

Early Measures of Perfusion and Diffusion Changes Using a Standardized Analysis Platform Evaluated in Brain Metastases Treated with Stereotactic Radiosurgery

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Background

Imaging systems need to perform as quantitative, precise measuring tools if they are to contribute to the goals of personalized and precision cancer medicine. This is especially true in radiation oncology where non-invasive imaging methods promise to probe the tissue/tumor for anatomical and physiological characteristics that affect both the decision to treat as well as the distribution of radiation dose to be delivered. Analysis of these imaging signals over time can also help monitor dynamic response to treatment, thereby enabling personalized management of solid tumors through treatment adaptation based on individual measurements. Quantitative imaging needs investment and adoption by industry, academia, and

healthcare providers to live up to its potential. For imaging techniques to become truly quantitative, a high level of standardization and novel quality assurance methods are needed to minimize the noise in the measurements so that even small changes in imaging characteristics associated with a patient's clinical outcome can be detected early enough to adapt and personalize treatment. For example, the emerging potential to alter the location and prescription of the applied radiation dose in response to images acquired through the course of treatment requires a high degree of reliability for the quantitative performance of the imaging performed.

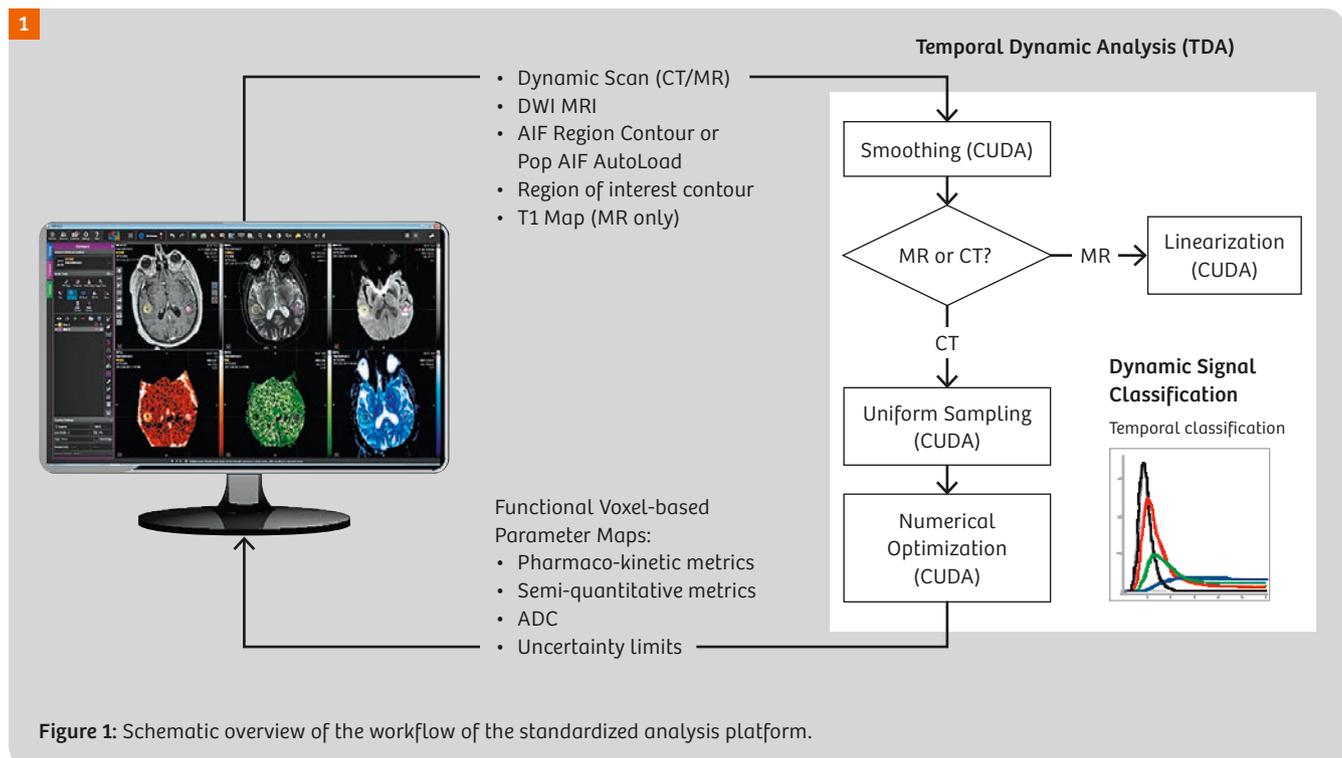


Figure 1: Schematic overview of the workflow of the standardized analysis platform.

Dynamic Contrast Enhanced (DCE) MRI is one such (functional) technique aimed at evaluating tissue and tumor perfusion parameters. DCE MRI techniques have seen a rapid growth in translation into radiation therapy clinical trials [1, 2] but DCE MRI measures of tumor vascular physiology have shown heterogeneous results across studies: this may reflect variability in the MR acquisition and analysis approaches across different studies, institutions, and even MR vendors [3–5]. Given the potential for DCE MR imaging metrics to provide early indicators of therapy-induced changes in the tumor micro-environment, it is imperative to obtain a better understanding of these imaging biomarkers to guide adaptive and potentially individualized therapy approaches in the future.

Pharmaco-kinetic modelling

