Imaging in Clinical Trials

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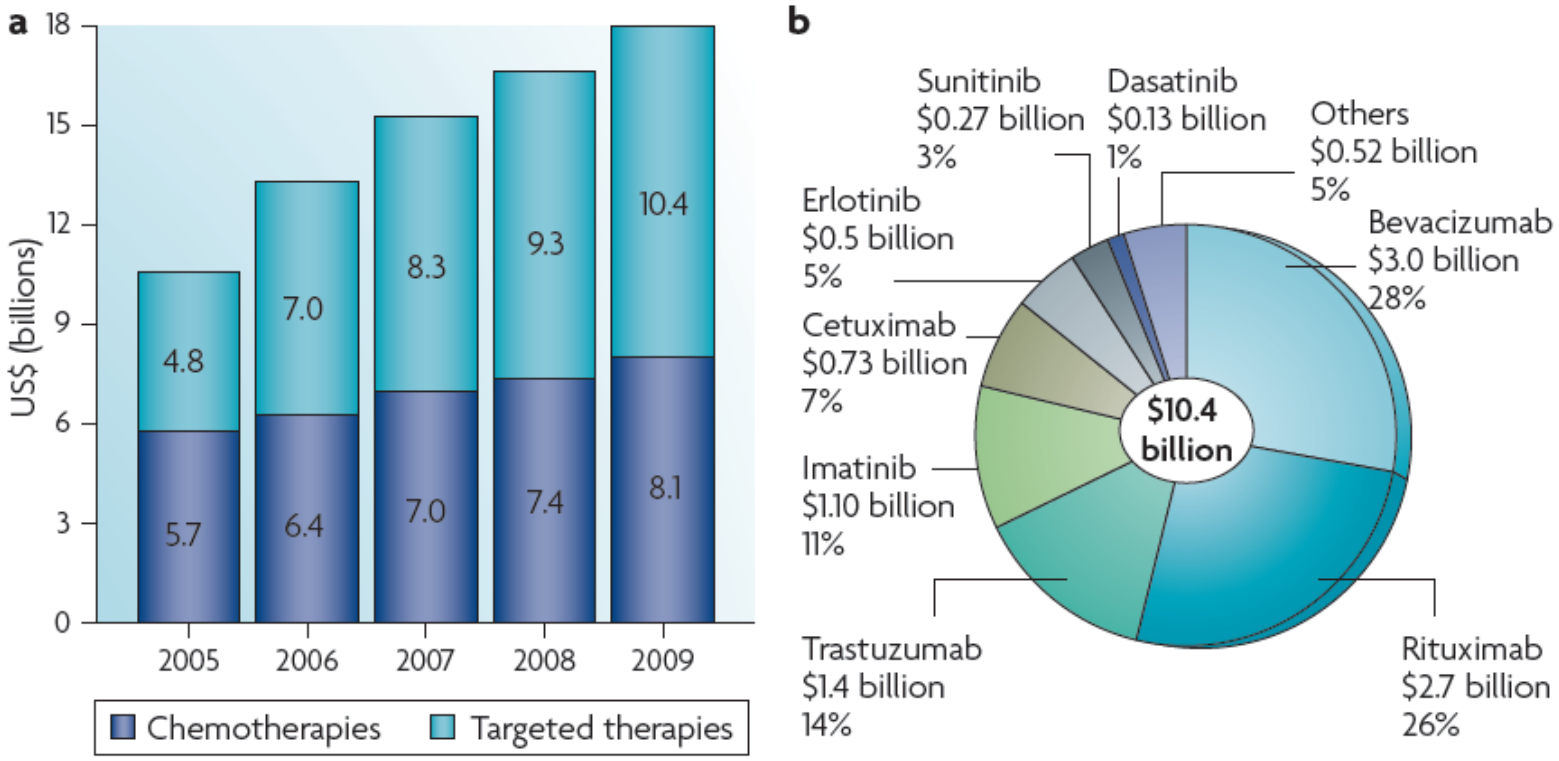
Clinical Trials in Perspective



16,000 cancer related trials listed in Clinical Trials.gov (2009)

Aggarwal S. NATURE REVIEWS | DRUG DISCOVERY VOLUME 9 | JUNE 2010 | 427

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Challenges for Imaging in Cancer

Tumour Phenotyping	Assessment of treatment response
Can we improve tumour phenotyping? - Important biological characteristics may not be depicted by conventional imaging	Can we improve imaging response assessment? - Better responsive/predictive biomarkers? - Detect response at an earlier stage?

Types of Clinical Trials

Phase I	Phase II	Phase III
▪ Small no. of patients ▪ Safety/Toxicity/Dosage	▪ Small no. of patients ▪ Drug effectiveness ▪ Safety	▪ Large no. of patients ▪ Randomisation ▪ Tested vs standard treatment

Question: Is the agent safe & is there biological activity?

Question: Does the drug work sufficiently well?

Question: How well does the drug work compared to what we have?

Go/No go

Go/No go

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Role of Imaging ?

Phase I	Phase II	Phase III
▪ Small no. of patients ▪ Safety/Toxicity/Dosage	▪ Small no. of patients ▪ Drug effectiveness ▪ Safety	▪ Large no. of patients ▪ Randomisation ▪ Tested vs standard treatment

- Prospective end-point to estimate the benefit of treatment

- Objective treatment response (RR)
- Classification of response:
  - Complete remission
  - Partial remission
  - Stable disease
  - Progressive disease

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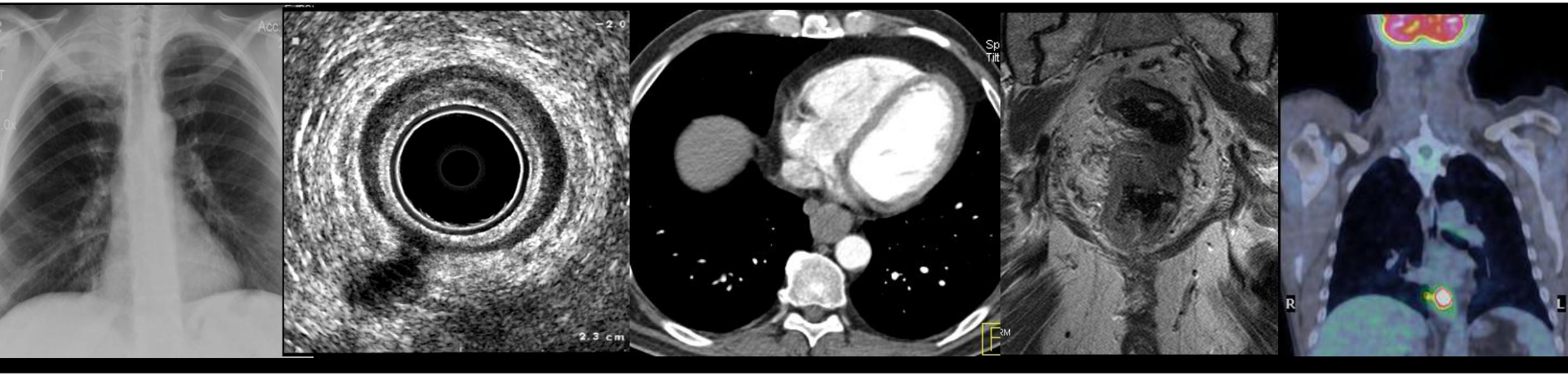
Role of Imaging ?

Phase I	Phase II	Phase III
▪ Small no. of patients ▪ Safety/Toxicity/Dosage	▪ Small no. of patients ▪ Drug effectiveness ▪ Safety	▪ Large no. of patients ▪ Randomisation ▪ Tested vs standard treatment

- End-point to selecting drugs for further Phase III studies

- Objective treatment response (RR)
- Classification of response:
  - Complete remission
  - Partial remission
  - Stable disease
  - Progressive disease

Imaging Modalities Used For Response Assessment



X-ray Ultrasound CT MRI PET

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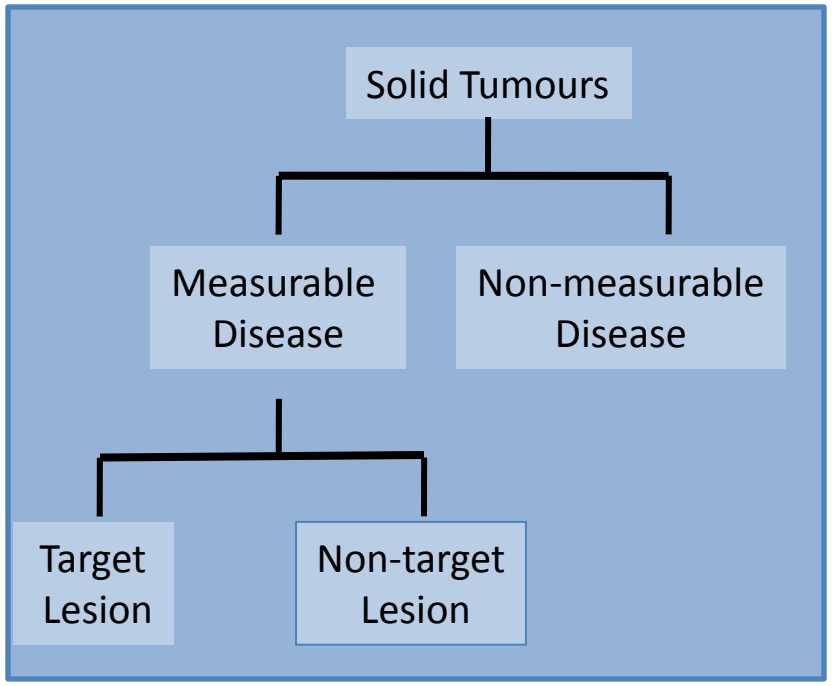
RECIST 1.1: Response Assessment



EJC
EUROPEAN JOURNAL OF CANCER

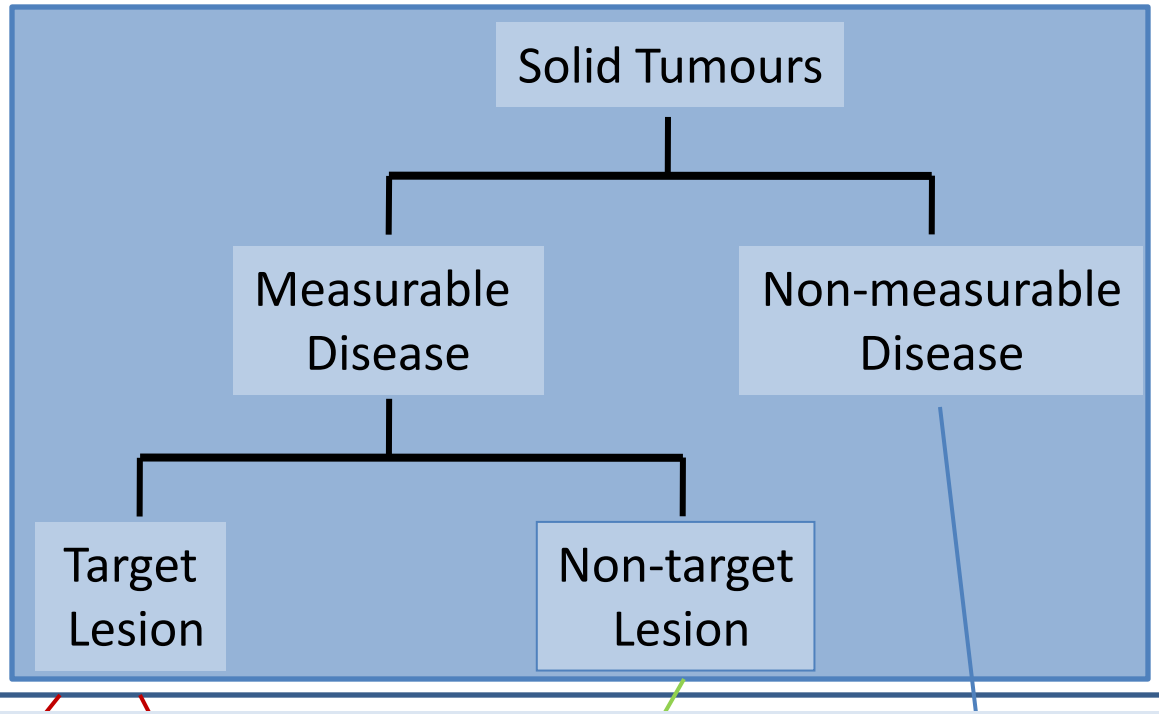
New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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]

Eisenhauer et al. Eur J Cancer 2009;45:228–47

Lesion >1cm
Reproducibly measured
Selection must reflect different sites
Max: 5 lesions; 2 per organ

- Classification of Response:
  - Complete remission
  - Partial remission
  - Stable disease
  - Progressive disease



- Response criteria for solid tumours
- Response based on changes to sum of the longest diameters of **target** lesions
  - Longest diameter irrespective of shape change subsequently
  - Nodes: short axis NOT longest dimension
- Changes in burden of **non-target** lesions & **non-measurable** disease also taken into account

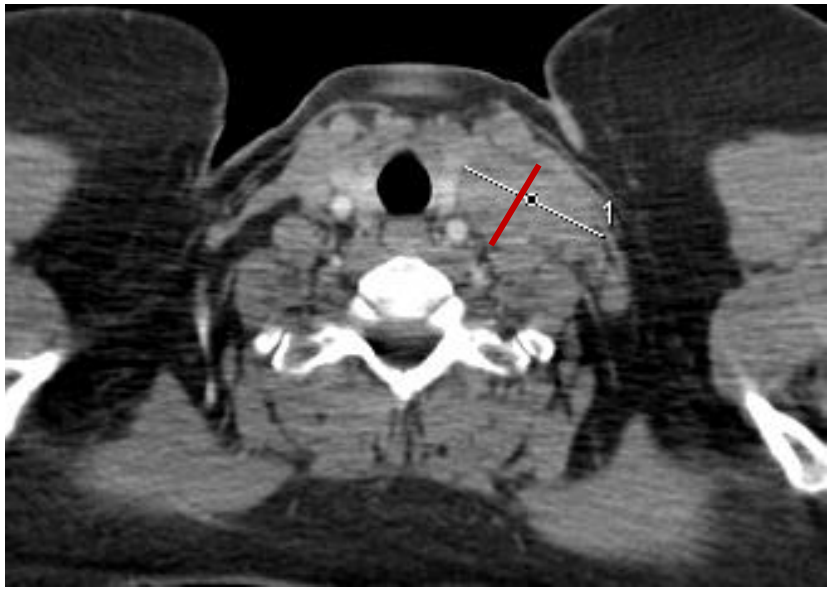
RECIST 1.1: Response Assessment

Response criteria for evaluation of target lesions
Complete Response (CR): Disappearance of all target lesions (TL). All nodes <10 mm
Partial Response (PR): >30% decrease in the sum of TL diameters
Stable Disease (SD): Neither PR nor PD
Progressive Disease (PD): > 20% increase in the sum of TL diameters Absolute increase of at least 5 mm Any new lesion = progressive disease

