MR Functional Imaging to Guide Radiotherapy: Challenges and Opportunities

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Abstract

MR Functional Imaging

• Predict local control and survival
• Early response assessment (clinical trials)
• Target identification and delineation
• Dose escalation (radioresistant regions)
• Treatment adaptation

Personalized Radiation Medicine

Anatomic targeting

Molecular targeting

Complementary strategies to improve tumor control and reducing side effects

Goals of functional imaging
MR Functional Imaging

- Dynamic contrast enhanced MR
- Diffusion weighted MR imaging
- Blood Oxygen Level Dependent (BOLD) MR
- MR spectroscopy

Cervical Cancer

- Primary tumor
- Lymph node metastasis

Tumor Regression During RT

- Gy 20 Gy
- Gy 38 Gy
- Gy 48 Gy

Pre-Tx
Abnormal Tumor Vasculature

Konerding, 2001; Miller, 2005

Tumor vessels

Tumor Microenvironment

Cairns and Denko, 2006

Hypoxia
Acidosis
High IFP

MR Enhancement Dynamics

Enhancement pattern influenced by:
- Imaging parameters
- Contrast injection
- Contrast characteristics
- Vessel distribution
- Vessel permeability
- Blood flow
- Blood volume
- Blood transit time
- Extra-cellular volume
- Extra-cellular composition

Dynamic MR imaging of cervix cancer
Haider, Yeung, Milosevic
### DCE MR and Clinical Outcome

Cervical cancer: DCE MR and clinical outcome

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Parameter</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawighorst, 1998</td>
<td>57</td>
<td>Low $k_{ep}$</td>
<td>Survival</td>
</tr>
<tr>
<td>Yamashita, 2000</td>
<td>36</td>
<td>High “permeability”</td>
<td>Poor response</td>
</tr>
<tr>
<td>Mayr, 2000</td>
<td>16</td>
<td>$RSI_{10&lt;2.5}$</td>
<td>Local control</td>
</tr>
<tr>
<td>Loncaster, 2002</td>
<td>50</td>
<td>$A_{low}$</td>
<td>Survival</td>
</tr>
<tr>
<td>Zahra, 2009</td>
<td>13</td>
<td>High $K_{trans}$ or $k_{ep}$</td>
<td>Better regression</td>
</tr>
<tr>
<td>Semple, 2009</td>
<td>8</td>
<td>$K_{trans}$</td>
<td>Clinical response</td>
</tr>
<tr>
<td>Donaldson, 2010</td>
<td>50</td>
<td>$EF25s &gt;28%$</td>
<td>Survival</td>
</tr>
<tr>
<td>Andersen, 2011</td>
<td>81</td>
<td>Low $RSI_{10&lt;2.5}$, low AUC</td>
<td>Local control</td>
</tr>
</tbody>
</table>

EF25s: Enhancing fraction 25s post-injection

RSI<sub>10%</sub>: 10<sup>th</sup> percentile RSI at 90-120s post-injection

### DCE MR and Clinical Outcome

- DCE MR before and during RT
- Voxel-based analysis
- $RSI_{10<2.5}$: 10<sup>th</sup> percentile relative signal intensity at 90-120s post-injection

![Graphs showing local control, cause-specific survival, and overall survival.](image)

Mayr, 2010

### Uncertainties in DCE MR

- Image acquisition
- Analysis
- Modeling
- Reporting
- Need for validation and standardization

![Graphs showing relationships.](image)

Cenic, 2000 and Purdie, 2001
Standardization

Estimating Kinetic Parameters From Dynamic Contrast-Enhanced T1-Weighted MRI of a Diffusible Tracer: Standardised Quantities and Symbols

Workshop Report
The assessment of antiangiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations

Imaging vascular function for early stage clinical trials using dynamic contrast-enhanced magnetic resonance imaging

Clinical Questions

• DCE MR vs. DCE CT
  – CT is available in every radiation treatment department
• Timing of DCE MR during fractionated RT
• Identification and delineation of relevant volumes
• Analysis methods and reporting metrics
  – Volume averaged vs. pixel-based analysis
  – Intensity-time curve analysis vs. kinetic modeling
  – Which model?
• Biologic relevance

Region of Interest

Cervix
Uterus
Parametria

19 international experts in GYN radiation oncology
(T2W images)
**Region of Interest**

Is ADC more sensitive to microscopic residual tumor than T2 or DCE MR? Implications for adaptive RT planning?

**DWI in Cervix Brachytherapy**

Mean ADC

Restricted diffusion as a function of target volume:
- GTV: 37% low ADC < 1.2 × 10^{-3} mm²/s
- HR CTV: 22%
- IR CTV: 12%

Haack, 2010

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**Primary Endpoints**

**Recommendations**

- The primary end point should be either $K_{trans}$ (min⁻¹) or IAUGC (mm Gd/min).
- Vascularised tumour volume can be obtained by summing voxels with values above a predetermined threshold.
- Ideally, measurements of $K_{trans}$ or IAUGC should be made for each voxel in the ROI or VOI.
- In tissues with substantial motion, ROI or VOI average measurements may be more appropriate.
- Three-dimensional measurements are preferred, as single-slice measurements (in theory) may be prone to bias due to incomplete sampling and errors in positioning the slice.

