Quantitative DCE-MRI for Treatment Monitoring Rat HCC

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TUM
Hepatocellular carcinoma

Major health problem worldwide

3\textsuperscript{rd} most common cause of cancer-related death

> 500,000 new cases yearly

Curative treatments (5-15\% of patients)

Hepatic resection in non-cirrhotic patients

Percutaneous treatments (PEI, RFA)

Liver transplantation

Palliative treatments (85-95\% of patients)

Arterial embolization or chemoembolization

Multikinase inhibitor Sorafenib (Nexavar\textsuperscript{®})
Mechanism of HCC Development

### Angiogenesis in HCC: portalvein to hepaticartery

<table>
<thead>
<tr>
<th></th>
<th>normal liver tissue</th>
<th>RN, DN, early HCC</th>
<th>late HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>marker</strong></td>
<td>CD31- CD34- BNH9- EphB4</td>
<td>Genetic / epigenetic Environment Physiology</td>
<td>CD31+ CD34+ BNH9+ EphrinB2 a-SMA Laminin</td>
</tr>
<tr>
<td><strong>phenotype</strong></td>
<td>sinusoidal</td>
<td>Sprouting Intussusception Vesselcooption Vascularmimicry Progenitorcellincorporation</td>
<td>capillary</td>
</tr>
<tr>
<td><strong>Bloodsupply</strong></td>
<td>portalvein (80%)</td>
<td></td>
<td>hepaticartery</td>
</tr>
</tbody>
</table>
### Signal Quantification

<table>
<thead>
<tr>
<th>Pro</th>
<th>Contra</th>
</tr>
</thead>
</table>
| simple | • signal change reflects intra- and extravascular \( Ca \)  
| | • signal intensity affected by scan protocol (i.e. receiver gain) |

### Pharmacokinetic modeling (qDCE-MRI)

<table>
<thead>
<tr>
<th>Pro</th>
<th>Contra</th>
</tr>
</thead>
</table>
| independent of scan protocol | • complex numerical analysis (optimal fit?)  
| | • need for model selection |

#### qualitative / descriptive:
- MITR, IAUC90  
- wash in / out slope -> benign vs. malignant

#### quantitative:
- i.e. \( K^{\text{trans}}, v_e \)
## PK Modeling

### Modeling Techniques

<table>
<thead>
<tr>
<th>Individual level structural models</th>
<th>Population PK modeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIF</td>
<td>RR</td>
</tr>
<tr>
<td>Individual Arterial Input Function (iAIF)</td>
<td>Population Arterial Input Function (popAIF)</td>
</tr>
<tr>
<td>central compartment</td>
<td>RR compartment (representative)</td>
</tr>
</tbody>
</table>
Influence of heart rate and age on the arterial input function (AIF)

- combine CT and MR CA Gd-DTPA
- inducedefinitionchange in heart rate
- generate different population AIFs
- applypopulationAIFs to PK modeling
### Population AIF

**Siemens Somatom** (Erlangen, Germany)
**Philips Achieva, 1.5T** (Best, The Netherlands)

**Buffalo Rats (n=10)**

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>8-10</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>220±5</td>
<td>380±20</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>MMF</td>
<td>Iso</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>281±24</td>
<td>378±10</td>
</tr>
</tbody>
</table>
Data acquisition and processing

manual bolus injection (0.2mmol / kg BW)

sampling

\[ \Delta t_1 = 0.75 \text{s} \]
\[ \Delta t_2 = 38.5 \text{s} \]

HU dynamic -> conversion -> \( C_{\text{Gd,dynamic}} \)
Clinical dose Isovist400®

<table>
<thead>
<tr>
<th>tissue</th>
<th>VenaCava</th>
<th>Aorta</th>
<th>Tumor</th>
<th>Liver</th>
<th>muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δt (s)</td>
<td>4</td>
<td>8</td>
<td>10</td>
<td>26</td>
<td>34</td>
</tr>
</tbody>
</table>
population AIF

