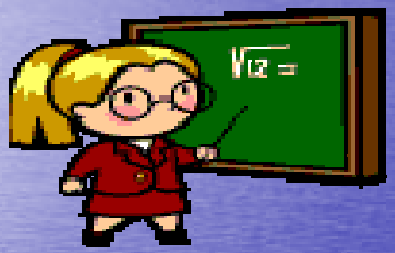
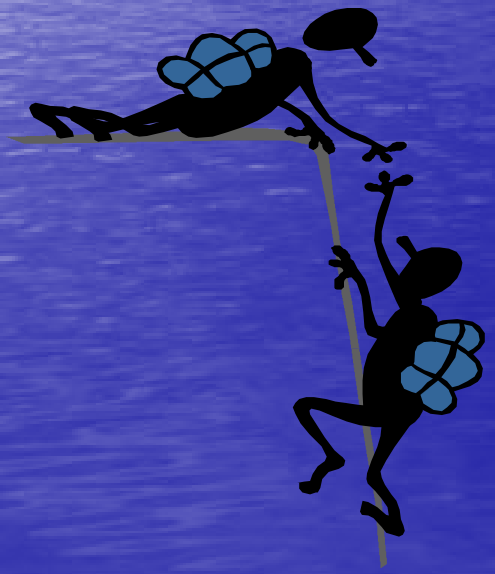
Why are ***YOU*** here ???

Treatment response criteria Which is perfect?

Mustafa ÖZGÜROĞLU
Cerrahpaşa Medical Faculty
Department of Medical Oncology

Why am *I* here ???





Outline

- Background:
  - Definition of response
  - Why measure response?
  - Response criteria in cancer trials
- Key aspects and comparison of WHO AND RECIST 1.0
- New version of RECIST 1.1
- FUTURE

Why Measure Response?

- The word "response" is used in a number of contexts:
  - To describe outcomes in daily practice ("my patient is responding to treatment")
  - As a *surrogate* for benefit (e.g. in randomized trial)
  - As the *primary* endpoint in phase II "screening" trials where a decision is being taken about future of drug or regimen

Why do we need response criteria?

- To assess the change in tumor burden for the clinical endpoints
  - Response
  - Time to progression
  - Progression free survival
- To assess the effect of treatment
  - For the indivial patient
  - in phase II trials
  - As surrogate for overall survival

Response Criteria in Clinical Trials I

- Clinical cancer research takes place in an international arena, thus we need a common, standard “language” for
  - Toxic effects: terms and grades
  - Time to event definitions
  - Tumour response definitions

Response Criteria in Clinical Trials II

- In early drug development:
  - Tumour *shrinkage* has long been used to provide a "signal" that new agents may be effective
  - Zubrod et al. : first clinical trial

- **Anatomic-based criteria** therefore required to describe and categorize patient outcomes
  - WHO/others defined CR, PR, SD, PD

Uniform criteria for reporting response

- WHO criteria 1979
- RECIST
  - version 1.0 Therasse et al. JNCI 2000
  - version 1.1 Eisenhauer EJC 2009

Important parameters in two guidelines

- Definition of the measurability of lesions at baseline
- Objective response
- Overall response
- Duration of response

WHO criteria

- Each lesion is measured in 2 dimensions on the same image
  - Maximum diameter in the transverse plane
  - Longest diameter perpendicular to the other measurement
  - Two measurements are multiplied to obtain a cross product

WHO criteria

Complete response CR	Disappearence of all target lesions
Partial response PR	>50% reduction in cross product
Progressive disease PD	25% increase in the cross product or any new lesion
Stable disease SD	<50% in the cross product or 25% increase in cross product

Shortcomings of WHO

- Complexity (bidimensional measurements)
- New technologies (CT) , MRI or PET-CT?
- Silent on many areas so open to varying interpretation
  - *i.e. the "standard" was no longer standard*

SPECIAL ARTICLE

New Guidelines to Evaluate the Response to Treatment in Solid Tumors

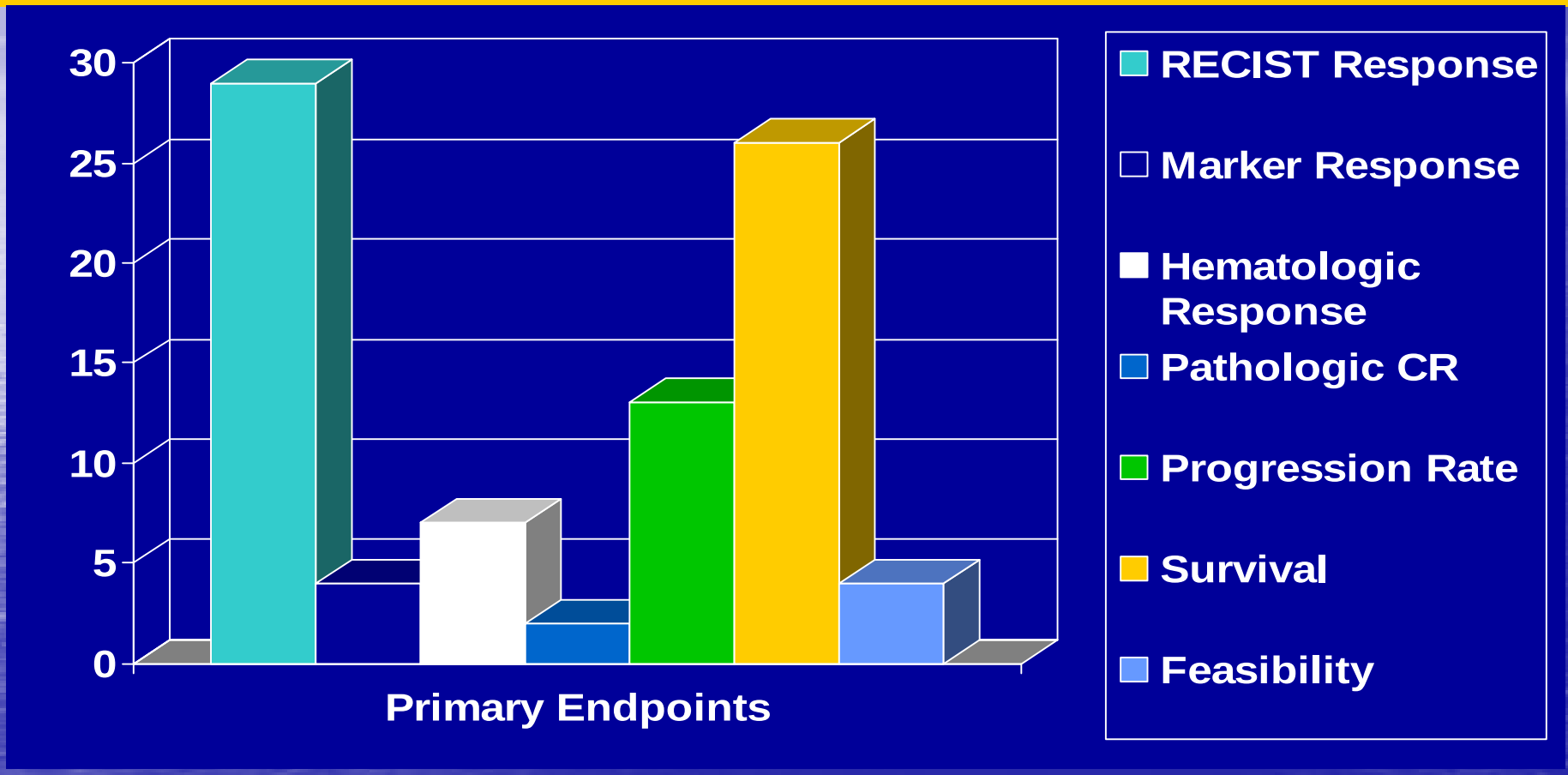
Patrick Therasse, Susan G. Arbuck, Elizabeth A. Eisenhauer, Jantien Wanders, Richard S. Kaplan, Larry Rubinstein, Jaap Verweij, Martine Van Glabbeke, Allan T. van Oosterom, Michaele C. Christian, Steve G. Gwyther

