Mini-Symposia Title:

The Evolving Science and Engineering of Tumor Treating Fields:-Part I

Mini-Symposia Organizer Name & Affiliation:

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Mini-Symposia Speaker Name & Affiliation 2:

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Jimm Grimm, Geisinger Medical Center

Mini-Symposia Speaker Name & Affiliation 6:

Lynn Oxenberg, Glioblastoma Patient

Theme:

- ○ 01. Biomedical Signal Processing
- ○ 02. Biomedical Imaging and Image Processing
- ○ 03. Micro/ Nano-bioengineering; Cellular/ Tissue Engineering &
- ○ 04. Computational Systems & Synthetic Biology; Multiscale modeling
- ○ 05. Cardiovascular and Respiratory Systems Engineering
- ○ 06. Neural and Rehabilitation Engineering
- ○ 07. Biomedical Sensors and Wearable Systems
- ○ 08. Biorobotics and Biomechanics
- ◉ 09. Therapeutic & Diagnostic Systems and Technologies
- ○ 10. Biomedical & Health Informatics
- ○ 11. Biomedical Engineering Education and Society
- ○ 12. Translational Engineering for Healthcare Innovation and Commercialization

Mini-Symposia Synopsis— Max 2000 Characters

Tumor Treating Fields (TTFields) is a therapy utilizing alternating electric fields to inhibit cancer cell division. TTFields are aprpoved for the treatment of Glioblastoma Multiforme and Mesothelioma. Ongoing clinical trials are testing the efficacy and safety of TTFields for treating other malignancies including non small cell lung, pancreatic ovarian and hepatocellular cancer. We are planning two symposia in which experts in the field of TTFields will discuss recent scientific and engineering developments.The sessions will include talks discussing recent studies on the mechanism of action of TTFields, simulation-based studies on TTFields therapy and clinical research regarding imaging of response to TTFields and combination of TTFields with radiation therapy. The sessions will also include a talk from a patient, who is currently being treated with TTFields, thereby providing a unique perspective on how the journey cancer patients go through, and how they integrate TTFields into their lives.We believe this session will stimulate new opportunities for collaboration and increase involvement of the biomedical engineering community in this new and exciting field.

Novel Imaging Biomarkers to Assess Effectiveness of TTFields in Patients with Glioblastoma

Suyash Mohan MD, PDCC, Sumei Wang, MD, Lynn Oxenberg, Sanjeev Chawla PhD

Abstract— **Glioblastoma (GBM) is the most common malignant brain tumor and accounts for 70% of all primary brain tumors in adults. Despite aggressive multi-modal therapy including surgery, radiation, and chemotherapy, the prognosis remains poor with a median survival of around 2 years. Tumor-treating fields (TTFields), is a new frontier in cancer therapy, and has been recently approved for the treatment of GBM. We will discuss recent neuroimaging advances including novel physiologic and metabolic neuroimaging techniques and their role in monitoring treatment related temporal characteristics and assessing response to this unique treatment modality.**

I. Introduction

Tumor treating fields (TTFields) is a novel therapeutic modality recently approved for the management of patients with glioblastoma (GBM). It interferes with tumor cell division and organelle assembly by delivering low-intensity, intermediate frequency alternating electric fields to rapidly dividing neoplastic cells, resulting in apoptosis. This approach comprises of a portable device delivering alternating electric fields aiming at selectively inhibiting cellular proliferation of neoplastic cells, with minimal effect on normal quiescent cells. Promising findings of recent practice changing large-scale multinational randomized clinical trials have demonstrated that the addition of TTFields to maintenance temozolomide chemotherapy resulted in statistically significant improvement in progression-free survival (PFS) and overall survival (OS) compared to patients receiving standard chemo-radiation therapy (CRT). We will review the recent neuroimaging advances including novel physiologic and metabolic neuroimaging techniques and their role in monitoring response to this unique treatment modality. The purpose of our study was to evaluate the effects of TTFields in GBM patients using diffusion tensor imaging (DTI), perfusion weighted imaging (PWI) and 3D-echoplanar spectroscopic imaging (EPSI).