DCE-CT

Venacavapeakehancement

Aorta peakehancement
population AIF

AIF modeling

\[
C_p(t) = \sum_{n=1}^{2} \frac{A_n}{\sigma_n \sqrt{2\pi}} \exp\left(-\frac{(t-T_n)^2}{2\sigma_n^2}\right) + \sum_{m=1}^{2} \frac{\alpha_m \exp(-\beta_m t)}{1 + \exp(-s(t-\tau))}
\]

Parker et al. MRM 2006
### Population AIF

**HR low vs high**
- Slower initial rise
- Broader 1\textsuperscript{st} pass peak
- Later initial peak, recirculation

**age/weight low vs high**
- Lower initial peak
- Narrow peak

<table>
<thead>
<tr>
<th></th>
<th>HR (\uparrow) young</th>
<th>HR (\downarrow) young</th>
<th>HR (\uparrow) old</th>
<th>HR (\downarrow) old</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>21.69</td>
<td>15.34</td>
<td>36.38</td>
<td>54.56</td>
</tr>
<tr>
<td>A2</td>
<td>11.26</td>
<td>18.72</td>
<td>16.42</td>
<td>16.90</td>
</tr>
<tr>
<td>T1</td>
<td>1.69</td>
<td>2.82</td>
<td>2.26</td>
<td>3.93</td>
</tr>
<tr>
<td>T2</td>
<td>4.59</td>
<td>5.33</td>
<td>4.71</td>
<td>8.67</td>
</tr>
<tr>
<td>sigma1</td>
<td>0.64</td>
<td>0.67</td>
<td>0.78</td>
<td>1.27</td>
</tr>
<tr>
<td>sigma2</td>
<td>1.65</td>
<td>2.91</td>
<td>2.62</td>
<td>3.52</td>
</tr>
<tr>
<td>alfa1</td>
<td>2.34</td>
<td>3.21</td>
<td>6.32</td>
<td>5.41</td>
</tr>
<tr>
<td>beta1</td>
<td>0.052</td>
<td>0.020</td>
<td>0.066</td>
<td>0.030</td>
</tr>
<tr>
<td>s</td>
<td>43.73</td>
<td>40.00</td>
<td>40.02</td>
<td>39.81</td>
</tr>
<tr>
<td>tao</td>
<td>2.64</td>
<td>3.33</td>
<td>3.40</td>
<td>2.29</td>
</tr>
<tr>
<td>(\alpha)2</td>
<td>0.51</td>
<td>0.06</td>
<td>0.99</td>
<td>0.89</td>
</tr>
<tr>
<td>(\beta)2 (fix)</td>
<td>0.00048</td>
<td>0.00048</td>
<td>0.00048</td>
<td>0.00048</td>
</tr>
</tbody>
</table>
- HCC bearing Buffalo rats (n=10)
- HR low (MMF)
- Achieva 1.5T
- Gd-DTPA bolus (0.2mmol / kg bw)
- Dynamic Radial T1 mapping DCE-MRI
- PK modeling with population AIF (HR low and high)
DCE-MRI set up
Data analysis:

- Apply population AIF HR low and HR high PK modeling (opentwo-compartment)

\[ C_t(T) = K^{\text{trans}} \int_0^T C_p(t) \exp\left(-\frac{K^{\text{trans}}}{v_e}(T-t)\right) dt \]
Results I: qDCE-MRI Tumor

- **Ktrans (min⁻¹)**
  - HR high
  - HR low

- **ΔKtrans (%)**
  - %diff

- **ve**
  - HR high
  - HR low

- **Δve (%)**
  - %diff
Results II: qDCE-MRI Muscle
Summery

• DCE-CT with Gd-DTPA allows determination of a rat population AIF

• Different anaesthesia protocols induced different heartrates

• Derived population AIFs reflected the induced systemic change and also showed dependency on age/weight.

