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Clinical Investigation

Correlation of Tumor Treating Fields Dosimetry to Survival Outcomes in Newly Diagnosed Glioblastoma: A Large-Scale Numerical Simulation-Based Analysis of Data from the Phase 3 EF-14 Randomized Trial

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Summary

This simulation-based study investigated the relationship between Tumor Treating Fields (TTFields) dosimetry and survival in 340 patient cases from the phase 3 EF-14 study. Delivery of TTFields to the patients was simulated and the spatial distribution of the fields analyzed. The analysis yielded a robust definition for TTFields dose, which was correlated to patient survival. This work sets a conceptual framework for defining TTFields dosimetry and treatment planning procedures.

Introduction: Tumor Treating Fields (TTFields) are approved for glioblastoma based on improved overall survival (OS) and progression-free survival (PFS) in the phase 3 EF-14 trial of newly diagnosed glioblastoma. To test the hypothesis that increasing TTFields dose at the tumor site improves patient outcomes, we performed a simulation-based study investigating the association between TTFields dose and survival (OS and PFS) in patients treated with TTFields in EF-14.

Methods and Materials: EF-14 patient cases (N = 340) were included. Realistic head models were derived from T1-contrast images captured at baseline. The transducer array layout on each patient was obtained from EF-14 records; average compliance (fraction of time patient was on active treatment) and average electrical current delivered to the patient were derived from log files of the TTFields devices used by patients. TTFields intensity distributions and power densities were calculated using the finite element method. Local minimum dose density (LMiDD) was defined as the product of TTFields intensity, tissue-specific conductivities, and patient compliance. The average LMiDD within a tumor bed comprising the gross tumor volume and the 3-mm-wide peritumoral boundary zone was calculated.

Results: The median OS and PFS were significantly longer when the average LMiDD in the tumor bed was $\geq$0.77 mW/cm^3: OS was 25.2 versus 20.4 months (P = .003, hazard ratio [HR] = 0.611) and PFS was 8.5 versus 6.7 months (P = .02,

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HR = 0.699). The median OS and PFS were longer when the average TTFields intensity was >1.06 V/cm: OS was 24.3 versus 21.6 months (P = .03, HR = 0.705) and PFS was 8.1 versus 7.9 months (P = .03, HR = 0.721).

Conclusions: In this study we present the first reported analysis demonstrating patient-level dose responses to TTFields. We provide a rigorous definition for TTFields dose and set a conceptual framework for future work on TTFields dosimetry and treatment planning.

Introduction

Despite decades of investigation, there has been only a modest improvement in outcomes for patients with glioblastoma (GBM). In the 1970s, surgical resection and whole brain radiation resulted in a median overall survival (OS) of 9 months. By the early 2000s, smaller radiation field sizes and the addition of temozolomide (TMZ) chemotherapy resulted in median survival of 15 months.[1,2]

Stupp et al initiated the EF-14 phase 3 randomized trial of 695 patients newly diagnosed with GBM, comparing TMZ chemotherapy with radiation followed by monthly TMZ versus the same regimen with the addition of a novel cancer treatment modality, Tumor Treating Fields (TTFields).[3] The EF-14 trial demonstrated that adding TTFields to standard therapy improved OS (5-year OS: 13% vs 5%, P = .004) with no negative impact on quality of life.[4,5] The National Comprehensive Cancer Network guidelines for central nervous system cancers now include TTFields as a category 1 recommendation for patients with newly diagnosed GBM.[6]

TTFields are intermediate-frequency alternating electric fields delivered to the tumor site via an array of electrodes applied to the scalp. TTFields act like other cytotoxic modalities by interfering with key components of cell division. The currently accepted mechanism of action is that TTFields disrupt the spatial orientation of highly polarized molecules required for successful mitosis. Preclinical investigations have defined a relationship between TTFields' antimitotic effects and exposure time (in hours), frequency (in kHz), and field intensity (in V/cm). A retrospective post hoc analysis of the EF-14 clinical trial confirmed that OS increases with increasing TTFields compliance (defined as the fraction of time a patient is on active treatment); this beneficial effect is independent of MGMT status, age, and performance status.[7]

