

RECIST: Applying the Rules

Assessing response to therapy allows for prospective end point evaluation in clinical trials and serves as a guide for decision making for clinician and patient/study subject.

In oncology clinical trials there are several standards that are used. This module will focus on the standard used for solid tumors: Response Evaluation Criteria for Solid Tumors (RECIST). By the end of the module you will be able to:

- Describe two criteria used to select target lesions for RECIST 1.0 and 1.1.
- Discuss how to use target and non-target lesions when determining overall response for RECIST 1.0 and 1.1.
- Define what is meant by a partial response for RECIST 1.0 and 1.1.

RECIST is being used in most of the CCR's solid tumor protocols to assess tumor response. However, not all studies will be using RECIST. This module is intended to assist you in understanding how to apply the RECIST "rules" using RECIST version 1.0. The end of the module will highlight some of the changes in version 1.1.

Consult your protocol for specifics of assessing tumor response.

Background

- Initial attempts to standardize assessing tumor response began in 1960s
- 1979 World Health Organization
 - Standardized criteria for response assessment

Problems with WHO criteria

- Interpretation of WHO guidelines vary amongst groups
- Minimum lesion size number of lesions to be recorded vary
- Definition of progressive disease (PD) varied
- Maturation of imaging technology not taken into consideration
- Discrepancies identified during independent review

Development of RECIST

- 1994 international task force
 - European Organization for Research and Treatment of Cancer (EORTC)
 - National Cancer Institute (NCI) of the U.S.
 - National Cancer Institute of Canada Clinical Trials Group
- Review of 4000 patients for tumor response
- Recommendation to simplify response evaluation
- 1999: Criteria was publicly presented/accepted the American Society for Clinical Oncology meeting
- 2000: Published in *Journal of the National Cancer Institute* in 2000
- Intended for solid tumor response assessment in Phase II clinical trials but is actually being used for response assessment in all Phases

RECIST Terminology

To understand RECIST rules, you need to understand the following terms:

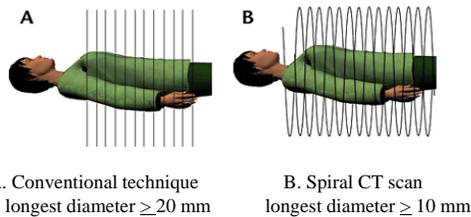
- Measurable disease
- Nonmeasurable disease
- Target lesion
- Non-target lesion

The next several slides will provide definitions.

Measurable Disease

- Disease which has at least 1 lesion that can be accurately measured in at least one dimension using calipers or ruler
- Measurement must be at least 20 mm using conventional techniques or 10 mm using spiral CT scan

Measurable Lesions



Non-measurable Disease

- Non-measurable disease is all other lesions, < 20 mm/10mm
- Includes:
 - Bone lesions
 - Leptomeningeal disease
 - Ascites
 - Pleural/pericardial effusion
 - Inflammatory breast disease
 - Cystic lesions

Target Lesions

- Chosen, measured, and recorded at baseline
- May include all measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, which represent all involved organs (e.g.: disease in lung, liver and brain – select lesions from all 3 sites if size appropriate)
- Selected on the basis of their size and suitability for accurate repeated measurements
- If there is a single measurable lesion, the lesion carcinoma status should be confirmed with cytology

Non-Target Lesions

- Any lesion or site of disease not classified as a target lesion (e.g.: pleural effusion, 5 mm lung nodule)
- Measurement of the lesions is not required
- Required to be identified and recorded at baseline
- For follow-up, non-target lesions are noted as either present or absent

Summary Table

Target lesions:

- Measurable lesions
- Maximum 5 per organ
- Maximum 10 lesions total
- Representative of all involved organs

Non-target lesions:

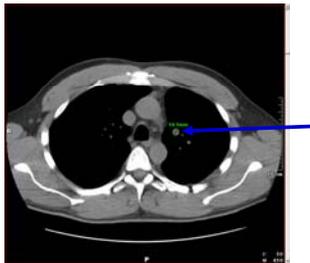
- All other lesions
- Measurements are not required (present/absent)

Imaging and RECIST...

