Monitoring Tumor Response: 2D/3D/HU or Function

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Disclosures

Research Grant Support from GE Healthcare
CT Oncology Imaging

- Volume
- Viability
- Staging
- Size
- Density
- Function
Image Biomarker

- Biomarker Expectations
- Quantitative
- Reproducible
- Robust
- Coverage
- Applicable in clinical trials
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><strong>CR</strong> (Complete Response)</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>
</tr>
<tr>
<td><strong>PD</strong> (Progressive Disease)</td>
<td>20% increase</td>
<td>25% 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>
</tr>
</tbody>
</table>

- **Type of metric**: Uni-dimensional vs. Bi-dimensional (CP) MAD X LPD
- **CR (Complete Response)**: Total disappearance
- **PR (Partial Response)**: 30% decrease, 50% decrease
- **PD (Progressive Disease)**: 20% increase, 25% increase
- **SD (Stable Disease)**: Neither PR or PD criteria met
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

## 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></td>
<td>Uni-dimensional</td>
<td>Bi-dimensional</td>
<td>Volume</td>
</tr>
<tr>
<td></td>
<td>MAD X LPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CR</strong> (Complete</td>
<td>Total disappearance</td>
<td>Total disappearance</td>
<td>Total disappearance</td>
</tr>
<tr>
<td>Response)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PR</strong> (Partial</td>
<td>30% decrease</td>
<td>50% decrease</td>
<td>65% decrease</td>
</tr>
<tr>
<td>Response)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PD</strong> (Progressive</td>
<td>20% increase</td>
<td>25% increase</td>
<td>40-73% increase*</td>
</tr>
<tr>
<td>Disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SD</strong> (Stable</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>
<tr>
<td>disease)</td>
<td></td>
<td></td>
<td></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/ Yittrium
  – 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>

### Challenges
- Technologically demanding
- Labor intensive
- Automation
- Structural changes not factored
Tumor Density and Necrosis

Tumor Necrosis: EASL

## Modified RECIST Criteria (mRECIST)

<table>
<thead>
<tr>
<th>Type of metric</th>
<th>RECIST</th>
<th>mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of metric</td>
<td>Uni-dimensional</td>
<td>Enhancement</td>
</tr>
<tr>
<td>CR (Complete Response)</td>
<td>Total disappearance of lesions</td>
<td>Total disappearance of enhancing tumor</td>
</tr>
<tr>
<td>PR (Partial Response)</td>
<td>30% decrease in tumor burden</td>
<td>30% decrease in sum of enhancing component</td>
</tr>
<tr>
<td>PD (Progressive Disease)</td>
<td>20% increase</td>
<td>20% increase in sum of enhancing</td>
</tr>
<tr>
<td>SD (Stable disease)</td>
<td>Neither PR or PD criteria met</td>
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</tbody>
</table>
Segmentation for estimation of total tumor volumes and non-necrotic (viable) volumes

Structure segmentation, extraction and feature computation for semi-automated/CAD quantification algorithm. Tissues within a defined range of Hounsfield unit (HU) values.

Margins outlined: Outer tumor boundaries for TTV; Necrotic portion outlines (10-35 HU). Subtracted region = Non-necrotic fraction.
Kaplan Meier curves for overall patient survival by RECIST, TTV and proposed NNV criteria

$\text{rr} = \text{RECIST criteria}, \text{tt} = \text{Total tumor volumetry (TTV) criteria}, \text{nn} = \text{proposed non necrotic tumor volume criteria}.$

Group 0 = stable disease or partial response; Group 1 = disease progression.
**Tumor Density (HU): 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>PRE</th>
<th>POST</th>
<th>PRE</th>
<th>POST</th>
</tr>
</thead>
<tbody>
<tr>
<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

### Overall Tumor Response (Revised CT evaluation criteria)

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

*Choi et al J Clin Oncol 2007, Choi et al The Oncologist 2008*
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
FDG-PET Imaging of Imatinib (Gleevec, Novartis) on GIST

## Monitoring Response: EORTC Criteria for FDG-PET

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>SUV increase &gt;25%&lt;br&gt;Visible increase of FDG uptake&lt;br&gt;Appearance of new focus</td>
</tr>
<tr>
<td>SD</td>
<td>SUV increase &lt;25% or decrease &lt;15%&lt;br&gt;No visible increase of the extent of FDG uptake</td>
</tr>
<tr>
<td>PR</td>
<td>SUV drop 15-25% after one cycle;&lt;br&gt; &gt;25% after more than one treatment cycle</td>
</tr>
<tr>
<td>CR</td>
<td>Complete resolution of FDG uptake</td>
</tr>
</tbody>
</table>

**EORTC** = European Organization for Research and Treatment of Cancer
Bile Duct Tumor: PFS > 6 months
FDG PET vs RECIST

The metabolic response measured by FDG PET was a better predictor of PFS than RECIST

Sahani et al. SGR 2009, Zhu et al. Lancet Oncology 2010
Novel Oncologic Drugs

- Bevacizumab
- VEGF-Trapping
- Vascular endothelial cell plasma membrane
- Vascular permeability
- Endothelial cell survival
- Endothelial cell migration
- Endothelial cell proliferation
- Sorafenib
- Sunitinib
- Vatalanib
- PI3K
- Akt/PKB
- p38MAPK
- MEK
- Erk
- Raf
- VEGFR-2
Mechanistic Antiangiogenic Effects in Malignancy

- Investigating Anti-angiogenesis and the “vascular normalization” hypothesis

Jain, Science 2005 307:61
Imaging Biomarker Selection: Drug Mechanism

Baseline: 40 ml/100gm/min

2 weeks following therapy: 90 ml/100gm/min

Image Biomarker-Good Response

Pre-treatment

10 days Post-Avastin
Image Biomarker - Poor Response

Pre-treatment

10 days post-Avastin
Perfusion CT

Characterization
- Necrosis
- Recurrence
- Prostate
- Lung Nodule

Biology
- Tumor Grade
- Angiogenesis

Angiogenesis
- Soft Tissues
- Lymph Nodes
- Pancreas
- Liver

Challenges
- Limited coverage
- Standardization
- Kinetic modeling
- Radiation Dose
Iodine (perfusion) Imaging

**Qualitative**

**Quantitative**

RM - 3.0 mg/cc
RP - 5.2 mc/cc
**Base line**
Contrast enhanced CT (RECIST)

**Post BVZ**
Contrast enhanced CT (RECIST)

**Treatment completion**
Contrast enhanced CT (RECIST)

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FDG PET Mean SUV 7.62

FDG PET Mean SUV 4.01

FDG PET Mean SUV 2.1
Summary

- Imaging integral to monitoring treatment response in Oncology
  - Expectations are changing
  - Beyond 2D measurements
    - Volume/Viability
    - Density
    - Function
    - Combination
  - Modality selection is dependent on the drug mechanism and local expertise
  - Early antiangiogenic changes are better appreciated with perfusion
Tumor Response Evaluation

Tumor burden
CT/MR Tumor measurement RECIST/WHO

Metabolism
FDG-PET

Angiogenesis
CT-perfusion MR-perfusion MR-diffusion

[Images of medical scans and measurements]