



RECIST Overview

Introduction

- What is RECIST?
- RECIST Endpoints in << enter study name >>
- Definitions
 - ◆ Measurable & non-measurable disease
 - ◆ Target lesions, Non-target lesions, New Lesions
- Methods of Assessment
- Schedule of Assessments
- Evaluation of tumour response
- Minimum Source Data Requirements
- Special cases
- Summary

What is RECIST?

Response Evaluation Criteria In Solid Tumours

- A set of published rules that define when cancers improve (Respond), stay the same (Stable) or worsen (Progress) during treatment*
- Standardises solid tumour response evaluation => uniform reporting of clinical study outcomes

***Therasse *et al*; New Guidelines to Evaluate the Response to Treatment in Solid Tumours, J Natl Cancer Inst 2000; 92 (3): 205-216**


Optional slide

<<Enter Study name or number>>
RECIST Study Endpoints

- Primary endpoint:
 - ◆ Progression Free Survival (PFS)

- Secondary endpoints:
 - ◆ Objective response (CR+PR)
 - ◆ Clinical benefit (CR+PR+SD \geq 24 weeks)
 - ◆ Duration of response

Definitions

- Measurable lesions
 - Non-measurable lesions
 - Target lesions
 - Non-target lesions
 - New lesions
- 

Definitions

➤ Measurable lesions

- ◆ Can be accurately measured in at least one dimension
- ◆ Longest diameter must be:
 - ✦ ≥ 20 mm with conventional techniques (see methods of assessment)
 - ✦ ≥ 10 mm with spiral CT scan

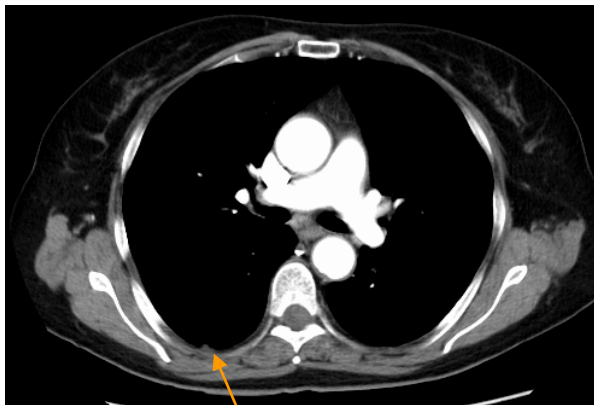


Internal iliac adenopathy

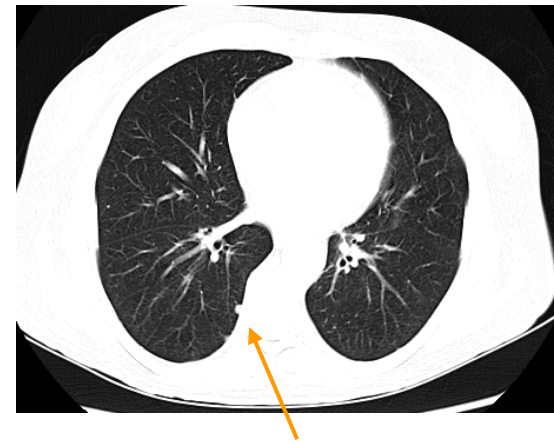
Definitions

➤ Non-measurable lesions

- ◆ All other lesions, including:
 - ★ Small lesions < 20 mm with conventional techniques or < 10 mm with spiral CT
 - ★ Bone lesions
 - ★ Previously irradiated lesions
 - ★ Ascites, pleural / pericardial effusion, cystic lesions etc



**Sub-pleural nodule
(small lesions)**



Definitions

➤ Target lesions

- ◆ Selected at baseline
- ◆ All measurable lesions
 - ★ minimum of 1, maximum of 10
 - ★ no more than 5 per organ
 - ★ representative of all involved organs
- ◆ Selection based on size and suitability for accurate repeated measurements
- ◆ Unidimensional measurements (longest diameter) required for each target lesion at all assessed time points

Definitions

➤ Non-target lesions

- ◆ Selected at baseline
- ◆ All other lesions that are not selected as target lesions
 - ★ Excess measurable lesions (eg when 10 have already been identified as Target lesions)
 - ★ All non-measurable lesions
- ◆ Measurements are not required

Definitions

➤ New lesions

- ◆ Any lesion present on a follow-up tumour assessment that was not present at baseline

Methods of Assessment

Target Lesions	Non-target Lesions & New Lesions
<ul style="list-style-type: none">➤ Recommended<ul style="list-style-type: none">◆ CT (preferred)◆ MRI ➤ Accepted<ul style="list-style-type: none">◆ Clinical examination with digital photography + ruler◆ Chest X-ray	<ul style="list-style-type: none">➤ Recommended<ul style="list-style-type: none">◆ CT (preferred)◆ MRI ➤ Accepted<ul style="list-style-type: none">◆ Clinical examination◆ X-ray (plain and chest)◆ Ultrasound◆ Endoscopy

Methods of Assessment

- Important to use same imaging methods to follow lesions
 - ◆ Baseline method of assessment must be followed throughout the trial
 - ◆ Change in method of assessment will invalidate the patients results
- Bone scan, PET scan, mammography, angiography, tumour markers and cytology/histology are not acceptable methods as part of RECIST framework

Schedule of Assessments

<<Refer to study plan in protocol>>

- Baseline tumour assessment
 - ◆ Within 28 days before start of treatment

- Follow-up tumour assessments
 - ◆ Assessments of all TL and NTL performed every X weeks (+/- Y weeks) from randomisation date, even if a patient has a complete response or partial response
 - ◆ Until disease progression
 - ★ Even if study treatment discontinued prior to disease progression, unless patient withdraws consent
 - ★ Even if patient receives another subsequent cancer therapy

