

Recent advances in PET Monte Carlo simulations and PET image quantification towards enhancement of the role of PET in cancer patients

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Where are we located?



25 km south of Paris



The lab

- CNRS lab (Centre National de la Recherche Scientifique)
- IMNC: Imaging and Modeling in Neurobiology and Cancerology
- Head: Yves Charon

Staff of ~40 in 5 teams

- Instrumentation for intraoperative imaging (nuclear and optical)
- Instrumentation for small animal imaging (nuclear and optical)
- Metabolism, imaging and olfaction (biologists)
- Modelling of dynamic systems (bkgd of theoretical physics)
- Quantification in Molecular Imaging (QIM)

The QIM group

Yolanda Prezado, CNRS junior scientist

Sébastien Jan, CEA-SHFJ

Claude Comtat, CEA-SHFJ

Irène Buvat, CNRS senior scientist

Charlotte Robert, post-doc ENVISION FP7

Mohamed Mesradi, post-doc hGATE

Jacques-Antoine Maisonobe, PhD student

Didier Benoit, GATE engineer

Pauline Huet, PhD student

Julien Bonte, engineer

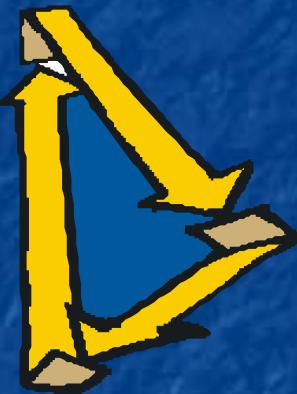
Nicolas Fourrier, MSc student

Fanny Orlhac, MSc student

Our research in the lab

Instrumentation in
medical imaging for
very specific
applications

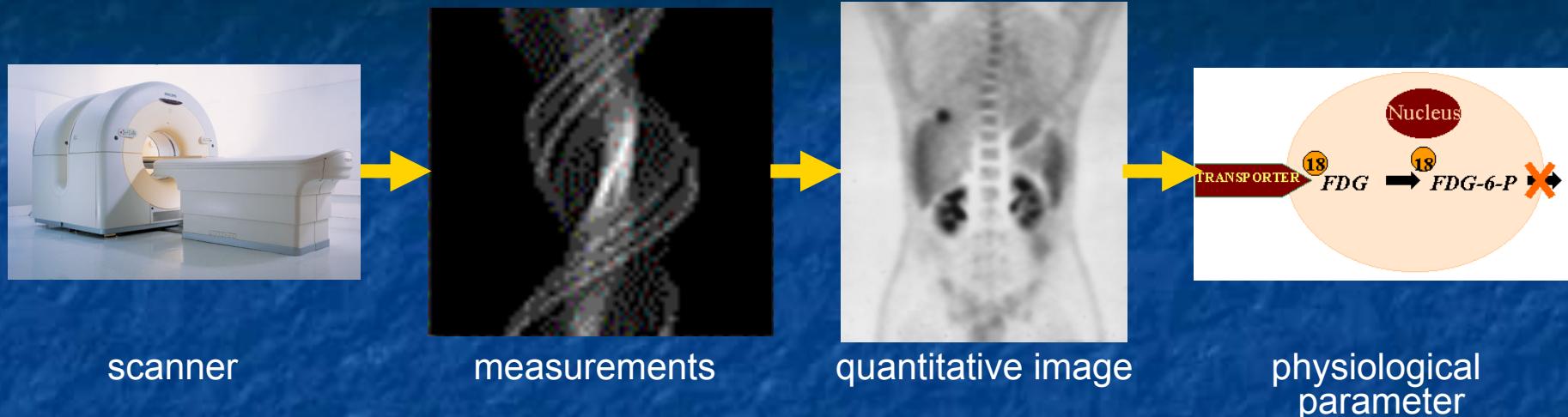
Modelling of
biological
phenomena like
tumour growth



Simulations and methods
for functional imaging
(mostly PET and SPECT)

Key words: molecular imaging, SPECT, PET, quantification,
Monte Carlo simulation, image-based monitoring in
hadrontherapy

QIM research axes



1. **Simulation** of hyper-realistic SPECT and PET scans for a better understanding of the imaging process and associated biases
2. **Quantitative reconstruction** of SPECT and PET images, and associated corrections (among which partial volume effect)
3. **Quantitative characterization** of physiological processes (tumor metabolism, inflammation) or physical processes (dose deposit) from PET/CT or SPECT/CT images

Simulations

Brief state of the art

1. There are currently several Monte Carlo codes supporting simulations of SPECT and PET scans
2. Most popular codes include:
 - SIMIND (SPECT only): Michael Ljungberg, Lund, 1989
 - SIMSET (PET and SPECT): Robert Harrison + Paul Kinahan Seattle, 1993
 - GATE (SPECT, PET, CT, Radiotherapy, Hadrontherapy): developed by the OpenGATE collaboration, first release in 2004

GATE was initially developed to overcome the limitations of SIMIND, SIMSET and general purpose codes (MCNPX, EGS4) in the context of SPECT and PET simulations

GATE V6

- First dedicated code supporting simulations of imaging devices and radiotherapy system in the same framework (e.g., from the beam to the PET scanner)

Jan et al Phys Med Biol 2011

- GATE uses the physics of Geant4
- What we have been doing recently with GATE:
 1. Study how scans indistinguishable from real scans could be simulated (Stute et al, *Phys Med Biol* 2011: 6441-6457)
 2. Simulate highly realistic scans including tumors for evaluation purpose (Stute et al, *IEEE Trans Nucl Sci* 2012: in press)

Simulation of highly realistic scans: motivation

- Why? For evaluation purpose in two contexts:
 - for detectability studies: characterizing the detectability of lesions as a function of the contrast, noise level, noise structure, lesion location, ...
 - for assessing the accuracy and precision of quantification methods

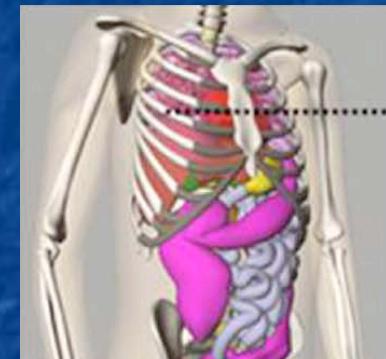
Question: how to simulate a SPECT or PET scan that cannot be distinguished from a real one so that it is a realistic dataset for evaluation purpose?

Simulation of highly realistic scans: state of the art

- There are currently two approaches to simulate patient scans:
 - Analytical description of the patient: sophisticated XCAT phantom (see Proceedings of the IEEE; 97:1954-1968, 2009)



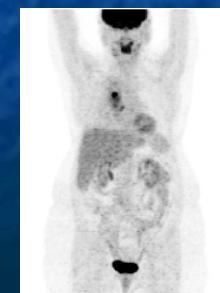
- Precise and high resolution anatomical modeling including models of organ motions
- Hard to match a specific patient (feasible but extremely tedious)
- Piecewise constant activity distribution
- Need to develop models of lesions



- Voxelized description of the patient: Define the activity and attenuation maps from a real patient PET/CT or SPECT/CT



- All patient features can be accurately reproduced, including uptake pattern within organs
- A real PET or SPECT scan is already inaccurate (noisy and with limited spatial resolution), hence errors will propagate through the simulation process