Taken together, these data suggest that although TTFields are nonionizing, a conceptual framework similar to that used for ionizing radiation might be clinically applicable. Radiation oncologists routinely visualize and quantify the radiation dose to 3-dimensional target volumes and correlate tumor response or local disease control to the amount of radiation delivered (ie, the dose-response relationship). Computer simulations are routinely used to calculate and visualize dose distributions and perform treatment planning. In the current analysis, we define and quantify the dose density of TTFields. We present the physical rationale behind this measure and provide a methodology for calculating TTFields dose-density distributions in patients using computer simulations. Finally, we demonstrate a clear correlation between TTFields dose at the tumor bed and survival in patients treated with TTFields in the EF-14 trial.

Methods and Materials

Patient model creation

TTFields distribution within the brain depends on the electric properties of tissues, which are not measurable from standard imaging data (neither computed tomography nor magnetic resonance imaging). Therefore, when simulating delivery of TTFields, 3-dimensional patient models are created by segmenting the images to identify the tissue type in each voxel, and electric properties are assigned to each tissue type based on empirical data.[8-10] In this study, patient models were created using a previously described method[8] in which a user contours various regions in the tumor in a semiautomatic manner, and the full patient model is created using a healthy head model that serves as a deformable template.

The transducer array layouts assigned to the patients, their average monthly compliance, and the average electric current delivered to each patient, calculated from log files of the TTFields device were derived from patient records. While receiving TTFields, patients met monthly with device specialists to ensure proper placement of the transducer arrays and to generate the log files by downloading usage data directly from the memory bank of the device. To simulate delivery of TTFields, virtual transducer arrays were automatically placed on the models according to the assigned layouts, and the field intensity distributions within the models were calculated using the Sim4Life v3.0 quasielectrostatic solver (ZMT Zurich, Zurich, Switzerland). Standard electric properties were assigned to the various tissue types and materials in the model according to Table 1. Boundary conditions were set so that the total

Table 1 Standard electric properties of tissues used in simulations[8]

Tissue type	Conductivity, S/m	Relative permittivity
Scalp	0.3	5000
Skull	0.08	200
Cerebrospinal fluid	1.79	110
Gray matter	0.25	3000
White matter	0.12	2000
Enhancing tumor	0.24	2000
Enhancing nontumor	0.36	1170
Resection cavity	1.79	110
Necrotic tumor	1	110
Hematoma	0.3	2000
Ischemia	0.18	2500
Atrophy	1	110
Air	0	0

current delivered to the patient was equal to the average current delivered to the patient during the first 6 months of treatment.

Calculating TTFields dose density

Previous studies have investigated the effect of TTFields as a function of electric field intensity, which has been used as a surrogate for dose.[11,12] In radiation therapy, (absorbed) dose is defined as the mean energy imparted by ionizing radiation to material of mass[13] and is measured in units of gray (J/kg). Field intensity quantifies the force that a field exerts on charged objects within it and not the energy imparted by the field on the material. Hence, alternative physical quantities quantifying the energy imparted by TTFields to tissue may provide a measure of TTFields dose, more analogous to radiation dose in meaning than electric field intensity. Consequently, in this study, in addition to field intensity, we incorporated power loss density into measures of TTFields dose. TTFields power loss density represents the energy per unit of time deposited by TTFields within the body and is calculated per Equation 1:

$$P = \frac{1}{2}\sigma E^2$$

Here P is the power loss density (W/volume), σ is the tissue conductivity (Siemens/m), and E is the magnitude of the electric field (V/cm).

To account for the fact that TTFields are delivered in 2 orthogonal directions during treatment, the following quantities were defined:

1. Local minimum field intensity (LMiFI): the lower of the 2 field intensities delivered to each point in the brain.

2. Local minimum power density (LMiPD): the lower of the 2 power loss densities delivered to each point.

To assist in defining dose at the tumor bed, the average of these quantities was calculated in a volume combining the enhancing tumor and a 3-mm-thick proximal boundary zone surrounding the enhancing tumor, necrotic regions, and resection cavity. Throughout the rest of the paper we will refer to the average field intensity and average power loss density in the tumor bed as LMiFI and LMiPD, respectively.

