Imaging Biomarkers as Predictive and Prognostic Biomarkers in Oncology

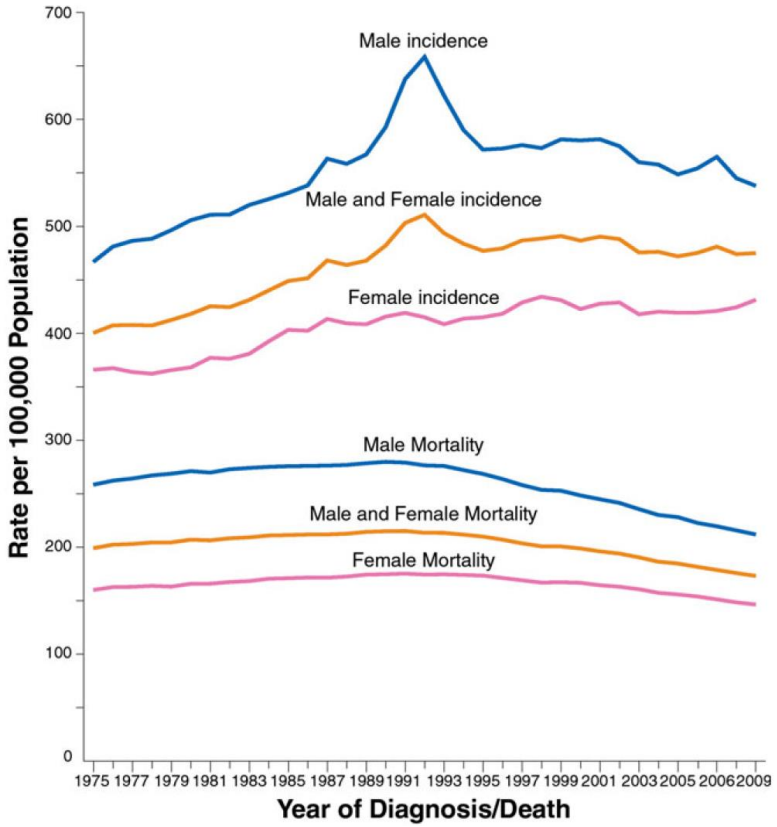
Benoit GALLIX

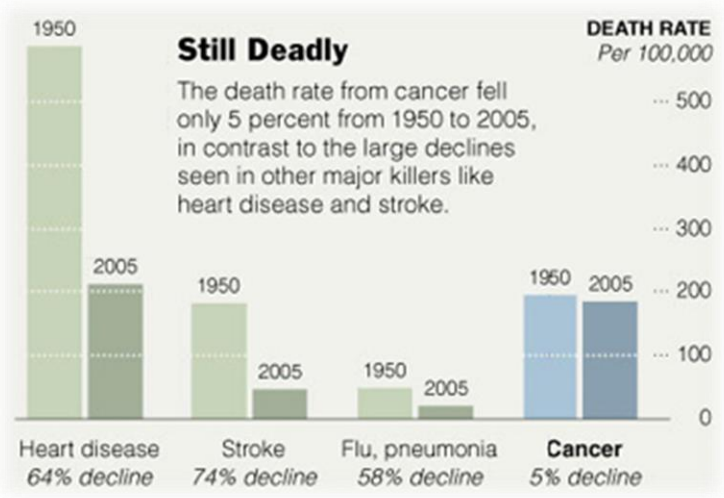
McGill

Bad news !

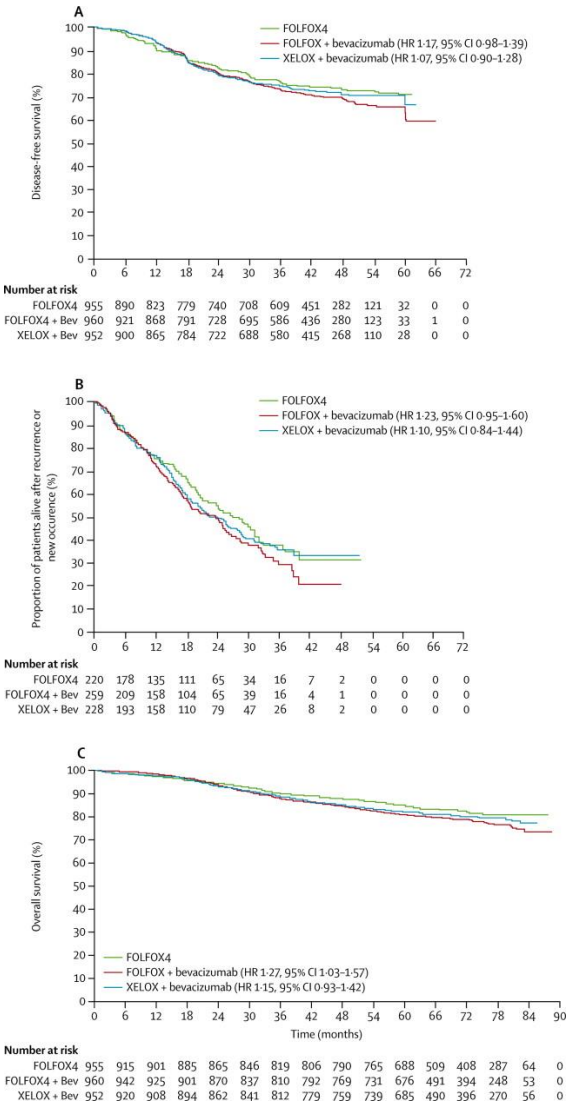
Despite advances in cancer treatment and genetics, ***we are not "curing" Cancer***

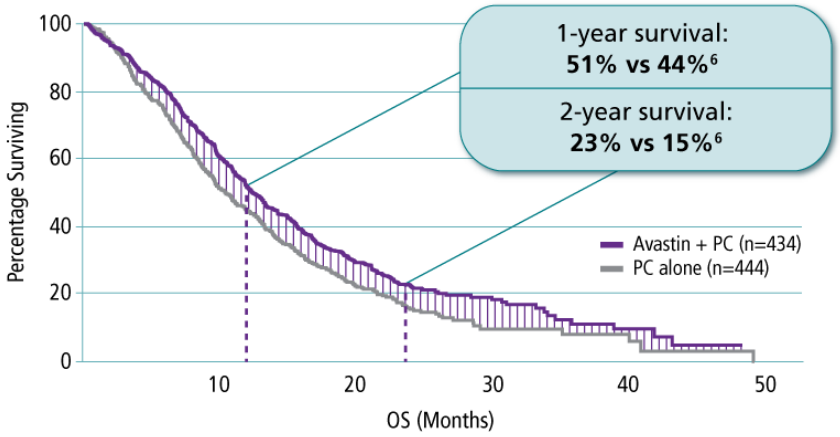
Unlike Other Major Disease Killers, Cancer Continues to Take Nearly the Same Toll as it did in 1950

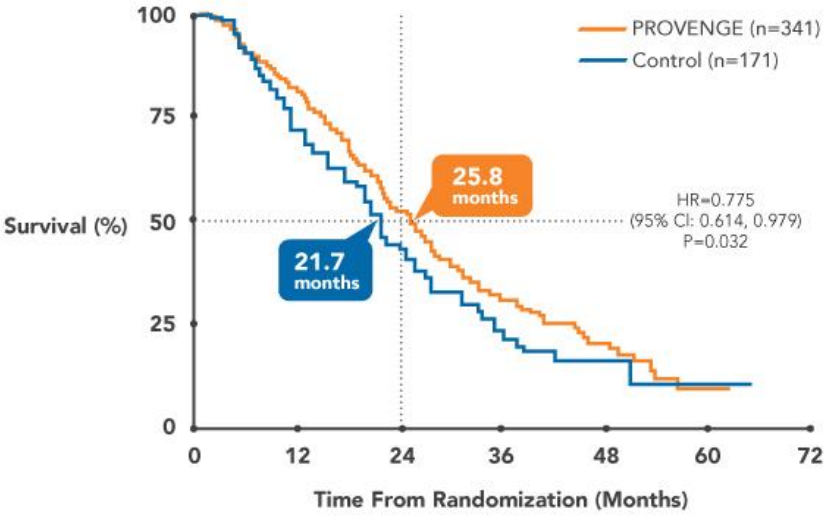




Even when we know target and have a great drug, benefit is measured in months







Traditional Clinical Trial Approaches

- Have protected us from false claims resulting from post-hoc data dredging not based on pre-defined biologically based hypotheses
- Have led to widespread over-treatment of patients with drugs to which many don't need and from which many don't benefit
- May have resulted in some false negative results

Traditional Clinical Trial Approaches

- Based on assumptions that
  - ➔ One type of cancer will respond to a specific treatment
  - ➔ "Costs" of over-treatment are less than "costs" of under-treatment
- Neither of these assumptions is valid with most new molecularly targeted oncology drugs

Prognostic & Predictive Biomarkers

- Most cancer treatments benefit only a minority of patients to whom they are administered
- Being able to predict which patients are or are not likely to benefit would
  - ➔Save patients from unnecessary toxicity, and enhance their chance of receiving a drug that helps them
  - ➔Control medical costs
  - ➔Improve the success rate of clinical drug development

Diagnostic Markers

- Predictive biomarkers
  - ➔Measured before treatment to identify who is likely or unlikely to benefit from a particular treatment
- Prognostic biomarkers
  - ➔Measured before treatment to indicate long-term outcome for patients untreated or receiving standard treatment
    - Can be used to identify patients with such good prognosis on limited treatment that they do not require more aggressive approaches

Quantitative Imaging

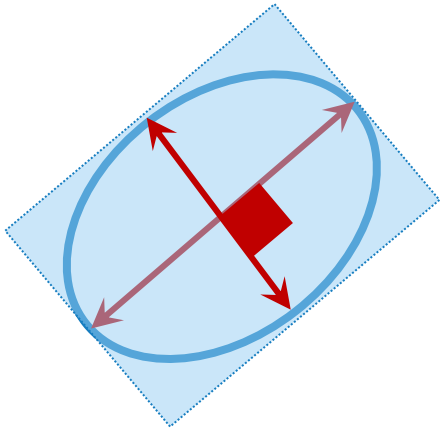
- Tumor measurement (RECIST) do not reflect the complexity of tumor morphology or behavior
- In many cases, changes in these measures are not predictive of therapeutic benefit
- Imaging Biomarkers
  - ➔ Image acquisition and reconstruction
  - ➔ Image segmentation and rendering
  - ➔ Feature extraction and qualification
  - ➔ Data storage and sharing
  - ➔ Ad hoc informatics analyses

Response Criteria in Clinical Oncology

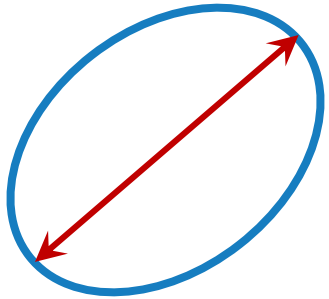
- We need a common, standard “language” to describe key methods and definitions for patient outcomes, such as
  - ➔Toxic effects: terms and grades
  - ➔Time to event definitions
  - ➔Tumour response definitions

Guideline for Response Evaluation

- **WHO (2D) :**



- **RECIST (1D) :**



Tumor Response Criteria

Tumor response criteria world health organization (who)

WHO Handbook for Reporting Results of Cancer Treatment

World Health Organization Offset Publication No. 48
Geneva, Switzerland, 1979

Reporting Results of Cancer Treatment

AB Miller, B Hogestraeten, M Staquet, A Winkler

Cancer 47:207–14, **1981**

Response evaluation criteria in solid tumors (recist)

New Guidelines to Evaluate the Response to Treatment in Solid Tumors

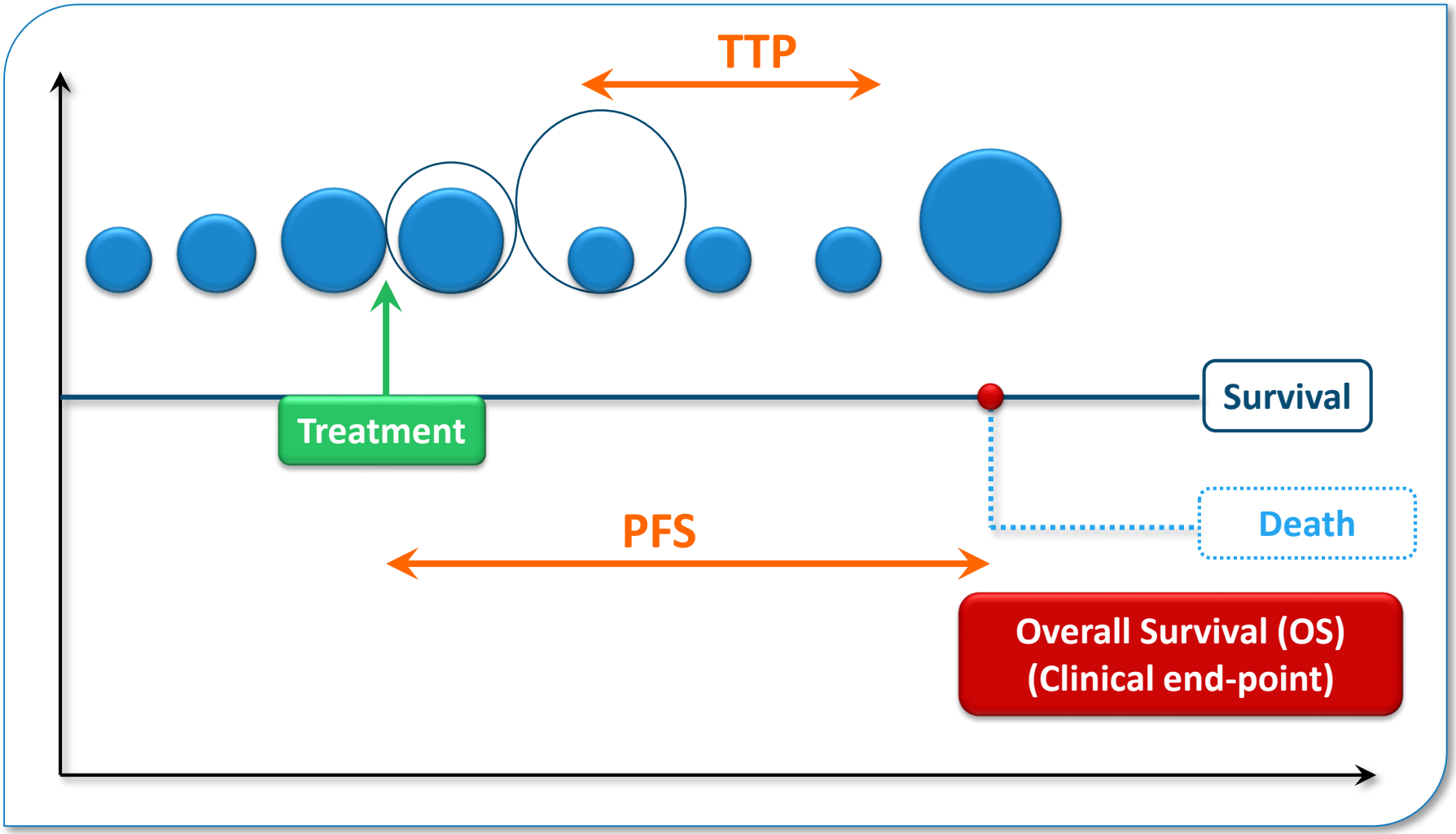
P Therasse, SG Arbuck, EA Eisenhauer, J Wanders, RS Kaplan, L Rubinstein, J Verweij, M Van Glabbeke, AT van Oosterom, MC Christian, SG Gwyther

Journal of the National Cancer Institute 92: 205-216, **2000**

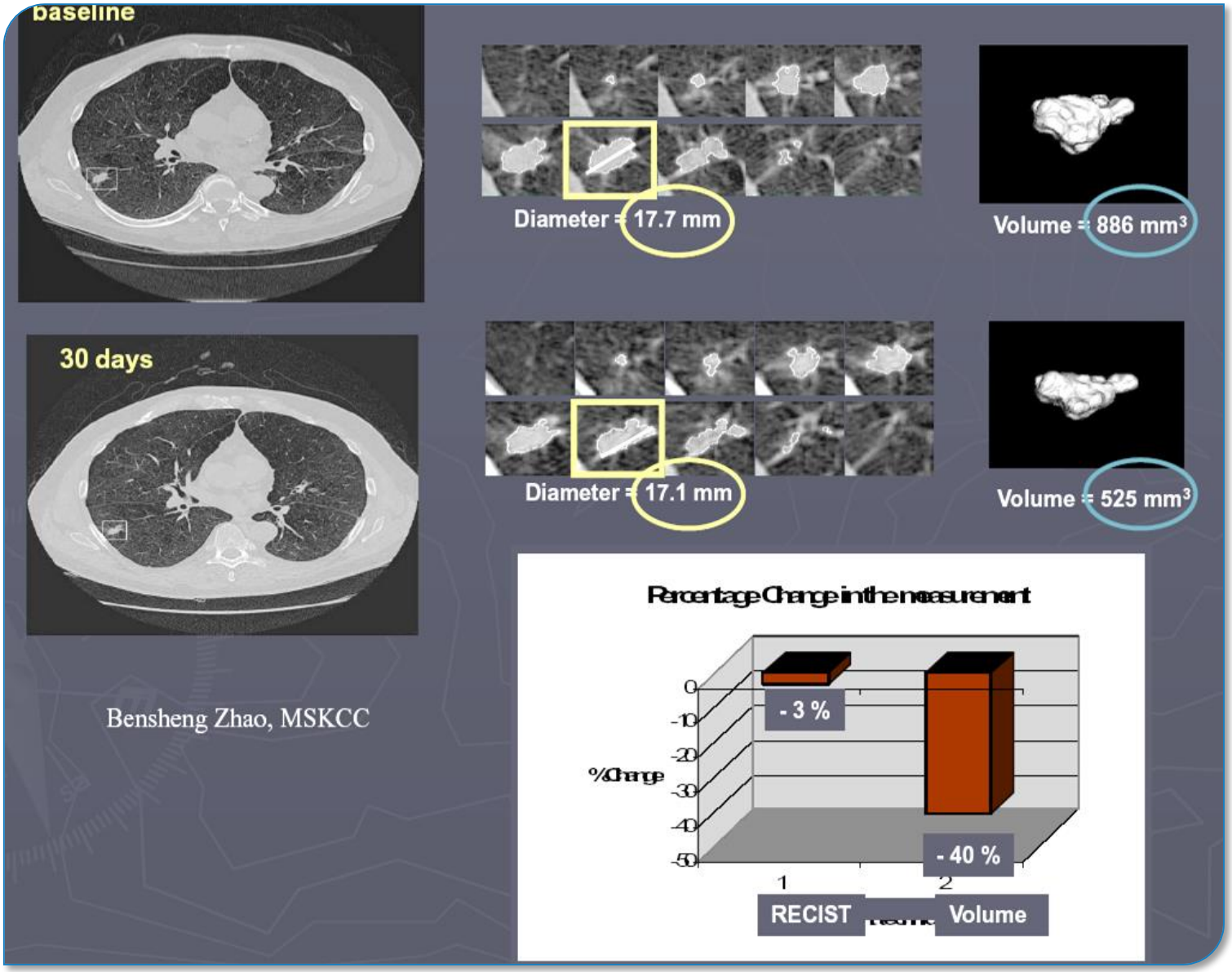
EORTC European Organisation for Research and Treatment of Cancer

NATIONAL CANCER INSTITUTE

Surrogate Endpoints: Progression Free Survival (PFS) Time to Progression (TTP)

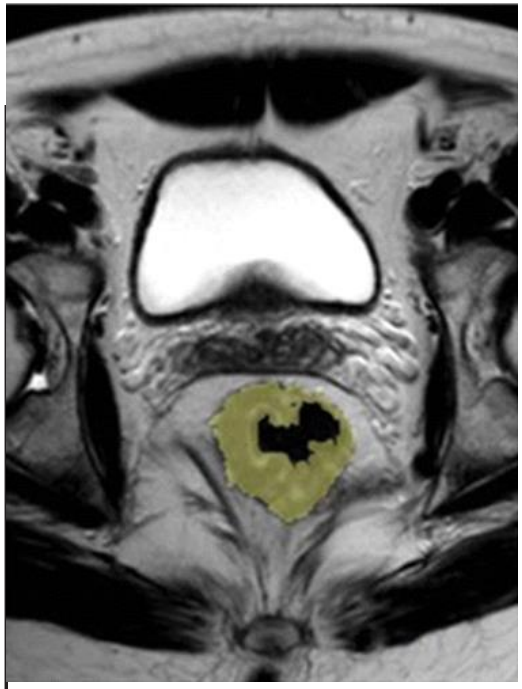


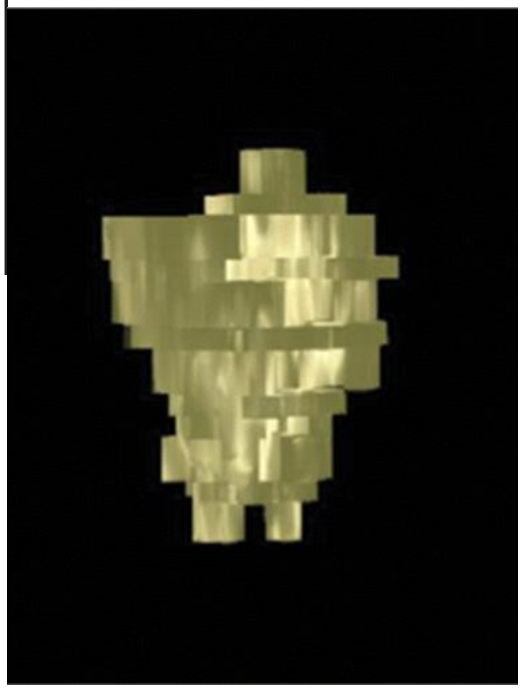
RECIST… limitations



MR Volumetric Measurement of Low Rectal Cancer Helps Predict Tumor Response and Outcome after Combined Chemotherapy and Radiation Therapy[1]

Purpose: To retrospectively determine whether magnetic resonance (MR) volumetry of rectal cancer is a reproducible method for predicting disease-free survival (DFS) in patients with locally advanced low or midrectal tumors who undergo combined chemotherapy and radiation therapy (CRT) before total mesorectal excision.

