

RECIST 1.1

Criteria Handout



Medical Imaging

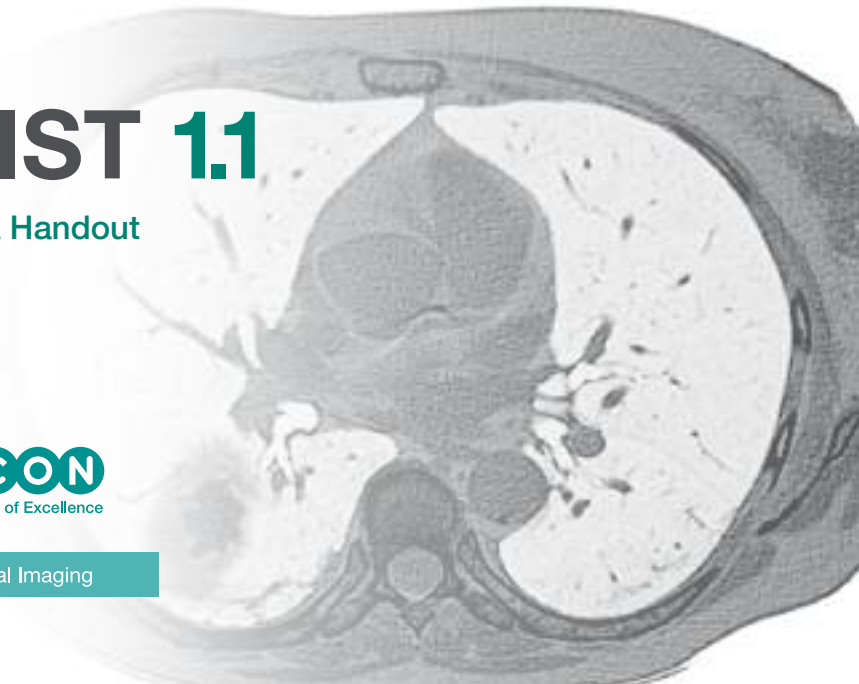


Table of Contents:

Basic Paradigm	3
Image Acquisition	4
Measurable Lesions	5
Non-Measurable Lesions	6
Special Lesion Types	7
Baseline Lesion Burden.....	8
Target Lesions	9
Baseline Documentation	10
Lesions with Prior Local Treatment.....	11
Evaluating Response at Each Timepoint	12
Target Lesion Evaluation.....	13–14
Missing Assessments and Non-evaluable Designation	15
Non-Target Lesion Evaluation.....	16
New Lesions.....	17
FDG-PET	18
Recurrence of Lesions	19
Evaluation of Overall Timepoint Response for Patients with Measurable Disease at Baseline.....	20
Evaluation of Overall Timepoint Response for Patients without Measurable Disease at Baseline.....	21
Confirmation.....	22
What Has Changed: RECIST 1.0 – RECIST 1.1.....	23
Modifications and Variants	24
References	25

Basic Paradigm

- Assess at baseline
 - Look for measurable lesions
 - Select target and non-target lesions
 - Measure target lesions
 - Add up to get tumor burden
- Treat patient
- Follow-up evaluation
 - Measure target lesions
 - Assess non-target lesions and look for new lesions
 - Calculate timepoint response

Image Acquisition

- CT
 - Slice thickness ≤ 5 mm if possible, contiguous
 - IV and oral contrast used (3-phase liver if appropriate)
 - Field of view adjusted to body habitus (include the whole body, out to the skin)
- MRI
 - Axial T1 and T2, axial T1 post contrast
 - ≤ 5 mm contiguous slices if possible
 - Use the same machine for all timepoints
- PET/CT
 - Not required, but may be useful for assessment of new lesions on future timepoints (see page 18)
 - CT portion of PET/CT is usually of lower quality, and should not be used instead of dedicated diagnostic CT. If the CT is of high quality, with oral and IV contrast, use with caution. Additional information from PET may bias CT assessment.
 - Use the same machine for all timepoints
- Calipers – Hard to use reproducibly
 - Include ruler in photograph for skin lesions
- Chest x-ray (CXR) – Use CT instead (if possible)
- Ultrasound – Not reproducible

Measurable Lesions

- Tumor ≥ 10 mm in longest diameter (LD) on an axial image on CT or MRI with ≤ 5 mm reconstruction interval
 - If slice thickness > 5 mm, LD must be at least 2 times the thickness
- Tumor ≥ 20 mm LD by chest x-ray (if clearly defined & surrounded by aerated lung); CT is preferred (even without contrast)
- Tumor ≥ 10 mm LD on clinical evaluation (photo) with electronic calipers; skin photos should include ruler
 - Lesions which cannot be accurately measured with calipers should be recorded as non-measurable
- Lymph nodes ≥ 15 mm in short axis on CT (CT slice thickness recommended to be no more than 5 mm)
- Ultrasound cannot be used to measure lesions

