Standardisation of FDG PET/CT imaging for tracer uptake quantification and automated metabolic volume assessment

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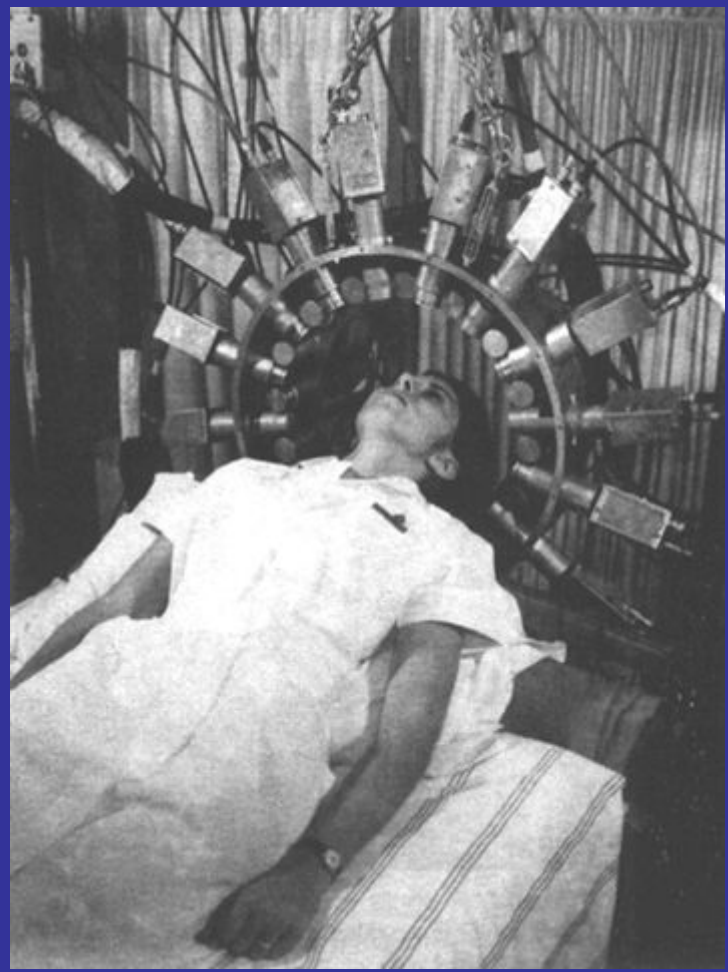
The Netherlands



1975

Positron emission tomography (PET) features

- **Molecular imaging technique – tracer principle**

- **Provides functional, metabolic,.. information**
  - can measure changes in metabolism/function before structural changes occur

