Incontro con gli esperti - XIV Edizione

Appropriatezza dell'Imaging nella Diagnostica e Radioterapia dei Tumori Gastrointestinali

Appropriatezza dell'Imaging in funzione dei trattamenti

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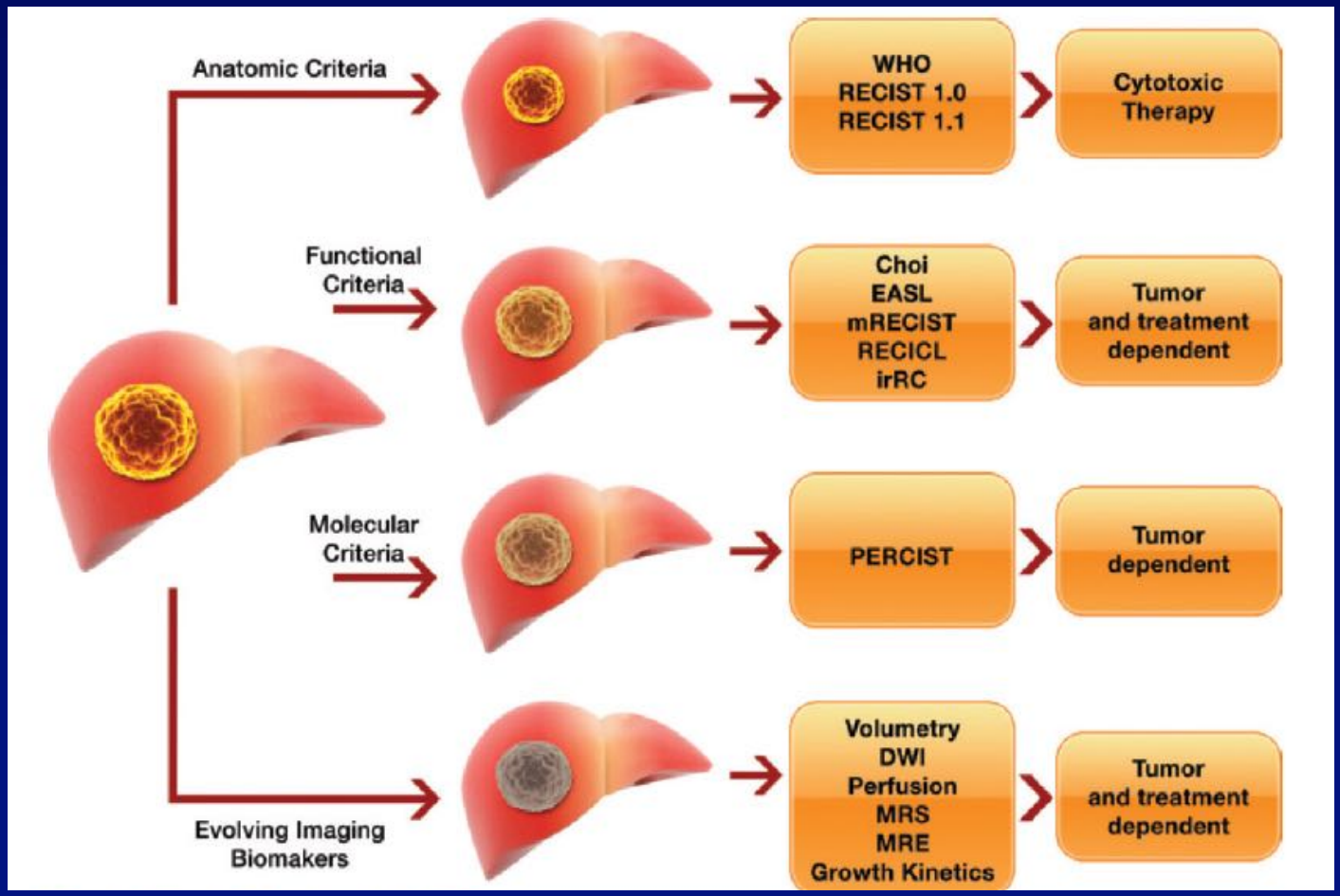
Appropriatezza dell'Imaging in funzione dei Trattamenti



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Appropriatezza dell'Imaging in funzione dei Trattamenti

Clinical need

- *To measure treatment effect early in a treatment course*
- *To stratify patients into responders and non-responders*
- *Advantage for non-responding:*
  - *shifting to other therapies early in the treatment course*
  - *avoiding unnecessary side-effects of inefficient treatment*

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Clinical need

Response monitoring has therefore become increasingly important as it can allow for *individualized tailored therapy*

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Clinical need

- *treatment paradigms have diverged*
- *development of antiangiogenic agents, vascular and molecularly-targeted agents*

- the multidisciplinary team (MDT)
- review of volumetric measurements/morphological criteria

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Appropriatezza dell'Imaging in funzione dei Trattamenti

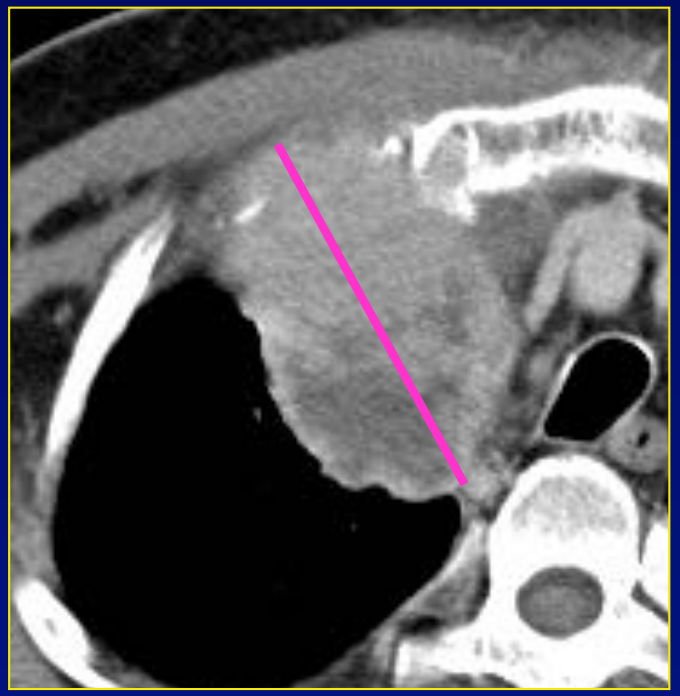
Which Imaging Criteria?

- In clinical studies treatment monitoring can be performed using the Response Evaluation Criteria In Solid Tumors (RECIST). The RECIST criteria are based on anatomical tumor burden measured by computed tomography (CT). In 2009, an updated version of the RECIST guideline, RECIST 1.1, was published.

RECIST 1.1

- one-dimensional measurements

longest diameter (sum of diameters of multiple lesions)



- <<< number of lesions (maximum of 5 [2xorgan]
- Inf as target lesions

CR disappearance of target lesions

PR ≥ 30% decrease, baseline as reference

PD > 20% increase, smallest measurement as reference, and absolute increase of at least 5 mm; appearance of new lesions

NC neither PR nor P, smallest measurement as reference

Eisenhauer EA – Eur J Cancer 2009; 45:228

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Appropriatezza dell'Imaging in funzione dei Trattamenti

Which Imaging Criteria?

- In clinical studies treatment monitoring can be
  Response Evaluation Criteria In Solid Tumors (
  criteria are based on anatomical tumor burden
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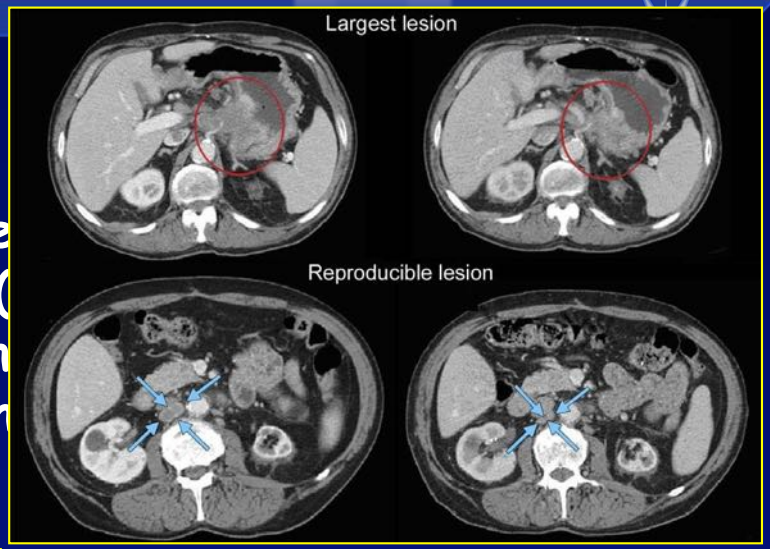
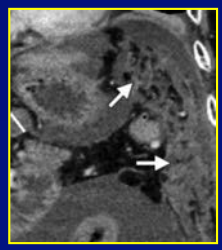
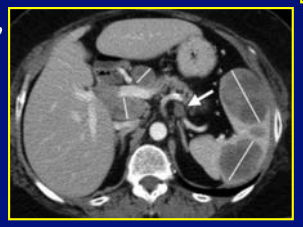


➢ *one-dimensional measurements*





measurable lesions

- ✓ *d. ≥ 10 mm by CT*

non-measurable lesions

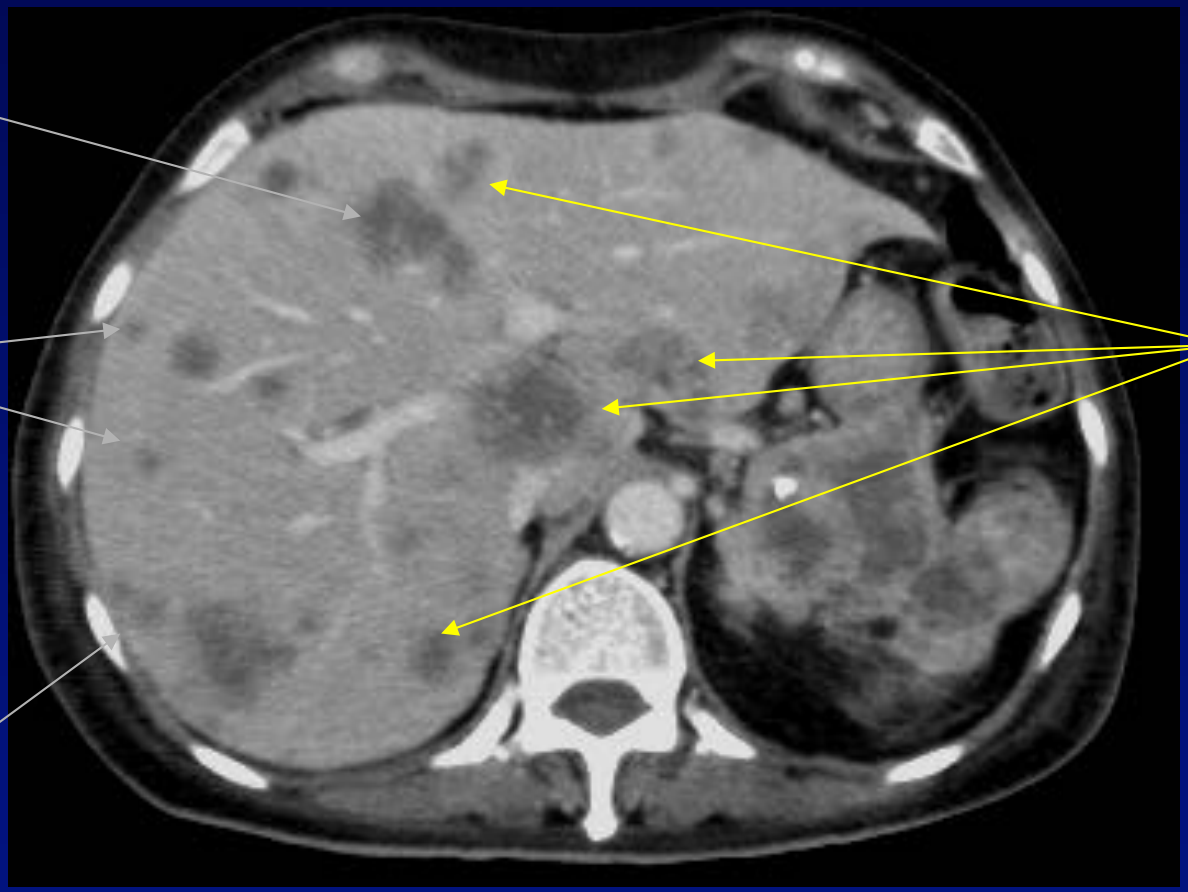
- ✓ *d. < 10 mm*
- ✓ *leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitic involvement of skin or lung*

target lesions

- ✓ *a maximum of 5 lesions total (max 2 lesions per organ)*
- ✓ *reproducible repeated measurements*