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

Why "Response Evaluation Criteria in Solid Tumors" – RECIST needed?

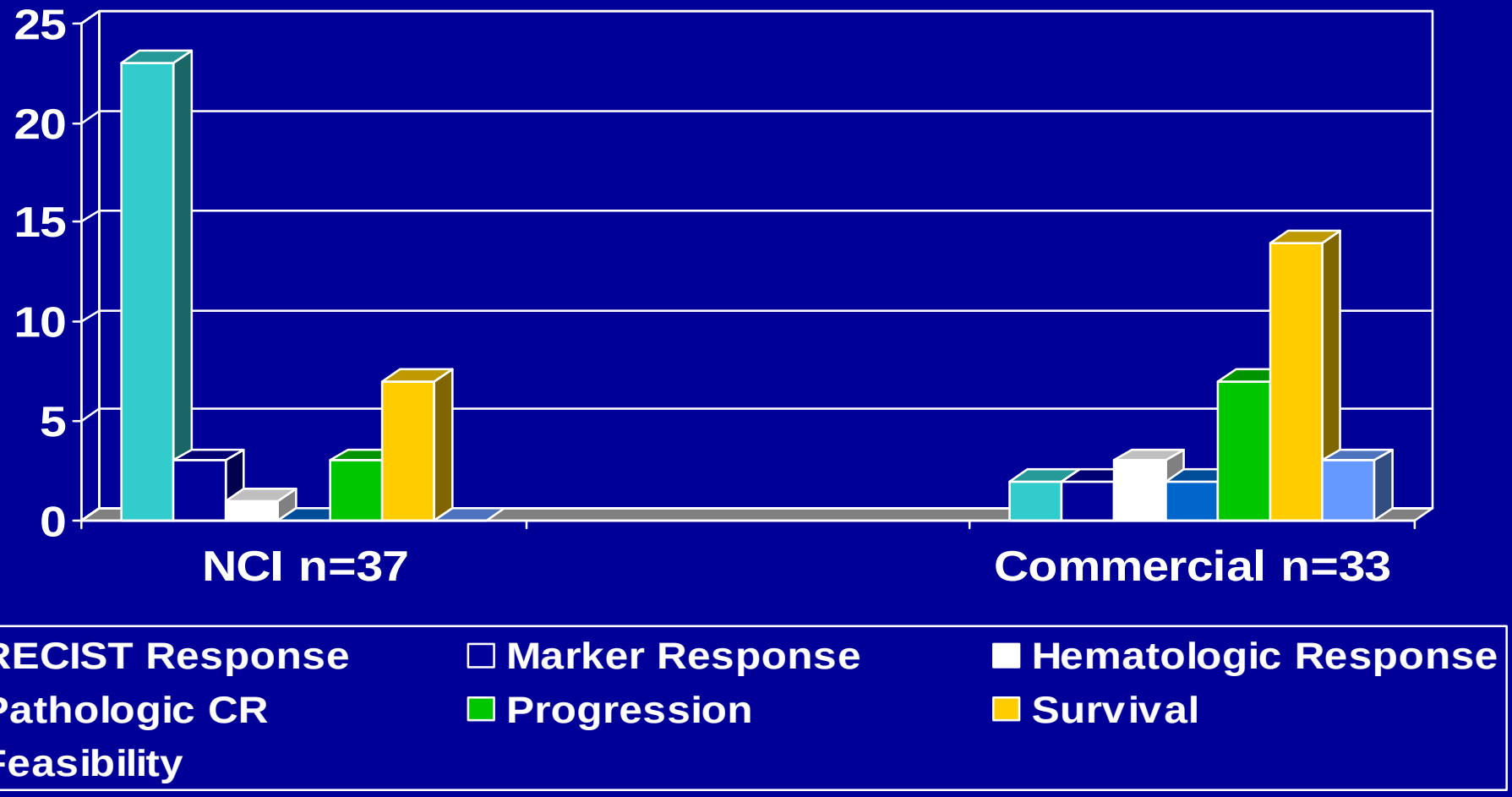
- Intended for use in clinical trials with primary endpoint of objecive response
- Easier unidimensional assessment
- 4 categories of response: CR,PR SD,PD
- Widely adopted by cooperative groups, industry, academia

Endpoints Used in SWOG Phase II Trials



- 86 Phase II studies numbering from S9902-S0517

Does Source of Drug Affect Endpoint Selection in SWOG Phase II Trials?



Method of assessment in RECIST

- Same method and same technique should be used at baseline and follow up
  - Clinical examination
  - Spiral CT should be performed by use of a 5mm contiguous reconstruction
  - Sonography should not be used

RECIST guidelines are more specific than the WHO

- Specific size requirements for measurable lesion at baseline
- Distinguishes target from nontarget
- Gives the maximum number of target lesions to be followed
- Gives a baseline tumor burden for determining progressive disease
  - All TL to be measured , instead of one or more measurable lesions in who

Key RECIST Elements

- Unidimensional measurement of longest diameters
- Measurable lesion ≥ 20 mm (10 mm Spiral CT)
- Identify up to 10 measurable TARGET lesions; maximum 5 per organ. Follow sum of longest diameters (SLD)
- Response Categories:
  - PR = 30% decrease in SLD compared to baseline
  - PD = 20% increase in SLD compared to lowest value on study
- CT scan preferred imaging modality. No ultrasound.

