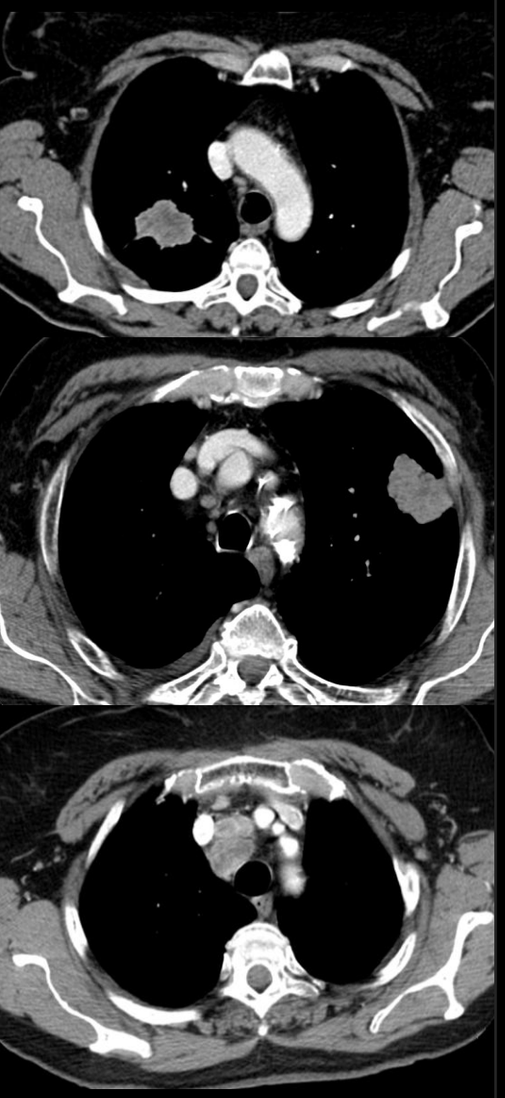

RECIST 1.1

Why, What, How ?

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February 15th 2011

RECIST

Response
Evaluation
Criteria
In
Solid
Tumors

1. Why RECIST criteria ?

Background

Background

- Cancer will become the most common cause of death worldwide
- The ultimate goal of new cancer therapies is cure. A goal that has rarely been achieved in disseminated solid cancers.
- For many common cancers, treatment of disseminated disease is often noncurative, toxic and costly.
- There is great interest in surrogate metrics for survival after investigational cancer treatments, such as response rate, time to tumor progression or progression-free survival.

Background

- Assessment of the change in tumor burden

  = important feature of the clinical evaluation of cancer therapeutics

- Important endpoints in clinical trials
  - Tumor shrinkage (objective response)
  - Time to development of disease progression or progression-free survival
  - → only useful if based on widely accepted and readily applied standard criteria based on anatomical tumor burden

Background

- World Health Organisation (WHO)
  - 1981: publication of tumor response criteria
  - Use in trials where tumor response was the primary endpoint
  - Introduced the concept of overall assessment of tumor burden by summing the products of bidimensional lesion measurements
  - Determined response to therapy by evaluation of change from baseline
  - Pharmaceutical companies ‘modified’ these criteria, which led to confusion in interpretation of trial results → leading to very different conclusion

2. WHAT are the RECIST criteria ?

Past – Present – Future

RECIST: the PAST

- Mid 1990's: International working party was formed, including
  - European Organization for Research and Treatment of Cancer (EORTC)
  - National Cancer Institute (NCI) of the United States
  - National Cancer Institute of Canada Clinical Trials Group
- Goals: Standardise / Simplify response criteria
- 2000: RECIST criteria 1.0

PAST

RECIST 1.0

- Key features
  - Minimum size of target lesions ≥ 10 mm CT/MRI
  - Number of measurable lesions : up tot 10 – maximum five per organ
  - Measurement: UNI-dimensional
  - No lymph node measurements

PAST

RECIST 1.0

- Questions and issues
  - Fewer than 10 lesions can be assessed without affecting the overall assigned response
  - How to apply RECIST in randomised phase III trials where progression, not response, is the primary endpoint
  - Whether or how to utilize newer imaging technologies, such as FDG-PET and MRI
  - How to handle assessment of lymph nodes
  - Applicability of RECIST in trials of targeted non-cytotoxic drugs
  - …

RECIST: the PRESENT

- RECIST 1.1. development : RECIST working group
  - Clinicians with expertise in early drug development from academic research organisations – government – industry
  - Imaging specialists
  - Statisticians

- EORTC database > 6500 patients > 18.000 target lesions, was utilized to investigate the impact of a variety of questions on response and progression-free survival outcome

PRESENT

RECIST 1.1

- Published in January 2009
- Used in the majority of clinical trials evaluating cancer treatments
- RECIST: SOLID tumors

- New version: RECIST 1.1 – Why not RECIST 2.0 ?

> The fundamental approach to assessment remains grounded in the anatomical, rather than functional assessment of disease

PRESENT

Methods of measurement

- Baseline evaluations should be performed as close as possible to the treatment start
- Never more than 4 weeks before the beginning of the treatment

- Method of assessment
  - General rule: imaging assessment is preferred
  - Chest X-ray: lesion size > 20 mm
  - CT : best currently available and reproducible method – CT slice thickness of 5 mm or less
  - MRI: acceptable in certain situations
  - Ultrasound: not useful

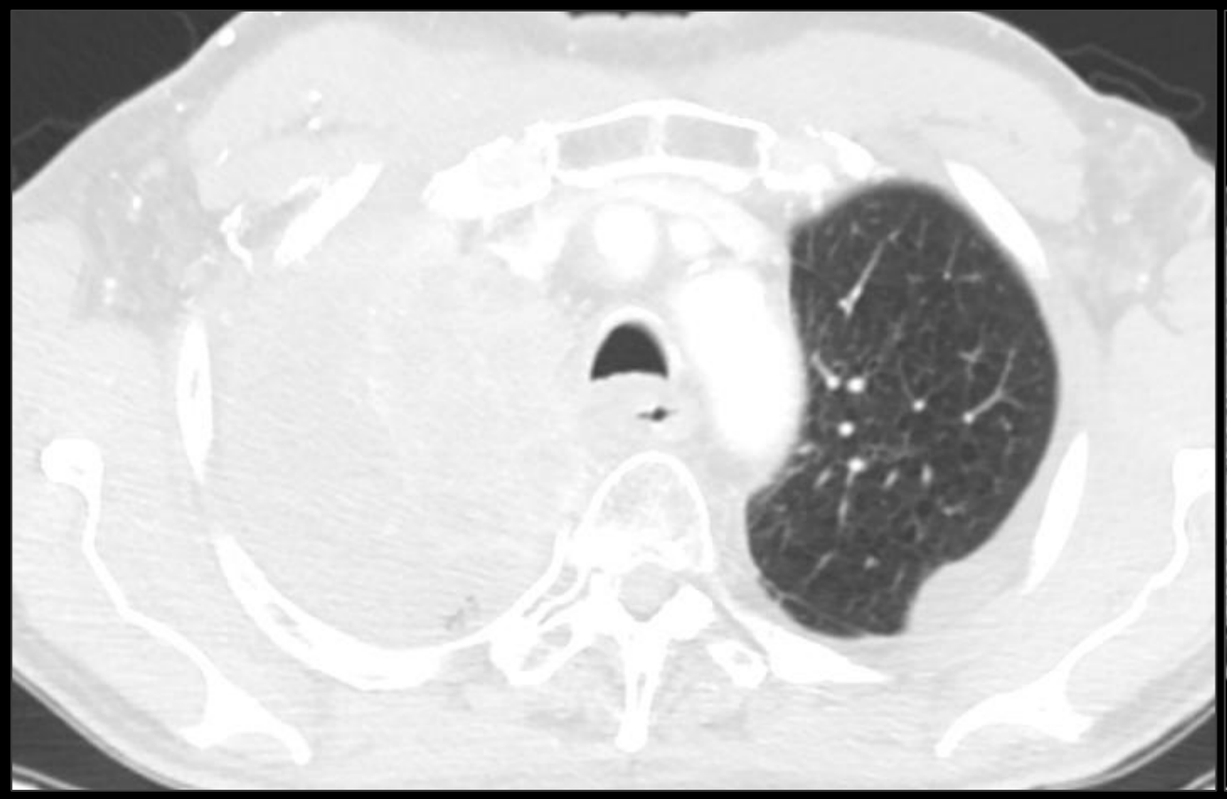
PRESENT

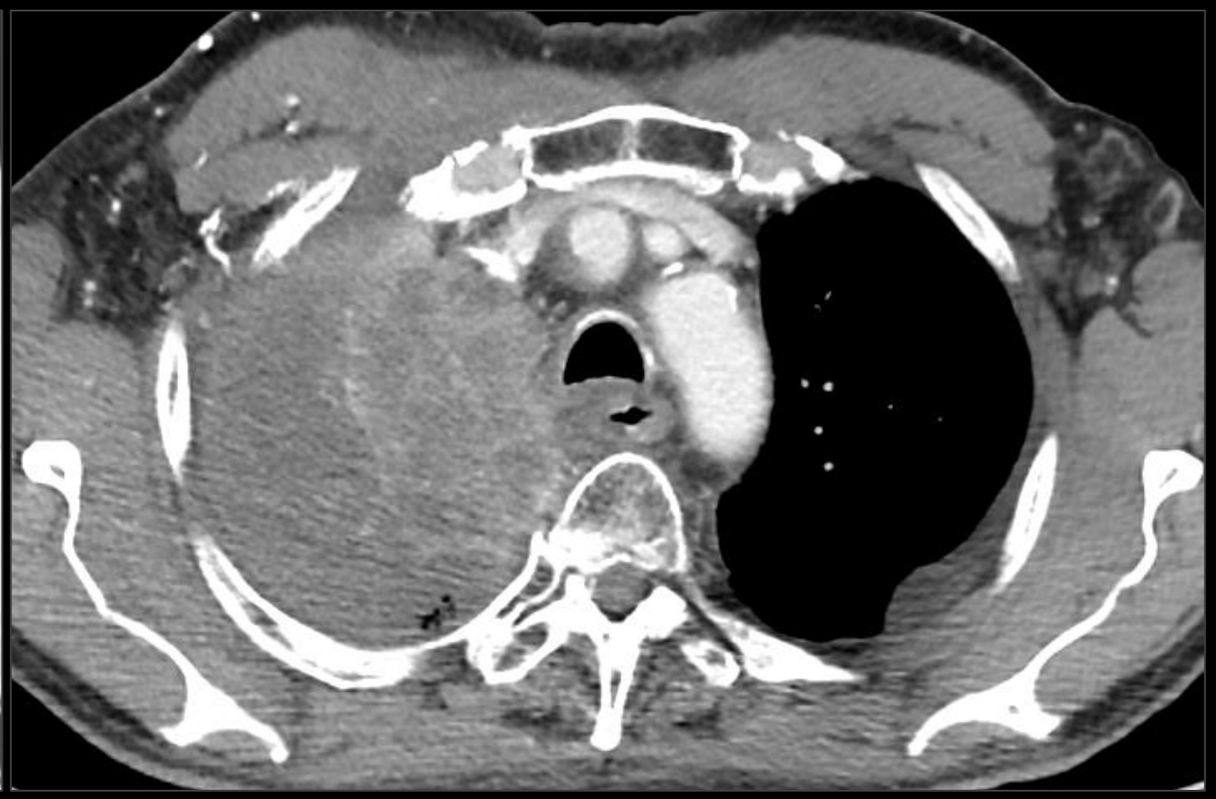
Measurability of tumor at baseline

measurable or non-measurable

- MEASURABLE
  - Tumor lesions
    - Accurately measured in at least one dimension
    - LONGEST diameter – axial plane
    - Minimum size of 10 mm by CT scan – slice thickness no greater than 5 mm
  - Malignant lymph nodes
    - Pathologically enlarged and measurable → lymph node must be ≥ 15 mm in SHORT AXIS, assessed on CT-scan.

In practice: chest CT
Window setting: lung parenchyma or mediastinal window ?



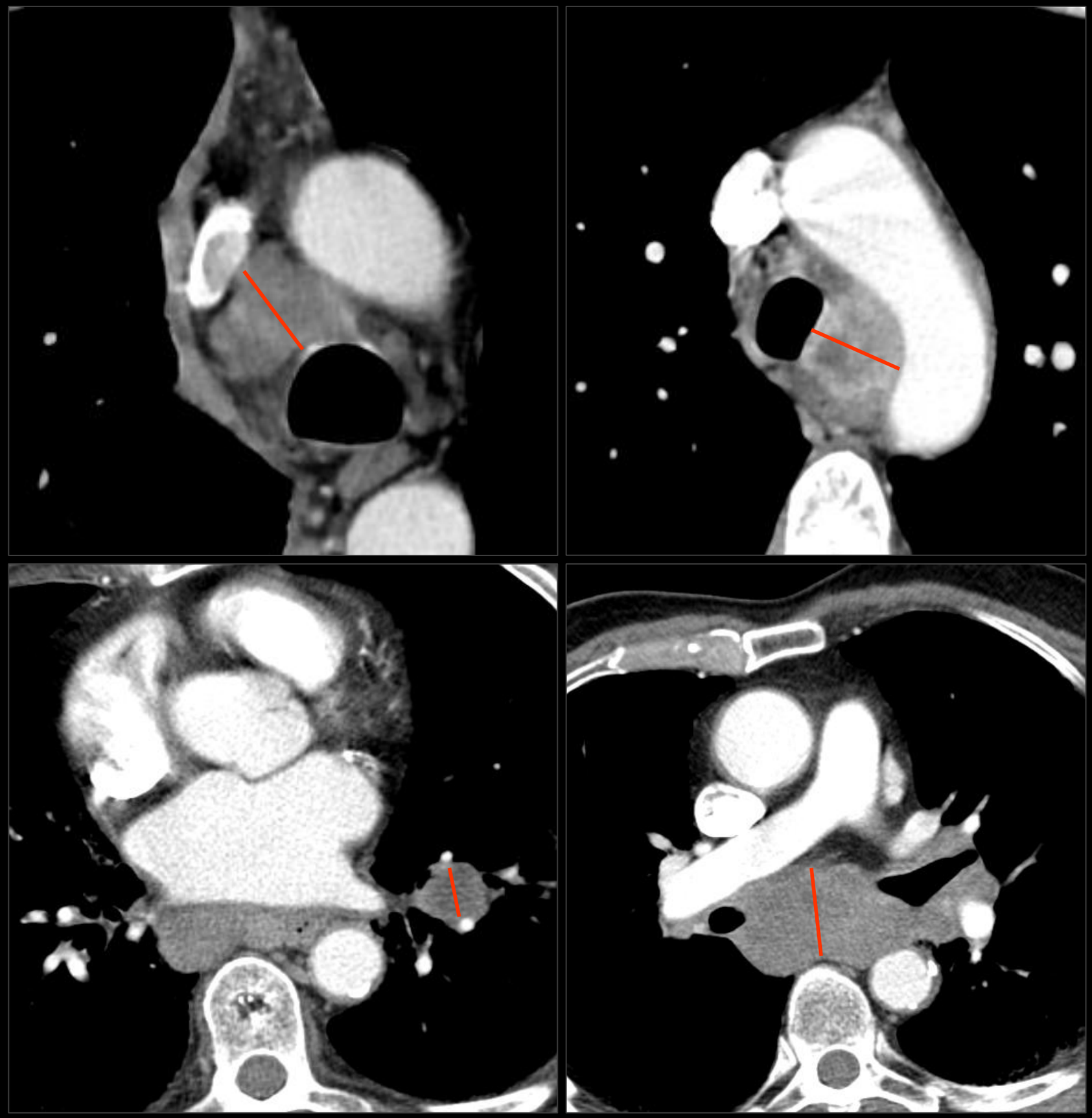


Lymph nodes: measure
SHORT AXIS !