Non-Measurable Lesions

- All other definite tumor lesions
 - Masses <10 mm
 - Lymph nodes 10-14 mm in short axis
 - Leptomeningeal disease
 - Ascites, pleural or pericardial effusion
 - Inflammatory breast disease
 - Lymphangitic involvement of skin or lung
 - Abdominal masses or organomegaly identified by physical exam which cannot be measured by reproducible imaging techniques
- Benign findings are NEVER included. Also, do not include equivocal (“cannot exclude”) findings

Special Lesion Types

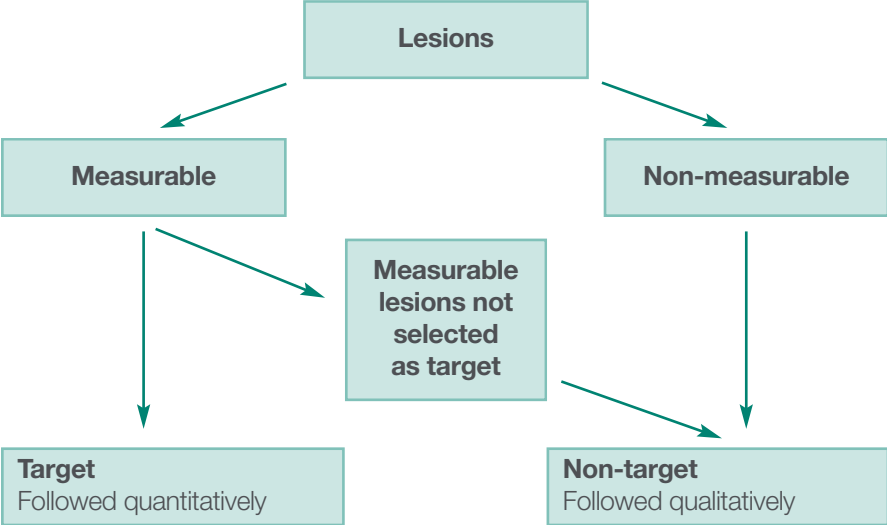
● Bone Lesions

- NMBS, PET scans & plain films can be used to confirm the presence or disappearance of bone lesions, but NOT for measurement
- Bone lesions with identifiable soft tissue components seen on CT or MR can be measurable if the soft tissue component meets the definition above
- Blastic bone lesions are unmeasurable

● Cystic Lesions

- Simple cysts are not included as lesions
- Cystic metastases may be selected, but prefer to use non-cystic lesions as “target”
- Clarify with sponsor as to their acceptability before study start

Baseline Lesion Burden



Target Lesions

- Choose up to 5 lesions
 - Up to 2 per organ
- Add up longest diameters (LD) of non-nodal lesions (axial plane)
- Add short axis diameters of nodes
- This is the “sum of diameters”

Baseline Documentation

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

● Target Lesions

- A maximum of five (5) target lesions in total (up to two (2) per organ)
- Select largest reproducibly measurable lesions
- If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be

● Non-Target Lesions

- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”)



Lesions with Prior Local Treatment

- Lesions in previously irradiated areas (or areas treated with local therapy) should not be selected as target lesions, unless there has been demonstrated progression in the lesion
- Conditions in which these lesions would be considered target lesions should be defined in study protocols

Evaluating Response at Each Timepoint

- 1 Measure previously chosen target lesions
 - Even if they are no longer the largest
- 2 Evaluate all previously identified non-target lesions
- 3 Look for new definite cancer lesions
- 4 Combine lesion responses into timepoint response using appropriate table

Target Lesion Evaluation

- Measure LD (axial plane) for each non-nodal target lesion
- Measure short axis for target lymph nodes
- Add these measurements to get the sum of diameters
- If too small to measure, a default value of 5 mm is assigned. If the lesion disappears completely, the measurement is recorded as 0 mm. If an accurate measurement can be obtained, use actual measurement even if smaller than 5 mm.
- Splitting or coalescent lesions
 - If a target lesion fragments into multiple smaller lesions, the LDs of all fragmented portions are added to the sum
 - If target lesions merge, the LD of the resulting merged lesion is added to the sum

Target Lesion Evaluation

Response	Definition
Complete Response (CR)	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
Progressive Disease (PD)	Sum of diameters increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The sum of diameters must also demonstrate an absolute increase of at least 5 mm. (Two lesions increasing from 2 mm to 3 mm, for example, does not qualify)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

