Supporting Information

Computer model

Mathematical model of radiofrequency heating

Similar to prior studies, we coupled a heat-transfer model simulating RF ablation heating with a drug delivery model, and simulated these in 3-D via Finite Element Method [1, 2]. In the heat-transfer model, the temporally and spatially varying tissue temperature profile resulting from RF heating was calculated by solving Pennes’ Bioheat equation [3]. Perfusion is altered in response to hyperthermic and ablation range temperatures [4], and thus affects both RF tissue heating and drug delivery. In prior modeling studies [2], hyperthermia induced perfusion change was modeled based on small animal tumor studies [5]. Since here we modeled normal liver tissue, we considered perfusion temperature dependence based on measurements in normal porcine kidney [6], as similar data on liver was not available. Detailed equations and parameter values are listed in the Supplementary Materials.

The main governing equation that has established to model the temperature distribution in biological tissues is the Bioheat equation and is based on the general equation for conservation of energy [3]:

$$\rho c \frac{\partial T}{\partial t} = k \nabla^2 T + Q_{\text{rf}} - Q_P,$$  \hspace{1cm} (1)

where $\rho$ is the density (kg·m⁻³), $c$ is the specific heat (J·kg⁻¹·K⁻¹), $k$ is the thermal conductivity (W·m⁻¹·K⁻¹), $Q_{\text{rf}}$ (W·m⁻³) is the heat generated by RF current, and $Q_P$ (W·m⁻³), is the heat loss due to blood perfusion. The energy generated by the metabolic processes is neglected since it is orders of magnitude lower than $Q_P$.

$$Q_P = \rho_{\text{bl}} c_{\text{bl}} w_{\text{bl}} (T - T_{\text{bl}}),$$  \hspace{1cm} (2)

$T_{\text{bl}}$ is the temperature of the blood (commonly assumed to be 37 °C), $\rho_{\text{bl}}$ is the blood density (kg·m⁻¹), $c_{\text{bl}}$ is the specific heat of human blood (J·kg⁻¹·K⁻¹), and $w_{\text{bl}}$ is the blood perfusion (s⁻¹). The temperature dependence of the blood perfusion term $w_{\text{bl}}$ was implemented as described in a prior publication [7], with an initial increase in perfusion followed by vascular stasis (Fig. S1). This temperature dependence was implemented based on a first-order kinetic Arrhenius model. A variable “degree of stasis” (DS) was modeled according to following equation with $A$ as the frequency factor ($1.98 \times 10^{106}$ s⁻¹), and $\Delta E$ is the activation energy ($6.67 \times 10^5$ J·mole⁻¹) [7]:

$$DS = 1 - \exp(-\int_0^t A e^{-\Delta E/(RT(\tau))} d\tau)$$  \hspace{1cm} (3)

Based on DS, perfusion was varied according to Figure S1.
Fig. S1. Relative perfusion vs. degree of stasis (DS) used to model dose dependent perfusion change.

For RF heating at frequencies between 300 kHz and 1 MHz, tissue can be considered as purely resistive as the as the displacement currents are negligible. Thus heating around the active electrode due to dissipating electrical power $Q_h$ (Joule loss) can be modeled via quasi-static approach:

$$Q_{rf} = J \cdot E,$$  \hspace{1cm} (4)

where $J$ (Am$^{-1}$) is the current density and $E$ (Vm$^{-1}$) is the electric field intensity [8, 9] which can be evaluated from the Laplace’s equation $\nabla \cdot (\sigma \nabla V) = 0$, thus $Q_h$ can be expressed as:

$$Q_{rf} = \sigma |\nabla V|^2,$$  \hspace{1cm} (5)

where $\sigma$ is the electrical conductivity and $V$ is the electric potential (Volts).

Table S1. Parameters of heat-transfer model.

| Symbol | Description                        | Value       | Source |
|--------|------------------------------------|-------------|--------|
| $\rho$ | Mass density of tissue             | 1060 kg m$^{-3}$ | [10]   |
| $c^*$  | Specific heat of tissue            | 3600 J kg$^{-1}$ K$^{-1}$ | [10]   |
| $k^*$  | Thermal conductivity of tissue     | 0.52 W m$^{-1}$ K$^{-1}$ | [10]   |
| $\sigma^*$ | Electrical conductivity       | 0.333 S m$^{-1}$ |        |
| $c_{bl}$| Specific heat of blood             | 3800 J kg$^{-1}$ K$^{-1}$ | [10]   |
| $w_{bl}$| Blood perfusion rate               | 0.018 s$^{-1}$ | [11]   |
| $T_{bl}$| Arterial blood temperature         | 37 °C       | NA     |
| $k_p$  | Controller parameter (proportional term) | 0.2        | NA     |
| $k_i$  | Controller parameter (integral term)  | 0.01       | NA     |
In Table 1, temperature dependence of electrical conductivity of liver tissue was assumed with $1.6 \, ^\circ \text{C}^{-1}$ [12]. Temperature dependence of the thermal conductivity of liver tissue was implemented according to ex-vivo measurements from a prior study [13]. The value of latent heat of vaporization for water was used for liver tissue as in previous studies [14, 15].

