Imaging data and RECIST criteria for the evaluation of tumor response

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A little bit of history

1979 WHO

1990 RECIST (1.0)

2000 RECIST 1.1

2009
Response Evaluation Criteria in Solid Tumors (RECIST)

Therasse et al JNCI 2000

- Intended for use in clinical trials with primary endpoint of objective response
- Measurable lesion \( \geq 20 \) mm (10 if spiral CT)
- Unidimensional assessment: Tumor burden assessed by summing longest diameters of all measurable lesions up to 10 (5 per organ)
- Four categories of response: CR*, PR*, SD, PD
- RECIST widely adopted by cooperative groups, industry, academia

* Required confirmation
### Summary:

**What **HAS** changed in RECIST 1.1**

<table>
<thead>
<tr>
<th></th>
<th>RECIST 1.0</th>
<th>RECIST 1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring tumor burden</td>
<td>10 targets 5 per organ</td>
<td>For response: 5 targets (2 per organ)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>Measure long axis as for other lesions. Silent on normal size</td>
<td>Measure short axis. Define normal size.</td>
</tr>
<tr>
<td>Progression definition</td>
<td>20% increase in sum</td>
<td>20% increase and at least 5 mm absolute increase</td>
</tr>
<tr>
<td>Non-measurable disease PD</td>
<td>“must be unequivocal”</td>
<td>Expanded definition to convey impact on overall burden of disease. Examples.</td>
</tr>
<tr>
<td>Confirmation</td>
<td>required</td>
<td>Required when response primary endpoint—but not PFS</td>
</tr>
<tr>
<td>New lesions</td>
<td>--</td>
<td>New section which includes comment on FDG PET interpretation</td>
</tr>
</tbody>
</table>
RECIST: a standardized tool

Simple, objective and uniform
• Across tumour types
• Across sites participating in a clinical trial
• Across clinical trials

While some diversifications can be implemented, RECIST cannot accommodate for all possible protocol specificities (Verweij et al EJC 2009)

Criticisms of RECIST 1.1 include
• not adapted to specific tumor type
• purely based on anatomical burden (“size”)
• there are more refined imaging techniques
• not validated for targeted agents
The road ahead

Targeted agents:
• Different mode of action not necessarily leading to obvious tumor shrinkage
• We compiled a database of **50 clinical trials** (academia and industry) on approx **23,000 patients**

Advanced imaging techniques – FDG-PET:
• Playing an important role in clinical practice, but results from clinical trials are difficult to compare. Lack of harmonization is an important obstacle
• We pooled data from **9 studies** (academia and industry) on approx **200 patients** to study the sources of heterogeneity of FDG-PET by looking at repeatability data
• We compiled a database of **18 clinical trials** (academia and industry) on approx **1,000 patients** to study its added value to the current RECIST

Immunotherapy
• Immune-related response patterns may challenge the classical concepts of progression
• RECIST Working Group is trying to initiate a high-level collaboration with partners from academia, industry and regulatory to address this
What do we need for a new version of RECIST?

• Some biological rationale

• **Standardized protocol** for interpreting measurements
  - Understanding sources of variability: imaging methodology, reader variability, patient heterogeneity, role of missing data

• Understanding of its **limitation(s)**

• Evidence of correlation with a **true endpoint**
  - Patient benefit (PRO?, OS?)
  There is no real ‘consistent’ **gold standard**
Evidence of correlation: surrogacy?

When an event on the “surrogate” leads to a change in treatment decision, the relationship will be obscured.
What else is needed?

Collecting data for validation requires time, persistence and a lot (!) of data sharing negotiation

• Patient privacy
• Patient data anonymization
  • Digital images vs reported data
  • Resources
• Agreements not to report/repeat study level analyses
The clinical trial data as limiting factor

• **Elephant number 1: the chicken and egg issue of progression**
  • Sharing of scanned results **starts with the study and stops at RECIST PD**
  • Typically in advanced disease setting, this leaves us with few observations
  • ... so we cannot assess less stringent definitions of “PD” because of lack of data

• **Elephant number 2: incomplete data.** In the RECIST 1.1 data warehouse
  • for **14%** of patients no tumor lesion measurements provided at time of non-target progressive disease or new lesions
  • for **10%** of patients measurements incomplete for target lesions at time of progression (i.e. **only progressive lesion** reported) resulting in a non-evaluable result
The clinical trial data as limiting factor

- Elephant number 3: the role of non-target and new lesions?

### Table 1
Reason to stop follow-up of target lesion measurements (note that categories are not mutually exclusive).

<table>
<thead>
<tr>
<th>Reason</th>
<th>Breast cancer (n = 1141)</th>
<th>Lung cancer (n = 1853)</th>
<th>Colorectal cancer (n = 734)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of a new lesion</td>
<td>507 (44%)</td>
<td>530 (29%)</td>
<td>309 (42%)</td>
</tr>
<tr>
<td>Non-target progressive disease</td>
<td>280 (25%)</td>
<td>505 (27%)</td>
<td>247 (34%)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (0.4%)</td>
<td>1 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up†</td>
<td>28 (2.5%)</td>
<td>8 (0.4%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Progression of target lesions§</td>
<td>437 (38%)</td>
<td>961 (52%)</td>
<td>417 (57%)</td>
</tr>
<tr>
<td>End of follow-up†</td>
<td>320 (28%)</td>
<td>552 (30%)</td>
<td>197 (27%)</td>
</tr>
</tbody>
</table>

† Last measurement reported is also last known date to be alive.
† Defined as none of the above.
§ Progression = increase from smallest sum of target lesions.

Litière et al. EJC 2014
Final remark

• New technologies should be incorporated rapidly but this should be based on evaluation of fairly massive data (i.e. validated)

• Therefore, in order to validate new biomarkers and/or response criteria we need the community to pull together to
  • ensure standardization and harmonization of the data collection across different sites, and
  • pool the data in the context of large international collaborative efforts such as RECIST
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  • Gaëlle Isaac
  • Zeina Tayah

http://www.eortc.org/recist/
Thank you

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