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Appendix E1

1. Introduction

A hyperthermia-by-ultrasound model was developed using a combination of TARDOX case data and finite element calculations to specify FUS parameters and to estimate temperature histories for candidate treatment plans. Model inputs consisted of i) participant-specific anatomic data, ii) tissue acoustic and thermal properties, and iii) thermometric and radiologic results from the first two Part I participants. Model outputs for each trial participant were i) a treatment recommendation (FUS power and duty cycle, and a recommended treatment volume) and ii) acoustic (pressure, intensity) and thermal (temperature, cumulative exposure) predictions within and surrounding the treatment volume. This document describes model development, validation, usage and limitations.

2. Participant Data

Anonymized participant CT and MRI images were reviewed by the research team (F.W., F.V.G., M.A., P.C.L., C.C.C.) to identify a target tumor and a preferred intercostal route for extracorporeal FUS access. Once the target had been identified, tissue types and characteristic dimensions were determined (P.C.L., D.Y.F.C., M.D.G.) using RadiAnt DICOM viewer (proprietary, v4.0, Medixant, Poznan, Poland) software. Dimensions were reported to the nearest millimeter. This information was used in the power, pressure and temperature calculations described in the following sections.

3. FUS Power Prediction

The required FUS power was predicted through a simple geometric scaling process based upon relative ultrasonic propagation losses between a reference case and the case for which treatment was being designed. During initial model development, the first and second participants from trial Part I (referred to as I.01, I.02, and whose exposure settings were optimized in vivo using implanted thermistors) served as reference cases, as their thermometry and microscopy results indicated adequate hyperthermia and drug release, respectively. The ultrasound power scaling procedure was based on the estimated ultrasonic intensity loss to the target, which is a function of target depth (z_t) and an effective attenuation (α_{eff}) comprised of path absorption, scattering refraction, and rib obstruction.

For initial model development, the losses were taken purely based on the path averaged soft tissue attenuation:

$$\alpha_{eff,lit} = \left(\frac{z_{fat}\alpha_{fat}+z_{mus}\alpha_{mus}+z_{cart}\alpha_{cart}+z_{liv}\alpha_{liv}+z_{met}\alpha_{met}}{z_{fat}+z_{mus}+z_{cart}+z_{liv}+z_{met}}\right) \quad (1)$$

where representative tissue thicknesses z_{tissue} were extracted from CT or MRI data, and tissue-specific attenuation values α_{tissue} were taken from the literature for fat, muscle, cartilage, normal

liver, and metastatic liver tumor tissue (30–32). The acoustic intensity signal loss (L) relative to propagation in water was then estimated from: $L_{lit} = \mathrm{e}^{-2\alpha_{eff,lit} z_t}$.

Predictions for participants I.05–06 and II.01–04 used loss calculations (including refraction and rib obstruction) from three-dimensional finite element body models (FEM) described below. For these cases, the estimated intensity signal loss came from the ratio of in situ and in-water focal plane FUS intensities: $L_{FEM} = I_{in\ situ} / I_{water}$.

The continuous power prediction W_n for participant n was found from the average of the scaled estimates for the two reference cases using:

$$W_n = \frac{1}{2}\sum_{i=1}^{2} W_i \left({}^{L_i}/_{L_n}\right) \quad (2)$$

where W_i are the reference case FUS powers. The primary assumption made for the above calculation was that the FUS power required for sustained mild hyperthermia scaled with tissue path length and attenuation. Mechanical and thermal tissue properties (including perfusion) for each tissue type were taken to be time-invariant and identical across all participants, and absorption was taken to be equal to attenuation in the target tumor (33). The estimated effect of nonlinearity and its contribution to heating was accounted for separately (see section 6 of this document).

