Imaging Methods for Tumor Response Assessment And Monitoring Angiogenesis

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Conventional method of monitoring treatment response is change in tumor size

10 Target Lesions (>1-2 cm)
5 max in an organ
Non-target lesions

RECIST= Response Evaluation Criteria in Solid Tumors
WHO = World Health Organization
# Monitoring Response to Chemotherapy

<table>
<thead>
<tr>
<th>Type of metric</th>
<th>RECIST</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of metric</strong></td>
<td>Uni-dimensional</td>
<td>Bi-dimensional (CP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MAD X LPD</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>Total disappearance</td>
<td>Total disappearance</td>
</tr>
<tr>
<td>(Complete Response)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>30% decrease</td>
<td>50% decrease</td>
</tr>
<tr>
<td>(Partial Response)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>20% increase</td>
<td>25% increase</td>
</tr>
<tr>
<td>(Progressive Disease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>Neither PR or PD criteria met</td>
<td>Neither PR or PD criteria met</td>
</tr>
<tr>
<td>(Stable disease)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Monitoring Response to Chemotherapy: Tumor Volume

Tumor volumetry is a better representative of tumor burden

Liver tumor treated with chemotherapy
## Monitoring Response to Chemotherapy

<table>
<thead>
<tr>
<th>Type of metric</th>
<th>RECIST</th>
<th>WHO</th>
<th>Volumetry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of metric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uni-dimensional</td>
<td></td>
<td>Bi-dimensional</td>
<td>Volume</td>
</tr>
<tr>
<td>Bi-dimensional</td>
<td></td>
<td>MAD X LPD</td>
<td>Volume</td>
</tr>
<tr>
<td><strong>CR</strong> (Complete Response)</td>
<td>Total disappearance</td>
<td>Total disappearance</td>
<td>Total disappearance</td>
</tr>
<tr>
<td><strong>PR</strong> (Partial Response)</td>
<td>30% decrease</td>
<td>50% decrease</td>
<td>65% decrease</td>
</tr>
<tr>
<td><strong>PD</strong> (Progressive Disease)</td>
<td>20% increase</td>
<td>25% increase</td>
<td>40-73% increase*</td>
</tr>
<tr>
<td><strong>SD</strong> (Stable disease)</td>
<td>Neither PR or PD criteria met</td>
<td>Neither PR or PD criteria met</td>
<td>Neither PR or PD criteria met</td>
</tr>
</tbody>
</table>

* 25% increase in 2D product (WHO) corresponds to 40% increase in volume, while 20% increase in RECIST corresponds to 73% change in volume.
Targeted Treatment Planning

- Intra-arterial radiation therapy
  - Therasphere
  - SIRT
- Calculation of tumor burden and total and liver volume
  - To calculate the dose
  - Limit toxicity
# Liver Tumor Volumetric Case

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Volume (cc)</td>
<td>78.65</td>
<td>307.85</td>
<td>496.62</td>
</tr>
<tr>
<td>Liver Volume (cc)</td>
<td>1783.09</td>
<td>1988.26</td>
<td>1907.84</td>
</tr>
<tr>
<td>Tumor Volume %</td>
<td>4.41%</td>
<td>15.48%</td>
<td>26.03%</td>
</tr>
<tr>
<td>Left Robe (cc)</td>
<td>13.83</td>
<td>193.55</td>
<td>166.31</td>
</tr>
<tr>
<td>Right Lobe (cc)</td>
<td>64.82</td>
<td>114.31</td>
<td>330.31</td>
</tr>
</tbody>
</table>
Tumor Density-Choi criteria

<table>
<thead>
<tr>
<th>Good Responders</th>
<th>Poor Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 15% decrease in tumor density</td>
<td>&lt;15% decrease in tumor density</td>
</tr>
</tbody>
</table>

* ROI drawn around the margin of the entire tumor
† Portal venous phase images for the tumor density measurement in abdomen
‡ Multiple lesions - Mean HU of all the lesions

PRE | POST | PRE | POST
---|---|---|---
96HU | 54HU | 28HU | 25HU

Overall Tumor Response (Revised CT evaluation criteria)