- Unscheduled tumour assessments

Baseline tumour assessment

- Baseline tumour assessments must be performed as close as possible to the beginning of treatment
 - ◆ Within 28 days before start of treatment
 - ◆ Important that timing of screening assessments are planned appropriately
- Identify and record all sites of disease
- Select and record Target and Non-target lesions in source documentation
 - ◆ The longest diameter (LD) of each TL is measured => baseline sum of LD
 - ◆ Lesion measurements not required for NTLs

Follow-up tumour assessments (1)

- At each protocolled RECIST visit, assessments are performed to assess response of TL, NTL and the presence of any new lesions

- Target Lesions
 - ◆ Continue to track and measure the same target lesions even
 - ◆ The sum of LDs at each follow up visit should then be compared to
 - ✦ Baseline sum of LD
 - ✦ Smallest sum of LD previously recorded
 - ◆ A TL response for each visit is determined depending on changes in the sum of the LD

Follow-up tumour assessments (2)

➤ Non-target lesions

- ◆ Continue to assess all of the NTLs
- ◆ Provide an overall assessment of the NTL response

➤ New Lesions

- ◆ Any lesion that was not present at baseline
- ◆ If there is doubt over the presence of a new lesion, continue treatment and reassess at the next tumour assessment
 - ★ If presence of new lesion is clear at this next visit record the date and details of new lesion at the earlier visit
 - ★ If no evidence of a new lesion at this next visit then continue treatment until evidence of progression

Unscheduled Tumour Assessments

- An unscheduled visit is one which is performed outside the scheduled tumour assessment time window
 - ◆ If an unscheduled assessment occurs and the patient has not progressed, the next scheduled assessment must be performed at the planned time according to the study plan
 - ◆ If an unscheduled assessment occurs and the patient has progressed, no further RECIST assessments are required
- Tumour assessments must be performed in accordance with visit schedule to avoid bias

Missed Visits

- I've missed my last scheduled assessment, should I perform a scan now or wait for the next scheduled assessment?
 - ◆ It is imperative that the next scheduled assessment (and all subsequent assessments) are performed in accordance with the protocol schedule
 - ◆ In addition, it is left to Investigators discretion whether to perform a scan now in order to assess the patient's disease status

Adherence to Visit Schedule Vital to Avoid Bias

- Unlike date of death, date of progression only known within an interval
 - E.g. Patient hadn't progressed at wk 18 but had progressed by wk 24
- Bias is introduced if one arm is assessed more frequently than another*
 - Progression likely to be detected earlier in arm with frequent assessments
 - ⇒ **Adherence to visit schedule essential**

* Williams G, He K, Chen G, Chi G, and Pazdur R. Operational bias in assessing time to progression (TTP). Proc Am Assoc Cancer Res 2002; abst 975

Evaluation of tumour response



Target Lesion Visit Response

Complete Response: (CR)	All TL have disappeared completely (diameters=0)
Partial Response: (PR)	Sum of LD of the TLs have shrunk by $\geq 30\%$ compared to sum of LD from baseline
Progressive Disease: (PD)	Sum of LD of the TLs have grown by $\geq 20\%$ compared to smallest sum of LD previous recorded (Note: not necessarily baseline)
Stable disease: (SD)	Neither sufficient shrinkage for PR or growth for PD (ie Conditions of PD, CR and PR are not satisfied)
Not Evaluable: (NE)	Any missing TL data

Non-target Lesion Visit Response

- Complete Response:** The disappearance of all NTLs
(CR)
- Progressive Disease:** Unequivocal progression in NTLs may be due to an important progression in one lesion only or in several lesions. In all cases the progression **MUST** be clinically significant for the physician to consider changing (or stopping) therapy
(PD)
- Incomplete response :** The persistence of one of more NTLs
/Stable disease (IR/SD)
- Not Applicable:** No NTLs at baseline
(NA)
- Not Evaluable:** As assessed by Investigator (eg if insufficient non-target lesion assessments performed to be able to provide an overall NTL response assessment)
(NE)