Eisenhauer EA – Eur J Cancer 2009; 45:228

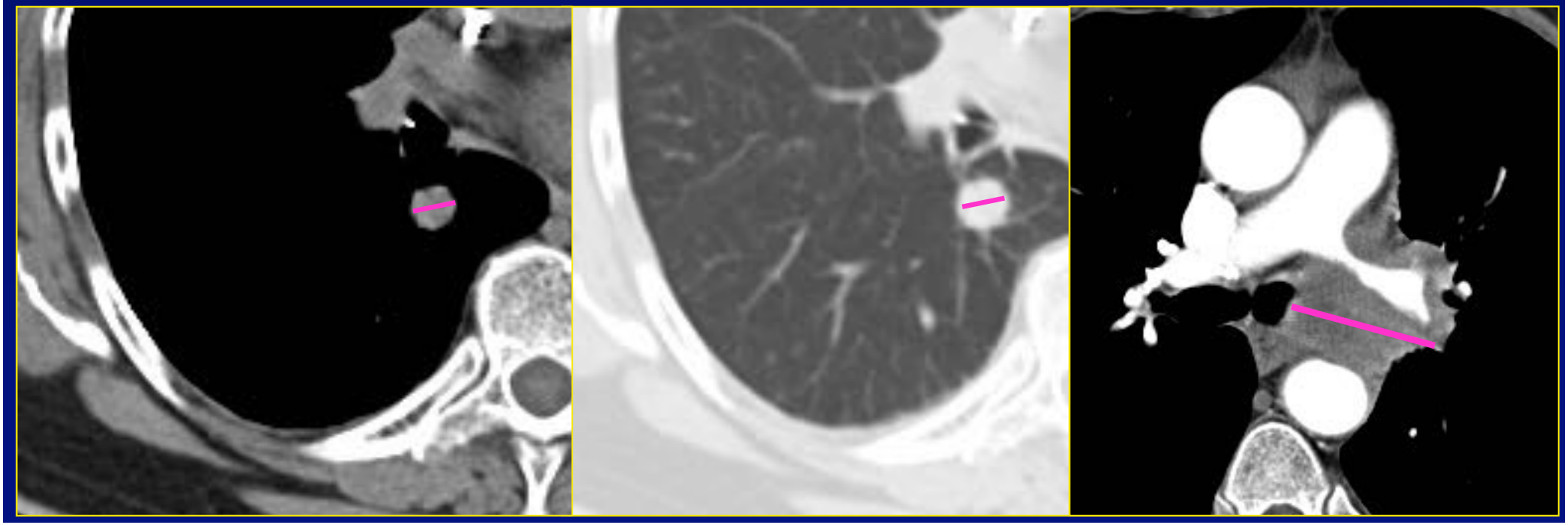
Target vs Non Target



RECIST 1.1 – Clinical applications

consistency of measurements

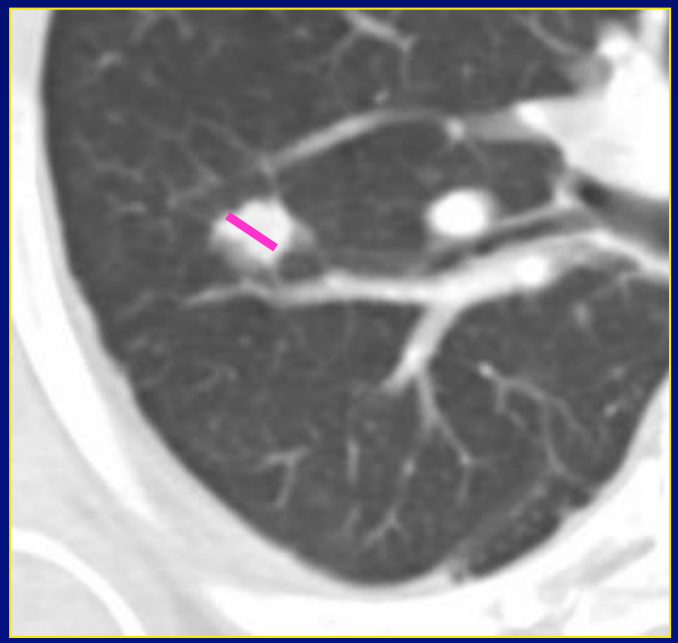
- unequivocal identification of the target lesion (s)
- use of a costant window-setting to measure the target lesion on each examination (parenchymal window)
- exclusion of normal anatomic structures from the measurement

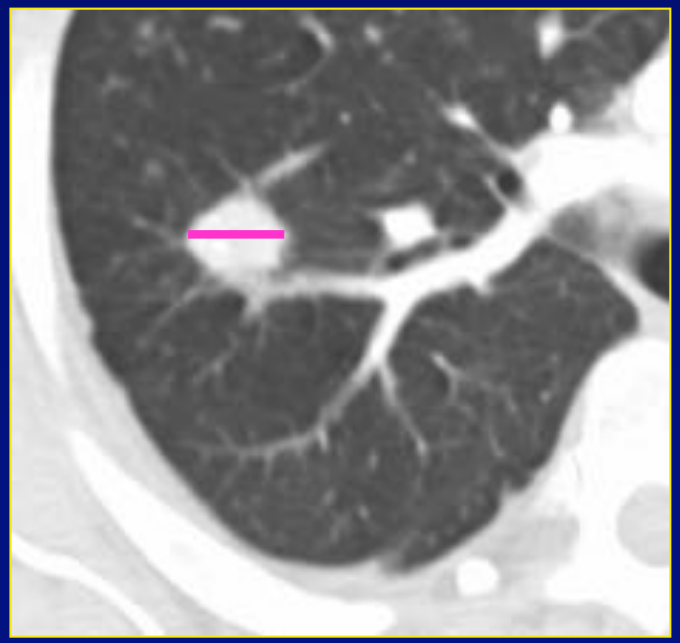


RECIST 1.1 – Clinical applications

consistency of measurements

- unequivocal identification of the target lesion (s)
- use of a constant window-setting to measure the target lesion on each examination (parenchymal window)
- exclusion of normal anatomic structures from the measurement





always measure the longest diameter

RECIST 1.1 – Clinical applications

consistency of measurements

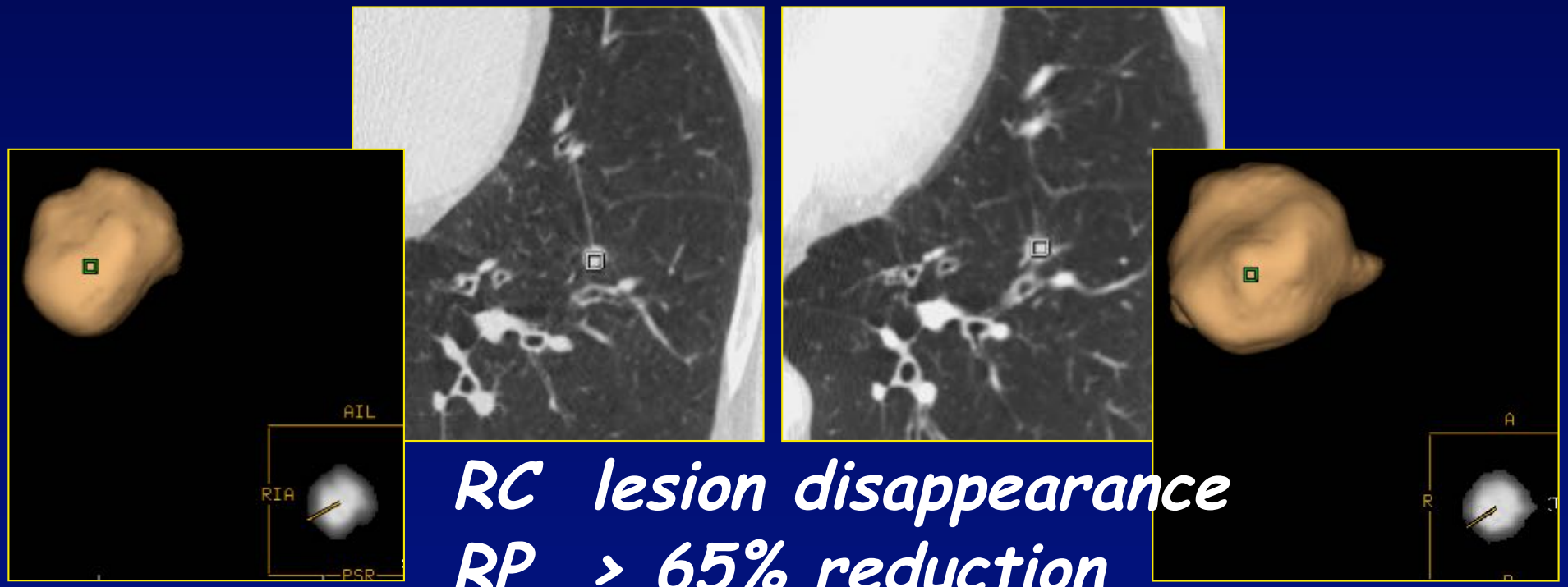
- unequivocal identification of the target lesion (s)
- use of a constant window-setting to measure the target lesion on each examination (parenchymal window)
- exclusion of normal anatomic structures from the measurement
- substantial variability within and among readers (~ 24% of errors)*

  - ✓ small size lesions
  - ✓ lesions with irregular margins
  - ✓ lesions with asymmetric or irregular growth patterns

* Marten K – Eur Radiol 2006; 16:781

RECIST 1.1 – Clinical applications

is there a role for volumetry?



RC lesion disappearance

RP > 65% reduction

PD > 73% increase

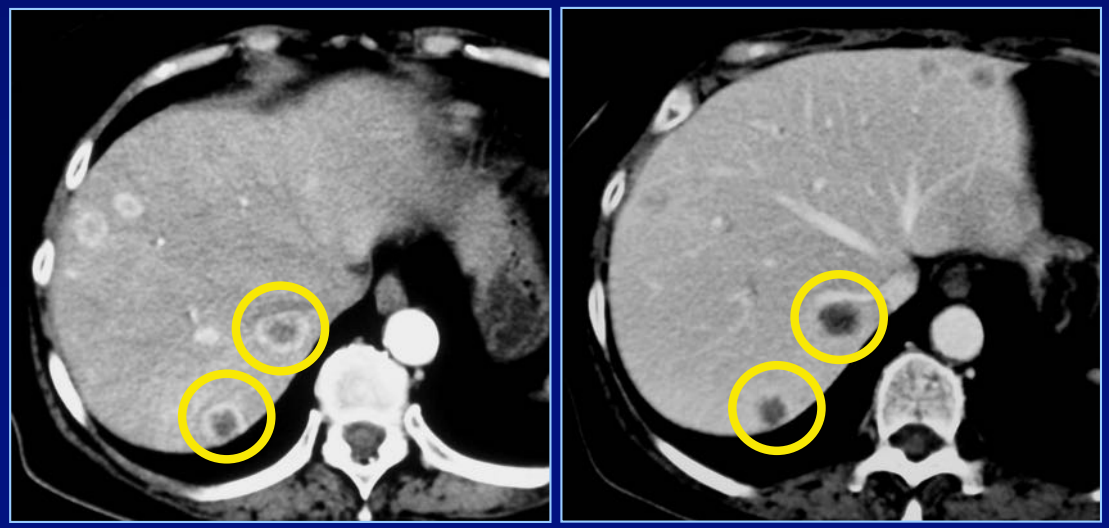
NC < 65% reduction; <73% increase

* Marten K – Eur Radiol 2006; 16:781

RECIST 1.1 – Practical applications

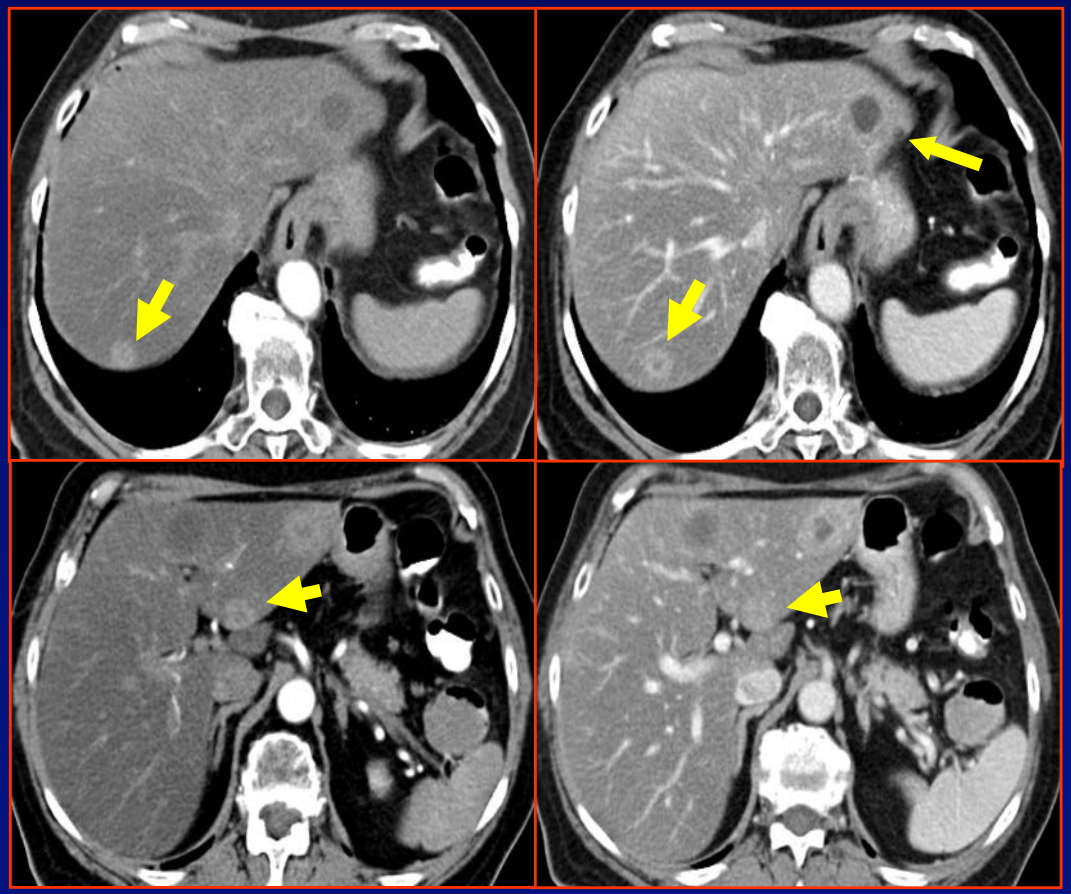
consistency of measurements

- unequivocal identification of the target lesion (s)
- use of the same enhanced phase to measure the target lesion on each examination
- exclusion of normal anatomic structures from the measurement



