Probing tumour vascular microenvironment using DCE-MRI

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Vascular Features of Angiogenic Tissue

Active Angiogenesis
- Regional Ischaemia
- VEGF / Cytokine Production
- Increased endothelial permeability
- Endothelial cell in-growth

Established Angiogenesis
- Increased proportion of blood vessels
- Abnormal structure and Flow Patterns
- Changes in physiological reactivity
Commonly Used MR biomarkers

- **CBV**: from VASO, DSCE or DRCE-MRI

- **$K^{\text{trans}}$**: from DSCE or DRCE-MRI, meaning depends on the model used to calculate it.

- **Flow ($F$)**: from ASL, DSCE or DRCE-MRI or DCE-CT, $H_2^{15}$O PET or Xe-CT
Characterizing the Microvasculature

1: Increased Proportion of Blood Vessels

(What has Happened)
Enhancing Tissues (T1 Shine through)
Relationship between rCBV and Grade
Clinical Value of DSCE-MRI CBV

- Correlates with grade and prognosis
- Accurate targeting of biopsy
- Correlates with histological evidence of aggressiveness
- Close agreement with FDG-PET
- Better relation to grade than Thallium SPECT
- Better detection of recurrence than Thallium SPECT
- Differentiation between Glioma and Met
- Differentiation between Glioma and Abscess
Cerebral Lymphoma

Low CBV despite enhancement

Radiology 2002; 223:11–29
Image Guided Biopsy

Soonmee Cha, MD
Edmond A. Knopp, MD
Glyn Johnson, PhD
Stephan G. Wetzel, Dr med
Andrew W. Litt, MD
David Zagzag, MD, PhD

Radiology 2002; 223:11–29
Characterizing the Microvasculature

2: Abnormal Flow Patterns

What Is Happening Now
Vascular Tortuosity
(The Mother in Law effect)

Relative Recirculation (rR)
Relationship between rR and Tumour Grade

![Graphs showing the relationship between rR and tumour grade.](image)
Relationship between $rR$ and Tumour Grade
Characterizing the Microvasculature

3: T1 weighted Dynamic Imaging
DRCE-MRI

Measuring Permeability

What Will Happen?
Why Measure Endothelial Permeability?

1. Direct immediate effect of VEGF
2. Reflects current status of Angiogenic drive
3. Rapidly reversed with cytokine blockade
4. Potential marker of drug activity
5. Potential prognosticator
Quantifying Endothelial Permeability

Contrast agent concentration, $C_p$

Capillary vascular plasma space, $V_p$

Contrast agent concentration, $C_e$

Extracellular Space, $v_e$

Intracellular space, $v_i$

Flow, $F$

Permeability, $PS$
What is $K_{trans}$

- Mathematical constant which describes the relationship between contrast concentration in the blood and the tissue

What does it mean?
- Depends on complexity of pharmacokinetic model
  - St Lawrence: $K_{trans}, v_e, v_p, F$
  - Larson: $K_{trans}, v_e, v_p$
  - Tofts: $K_{trans}, v_e$
Pseudopermeability

$k$  $k_{fp}$
Grading Glioma

![Graph showing relationship between CBV and Ki67 (95%) and glioma grade.](image-url)
Predicting Prognosis: Glioma
Predicting Prognosis: Glioma

Survival Kfp (grade 4 only)

Cum Survival

Survival (months)
The problem: Epithelial cancer

- Lung: 23%
- Colon: 11%
- Breast: 9%
- Ovary: 6%
- NHL: 9%
- Bladder: 11%
- Pancreas: 6%
- Oesophagus: 6%
- Prostate: 9%
- Stomach: 30%

Cisplatin, cyclophosphamide, paclitaxel
Anti-angiogenic therapy

Expected Mechanistic Effects

- Inhibition of growth factor support of neovasculature.
- Reduced permeability.
- Reduced perfusion.
- Reduced blood volume.