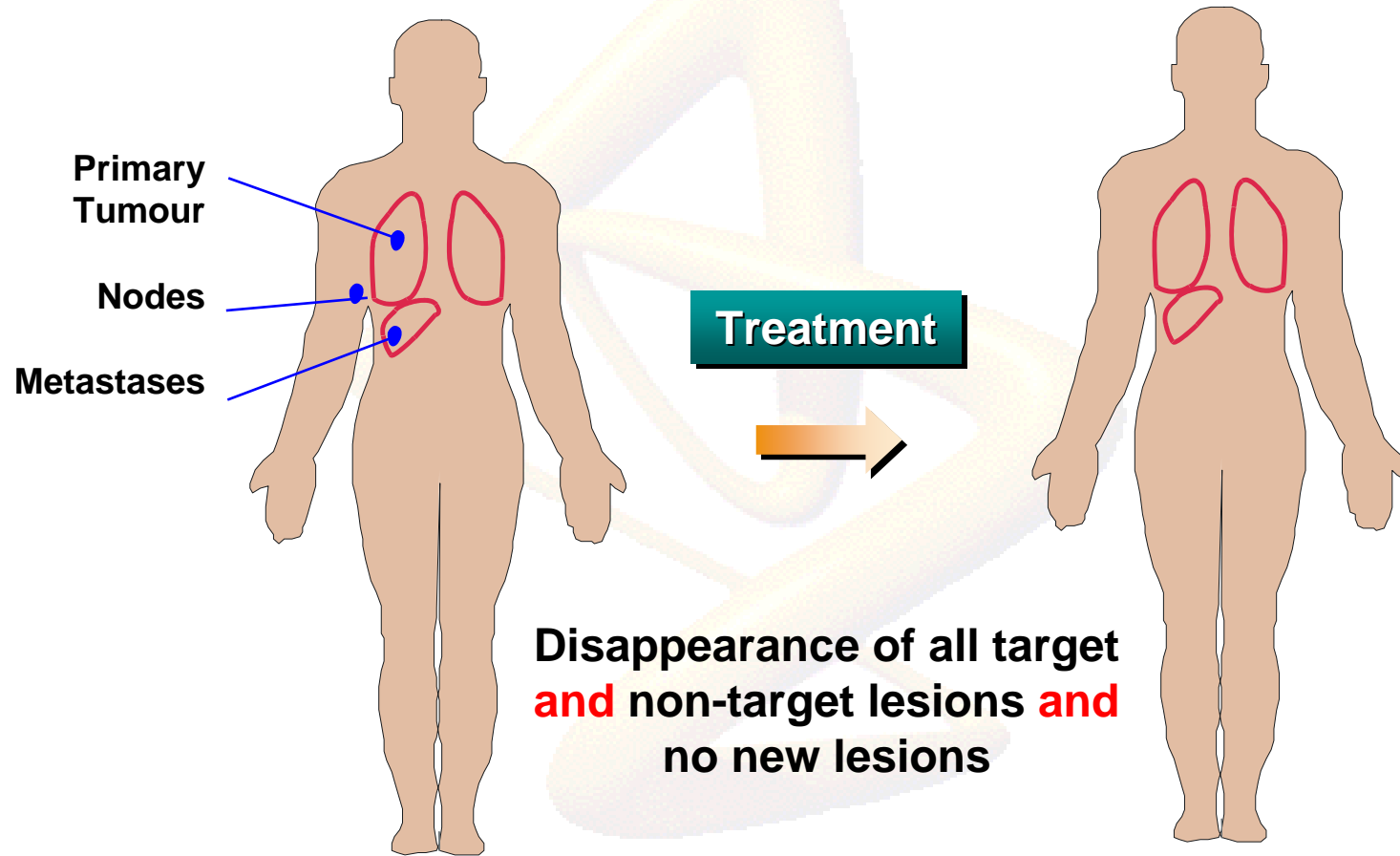
New Lesion Visit Response

- The presence or absence of new lesions must be recorded at each tumour assessment visit
- Detection of a new lesion = progressive disease
- If in doubt, confirm presence before recording on CRF