RECIST 1.1 – Practical applications

History of BRC and CRC

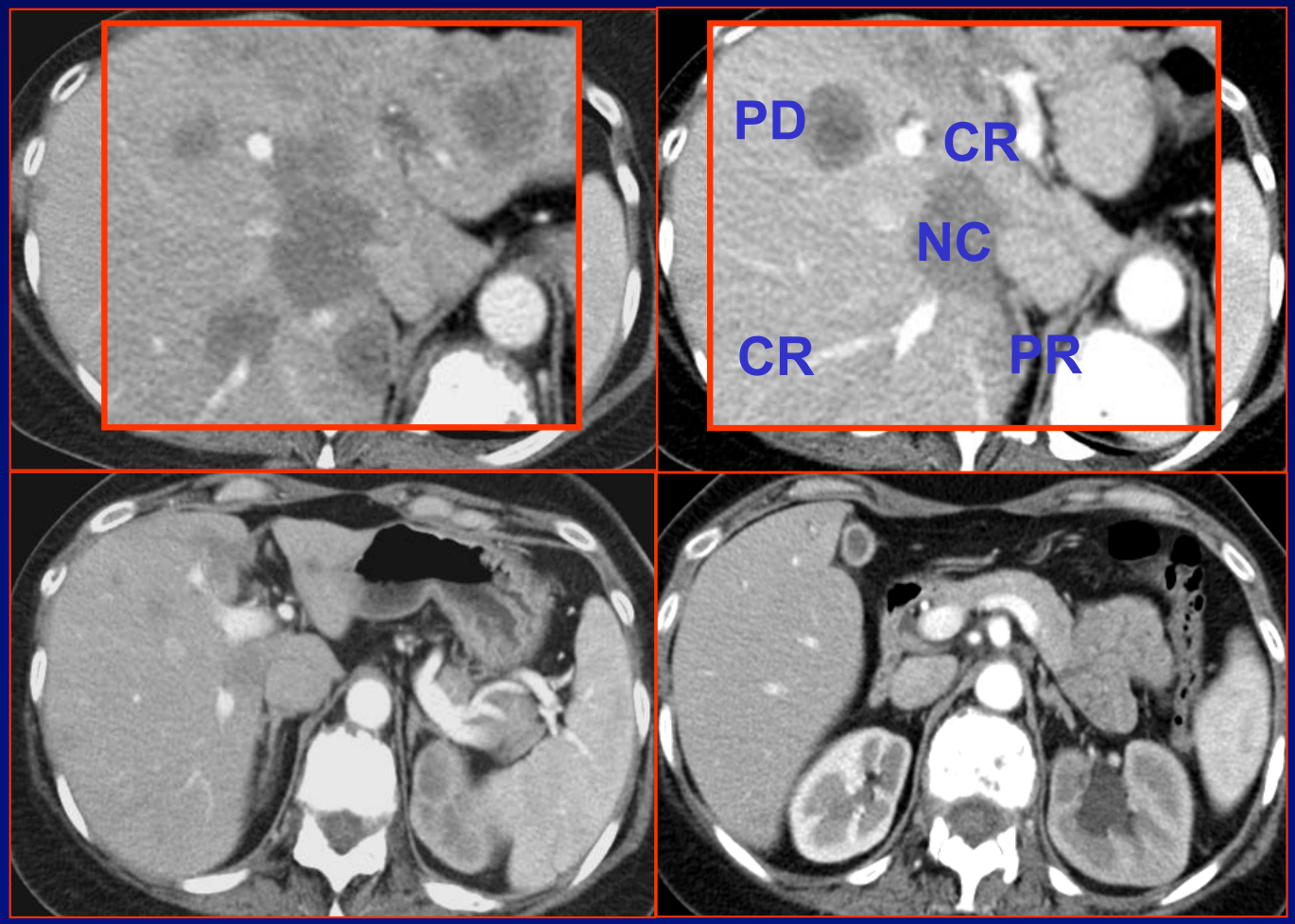


- Mixed vascularization (mixed types)
- One probably missed on pvp only

RECIST 1.1 – Practical applications

Pancreatic Cancer

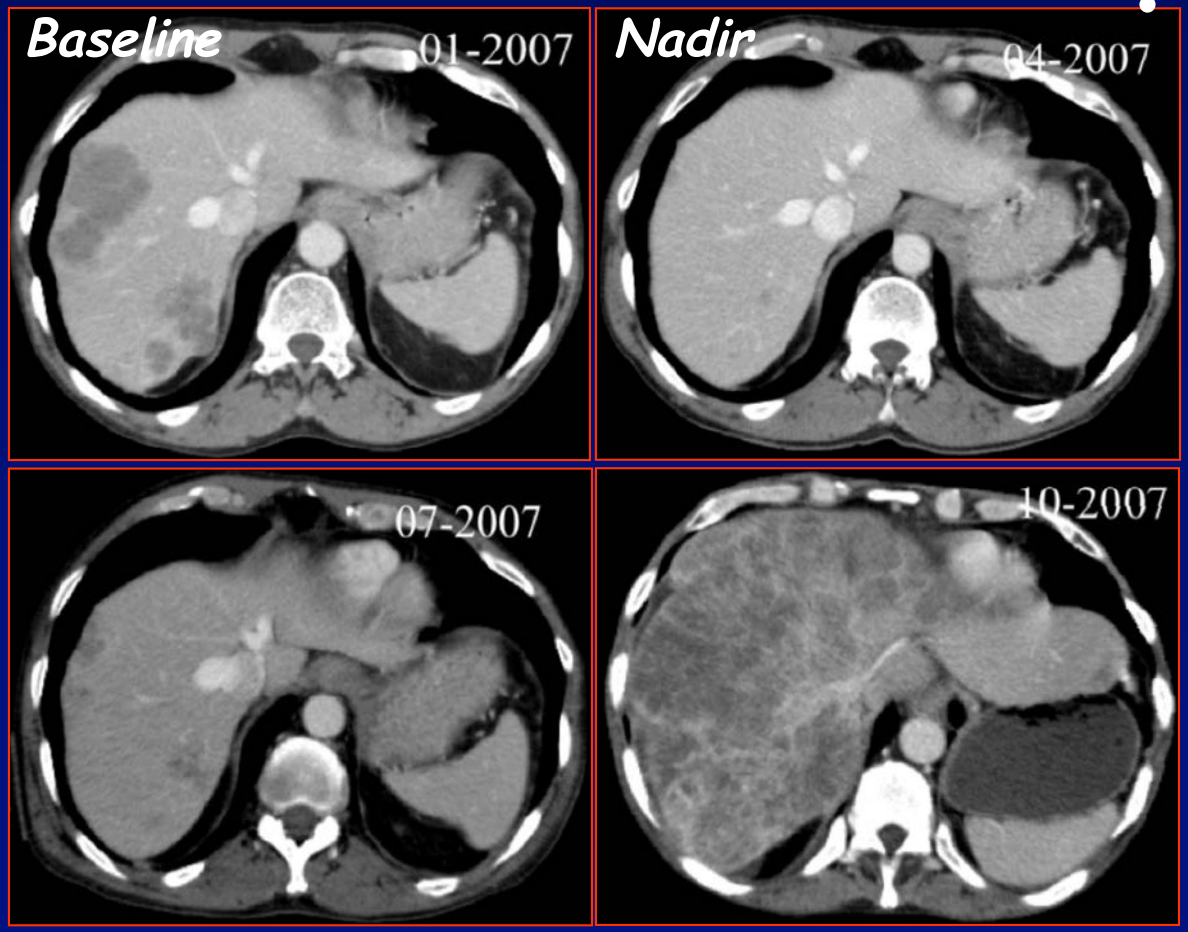
3 months f-up after Gemcitabine



Mets of same origin may respond differently

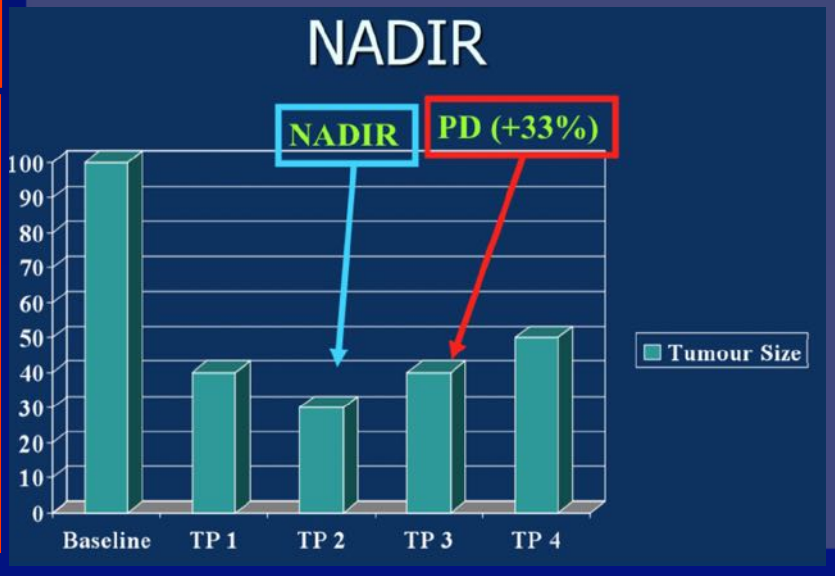
RECIST 1.1 – Practical applications

- What is the response?

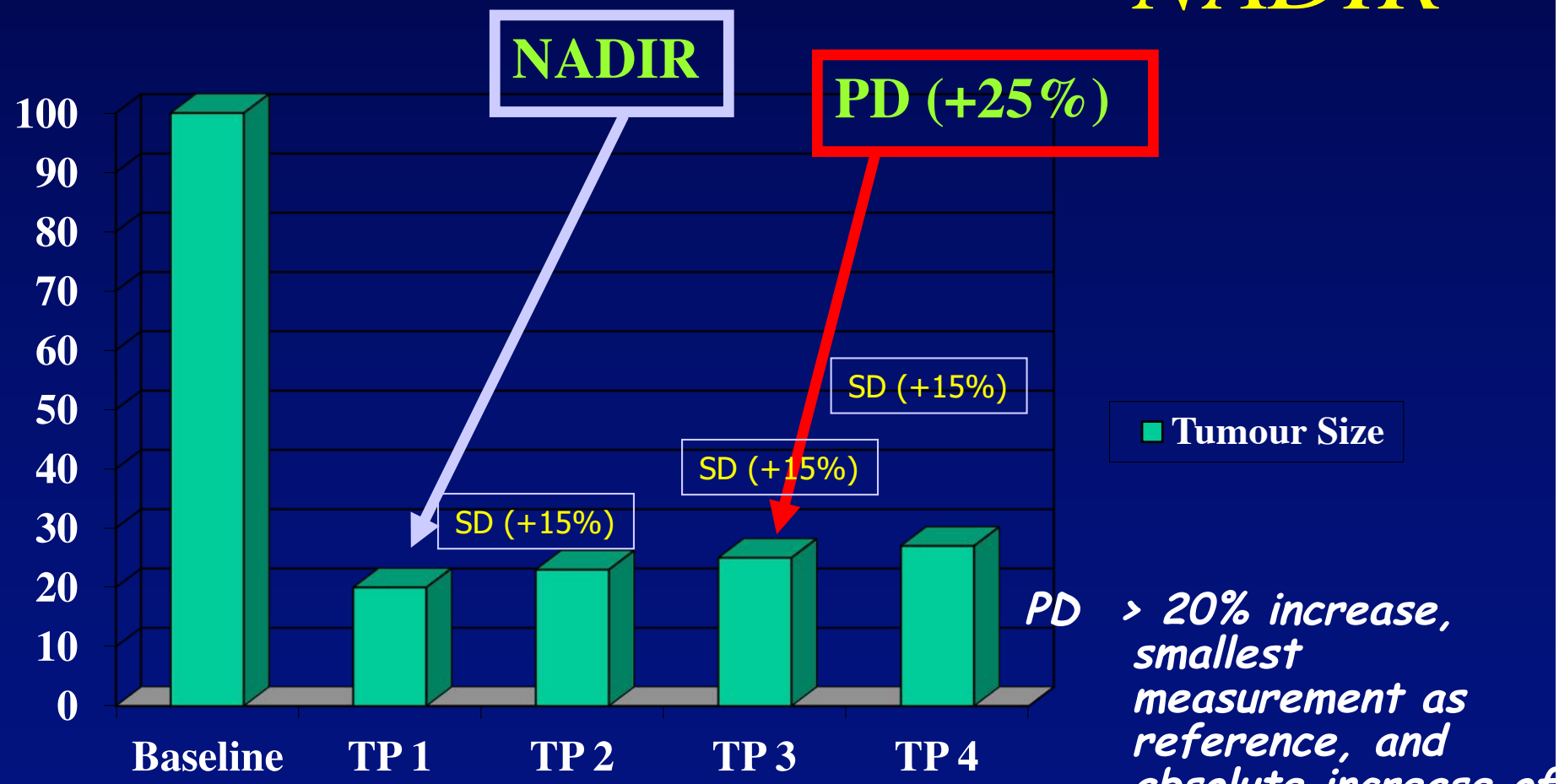


… Baseline and Nadir

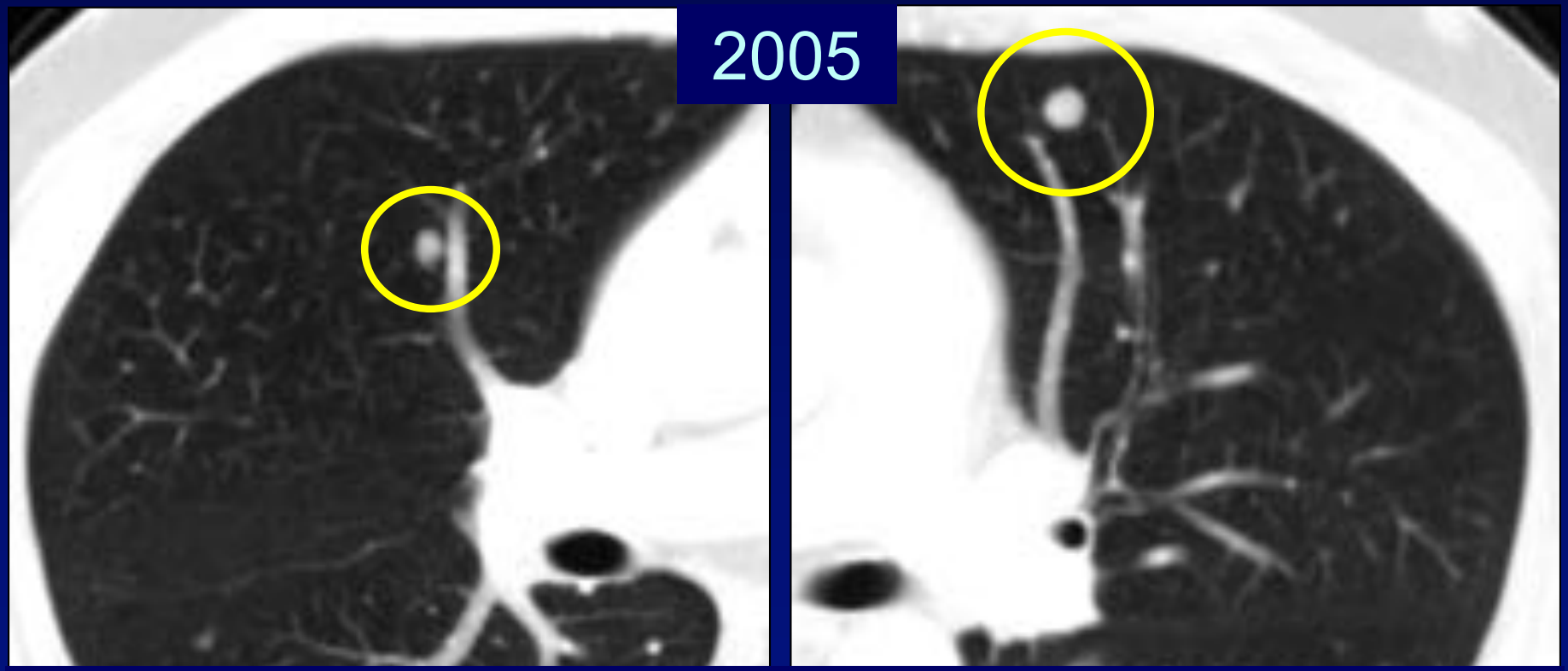
- NADIR : the smallest size of target tumors obtained by the treatment
  - NADIR is the reference for Progression
  - NADIR is NOT necessarily the last examination