Mathematical drug delivery model

**Fig. S2. Drug delivery model overview.** Intravascular temperature-dependent release of Dox from TSL, uptake by interstitium (EES), and cell uptake are simulated. Local temperature and perfusion are fed into the drug delivery model from the heat transfer model.

The tissue temperature and perfusion were fed into the drug delivery model to calculate intravascular release from TSL-Dox, transport from plasma into tissue interstitium (extracellular-extravascular space (EES)), and uptake by liver cells (Fig. S2), similar to prior studies [1, 2]. Similar to prior models, the targeted liver tissue and body compartments were modeled separately [2]. Liver tissue was modeled via three compartments: plasma, extracellular-extravascular space (EES), and intracellular space. The body was modeled via tissue compartment (representing all body tissues except tumor i.e. organs with a significant drug uptake) and plasma compartment. These systemic plasma and tissue compartments were not considered spatially varying.

In order to simulate spatio-temporal release and transport of Dox the tumor was modeled by spatially varying compartments; i.e. each location within the tumor was represented by its own sub-compartment. The normal tissue was represented by a single compartment without considering spatial variation and the systemic plasma compartment included the total blood plasma volume with exception of the tumor. The administered TSL-Dox at a dose of 30 mg is modeled as a 30 min continuous infusion into the systemic plasma compartment. Pharmacokinetics (PK) of Dox after release was based on prior studies [16], as were PK and release kinetics of TSL-Dox [2, 17]. Note that we considered uptake kinetics of normal liver cells [18] rather than tumor cells as in prior studies [2], to allow direct comparison to the in vivo studies that were performed in normal porcine liver.

We used equations from Gasselhuber et al. [2] to model the transport of Dox from the systemic plasma compartment with the normal tissue compartment and with the tumor plasma space, and from the tumor plasma transport of Dox into the tumor interstitium. Gasselhuber et al. used a cell uptake model developed El-Kareh et al. [19], based on in vitro studies on lung cancer cells [20]. Since in the current study the computer model...
was compared to in vivo studies in normal liver, a cell uptake model for normal liver cells was used, based on prior in vivo studies [18]. In addition, we added a source term in equation (5) to model infusion, rather than bolus administration as in the prior model [2].

\[
\frac{dc_{p,TSL}}{dt} = \frac{D / V_p^B}{T_{inf}} - k_{e,TSL} c_{p,TSL} - R_{RS3} c_{p,TSL} \tag{6}
\]

TSL-Dox concentration in systemic plasma (encapsulated drug)

\[
\frac{dc_p^B}{dt} = \frac{\int (F_{p,v}^T c_p^T v_p^T) dV}{V_p^B} + c_{p,TSL} R_{RS7} - k_e c_p^B - k_i c_p^B + k_i c_i - c_p \frac{\int F_{p,v}^T dV}{V_p^B} v_p^T \tag{7}
\]

Dox concentration in systemic plasma (unencapsulated drug)

\[
\frac{dc_i^B}{dt} = k_p c_p^B - k_i c_i \tag{8}
\]

Dox concentration in systemic tissue

\[
\frac{dc_p^T}{dt} = -\frac{1}{v_p^T} PS \cdot (c_p^T - c_e^T) - F_{p,v}^T c_p^T + F_{p,v}^T c_e^B + c_{p,TSL} R \tag{9}
\]

Dox concentration in liver plasma

\[
\frac{dc_e^T}{dt} = \nabla \cdot (\text{Diff} \cdot \nabla c_e^T) + \frac{1}{v_p^T} PS \cdot (c_p^T - c_e^T) - k_e c_e^T + k_i c_i^T \tag{10}
\]

Dox concentration in liver EES

\[
\frac{dc_{i,u}}{dt} = k_i c_e^T - k_i c_{i,u} - k_{i,u} c_{i,u} \tag{11}
\]

Dox concentration in liver cells (unbound)

\[
\frac{dc_{i,b}}{dt} = k_{i,b} c_{i,u} \tag{12}
\]

Dox concentration in liver cells (bound)

Within the EES, spatial diffusion was considered based on diffusion coefficients experimentally measured in liver tissue [21].
Release rate calculation