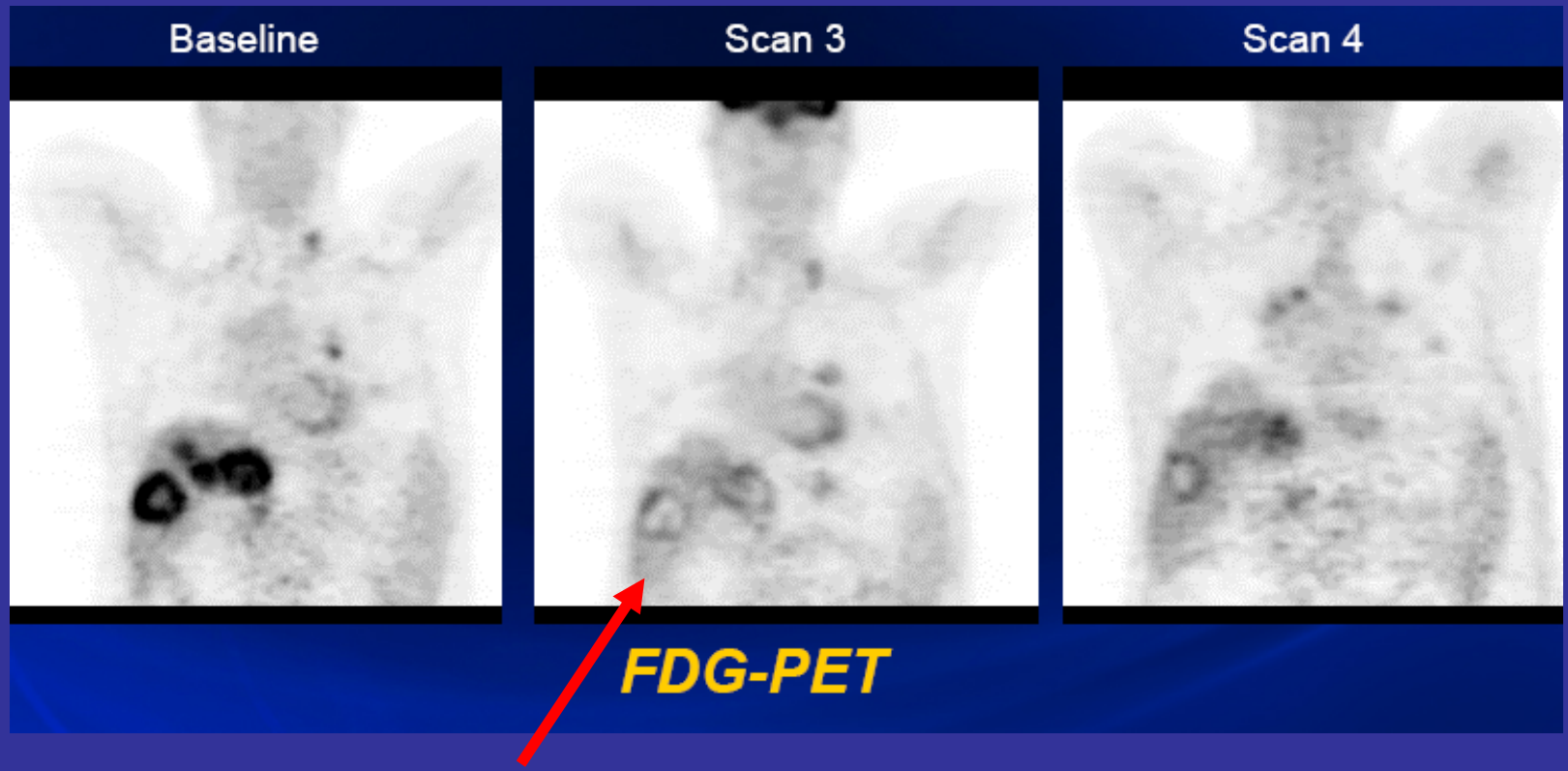
- **Various tracers and probes are available**
  - Onco: FDG, FLT, H_2O, F-MISO, F-AZA,…….labeled mAb or drug etc.
  - Cardio: NH_3, Rb, H_2O
  - Brain: various ^{18}F and ^{11}C labeled neuroreceptor tracers
  - Various inflammation tracers

- **Essentially quantitative imaging technique, <u>provided</u> it is used in a quantitative manner !**

Some examples of use of quantitative (FDG) PET/CT imaging (oncology)