Eisenhauer et al. Eur J Cancer 2009;45:228–47

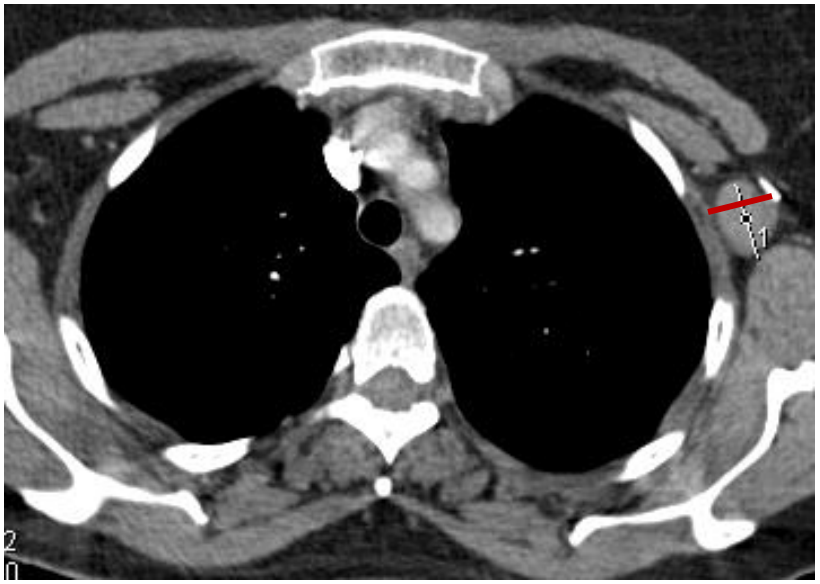
RECIST 1.1: Response Assessment

Target lesion



Node: Short axis: 2.5cm

Non-target lesion



Node: Short axis: 1.0-1.5cm

Baseline

Sum of maximal diameter = 2.5 cm

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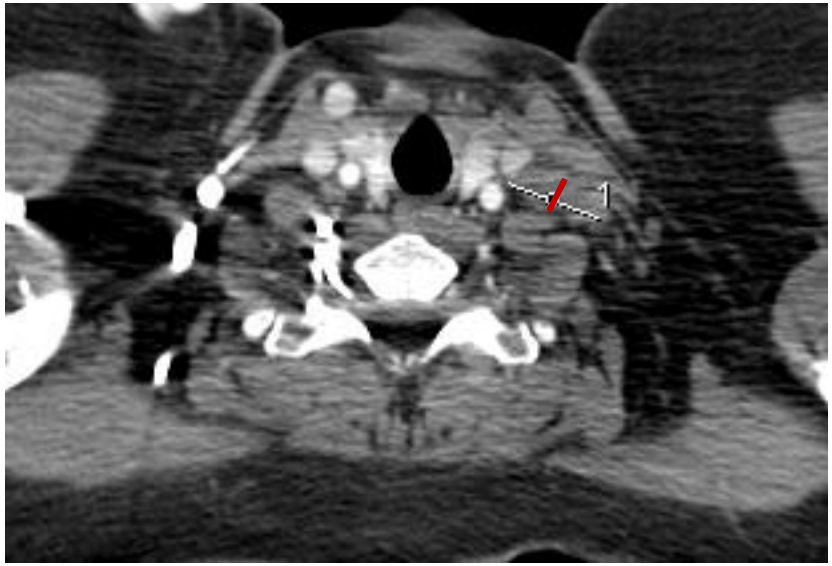
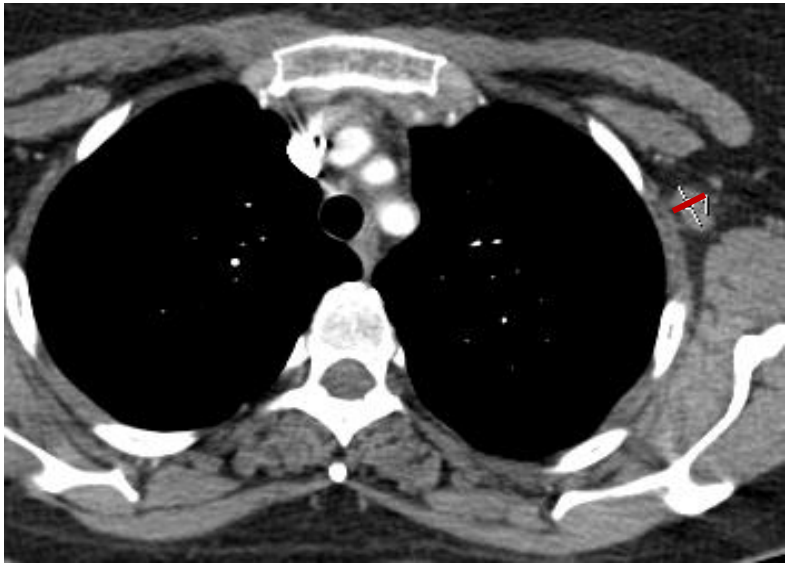
RECIST 1.1: Response Assessment

Target lesion



Node: Short axis: 1.0 cm

Non-target lesion



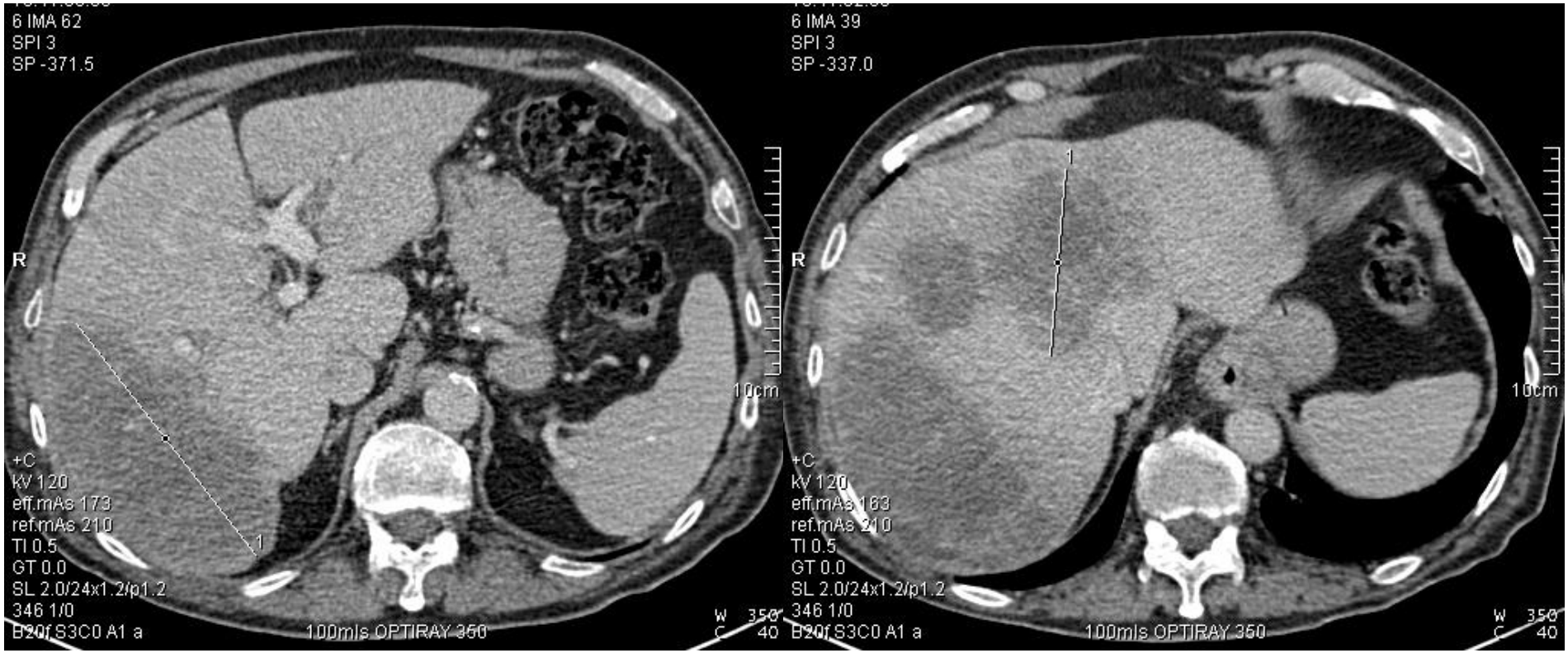
Node: Short axis: <1.0cm

Post 2 cycles

% change: 2.5-1/2.5*100=60% decrease

Partial Response

RECIST 1.1: Response Assessment



Baseline

Sum of maximal diameter = 12.9 + 8.3 = 21.2 cm

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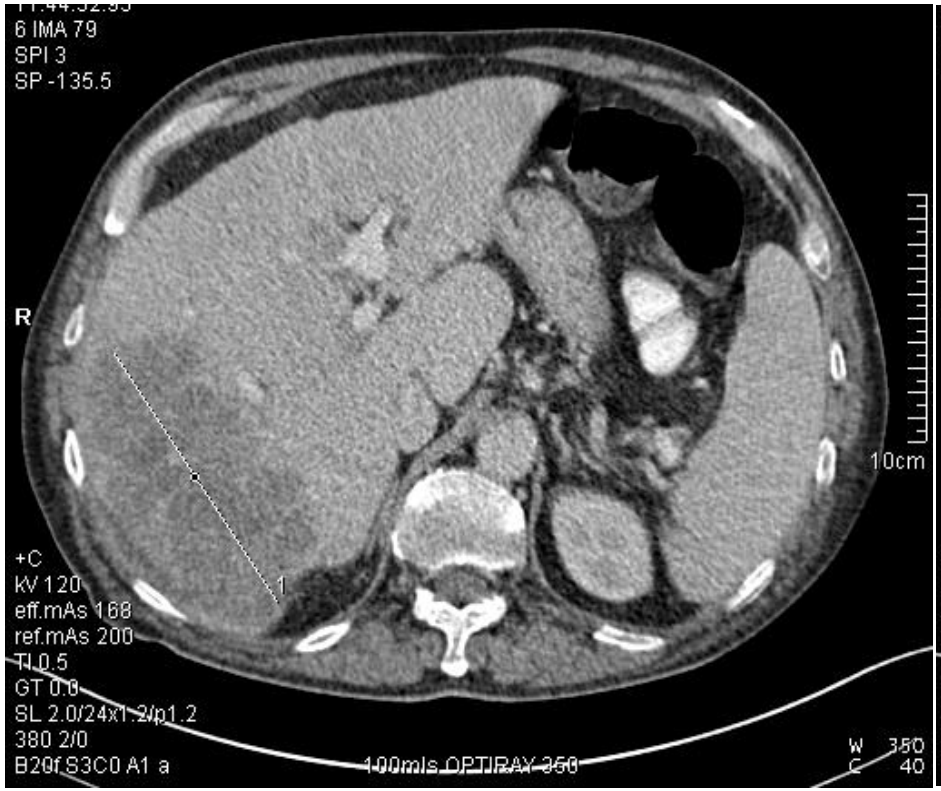
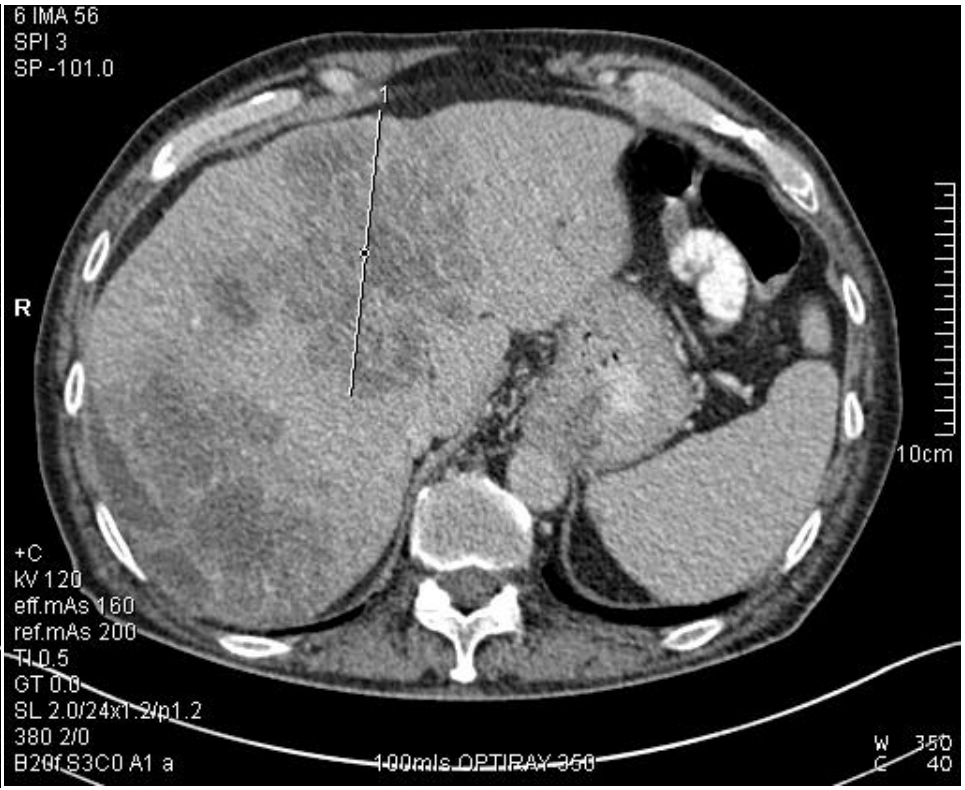
RECIST 1.1: Response Assessment





Post 2 cycles

Sum of maximal diameter = 12.1 + 11.3 = 23.4

% change = (23.4-21.2)/21.2*100 = 10% increase

Stable Disease

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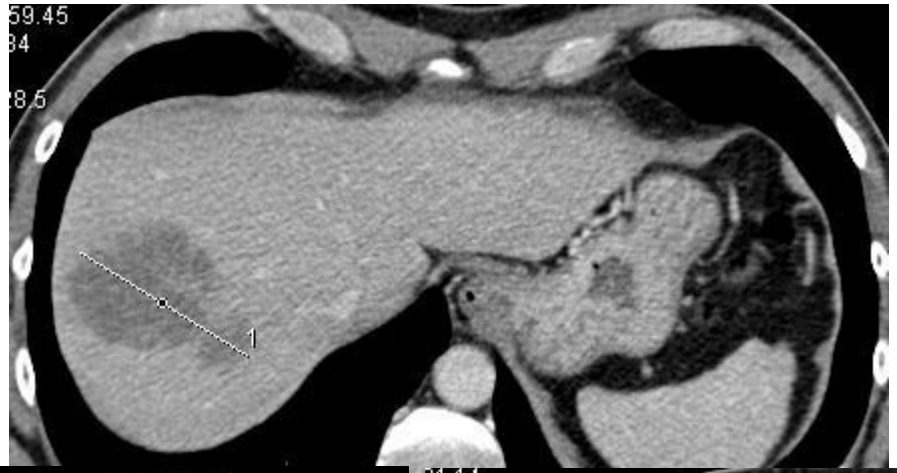
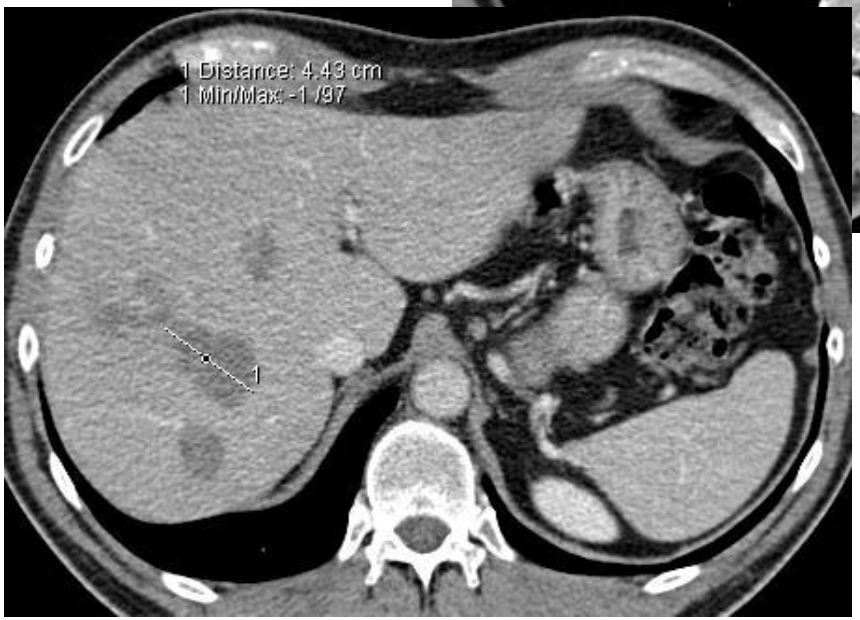
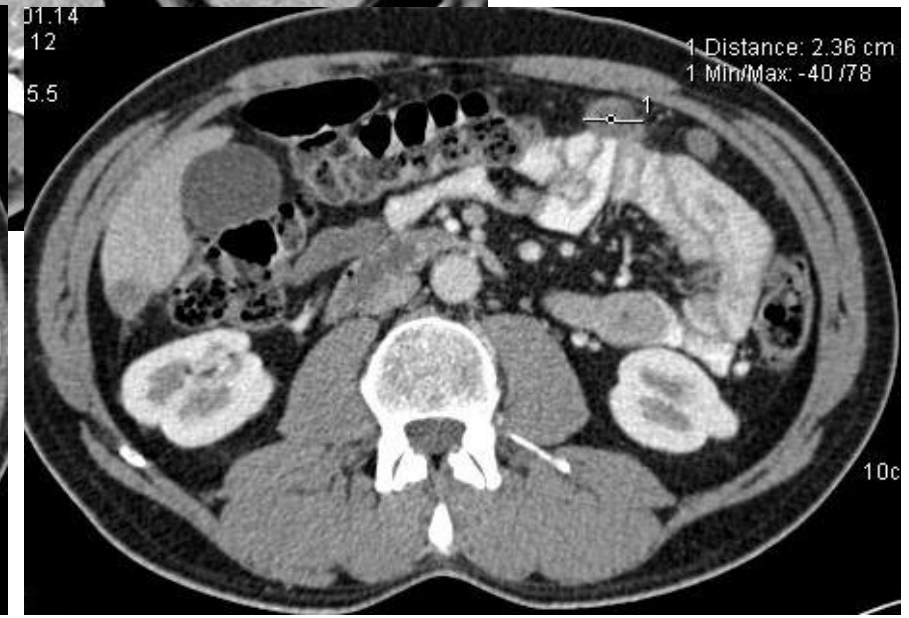
RECIST 1.1: Response Assessment