≥ 15 mm = target lesion

≥ 10 mm and < 15 mm = non-target lesion

< 10 mm = “normal”



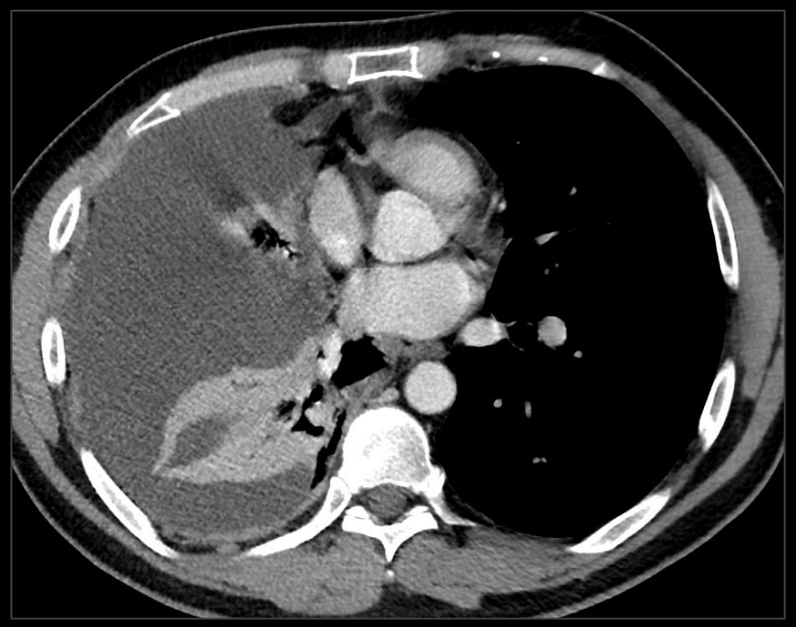
PRESENT

Measurability of tumor at baseline

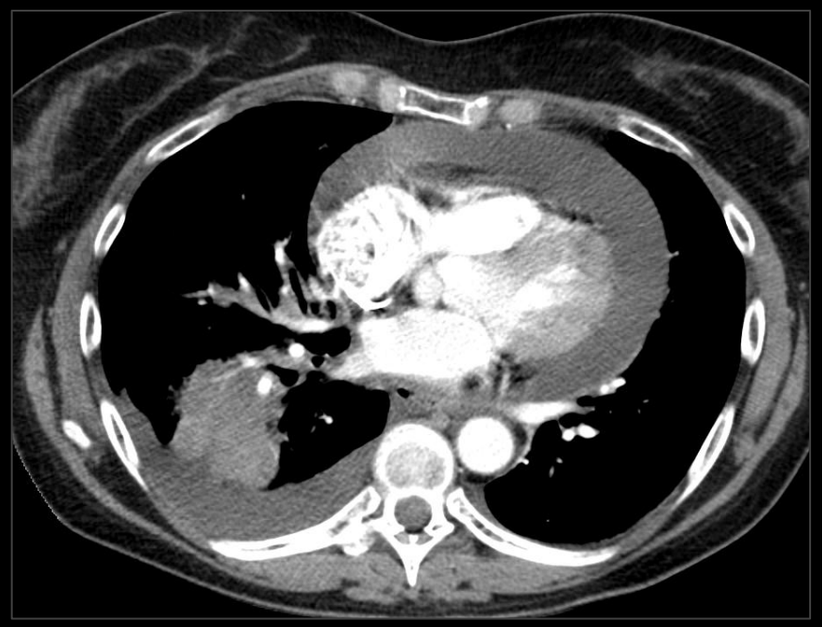
measurable or non-measurable

- NON-MEASURABLE
  - All other lesions (<10 mm longest diameter – 10 mm ≤ LN < 15 mm short axis)
  - Truly non-measurable lesions
    - Pleural or pericardial effusion
    - Ascites
    - Leptomeningeal disease
    - Inflammatory breast disease
    - Lymphangitic involvement of skin or lung
    - Abdominal organomegaly
    - …

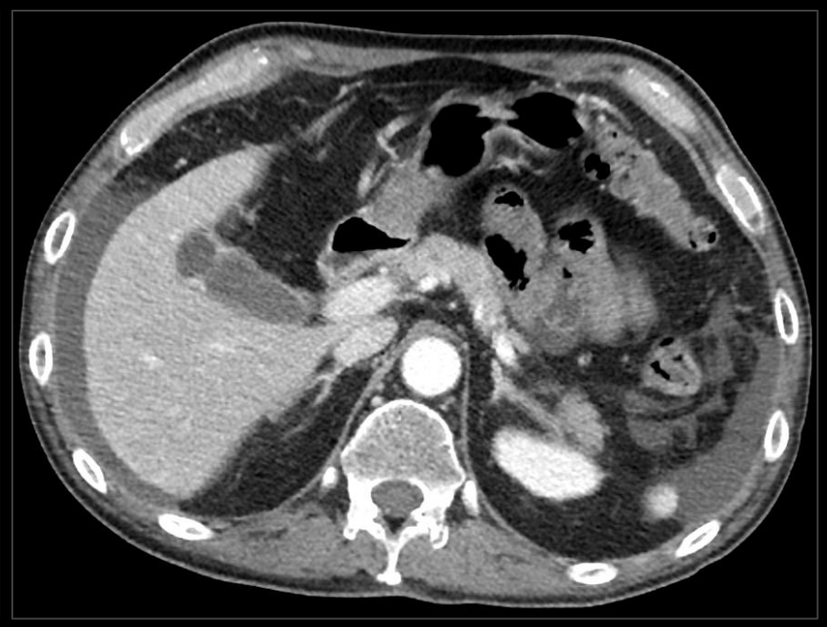
Non-measurable lesions



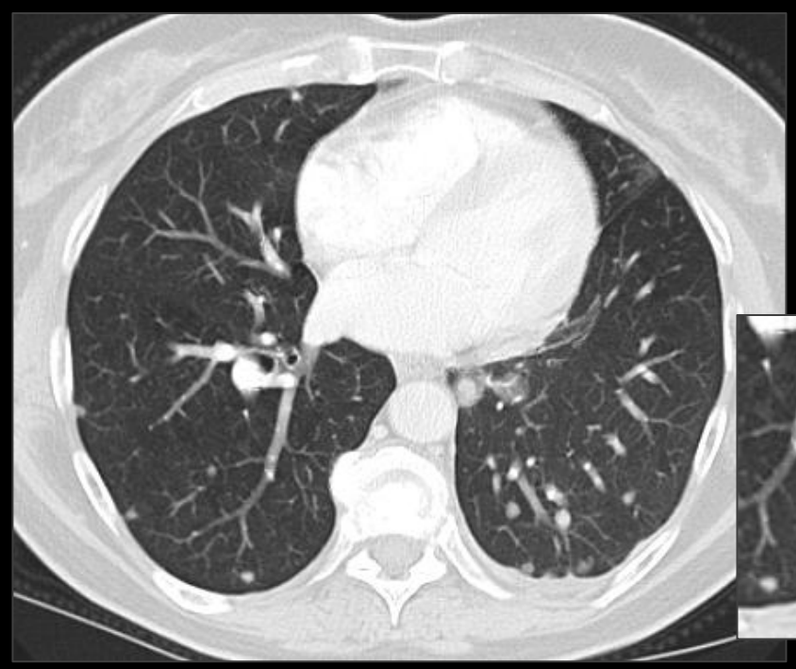
Pleural fluid

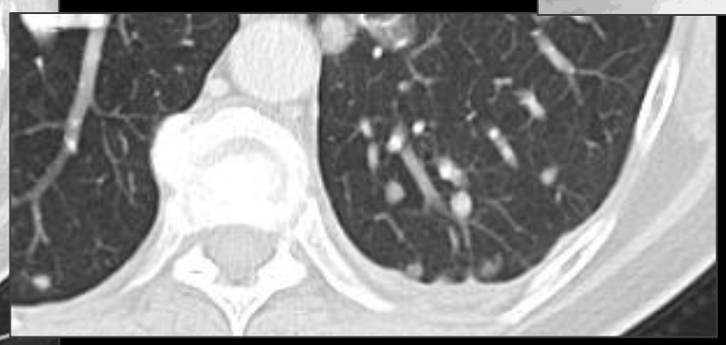


Pericardial fluid

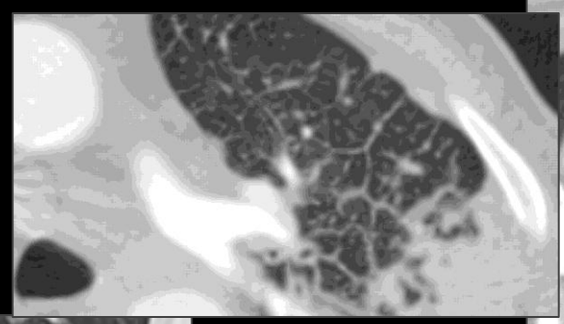


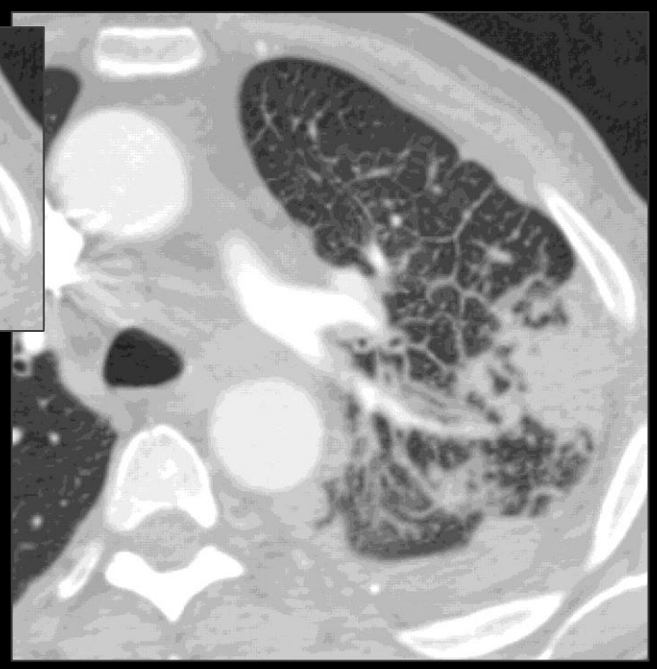
Ascites – peritoneal carcinomatosis





Numerous pulmonary metastases





Lymphangitic carcinomatosis

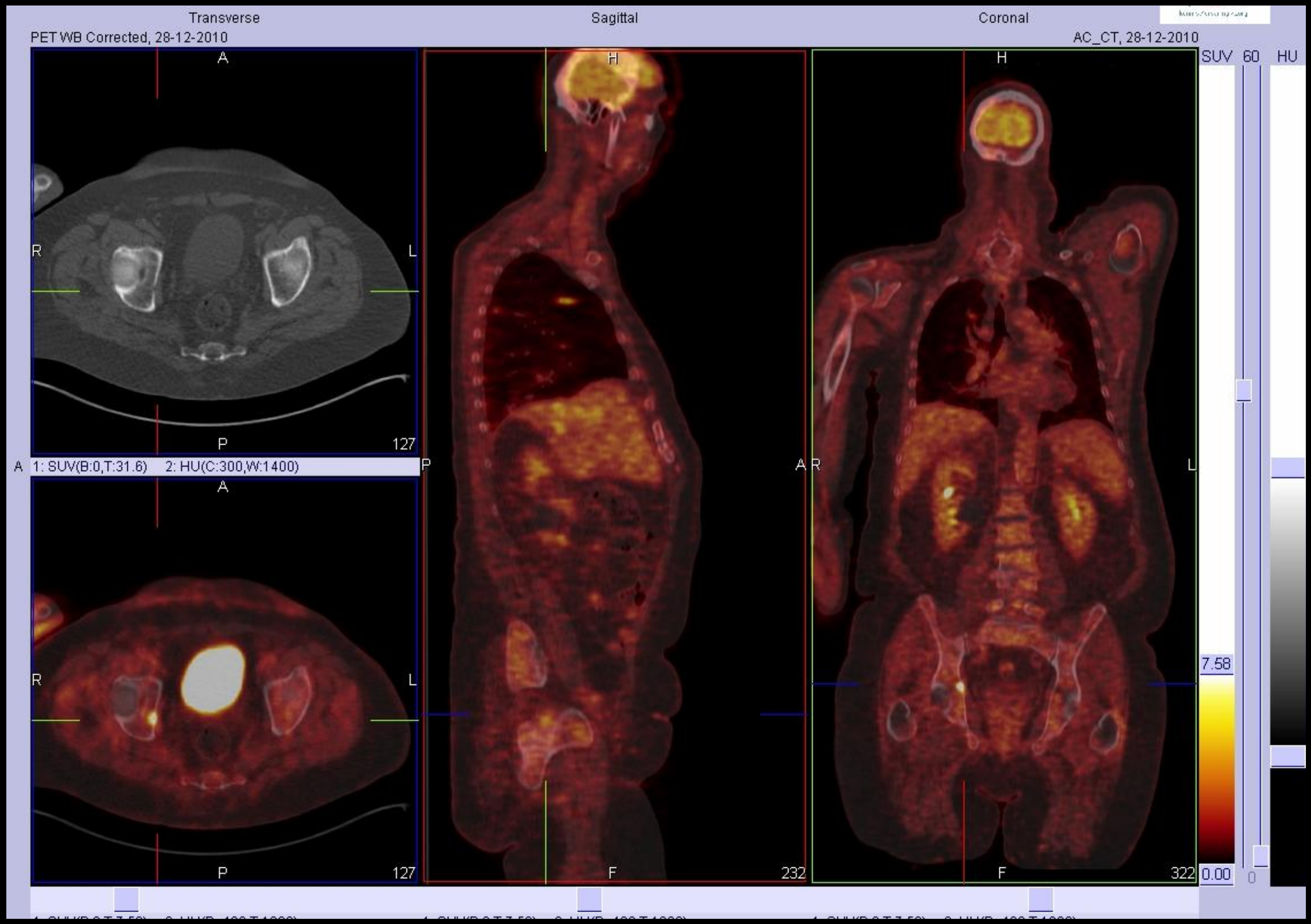
PRESENT

Special considerations

Lesion measurability

- BONE LESIONS
  - Bone scan – PET scan – plain films:
    - not considered adequate imaging techniques to measure bone lesions
    - can be used to confirm the presence or disappearance of bone lesions