The in vitro measured TSL release data in Fig. S3 was modeled by a bi-exponential fit (represented by solid lines). The drug fraction released from TSL depends on both local temperature, and on the time the plasma requires to pass through the heated tissue volume (=transit time, $t_T$) – i.e. the time TSL are exposed to heat. This transit time ($t_T$) depends on plasma perfusion as follows:

$$t_T = \frac{1}{F_{pv}}$$

The release rate is then calculated as follows, where $rf(T,t_T)$ is the release fraction, i.e. fraction of drug released at a particular temperature ($T$), after time ($t_T$), corresponding to the data plotted in Fig. S3:

$$R_R(T,F_{pv}^{T}) = \frac{rf(T,t_T)}{t_T} = rf(T) \cdot F_{pv}^{T}$$
For a specific temperature, the release rate was interpolated between the temperatures
where data was measured (see Fig. S3), by using linear interpolation of \( rf(T,t_T) \) between
neighboring temperatures. The data for Fig. S3 was acquired in a prior study during \textit{in vitro}
studies, where TSL were immersed in plasma samples of varying temperatures,
while measuring fluorescence of released drug. The method is described in more detail
in the study where these data were initially published \cite{2}.

![Image]

**Fig. S3. TSL release kinetics.** Drug release fraction, dependent on temperature and time, from \textit{in vitro}
measured data. Figure reproduced from Gasselhuber et al. \cite{2}

Release at body temperature (37 °C) was treated differently than described above. This
was necessary since TSL are exposed to 37 °C continuously after administration rather
than just for a few seconds (i.e. transit time, \( t_T \)) as is the case for hyperthermic
temperatures. Based on the derivative of the release curve for 37 °C from Fig. S3, a
temporally varying release rate \( R_{37}(t) \) was devised for equations (5) and (6).

**Model geometry**

Two model geometries were developed to simulate a single cooled needle electrode
(model 1), and three cooled needle electrodes arranged in a triangular cluster, 2 cm
apart (model 2, Fig. S4). Model 1 was employed to simulate RF ablation for 5, 12 and
30 minutes. In addition, a 12-minute ablation (the clinically used duration for this type of
electrode) was simulated starting either immediately, 60 min, or 120 min after
administration of TSL-Dox. In Model 2, three sequential 12-minute ablations were
simulated, emulating clinical practice where multiple sequential ablations are employed
to cover a large tumor.
RF electrode array

Figure S4. 3-D Model geometry. Three-electrode array (2 cm apart) is inserted into the tissue domain (diameter=12cm, height=6.5cm)

The commercial software Comsol 4.3 was used to simulate RF heating and drug delivery. For Model 1, a 2D-axially symmetric geometry was used, whereas Model 2 required a 3-D geometry (see Supplementary Materials). Model 1 consisted of ~20,000 triangular elements and model 2 consisted of 185,000 tetrahedral elements. Convergence tests were performed to ensure adequate mesh size. The temporal resolution for the models was 0.3–2 s.

Initial and boundary conditions
An initial temperature of 37 °C was assumed throughout the model domain. Cooling of the needle electrode was simulated by setting electrode temperature constant to 20 °C. Electric ground potential was assigned to the boundaries of the model domain, and $V_{cc}$ was assigned to the active electrode tip. The voltage $V_{cc}$ was varied throughout the simulation based on proportional-integral (PI) control algorithm to keep maximum tissue temperature at 100 °C.
Calibration curve for conversion of fluorescence to doxorubicin concentration

Figure S5 shows the calibration curve used to convert fluorescence to tissue drug concentration. Since at very low concentrations the relationship between concentration and fluorescence is linear, we likely introduce an error at low concentrations (<~2 μg/g).

Fig. S5. Fluorescence calibration curve. A calibration curve was created based on four samples (blue diamonds) of known tissue doxorubicin concentration, and modeled by bi-exponential equation (black curve). This equation was employed to convert fluorescence intensity to tissue drug concentration.
Fluorescence images

Figure S6 shows fluorescence images of all 4 ablation samples. Fluorescence is visualized in gray scale (12 min: ablation 1,3; 5 min: ablation 2,4). Angular segments were the visible coagulation zone was less than ~5 mm from the organ boundary were excluded from evaluation, indicated in each image by red angular sections. The voids in drug distribution are likely due to adjacent large vessels (see Figure S7).

Fig. S6. Fluorescence images of all four ablations. (A) Photographic image of an ablation close to a blood vessel. (B) Fluorescence image shows how the vessel reduces perivascular drug delivery, presumably due to vascular mediated cooling. Figure reproduced from Swenson et al. [29].
Statistical Analysis

Individual data points consisted of concentration values located along a radial path with distance relative to the boundary. At each measured distance, data were averaged over all the radial paths to estimate the average concentration as a function of relative distance from the boundary. Two separate sets of results were available for the 5 minute ablation, and two sets for the 12 minute ablation. Visual inspection of the plotted data suggested the data could be reasonably modeled using a piecewise linear regression model [30], assuming linearity between and outside of three breakpoints. Separate segmented linear regression models were constructed for each ablation time to estimate concentration as a function of distance using R [31], one model constructed for 5-minute data and one model for 12 minute data, both between the distances of -5mm to +12.6mm relative to the boundary (Fig. S8, Table 3). Break-points were allowed to be different between the two models. Predicted results for “Distance” were determined with their respective standard errors for each regression model, and estimated differences were calculated starting at -5mm, and each +1mm interval thereafter (Table 4). Wald tests were used to determine if the differences were significantly different from zero at each point, using $\alpha = 0.05$. To maintain a family-wise $\alpha = 0.05$ using the Bonferroni method to adjust for multiple comparisons ($n$ comparisons = 18), a $p$-value < 0.003 would be considered significant.