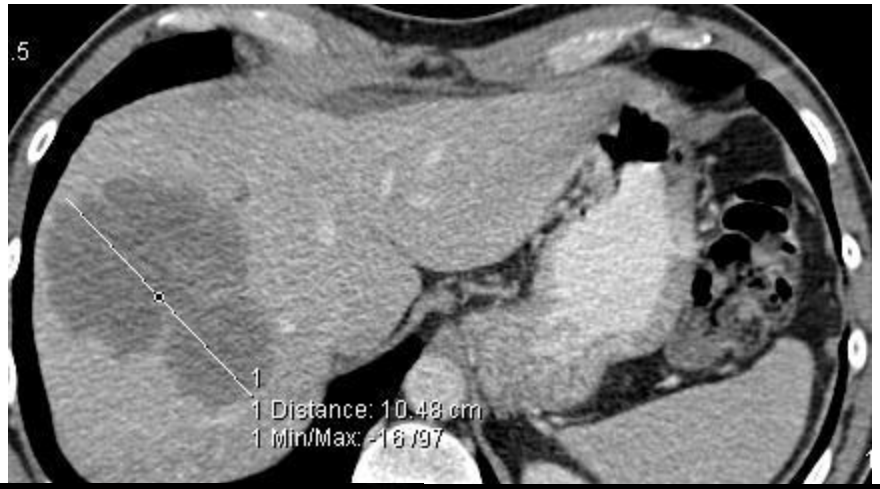
Baseline



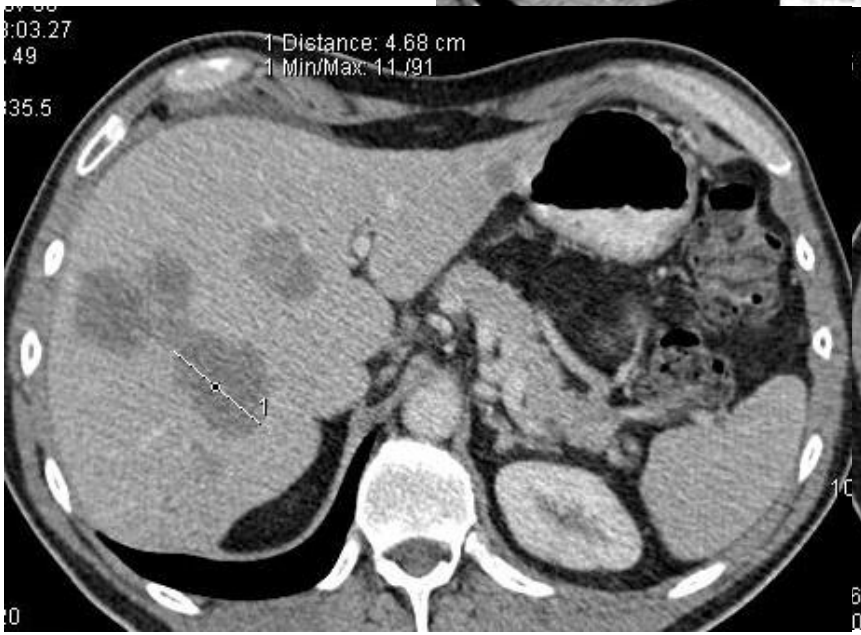


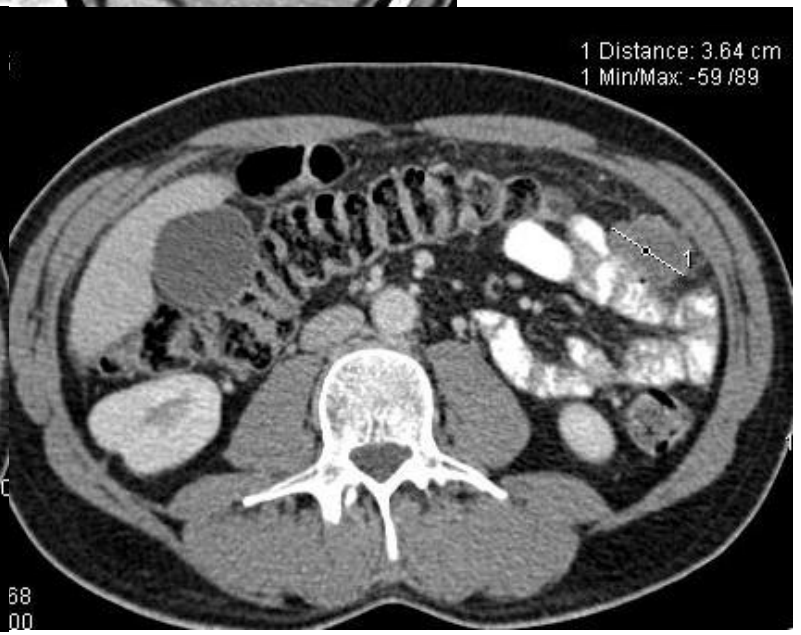
Sum of max diameters= 7.5 +4.5 + 2.4 = 14.4

RECIST 1.1: Response Assessment



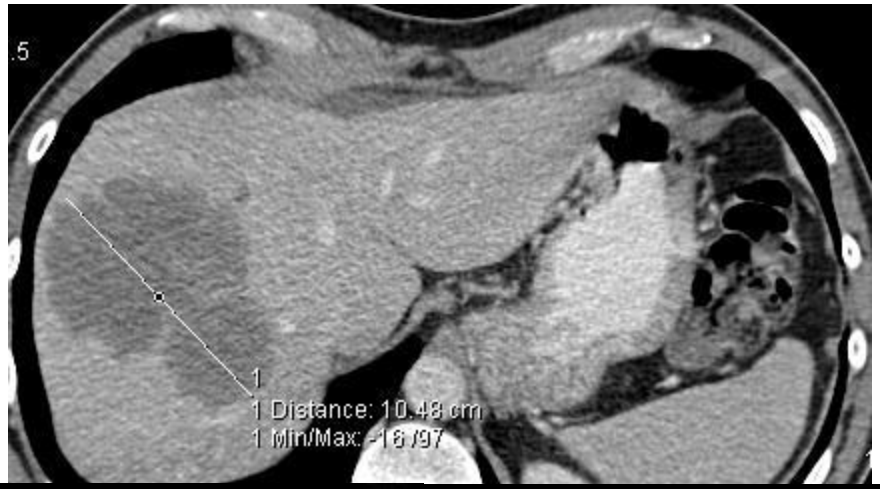
Post 2 cycles



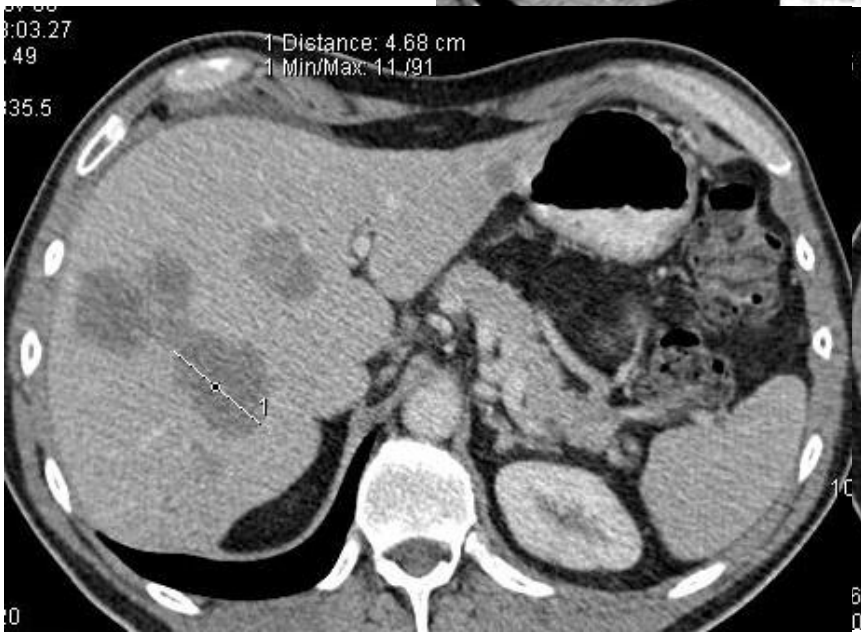


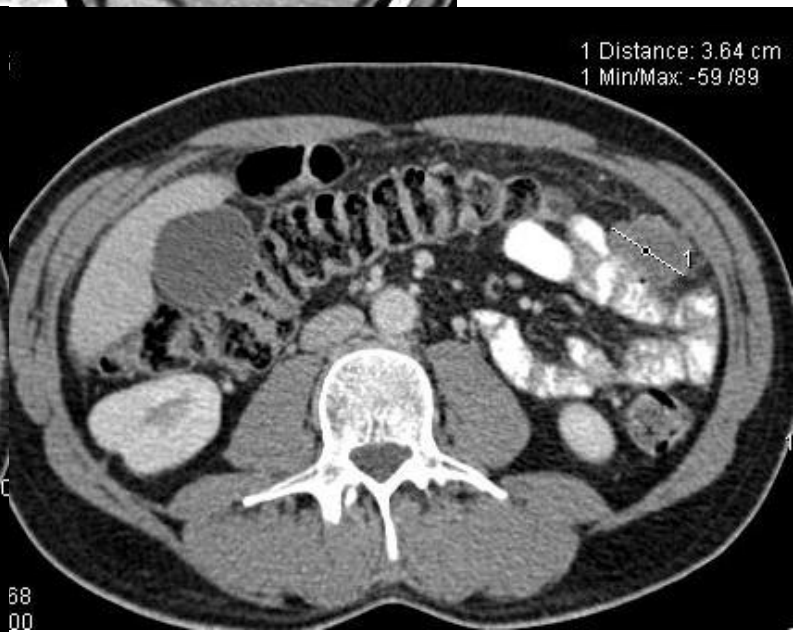
Sum of max diameters= 10.5 + 4.7 + 3.6 = 18.8

RECIST 1.1: Response Assessment



Post 2 cycles

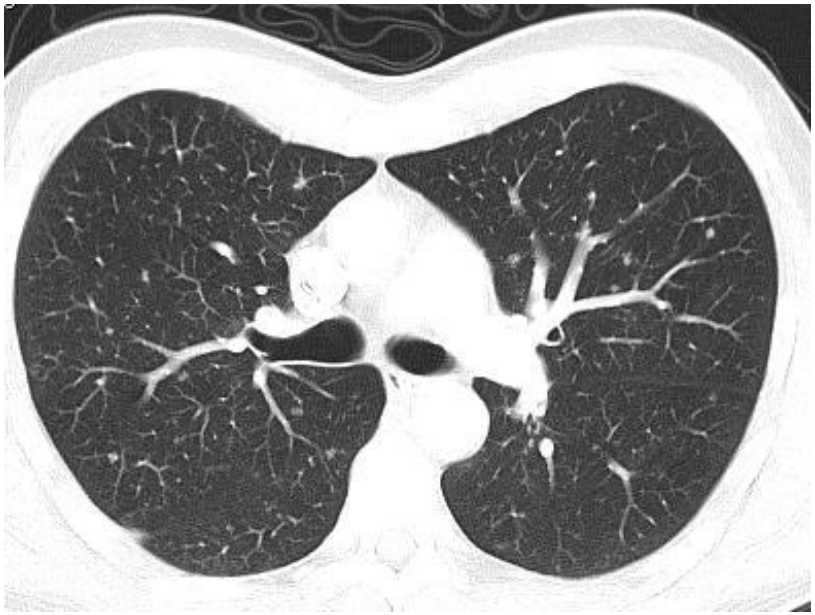




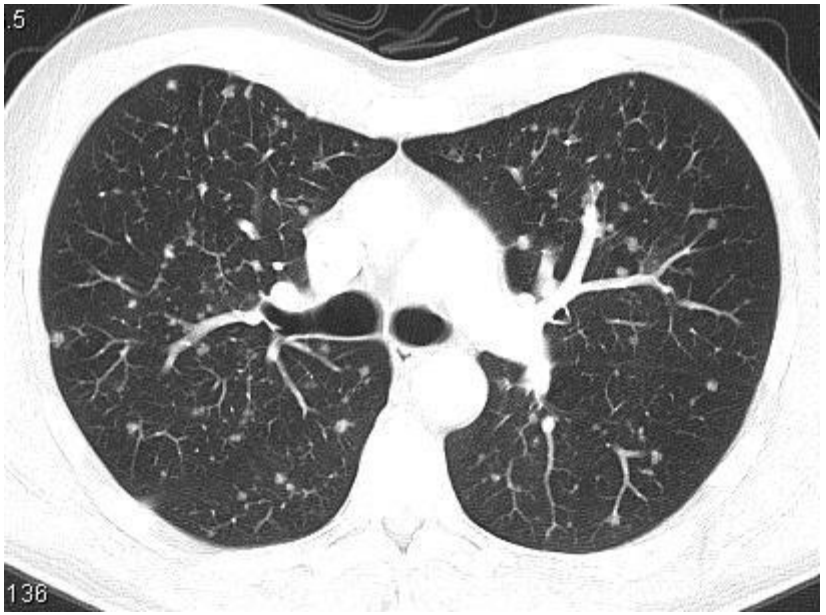
% change = 18.8- 14.4 / 14.4 * 100 = 30.6 increase%

RECIST 1.1: Response Assessment

Baseline



Post 2 cycles



Non Measurable Disease: Increase

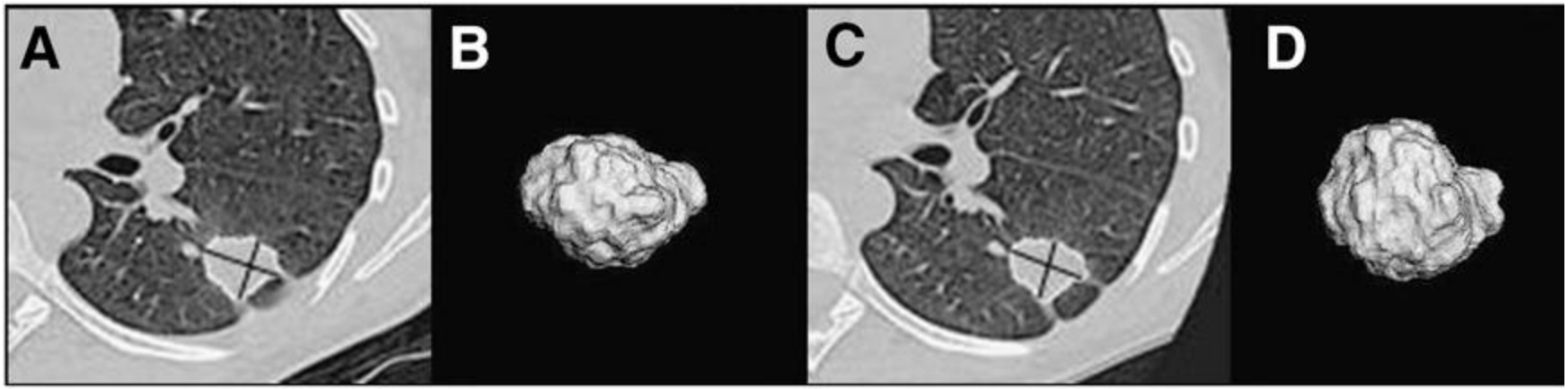
Progressive Disease

RECIST 1.1 Assessment

Does it work in practice?

- Imaging established & widely available in the clinic
- High patient acceptability
- Reproducible
- Response categorisation clinically meaningful & reflects clinical outcome

Imaging Evaluation: Limitations

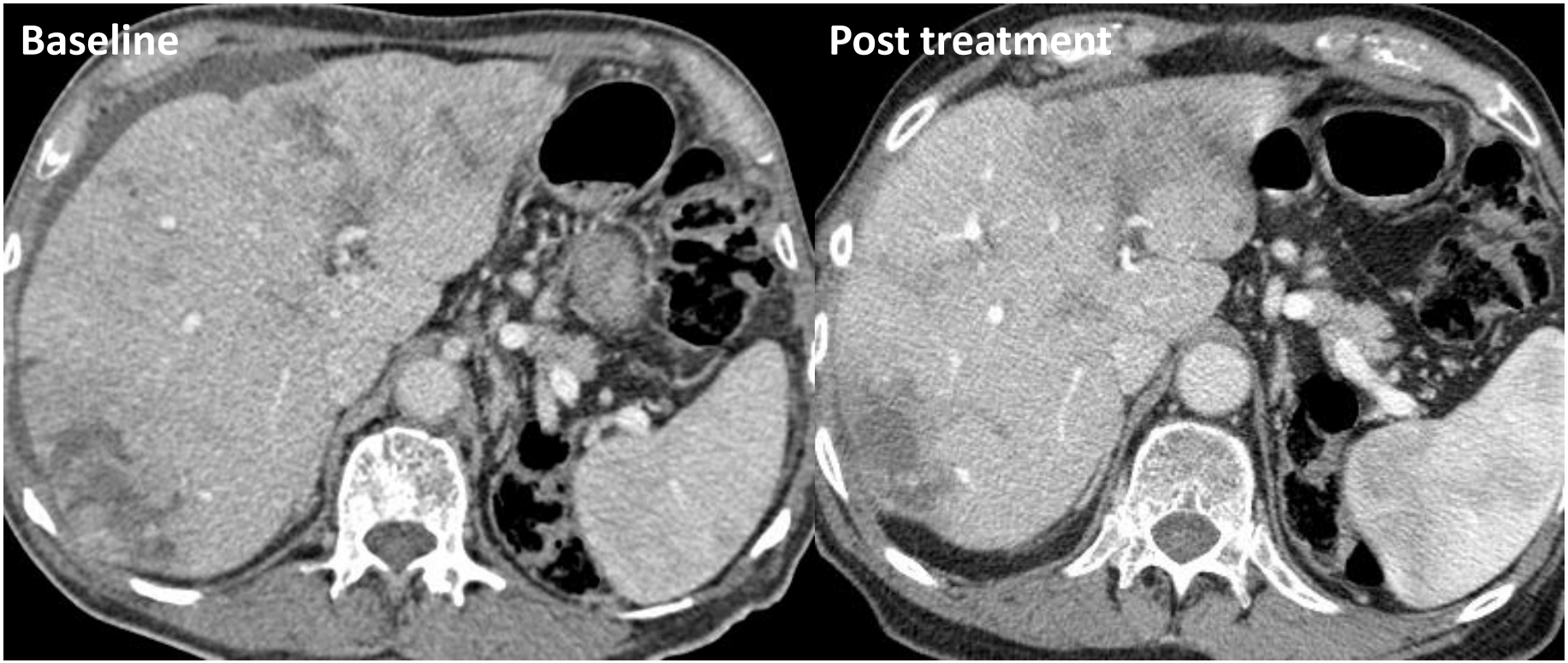


Change in uni, bi-dimensional measurements & volume: 0.4%, 24.4%, & 33.2%

From: Zhao et al. JNM 2009

- May not reflect changes in z-axis
- Uni & bi-dimensional measurements are adequate surrogates for changes in tumour volume only if these changes occur in a spheroid manner