Example Agents

- Vatalanib (PTK787/ZK222584) protein tyrosine kinase inhibitor
- Avastin (bevacizumab) anti-VEGF monoclonal antibody
- ZD6474 VEGF-2 receptor antagonist
- SU11248 Protein Tyrosine Kinase (PTK) inhibitor
- AGM-1470 Inhibits endothelial cell migration, endothelial cell proliferation, and capillary tube formation
What Use are They?
Drug Development

k
Pre-Treatment

rCBV
What Use are They?
Drug Development

% maximum permeability

- 0.3 mg/kg
- 1-10 mg/kg

Day 0
Day 2
Day 35
Anti VEGF-KDR receptor antibody

14 patients colorectal metastases in liver

0.2 – 4.0 mg/kg escalating dose

Changes in K and enhancement fraction in 11/14

Increased number of stable disease at high dose levels (NS)

Posey et al; Clin Cancer Res; 2003; 9:1323
VEGF Receptor Tyrosine Kinase Inhibition
PTAC Workshop Consensus Recommendations

- The primary end point should be either $K_{\text{trans}} (\text{min1})$ or IAUGC (mMGd min).
- Vascularised tumour volume can be obtained by summing voxels with values above a predetermined threshold.
- Ideally, measurements of $K_{\text{trans}}$ or IAUGC should be made for each voxel in the ROI or VOI.
- 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.
- Tumour volume should be measured.
- All data including ROI definition and analysis should be recorded and traceable to support external review.
STUDY DESIGN: EFFECTS OF BEVACIZUMAB ON CRC LIVER METS

Baseline

Pre-therapy

Cycle 1

Cycle 2 - 13

CT evaluation

EC5  EC9  EC13

DCE-MRI assessment

Wolfson Molecular Imaging Centre

University of Manchester
EXAMPLE $\kappa_{\text{trans}}$ MAPS

$\kappa_{\text{trans}}$ (min\(^{-1}\))

1.5

0
GROUP % CHANGE MEDIAN $K_{trans}$

Median $K_{trans}$

<table>
<thead>
<tr>
<th>Day</th>
<th>Mean % change</th>
<th>95% CI</th>
<th>p value</th>
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<tr>
<td>4 hours</td>
<td>-18.3</td>
<td>-9.7 to -26.9</td>
<td>&lt;0.001</td>
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<td>Day 3</td>
<td>-23.9</td>
<td>-10.8 to -37.0</td>
<td>0.001</td>
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<td>Day 8</td>
<td>-20.7</td>
<td>-9.8 to -31.5</td>
<td>0.001</td>
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<tr>
<td>Day 12</td>
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### MEAN % CHANGE $\nu_p$

<table>
<thead>
<tr>
<th>Day</th>
<th>$\Delta\nu_p$</th>
<th>Median $\nu_p$</th>
<th>95% CI</th>
<th>p value</th>
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<tr>
<td>4 hours</td>
<td>-34.5</td>
<td>-21.5 to -47.4</td>
<td>&lt;0.001</td>
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<tr>
<td>Day 3</td>
<td>-34.2</td>
<td>-16.6 to -51.8</td>
<td>&lt;0.001</td>
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<td>Day 8</td>
<td>-33.5</td>
<td>-12.8 to -54.3</td>
<td>0.003</td>
<td></td>
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<tr>
<td>Day 12</td>
<td>-28.3</td>
<td>-13.5 to -43.1</td>
<td>0.001</td>
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PURE VEGFR2i DO NOT MODULATE $k^{\text{trans}}$

CDP791 biochemically active Volumetrics: Dose response

Vandetanib (AZD6474) VEGFR2, EGF
No impact on IAUC, $K^{\text{trans}}$

Mross GI ASCO 2008
IMAGING VASCULAR HETEROGENEITY AS A PROGNOSTIC BIOMARKER FOR VEGFi
Perfusion in pulmonary metastasis from renal cancer