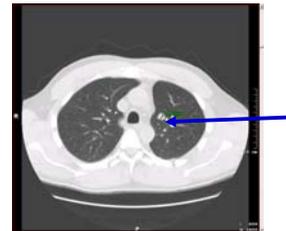
- Window settings refer to the brightness of the image. Window settings can be adjusted to accentuate various anatomical structures.
- Consistency is important when following these lesions over time, as measurements should be performed using the same window setting on each follow-up imaging study



This is an example of a chest CT, shown with chest windows. Note that the structures in the mediastinum and the borders on the lesion in the L lung can be easily identified. The L lung lesion measurement is 10.5 mm.



This is the same CT image, shown with lung windows. The mediastinal structures are more difficult to identify. The lesion measurement differs using this window (11.8), which reinforces the need to be consistent with windows when reviewing images for response.



... Imaging and RECIST ...

- All images in a series should be reviewed for new disease rather than reviewing selected target lesion images only
- Oral contrast to help differentiate the bowel from other soft tissue in the abdomen
- MRI scans may be used to identify target lesions, perform lesion measurements, and follow the lesions over time, although CT is the preferred modality of choice.
 - Recommended that ideally the same MRI scanner be used to obtain repeat images and the same anatomic place when following lesions over time using MRI images

... Imaging and RECIST ...

- Clinical examination may be used to follow superficial lesions over time.
 - Recommended that skin lesion assessment include taking a lesion color picture with a ruler to document the size of the lesion



...Imaging and RECIST

- Ultrasound examinations may be used to perform superficial target lesions measurements, such as subcutaneous lesions and thyroid
 - Should not be used to follow deeper lesions
- Chest x-ray may be used to identify, measure, and follow lesions over time, as long as the lesion borders are clearly defined and surrounded by aerated lung.
 - CT scanners are readily available and are the preferred imaging modality since CT images can also be used to follow mediastinal and thoracic wall lesions.

Response Assessment

Response assessment using RECIST 1.0 involves determining:

- target lesion response
- non-target lesion response
- appearance of new lesions

Target Lesion Response

- **Complete Response (CR)**
 - All target lesions gone
- **Partial Response (PR)**
 - $\geq 30\%$ decrease from baseline
- **Progressive Disease (PD)**
 - $\geq 20\%$ increase from smallest sum of longest diameter recorded since treatment started (best response)
- **Stable Disease (SD)**
 - Neither PD nor PR

Non-target Lesion Response

- **Complete Response (CR)**
 - All non-target lesions gone
 - Tumor markers to normal levels
- **Stable Disease (SD)**
 - Persistence of ≥ 1 non-target lesion
 - Tumor marker level elevated
- **Progressive Disease (PD)**
 - Enlargement of non-target lesions

Overall Response Table

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Lesion Re-evaluation

- Evaluating the frequency of response assessments is listed in the protocol
- If confirming a response:
 - Repeat assessment in 4 weeks for PR or CR
 - Repeat assessment in 6-8 weeks for SD

Calculation of Target Lesions Sum

- Add target lesion measurements together = current target lesion sum
- Divide current sum by baseline sum, subtract 1, multiply by 100 = % change from baseline
- Substitute best response sum for baseline sum to calculate % change from best response
- The next several slides illustrates an example of how to use the formula above to measure a set of target lesions.