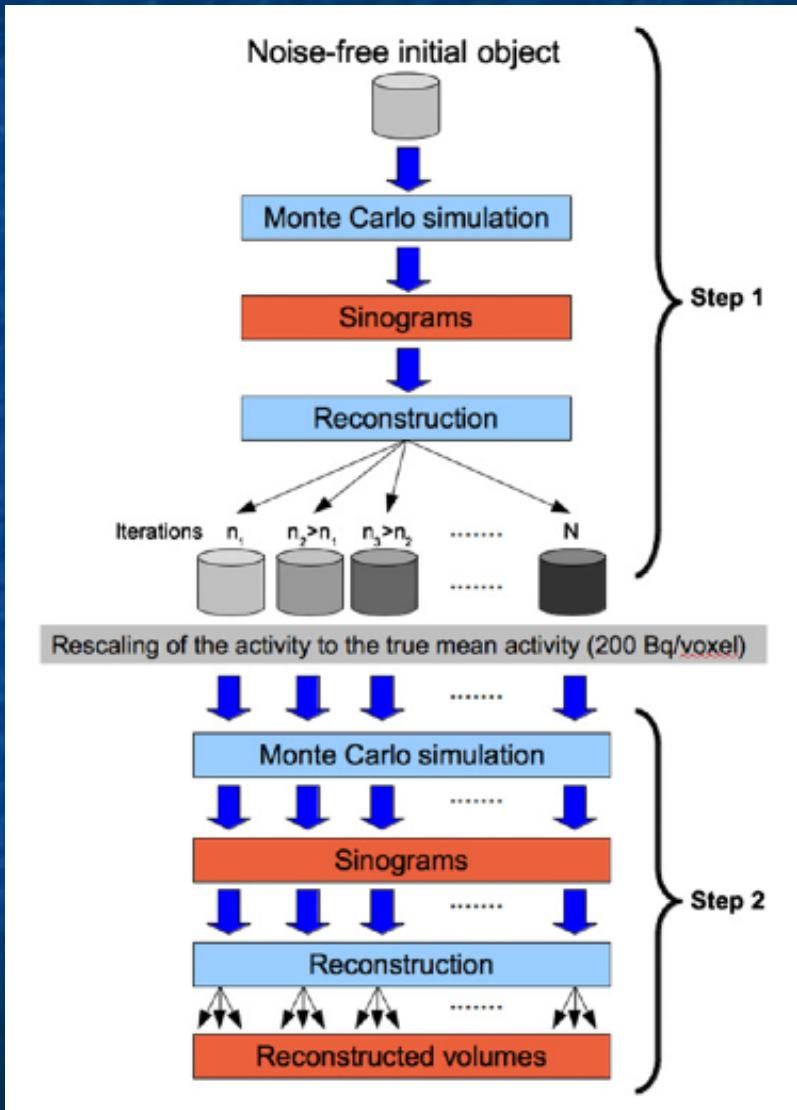
Simulation of highly realistic scans

Aim of our study: how to set up a simulation from real data in order to obtain reconstructed images very close to real images?

Question: how do the errors in the input activity maps propagate through the simulation / reconstruction processes?

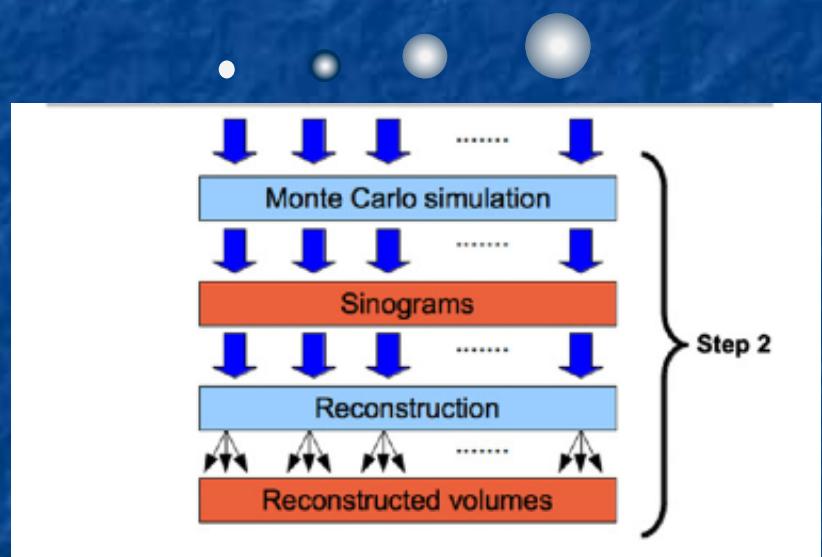
Simulation of highly realistic scans: method

Noise study



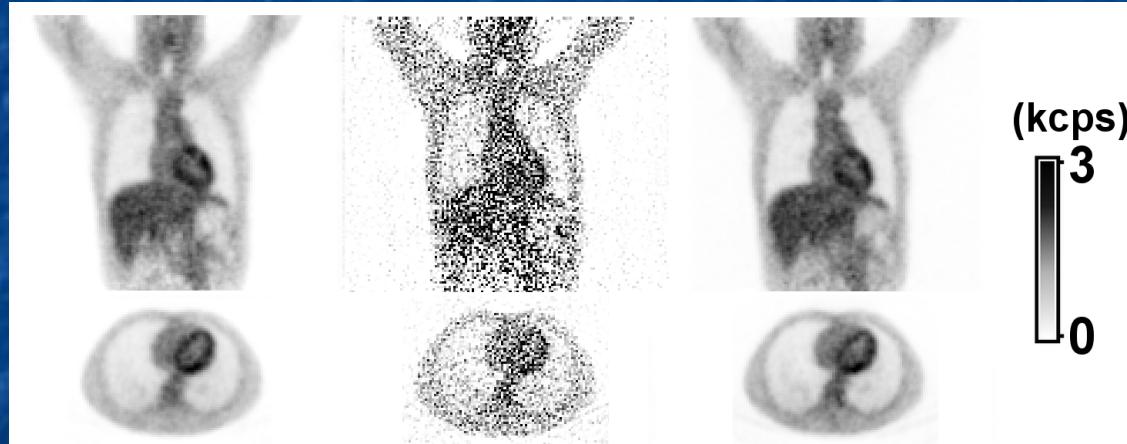
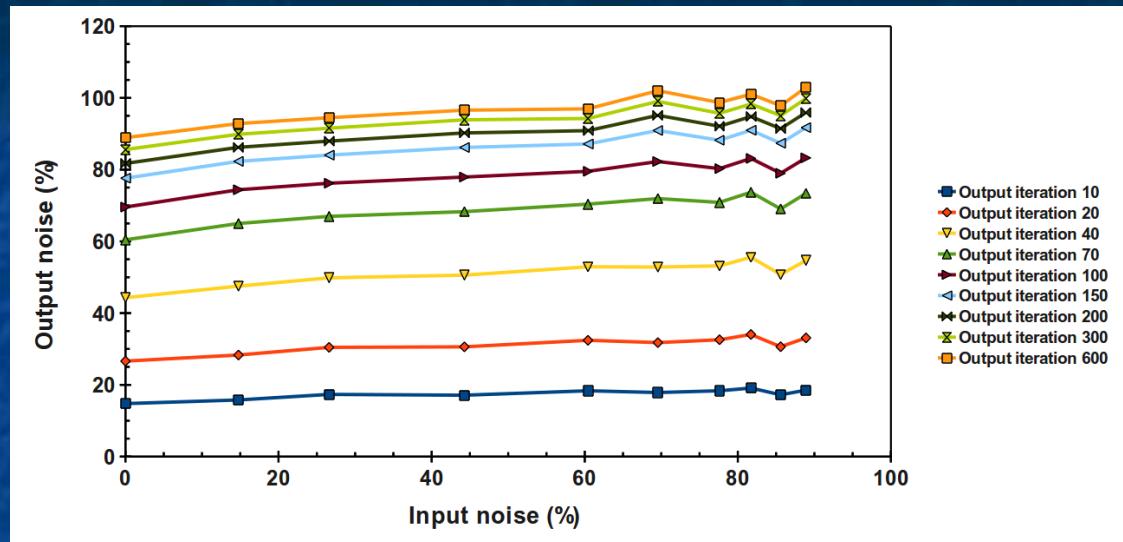
Spatial resolution study

Point source with FWHM varying from 1 to 40 mm



Simulation of highly realistic scans: results

Noise study



Patient scan

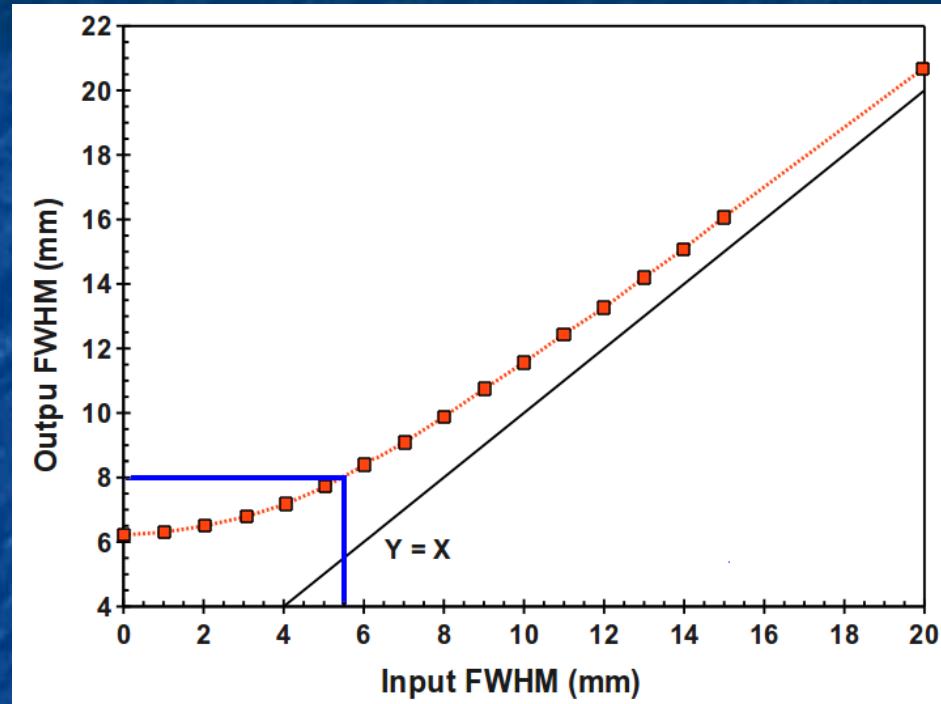
Input activity map

Reconstructed image

Images reconstructed from the simulated data are almost insensitive to the noise present in the input activity map

