Comparison of one- and two-compartment kinetic models in DCE-MR images of hepatocellular carcinomas

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Purpose

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide. It is usually related to either a viral infection (hepatitis B or C) or cirrhosis (mainly due to alcoholism). The usual outcome is poor, as it is very difficult to remove the tumor completely after surgery [1].

One of the mechanisms that stands in the spotlight of HCC development is angiogenesis, which can be defined as the formation of new vessels either from pre-existing vasculature or from embryo cells. When the tumor is developing, at a certain step of growth (approximately 1 mm) it needs an autonomous blood supply to keep on growing [2]. There is also a progressive change of the vascularization origin, from a predominant portal blood supply, as in normal conditions, towards an arterial dominance [3].

Kinetic analysis of dynamic contrast-enhanced MR images (DCE-MRI) is currently used in many research and clinical centers to assess the microvascular properties of tissues. Among its potential clinical applications, the study of tumors has demonstrated that DCE-MRI kinetic modeling can be used to quantify physiological parameters such as permeability, interstitial space, vascular space and contrast agent washout rate [4].

In normal livers there is a predominant venous contribution in the uptake curves. This means that the curve maximum takes place just after the maximum of the portal vein enhancement curve. In this situation, it has been demonstrated that it is not necessary to include a vascular term in the model (i.e. a second compartment), as this term focuses particularly on the arterial contribution. However, when there is a significant arterial contribution, such as in HCCs, the one-compartment approach models this new information through the volume transfer constant, masking the vascular volume and overestimating the flow and permeability values [5].

The purpose of this work is to evaluate if the application of one- and two-compartment kinetic models in DCE-MR images of hepatocellular carcinomas (HCC) shows different results.
Methods and Materials

Patients and image acquisition

The study included thirteen cirrhotic patients not treated previously with defined expansive HCC (7 men, 6 women, 63±13 years). Written consent was obtained from all the patients for the MR examination and from the Ethics Committee for data processing and evaluation. All patients were imaged in a 1.5 T scanner (Intera, Philips Healthcare, The Netherlands) using a 4-channel phased-array surface coil. The patients were asked to breathe smoothly during the dynamic study. Apart from the usual MR examination, two additional sequences were acquired, a multiple flip angle sequence for T1 calculation and a high temporal resolution contrast-enhanced perfusion sequence. These sequences were necessary to apply the pharmacokinetic models afterwards.

- Sequence 1: transversal T1-weighted spoiled gradient echo, TR = 87 ms, TE = 1.1 ms, resolution = 0.8 x 0.8 x 7.5 mm, $\alpha$ = 5º, 15º, 30º, 45º, 70º, slices = 24.
- Sequence 2: transversal T1-weighted contrast-enhanced spoiled gradient echo, TR = 70 ms, TE = 1 ms, resolution = 0.8 x 0.8 x 7.5 mm, $\alpha$ = 60º, slices = 24, dynamic time = 3.7 s, dynamics = 40, acquisition time = 2 minutes and 28 seconds, contrast dose = 0.05 ml/kg (Gd-BOPTA, Multihance, Rovi, Spain), saline flush = 40 ml, injection speed = 4 ml/second.

Image analysis

All images were transferred to a dedicated workstation for post-processing. A registration software was applied to correct motion artifacts caused by breathing (SPM, Wellcome Trust Center for Neuroimaging, London, UK). This software generated a secondary series of images where movement was corrected according to a reference volume. In this study, a volume obtained as the mean of the whole dynamic series of volumes was used as reference.

A multiple flip angle sequence was used to obtain the T1 values of the liver before contrast administration. These T1 values are necessary for the conversion of signal intensity into contrast concentration. From this sequence it is possible to express the signal intensity as a function of the flip angle (figure 1).

For each study the aorta and the portal vein were manually selected as vascular inputs to the models. Also, large regions of interest were selected for the livers and the tumors (figure 2). All curves were converted from signal intensity into contrast concentration (figure 3).
Both the one-compartment (only interstitial space) and two-compartment (interstitial and vascular spaces) models were applied to the contrast uptake curves (figure 4), obtaining the pharmacokinetic parameters $K_{\text{trans}1}$ (arterial transfer constant), $K_{\text{trans}2}$ (venous transfer constant), $k_{\text{ep}}$ (washout constant), $v_e$ (interstitial space) and $v_p$ (vascular space, only in the two-compartment model). The interstitial space fraction, $v_e$, is obtained as $(K_{\text{trans}1} + K_{\text{trans}2})/k_{\text{ep}}$ [6].

**Statistical analysis**

The Pearson correlation coefficient and the Student’s t test were used to establish the relationship and the differences between the one- and two-compartment pharmacokinetic parameters. The differences between liver and tumor were assessed with the Student’s t test. A p-value < 0.05 was considered as statistically significant.
Fig. 0: Figure 1. Relationship between signal intensity and flip angle, where $S(\alpha, x, y)$ is the signal intensity for the pixel in coordinates $x, y$ and the flip angle $\alpha$, and $M$ is a factor which is associated to the equipment gain and the proton density.

