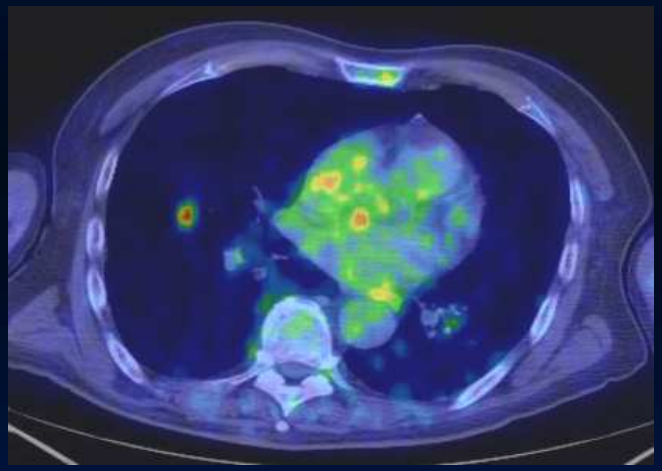
MOLECULAR METABOLIC IMAGING FOR RADIOTHERAPY PLANNING

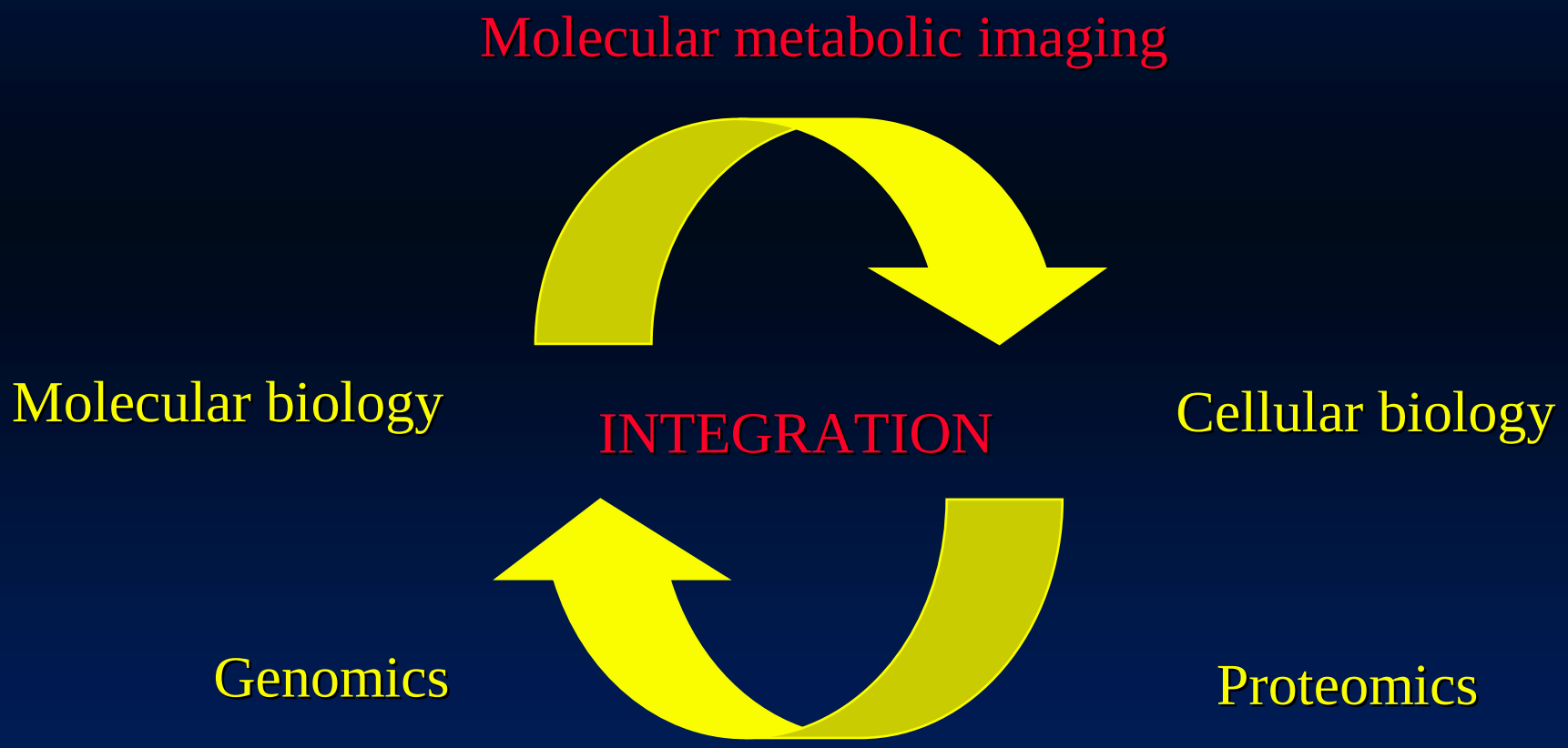


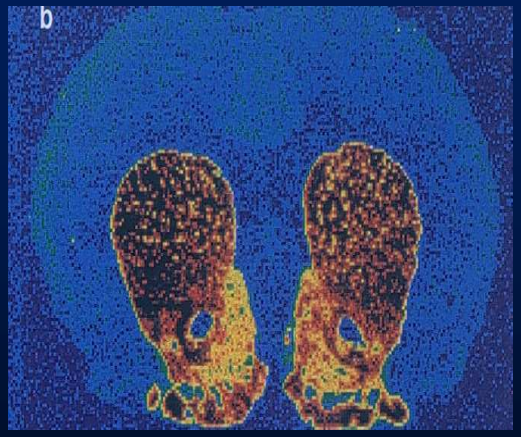
Isabella Castiglioni

IBFM-CNR,

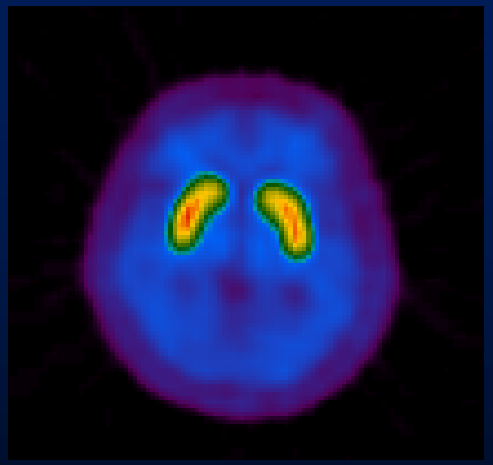
Scientific Institute H.S.Raffaele, University of Milan-Bicocca

