Radiographic Assessment of Response

An Overview of RECIST v1.1

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Presentation Objectives

- To understand the purpose of RECIST guidelines
- To describe the characteristics that are important in selecting target lesions
- To apply RECIST v1.1 guidelines in assessing response to therapy

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RECIST

- **R**esponse **E**valuation **C**riteria **I**n **S**olid **T**umors
  - Guidelines published in 2000
  - Updated guidelines (v1.1) published in 2009
- Guidelines are a tool to assess response to treatment

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. Gwyther[i], M. Mooney[g], L. Rubinstein[g], L. Shankar[g], L. Dodd[g], R. Kaplan[j], D. Lacombe[c], J. Verweij[k]

EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247

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Response

- Critical endpoint for many clinical trials
  - Reflects changes in tumor burden
  - Historically represented drug activity
  - Related to other clinical outcomes
    - Correlation with survival *(Paesmans et al 1997, Buyse et al 2000)*
- Criteria for assessing response and progression are critical when RR is the primary endpoint
  - Time to progression and progression free survival are based on assessment of progression

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Assessing Response

- Integral part of clinical oncology
  - Systematic observation is a basic principle of oncology
  - Radiographic assessment routinely performed and guides patient care but…
    - Inconsistent use of terms like “response” and “progression”
    - Reproducibility and comparisons across institutions are challenging
    - No clear rules on how to approach a mixed response

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Assessing Response

- Formal guidelines standardize assessment
  - Facilitate comparison within and among trials
- Goal is consistency and reproducibility

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Assessing Response

THE EFFECT OF MEASURING ERROR ON THE RESULTS OF THERAPEUTIC TRIALS IN ADVANCED CANCER

CHARLES G. MOERTEL, MD,* AND JAMES A. HANLEY, PHD†

Cancer 38:388–394, 1976.

- Need for a surrogate endpoint was clear
  - For cytotoxic therapy, response rate was an early endpoint
- Study simulated clinical conditions
  - Establish what is reproducible (not necessarily significant)
  - 12 spheres of varying diameter placed under a soft mattress of foam rubber to represent masses / lymph nodes
  - 16 experienced physicians measured each diameter
  - Consistent results obtained when the product of perpendicular diameters was reduced by 50%
    - Reduction by 25% led to more inconsistency

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Assessing Response

- World Health Organization (WHO)
  - First international criteria published in 1979
    - Standardized reporting of results
    - Defines response and progression
      - Response was a reduction in the product of perpendicular diameters by 50%
  - Was left open to interpretation and led to variations and "modified WHO criteria"
    - Identification of measurable lesions
    - Number of lesions to measure
    - Progression and mixed responses
    - Accounting for new technology

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Assessing Response

- RECIST criteria
  - Collaboration of NCI, EORTC, NCIC
  - International membership
  - Representatives from academia, industry, clinical research, image acquisition
  - Employed a data warehouse
    - 6500 patients, 18000 lesions
    - Simulation studies estimate the impact of changes in guidelines

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Assessing Response

- RECIST criteria
  - Target and non-target lesions
    - Quantitative assessment of target lesions
    - Qualitative assessment of non-target lesions
  - Updated WHO criteria
    - Fewer measured lesions
    - Updated definitions of progression
    - Unidirectional instead of bidirectional

	Diameter, $2r$	Product, $(2r)^2$	Volume, $4/3\pi r^3$
Response	Decrease	Decrease	Decrease
	30%	50%	65%
	50%	75%	87%

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Journal of the National Cancer Institute, Vol. 92, No. 3, February 2, 2000

Assessing Response

- Subsequently validated
  - Exceptions include mesothelioma, lymphoma
  - Updated in 2008 (version 1.1) for further clarification, simplification and standardization

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RECIST v1.1 Criteria

- The purpose of RECIST guidelines is to standardize response assessment
- Most trials assessing response utilize RECIST
  - Understanding RECIST criteria is critical to trial conduct and interpretation of results
    - Eligibility
    - Continuation of effective therapy
    - Discontinuation of ineffective therapy