Nontarget lesions

- Bone lesions
- Leptomeningeal disease
- Ascites
- Pleural/pericardial effusion
- Inflammatory breast disease
- TARGET lesions more than 10
- Lesions within previously irradiated area

Comparison of WHO **and** RECIST

Measurability of lesions at baseline

WHO	RECIST
Measurable, bidimensional -product of LD and greatest PD	Measurable, unidimensional -LD only, conventional >20mm, spiral CT >10mm
Nonmeasurable/evaluable -lympangitic pulmonary metastases, effusion	Nonmeasurable: all other lesions including small lesions. Evaluable is not recommended

OBJECTIVE RESPONSE I

	WHO	RECIST
Measurable disease	Change in sum of products of LDs-PDs, no max. lesions specified CR: disappearence of all known disease confirmed at 4 weeks PR: >50% decrease from BL PD: 25% increase of one or more lesions or apearence of new lesions NC: neither PR or PD criteria met	Target lesions:Change in sum of LDs, maximum of 5 per organ,up to 10 total CR:disappearence of all target lesions confirmed at 4 weeks PR: 30% decrease from baseline PD:20% over smallest sum Or new lesions SD: Non-PR nonPD

OBJECTIVE RESPONSE II

	WHO	RECIST
Nonmeasurable	CR: disappearence of all known disease PR: estimated decrease >50% PD: estimated increase >25% in existent lesions or new lesions NC: neither PR or PD met	Nontarget lesions CR:disappearence of all nontarget lesions and normalization of tumor markers PD: unequivocal progression of nontarget lesions or new lesions Non-PD: persistence of nonTG or tm markers above normal limits

Best Overall Response I

	WHO	RECIST
Overall response	Best response recorded in measurable disease	Best response in from treatment start to PG
Duration of response	CR : first met to date PD first noted Overall response: date of treatment start to date of PD	Overall CR: Date CR first met to date recurrent disease first noted Overall response: Date CR or PR first met to date of PD SD: date of treatment start to PD

Best Overall Response II

- Patients with global deterioration requiring discontinuation of treatment are classified as "symptomatic deterioration"

- Every effort should be made to document objective progression even after treatment discontinued.

CONFIRMATION OF RESPONSE IN RECIST

- In order to avoid overestimating response
- Especially in nonrandomized trials
- Tumor measurements must be confirmed 4 weeks later

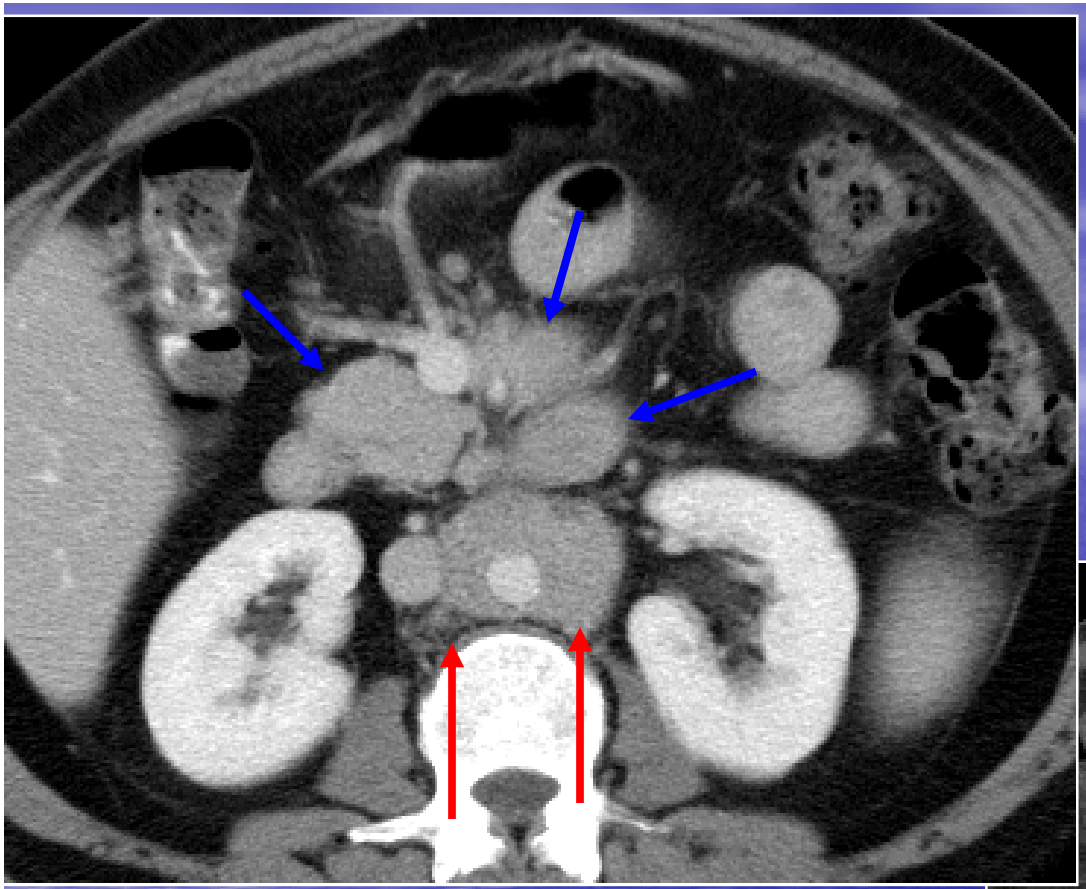
RECIST GRID: OVERALL RESPONSE

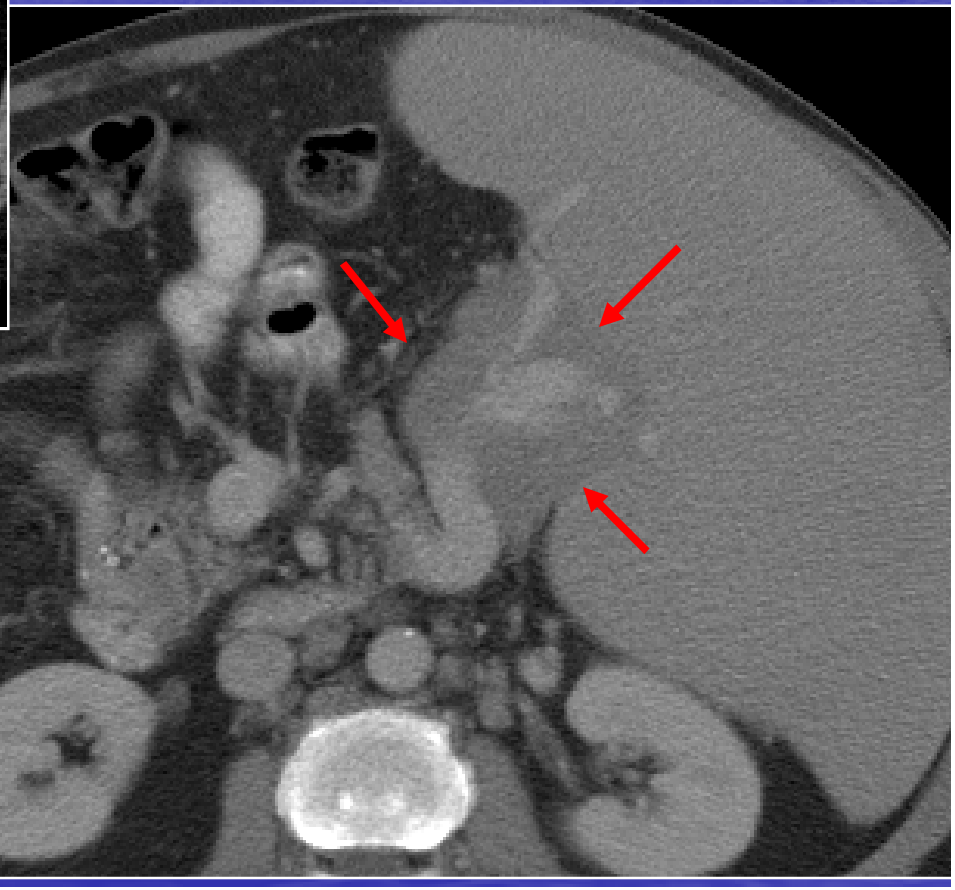
TARGET	NONTARGET	NEW LESION	OVERALL
CR	CR	NO	CR
CR	Non CR/PD	NO	PR
PR	Non-PD	NO	PR
SD	Non-PD	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES OR NO	PD