POST-GENOMIC MOLECULAR METABOLIC IMAGING

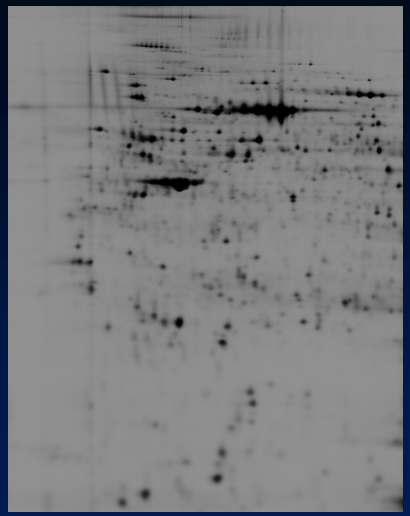


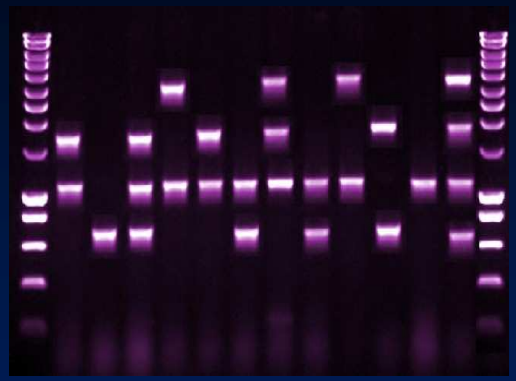


EX-VIVO
HISTOPATHOLOGY



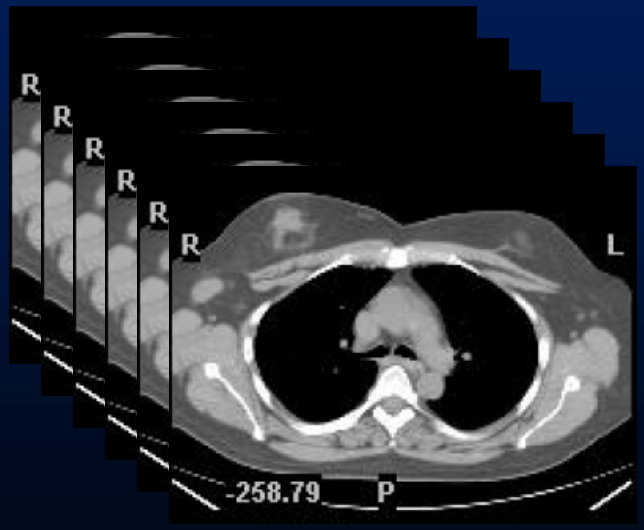
IN-VIVO
HISTOPATHOLOGY

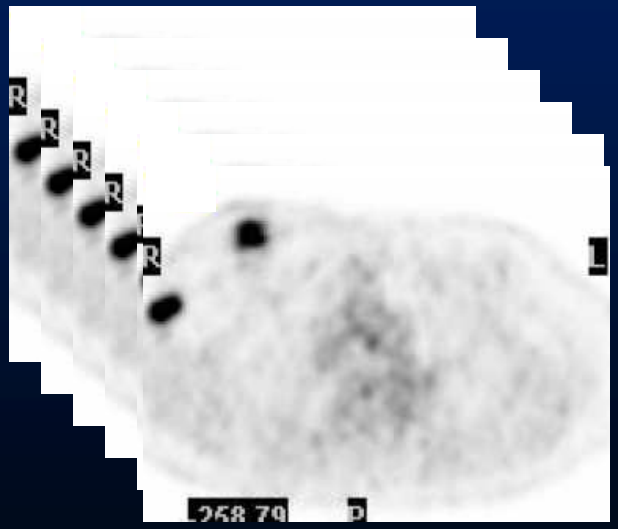


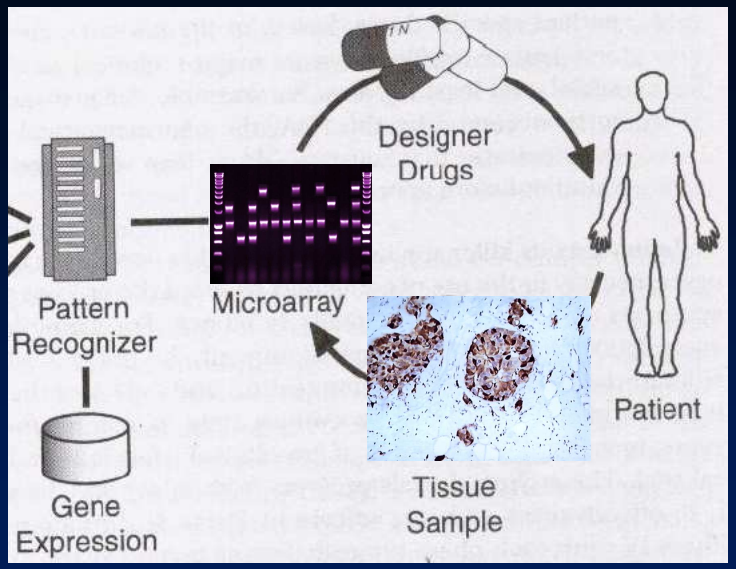


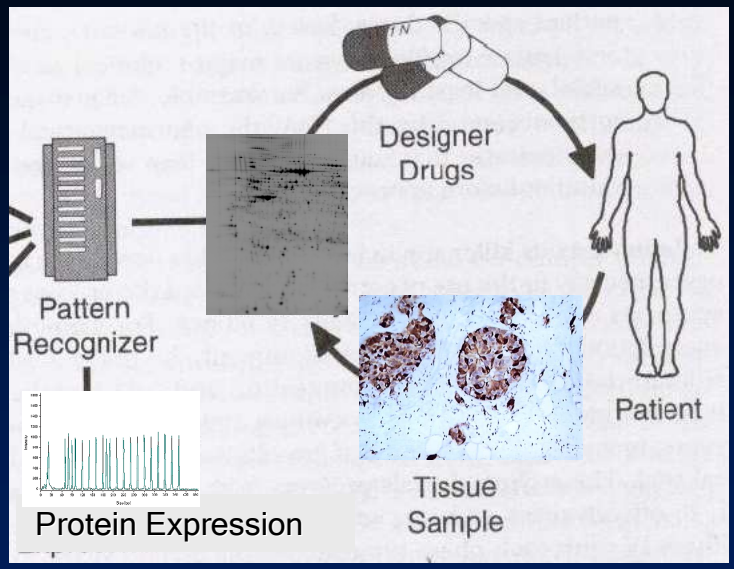
IN-VITRO HISTOPATHOLOGY

INTEGRATED PROTOCOLS

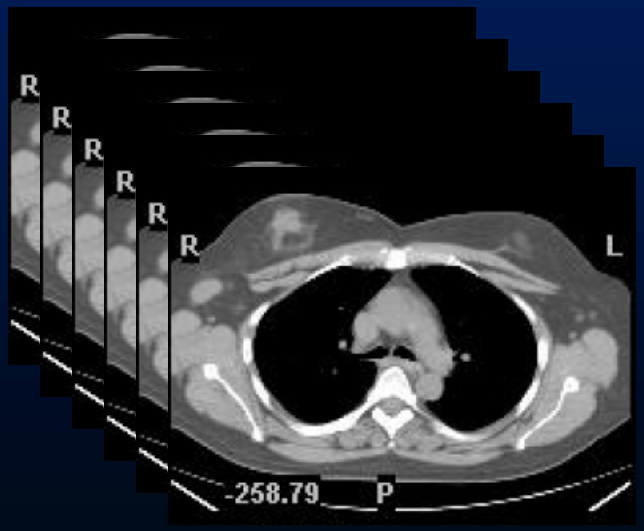


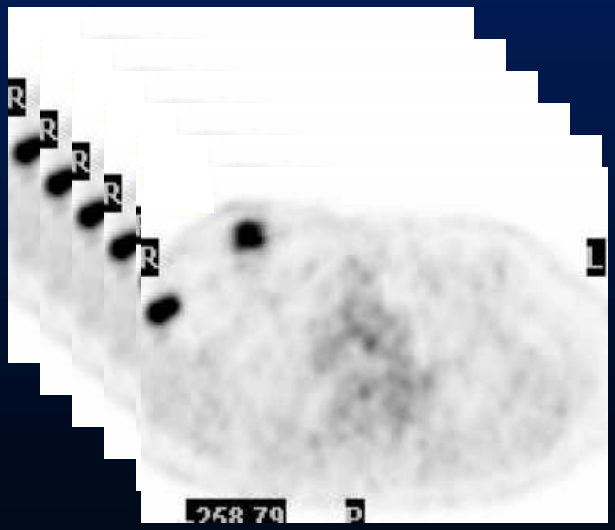




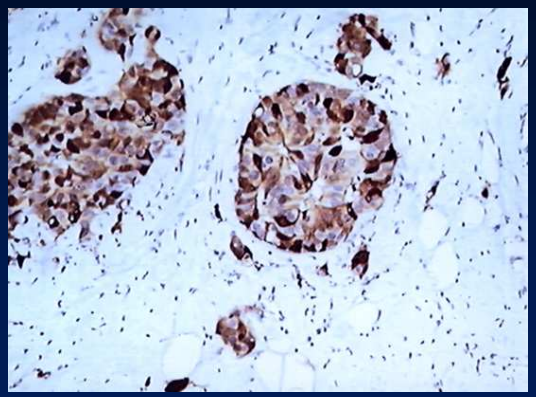


DATA TO BE INTEGRATED



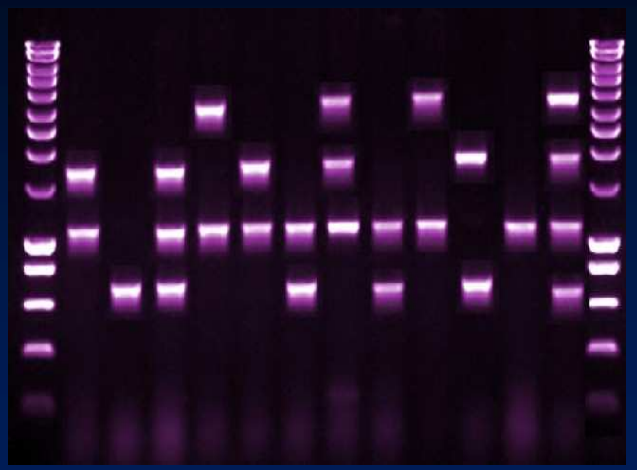


^{18}F-PET/CT glucose metabolism for breast carcinoma



pTnm

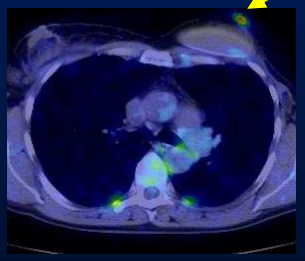
overexpressed proteins

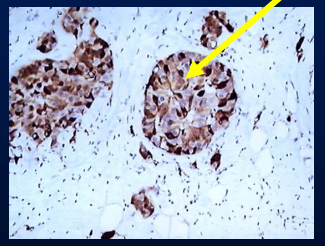


modified genes

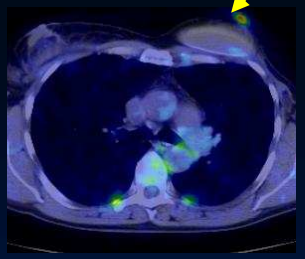
INTEGRATION

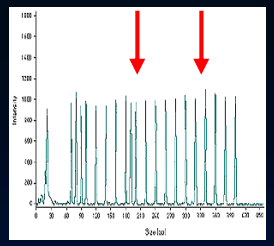
PET + vs Cancer aggressiveness



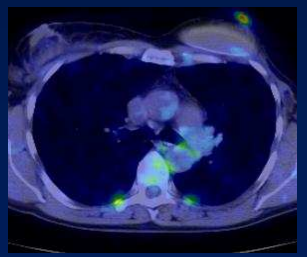


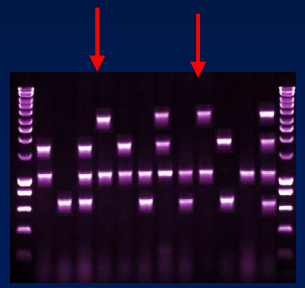
PET + vs Protein expression levels





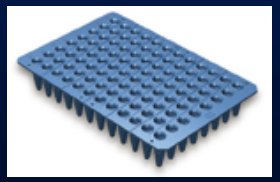
PET + vs modified genes



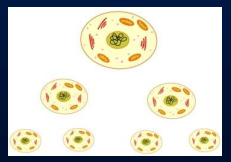


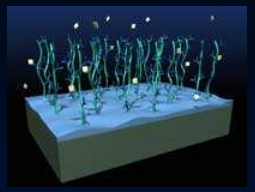
THE CHALLENGE

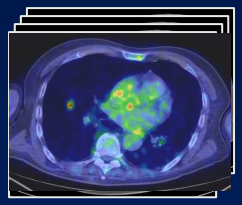
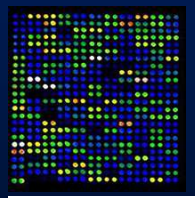
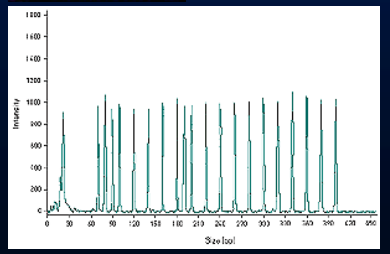
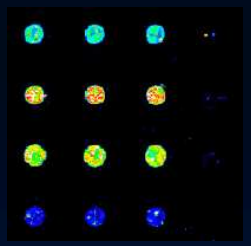
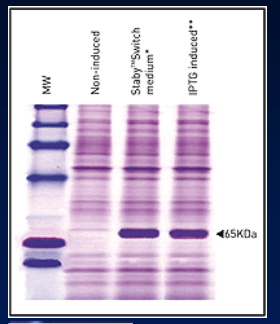
To determine genetic/biochemical characteriscs in vivo & non invasively