Imaging Evaluation: Limitations



Background changes may make response evaluation difficult: Schirrous change in liver

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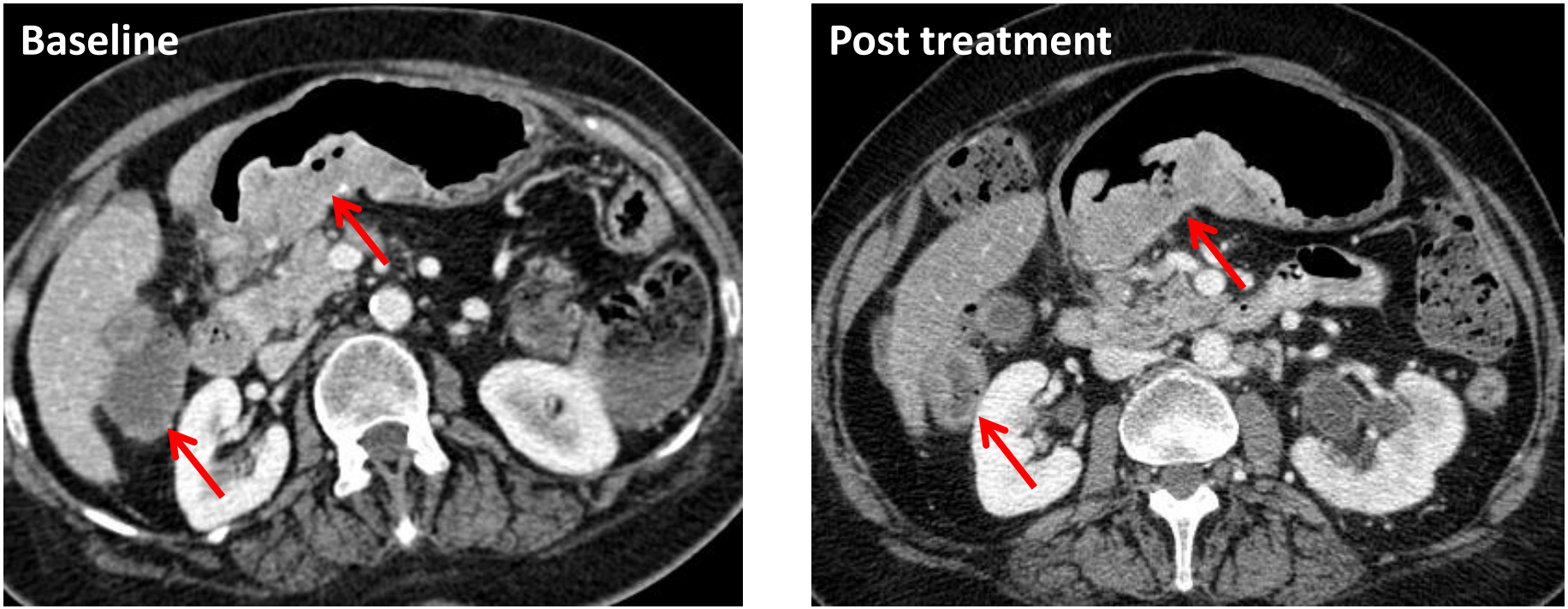
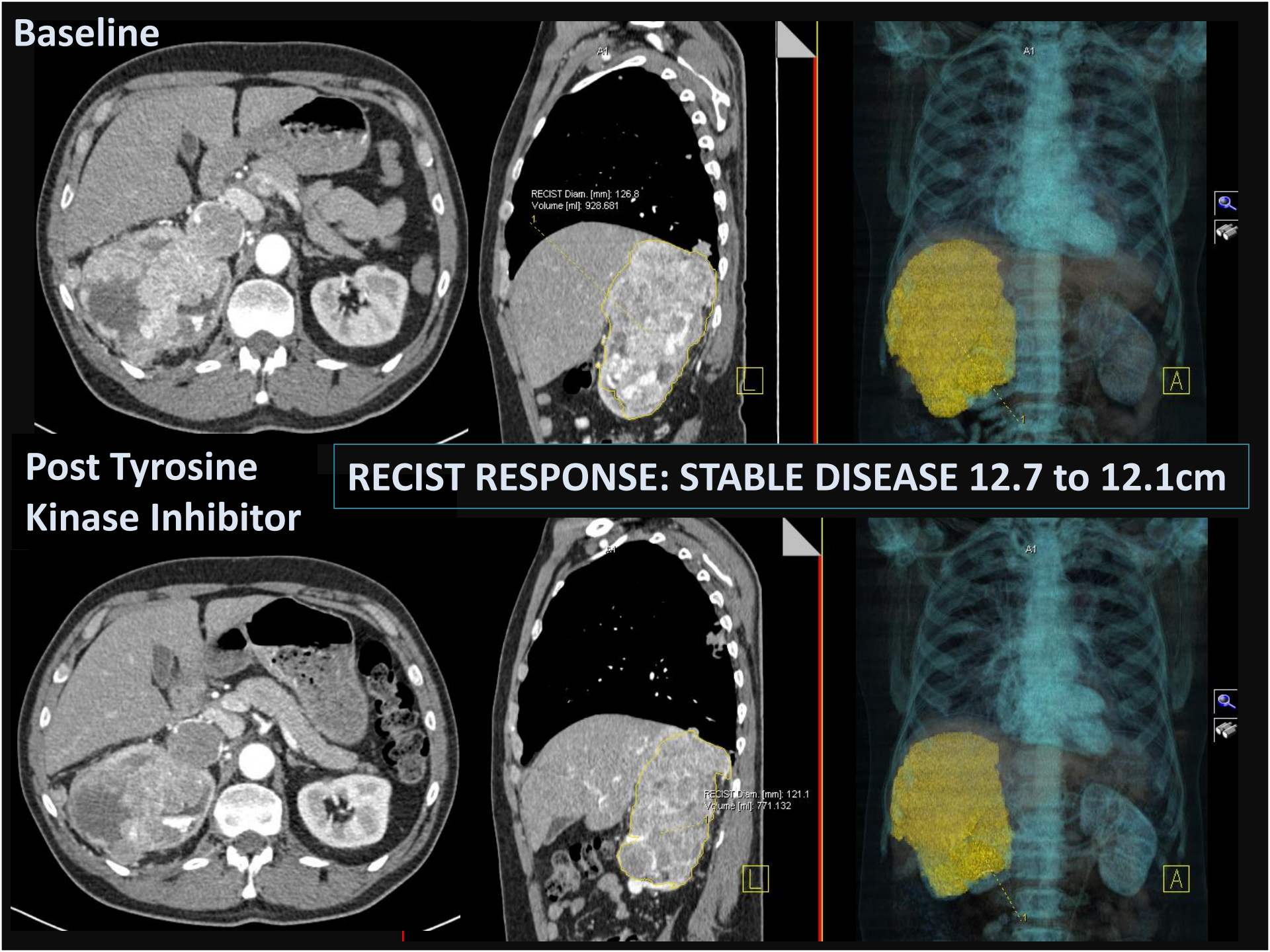
Imaging Evaluation: Limitations



Target lesions: Change in other morphological characteristics are not part of categorisation

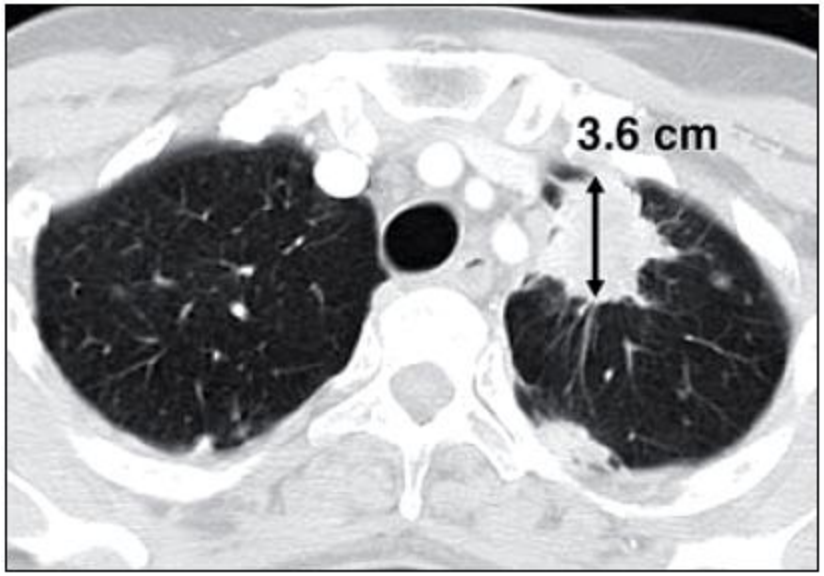

Baseline
RECIST Diam. [mm]: 126.8
Volume [ml]: 928.681
Post Tyrosine Kinase Inhibitor
RECIST RESPONSE: STABLE DISEASE 12.7 to 12.1cm
RECIST Diam. [mm]: 121.1
Volume [ml]: 771.132

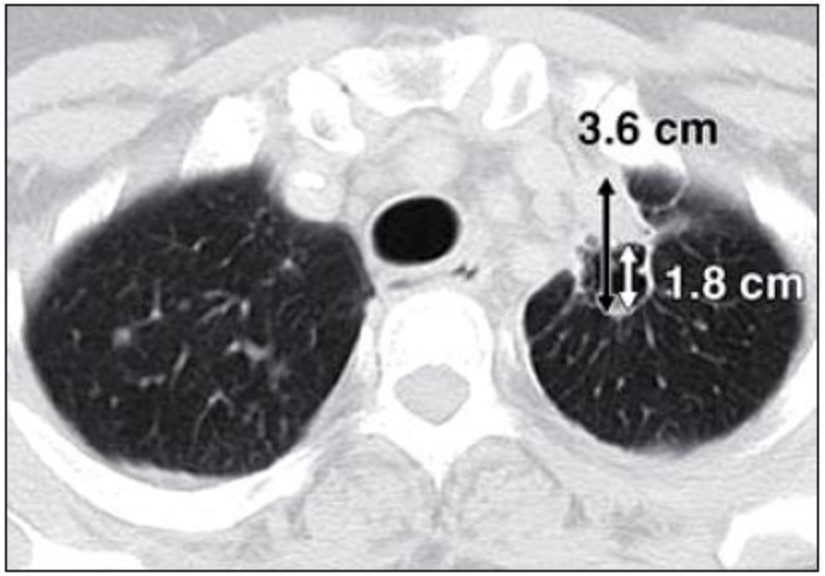
Response Assessment: Beyond RECIST

Response criteria	Based on	Tumour type
Modified RECIST	Size (Arterial phase)	HCC
EASL	Size (Arterial phase)	HCC
Crabb	Size & cavitation	NSCLC
Lee	Size & cavitation	NSCLC
Choi	Size & enhancement	GIST
Modified Choi	Size & enhancement	Renal cell cancer
MASS/SACT	Size & enhancement	Renal cell cancer
PERCIST	Size & metabolic response	All

Ongoing work on validation in clinical trials

Size & Cavitation: Crabb





From: Nishino et al. AJR 2012; 198:737–745

Cavitation is taken into account & subtracted from the total diameter

Crabb et al. J Clin Oncol 2009; 27:404–410

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Size & enhancement: Choi & Modified Choi Criteria

Response Criteria	Partial Response	Stable Disease	Progressive Disease
RECIST	>30% size reduction	<30% size reduction or <10% size increase	>10% size increase
Choi	>10% size reduction OR >15% attenuation reduction	<10% size reduction OR <15% attenuation reduction	>10% size increase & does not meet attenuation criteria of PR New lesions
Modified Choi*	>10% size reduction AND >15% attenuation reduction	<10% size reduction AND <15% attenuation reduction	>10% size increase & does not meet attenuation criteria of PR New lesions

***Nathan et al. Cancer Biol Ther. 2010;9:15-9**

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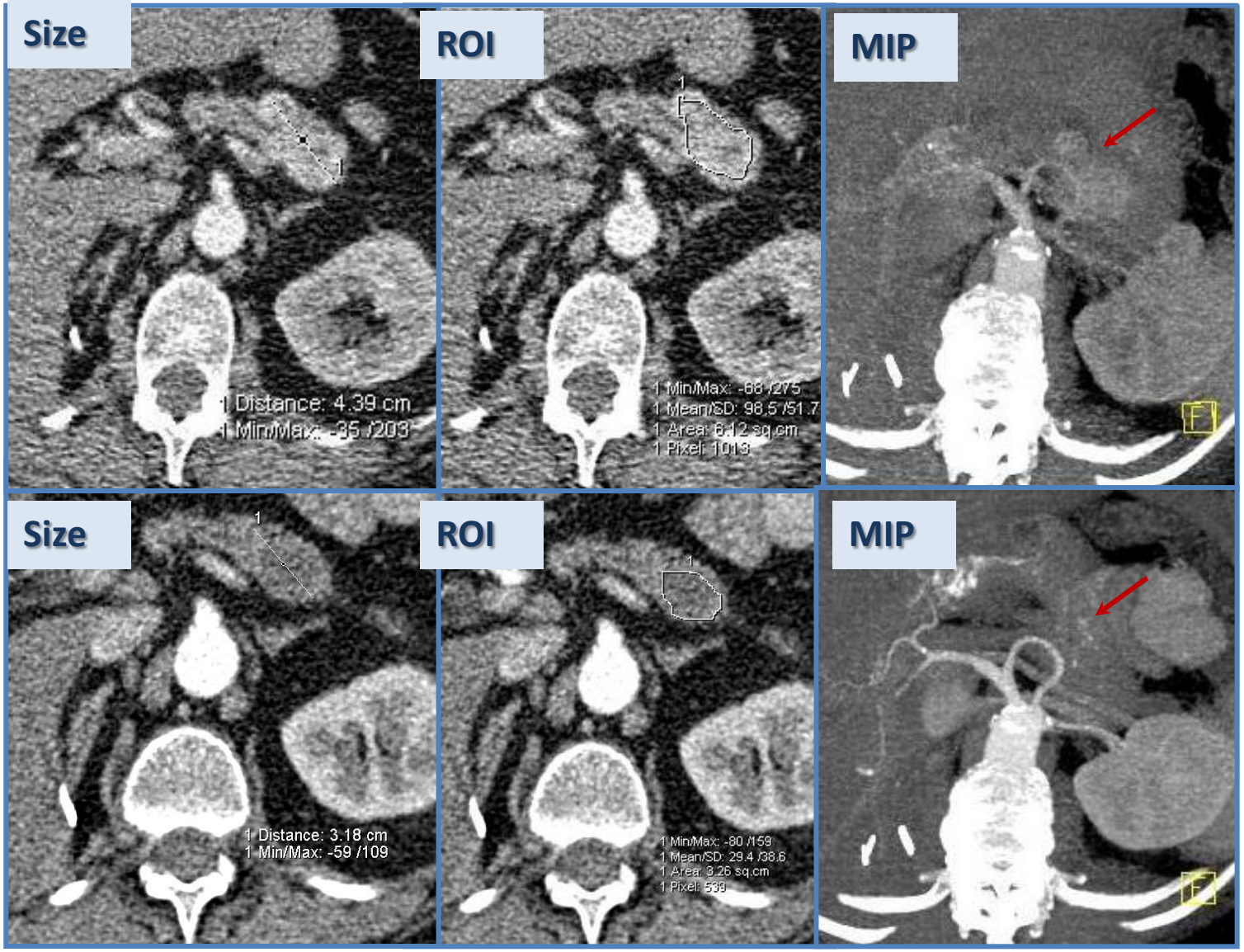

Size change 29%, density change 71%

SD by RECIST & **PR** by Choi & modified Choi criteria

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Size & metabolic response: PET response criteria

