Reproducibility and Cross-Validation of DCE-MRI and DCE-CT Perfusion Parameters in a Rat Tumor Model

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Introduction: K^{trans} is commonly used as a biomarker of drug efficacy in tumors, but its interpretation is complex when using clinically available low molecular weight contrast agents. Dynamic CT (DCE-CT) potentially provides independent measures of perfusion and permeability. The goals of this study were (1) to compare the reproducibility (scan-rescan) of DCE-CT and DCE-MRI biomarkers, and (2) to compare parameter values measured in a rodent xenograft using DCE-CT to those measured using DCE-MRI with a Tofts model (1).

Methods & Materials: MR studies were performed using a Bruker 7.0T/30 cm system (Bruker BioSpin, Billerica, MA). CT studies were performed using a GE LightSpeed 4-detector system (GE Healthcare, Waukesha, WI). Prior to imaging, an indwelling catheter was placed in the jugular vein. During imaging, animal temperature and blood pressure were continuously monitored. Temperature was maintained using a closed loop heating system. For DCE-MRI studies, a 0.2 mmol/kg dose of Magnevist (Bayer Healthcare Pharmaceuticals), followed by a saline flush, was delivered by an MR-compatible injection system. For DCE-CT studies, a 1.5 ml/kg dose of Optiray 320 (Covidien Imaging Solutions) at 5 ml/min was delivered using the same injection system. Animals were anesthetized with 1-2% isoflurane in a 1 l/min O_2 flow. All studies were approved by the Institutional Animal Care and Use Committee.

Eight nude rats were inoculated with 5000 C6 glioma cells and tumors allowed to grow until they reached a nominal size of approximately 1 cm^3. Each rat was subsequently scanned three times (on consecutive days). During each session, the rat was scanned first on CT and then on MR. The CT scanning protocol consisted of continuous cine acquisition for 50 sec over the tumor (4x2.5mm collimation). The MR scanning protocol consisted of the acquisition of sagittal and axial T_2-weighted images, axial T_1-weighted images, axial DCE images, and post-Gd axial T_1-weighted images. For the DCE-MR acquisition, a 3D fast spoiled gradient echo sequence was used with TE= 1.8 ms, TR= 5.3 ms, 10 degree flip angle, 12 2-mm sections, 128x96 matrix, 60 mm FOV, temporal resolution of 6.6 sec, and a total scan time of 6.5 min. Contrast agent was administered after 10 baseline scans were acquired.

DCE-CT data were analyzed using CT Perfusion 3 (GE Healthcare, Waukesha, WI) to yield parametric maps of blood volume (*BV*), blood flow (*BF*), mean transit time (*MTT*), and permeability-surface area product (*PS*). Regions of interest (ROIs) were defined in each imaging section containing tumor. The results from the two sections with largest tumor cross-section were averaged. DCE-MRI data were analyzed using the Kinmod module within the CineTool environment (GE Healthcare, Waukesha, WI) to yield parametric maps of endothelial transfer constant (K^{trans}), extracellular, extravascular space volume fraction (v_e), and contrast agent reflux rate constant (k_{ep}). As it was difficult to consistently obtain an arterial input function from the DCE-MRI data, a model contrast agent clearance curve was used and, therefore, the fractional plasma volume fraction (v_p) was not computed. As for the DCE-CT data, the results from the ROIs in the two imaging section representing the largest cross-section of tumor were averaged. For both DCE-CT and DCE-MRI, root mean square (RMS) coefficients of variation across the three scan sessions were used to assess reproducibility.

Results. The tumors were mostly well-vascularized, showing little apparent inter-animal variability. The mean DCE-CT and DCE-MRI parameter values with ranges and intra-animal (over three time points) RMS coefficients of variation with ranges are given in Table 1. In addition, the inter-animal (over eight animals) RMS coefficients of variations of the mean are given in Table 1 for each DCE-CT and DCE-MRI parameter.

	K^{trans} (min^{-1})	k_{ep} (min^{-1})	v_e	*BF* (ml/min/100g)	*BV* (ml/100g)	*MTT* (s)	*PS* (ml/min/100g)
Mean	0.13	0.94	0.13	40.4	5.3	11.5	13.7
Range	0.06 – 0.18	0.68 – 1.23	0.09 – 0.17	28.4 – 61.6	4.1 – 6.9	8.8 – 14.4	7.6 – 19.6
intra-animal CV%	19.9	16.6	17.5	32.9	31.3	17.0	26.4
Range	2.5 – 39.7	2.4 – 33.8	11.6 – 25.9	4.6 – 76.3	3.6 – 66.1	8.0 – 20.4	7.4 – 52.9
inter-animal CV%	33.5	19.2	22.1	25.7	16.3	20.6	24.3

Table 1: DCE-MRI and DCE-CT parameters, ranges, and RMS coefficients of variation across time points (n=3) and across animals (n=8).

Discussion: According to the Tofts model (1), if flow rates are high, K^{trans} should approximate to *PS*. C6 is a well-perfused tumor, evident from the high BF and BV in Table 1. Assuming unit tumor density, the DCE-MRI K^{trans} of 0.13 min^{-1} is in excellent agreement with 0.14 min^{-1} from DCE-CT. In general, the reproducibility of the DCE-MRI parameters, as assessed by the CV% across time points, was better than for the DCE-CT parameters. Thus for the same reduction in *PS*, DCE-MRI would be preferred as fewer animals would be required for the same statistical power. However, unlike traditional anti-VEGF approaches (2), future antiangiogenic targets may modulate flow independently of permeability, thus confounding the interpretation of K^{trans}: in that case the ability of DCE-CT to potentially separate BF from PS may be essential.

References: (1) Tofts PS *et al.* J Magn Reson Imaging 10:223-32, 1999; (2) Bradley DP *et al* Magn Reson Imaging, in press, 2008