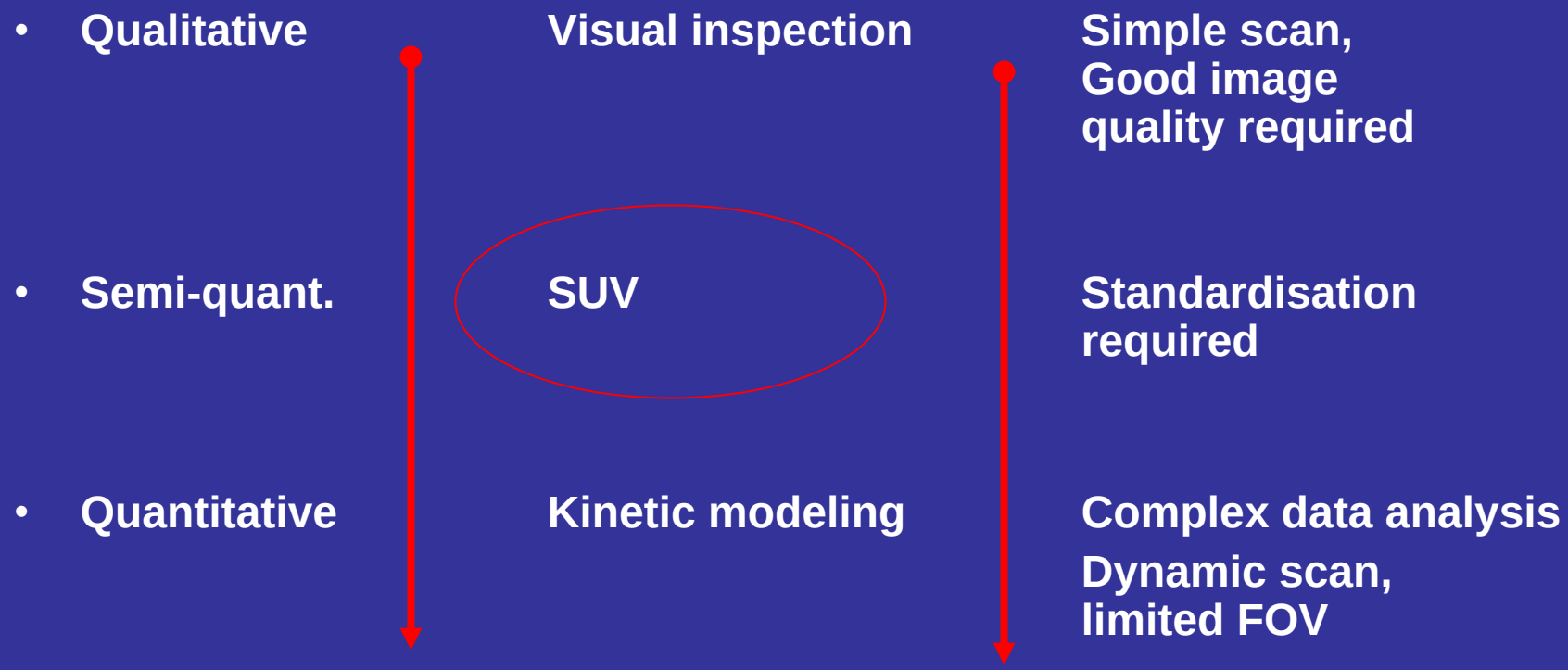
- Patient selection
  - Staging/inclusion criteria
- Stratification
  - High versus low risk arm
    (or identify possible poor vs good responders)
- Proof of mechanism/concept
  - E.g. using labeled drugs (^{11}C !) or displacement studies
- Occupancy – dose scheduling
- Drug efficacy – response assessment
  - Presently much interest by pharma
- RT – 'biological' target volume

Example of response assessment

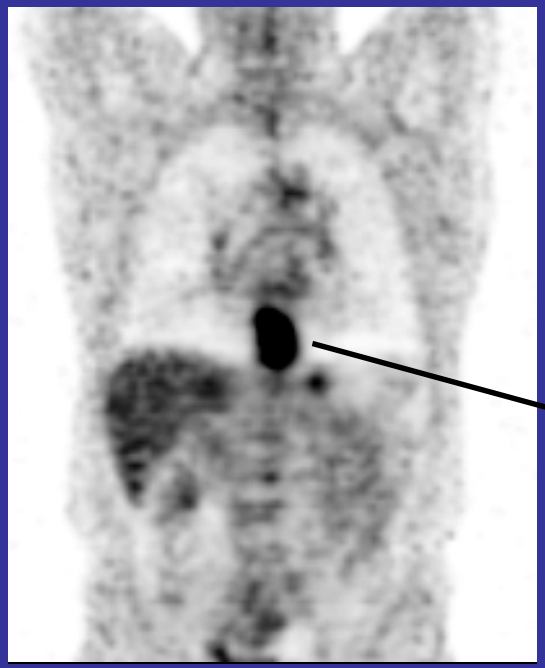


3 weeks after start of treatment

Methods of FDG PET quantification in oncology



Standard Uptake Value



$$SUV_{TBW} = \frac{c_t\,[kBq/ml]}{Dose[MBq]/weight[kg]}$$

SUV ‘is’ activity concentration ratio

Weight is sometimes replaced by BSA, LBM, BMI…

PET imaging / SUV uncertainties

Technical factors

– Relative calibration between PET scanner and dose calibrator (10%)
– Residual activity in syringe (5%)
– Incorrect synchronization of clocks (10%)
– Injection vs calibration time (10%)
– Quality of administration (50%)