Initially, the scaling calculation above only specified continuous power, leaving pressure amplitude and duty cycle unconstrained. Following participants I.04 (where a partial radiologic response was observed in the target tumor by modified Choi criteria) and I.05 (where no formal radiologic response was observed), a mid-target peak to peak pressure was fixed at the estimated value for I.04: 18.0 MPa based on linear estimates. Doing so allowed specification of JC200 power and duty cycle from the following procedure. The relationship between JC200 specified power and peak-to-peak pressure was measured (29) for acoustic powers < 50 Watts (W) and fit to:

$$p_{water} = 1.91\sqrt{W_{jc200}} + 5.5 \ \ (MPa) \quad (3)$$

The in situ pressure is related to the pressure in water by a tissue derating factor based on the attenuation described above:

$$p_{insitu} = p_{water} e^{(-\alpha_{eff} z_t)} \quad (4)$$

Combining Equation 3 and 4, the required drive power to achieve the desired pressure is

$$W_{jc200} = \left(\frac{p_{insitu}\, e^{(\alpha_{eff} z_t)} - 5.5}{1.91}\right)^2 \quad (5)$$

Finally, the duty cycle (as a percentage) was found from the ratio of the power scaling estimate in Equation 2 and the pressure-based estimate in Equation 5:

$$DC_{jc200} = 100 * \left({}^{W_n}/_{W_{jc200}}\right) \quad (6)$$

From Equations 4–6, the FUS settings were defined for pulsed power (W_{jc200} at DC_{jc200}) for a target pressure of p_{insitu}, which was fixed at 18.0 MPa peak-to-peak. Calculations were performed in MATLAB (R2015b, Mathworks, Natick, MA), with execution time under one second on a circa-2015 desktop PC running Windows 7.

Uncertainties in the values computed from the above equations were estimated using conventional error propagation analysis (34), which can be written as:

$$\Delta v = \left(\sum_j \left(\frac{\partial v}{dx_j} \right)^2 (\Delta x_j)^2 \right)^{\frac{1}{2}} \quad (7)$$

where Δv is the uncertainty in the dependent variable (p_{insitu} (Eq 4), W_{jc200} (Eq 5) and DC_{jc200} (Eq 6)), and Δx_j are the uncertainties in each of the input independent variables. The dominant uncertainty in the acoustic pressure in water (p_{water}) came from the hydrophone calibration, while uncertainties in the attenuation values were found from the tissue-specific literature, and the thickness of each tissue estimated from CT or MR scans was taken to be ± 1.0 mm. The total uncertainty varied with each participant, since each had different tissue morphologies. Estimated values are listed in Table E1 for p_{insitu}, W_{jc200}, and DC_{jc200}.

Pressure estimation uncertainties were dominated by the hydrophone calibration, while the power and duty cycle estimates were also influenced by tissue composition. Participant II.01, who had the thickest layer of peripheral fat, had largest power and duty cycle uncertainties, owing to the uncertainty in fat attenuation values in the literature. Valuable improvements to future clinical modeling efforts could be brought about through improvements in the accuracy of instrumentation used for FUS system calibration, and through estimation of participant-specific in vivo acoustic tissue properties.

4. Pressure and Temperature Prediction

An analytical capability was developed for the purpose of predicting in vivo temperature and acoustic pressure fields during candidate mild hyperthermia treatment plans without direct use of prior participant treatment outcome data. This branch of the model used 3D acoustic and thermal calculations incorporating participant radiologic image data as described below.

4.1. FUS Source Model

The JC200 clinical system employs a single element source with a fixed spherical focus. Since it is both physically large (200 mm active diameter) and its beam is unsteerable (not an array-based radiator), it was both computationally burdensome and unnecessary to recompute the full source incident field for every position of interest in the volumetric hyperthermia scan. As an alternative, the radiated field from the source was computed once, retaining both the focal and prefocal data, with the latter used to create a boundary load to the 3D body model (Fig E1). The source fields were calculated in PZFlex (v2015, PZFlex LLC, Cupertino, CA, proprietary software) using an axisymmetric formulation, using both linear and nonlinear materials to assess harmonic generation and nonlinear contributions to heating. Ultimately, it was found that the

predicted nonlinear heating contributions were small (< 10%, see Section 6) for all TARDOX participants.

4.2. 3D Acoustic Model

Tissue geometry information from the screening CT and MRI reviews were used to build a three-dimensional body model in the vicinity of the target tumor. PZFlex was again used for this purpose. Tissue types were assigned into five categories-fat, muscle, cartilage, liver and compact bone–the acoustic properties of which were taken from the IT'IS database (31) except for bone shear speed (35). Rather than segmenting and mapping imaging data into the acoustic model, tissue morphologies were approximated with simpler geometric forms to accelerate the model generation and computation processes (Fig 3b in the main manuscript). This was also done in recognition that tissue morphologies as seen in the screening data may differ from those on the day of treatment simply due to participant positioning. MR-guided systems can adapt to such issues since imaging is performed as part of the treatment. Given the uncertainties in tissue positions and properties, and the emphasis on volumetric rather than single site treatment, the level of effort and complexity involved in fine scale image-segmentation and mapping into the models was deemed unjustifiable.