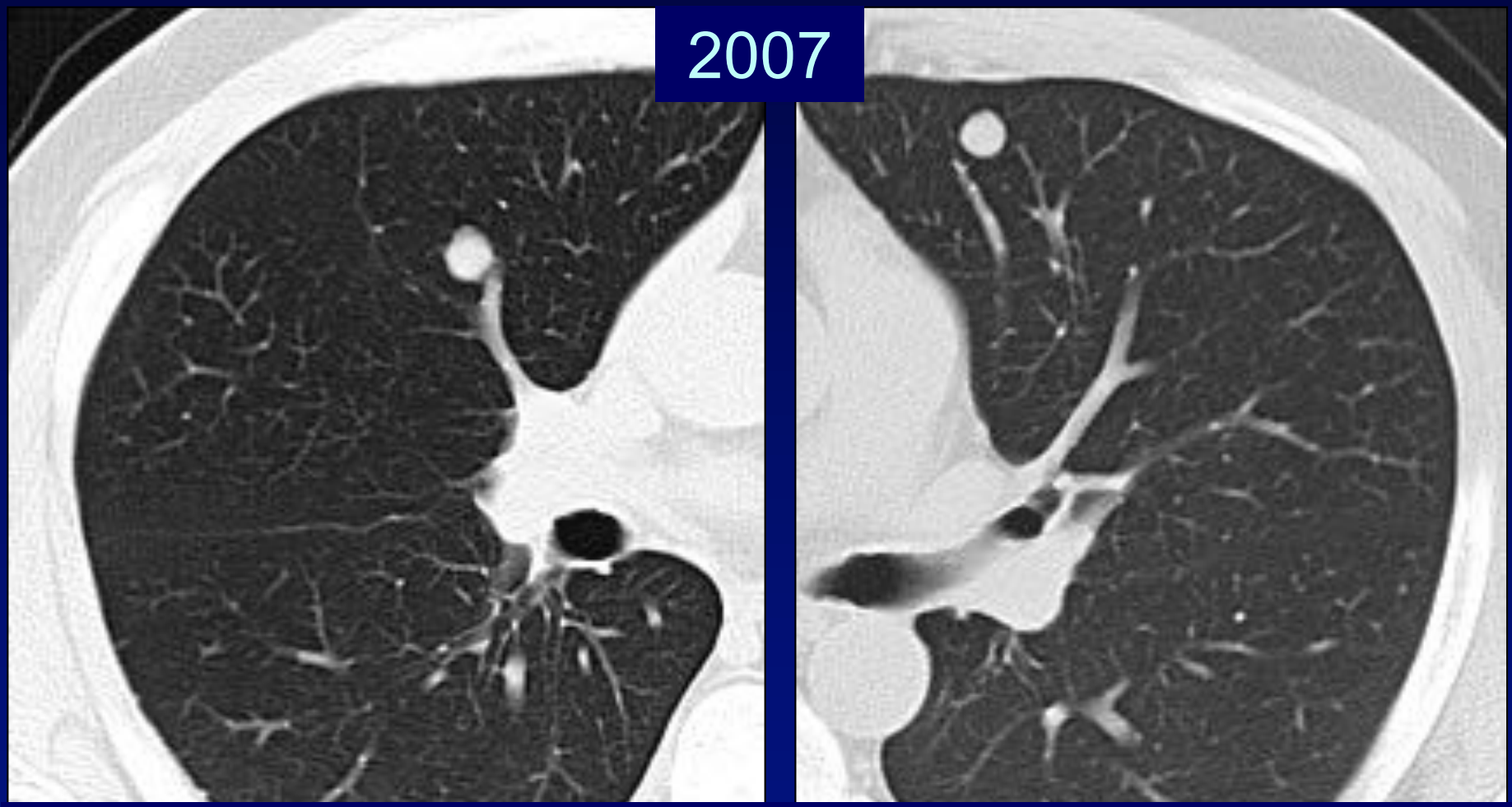
RECIST 1.1 – Practical applications



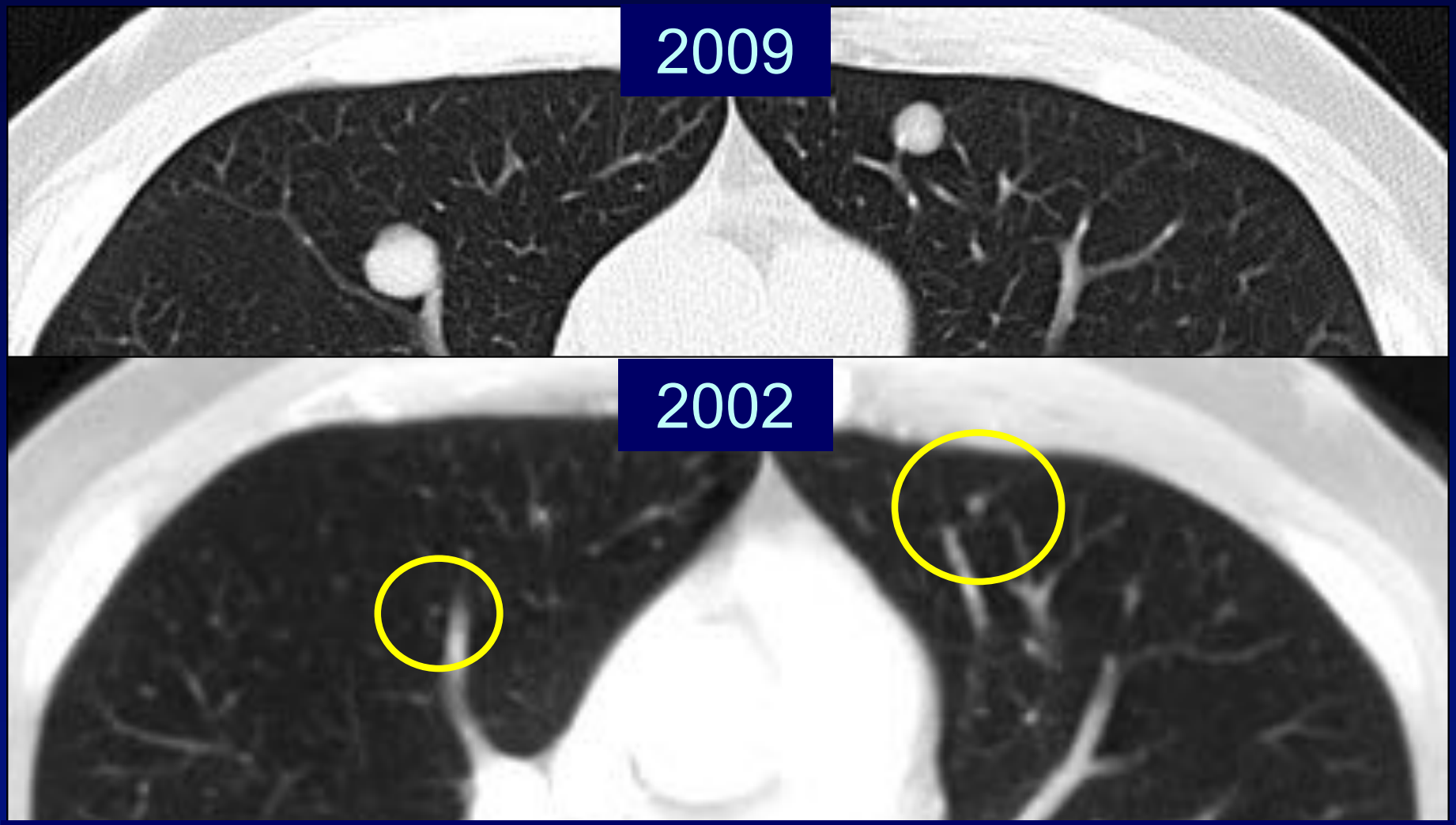
Extraskeletal myxoid chondrosarcoma (thigh, 1997)



"Since 2002, three subcentimeter nodules in lungs, 2 of which are unchanged and third was likely present. No evidence of metastatic disease."

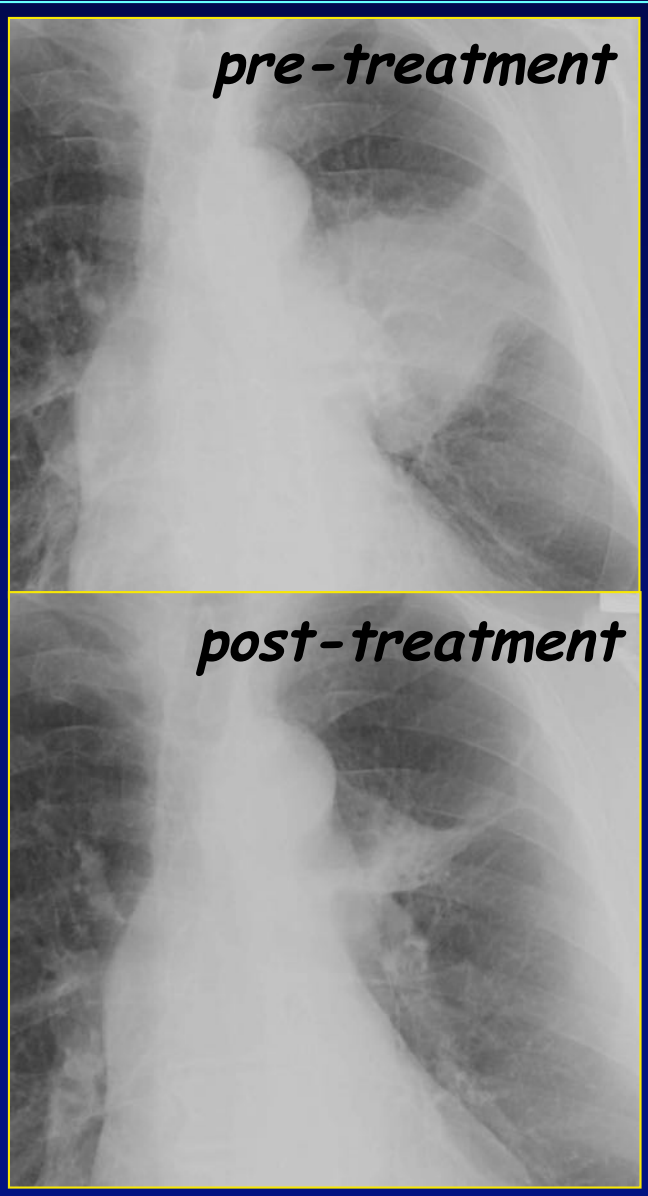


"Since 6 months ago, stable bilateral subcentimeter pulmonary nodules."

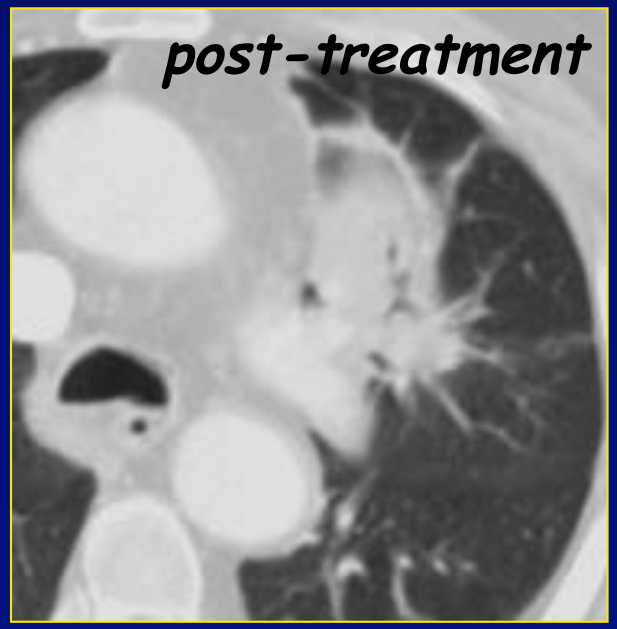


"Since 2007, the dominant left upper and right upper pulmonary nodules show subtle size increase (1-2 mm), with significant size increase compared to 2002."

RECIST 1.1 – issues of debate



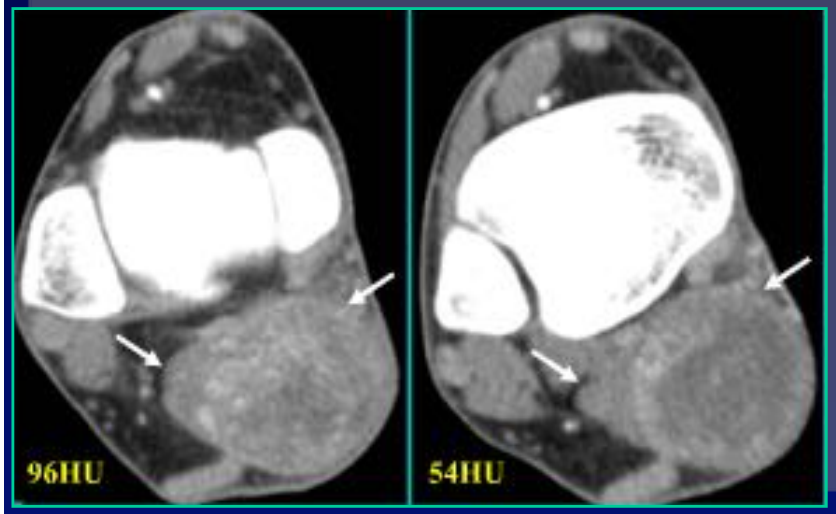
- reduction in tumor size does not always correlate with tumor response