Data analysis

Three hundred forty of the 466 patients randomized to TTFields or TMZ in the EF-14 trial were included in the simulation analysis. Patients who were on treatment for less than 2 months (n = 87) and patients whose magnetic resonance imaging quality was insufficient for model creation (n = 39) were excluded from the study.

To test the hypotheses that LMiFI and LMiPD are associated with patient outcome, threshold values that divided the patients into 2 groups with the most statistically significant difference in OS were determined. Searches for the optimal thresholds were performed within ranges of less than ±20% around the median values. The median OS and progression-free survival (PFS) for each group were estimated from Kaplan−Meier curves; the *P* values of the differences in the curves were calculated using a stratified log rank test. The hazard ratios (HRs) were evaluated from a Cox proportional hazards model controlling for compliance (defined as the average daily device usage over the first 6 months of therapy), age, sex, Karnofsky performance status, MGMT status, tumor location, and resection status. Annual survival rates and the rate of PFS at 6 months were compared between groups using a 1-sided Z distribution of the Kaplan−Meier estimates of the survival rates at the defined time point. Time to deterioration fraction of global health status was defined previously as the time to a >10-point deterioration in scores from baseline without a subsequent ≥10-point improvement in scores compared with baseline and was analyzed in the same way as OS and PFS.[5] All analyses were performed using SAS v9.4 (SAS, Cary, NC).

Results

TTFields dose calculations

Figure 1 shows (a) an axial slice through the head of a patient who was treated with TTFields in the EF-14 study and (b) the corresponding patient computational model and color maps depicting the distribution of the (c) LMiFI and (d) LMiPD calculated within this slice. Visual observation of the color maps suggests a degree of spatial correlation between the 2 measures. However, there are some clear differences between the 2 color maps. In particular, the LMiFI tends to be low in regions of high conductivity such as the ventricles and resection cavity. However, the LMiPD

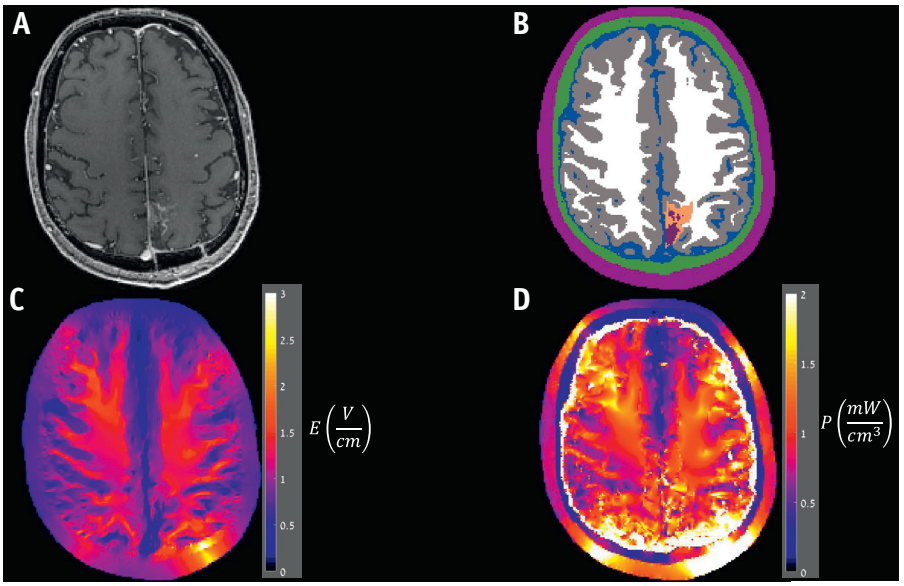

Fig. 1. (A) Axial slice of T1 postcontrast magnetic resonance imaging of a patient who participated in the EF-14 trial and (B) the corresponding slice through the computational model of the patient. The color maps show the distribution of the (C) LMiFI and (D) LMiPD within the corresponding slice. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2019.04.008.)

in these regions remains relatively high, indicating that although the electric field intensity is low in these regions, the power deposited by the field within them is high.