From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors

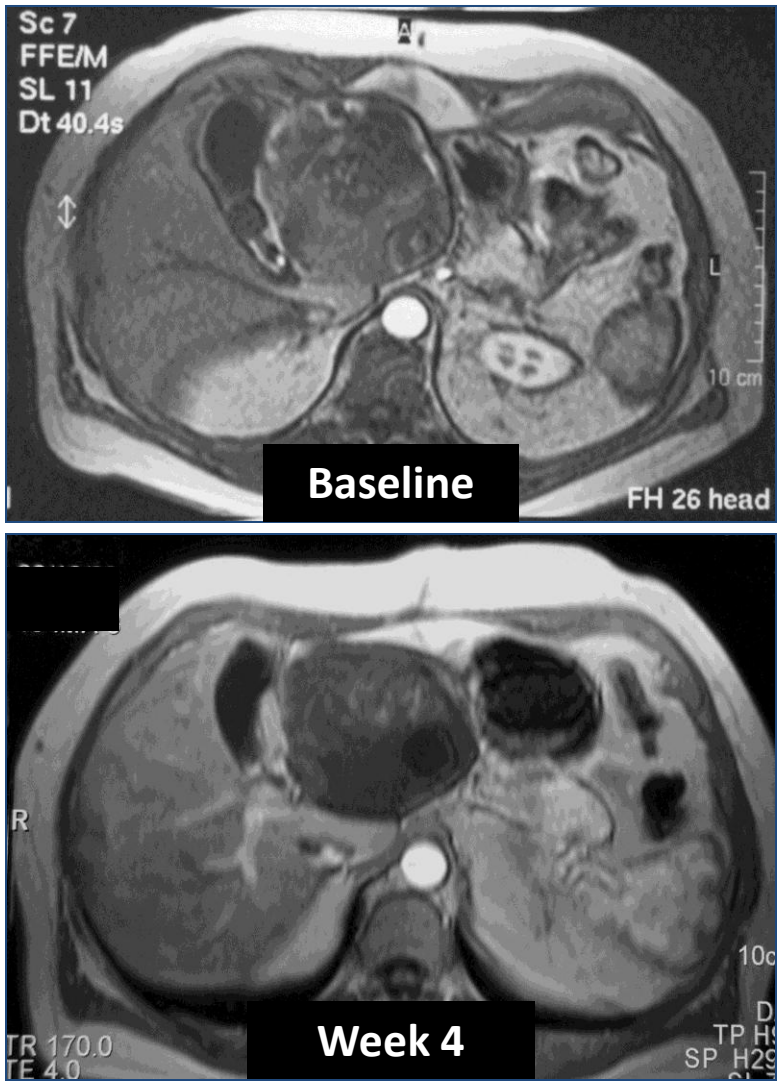
Richard L. Wahl[1,2], Heather Jacene[1], Yvette Kasamon[2], and Martin A. Lodge[1]

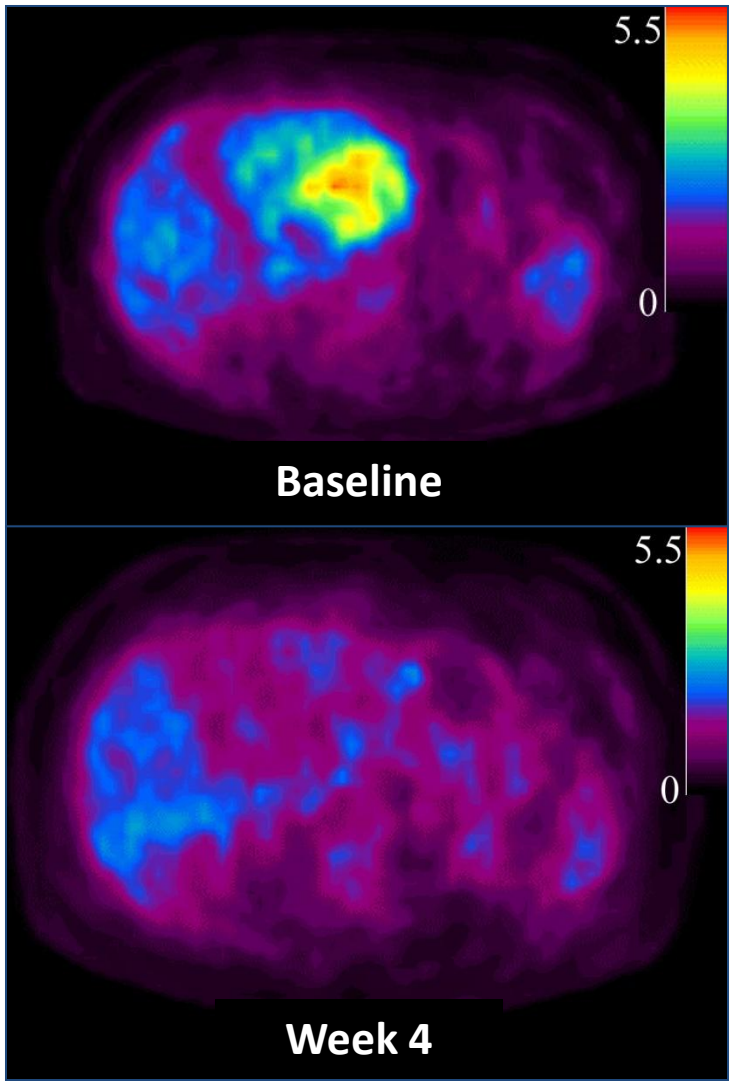
[1]Division of Nuclear Medicine, Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland; and
[2]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland

J Nucl Med 2009; 50:122S–150S

MRI: T1 + contrast

^{18}F-FDG PET





Rate metabolic response is achieved reflects cell kill:
> 10^7 cells lower limit of PET detection

PERCIST

PERCIST 1.0

1. Measurable target lesion is hottest single tumor lesion SUL of "maximal 1.2-cm diameter volume ROI in tumor" (SUL peak). SUL peak is at least 1.5-fold greater than liver SUL mean + 2 SDs (in 3-cm spherical ROI in normal right lobe of liver). If liver is abnormal, primary tumor should have uptake > 2.0 × SUL mean of blood pool in 1-cm-diameter ROI in descending thoracic aorta extended over 2-cm *z*-axis.
2. Tumor with maximal SUL peak is assessed after treatment. Although typically this is in same region of tumor as that with highest SUL peak at baseline, it need not be.
3. Uptake measurements should be made for peak and maximal single-voxel tumor SUL. Other SUV metrics, including SUL mean at 50% or 70% of SUV peak, can be collected as exploratory data; TLG can be collected ideally on basis of voxels more intense than 2 SDs above liver mean SUL (see below).
4. These parameters can be recorded as exploratory data on up to 5 measurable target lesions, typically the 5 hottest lesions, which are typically the largest, and no more than 2 per organ. Tumor size of these lesions can be determined per RECIST 1.1.

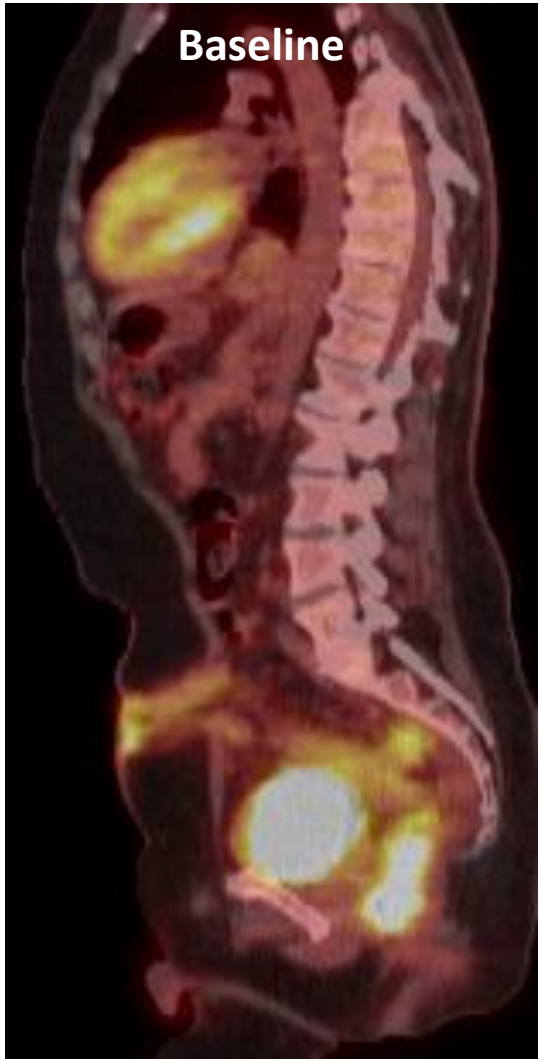
- **Complete Response:** Disappearance of all disease
- **Partial Response:** >30% decrease FDG SUL_{peak} (AND -0.8 SUL units), <30% size increase & no new sites
- **Stable disease:** Neither PR not PD
- **Progressive Disease:** >30% increase FDG SUL_{peak} (AND +0.8 SUL units), increase in TLG volume, new lesions

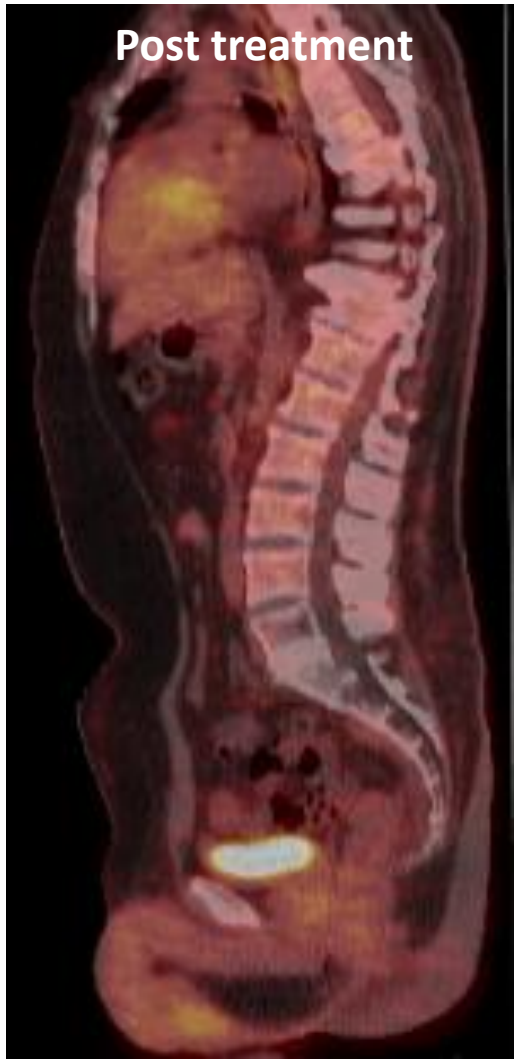
EORTC PET Response Criteria

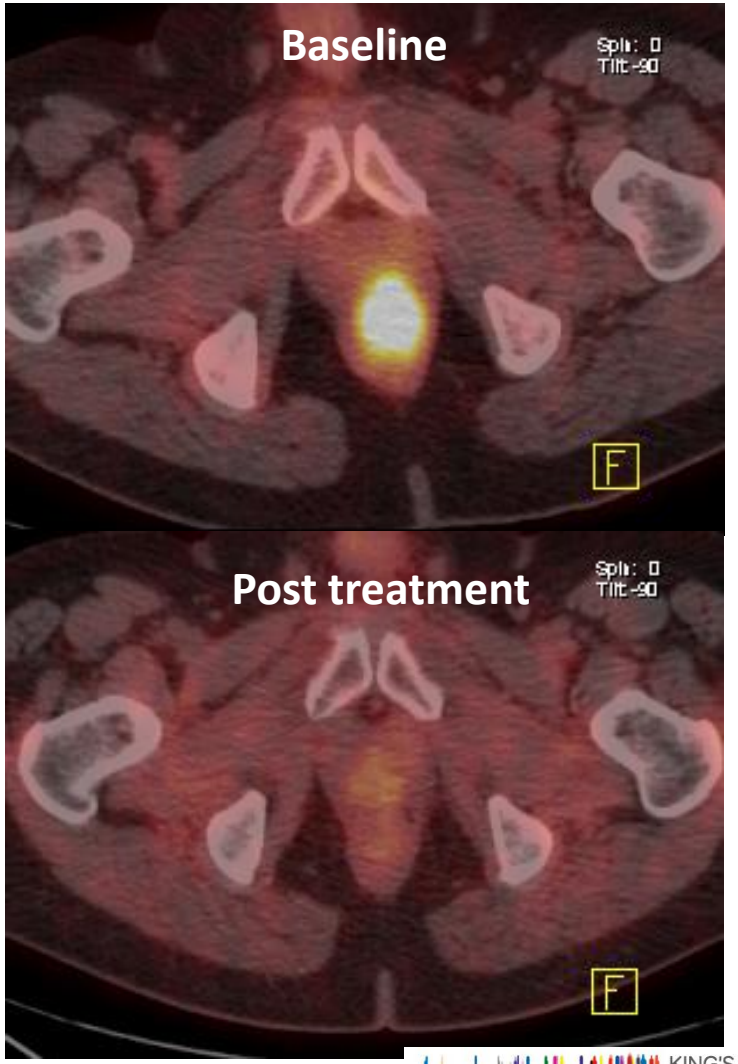
- **Complete Response:**
  Disappearance of all uptake
- **Partial Response:**
  >25% decrease FDG SUV_{mean} A reduction in the extent of the tumour [18F]-FDG uptake is not a requirement for partial metabolic response
- **Stable disease:**
  Neither PR not PD
- **Progressive Disease:**
  >25% increase FDG SUV_{mean} visible increase in the extent of [18F]-FDG tumour uptake (20% in the longest dimension) or the appearance of new [18F]-FDG uptake in metastatic lesions

Young et al. Eur J Cancer. 1999;35:1773–1782.

Complete Metabolic Response







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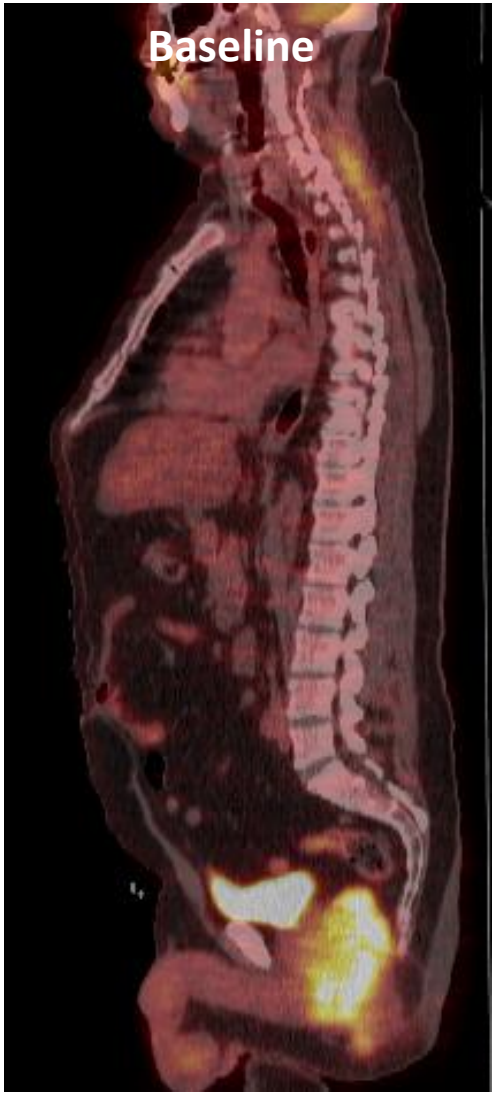
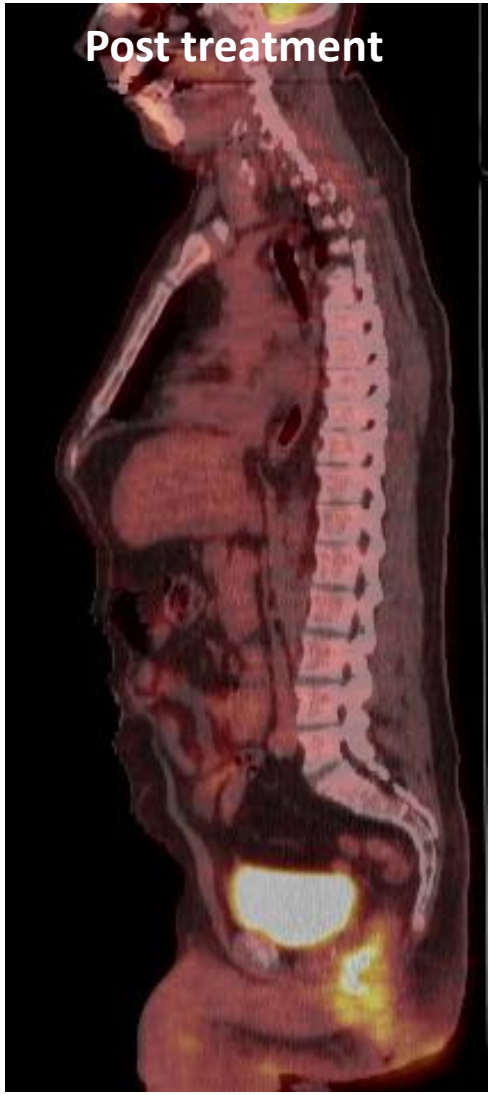
Partial Metabolic Response





Role of Imaging ?

Phase I	Phase II	Phase III
▪ Small no. of patients ▪ Safety/Toxicity/Dosage	▪ Small no. of patients ▪ Drug effectiveness ▪ Safety	▪ Large no. of patients ▪ Randomisation ▪ Tested vs standard treatment

- Exploratory imaging biomarker of drug efficacy

What Determines Choice of Imaging Method?

