Analyzing Intratumoral Chemotherapeutic Drug Penetration in Ablated Tumors Using Finite Element Methods

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Statement of Purpose: Intratumoral drug delivery implants have significant benefits over traditional systemic chemotherapy to treat solid tumors. One advantage is their ability to deliver relatively high concentrations of drug to target tissues while avoiding undesirable systemic side effects. However, due to limitations in penetration depth leading to incomplete treatment, there have been few uses of these devices in clinical settings. Previous *in vivo* studies conducted by our group have suggested that combining radiofrequency (RF) ablation with intratumoral drug delivery may allow us to overcome these drug penetration limitations (1). To quantify this experimentally observed result and design a better treatment strategy, we have developed a finite element method (FEM) model of drug transport in ablated and non-ablated tumors.

Methods: To simulate doxorubicin transport from our implants into ablated and non-ablated tumor, we apply a two-dimension dynamic mass balance incorporating diffusion and elimination:

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2}\right) - \gamma c$$

We used a two-dimensional (2-D) geometry with an implant in the center of a 2 cm diameter tumor surrounded by normal liver tissue (Fig 1A). The ablated tumor geometry consisted of an additional ablated inner tumor region corresponding to 90% of the tumor radius. For our initial conditions we assumed all drug was confined to the implant at time zero. At the outer boundary of the implant-tissue interface, the drug concentration was defined by a drug release function obtained from previous experimentally measured values (2). The drug concentration at the outer normal tissue boundary was set to zero, and a continuous flux condition was applied to all interior boundaries. All tissue diffusion and elimination parameter values were estimated from previous *in vivo* experiments and are shown in Table 1. Diffusion in ablated tissue decreases linearly with increasing tumor radius until it reaches the diffusion value in tumor, while elimination increases linearly with time after 4 days due to the wound healing response. Once geometry, parameters, and conditions were defined, concentration profiles for both ablated and non-ablated tumor models were solved for zero to eight days after implant placement. All described simulations were calculated using COMSOL Multiphysics (COMSOL, Burlington, Ma).

Table 1 Tissue drug distribution properties.

	D (m^2s^{-1})	**γ (s^{-1})**
Ablated Tissue	10.6×10^{-11} - f(r)	0 + f(t)
Tumor Tissue	5.0×10^{-11}	5.9×10^{-5}
Normal Tissue	6.7×10^{-11}	9.6×10^{-4}

Results/Discussion:

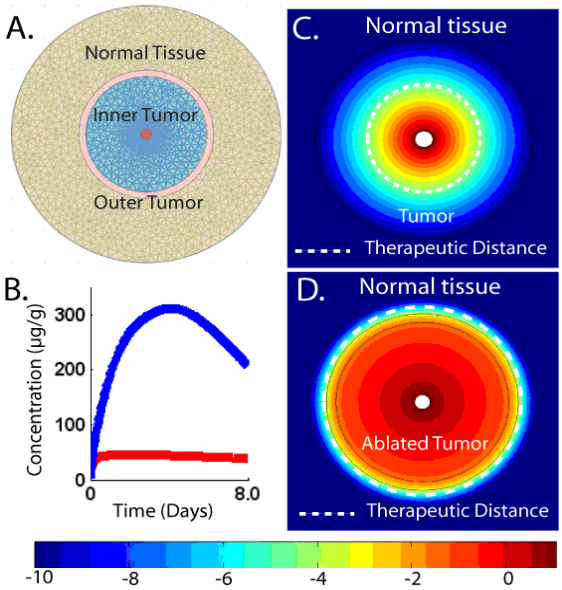

Fig 1 The model geometry (**A**) was meshed with 3890 elements and consisted of our implant, (red), embedded in a 2 cm tumor, (blue inner tumor, pink outer tumor), surround by normal tissue, (brown). The model was solved and the average tumor drug concentration (**B**) over time shows much higher dosages in ablated tumor (blue line) than in non-ablated tumor (red line). The therapeutic drug dosage, 6.4 µg/g, penetrates 0.52 cm in non-ablated tumor (**C**) compared to a penetration depth of 1.05 cm in ablated tumor (**D**). Concentration distributions are shown as log scale of the molar drug concentration

Our model shows that a much greater penetration depth and average tumor concentration can be achieved by our implant in ablated tumor than in non-ablated tumor (Fig. 1B-D). These findings in ablated tumor are mostly likely due to the destruction of all tissues capable of eliminating drug from the treatment region. However, as drug reaches normal tissue it is rapidly eliminated, thereby confining it to the treatment region.

Conclusions: Our study shows that by combining intratumoral drug delivery with RF ablation we are able to deliver a much greater therapeutic concentration of chemotherapy for solid tumor treatment. Future goals include expanding this model to a more realistic three-dimensional geometry, to facilitate design of clinically-relevant combination treatments for tumors of varying shapes and sizes.

References:

1. Qian, F., J Control Release. 2003;91:157-166.
2. Weinberg BD. J Biomed Mater Res A. 2006;In Press