Response Evaluation Assessment in HCC: modified RECIST

So Yeon Kim
Department of Radiology
University of Ulsan, Asan Medical Center
Endpoint of Cancer Research

- **Overall survival**
- **Tumor burden**
  - Predictive better survival
  - Tumor shrinkage
  - Time to progression

Paesmans M, Eur J Cancer 1997
Buyse M. Lancet 2000
Tumor Response Criteria

► WHO criteria
  Miller AB, Cancer 1981

► RECIST (Response Evaluation Criteria in Solid Tumors)
  Therasse P, J Natl Cancer Inst 2000
  – International Working Party of JNCI
  – Simplified response criteria
  – Revised RECIST criteria (Ver 1.1)
  Eisenhauer EA, Eur J Cancer 2009
WHO vs. RECIST
WHO vs. RECIST

WHO criteria (bidimesional) = (A × B) + (C × D)

RECIST criteria (unidimensional) = A + B
RECIST

- Standard methods for measuring the tumor response
- Designed primarily for cytotoxic agent resulting in tumor shrinkage

Problems of application of RECIST in HCC?
RECIST in HCC

Stable disease??
Residual tumor??
RECIST in HCC

Progression of disease??

2cm

4.5cm
RECIST in HCC

HCC treated with sorafenib

Baseline

Timepoint 1

No response at all??

Courtesy of Choi JI, St Mary H.
Problems of RECIST in HCC

Locoregional treatment (RFA, TACE)

- To obtain tumor necrosis, regardless of the shrinkage of the lesion
- Complete necrosis $\propto$ Better survival

Sala M, Hepatology 2004

- Poor correlation btw clinical benefit & RECIST

Forner A. Cancer 2009
Problems of RECIST in HCC

► Cytostatic agent
  – Sorafenib
  – Shrinkage of tumor would not be expected.

Llovet JM. JNCI 2008

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Objective response</th>
<th>Survival benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional treatments in HCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local ablative therapies (RF ablation and/or PEI)</td>
<td>70–80% (CR)</td>
<td>Yes</td>
</tr>
<tr>
<td>Chemoembolization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal radiation (I131, Y90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraarterial chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular targeted therapies in oncological practice†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small-molecule kinase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR: erlotinib (NSCLC) (41)</td>
<td>9% (PR)</td>
<td>Yes</td>
</tr>
<tr>
<td>Raf/VEGFR: sorafenib (HCC) (18)</td>
<td>2.7% (PR)</td>
<td>Yes</td>
</tr>
<tr>
<td>mTOR: temsirolimus (RCC) (42)</td>
<td>8% (PR)</td>
<td>Yes</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-VEGF: bevacizumab (metastatic CRC) (43)</td>
<td>10% (PR)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Improved survival with an objective response rate less than 10%
Problems of RECIST in HCC

► Underestimate tumor response
► Missed all CR

► For problem solving
  – Not just reduction in overall tumor size
  – Consideration of viable tumor & necrosis
Response Evaluation for HCC

Reduction of viable tumor volume
= Measure enhancing area only

- EASL guideline
  - WHO criteria

- Modified RECIST (mRECIST) criteria
  - RECIST criteria
  - AASLD-JNCI guideline

Bruix J. J Hepatol 2001
Llovet JM, JNCI 2008
Lencioni R. Semin Liver Dis 2010
mRECIST

Table 1  Summary of Conclusions of the AASLD-JNCI Guidelines for Trial Design in HCC

Endpoints: Survival or time to recurrence (phase III), time to progression (phase II)

Trial strategy: Test drugs in the setting of randomized phase II before moving to phase III

HCC Classification: BCLC staging system is recommended for selection of target population and stratification

Assessment of response and TTP: Should follow the AASLD-JNCI amendments, which are summarized in the current article

<table>
<thead>
<tr>
<th>HCC Subclass (Standard of Care)</th>
<th>1st Line Treatment</th>
<th>2nd Line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCLC 0 or A—Early stages (resection, transplantation, local ablation)</td>
<td>Adjuvant: drug vs. placebo</td>
<td>–</td>
</tr>
<tr>
<td>BCLC B—Intermediate stage (Chemoembolization-TACE)</td>
<td>TACE vs. TACE + drug</td>
<td>–</td>
</tr>
<tr>
<td>BCLC C—Advance stage (Sorafenib)</td>
<td>TACE vs. drug or device†</td>
<td>Sorafenib vs. sorafenib + drug</td>
</tr>
<tr>
<td></td>
<td>Sorafenib vs. drug†</td>
<td>Drug vs. placebo</td>
</tr>
</tbody>
</table>