Simulation of highly realistic scans: results

Spatial resolution study



- Limited spatial resolution in the input activity map reduces the spatial resolution in the reconstructed images

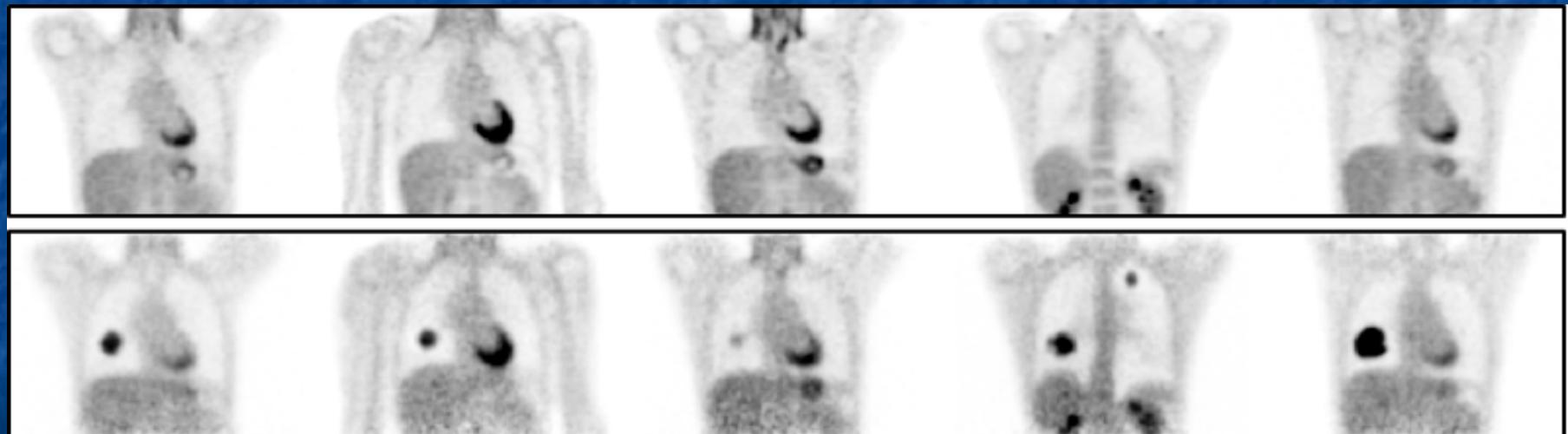
To simulate images with the same spatial resolution as in routine, input activity maps should be very high resolution (regardless of the noise)

Simulation of highly realistic scans: overall conclusion

Highly realistic PET and SPECT images can be simulated using the Monte Carlo approach, by using ultra-high resolution activity maps as input (regardless of the noise).

Such ultra high resolution activity maps can be obtained using a high number of iterations during iterative reconstruction

Real serial PET scan in a patient



Simulations of serial PET scan of the same patient with a lung tumour

Stute et al, *IEEE Trans Nucl Sci* 2012: in press

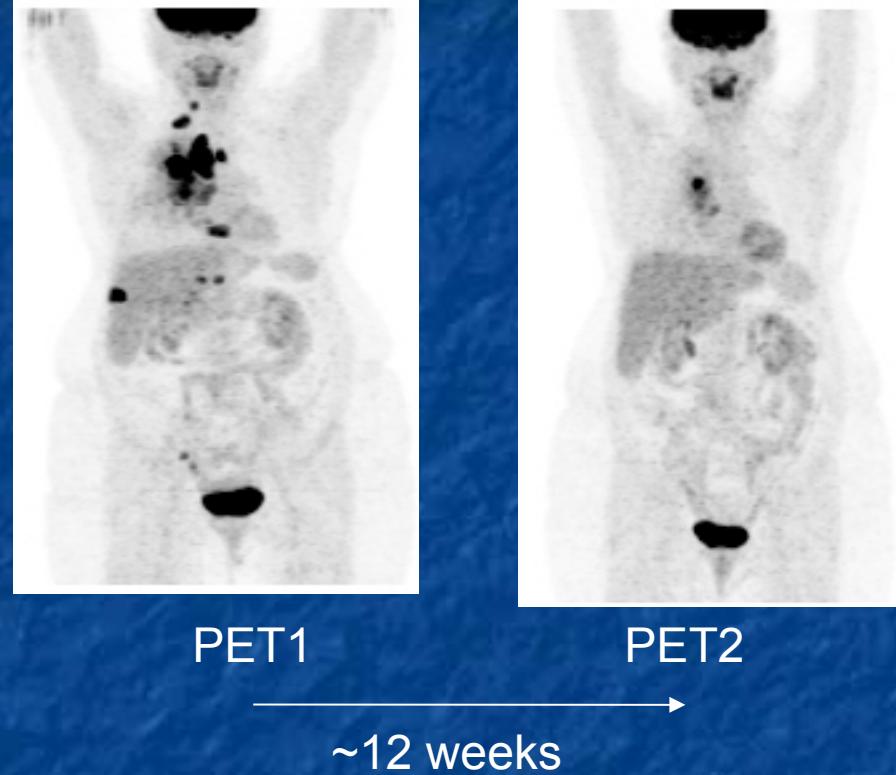
Maastro clinic – February 8th, 2012 - 16

Quantification in PET in cancer patients

Recent research axes

- How to best compare two or serial PET scans in a patient in the context of patient monitoring?
 - Parametric imaging to compare 2 PET scans
 - Parametric imaging to characterize tumour change over the course of therapy when >2 PET scans are available
- What is the impact of partial volume correction in PET-based patient monitoring?

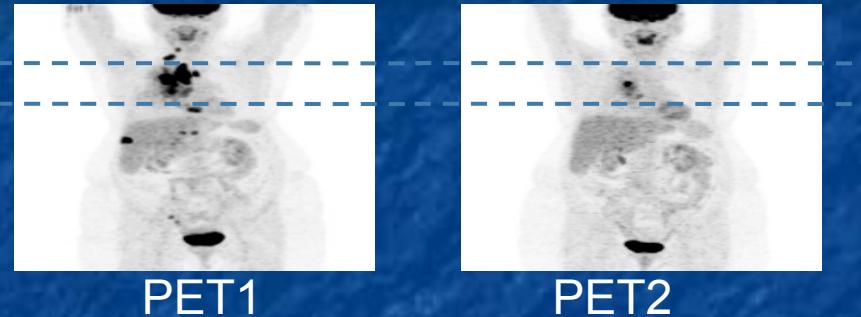
Comparison of 2 PET scans: motivation



How to best identify what has changed and by which amount?

A parametric imaging approach: step 1

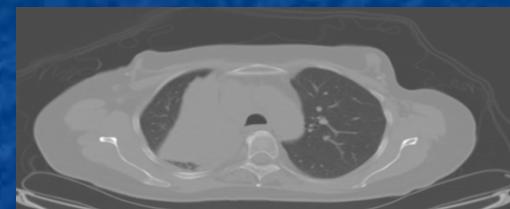
Step1: registration of the 2 scans based on the CT



Identification of a local transform T_{21}

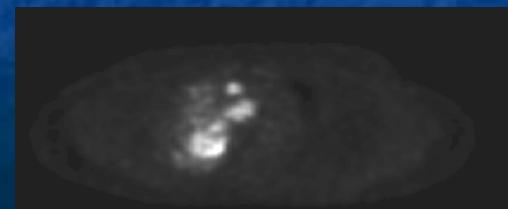


T_{21}
(rigid transform using
Block Matching)