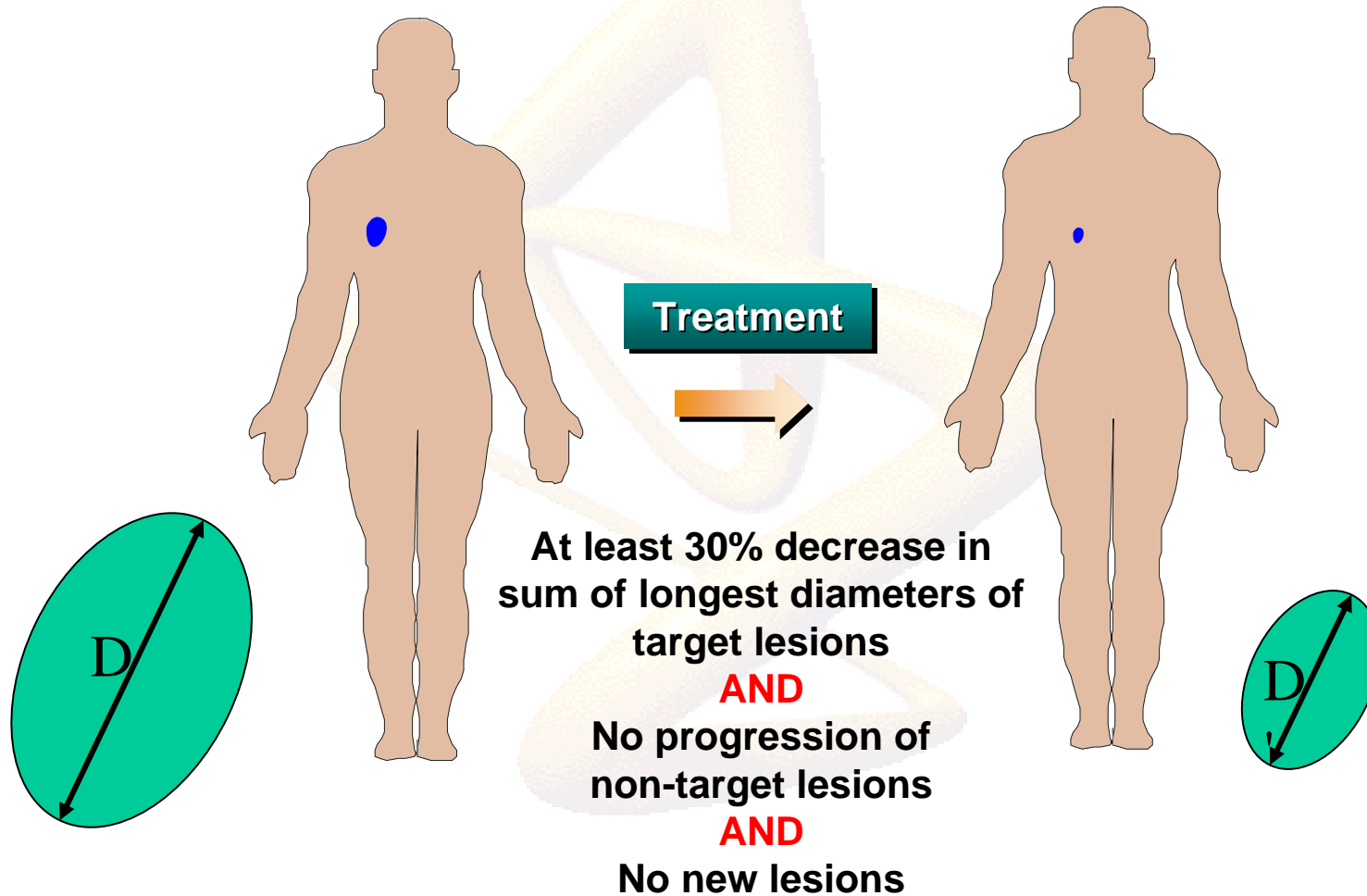
Response Calculation via eCRF

- To aid your assessment of response:
 - eCRF system calculates response of TLs
 - Combines TL response with your assessment of NTLs and presence/absence of new lesions
 - Calculates Overall Visit Response as shown on following slides