Longest Target Lesion Diameter (cm): BL & #1

Lesion	BL	#1
Rt.Lung #1	3	2
Rt.Lung #2	2.5	2
Lt liver lobe	6	5
Rt Liver lobe	2.5	2
Total Length	14	11
% Change		-21%
Disease Status		SD

- $11/14 = 0.79$
 - $0.79 - 1 = (-0.21)$
 - $(-0.21) \times 100\% = -21\%$
- Not 30% decrease = SD

Longest Target Lesion Diameter (cm): BL, #1, #2

Lesion	BL	#1	#2
Rt.Lung #1	3	2	2
Rt.Lung #2	2.5	2	2
Lt liver lobe	6	5	3
Rt Liver lobe	2.5	2	2
Total Length	14	11	9
% Change		-21%	-36%
Disease Status		SD	PR

- $9/14 = 0.64$
 - $0.64 - 1 = (-0.35)$
 - $(-0.35) \times 100\% = -36\%$
- PR = > 30% decrease

Longest Target Lesion Diameter (cm): BL, #1, #2, #3

Lesion	BL	#1	#2	#3
Rt.Lung #1	3	2	2	2
Rt.Lung #2	2.5	2	2	2
Lt liver lobe	6	5	3	3
Rt Liver lobe	2.5	2	2	2
Total Length	14	11	9	9
% Change		-21%	-36%	-36%
Disease Status		SD	PR	PR

- $9/14 = 0.64$
 - $0.64 - 1 = (-0.35)$
 - $(-0.35) \times 100\% = -36\%$
- PR = > 30% decrease

Longest Target Lesion Diameter (cm): BL, #1, #2, #3, #4

Lesion	BL	#1	#2	#3	#4
Rt.Lung #1	3	2	2	2	3
Rt.Lung #2	2.5	2	2	2	3
Lt liver lobe	6	5	3	3	5
Rt Liver lobe	2.5	2	2	2	2
Total Length	14	11	9	9	13
% Change		-21%	-36%	-36%	+44%*
Disease Status		SD	PR	PR	PD

- $13/9 = 1.44$
 - $1.44 - 1 = (0.44)$
 - $(0.44) \times 100\% = 44\%$
- PD = > 20% increase from nadir
- Best Response = PR

* Change from nadir

RECIST documentation

- Ideally all radiology reports should include tumor measurements but this may not be done using RECIST.
- Response needs to be assessed in clinic to make a decision of therapy continuation, so measurements should be documented at that time.
- CRIS has RECIST documentation flowsheet

Issue Since RECIST 1.0

Several issues have been identified with RECIST version 1.0 including:

- Where 10 lesions needed?
- Was confirmation needed?
- How to assess PD in subjects with non-measurable disease?
- Were lymph nodes being adequately assessed?
- Should functional imaging be used instead of anatomical imaging?

RECIST Version 1.1

- Working group call together again CTG
- Use evidence-based approach:
 - Literature
 - Data analysis
- Proposed changes distributed for comments
- Revised RECIST 1.1 published January 2009



New response evaluation criteria in solid tumours:
Revised RECIST guideline (version 1.1)

E.A. Eisenhauer^{a,*}, P. Therasse^b, J. Bogaerts^c, L.H. Schwartz^d, D. Sargent^e, R. Ford^f, J. Dancey^g, S. Arbuck^h, S. Gwytherⁱ, M. Mooney^j, L. Rubinstein^k, L. Shankar^l, L. Dodd^l, R. Kaplan^l, D. Lacombe^e, J. Verweij^g

- The next several slides will highlight the changes in RECIST version 1.1, but for more details, review the article and the resource listed below:
 - <http://www.eortc.be/recist/> (link to publications and presentation)
 - <http://www.recist.com/>
 - http://ctep.cancer.gov/protocolDevelopment/docs/recist_measurement_of_effect.doc (link to word document containing protocol templated language used for CTEP sponsored trials, but also can be used for CCR protocols)

What HAS NOT Changed

- Measurable lesions still longest diameter
- Tumor burden still sum of diameters
- Categories of response:
 - CR
 - PR
 - SD

What HAS Changed

- Assessment of tumor burden
- Assessment of lymph nodes
- Confirmation of response
- Clarification of Progressive Disease
- Clarity regarding new lesions
- Imaging guidance

Overview of Differences Between RECIST 1.0 and 1.1

RECIST 1.0

- Target lesion max of 10 (5/organ)
- Long axis measure for LN, no normal defined
- PD = $\uparrow 20\%$
- Non-measurable PD = unequivocal
- Confirmation required

