MR Functional Imaging to Guide Radiotherapy: *Challenges and Opportunities*

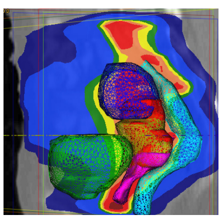
Michael Milosevic, MD

Department of Radiation Oncology, University of Toronto
Radiation Medicine Program, Princess Margaret Hospital
Toronto, Canada

Radiation Oncology
UNIVERSITY OF TORONTO

Princess Margaret Hospital
University Health Network

Personalized Radiation Medicine



Anatomic targeting

Molecular targeting

Complementary strategies to improve tumor control and reducing side effects

MR Functional Imaging

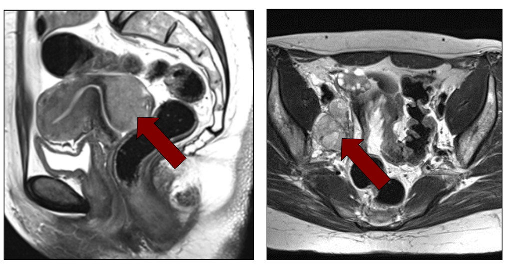
Goals of functional imaging

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

MR Functional Imaging

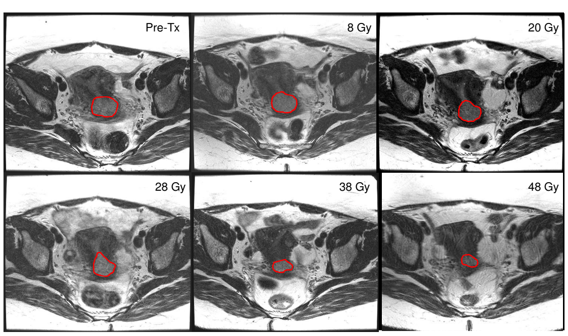
- Dynamic contrast enhanced MR
- Diffusion weighted MR imaging
- Blood Oxygen Level Dependent (BOLD) MR
- MR spectroscopy

Cervical Cancer

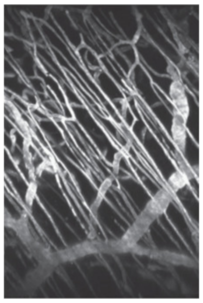


Primary tumor   Lymph node metastasis

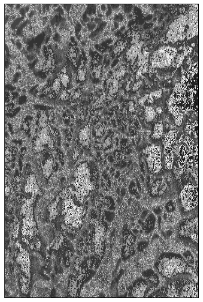
Tumor Regression During RT



Abnormal Tumor Vasculature



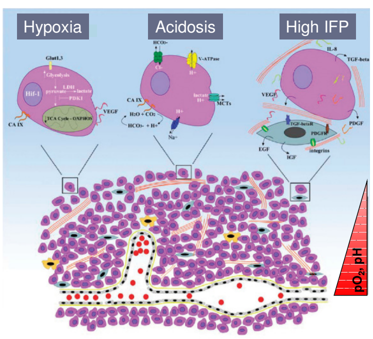
Normal vessels



Tumor vessels

Konerding, 2001; Miller, 2005

Tumor Microenvironment



Cairns and Denko, 2006

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

Author	n	Parameter	Outcome
Hawighorst, 1998	57	Low k_{ep}	↓ Survival
Yamashita, 2000	36	High "permeability"	"Poor response"
Mayr, 2000	16	$RSI_{10\%}$ <2.5	↓ Local control
Loncaster, 2002	50	*Low* A_{Brix}	↓ Survival
Zahra, 2009	13	High K^{trans} *or* k_{ep}	"Better regression"
Semple, 2009	8	K^{trans}	"Clinical response"
Donaldson, 2010	50	EF25s >28%	↓ Survival
Andersen, 2011	81	Low $RSI_{10\%}$, low AUC	↓ Local control

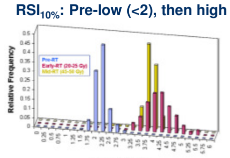
EF25s: Enhancing fraction 25s post-injection

$RSI_{10\%}$: 10th percentile RSI at 90-120s post-injection

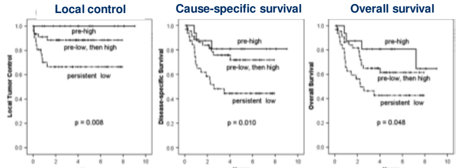
DCE MR and Clinical Outcome

- DCE MR before and during RT
- Voxel-based analysis
- $RSI_{10\%}$: 10th percentile relative signal intensity at 90-120s post-injection