TDM1

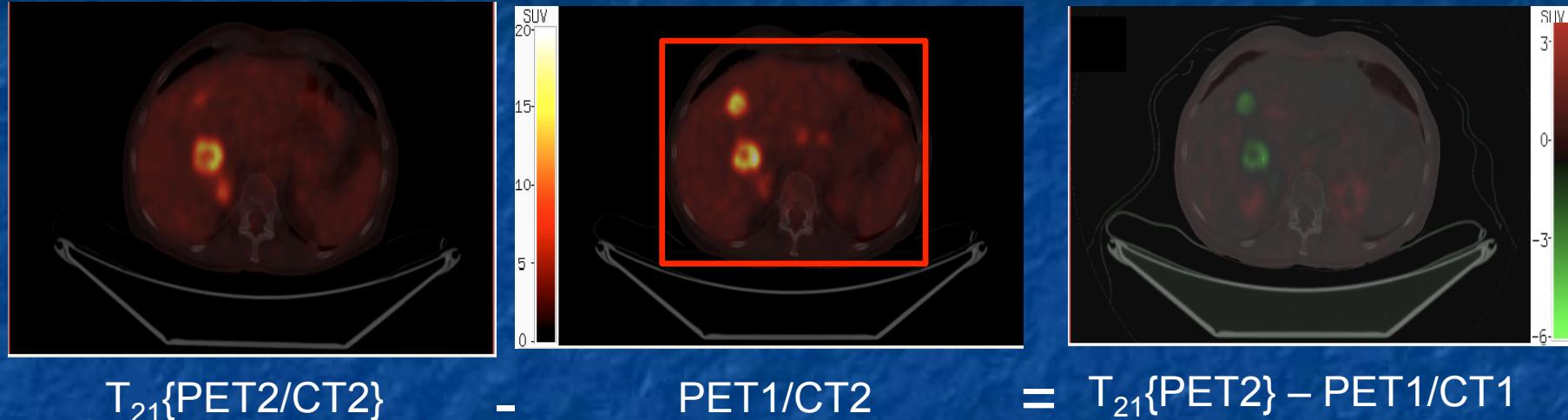
Registration of PET2 to PET1 using T_{21}



PET1

A parametric approach: steps 2 and 3

Step 2: subtraction of the 2 registered PET scans (in SUV units)



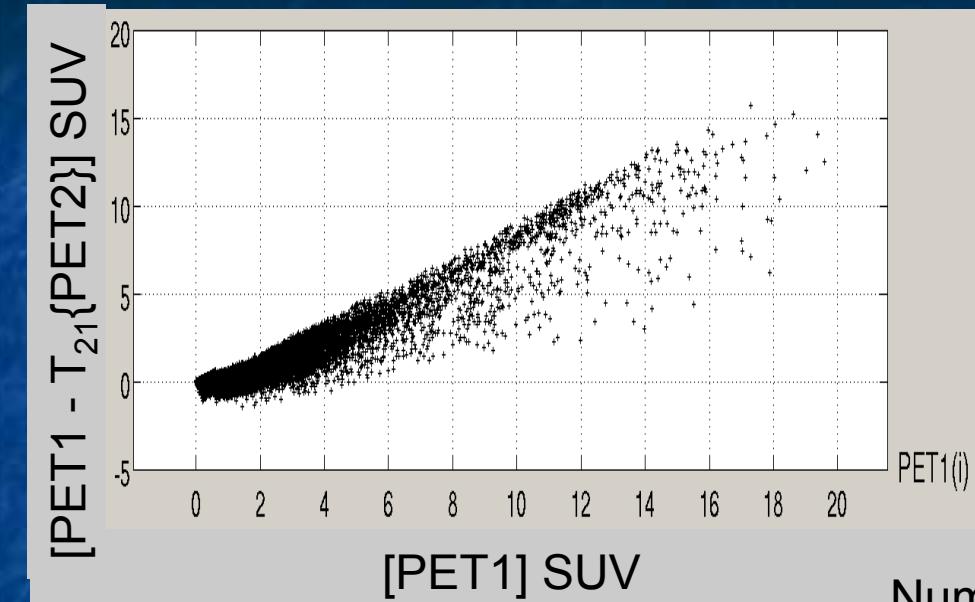
Step 3: identification of tumour voxels in the subtracted volume using a Gaussian mixture model