The models included solid ribs (as compact bone) to allow assessment of their scattering, absorption and resultant heating. However, the large focal gain of the FUS source (ratio of focal to surface pressures in water ~56) meant that the acoustic intensity incident upon the ribs would usually be 2–3 orders of magnitude smaller than at the focus for the treatments in our study. This, combined with the relatively low drive powers (compared with those used for ablation) and brief source position dwell times minimized the risk of prefocal rib heating.

The prefocal FUS source data sets were used to specify the incident ultrasonic field in water, just prior to entering the body. In situ pressure field changes with respect to FUS source position were calculated by translating the prefocal source data in 3–5 mm steps laterally (for synthesis of scan lines at a fixed depth) and 8–12 mm axially (for accumulating scan lines at multiple depths to form treatment 'slices'). Mesh convergence was tested within the memory limits of existing hardware by progressively lowering the grid size until the field peak amplitude changed less than 2%.

4.3. Heat Source Distribution

Pressure field maps saved from 3D acoustic model runs were exported to MATLAB and used to estimate the distribution of heat generation sources from $\dot{q} = 2\alpha I_{pa}$, where the absorption α was taken to be equal to the attenuation in liver at the FUS fundamental frequency, and the pulse averaged intensity $I_{pa} = \frac{1}{\rho c \tau_p} \int_{t=0}^{\tau} p^2 dt$, was calculated with pulse time τ_p and total record time τ. The use of this form ignores nonlinear contributions to heating–an assumption that is discussed and mitigated in Section 6. Heat generation terms for FUS source locations not explicitly run in PZFlex were estimated by linearly interpolating between nearest available calculations. Since the FUS source emits a pulse at on the order of 100 unique positions per scan line, and on the order of 10^4 unique positions per scan volume, the spatial interpolation step allowed thermal predictions to be completed in a manageable time frame with respect to the time window between participant screening and therapeutic treatment. Specifically, eight to ten full models

spanning the maximum anticipated scan line width (based on the width of the intercostal space selected during screening) were run to define an effective field taper profile that approximately described rib shadowing and soft tissue refraction effects.

4.4. Thermal FEM

The heat source terms found in the previous step were imported back into a PZFlex thermal finite element calculation incorporating thermal tissue properties taken from the IT'IS database (31). Temperature elevations were found by driving each heat source for 20 msec (1/5th the typical pulse repetition period used in the trial) and calculating the temperature field for 240 s. Thermal boundary conditions were set to be infinite, the starting field was at a uniform temperature, and all thermal properties were taken to be temperature-independent. Liver perfusion rates were varied between zero and published values (36) to assess sensitivity. Convergence studies were performed to determine the spatial and temporal step sizes that adequately described the field evolution. Values were chosen by progressively decreasing the step size until the maximum temperature, location and time changed no more than 2%.

4.5. Volume Heating

Temperature fields generated in PZFlex for individual heat source distributions (corresponding to a single FUS source position with respect to the fixed participant body) were superposed in MATLAB to form volumetric temperature elevation estimates. Specifically, a line scan temperature profile was synthesized by adding fields from successive source positions, with sequential time delays defined by the ratio of thermal grid step size and the source translation speed. Two-dimensional slices were synthesized from the addition of line scans at multiple tissue depths, and volume scans were formed from the addition of multiple slices. The validity of using superposition was verified for a scan line by comparison with an explicit translating source model generated entirely within PZFlex.

The final outputs of the model was a temperature history in a three-dimensional grid encompassing the target tumor, along with statistical descriptions of volume heating and cumulative exposure. The administrative burden associated with transferring data between programs as described above was more than offset by the enhanced control over problem size and memory allocation. All processing described here was conducted on a single PC workstation with 256 GB RAM. While the calculations were tailored to run on this system, the broader objective was to assess the ability to make trustworthy pressure and temperature estimates in support of mild hyperthermia treatment planning, using modest facilities to complete the first estimate and a small number of iterations in a timeframe well within the window between participant screening and scheduled treatment (as few as three weeks).

