Delayed bolus arrival time with high molecular weight contrast agent, an indicator of necrosis

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INTRODUCTION: The bolus arrival time (BAT) is the time at which the contrast agent arrives at a location in the tumour following injection, and signal enhancement begins. In any DCE-MRI data set, a number of scans will be collected before injection of the bolus of contrast agent. It is necessary to find the point in the dataset where the bolus arrival occurs for pharmacokinetic modelling of the data. In this study, the bolus arrival time is compared for a standard clinical contrast agent, and a high-molecular-weight contrast agent. Resulting parameter maps are compared to whole tumour histology sections showing necrotic and healthy tissue. In areas of BAT maps matching necrotic areas in histology, BAT is delayed, particularly in larger areas of necrosis, and when using the high molecular weight contrast agent.

METHODS:

MRI: Imaging was performed on a Bruker Biospec 70/30 using a combination of volume (Tx) / surface (Rx) coil. T1 measurements, and flip angle mapping are performed using a single slice FLASH variable flip angle experiment (FLASH TR/TE = 500/2.75, FA = 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 215). DCE-MRI data was collected at 2.24 s time resolution (FLASH; TR/TE = 35/2.75; FA = 40; NR = 1200). Images are single slice, with $0.33\times0.33\times1$ mm^3 resolution.

Mice: HT29 human colorectal carcinoma xenografts in six NOD/SCID mice were imaged when tumours reached 300 mm^3. A DCE protocol was used to image mice on day 0 during injection of Gadovist and on day 1 during injection of HPG. Mice were euthanized 60-70 min after the second contrast agent injection.

Contrast Agents: Hyperbranched polyglycerol (HPG) was derivatized with p-NH_2-benzyl-DOTA in the Faculty of Pharmaceutical Sciences at UBC [1] and contained 20 µg Gd per mg HPG. HPG-Gd was administered as a 6 µL/g bolus i.v. dose from a 0.2 mM solution. The relatively low molecular weight agent, Gadovist (Bayer Healthcare), was administered as a 5 µL/g bolus i.v. dose at 60 mM.

Histology: At indicated time points animals were euthanized and tumours were immediately collected and frozen. A 10 µm cryosection was obtained from the region corresponding to MR images. Sections were stained with Hoechst for cell nuclei, and imaged using a robotic microscope and camera to obtain tiled images of whole tumour sections [3]. Images for individual tumours were cropped to tumour tissue boundaries with artefacts and non-viable tissue removed, to create masks. Histological image analysis was done using ImageJ.

Bolus arrival time: A region of interest (ROI) was chosen in each image to select the tumour. The BAT for each tumour was found by searching for the first enhancing time point in a contrast agent concentration time curve at each voxel within the ROI. Changes from the mean concentration are searched for using a control chart decision criteria [2]. The control chart was originally developed by Walter Shewart for quality control. A control chart defines a set of rules indicating when a process fails to remain under a state of control. In this work, a change in contrast agent concentration from baseline is detected when:

I. any given point falls outside of 3σ from the centre line (the average of baseline concentrations),
II. 2 out of 3 consecutive points fall above the 2σ,
III. 4 out of 5 consecutive points fall above the 1σ limit, or
IV. 8 consecutive points all fall above the centre line.

We additionally require that three points in a row must indicate a change from baseline. Should more than one of the decision rules be violated, the one indicating the earliest BAT was chosen. Figure 1 shows an example where the bolus arrival occurs at scan number 30. Analysis of MR images was performed in MATLAB. ROIs were drawn in ImageJ.

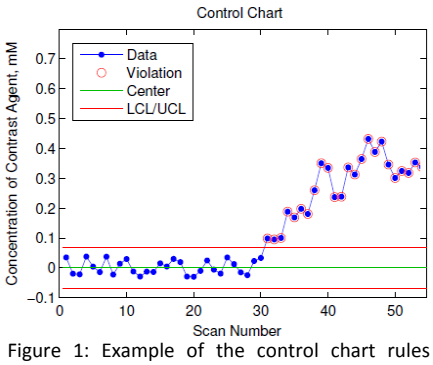

Figure 1: Example of the control chart rules applied to a contrast agent curve. This data set indicates a BAT at scan 30.

RESULTS:

Images of BAT for both low and high molecular weight agents are shown in Figure 2 with correlating histology. Histology masks show healthy tissue, where necrotic tissue is masked out. Regions of very late BAT (≳ 1 minute later than surrounding tissue) appear to correspond with large areas of necrosis.

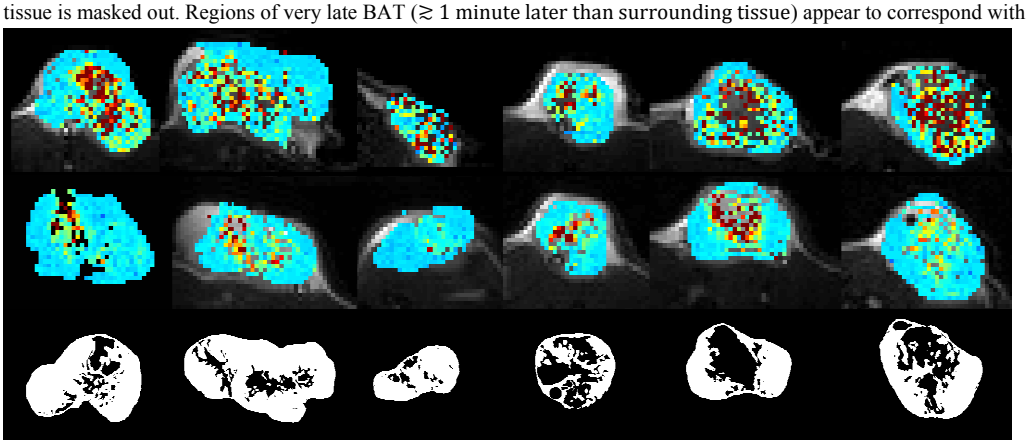

Figure 2. BAT maps are overlaid on corresponding T2-weighted images to indicate orientation. BAT maps for HPG (top row) are shown with corresponding BAT maps for Gadovist (centre row) and corresponding histology maps (bottom row) showing masks of healthy tissue. Histology masks are aligned to correspond to the centre row. Each column indicates a different subject. BAT is in seconds from the beginning of the DCE MRI series

DISCUSSION AND CONCLUSIONS:

Regions with very delayed BAT (≳ 1 minute later than surrounding tissue) in the parameter maps correspond to large areas of necrosis in histology maps. Longer delays occur with HPG-Gd than with Gadovist. Thus, BAT is not only an important input parameter for pharmacokinetic modelling, but also a reproducible, phenomenological parameter in its own right. In larger necrotic areas, the contrast agent is likely to reach the area via diffusion, instead of delivery through blood vessels. Identification of necrotic areas is important cancer research. Effective identification of the BAT is important for pharmacokinetic modelling of DCE-MRI data. If modelling were to be performed using the same BAT for the whole tumour, errors in pharmacokinetic model parameters may be introduced, especially in large necrotic areas.

REFERENCES:

[1] Saatchi, et al *Submitted to* ***Bioconjugate Chemistry,*** June 1,2011. [2] Shewhart. *ASQ Quality Press*, (1931). [3] Baker et al., *Clin Canc Res* (2008) 14(7); 2171.