Physics related factors

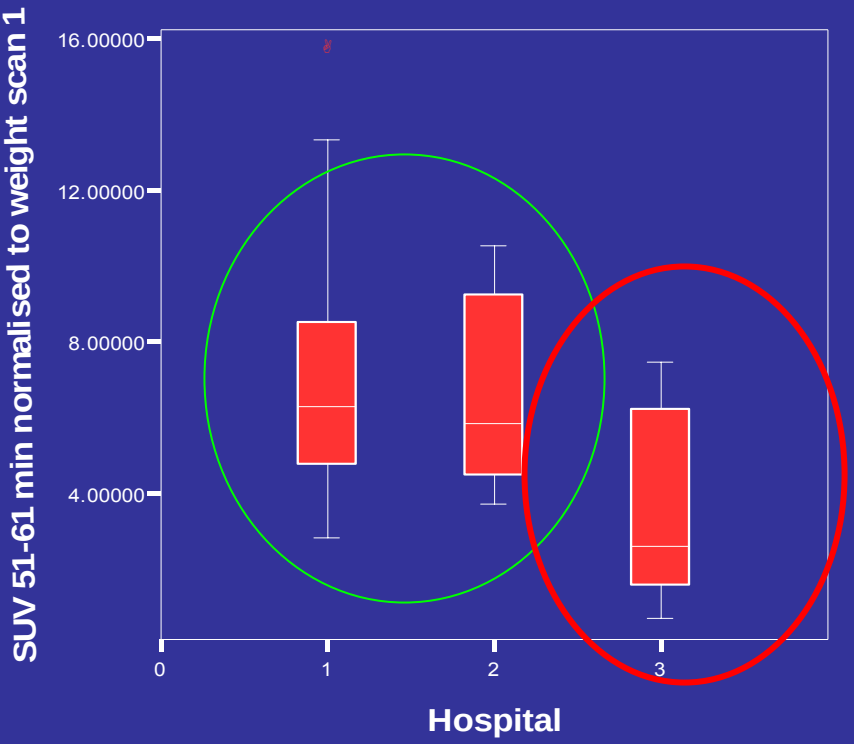
– Scan acquisition parameters (15%)
– Image reconstruction parameters (30%)
– Use of contrast agents (15%)
– ROI (50%)

Biological factors

– Uptake period (15%)
– Patient motion and breathing (30%)
– Blood glucose levels (15%)

R. Boellaard 2009, J Nucl Med Supplement Issue 50: 11S

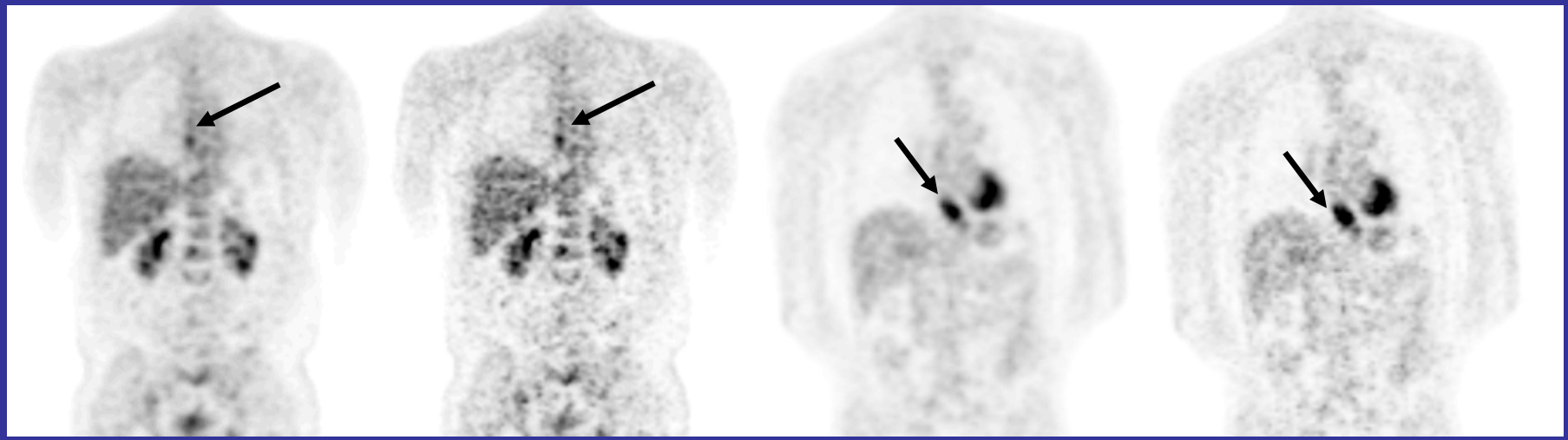
Why do we need a guideline for quantitative FDG PET ?