<table>
<thead>
<tr>
<th>Complete Response (CR)</th>
<th>Partial Response (PR)</th>
<th>Stable Disease (SD)</th>
<th>Progressive Disease (PD)</th>
</tr>
</thead>
</table>
| ● Disappearance of all lesions
   ● No new lesions | ● A decrease in size of ≥ 10%
   ● A decrease in tumor density (HU) ≥ 15% on CT
   ● No obvious progression of non-measurable disease | ● Does not meet the criteria for CR, PR or PD
   ● No symptomatic deterioration attributed to tumor progression | ● An increase in tumor size of ≥ 10% and does not meet criteria of PR by tumor density (HU) on CT
   ● New lesions
   ● New intratumoral nodules or increase in the size of the existing intratumoral nodules |

Conventional Imaging Limitations

- Evaluates the gross anatomical change of molecular events
- Time lag—typically weeks to months elapse before change observed
- Cannot measure early changes of disease process
- Changes do not necessarily correlate with disease process
- Cannot measure drug distribution
Novel Oncologic Drugs
Angiogenesis

• The development of new vessels from preexisting ones*
• Essential step in establishment and growth of malignancies
• Essential for ... metastatic process of malignant tumors*

Angiogenesis: Microvessel Density (MVD) Count

Tumor response after one infusion of bevacizumab alone

Immunohistochemistry in biopsy tissues

Willett et al., Journal of Clinical Oncology (2005)
Potential pharmacodynamic biomarker

<table>
<thead>
<tr>
<th>Biomarker/Trial</th>
<th>Rectal cancer (BEVACIZUMAB)</th>
<th>Recurrent GBM (CEDIRANIB)</th>
<th>Advanced HCC (SUNITINIB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>Increased (p&lt;0.0001)</td>
<td>Increased (p&lt;0.0001)</td>
<td>Increased (p&lt;0.0001)</td>
</tr>
<tr>
<td>PlGF</td>
<td>Increased (p&lt;0.0001)</td>
<td>Increased (p&lt;0.0001)</td>
<td>Increased (p&lt;0.0001)</td>
</tr>
<tr>
<td>SDF1α</td>
<td>N.S.</td>
<td>Increased (p&lt;0.001)</td>
<td>Increased (p&lt;0.001)</td>
</tr>
<tr>
<td>bFGF</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>sVEGFR1</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>sVEGFR2</td>
<td>Transiently increased (p&lt;0.001)</td>
<td>Decreased (p&lt;0.0001)</td>
<td>Decreased (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

Why Image Biomarker?

- Imaging is *in vivo* and non-invasive
- Quantitative
- To provide early indications of compound’s bioeffectiveness
  - Can also lead to early termination of unpromising compounds
- To select patients for targeted therapy
- Monitor early treatment effects
  - time lag between functional and anatomic changes
- Predict outcome
Drug Development

– It takes an average of $802M and 12 years to bring a new drug to the market

From: DiMasi, 2003
FDG-PET Imaging of Imatinib (Gleevec, Novartis) on GIST

## Monitoring Response: EORTC Criteria for FDG-PET

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
</table>
| **Progressive disease** | SUV increase >25%  
                         Visible increase of FDG uptake  
                         Appearance of new focus         |
| **Stable disease**      | SUV increase <25% or decrease <15%  
                         No visible increase of the extent of FDG uptake |
| **Partial response**    | SUV drop 15-25% after one cycle;  
                         >25% after more than one treatment cycle |
| **Complete response**   | Complete resolution of FDG uptake                                            |

*EORTC = European Organization for Research and Treatment of Cancer*
The metabolic response measured by FDG PET was a better predictor of PFS than RECIST.

Sahani et al. SGR 2009
Imaging Biomarker Selection: Drug Mechanism

Image Biomarker-Good Response

Pre-treatment

10 days Post-Avastin
Image Biomarker - Poor Response

Pre-treatment

10 days post-Avastin
Microvascular Structure

Organized
Artery-venous network

Dilated
Spatially heterogeneous

Normal tissue
Tumor tissue

Jain et al., Nat Rev Cancer 38:266, 2002
Tumor Vasculature Abnormalities Influences Contrast Enhancement Kinetics on DCE CT/MR

- Blood Flow
- Blood Volume
- Mean Transit Time
- Permeability
Why CT?