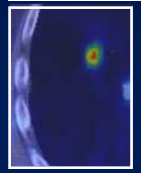






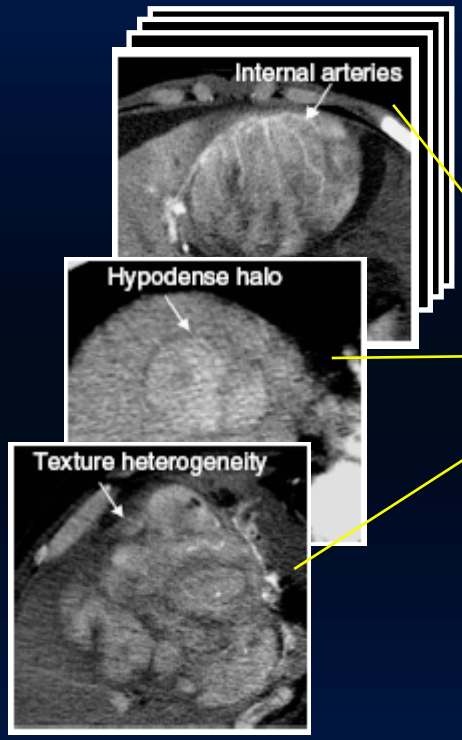








Segal E. et al, Nature Biotecnology, June 2007

A correlation exixts between CT traits and gene expression in HCC cells

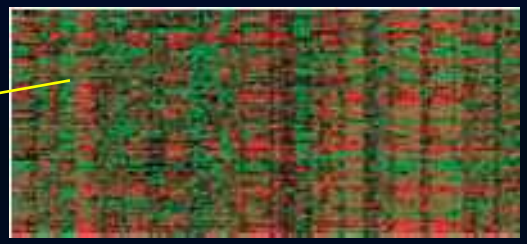
hepatic syntetic functions
cellular proliferation
prognostic factors



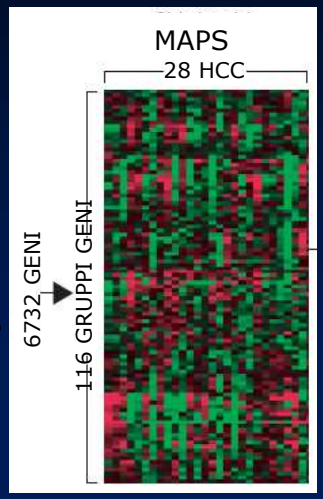
138 “traits” CT

Combinations, logical relations

AND OR



6732 genes

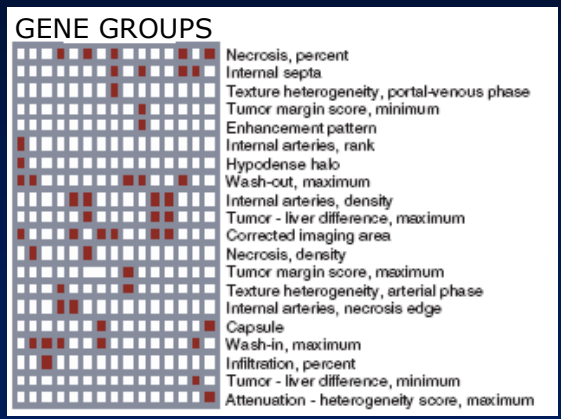


RESULTS

28 infomative HCC traits

116 groups of genes with coherent variations

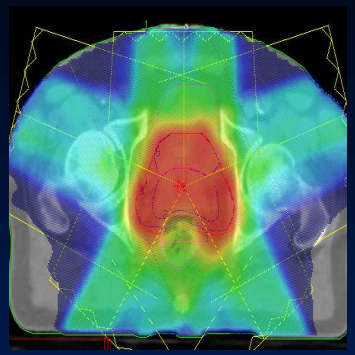
Every gene group is associato con associated with a combination of traits



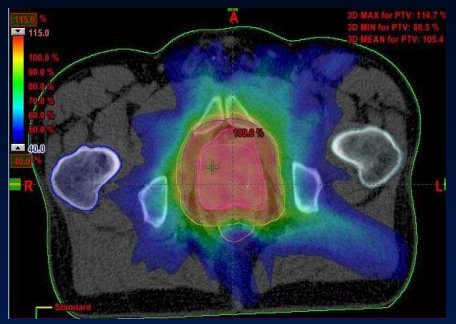
POST-GENOMIC RADIOTHERAPY

RADIOTHERAPY & HIGH TECH

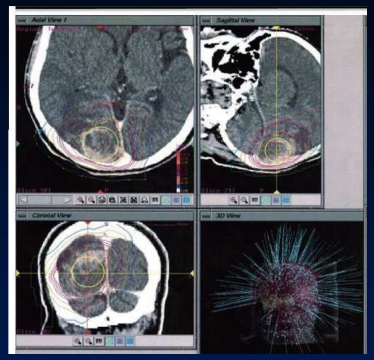
- **High conformal radation dose**
- **Steep dose gradients**



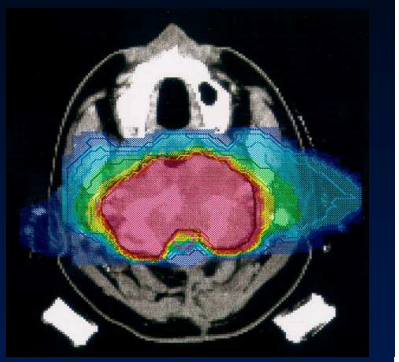
IMRT



VMAT



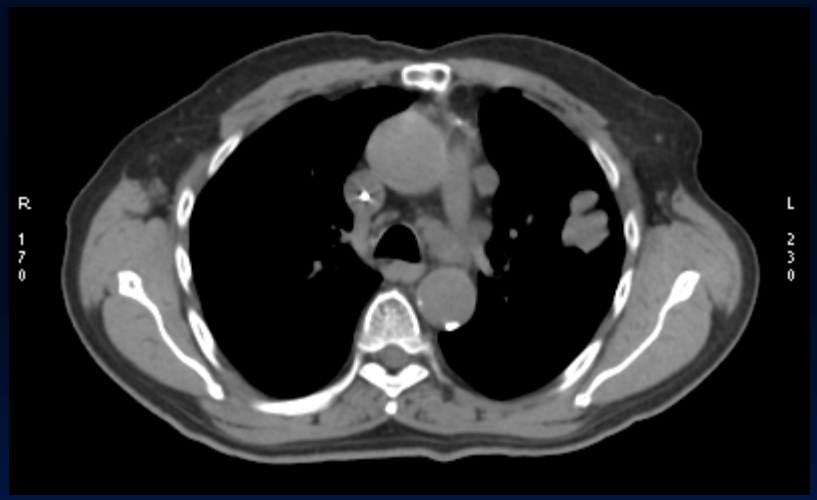
CK

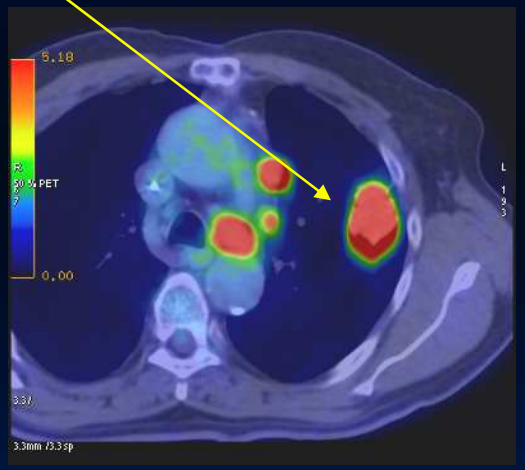


HIT

MOLECUALAR METABOLIC IMAGING for RADIOTHERAPY PLANNING

BTV





^{18}F-FDG PET

Molecular metabolic imaging: 18F-FDG PET

- Efficacy of 18F-FDG PET in a wide variety of malignant tumours
- Sensitivity, specificity and accuracy ~ 90%

- Better patient management and changes in the treatment plans in 25–50% of the cases

MOLECULAR METABOLIC IMAGING & HIGH TECH

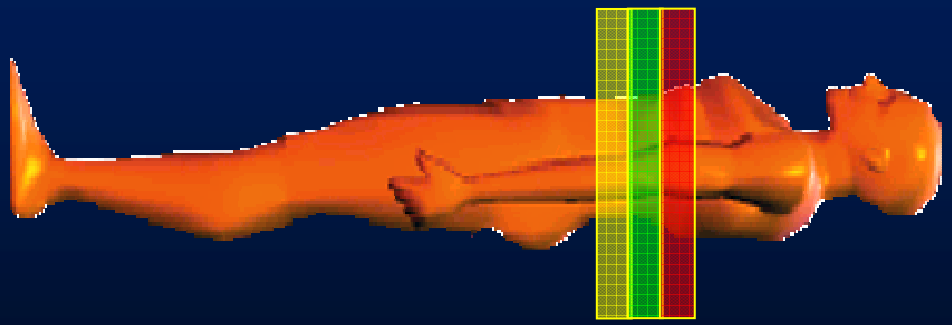
Compensated lesion motion → 4D PET/CT gating

Increased spatial resolution (up to 3-4mm) → High-tech PET-CT systems & improved reconstruction alghorithms

↓

Better BTV definition

4D CT-PET Data Acquisition



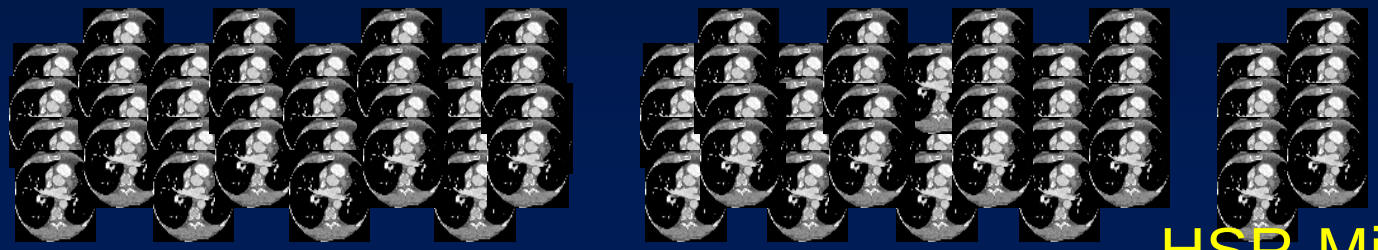
RPM Signal

CT Acq.

