Combining DCE-MRI and microbubble ultrasound to evaluate response to Sunitinib in patients with renal cell carcinoma

C. Bailey[1,2], R. Williams[2], G. Lueck[2], M. Atri[3], P. N. Burns[1,2], G. J. Stanisz[1,2], and G. A. Bjarnason[4]

[1]Medical Biophysics, University of Toronto, Toronto, ON, Canada, [2]Imaging Research, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [3]Medical Imaging, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [4]Medical Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

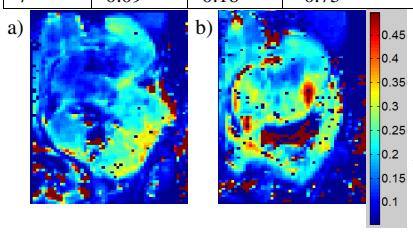
INTRODUCTION: As more anti-angiogenic drugs are developed, assessment of patient response during therapy is becoming crucial. DCE-MRI has been proposed as a way of detecting changes in the vasculature. For example, the Tofts model (1) provides the volume transfer constant, K_{trans}, which describes permeability and flow, and v_e, the extravascular, extracellular volume fraction. It has been shown (2), however, that parameters obtained from DCE-MRI using low-molecular weight contrast agents, such as Gd-DTPA, are not sensitive to vascular changes caused by anti-angiogenic drugs. These contrast agents leak into the extravascular extracellular space, so that they reflect not only blood volume and flow, but also vessel permeability. Microbubble contrast agents (Definity, Lantheus), in conjunction with ultrasound, are intravascular and can therefore be used to evaluate changes in blood flow and volume fraction. This study compares the results of DCE-MRI with ultrasound disruption-replenishment measurements using microbubbles in patients being treated for renal cell carcinoma with the multi-targeted receptor tyrosine kinase inhibitor Sunitinib (Sutent). The relevance of the parameters obtained by each technique to vascular and extracellular changes are discussed.

METHODS: Seven patients with renal cell carcinoma were scanned using ultrasound and MRI before and two weeks after the beginning of Sunitinib treatment. DCE-MRI data were acquired at 1.5 T (GE Signa, Milwaukee, WI) with a multiphase 3D LAVA sequence (fat-saturated SPGR, 15 degree flip angle, TE=0.968 ms, TR=3.173 ms, 0.75 NEX, 8 mm slice thickness, 12 slices) for 80 phases, resulting in a scan time of five minutes. After 20 s of scanning, 0.2 mmol/kg Gd-DTPA-BMA (Omniscan, GE Healthcare) was injected. Analysis was performed on at least three radiologist-selected ROIs in each patient and up to four ROIs when tumour size permitted. The average signal from a region of interest in the descending aorta just above the renal arteries provided the arterial input function (AIF) and data in the tumour ROIs were fitted by the Tofts model to give the volume transfer constant, K_{trans}, and the extracellular volume fraction, v_e. A third model parameter accounted for delay between the AIF and the blood reaching the ROIs.
Ultrasound data were acquired with an iU22 Philips ultrasound system using the contrast agent Definity (1.1 mL in 50 mL saline drip infusion) and the disruption-replenishment method (30 s scan) (3). Seven 2-D tumour slices, spanning the lesion, were acquired for each patient. ROIs were drawn by a radiologist and the steady-state image intensity, which is related to the microbubble concentration in the scan plane, was used to infer the intravascular blood volume. The intensity during the second week of treatment was compared to the pre-treatment baseline value to obtain a relative blood volume.

RESULTS: Average K_{trans} values ranged from 0.14 to 0.73 min^{-1} across patients, with the standard deviation across the ROIs in one patient averaging 0.17 min^{-1}. The values of v_e ranged from 0.15 to 0.71, with a standard deviation of 0.11 across the ROIs on average. Table 1 shows the fractional change (Week2-Week0)/Week0 in the fit parameters for MRI and ultrasound for each patient. The DCE-MRI uptake curves for Patient 1 pre-treatment and in the second week of treatment are shown in Figure 1a normalized to the peak blood signal; in Figure 1b, the ultrasound disruption-replenishment curves are shown. Figure 2 presents a parametric map (from every 4 voxels) of v_e (a) pre-treatment and (b) two weeks into treatment.