• The induced systematic error in pop AIF resulted in a mean percent change for tumor $K_{\text{trans}}$ of $23 \pm 27\%$ and $v_e$ of $50 \pm 7\%$
## Modeling Techniques

<table>
<thead>
<tr>
<th>Individuallevelstructuralmodels</th>
<th>Population PK modeling</th>
</tr>
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<tbody>
<tr>
<td><strong>AIF</strong></td>
<td>RR</td>
</tr>
<tr>
<td>Individual Arterial Input Function (iAIF)</td>
<td>Multiple Reference Region (multiRR)</td>
</tr>
<tr>
<td>(popAIF)</td>
<td>(multiRR)</td>
</tr>
<tr>
<td>centralcompartment</td>
<td>RR compartment (representative)</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Population AIF versus RR model

- **Pre**
  - HR = 280 bpm
  - (n=20)

- **Post1**
  - **Group 1**
    - (n=5)
    - HR = 280 bpm
  - **Group 2**
    - (n=10)
    - HR = 360 bpm

- **Post2**
  - **Group 1**
    - (n=4)
    - HR = 280 bpm
  - **Group 2**
    - (n=12)
    - HR = 360 bpm
Population AIF versus RR model
Post_Embolisation

**T1 curve**

- T1 [ms]
- Time [s]

**Gd concentration**

- Gd conc [mM]
- Time [s]
pretreatment $K^{\text{trans}}$ and $v_e$

population AIF vs RR
group 1 $K_{\text{trans}}$ and $v_e$

population AIF vs RR
group 2 $K^{\text{trans}}$ and $\nu_e$

population AIF vs RR
population AIF versus RR

Bland-Altman analysis

\textbf{group 1} \textbf{group 2}
<table>
<thead>
<tr>
<th></th>
<th>group 1</th>
<th></th>
<th>group 2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta K^{\text{trans}}$ [%]</td>
<td>$\Delta v_e$ [%]</td>
<td>$\Delta K^{\text{trans}}$ [%]</td>
<td>$\Delta v_e$ [%]</td>
<td></td>
</tr>
<tr>
<td>post1</td>
<td>4±19</td>
<td>4±12</td>
<td>-45±7 *</td>
<td>-31±7 *</td>
<td></td>
</tr>
<tr>
<td>post2</td>
<td>-8±1</td>
<td>6±21</td>
<td>-41±3 *</td>
<td>-26±7 *</td>
<td></td>
</tr>
</tbody>
</table>
Summery

- induced increase in HR results in a systematic offset in $K^{\text{trans}}$ and $v_e$ (45 and 31 %)
- RR model is sensitive to systemic changes, indicating that essential features of the AIF are represented in the spinal muscle
- RR model valuable modeling technique for qDCE-MRI in longitudinal studies
## Modeling Techniques

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<td>Population Arterial Input Function (popAIF)</td>
</tr>
<tr>
<td>Multiple Reference Region (multiRR)</td>
<td>Individual Reference Region (iRR)</td>
</tr>
<tr>
<td>Gd_{conc} DV_{1-n} (representative of AIF)</td>
<td>DV_{1-n} (representative)</td>
</tr>
</tbody>
</table>

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<th>Individual Arterial Input Function (iAIF)</th>
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<tbody>
<tr>
<td>RR compartment (representative)</td>
<td>DV_{1-n} (representative)</td>
</tr>
</tbody>
</table>
Components of a population pharmacokinetic model

Statistical model
- Measurement error (i.e. movement)
- Systematic error (i.e. wrong model)
- Interindividual differences (Variance)

PK model
- Compartment elimination

Covariate model
- Tumorsize
- Renal clearance
- Sex / Age

Population PK modeling
- Population
- $Gd_{conc}$ $DV_{1-n}$ (representative of AIF)
- $(Pop)$
- $DV_{1-n}$ (representative)
Visual Predictive Check (VPC) 3 compartment model
### Individual Population Fits

#### 3 compartment model

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Tumor</th>
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<td>10</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Muscle</th>
<th>Muscle</th>
<th>Muscle</th>
<th>Muscle</th>
<th>Muscle</th>
<th>Muscle</th>
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<td>10</td>
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<td>12</td>
<td>13</td>
<td>14</td>
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</table>

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<tr>
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<td>4</td>
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<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>

