CT Perfusion Imaging: Technique and Applications in the Body

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Monitoring Response to Conventional Chemotherapy

Conventional method of monitoring treatment response is change in tumor size

**RECIST 1.0**
- 10 Target Lesions (>1-2 cm)
- 5 max in an organ
- Non-target lesions

**RECIST 1.1**
- 5 Target Lesions (>1 cm)
- 2 max in an organ
- Short-axis of LN>15 mm

Therasse P et al. JNCI 2000
Therasse P et al. EJC 2006
Eisenhauer EA et al. EJC 2009

**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>CR (Complete Response)</td>
<td>Total disappearance</td>
<td>Total disappearance</td>
</tr>
<tr>
<td>PR (Partial Response)</td>
<td>30% decrease</td>
<td>50% decrease</td>
</tr>
<tr>
<td>PD (Progressive Disease)</td>
<td>20% increase</td>
<td>25% increase</td>
</tr>
<tr>
<td>SD (Stable disease)</td>
<td>Neither PR or PD criteria met</td>
<td>Neither PR or PD criteria met</td>
</tr>
</tbody>
</table>

**Type of metric**
- Uni-dimensional
- Bi-dimensional (CP) MAD X LPD
Limitations of RECIST guidelines

- **Tumor morphology**
  - Confluent, Irregular borders
  - Unusual configuration; Circumferential (e.g., mesothelioma)
  - Lesion length > 1.5-2 times lesion width

- **Discordant results due to RECIST technique**
  - Uni-dimensional measurement
  - Shape changes may confound results
Monitoring Response to Chemotherapy: Tumor Volume

Tumor volumetry is a better representative of tumor burden

Liver tumor treated with chemotherapy

# 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>

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>PRE</th>
<th>POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>96HU</td>
<td>54HU</td>
<td>28HU</td>
<td>25HU</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

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
Angiogenesis

• The development of new vessels from pre-existing ones*
• Essential step in establishment and growth of malignancies
• Allow tumor progression from *in-situ* lesion to invasive

*(Risau W., 1997) *(J. Folkman, 1995)*

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

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
Tortuous
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)
- CT attenuation

\[ \text{Iodine Concentration (mg/ml)} \sim \text{linear related} \]

\[ \text{CT attenuation} \]

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

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

Sahani DV et al. Radiology 05/07
Goh V et al. Radiology 06, ER 07
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

Sahani DV et al. Radiology 05/07
Goh V et al. Radiology 06, ER 07
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</td>
<td>Inadequate $PS$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less radiation</td>
<td>measurement</td>
</tr>
<tr>
<td>Permeability ($PS$)</td>
<td>Cine 45-120 sec Limited</td>
<td>Permeability</td>
<td>Susceptible to Motion</td>
</tr>
<tr>
<td></td>
<td>scan every 10-20 seconds</td>
<td></td>
<td>More radiation</td>
</tr>
<tr>
<td></td>
<td>for 4-6 minutes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, (\alpha)</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>
</tbody>
</table>
| **Advantages**       | BF, BV, MTT and PS can be calculated using a single CT study | 1. Simple analysis  
2. Efficient in calculation of rate constant \(K\) value | 1. Short scan duration  
2. “No venous outflow” is true  
3. No recirculation |
| **Limitations**      | Partial volume averaging correction required                | Assumes that back flux of CM from EVS to IVS is negligible for first 1-2 min | Sensitive to image noise |

\(^1\)Sahani et al, Radiology 2005, \(^2\)Ng 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>
</tbody>
</table>
## Staging, Grading and Prognosis

<table>
<thead>
<tr>
<th>Clinical Application</th>
<th>Author (Journal/Year)</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung</strong></td>
<td>Li et al (Clinical Radiology 2008)</td>
<td>Lung cancers with distant metastases have <strong>high BF, BV and</strong> and different histological types of lung cancer show no difference in perfusion characteristics.</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td>Hirasawa et al (Acad Radiol 2007)</td>
<td>Nonncirrhous carcinomas have <strong>high BF</strong> values compared to scirrhous carcinomas.</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>Zhu et al (The Oncologist 2008) Sahani et al (Radiology 2007)</td>
<td>Patients with progressive disease (HCC) had lower baseline MTT values. Well differentiated HCCs show <strong>high BF, BV, PS and low MTT</strong> values than poorly differentiated HCCs.</td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td>d’Assignies et al (Radiology 2008) Park et al (Radiology 2009)</td>
<td>Benign endocrine tumors have <strong>high BF</strong> values. Malignant tumors with liver &amp; lymphnodal metastases have <strong>long MTT</strong>. Pancreatic cancers with <strong>high baseline K_{Trans}</strong> values responded better to concurrent chemoradiation.</td>
</tr>
<tr>
<td><strong>Colon and Rectum</strong></td>
<td>Sahani et al (Radiology 2005) Bellomi et al (Radiology 2007)</td>
<td>Rectal cancers with <strong>high baseline BF and low MTT</strong> responded poorly to chemoradiation. Rectal cancers with <strong>high baseline BF and BV</strong> showed good response to chemoradiation.</td>
</tr>
</tbody>
</table>
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</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

Blood Flow = 86.3 ml/100g /min
Permeability Surface = 8.57 ml/100g /min

Post CXT

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

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<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>
Sarcoma: Antiangiogenic T/t

Pre- Avastin

Post- Avastin
Monitoring Antiangiogenic (Avastin) Response in Rectal Cancer

Rectal Cancer: CTp changes following Treatment

MGH Experience

Willett C et al. JCO 2009
# Validation and Reproducibility

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<tbody>
<tr>
<td><strong>Lung</strong></td>
<td>Ma et al (BMC Cancer, 2008)</td>
<td><em>BF, BV and PS</em> values of peripheral lung cancer correlated positively with MVD</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>Sahani et al (Radiology 2007)</td>
<td>Reproducibility of <em>BF, BV, PS and MTT</em> values with high correlation and variability of 4% in HCC</td>
</tr>
</tbody>
</table>
| **Pancreas**         | d’Assignies et al (Radiology 2008)  
Good linear correlation of *BF* measured by and CTp in pancreatic tumors |
| **Colon & Rectum**   | Goh et al (Am J Roentgenol 2006)  
Li et al (World J Gastroenterol 2005) | *Quantitative perfusion* measurements are reproducible in colorectal cancer  
*BF* values of colorectal carcinomas did not correlate with MVD |

- Chan NG et al. CTp  JCAT 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
FDA: High Radiation Doses at Cedars-Sinai Hospital
Radiation Overdoses Point Up Dangers of CT Scans

• Appropriate indication
Strategies to Lower CTP Dose

- Appropriate indication
- Compromise resolution and SNR
  - 5-10 mm thickness
  - Low dose kVp 80-100 mA 100-160
  - 2 second temp resolution
  - Cine < 40 sec
  - Appropriate scan delay based on the circulation time
Summary

• Imaging integral to monitoring treatment response in Oncology trials and decision-making
  – Expectations are changing
  – Beyond 2D measurements
    • Volume
    • Density
    • Function
    • Combination
Summary

- CT perfusion imaging is an evolving field
  - redefines CT as a technique that can now depict vascular physiology in addition to detailed anatomy
  - is getting increasingly important in trials for targeted therapies

- Protocol customization is mandatory
  - to enable relevant tumor vascular physiology data
  - Radiation dose optimization

- Data is specific to protocol and processing method
THANK YOU