PET: lesion detection and staging



PRESENT

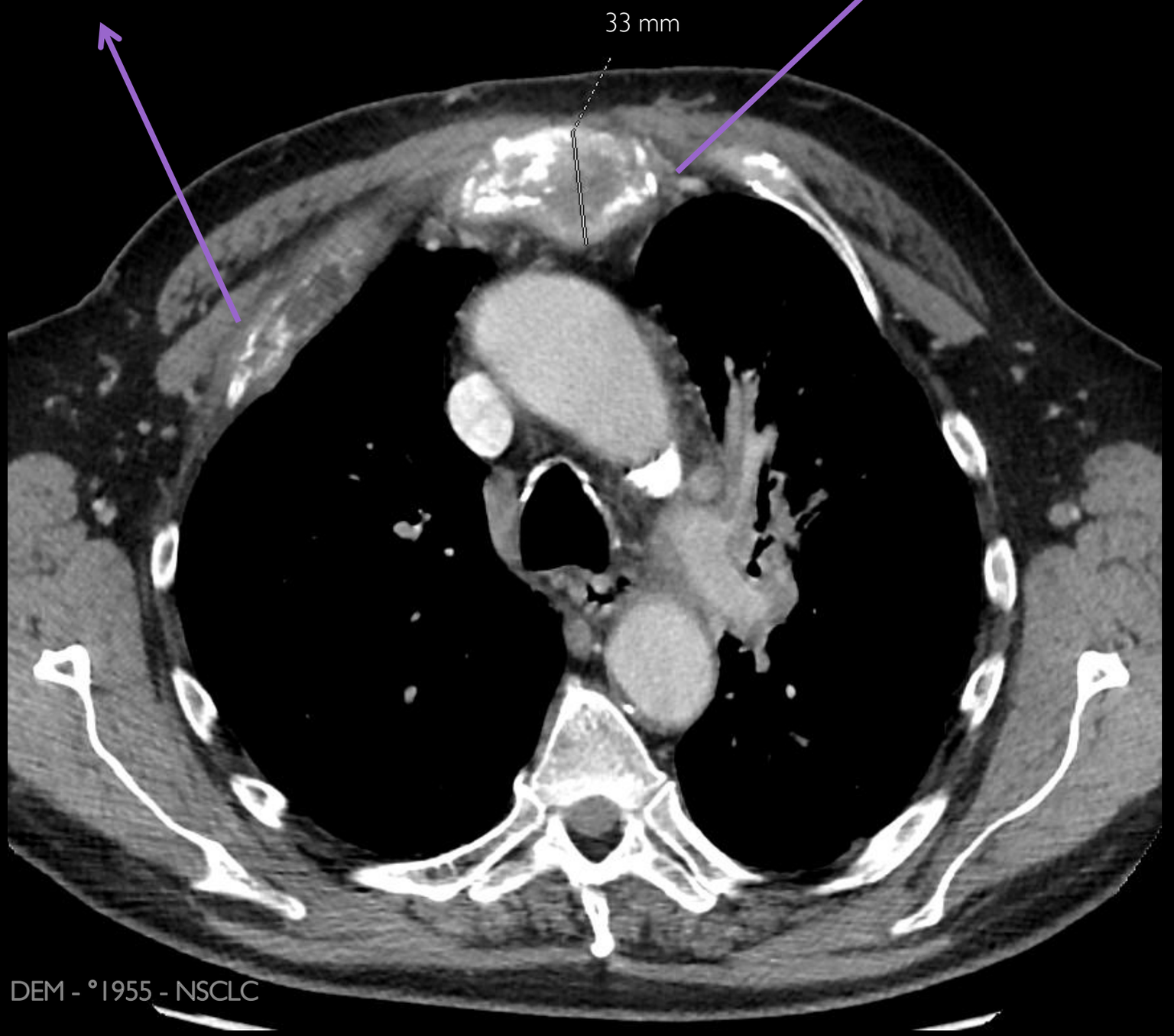
Special considerations

Lesion measurability

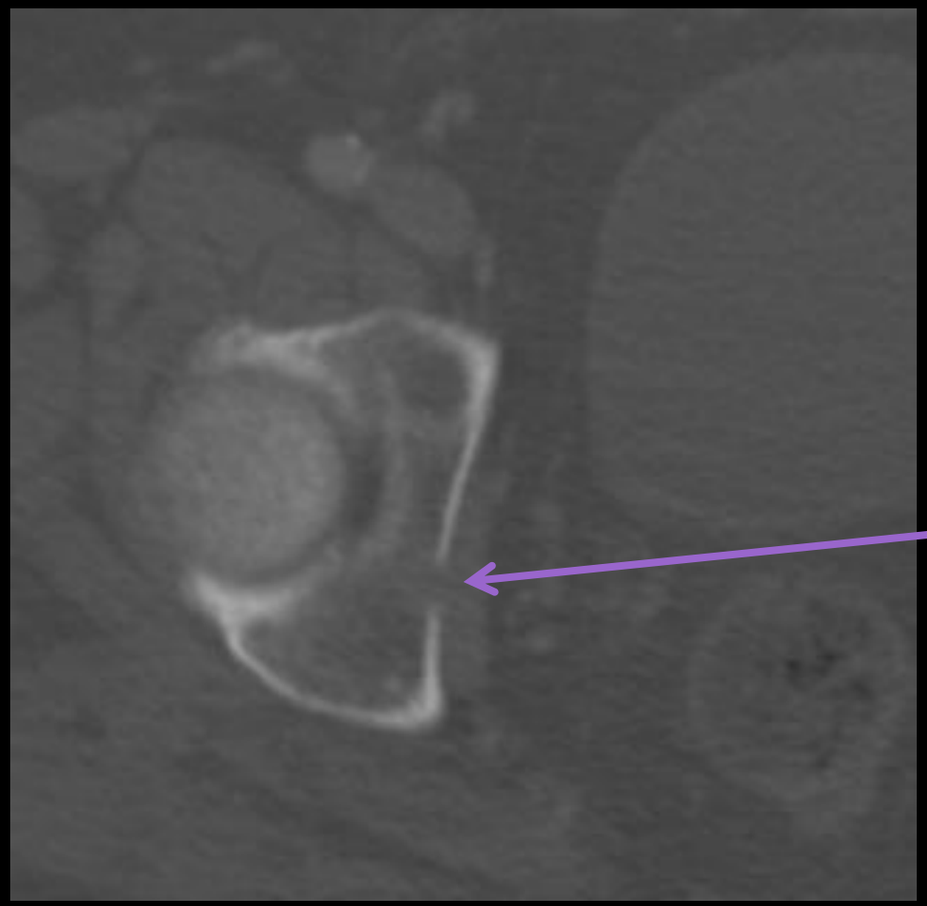
- BONE LESIONS
  - Bone scan – PET scan – plain films:
    - not considered adequate imaging techniques to measure bone lesions
    - can be used to confirm the presence or disappearance of bone lesions
  - Lytic bone lesions or mixed lytic-blastic lesions
    - with identifiable soft tissue components
    - evaluated by CT or MRI
    - considered as measurable lesions if the soft tissue component is larger than 10 mm
  - Blastic bone lesions: non-measurable

Lytic lesion with soft tissue component
Measurable disease → Target lesion

Osteolytic rib destruction
Non-measurable disease → Non-target lesion



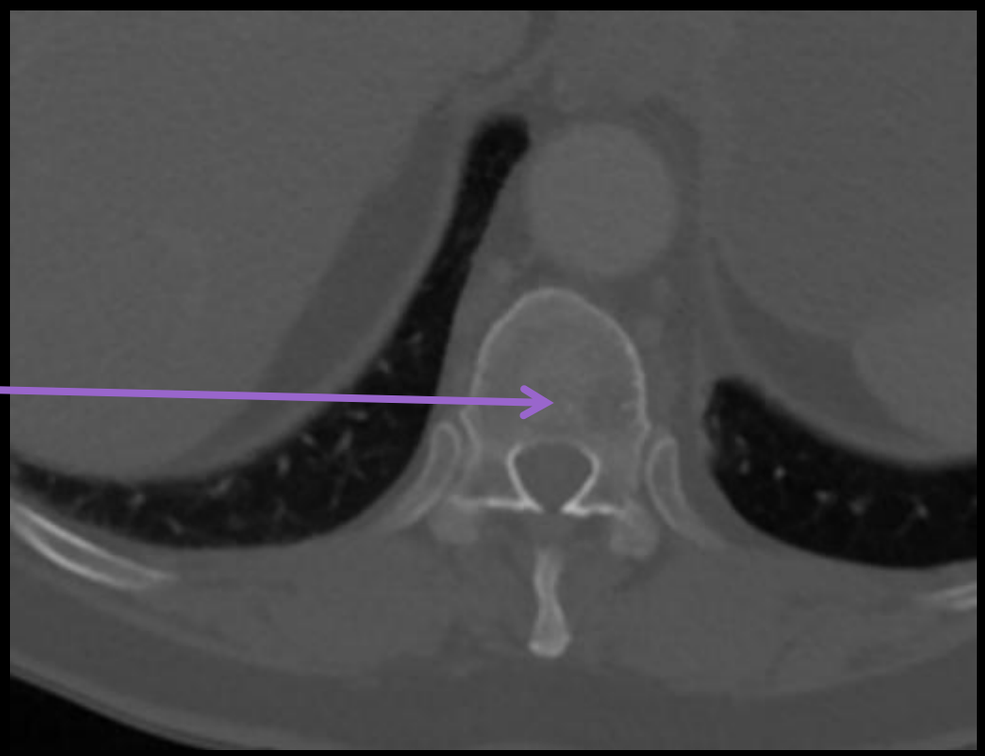
DEM - °1955 - NSCLC



Only cortical osteolysis, even if larger →
Non-measurable disease → Non-target lesion

AW - °1942 - NSCLC

Lytic bone lesion with no soft tissue component →
Non-measurable disease → Non-target lesion



CJ - °1945 - NSCLC

PRESENT

Special considerations

Lesion measurability

- CYSTIC LESIONS
  - Truly cystic lesions can not be considered malignant
  - Cystic “metastatic” lesions: measurable lesions if > 10 mm
  - Non-cystic lesions present in the same patient: preferred for selection as target lesions

- LESIONS WITH PRIOR LOCAL TREATMENT
  - Tumor lesions in a previously irradiated area or after locoregional therapy, are usually not considered measurable, unless there has been demonstrated progression in the lesion

PRESENT

Tumor response evaluation

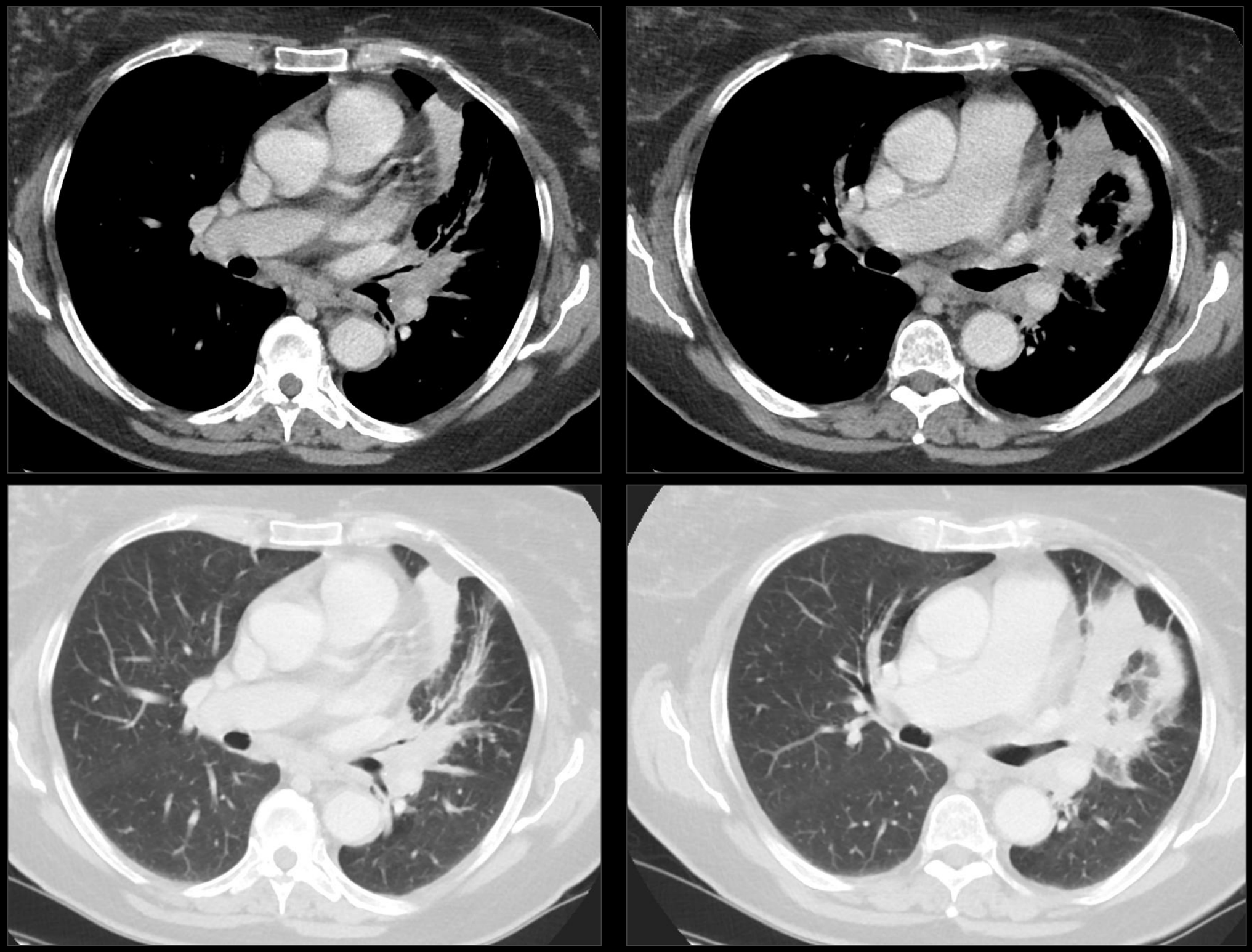
- ! Estimation of overall tumor burden at baseline
- Only patients with measurable disease
- At least one measurable lesion
- Patients only having non-measurable disease: specific protocols

PRESENT

“Target” lesions

- One measurable lesion: one target lesion
- More than one measurable lesion:
  - Maximum of five lesions total
  - Maximum of two lesions per organ

- Selection of target lesions:
  - On the basis of their size (lesions with longest diameter)
  - Representative of all involved organs
  - Lesions that lend themselves to reproducible repeated measurements



Central tumor with retro-obstructive atelectasis

Target: Lesions that lend themselves to reproducible repeated measurements ?