**TIME**

- **Tumor**
- **Muscle**
- **Blood**
Individual Population Fits

3 compartment model

![Graph showing tumor, muscle, and blood changes over time](image-url)
Diethylnitrosamine (DEN) induced liver cirrhosis and HCC

- **chemical carcinogen** metabolized into reactive electrophilic reactants (alkylation of DNA) -> chromosomal aberration
- multifocal hepatocellular carcinoma (HCC) superimposed on liver cirrhosis
- **heterogenous** HCC morphology (number, size, vascularization, grade of differentiation)

- relevant for imaging and treatment studies
  - suggested by comparative genomic studies
  - orthotopic location
  - blood supply
  - metastatic potential
  - therapeutic responsiveness
DEN characterization

- **T2w DWI DCE-MRI**
  - Week 10
- **T2w DWI DCE-MRI**
  - Week 11
- **T2w DWI DCE-MRI FDG-PET**
  - Week 16
- **T2w DWI DCE-MRI**
  - Week 20

**Histology**

**Images:**
- **T2-weighted MRI**
- **Diffusion Weighted MRI (b600)**
DEN induced liver fibrosis

- irregular architecture
- enlarged hepatocytes with cytoplasmatic and canalicular PAS positive precipitations
- enlarged portal fields with beginning fibrosis and ductal reaction

<table>
<thead>
<tr>
<th>DEN</th>
<th>γGT</th>
<th>CHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>-0.5</td>
<td>100</td>
</tr>
<tr>
<td>4 weeks</td>
<td>-0.6</td>
<td>71</td>
</tr>
<tr>
<td>6 weeks</td>
<td>1.3</td>
<td>190</td>
</tr>
<tr>
<td>8 weeks</td>
<td>1.3</td>
<td>199</td>
</tr>
</tbody>
</table>
Heterogenous growth
Heterogeneous perfusion

Tumor perfusion
745 (early)

Tumor perfusion
746 (early)

Tumor volume

Time (weeks)

Tumor volume (mm$^3$)
<table>
<thead>
<tr>
<th>ID</th>
<th>location</th>
<th>T/M</th>
<th>T/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>741</td>
<td>caudal</td>
<td>6.75</td>
<td>2.44</td>
</tr>
<tr>
<td></td>
<td>apikal</td>
<td>3.56</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>liver</td>
<td>2.77</td>
<td></td>
</tr>
<tr>
<td>745</td>
<td>central</td>
<td>10.71</td>
<td>3.04</td>
</tr>
<tr>
<td></td>
<td>ventral_R</td>
<td>5.45</td>
<td>1.55</td>
</tr>
<tr>
<td></td>
<td>ventral_L</td>
<td>4.88</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>liver</td>
<td>3.52</td>
<td></td>
</tr>
<tr>
<td>747</td>
<td>center</td>
<td>1.77</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>liver</td>
<td>1.53</td>
<td></td>
</tr>
</tbody>
</table>
Thanks!

**C4**
- Sufyan Sayyed
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- Markus Settles
- Carl Ganter

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- Frauke Neff

**Z3**
- Sybille Reder

**ETH Zürich**
- Andreas Steingötter
- Dieter Menne
Multiparametric Imaging

- establish longitudinal multiparametric imaging
- detect early therapy response

- correlate imaging data (day-1, +1 and +3) with quantitative histological data (vital tissue, vital tumor)
## Multiparametric Imaging