II. Methods

Twelve patients (both newly diagnosed & recurrent GBM patients) previously treated with standard of care maximal safe resection and CRT received TTFields. Patients underwent baseline (prior to TTFields) and two follow-up (one & two months post initiation of TTFields) MR imaging on a 3T MR system. DTI data were acquired using 30 directions with a single-shot spin-echo EPI sequence. After motion and eddy current correction of raw DTI data, parametric maps [mean diffusivity (MD), fractional anisotropy (FA)] were generated using in-house developed algorithm. For PWI, T2* weighted gradient-echo EPI sequence was acquired with a temporal resolution of 2.1s. Leakage corrected cerebral blood volume (CBV) maps were constructed. 3D-EPSI was acquired using a spin-echo based sequence. EPSI data were processed using metabolic imaging and data analysis system (MIDAS) package. DTI (MD, FA), EPSI [choline (Cho)/creatine(Cr)], CBV maps and FLAIR images were co-registered to post-contrast T1-weighted images and a semi-automated algorithm was used to segment the contrast-enhancing region of neoplasms. Median values of MD, FA, relative CBV (rCBV) and Cho/Cr were computed at each time point. The 90th percentile rCBV (rCBVmax) values were also measured. Percent changes of each parameter between baseline and follow-up time points were evaluated.

III. Results/Discussion

There was an increasing trend in MD (~3%) and declining trend in FA (~8%) at the 2-month follow-up relative to baseline. Additionally, from baseline to post- TTFields, reductions in Cho/Cr and rCBVmax were also observed from most of the patients. All patients were clinically stable at 2-month follow-up. The inhibition of cellular growth may account for increase in MD, decrease in FA and Cho/Cr. Reducing trends in rCBVmax may indicate anti- angiogenic effects of TTFields and decreased perfusion within the tumor bed after the therapy. Conclusion: Our preliminary results suggest that advanced MR imaging may be useful in evaluating TTFields related temporal characteristics and response assessment to TTFields in GBM patients. However, these findings need to be validated in a larger patient cohort and correlated with clinical endpoints of PFS and OS. Future work correlating advanced imaging findings with field intensity distribution patterns derived from simulations is underway to further optimize treatment in real-time.

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Modeling Ionic Conductance, Capacitance and Power Dissipation of Microtubules and Their Networks Due to The Action of TTFields

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Abstract— **In this paper we provide a theoretical and computational overview of the ionic conduction properties of microtubules and microtubule networks in living cells. We discuss ionic concentration dependence of the microtubule conductance, capacitance and inductance based on computational predictions and some available experimental data. We compute the values of currents and the power dissipated via microtubules and microtubule networks when exposed to typical values of potential differences generated by TTFields. We compare these estimates to those for the cytoplasm.**

I. INTRODUCTION

Microtubules (MTs) form parallel bundles that provide the structure of mitotic spindles in dividing cells generating substantial mechanical forces (approx. 700 pN) required for chromosome segregation. They have also been implicated in electrical signaling in neurons, possibly due to their ionic conduction properties. Hence, they may act as biological nanowires. In this connection, relatively weak AC electric fields with frequencies 100<f<300 kHz and low intensities in the range ~1-2.5 V/cm, called Tumor Treating Fields (TTFields), have been shown to arrest cancer cells' mitosis, which led to therapeutic advances in cancer, especially GBM. In recent experimental studies measurements of AC conductivity and capacitance of MTs as a function of frequency between 1kHz and 1MHz have been performed in order to elucidate the mechanism of action of TTFields. Specifically, different tubulin concentrations and ionic strengths were used in the determination of the conductance and capacitance of the following samples: (a) buffer solution itself, (b) unpolymerized tubulin and (c) microtubules stabilized by taxol. The experimental data indicate major effects of tubulin polymerization on these properties as well as strong dependence of ionic concentration on the conductive and capacitive properties of the sample [1-3].

II. METHODS

We generated a theoretical basis for the results observed, by analyzing the response of ions as the principal charge carriers attracted to MTs and tubulin. The methods used involve Kirchhoff's equations for RLC electrical networks and their extension in the continuum approximation to nonlinear differential cable equations. We have also performed a computational analysis using random networks representing MTs in solution as a function of frequency of the applied AC signal and observed a transition from real to imaginary impedance as the frequency crosses a threshold.