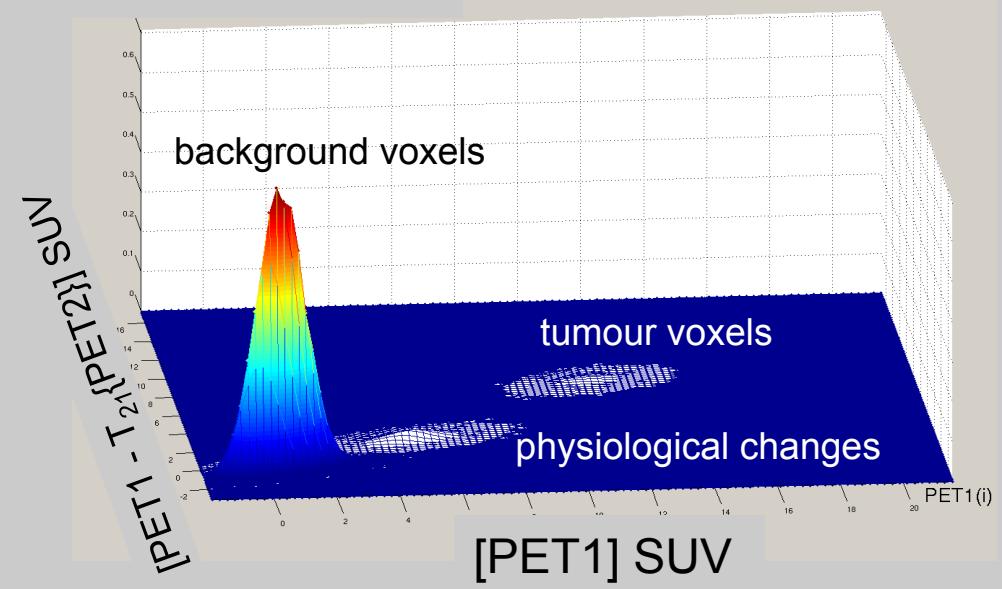
ΔV : volume that has changed

ΔSUV : magnitude of change

The Gaussian mixture model approach

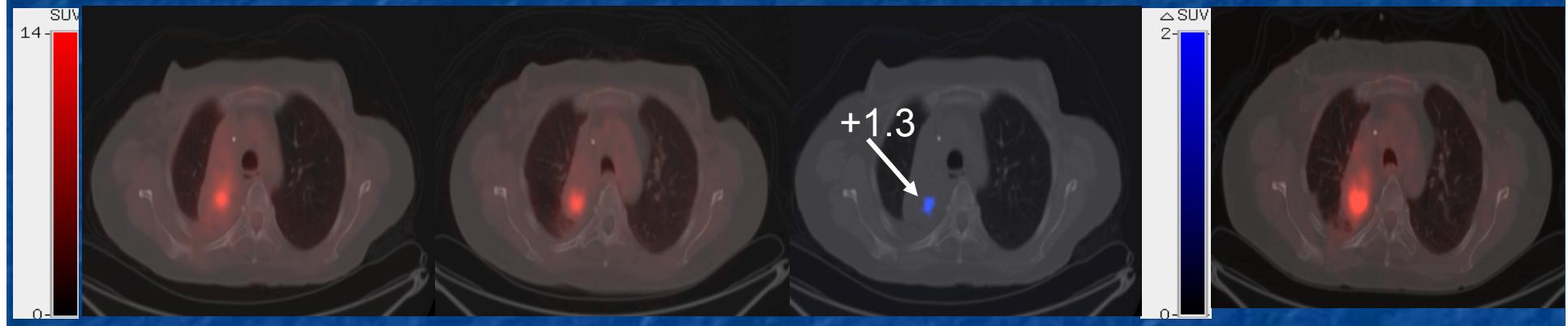


Number of voxels



Example

Identification of small changes

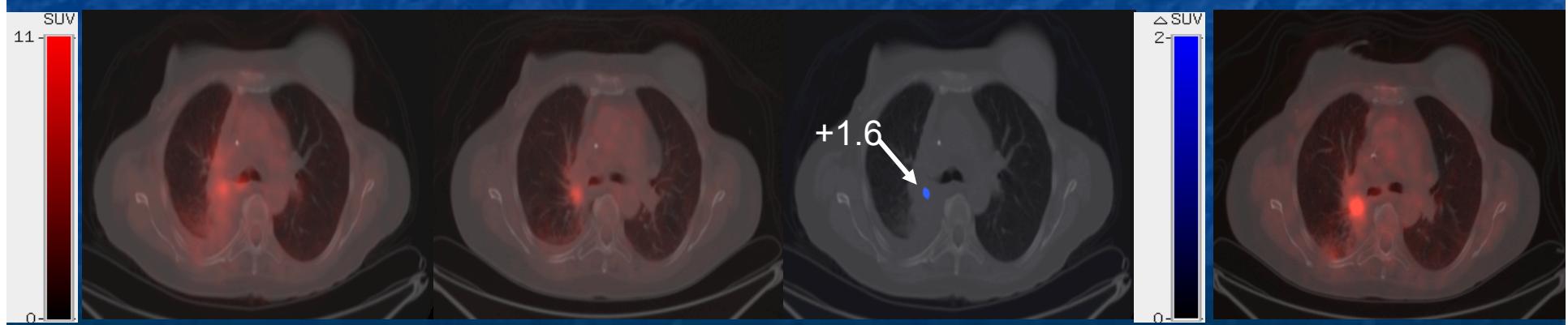


PET1

$T_{21}\{\text{PET2}\}$

$T_{21}\{\text{PET2}\} - \text{PET1}$
with tumour voxel selection

PET3



PET1

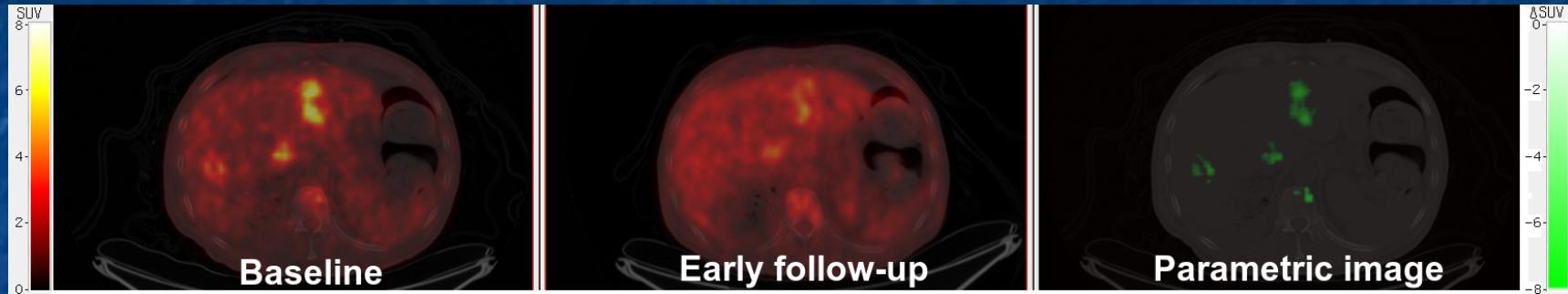
$T_{21}\{\text{PET2}\}$

$T_{21}\{\text{PET2}\} - \text{PET1}$
with tumour voxel selection

PET3

Clinical validation: 28 patients with metastatic colorectal cancer

78 tumours with baseline PET/CT and PET/CT @ 14 days



	NPP	PPV	Sensitivity*	Specificity
EORTC	91%	38%	85%	52%
PI	100%	43%	100%	53%

* of detecting responding tumours

All tumours classified as progressive @ 14 days were confirmed as such using the RECIST criteria 6-8 weeks after therapy initiation

Among the 14 tumors identified as progressive tumours with RECIST:

- 12 were identified as progressive @ 14 days using PI
- 1 only using the EORTC criteria and SUVmax

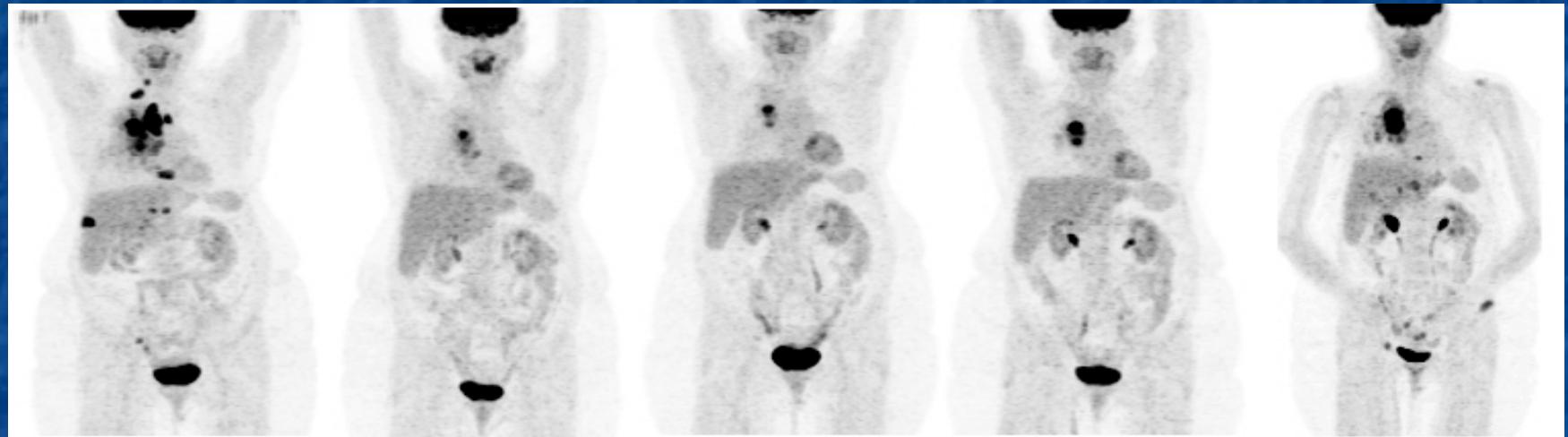
Conclusion for this parametric imaging method

The parametric imaging method :

- Does not require any precise delineation of region of interest
- Makes it possible to detect subtle changes not seen using the conventional regional analyses
- Makes it possible to visualize heterogeneous tumour changes (like necrosis)

Comparaison of more than 2 scans

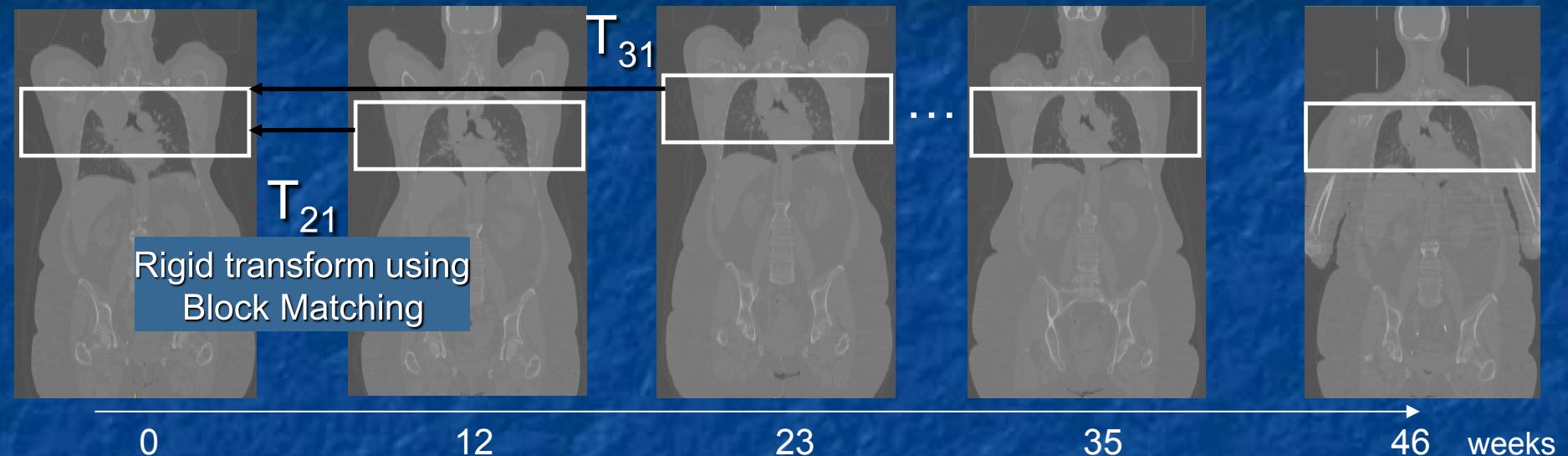
Serial PET/CT scan for patient monitoring