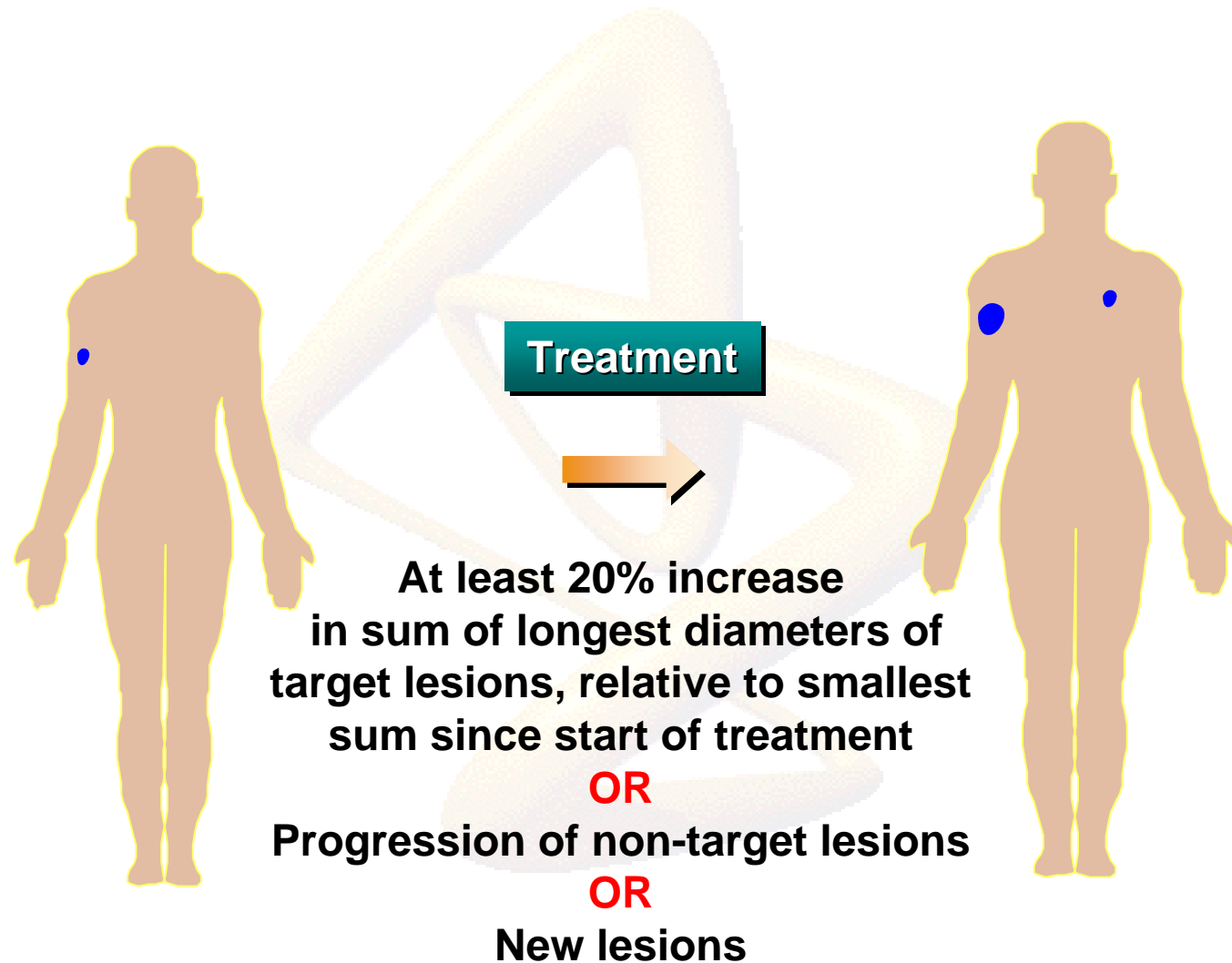
Complete Response



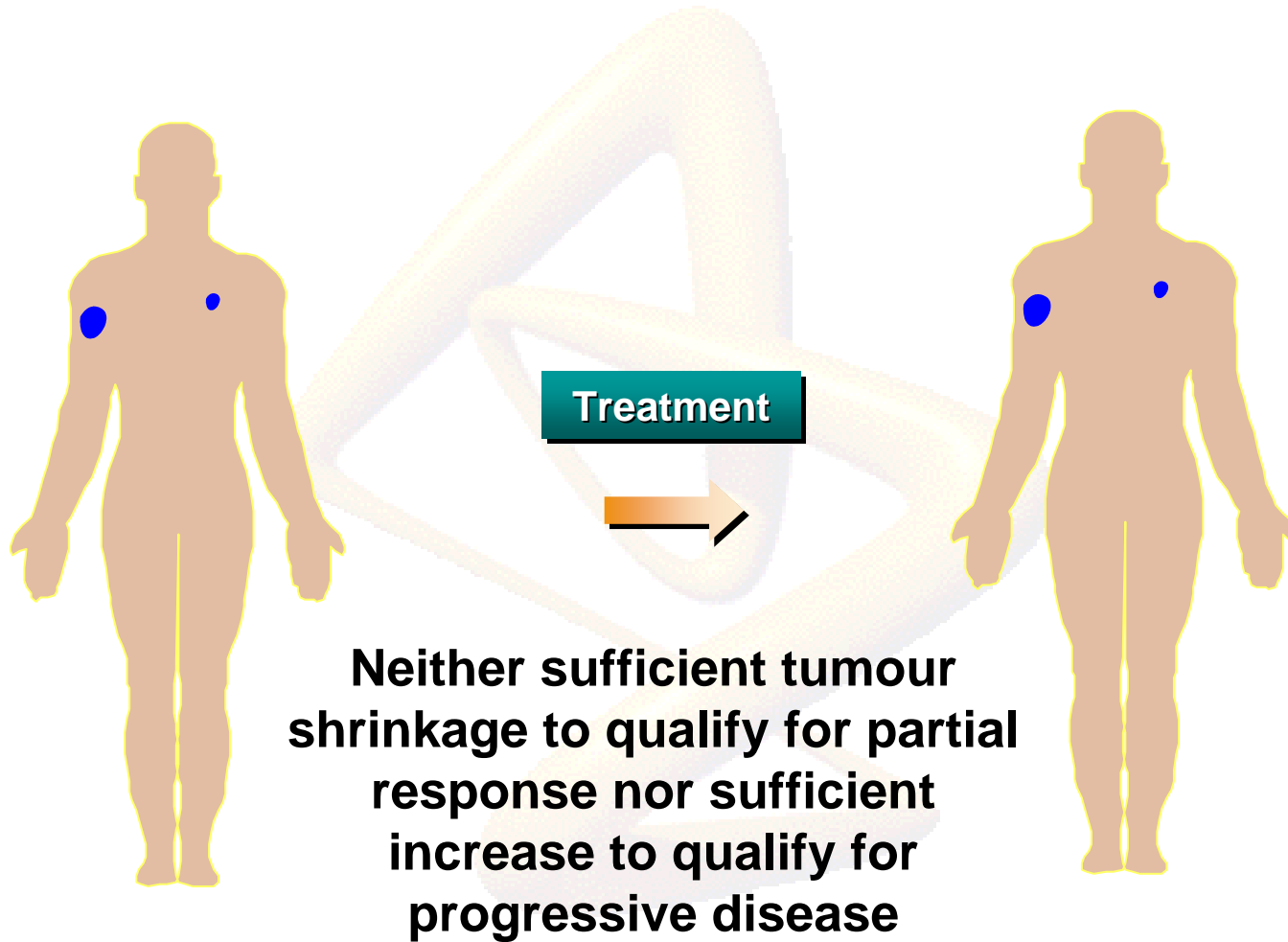
Partial Response



Progressive Disease



Stable Disease



Overall Visit Response

- Combination of TL response, NTL response and presence / absence of new lesions
- RECIST overall visit response categories
 - ◆ Complete response (CR)
 - ◆ Partial response (PR)
 - ◆ Stable disease (SD)
 - ◆ Progressive disease (PD)
 - ◆ Not Evaluable (NE)
- If patient has PD of TL, NTL or an appearance of a new lesion, the overall visit response will be PD (PD always overrides)
- If TL or NTL assessment is NE, then the overall assessment will also be NE unless there is clear evidence of progression eg a new lesion

Summary of Overall Visit Response

Target lesions	NTLs	New Lesions	Visit Response
CR	CR (or NA)	No	CR
CR	IR/SD	No	PR
PR	CR, IR/SD (or NA)	No	PR
SD	CR, IR/SD (or NA)	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NE	Non-PD	No	NE
Non-PD	NE	No	NE
Non-PD	Non-PD	NE (missing response)	NE

CR = complete response; PR = partial response; SD = stable disease; IR/SD = Incomplete Response/Stable disease; PD = progressive disease; NA = Not applicable; NE = not evaluable

Confirmation of Response

<<refer to protocol>>

- A responder is defined as a patient who has a confirmed CR or PR

- What do we mean by confirmed?
 - ◆ Initial overall visit response of CR or PR
 - ◆ Confirmation of response (overall visit response of CR or PR) at the next scheduled tumour assessment visit (no less than 4 weeks later)

- Why do we confirm responses?
 - ◆ To avoid overestimating the response rate observed

Minimum Source Data Requirements

- Target lesions and Non-target lesions at baseline and follow-up
 - ◆ Site and location
 - ◆ Date of assessment and method used
 - ◆ Any lesion interventions (eg irradiation, surgery)
 - ◆ Longest diameter measurements (target lesions only)
 - ◆ Reasons for any missing or non-evaluable assessments
 - ◆ Reasons for any inconsistencies between radiology report and patient's notes
- Details of any new lesions (site, location, date of assessment and method used)
- Overall assessment of Non-target lesion response
RECIST response calculated by Investigator
- Investigator's opinion of response

Local site management – key considerations

- How will imaging requisitions be flagged to Radiology for a RECIST assessment?
- Who will select the target and non-target lesions at baseline and how will they be documented / reported?
- What steps will be necessary to ensure that target and non-target lesions are followed up by the same type and method of assessment and documented / reported consistently?