PRESENT

"Target" and "non-target" lesions: LYMPH NODES

- Pathologic nodes: measurable and target lesions
  → short axis of ≥ 15 mm by CT scan
- Nodes with short axis ≥ 10 mm and < 15 mm : should be considered as non-target lesions
- Nodes with short axis < 10 mm: should not be recorded or followed

PRESENT

“Target” lesions

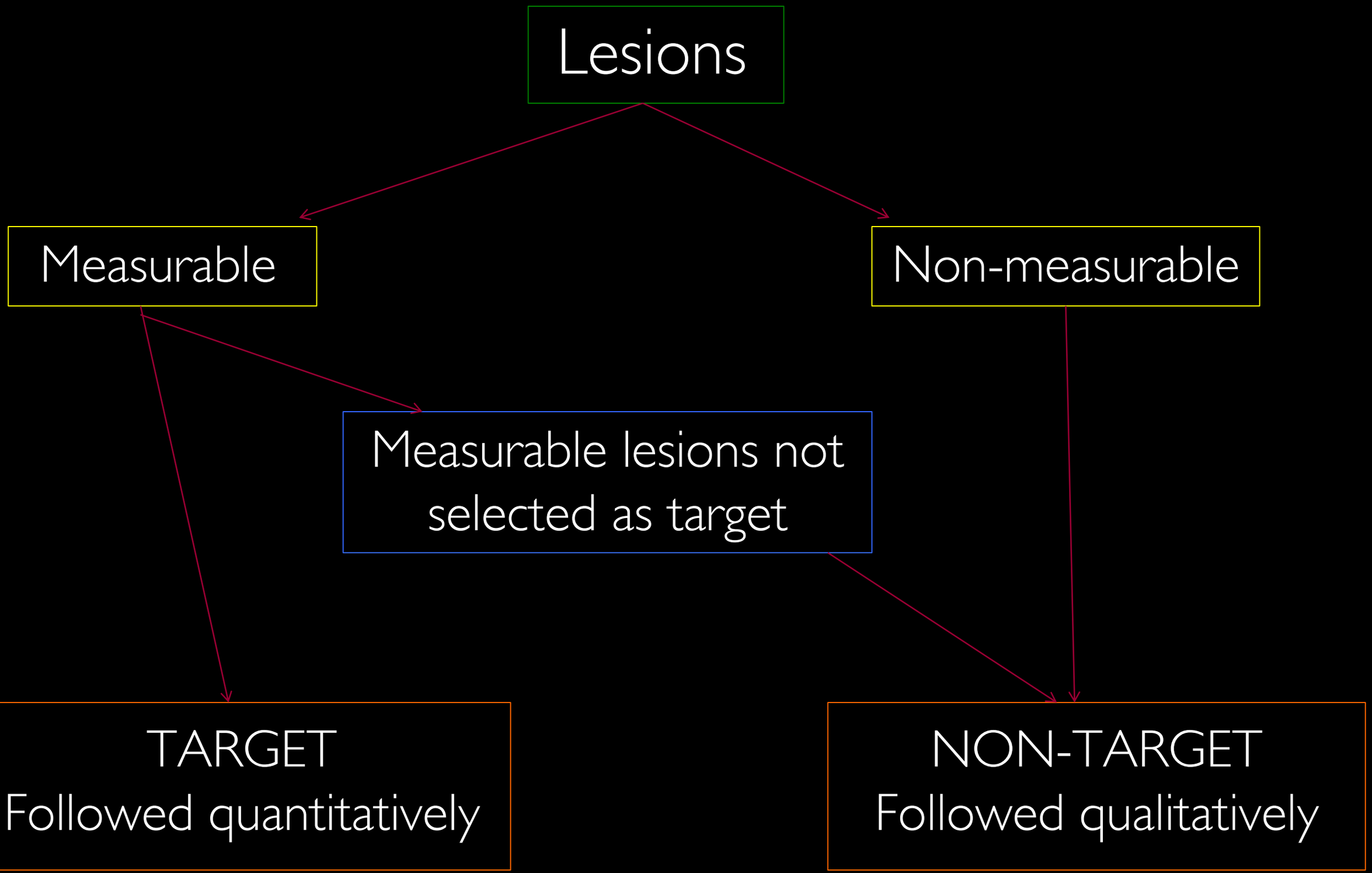
Sum of the diameters for all target lesions will be calculated and reported as the BASELINE SUM DIAMETERS

PRESENT

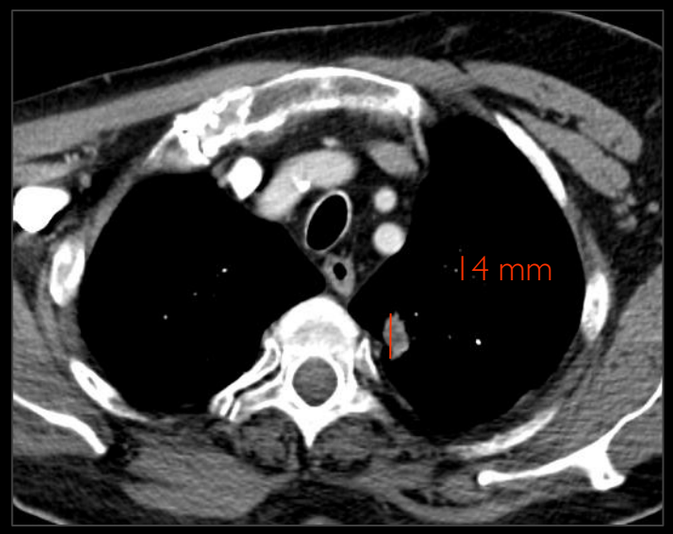
“Non-target” lesions

- All other lesions or sites of disease should be identified as non-target lesions
- Should also be recorded at baseline !
- Not measured
- Should be followed:
  - Present
  - Absent
  - Rare cases: unequivocal progression
  - Possible to record multiple non-target lesions involving the same organ as a single item: e.g. “multiple liver metastases”

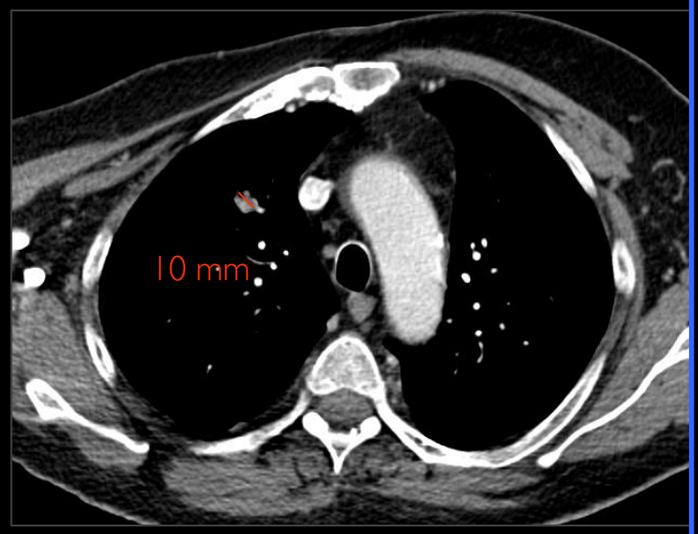
Baseline lesion burden



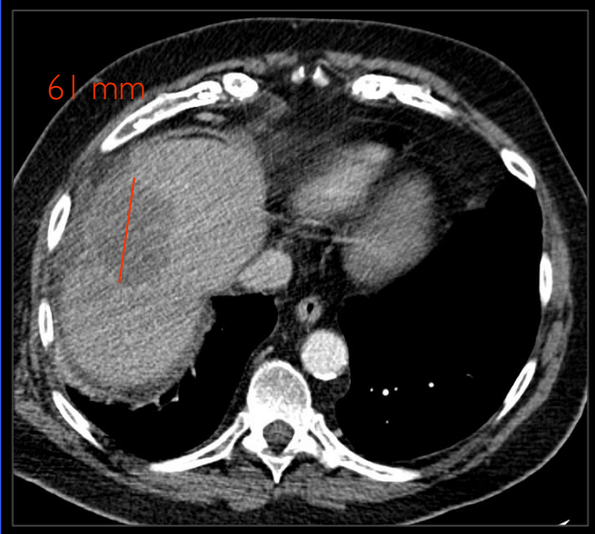
AW - °26/01/1945 – NSCLC



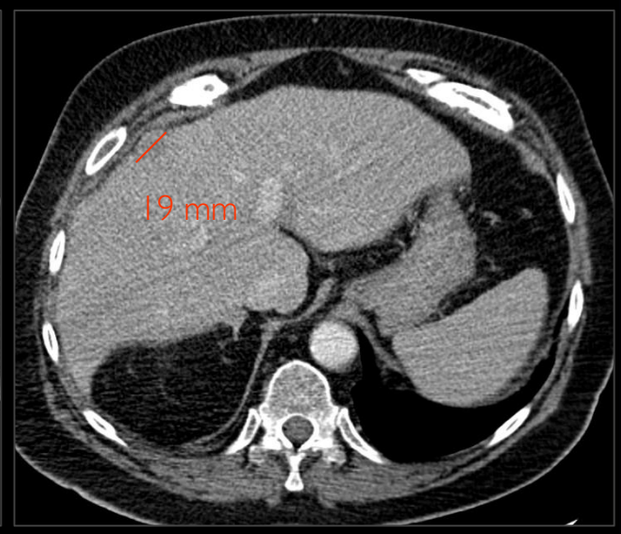
Target lesion 1
Primary tumor



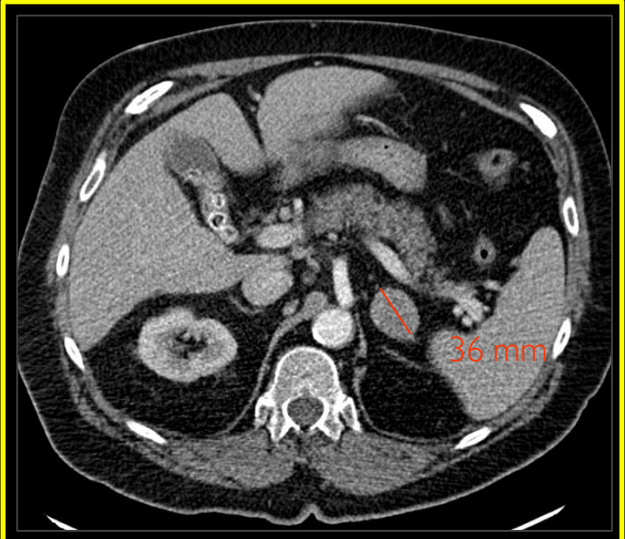
Target lesion 2
Pulmonary mass
≥ 10 mm



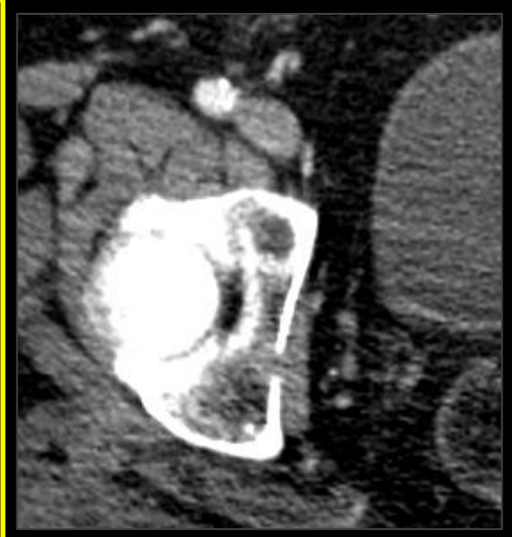
Target lesion 3
Liver metastasis



Target lesion 4
Liver metastasis



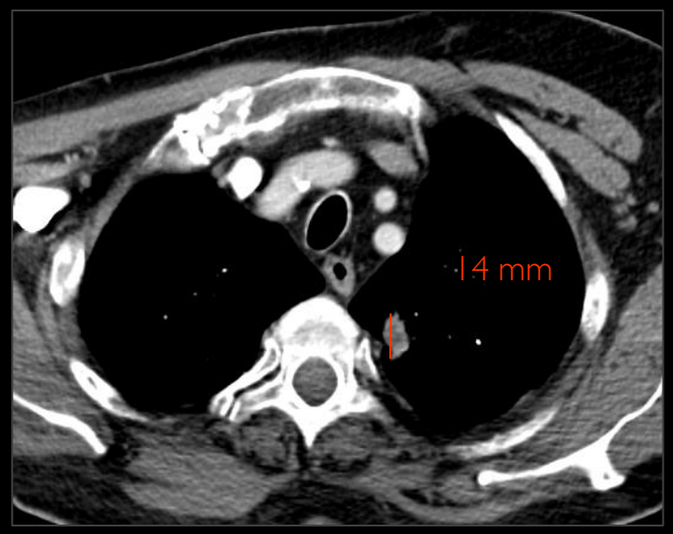
Target lesion 5
Adrenal gland metastasis



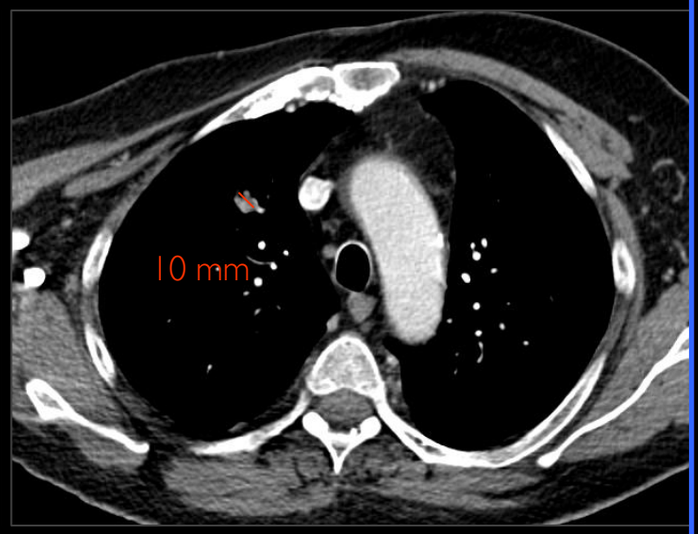
Non-target lesion (+)
Lytic bone metastasis