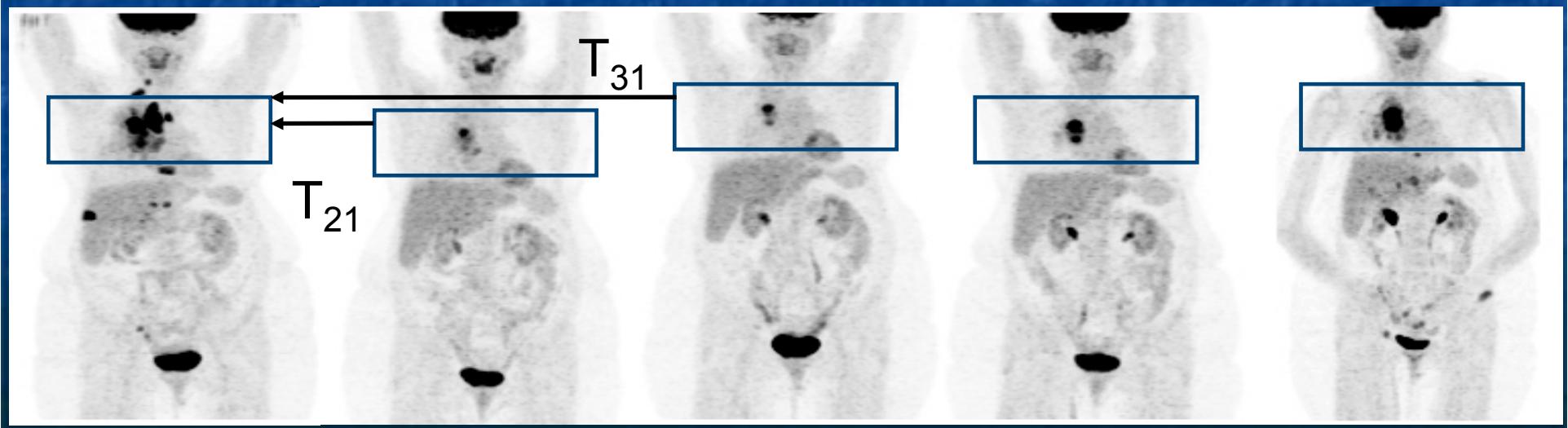
Motivation: get a synthetic representation of the uptake changes over time

Parametric imaging for serial scans: step 1

Step1: registration of the scans based on the CT



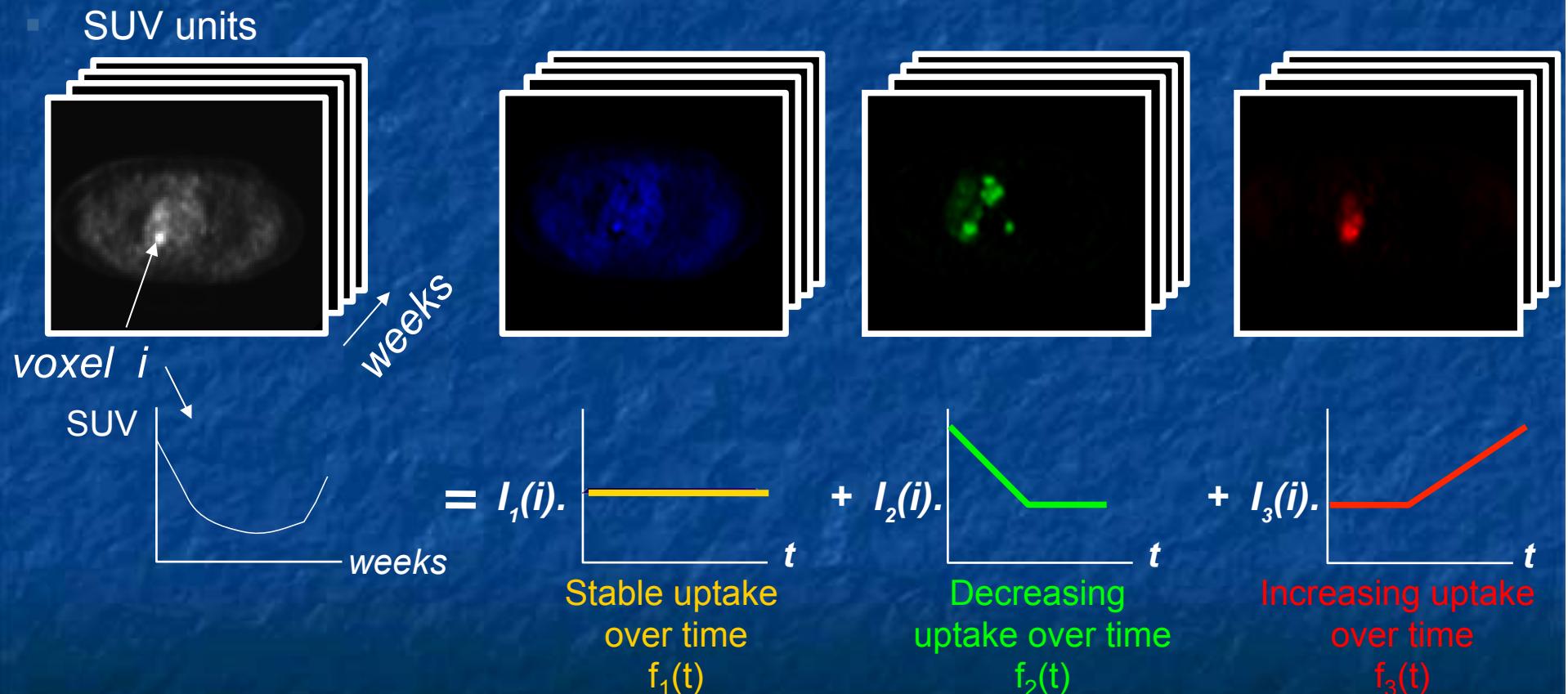
Registration of all PET scan with respect to the first PET using the T_{t1} transforms



Parametric imaging for serial scans: factor analysis

Linear model

$$\text{uptake}(i, t) = \sum_{k=1}^K l_k(i) \cdot f_k(t) + \varepsilon_k(t)$$



Model solution: identification of the model components

$$\text{uptake}(i, t) = \sum_{k=1}^K l_k(i) \cdot f_k(t) + \varepsilon_k(t)$$

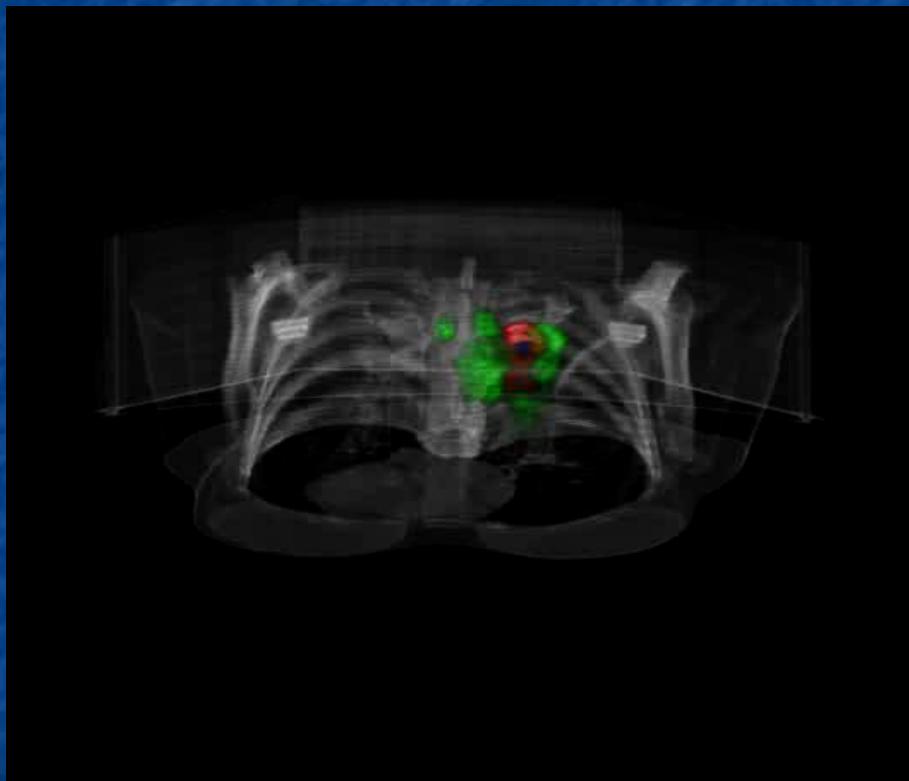
Priors:

- The $l_k(i)$ coefficients should all be positive
- The $f_k(t)$ values should all be positive
- Variance of reconstructed voxel values roughly proportional to the mean

Iterative identification of $l_k(i)$ and $f_k(t)$ (Buvat et al Phys Med Biol 1998)