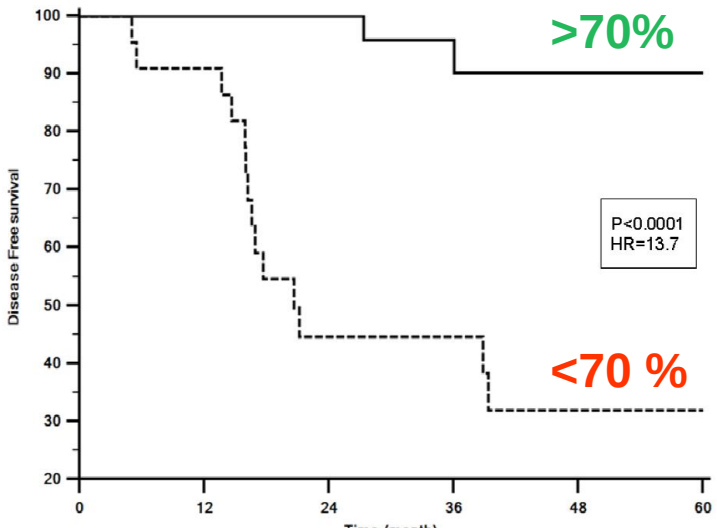




Nougaret S, Gallix B. Radiology, 2012

Volume response / PFS

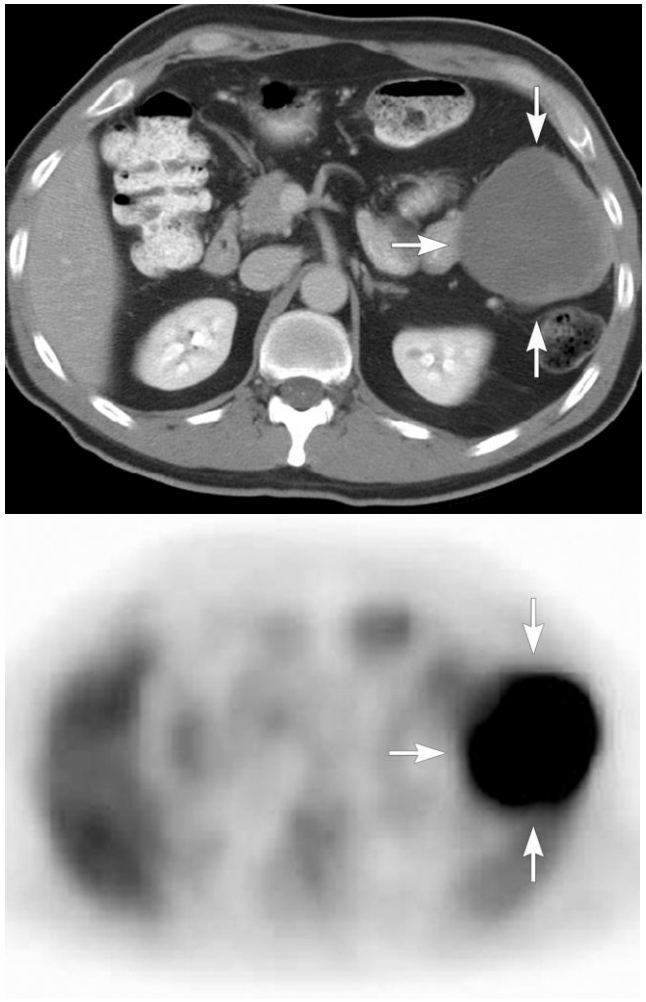
Tumor Reduction Volume ≥ 70%	HR=13.7	[95% CI: 4.00-31.93]	p<0.0001
Downstaging	HR=7.1	[95% CI: 3.04-26.19]	p=0.0001
EMS less than 5mm	HR=5.2	[95% CI: 1.60-11.61]	p=0.0038
No CRM involvement	HR=3.9	[95% CI: 1.79-17.56]	p=0.003



Tumor Reduction Volume

CT for GIST response to imatinib (Gleevec)

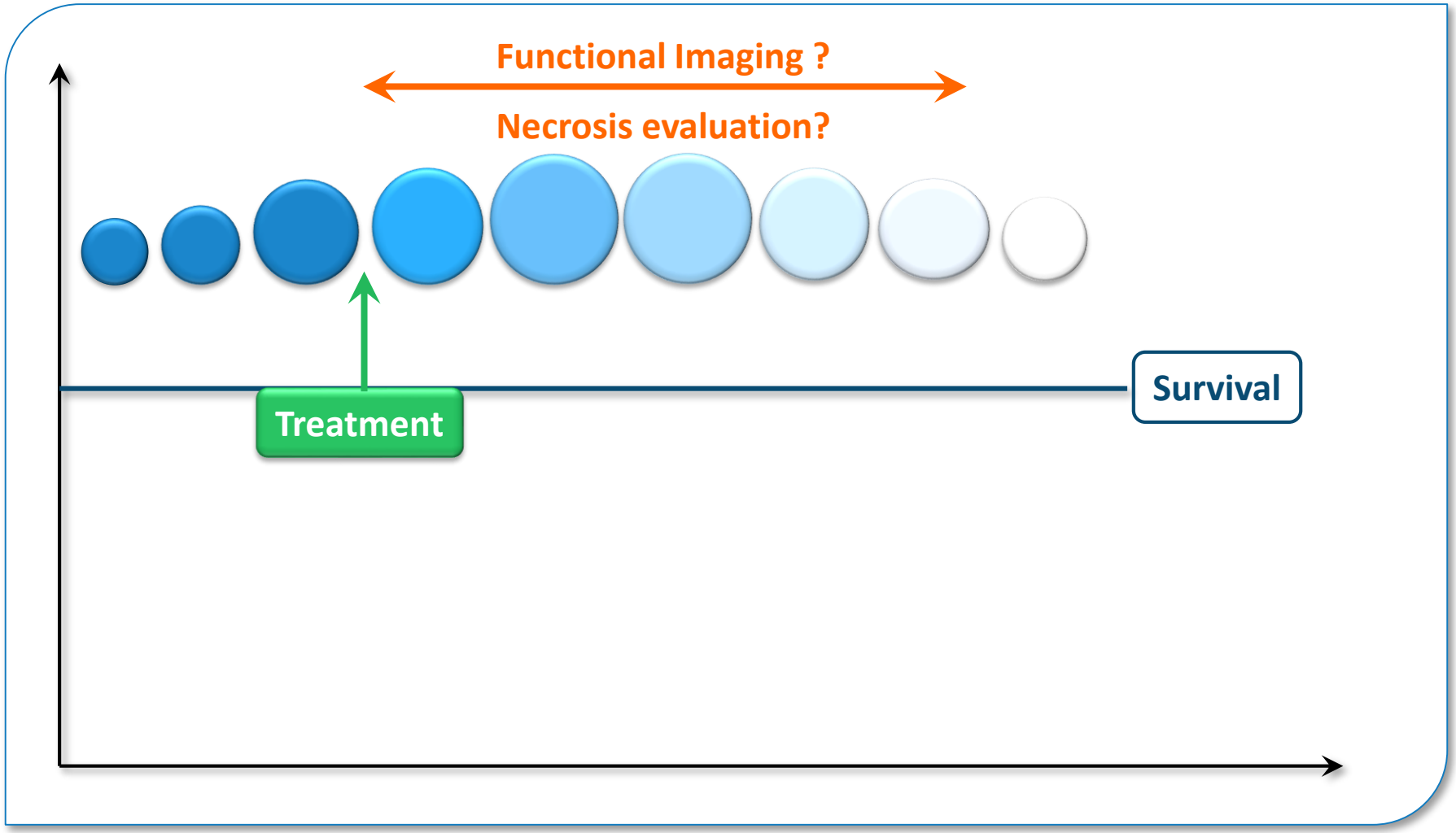
Baseline



2 month

CHOI JCO 2007

How to evaluate the response to target therapy ?

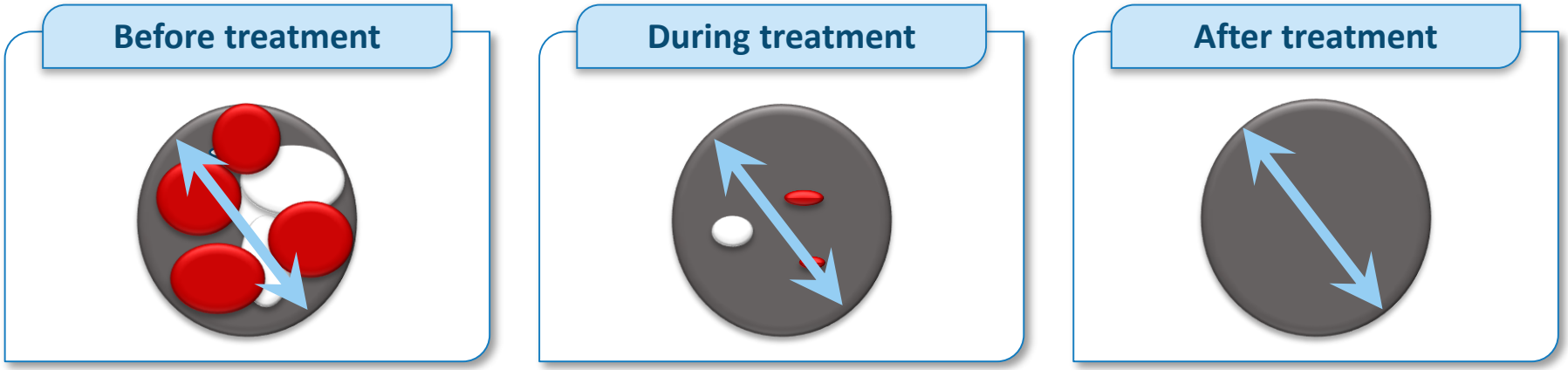


Response to target therapy ?

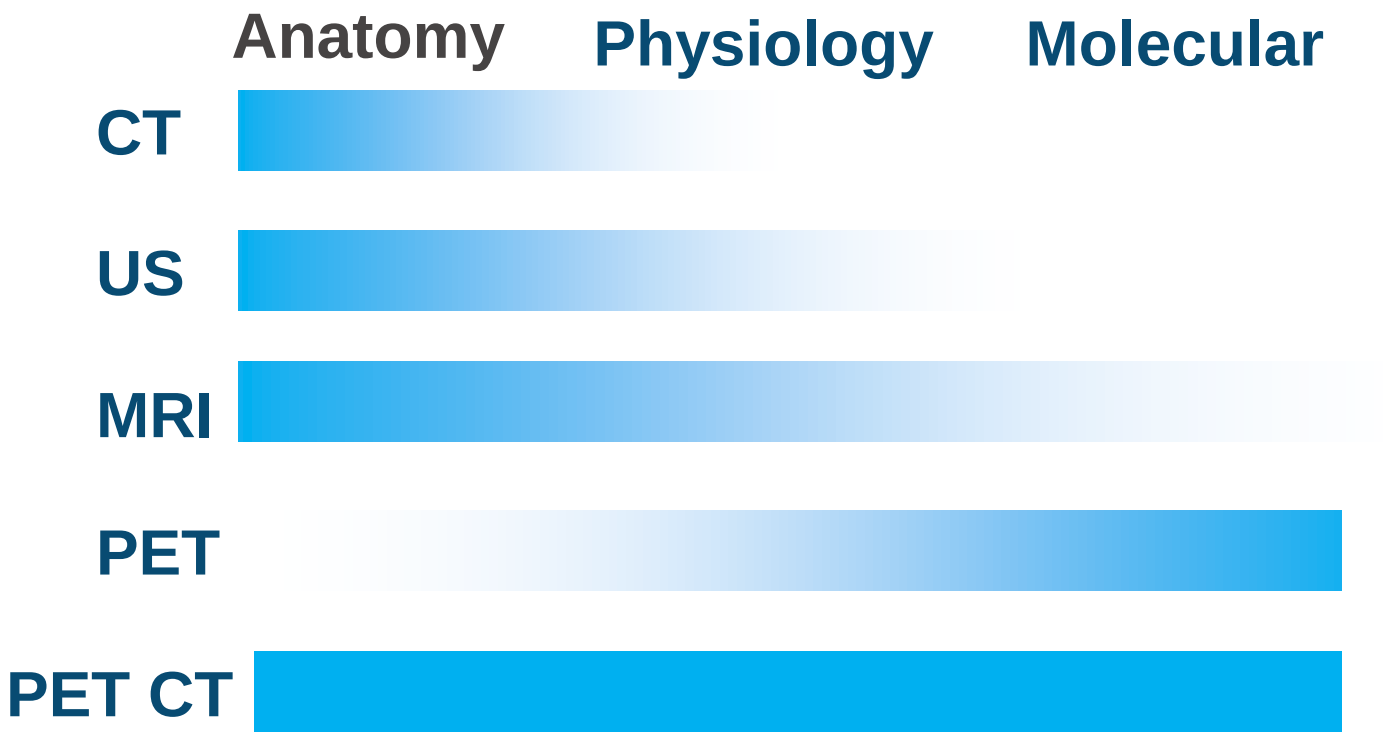
- **Anti-angiogenics, necrosis , fibrosis, …**
- **No tumoral volume changes at the beginning**

RECIST criteria not adequate
(Schwarz RSNA 2005, Benjamin ASCO 2006, Jaffer JCO 2006)

➔ **Need for functional imaging and quantification**

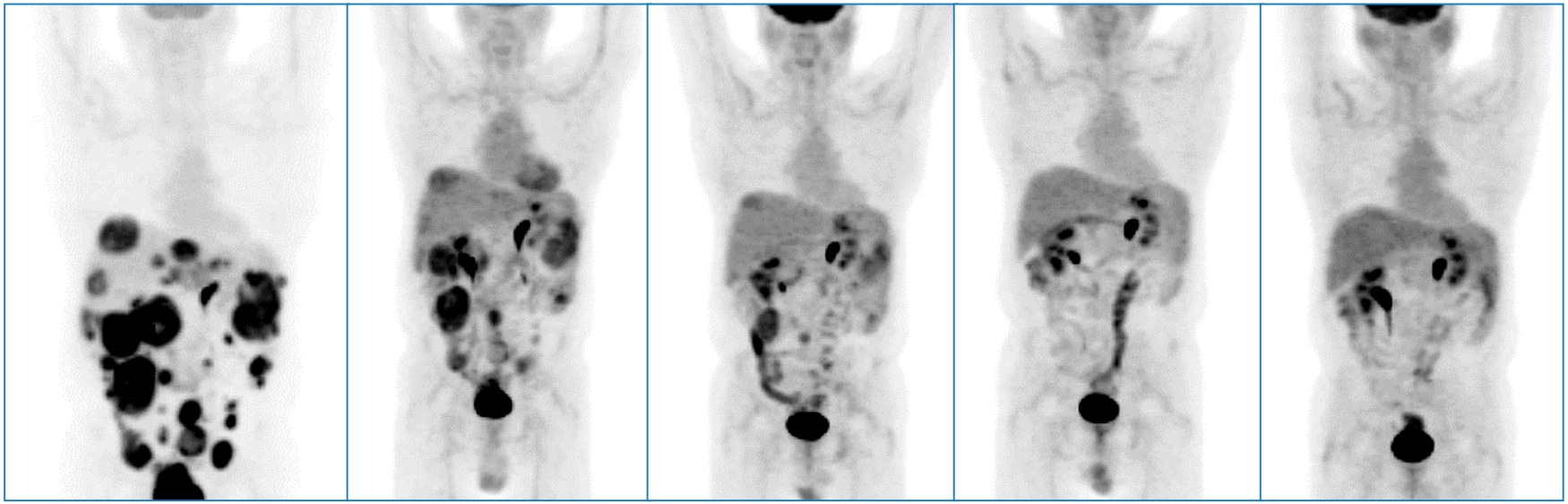


Imaging Modalities



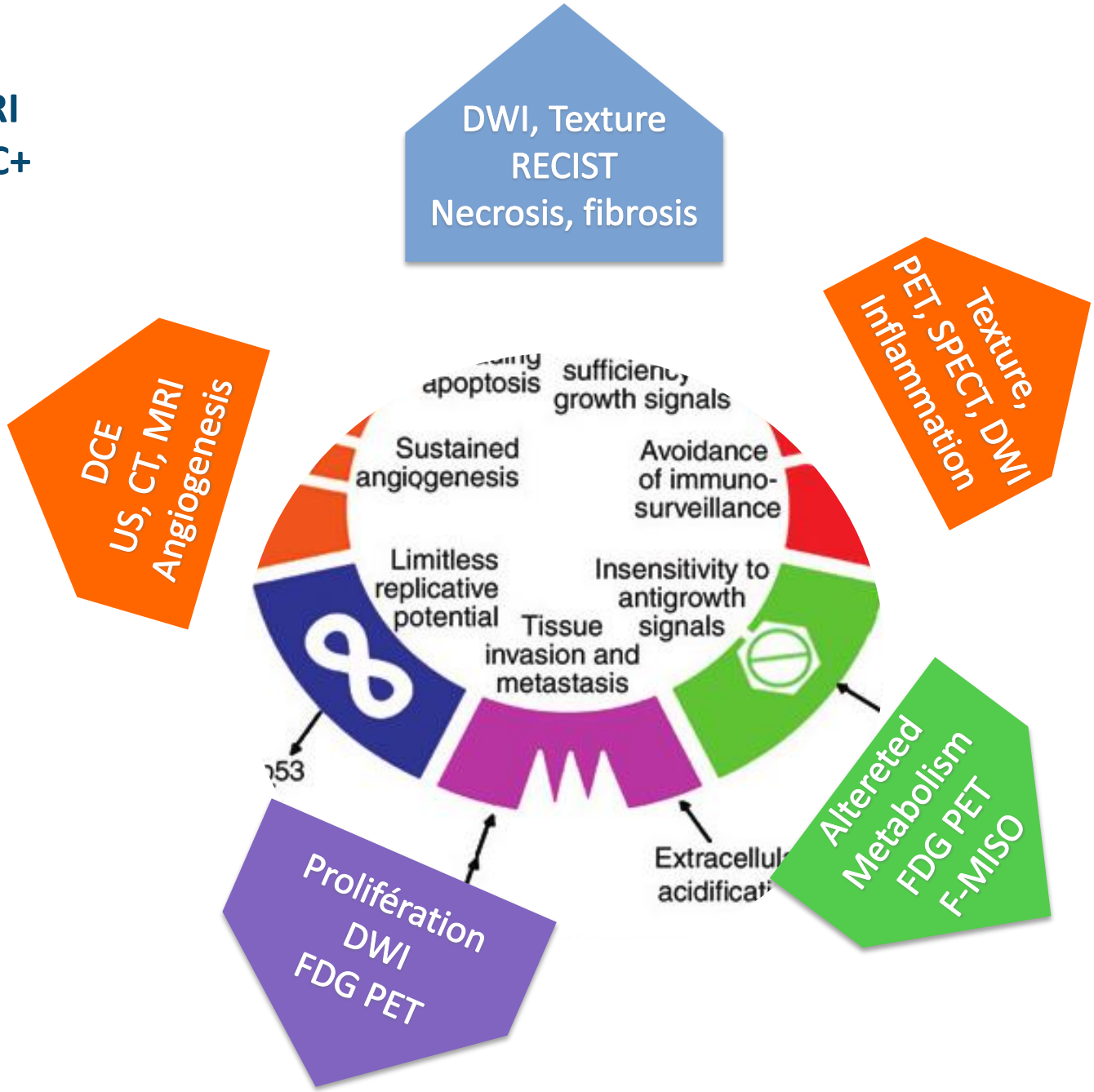
Metabolic Imaging

PET/CT for GIST response to imatinib (Gleevec)