4.6. Calculated Quantities and Metrics

The above procedures generated pressure, intensity and temperature fields from each individual transmission at a subset of the source locations used in the planning simulation for each participant. From the latter, treatment-cumulative temperature fields were computed, from which several metrics were found: i) volume-averaged temperature history, ii) T_{50} and T_{10} (temperature exceeded 50 and 10% of the tumor volume, respectively) time history, iii) spatially integrated temperature to mimic the performance of the invasive thermometry devices (which have distributed sensitive areas–see (29)), and iv) cumulative thermal dose (CEM_{43} (37),) based on T_{50}

and T_{10}. PIR (percent in range) was calculated to describe the portion of the treatment volume between the liposomal release threshold (39.5°C) and a short duration safe exposure threshold (47.0°C, see (38)). Similarly, TIR (time in range) quantified the amount of time that at least 50% of treatment volume was between 39.5–47.0°C.

5. Model Validation

5.1. Pressure

Pressure field predictions were experimentally evaluated using a preclinical configuration shown in Figure E2, *A*. A single element spherically-focused source resembling a scaled-down version of the JC200 transducer (H102, Sonic Concepts, Bothell, WA) was driven with a tone pulse, and the resulting field was measured in a 2D plane using a needle hydrophone (200 μm, Precision Acoustics, Dorchester, UK). The effect of rib-like structures was simulated using a pair of PVDF rods (mass density = 1780 kg/m^3, bulk speed = 2430 m/s), with cross sectional dimensions representative of ribs encountered in early trial participants. Pressure fields were first determined without ribs, and subsequently for several target locations between and ultimately behind ribs.

Figure E2, *B*, shows a comparison of predicted and measured pressure amplitude as function of lateral and axial position for the case where the source focus was centered between ribs. Pressure amplitudes were normalized by the focal plane peak in water and displayed in decibels, so that a value of 0 dB at the focus indicates no attenuation. In the 3D illustration to the right of the two plots, the gray box indicates the plotted field boundaries, and the dashed magenta lines inside the plots indicate the focal 'cone' of the FUS source. Rib effects were apparently negligible in the geometry of Figure E2, *B*, and the simulation and measurement were in good agreement. In the case where the geometric focus of the source was aligned with a rib edge (Fig E2, *C*), the field levels and shapes were still similar, but with modestly larger differences than in Figure E2, *B*. Additional FEM calculations (data not shown) indicated that material properties weakly influenced the fields, and the discrepancies were likely arising from differences between modeled and constructed rib cross sections. Figure E2, *D*, shows the focal plane summary pressures as a function of source lateral shift (ordinate) in 2 mm steps. The trends were in good agreement between measurement and prediction. Within the rib space (0–12 mm), the pressure amplitudes drop by approximately half, so that the heating rate would drop by approximately a factor of four. As expected for shallow target scenarios such as those illustrated here, treating over/through dense obstructions is highly inefficient.

5.2 Temperature

Thermal model validation was carried out using the above preclinical configuration modified by the presence of an agar-based soft tissue mimicking phantom (39) as in Figure E3, *A*. Phantom heating as a result of ultrasound absorption was monitored using a pair of fine needle thermocouples (HYP0–33–1-T, Omega, Stamford, CT) whose responses were logged with a USB reader (TC-08, Pico Technology, St. Neots, UK). A small fixed focus transducer (Panametrics V320, 7.5MHz, 2.95" spherical focus, Olympus NDT) was coaxially aligned with the source and used as a passive cavitation detector (PCD) to ensure that all heating experiments were done in the absence of cavitation. The PCD transducer was also used in pulse-echo mode for alignment to and localization of the thermocouples. Heating experiments were conducted while driving the source with a continuous signal for 20 seconds. To support comparison with

models, the sound speed, mass density and ultrasound attenuation were all measured using conventional methods and provided as inputs to the simulations. Thermal properties for the phantom were taken from several sources (40,41) to assess sensitivity.