Example of results

Analysis of a series of 5 PET/CT scans in a patient with lung tumours

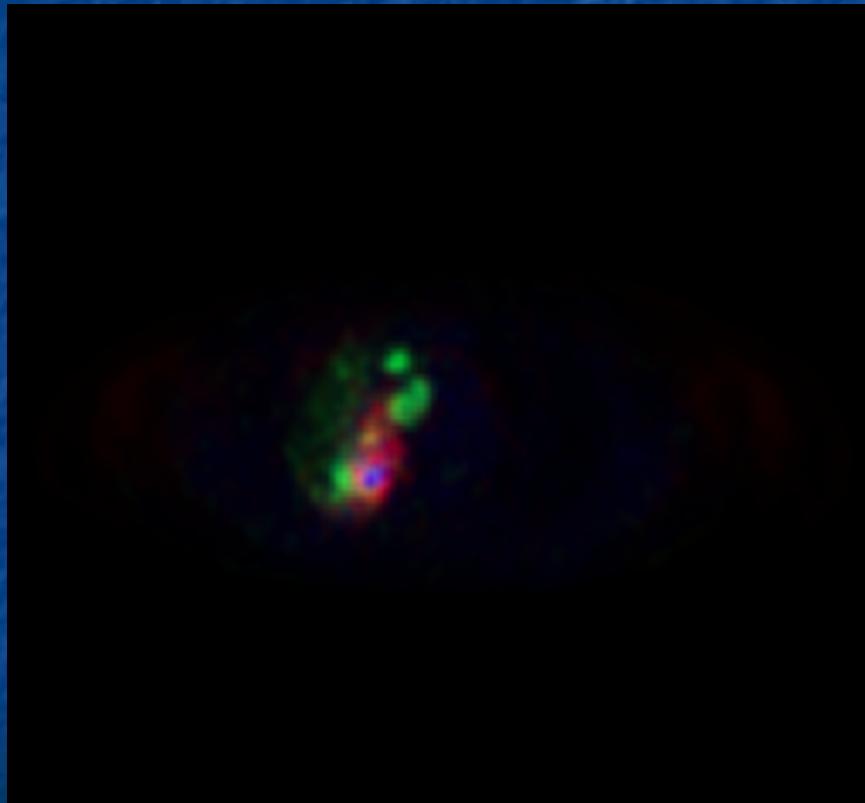


Normalized SUV



Example

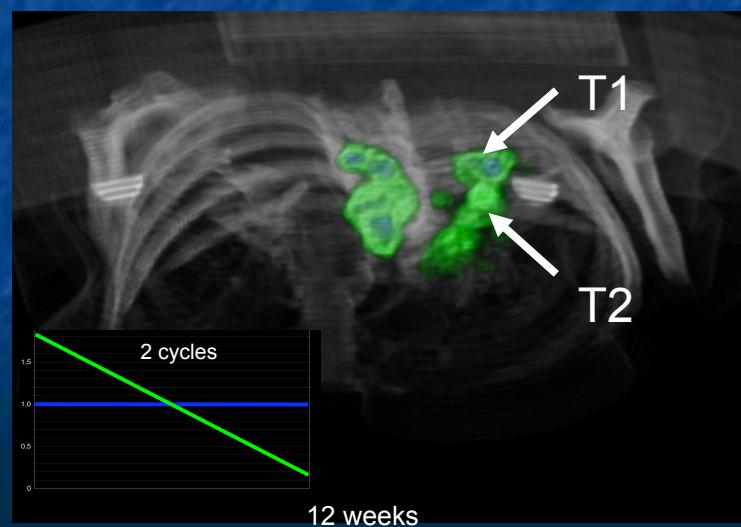
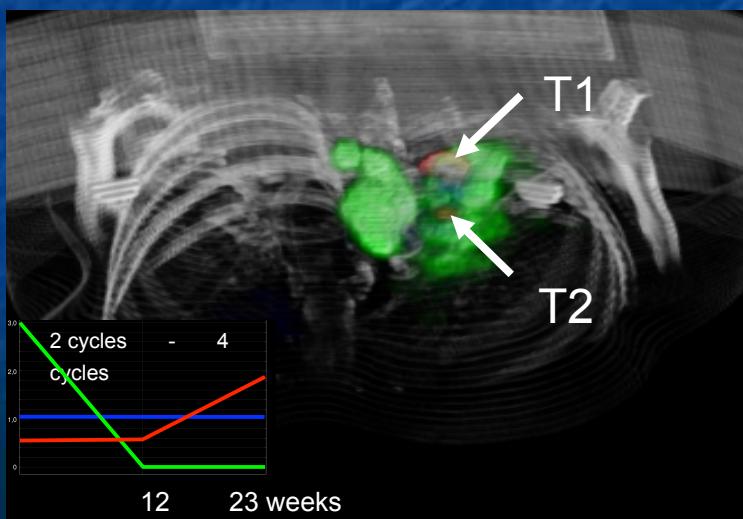
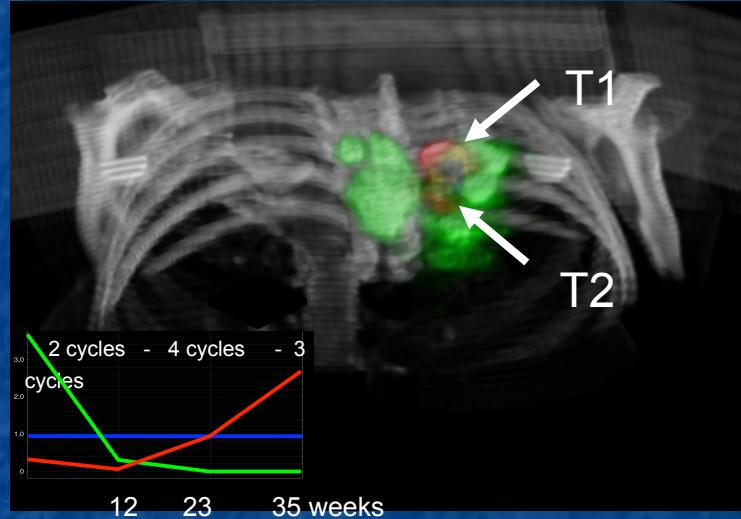
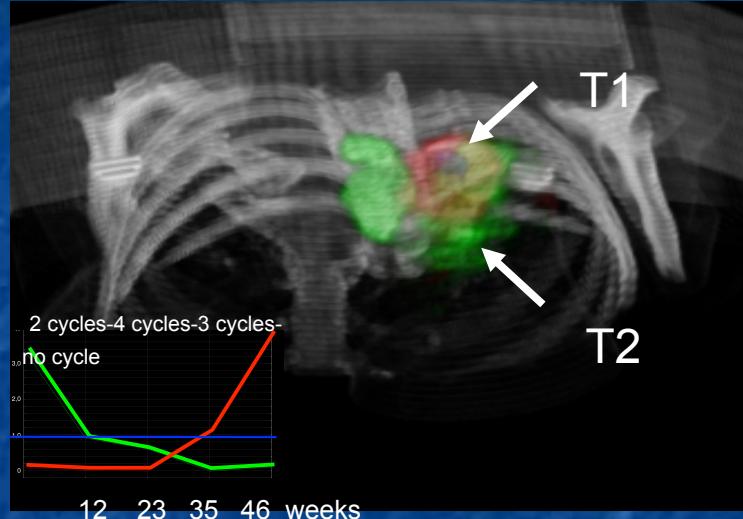
Using this approach, heterogeneous tumour response can be easily appreciated



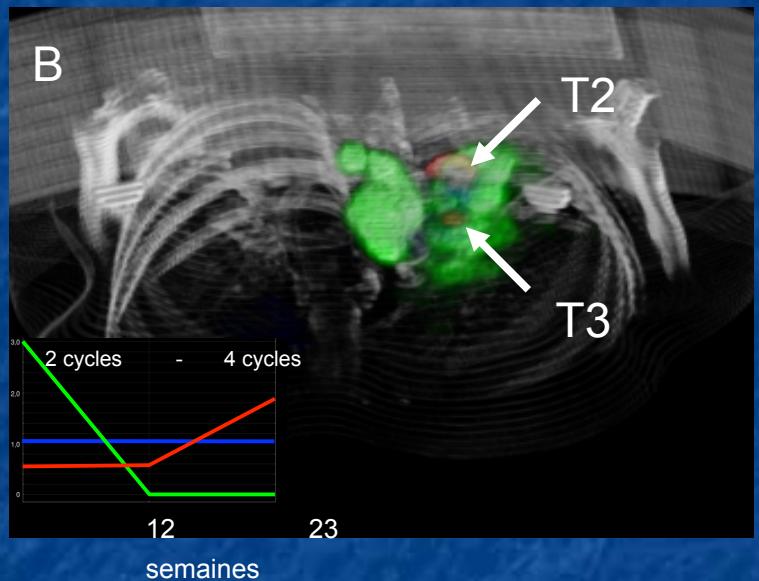
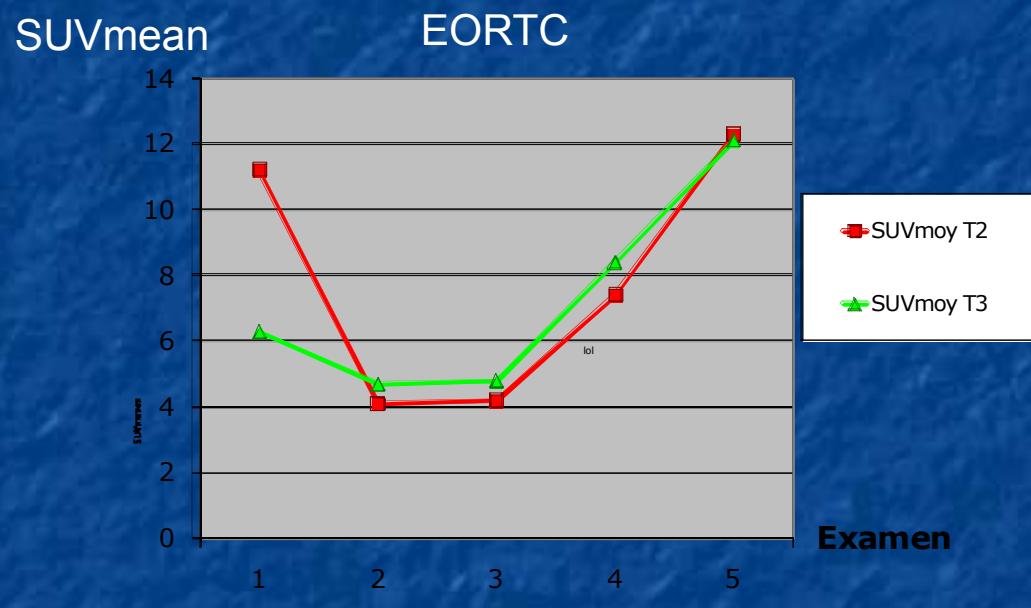
Normalized SUV



