Integration of diffusion weighted magnetic resonance imaging data into a simple mathematical model of tumor growth

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INTRODUCTION

The integration of imaging data with mathematical models of tumor growth and treatment response can be used to make predictions that are patient specific and which can readily be checked against actual measurements obtained at later time points. Here we build on previous work [1, 2] to show how diffusion weighted MRI (DW-MRI) data can be used to separate treatment groups early in the course of therapy, and predict tumor cell numbers at later time points.

METHODS

MRI Acquisition 13 male Fischer 344 rats were implanted with 9L tumors which were left to grow for 11-12 days. 8 rats were treated with a chemotherapeutic drug BCNU and 5 rats were tumor bearing controls. Diffusion weighted images at different *b* values were acquired from all rats immediately before treatment (day 0), and days 1 and 3 after treatment. An identical central portion of the tumor was identified on days1 and 3 using rigid registration and then imaged with the same protocol as day 0. ADC maps were calculated for each imaging day. For each animal, an ROI around the tumor was selected from day 0 and copied onto days 1 and 3. ROI and voxel-by-voxel based mathematical modeling was then performed for each data set.

*Mathematical Modeling*The logistic model for tumor growth, Eq. (1), was used for mathematical modeling [4]. $N(r,t)$ and $N(r,0)$ are the number of cells in voxel r at time $t$and t=0respectively. $k(r)$ is the cell proliferative rate at voxel r, and θ is the maximum number of cells in a voxel (i.e., the carrying capacity). In controlled settings, theADC has been shown to correlate with cell number as shown in Eq. (2) [5];

$$N(r,t)=\frac{\theta N(r,0)}{N(r,0)+(\theta-N(r,0))e^{-k(r)*t}} \quad (1) \qquad ADC(r,t)=ADC_w-\lambda N(r,t) \quad (2) \qquad \left(\frac{ADC(r,t)-ADC_{\min}}{ADC(r,t)-ADC_w}\right)=\left(\frac{ADC(r,0)-ADC_{\min}}{ADC(r,0)-ADC_w}\right)e^{-k(r)*t} \quad (3)$$

ADC_w is the ADC of free water, $ADC(r,t)$ is the ADC at position r and time t,and λ is a proportionality constant calculated by assuming that the minimum ADC occurs at θ. For ROI modeling, the mean ADC for the tumor at days 0 and 1 was calculated and used in Eq.(3) to yield k_{mean}[2].The mean ADC for days 1 and 3 was then used in Eq.(2) to yield $N_{exp\_mean}(1)$ and $N_{exp\_mean}(3)$ (i.e., mean number of cells in days 1 and 3, respectively). For the voxel based analysis, the ADC values of the individual voxels wasused in Eq.(3) to yield $k(r)$. The ADC values of days 1 and 3 were then converted to numbers of cells on days 1 and 3($N_{exp}(r,1)$, and $N_{exp}(r,3)$, respectively) using Eq. (2). k_{mean} and $N_{exp\_mean}(1)$ were then used in conjunction with Eq. (1) to yield $N_{cal_mean}(3)$for the ROI analysis; similarly, $k(r)$ and $N_{exp}(r,1)$ were used to generate $N_{cal}(r,3)$ for the voxel analysis. The $N_{exp\_mean}(3)$ and $N_{cal\_mean}(3)$ for all the rats grouped together and the $N_{exp}(r,3)$and $N_{cal}(r,3)$ for each rat were compared using a Pearson and concordance correlation coefficient.We hypothesized that the treated rats would have more voxels with negative $k(r)$values than the control rats. Thus, we computed the "proliferation value ratio"(PVR) *via* Eq. (4): A Wilcoxon test was used to compare the PVR and mean ADC of the groups.

$$PVR=\frac{\sum(k(r)<0)}{\sum(k(r)<0)+\sum(k(r)>0)} \quad (4)$$

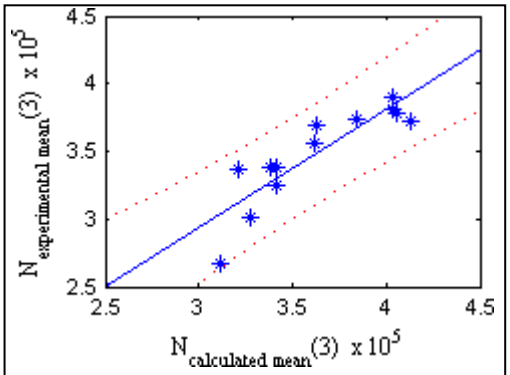

Figure 1: ROI averaging $N_{cal\_mean}(3)$ and $N_{exp\_mean}(3)$ for each rat with 95% CI.

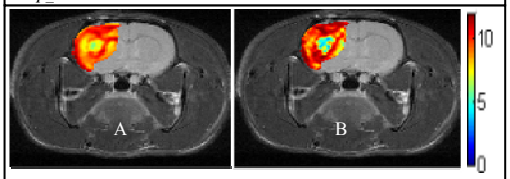

Figure 2: Panel A and B are the experimental and the calculated number of tumor cells ($x10^4$) at day 3 respectively

RESULTS

Figure 1 shows the $N_{exp\_mean}(3)$ and the $N_{cal\_mean}(3)$ for all rats; the correlation coefficient is 0.88 (p=0.0001) with a concordance correlation coefficient of 0.80. Figure 2 is the $N_{cal}(r,3)$ and the $N_{exp}(r,3)$ of one of the animals.The correlation coefficient for the voxels for this rat is 0.65 (p<2.2E-16).While the absolute values of the two methods do not quite match, there is general agreement in spatial distribution between the two, including the necrotic core and cellular dense rim. This indicates that the modelling scheme can describe fundamental tumor features in this animal. The Pearson correlation coefficient of all the rats ranged from -0.06 to 0.65 with an average of 0.34. The concordance correlation ranged from -0.06 to 0.58 with an average of 0.24. The treated and the control rats PVR was separable with the Wilcoxon test (p<0.05) after day 1, while the mean ADC values were not separable (p=0.62) after day1. The ADC was separable after day 3(p=0.002).

CONCLUSION

Sequential ADC data incorporated in a mathematical model can be used to predict the number of tumor cells at a later time point. It can also be used to separate treated and control animals as early as 1 day after treatment. Future work includes a longer longitudinal study with a higher SNR in order to increase the correlation between the rats. Also, we are working to include vascularcharacteristics into the modeling through DCE MRI data.

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REFERENCES1. Atuegwuet al. Phys Med and Bio, 2010. 55:2429-49.2. Yankeelov et al., Integr Biol, 2010:338-45.3. Colvinet al., Magn Reson Imag,in press.4. Bryne, Preziosi, Editors. 2003;75-120.5. Anderson, et al., Magn Reson Imag 2000;18:689-95.