<table>
<thead>
<tr>
<th></th>
<th>ADC</th>
<th></th>
<th>FDG</th>
<th></th>
<th>Vol</th>
<th></th>
<th>ktrans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vital tissue</td>
<td>vital tumor</td>
<td>vital tissue</td>
<td>vital tumor</td>
<td>vital tissue</td>
<td>vital tumor</td>
<td>vital tissue</td>
</tr>
<tr>
<td>pre</td>
<td>0.06</td>
<td>0.04</td>
<td>0.18</td>
<td>0.16</td>
<td>0.63</td>
<td>0.37</td>
<td>0.15</td>
</tr>
<tr>
<td>post1</td>
<td>0.8</td>
<td>0.74</td>
<td>0.12</td>
<td>0.17</td>
<td>0.52</td>
<td>0.28</td>
<td>0.43</td>
</tr>
<tr>
<td>post2</td>
<td>0.86</td>
<td>0.63</td>
<td>0.16</td>
<td>0.18</td>
<td>0.05</td>
<td>&lt; 0.05</td>
<td>0.4</td>
</tr>
<tr>
<td>Δ pre-post1</td>
<td>0.44</td>
<td>0.51</td>
<td>0.03</td>
<td>0.09</td>
<td>0.48</td>
<td>0.56</td>
<td>0.11</td>
</tr>
<tr>
<td>Δ pre-post2</td>
<td>0.48</td>
<td>0.56</td>
<td>0.11</td>
<td>0.26</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Diagrams
- Pre: ADC, Vol, ktrans vs. % vital tissue
- Post 2: ADC, Vol, ktrans vs. % vital tissue
- Post 1: ADC, Vol, ktrans vs. % vital tissue
- Post 1: FGD, V0 vs. % vital tumor
- Δ pre-post2: FGD, V0 vs. % vital tumor
Multiparametric Imaging

Conclusion

Multiparametric imaging of orthotopic rat HCC is feasible.

$pre \text{Vol}_{\text{MRI}}$ was the only predictive marker.

$post2 \text{ADC}$ values showed highest sensitivity and specificity.

$\text{FDG}_{\text{Ratio}}$ specificity was higher compared to sensitivity.

$K_{\text{trans}}$, $v_e$ and $\text{FDG}_{\text{Ratio}}$ showed only moderate correlation with detected necrosis level.
AIF models

Input:
AIF$_i$ = $C_{pi}(t)$
popAIF = $E\{C_{pi}(t)\}$
AIF = $C_p(t)$

Output:

Output:
$K_{trans i}, v_{ei}$
(Intravascularcompartment ignored,
$C_{EES} = C_e/v_e$)

Reference Region model

Input:
RR = $C_{RR}(t)$
$K_{trans RR}, v_{eRR}$

Output:

Output:
$K_{trans i}, v_{ei}$
## Signaling Pathways in HCC

<table>
<thead>
<tr>
<th></th>
<th>Inflammation</th>
<th>Proliferation &amp; Cell Survival</th>
<th>Differentiation &amp; Apoptosis</th>
<th>Angiogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ligands</strong></td>
<td>IL6, IFN, TNFa</td>
<td>TGFα, EGF, IGF2, HGF</td>
<td>WNT, HH, TGFβ</td>
<td>VEGF/ PGF (5)</td>
</tr>
<tr>
<td><strong>Receptors</strong></td>
<td>Gp130, IFNR</td>
<td>EGFR, IGF-IR, MET</td>
<td>FZD, NOTCH1-4</td>
<td>VEGFR / NRP (5)</td>
</tr>
<tr>
<td><strong>Mediators</strong></td>
<td>HSP90, JAK/STAT</td>
<td>AKT, mTOR, ERK, BRAF</td>
<td>B-catenin, BIRC5, MYC, CCND1</td>
<td>AKT, MAPK</td>
</tr>
</tbody>
</table>

**VEGF/PGF (5)**
**FGF (23)**
**PDGF**
**Ang (2)**
Results I: DCE-CT

<table>
<thead>
<tr>
<th>Isofluorane</th>
<th>MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF_high_young</td>
<td>CF_low_young</td>
</tr>
<tr>
<td>CF_high_old</td>
<td>CF_low_old</td>
</tr>
</tbody>
</table>

Gd Concentration (mmol) vs. time (s)
Methods I

Transarterial embolization procedure in HCC-bearing rats

TransArterialChemoEmbolization

Abdominal aorta
Proper hepatic a.
Gastroduodenal a.
Common hepatic a.
Abdominal aorta
Posterior pancreaticoduodenal arcade
Basic Goodness of Fit

3 compartment model
Basic Goodness of Fit

NONMEM: 3 compartment model

Variance

GOF