Communication pathways between Investigator, Radiology and monitors are very important

Special Cases



Overview of common special cases

- Occasionally, it may be unclear how to arrive at a longest diameter
 - ◆ Lesions that become too large / small to measure
 - ◆ Lesions that disappear
 - ◆ Lesions that merge / split
 - ◆ Lesions that are irradiated during the trial
 - ◆ Bone lesions

Target Lesion too Large to Measure

- Target Lesion too large to measure
 - ◆ If a lesion becomes too large to measure during the trial, record the diameter above which it cannot be accurately measured and indicate that the lesion was too large to measure
 - ✦ eg If a lesion is too large to measure, but is known to be >150 mm, record LD as 150 mm on the CRF and indicate that this lesion has become too large to measure using box provided
 - ◆ A response of progressive disease will automatically be assigned in this instance

Target Lesion too Small to Measure

- Assigning measurements to lesions that are too small to measure
 - ◆ When tumours shrink in response to therapy it is possible for them to become too small to measure accurately
 - ◆ Record on the CRF the size below which the tumour cannot accurately be measured and indicate on the CRF that the lesion is too small to measure
 - ★ eg If <6 mm record diameter = 6 mm and indicate that this lesion is too small to measure, using the box provided

Target Lesions that Disappear

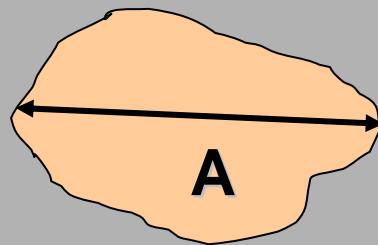
- If a target lesion disappears following therapy, record longest diameter = 0 mm
 - ◆ Note: Only record longest diameter = 0 mm if lesion has completely disappeared on all slices. If still visible, but too small to be accurately measured, see previous slide
 - ◆ Do not tick the 'too small to measure' box

Target Lesions that Disappear then Reappear

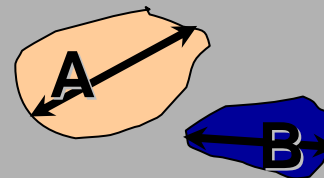
- If a TL is recorded as 0 mm at one visit then it should be recorded as 0 mm at all subsequent visits
- If at a subsequent visit a lesion is now present in the same location then there are two possibilities
 - ◆ The lesion had not truly disappeared but was too small to measure at the previous visit
 - ✦ The previous visit (where it was recorded as 0 mm) should be amended to follow the procedure for lesion too small to measure
 - ◆ If the lesion truly had disappeared then the appearance of a lesion in the same location is considered a new lesion and should be recorded as a new lesion on the CRF

Target Lesions that Split in Two

- The longest diameter of the two lesions should be measured, summed, and reported as one lesion
 - ◆ Example
 - ★ At baseline 3 target lesions
 - ★ At follow-up lesion 3 has split in two
 - ★ Measure both lesions and sum the longest diameters
 - ★ Record the sum in the space provided for lesion 3 on CRF



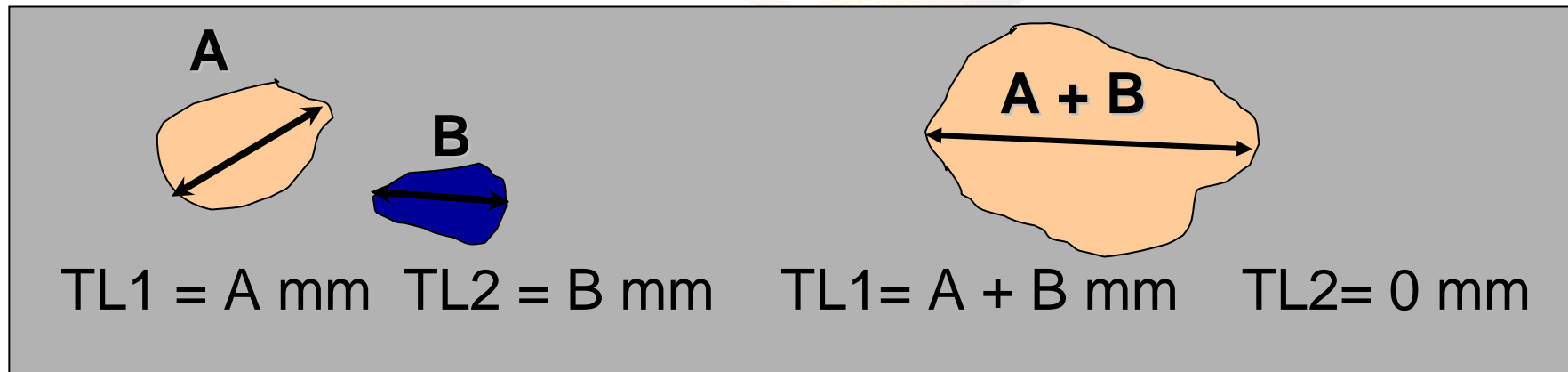
TL LD = A



TL LD = A + B

Two Lesions that Merge

- If two target lesions merge
 - ◆ eg Patient has two target lesions at baseline that merge at follow-up
 - ★ Measure and record longest diameter of merged lesions as lesion 1
 - ★ Record longest diameter = 0 mm for lesion 2



New Lesions

- People often try to record new lesions as a TL (if the new lesion is measurable) or include as part of the NTL assessment
 - ◆ Neither is correct
 - ◆ All TLs and NTLs should be identified at baseline and should capture all measurable and non-measurable disease at entry to the study
 - ◆ Any new lesions detected during the study should be recorded on the CRF as a “New Lesion”
 - ★ New lesions are indicative of progression