The predicted and measured temperature elevations in the agar phantom are shown in Figure E3, *B*, when aligned over a single thermocouple. Predicted temperatures shown for three sets of agar thermal properties closely bound the measured values while the source is on (20s), and slightly overestimate the short-term cooling rate.

6. Nonlinearity Assessment

The impact of nonlinear propagation on the prediction of target pressure and heating was assessed using PZFlex, with values for coefficient of nonlinearity taken from the IT'IS database (31). Since nonlinear propagation expands signal bandwidth, the model mesh size was refined to adequately capture harmonic generation. This placed enormous demands on computational resources: halving the grid dimension raised the required machine memory by four and eight for 2D axisymmetric and 3D models, respectively. The latter scaling made 3D nonlinear calculations relevant to TARDOX untenable on the available workstation. Instead, nonlinearity assessments were carried out using axisymmetric models of the JC200 FUS source into tissue models consisting of layers of fat, muscle cartilage and liver on a participant-by-participant basis. A baseline mesh grid dimension of 25 μm (approximately 62 wavelengths of f_0 = 0.96 MHz in water) was chosen based on prior convergence studies, and a 16 μm grid was used for convergence out to the 3rd harmonic for the nonlinear model. Note that in addition to the geometric scaling, the model time step scales with element size for computational stability reasons (42). This further elevates the total nonlinear problem computation time.

The predicted effect of nonlinear propagation on the focal pressure spectrum is shown in Figure E4, *A*, for participant I.01, using a source drive signal consisting of a five cycle sine wave at the FUS fundamental frequency (0.96 MHz), with an amplitude consistent with the I.01 treatment power (50 W). The linear tissue result (red) has a spectrum peak centered at the drive frequency, with sidelobes as expected from the use of a short tone pulse. The nonlinear result (blue) shows modest harmonic generation, with 2nd and 3rd harmonic levels approximately a factor of five and twenty three lower than that of the fundamental. Their intensity contributions are approximately quadratic in pressure, with commensurate reduction of the ultrasonically generated heating rate.

Figure E4, *B*, shows the on-axis heating rate ($\dot{q} = 2\alpha I$ integrated over frequency) for the midtarget treatment depth as computed for linear and nonlinear propagation, presuming an ultrasonic absorption of $\alpha = 0.06 f^{1.0}$ np/cm/MHz. Both beam peaks are shifted slightly toward the FUS source as a result of refraction in the tissue layers. Inclusion of nonlinear effects raised the estimated spatial peak heating rate by 5.1%, and by 2.5% when integrated over the FUS beam main lobe. These biases are small compared with all other uncertainties in the predictive process (eg, acoustic and thermal properties, target position, JC200 calibration). Capturing the observed nonlinear effects up through the third harmonic required a factor of 16.1 growth in computation time.

Summary beam-averaged heating rate enhancements calculated for all TARDOX participants are listed in Table E2. Even when higher drive powers were used for treatment of deeper targets, the nonlinear effects were offset by path attenuation, so that the net effect was no

greater than 9% (4.7% mean, 2.7% standard deviation across all ten participants). The nonlinear calculations were performed in the absence of ribs, and therefore provided a likely upper bound. It therefore seemed highly unlikely that nonlinear heating would be a major factor in the proposed moving beam hyperthermia scheme, and computations of full 3D nonlinear fields were unwarranted. Instead, the heating enhancement ratios in Table E2 were applied as scale factors to volume heating calculations (section 4.3 of this document) as an upper bound on the impact of nonlinear effects. The resulting thermal statistics are presented and discussed in the *Results* section of the main manuscript.

An added value of the nonlinear models was in estimation of peak negative pressure and associated mechanical index (MI). Again, these estimates did not include any effects associated with ribs, and therefore were likely to overestimate the pressures in situ. The largest rarefactional pressures were in the range of 8.0 MPa, which exceeds the estimated in vivo thermally significant cavitation threshold in dog thigh at 1 MHz (43). However, the duration of TARDOX exposures at any one site were at least an order of magnitude shorter than in the dog study, with a significantly reduced cavitation risk (44). This-together with rib-shadowing, beam distortion in 3D refracting media, and the continuously moving beam used for most treatments-suggested that there would be minimal cavitation enhancement of heating. Enhanced drug transport due to thermally insignificant cavitation may still be possible (24), but this effect was not assessed in our study. Had higher pressures for greater temperature elevations been of interest (for ablation or histotripsy treatment, for example), three-dimensional nonlinear models would have been required, and other computation resources would have been sought.