Limitations of RECIST guidelines I

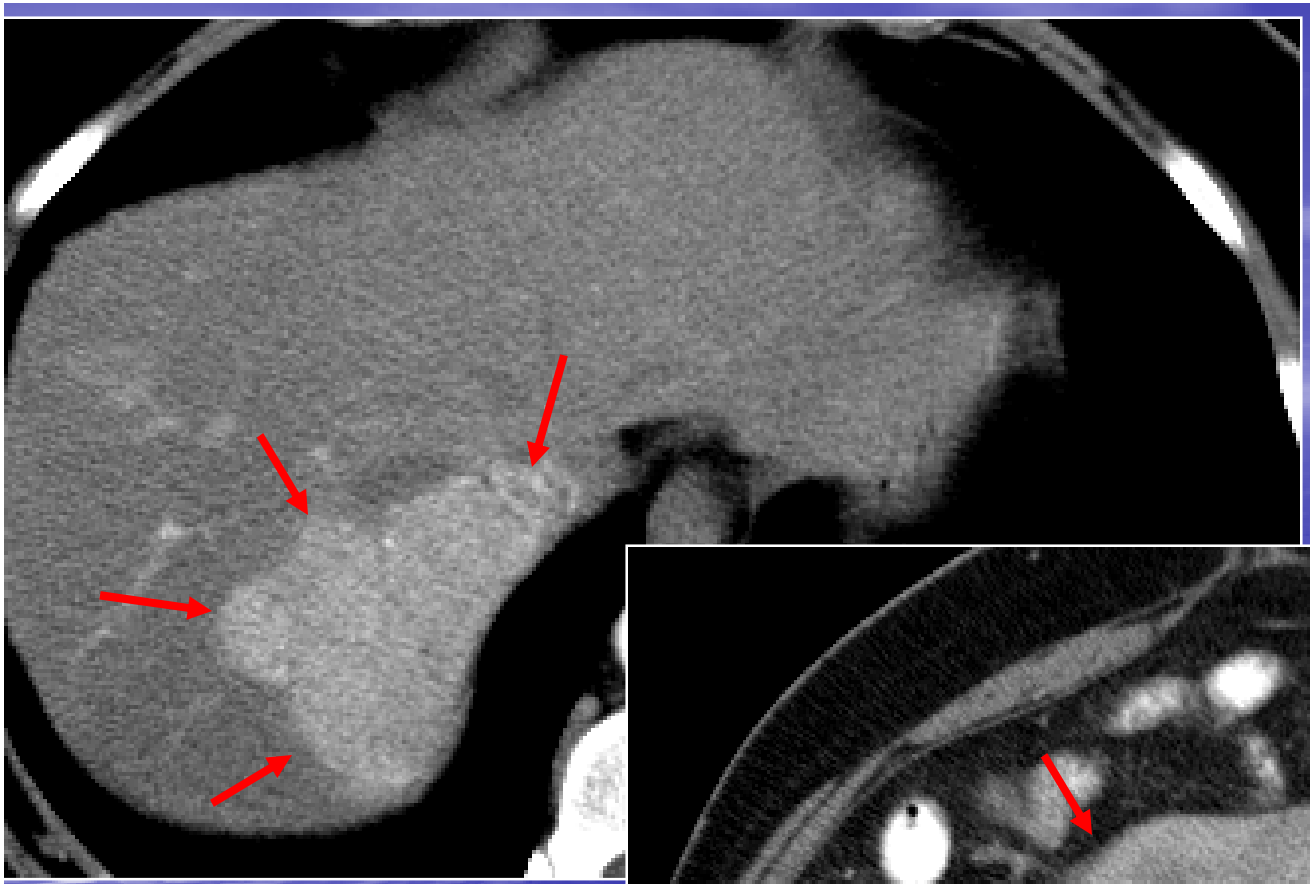
- Tumor morphology
  - Confluent, Irregular borders
  - Unusual configuration; Circumferential (eg. mesothelioma)
  - Lesion length > 1.5-2 times lesion width
- Discordant results due to RECIST technique
  - Uni-dimensional measurement
  - Shape changes may confound results

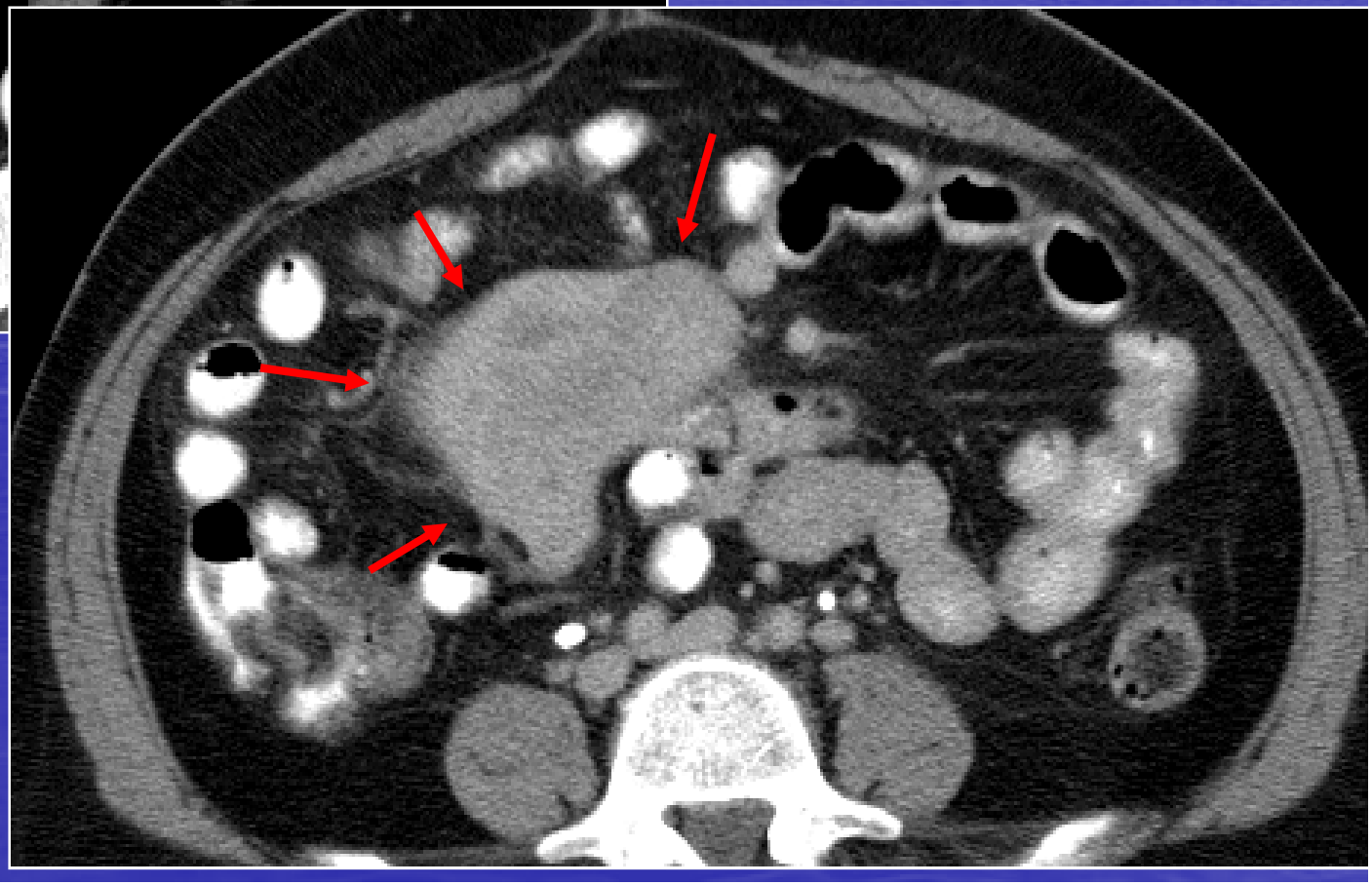
Lesion Confluence and Relationship to Normal Anatomical Structures