RECIST 1.1

- Target lesion max of 5 (2/organ)
- Short axis measure for LN, normal is < 10 mm
- PD = $\uparrow 20\% + 5$ mm absolute \uparrow
- Non-measurable PD = impact on overall disease burden
- Confirmation required only if response 1^o endpoint
- New lesions
- FDG-PET

Assessment of Tumor Burden

- Minimum size of measurable non-nodal lesions
 - CT scan 5 mm slice: measurable ≥ 10 mm
 - CT scan > 5 mm slice: measurable is 2x slice thickness
- Up to 5 measurable lesions (2/organ)

Assessment of Lymph Node

- Lymph nodes are measured on short axis
- To be a target lesion, lymph node has to be ≥ 15 mm
- To be a non-target lesion, lymph node has to be <15 mm
- If lymph node is considered normal if <10 mm
 - Implication for response assessment
 - If residual nodes <10mm, response is a CR, not a PR as with version 1.0

Clarification of Disease Progression

- Still $\uparrow 20\%$ in sum of target lesions PLUS a 5 mm absolute \uparrow over lowest sum
- Guidance on “unequivocal progression” of non-measurable/non-target lesions
 - Overall status of PD and therapy should stop
 - Magnitude of \uparrow should be substantial
 - Comparable to \uparrow that would be PD for measurable disease

Confirmation of Response

- If response is primary endpoint (e.g., Phase II), confirmation IS required
- If response is secondary endpoint (e.g., RCT w/PFS or OS): confirmation IS NOT required
 - Control arm provides ability to interpret results

Clarification of New Lesions

- Must be unequivocal and not attributed to different scanning technique or non-tumor
- When in doubt, continue to treat and repeat
- If scan showing new lesions is of anatomical region which wasn't included in BL, it is still PD

Imaging Guidance: FDG-PET

- “-” FDG-PET at BL and “+” at follow-up = PD
- No FDG-PET at BL and “+” at follow-up:
 - PD: corresponds to new site in CT
 - Equivocal: no new site on CT. Repeat CT and if new sit, PD date is that of initial “+” FDG-PET
 - Not PD: corresponds to pre-existing site on CT that is not progressing

Response Assessment

- Response assessment using RECIST 1.1 involves determining:
 - target lesion response
 - non-target lesion response
 - appearance of new lesions
- Best response is based on if there are measurable disease or just non-measurable disease.
- The next few slides will describe the response definitions and overall response assessments.

Target Lesion Response

- **Complete Response (CR)**
 - Disappearance of all target lesions
 - Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
- **Partial Response (PR)**
 - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
- **Progressive Disease (PD)**
 - At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).
 - In addition to the relative increase of 20%, sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD)**
 - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Non-target Lesion Response

- **Complete Response (CR)**
 - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
 - Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD**
 - Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
- **Progressive Disease (PD)**
 - Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions.
 - *Unequivocal progression* should not normally trump target lesion status.
 - It must be representative of overall disease status change, not a single lesion increase.

Best Response for Patients with Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	≥4 wks. Confirmation**
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
 ** Only for non-randomized trials with response as primary endpoint.
 *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
 Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Best Response for Patients with Non-measurable Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

References

- James, K., Eisenhauer, E., Christian, M., Terenziani, M., Vena, D., Muldal, A., and Therasse, P. (1999). Measuring response in solid tumors: unidimensional versus bidimensional measurement. *Journal of the National Cancer Institute*, 91, 523-528.
- Therasse, P., Arbuck, S., Eisenhauer, E., Wanders, J., Kaplan, R., Rubinstein, L., Verweij, J., Van Glabbeke, M., van Oosterom, A., Christian, M., and Gwyther, S. (2000). New guidelines to evaluate the response to treatment in solid tumors. *Journal of the National Cancer Institute*, 92, 205-216.
- Eisenhauer, E., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., et al. (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European Journal of Cancer*, 45, 228-247.

Evaluation

Please complete the [evaluation form](#) and fax to Elizabeth Ness at 301-496-9020.



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