Irradiated Lesions

- At baseline, previously irradiated lesions are not considered measurable and should be assessed as NTLs
- If a TL is irradiated during the study the following procedure should be followed
 - ◆ Measurements should continue to be collected and recorded for the irradiated lesions
 - ◆ The CRF contains a check box asking if the lesion has had an intervention — this box should be marked from this visit onwards
 - ◆ The patient should still be followed until progression
 - ✦ If there is no evidence of progression patient can be assigned visit response of SD

Bone Lesions

- If patient has a bone lesion at entry which is covered by the protocolled scans (abdomen, chest and pelvis if clinically indicated) then this bone lesion should be recorded as a NTL at baseline and followed up at every RECIST visit
- If patient has a bone lesion outside of the protocolled scanning area then this does not need to be recorded as a NTL at baseline
 - ◆ Regular imaging is not required
 - ◆ If new or worsening symptoms occur then this should trigger additional imaging to be performed
 - ◆ Confirmation of disease progression via imaging should be recorded as a new lesion
 - ★ Confirmed by CT, MRI or X-ray

Summary

- RECIST used to standardise tumour response evaluation
- Baseline documentation of tumour burden in terms of Target and Non-target lesions
- Target lesions are selected on the basis of their size and suitability for accurate, repeated measurements
- Ensure all Target and Non-target lesions are followed up at each tumour assessment visit by the same methods and techniques used at baseline
- Tumour assessments must be performed in accordance with visit schedule to avoid bias
- All patients must be followed for progression even if:
 - ◆ Discontinued randomised treatment
 - ◆ Started another anti-cancer treatment



RECIST Imaging Methods

Imaging Based Evaluation

Response Evaluation Criteria In Solid Tumours (RECIST) are easily applicable criteria for measuring tumour response using CT, MRI and X-ray

➤ **Recommended**

- ◆ CT — conventional or spiral (preferable)
- ◆ MRI

➤ **Acceptable**

- ◆ X-ray

➤ **Not allowed**

- ◆ Ultrasound

CT Scans

- Definition — a computed tomography scan (CT scan, also called a CAT scan) uses computer-controlled X-rays to create images of the body
- Important characteristics
 - ◆ A CT scan is three-dimensional
 - ◆ Shows not only if a tumour is present, but roughly how deep it is in the body
 - ◆ A contrast agent may be given to more clearly show the boundaries between organs or between organs and tumours

CT Scans — Mode Of Action

Figure A : Conventional CT Scan

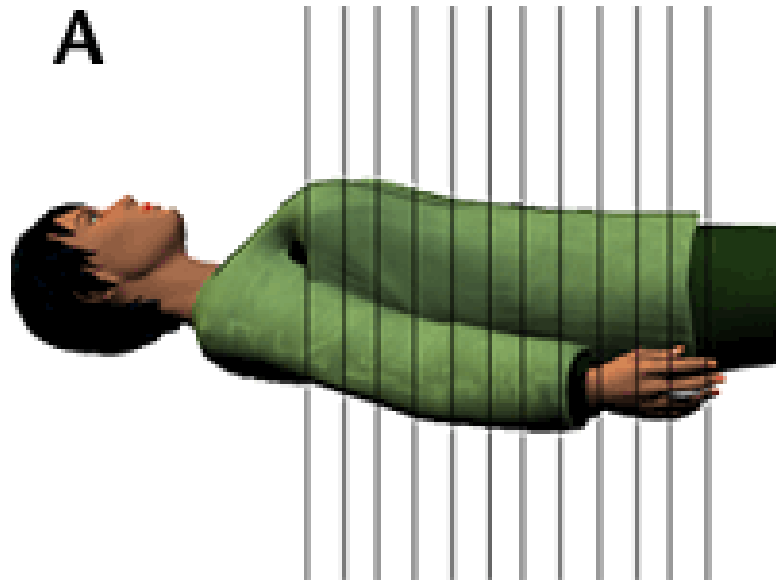
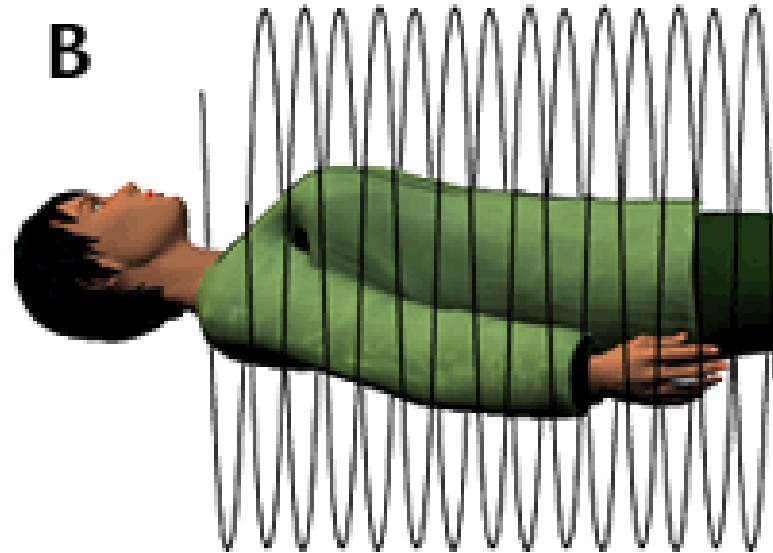


Figure B : Spiral CT Scan



Main Characteristics

➤ Spiral CT

- ◆ Takes continuous pictures of the body in a rapid spiral motion
- ◆ Uses a process called multi-slice or helical (spiral) scanning
- ◆ Acquires the data for the whole volume imaged in a single breath hold of about 20–30 seconds
- ◆ The minimum size of the lesion at baseline may be 10mm if images are reconstructed contiguously at 5mm intervals
- ◆ The standard in most hospitals