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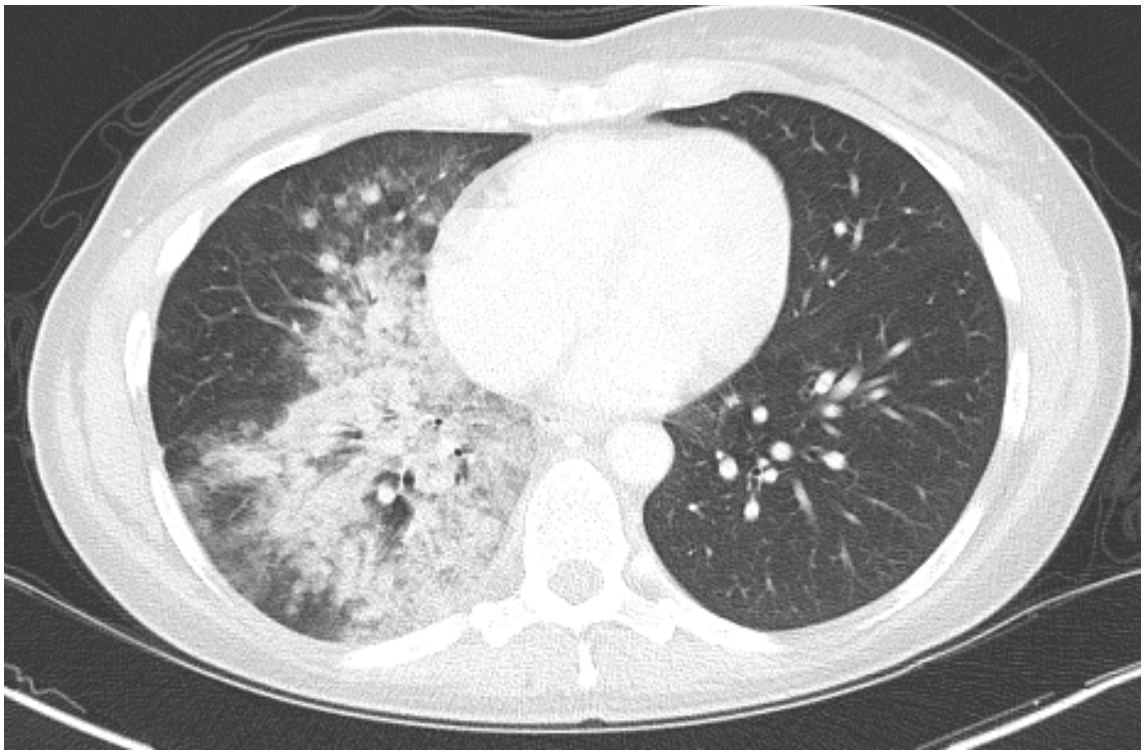
Measurable Disease

- "Measurable" disease is more than just *"measurable"*
  - Dimensions on a radiology report are not enough!



