Parameterizing the Logistic Model of Tumor Growth by DW-MRI and DCE-MRI to Predict Breast Tumor Cellularity During Neoadjuvant Chemotherapy

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INTRODUCTION

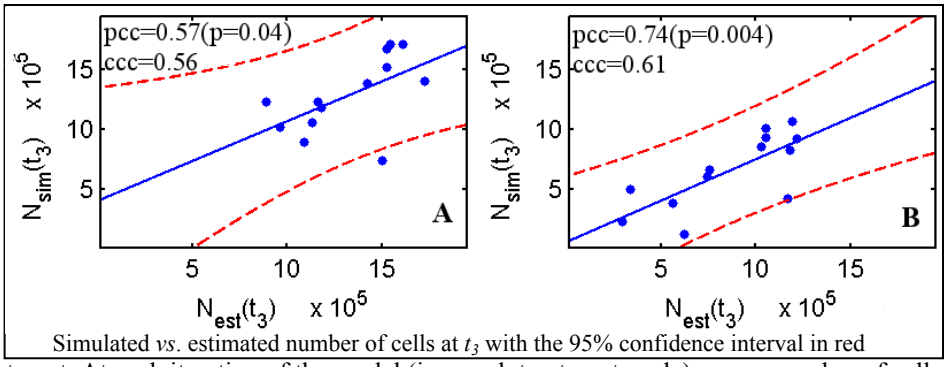
The impact of mathematical models on predicting tumor growth can be enhanced by imaging data that can be obtained noninvasively, in 3D, longitudinally, and specifically for each patient. Here we build on previous work [1] to show how diffusion weighted MRI (DW-MRI) and dynamic contrast enhanced MRI (DCE-MRI) data obtained early in therapy may be used to predict the proliferation rate of human breast tumors and how these proliferation values can then be used to estimate the number of tumor cells at a later time point.

METHODS

MRI Acquisition Thirteen patients with locally advanced breast cancer were treated on a phase II clinical trial with cisplatin, paclitaxel with and without RAD001. DCE and DW-MRI data was obtained prior to (t_1), after one cycle of therapy (t_2) and after completion of chemotherapy (t_3). MRI data were acquired with a 3T Achieva MR scanner (Philips Healthcare, Best, The Netherlands). DW-MRIs were acquired with a single-shot spin-echo echo planar imaging sequence in three orthogonal diffusion encoding directions (x, y, and z), b=50 and 600 s/mm^2, FOV = 192×192, TR\TE = 3080 ms\43ms, Δ = 20.7ms, and δ = 11.6ms. A SENSE factor of 2 and spectrally-selective adiabatic inversion recovery (SPAIR) fat saturation were implemented to reduce image artifacts. DCE-MRI data were acquired with a 3D RF-spoiled gradient echo sequence with TR\TE\α = 7.9 ms\1.3 ms\10^o, FOV =25.6 x 25.6 cm^2, acquisition matrix of 192×192×20 and a SENSE = 2. Each 20-slice set was collected in 16.5 seconds at 25 time points. A catheter was used to deliver 0.1 mmol/kg of Gd-DTPA at a rate of 2 ml/s (followed by a saline flush) after the acquisition of three baseline dynamic scans for the DCE study. ADC maps were calculated from the DW-MRI, while v_e and v_p maps were calculated from the DCE data for the 3 time points. Tumor ROIs were manually selected for all the time points, and the mean values of ADC, v_e, and v_p within the ROIs were calculated.

Mathematical Modeling The logistic model of tumor growth, Eq. (1), was used for the mathematical modeling [2]. $N(t)$ is cell density at time t, θ is the maximum number of cells that can be contained within a voxel (i.e., the carrying capacity), and k is the proliferation rate. The mean ADC in the tumor ROI can be related to the mean number of cells using Eq. (2), where $ADC(t)$ is the ADC at any time t, ADC_w is the ADC of water and λ is a proportionality constant [3]. To calculate λ, the minimum ADC in the tumor volume is assumed to occur at θ which is calculated using Eq. (3). The mean ADC values at t_1 and t_2 were used to calculate k for each patient *via* Eqs. (1)-(3). θ, ADC of t_2 and t_3 were used to estimate the number of tumor cells at t_2 and t_3 ($N_{est}(t_2)$ and $N_{est}(t_3)$), respectively. The logistic model was allowed to run in a pulsed fashion with the model switched "on" for the day of treatment, and switched "off" one day after treatment. At each iteration of the model (i.e., each treatment cycle), a new number of cells was calculated. For the first model update, $N_{est}(t_2)$, θ and k in conjunction with Eq. (1) were used to calculate the number of cells at the end of the first cycle. The newly calculated number of cells was then used in conjunction with k and θ to calculate the number of cells for the next cycle. This was repeated for all cycles to yield the simulated number of tumor cells at the completion of therapy, $N_{sim}(t_3)$. $N_{est}(t_3)$ and $N_{sim}(t_3)$ were then compared using Pearson's and concordance correlation coefficients.

$$N(t)=\frac{\theta N(0)}{N(0)+(\theta-N(0))e^{-k*t}} \quad (1) \qquad ADC(t)=ADC_w-\lambda N(t) \quad (2) \qquad \theta=\left(1-v_e-v_p\right)\left(\frac{V_{voxel}}{V_{cell}}\right) \quad (3)$$



Simulated *vs.* estimated number of cells at t_3 with the 95% confidence interval in red

RESULTS

The mean number of cells at t_3 for both the simulated, $N_{sim}(t_3)$, and the estimated, $N_{est}(t_3)$, number of cells with the 95% confidence interval are shown in the Figure. Each point in the figure represents a patient. Panel A is calculated without using v_e and v_p to inform θ, while the plot in Panel B includes those data. The Pearson's and concordance correlation coefficient increases as v_e and v_p are incorporated into the model, and all patients data points are within the 95% confidence interval unlike Panel A.

DISCUSSION

Sequential DW and DCE-MRIs of the breast were used to determine the tumor proliferation rate early in the course of therapy and to estimate the number of cells at the completion of therapy. The Pearson's and concordance correlations increase as v_e and v_p are added to the model. Future work will involve voxel based analysis and also correlating the mathematically predicted tumor cell numbers to histology and patient outcome.

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