7. Usage and Limitations

Model results were combined (M.D.G.) into a single treatment recommendation provided for consensus review by the research team. The recommendation included FUS parameters (power, duty cycle), scan volume (dimensions, slice thickness and depth partitioning into lines per slice), estimated in situ pressures, and a reminder of assumptions used. For Part I, settings from the predictive model were used as a starting point, but optimization and acceptance (based on test FUS transmissions and preliminary thermometry) were at the discretion of the radiology clinical fellow (P.C.L.) and the FUS clinician (F.W.). In all cases the treatment was monitored by the FUS clinician, who specifically looked for B-mode enhancement as evidence of bubble formation as an indication of FUS parameters that were delivering excessive exposure. No such echo enhancement was observed in the trial, thus reassuring the clinical team that FUS parameters were in a safe hyperthermia regimen.

Restrictions imposed by the FUS system served to greatly condense the optimization parameter space. FUS power and duty cycle could not be varied pointwise during a treatment without halting and restarting, so one set of values must be chosen for tumor volumetric coverage. The single element fixed focus transducer could not be dynamically steered or apodized, so geometric positioning was the only option available to maximize intercostal targeting while minimizing direct rib exposure. Transducer motion was limited to linear translation, so circular (6) or other arbitrary trajectories could not be efficiently implemented. Further simplifications were made following a series of preclinical temperature measurements (29), leading to the use of a fixed pulse repetition period (100 ms), linear translation speed (6 mm/s, the maximum attainable), slice thickness (2 mm), and slice skip (8 mm, distance between consecutively treated treatment planes). As a result, ultrasound power, duty cycle and treatment

volume geometry (number and size of lines and slices) were the only exposure parameters varied in the planning calculations.

8. Supplemental Results and Discussion

8.1 Thermometry and Thermal Modeling Results

Review of the measured and predicted thermometry data in Table E3 for all trial participants reveals several noteworthy trends. The treatment averaged temperature from the implanted sensor in Part I participants was within 0.1–0.3°C of the model prediction (time average of T_{50}) for the three participants with treatment volumes ≤ 52 cm^3 (I.01, 02, and 06). The similarity of these temperature values also suggests that cavitation (24) was an unlikely heating mechanism.

Time in range (39.5–47.0°C) measurements and predictions (cumulative time where PIR ≥ 50%) were most similar for the smallest treatment volumes. For participants with larger treatment volumes (I.04, 05), the time-averaged temperature prediction was 1.4–1.7°C below the sensor-based value, suggesting that as expected, the small sensor was not a good indicator of the median temperature of the larger targeted regions.

A review of histologic (R.G.) and day +1 MRI data (F.V.G., P.C.L.) showed no clear evidence of instantaneous tissue ablation. Interestingly, while the $CEM_{43}T_{50}$ estimates for all participants were less than 30 minutes, the predicted $CEM_{43}T_{10}$ values substantially exceeded 240 minutes in cases I.04, I.06, II.01 and II.03. Since the model does not account for temperature-induced perfusion changes or other physiologic responses in tumors, the predicted peak temperatures and corresponding T_{10} metrics may be unrealistically high. Safe exposure recommendations described in prior ultrasound heating studies were derived from either stationary (30) or fixed orbit (7) sources treating volumes ≤ 1 cm, and therefore may not be directly applicable for the combination of source motion and tumor size in the present study.

The treatment time-averaged PIR values (26.2%–60.0%) indicate a nonuniform temperature field within the prescribed volume at any point in time. The moving FUS beam approach was predicted to elevate the temperature of the entire prescribed volume, but with preferential short-term temperature elevation centered in a sub-volume around the current FUS treatment line and slice (Fig 1b).