Fig. S8. Regression model predictions. Result curves predicted for 5 and 12 min based on the piecewise linear regression model.
Table S3. Regression Model Summary

| Model Regression Coefficients | 5-Minutes Estimate (Std. Error) | 12-Minutes Estimate (Std. Error) |
|-------------------------------|----------------------------------|----------------------------------|
| Intercept ($\beta_0$)        | 3.87 (0.249)                    | 3.86 (0.570)                    |
| Distance ($\beta_1$)         | 0.52 (0.072)                    | 0.46 (0.159)                    |
| U1.Distance ($\beta_2$)      | -2.01 (0.236)                   | -1.14 (0.257)                   |
| U2.Distance ($\beta_3$)      | 2.64 (0.269)                    | 3.76 (0.325)                    |
| U3.Distance ($\beta_4$)      | -1.25 (0.147)                   | -3.61 (0.256)                   |

Model Break-Points

| Point 1 ($P_1$)              | -1.71 (0.119)                   | -1.99 (0.353)                   |
| Point 2 ($P_2$)              | -0.17 (0.099)                   | 0.52 (0.116)                    |
| Point 3 ($P_3$)              | 1.87 (0.152)                    | 2.73 (0.098)                    |

Model Segment Slopes

| Slope 1                      | 0.52 (0.072)                    | 0.46 (0.159)                    |
| Slope 2                      | -1.49 (0.225)                   | -0.68 (0.202)                   |
| Slope 3                      | 1.15 (0.146)                    | 3.09 (0.254)                    |
| Slope 4                      | -0.09 (0.012)                   | -0.53 (0.026)                   |

To calculate estimated concentrations:

For distance $x_d < P_1$, Conc. = $\beta_0 + \beta_1 x_d$

For distance $P_1 < x_d < P_2$, Conc. = $\beta_0 + \beta_1 P_1 + (\beta_1 + \beta_2)(x_d - P_1)$

For distance $P_2 < x_d < P_3$, Conc. = $\beta_0 + \beta_1 P_1 + (\beta_1 + \beta_2)(P_2 - P_1) + (\beta_1 + \beta_2 + \beta_3)(x_d - P_2)$

For distance $x_d > P_3$, Conc. = $\beta_0 + \beta_1 P_1 + (\beta_1 + \beta_2)(P_2 - P_1) + (\beta_1 + \beta_2 + \beta_3)(P_3 - P_2) + (\beta_1 + \beta_2 + \beta_3 + \beta_4)(x_d - P_3)$

Table S4. Predicted values for 5 and 12 min ablation, and p-value for comparison at each 1 mm increment

| Distance | Predicted 5-Minute | Predicted 12-Minute | Difference (12-5min) | P-value |
|----------|--------------------|---------------------|----------------------|---------|
| -5       | 1.25               | 1.54                | 0.29                 | 0.35    |
| -4       | 1.78               | 2.01                | 0.23                 | 0.20    |
| -3       | 2.30               | 2.47                | 0.17                 | 0.32    |
| -2       | 2.82               | 2.93                | 0.11                 | 0.71    |
| -1       | 1.93               | 2.27                | 0.35                 | 0.06    |
| 0        | 0.90               | 1.60                | 0.70                 | 0.006   |
| 1        | 2.05               | 2.75                | 0.70                 | 0.004   |
| 2        | 3.04               | 5.84                | 2.80                 | <0.001  |
| 3        | 2.95               | 7.96                | 5.01                 | <0.001  |
| 4        | 2.86               | 7.44                | 4.58                 | <0.001  |
|   |     |     |     |     |
|---|-----|-----|-----|-----|
| 5 | 2.76| 6.91| 4.15| <0.001 |
| 6 | 2.67| 6.39| 3.72| <0.001 |
| 7 | 2.58| 5.86| 3.28| <0.001 |
| 8 | 2.49| 5.34| 2.85| <0.001 |
| 9 | 2.39| 4.81| 2.42| <0.001 |
| 10| 2.30| 4.29| 1.99| <0.001 |
| 11| 2.21| 3.76| 1.55| <0.001 |
| 12| 2.11| 3.24| 1.12| <0.001 |
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