*British Journal of Cancer (2005) 92, 1599–1610*
Tumor Heterogeneity

Red: Vessels, Green: Hypoxia, Blue: Doxorubicin
Courtesy of Ian Tannock

Accounting for Heterogeneity

Pixel-based analysis of 13 patients with cervical cancer

Analysis of at least 3 slices is necessary to assure that between-patient variability exceeds within-patient variability

Voxel-Based Analysis

Relative signal intensity (RSI)

Map of Log-rank p-values for locoregional control
Best locoregional control
Andersen, 2012
Generalized Kinetic Model

Generalized kinetic model
\[
\frac{dC(t)}{dt} = K^{\text{max}} \cdot C(t) - k_{e} \cdot C(t)
\]

where \( K^{\text{max}} = F \cdot \rho \cdot (1 - \text{Hct}) \)
for flow-limited conditions

and \( K^{\text{max}} = PS \cdot \rho \)
for permeability-limited conditions

Tofts, 1999 and Zahra, 2007

Two compartment model

Generalized Kinetic Model

Generalized kinetic model
\[
\frac{dC(t)}{dt} = K^{\text{max}} \cdot C(t) - k_{e} \cdot C(t)
\]

Uncertainties:
- \( C(t) \) from \( S(t) \)
- Arterial input function \( C_{p}(t) \)
- Microvascular Hct

Tofts, 1999 and Zahra, 2007

Two compartment model

DCE MR Arterial Input Function

Average AIF’s from 38 patients with cervix cancer

MRTM: Multiple reference tissue method
EIA: Measured from external iliac artery
Parker: Published population AIF (Parker et al, 2006)

Cheng Yang, 2010
DCE CT-MR Comparison

38 patients, MR AIF from MRTM

DCE CT-MR Comparison

38 patients with cervix cancer

<table>
<thead>
<tr>
<th></th>
<th>Mean $K_{trans}$</th>
<th>Mean $k_{ep}$</th>
<th>Mean $v_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>0.16 min$^{-1}$</td>
<td>0.65 min$^{-1}$</td>
<td>0.04</td>
</tr>
<tr>
<td>MR - MRTM AIF</td>
<td>0.09 (r=0.6)</td>
<td>0.50 (r=0.8)</td>
<td>0.02 (r=0.3)</td>
</tr>
<tr>
<td>MR - Published AIF</td>
<td>0.18 (r=0.6)</td>
<td>0.56 (r=0.8)</td>
<td>0.02 (r=0.6)</td>
</tr>
</tbody>
</table>

MRTM: Multiple reference tissue method
Published AIF: Parker et al, 2006

Vascular-Targeted Therapy

Phase I-II study of RTCT + Sorafenib

Phase I: Sorafenib dose escalation, 3 patients / dose level
Phase II: Sorafenib at MTD

External RT + Cisplatin 40 mg/m$^2$

Markers of biologic response
($pO_2$, IFP, DCE CT, DCE MRI, Biopsies, Blood)
**DCE MR Response to Sorafenib**

Patient 1  
Cervix  
T2b N0  
Baseline | Day 7 of Sorafenib | Day 14, S+RT

Patient 2  
Cervix  
T1b N1  
Baseline | Day 7 of Sorafenib | Day 14, S+RT

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**K\text{trans}: Response to Sorafenib**

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**Biomarker Changes**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 1 week of Sorafenib</th>
<th>After 1 week of RTCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor volume</td>
<td>78 cm³</td>
<td>&quot;86 cm³&quot;</td>
<td>&quot;57 cm³&quot;</td>
</tr>
<tr>
<td>MR DCE K\text{trans}</td>
<td>0.016 s⁻¹</td>
<td>&quot;0.008 s⁻¹&quot;</td>
<td>0.018 s⁻¹</td>
</tr>
<tr>
<td>Mean pO₂</td>
<td>14 mm Hg</td>
<td>&quot;3 mm Hg&quot;</td>
<td>13 mm Hg</td>
</tr>
<tr>
<td>IFP</td>
<td>24 mm Hg</td>
<td>21 mm Hg</td>
<td>&quot;16 mm Hg&quot;</td>
</tr>
</tbody>
</table>

* Significant relative to baseline
**Future of DCE MR**

- Improved access to MR
- New, large MW or targeted contrast agents

![Integrated MR-RT Suite](image1)

**Contrast Agent Transport**

- Trans-Vascular Transport
- Interstitial Transport

![Contrast Agent Transport Diagram](image2)

**Imaging Convective Transport**

- Liposomal Contrast Agents
- Trans-Vascular Convection
- Interstitial Convection

![Imaging Convective Transport Diagram](image3)
Summary

- DCE MR can provide valuable information to guide personalized cancer treatment.
- Optimization, standardization and validation are required to obtain biologically and clinically relevant information.
- Sharing of data sets would facilitate model development and validation and a better understanding of clinical value.

Voxel-Based Analysis

Map of Log-rank p-values for progression-free survival

Best progression-free survival

Andersen, 2012