Llovet JM, JNCI 2008
mRECIST

- Image acquisition
- Image interpretation
  - Assessment of the tumor lesions at baseline
  - F/U image analysis
- Defining treatment response & tumor progression
Image Acquisition

- IV contrast for all CT or MR
- Dual-phase imaging of the liver
- Contiguous slice

Slice thickness: 5mm
Interval: 5mm

Slice thickness: 5mm
Interval: 10mm
mRECIST

Image Interpretation

- **Baseline imaging**
  - To determine the overall tumor burden
  - As a comparator for subsequent measurement

- **At each f/u imaging time point**
  - Tumor response evaluation
mRECIST

Image Interpretation

Lesions

Measurable

Non-measurable

Measurable lesions not selected as target

Target
to be recorded on the Analysis form

Non-target
to be recorded on the Analysis form
mRECIST

Baseline Images
mRECIST

Measurable Lesion

The longest diameter $\geq 1\text{cm}$
$LN \geq 1.5\text{cm}$ in the shortest diameter
Suitable for repeat measurement
Maximum 2 lesions/organ
5 lesions in total
mRECIST

Target Lesions

► RECIST measurable lesion
  – The longest diameter ≥ 1cm
  – LN ≥ 1.5cm in the shortest diameter

► Suitable for repeat measurement

► Maximum 2 lesions/organ

► 5 lesions in total

Intratumoral arterial enhancement
mRECIST

Target Lesions at F/U

Baseline

Arterial enhancement
Not include any intervening areas of necrosis

2 cm

RFA

105% increase in size
→ Progression?

4.1 cm

45% decrease in size
→ Partial response

1.1 cm

Timepoint 1
Target Lesions at F/U

Baseline

5 cm

Timepoint 1

1.1 cm

78% decrease in size → Partial response

Timepoint 2

1.5 cm

74% decrease in size → Partial response

36% increase in size → Progressive disease?
Target Lesion Assess

100% Sum of diameters

100% decrease in size → Partial response

75%

75% 25% increase in size → Progressive disease

60%

PR

1st F/U 2nd F/U Time
<table>
<thead>
<tr>
<th>Response</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (complete response)</td>
<td>Disappearance of any intratumoral arterial enhancement in all target lesions</td>
</tr>
<tr>
<td>PR (partial response)</td>
<td>At least a 30% decrease in the sum of diameters of viable (enhancing) target lesions Reference - Baseline sum</td>
</tr>
<tr>
<td>SD (stable disease)</td>
<td>Not qualify for either PR or PD</td>
</tr>
<tr>
<td>PD (progressive disease)</td>
<td>An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions Reference - Smallest sum since treatment started</td>
</tr>
</tbody>
</table>
mRECIST

Non-target Lesions

- Not selected or identified as target lesions
  - Excess measurable lesions
  - All non-measurable lesions

- Identify all areas of non-target disease at baseline

- Follow as present or absent
mRECIST

Non-target Lesions

Infiltrative HCC
PV thrombosis
mRECIST

Special consideration for nontarget lesions

- Previous treated with locoregional or systemic therapy
- Portal hepatis LN >20mm in short axis
- Pleural effusion or ascites
  - Cytopathologic confirmation when the measurable tumor has met criteria for response or stable disease.
Intratumoral arterial enhancement

**Response**

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<th>Description</th>
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<tbody>
<tr>
<td>CR (complete response)</td>
<td>Disappearance of all nontarget lesions</td>
</tr>
<tr>
<td>IR (incomplete response) /SD (stable disease)</td>
<td>Persistence of one or more nontarget lesions</td>
</tr>
<tr>
<td>PD (progressive disease)</td>
<td>Appearance of new lesions, Unequivocal progression of existing nontarget lesions</td>
</tr>
</tbody>
</table>

mRECIST

Nontarget Lesion Assess
New lesion
- The longest diameter ≥ 1cm
- Typical vascular pattern

Lesion > 1cm without typical vascular pattern?
- At least 1cm interval growth in subsequent scan
# mRECIST

## Overall response assessment

<table>
<thead>
<tr>
<th>Target</th>
<th>Nontarget</th>
<th>New</th>
<th>Overall responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>IR/SD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>
mRECIST

- Arterial enhancement → viable tumor
- No enhancement → necrosis
- A reliable method for assessing tumor response in HCC clinical trial
- Prototype used in SHARP trial

Llovet JM. NEJM 2008
THANK YOU FOR YOUR ATTENTION!