Wolfson Molecular Imaging Centre
University of Manchester

STATISTICAL ANALYSIS OF DATA IS PROBLEMATIC

From Liu JCO 2005
Complex Models

<table>
<thead>
<tr>
<th>Grade</th>
<th>F (ml/100ml/min)</th>
<th>V_b (ml/100ml)</th>
<th>PS (ml/100ml/min)</th>
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<tr>
<td>2 (n=1)</td>
<td>11.2</td>
<td>0.6</td>
<td>0.0</td>
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<tr>
<td>3 (n=3)</td>
<td>35 (±11)</td>
<td>3.8 (±2.0)</td>
<td>3.2 (±0.6)</td>
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<tr>
<td>4 (n=9)</td>
<td>63 (±65)</td>
<td>4.9 (±2.0)</td>
<td>6.5 (±4.4)</td>
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F 0.47 ml/min/ml
PS 0.12 ml/min/ml
V(b) 0.04 ml/ml
V(e) 0.20 ml/ml
IAUC 60
Modified Ketty

K<sub>trans</sub> < 0.5  
Ve < 1.0  
V<sub>p</sub> < 0.1  
SS < 5
How Accurate are They?
TK / fp / Hybrid
Inhibition of PDGF receptor signalling in tumour stroma enhances anti-tumour activity of chemotherapy

Pietras et al., Cancer Research 2002

Graphs showing:
- Tumor interstitial fluid pressure (mm Hg)
- Tumor uptake of $[^3H]$Taxol (dpm/g tumor tissue / dpm/ml blood)
- Tumor volume (cm$^3$)
binds and inhibits PDGF Rb

Jayson et al 2005; J Clin Oncol 23:973

Tumour volume

CT doubling times

MR doubling times (Origin-derived)

Times (days)

Days

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volume interdependence

vascularised volume (ml)

total tumour volume (ml)
ENHANCING FRACTION PREDICTS OUTCOME IN OVARIAN CANCER

Human Monoclonal Antibody to the Human Integrin Receptors ανβ3 and ανβ5 (CNTO 95)

**MR outcome**

<table>
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<tr>
<th>MR outcome</th>
<th>MR stable</th>
<th>MR progressive</th>
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<tr>
<td>Baseline</td>
<td>0.4</td>
<td>0.7</td>
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<tr>
<td>Day 1</td>
<td>0.3</td>
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<tr>
<td>Day 7</td>
<td>0.2</td>
<td>0.5</td>
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<tr>
<td>Day 49</td>
<td>0.1</td>
<td>0.4</td>
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**Proportional enhancing tumour (%)**

<table>
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<th>MR outcome</th>
<th>MR stable</th>
<th>MR progressive</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>80</td>
<td>60</td>
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<tr>
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<td>Day 7</td>
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<td>20</td>
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<tr>
<td>Day 49</td>
<td>20</td>
<td>10</td>
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IMPACT OF BEVACIZUMAB ON ENHANCING FRACTION

EF reduced from baseline d1 $p = 0.003$ and at d3, 8 and 12 $p < 0.001$ (Wilcoxon signed rank test)
IMPROVING THE SENSITIVITY OF VASCULAR IMAGING

Intervention Studies
Calculating Growth Rates
Before Drug Administration

Dynamic Functional Assessment of Vasculature
O$_2$-enhanced imaging
**FIGURE 1**

Sequence: $T_1$-w, $T_2$-w  |  OE-MRI: 96 $T_1$ maps  |  DCE-MRI  |  $T_1$-w

Time (min): 0  |  2  |  10  |  26  |  34  |  42  |  43

Gas order: AIR  |  OXYGEN  |  AIR
CONCLUSIONS

Imaging is contributing to drug development
- Imaging research parallels drug development
- Drug development and imaging research informing each other
- Scheduling

Imaging science is furthering understanding of cancer biology
- Heterogeneity
- Dynamic change (and baseline measurements) may help individualise therapy

Immediate needs
- Global standardisation of imaging strategies
- Volumetrics: a sensitive biomarker for impact on cancer biology
- Integration of high quality blood biomarkers and imaging
- Phase IV biomarker research to guide development of combination regimens
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