Recent (2009) observation on site differences in SUV
-Site 1 & 2 closely followed NL standardized protocol
-Site 3 did not – almost factor 2 lower SUV on average

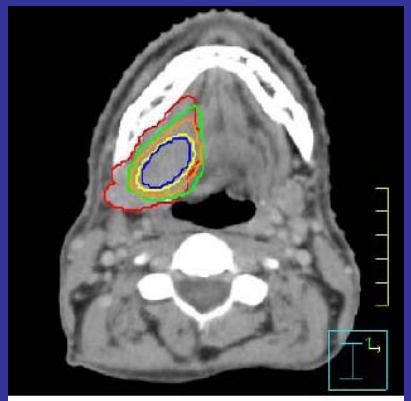
Example showing effect of image reconstruction

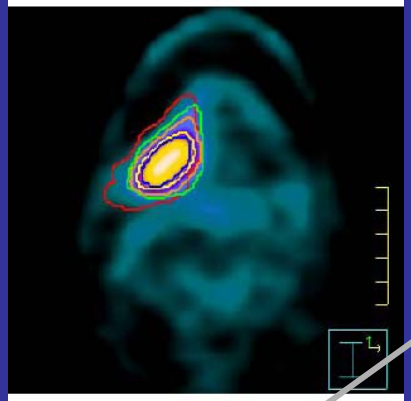
Effects of different number of OSEM iterations, as seen in the Netherlands, on SUV

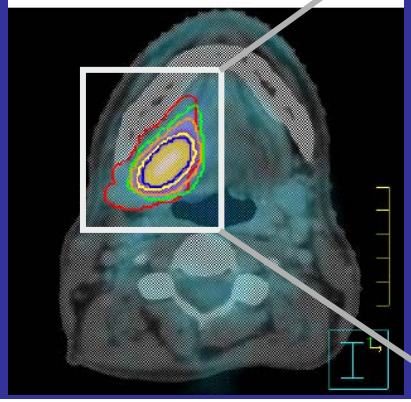


SUVmax = 4.0	5.9	6.4	8.6
SUV 50%= 3.0	4.1	4.6	5.9

Definition of target volume with PET/CT: which method?







Results depend on segmentation method being used:

CT:

GTV - CT 47.5 cm^3 (**rood**)

PET:

GTV - visueel 43.8 cm^3 (**groen**)