$RSI_{10\%}$: Pre-low (<2), then high



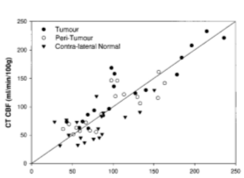
Local control **Cause-specific survival** **Overall survival**

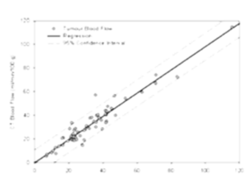


Mayr, 2010

Uncertainties in DCE MR

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





Cenic, 2000 and Purdie, 2001

Standardization

Estimating Kinetic Parameters From Dynamic Contrast-Enhanced T_1-Weighted MRI of a Diffusable Tracer: Standardized Quantities and Symbols

JOURNAL OF MAGNETIC RESONANCE IMAGING 10:223–232 (1999)

Workshop Report

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

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

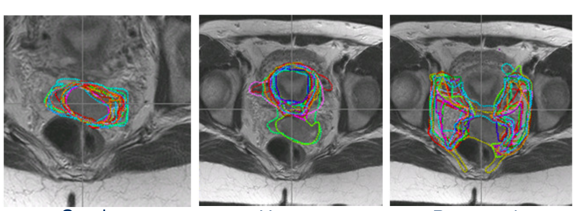
Imaging vascular function for early stage clinical trials using dynamic contrast-enhanced magnetic resonance imaging

Eur Radiol (2012) 22:1451–1464

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



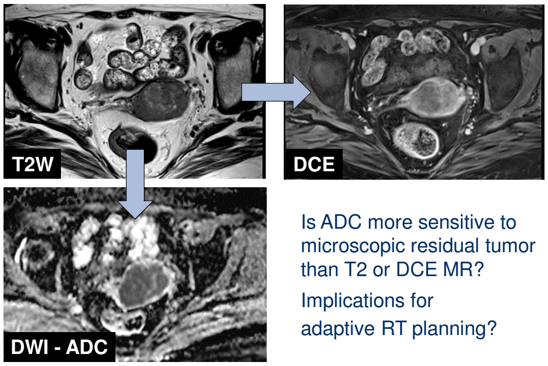
Cervix — Uterus — Parametria

19 international experts in GYN radiation oncology

(T2W images)

Karen Lim, 2010

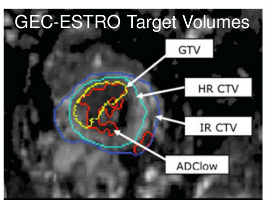
Region of Interest

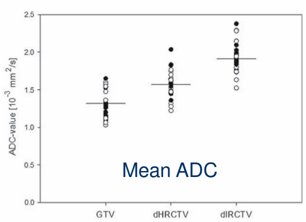


Is ADC more sensitive to microscopic residual tumor than T2 or DCE MR?

Implications for adaptive RT planning?

DWI in Cervix Brachytherapy





Restricted diffusion as a function of target volume:

GTV 37% low ADC <1.2X10^{-3} mm^2/s
HR CTV 22%
IR CTV 12%

Haack, 2010

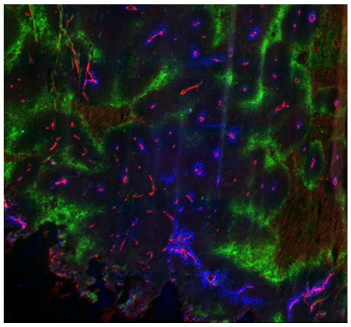
Primary Endpoints

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

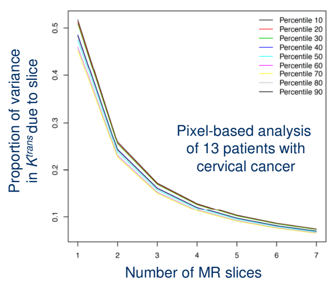
Tumor Heterogeneity



Red: Vessels, Green: Hypoxia, Blue: Doxorubicin

Courtesy of Ian Tannock

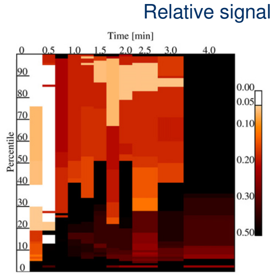
Accounting for Heterogeneity



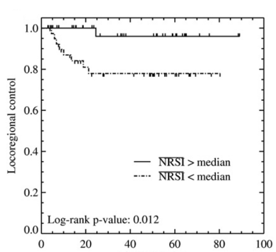
Analysis of at least 3 slices is necessary to assure that between-patient variability exceeds within-patient variability