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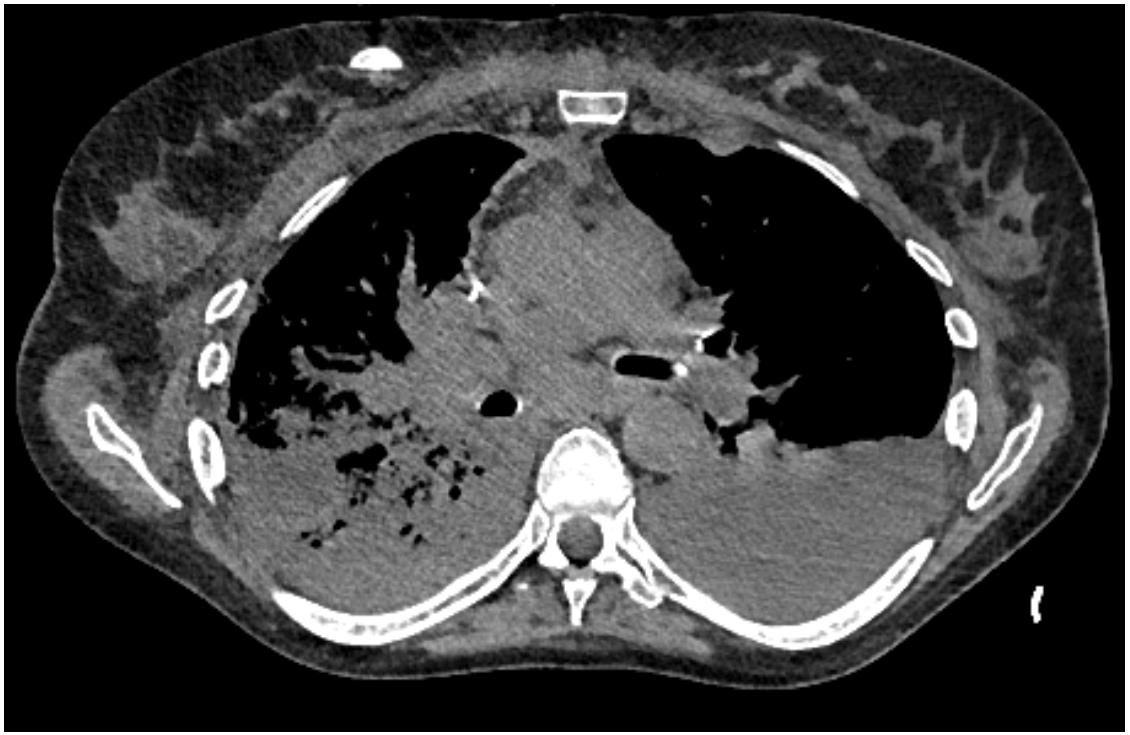

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Measurable Disease

- Tumor lesions
  - Measure in the plane in which images were acquired
    - For body CT, this is typically the axial plane
  - Must be accurately measured in at least one dimension with a minimum size (by long axis) of
    - 10 mm by CT scan
    - 10 mm by caliper measurement on clinical exam
    - 20 mm by chest x-ray
  - Based on a 5mm slice thickness
    - If slice thickness is > 5mm, use 2x the slice thickness as the minimum size

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Measurable Disease

- Malignant lymph nodes
  - Must be accurately measured in at least one dimension with a minimum size (by **short** axis) of
    - 15 mm by CT scan
  - Follow the **short** axis, not the long axis