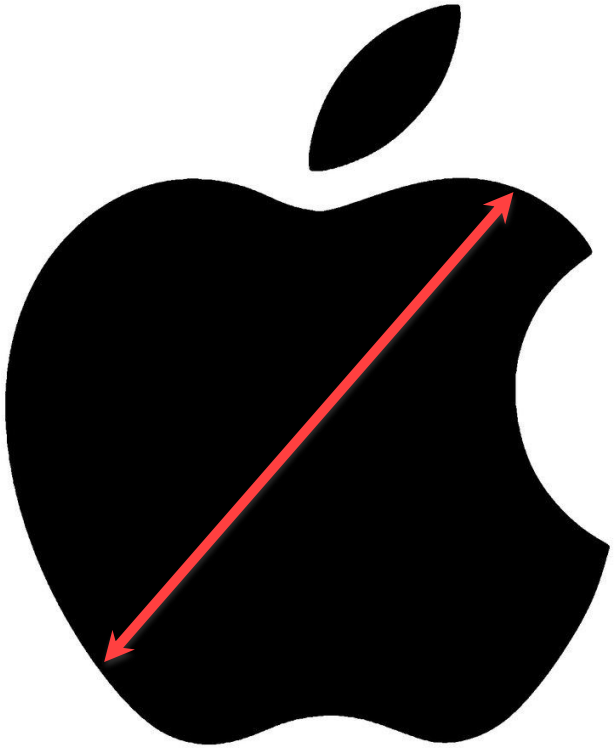
Baseline | 24 hours | 7 days | 2 months | 5.5 months

- RECIST
- VOLUME
- DCE US,CT, MRI
- Delayed post C+
- Early post C+
- FDG PET
- F-MISO -PET
- *-PET
- *-SPECT
- DWI
- …

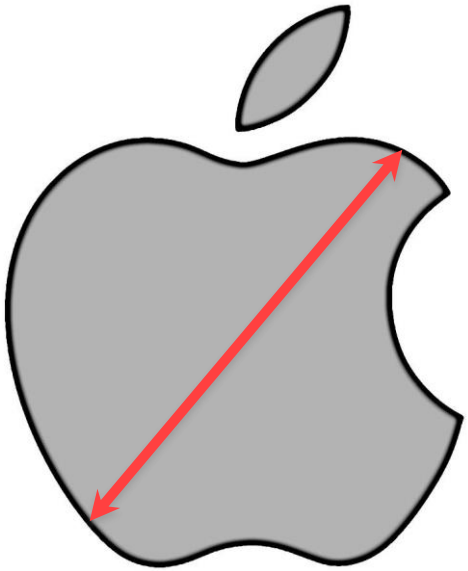


Composite morphological biomarkers

Morphological Imaging



Composite



New morphological biomarkers (composite)

	Parameters	Modality	Tumor type	Response
Newer Imaging Biomarkers	CHOI	CT	GIST	> 10% decrease in size or > 15% decrease in density
	EASL	CT, MR	HCC	Disappearance or decrease of intratumoral arterial enhancement
	mRECIST	CT, MR	HCC	Disappearance or decrease of viable target lesions
	MD Anderson ?	CT	CRC	Morphologic criteria (visual)

CT for GIST response to imatinib (Gleevec)

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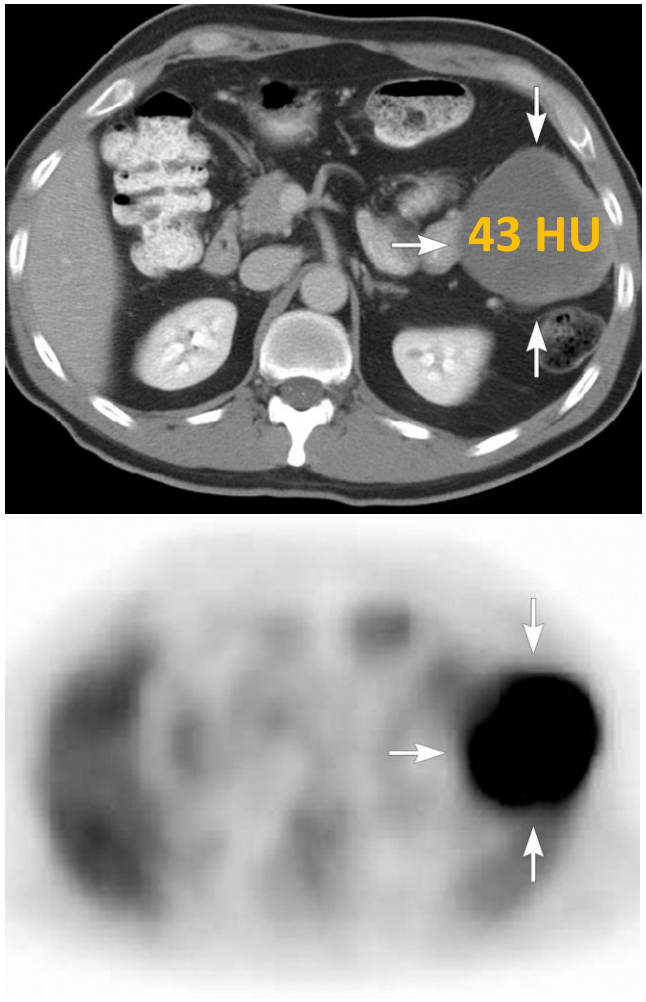
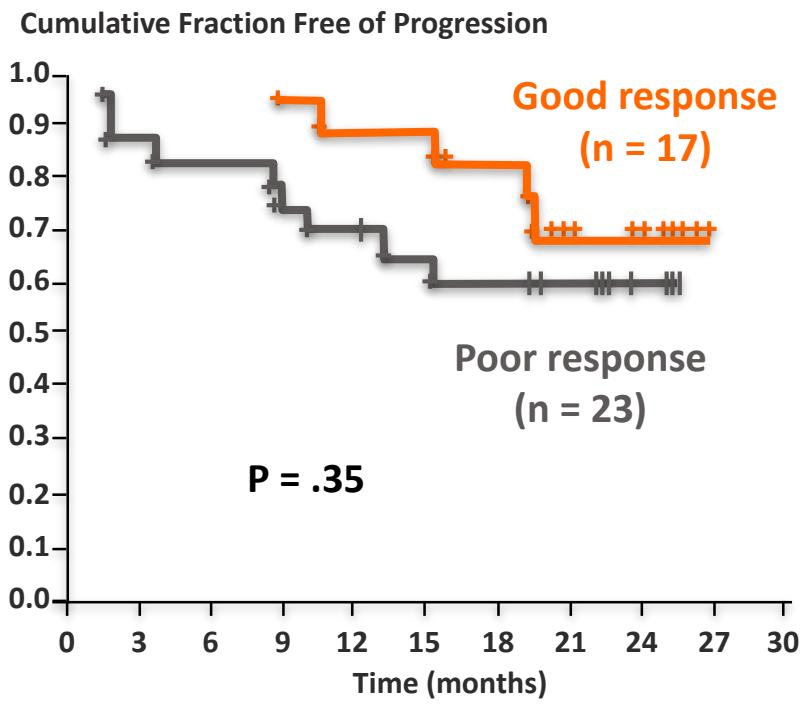


2 month

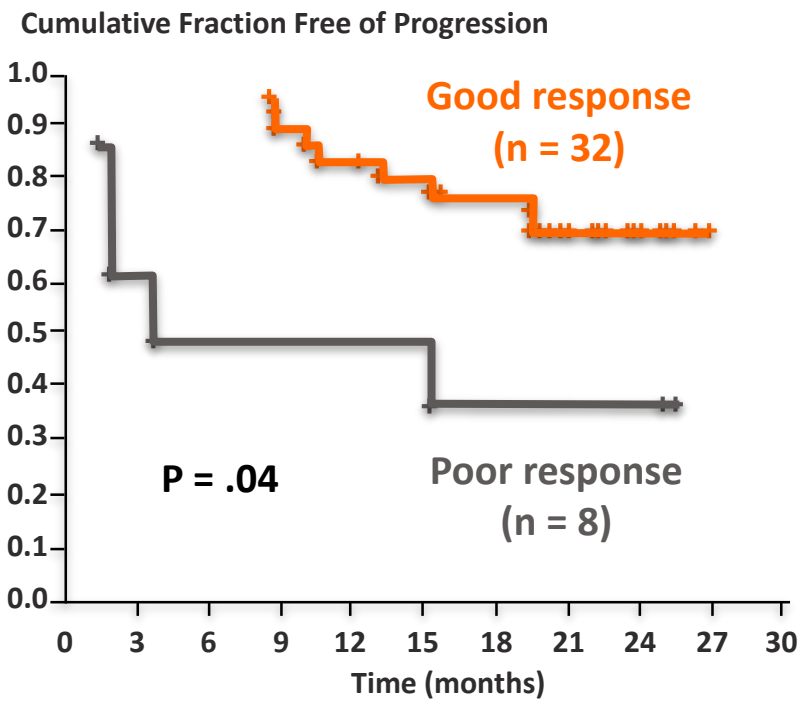
CHOI JCO 2007

PFS

CT – RECIST criteria



CT – CHOI criteria



CHOI JCO 2007

New composite biomarkers (CT, MR)

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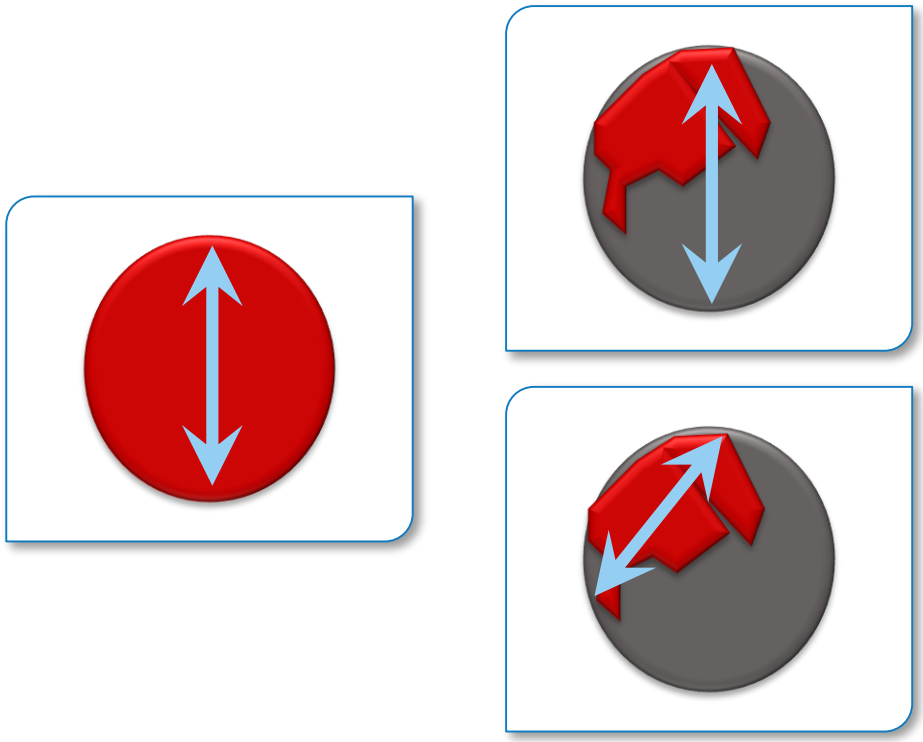
HCC response criteria
EASL → mRECIST
Arteriel Phase (CT / MR)



EASL : Bruix J, et al; EASL. J Hepatol 2001
Bruix J, Sherman M; AASLD. Hepatology 2005

mRECIST : Llovet JM; AASLD-JNCI. J Natl Cancer Inst 2008

New composite biomarkers (CT, MR)

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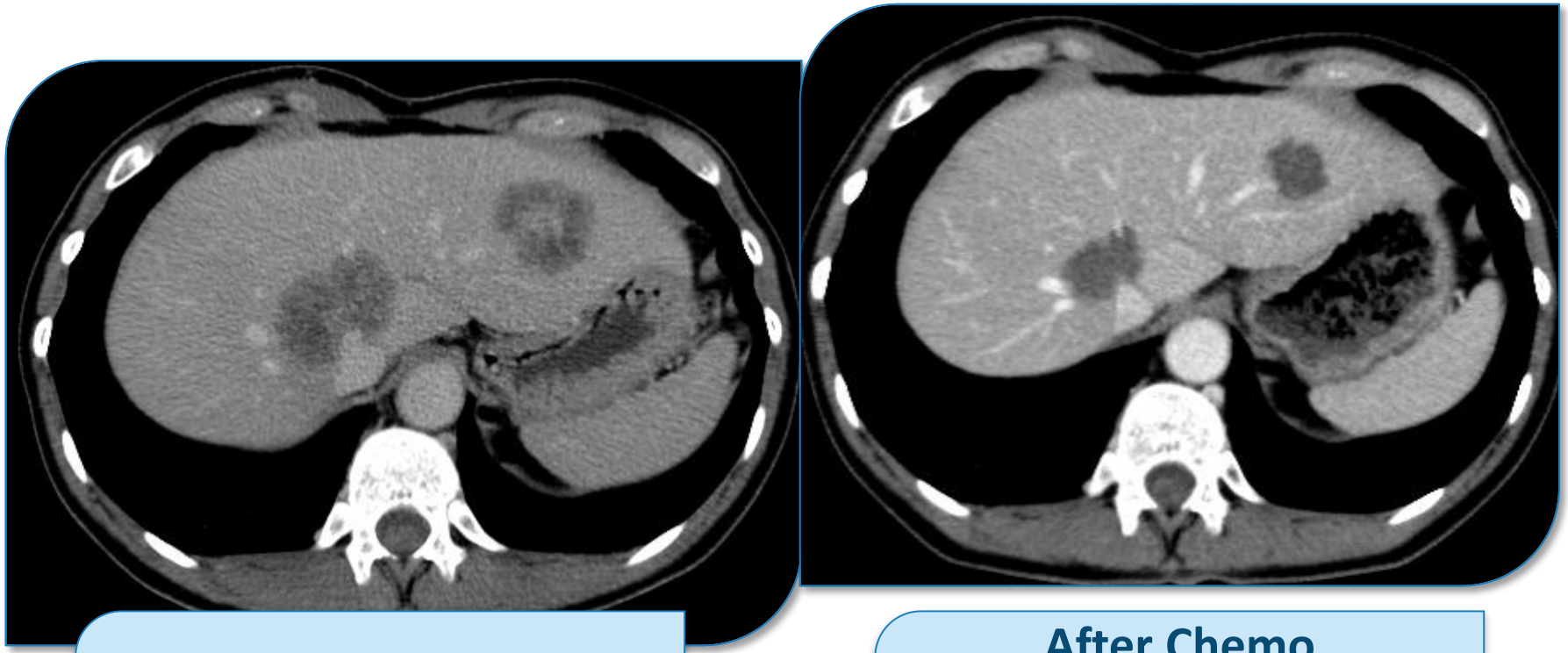
Chun YS *et al.* JAMA 2009

Morphological changes after target therapy



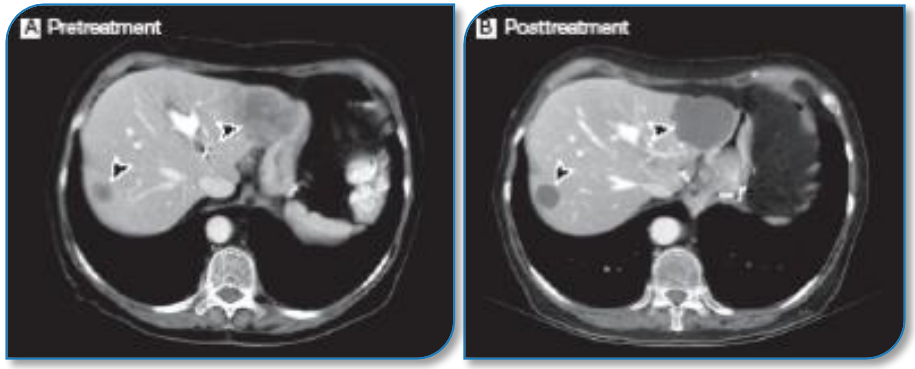
Baseline

After Chemo
+ Beva

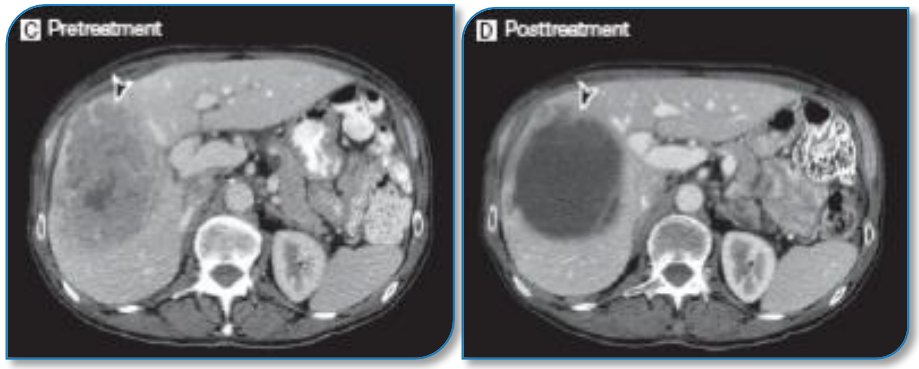
Morphological changes after target therapy