The FUS treatment parameter data for each participant was listed in Table 2 of the main manuscript. Across all participants, prescribed power scaled approximately with target depth, subject to details of tissue path morphology. For cases where model predictions were available at the time of treatment (I.04–06 and II.01–04), the collective differences between predicted and treatment-averaged implemented powers were not significant (3.5 Watt mean, $P = .33$). A larger prediction-implementation difference for Part I would not be surprising, given that thermometry readings were available to dynamically modify the FUS system settings if needed. One notable example of this was seen with I.05, where a successful predrug test exposure of model-prescribed parameters was followed by a near-doubling of treatment volume (for which the model had not been run) in an effort to treat more of the large target tumor. Still, these results indicate that the model consistently provided settings deemed safe by the lead radiologist and FUS clinician at the time of treatment.

Models were run retrospectively for participants I.01–03, who were treated prior to model availability. The largest prediction discrepancy was seen with I.03, where the target depth was

nearly 5 cm deeper than for any other participant. Based on thermometry (Table 3), the I.03 treatment was substantially under-powered, and use of the model-predicted settings (had they been available at the time) should have improved target heating.

8.2 Drug Delivery Results

Intratumoral biopsy drug concentration data in Table E3 is presented alongside the thermal modeling and thermometry results to enable assessment of the impact of heating on drug delivery. Across all patients, ultrasound-mediated drug delivery fold-enhancement (post-FUS/pre-FUS ratio) was 3.7 mean (1.3–9.3 range), with a 3.3 mean (1.3–5.2 range, $n = 6$) in patients monitored with thermometry and 4.2 mean (1.78–9.3 range, $n = 4$) in patients without thermometry (21). This suggests that the absence of real-time thermometry was not detrimental to the overall process of enhancing drug delivery. Pearson analysis of the data in Table E3 across all participants further demonstrates that there is no apparent correlation between the final post-FUS intratumoural drug concentration and median temperature (R = -0.43), Time-in-Range (R = -0.26), PIR (R = -0.22) or CEM43 (R = -0.32). Beyond the calculated characteristics of tumor heating, other clinical factors that may have similar impact on drug delivery and its quantification include tumor type, size, and vascularity, and small volume biopsy sampling as performed in this study.

8.3 Discussion

The vast majority of nonlithotriptic clinical experience with therapeutic extracorporeal ultrasound had been for soft tissue ablation. The TARDOX trial represents the first clinical noninvasive FUS application for mild hyperthermia–induced targeted drug delivery. Several challenges were faced in making the transition from the extensive body of work in ultrasound-induced hyperthermia for liposomal drug release in small animals to clinical application. Transcostal FUS propagation, uncertainties in constituent tissue properties, and participant motion were all of concern. However, operation in a sub-ablative realm appeared to simplify the physics of energy transduction from sound to heat, and commensurately eased constraints around treatment planning and monitoring.

The treatment planning model provided FUS parameters that required little if any modification by the FUS clinician when defining the treatment protocol. Model performance was quantifiable both from invasive thermometry and from intratumoural drug release as a surrogate for reaching the desired temperature range in the targeted region. Specifically, similar levels of doxorubicin were found when the treatments were performed with and without invasive thermometry (21).

These findings are probably not due to the point-by-point accuracy of the model, but rather to the fact that local response variations are spatially and temporally smoothed by conduction and perfusion over the course of a clinically relevant treatment. It is therefore conceivable that sophisticated control algorithms for tight temperature constraint (45) may not be necessary for mild hyperthermia protocols. Ensuring highly accurate trajectories of the FUS focus in a clinical context would be challenging based on the experience from this trial, and the simplest solutions may therefore clinically work best.

The relatively streamlined modeling approaches used here appeared to be justified given all the uncertainties in participant specific treatment planning, such as tissue acoustic and thermal properties, perfusion variability, temperature dependencies of all these parameters, and tissue

morphologies relative to preintervention CT and MRI scans which may have been done in a different body position/orientation than the actual treatment. The degree to which the modeling approach could be extended to more detailed planning optimization with more degrees of freedom (such as curved trajectories, position-adjustable powers) in a clinically useful timeframe is not known.

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Table E1: Estimated uncertainties in pressure, power and duty cycle calculation.

Participant		Uncertainty	
ID	p_{insitu}(MPa)	W_{jc200} (W)	DC_{jc200}(%)
I.01	2.1	9	17
I.02	1.8	10	14
I.03	1.6	15	11
I.04	2.4	14	11
I.05	2.3	13	12
I.06	2.7	11	9
II.01	2.8	29	25
II.02	2.7	17	15
II.03	2.6	21	15
II.04	2.6	10	10
Mean	2.3	15	14

p_{insitu} = in situ pressure uncertainty (peak to peak): compare with Table E2 mid-target pressures

W_{jc200} = FUS drive power uncertainty

DC_{jc200} = Duty cycle uncertainty

Table E2: Nonlinear simulation results.