The underlying process of DCE imaging is based on measuring the flow of an intravenously administered, low-molecular weight contrast agent such as Gadolinium and performing pharmaco-kinetic analysis. This involves modelling the transport of these contrast molecules between the intra-vascular and extra-vascular space. Different parameter models for contrast material exchange have been developed to quantify physiological properties of the microcirculation, such as tissue perfusion, vascular permeability, and blood volume. Most of these pharmaco-kinetic models are simplified, compartmentalized descriptions of transfer rates between intra-vascular and extra-vascular blood pools where a uniform contrast agent distribution is assumed. As such it is not surprising that the reproducibility and accuracy of model-based physiological parameters has been challenging, especially in flow-limited situations like hypoxic and necrotic tissue regions. Although the type of contrast agents used for other imaging techniques such as DCE CT and PET imaging will vary in size, osmolality, weight, etc., this fundamental analysis problem is shared by all.

Reproducibility of either DCE CT or DCE MRI alone has been low [6, 7] and output parameters from either imaging technique have not correlated well. This has been the case even in direct, *in-vivo* comparisons of the same tumor and in these situations the variability in kinetic parameters has been attributed mostly to differences in contrast agents and tumor dynamics between DCE CT and MRI. However, we hypothesized that two other factors are perhaps equally important:

- 1) Often, different kinetic models or model implementations are used for the DCE CT and MRI analysis despite both using low-molecular weight contrast agents;
- 2) notwithstanding advances in voxel-based DCE image acquisitions, analysis results are mostly reported in median values, hence losing the opportunity to investigate tumor heterogeneity and masking any correlations.

A recent 4D temporal dynamic analysis (TDA) method, which enables voxel-based, parametric analysis based on

patient-specific dynamic behaviour of contrast flow, might provide a more standardized approach for DCE MRI analysis, including its validation against DCE CT [8] given its linear relation between signal and contrast agent concentrate. It was shown that this TDA approach to DCE CT pharmacokinetic modelling provides more robust measures of change in perfusion following stereotactic radiosurgery (SRS) for brain as well as liver lesions [9].