Field intensity and power density related to survival

Within the cohort of 340 patients tested, LMiFI varied in the range of 0.52 to 1.74 V/cm with a median and mean of 0.96 V/cm and 0.99 V/cm, respectively. LMiPD varied in the range of 0.31 to 3.2 mW/cm^3 (median, 0.97 mW/cm^3; mean, 1.06 mW/cm^3), and average patient compliance over the first 6 months of treatment varied from 0% to 98% (median, 79%; mean, 72%).

A search for the threshold LMiFI that divided the patient population into groups with the most statistically significant difference in OS was performed for values of LMiFI ranging from 0.96 to 1.1 V/cm. A table showing *P* values versus threshold LMiFI is given in Material E1 (available online at https://doi.org/10.1016/j.ijrobp.2019.04.008). The optimal cutoff for LMiFI was 1.06 V/cm. For this cutoff, the median survival duration was 24.3 months (95% confidence interval [CI], 19.6-33.0) when the LMiFI in the tumor bed was $\geq$1.06 versus 21.6 months (95% CI, 18.7-24.1) in the LMiFI <1.06 group, ($P = .0298$; stratified log rank test; Fig. 2A). Similarly, the PFS was 8.1 months (95% CI, 6.1-10.6) for patients treated with LMiFI $\geq$1.06 versus 7.9 months (95% CI, 6.1-8.4) for patients treated with LMiFI <1.06, ($P = .034$; stratified log rank test; Fig. 2B). After accounting for the influence of patient, tumor, and treatment characteristics (including TTFields compliance), HRs confirmed that a higher LMiFI independently improved outcomes. The proportional HR was 0.694 (95% CI, 0.512-0.942) for OS and 0.708 (95% CI, 0.530-0.945) for PFS.

A search for the threshold LMiPD that divided the patient population into groups with the most statistically significant difference in OS was performed for values of LMiPD around the value of ranging from 0.9 mW/cm^3 to 1.25 mW/cm^3. A table showing *P* values versus threshold LMiPD is given in Material E1 (available online at https://doi.org/10.1016/j.ijrobp.2019.04.008). The threshold LMiPD that divided the patient population into groups with the most statistically significant difference in OS was 1.15 mW/cm^3. In the LMiPD $\geq$1.15 mW/cm^3 group, the OS was 24.9 months (95% CI, 20.8-37.4) versus 21.5 months (95% CI, 18.7-23.9) in the LMiPD <1.15 mW/cm^3 group ($P = .014$; stratified log rank test; Fig. 2C). The median PFS between these 2 groups was 8.2 months (95% CI, 6.4- 11.2) with LMiPD $\geq$1.15 mW/cm^3 versus 7.9 months (95% CI, 5.8-8.2) in the LMiPD <1.15 mW/cm^3 group ($P = .0097$; stratified log-rank test; Fig. 2D). After accounting for the influence of patient, tumor, and treatment characteristics (including TTFields compliance), HRs confirmed that higher LMiPD independently improved outcomes. The proportional HR was 0.687 (95% CI, 0.503-0.938) for OS and 0.647 (95% CI, 0.478-0.875) for PFS.

Because the degree of TTFields compliance was previously shown to be associated with both OS and PFS, we created a new term to reflect both compliance and power density as a single variable. We refer to this unifying term as dose density or LMiDD (equal to LMiPD multiplied by the average patient compliance with treatment as derived from the logs of the Optune devices used by the patient;