III. RESULTS

We observed that MTs measurably increase the solution's conductance compared to free tubulin at lower ionic concentrations while the opposite is true at high ionic concentrations. We quantify this effect using the Debye-Hueckel model as due to the formation of a counter-ionic layer whose thickness is concentration and temperature dependent according to the Debye length formula. At high ionic concentrations MTs act as low-resistance cables while at low ionic concentrations their contribution to impedance is mainly capacitive. At the peak value, the intrinsic conductivity of MTs has been found to be two orders of magnitude greater than that of the buffer solution. Moreover, we found that at 100 kHz the conductance of MTs reaches its peak. On the other hand, at low protein concentration, free tubulin dimers decrease solution's conductance, and we model this as being due to tubulin attracting ionic charges and lowering their mobility. Both tubulin and MTs were found to increase capacitance of buffer solutions, due to their formation of ionic double layers.

III. DISCUSSION & CONCLUSION

These results point to MTs being very sensitive to AC electric fields in the 100 kHz range and further support their electrical ionic conductivity function in cells. We estimated the power dissipated through MTs during the action of TTFields and found it to be comparable to the power generated by mitochondria in living cells indicating this as a possible physiologically relevant finding. These results bring insight into MTs ability to modulate the capacitance and conductance of the cytoplasm and act as low resistance pathways for ions, which has implications for understanding of the action of TTFields on cancer cells.

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Current injection during TTFields therapy: new methods to increase effective treatment time

Nichal Gentilal and Pedro Miranda

Abstract— **We used a realistic head model to study new ways to inject current during TTFields therapy to overcome the need to shutdown the fields when transducers' temperature surpassed 41ºC. We found out that decreasing the amount of injected current to values below a certain threshold might lead to a continuous treatment time. Another approach is by controlling the current at the transducer level and temporarily decrease it to zero just on the transducers that reached the critical temperature. Further investigation of the applicability of these new operating modes should be performed to assess their value.**

I. INTRODUCTION

Tumor-Treating Fields (TTFields) is a cancer treatment technique for glioblastoma multiforme (GBM). It consists in applying an electric field with a frequency of 200 kHz in two perpendicular directions (e.g.: Anterior-Posterior or AP and Left-Right or LR) alternately. Pos-hoc analysis of data from clinical trials showed that a high daily usage of this technique leads to significantly better outcomes. In recurrent cases a minimum of 18 hours per day is recommended, whereas for newly diagnosed patients the lowest daily compliance suggested is 12 hours. In these situations, the Joule heating effect is non-negligible. To avoid burns Optune, the device used to apply this technique in real subjects, monitors the temperature of the transducers and ensures that it does not surpass 41ºC by controlling the current injected into the arrays. Our aim is to investigate new ways to inject current to maximize the time that the patient is under treatment considering the thermal restrictions of the device. Additionally, we also analyze the thermal impact that each new operating mode might produce.

II. METHODS

We used a realistic head model created from MR images [1] and run several simulations in COMSOL Multiphysics, using the AC/DC and the Heat Transfer modules. The spatial and temporal variation of the temperature were determined by solving Pennes equation with the usual terms: conduction, blood perfusion, metabolic heat and Joule heating. Convection, radiation and sweat losses at the surface were considered. The Joule heating term was taken alternately from the electric field solutions for the AP and LR configurations for periods of 1 s each. In the simulations where current shutdown was implemented, we set this term to zero whenever the temperature of a transducer reached 41 °C. The values for the physical parameters were taken from the literature.

III. RESULTS

The thermal restrictions of Optune limit how long current is being injected which might have an impact on treatment outcomes as we reported previously [2]. Our model predicts an intermittent operating mode of the device, that is different for each configuration. We tested new possible ways to deliver the fields while maintaining a continuous treatment time. Decreasing the amount of injected current based on the maximum temperature that the transducers can reach showed to be one possible way. In our studies we also verified that there is one transducer that reaches the shutdown temperature quicker and thus that controls if the device is applying the fields or not. In line with these findings, we tested a new operating mode: reducing the current to zero temporarily just for the transducers that surpassed the threshold temperature to allow them to cool down.

IV. DISCUSSION & CONCLUSION

The approaches here suggested might lead to a reduction of the electric field intensity at the tumor bed and thus their applicability might be limited by tumor location. The benefits of this reduction on the electric field distribution may be compensated by a longer application of current for the most superficial tumors. The clinical relevance of these new operating modes must be confirmed with data from phantoms and/or clinical trials.

