Estimating Local Doxorubicin Transport Properties in Experimental Liver Carcinoma

Brent D. Weinberg[1], Ravi B. Patel[1], Agata A. Exner[2], Gerald M. Saidel[1], Jinming Gao[3]
[1]Dept. of Biomedical Engineering, Case Western Reserve University, Cleveland, OH 44106
[2]Dept. of Radiology, Case Western Reserve University, Cleveland, OH 44106
[3]Simmons Comprehensive Cancer Center University of Texas Southwestern Medical Center, Dallas, TX 75390

Statement of Purpose: Developing an intratumoral drug delivery implant to supplement radiofrequency (RF) ablation requires detailed knowledge of the drug transport properties in tumor tissue. Doxorubicin transport parameters in non-ablated and ablated rabbit VX2 liver carcinoma were estimated by fitting a drug transport model to experimentally measured drug distribution data. The estimated parameters provide unique insight about drug transport that can be used to intelligently design chemotherapeutic implants to supplement RF ablation for cancer treatment.

Methods: A one-dimensional (1-D), cylindrically symmetric model is applied to describe doxorubicin transport in normal and ablated tissues of liver.[1] This transport model incorporates parameters of diffusion, D, and elimination, γ, in each tissue: :

$$\frac{\partial C}{\partial t} = \frac{D}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C}{\partial r}\right) - \gamma C$$

where t is time, r is radial distance from the implant center, C is the doxorubicin. The implant was assumed to occupy the center, and was surrounded by non-ablated or ablated tumor and normal liver. A finite element method (FEM) was used for numerical solution in simulating drug distribution dynamics in the tissues. Comparisons were made with concentration distributions of doxorubicin 4 and 8 days after implantation of a poly(D,L-lactide-co-glycolide) (PLGA) device containing doxorubicin in rabbit VX2 liver carcinomas.[2] Optimal estimates of D and γ were obtained for non-ablated and ablated tumor by minimizing the sum of square residuals between the model output and experimental data. The parameters D and γ were estimated initially assuming they were independent of time and position in the tumor. As needed for the model simulation to match data, these parameters were allowed to change with time and/or position.

Results/Discussion: Optimal estimation resulted in realistic parameter values and doxorubicin concentration distributions that closely approximate the experimental data. A comparison between the experimental data and model output is shown in Figure 1. In non-ablated tumor, D was estimated at 5.0 x 10^{-11} m^2s^{-1} (25% slower than normal liver[1]), and γ was 5.9 x 10^{-5} s^{-1} (94% slower than normal liver[1]). These values indicate a fundamental difference between liver tumor and normal liver tissue that should be accommodated in implant design. In ablated tumor, diffusion was found to vary as a function of distance from the ablation center. Doxorubicin

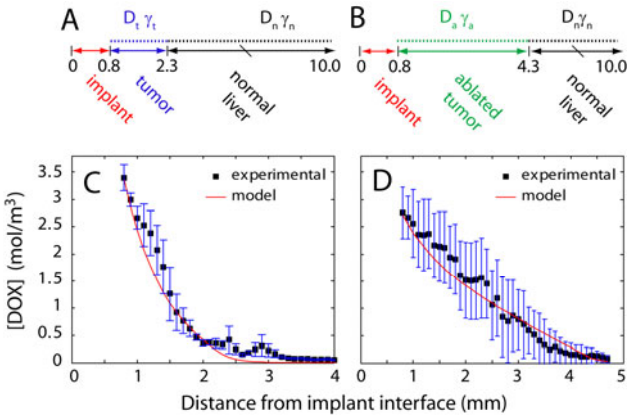

Figure 1. Doxorubicin distribution data in VX-2 tumors. Parameters and locations for non-ablated (A) and ablated tumors (B). Experimental drug distribution (squares) compared with model output (line) on Day 4 for non-ablated (C) and ablated (D) tumor. Error bars show the standard error of each measurement.

diffusion near the center was 10.6 x 10^{-11} m^2s^{-1} (58% faster than normal liver[1]), but in the periphery of the ablation it decreased to levels associated with normal liver. In contrast, the elimination rate was homogeneous throughout the ablated tumor, but varied as a function of time. Before day 4, γ was near 0 and increased linearly between days 4 and 8 to 5.7 x 10^{-5} s^{-1}, a value similar to that of non-ablated tumor. Both the increased diffusion and decreased elimination of ablated tumor lead to an increase in drug penetration. RF ablation likely creates these changes by destroying the tissue structure and vasculature, which reduces impediments to drug diffusion while minimizing drug elimination.

Conclusions: This study has shown that the transport properties of normal liver, non-ablated tumor, and ablated tumor differ substantially. By increasing D and reducing γ for higher doxorubicin concentration in tumor tissue, RF tissue ablation increases local drug distribution around an intratumoral implant. Knowledge of these tissue properties can be used to design better treatments that maximize drug delivery to tumor areas which are most at risk for recurrence. Future work will focus on using these parameters to simulate treatment of larger liver tumors using implantable drug delivery devices.

References:

1. Qian F. J Control Release. 2003;91:157-66.
2. Weinberg BD. J Biomed Mater Res A. 2006; In Press.