Voxel-Based Analysis

Relative signal intensity (RSI)



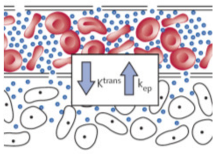
Map of Log-rank p-values for locoregional control



Best locoregional control

Andersen, 2012

Generalized Kinetic Model



Two compartment model

Generalized kinetic model

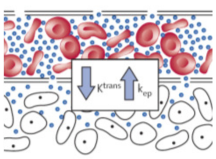
$$\frac{dC_t(t)}{dt} = K^{trans} \cdot C_p(t) - k_{ep} \cdot C_t(t)$$

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

and $K^{trans} = PS \cdot \rho$
for permeability-limited conditions

Tofts, 1999 and Zahra, 2007

Generalized Kinetic Model



Two compartment model

Generalized kinetic model

$$\frac{dC_t(t)}{dt} = K^{trans} \cdot C_p(t) - k_{ep} \cdot C_t(t)$$

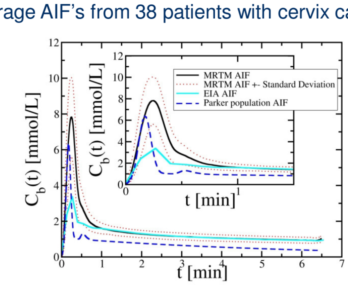
Uncertainties:

- $C_t(t)$ from $S_t(t)$
- Arterial input function $C_p(t)$
- Microvascular Hct

Tofts, 1999 and Zahra, 2007

DCE MR Arterial Input Function

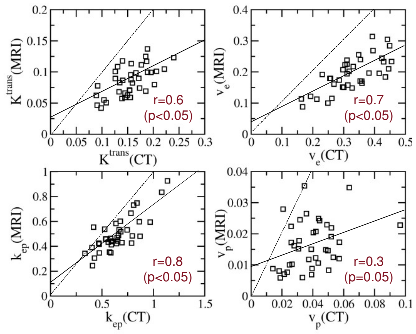
Average AIF's from 38 patients with cervix cancer



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

Cheng Yang, 2010

DCE CT-MR Comparison

38 patients with cervix cancer

	Mean K^{trans}	Mean k_{ep}	Mean v_p
CT	0.16 min^{-1}	0.65 min^{-1}	0.04
MR - MRTM AIF	0.09 (r=0.6)	0.50 (r=0.8)	0.02 (r=0.3)
MR - Published AIF	0.18 (r=0.6)	0.56 (r=0.8)	0.02 (r=0.6)