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Dose-dependent progression patterns in patients treated with Tumor Treating Fields

Ze'ev Bomzon, Novocure Ltd., Haifa, Israel

Abstract- **Here we will review recent studies analyzing recurrence patterns in newly diagnosed patients that participated in the phase 3 EF-14 trial. This trial compared outcome for newly diagnosed glioblastoma patients treated with chemoradiation+Tumor Treating Fields (TTFields) with outcome for patients treated with chemoradiation alone. Our analysis shows that TTFields therapy alters tumor progression patterns, with higher rates of distal progression occurring in the TTFields arm. Further analysis combining patient-specific modelling of field distributions showed that within the TTFields arm, recurrence was more likely to occur in regions of the brain that received lower doses of TTFields. This analysis supports the rationale for adaptive TTFields treatment treatment planning.**

I. INTRODUCTION

The phase 3 EF-14 trial revealed superior overall survival in patients treated with chemoradationa+ Tumor Treating Fields (TTFields) vs. patients treated with chemoradiation alone. A recent post-hoc analysis of the trial, in which delivery of TTFields was simulated in a patient-specific manner, revealed that a positive correlation between TTFields dose at the tumor bed and patient outcome. Dose being defined as average power loss density multiplied by fraction of usage time [1]. The positive connection between dose, combined with preclinical data showing that the anti-proliferative effects of TTFields are dose dependent [2], lead to the hypothesis that tumor progression in TTFields treated patient depends on the dose distribution within the brain. Here we review analysis testing this hypothesis.

II. METHODS

The study included two parts. In the first part compared progression patterns between patients treated with TTFields+chemoradiation and patients treated with chemoradiation alone were compared. In the second part, the connection between field distribution within the brain and the progression patterns were examined utilizing numerical simulations in which delivery of TTFields to patient-specific computational models was simulated. Participants of the EF-14 trial who exhibited radiological progression were included in this study (treatment: N=306/466, control: N=122/229). Enhancing tumor was segmented on T1c MRIs at baseline and progression. For the first part of the study, regions of progression disconnected from the original lesion were defined as distal. The rates of occurrence and distances of distal progressions from primary lesions were compared between the arms. For the second part of the study, computational head models

were created and delivery of TTFields numerically simulated for n=229 patients in treatment for over 2
months for whom image quality was sufficient to create patient-specific computational models. TTFields Dose in regions of progression was compared to TTFields dose in regions where no progression occurred.

III. RESULTS

Distal lesions appeared at larger distances within the TTFields-treated arm (control: 14.2±14.4 mm, TTFields 23.2±29.8 mm, p=0.03 Wilcoxon rank-sum). Outside of a 20 mm boundary zone around the primary tumor, a higher rate of distal progressions was observed in the treatment arm. (Control: 10/122, TTFields: 53/306 p<0.02 chi-squared). In the vicinity of the primary lesion (a 3 mm ring around the tumor), lower doses of TTFields were observed in regions f progression, than in regions where no progression occured (0.73 mW/cm^3 vs. 0.79 mW/cm^3 p<0.0001 t-test)

IV. DISCUSSION & CONCLUSION

This analysis shows a clear connection between TTFields dose and progression patterns, with progression more likely to occur in regions that receive lower doses of TTFields. The study supports the rationale for adaptive TTFields treatment planning, in which placement of the transducer arrays is periodically modified to optimize dose in regions of progression, with the aim of effectively inhibiting tumor growth within these regions.

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Avoiding Skin Toxicity with Concurrent TTFields and Radiation Therapy for Glioblastoma

Jimm Grimm, Greg Stachelek, Rachel Grimm, Khadija Sheikh, Kenneth Forster, Carla Scofield, Ian Butterwick, Kristin J. Redmond, Lawrence R. Kleinberg, Michel Lacroix and Anand Mahadevan

***Abstract*— Skin dose tolerance to radiation therapy when combined with concurrent TTFields anti-mitotic therapy has been a concern, therefore we analyzed dose distributions in anthropomorphic head phantom tests. Although surface dose was somewhat higher with the TTFields array, we found that the patient's skull acts as a transition region enabling the skin dose to remain below clinically meaningful tolerance levels.**

V. INTRODUCTION

Tumor treating fields (TTFields) is a regional, noninvasive anti-mitotic tumor treatment, offering improved survival for patients with newly-diagnosed and recurrent glioblastoma (GBM) (1-3). Usually patients complete an 8-week course of radiation prior to TTFields therapy; if safety and efficacy of concurrent therapy could be ensured they could begin TTFields therapy 8 weeks sooner. We performed phantom testing to study the increased skin dose owing to bolus effect from the ceramic TTFields array which shifts the radiation dose distribution toward the skin surface.