Missing Assessments and Non-evaluable Designation

- If all lesions cannot be evaluated due to missing data or poor image quality the patient is inevaluable (NE) at that time point
- If only a subset of lesions can be evaluated at an assessment, the visit is also considered NE, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response
 - E.g. PD based on other findings

Non-Target Lesion Evaluation

Response	Definition
Complete Response (CR)	<ul style="list-style-type: none">■ Disappearance of all extranodal non-target lesions■ All lymph nodes must be non-pathological in size (<10 mm short axis).■ Normalization of tumor marker level
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)	Unequivocal progression of existing non-target lesions. (Subjective judgement by experienced reader)*

*Be cautious when calling progression based on non-target lesions. If target lesions are also present, there must be substantial worsening in non-target disease overall such that, even in presence of SD or PR in target disease, the disease burden has increased enough to merit discontinuation of therapy. A modest increase in non-target lesions is usually not sufficient to qualify for unequivocal progression status.

New Lesions

- Should be unequivocal and not attributable to differences in scanning technique or findings which may not be a tumor
 - Does not have to meet criteria to be “measurable”
- If a new lesion is equivocal, continue to next timepoint. If confirmed then, PD is assessed at the date when the lesion was first seen.
- Lesions identified in anatomic locations not scanned at baseline are considered new
- New lesions on US should be confirmed on CT/MRI

FDG-PET

● **FDG-PET can be used to help detect progression**

- A 'positive' FDG-PET scan lesion means one with uptake greater than twice that of the surrounding tissue on the attenuation corrected image.
- Negative PET at baseline and positive PET at follow-up: Progressive Disease (PD) based on a new lesion.
- No PET at baseline and positive PET at follow-up: If there is a corresponding new or growing lesion on CT, this is PD. If a later CT confirms appearance or growth of a lesion, the date of PD is the date of the initial positive PET scan.
- No PET at baseline and positive PET at follow-up: If there is a corresponding pre-existing lesion on CT that is stable, this is not PD.

Recurrence of Lesions

- For a patient with Stable Disease (SD)/Partial Response (PR), a lesion which disappears and then reappears will continue to be measured and added to the sum
 - Response will depend on the status of the other lesions
- For a patient with Complete Response (CR), reappearance of a lesion would be considered Progressive Disease (PD)

Evaluation of Overall Timepoint Response for Patients with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE*	No	PR
SD	Non-PD or NE*	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = Inevaluable

*When target lesions show SD/PR and some subset of non-target lesions is inevaluable, a careful decision must be made whether to call the overall response at this timepoint SD/PR or NE. This is based on whether the inevaluable lesions, if they showed growth, could cause an overall response of PD in the context of the other lesion responses seen. If the inevaluable non-target lesions comprise a significant proportion of the overall disease burden, the appropriate timepoint response is NE.

Evaluation of Overall Timepoint Response for Patients without Measurable Disease at Baseline

Non-Target	New	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal Progression	Yes or No	PD
Any	Yes	PD

**CR = Complete Response,
PD = Progressive Disease, NE = Inevaluable**

Confirmation

- Confirmation of Partial Response (PR)/Complete Response (CR) is only required for non-randomized trials where response is the primary endpoint
- In these trials, subsequent confirmation of PR with one interim time point of Inevaluable (NE) is acceptable

What Has Changed: RECIST 1.0 – RECIST 1.1

	RECIST 1.0	RECIST 1.1
Tumor Burden	10 Targets (5 per organ)	5 Targets (2 per organ)
Lymph Nodes	Measure like any other lesion	Measure short axis Defined normal size
PD Definition	20% increase in SLD	20% increase in sum of diameters 5 mm absolute increase
Non-measurable PD	“Unequivocal”	More details and examples
Confirmation	Required for PR and CR	Required in non-randomized trial with response as 1 ^o endpoint
New Lesions		Section on FDG-PET
Inevaluable Non-target Lesions	Forces timepoint NE	Does not force timepoint NE

Modifications and Variants

- RECIST is not set in stone
- Modifications for specific disease processes have been documented
- Modifications may be made to meet the needs of individual trials

References

Print Version:

“Response assessment in solid tumours (RECIST): Version 1.1 and Supporting Papers.” *European Journal of Cancer*, Volume 45, Issue 2 Jan. 2009: 225-310. Print.

Online Version: <http://www.eortc.be/Recist/Default.htm>



A Symbol of Excellence

Medical Imaging

To learn more about how ICON Medical Imaging
will benefit your clinical trial, contact us:

Headquarters Office

2800 Kelly Road
Suite 200
Warrington, PA 18976, USA
Telephone: +1 267 482 6300

European Office

Zeltweg 46
CH-8032 Zurich
Switzerland
Telephone: +41 44 582 41 00

Email: imaging@iconplc.com