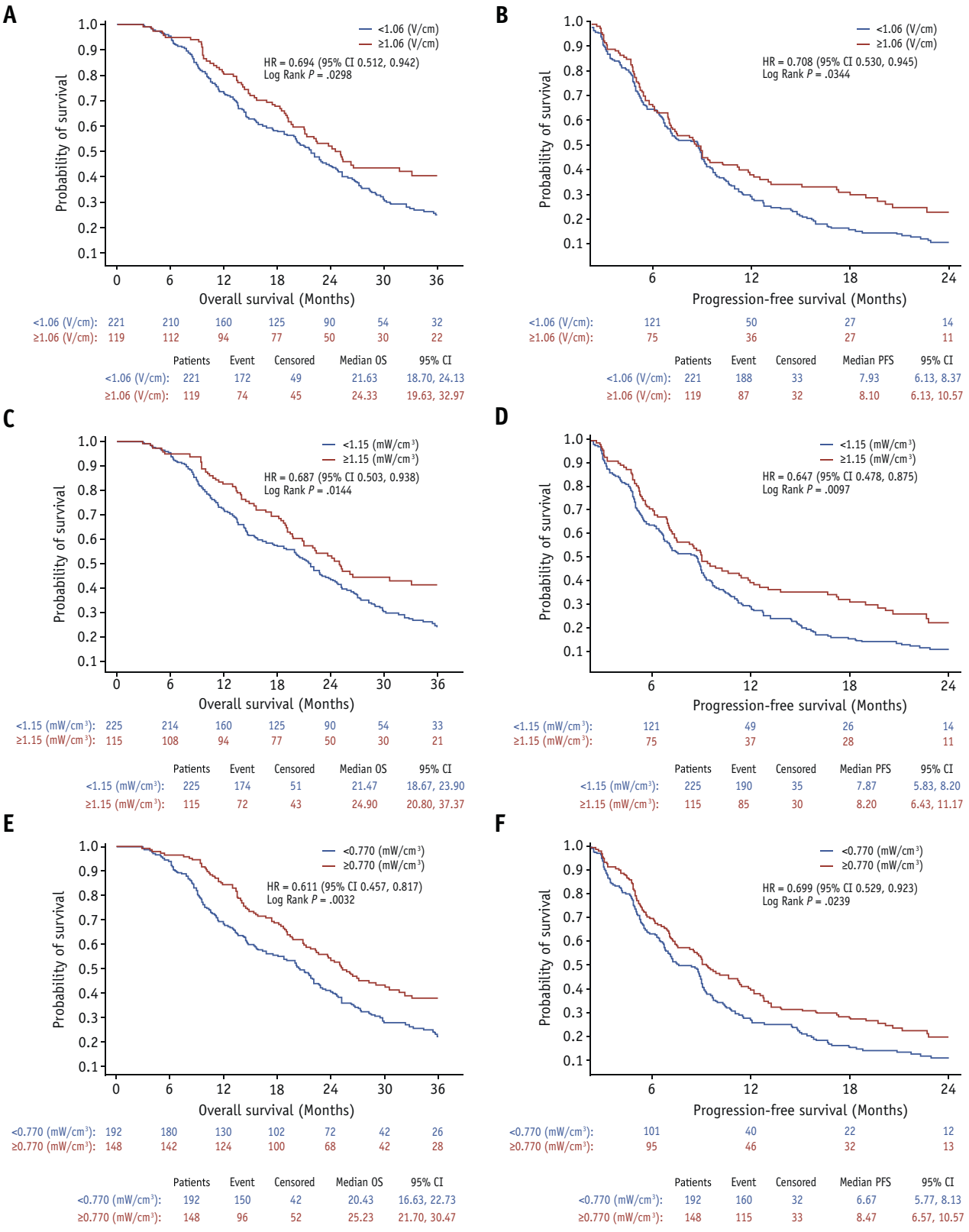

Fig. 2. Kaplan–Meier curves showing overall survival and progression-free survival when splitting the patient population according to threshold values of average (A, B) LMiFI = 1.06 V/cm, (C, D) LMiPD = 1.15 mW/cm^3, and (E, F) LMiDD = 0.77 mW/cm^3.

expressed as mW/cm^3). A search for the threshold LMiDD that divided the patient population into groups with the most statistically significant difference in OS was performed for values of LMiDD ranging from 0.72 mW/cm^3 to 0.97 mW/cm^3. This range is centered around the value of 0.85 mW/cm^3, which is equal to the optimal LMiPD (1.15 mW/cm^3) multiplied by 75% usage. A table showing *P* values versus threshold LMiDD is given in Material E1 (available online at https://doi.org/10.1016/j.ijrobp.2019.04.008). When dividing the patient population into 2 groups based on an optimal threshold value of average LMiDD (in the tumor bed) of 0.77 mW/cm^3, the OS was 25.2 months (95% CI, 21.7-30.5) in the LMiDD ≥0.77 group versus 20.4 months (95% CI, 16.6-22.7) in the LMiDD <0.77 group ($P = .003$; stratified log rank test; Fig. 2E). The median PFS was 8.5 months (95% CI, 6.6-10.6) for patients treated with LMiDD ≥0.77 and 6.7 months (95% CI, 5.8-8.1) for patients treated with LMiDD <0.77 ($P = .024$; stratified log-rank test; Fig. 2F). After accounting for the influence of other patient, tumor, and treatment characteristics, HRs confirmed that a higher LMiDD independently improved outcomes. For OS, the proportional HR is 0.611 (95% CI, 0.46-0.82), and for PFS the proportional HR is 0.699 (95% CI, 0.53-0.92).