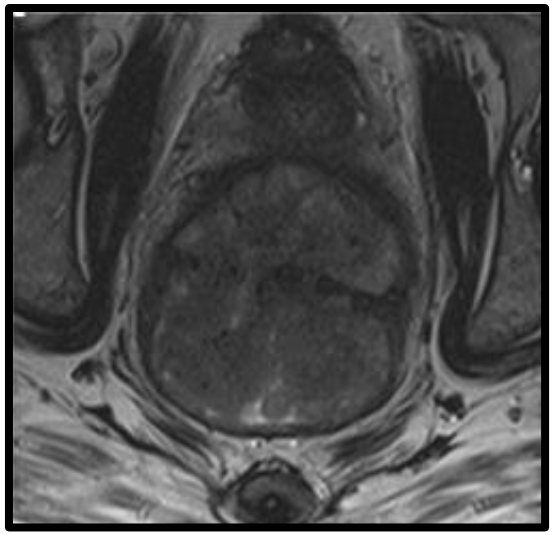
Phase I	Phase II	Phase III
▪ Small no. of patients ▪ Safety/Toxicity/Dosage	▪ Small no. of patients ▪ Drug effectiveness ▪ Safety	▪ Large no. of patients ▪ Randomisation ▪ Tested vs standard treatment

- Purported mechanism of action of drug
- End points being collected
- Appropriateness of imaging method
  - Technical issues : Reproducibility, etc.
  - Local expertise
  - Cost

What Can We Measure?

- Cellular metabolism
- Vascularization
  - Perfusion
  - Angiogenesis
  - Hypoxia
- Cellular proliferation, differentiation, survival & apoptosis

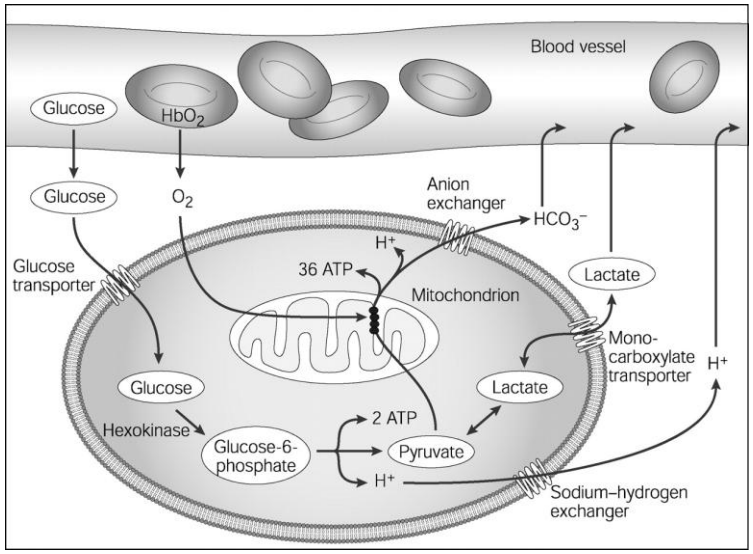
FDG	
H_20	**DCE-CT**
Integrin	**DCE-MRI**
F-MISO	**ISW-MRI**
Cu-ATSM	
Choline	**DW-MRI**
FLT	**1H-MRS**
(Annexin)	



Cellular Metabolism

FDG PET/CT

Assessment of cellular metabolism



From: Warburg. J Gen Physiol 1927; 8:519-530.

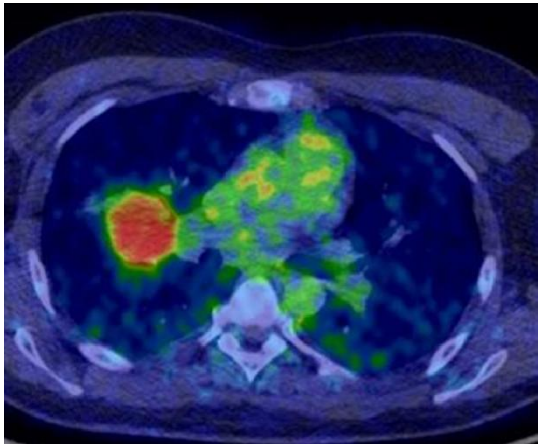
- Change from oxidative phosphorylation to glycolysis may occur despite adequate oxygen supply in tumours
- Upregulation of glucose transporter protein in tumours

FDG PET/CT

Perfusion & Angiogenesis

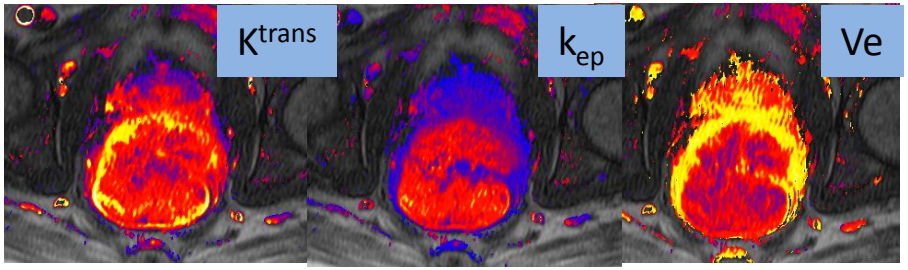
Water PET:
Provides information regarding perfusion

Integrin ($\alpha_v\beta_3$) PET: ^{18}F-Galacto-RGD
Provides information of the degree of tumour angiogenesis

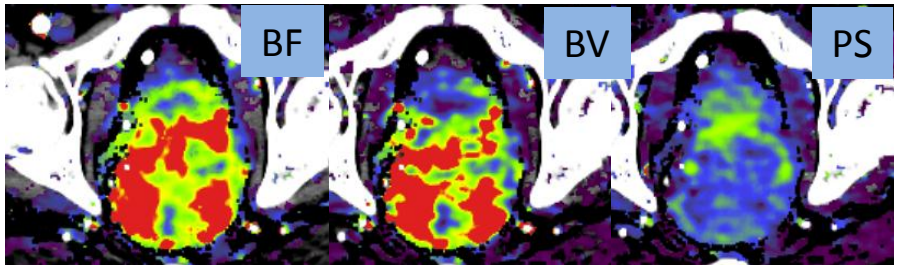


: ^{18}F-Galacto-RGD PET/CT

DCE-MRI and DCE-CT
Parameters indirectly reflect perfusion, hypoxia & the functioning microvasculature



Dynamic contrast enhanced MRI

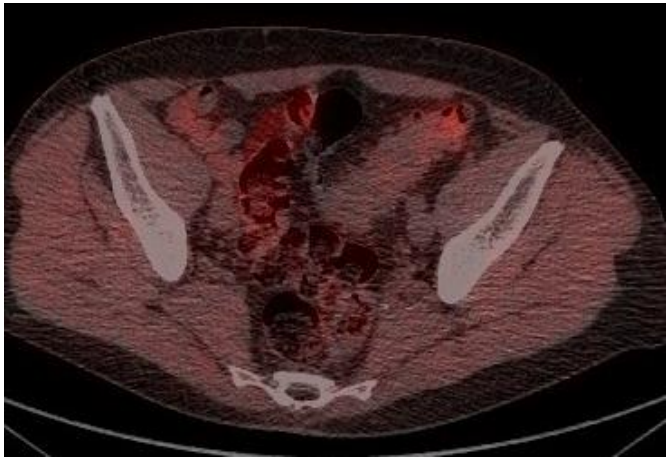


Dynamic contrast enhanced CT

Hypoxia

Hypoxia PET
Provides information of
the level of perfusion &
tumour oxygenation

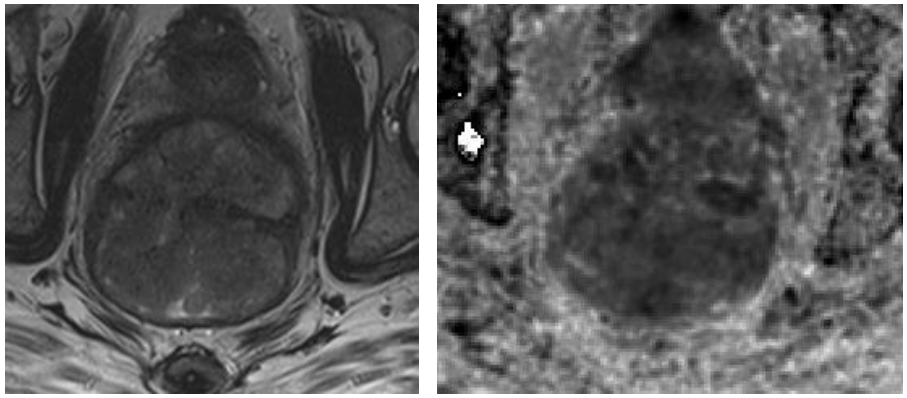
^{18}F-fluoroimidazole (F-MISO) PET
^{64}Cu-ATSM PET



F-MISO PET/CT

Intrinsic susceptibility weighted MRI
Sensitive to paramagnetic
deoxyhemoglobin in red blood
cells in perfused vessels

Provides information of
red cell delivery & level of blood
oxygenation

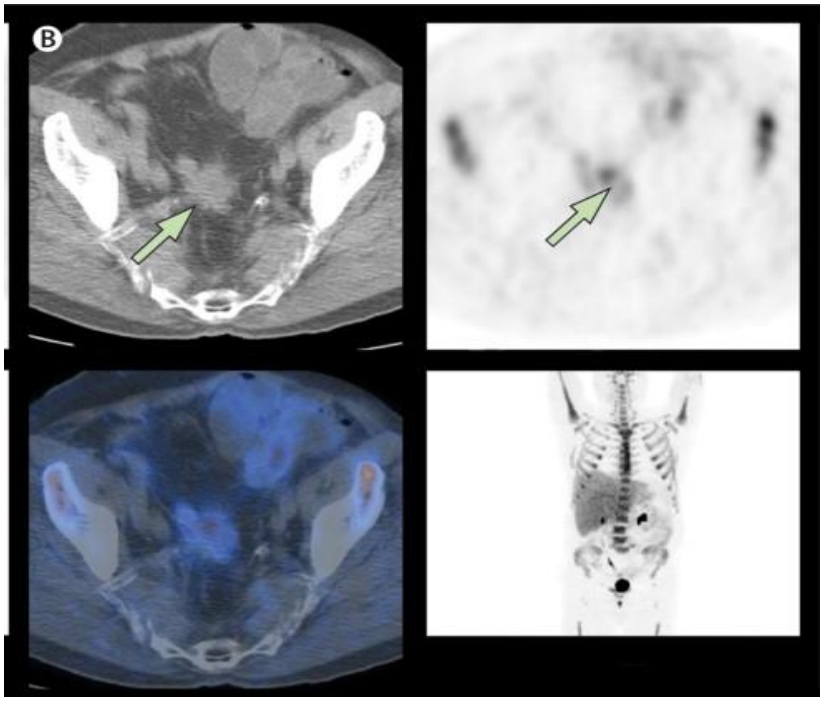


Intrinsic susceptibility weighted MRI

Proliferation
Apoptosis

3´-deoxy-3´-^{18}F-fluorothymidine (FLT) PET
Informs on active DNA synthesis

Annexin-PET
Informs on apoptosis.
^{124}I-labelled or ^{18}F-labelled annexin
Have showed potential in animal studies

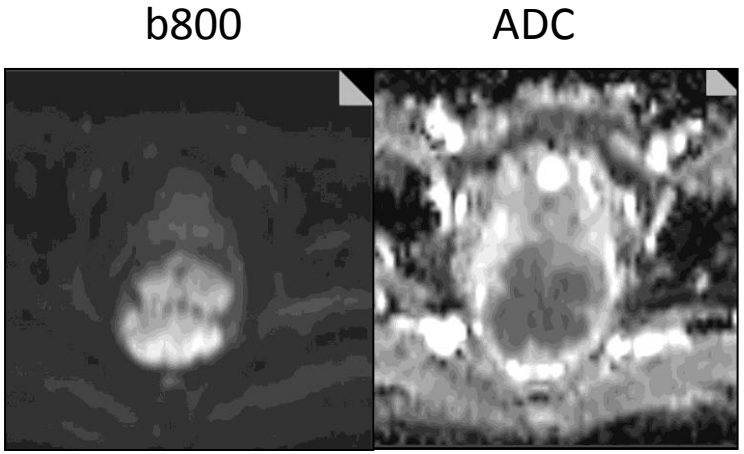


The Lancet Oncology Volume 8, Issue 9 2007 822 - 830

Proliferation
Apoptosis

Diffusion weighted MRI
Assessment of water diffusion

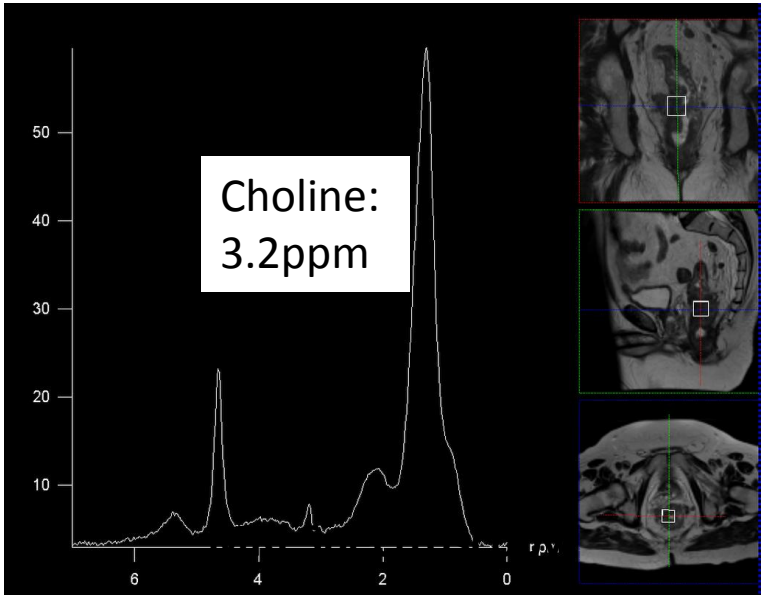
Informs on cell density,
extracellular space tortuosity
& integrity of cellular membranes



Diffusion weighted MRI

1H-MRI Spectroscopy
Informs on cell density,
& cellular membrane turnover

Common metabolites:
Choline: cell membrane synthesis & degradation
Free Lipids: necrosis & apoptosis



Water:
4.7ppm

Lipid:
0.9-2.2ppm

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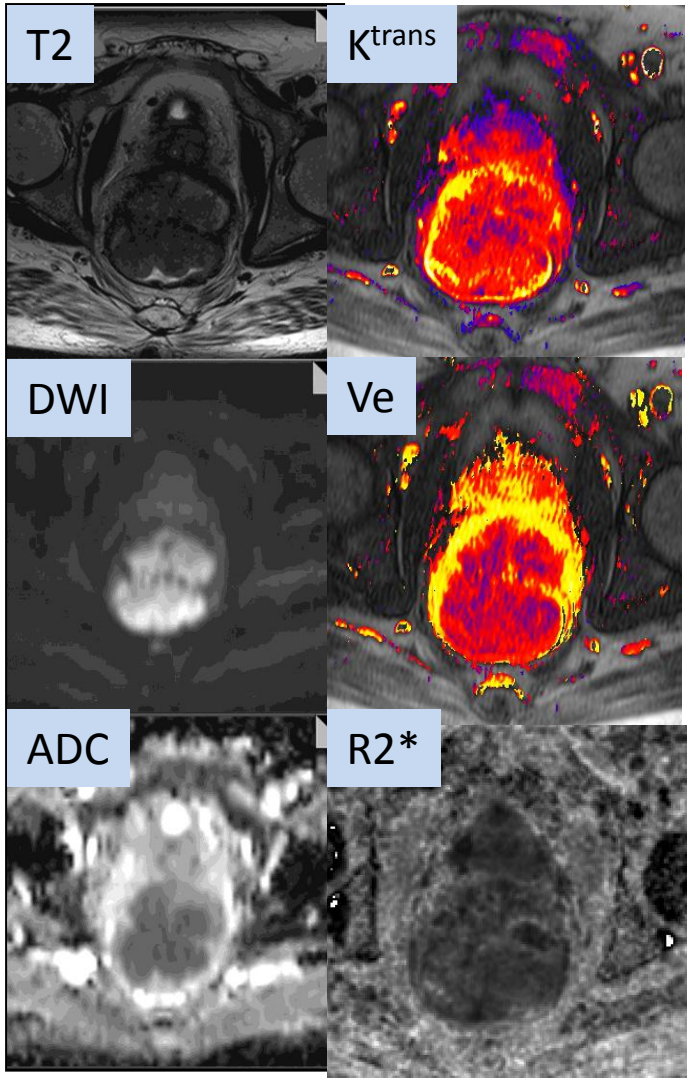
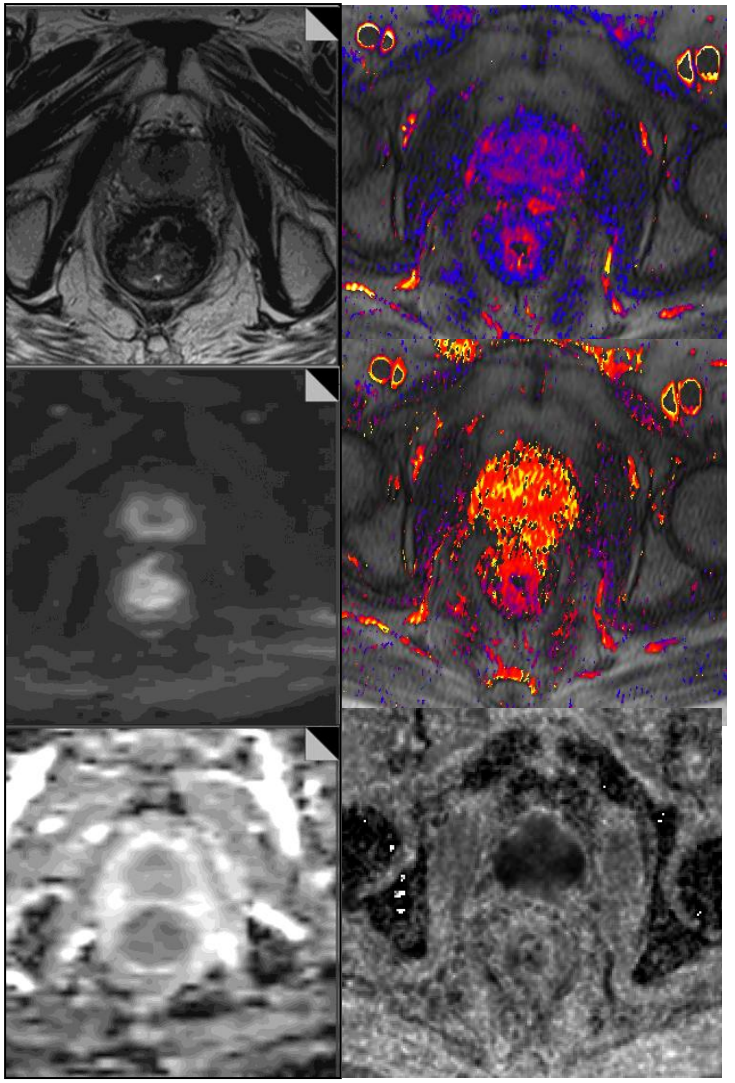
Imaging Signatures

