Tumor Response Assessment in Adult Clinical Trials

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A National Cancer Institute Comprehensive Cancer Center
Objectives: To discuss-

- Conventional imaging response criteria in solid tumors
  - RECIST 1.1
  - Beyond RECIST
- Best methods to enable response assessment
  - Recording and reporting the data
Why Tumor Response Criteria

- It remains critically important to the conduct and outcome of clinical trials
- Need to be able to compare results across non-randomized clinical trials
- Need to be able to compare results among sites within a clinical trial
Why Tumor Response Criteria

- In clinical reads, radiologists usually describe tumors subjectively and often ambiguously, and
- Lesion measurements are not recorded in a format that permits reproducibility, making it difficult to evaluate response
2009-New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

RECIST 1.1

- Three components:
  - Target lesion evaluation
  - Non-target lesion evaluation
  - New lesion detection
- CT scan preferred imaging modality
- MRI can be substituted
- NO ultrasound
- Reconstruction slice thickness $\leq 5$mm
- Measure in axial plane
RECIST 1.1 Target Lesions

- Measurable and reproducible
- ≤5 lesions, ≤2 per organ
- Non-nodal lesions long axis > 10 mm
- Lymph nodes short axis ≥ 15 mm
- Bone lesions with a lytic component and measurable soft tissue mass
Example: Non-nodal Target Lesions

- > 10 mm long axis, ≤ 2 per organ

Chalin et al RadioGraphics 2011; 31:2093-2105
Liver Lesions as Target Lesions

- The rim should be included in the measurements
- View at liver windows

Van Meerten Eur Radiol 2010; 20:1456-1467
RECIST 1.1

IV contrast is mandatory

If there is no IV contrast at baseline, cannot assess full tumor burden or response
Reproducible Defined Margins

Sharp margins
Ideal to measure

Irregular margins

Imperceptible margins

Reproducible measurements unlikely

Jaffe J Clin Oncol 2006; 24:3245
RECIST 1.1 Lymph Node Assessment

- Measure SHORT axis (not long axis)
  - > 15 mm: target lesion status
  - 10 to <15 mm: non-target
  - < 10 mm: normal
Lymph Nodes as Target Lesions

2 cm Target lesion

9 mm normal
Lymph Node Specifications

0.7 cm normal

1.6 mm abnormal
Specifications on Bone Lesions

• Bone lesions may be target lesions if--
  – they are either lytic or mixed lytic-blastic with a measurable soft tissue component
  – PET, bone scintigraphy, or radiography cannot be used when measuring disease response

• Blastic bone lesions are non-measurable
Bone Lesions as Target Lesions

Non-Target blastic

Measurable ST component

Chalin et al RadioGraphics 2011; 31:2093-2105
Non-Target Lesions

- Solid lesions < 10 mm
- Nodes 10 to <15 mm
- Lesions with poorly visualized margins
- Bone lesions without measurable components
- Previously irradiated lesions
- Blastic bone lesions

DO NOT MEASURE
Non-Target Lesions

9mm nodule

Poorly defined margins

Nodes 10 to <15 mm

Van Meerten Eur Radiol 2010; 20:1456-1467
What is totally excluded from imaging response assessment

- These are **not recorded** at baseline or followed
  - Nodes <1 cm in short diameter ("normal")
  - Pleural/pericardial effusion/ascites
  - Simple cysts
Follow Up Evaluation
• Target lesions - sum the measurements at baseline and follow up and calculate % change from Baseline or Nadir

• Non-target lesions - record status as absent, present, or unequivocal progression

• Look for new definite lesions
Target Lesion Response: PR

Baseline

Follow up

• 40% decrease in SOD \[\left(\frac{10 - 6 \text{ cm}}{10 \text{ cm}} \times 100\right)\]

Nishino AJR:195, August 2010
New Lesions

• New lesions are reported as “yes” or “no”

• Should be unequivocal
  – i.e., represent malignant disease rather than a benign process and is not due to difference in scanning technique

When in doubt continue treatment, repeat evaluation, including with FDG-PET
Unequivocal PD
New Liver metastases

Eisenhauer et al. ORTC-NCI-AACR 2008 meeting
New Liver Lesion – Equivocal Does Not Mandate PD