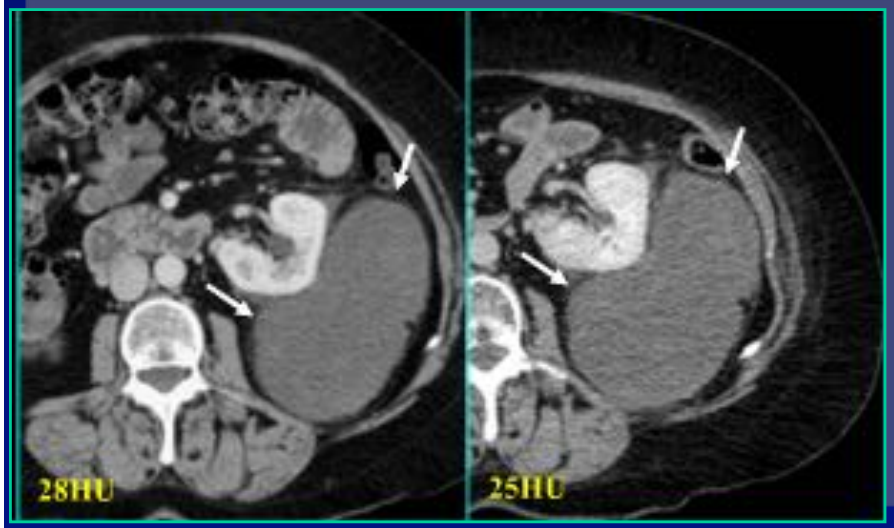
pTo pNo

Van Meerten EL – Eur Radiol 2009

RECIST 1.1 – issues of debate



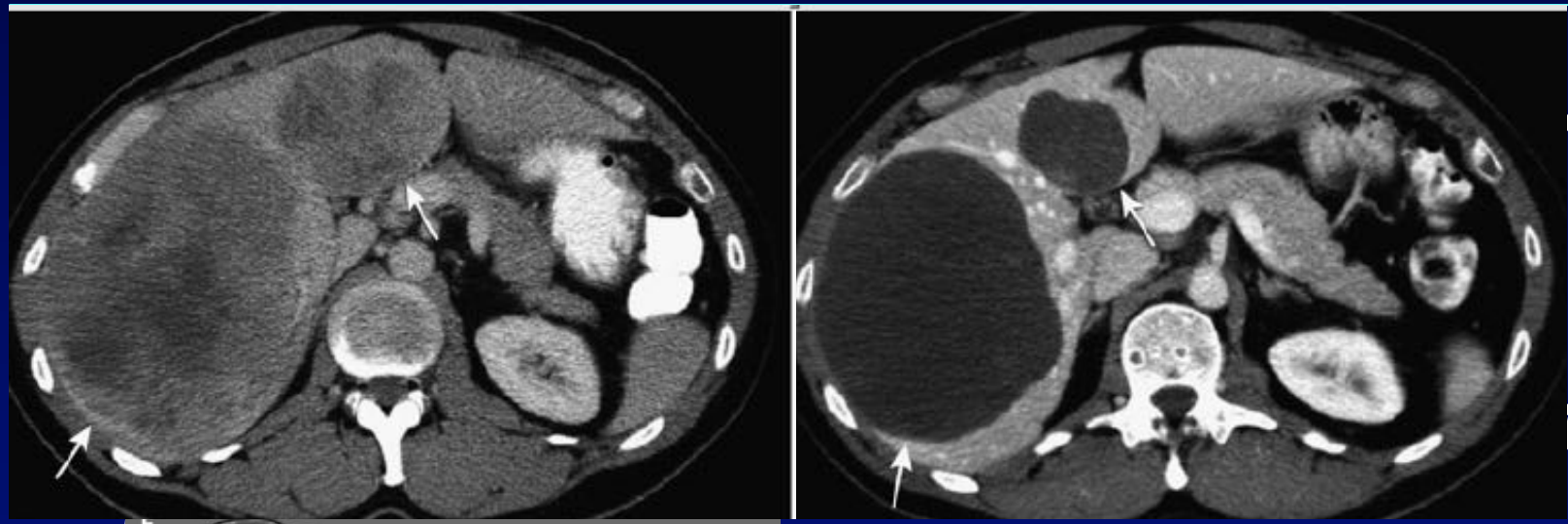
- reduction in tumor size does not always correlate with tumor response
- tumor shrinkage may not be an appropriate end-point when cytostatic agent are used

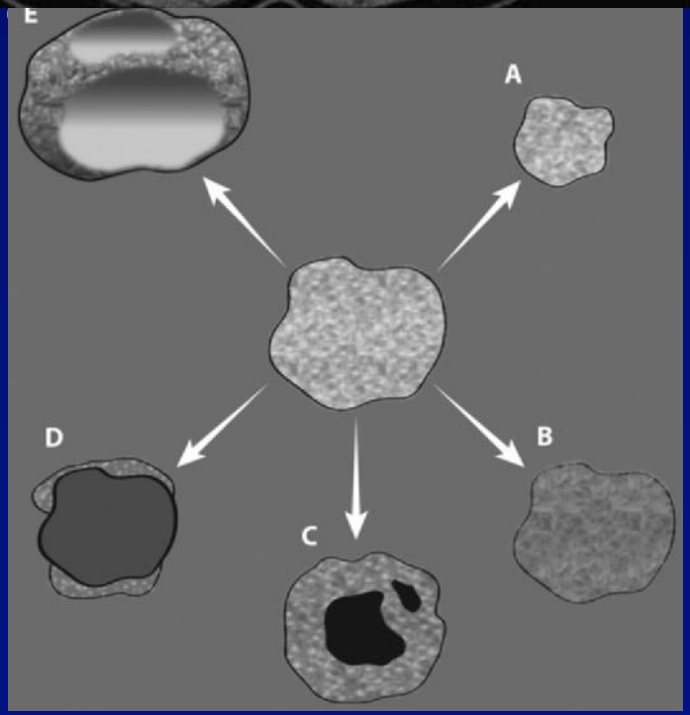


Tumor Density: Choi criteria

Van Meerten EL – Eur Radiol 2009

RECIST 1.1 – issues of debate





- A: conventional CHT
- B: decrease in lesion vascularity
- C: stability or decrease in size with cavitation
- D: cystic changes
- E: intratumoral hemorrage

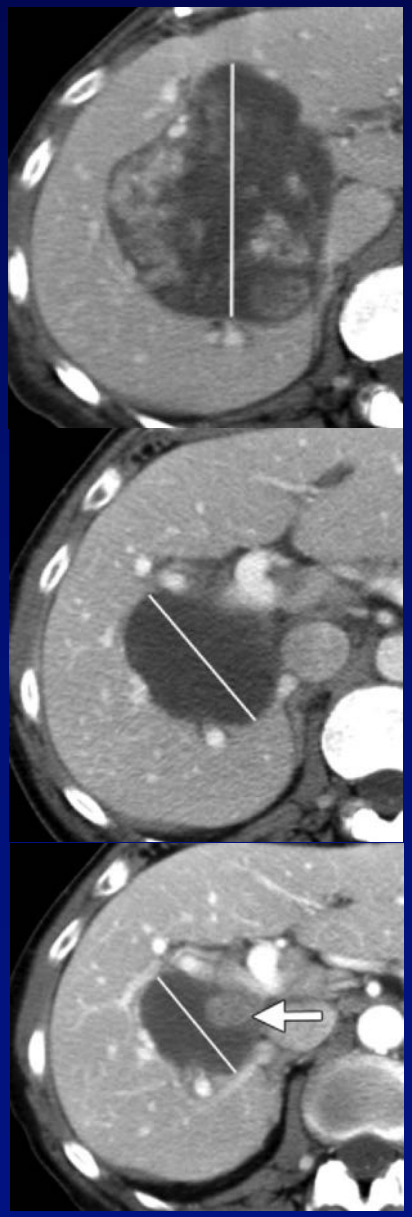
RECIST 1.1 – issues of debate

Tumor Density: Choi criteria

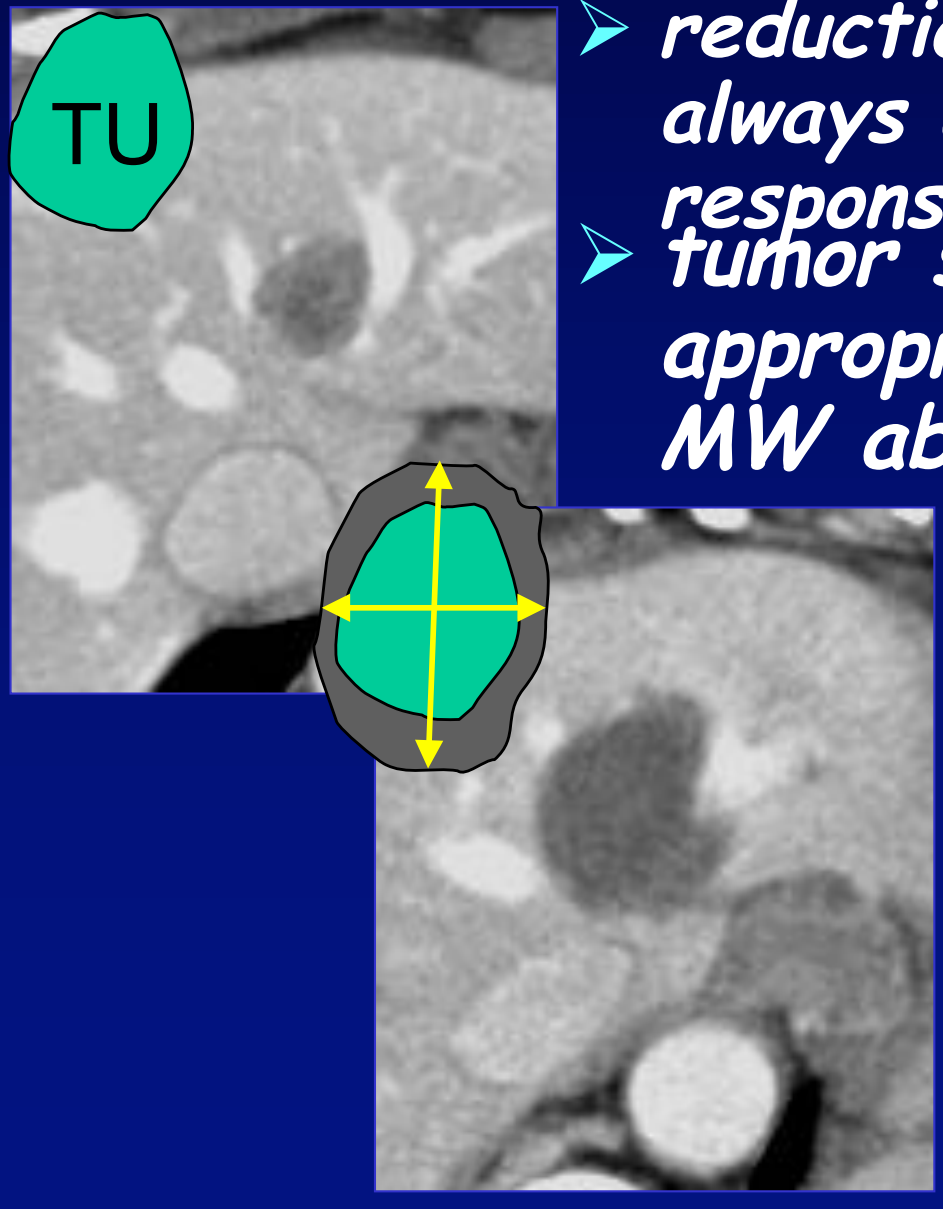
Overall Tumor Response (Revised CT evaluation criteria)

Complete Response (CR)	• Disappearance of all lesions • No new lesions
Partial Response (PR)	• A decrease in size of ≥ 10% • A decrease in tumor density (HU) ≥ 15% on CT • No obvious progression of non-measurable disease
Stable Disease (SD)	• Does not meet the criteria for CR, PR or PD • No symptomatic deterioration attributed to tumor progression
Progressive Disease (PD)	• An increase in tumor size of ≥ 10% and does not meet criteria of PR by tumor density (HU) on CT • New lesions • New intratumoral nodules or increase in the size of the existing intratumoral nodules

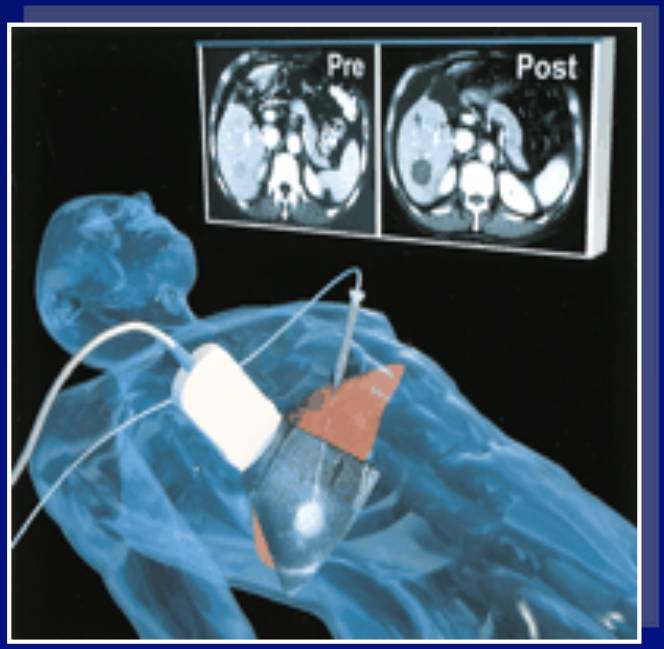
Choi et al J Clin Oncol 2007, Choi et al The Oncologist 2008



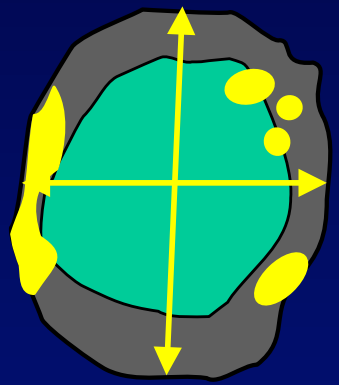
RECIST 1.1 – issues of debate



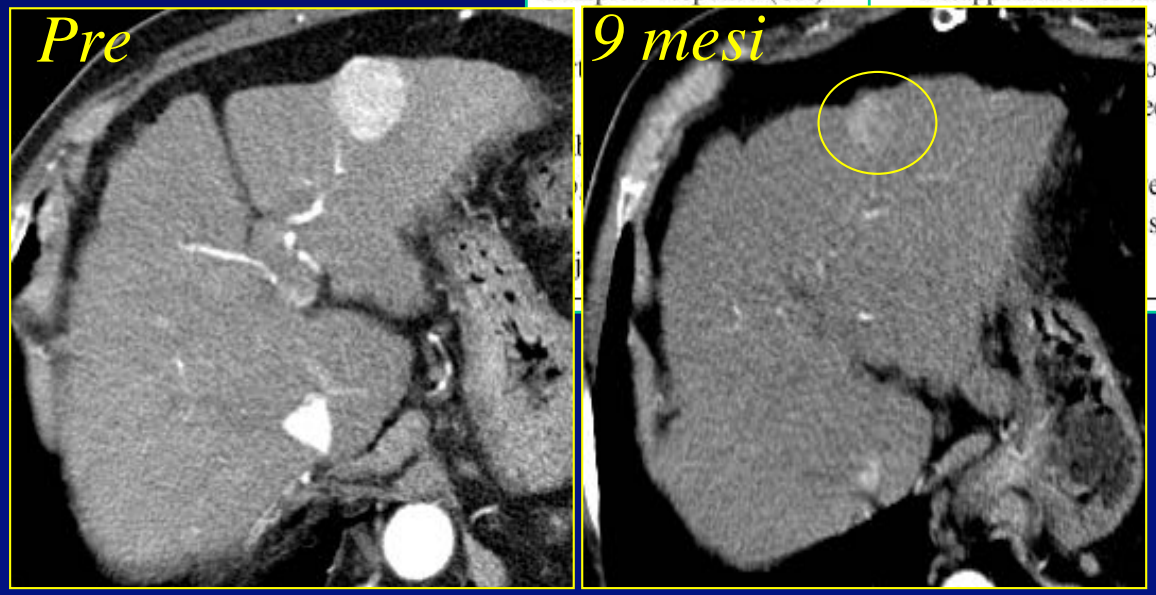
- reduction in tumor size does not always correlate with tumor response
- tumor shrinkage may not be an appropriate end-point when RF o MW ablation are used



RECIST 1.1 – issues of debate



Variables	RECIST	EASL
Characteristics		
Lesions assessed	Target lesions (five lesions or up to ten if more than one organ involved)	Measurable lesions (all lesions)
Type of assessment	Change in sum of largest diameter	WHO criteria, but change in diameter of viable tumour volume (enhanced areas within the tumour by CT-scan) instead of diameter of the lesion
Type of response		
Complete response (CR)	Disappearance of all target lesions,	WHO criteria, by spiral CT-scan or MRI 4 weeks after treatment*
	eeks	*
	om baseline,	
	eeks	*
	er smallest sum	*
	sions	
		CR + PR



Bruix J et al. Clinical management on hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL Conference. J Hepatol 2001;35:421–430

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Which Imaging Criteria?