RELIABLE:
Iodine Concentration (mg/ml) = linear related CT attenuation

CONVENIENT:
• Available technique
• High spatial resolution
• Low inter-tester variability
• Software is commercially available

Miles KA. Acad Radiol 2000;7:840–50
Technique: Patient Preparation

- **Peripheral I.V**
  - 18-20 gauge in the arm
- **For hollow organs (rectum/colon/stomach)**
  - Distention with negative contrast 300-500mL
- **Contrast material**
  - 50-70 cc 300-370mgI/mL
Technique: Site selection

- Non-contrast CT to cover the entire organ
  - 5mm helical
- 2 cm tumor/4 slices (non-necrotic portion) to be covered for dynamic imaging is selected
- 4 cm with 64-MDCT
Scanning Technique

- **Contrast injected at 4-7 cc/sec**
- **Delay = 5-8 sec (abd) 10 sec (pelvis)**
- **Cine acquisition**
  - 4 contiguous 5 mm slices X 30-120 sec (every 1-2 sec)
  - kVp 80-100 and mA 100-160
  - Limited data
  - 4 slices once every 10-20 sec for 4-6 minutes
CTp Technique: Rectum
CTp Technique: Abdomen
## CTp Techniques and Protocols

<table>
<thead>
<tr>
<th>Technique</th>
<th>Protocol</th>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>First pass</td>
<td>20-30 sec cine</td>
<td>Breath-hold, Less radiation</td>
<td>Inadequate PS measurement</td>
</tr>
<tr>
<td>Permeability (PS)</td>
<td>Cine 45-120 sec, Limited scan every 10-20 seconds for 4-6 minutes</td>
<td>Permeability</td>
<td>Susceptible to Motion, More radiation</td>
</tr>
</tbody>
</table>
CT Perfusion

- **Protocol Panel**
  - Provides access to algorithms for image processing.
  - Deconvolution kinetic modeling is used.
Parameters computed

- BF = Blood flow
- BV = Blood volume
- MTT = Mean transit time
- PS = Permeability surface

Parameters dependent on the scanning technique and mathematic modeling
<table>
<thead>
<tr>
<th></th>
<th>CT Perfusion (GE)¹</th>
<th>Functional CT (Siemens)²</th>
<th>Brilliance (Philips)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mathematic Model</strong></td>
<td>Deconvolution method</td>
<td>Two-compartment model</td>
<td>Slope method</td>
</tr>
<tr>
<td><strong>Principle of the Model</strong></td>
<td>Impulse residue function (IRF) which is time enhancement curve of tissue due to idealized instantaneous injection of one unit of contrast</td>
<td>One way transfer of CM from intra to extra-vascular space proportionate to blood clearance constant, α</td>
<td>Perfusion is ratio of max slope of tissue enhancement curve to max arterial enhancement</td>
</tr>
<tr>
<td><strong>Parameters measured</strong></td>
<td>BF, BV, MTT, PS</td>
<td>BV and Permeability</td>
<td>MTT, time to peak enhancement</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>BF, BV, MTT and PS can be calculated using a single CT study</td>
<td>1. Simple analysis 2. Efficient in calculation of rate constant K value</td>
<td>1. Short scan duration 2. “No venous outflow” is true 3. No recirculation</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Partial volume averaging correction required</td>
<td>Assumes that back flux of CM from EVS to IVS is negligible for first 1-2 min</td>
<td>Sensitive to image noise</td>
</tr>
</tbody>
</table>

¹Sahani et al, Radiology 2005, ²Ng et al, Radiology 2006
## Perfusion CT Parameters and Significance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BF</th>
<th>BV</th>
<th>MTT</th>
<th>PS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Flow rate through vasculature in tissue region</td>
<td>Volume of flowing blood within a vasculature in tissue region</td>
<td>Average time taken to travel from artery to vein</td>
<td>Total flux from plasma to interstitial space</td>
</tr>
<tr>
<td><strong>Marker</strong></td>
<td>Tumor Vascularity</td>
<td>Mitotic activity and vascularity.</td>
<td>Perfusion pressure</td>
<td>Immature leaky vessels.</td>
</tr>
<tr>
<td></td>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Staging, Grading and Prognosis