Example: early detection of tumour recurrence (1)



Example: early detection of tumour recurrence (2)



Conclusion for this parametric imaging method

The parametric imaging method for serial scans:

- Does not require any precise delineation of region of interest
- Makes it possible to detect subtle changes at the voxel level
- Makes it possible to visualize heterogeneous tumour changes in a large FOV
- Also works for monitoring patients undergoing radio-chemotherapy (study in progress)

Impact of PV correction in PET-based therapy monitoring

Does partial volume correction help accurately characterize the tumour response to therapy?

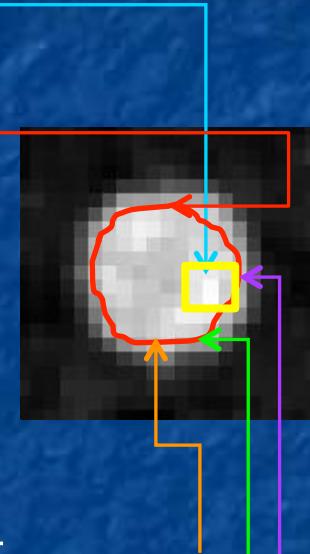
Clinical study (after an initial study on simulation was performed)

- 40 patients with metastatic colorectal cancer treated with chemotherapy
- PET/CT at baseline and 14 weeks after therapy initiation
- GE Discovery LS scanner
- OSEM (2 iterations, 28 subsets) + Gaussian post-filtering (FWHM=5.45 mm)
- Calculation of 7 indices to characterize the tumour and the tumour changes
- Gold standard : RECIST 1.0 classification based on a CT performed 5 to 8 weeks after therapy initiation
- Using RECIST, 2 groups of lesions were defined:
 - Responding lesions= total or partial response to therapy (27 lesions)
 - Non responding lesions= stable or progressive lesions (74 tumours)
- ROC curves were calculated for the 7 indices

Indices

3 SUV without partial volume correction

- **SUVmax** : max SUV in the lesion
- **SUVmean** : mean SUV in a region delineated using Nestle et al (J Nucl Med 1995) method
- **SUVpeak** : mean SUV in a $3 \times 3 \times 3$ voxels region around the max



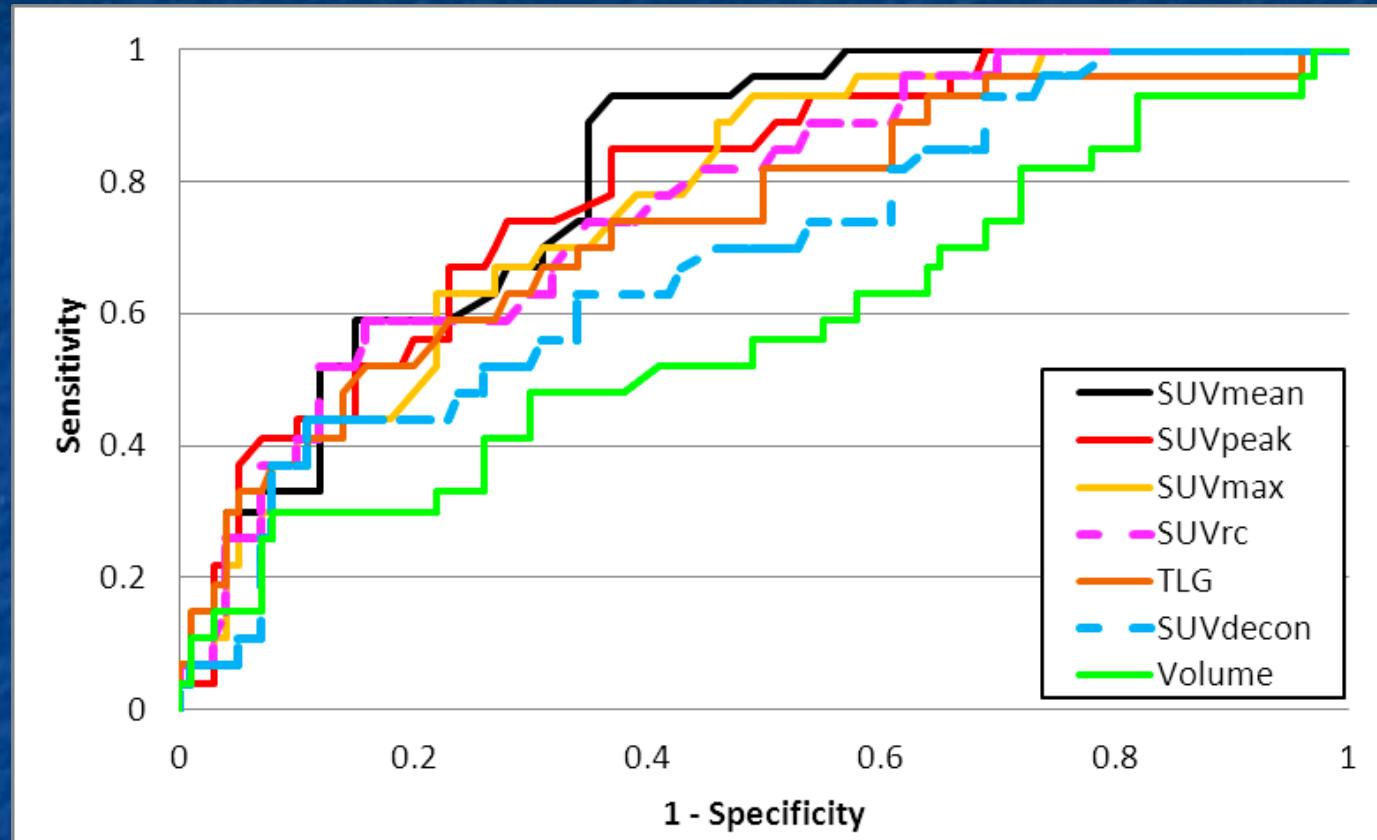
2 SUV with PV correction

- **SUVmeanRC** : SUV corrected using a Recovery Coefficient
- **SUVdecon**: mean SUV on the image deconvolved with the Van Cittert algorithm, with mean calculated in an isocontour set to 70% of the max in the original image

2 index accounting for the tumour volume

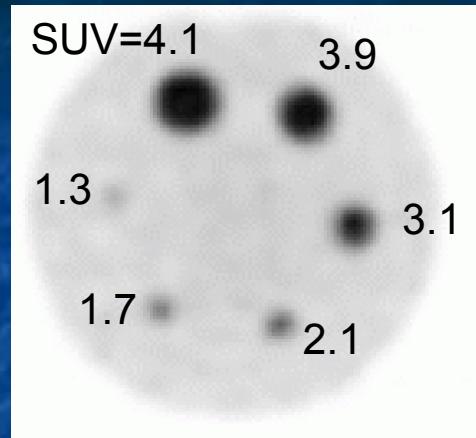
- **Volume** : volume delineated for SUVmean calculation
- **TLG** : Volume \times SUVmean

Summary of results: ROC curves



PVC did not help identifying responding from non-responding tumours in this group

Discussion / conclusion



Without PV correction and in small or medium-sized tumours, SUV reflects both the metabolic activity and the metabolically active volume

PV-corrected SUV only reflects the metabolic activity

Our study suggests that change in metabolic volume is a useful piece of information to appreciate tumour response

PV correction, by making SUV immune to metabolic volume, actually removes some information potentially useful to characterize the tumour response

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Frank and you all !

Articles available on <http://www.guillemet.org/irene/articles>