- The change in tumor size after treatment is often used as a surrogate marker of survival in clinical studies, as for many cancer types, tumor shrinkage has
- In RECIST 1.1, 18F-FDG PET measurements have been incorporated; however, only as an adjunct to determination of progression by identification of new lesions. The new guideline includes comments on the possibility for future use of PET for treatment evaluation in clinical trials when the technique becomes more standardized and widespread available
- The PERCIST guideline proposes the use of 18F-FDG PET for tumor response assessment. In this guideline it is argued that treatment can be effective despite minimal changes in tumor size which is a concern especially during treatment with cytostatic therapies.

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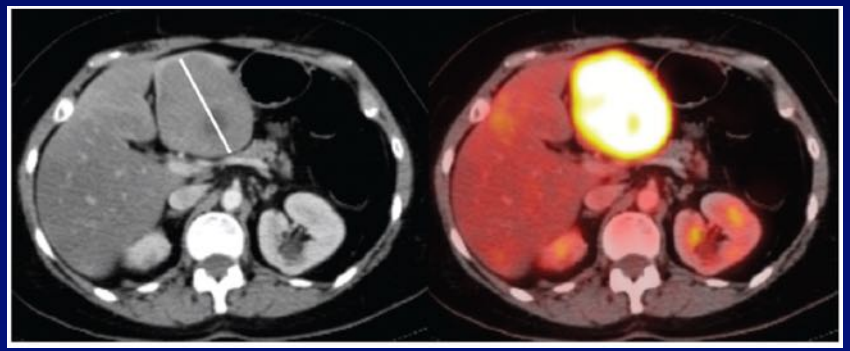
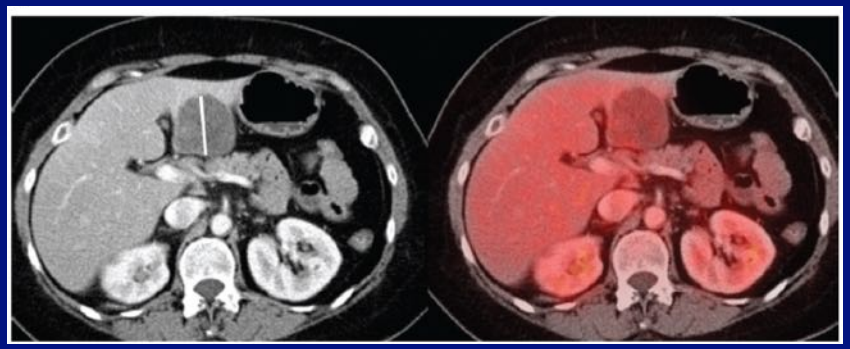
Appropriatezza dell'Imaging in funzione dei Trattamenti

Which Imaging Criteria?





Comparison of WHO, RECIST 1.1, Choi, mRECIST, and PERCIST Tumor Response Criteria

Response	WHO*	RECIST 1.1	Choi†	mRECIST‡	PERCIST§
Complete response	No lesions detected for at least 4 weeks	Disappearance of all target lesions or lymph nodes <10 mm in the short axis	Disappearance of all target lesions	Disappearance of arterial phase enhancement in all target lesions	Disappearance of all metabolically active tumors
Partial response	≥50% decrease in SPD (confirmed at 4 weeks)	>30% decrease in sum of longest diameters (SLD) of target lesions	≥10% decrease in tumor size or ≥15% decrease in tumor attenuation at computed tomography (CT); no new lesions	>30% decrease in SLD of "viable" target lesion (arterial phase enhancement)	>30% (0.8-unit) decline in SUL peak between the most intense lesion before treatment and the most intense lesion after treatment
Progressive disease	≥25% increase in SPD in one or more lesions; new lesions	>20% increase in SLD of target lesions with an absolute increase of ≥5 mm; new lesions	≥10% increase in SLD of lesions; does not meet the criteria for partial response by virtue of tumor attenuation, new intratumoral nodules, or an increase in the size of the existing intratumoral nodules	>20% increase in SLD of "viable" target lesion (arterial phase enhancement)	>30% (0.8-unit) increase in SUL peak or confirmed new lesions
Stable disease	None of the above	None of the above	None of the above	None of the above	None of the above

SUL = lean body mass–normalized standardized uptake value (SUV).

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Appropriatezza dell'Imaging in funzione dei Trattamenti

Which Imaging Criteria?

Cheson Response Criteria for Malignant Lymphomas

Definitions of Treatment Response According to Cheson Criteria

Response	Nodal Masses	Spleen and Liver	Bone Marrow
Complete response	All previously enlarged FDG-avid or PET-positive lymph nodes regressed to normal size (≤1.5 cm in greatest diameter)	Regressed in size and not palpable at physical examination, disappearance of nodules	Clearance of infiltrate at repeat biopsy; if findings at morphologic analysis are indeterminate, immunohistochemical findings should be negative
Partial response	≥50% decrease in SPD of up to six largest dominant masses, no increase in size of other nodes; FDG avid or PET positive before therapy, one or more nodes PET positive at previously involved site, or variably FDG avid or PET negative with regression at CT	≥50% decrease in SPD of nodules, no increase in size of liver or spleen	Irrelevant if findings are positive before therapy, cell type should be specified
Stable disease	FDG avid or PET positive before therapy, PET positive at prior sites of disease and no new sites at CT or PET, or variably FDG avid or PET negative with no change in size of previous lesions at CT	. . .	. . .
Relapse or progressive disease	Appearance of one or more new lesions >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in the longest diameter of a previously identified node >1 cm in the short axis; lesions PET positive if FDG-avid lymphoma or PET positive before therapy	>50% increase from nadir in SPD of any previous lesions	New or recurrent involvement

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Appropriatezza dell'Imaging in funzione dei Trattamenti

Which Imaging Criteria?

IrRC Response Criteria for Immunotherapy

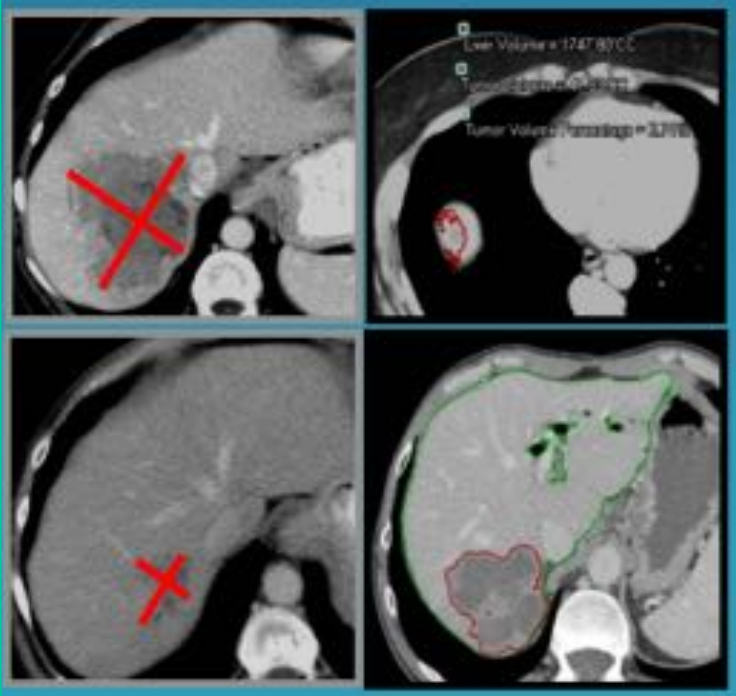
WHO versus IrRC Criteria

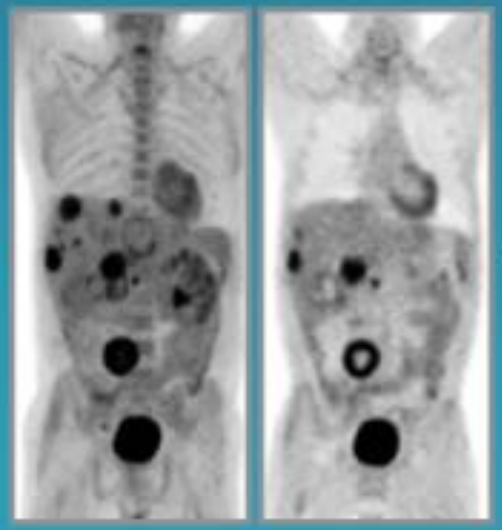
Response	WHO	IrRC
Complete response	Disappearance of all lesions at two consecutive observations ≥4 weeks apart	Disappearance of all lesions (including nonindex lesions) at two consecutive observations ≥4 weeks apart, no new nonmeasurable disease
Partial response	50% decrease in SPD of all lesions (confirmed at 4 weeks)	50% decrease in tumor burden (confirmed at 4 weeks)
Progressive disease	25% increase in SPD or new lesions (measurable or nonmeasurable)	25% increase in tumor burden (confirmed at 4 weeks), new measurable lesions included within tumor burden
Stable disease	None of the above	None of the above

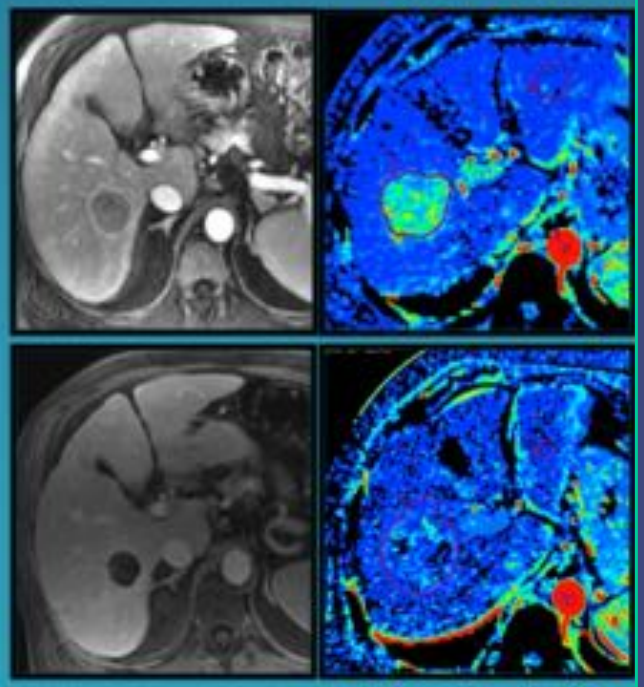
RECIST 1.1 – issues of debate

Tumor measurement + Oncologic Markers + Functional Imagi

Tumor Burden	Metabolism	Angiogenesis
CT/MRI tumor measurement RECIST/WHO	FDG/PET	CT perfusion MR perfusion MR diffusion







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Appropriatezza dell'Imaging in funzione dei Trattamenti

Functional Imaging: Overcoming the Problems of Morphologic Imaging?

- Positron emission tomography (PET),
- Magnetic Resonance Spectroscopy (MRS),
- Dynamic contrast-enhanced (DCE) MRI,
- Diffusion-weighted (DW) MRI

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Appropriatezza dell'Imaging in funzione dei Trattamenti

Imaging biomarkers: ^{18}F-FDG-PET-CT

- FDG-PET has been applied in the evaluation of treatment response
  to targeted therapies, such as tyrosine kinase inhibitors (TKIs) [15], epidermal growth factor receptor inhibitors, angiogenesis inhibitors, endocrine therapies, and androgen receptor blockade [19]. To improve anatomic localization, PET images are usually combined with CT or MR images

- *not all malignancies are FDG-avid and not all FDG-avid lesions are malignant*
- *cancers are usually diagnosed when they reach a size of 10^8 to 10^9 cells.*

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Appropriatezza dell'Imaging in funzione dei Trattamenti

Imaging biomarkers: MR spectroscopy

- By detecting signal from molecules containing the targeted atoms, MR spectroscopy (MRS) is a noninvasive technique used to study metabolism through quantification of the molecular component of tissues
- Evaluation of treatment response may be accomplished by quantification of tumor-specific compounds, such as choline, or tissue-specific compounds, such as citrate and *N*-acetyl aspartate (NAA)
- MRS has been applied in the evaluation of treatment response to radiotherapy, hormone therapy, and cryosurgery in brain, breast, and prostate] malignancies