<table>
<thead>
<tr>
<th>Clinical Application</th>
<th>Author (Journal/Year)</th>
<th>Observations</th>
</tr>
</thead>
</table>
| **Head and neck**    | Zima et al (Am J Neuroradiol 2007)  
                       | Hermans et al (Int J Radiat Oncol Biol Phy 2003) | Upper aerodigestive tract cancers with *high BF and BV* values respond well to induction chemotherapy  
Head and neck cancers with *lower perfusion rate (BF)* show poor response to radiotherapy (high local failure). |
| **Lung**             | Li et al (Clinical Radiology 2008) | Lung cancers with distant metastases have *high BF, BV* and and different histological types of lung cancer show no difference in perfusion characteristics |
| **Breast**           | Hirasawa et al (Acad Radiol 2007) | Nonscirrhous carcinomas have *high BF* values compared to scirrhous carcinomas |
| **Liver**            | Zhu et al (The Oncologist 2008)  
                       | Sahani et al (Radiology 2007) | Patients with progressive disease (HCC) had lower baseline MTT values  
Well differentiated HCCs show *high BF, BV, PS and low MTT* values than poorly differentiated HCCs |
| **Pancreas**         | d'Assignies et al (Radiology 2008)  
                       | Park et al (Radiology 2009) | Benign endocrine tumors have *high BF* values. Malignant tumors with liver & lymphnodal metastases have *long MTT*  
Pancreatic cancers with *high baseline KTrans* values responded better to concurrent chemoradiation |
| **Colon and Rectum** | Sahani et al (Radiology 2005)  
                       | Bellomi et al (Radiology 2007) | Rectal cancers with *high baseline BF and low MTT* responded poorly to chemoradiation  
Rectal cancers with *high baseline BF and BV* showed good response to chemoradiation |
Monitoring Antiangiogenic Response: CT perfusion

Pre- Avastin  →  10 day Post- Avastin

Favourable Response
Drop in Blood Flow
Drop in Blood Volume
## Monitoring Response to Antiangiogenic (Avastin) Therapy in HCC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre Avastin</th>
<th>Post Avastin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Flow (ml/100mg/min)</td>
<td>105 ± 92.9</td>
<td>50 ± 28.8</td>
<td>0.014</td>
</tr>
<tr>
<td>Blood Volume (ml/100mg)</td>
<td>5.4 ± 3.9</td>
<td>2.7 ± 1.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean Transit time (sec)</td>
<td>7.3 ± 2.8</td>
<td>8.8 ± 2.3</td>
<td>0.009</td>
</tr>
<tr>
<td>Permeability Surface (ml/100mg/min)</td>
<td>34.28 ± 14</td>
<td>21.9 ± 8.2</td>
<td>0.003</td>
</tr>
</tbody>
</table>

P value from ‘paired student t test’ between the means of pre and post Avastin

Zhu et al. The Oncologist (2007)
Lung Cancer Response to CXT

Baseline

Post CXT

Permeability Surface = 8.57 ml/100 g/min
Blood Flow = 86.3 ml/100 g/min
Permeability Surface = 5.24 ml/100 g/min
Blood Flow = 47.6 ml/100 g/min
## Monitoring Treatment Response

<table>
<thead>
<tr>
<th>Clinical Application</th>
<th>Author (Journal/Year)</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Zhu et al (The Oncologist 2008)</td>
<td>Fall in $BF, BV, PS$ and rise in $MTT$ after antiangiogenic treatment in HCC</td>
</tr>
<tr>
<td>Rectum</td>
<td>Sahani et al (Radiology 2005)</td>
<td>Fall in $BF$ and rise in $MTT$ after chemoradiation in rectal cancer</td>
</tr>
<tr>
<td></td>
<td>Bellomi et al (Radiology 2007)</td>
<td>Fall in $BF, BV and PS$ after chemoradiation in rectal cancer</td>
</tr>
<tr>
<td></td>
<td>Willett et al (Nature Medicine 2004)</td>
<td>Fall in $BF$ and $BV$ after antiangiogenic treatment in rectal cancer</td>
</tr>
</tbody>
</table>
Rectal Cancer: CTp changes following Treatment

MGH Experience

Willett C et al. JCO 2009
CTp Challenges

- Limited sample volume (2-4 cm)
  - Choice of location for the investigation critical
- The CTp parameters are estimates of tissue perfusion
- Patient motion can impact perfusion values
- Radiation dose is an issue
MR Perfusion: Dynamic imaging

