximal decrease in intensity by as much as 52%.14 However, glioblastoma is a locally infiltrative disease and tumor cells characteristically invade the surrounding brain parenchyma. Therefore, the associated edema is unlikely to be solely from vasogenic sources but a mixture of vasogenic edema plus increased cellularity within the edematous region. In contrast, edema from brain metastasis does not typically have infiltrative tumor cells and therefore the vasogenic edema is unadulterated compared with that from glioblastoma.

Although our modeling study applied methods similar to that used by Lang et al,14 there are key differences. First, as shown in Fig. 3, our study revealed that there exists a patient-specific correlation between volume of edema and electric field coverage within the GTV. The different distributions between the models presenting with and without a necrotic core in WD001 further

| Table 3 Contribution of necrotic core in PQM for electric fields, SAR, and CD* |
|-----------------------------------|----------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                  | Structure                        | E95% (Pre-Diagnosis) | E50% (Pre-Diagnosis) | E5% (Pre-Diagnosis) | SAR95% (Pre-Diagnosis) | SAR50% (Pre-Diagnosis) | SAR5% (Pre-Diagnosis) | CD95% (Pre-Diagnosis) | CD50% (Pre-Diagnosis) | CD5% (Pre-Diagnosis) |
| Pre-Diagnosis with GTV & NC vs. Pre-Diagnosis with GTV & No NC (% Difference) | Bilateral Ventricles | -1.1 | -1.6 | 0.2 | -3.5 | -3.9 | -3.4 | 0.3 | -1.5 | -0.9 | 0.2 |
|                                  | Brainstem                        | 0.0 | -0.1 | -0.3 | 0.0 | -0.1 | -0.6 | 0.1 | 0.0 | -0.4 | 0.0 |
|                                  | Cerebellum                       | 0.1 | 0.1 | 0.0 | -0.1 | -0.1 | -0.1 | -0.2 | 0.1 | 0.0 | 0.0 |
|                                  | CSF                              | 0.0 | 0.0 | 0.0 | 0.1 | 0.2 | 0.1 | 0.0 | 0.1 | 0.1 | 0.0 |
|                                  | Dura Mater                       | 0.0 | 0.1 | 0.0 | 0.3 | 0.2 | 0.1 | 0.1 | 0.0 | 0.0 | 0.0 |
|                                  | Grey Mater                       | 0.1 | 0.0 | 0.0 | 0.1 | -0.2 | 0.1 | 0.0 | 0.0 | 0.0 | 0.0 |
|                                  | GTV                              | 37.5 | 2.1 | -8.2 | 33.5 | 34.8 | 0.5 | 21.8 | 2.3 | -11.1 | 0.0 |
|                                  | Orbits                           | 0.2 | 0.1 | 0.0 | 0.1 | 0.2 | 0.2 | 0.1 | 0.1 | -0.2 | 0.0 |
|                                  | Scalp                            | 0.0 | -0.1 | 0.0 | 0.1 | -0.3 | 0.1 | 0.2 | 0.0 | 0.1 | 0.1 |
|                                  | Skull                            | 0.4 | 0.1 | 0.0 | 0.3 | 0.0 | 0.0 | 0.2 | 0.0 | 0.0 | 0.0 |
|                                  | White Matter                     | 0.2 | -0.1 | -0.2 | 1.3 | 0.0 | -0.7 | 0.2 | -0.1 | -0.4 | 0.0 |

Abbreviations: CD = current density; CSF = cerebrospinal fluid; E = electric field; GTV = gross tumor volume; NC = necrotic core; PQM = plan quality metrics; SAR = specific absorption rate.

Red denotes increased values and blue denotes decreased values.