Lesions ≥ 10 mm
Up to 5 lesions in total
Maximum of 2 lesions per organ

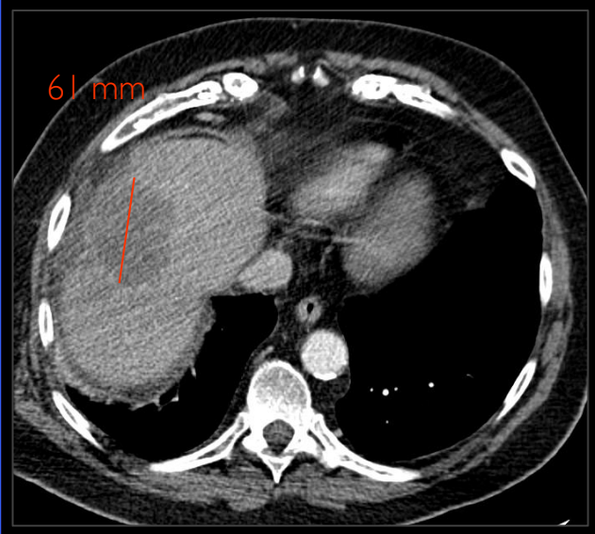
AW - °26/01/1945 – NSCLC



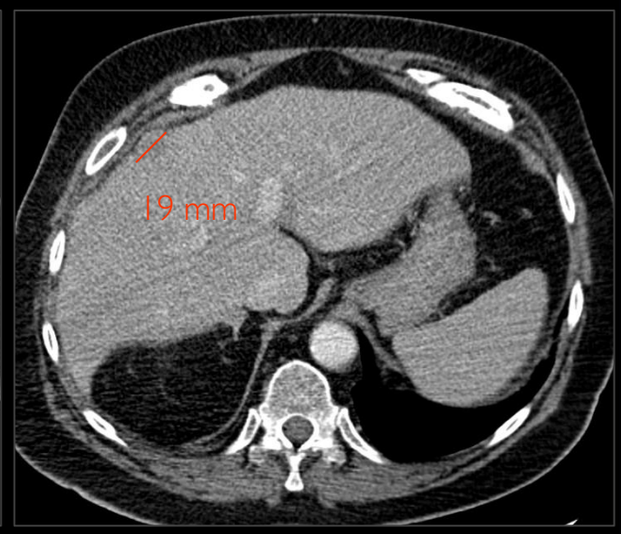
Target lesion 1
Primary tumor



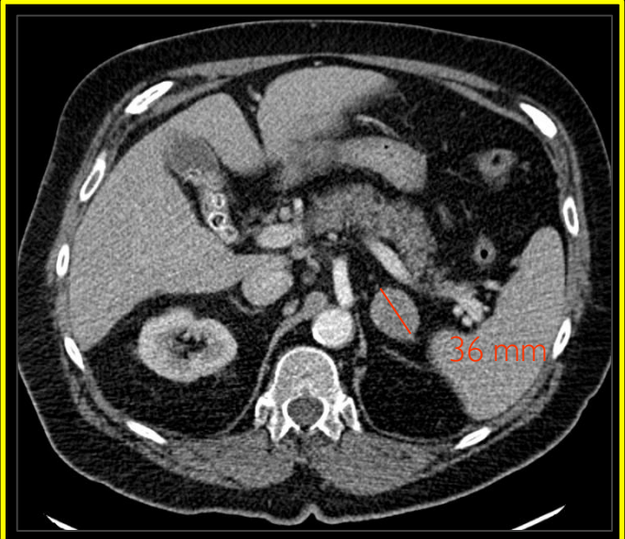
Target lesion 2
Pulmonary mass
≥ 10 mm



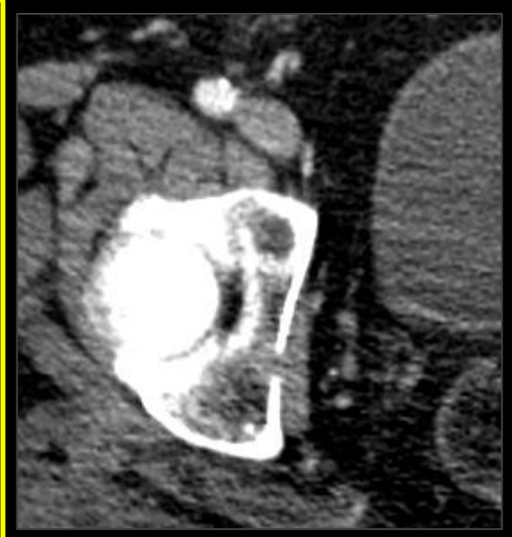
Target lesion 3
Liver metastasis



Target lesion 4
Liver metastasis



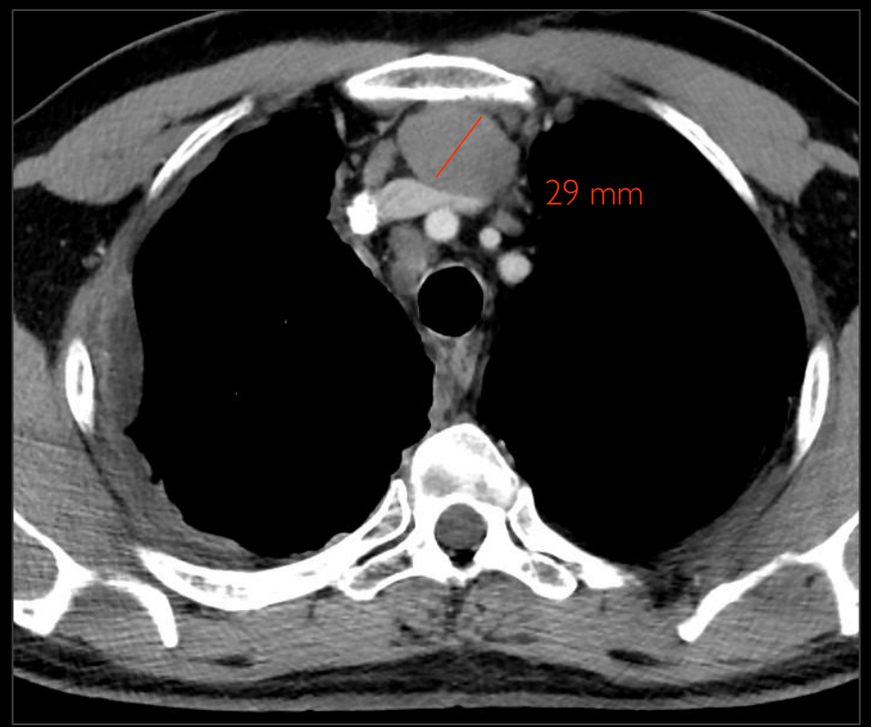
Target lesion 5
Adrenal gland metastasis



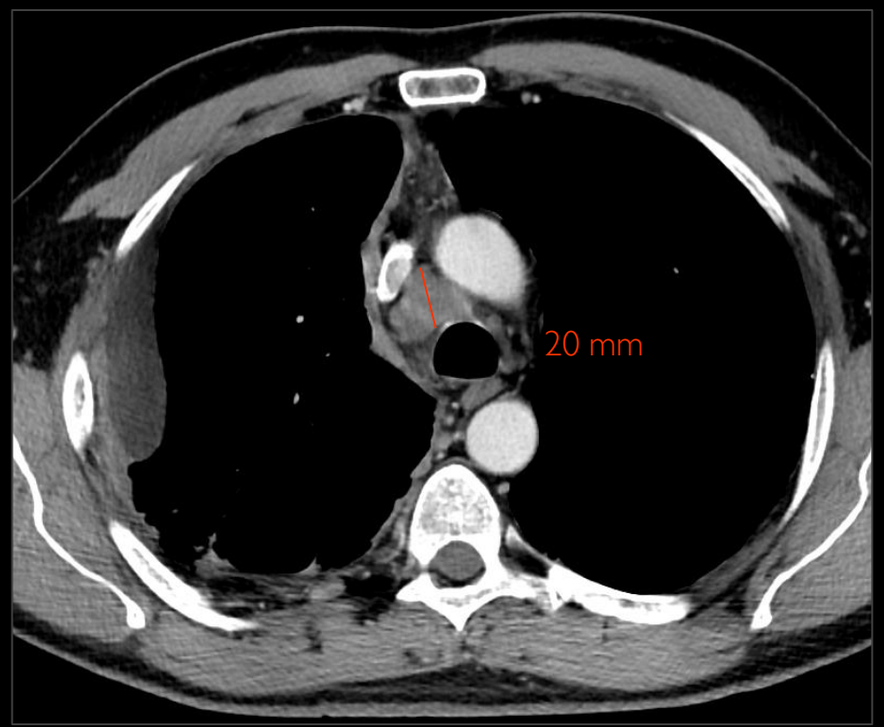
Non-target lesion (+)
Lytic bone metastasis

Target lesion 1	Primary tumor	14 mm
Target lesion 2	Pulmonary mass	10 mm
Target lesion 3	Liver metastasis	61 mm
Target lesion 4	Liver metastasis	19 mm
Target lesion 5	Adrenal gland met.	36 mm
Non-target lesion	Lytic bone met.	+
Baseline sum diameters		140 mm

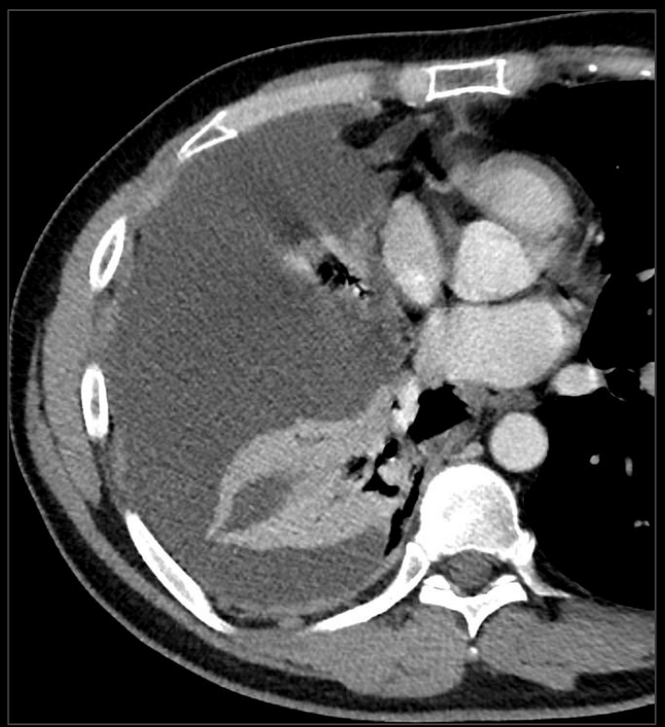
BASELINE EXAMINATION



Target lesion 1
Metastatic LN



Target lesion 2
Metastatic LN

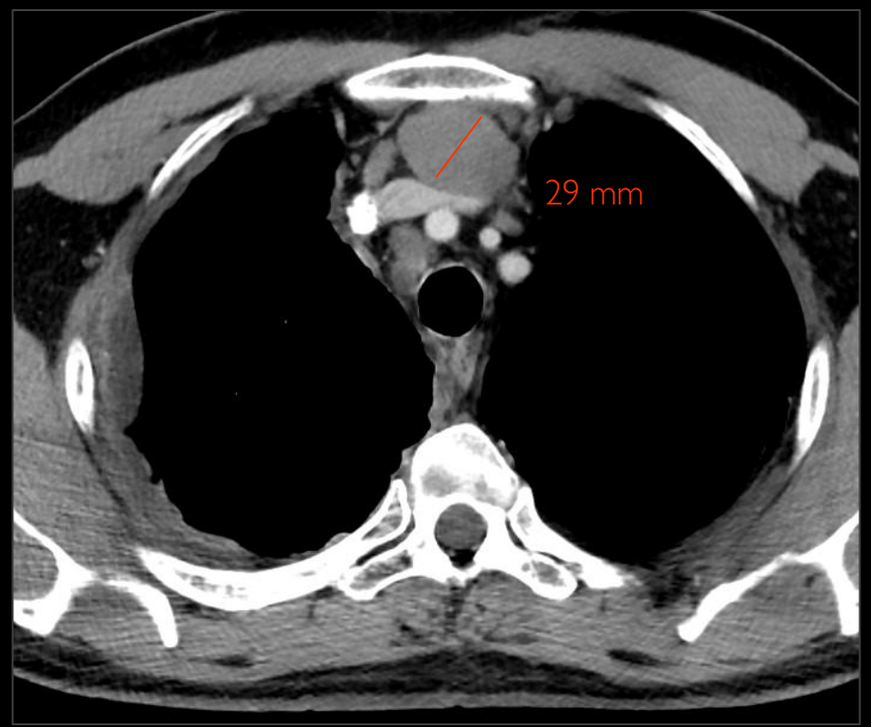


Non-target lesion
Metastatic pleural fluid

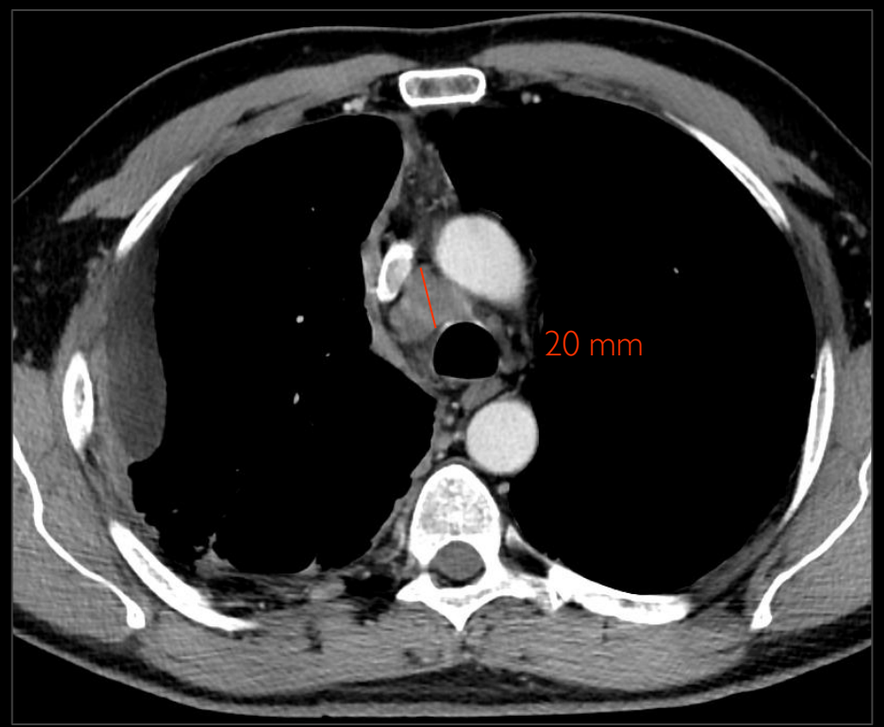
Lymph nodes: measure SHORT AXIS !

