Estimation of R1 changes from Dual bolus DCE-MRI in Vestibular Schwannomas and Meningiomas of Patients Undergoing Treatment of Bevacizumab

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**Target audience:** Investigators using DCE-MRI in tumor studies

**Purpose:** Mapping 3D tissue T1 relaxation rate, R1 (1/T1) is essential in converting DCE-MRI to 4D contrast concentration images. The purpose of this study was 1) to test reliability of R1 mapping methods; 2) to estimate R1 changes between two bolus injections of contrast agent (CA), the prebolus and the main dose, with the use of dual temporal resolution approach (DTR)1. A group of patients with brain tumors undergoing antiangiogenic were used for the validation.

**Methods:** In DTR, the spatial distribution of R1 needs to be estimated twice. The first is to map the tissue native R1s before the administration of contrast media (CA). The second R1inst is estimated immediately before administration of the main dose of CA. R1inst might be higher than R1s if CA from the prebolus was not entirely eliminated from the brain tissue and lesions. Alternatively, the changes of R1 from R1s to R1inst can be estimated from fitting the prebolus CA concentration time curve with a pharmacokinetic model. e.g. the Kety model, then extending the theoretical curve to the start of the 2nd injection:

\[
C(t) = v_p C_p(t) + K_{\text{vasc}} \int_0^t C_v(t-r) \exp \left(-\frac{K_{\text{vasc}}}{v_p}(t-r) \right) dr
\]

and

\[
R1_{\text{inst}} = R1_s + C(v_p) \Delta r
\]

where \(\Delta r\) is the time between the injections of first and second bolus. \(r1\) is the longitudinal relaxivity of gadoterate meglumine (Gd-DOTA: Dotarem), which has an elimination half-life of 90 minutes.

DTR-DCE data were acquired from five patients with type 2 neurofibromatosis (NF2) with vestibular schwannomas (VS) and meningiomas (Me). They underwent 3 scans: baseline, 2 and 90 days post-treatment with the anti-vascular endothelial growth factor antibody, bevacizumab. Large volume high temporal resolution (HT, \(\Delta t = 1s\)) DCE MRI followed a small dose (0.02 mM/kg body weight) prebolus and high spatial resolution (HS, voxel size = 1x1x2 mm) was acquired following a standard dose (0.1 mM/kg). Two sets of variable flip angle (VFA) GRE images were acquired for R1 mapping.

\(R1_{\text{HT}} (=R1_s)\) and \(R1_{\text{HT}} (=R1_{\text{inst}})\) maps were calculated (Fig 1). Three longitudinal HT and HS DCE series and associated R1 maps, (baseline, 2 days, 3 months) were spatially (4D) co-registered to baseline HS DCE-MRI images acquired on day0. 3D parametric maps of the transfer constant (\(K^{\text{vasc}}\)), the fractional plasma volume (\(v_p\)) and the fractional volume of extravascular extracellular space (\(v_e\)) were calculated. WM, GM and tumors were automatically segmented for voxel-by-voxel analysis in a region of interest, i.e. tumor, GM and WM (Fig. 2). Figure 3 shows \(K^{\text{vasc}}\) images calculated from two DCE-MRI series following prebolus and main dose, \(K_{\text{HT}}\) and \(K_{\text{HS}}\), in a patient who had 5 scans from day0 to day450. Visual inspection shows the similar features of change of \(K^{\text{vasc}}\) intensity on the low dose maps following treatment of bevacizumab. Both show earlier response to bevacizumab treatment in VS (2 days onwards) and late response in Me (7 month onwards).

Table 1. Day0, R1s (R1HT) and R1inst (R1HS) of tumor, WM and GM

<table>
<thead>
<tr>
<th>Tissues</th>
<th>R1s</th>
<th>R1HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS</td>
<td>.66±.03</td>
<td>.88±.03*</td>
</tr>
<tr>
<td>Me</td>
<td>.88±.10</td>
<td>.99±.06†</td>
</tr>
<tr>
<td>GM</td>
<td>.83±.04</td>
<td>.82±.04</td>
</tr>
<tr>
<td>WM</td>
<td>1.18±.05</td>
<td>1.26±.05</td>
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</tbody>
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*\(p < 0.0001\), †\(p = 0.07\)

Table 2 shows \(K_{\text{HT}}\) and \(K_{\text{HS}}\) on day0, day2 and day90. In agreement with the visual inspection, there is significant early reduction (day0 onwards) of both \(K_{\text{HT}}\) and \(K_{\text{HS}}\) in the progressive VS, but not in Me. There is no significant change of mean values of R1 in brain tissue or tumors in the repeated studies.

**Discussion:** We have demonstrated significant R1 increase from R1s to R1inst resulting from Gd-DOTA retained in the interstitial space in VS and Me. The amount of increase can be estimated using the Kety model. As expected R1 increase in WM and GM were much less than tumors since little contrast diffuses across capillary endothelium in normal brain tissues. This study also shows that the variable flip angle (VFA) method provides fast and robust measurement of R1, which is the key step in converting DCE-MRI to 4D concentration images. Finally, we present 3D maps of \(K_{\text{HT}}\) from one-fifth dose of Gd-DOTA. The maps were comparable to the 3D \(K_{\text{HS}}\) maps where a full dose of CA was injected so that the \(K_{\text{HT}}\) achieved the same detection of changes in VS and Me induced by VEGF blockade. In conclusion, the VFA is a fast 3D T1 mapping technique. Although the R1inst can be estimated in theory, we still recommend acquiring two VFA R1 series, one for R1s and the other for R1inst, instead of one, especially when different scan sequences or scan parameters were used for the prebolus and main dose DCE.

**References:**