Table 2 shows the characteristics of the patients in the LMiDD ≥0.77 mW/cm^3 and LMiDD <0.77 mW/cm^3 groups. The demographics of the 2 groups were similar in most parameters except for age, sex, tumor position, and resection status. To reject the effect of these characteristics on survival prolongation in all 3 groups, the HRs were evaluated using a Cox proportional hazards model, which demonstrated that the effect of LMiDD ≥0.77 remained independently significant for improved outcomes. These findings were also true for LMiFI ≥1.06 and LMiPD ≥1.15.

Dose density not only predicts improved PFS and OS but is also associated with the patient's quality of life. Global health status as measured by a self-reported quality-of-life questionnaire revealed that patients with higher values of LMiDD had a statistically significant prolongation of survival until deterioration of global health (18.0 months [95% CI, 12.2-21.0] vs 9.1 months [95% CI, 7.7-13.1]; HR 0.676 [95% CI, 0.479-0.955], $P = .004$). Similar results were achieved from LMiFI and LMiPD (data not shown).

Table 2 Patient demographics for LMiDD

Characteristics	LMiDD <0.77 mW/cm^3 (N = 192)	LMiDD ≥0.77 mW/cm^3 (N = 148)	*P* value
Age, y			
Mean (SD)	56.4 (11.65)	52.2 (11.26)	.001
Median (range)	56.5 (19-83)	54.0 (22-74)	
Sex, n (%)			
Male	121 (63.0%)	109 (73.6%)	.038
Female	71 (37.0%)	39 (26.4%)	
Region, n (%)			
United States	96 (50.0%)	63 (42.6%)	.173
Rest of world	96 (50.0%)	85 (57.4%)	
Extent of resection, n (%)			
Biopsy	29 (15.1%)	13 (8.8%)	.017
Partial resection	70 (36.5%)	41 (27.7%)	
Gross total resection	93 (48.4%)	94 (63.5%)	
MGMT tissue available and tested, n (%)	161 (83.9%)	125 (84.5%)	
Methylated	54 (33.5%)	51 (40.8%)	.446
Unmethylated	89 (55.3%)	61 (48.8%)	
Invalid	18 (11.2%)	13 (10.4%)	
Tumor position, n (%)			
Corpus callosum	12 (6.3%)	6 (4.1%)	.000
Frontal lobe	66 (34.4%)	79 (53.4%)	
Occipital lobe	25 (13.0%)	16 (10.8%)	
Parietal lobe	53 (27.6%)	50 (33.8%)	
Temporal lobe	110 (57.3%)	34 (23.0%)	
Missing	1 (0.5%)		
Tumor location, n (%)			
Left	85 (44.3%)	69 (46.6%)	.882
Right	106 (55.2%)	75 (50.7%)	
Both	2 (1.0%)	2 (1.4%)	
Corpus callosum	7 (3.6%)	4 (2.7%)	
Karnofsky performance score			
Mean (SD)	87 (10)	90 (10)	.014
Median (range)	90 (70-100)	90 (70-100)	
Time from last day of radiation therapy to randomization, d			
Mean (SD)	37.3 (9.94)	37.1 (7.24)	.830
Median (range)	37.0 (15-128)	36.0 (22-54)	
Time from diagnosis to randomization, d			
n	192	144	
Mean (SD)	112.8 (15.07)	114.5 (16.58)	.333
Median (range)	111.5 (77-162)	113.5 (63-165)	

Abbreviations: LMiDD = local minimum dose density; SD = standard deviation.