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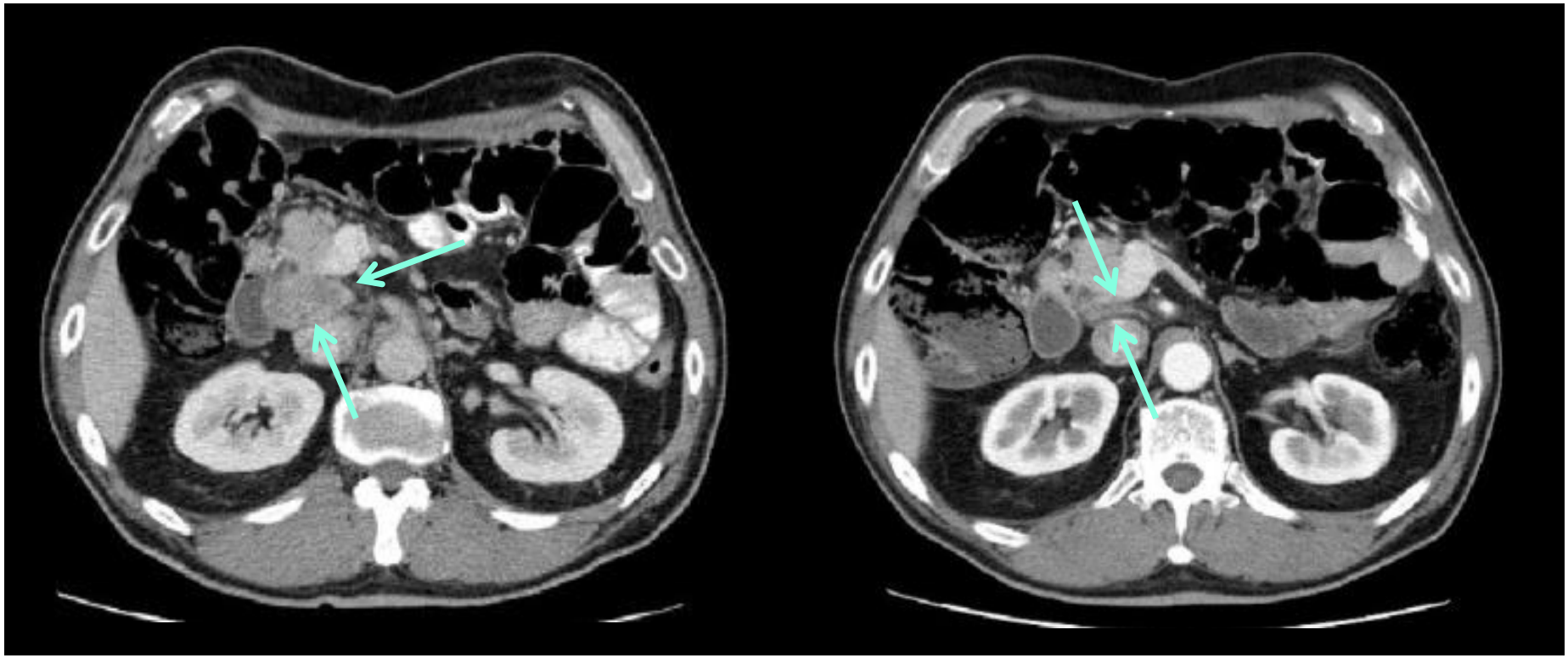
Lymph Node – Short Axis



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Eisenhauer, EORTC 2008

Non-Measurable Disease

- All other lesions are non-measurable
  - Smaller lesions
  - Leptomeningeal disease
  - Lymphangitic disease of skin or lung
  - Ascites
  - Effusions
  - Inflammatory breast disease
- Lymph nodes with a short axis < 10mm are considered non-pathological and should not be recorded or followed

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Non-Measurable Disease

- Bone lesions
- Cysts
- Previously treated lesions
  - Unless there is documented progression in the lesion following prior treatment

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Modality

- Image-based assessment preferred to clinical exam
- Consistency should be maintained
  - Chest X-ray is acceptable but not preferred
  - MRI can be used
    - Preferred for neoadjuvant studies in breast cancer
  - CT is otherwise the preferred modality
  - Ultrasound cannot be used
    - Not reproducible
    - Operator dependent and subjective
    - Obstructed by gas

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Selecting Target Lesions

- Careful planning prior to therapy is critical
  - Ensure eligibility
  - Minimize challenges in the future
- Target lesions
  - Largest and most easily and reproducibly measurable
  - Representative of the disease
- Non-target lesions
  - Represents all other manifestations of the disease
  - Includes
    - Non-measurable lesions
    - Measurable lesions not selected as target lesions

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Selecting Target Lesions

- How to choose your target lesions
  - Radiographic assessment preferred over clinical exam
  - CT preferred over chest X-ray or MRI
    - Use the same modality going forward
- Remember which diameter to use
  - Tumor lesions always use longest diameter
  - Lymph nodes always use shortest diameter

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Selecting Target Lesions

- Each case is unique
- Select lesions with well-defined edges or margins
- Choose lesions in a stable position
  - Mesenteric masses will often change position
- Think ahead
  - Avoid lesions in close proximity that may coalesce
- Capture the disease distribution
  - Limited to 5 target lesions and 2 per organ