* The percentage change in E95%, E50%, E5%, SAR95%, SAR50%, SAR5%, CD95%, CD50%, and CD5%, from the models containing WD001 GTV and necrotic core versus GTV without necrotic core, were calculated using the prediagnosis scans. The percentage change in E95%, E50%, E5%, SAR95%, SAR50%, SAR5%, CD95%, CD50%, and CD5%, from the models containing WD001 GTV and necrotic core versus GTV without necrotic core, were calculated using the initial diagnosis scans.
affirms a need for patient-specific modeling of TTFields, especially when the volumetric ratio between edema and GTV is small. This may be due to the fact that the total volume of the highly conductive necrotic core within the GTV dramatically redirects current flow away from the GTV. This phenomenon is analogous to estimating the electric field inside a perfectly conducting spherical shell where it is close to or equals to zero according to Gauss’ law. Because biological tissues are not perfectly conducting, the electric fields then are highly dependent on the conductivities in each adjacent layer of tissues.15 Previous studies have shown similar results where the presence of a necrotic core within the GTV decreases electric field coverage at the GTV.13,16 It is important to note that in our modeling, when the size of GTV is multiplied within the edema volume, the absolute volume of edema decreases, and thus the GTV-to-edema volume ratio increases. Therefore, this may underestimate the real effect of the necrotic core within a GTV. Second, the presence of edema in the brain significantly alters TTFields distribution throughout the entire supratentorial brain. As shown in Fig. 1, higher field strength was seen at initial diagnosis throughout the normal brain not only volumetrically, but in magnitude as well, in both GN003 and WD001. This effect has potential clinical implications such as patient survival and that may warrant electric field modulation by means of skull remodeling to compensate for the loss in field strength due to the presence of a large area of cerebral edema.19

TTFields coverage in GTV, necrotic core and edema varies according to the category of cerebral edema, namely cytotoxic, vasogenic, and interstitial types. First, cytotoxic edema is composed of swollen cells, most commonly seen in patients with cerebral ischemia, where cells lose energy and their ability to maintain ATP-dependent sodium and potassium ion pump, and thus potassium ions are accumulated intracellularly along with water molecules.18 On MR imaging, the margins between gray and white matter are lost and the fractional diffusion of water molecules between cells is attenuated, which results in high signal intensity in the diffusion weighted imaging sequence.19 Therefore, when modeling cytotoxic edema, we chose to apply gray matter-equivalent conductivity and other material properties to the edema region.20 Second, the most electrically conductive form of cerebral edema is interstitial edema, which primarily is composed of highly conductive cerebrospinal fluid (CSF).21 This type of edema is usually associated with communicating or noncommunicating hydrocephalus where malabsorption or obstruction, respectively, causes CSF back up into the interstitial space. Lastly, patients with brain metastasis most commonly have vasogenic edema, which is a result of plasma leakage from hyperpermeability tumor-induced vasculature and associated with the breakdown of the blood-brain barrier. For this type of edema, blood plasma conductivity and material properties are applied.22 Blood plasma is not as electrically conductive as CSF but is more conductive than gray matter. When applying properties from all 3 types of edemas in our models, we found that increasing electric conductivity of edema correlated very strongly with decreasing electric field strength and magnitude of SAR within the GTV, necrotic core and the edema itself. In contrast, increasing electric conductivity of edema correlated with increasing current density, and this is not unexpected because tissues with higher conductivity allow greater electric charge flow through it. Therefore, TTFields treatment planning will need to account for not only the GTV and necrotic core, but also the edematous region surrounding the tumor.

Our findings have clinical relevance because cerebral edema can be minimized by corticosteroid or antiangiogenesis agents. Dexamethasone decreases the permeability of vascular endothelium but it also suppresses the immune system and therefore counteracts the immunotherapies that are being increasingly used to treat patients with metastatic NSCLC.23-25 Bevacizumab may be a better alternative because it may potentiate the efficacy of immunotherapy.26 However, the antiedema effect from antiangiogenic tyrosine kinase inhibitors is less clear. Therefore, future efforts are needed to find the ideal agent that can decrease peritumoral edema without compromising TTFields efficacy.

Conclusion

Cerebral edema plays an important role in modulating applied TTFields to the head. Our modeling study demonstrated that changes in the conductivity of cerebral edema altered the PQM of electric field, SAR, and CD at the GTV and the edema region. The ratio of tumor-to-edema is also important because the PQM increased linearly as a function of increasing GTV volume. However, the conductive necrotic core draws in TTFields and thereby increases the quantitative metrics. Therefore, developing a means to increase TTFields intensity applied to the head may help to counteract the attenuation from cerebral edema.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101046.

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