Given that both DCE and diffusion-weighted imaging (DWI) modelling approaches probe the tumor micro-environment on a similar scale and are clearly linked in its biomechanical description, we designed a multi-modal architecture to analyse various complimentary solute transport processes in a common framework. The aim was to allow for a direct, voxel-to-voxel comparison of tumor perfusion, permeability and diffusion parameters from registered DCE CT, DCE MRI and DWI-MRI data using a shared pharmacokinetic model implementation. It was **hypothesized** that

- a) this unified platform would result in better correlations between parametric maps from DCE CT and MRI than previously reported; and that
- b) a high correlation would exist between the Apparent Diffusion Coefficient (ADC) and extravascular extracellular volume fractions, V_e , given their physiological connection describing the diffusion of water molecules inside the extravascular extracellular space.

A unified pipeline could streamline and perhaps improve even the reproducibility of individual functional imaging techniques and enable cross-validation of physiological response measures across imaging techniques and modalities. Once a shared pharmaco-kinetic platform is established, other voxel-based features of the tumor – such as cell density, or lipid and metabolites as obtained from MRI spectroscopy – could be incorporated in order to provide complementary information so that together a more comprehensive description of the tumor microenvironment can be evaluated.

Multi-functional analysis platform

In order to achieve this goal of rich, combined descriptions of the micro-environment, one must realize the amount of data associated with functional imaging techniques is significant. A typical brain perfusion CT scan can be 10 GB, which creates special viewing, processing, and data transfer requirements to enable reliable and practical integration into the clinical decision making process. Automation is therefore essential to conduct voxel-based image analysis on this scale, so we developed a platform to streamline and automate the analysis.

An overview of the platform pipeline is shown in a schematic in Figure 1. The core component is the computationally intensive TDA method [10] which was remodelled to enable GPU-based optimization on a high-throughput cluster [11] using CUDA. Briefly, this method applies a classification

scheme to each voxel, based on the temporal characteristics of the voxel's contrast enhancement over time and then iteratively improves the pharmaco-kinetic modelling based on this classification and its resulting parameter sensitivity. The Modified Tofts model [12] is commonly used in brain perfusion, based on the hypothesis of weak vascularization and increased permeability in tumors [13, 14] and this is what was used in the following evaluation in brain metastases. In addition to semi-quantitative measures, such as the integrated area under the enhancement curve (iAUC₉₀), the resulting functional parameters of interest were: K_{trans} , the transfer constant from the blood plasma into the extra-cellular extra-vascular space (EES); K_{ep} , the transfer constant from the EES back to the blood plasma and V_e , the extra-vascular extra-cellular volume. The haematocrit value, H_{ct} , was assumed to be 0.4 for all cases.

Additional image registration between DCE MRI and DWI-MRI modalities allowed ADC values to be calculated on the same voxels as from DCE-MRI. The directional diffusion images were averaged on a voxel-by-voxel basis to non-directional diffusion images within the TDA framework and then ADC values were calculated for each voxel by fitting the mono-