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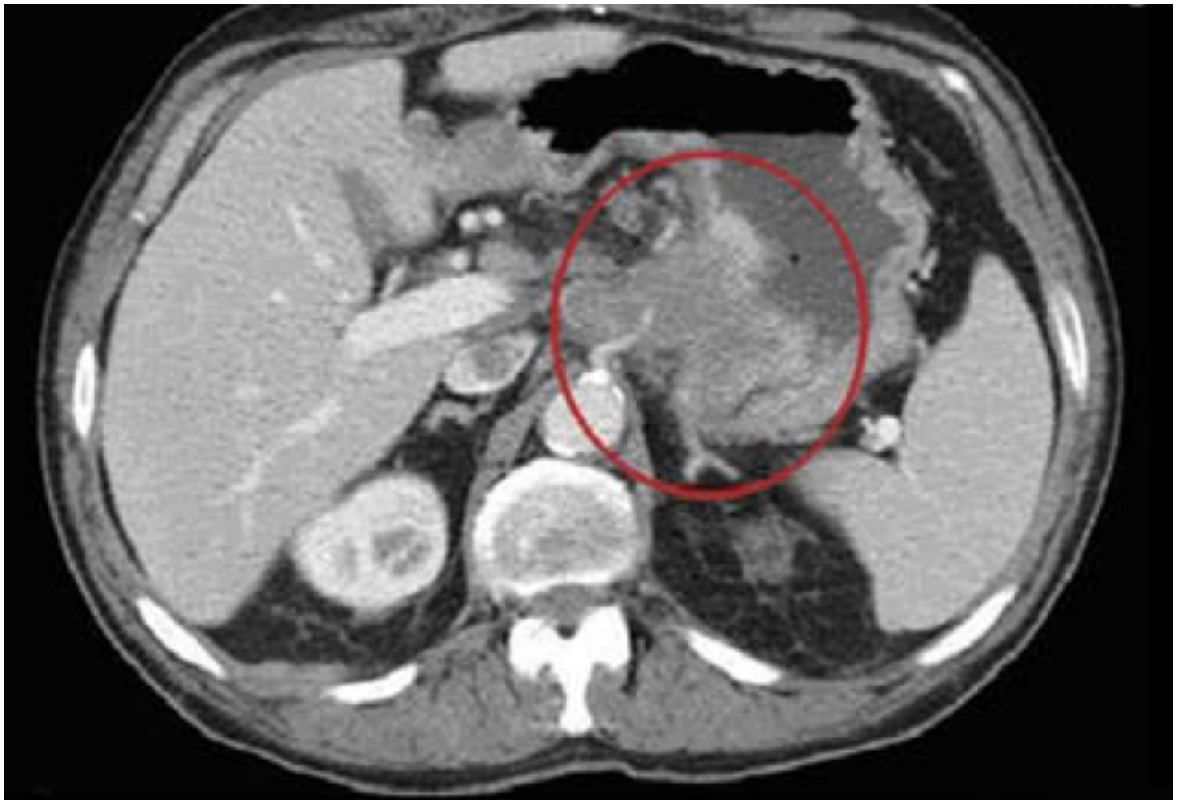
Measurable Disease

- Largest lesion may not be the best lesion



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Eisenhauer, Eur J Cancer 2008

Assessing Response

- The sum of the diameter for all target lesions will be used to calculate response
- Each target lesion will be followed
  - If lesion is no longer measurable, it will still be counted
  - Longest diameter should be used, not orientation or slice
  - If visible but “too small to measure”, use 5mm as the value
    - If a value is provided under 5mm, use the measured value

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Response Definitions

- Complete response (CR)
  - Disappearance of all target lesions (LN < 10mm short axis)
- Partial response (PR)
  - At least a 30% decrease in the sum of diameters of target lesions relative to the baseline sum