Enhancement depends on
- Blood flow
- Vascular volume fraction
- Permeability
- Distribution volume fraction
DCE MRI Enhancement Curve

Recommendations for MRI Measurements

- From: Workshop on assessment of antiangiogenic and antivascular therapies in early clinical trials using MRI

- Primary End Points
  - Initial area under curve (IAUC) (Arbitrary, non-physiological, semi-quantitative)
  - Volume transfer constant, Ktrans (Physiological, quantitative)

Leach et al 2005 Br J Cancer 92:1599
MR Perfusion (DCE-MR)

From McDonald 2003
Volume Transfer Constant ($K_{\text{trans}}$)

- Reflects delivery of contrast agent and vascular endothelium permeability
- Must be derived from concentration time curve (not signal intensity)
  - Requires quantitative $T_1$ measurements
  - Computationally demanding analysis; requires custom software
- May fail to fit model in highly vascular or poorly perfused regions
- Vulnerable to physiological motion and instrument noise
- Within patient CoV, 0.2 - 7.7% (brain); 24% (other)

JC Miller et al., 2005, JNCI, 97:172
Dynamic MR perfusion measures changes in perfusion and vessel permeability of tumor vasculature after gadolinium administration.

- **Positive tumor response**
  - 96% drop in K-Trans
  - 57% reduction in IAUC

K-Trans = Volume Transfer constant

IAUC = Initial area under curve

Zhu A, Sahani D et al. JCO (May 2009)
HCC permeability (K-trans) : Pre and 2 weeks post Sunitinib

K_{trans} decreased by an average of 38%

Zhu A, Sahani D et al. JCO (May 2009)
<table>
<thead>
<tr>
<th>Parameters</th>
<th>CTp</th>
<th>MRp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage</td>
<td>2-4 cm with 16/64 MDCT</td>
<td>Entire organ</td>
</tr>
<tr>
<td>CM Injection</td>
<td>40-70 mL @ 4-7 cc/sec</td>
<td>20-30 mL 2-3mL/sec</td>
</tr>
<tr>
<td>Data Capture</td>
<td>Cine-continuous</td>
<td>Sequential</td>
</tr>
<tr>
<td>Computation</td>
<td>Simpler</td>
<td>Complex</td>
</tr>
<tr>
<td>Parameters</td>
<td>BF, BV, MTT, PS</td>
<td>IAUC, K trans (perm)</td>
</tr>
<tr>
<td>Limitations</td>
<td>Radiation risks</td>
<td>Motion Reproducibility</td>
</tr>
</tbody>
</table>
Issues to Consider for Clinical Trials

- Imaging study feasibility
- Repeat scans practical and acceptable to patients
- Imaging protocol standardized, validated
- Implementable in multicenter study
- Robust and reliable analysis
  - ROI selection
  - Averaged data or voxel-by-voxel
- Statistical power
## Course of antiangiogenic therapy

<table>
<thead>
<tr>
<th></th>
<th>Baseline biomarkers</th>
<th>Dynamic biomarkers</th>
<th>Escape biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological:</td>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Gene level:</td>
<td>VEGF or IL-8 genotype</td>
<td>Perfusion CT</td>
<td>SDF1α, IL-6 or bFGF, CPCs</td>
</tr>
<tr>
<td>Imaging:</td>
<td></td>
<td>Vascular MRI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>parameters ($K_{\text{trans}}$, $CBV$)</td>
<td></td>
</tr>
<tr>
<td>Circulating:</td>
<td>sICAM1, LDH or VEGF(?)</td>
<td>Collagen IV</td>
<td></td>
</tr>
</tbody>
</table>

Summary

- Functional imaging is an evolving field
  - Is getting increasingly important in oncology trials
- Facilitates early Identification
  - Responders vs. non responders
- Protocol customization is mandatory
  - To enable relevant tumor vascular physiology data
- Modality selection
  - Drug mechanism and local expertise
Tumor Response Evaluation

Tumor burden
CT/MR
Tumor measurement
RECIST/WHO

Metabolism
FDG-PET

Angiogenesis
CT-perfusion
MR-perfusion
MR-diffusion
THANK YOU