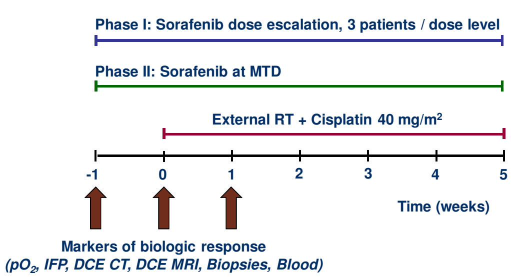
MRTM: Multiple reference tissue method

Published AIF: *Parker et al, 2006*

Cheng Yang, 2010

Vascular-Targeted Therapy

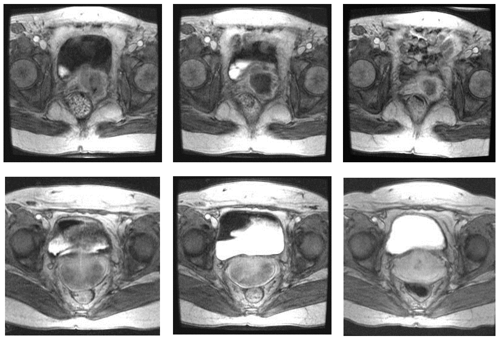
Phase I-II study of RTCT + Sorafenib



DCE MR Response to Sorafenib

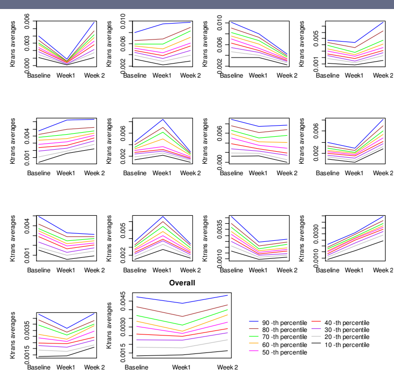
Patient 1
Cervix
T2b N0

Patient 2
Cervix
T1b N1



Baseline | Day 7 of Sorafenib | Day 14, S+RT

K^{trans}: Response to Sorafenib



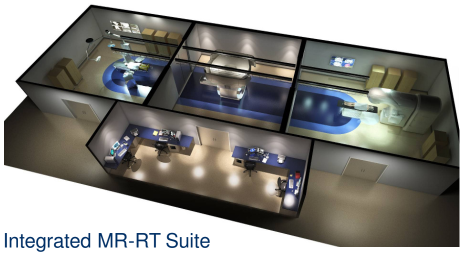
Biomarker Changes

	Baseline	After 1 week of Sorafenib	After 1 week of RTCT
Tumor volume	78 cm^3	*86 cm^3	*57 cm^3
MR DCE K^{trans}	0.016 s^{-1}	*0.008 s^{-1}	0.018 s^{-1}
Mean pO_2	14 mm Hg	*3 mm Hg	13 mm Hg
IFP	24 mm Hg	21 mm Hg	*16 mm Hg

* Significant relative to baseline

Future of DCE MR

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



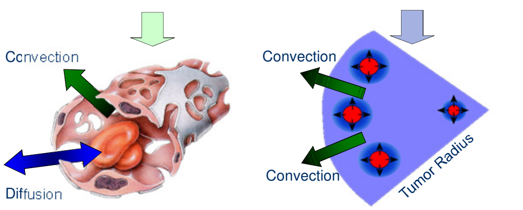
Integrated MR-RT Suite

Courtesy of David Jaffray

Contrast Agent Transport

Trans-Vascular Transport (Convection, Diffusion) — Interstitial Transport (Convection, Diffusion)

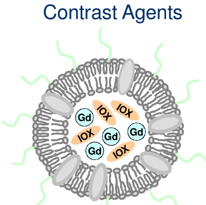
$$\frac{\partial C_i(\vec{r},t)}{\partial t} = \phi_v(\vec{r})\cdot(1-\sigma)\cdot C_p(t) + \frac{PS}{V}(C_p(t) - C_i(\vec{r},t)) - \nabla\bullet(f\cdot v(\vec{r})\cdot C_i(\vec{r},t) - D\cdot\nabla C_i(\vec{r},t))$$



Courtesy of Shawn Stapleton

Imaging Convective Transport

Liposomal Contrast Agents



Cholesterol
Polyethylene glycol
IOX Iohexol
Gd Gadoteridol

MW ~ 1E8 Da
D = 80 nm

Trans-Vascular Convection — Interstitial Convection

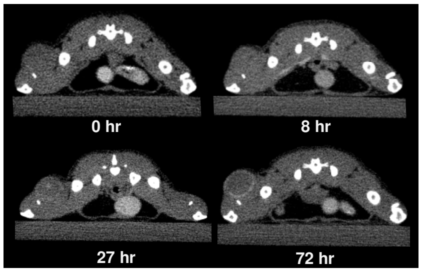
$$\frac{\partial C_i(\vec{r},t)}{\partial t} = \phi_v(\vec{r})\cdot(1-\sigma)\cdot C_p(t) - \nabla\bullet(f\cdot v(\vec{r})\cdot C_i(\vec{r},t))$$

Driven by trans-vascular pressure gradient

Driven by interstitial pressure gradients

Courtesy of Shawn Stapleton and David Jaffray

Imaging Convective Transport



Courtesy of Mike Dunne and Shawn Stapleton

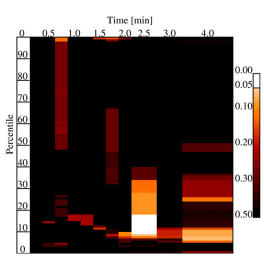
Summary

- 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.

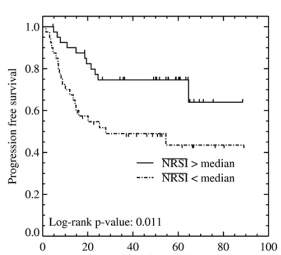
Radiation Oncology
UNIVERSITY OF TORONTO

Princess Margaret Hospital

Voxel-Based Analysis



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



Best
progression-free survival

Andersen, 2012