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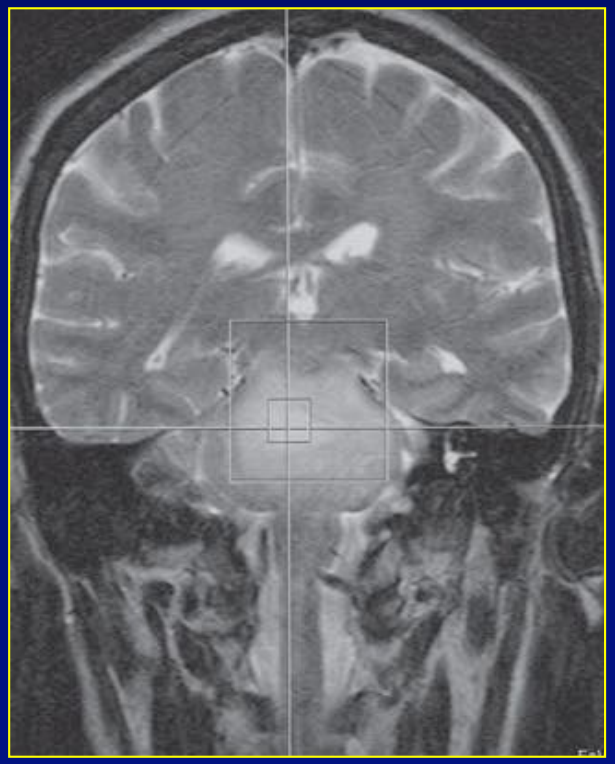
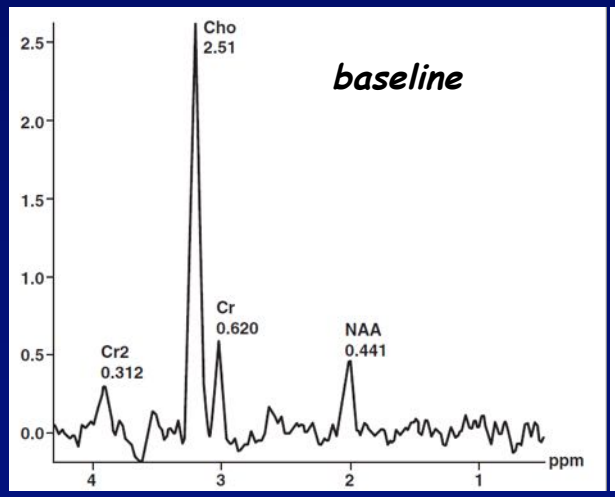
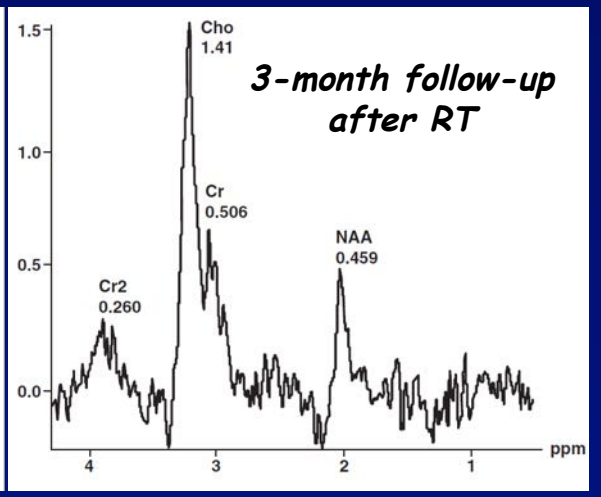
Appropriatezza dell'Imaging in funzione dei Trattamenti

Imaging biomarkers: MR spectroscopy







Coronal MR image obtained at baseline and MR spectroscopic images obtained at baseline and follow-up 3 months after radiation therapy. Choline/ creatine and choline/*N*-acetyl aspartate ratios decreased from 4.04 and 5.69 at baseline to 2.78 and 3.07, respectively, corresponding with interval improvement and
favorable response to treatment

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Appropriatezza dell'Imaging in funzione dei Trattamenti

Imaging biomarkers: DCE-MRI

- Angiogenesis is a critical step for tumor growth and metastasis
- Inhibitors of vascular endothelial growth factor (VEGF) have become an emerging class of antineoplastic agents, and evaluation of their therapeutic effect has been of great clinical interest
- Noninvasive assessment of angiogenesis may be performed with evaluation of tumor perfusion by dynamic contrast-enhanced techniques
- Evaluation of treatment response relies on quantification of transfer constants, which should ideally decrease in response to VEGF inhibitors

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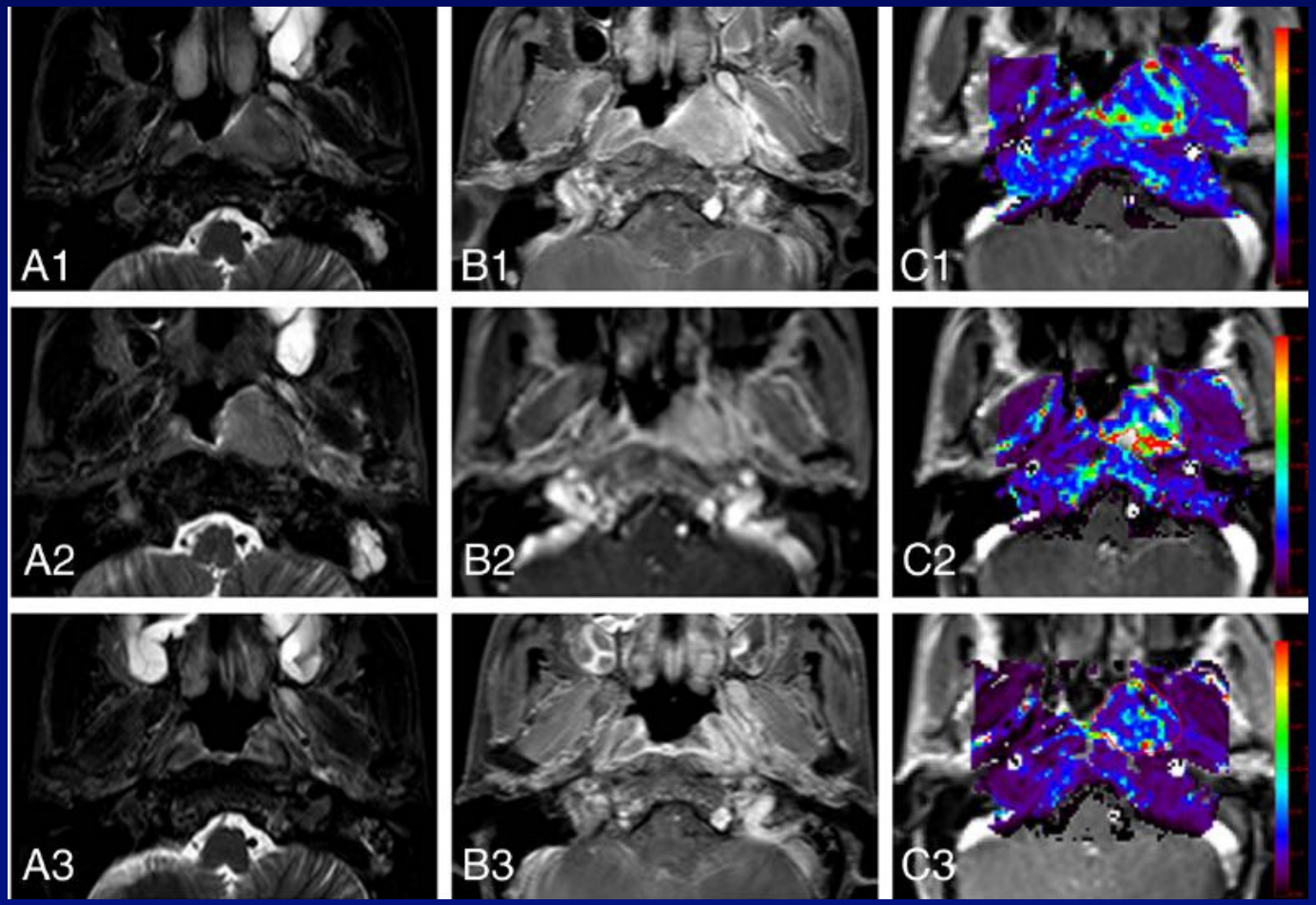
Appropriatezza dell'Imaging in funzione dei Trattamenti



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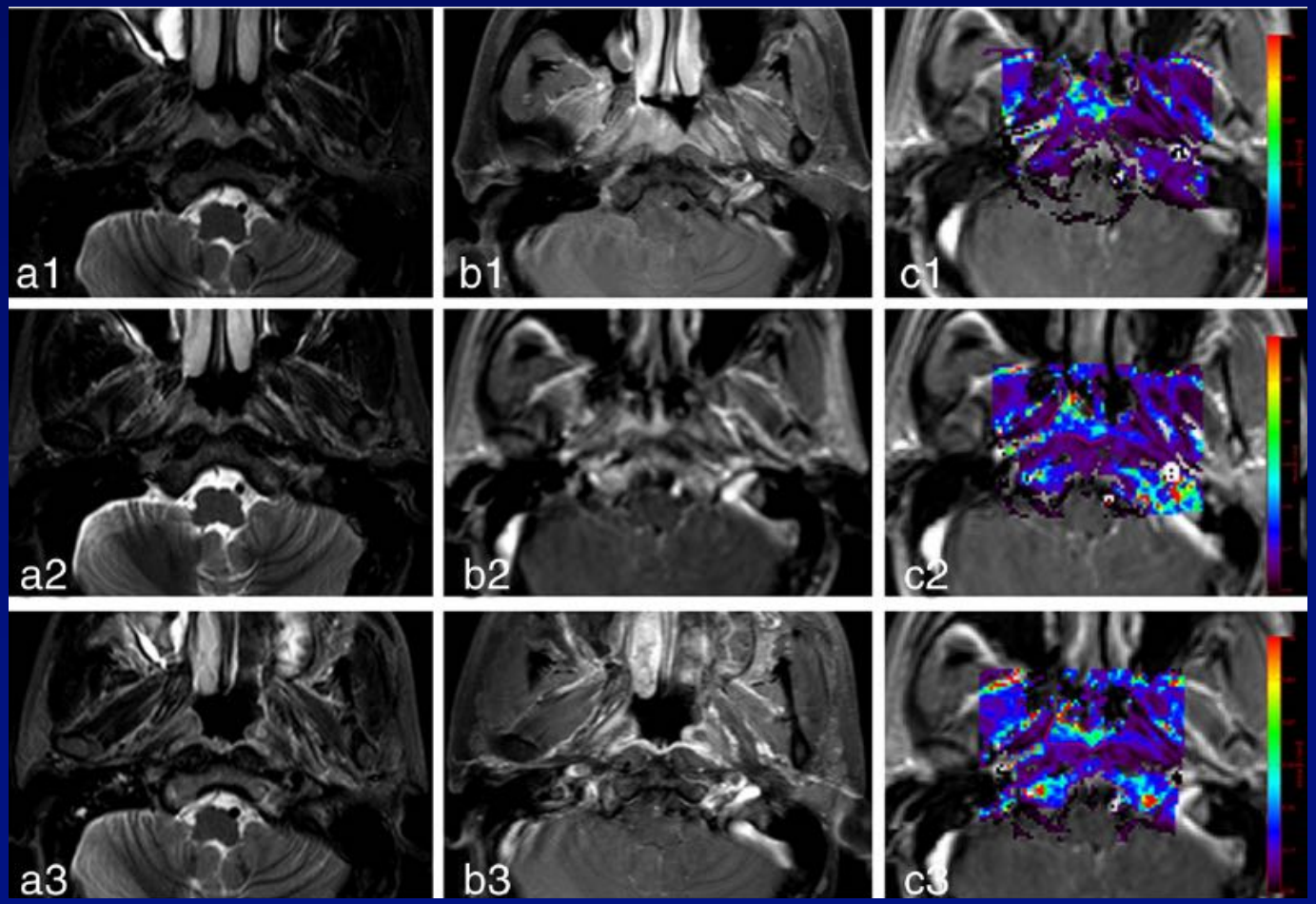
Appropriatezza dell'Imaging in funzione dei Trattamenti



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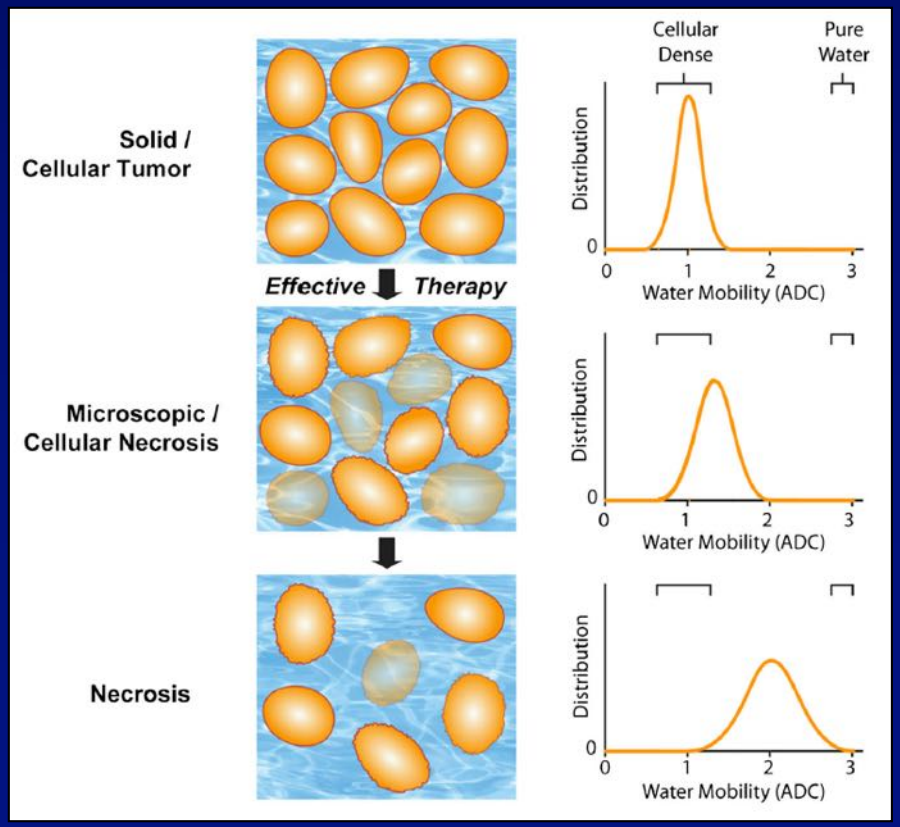
Appropriatezza dell'Imaging in funzione dei Trattamenti

Imaging biomarkers: DWI-MRI



Clinical cancer studies on the efficacy of DW-MRI as a surrogate imaging biomarker of the tumor treatment response have demonstrated that treatment-induced cell death can be detected in responding tumors as an increased ADC value in these regions

Diffusion-weighted MRI for monitoring therapy has already been applied in a wide variety of cancer types and organ sites, including the liver, breast, bone, soft tissue tumors, cervical tumors, head and neck tumors, as well as rectal cancer

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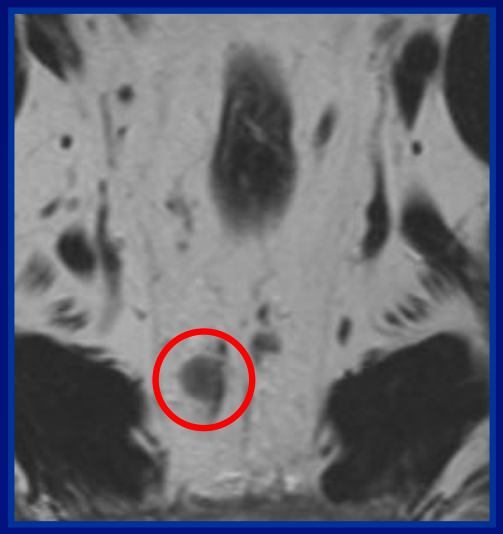
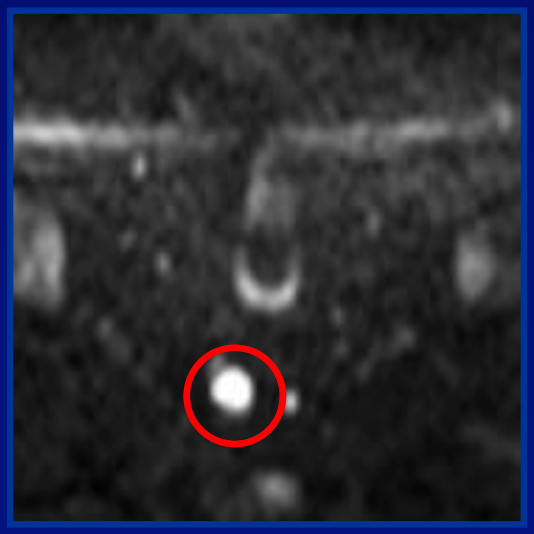
Appropriatezza dell'Imaging in funzione dei Trattamenti