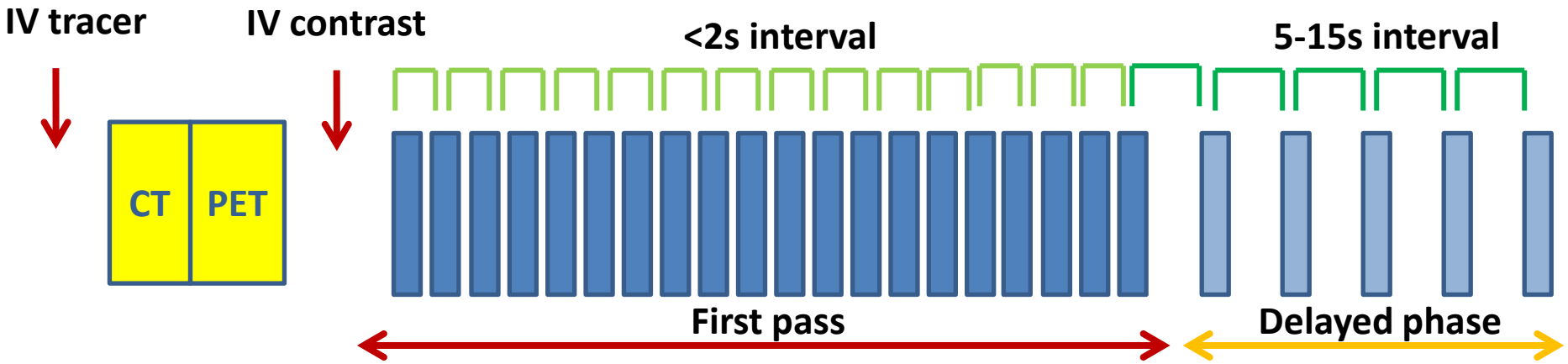


Pre therapy



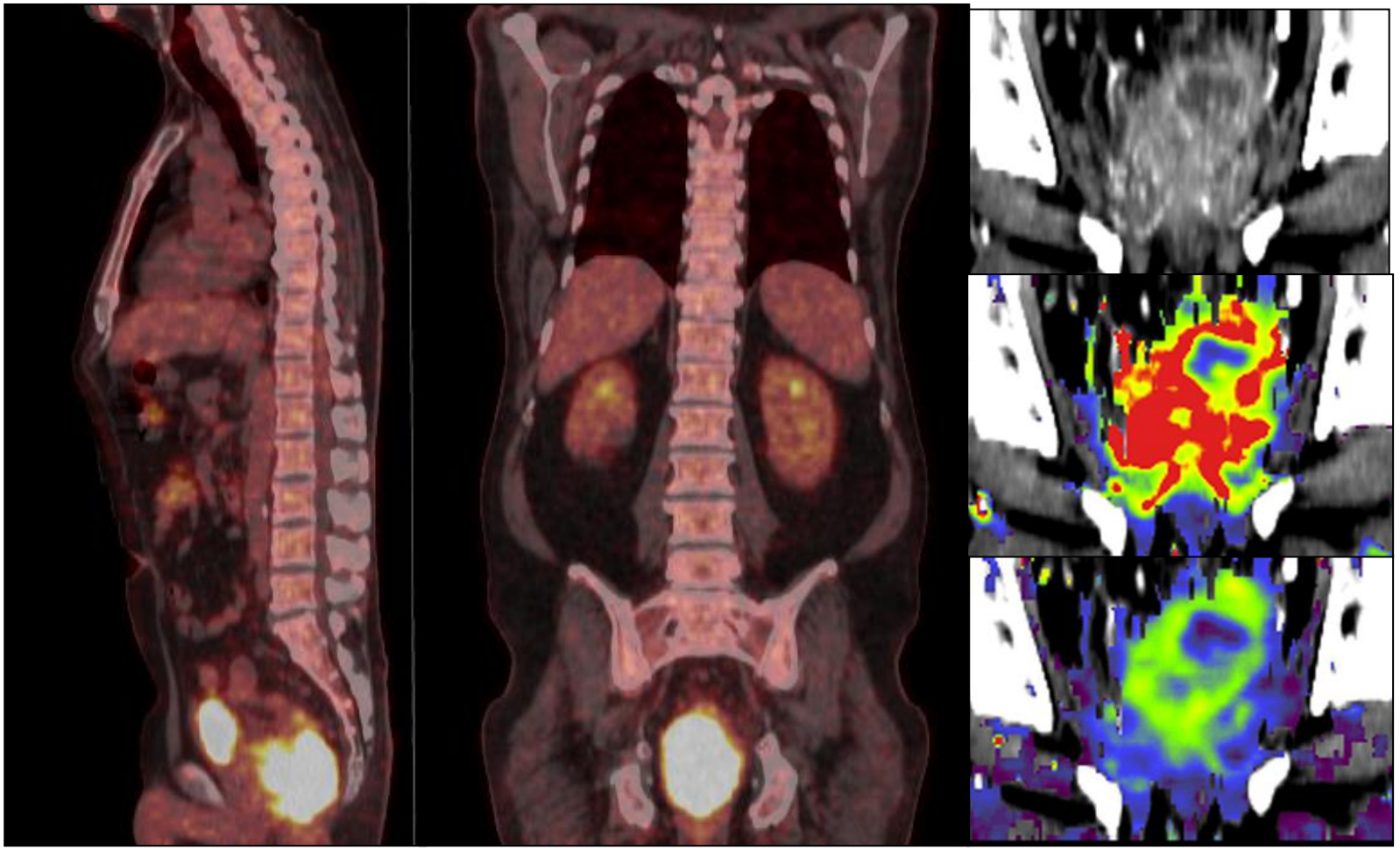
Post therapy

Multi-modality approaches



Single combined examination

Multi-modality approaches

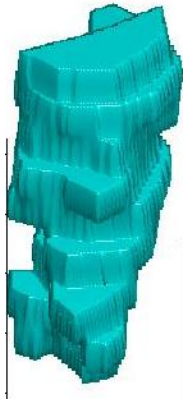


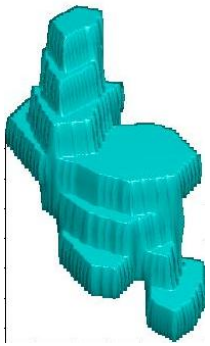
Vascular – metabolic relationship

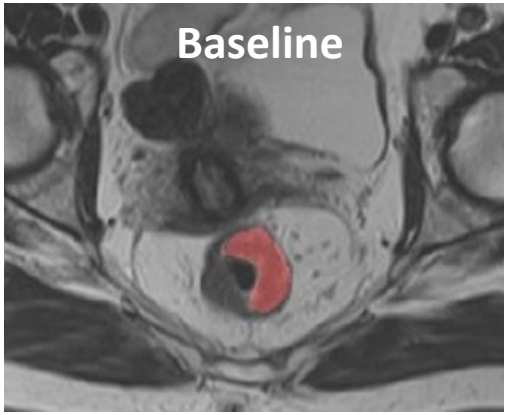
Imaging Response

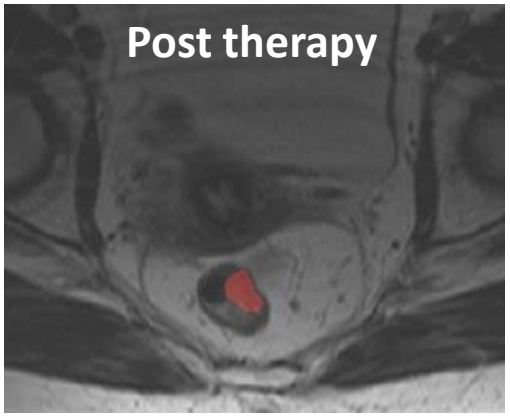
Criteria	Response	Response	Response	Response
Tumour Size Change	+	-	-	-
Vascular Response	+	+	+/-	-
Cellular Response	+	+	+/-	-
Overall response	**Responder**	**Functional Responder**	**Partial Functional responder**	**Non-responder**
Outcome	**Good**			**Poor**

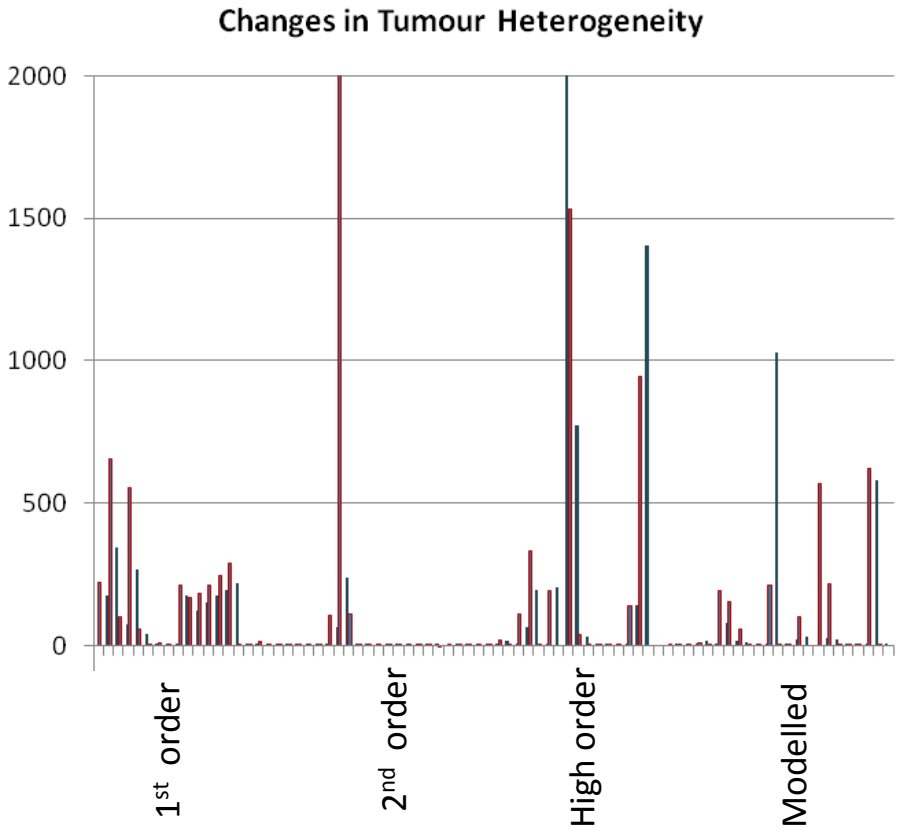
Functional Mapping of Heterogeneity in Treatment Response











Primary rectal cancer

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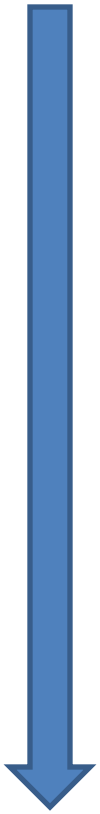
Challenges for Novel Imaging Methodologies in Clinical Trials

- **Novel imaging biomarkers**
  - Increasing number available
  - Challenges for translation
    - Technical validation
    - Biological validation

  - Validation as a trial end point
  - Health economic evaluation



Single expert Centre

Several key Centres

Multiple Centres

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Challenges for Novel Imaging Methodologies in Clinical Trials

Validation of novel imaging methodologies for use as cancer clinical trial end-points

D.J. Sargent[a,], L. Rubinstein[b], L. Schwartz[c], J.E. Dancey[d], C. Gatsonis[e], L.E. Dodd[b], L.K. Shankar[b]*

Criteria necessary prior to definitive evaluation studies

Technology stable & broadly available

Imaging acquisition parameters specifiable

Normal ranges defined

Standardised interpretation

Documented reproducibility

Sargent et al. EJC 2009

Challenges for Novel Imaging Methodologies in Clinical Trials

Validation of novel imaging methodologies for use as cancer clinical trial end-points

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Table 2 – Early and late phases of end-point validation.

Attribute	Early phase validation	Late phase validation
Goal	Individual patient level outcome prediction	Trial level outcome prediction
Setting	Single randomised trials or uniformly treated patients from non-randomised trials	Meta-analysis of randomised clinical trials
Methods	Correlation analyses between end-points within patients	Correlation analyses between trial level effects on both end-points

For an imaging end point to serve as an early accurate indicator of promising treatment effect it needs to correlate with Phase III end points i.e. PFS, OS

Sargent et al. EJC 2009

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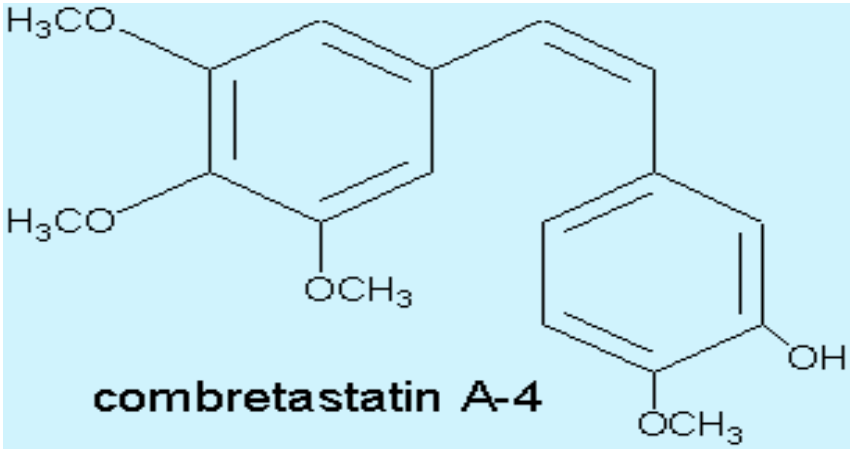
Summary

- Imaging has an important role in clinical trials
- Objective response assessment; trial end point
- RECIST 1.1 remains the international standard for response assessment
- Other response criteria may be appropriate but require further validation
- Imaging biomarkers may have a role in early phase clinical trials as a PD tool
- Challenges remain to implementation of novel imaging biomarkers

Case Example: CA4P

- *Combretum caffrum*
- Bark of the African Bush Willow tree
- Used as a tonic, as well a poison for Zulu spears