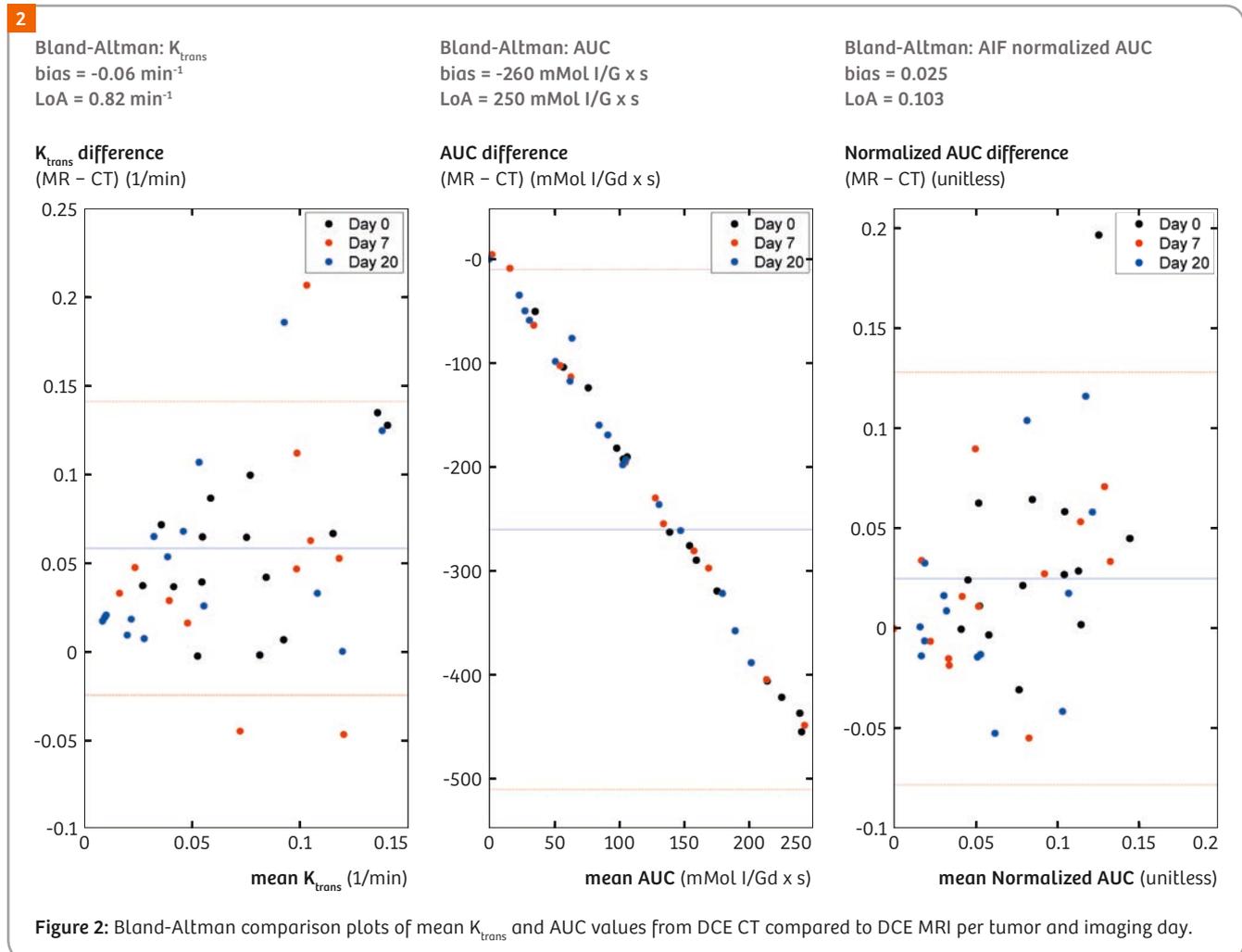
exponential model equation to four-point plots of signal intensity by using a linear least square fit algorithm [15].

A 3D Voxel Mask was created for each functional parameter as well as a separate sum of squared errors (SSE) mask to show the transport model quality-of-fit. Finally, a histogram moment analysis was done for each parameter inside the tumor mask assessing the standard deviation, skew and kurtosis of the histogram shape.

Early treatment response following SRS for brain metastases

Comparison of DCE CT to DCE MRI

Our initial clinical experience with tumor imaging biomarkers following SRS for brain metastases used volumetric DCE CT and DCE MRI in the same patients supported by this common TDA framework [16]. Patients were treated with SRS as part of REB-approved clinical trials and underwent volumetric DCE CT and DCE MRI scans at baseline, then 7 and 21 days post-SRS. TDA was used to create 3D pharmaco-kinetic parameter maps for both modalities. The arterial input function (AIF_{CT}) was chosen in the carotid artery for DCE CT and compared against a vascular input function (VIF_{CT}) in