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Fig. 0: Figure 2. Selection of the arterial (red) and venous (blue) input functions, liver parenchyma (green) and lesion (brown). Liver and lesion enhancement curves are extracted and analyzed pixel-by-pixel.

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\[ C(t,x,y) = \frac{1}{T1(t,x,y)} - \frac{1}{r1} \]

**Fig. 0:** Figure 3. Relationship between contrast concentration and T1 variation, where \( C(t,x,y) \) is the contrast concentration at time \( t \) pro pixel in coordinates \( x,y \), \( r1 \) is the contrast longitudinal relaxivity \((4.5 \text{ mM-1s-1 at } 37^\circ \text{C})\) and \( T1(t,x,y) \) is the variation of the T1 with time.

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\[
C_i(t) = \int_0^t \left( K^{\text{trans}1-1c} C_a(\tau) + K^{\text{trans}2-1c} C_v(\tau) \right) e^{-k_{ep}1c(t-\tau)} d\tau \\
C_i(t) = \nu_p^{2c} C_a(t) + \int_0^t \left( K^{\text{trans}1-2c} C_a(\tau) + K^{\text{trans}2-2c} C_v(\tau) \right) e^{-k_{ep}2c(t-\tau)} d\tau
\]

**Fig. 0:** Figure 4. Equations for the 1- (1c) and 2-compartment (2c) pharmacokinetic models, where \( t \) denotes time, \( C_t \) is the contrast concentration in the tissue, \( C_a \) is the contrast concentration in the aorta and \( C_v \) is the contrast concentration at the porta. \( K^{\text{trans}1} \) denotes the arterial transfer constant, \( K^{\text{trans}2} \) the venous transfer constant, \( k_{ep} \) the washout constant, \( \nu_p \) the interstitial space and \( v_p \) the vascular space (only in the two-compartment model). The interstitial space fraction, \( \nu_p \), is obtained as \((K^{\text{trans}1} + K^{\text{trans}2})/k_{ep}\).

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Results

Figure 5 shows a table with the correlation values and the statistical significance for each couple of pharmacokinetic parameters, both in the liver and the tumor. It also shows the differences between liver and tumor for all the parameters. Although there were no statistically significant differences, it can be seen that the one-compartment model showed much higher mean values in the tumor for $K^{\text{trans}1}$, $K^{\text{trans}2}$ and $k_{\text{ep}}$, while $v_e$ remained in the same range. On the other hand, both models showed similar results in the liver. All correlation coefficients were high and strongly significant.

Both the one- and two-compartment parameters offered similar results for the differentiation between liver and tumor, especially $K^{\text{trans}1}$ ($p<0.001$). For the two-compartment model, $v_p$ also showed good results ($p=0.001$). Figure 6 depicts a set of coloured parametric maps showing the differences between liver and lesion.
<table>
<thead>
<tr>
<th>Region</th>
<th>$K_{101\text{max}}$</th>
<th>$K_{202\text{max}}$</th>
<th>$k_{op}$</th>
<th>$v_{r}$</th>
<th>$v_{p}$</th>
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<tr>
<td></td>
<td>1c</td>
<td>2c</td>
<td>1c</td>
<td>2c</td>
<td>1c</td>
</tr>
<tr>
<td>Liver</td>
<td>47.9±40.9</td>
<td>40.2±36.8</td>
<td>133.9±184.0</td>
<td>134.2±169.9</td>
<td>369.5±396.6</td>
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<tr>
<td>r</td>
<td>0.99 (p&lt;0.001)</td>
<td>1.00 (p&lt;0.001)</td>
<td>1.00 (p&lt;0.001)</td>
<td>0.99 (p&lt;0.001)</td>
<td>-</td>
</tr>
<tr>
<td>p</td>
<td>0.619</td>
<td>0.997</td>
<td>0.957</td>
<td>0.966</td>
<td>-</td>
</tr>
<tr>
<td>Tumor</td>
<td>216.5±99.6</td>
<td>150.4±70.4</td>
<td>105.6±126.4</td>
<td>59.2±60.0</td>
<td>750.6±445.0</td>
</tr>
<tr>
<td>r</td>
<td>0.93 (p&lt;0.001)</td>
<td>0.83 (p&lt;0.001)</td>
<td>0.77 (p&lt;0.002)</td>
<td>0.99 (p&lt;0.001)</td>
<td>-</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.652</td>
<td>0.146</td>
<td>0.030</td>
</tr>
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</table>

**Fig. 0:** Figure 5. Comparison of the results obtained from the application of the one- and two-compartment pharmacokinetic models.

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**Fig. 0:** Figure 6. Coloured parametric maps for (a) Ktrans1 (ml/min/100ml), (b) Ktrans2 (ml/min/100ml), (c) kep (ml/min/100ml), (d) ve (no units) and (e) vp (no units).

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Conclusion

Although there are no differences in normal liver tissue, it seems necessary to include a vascular compartment when analyzing highly arterialized lesions such as HCCs, as the one-compartment approach overestimates the transfer constants.
References


Personal Information

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