Main Characteristics

- Conventional CT
 - ◆ Conventional CT scans take pictures of slices of the body (like slices of bread)
 - ◆ Acquires the information only for the particular slice thickness scanned
 - ◆ The next slice thickness needs to be scanned before it can be imaged (can not scan the whole volume at once)
 - ◆ The minimum size of the lesion at baseline may be 20mm if images are reconstructed contiguously at 10mm intervals

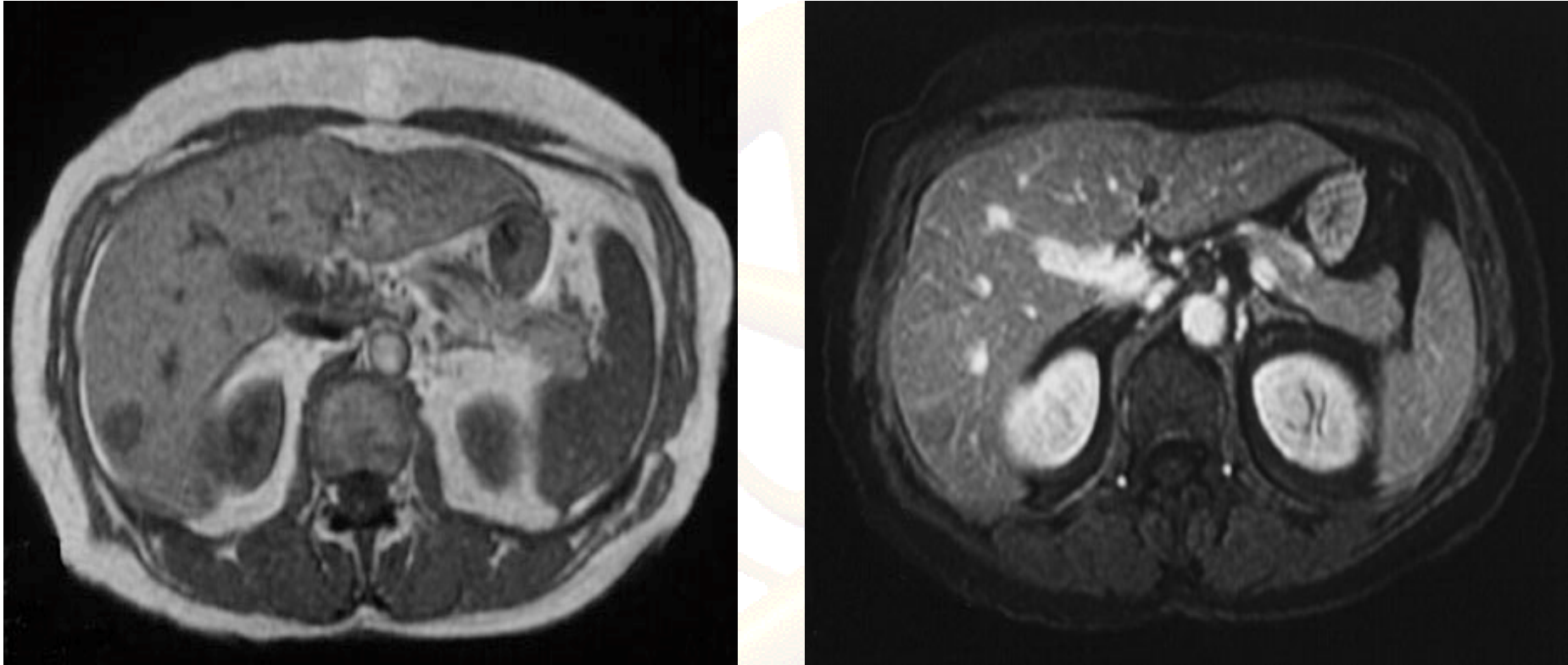
Advantages of Spiral vs Conventional CT

- Dramatically increased speed and effectiveness
- Improved lesion detection due to
 - ◆ Elimination of respiratory (motion) artefacts (single breath hold acquisition)
 - ◆ Ability to reconstruct overlapping images
 - ◆ Capability of optimising enhancement with i.v. contrast agent
 - ◆ Better visualisation of vascular lesions
- Rapid examination time
- Reduced radiation dose due to decreased exposure

Magnetic Resonance Imaging (MRI)

- Definition — Magnetic Resonance Imaging (MRI) uses radio waves in the presence of a strong magnetic field
- Important characteristics
 - ◆ Different tissues (including tumors) emit a more or less intense signal based on their chemical makeup, so a picture of the body organs can be displayed on a computer screen
 - ◆ MRI should not be the first choice for lung lesions assessment
 - ◆ If CT is contraindicated, MRI would be recommended for abdomen and non contrast enhanced CT for the chest
 - ◆ A contrast agent may be given to enhance the lesions

Magnetic Resonance Imaging (MRI)



(Left) MRI scan without contrast showing possible tumour in the liver. (Right) MRI scan of the same patient using contrast

X-Ray Imaging

- Definition — Images produced by X-rays are due to the different absorption rates of different tissues
 - ◆ Calcium in bones absorbs X-rays the most, so bones look white on a radiograph
 - ◆ Fat and other soft tissues absorb less and look grey
 - ◆ Air absorbs least, so lungs look black
 - ◆ Chest radiographs are often used for early cancer detection or to see if cancer has spread to the lungs
 - ◆ Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung

Important Points To Remember !!!

- CT is the imaging modality of choice
- Same imaging modality must be used throughout the study
- Different imaging techniques have different sensitivity
- Any given lesion may have different dimensions if measured with different modalities, therefore they are not interchangeable