Discussion

In this study, we present the first reported analysis demonstrating patient-level dose responses to TTFields. Using patient data from the cohort of patients receiving TTFields in the EF-14 trial, we confirmed the correlation between TTFields magnitude at the tumor and patient survival. In our analysis, we show that TTFields dose can be defined as the product of the TTFields average power loss density at the tumor and device usage (compliance). Furthermore, higher doses of TTFields resulted in improved patient survival, thereby corroborating and elaborating on the reasons why increased device use in the EF-14 trial resulted in increased survival.[7]

The EF-14 trial confirmed the time-dependent nature of TTFields' antimitotic effects. Giladi et al had examined the

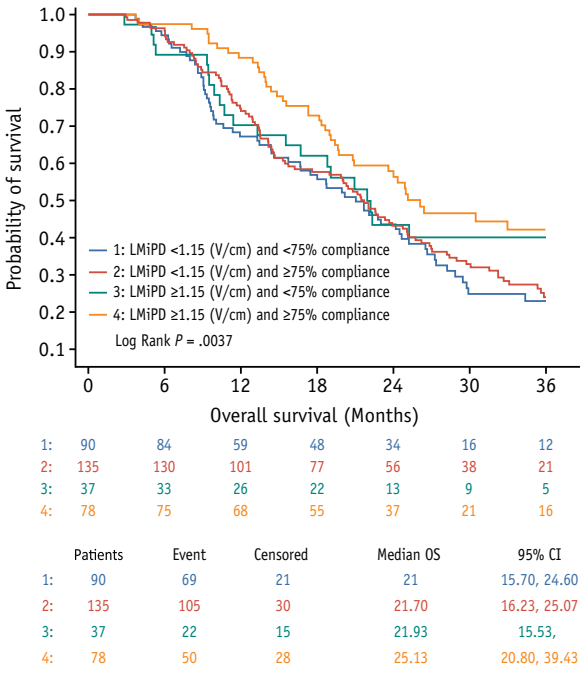

Fig. 3. Overall survival when dividing the patient population into 4 groups based on threshold values of LMiPD and compliance (log rank $P = .0037$).

effects of exposure time on glioma cell cultures and showed that the efficacy of TTFields increased with exposure time.[11] Likewise, in the EF-14 trial, OS increased in a stepwise fashion as the percentage of monthly usage of TTFields increased, validating the preclinical findings.[11,12] Our current analysis confirms a second basic tenet of TTFields' antimitotic effects: Within a fixed TTFields frequency, the antimitotic effect is intensity dependent. Kirson et al had studied the intensity dependence of TTFields in 4 different cell cultures and defined a dose-response relationship wherein inhibition of cell division and cell death increased as the intensity of the field increased.[11] In their analysis, a threshold effect of 1 V/cm was seen, where inhibition and cell death increased considerably.[11] In the current analysis, we not only confirmed the significance of TTFields intensity but also demonstrated that 1 V/cm is a clinically significant threshold value.

Previous studies have shown that maximizing patient compliance with TTFields treatment leads to improved outcomes; we hypothesized that a combination of high compliance and high power density (or field intensity) values in the tumor bed would improve patient outcomes. Indeed, the data presented confirm this hypothesis. Figure 3 shows the Kaplan−Meier curves for OS in 4 groups of patients based on LMiPD (<1.15 mW/cm^3 vs ≥ 1.15 mW/cm^3) and average compliance ($<75\%$ vs $\geq 75\%$). As predicted, patients with the highest compliance and the highest LMiPD had the highest OS (median survival 25 months, 95% CI, 20.8-39.4), whereas those with the lowest compliance and the lowest LMiPD had the lowest survival (median survival 21 months, 95% CI, 15.7-21).

To combine the factors of power density and compliance into a single measure of dose, we defined LMiDD as the product of LMiPD and patient compliance. Indeed, a survival benefit of 4.8 months was observed for the group of patients for whom LMiDD was ≥ 0.77 mW/cm^3. It is important to note that the demographics of the 2 groups formed when splitting patients according to a threshold value of 0.77 mW/cm^3 are unbalanced, with demographics (primarily age and sex) favoring increased survival in the LMiDD ≥ 0.77 mW/cm^3 group. This raises the possibility that the 4.8-month difference in OS between the 2 groups overestimates the survival benefit associated with LMiDD ≥ 0.77 mW/cm^3. However, the HR for LMiDD was calculated using a Cox proportional hazards model that accounts for the differences in demographics between the groups. The statistical significance of this HR therefore confirms a survival benefit associated with higher TTFields dose at the tumor bed.