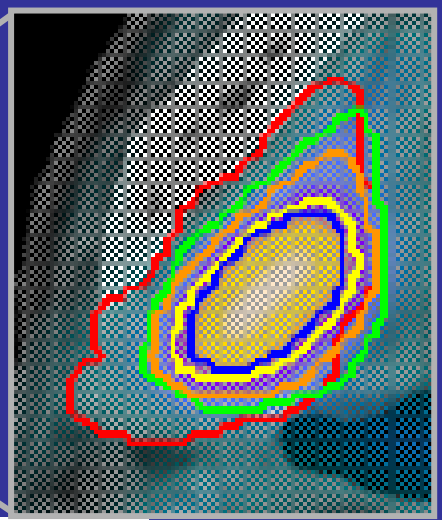
manual

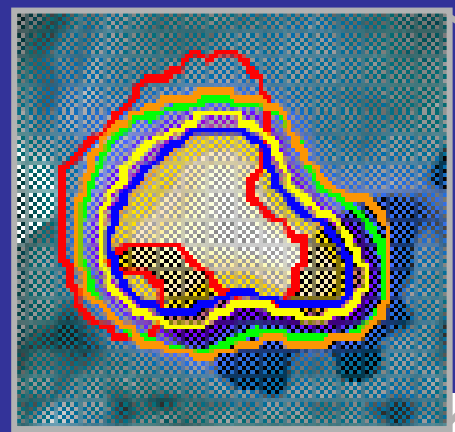
$GTV_{40\%}$ 20.1 cm^3 (**geel**)

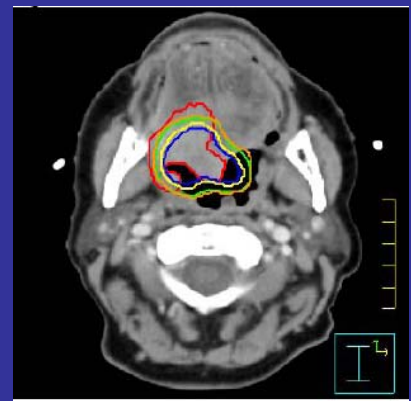
GTV_{SUV} 32.6 cm^3 (**oranje**)

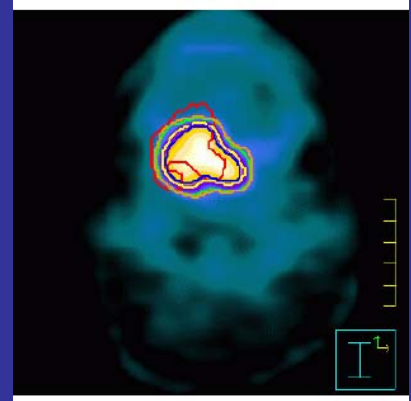
GTV_{SBR} 15.7 cm^3 (**blauw**)