Scan First Position

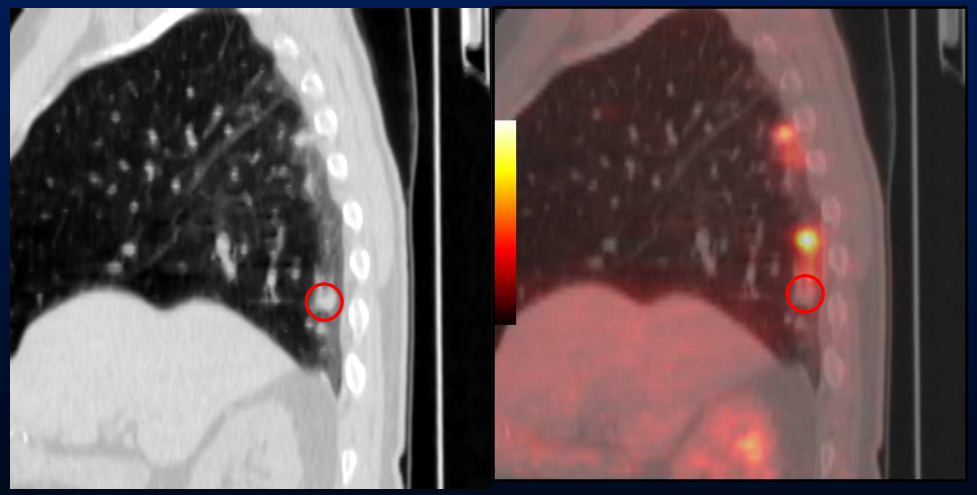
Scan Second Position

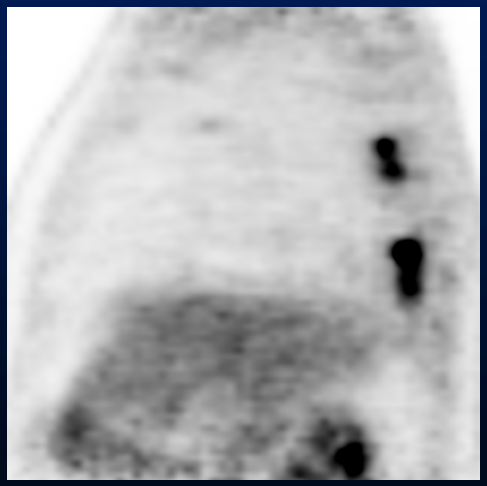
Scan



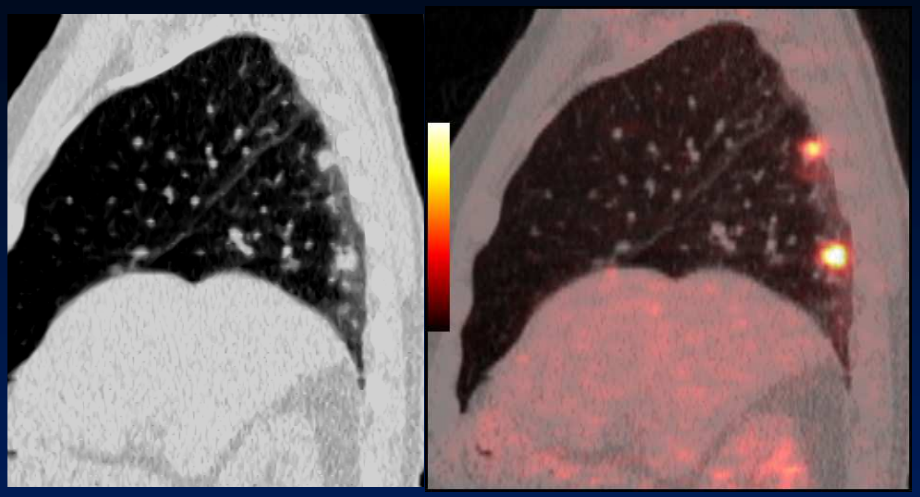
HSR-Milano

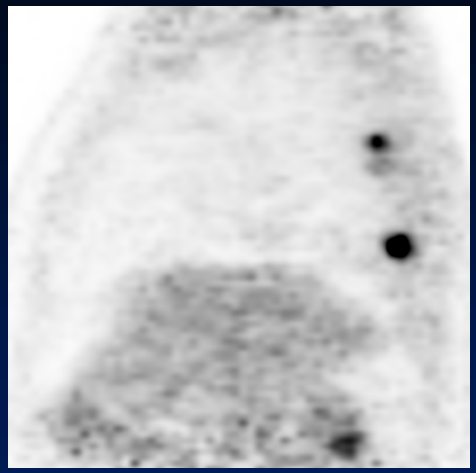
Conventional PET/CT





4D-PET/CT





HSR-Milano

BTV from PET images

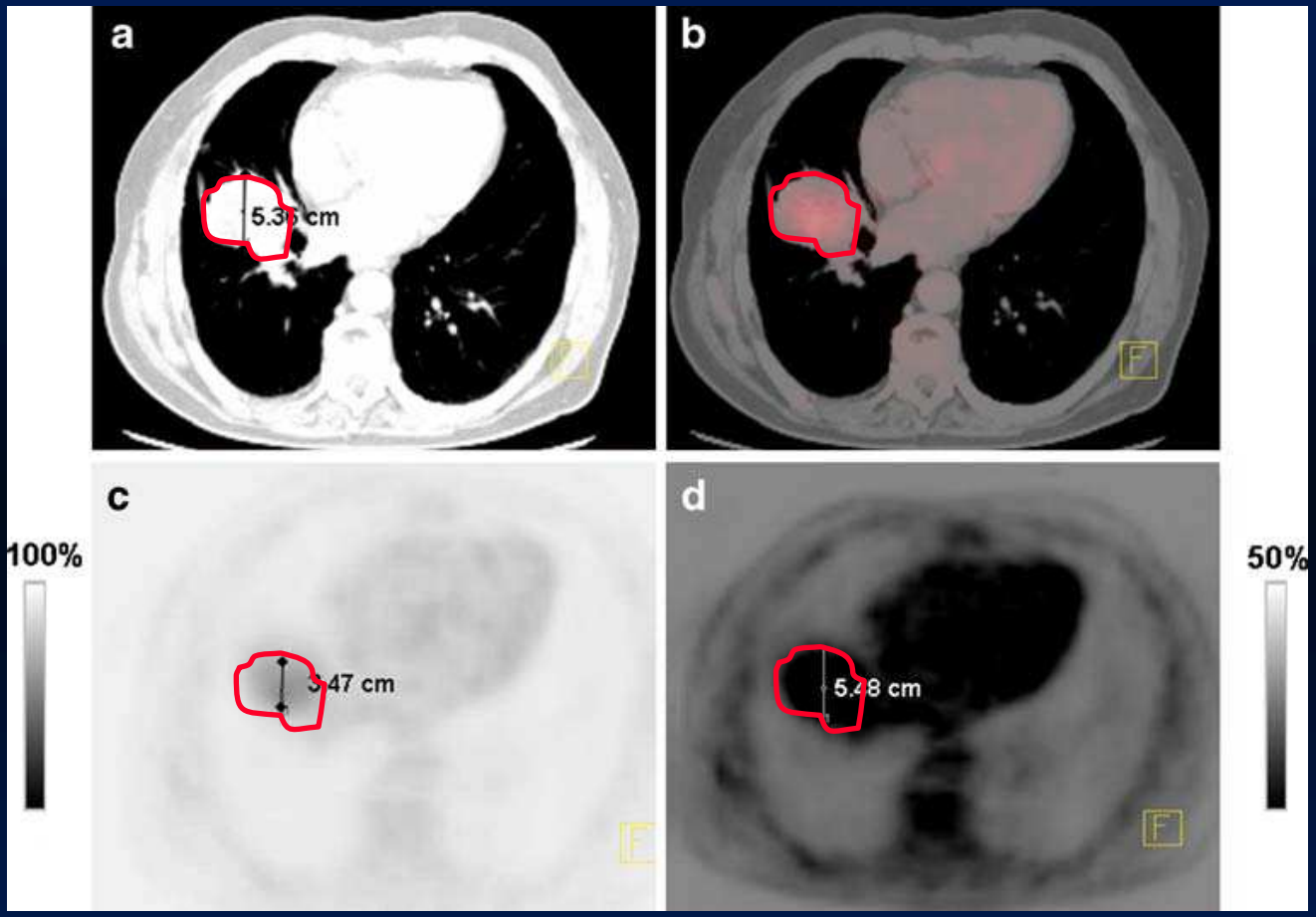
Segmentation techniques

Qualitative methods → Manual contourning

Quantitative methods → Semi-auto/image contouring

More reproducible, affordable

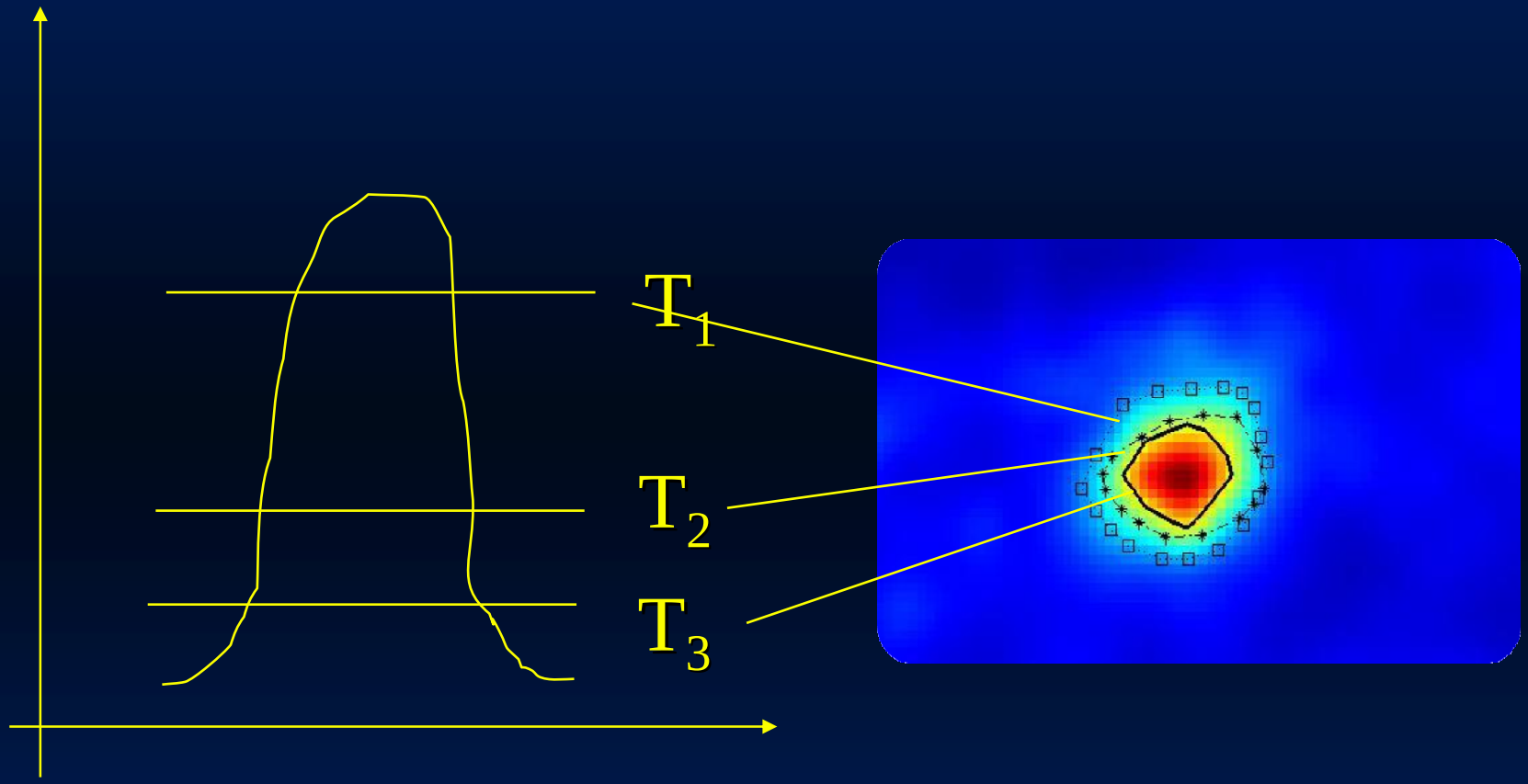
Qualitative methods



- Operator-dependent, image-modality dependent,image sampling dependent

Quantitative methods

Thresholding methods



$$\text{lesion} = T[I(x)] = \begin{cases} 1, & I(\mathbf{x}) \geq T \\ 0, & I(\mathbf{x}) < T \end{cases}$$

Thresholding methods

- absolute

~~T = 2,5 (SUV)~~

- vs SUV

$T = a + b \times SUV_{mean}$ Black et al., 1990

- vs V

$T = a + b \times \log_{10}(V) + q$ Biehl et al., 2006; Ford et al., 2006

2d) vs LB (adaptative)

$T = a + b \times 1/LB$ — Erdi et al.,1997

$T = \text{Contrast level} \times (L_{max} - B_{mean}) + B_{mean}$ — Drever et al., 2006

$T = a \times L_{mean\text{-}70\%} + B_{mean}$ — Nestle et al., 2005

$T = (a \times SUV_{mean\text{-}70\%} + b \times B_{mean})/SUV_{max}$ — Schaefer et al., 2008

$T = b /LB + c$ — Daisne et al. , 2003

2d) iterative

$T = a/V + b /LB + c$ — Jentzen et al., 2007

