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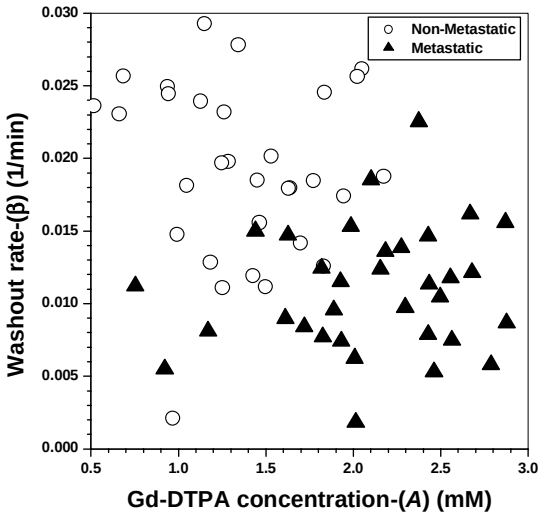
Differentiation of metastatic and non-metastatic rodent prostate cancer using a new mathematical model to fit dynamic contrast enhanced MRI data

Introduction: DCEMRI is used clinically to identify and stage tumors based on the physiological parameters. Pharmacokinetic models, such as the two compartment model, are employed to analyze DCEMRI data. However, simple pharmacokinetic models often do not provide adequate fits to experimental data from tumors. This is primarily because tumors are extremely heterogeneous on a microscopic level. Poor fits to experimental data reduce diagnostic accuracy (Fan et al., MRM 2003, in press). Therefore, we are developing an empirical mathematical model that fits experimental data accurately. The purpose of the current research is to determine whether this approach distinguishes between metastatic and non-metastatic rodent prostate tumors. Multi-slice DCEMRI data acquired with a low molecular weight contrast agent, Gd-DTPA (Berlex Laboratories) and a low diffusion agent P760, (Laboratoire Guerbet).

Methods: Prostate tumors, metastatic AT3.1 (n=13) and non-metastatic AT2.1 (n=13) were grown in the hind limbs of Copenhagen Rats. T_1-weighted spoiled gradient echo images were acquired using a SIGNA 1.5 Tesla MRI scanner (TR/TE = 15/6 ms, flip angle = 60°, readout bandwidth = 32 kHz, slice thickness = 3 mm, in-plane resolution ~ 500 μm, NEX=2). MRI signal from the tissue was detected using a three-inch surface coil. Five slices were imaged across the tumor with a time resolution of ~50 s per scan (~10 s per imaging). The calculated concentration curves $C(t)$ as a function of time (t) from MRI data were fitted using the empirical mathematical model (EMM) to describe the contrast agent uptake and washout in tissue:

$$C(t) = A \cdot \left(1 - e^{-\alpha t}\right)^{q} \cdot e^{-\beta t} \cdot \left(1 + e^{-\gamma t}\right) \Big/ 2 ,$$

where $\boldsymbol{A}$ is the upper limit of the maximum tracer concentration and is generally larger than the maximum concentration, α is the rate of contrast uptake (1/min), β is the overall rate of contrast washout (1/min), γ is the initial rate of contrast washout (1/min), and $\boldsymbol{q}$ is related to the curvature of $C(t)$ at the transition from first pass uptake to washout.



Results: The plots of $C(t)$ obtained for Gd-DTPA and P760 were accurately fit by the EMM for all the slices. For pooled data from all slices for both Gd-DTPA and P760, the statistic analysis showed that the washout parameter β was significantly smaller in the metastatic tumors than the non-metastatic tumors ($p < 0.002$). The ratio of parameter $\boldsymbol{A}$ (or β) at the tumor rim to tumor center was over ~1.5 in metastatic tumors, but almost the same in non-metastatic tumors. The figure on right shows a plot of parameters $\boldsymbol{A}$ v.s. β for all the slices obtained using Gd-DTPA for the tumor rim. The separation between the two types of tumors is highly statistically significant. The uptake rate constant, α, did not reliably distinguish metastatic and non-metastatic tumors.

Discussion: The combination of washout rate and maximum concentration effectively separated metastatic and non-metastatic tumors. The washout rate (β) was significantly slower in metastatic tumors than in non-metastatic tumor for both contrast agents Gd-DTPA and P760. In clinical practice, washout of contrast media is not sampled for an extended time due to practical considerations. However, the present results suggest that detailed sampling of washout for 30 minutes or more may provide important clinical information.

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