≥ 15 mm = target lesion
≥ 10 mm and < 15 mm = non-target lesion → report as + / -
< 10 mm = "normal" → do not record – do not follow

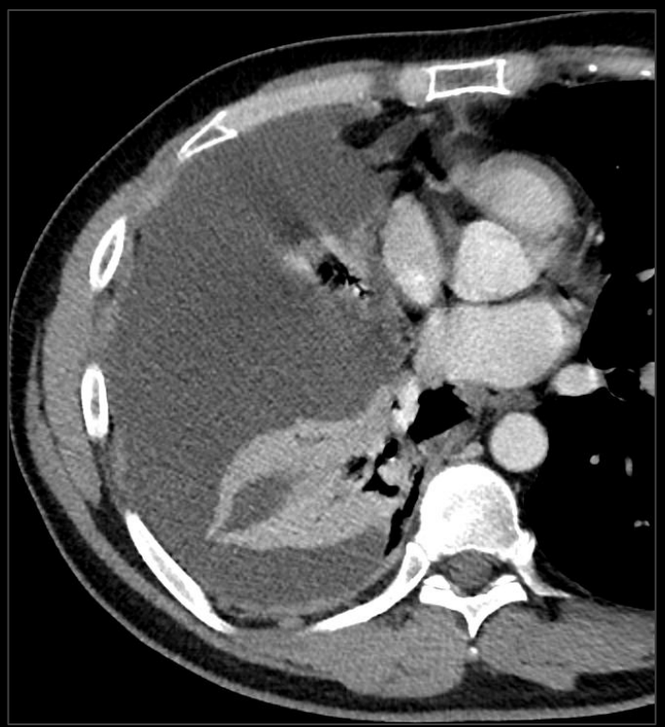
BASELINE EXAMINATION



Target lesion 1
Metastatic LN



Target lesion 2
Metastatic LN



Non-target lesion
Metastatic pleural fluid

Target lesion 1	Lymph node	29 mm
Target lesion 2	Lymph node	20 mm
Non-target lesion	Pleural fluid	+
Baseline sum diameters		49 mm

PRESENT

Follow-up: measurement of TARGET lesions

- Lesion measurability is defined at baseline
- Thereafter, actual measurements – even if < 10 mm – should be recorded
- Lesions that become very small: “too small to measure” → lesion that is still present = 5 mm
- If the radiologist believes the lesion has gone: default measurement of 0 mm

PRESENT

Response criteria: TARGET lesions

- COMPLETE RESPONSE
  - Disappearance of all target lesions
  - Pathologic lymph nodes must have reduction in short axis to < 10 mm
- PARTIAL RESPONSE
  - At least 30% decrease in the sum of diameters of target lesions
  - Reference: baseline sum diameters

PRESENT

Response criteria: TARGET lesions

- PROGRESSIVE DISEASE
  - At least a 20% increase in the sum of diameters of target lesions
  - Reference: the smallest sum on study (baseline or nadir)
  - Nadir: the smallest sum recorded since the treatment started
  - Absolute increase of 5 mm
  - Appearance of new lesions = always progressive disease !
- STABLE DISEASE
  - No progressive disease or partial response

PRESENT

Response criteria: NON-TARGET lesions

- COMPLETE RESPONSE
  - Disappearance of all non-target lesions and normalization of tumor marker level
  - Lymph nodes must be non-pathological in size

- PROGRESSIVE DISEASE
  - Unequivocal progression of existing non-target lesions

- NON-CR / NON-PD
  - Persistence of one or more non-target lesions and / or maintenance of tumor marker level above the normal limits

PRESENT

Unequivocal progression of non-target lesions

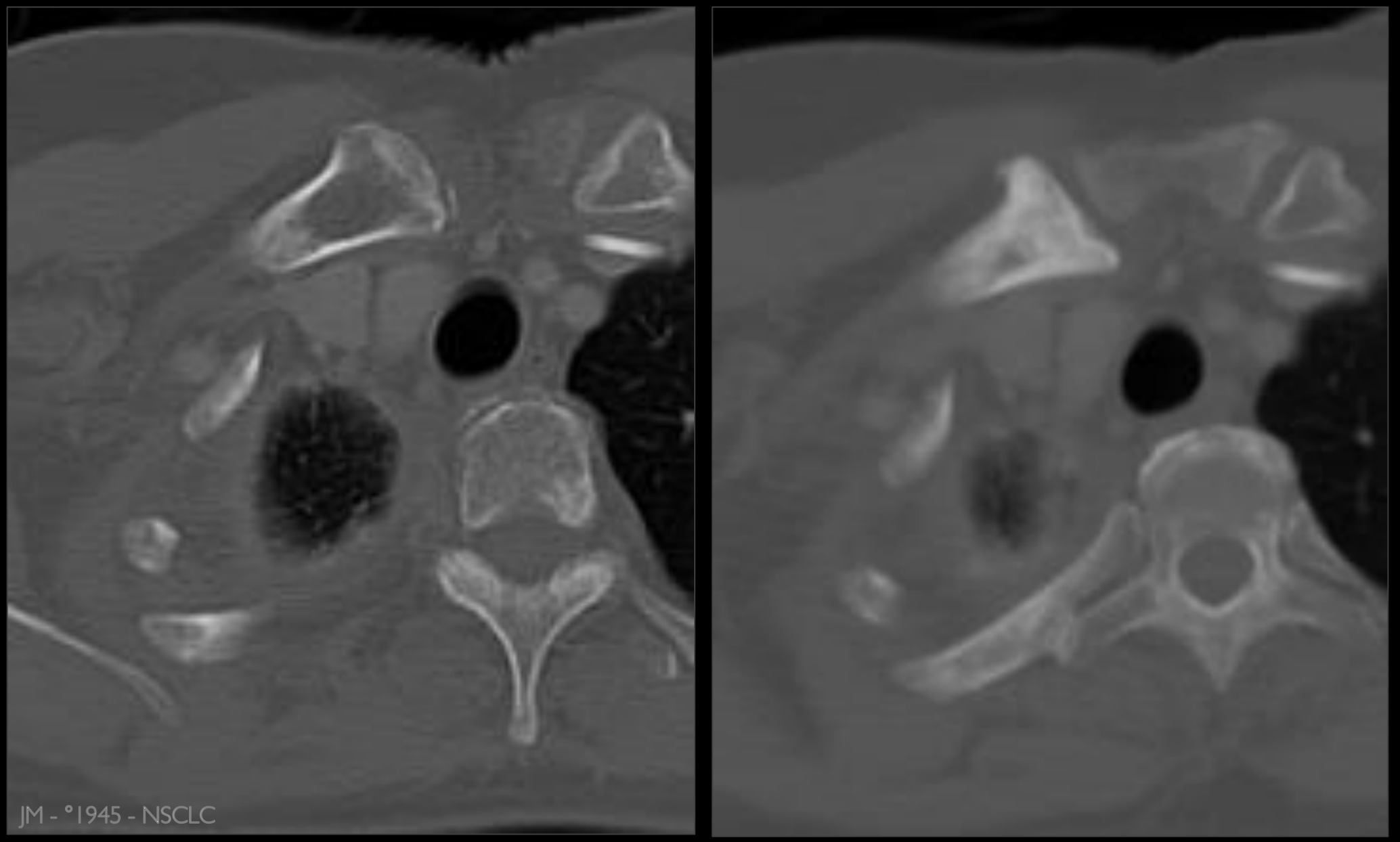
- Patient also has measurable disease
  - Unequivocal progression on the basis of non-target disease
  - → there must be an overall level of substance worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy
  - "modest increase" is usually not sufficient

- Patient has only non-measurable disease
  - Worsening in non-target disease cannot be easily quantified

PRESENT

Response criteria: NEW LESIONS

- Does not have to meet the criteria to be “measurable”
- Finding of a new lesion should be unequivocal
    - Not attributable to differences in scanning technique
    - Findings thought to represent something other than tumor → flare of pre-existing lesions



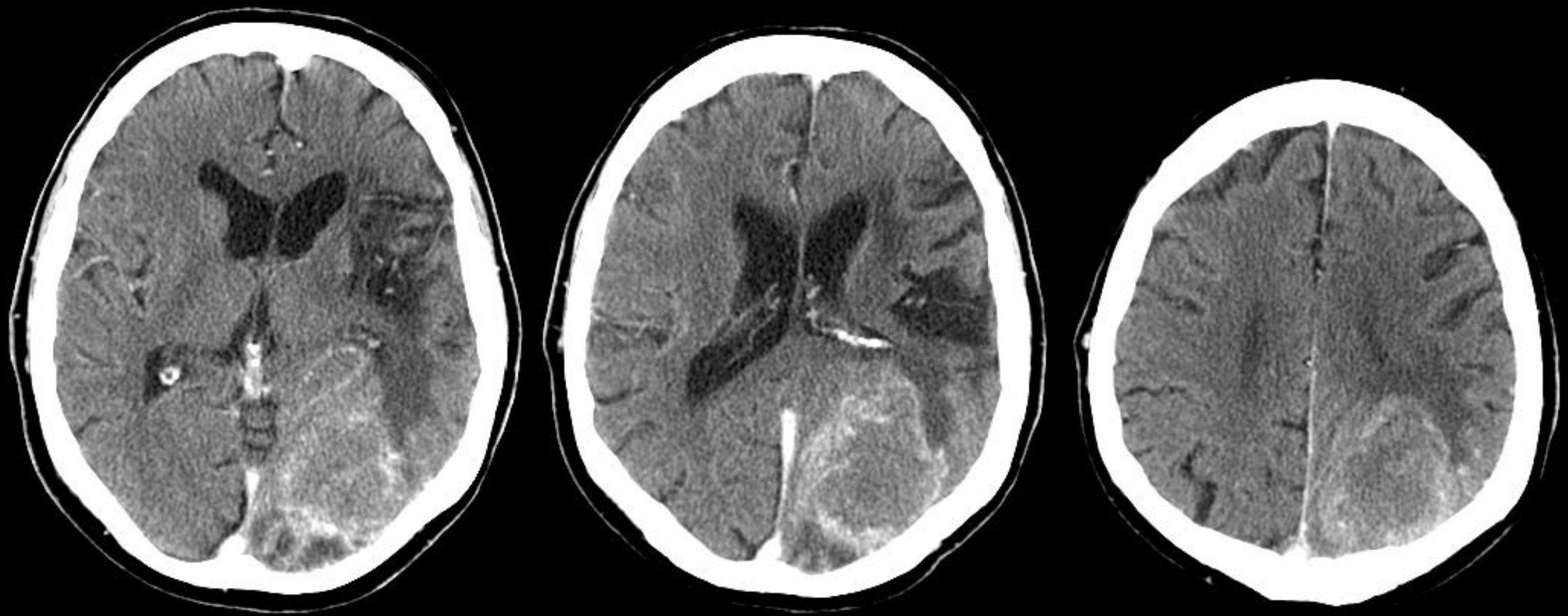
"Flare phenomenon"

Nuclear medicine → Bone scan flare phenomenon in non-small-cell lung cancer
= increase in the number or intensity of bone lesions with subsequent improvement while the patient is receiving chemotherapy

PRESENT

Response criteria: NEW LESIONS

- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline = considered a new lesion (e.g. brain metastases)
- FDG-PET imaging can be used to complement CT scanning in assessment of progression, particularly possible “new disease”



DLJ - °1945 - NSCLC

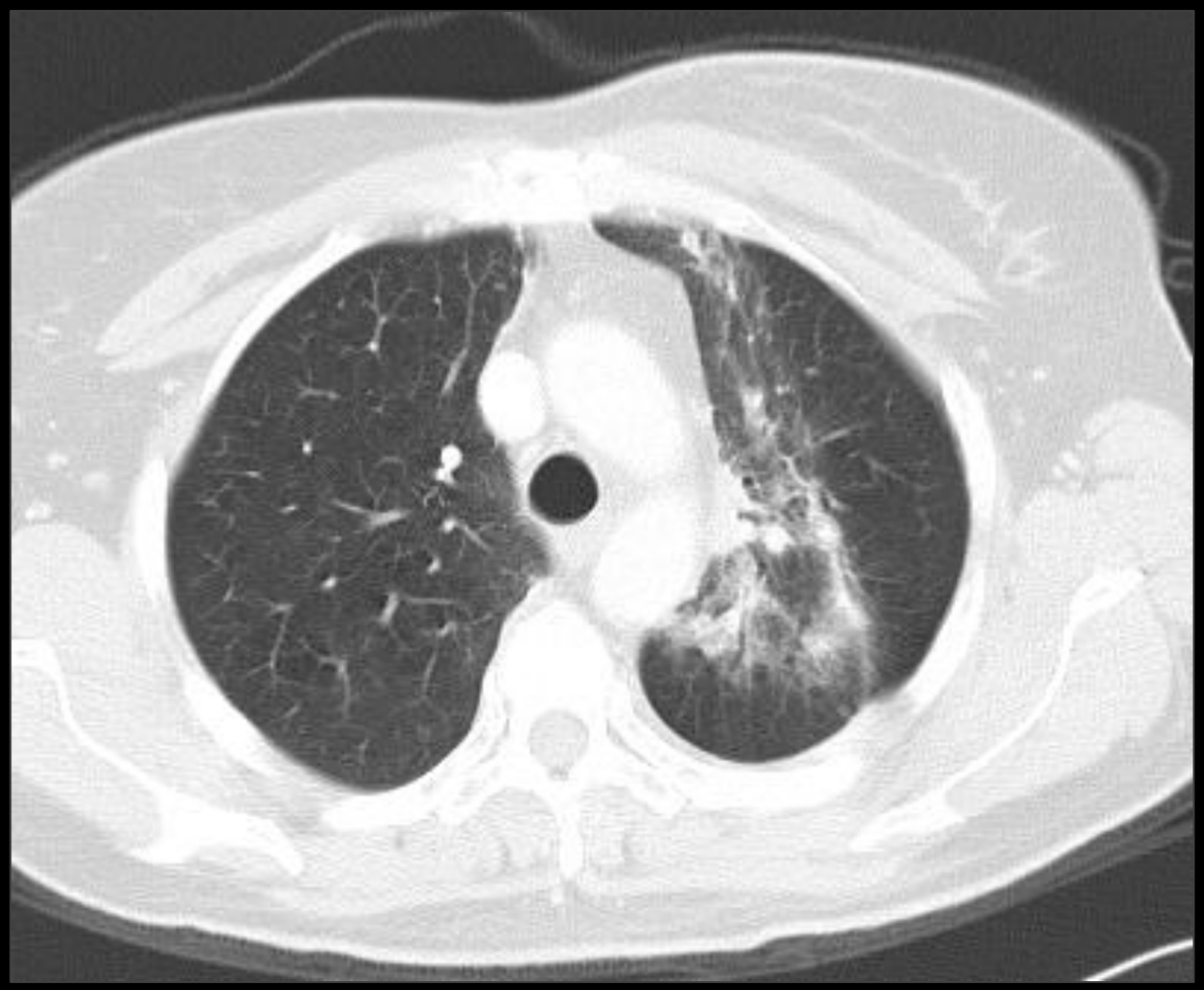
Follow-up examination
Chest CT: stable disease
CT brain: large brain metastasis with peritumoral edema

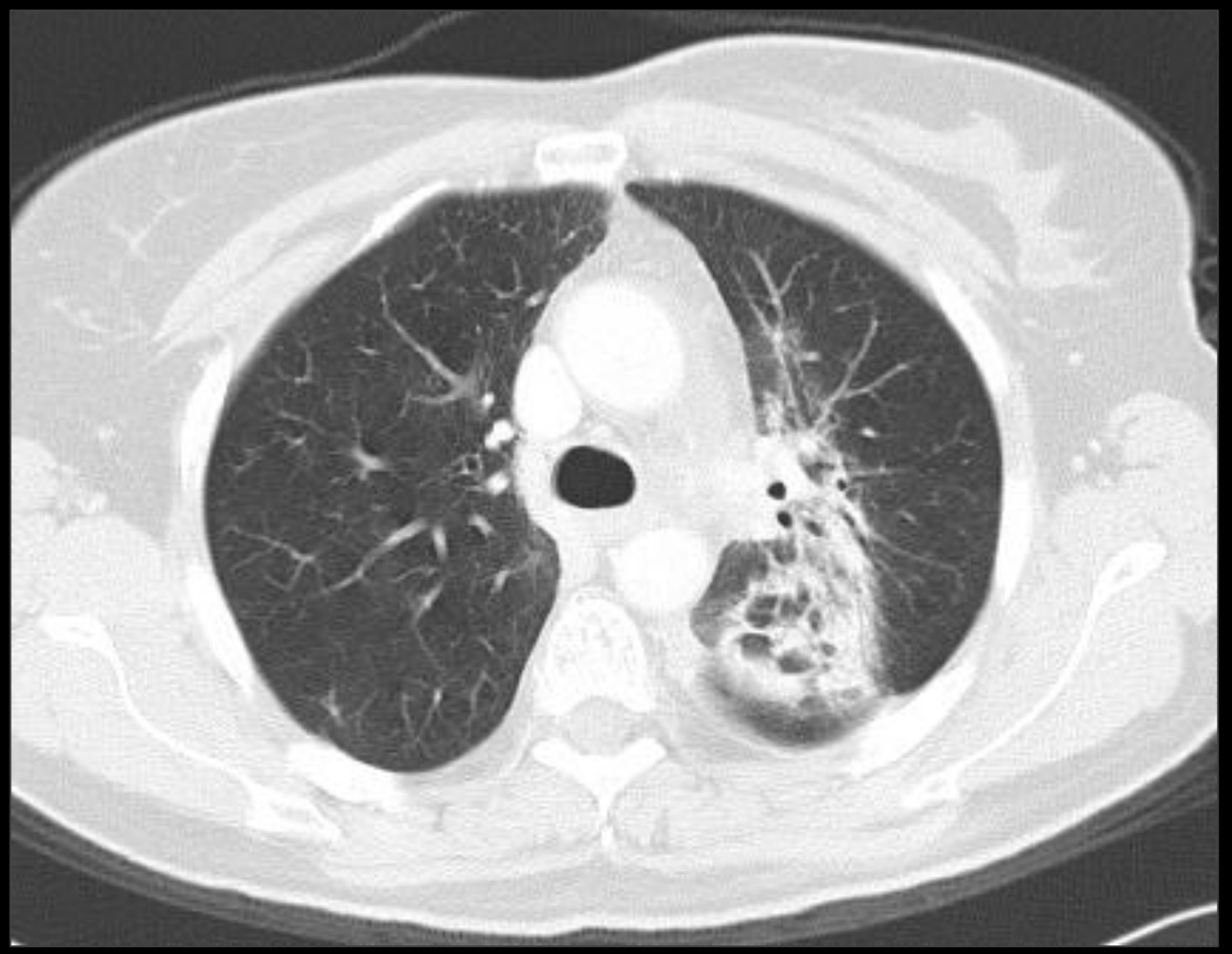
A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline = considered a new lesion (e.g. brain metastases)