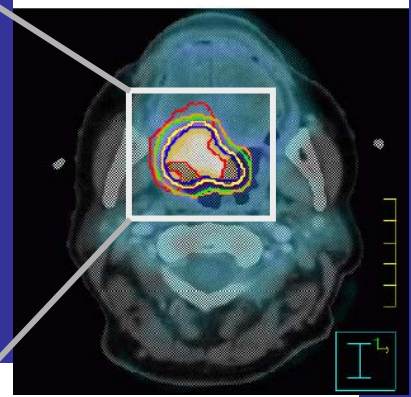
semi-automated





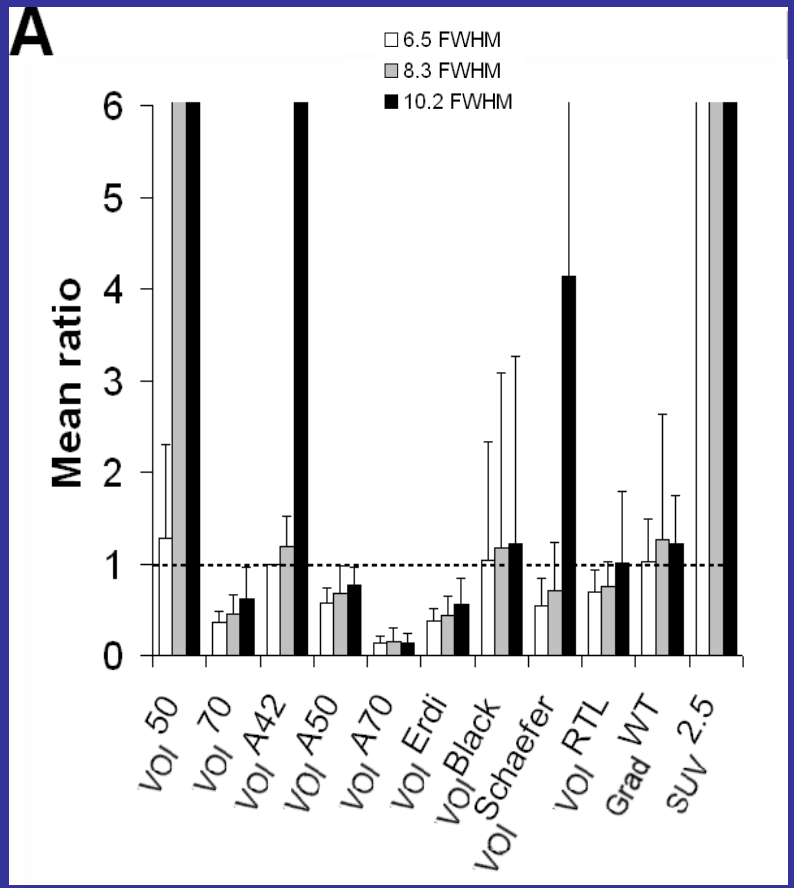


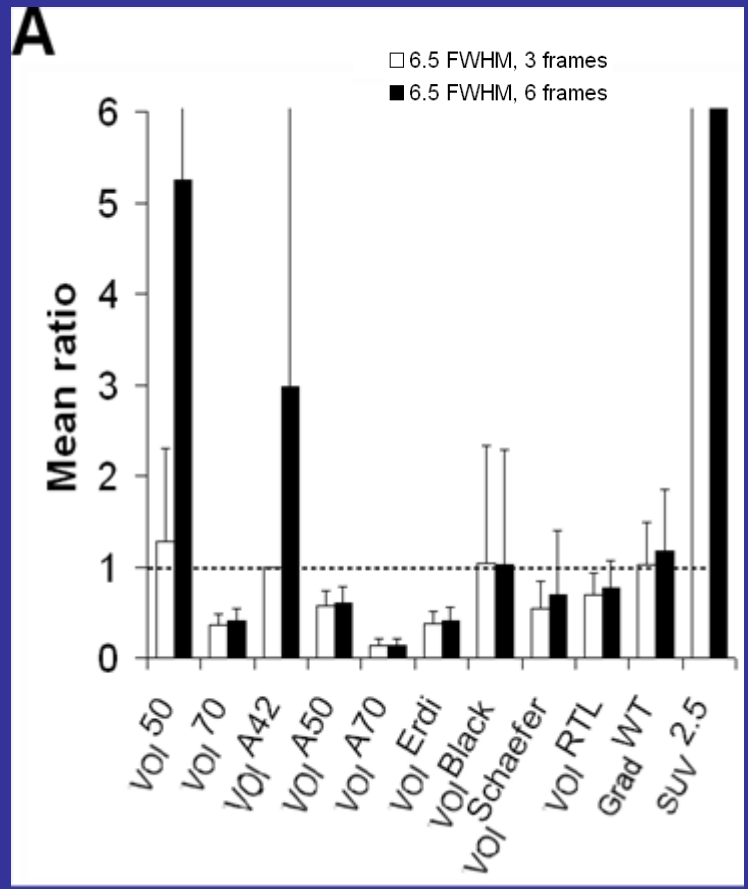




werk van D. Schinagl en W. Vogel 2006

However…..Impact of image characteristics on metabolic active volume assessment for several VOI methods (FDG)





Courtesy of P. Cheebsumon

FDG PET and PET/CT: EANM Procedure Guidelines for Tumour PET Imaging: version 1.0

Eur.J.Nucl.Med.Mol.Imag. 2010

Types of standards / recommendations

- Minimal performance standards:
  - "Focus" on accuracy
  - Lower threshold

- Harmonizing performance standards
  - "Focus" on reducing inter-institute, -scanner, -patient variability –'precision'
  - Lower and upper limits

The EANM guideline for FDG PET and PET/CT provides recommendations for:

- Minimizing physiological or biological effects by patient preparation guidelines
- Procedures to ensure accurate FDG administration
- Matching of PET study statistics ('image quality') by prescribing FDG dosage as function of patient weight, type of scanner, acquisition mode and scan duration
- Matching of image resolution by specifying image reconstruction settings and providing activity concentration recovery coefficients specifications (QC experiment)
- Standardization of data analysis by prescribing region of interest strategies and SUV measures
- Multi-center QC/QA procedures for PET and PET/CT scanners