CA4P Mechanism

Vascular disrupting agent

Selective to immature tumour vessels

Rapid change in endothelial cell shape

↓

Increase in permeability

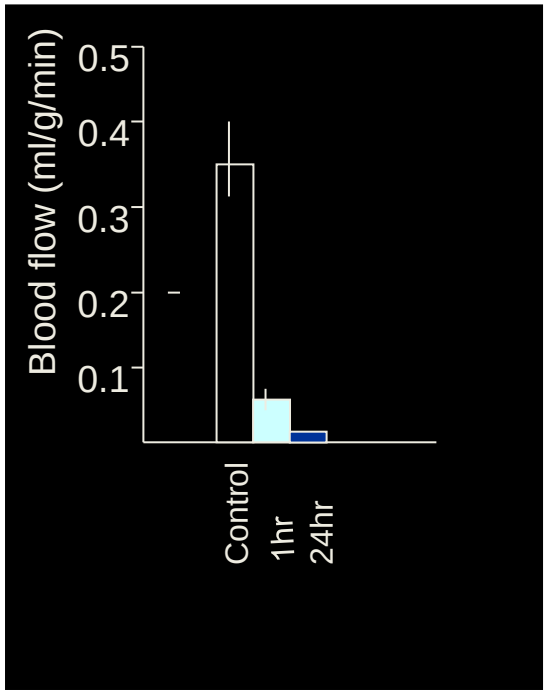
↓

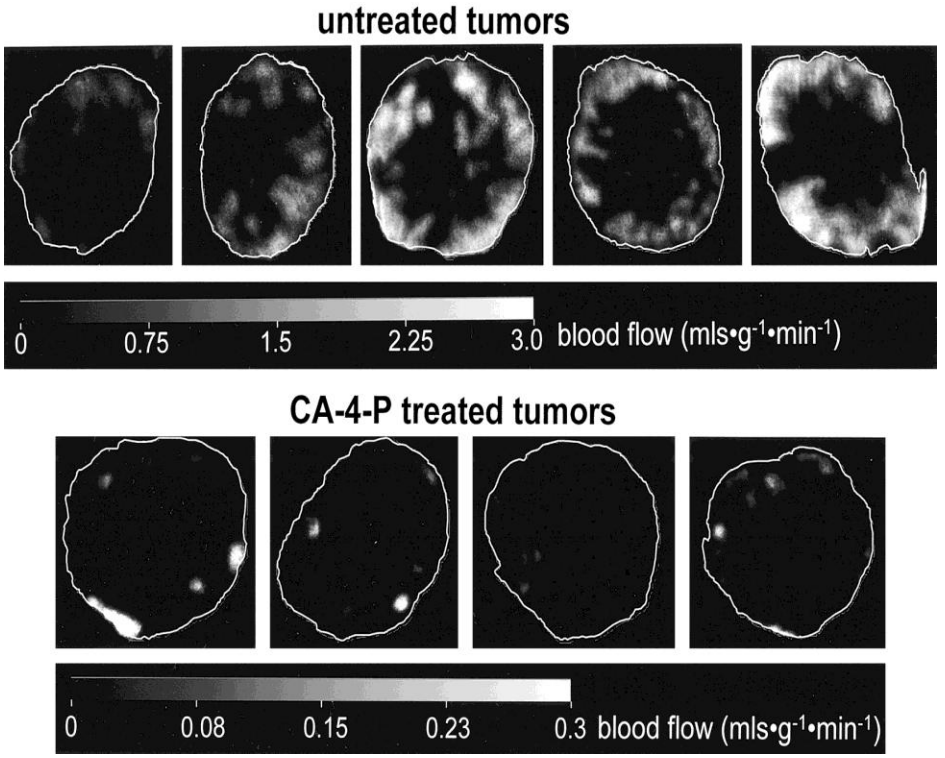
Further increase of already high interstitial fluid pressure

↓

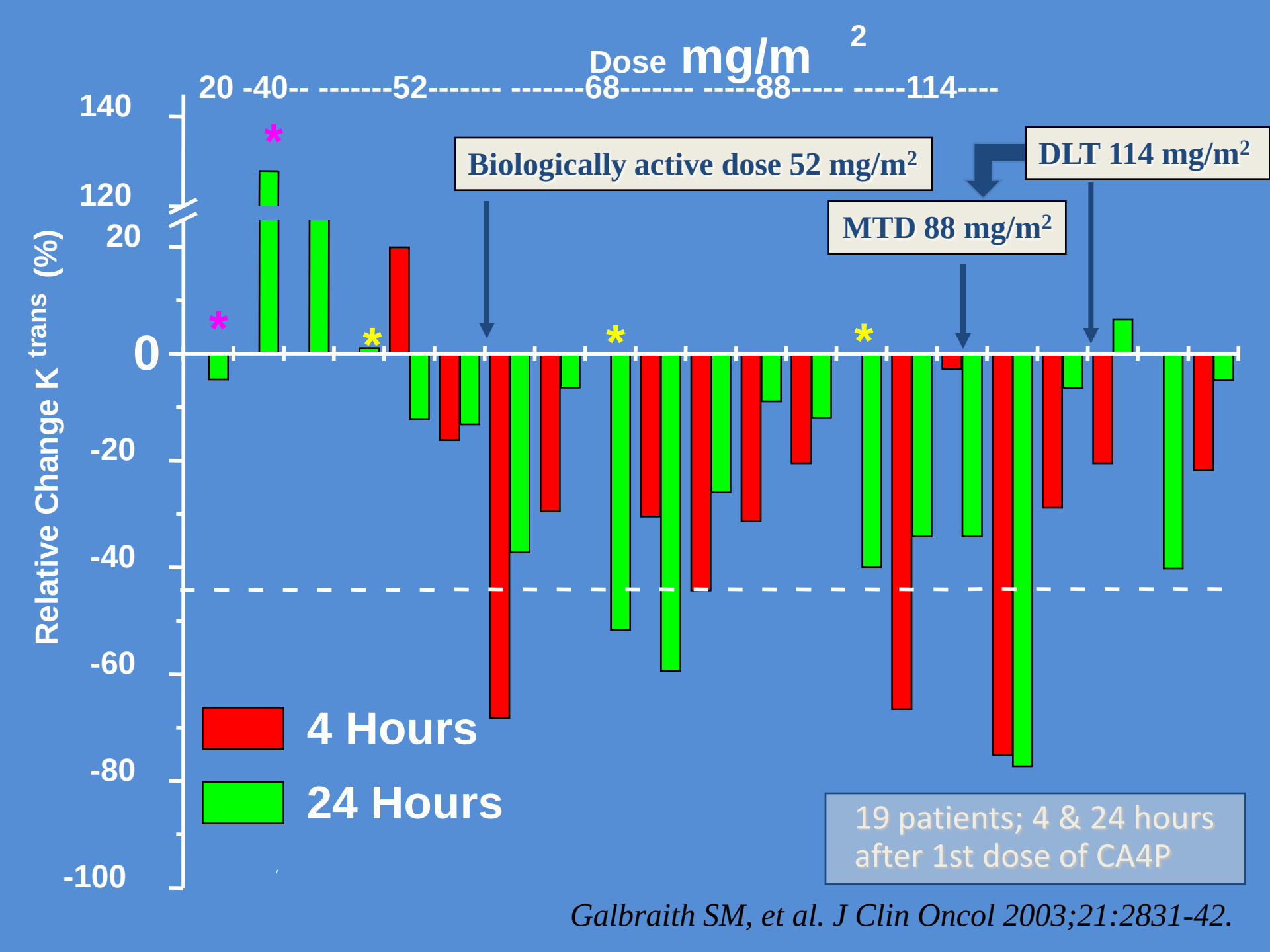
Vascular collapse and shutdown

CA4P Mechanism





Tozer et al. Cancer Res 1999



Galbraith SM, et al. J Clin Oncol 2003;21:2831-42.

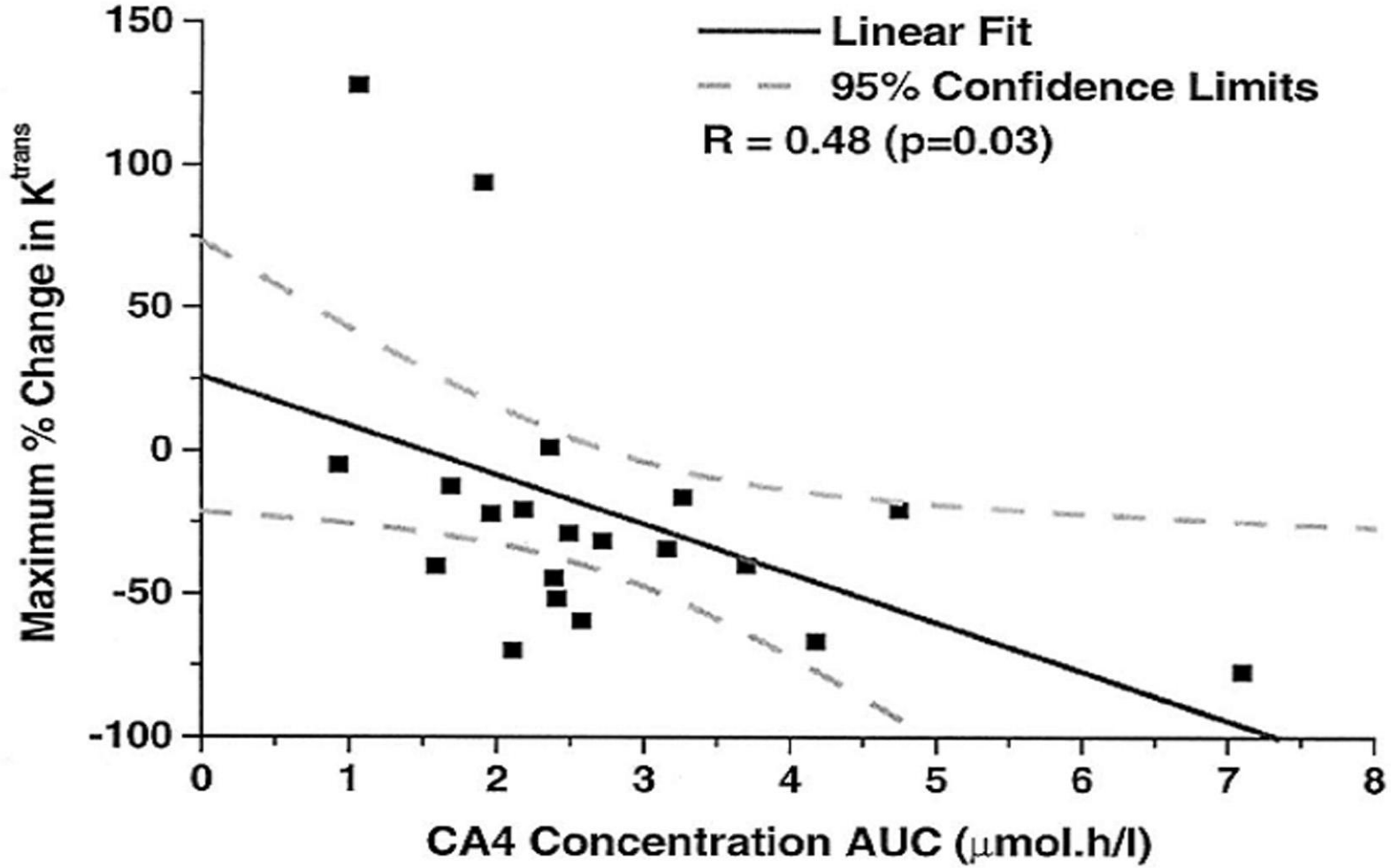


Fig 4. Absolute change in tumor $\log_{10} K^{trans}$ 4 and 24 hours after the first dose of combretastatin A4 phosphate for patients in the phase I trial.

Galbraith SM, et al. J Clin Oncol 2003;21:2831-42

Phase I – Toxicities[a]

- DLT – reversible ataxia at 114mg/m^2, vasovagal syncope and motor neuropathy at 88mg/m^2
- Other toxicities – tumour pain, dyspneoa, hypertension, QTc prolongation

[a] Rustin et al

Phase 1B study: CA4P & RT

- Rationale:
  - Potential synergy between CA4P and RT
  - CA4P targets blood vessels at the centre of the tumour
  - RT can target well vascularised viable tumour blood vessel at the tumour periphery
  - Non-overlapping toxicity

Cohort		Dose	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W	Th	F	S	S	M	T	W
1	NSCLC																																														
	Radiation	27 Gy	R			R				R			R				R			R																											
	CA4P	50 mg/m^2				C																																									
2	NSCLC																																														
	Radiation	27 Gy	R			R				R			R				R			R																											
	CA4P	50 mg/m^2				C							C							C																											
3	Prostate																																														
	Radiation	55 Gy	R	R	R	R	R			R	R	R	R	R			R	R	R	R	R			R	R	R	R	R																		
	CA4P	50 mg/m^2					C																																								
4	Prostate																																														
	Radiation	55 Gy	R	R	R	R	R			R	R	R	R	R			R	R	R	R	R			R	R	R	R	R																		
	CA4P	50 mg/m^2					C							C							C							C																		
5	Prostate																																														
	Radiation	55 Gy	R	R	R	R	R			R	R	R	R	R			R	R	R	R	R			R	R	R	R	R																		
	CA4P	63 mg/m^2					C							C							C							C																		
6	NSCLC																																														
	Radiation	27 Gy	R			R				R			R				R			R																											
	CA4P	50 or 63 mg/m^2	C			C				C			C				C			C																											
7	SCCHN																																														
	Radiation	66 Gy	R	R	R	R	R			R	R	R	R	R			R	R	R	R	R			R	R	R	R	R			R	R	R	R	R			R	R	R	R	R			R	R	R
	CA4P	50 or 63 mg/m^2					C							C							C							C																		

C, CA4P treatment; CA4P, combretastatin-A4-phosphate; NSCLC, non-small-cell lung cancer; R, radiation treatment; SCCHN, squamous cell carcinoma of the head and neck.

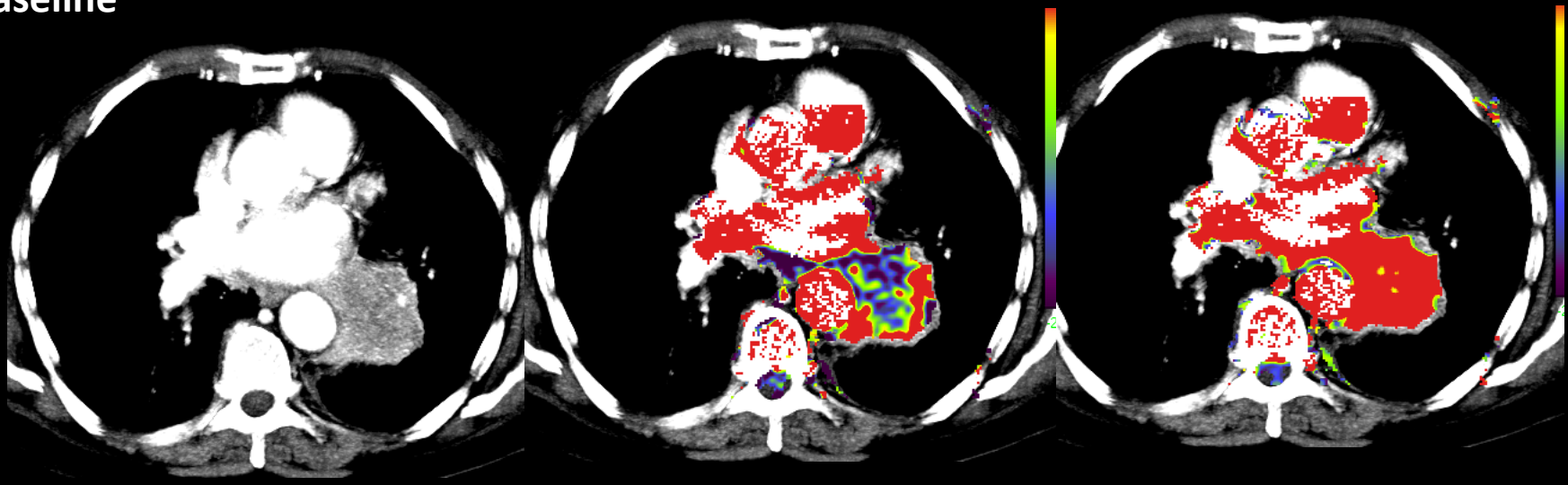
Ng et al. Ann Oncol 2012

n=39 received 121 doses of CA4P

DLTs at 63 mg/m2

No additional toxicity when administered with RT

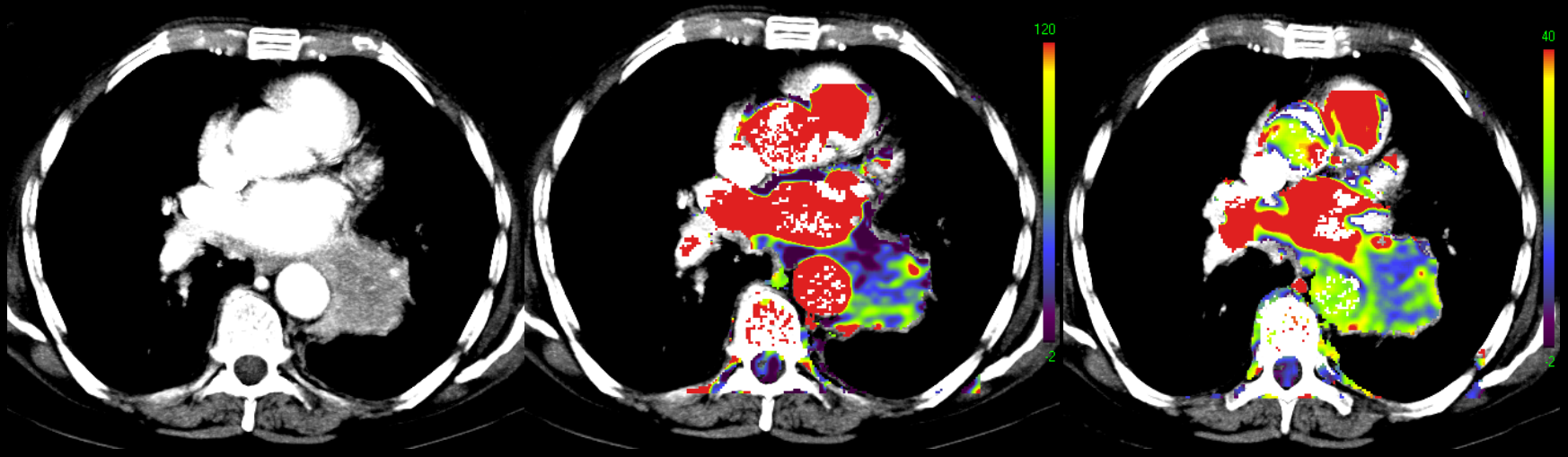
Baseline



Contrast enhanced CT

Blood Volume

Vessel Permeability



4 hours post administration vascular disrupting agent