TUMOUR RESPONSE ASSESSMENT USING VOLUMETRIC DCE-CT AND DCE-MRI IN METASTATIC BRAIN CANCER PATIENTS

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Introduction: Early change in tumour vascular physiology following stereotactic radiosurgery (SRS) is a potential biomarker of response. Although dynamic contrast enhanced (DCE) MRI is most commonly used to interrogate tumor vascular physiology, it has known uncertainties due to the complex relationship between MR signal and contrast concentration. In this context, DCE-CT presents as a consistent standard for tracer-kinetic validation. Progress in multi-slice CT technology now allows for volumetric CT acquisition with 4D temporal dynamic analysis (TDA) of perfusion. This enables voxel-based, parametric analysis based on patient-specific dynamic behaviour of contrast flow. This voxel-based approach may also improve DCE-MRI analysis. This study aims to evaluate the ability of DCE-MRI and DCE-CT to detect changes in tumor vascular physiology that predict for tumor response to SRS and to compare DCE-MRI analysis against DCE-CT supported by a common TDA framework to measure changes in vascular parameters in brain metastases treated with SRS.

Methods and Materials: **Methods and Materials**: Patients with brain metastases treated with SRS as part of REB-approved clinical trials underwent both volumetric DCE-CT (Toshiba, Aquilion ONE) and DCE-MRI (IMRIS 3T Verio, Siemens) scans at baseline then 7 and 21 days post-SRS. DCE-CT scan parameters were: 80kV, 100mA, 1sec rotation and 0.468x0.468x1mm reconstruction resolution. A total of 60 ml of Visipaque® 320 was injected intravenously at 5 ml/sec synchronized with the start of scanning. The DCE CT time sequence consisted of different sampling frequencies, scanning every 1.5 sec for the first 30 sec, then every 5 seconds up to 90 sec and every 10 sec up to 180 sec. Variable-flip-angle (VFA) T1 quantification and DCE MRI acquisitions used 3D-FLASH with matching echo times (1.86 msec), repetition times (4.8 msec), and geometric features (field-of-view 22 x 20 cm, 192x174 matrix, 1.15x.1.15 mm in-plane resolution, 40 slices at 1.5 mm each). VFA-T1 used flip angles of 2, 10, 20, and 30° degrees in 50 sec acquisitions. DCE-MRI used a 20° flip angle, and 45 frames were acquired with a temporal resolution of 5.8 sec DCE-MRI used a 20° flip angle, and 45 frames were acquired with a temporal resolution of 5.8 sec. Tumor regions of interest (ROIs) for each time point were contoured on the T1weighted Gadolinium-enhanced MR image sets by a singly expert observer and registered to the DCE-MR and DCE-CT images. Individual vascular input functions were selected in the internal carotid artery for DCE-CT while a population based AIF was utilized for DCE-MRI. Voxel-based whole brain TDA was performed on both the DCE-CT and DCE-MR images using in-house software for tracer-kinetic analysis. Modified Tofts and semi-quantitative kinetic parameters of perfusion and permeability (K_{trans}, V_e, AUC) were assessed within each tumour at every time point and a linear regression was done of the temporal changes in these parameters over treatment and the baseline parameters for the same patient. Correlation between these vascular parameters and treatment response, evaluated as stable or reduction in tumor volume was assessed. Tumour progression or response was assessed based on changes in gross tumour volume at Day 7 and 21 with a threshold of +/- 10%.

Results: A total of 14 tumours were evaluated with both DCE-CT and DCE-MR at Day 7 and 21 post SRS. At Day 21 only one tumor had a volume that remained larger than at baseline while the other tumors showed a decrease in volume of (mean of 53.6 +/- 31%). DCE-CT. With the 4D TDA approach, 3 of the 8 stable or responding tumours revealed a K_{trans} reduction of 44.6+/-36.6% ($p=0.056$) at Day 7 post-RS while 10 out of 13 responding tumours had a reduction in K_{trans} of 26.0 +/- 16.6 % by Day 20 ($p < 0.01$). Only one of the non-responding tumours showed a decrease in K_{trans} at Day 7 while none did at Day 20. Twelve out of the 13 stable/responding tumours showed a reduction in AUC (-49.6+/-20.2 % $p<0.01$) by day 20, however the one progressing tumour also showed a 10% decrease in AUC. DCE-MRI. 7 of the 8 stable or reducing tumours revealed a K_{trans} reduction of 17.4+/-16.6% ($p<0.05$) at Day 7 post-RS while 10 out of 13 responding tumours had a reduction in K_{trans} of 24.0 +/- 20.3 % by Day 20 ($p < 0.05$). However 3 of the non-responding tumours showed a decrease in K_{trans} at Day 7 as did the one at Day 20. Ten out of the 13 stable/responding tumours showed a reduction in AUC (-52.2+/-18.0 % $p<0.01$) by Day 20, however the one progressing tumour also showed a 19% decrease in AUC. Correlations between CT and MR. MRI results only showed weak overall correlations with the DCE-CT results at either Day 7 ($R2=-0.16$) or Day 20 ($R2 = 0.21$) for K_{trans}. However AUC showed a better correlation between the two modalities at both Day 7 ($R2=0.786$) and 20 ($R2=0.386$).

Discussion: This is the first study to evaluate the synchronised acquisition of perfusion parameters acquired by volumetric DCE CT and DCE MRI in a cohort of metastatic brain patients. In general, a reduction in K_{trans} was observed in the majority of responding tumors. But as only 1 tumor did not respond to SRS, using our definition of response as stable or smaller tumor volume at Day 21, it remains uncertain whether even non-responding tumors may show reductions in K_{trans}. One possible reason for observing a reduction in K_{trans} in both non-responding and responding tumors is the development of a necrotic core as the tumor grows or as the tumor responds to SRS, respectively. Therefore, methods that attempt to exclude the necrotic core may better predict response when using DCE biomarker approaches. Despite the promising results in both modalities to reveal response at early stages of treatment, the correlation between the two techniques is still weak. Given that a common perfusion analysis framework was used, one must also consider the impact of AIF on K_{trans} and as such it is possible that our initial analysis using individual AIF for CT and population AIF for MRI may explain the poor correlation. Analysis is ongoing to compare population AIF DCE-CT and population AIF DCE-MRI as well as individual AIF DCE-CT and individual AIF DCE-MRI results.

Conclusions: Early K_{trans} reduction at 20 days following SRS may be predict for eventual response to SRS in brain metastases using 4D TDA DCE imaging. Comparison between DCE CT and MRI is weak in this initial data set but issues such as sensitivity to AIF, differences in tumor type, etc might explain the lack of correlation more and are being investigated.