$T = a_0 + \exp[a+b/V + c\log V]$ — Nehmeh et al., 2009

Variational

Geometric function of surface deforming under internal (surface bending characteristics) and external (directional gradients) forces

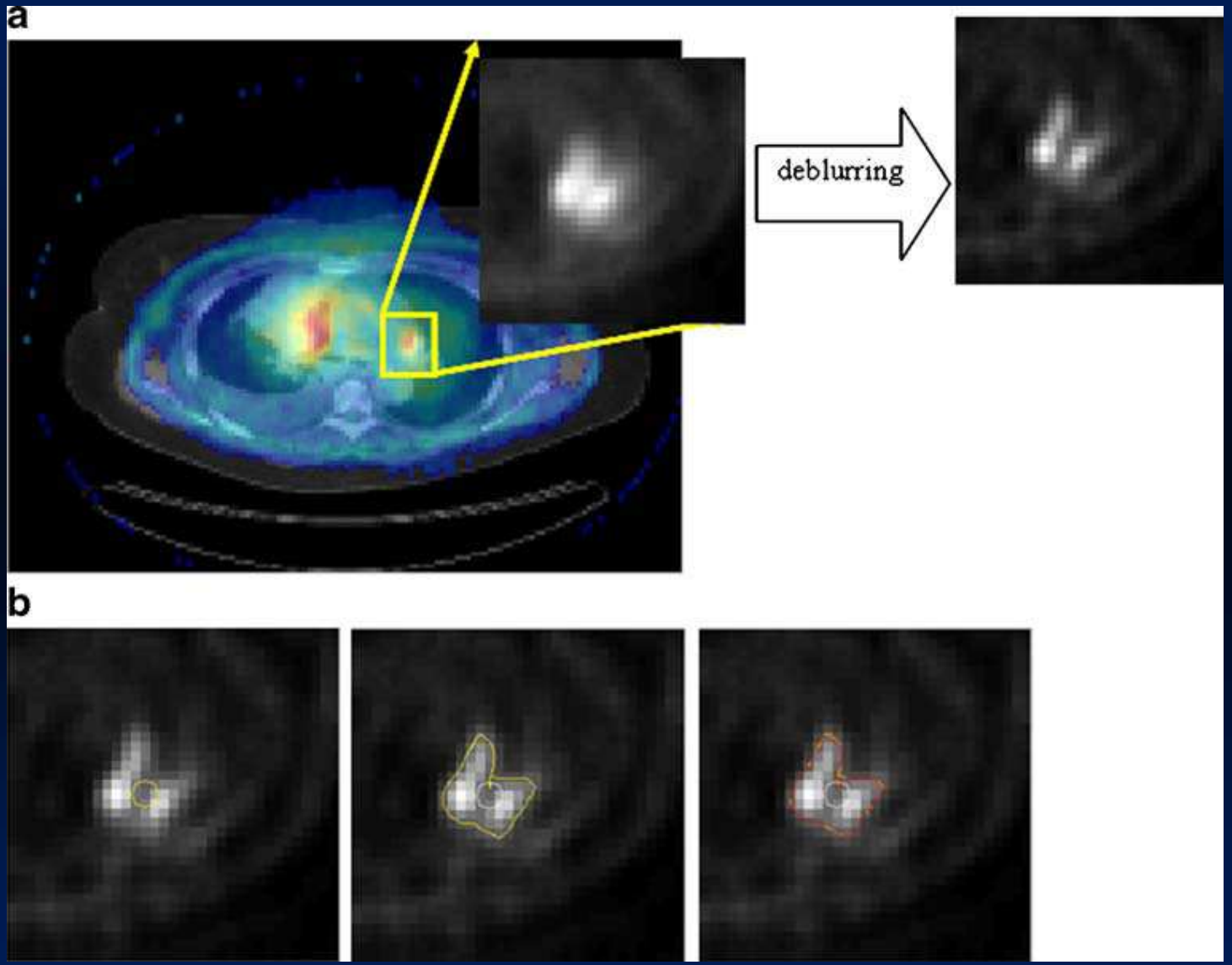
- edge detectors (Sobel operator) — Drever et al. , 2007

- ridge detectors (Watershed Transform, WT) — Drever et al. , 2007

- deformable active contour models (snakes) — El Naqa et al. , 2007; Li et al., 2008

Gradient Vector Flow (GVF), iterative evolutionary Poisson Differerential Equation (up to the balance between internal and external forces) (e.g. level set method, deblurring alghorithm)

level set method



1it 40 it convergence

Li et al. , 2008

Learning methods

learning task aims to discriminate L from B based on a set of extracted features

Supervised

Training sets of labelled images
+ unknown samples

Unsupervised

Unknown samples

Belhassen et al. , 2010

Classifiers

k-nearest neighbour (KNN)
Artificial neural network (ANN)
Support vector machine (SVM)

Clustering

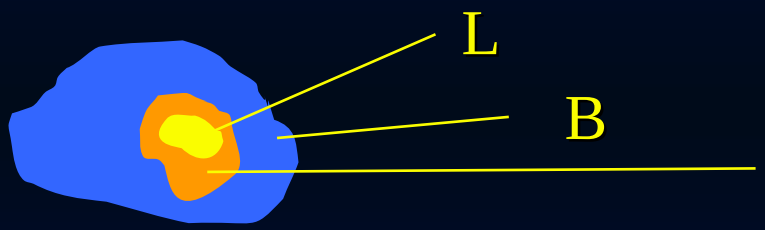
k-means
Fuzzy C-means (FCM)
Expectation maximization (EM)

Stocastic modeling

The intensity distribution of L and B are statistically different

Gaussian mixture model (GMM)

3 classes



EM (maximum likelihood) estimates the volumes by the probability of each voxel to belong to one of the three class