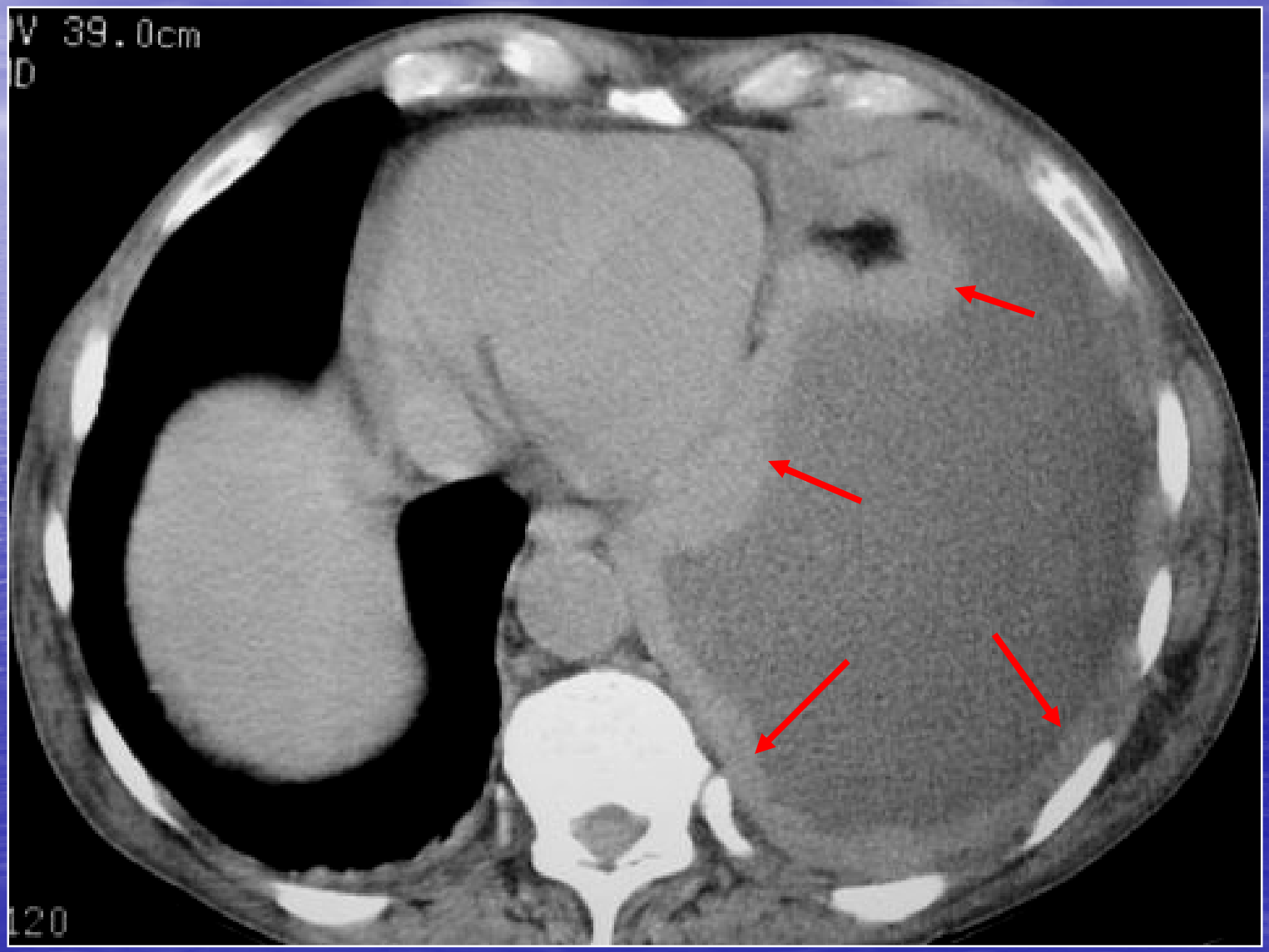


Unusual Lesion Configuration

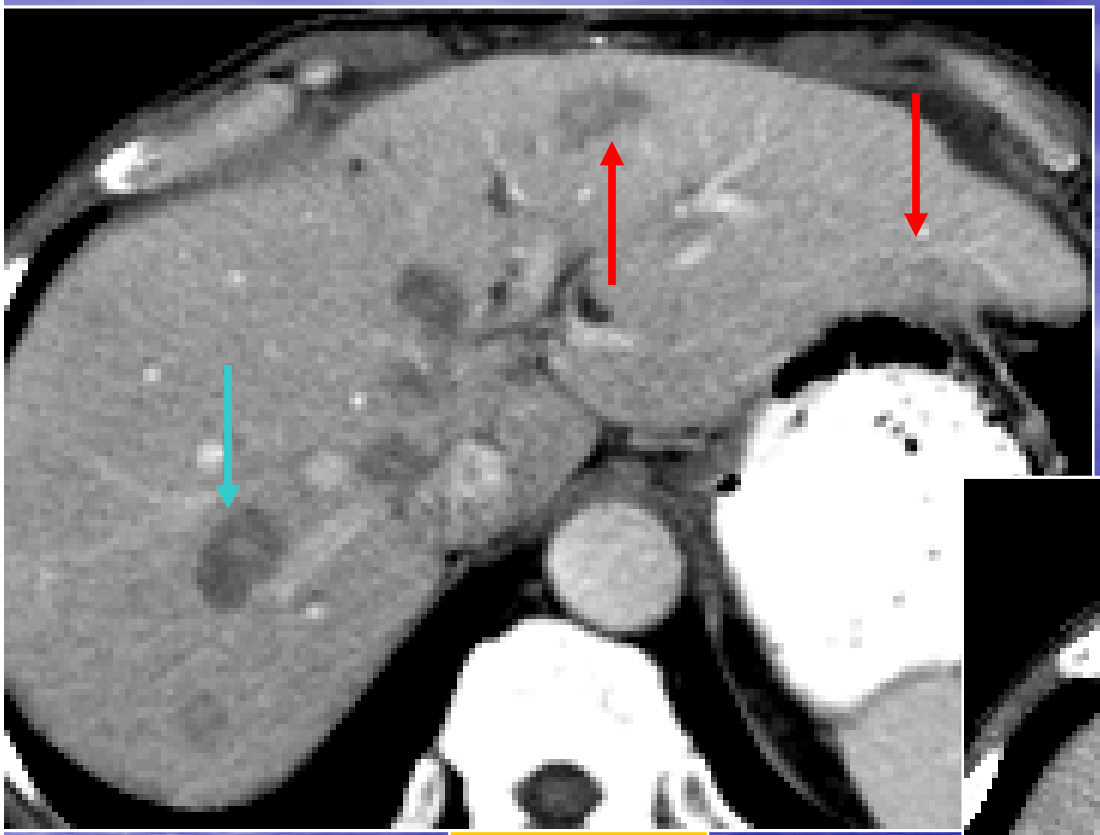




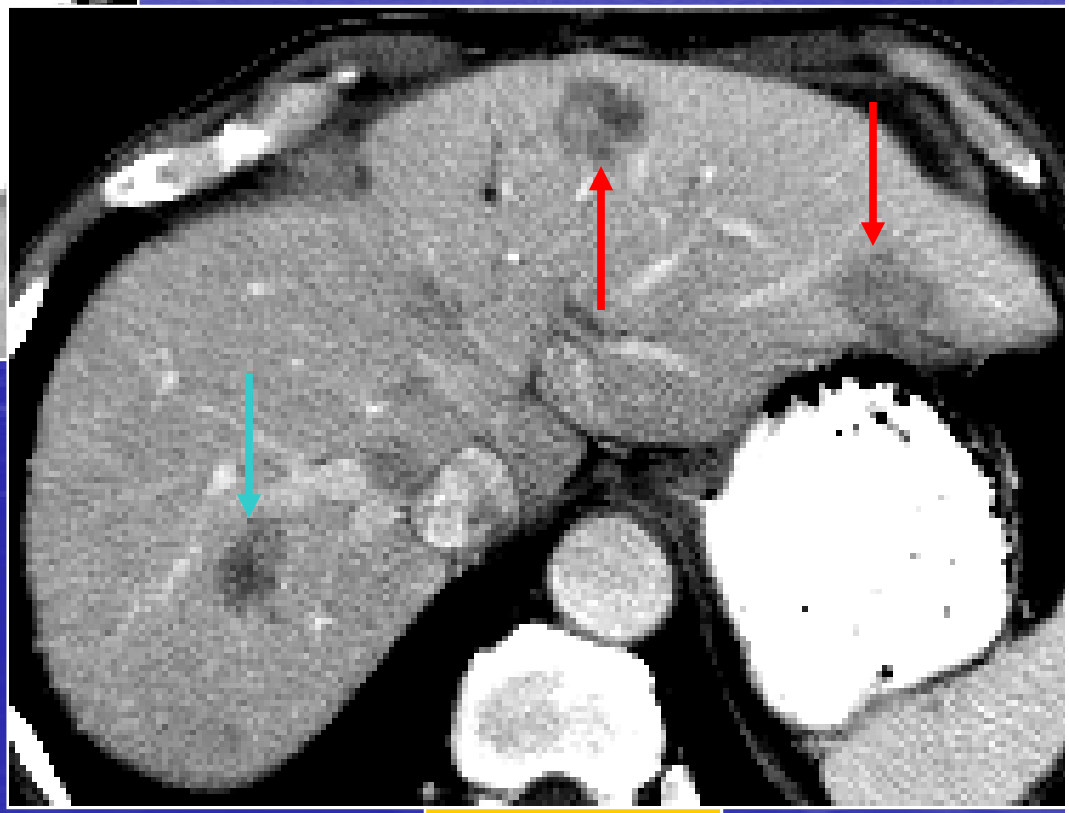
Lesion Morphology: Mesothelioma



Differential tumor behavior

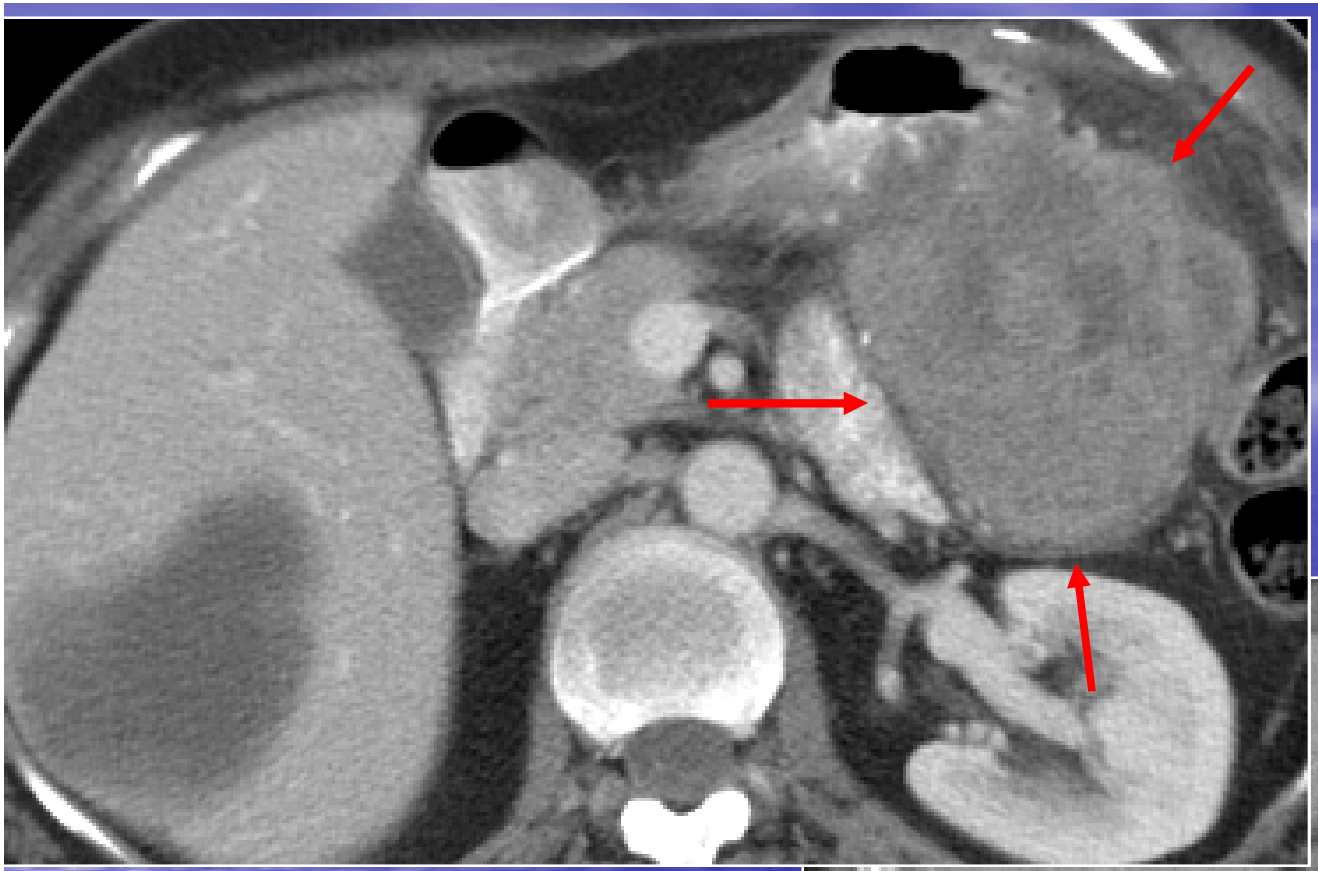


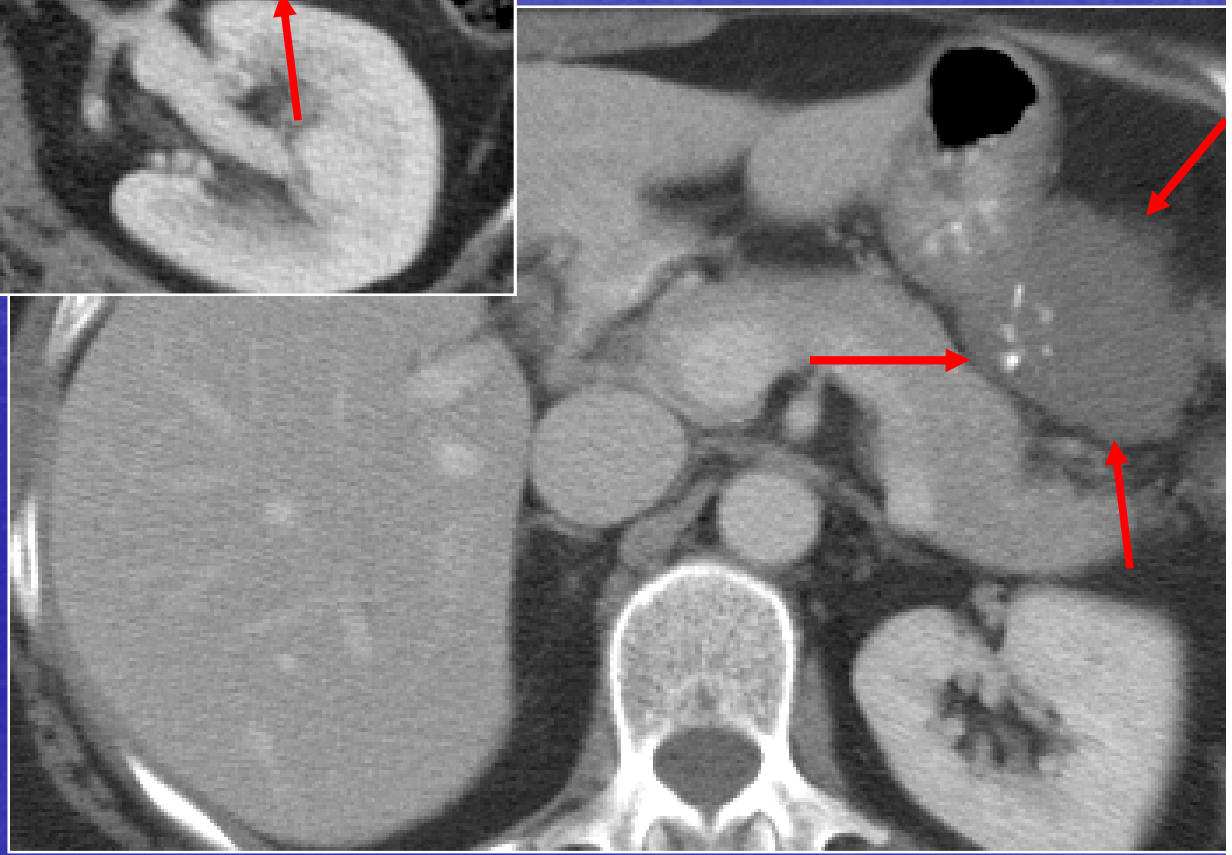
Pre



Post

Change in Tumor Form: From Solid to Non-Solid





Limitations of RECIST guidelines II

- No criteria for non-solid tumors
- No toxicity criteria
- Not applicable to Non-Cytotoxic drugs?
- Updated imaging technology not considered

Which method best assess the reduction of tumor volume?

- Is it better to use the product of perpendicular diameter
- Or the Longest diameter
- Or better to substitute **TUMOR VOLUME**

Which one is better?