	Computed Tomographic Tumor Characteristics		
Morphology Group	**Overall Attenuation**	**Tumor-Liver Interface**	**Peripheral Rim of Enhancement**
3	**Heterogeneous**	**Ill defined**	**May be present**
2	**Mixed**	**Variable**	**If initially present, partially resolved**
1	**Homogeneous and hypoattenuating**	**Sharp**	**If initially present, completely resolved**

RECIST-stable disease and morphologic optimal response



RECIST-stable disease and morphologic in complete response

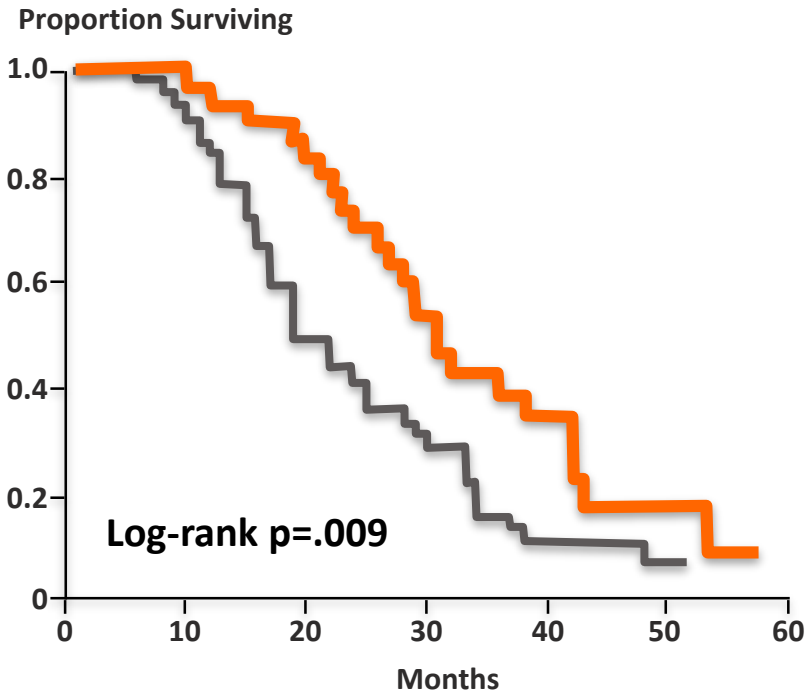


Chun YS *et al.* JAMA 2009

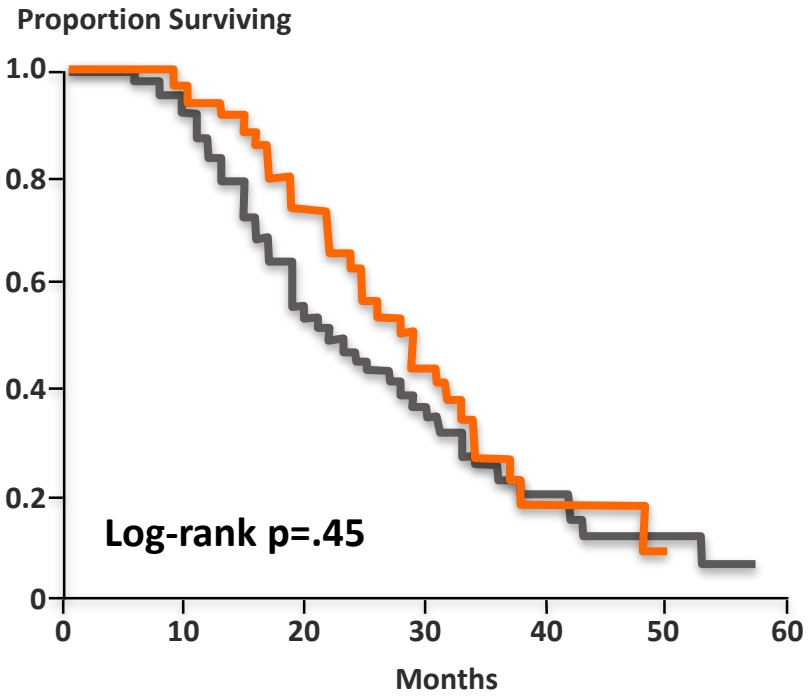
Morphological changes of LMs after chemotherapy

- Patients with unresectable tumor

Morphologic response criteria



RECIST



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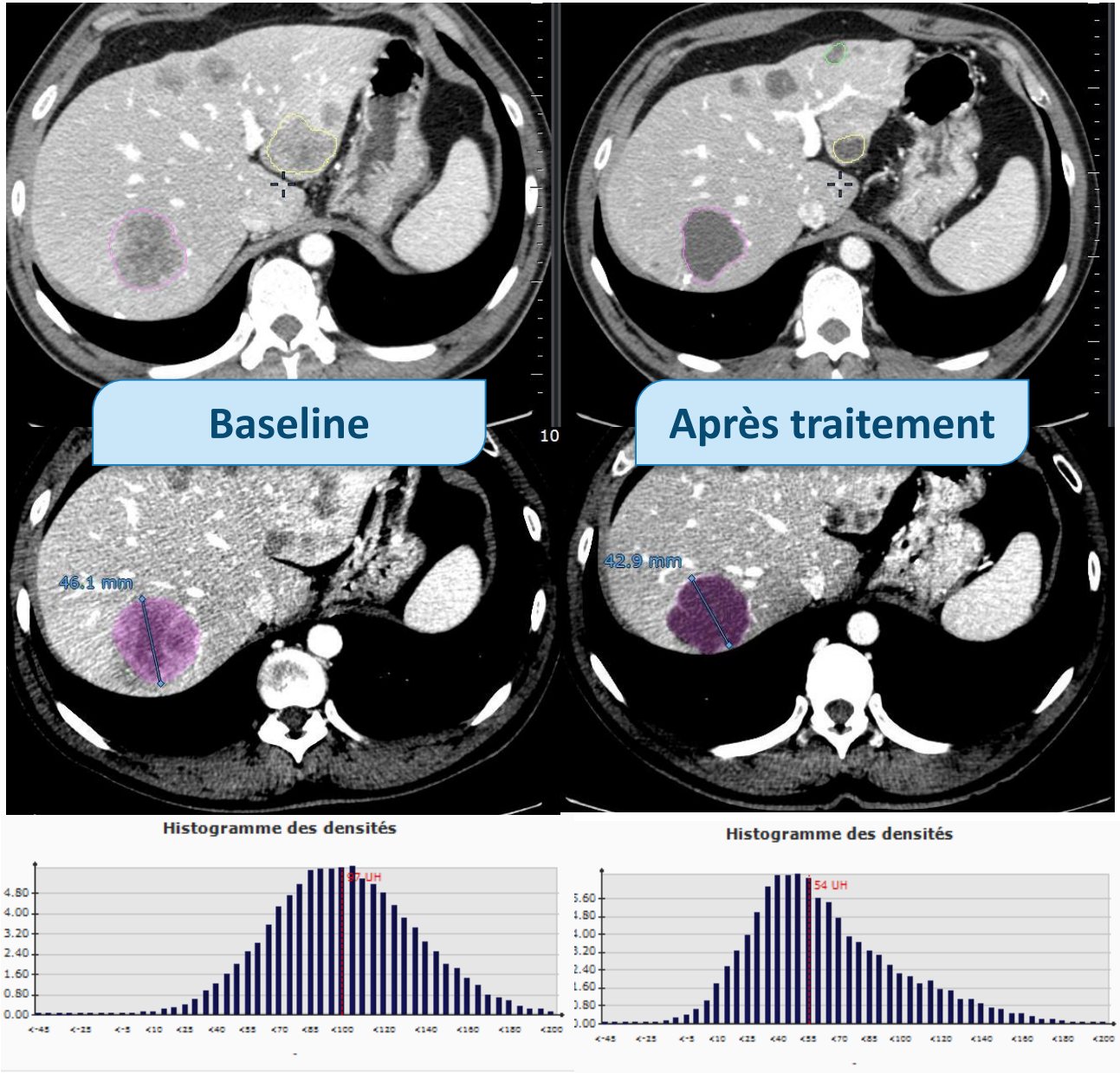


B.Gallix, submitted

Groupe de patients avec thérapies ciblées : Scanner 2 mois après le début du traitement

142 patients

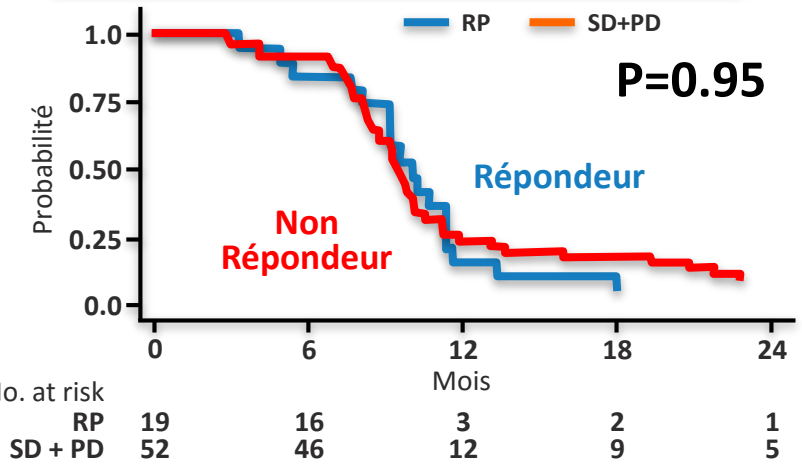
	PFS (n=71)		OS (n=71)	
	HR	95% CI	HR	95% CI
RECIST modified threshold / TDM 0-1				
< -15	1		1	
• -15	2.15	[1.25; 3.70]	2.67	[1.40; 5.09]
	0.007*		0.010*	
Densité // foie / TDM 0-1				
• -10	1		1	
< -10	2.25	[1.32; 3.84]	4.14	[1.69; 10.10]
	0.003*		0.012*	

* Test du rapport de vraisemblance

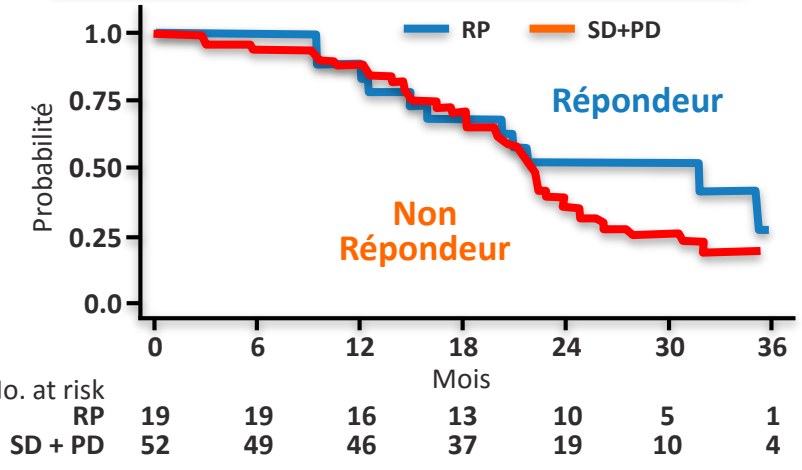
Analyse Multivariée

RECIST (-30%)

PFS – RECIST (TDM0-1)

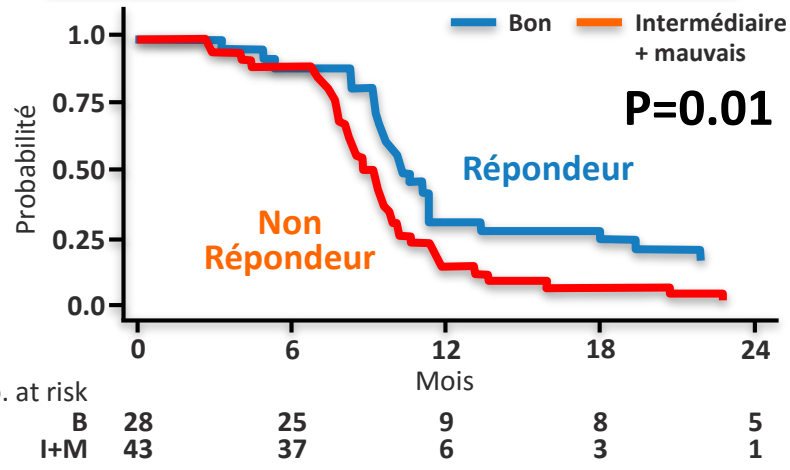


OS – RECIST (TDM0-1)

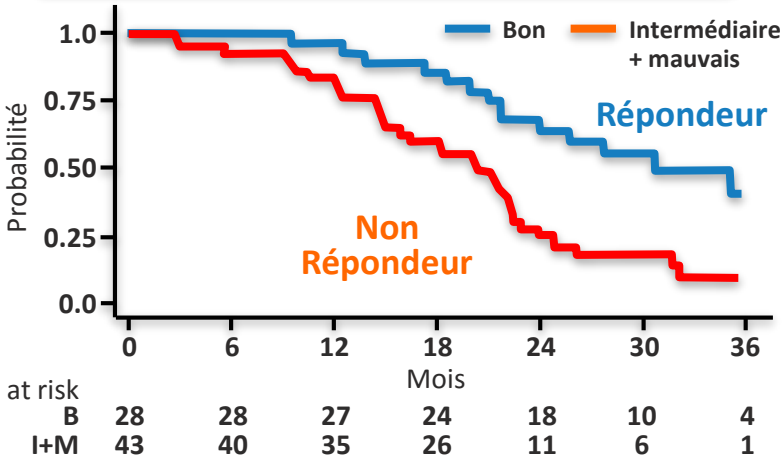


RECIST (-15%) & Densité (10%)