Hatt et al., 2010

Validation of BTV in clinical studies is crucial and still limited

by histological specimens

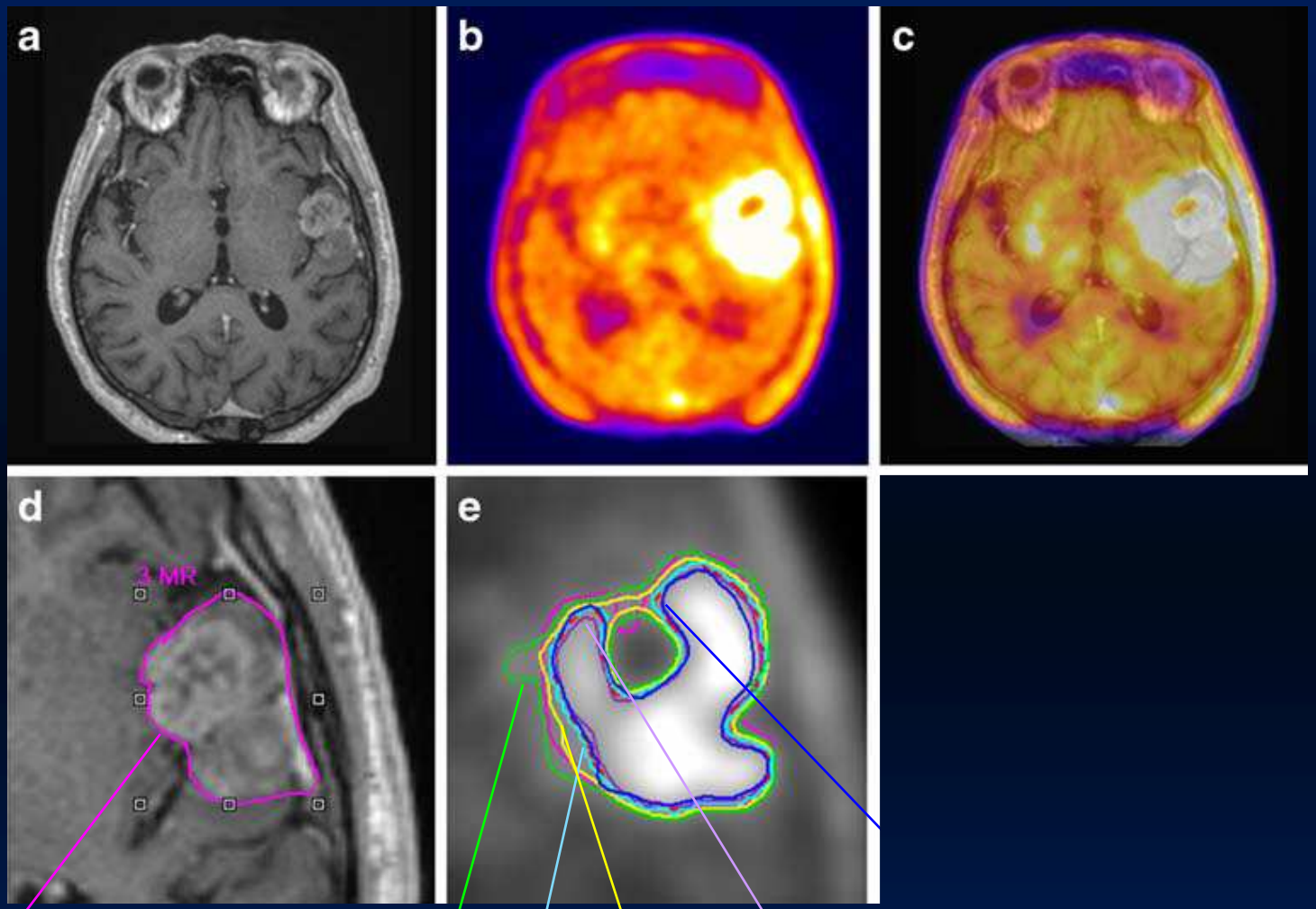
- PET reduces GTV
- PET BTV is more accurate with respect to CT/MRI GTV

Daisne et al., 2004

MRI

^{18}F-FET PET

MRI-PET



GTV_{MRI}

$BTV_{40\%}$

BTV_{man}

BTV_{LB}

$GTV_{2,5}$

BTV_{grd}

Vees et al., 2009

What is the best PET BTV?

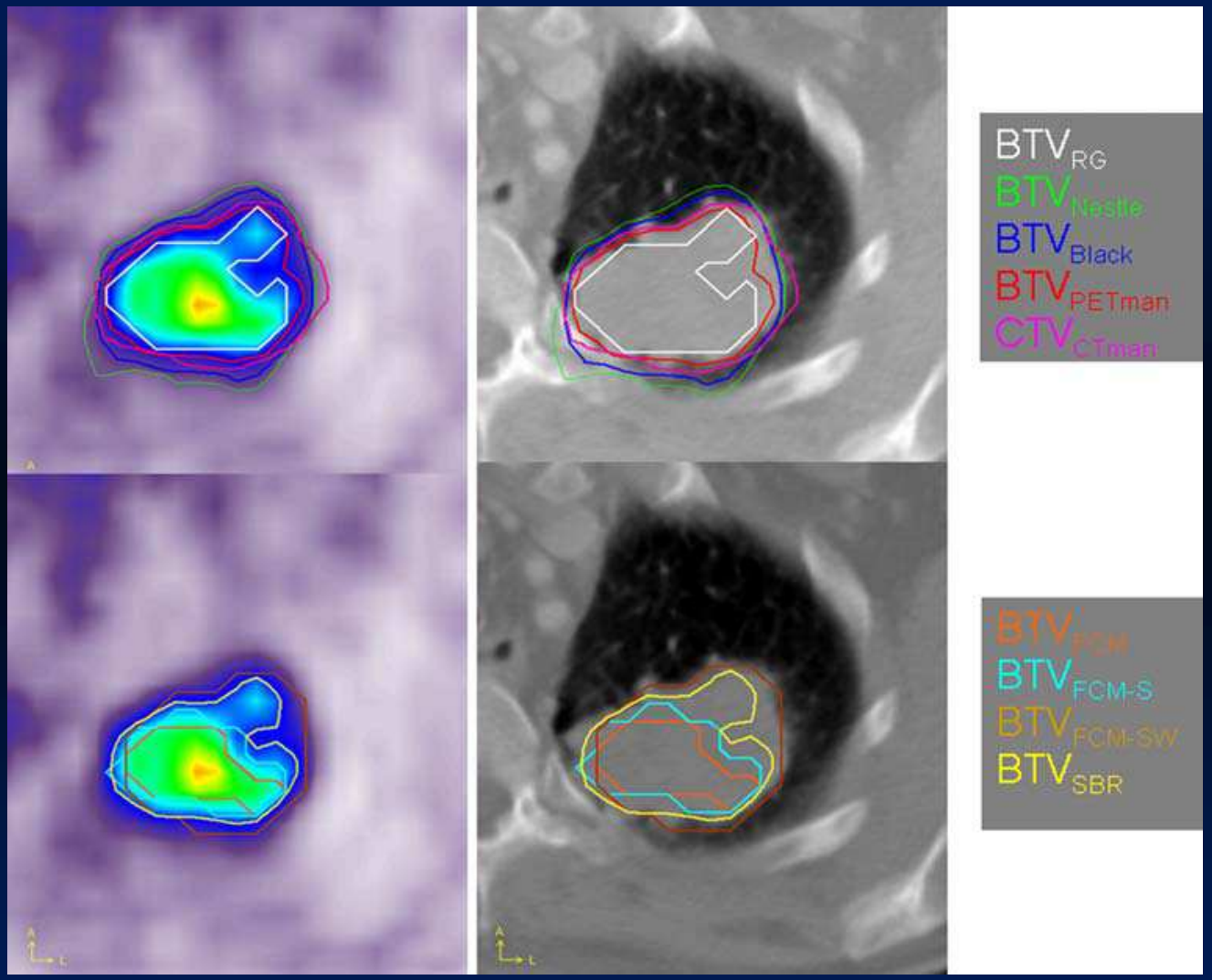
Validation of PET BTV in clinical studies is crucial and still limited

by histological specimens

- PET segmentation techniques extract similar d but different V

Belhassen et al., 2009

Comparison of 9 segmentation techniques



18F-FDG PET CT

Belhassen et al., 2009

	d_{max}(cm)	V (cc)
CT_{man}	6.5	98
PET_{man}	7.5	80
RG	6.0	61
Nestle	7.0	138
Black	6.5	117
SBR	6.5	65
FCM	4.8	32
FCM-S	5.5	45
FCM-SW	6.5	76

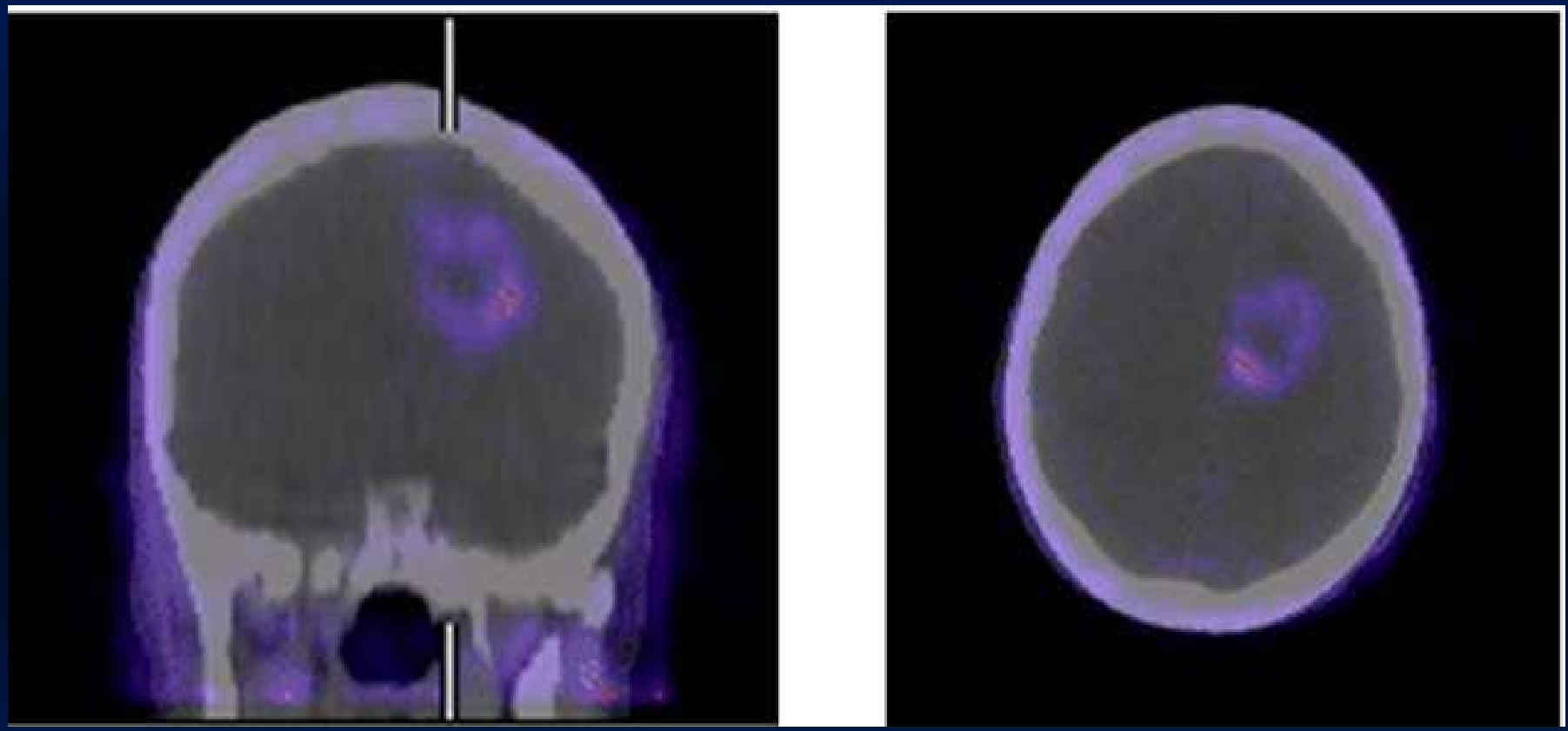
d_{GS}=7cm

Belhassen et al., 2009

PET Radiotracers

Tumour proliferation	*^{68}F-Fluorotimidine*
Aminoacid metabolism	*^{68}F-Fluoroethyltyrosine, ^{11}C-methionine, ^{11}C-tyrosine*
Cell membranes/ fatty acid metabolism	*^{11}C-acetate, ^{11}C-Choline, ^{18}F-Choline*
Somatostiatin receptors	*^{68}Ga-DOTA-TOC*
Apoptosis	*^{18}F-Annexin V*
Angiogenesis	*^{18}F-RGD peptide*
Hypoxia	*^{18}F-FMISO, ^{11}F-FAZA, ^{64}Cu-ATSM, ^{18}F-EF3, ^{18}F-EF5*