ALLIANCE
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Response Definitions

- Complete response (CR)
  - Disappearance of all target lesions (LN < 10mm short axis)
- Partial response (PR)
  - At least a 30% decrease in the sum of diameters of target lesions relative to the baseline sum
- Progressive disease (PD)
  - At least a 20% increase (and at least 5mm) in the sum of diameters of target lesions relative to smallest sum on study
  - Appearance of a new lesion is also progression

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Assessing Response

	10/31/14			
Sum of Target Lesions	6.4 cm			
Response	Baseline			

- Baseline uses long axis for tumor lesions and short axis for malignant lymph nodes

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Assessing Response

	10/31/14	12/15/14		
Sum of Target Lesions	6.4 cm	4.0 cm		
Response	Baseline	PR		

- Decrease from 6.4 cm to 4.0 cm
  - Reduction of 2.4 cm
  - Reduction of 38% from baseline (unconfirmed PR)

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Assessing Response

	10/31/14	12/15/14	2/2/15	
Sum of Target Lesions	6.4 cm	4.0 cm	2.2 cm	
Response	Baseline	PR	PR	

- Decrease from 6.4 cm to 2.2 cm
  - Reduction of 4.2 cm
  - Reduction of 66% from baseline (confirmed PR)

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Assessing Response

	10/31/14	12/15/14	2/2/15	3/27/15
Sum of Target Lesions	6.4 cm	4.0 cm	2.2 cm	3.2 cm
Response	Baseline	PR	PR	

- Decrease from 6.4 cm to 3.2 cm
  - Reduction
  - Reduction ≥ 30% baseline (confirmed PR)

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Assessing Response

	10/31/14	12/15/14	2/2/15	3/27/15
Sum of Target Lesions	6.4 cm	4.0 cm	2.2 cm	3.2 cm
Response	Baseline	PR	PR	PD

- Increase from 2.2 cm to 3.2 cm
  - Increase by 1.0 cm
  - Increase by 45% from baseline (PD)
    - PD: At least a 20% increase (and at least 5mm) in the sum of diameters of target lesions relative to **smallest sum on study**

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Response Definitions

- Complete response (CR)
  - Disappearance of all target lesions (LN < 10mm short axis)
- Partial response (PR)
  - At least a 30% decrease in the sum of diameters of target lesions relative to the baseline sum
- Progressive disease (PD)
  - At least a 20% increase (and at least 5mm) in the sum of diameters of target lesions relative to smallest sum on study
  - Appearance of a new lesion is also progression
- Stable disease (SD)
  - Does not qualify for any of the above

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Lymph Nodes

- Normal structures
  - Not considered pathologic when short axis < 10mm
  - Short axis diameter still recorded and included in the sum of target lesions
- In patients with a complete response, normal lymph nodes may persist
  - Sum of lesions may be greater than zero even in a CR