PFS – Score RECIST & Densité // foie

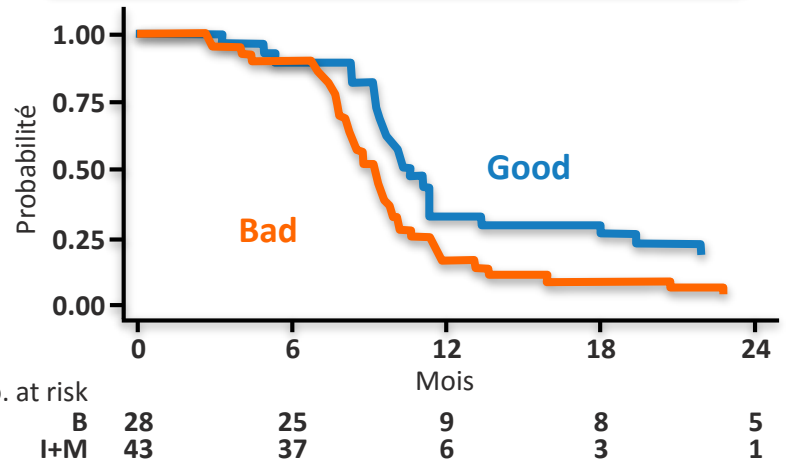


OS – Score RECIST & Densité // foie



Chemo + biotherapy

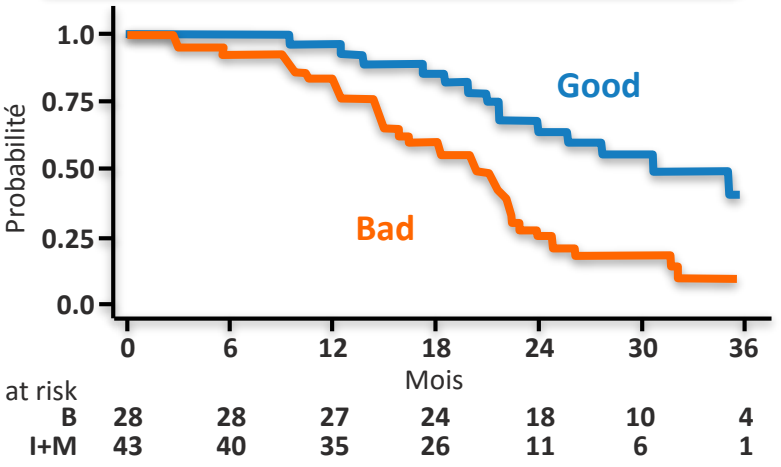
PFS – Score RECIST & Densité // foie



No. at risk

B	28	25	9	8	5
I+M	43	37	6	3	1

OS – Score RECIST & Densité // foie

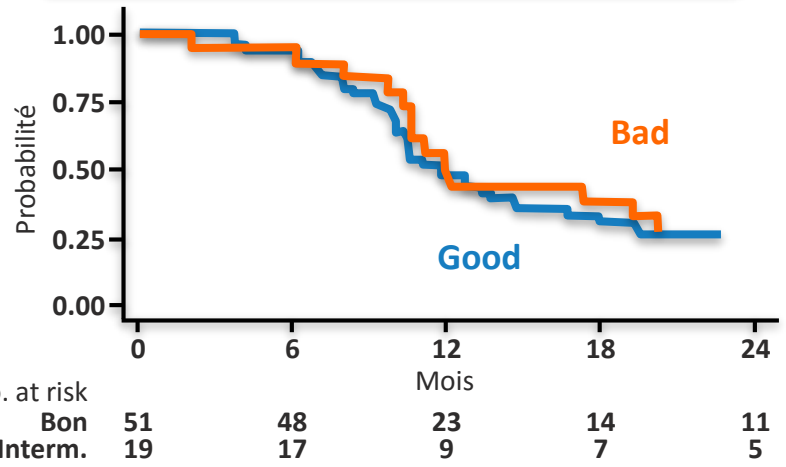


No. at risk

B	28	28	27	24	18	10	4
I+M	43	40	35	26	11	6	1

Chemo alone

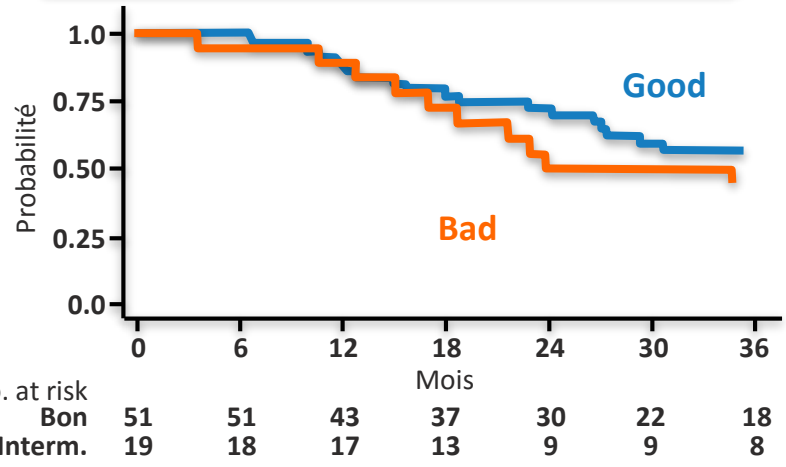
PFS



No. at risk

Bon	51	48	23	14	11
Interm.	19	17	9	7	5

OS



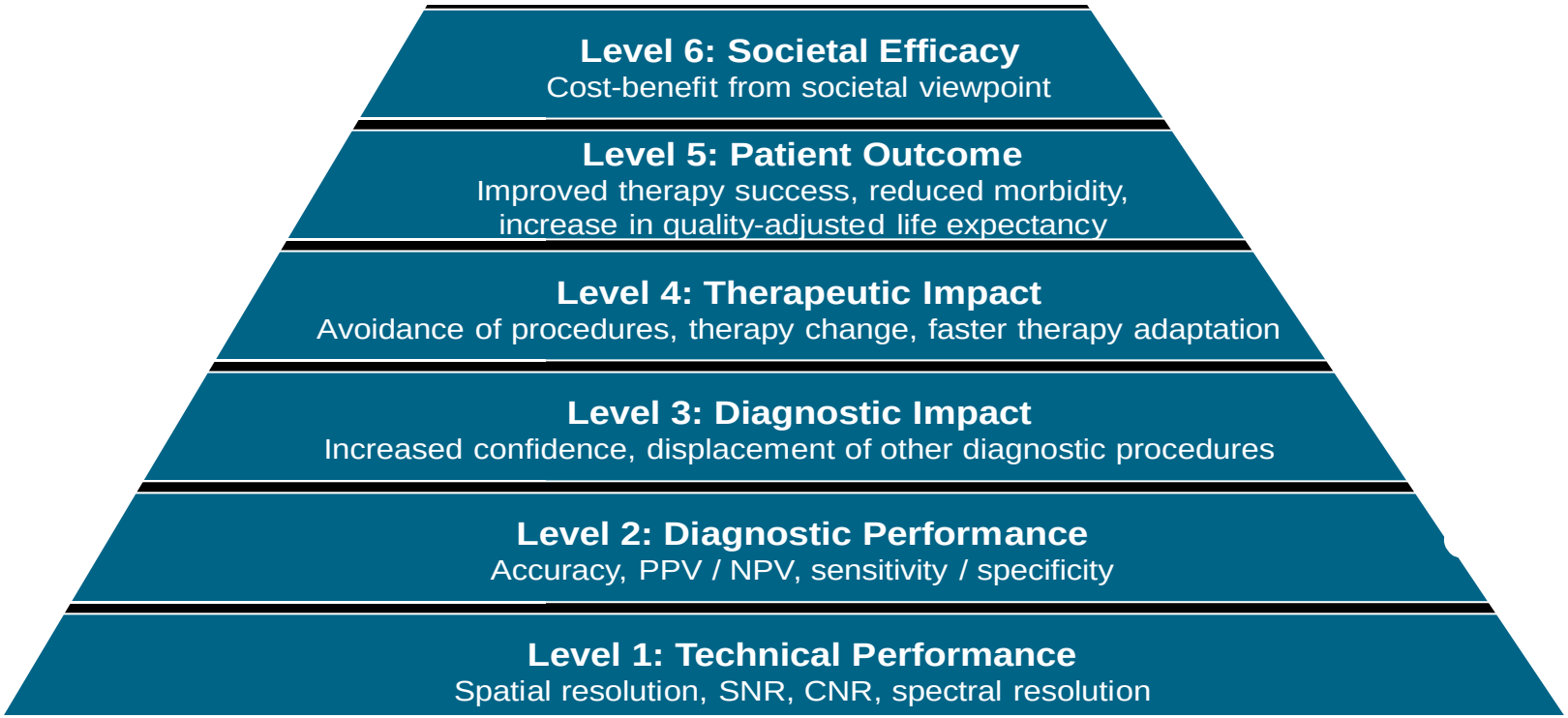
No. at risk

Bon	51	51	43	37	30	22	18
Interm.	19	18	17	13	9	9	8

Quantitative Imaging

- Imaging Biomarkers
  - ➔ **Image acquisition and reconstruction**
  - ➔ Image segmentation and rendering
  - ➔ Feature extraction and qualification
  - ➔ Data storage and sharing
  - ➔ Ad hoc informatics analyses

Imaging Test: Stage validation



Quantitative Imaging

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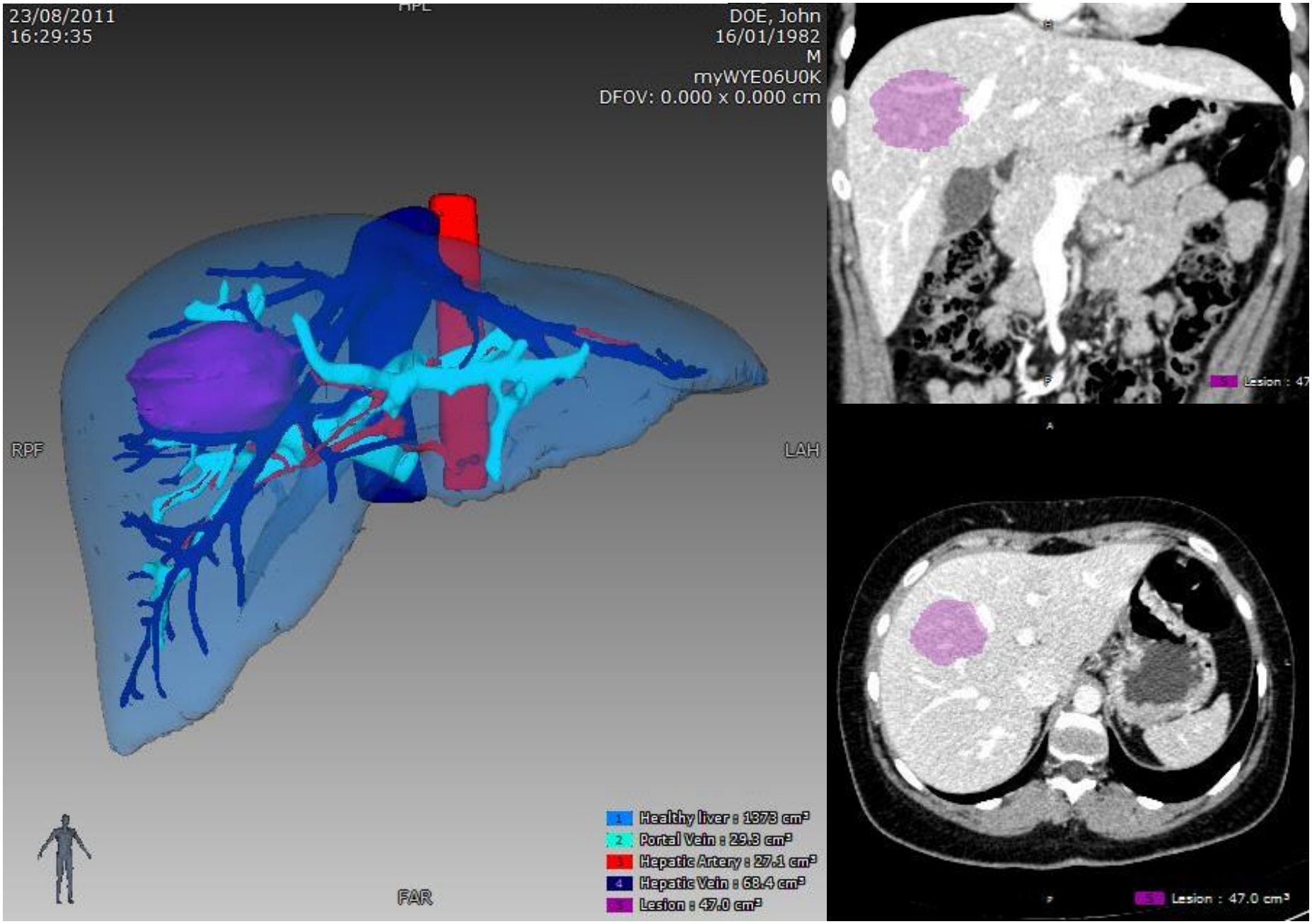
23/08/2011
16:29:35
DOE, John
16/01/1982
M
myWYE06U0K
DFOV: 0.000 x 0.000 cm
RPF
LAH
FAR
1 Healthy liver : 1373 cm³
2 Portal Vein : 29.3 cm³
3 Hepatic Artery : 27.1 cm³
4 Hepatic Vein : 68.4 cm³
5 Lesion : 47.0 cm³
Lesion : 47
Lesion : 47.0 cm³

Quantitative Imaging

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  - ➔ Image acquisition and reconstruction
  - ➔ Image segmentation and rendering
  - ➔ **Feature extraction and qualification**
  - ➔ Data storage and sharing
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Use of Archived Databases

Prospective – Retrospective Studies

- In some cases the benefits of a prospective trial can be closely achieved by the carefully planned use of archived database from a previously conducted randomized clinical trial

Use of Archived Images in Evaluation of Prognostic and Predictive Imaging Biomarkers

- Claims of medical utility for prognostic and predictive Imaging biomarkers based on analysis of archived images can be considered to have either a high or low level of evidence depending on several key factors.
- Studies using archived Databases, when conducted under ideal conditions and independently confirmed can provide the highest level of evidence.
- Traditional analyses of prognostic or predictive factors, using non analytically validated assays on a convenience sample of iimages and conducted in an exploratory and unfocused manner provide a very low level of evidence for clinical utility.

Use of Archived Images in Evaluation of Prognostic and Predictive Imaging Biomarkers

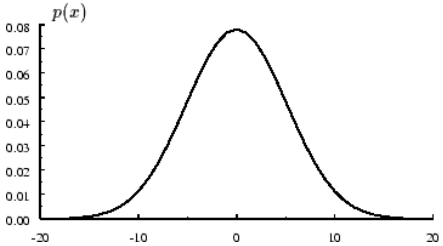
- Archives databases adequate for a successful assay must be available on a sufficiently large number of patients from a phase III trial so that the appropriate analyses have adequate statistical power and that the patients included in the evaluation are clearly representative of the patients in the trial.
- The test should be analytically and pre-analytically validated for use with these database
- The analysis plan for the Imaging biomarker evaluation should be completely specified in writing prior to the performance of the biomarker assays on archived images and should be focused on evaluation of a single completely defined classifier.
- The results from archived database should be validated using specimens from a similar, but separate, study.

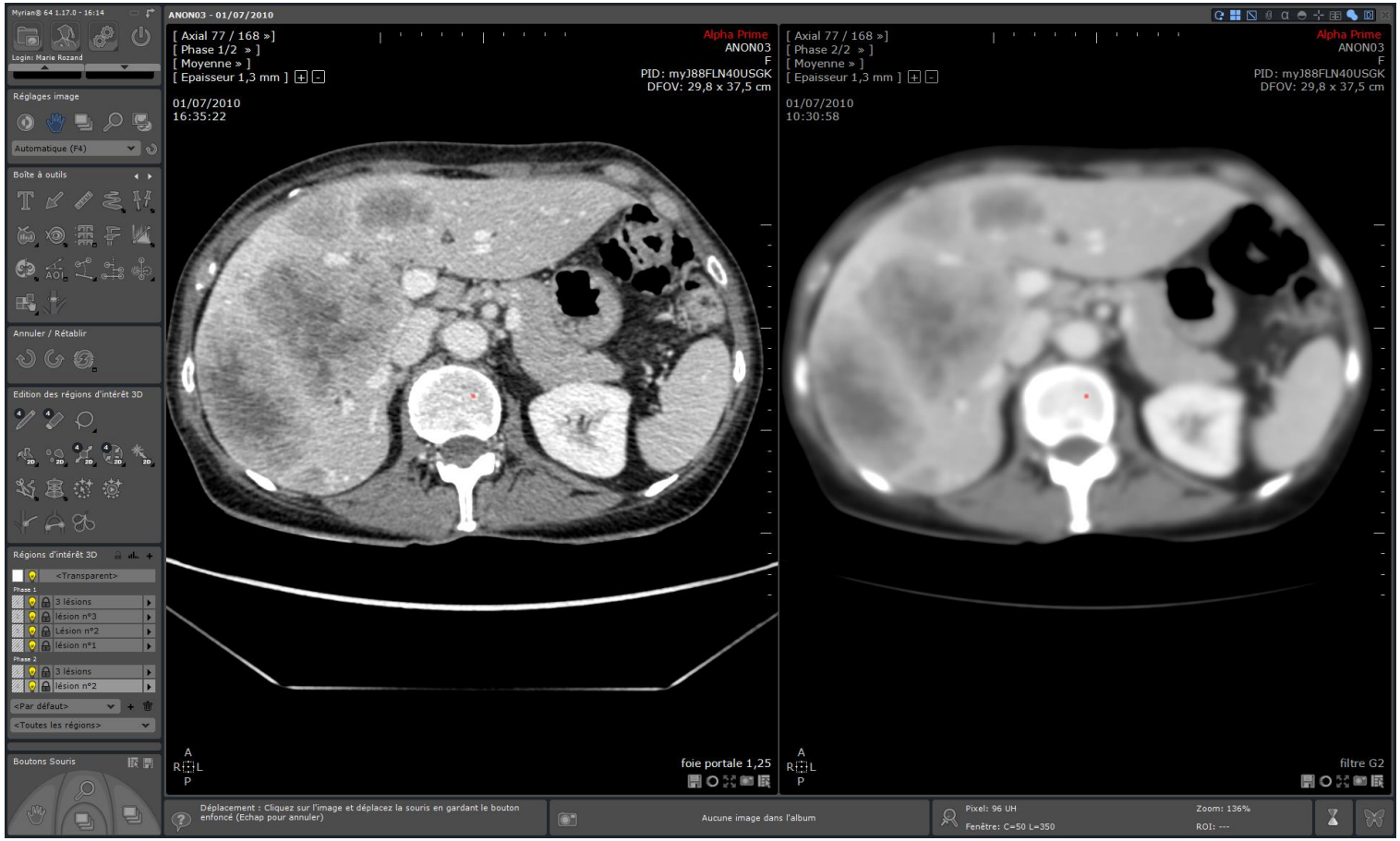
- RECIST
- VOLUME
- DCE US,CT, MRI
- Delayed post C+
- Early post C+
- FDG PET
- F-MISO -PET
- *-PET
- *-SPECT
- DWI
- …

Shape Analysis

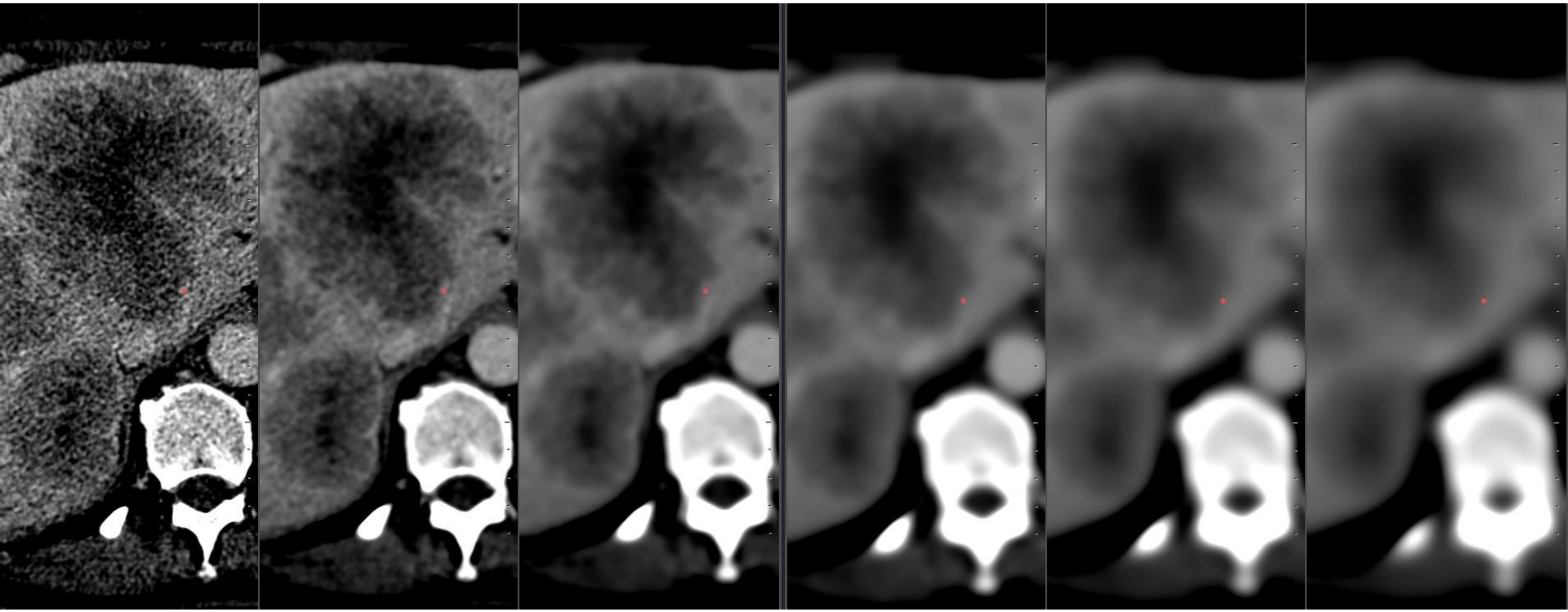
Texture Analysis

First step: Gaussian filter





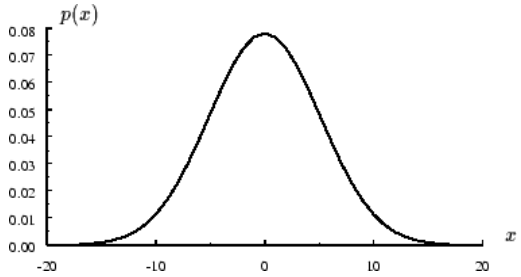
Size of the Gausssian Filter

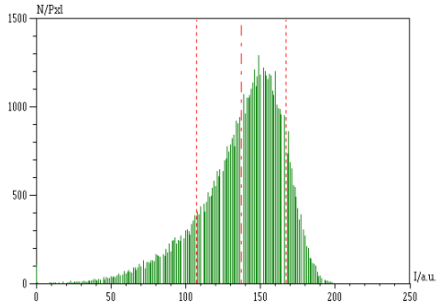


Non filtrée $\boldsymbol{\sigma} = 1\text{mm}$ $\boldsymbol{\sigma}=2\text{mm}$ $\boldsymbol{\sigma}=3\text{mm}$ $\boldsymbol{\sigma}=4\text{mm}$ $\boldsymbol{\sigma}=5\text{mm}$

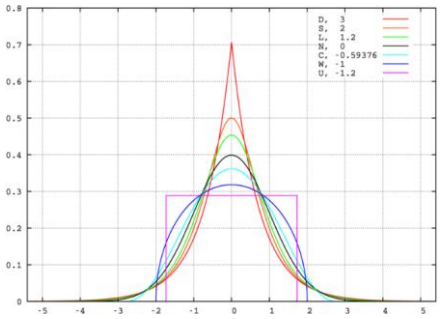
Second Step: Texture Analysis

- Sur l'histogramme :
  - ➔ Variance
  - ➔ Skewness





  - ➔ Kurtosis



  - ➔ Entropie = $-\sum \log(p(i))p(i)$
  - ➔ Energie (uniformity) = $\sum p(i)^2$
  - ➔ Signal sur bruit (coefficient de variation) = $\frac{MOY}{\sqrt{Var}}$

Coodurrence Matrix:

1	4	4	3
4	2	3	2
1	2	1	4
1	2	2	3

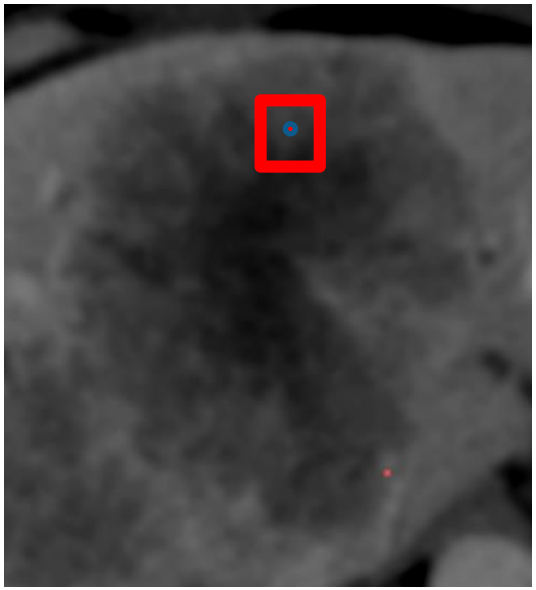
Image initiale

	1	2	3	4
1	0	2	1	2
2	1	1	1	0
3	0	1	0	0
4	1	0	1	1

Matrice de cooccurrence (d=1, θ=0°)associée

Parametric Map

Filtered Image



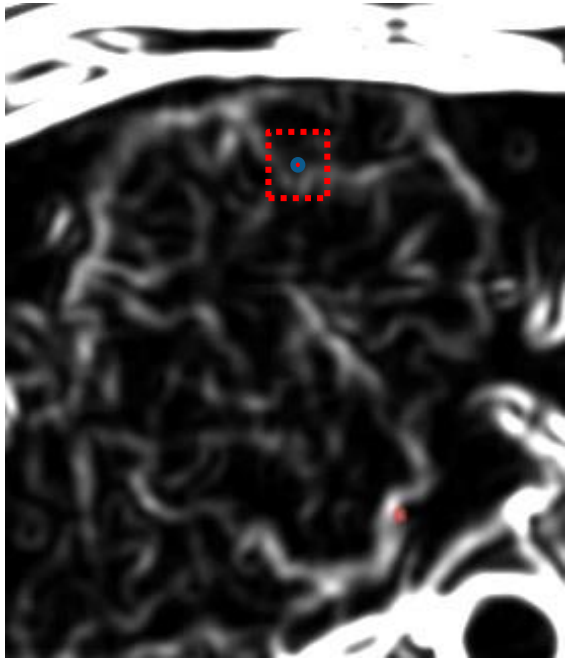
2D 5x5 voxels

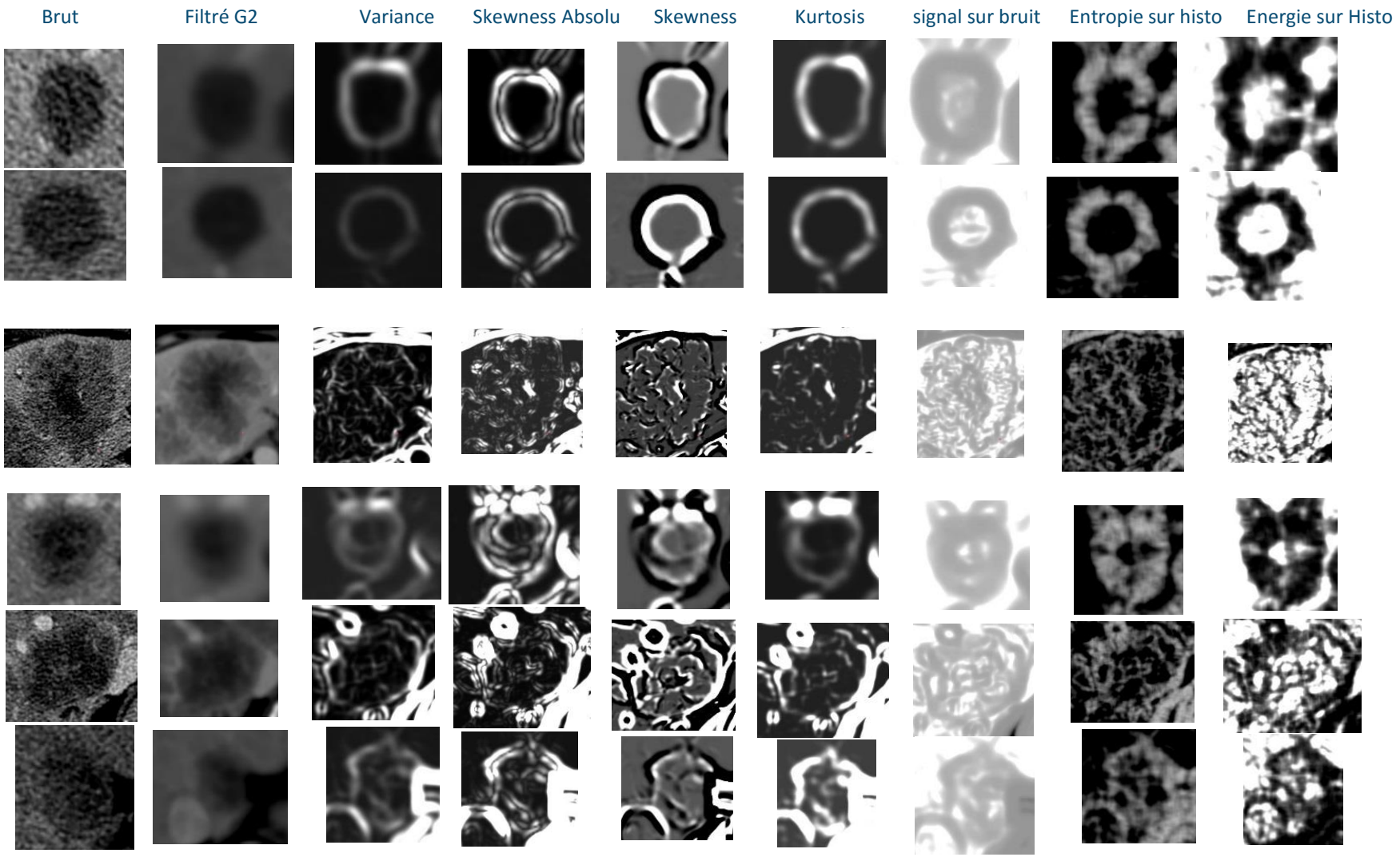
Calcul de la métrique sur le voisinage

$$\frac{1}{N}\sum(d(v) - M$$

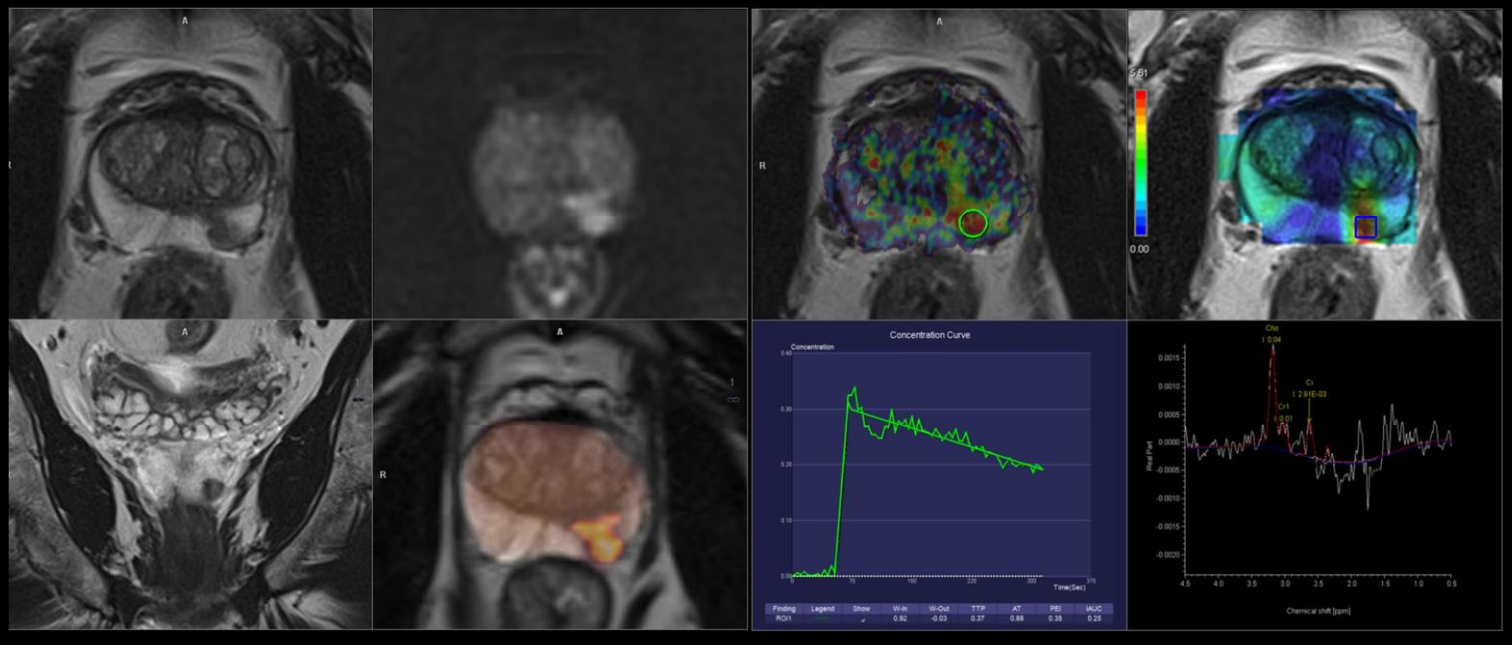
Valeur transformée en degré de gris

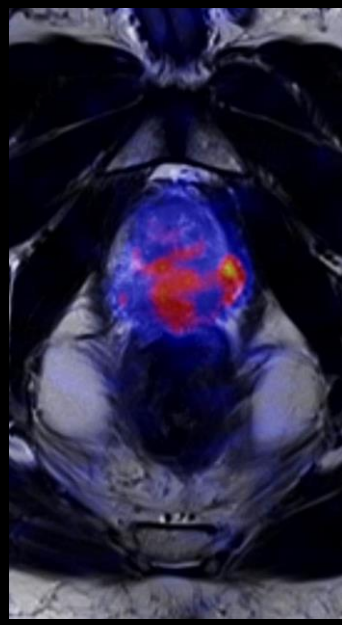
Variance map



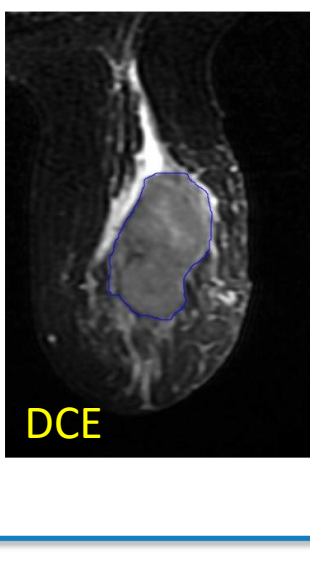

Brut
Filtré G2
Variance
Skewness Absolu
Skewness
Kurtosis
signal sur bruit
Entropie sur histo
Energie sur Histo

T2 | DWI | 4D Perfusion | Spectroscopy | mMR (^{68}Ga-PSMA*)



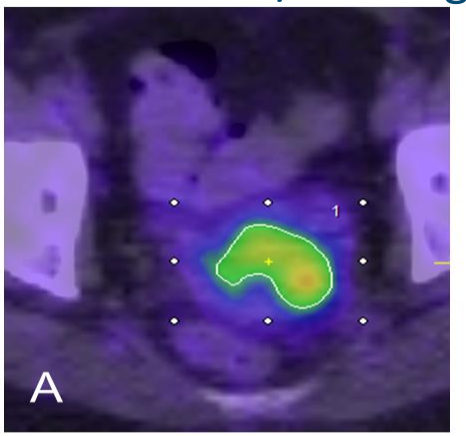


Breast MRI



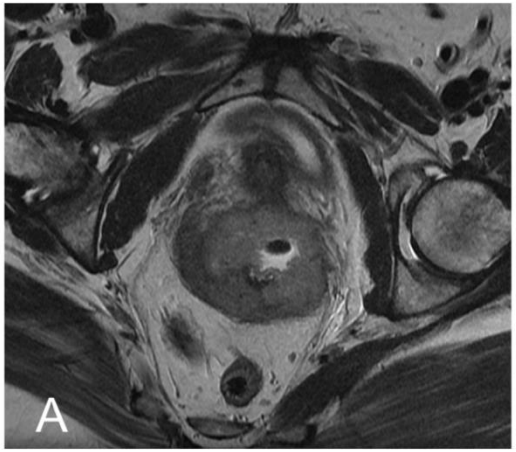
Comparison of FDG PET Metabolic Tumor Volume versus ADC Histogram: Prognostic Value of Tumor Treatment Response in Patients with Locally Advanced Uterine Cervical Cancer

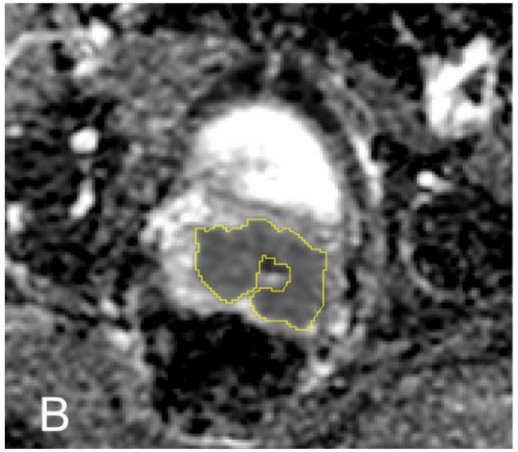
18F-FDG-PET/CT images depicting MTV (FIGO stage ⅢB cervical cancer)



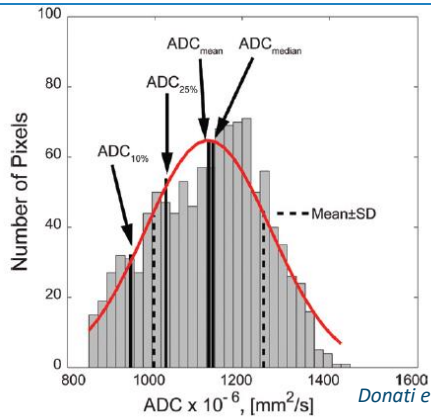
- MTV=metabolic tumor volume
  (the sum of all voxels with an SUV above 42% of SUVmax)
- TLG=total lesion glycolysis
  (the metabolic tumor volume multiplied by the average SUV of all voxels with an SUV above 42% SUVmax)

T2WI and ADC map (FIGO stage ⅢB cervical cancer)





Volume-based ADC histogram analysis



Donati et al. Radiology, 2014

The differences in the parameters between responders and non-responders of CCRT

	Group		
PET Parameter	Responder (n=15)	Non-responder (n=6)	P value
SUV_{mean}	8.20 ± 3.40	9.42 ± 1.80	0.55
SUV_{max}	13.04 ± 4.51	17.14 ± 4.20	0.14
MTV (mL)	34.81 ± 39.82	78.53 ± 47.40	0.04
TLG (g)	24.22 ± 19.62	68.81 ± 37.20	0.01
ADC parameter			
ADC_{mean} ($\times 10^{-3}$ mm²/s)	0.99 ± 0.18	1.06 ± 0.12	0.45
ADC_{min} ($\times 10^{-3}$ mm²/s)	0.45 ± 0.23	0.40 ± 0.21	0.55
ADC_{max} ($\times 10^{-3}$ mm²/s)	2.06 ± 0.70	2.18 ± 0.29	0.29
$ADC_{90\%}$ ($\times 10^{-3}$ mm²/s)	1.30 ± 0.28	1.34 ± 0.17	0.45
$ADC_{75\%}$ ($\times 10^{-3}$ mm²/s)	1.11 ± 0.20	1.17 ± 0.14	0.55
$ADC_{50\%}$ ($\times 10^{-3}$ mm²/s)	0.94 ± 0.16	1.01 ± 0.11	0.41
$ADC_{25\%}$ ($\times 10^{-3}$ mm²/s)	0.84 ± 0.10	0.91 ± 0.10	0.25
$ADC_{10\%}$ ($\times 10^{-3}$ mm²/s)	0.77 ± 0.15	0.84 ± 0.09	0.33
Skewness	0.82 ± 0.69	0.98 ± 0.16	0.72
Kurtosis	1.51 ± 0.92	1.42 ± 0.46	0.93

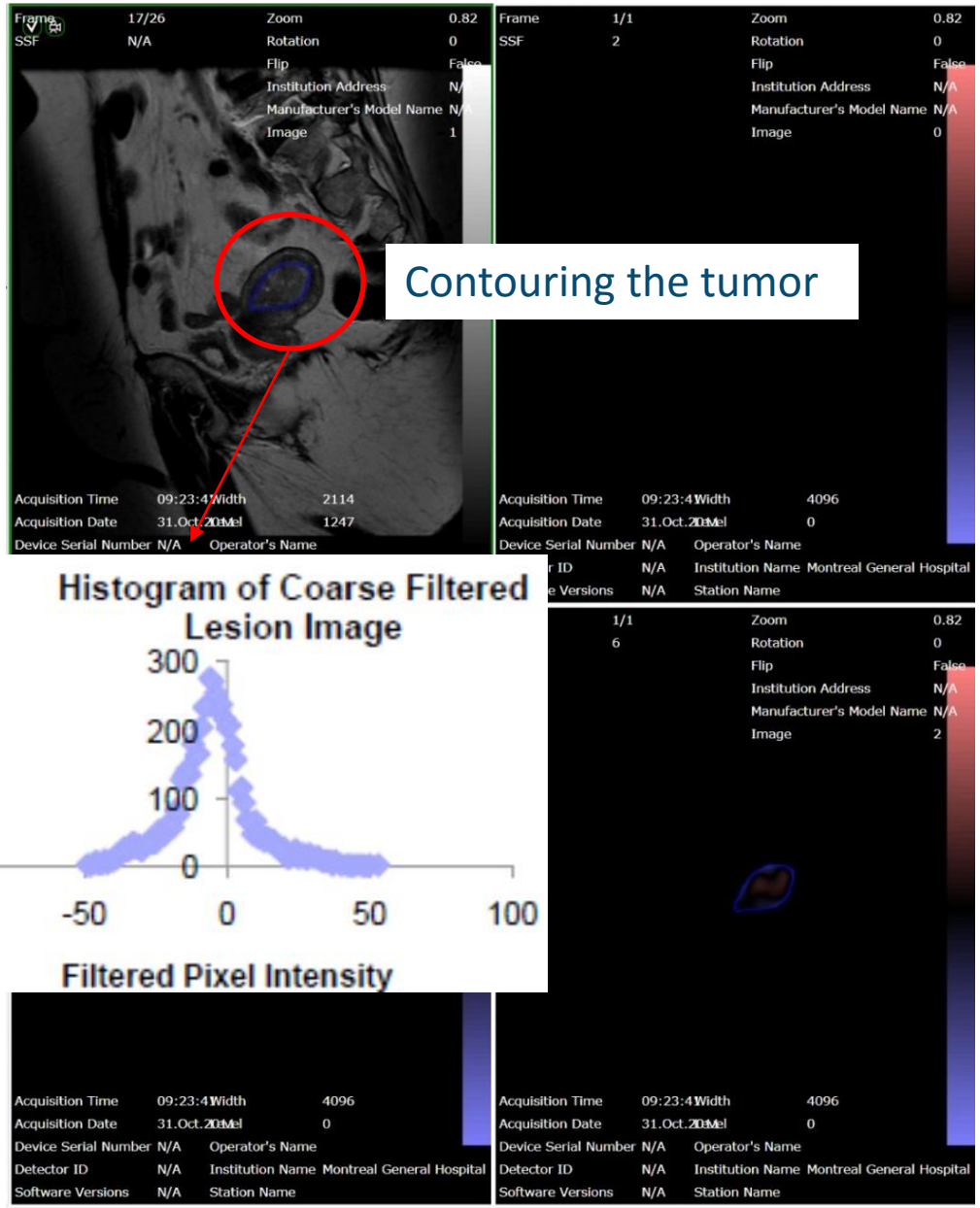
Ueno. Y, Reinhold. C, et al. [unpublished data]

Material and Methods with Texture analysis: TexRad®

Endometrial cancer

Texture parameters

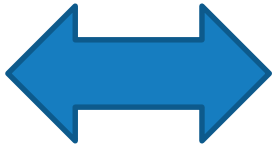
Mean
SD
Entropy
MPP
Skewness
Kurtosis
…



Material and Methods : Outcome

Texture parameters

Mean
SD
Entropy
MPP
Skewness
Kurtosis
…etc.