18^{F}-FAZA PET-CT



glioma

Postema et al., 2009

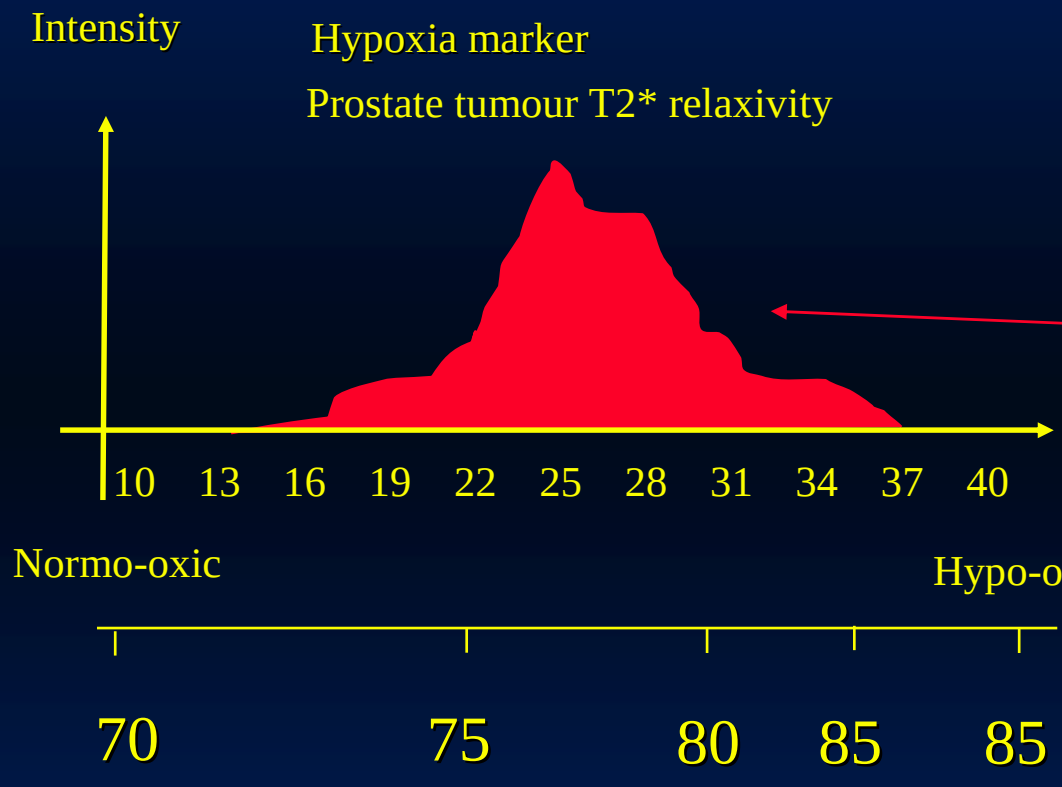
Hypoxia affects outcome of radiotherapy treatment

e.g. Nordsmark et al., 1996, 2000; Jomathan et al., 2006

Reduced perfusion correlate with therapy failure

e.g. Hermans et al., 2003; Vauper et al., 2004, 2005

"Dose painting by numbers" (Bentzen et al. *Lancet oncol*, 2005)



CTV from MR transferred on BOLD MR

inverse treatment-planning : pixel-driven dose distribution

Are we ready with dose painting by numbers?

1) Assess temporal and spatial stability of PET hypoxia maps

2) Assess time of reoxigenation of hypoxic areas

3) Improve quantification of PET hypoxia maps

1) Assess temporal and spatial stability of hypoxia maps

Hypoxia: 100μm

Intermittent hypoxia: minutes-hours

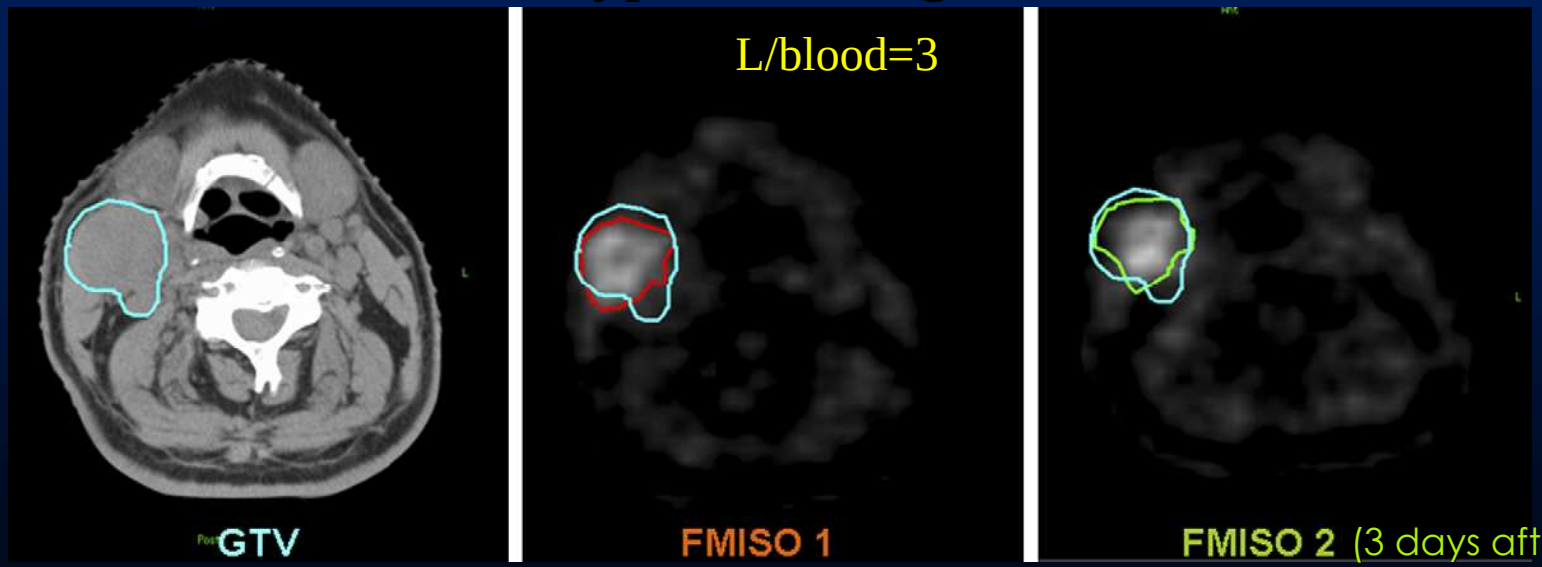
Hypoxia and normoxic areas can coexist in one PET voxel

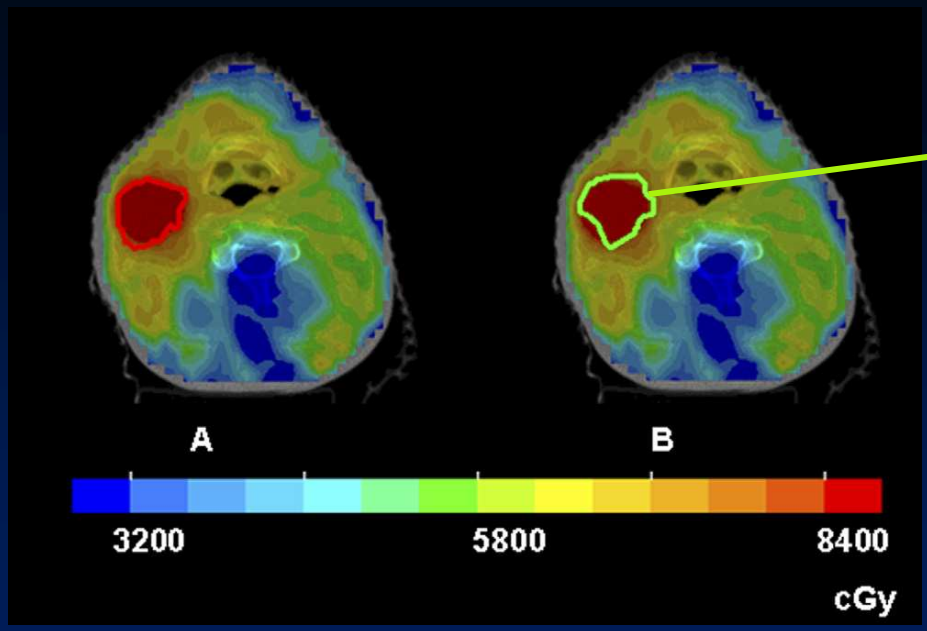
Multiparametric imaging (Dynamic/Multimodal (PET and CT/MRI)