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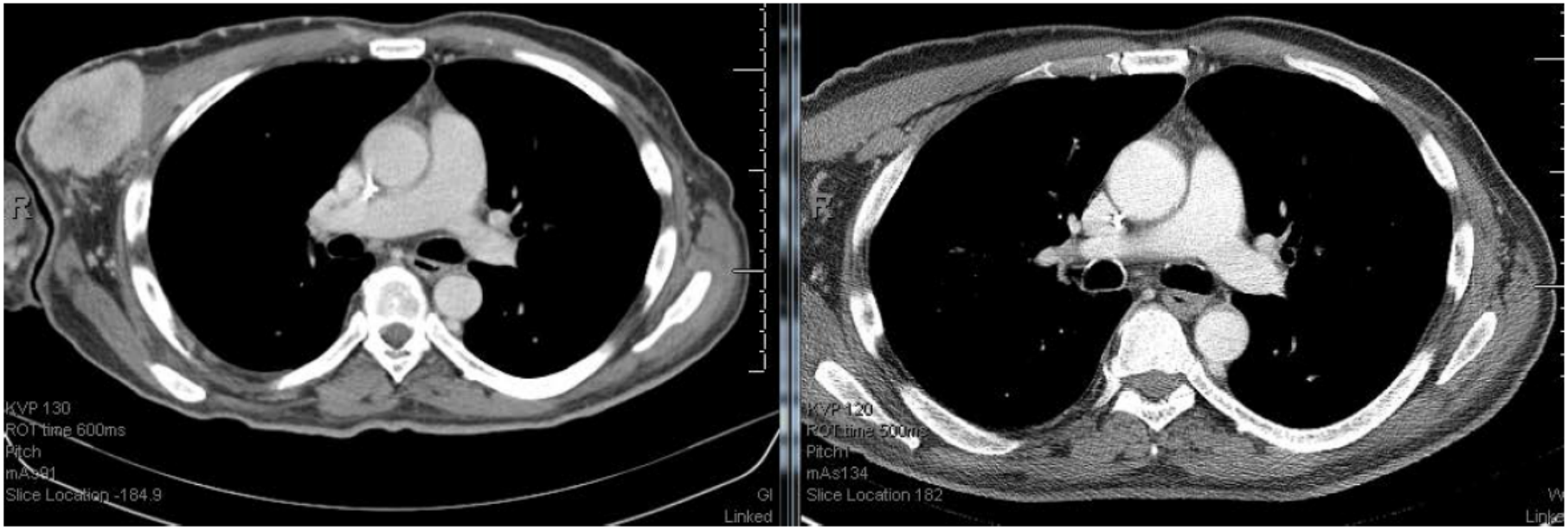
Complete Response



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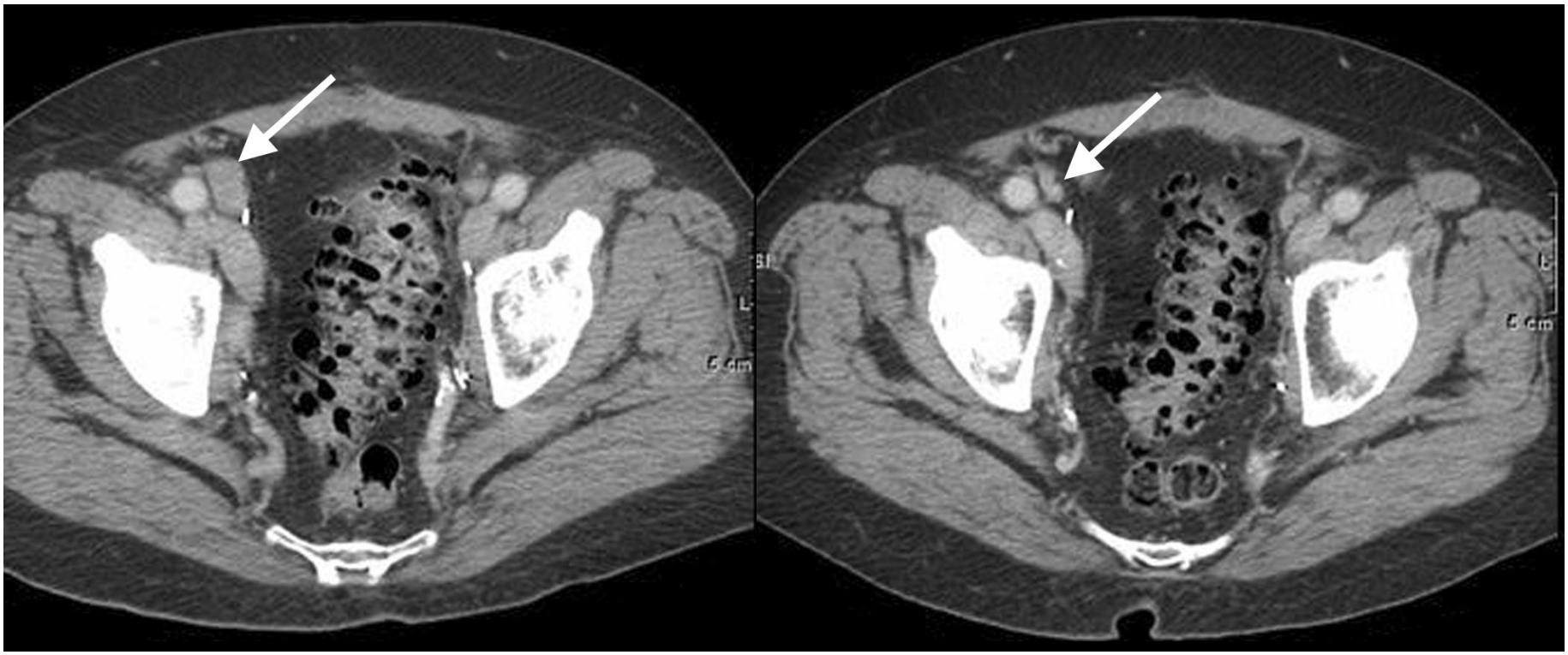
Lymph Node Normalization