- Measuring one dimension is simpler than two
- RECIST and WHO criteria were applied in 14 different trials
- No difference in the percentage of responders
- There was some difference in PR rates in 11 of the 14 trials, which could influence the conduct of phase I and phase II TRİALS of moderate size

Trials comparing RECIST and WHO

Author (Pt no)	Phase	Response rates WHO vs RECIST
Park et al(n=79)	II	31.6% vs 30.4%
Watanabe (n=120)	II	20% vs 19.3%
Prasad et al(n=38)	III	97% concordance

RECIST Revisited: SUMMARY

- In clinical cancer research, particularly phase II screening trials, standard criteria to describe change in burden of tumour are needed.
- RECIST criteria widely adopted for this need.

Issues since RECIST 1.0

- 10 lesions needed?
- Confirmation needed?
- Lymph node assessment?
- How to assess PD in nonmeasurable disease
- Role in trials of non-cytotoxics?
- Functional instead of anatomic imaging?

Progression in Phase III Trials

- Important issue, since as noted PFS and TTP becoming common primary endpoints.
- No problem if entry is restricted to patients with measurable lesions!
- But what about patients with non-measurable disease only?

What about Functional Changes in RECIST 1.0?

- RECIST:
  - Based on anatomical tumour *size*
  - Does *not* take into account phenomena such as tumour cavitation
  - Does *not* take into account metabolic function
  - Does *not* take into account blood flow parameters

Are RECIST Applicable in Trials of Non-Cytotoxics?