VI. METHODS

A series of dose measurements were made by orienting a sheet of film vertically in a rectangular phantom and directing a single 6MV radiation beam perpendicular to the film, for each of the four curves in Fig. 1A. Measurements were obtained using a single electrode of the ceramic Optune TTFields array aligned to the central axis of the beam, as well as for a piece of 5mm thick Superflab bolus in the beam, also for a sheet of brass bolus in the beam, and finally without any type of bolus for calibration purposes. calculated for three distinct positions of TTFields arrays, as in Fig. 1B.

VII. RESULTS

We observed that the bolus effect of the ceramic TTFields array electrodes is comparable to that of single-layer brass bolus and less than that of 5mm thick Superflab bolus. Average human skull thickness is 6.5mm which provides a transition region from the high dose in the tumor to a lower dose at the skin. An increased dose to skin surface due to bolus effect is observed, but in head phantom testing for all 10 cases, remained below clinical dose tolerance levels.

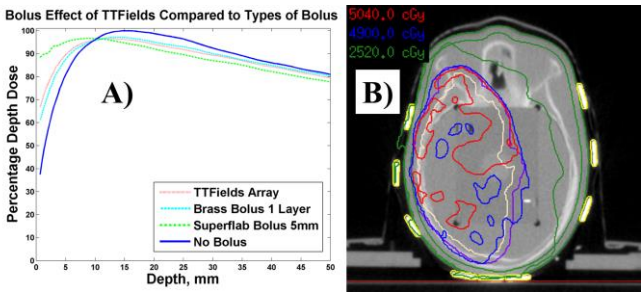

Figure 1. A) Depth dose curve for a single 6MV radiation beam through the TTFields Array, or brass bolus, or Superflab bolus, or no bolus. At the surface (depth 0) it may be seen that radiation dose with the TTFields array in place is about halfway between the dose of "no bolus" and 5mm of Superflab bolus, and is similar to one layer of brass bolus. B) Plan for a patient treated for glioblastoma, recalculated on an anthropomorphic head phantom with the TTFields array in place.

VIII. DISCUSSION & CONCLUSION

This work demonstrates that target volume dosimetry for glioblastoma radiation therapy is not excessively affected by the presence of tumor-treating fields electrode arrays. The skull acts as a transition region between the tumor and the skin, alleviating excess skin dose. The TTFields did increase the skin surface dose as in the case shown in Fig. 1B, but the surface dose was still about half of the prescription dose of 5040 cGy. Although skin dose was relatively higher, it still remained absolutely below tolerance levels. Nevertheless, it does present the need for close monitoring in patients undergoing concurrent therapy.

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Journey of a Glioblastoma Patient Treated with Tumor Treating Fields

Lynn Oxenberg

Before my glioblastoma diagnosis in December 2017, I was a hard working, barely sleeping, 67 year old wife, mother of 2, grandmother of 4, always on the go person, who, for 20 years, commuted two and a half hours each way for work, where I was the Controller, HR Manager and Circulation director for a newspaper group. And I participated in many evening activities as well.

In November 2017, I had a headache that lasted a full month. After an MRI that showed a mass and a seizure a few days later, I had emergency surgery to remove the mass...which was a glioblastoma. After 6 weeks of oral chemo (temozolomide) and daily proton radiation, and a month off of all treatments, I started wearing Optune in April 2018. My Optune compliance has always been 92-95%. I am no longer working but I am back to being on the go much of the time. As an Optune Ambassador, I speak at Optune Open Houses, answering questions from new Optune users. I also dance one night a week, work out with a personal trainer, play mahjong weekly, go to theatre, meditate and travel. Life goes on!