Appearance of a new malignant lesion

=

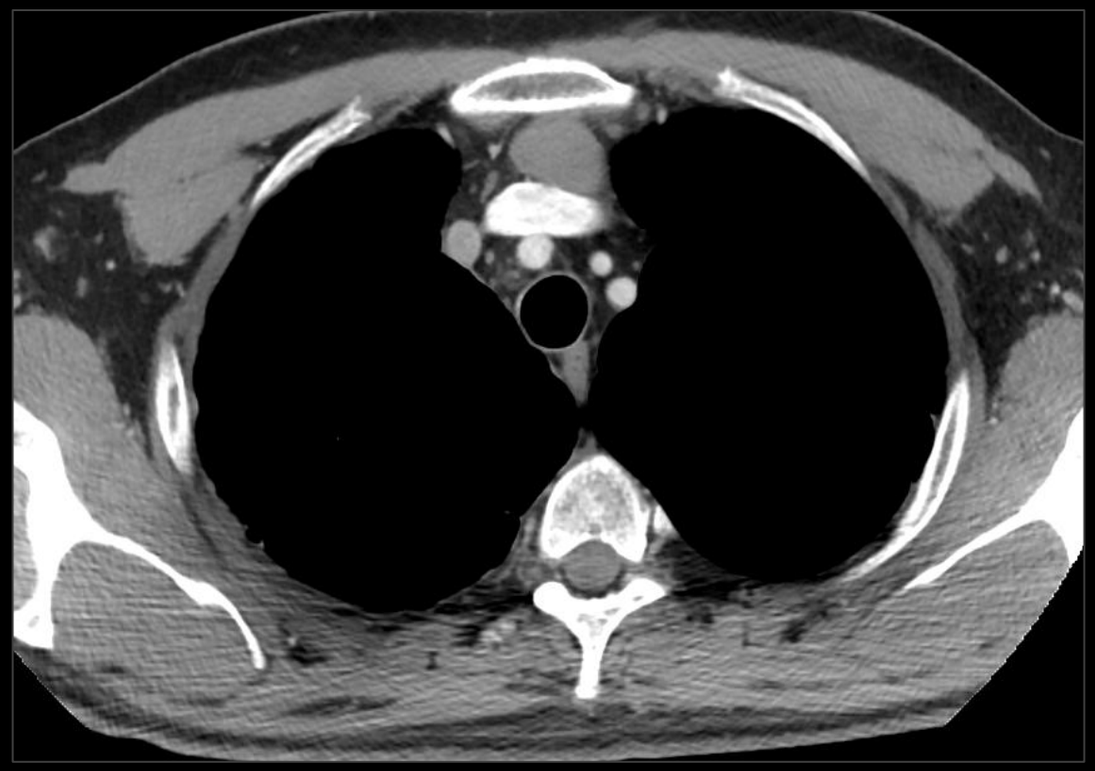
disease progression

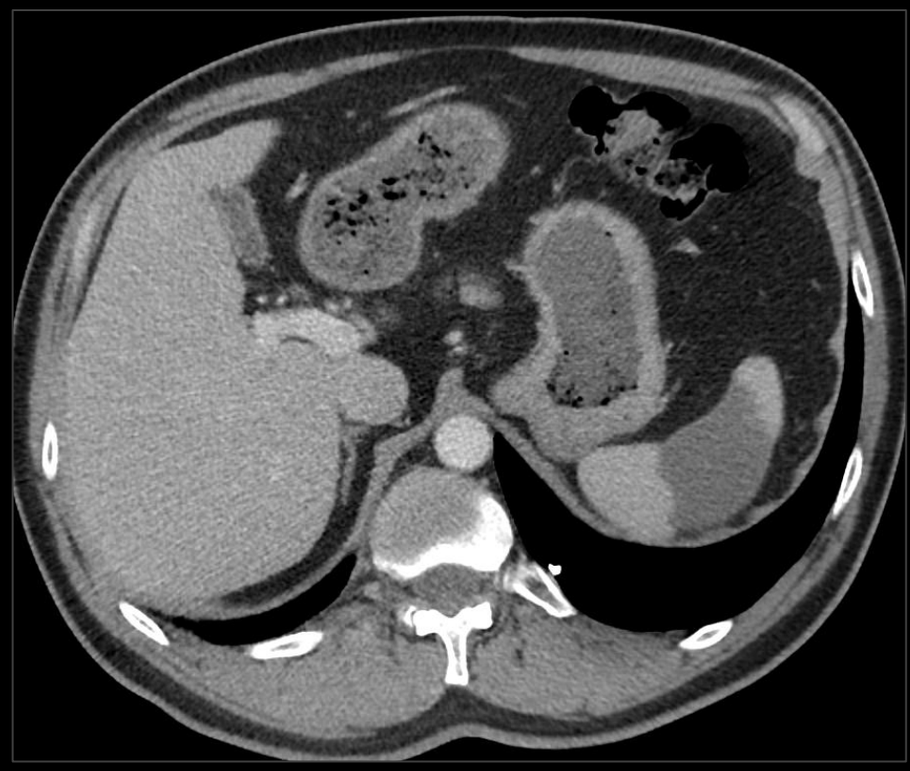


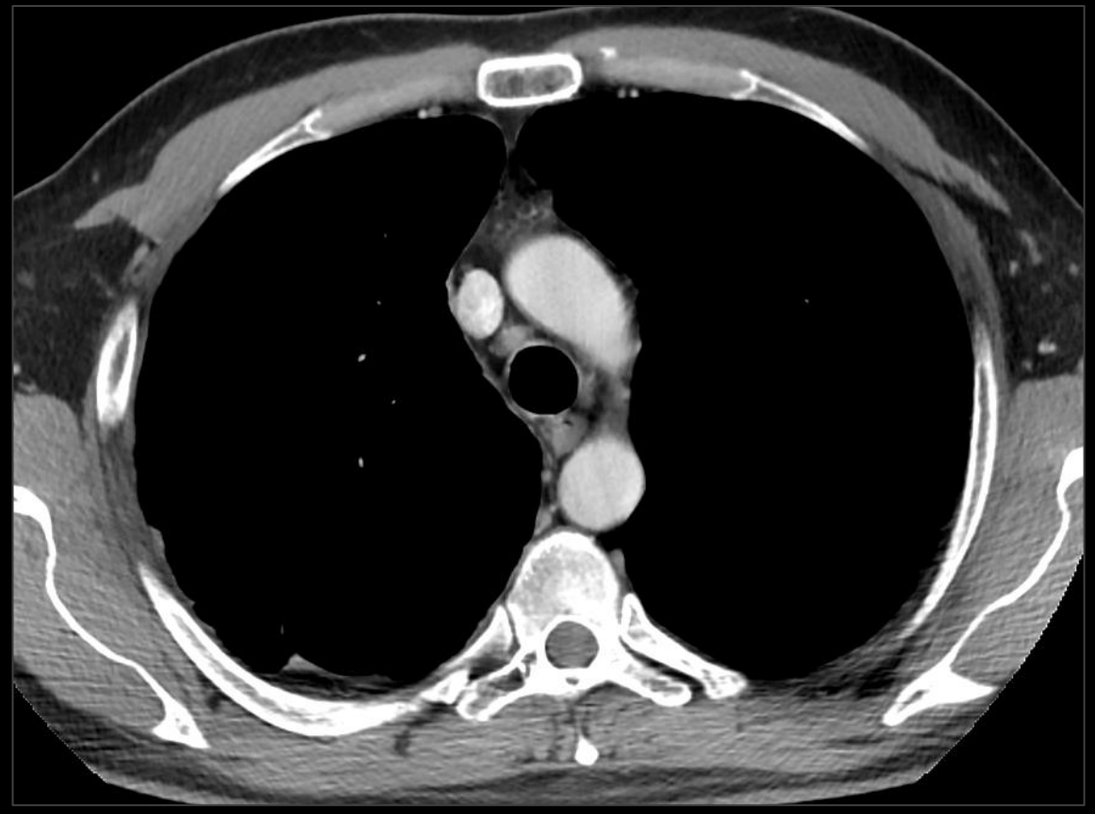


DSM - °1945 - NSCLC

Follow-up examination
Tumor shrinkage
Large new peritumoral consolidation
Paramediastinal anteroposterior orientation
→ Previous history → Radiotherapy !







BS - °1956 - NSCLC

Follow up examination

Short axis lymph nodes →
Splenic mass = new finding

If new lesion = progressive disease

But !
New lesion needs to be a malignant lesion !

This patient: splenic infarct !!!
→ No disease progression

Not every new lesion is a malignant lesion
If doubt: use other imaging techniques such as PET and MRI

PRESENT

Response criteria: Recurrence of lesions

- Patient with stable disease or partial response:
  - A lesions that disappears and then reappears will continue to be measured and added to the sum

- For a patient with complete response:
  - Reappearance of a lesion would be considered progressive disease

PRESENT

Evaluation of best overall response

- "Time point response"
  - At each protocol specified time point, a response assessment occurs
- "Best overall response"
  - = the best response recorded from the start of the study treatment until the end of treatment
  - On occasion, may not be documented until after the end of therapy
  - Will depend on the findings of both target and non-target disease

PRESENT

Evaluation of time point response

RECIST 1.1. Overall Response Tables

Target Lesion	Nontarget Lesion	New Lesion	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 – non-evaluable

Source: Perceptive Informatics, www.recist.com.

PRESENT

Evaluation of best overall response

- "Best overall response: all time points"
  - = determined once all the data for the patient is known
  - Differs from trials where confirmation of complete or partial response is not required and trials were confirmation of complete or partial response is required.

RECIST: the FUTURE

from RECIST to PERCIST ?

From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors
Richard L. Wahl, Heather Jacene, Yvette Kasamon, Martin A. Lodge
The Journal of Nuclear Medicine, Vol 50, No. 5 (Suppl), May 2009

the FUTURE: PET ?

- Anatomic imaging alone has limitations, particularly in assessing the activity of newer cancer therapies that stabilize disease
- It is clear that the biologic signal from 18F-FDG is important and often more predictive of histologic and survival outcomes than is anatomic imaging

- Some tumors do not have high uptake of may be too small to be reliably quantified
- Standardizing response assessment for PET in treatment monitoring is difficult but crucial to move the field forward and to allow comparisons from study to study

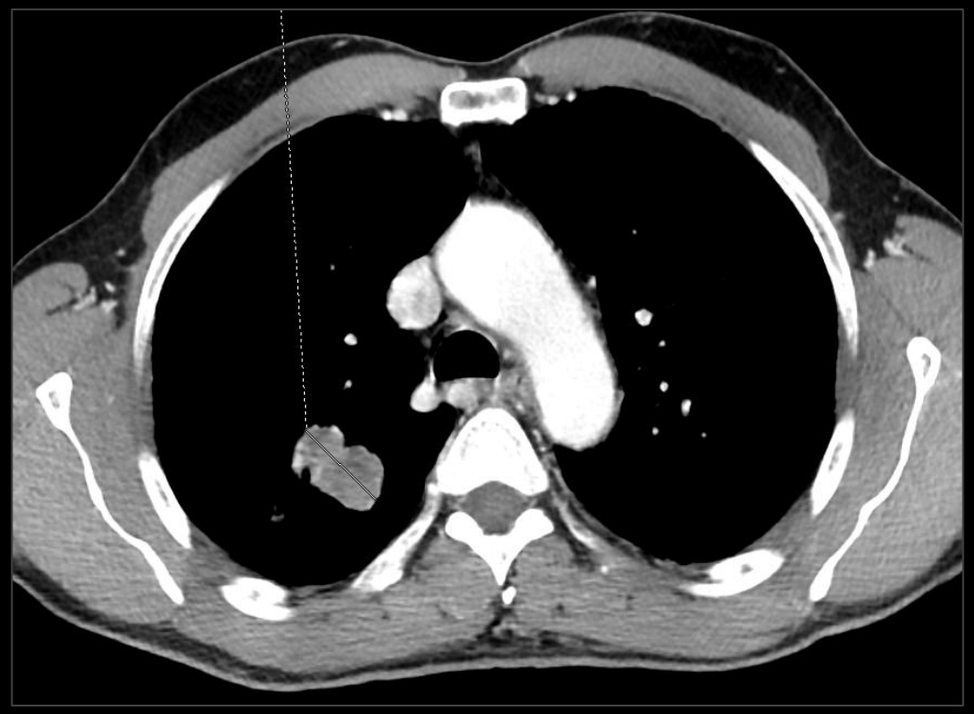
FUTURE

Issues remaining to be solved

- CAVITATION OF LUNG LESIONS
  - Commonly observed, especially in non-small lung cancer treated with antiangiogenic agents
  - Challenge to the radiologists who try to obtain the appropriate measurement that best represents tumor burden
  - Alternative measurement that excludes the area of cavitation
  - Needs to be further validated