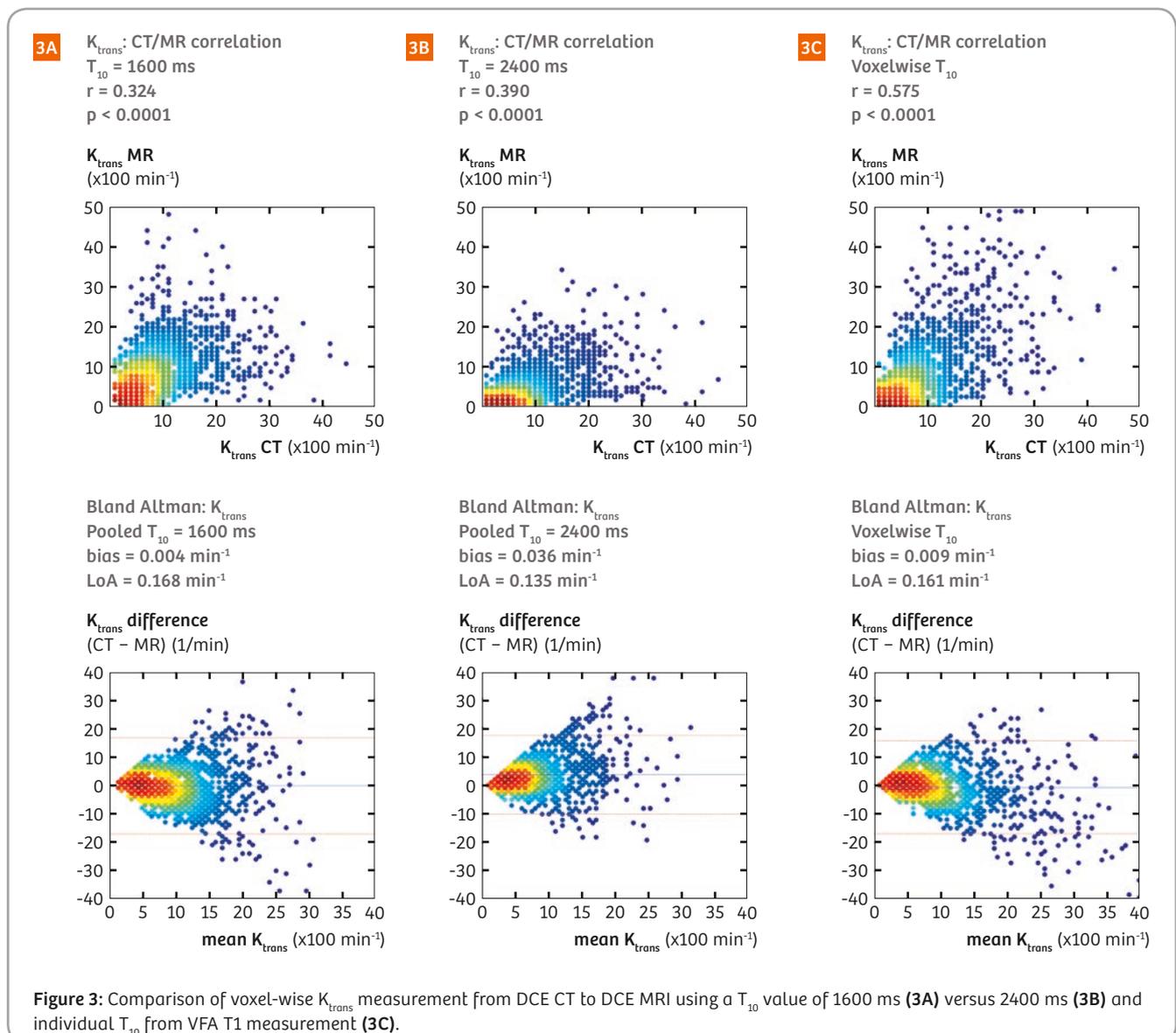
the sagittal sinus. For this study, a population-based input function (AIF_{MRI}) was used for DCE MRI analysis because of variability in flip angle between patients, and to allow for a robust comparison of the impact of the analysis methodology against DCE CT.