2) Assess time of reoxigenation of hypoxic areas

Multiple imaging sessions during RT

Hypoxia during RT





Lin et al., 2008

e.g. Eschmann et al., 2007; Thorwarth et al., 2007

Time of reoxigenation depends inversely from perfusion efficiency

Cell sensitivuty dependes from tracer retention

Early PET scans

Late PET scans

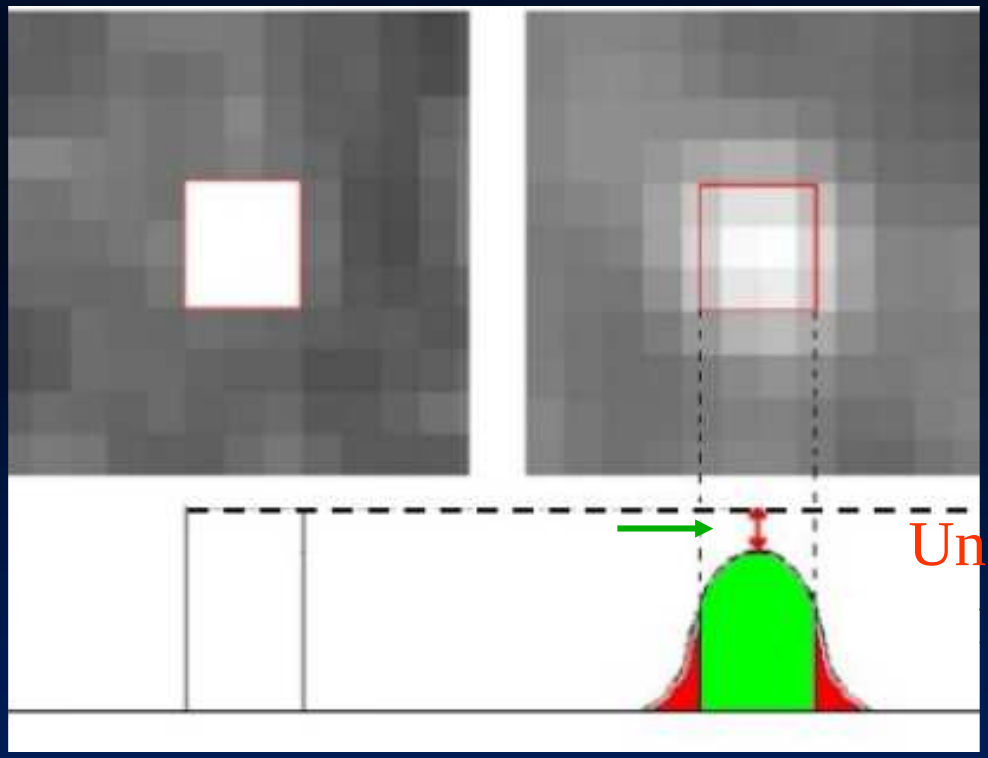
TCP can be used to stratify patients vs RT

3) Improve quantification of PET hypoxia maps

PET Partial Volume Effect

Ideal lesion

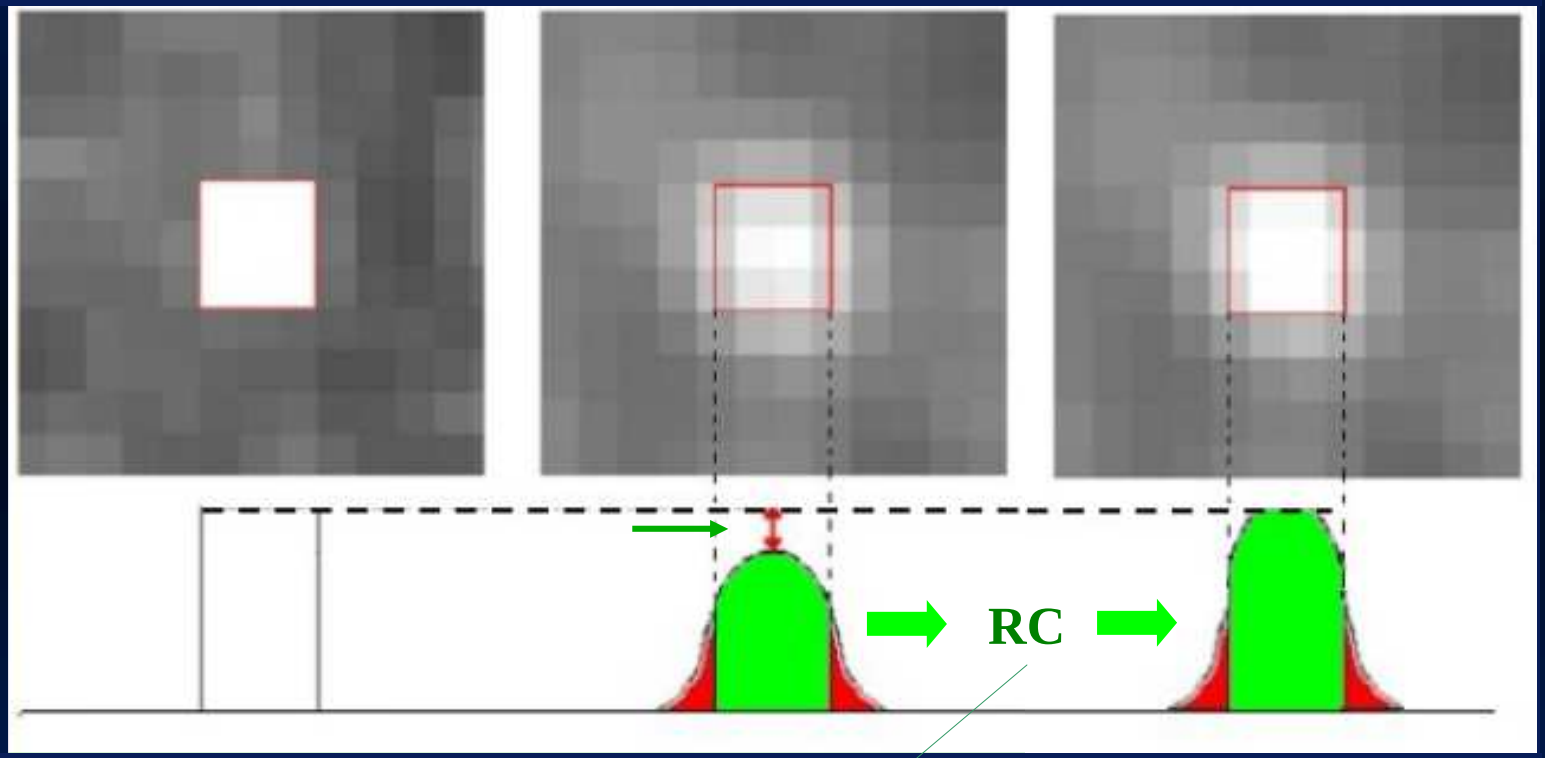
Real lesion



Underestimation

PVE PET correction

Ideal lesion | Real lesion | Corrected lesion



Measurement of RECOVERY COEFFICIENTS
(taking account of the system state)

Methods

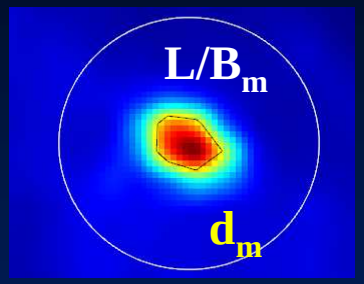
Recovery coefficients (RC) and RC curves from NEMA 2001 IQ phantom

$$RC = \frac{S/B_m}{S/B_{GS}}$$

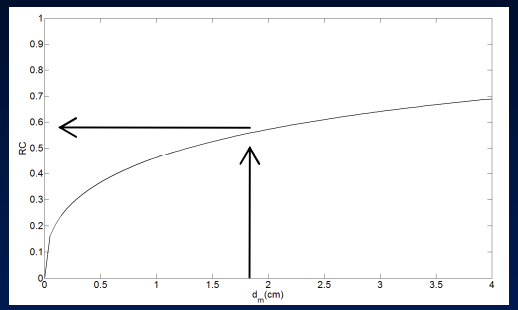
*GS = Gold Standard

RC function of measured sphere diameter (equivalent to V_m) and S/B_m

RC-based PVE correction method



RC



L/B_m

$$C_{corrected} = \frac{C_{uncorrected}}{RC}$$

$$SUV_{corrected} = \frac{SUV_{uncorrected}}{RC}$$

d_m

Castiglioni et al., 2009

Dose by BTV → Segmentation of qualitative PET metabolic images

Dose by BTV & subvolumes → Segmentation of qualitative PET hypoxia images

("dose painting") (Lyng et al. *Int J Radiat Oncol Biol Phys*, 2000)

Dose by PTV & numbers → Quantitative PET hypoxia images

("dose painting by numbers") (Bentzen et al. *Lancet oncol*, 2005)

Dose by PTV & numbers (“dose painting by numbers”)

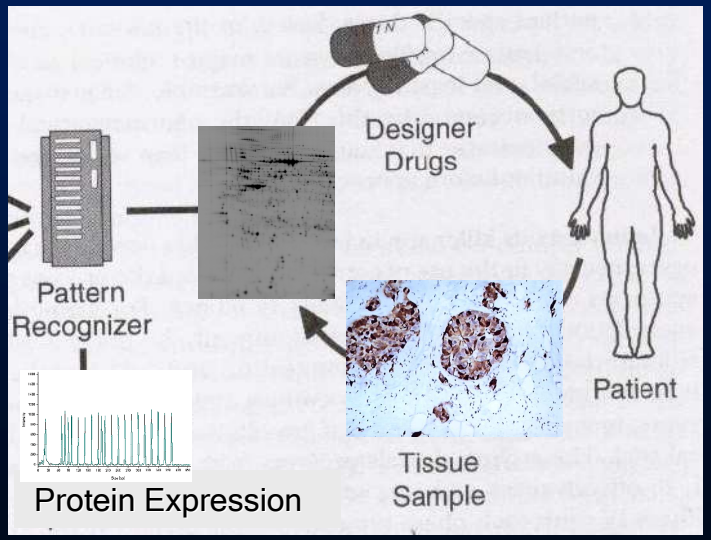
numbers = (PET voxels accurate numbers)

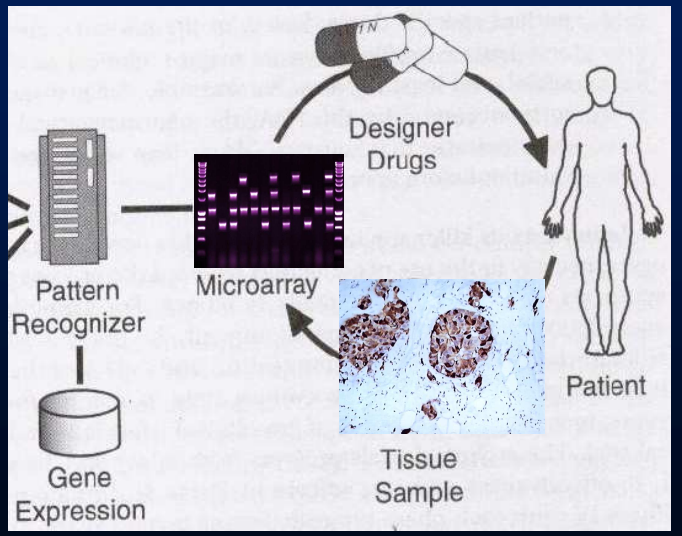
addressing to RT

RT planning

RT monitoring

Molecular imaging for RT





Ethiology, prognosis, tumour response to therapy

Personalized therapy periodically monitored