Participant ID	Midtarget Depth (cm)	JC200 Average Power (W)	Mid-Target Pressure (MPA)			Heating ratio ($q_{nonlinear}$/ q_{linear})
			p+	*p*-	MI	
I.01	5.6	50	9.9	6.7	7.6	1.03
I.02	8.5	70	7.5	5.6	7.4	1.01
I.03	12.9	100	6.3	5.0	7.7	1.00
I.04	7.6	140	11.8	7.7	9.2	1.05
I.05	5.8	120	11.1	7.3	8.8	1.04
I.06	4.1	116	13.6	8.2	9.3	1.05
II.01	5.9	123	13.2	7.9	9.6	1.09
II.02	4.5	114	13.2	8.0	9.4	1.06
II.03	7.0	140	12.5	7.9	10.0	1.06
II.04	4.1	110	12.9	8.0	9.0	1.08

Pressures and nonlinear heating enhancement ratios were calculated at mid-target depth.

p+ = peak positive pressure

p- = peak negative pressure

MI = Mechanical Index

$q_{nonlinear}$ = heating rate including nonlinear propagation

q_{linear} = heating rate assuming linear propagation

FUS = focused ultrasound

Table E3: Thermometry and drug delivery results.

Participant Information			Thermometry							Drug Delivery	
Partici-pant ID	Prescribed Volume (cm^3)	FUS Exposure Time (min)	T_{mean}, °C		Time in Range (minutes)		PIR_{mean} %	$CEM_{43}T_{50}$ (minutes)	$CEM_{43}T_{10}$ (minutes)	Dox Concentration (mg/g)	
			Sensor	Model	Sensor	Model	Model	Model	Model	Pre-FUS	Post-FUS
I.01*	11	33.2	39.8	39.7	23.1	28.8	52.2	0.5	115.6	2.56	5.32
I.02*	26#	74.6	39.3	39.4	27.4	38.6	51.1	2.1	75.7	1.78+	13.2**
I.03*	59#	72.4	38.9	38.3	0.1	7.5	26.2	0.1	5.2	4.09	7.89
I.04	73	66.0	41.5	40.1	63.0	40.6	46.4	2.3	2040.0	1.59	2.09
I.05	67#	80.0	40.1	38.4	56.6	21.4	27.6	0.2	14.9	2.23	11.50
I.06	52	64.5	40.6	40.9	35.9	52.3	55.0	5.7	2217.7	1.79+	6.41
II.01	41	55.1		41.7		43.8	57.4	29.2	4530.8		6.65
II.02	50	69.8		39.6		47.0	49.5	1.0	230.6		6.84
II.03	31	74.6		41.7		53.9	60.0	21.7	928.5		3.89
II.04	54	72.9		39.4		34.6	47.6	0.6	65.2		21.80

An asterisk next to the participant ID indicates that the model calculations were run retrospectively.

Model-generated values were calculated based on each actual treatment.

T_{mean} = Temperature averaged over treatment time for the sensor and model (using the median of the treatment volume)

PIR = percentage in range: portion of treatment volume between 39.5–47°C.

TIR = time in range: total time during which at least 50% of the treatment volume was between 39.5–47°C.

CEM_{43} T_{50} = cumulative equivalent minutes of exposure at 43°C, calculated for the median temperature in the treatment volume as a function of time

CEM_{43} T_{10} = cumulative equivalent minutes of exposure at 43°C, calculated for the temperature exceeded by the warmest 10% of the treatment volume as a function of time

FUS = Focused Ultrasound

Dox = Doxirubicin

+ For I.02 and I.06, the pre-FUS responses in the biopsy extracts were significantly below those seen for the lower limit of quantification. The values shown for these patients are upper-bound estimates, and as such, the Part I Pre-FUS mean comparator is likely an over-estimate of the true concentration (21).

** The post-FUS value for I.02 is an estimate, and is likely below the true concentration (21).

Table entries marked with (#) are time-averaged over the treatment.