Baseline / 08-07-2010

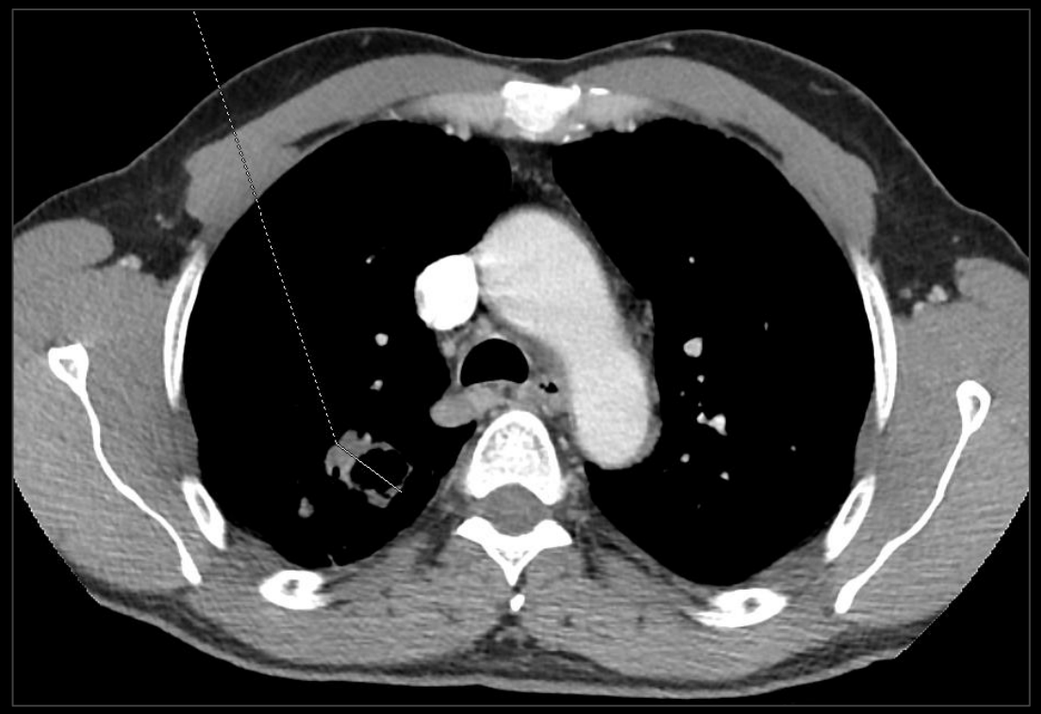
30 mm



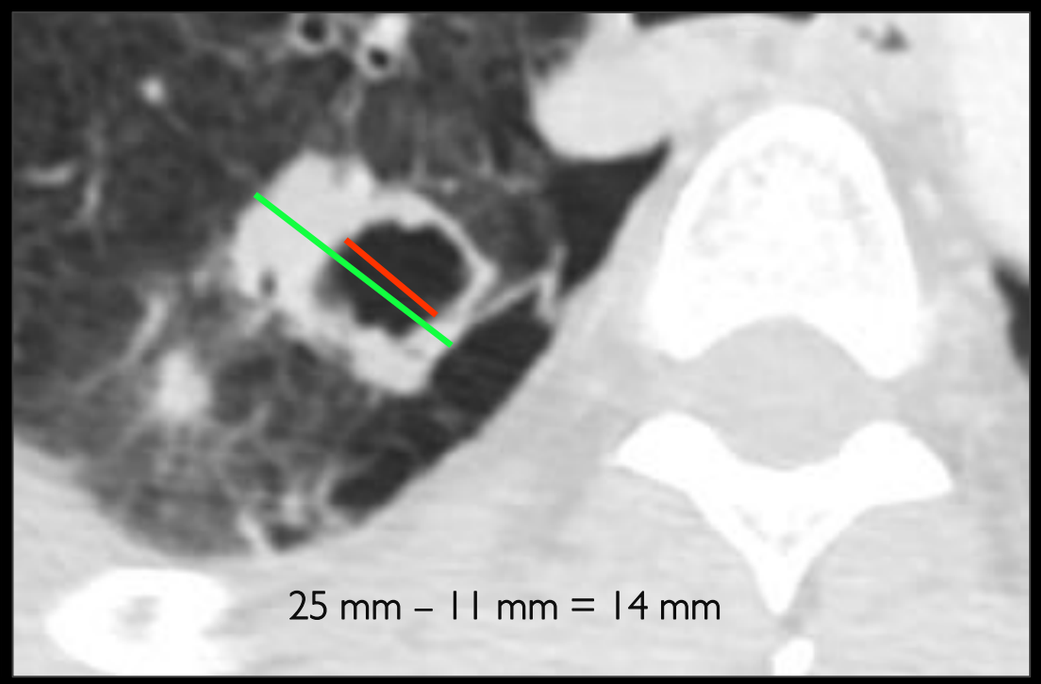
30 mm → 25 mm =
-17%
Stable disease ☹

Follow-up 1 / 13-09-2010

25 mm



30 mm → 14 mm =
-53%
Partial response ☺

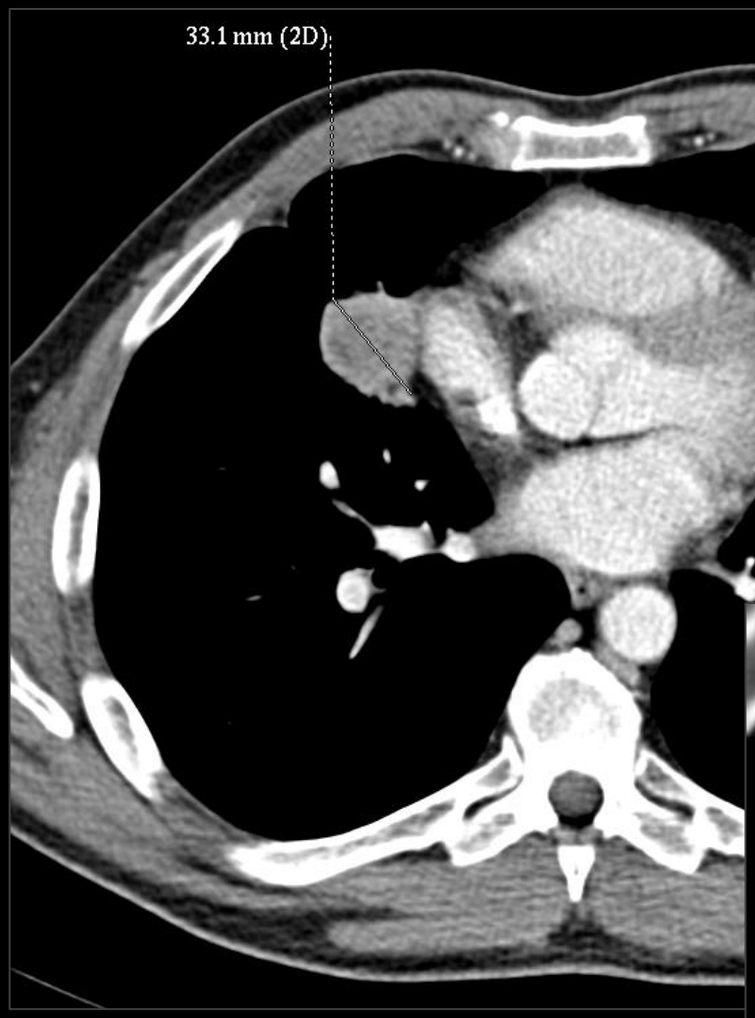


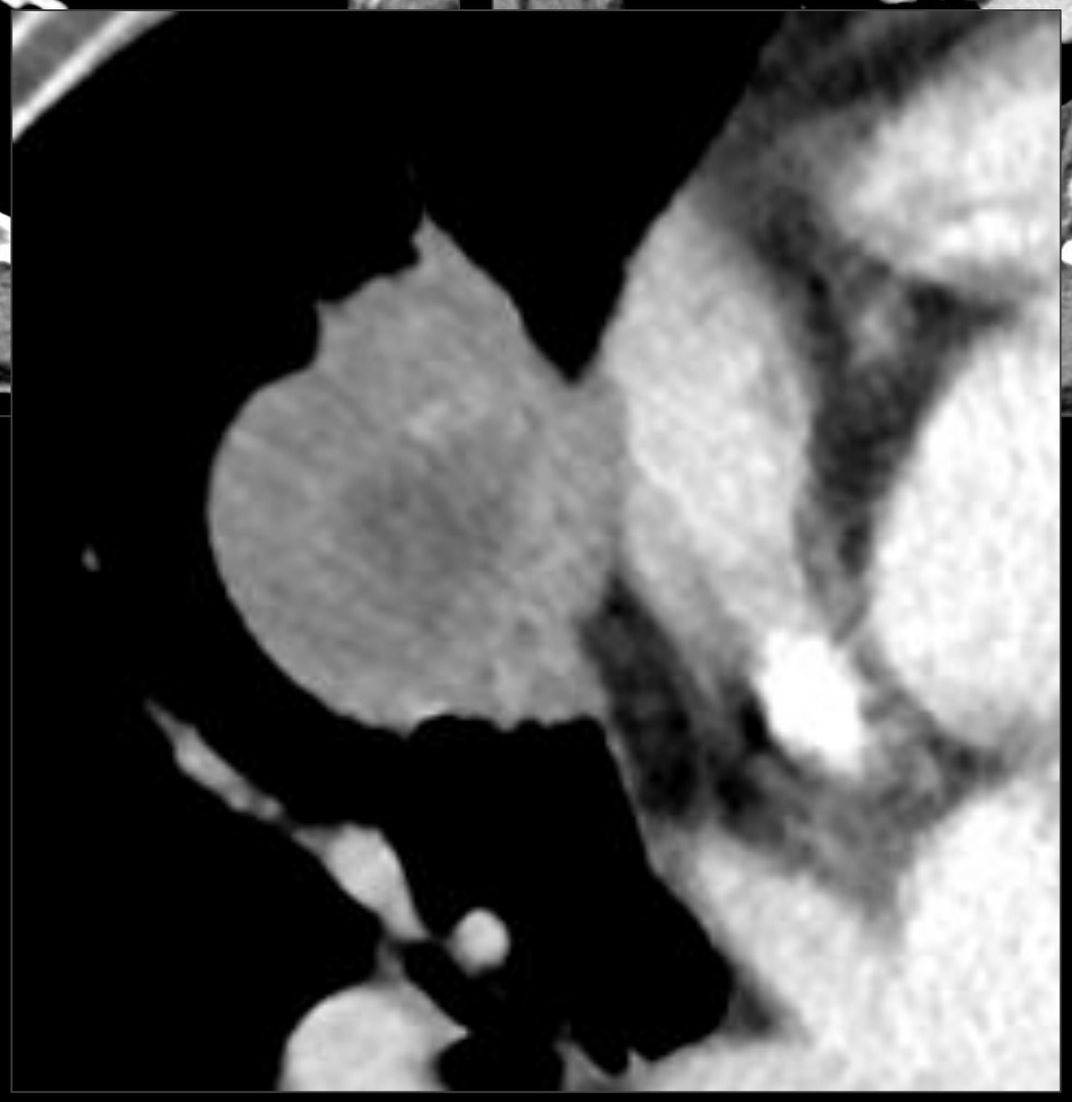
FUTURE

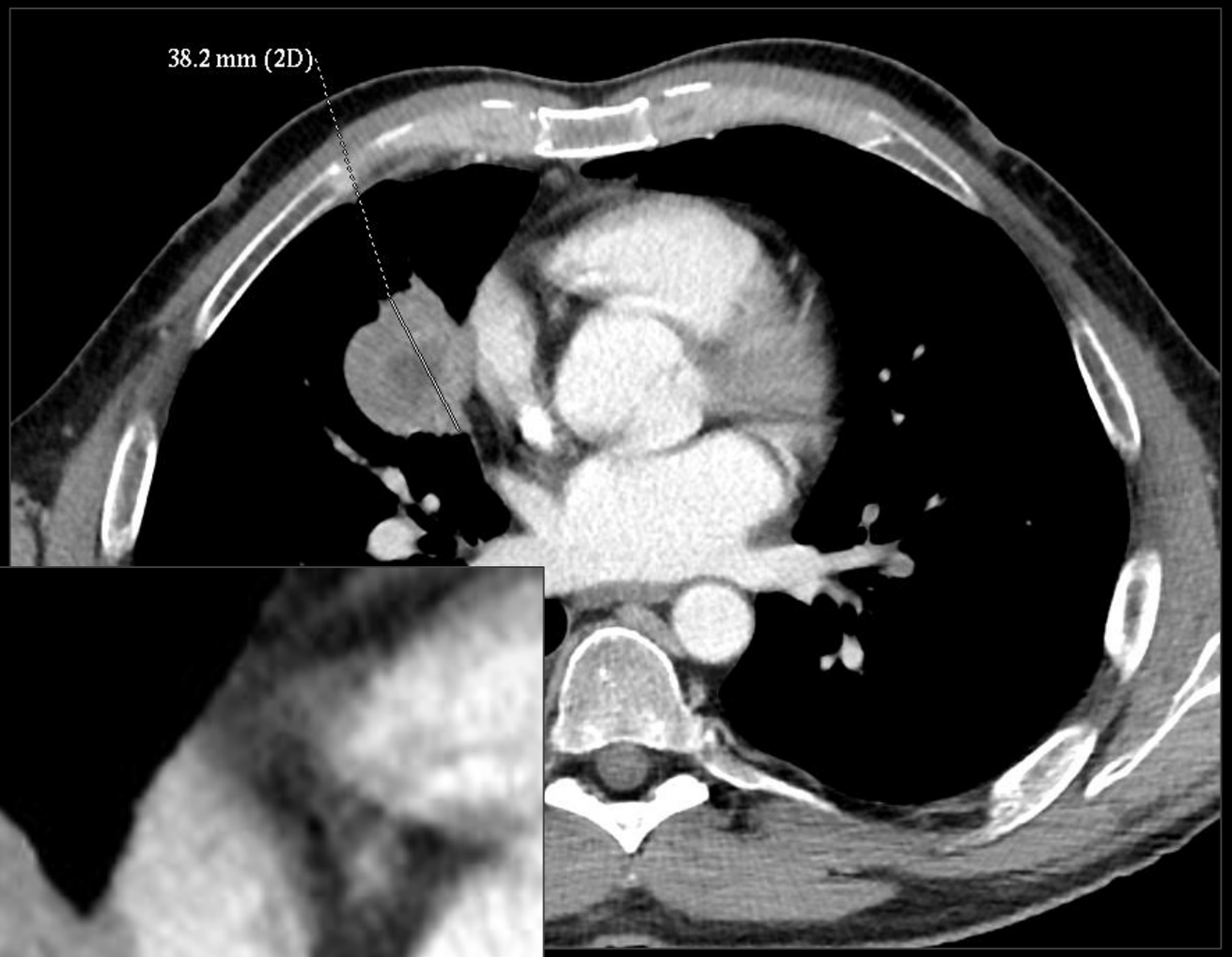
Issues remaining to be solved

- PARADOXICAL INCREASE OF TUMOR SIZE
  - Targeted anticancer therapy using antiogenesis agents or tyrosine kinase inhibitors
  - → may cause a paradoxical increase of tumor size despite response
  - ~ hemorrhage and necrosis
  - Should not be mistaken for PD → MRI or FDG PET

WJ–25-11-1959– NSCLC







Take home messages

RECIST

- Familiarity with the revised RECIST is essential in day-to-day cancer imaging
- Target lesions: longest diameter – 5 lesions – 2 per organ
- Lymph nodes: short axis ≥ 15 mm
- Non-target lesions: absent – present – progression
- New malignant lesion = progressive disease
- Future: RECIST 2.0 ? PERCIST ? → functional imaging will play a more important role

Thank you!

New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1.)
E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, et al.
European Journal of Cancer 45 (2009) 228 - 247