The methods and analysis presented in this report not only confirm the clinical significance of higher TTFields intensity but also provide the framework necessary to express intensity distributions in a clinically relevant manner. The 3 components of this framework are the ability to rapidly and accurately perform numerical simulations of TTFields distributions within the tissues of individual patients, the ability to visualize these TTFields distributions, and the ability to correlate dose to patient outcome. Using magnetic resonance imaging scans, we have shown that patient-specific models can be created rapidly using previously described algorithms and that TTFields distributions can be calculated using standard numerical tools. Although it has been shown that adapting array layouts to specific regions significantly increases field intensity within the tumor bed,[9] the current analysis demonstrates that higher field intensity (LMiFI) and power loss density (LMiPD) actually translates into improved OS. The situation, therefore, is analogous to radiation therapy planning, where radiation dose distributions are calculated, visualized, and manipulated to improve target coverage and local disease control.

Despite providing a clinically valid platform for expressing TTFields distributions, it is important to recognize the limitations and assumptions of the current analysis. The tumor bed was manually segmented into specific structures and assigned specific conductivities. However, the interface between scalp, skull, gray matter, white matter, and cerebrospinal fluid was created using a presegmented healthy head model that served as a deformable template. This process provides an accurate representation of most structures except for the gray−white matter interface. Although this might be viewed as a limitation, it is important to note that field intensity in a specific region of the head is determined primarily by the spatial relationship between the arrays and the electric

conductivity of the tissue within the vicinity of the specific region. The process used to create the models leads to a relatively accurate representation of the tumor bed, and therefore it is likely that the field distribution within this region is largely accurate within the models.

Although the quantities of field intensity (LMiFI) and power loss density (LMiPD) are not equivalent, they are also not independent (see Equation 1). Therefore, it is not surprising that the average values of both quantities in the tumor bed are predictive of patient outcome, and both are physical quantities that could be considered as definitions for TTFields dose.

However, radiation dose is defined in terms of energy imparted by ionizing radiation to tissue. If a definition of TTFields dose analogous to the definition of radiation dose is desirable, then TTFields dose should also be described in terms of energy imparted to the tissue by the field. Power loss density is equal to the rate at which energy is imparted by the field to tissues. Thus, LMiPD is the quantity that should be incorporated into the definition of TTFields dose. Calculating the energy imparted to tissues from the rate of energy deposition is done by multiplying the energy deposition rate by the amount of time during which energy was deposited. Hence, the second factor needed to complete a definition of TTFields is patient compliance (usage). TTFields dose density (LMiDD), the product of LMiPD and compliance, is therefore the unifying expression of the 2 most important clinical features of TTFields treatment and provides a unique opportunity for radiation oncologists and patients. Although radiation-planning software provides a visual representation of energy deposited in tissue by a beam of radiation, it is likely that future iterations of TTFields software could visually represent both power delivered by the Optune device and the degree of patient compliance. This could create a powerful platform for patient engagement wherein physicians can visualize dose distributions and manipulate array layouts while patients can visualize dose distributions and manipulate their compliance with treatment.

We also suggest that radiation oncology clinics are well positioned to integrate this novel device-based therapy into their existing clinical workflow. Radiation oncologists already visualize and manipulate ionizing radiation dose distributions in 3 dimensions and could similarly manipulate array layouts to maximize TTFields delivery to regions of interest. Similarly, radiation oncology nurses are well versed in managing the skin toxicity of external beam radiation and could easily manage the minor skin irritation caused by TTFields therapy and help to overcome any compliance issues.

Conclusions

The current analysis suggests that the conceptual framework used for ionizing radiation is clinically applicable to TTFields therapy, and as we better understand the relationship between TTFields dose distribution and survival, it is likely that the radiation oncology team will be more involved.

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