Direct voxel-voxel Pearson's analysis showed statistically significant correlations between CT and MR which peaked at Day 7 for K_{trans} ($R = 0.74$, $P < 0.0001$, $n = 40$). The strongest correlation to DCE-CT measurements was found with DCE-MRI analysis using voxelwise T_{10} maps ($R = 0.575$, $p < 0.001$, all cases) instead of assigning a fixed T_{10} value. Comparison of histogram features demonstrated statistically significant correlations between modalities over all tumors for median K_{trans} ($R = 0.42$, $P = 0.01$), median $iAUC_{90}$ ($R = 0.55$, $P < 0.01$) and $iAUC_{90}$ skewness ($R = 0.34$, $p = 0.03$).

This is illustrated in Figures 2 and 3 with Figure 2 showing the mean tumor correlation by ways of Bland-Altman

comparison for all imaging days derived from DCE MRI and DCE CT. The correspondence is relatively scattered and indicates a slight bias towards higher K_{trans} values from MRI. Statistical significance improved significantly when comparing the voxelwise correlations taking into account tumor heterogeneity as shown in Figure 3 where no bias is present.

Based on DCE CT data, AIF and VIF appear to be interchangeable in generating similar K_{trans} values [16]. This confirms that use of individual VIF in DCE MRI analysis is a reasonable approach if it can be accurately measured. In contrast, the application of different T_{10} values impacted the K_{trans} value more dramatically and the inclusion of individualized voxel-wise pre-contrast relaxation times in the pharmaco-kinetic analysis is essential when evaluating parametric tumor heterogeneity [16, 17].



Correlation between ADC and DCE MRI

Statistically significant correlations were also present between ADC values and V_e from both DCE MRI and DCE CT, but a large variation was present across tumors (R^2 : 0.15–0.8). These correlations disappeared altogether when using the mean ADC values hence disregarding tumor heterogeneity as shown in Figure 4.

Summary

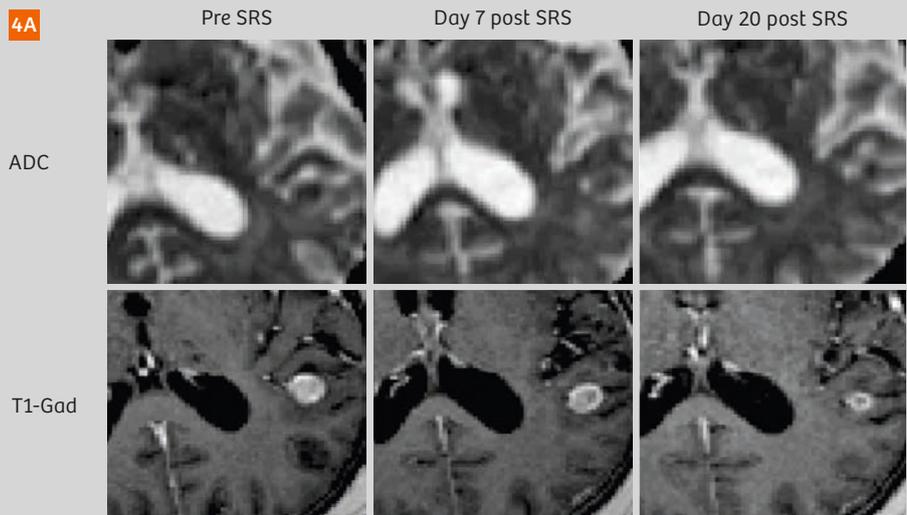
By analyzing contrast enhancement data from both DCE modalities in a unified and voxel-based approach, it was shown that the correlations between their parametric output values improved significantly compared to previously reported studies that used separate analysis software for both CT and MRI analysis. The high level of correlation between CT and MRI pharmaco-kinetic parameters supports the concept that low molecular weight contrast agents can

indeed help derive tumor permeability and perfusion heterogeneity independent of imaging modality, *provided the image analysis methods are standardised*. We also found correlations between ADC values and extravascular extracellular volume fraction parameters measured with DCE and DWI MRI when analysed using the TDA platform. This raises the potential to use this platform to further explore biophysical properties of different tumors and their microenvironments using multi-parametric imaging data.