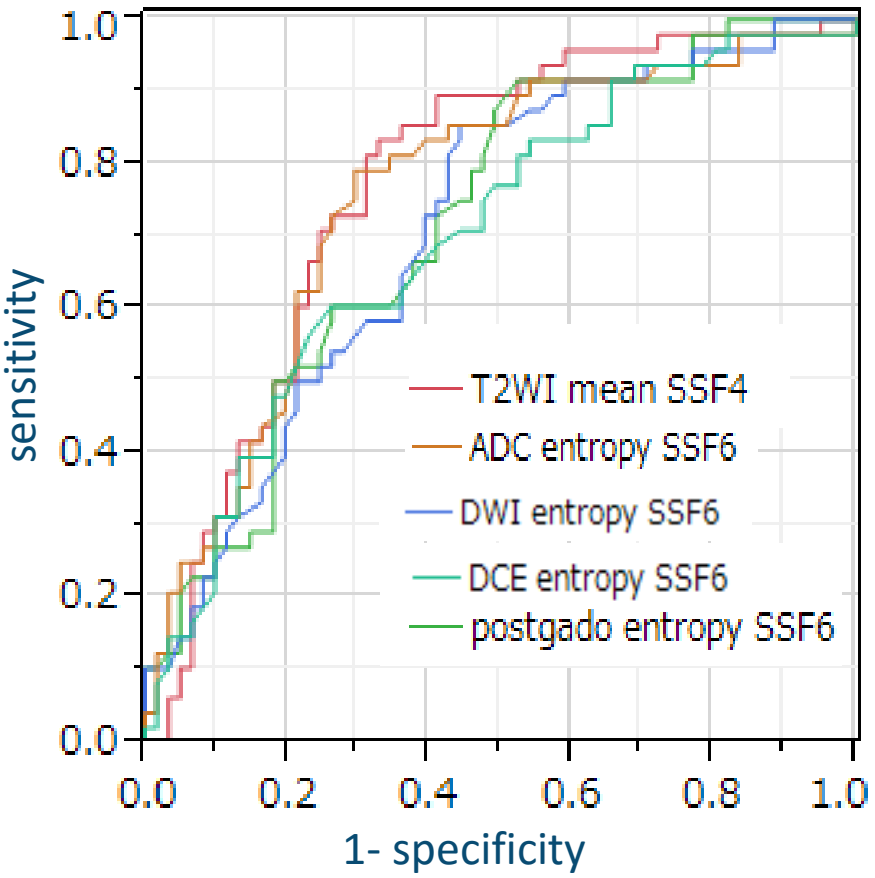


Clinicopathological prognosticators

FIGO stage,
Pathological grade,
LVSI +/-
…etc.

- Diagnostic performance of texture parameters for differentiation of prognosticators

Diagnostic capability of texture parameters for deep myometrium invasion in endometrial cancer patients



	AUC
T2WI mean SSF4	0.7742
ADC entropy SSF6	0.7597
postgado entropy SSF6	0.7208
DWI entropy SSF6	0.7140
DCE entropy SSF6	0.7018

	Naïve Bays (original data)
Accuracy %	78.12
Sensitivity %	85.71
Specificity %	72.22

Ueno. Y, Reinhold. C, et al. [unpublished data]

Materials and Methods
Patient selection

Local database was searched for reports of breast MRI between April 10th 2008 and March 12th 2015 containing the words : neoadjuvant chemotherapy : **N = 256**

Patient who actually had MRI before NAC for breast cancer were elligible: N = **107.** One patient had bilateral lesions. N=108

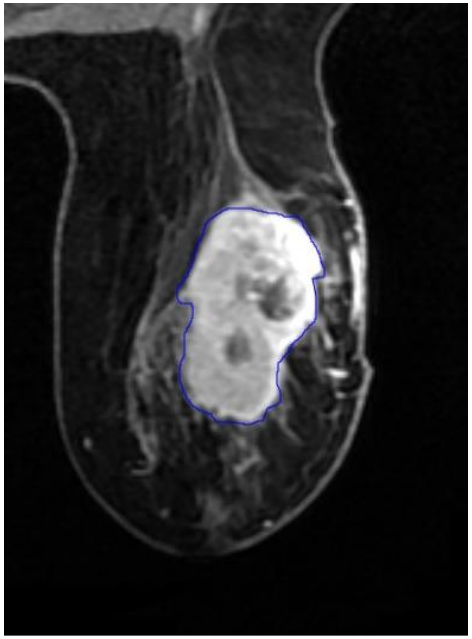
Patients with MRI performed outside (n=6) or substantial artifacts (n=1) or hardly visible lesions (n=2) or multifocal lesions (n=7) were excluded

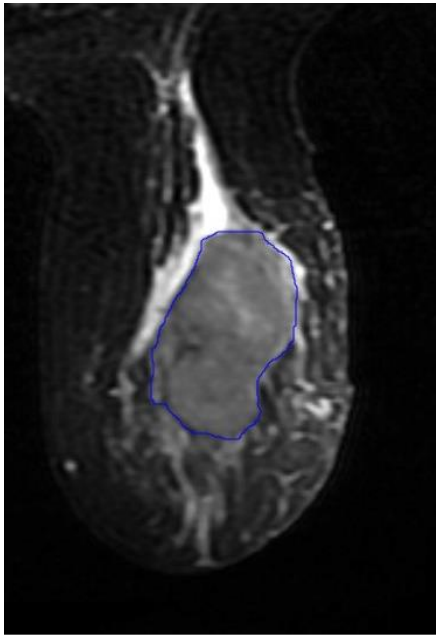
91 patients with 92 lesions elligible for texture analysis on MRI

No pre treatment (N=1) or post Treatment (N=5) histopathologic information

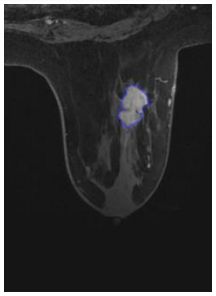
85 patients with 86 lesions finally included in the study

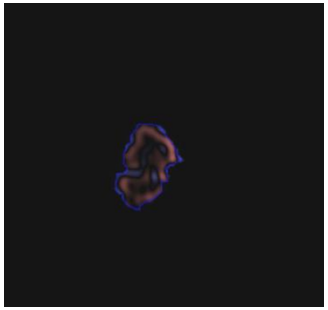
Materials and Methods
Image acquisition

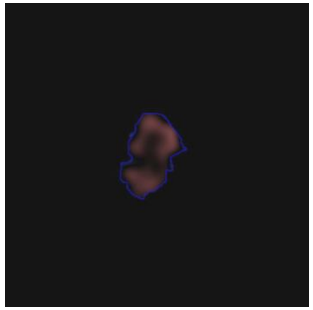


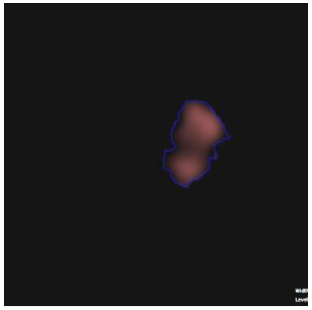


Materials and Methods
Image analysis









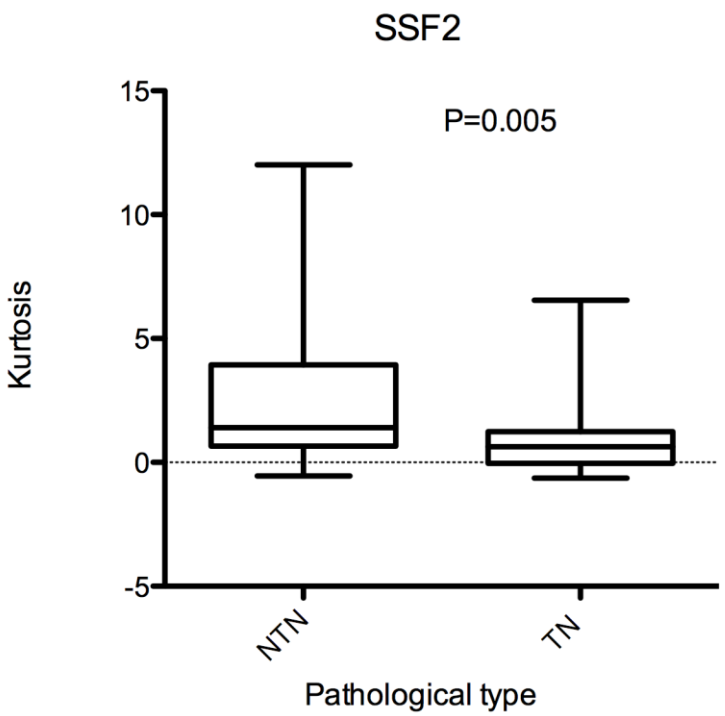
Roiid	Roiname	SSF	TX_sigma	mean	sd	entropy	mpp	skewness	kurtosis	total	algorithm
0	ROI_0	0	0	167.79	46.23	4.97	167.79	-1.02	0.64	1158	TexRAD_BRMRI
0	ROI_0	2	1.2	52.26	112.16	5.82	104.13	-0.05	0.57	1158	TexRAD_BRMRI
0	ROI_0	3	1.8	90.18	108.53	5.84	128.79	-0.16	-0.12	1158	TexRAD_BRMRI
0	ROI_0	4	2.4	127.52	109.34	5.83	154.53	-0.16	-0.39	1158	TexRAD_BRMRI
0	ROI_0	5	3	164.53	115.73	5.89	184.23	-0.1	-0.57	1158	TexRAD_BRMRI
0	ROI_0	6	3.6	200.52	124.03	5.94	212.82	-0.02	-0.68	1158	TexRAD_BRMRI

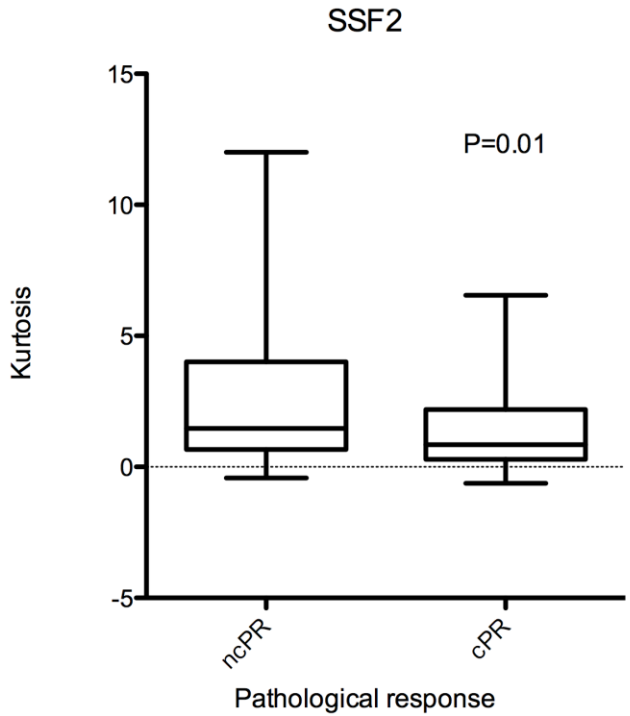
e value	NTN (N=70)	TN (N=16)	*P* value	NC PR	CPR	*P* value
MRI						
SSF0	1.14 [0.33; 2.30]	1.04 [0.08; 1.56]	*0.32*	**1.56** [0.41; 3.30]	**0.69** [0.07; 1.34]	*0.008***
SSF2	**1.4** [0.7; 3.9]	**0.63** [-0.04; 1.24]	*0.005***	**1.47** [0.67; 4]	**0.85** [0.29; 2.19]	*0.013**
SSF3	0.69 [0.02; 2.06]	0.37 [-0.29; 1.56]	*0.198*	**0.95** [0.04; 2.21]	**0.46** [-0.12; 0.48]	*0.036**
SSF4	0.28 [-0.16; 1.64]	-0.12 [-0.41; 0.78]	*0.12*	**0.29** [-0.11; 1.71]	**0.01** [-0.49; 0.83]	*0.042**
SSF5	0.08 [-0.36; 1.13]	-0.14 [-0.51; 0.11]	*0.052*	0.05 [-0.36; 1.34]	0.00 [-0.58; 0.24]	*0.12*
SSF6	**-0.03** [-0.53; 0.73]	**-0.40** [-0.75; -0.14]	*0.024**	**-0.10** [-0.42; 0.92]	**-0.30** [-0.82; 0.03]	*0.02**
CE MRI						
SSF0	0.12 [-0.47; 0.29]	0.23 [-0.37; 1.18]	*0.51*	0.03 [-0.43; 0.73]	0.58 [-0.45; 0.18]	*0.15*
SSF2	**0.43** [0.0; 1.02]	**-0.28** [-0.64; 0.52]	*0.004***	0.37 [0.601; 1.03]	0.14 [0.41; 0.67]	*0.085*
SSF3	0.03 [-0.33; 0.64]	-0.24 [-0.63; 0.47]	*0.11*	0.03 [0.04; 2.21]	0.19 [-0.28; 0.66]	*0.089*
SSF4	-0.07 [-0.44; 0.40]	-0.07 [-0.57; 0.18]	*0.32*	-0.06 [-0.44; 0.46]	-0.14 [-0.48; 0.20]	*0.16*
SSF5	-0.16 [-0.49; 0.24]	0.08 [-0.43; 0.44]	*0.44*	-0.13 [-0.46; 0.36]	-0.10 [-0.57; 0.28]	*0.52*
SSF6	-0.29 [-0.62; 0.19]	-0.13 [-0.60; 0.40]	*0.81*	-0.20 [-0.62; 0.46]	-0.40 [-0.861; 0.04]	*0.17*