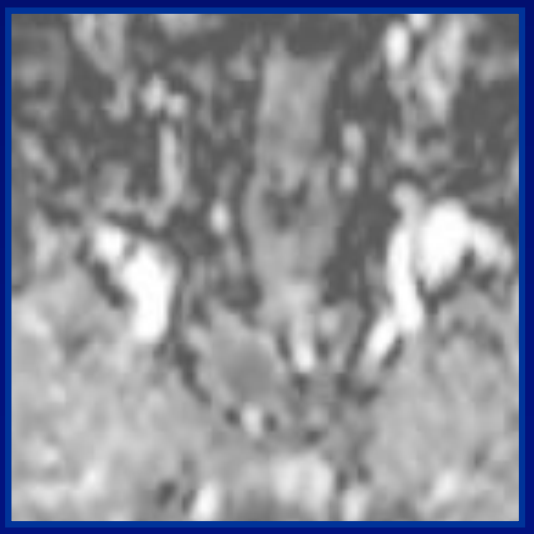
Imaging biomarkers: DWI-MRI



T2W FSE



DWI
(b 0,500,1000)



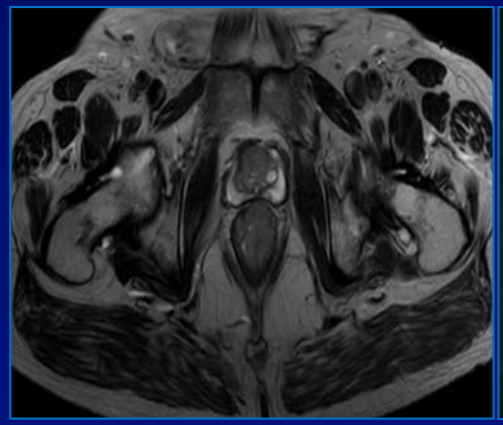
ADC

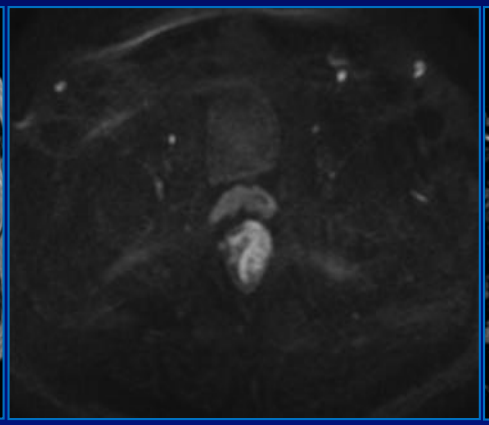
Endpoint 1- Discussion – WHAT DOES IT MEAN?

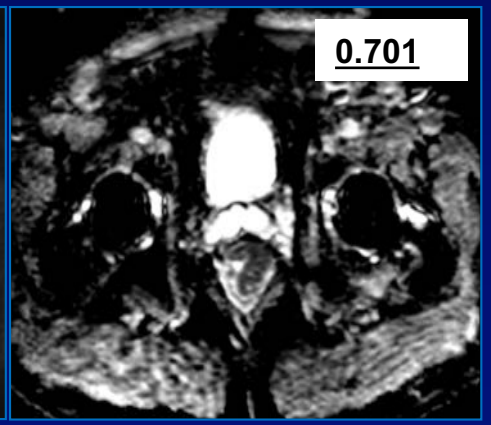
1.4 The best post-CRT mean ADC% increase cut off to differentiate responders from nonresponders with ROC was 29.5%

We suggested the cut-off value of a 29,5% ADC increase to predict tumor response.

It means that all those tumors that show a post-CRT ADC increase rate of ≥ 29.5%, have the potential to result of grade I or II at pathology, according to Mandard's classification, with a sensitivity of 83.3%, a specificity of 90%, a PPV of 91% and a NPV of 82%.



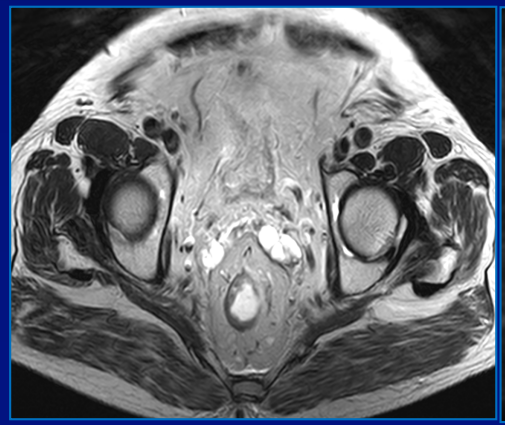


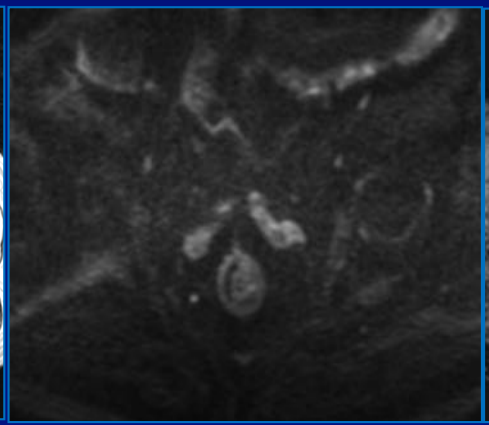


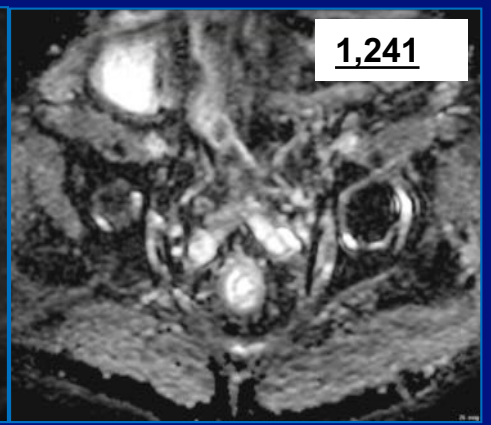
Before CRT

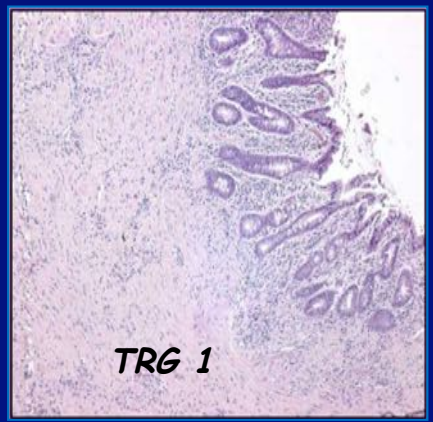
ADC% increase = 77%

After CRT







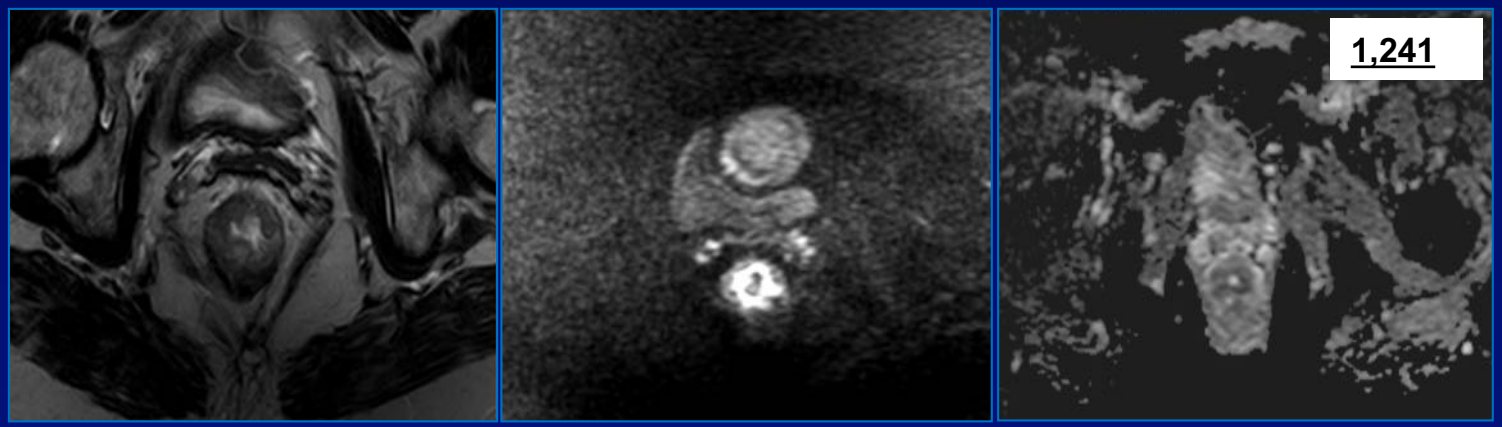


Endpoint 1- Discussion – WHAT DOES IT MEAN?

1.4 The best post-CRT mean ADC% increase cut off to differentiate responders from nonresponders with ROC was 29.5%

We suggested the cut-off value of a 29,5% ADC increase to predict tumor response.

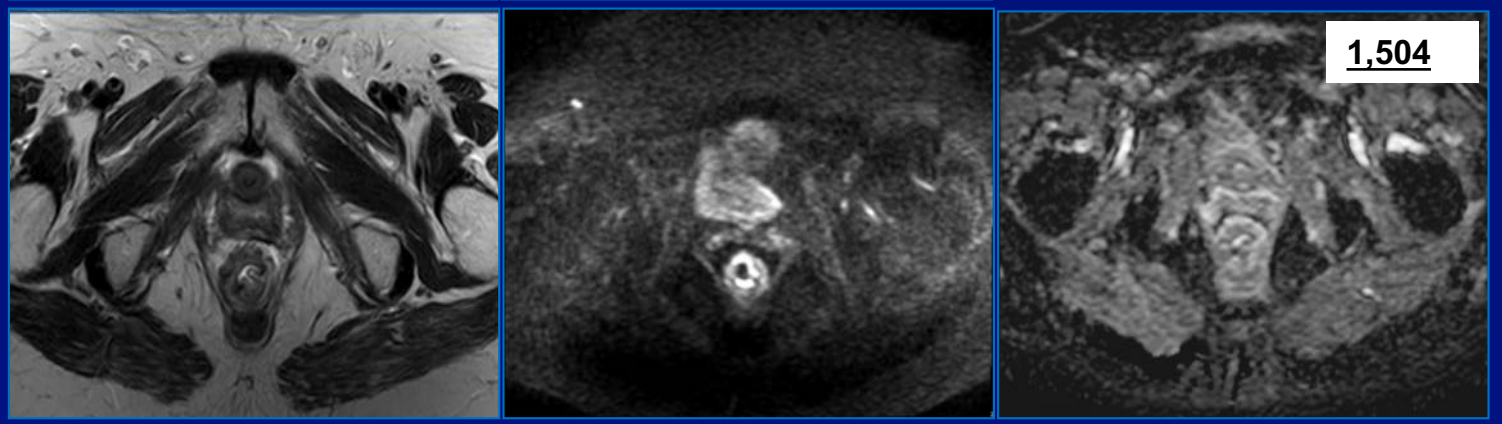
Conversely, all those tumors that show a post-CRT ADC increase rate less than 29.5%, have the potential to result of grade III or IV at pathology, according to Mandard's classification, with a sensitivity of 83.3%, a specificity of 90%, a PPV of 91% and a NPV of 82%.

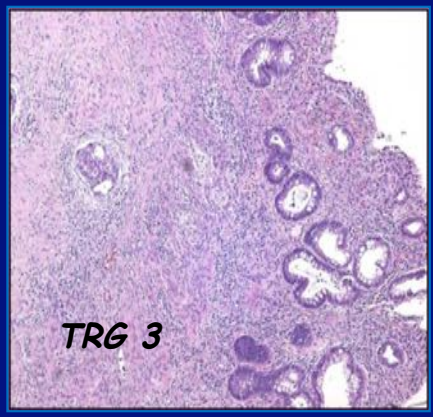


Before CRT

ADC% increase = 21%

After CRT





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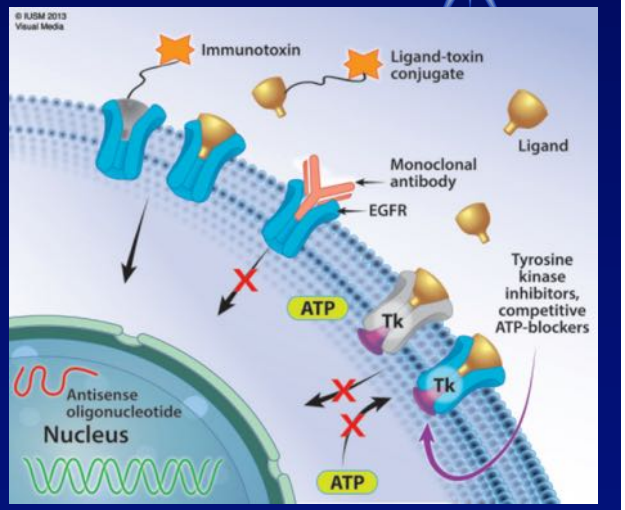
Appropriatezza dell'Imaging in funzione dei Trattamenti

Molecular Imaging

- labeling of the drug of interest with positron-emitting isotopes and evaluating pharmacokinetics and pharmacodynamics using PET;
- design of specific imaging probes directed to the receptors that interact with the drug of interest, such as trastuzumab PET;
- developing targeted agents with both therapeutic and diagnostic properties (theranostic approach)



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Appropriatezza dell'Imaging in funzione dei Trattamenti

Conclusioni

- Because of its wide availability, efficacy, results consistency and high reproducibility, CT has currently been the imaging method most utilized in dimensional evaluation
- MRI presents a greater potential to be adopted as a technique of choice, besides PET, in the functional and molecular tumor response evaluation, principally in the context of the increasing utilization of targeted therapies