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Eisenhauer, EORTC 2008

Non-Target Lesions

- No need for measurements
  - Qualitative assessment is required
- Complete response requires disappearance of all non-target lesions (all LN < 10mm in short axis)
- Progressive disease on the basis of non-target lesions only when there is unequivocal progression
  - A modest increase in size is not sufficient
  - Change must be sufficient to require a change in therapy

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New Lesions

- Represent progression regardless of measurability
- Should be unequivocal
  - New bone lesions may represent healing or a flare
  - Equivocal lesions should be confirmed
    - If subsequently shown to represent new disease, the date of progression should be the date of the initial scan
- When a lesion is seen in an anatomic area not included in the baseline scan, it is considered new and will constitute progressive disease
  - Obtaining the proper baseline scan is critical!

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PET

- Positive lesion has FDG avidity at least twice that of surrounding tissue on the attenuation corrected images
- If a PET is negative at baseline and positive at follow up, this is a sign of progressive disease
- If there is no PET at baseline
  - A new lesion confirmed by CT is progressive disease
  - A new lesion not seen by CT is not progressive disease
  - Increased FDG avidity in a pre-existing site that is not progressing based on CT is not progressive disease

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Unique Circumstances

- Lesions that split during treatment
  - Longest diameter of fragmented portions should be added together to calculate the target lesion sum
    - Document the process
- Lesions that coalesce
  - When a plane exists, use it to measure individual lesions
  - If lesions are truly coalescing, the vector of the longest diameter should be used as the longest diameter of the ‘coalesced lesion’ and represent the two target lesions

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Unique Circumstances

- Lesions that disappear and return
  - Continue to measure and include in the sum
    - Diameter will contribute to PR/PD evaluation
  - If the patient had achieved a complete response and a lesion reappears, this constitutes progressive disease

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Unique Circumstances

- Target lesion is now non-evaluable due to necessary changes in technique
  - Seek a baseline exam using the new technique
  - If no alternatives – judgment call
    - Delete the lesion from all forms
    - Make the overall interpretation inevaluable
    - Should be discussed with the site and study PI / monitor
  - Try to anticipate before the trial starts

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Tumor Markers

- Alone, tumor markers cannot assess response
- If elevated, they must normalize to meet criteria for a complete response
  - Published guidelines for CA-125 and PSA
  - Should be incorporated into protocols for specific diseases

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Conclusions

- Goal is accuracy and reproducibility
- Strict criteria on measurability
  - 10 mm for tumor lesions
  - 15 mm for lymph nodes (using the short axis)
- Select target lesions carefully
- When assessing response
  - PR – decrease in sum of diameters by 30% from baseline
  - PD – increase in sum of diameters by 20% from nadir (or emergence of unequivocal new lesions)
- Refer to the published guidelines and the protocol!

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