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JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Phase II Studies of Modern Drugs Directed Against New Targets: If You Are Fazed, Too, Then Resist RECIST

Mark J. Ratain, *University of Chicago, Chicago, IL;* and S. Gail Eckhardt, *University of Colorado, Denver, CO*

NONE IS PERFECT

WHAT ABOUT
NEW RECIST VERSION 1.1

What has not changed in RECIST 1.1

- Measurable lesions defined by unidimensional measurement
- Tumor burden based on sum of diameters
- Categories of response
  - CR
  - PR (30% decrease)
  - SD
  - PD (20%increase)

What has changed in RECIST1.1

- Measuring tumor burden
  - Clarify minimum size measurable non-nodal lesions
  - Up to 5 measurable lesions (2 per organ)
- Lymph node assessment
  - Measure short axis
  - Add actual short axis measurement to sum of longest diameter of non-nodal lesions
- Progressive disease
  - Requires not only 20% increase, but absolute increase
  - Definition of nonmeasurable disease expanded

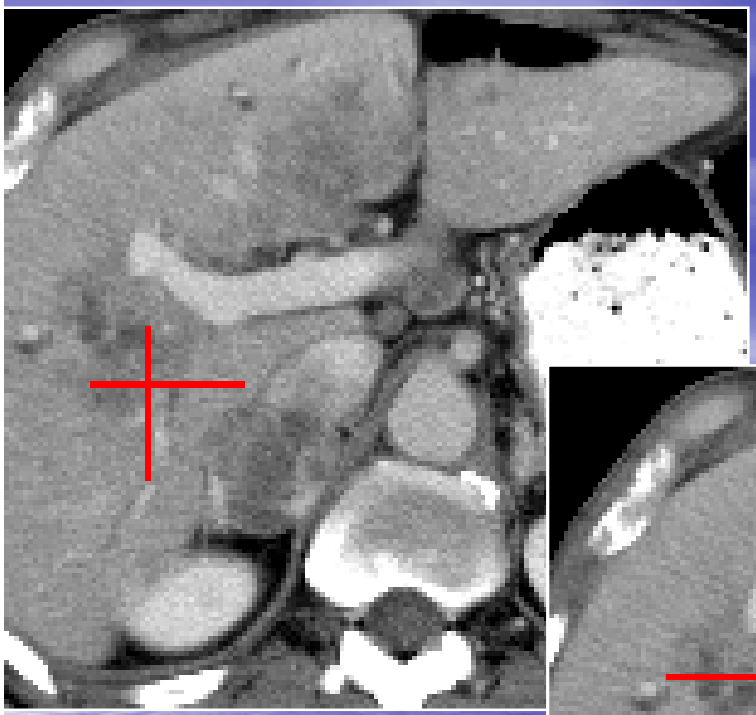
Summary of changes in RECIST 1.1

	Recist 1.0	Recist 1.1
Measuring tumor burden	10 targets 5 per organ	5 targets 2 per organ
Lymph node	Measure long axis	Measure short axis
PD definition	20% in sum	20% in sum 5 mm absolute increase
NON-Measurable disease PD	Must be unequivocal	Expanded definition
Confirmation	Required	Required when response primary endpoint
New lesions	-----	New section including PET

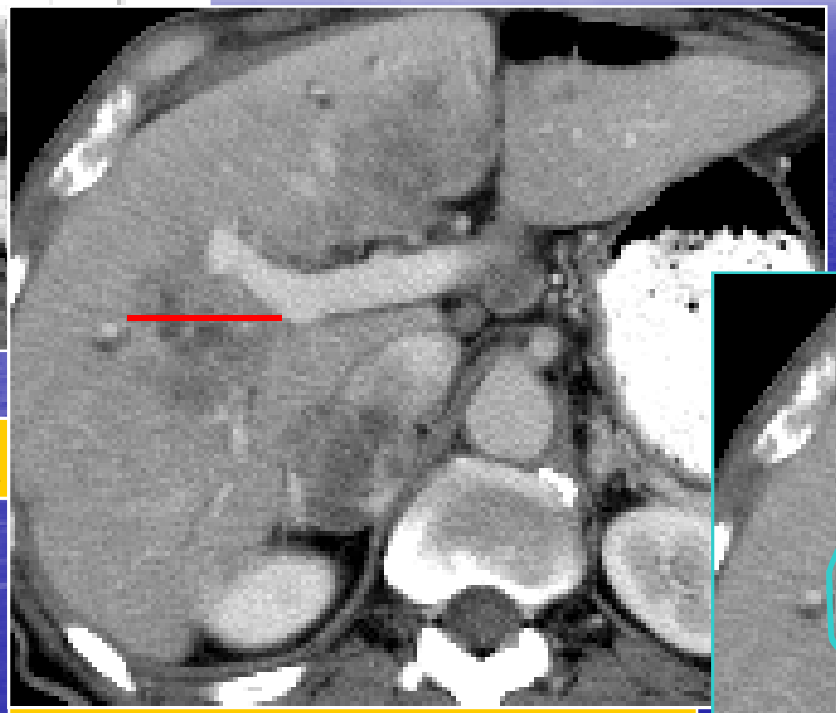
NEXT STEP: 3D VOLUMETRIC MEASURMENTS

- Can absolute **Tumor volumetrics** be used as a more accurate technique for evaluating tumor response?
- Computer assisted tumor volumetrics is now possible for applications in oncology.
- Its role and potential impact will need to be addressed by looking at real clinical trials.

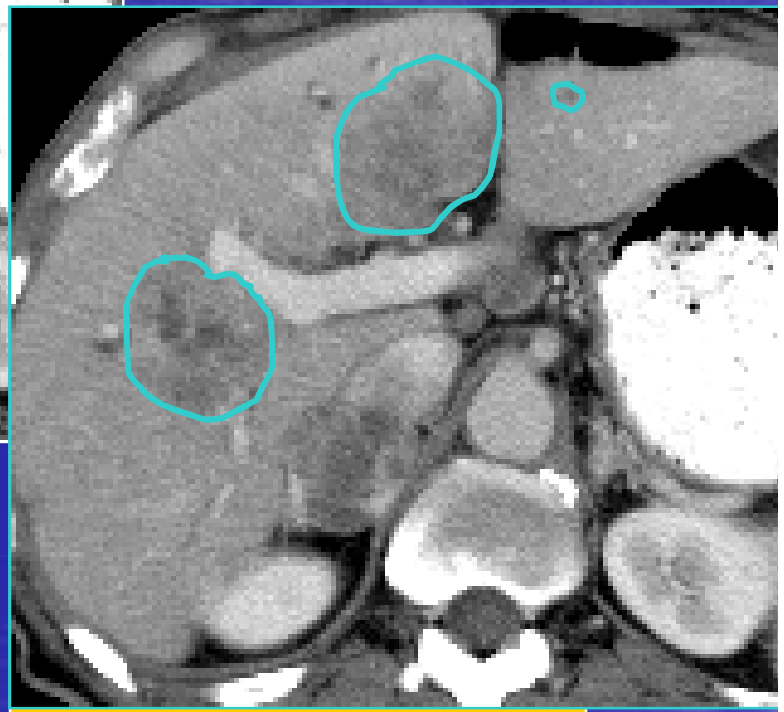
Future?



VHO-Bidimensional

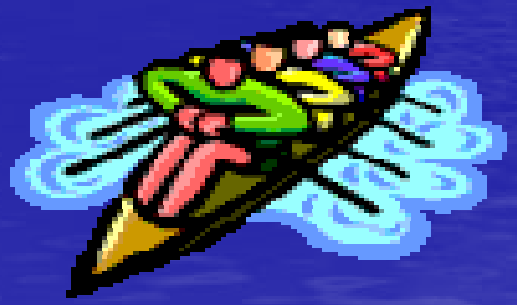


RECIST-Unidimensional



Volumetric

Why are ***WE*** here ???



Thank you for your attention!