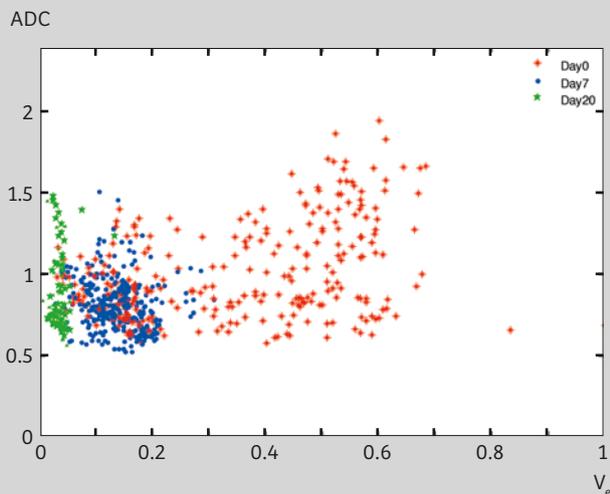
This research indicates that more reproducible, quantitative measures of the tumor micro-environment can be extracted using DCE MRI and DCE CT with appropriate pharmacokinetic models. Being able to non-invasively interrogate the tumor micro-environment in a reliable way finally opens the possibility of using these imaging techniques to guide precision cancer medicine by directing care and adapting treatment based quantitative imaging measures of tumor response.

Figure 4:

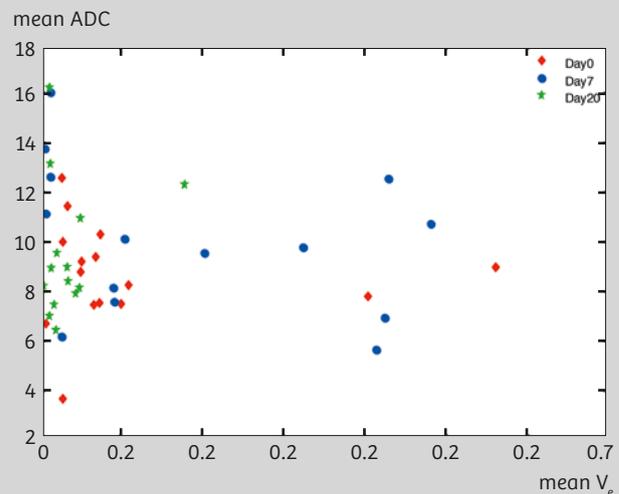
(4A) T1-weighted Gad and ADC pre-treatment; Day 7 and day 20 post-SRS for a typical tumor;
(4B) Voxelwise correlation of V_e and ADC for the same tumor;
(4C) Correlation between median ADC and mean V_e values per tumor over all imaging days.



4B ADC vs V_e
 $\times 10^3$



4C mean ADC vs mean V_e
 $\times 10^4$



The success of the early TDA platform formed the basis of the comprehensive and multi-centre Quantitative Imaging for Personalized Cancer Management (QIPCM) program now in place at the Princess Margaret Cancer Centre. The centralised storage and archiving system that underpinned TDA was greatly expanded and QIPCM currently also provides end-to-end QA, workflow, and analysis services for imaging in clinical trials including: equipment QA, protocol development, data anonymization, QC of data during accrual, centralized data storage with remote access, software tools, and image analysis. The program currently supports approximately 20 open clinical trials run under Cancer Care Ontario as well as a number of international and industrial partners aiming to use functional imaging. The GPU version of the TDA tool is being tested internally and will be released for external trials in the next couple of months.

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