T2

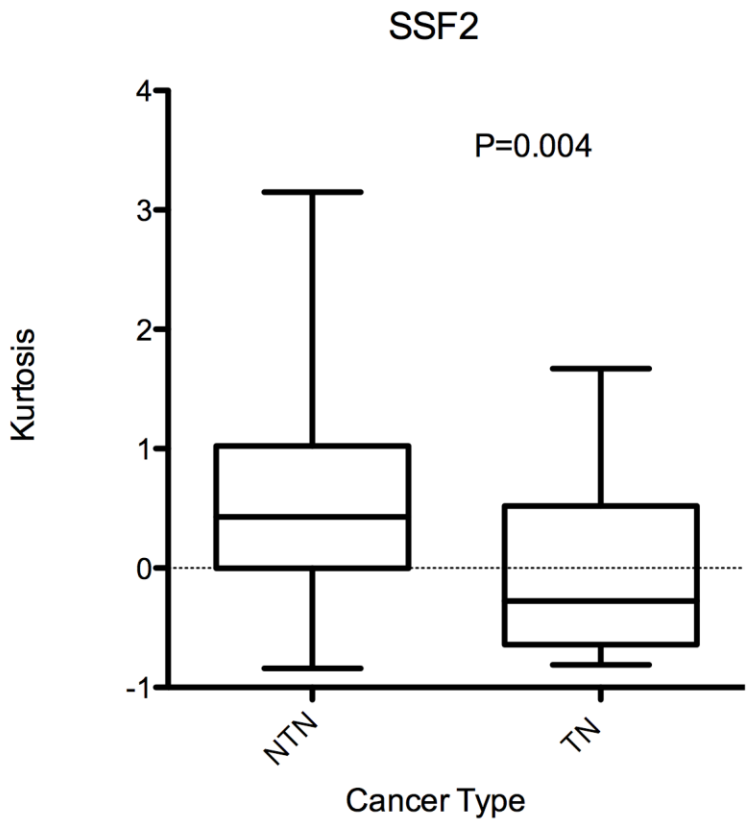
DCE

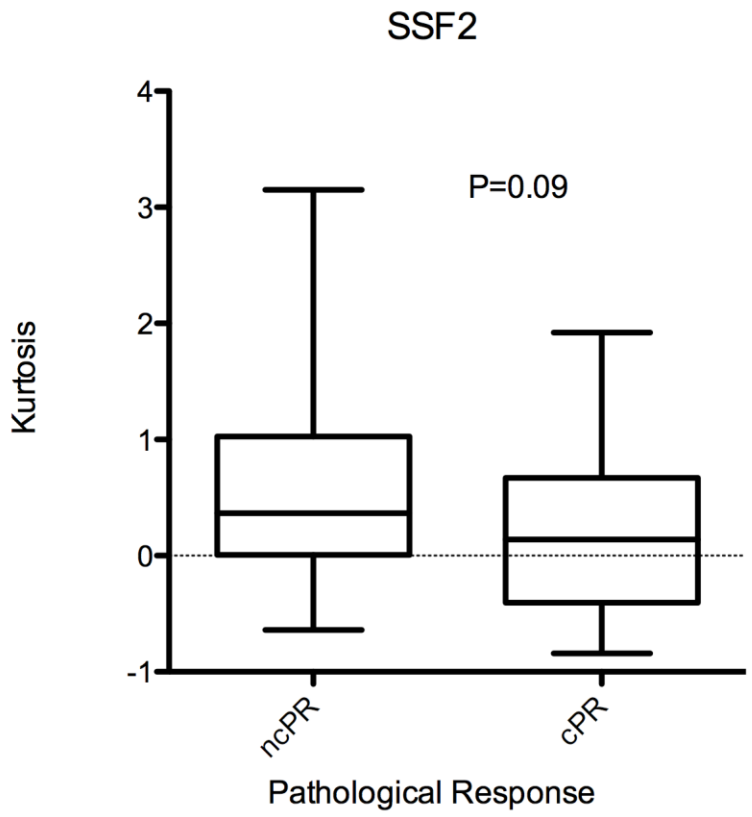
Results: T2


SSF2
P=0.005
Kurtosis
15
10
5
0
-5
NTN
TN
Pathological type

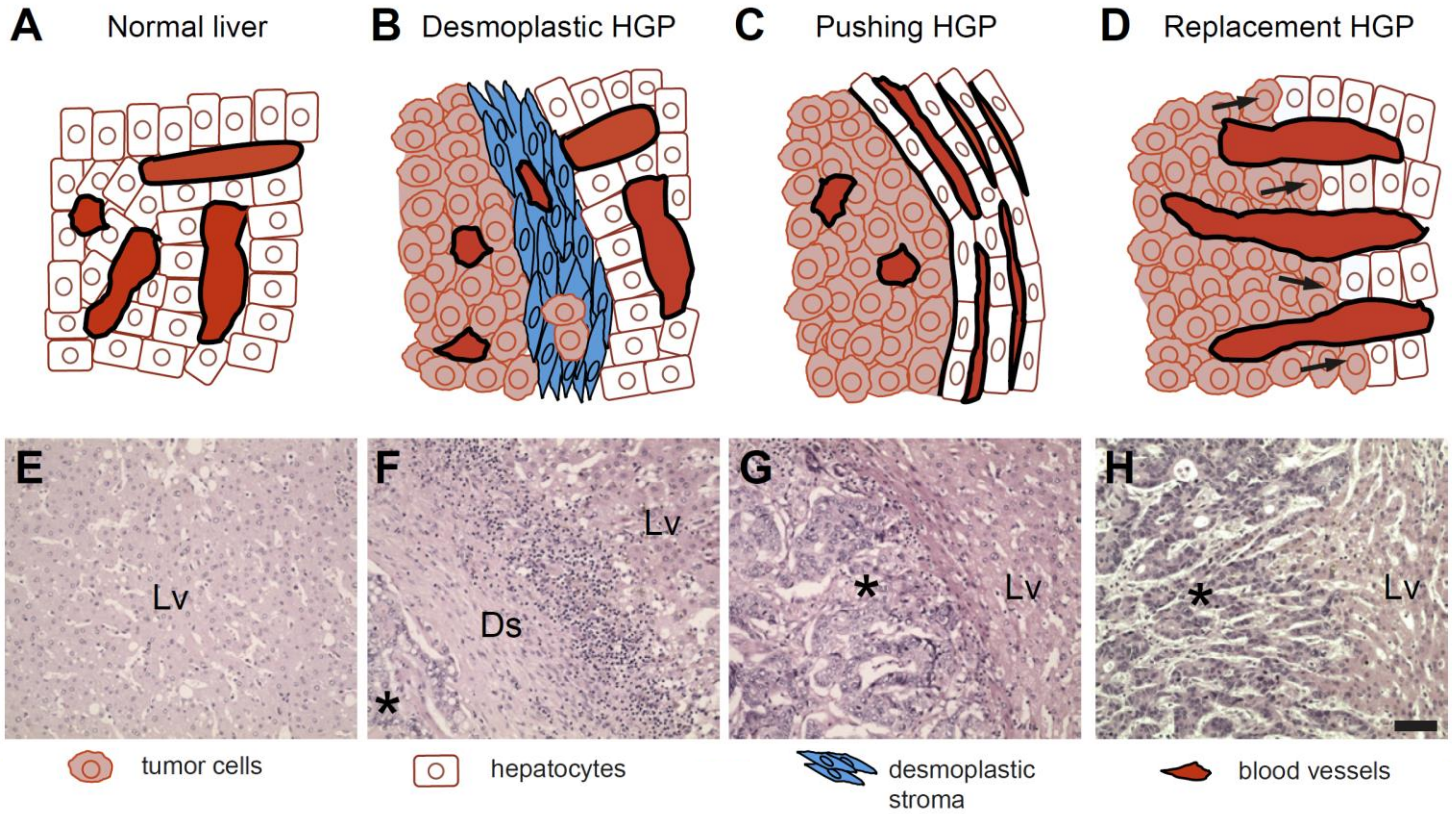

SSF2
P=0.01
Kurtosis
15
10
5
0
-5
ncPR
cPR
Pathological response

Results: DCE


SSF2
P=0.004
Kurtosis
4
3
2
1
0
-1
NTN
TN
Cancer Type

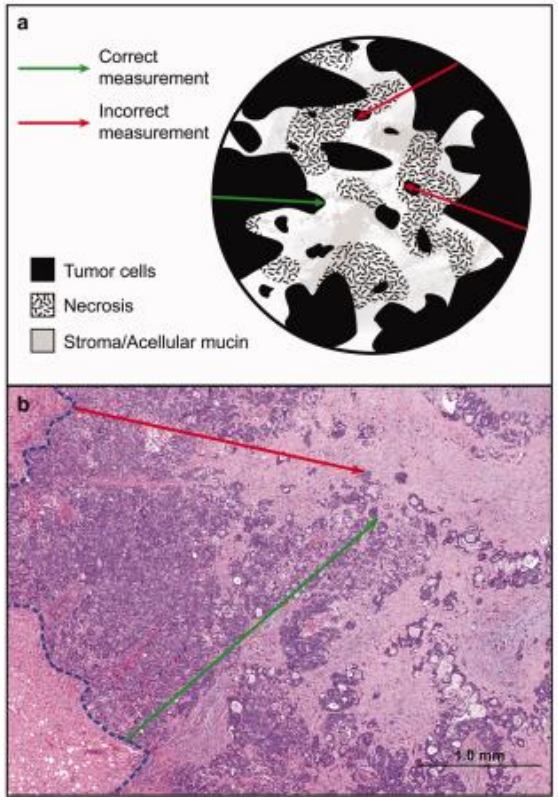

SSF2
P=0.09
Kurtosis
4
3
2
1
0
-1
ncPR
cPR
Pathological Response

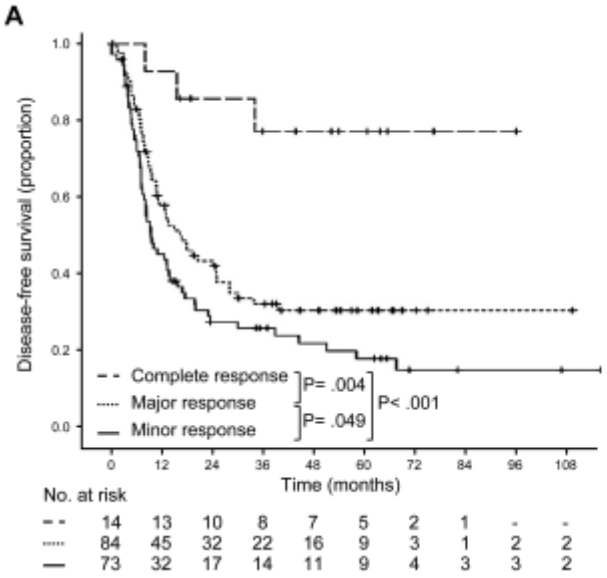
HGP of liver metastases from CRC

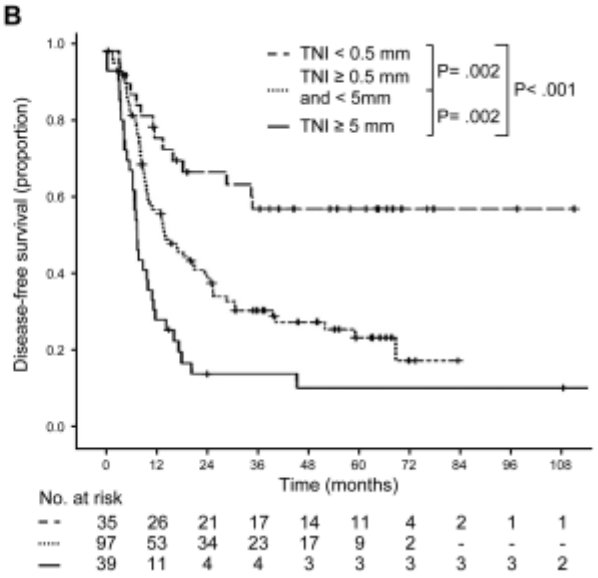


Adapted from manuscript of Reynolds A. etc.

Tumor thickness at the tumor-normal liver interface as independent predictors of disease-free survival after preoperative chemotherapy and surgery for colorectal liver metastases

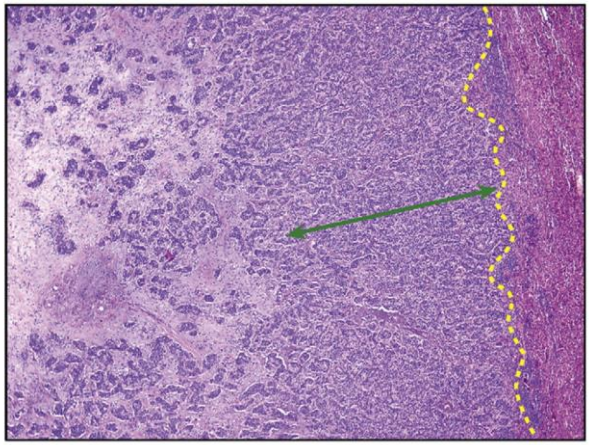


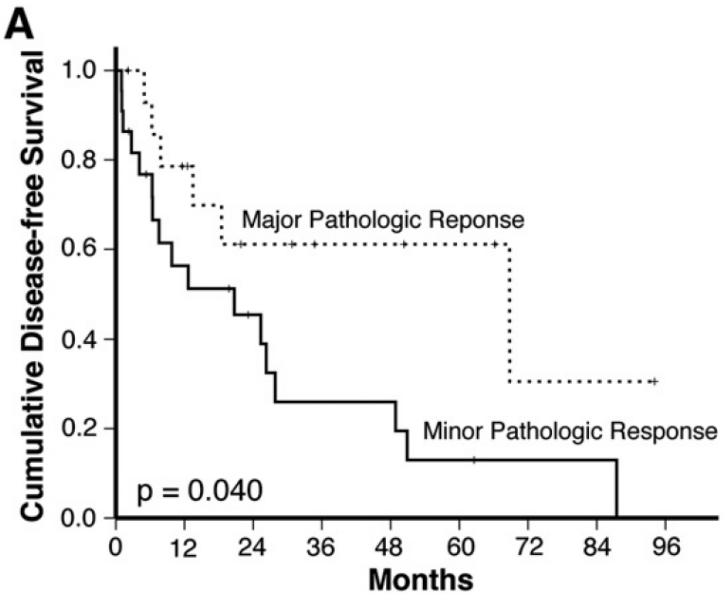


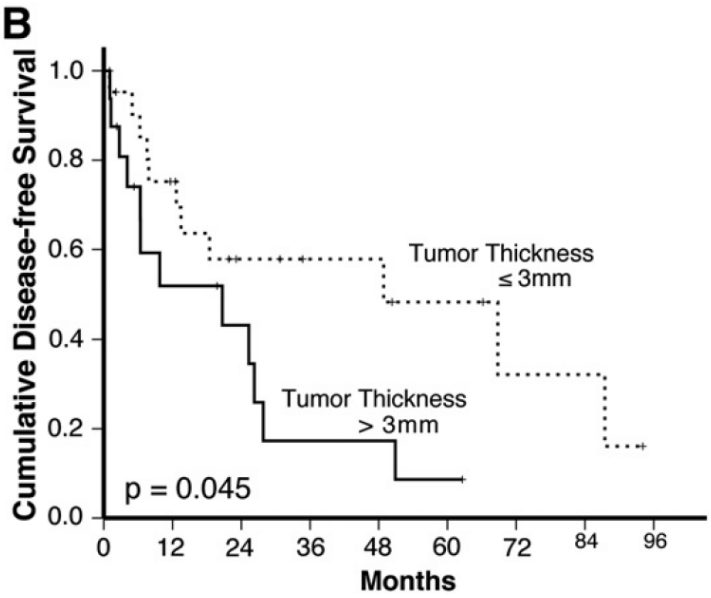


Cancer
Volume 119, Issue 15, pages 2778-2788, 23 APR 2013 DOI: 10.1002/cncr.28097
http://onlinelibrary.wiley.com/doi/10.1002/cncr.28097/full#cncr28097-fig-0001

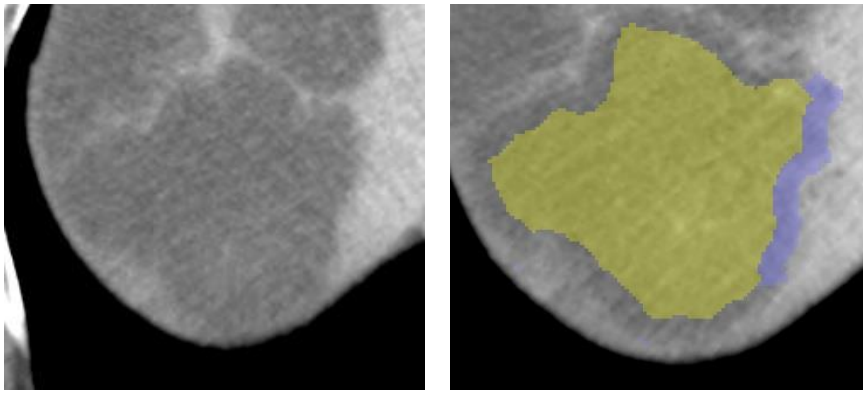
Tumor to normal tissue interface

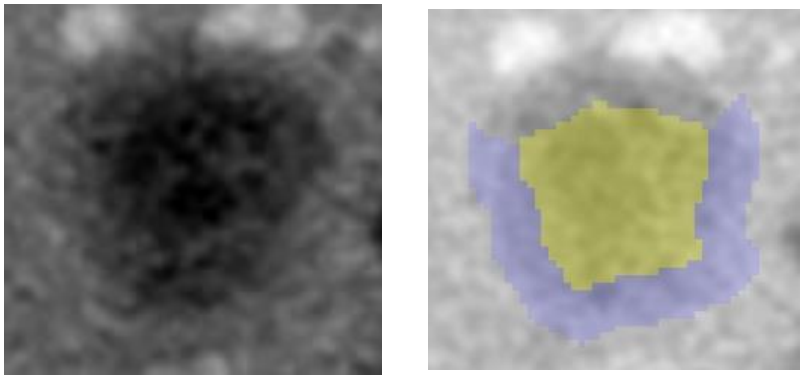




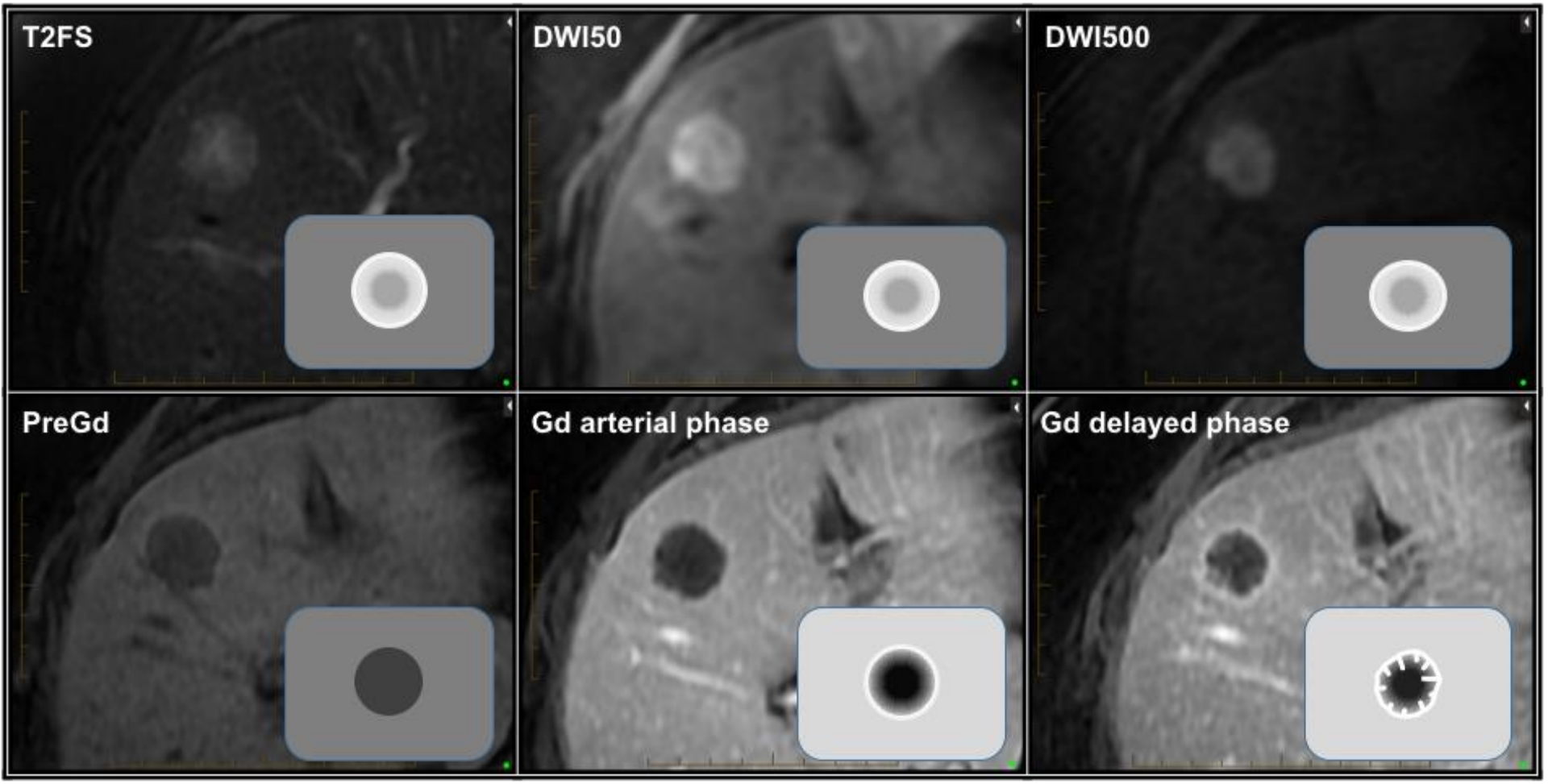


Boundaries of the tumor need a specific treatment

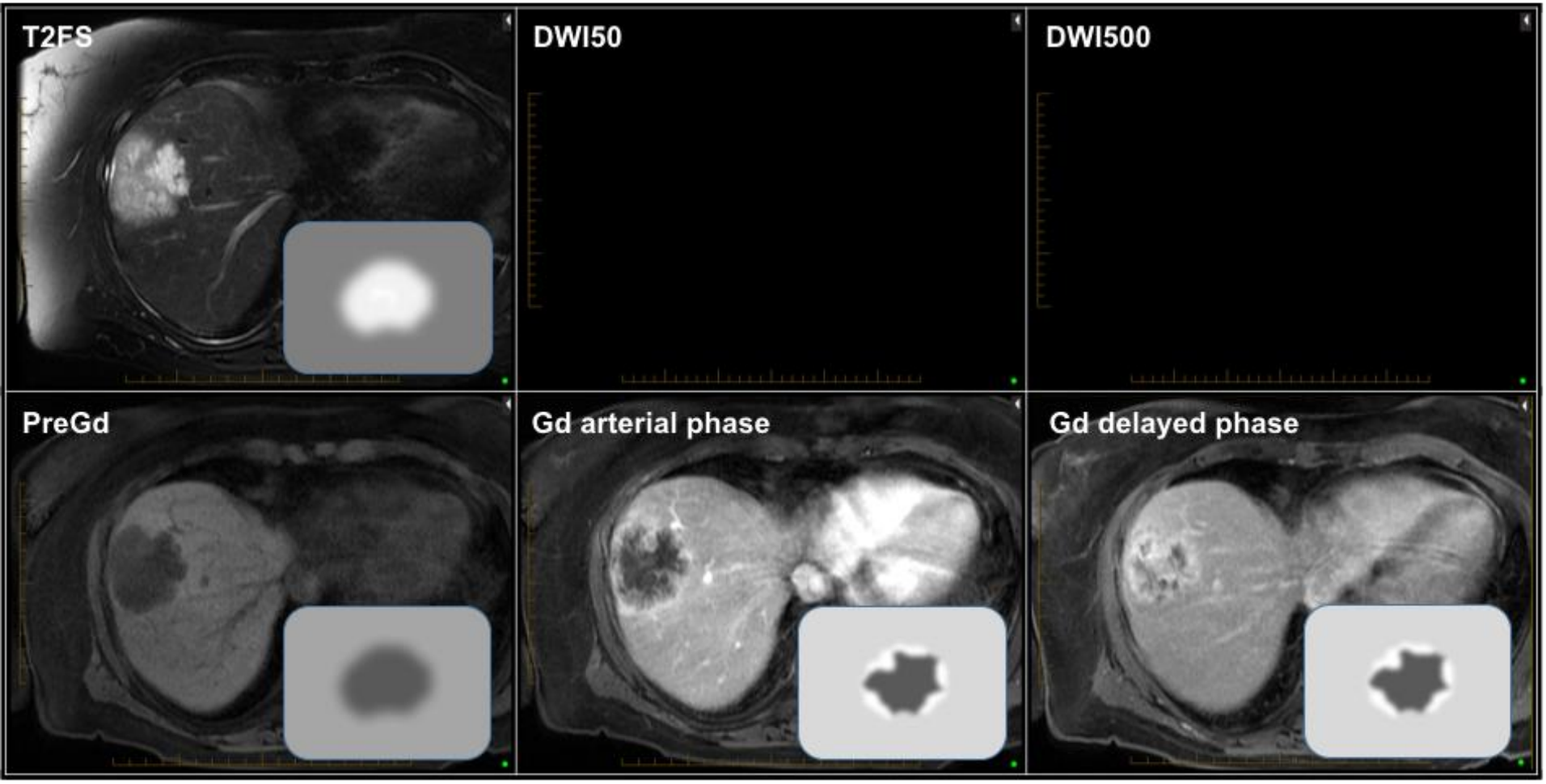




Desmoplastic pattern (C-D) – well defined border, thin irregular curvas and septa, normal liver parenchyma.



Replacement pattern (GJ) – poorly defined border, thick/irregular outline



Conclusion

- Spatially explicit mapping of tumor regions, for example by superimposing multiple imaging sequences, may permit patient specific characterization of intratumoral evolution and ecology, leading to patient- and tumorspecific therapies

- The future is mining large collections of image metadata to improve precision of practice

McGill