***Table 1**. Summary of fractional change in MRI and ultrasound fit parameters for uptake/replenishment curves. Averages over all ROIs reported for each patient were used to calculate changes.*

	MRI		Ultrasound
Patient	K_{trans}	v_e	RBV
1	1.97	1.37	-0.54
2	-0.42	-0.29	-0.71
3	-0.23	0.42	-0.01
4	-0.19	0.11	1.42
5	0.01	0.36	-0.89
6	-0.20	0.12	-0.91
7	0.09	0.18	-0.75



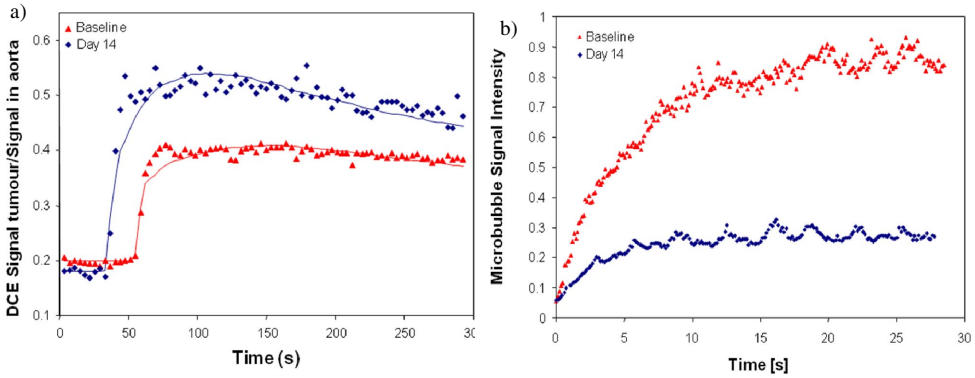


***Figure 1**. Sample curves of signal in an ROI as contrast agent flows into the tumour. (a) MRI uptake curves show an increase in normalized signal after two weeks of treatment. Solid lines indicate the fit to the model. (b) Ultrasound replenishment curves show a decrease in signal intensity after two weeks of treatment.*

***Figure 2.** Parametric maps of v_e for Patient 1 (a) pre-treatment and (b) two weeks into treatment show regions where extracellular space has increased, indicating decreased proliferation. A necrotic region in the tumour core was difficult to fit and has increased in size.*

DISCUSSION: The preliminary results of this clinical trial show a wide range of patient response to treatment, including the production of necrotic regions, which were preceded by changes in contrast agent kinetics. The ultrasound data in Table 1 demonstrated that most patients experienced a decrease in relative blood volume two weeks into Sunitinib treatment, consistent with the drug's anti-angiogenic effects. In contrast, the MRI parameter v_e was seen to increase in many cases. This parameter measures the fraction of extracellular space outside the vasculature and its increase in these patients indicates lower cell density. This is consistent with the fact that Sunitinib inhibits receptor tyrosine kinases involved in cell proliferation. The parameter K_{trans} is influenced by both blood flow and permeability of the vascular wall to the contrast agent. This was demonstrated by the data from Patient 1, where the uptake curves in Figure 1a actually showed an increase of Gd-DTPA-BMA uptake, while the disruption-replenishment curves in Figure 1b exhibited a decrease in microbubble perfusion. These results describe a situation where the relative blood volume in the tumour has decreased because of treatment, but the remaining blood vessels become leakier, leading to increased extravasation of the MRI contrast agent. Sutent is a known inhibitor of platelet-derived growth factor and can significantly reduce interstitial pressure in tumour tissue, altering permeability. This demonstrates that MRI and ultrasound contrast studies can be combined synergistically: ultrasound reveals changes in the vascular volume and DCE-MRI reveals changes in the quality of that vasculature, as well as the extravascular extracellular volume fraction.

REFERENCES: 1. Tofts, P.S. et al. 1991. *Magn. Reson. Med.* **17**: 357-367. 2. Turetschek, K. et al. 2004. *J. Magn. Reson. Imaging.* **20**: 138-144. 3. Burns, P.N. et al. 2006. *Ultrasound Quarterly.* **22**: 5-13.