7mm
Finally, Evaluate Overall Response
Response Categories

- CR = complete response
- PR = partial response
- PD = progressive disease
- SD = stable disease
Evaluate All Lesions in Combination Target, Non-target and New Lesions

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Target and non-target lesions resolved, nodes &lt; 10 mm</td>
</tr>
<tr>
<td>PR</td>
<td>$\geq 30%$ decrease sum of Target Lesions AND Non-target are non-PD</td>
</tr>
<tr>
<td>PD</td>
<td>$\geq 20%$ increase sum of target lesions AND $\geq 5 \text{ mm absolute increase from nadir}$ OR Non-target progress OR New lesions</td>
</tr>
<tr>
<td>SD</td>
<td>Does not meet PR or PD</td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; PD = progressive disease; SD = stable disease
New Challenge: Immunotherapy

• Associated with a delay between dosing and tumor response
• Response may occur after an initial increase in tumor burden
• Regression of initial lesions may occur despite development of new lesions
• Melanoma, renal cell cancer, NSCLC, prostate cancer
New Immunotherapy Response Criteria

- Immune-related response criteria (irRC)
- Immune-response RECIST (irRECIST)
- New lesions are incorporated into the total tumor burden
- New lesions are simply a change in tumor burden
- New lesions do not automatically qualify as PD
irRC
Immune-Related Response Criteria

• Tumor burden is measured by combining 'index' lesions with new measurable lesions
• CR - disappearance of all lesions and no new lesions
• PR - 50% drop in tumor burden from baseline
• PD - 25% increase in tumor burden from the lowest level recorded
• SD Everything else
irRECIST

- Tumor burden is measured by combining 'index' lesions with new measurable lesions
- CR  disappearance of all lesions; nodes < 10 mm
- PR  $\geq 30\%$ decrease in tumor burden compared to baseline
- PD  $> 20\%$ increase in tumor burden and minimum 5 mm increase in tumor burden compared to nadir
Tumor Response Assessment

- Understanding the variety of response criteria
- Recording and reporting the data

Trial response criteria  Recording the data  Reporting the data
Dedicated Automated Software

- Accessible from existing workstation or web browser
- Quantitative measurements for a variety of criteria
  - RECIST, irRC, irRECIST, mRECIST, Cheson, Lugano, Rano
- Automatic response classification
- Compares to nadir, baseline and prior time points
- Automated report communication
- **Summary data**
- **Snapshots of target lesions**
- **Graphical display**

<table>
<thead>
<tr>
<th>Lesion name</th>
<th>Baseline (05/09/2016 (CT))</th>
<th>Follow-up 1 (07/14/2016 (CT))</th>
<th>Follow-up 2 (09/12/2016 (CT))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T01 LUL Nodule</td>
<td>LA: 1.6 cm</td>
<td>LA: 1.5 cm</td>
<td>LA: 1.5 cm</td>
</tr>
<tr>
<td>T02 Lingula Nodule</td>
<td>LA: 2.0 cm</td>
<td>LA: 2.0 cm</td>
<td>LA: 2.1 cm</td>
</tr>
<tr>
<td><strong>Non-target lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT01 Lung nodule</td>
<td>Present</td>
<td>3.4 cm</td>
<td>3.6 cm</td>
</tr>
<tr>
<td><strong>Target sum</strong></td>
<td>3.7 cm</td>
<td>-6.5%ΔB / -6.5%ΔN</td>
<td>-2.7%ΔB / +4.1%ΔN</td>
</tr>
<tr>
<td><strong>Target response</strong></td>
<td>Stable Disease</td>
<td>Stable Disease</td>
<td>Stable Disease</td>
</tr>
<tr>
<td><strong>Non-target response</strong></td>
<td>Non-CR/Non-PD</td>
<td>Non-CR/Non-PD</td>
<td>Non-CR/Non-PD</td>
</tr>
<tr>
<td><strong>New lesions present</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Timepoint response</strong></td>
<td>Stable Disease</td>
<td>Stable Disease</td>
<td>Stable Disease</td>
</tr>
<tr>
<td><strong>Approval</strong></td>
<td>Approved by Marilyn J Siegel on 05/13/2016.</td>
<td>Approved by Marilyn J Siegel on 07/14/2016.</td>
<td>Approved by Marilyn J Siegel on 09/13/2016.</td>
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• Graphical display
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  – Beyond RECIST

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  – Automated technology for recording and reporting the data
Thank you!