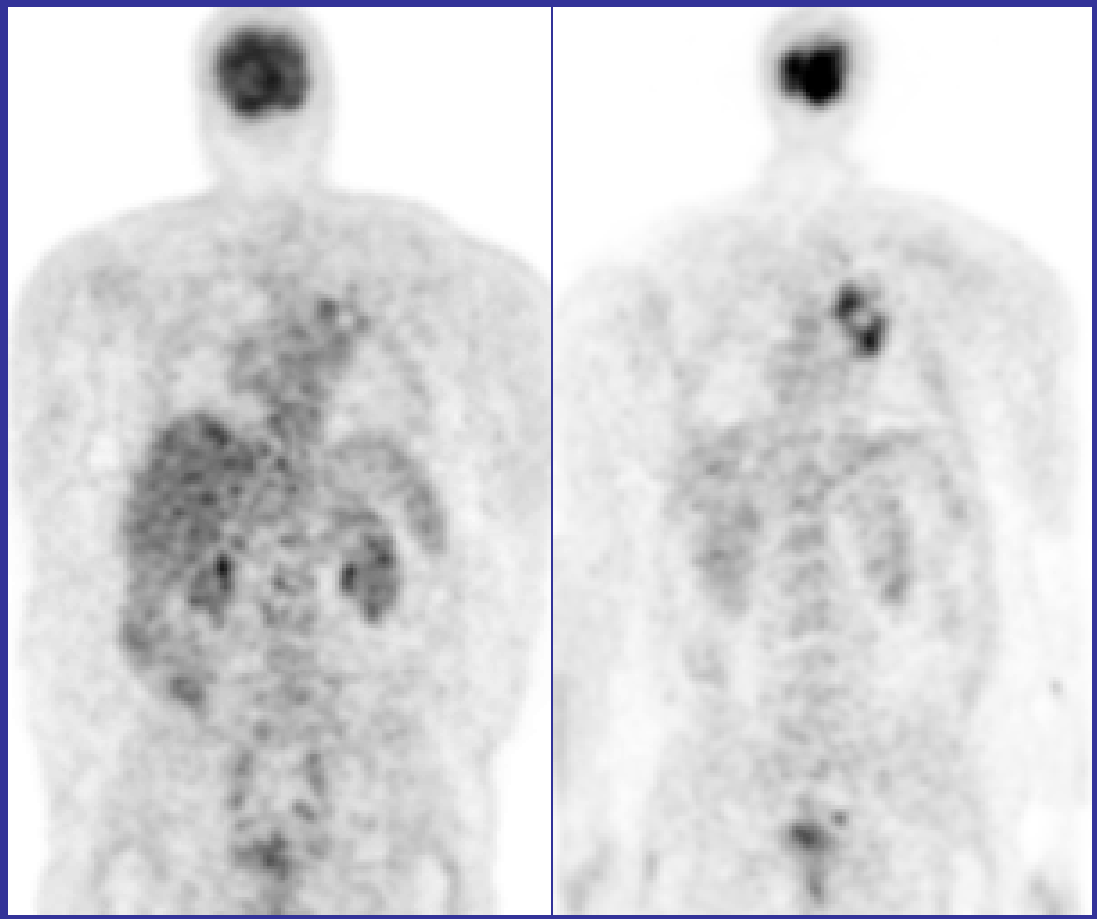
Patient preparation

Guidelines for patient preparation aim at optimizing uptake of FDG in tumors and minimizing uptake in surrounding tissue (muscle, brown fat). Secondly, to minimize patient related or physiological effects on SUV accuracy or reproducibility

- Short list of some items…
- Fasting
- Hydration before and during uptake period
- No or minimal exercise prior to study
- Blood glucose level
- Uptake period
- Patient comfort during uptake period, use of tranquilizers
- Patient weight and height
- Interval between PET and date of last cycle of chemotherapy etc

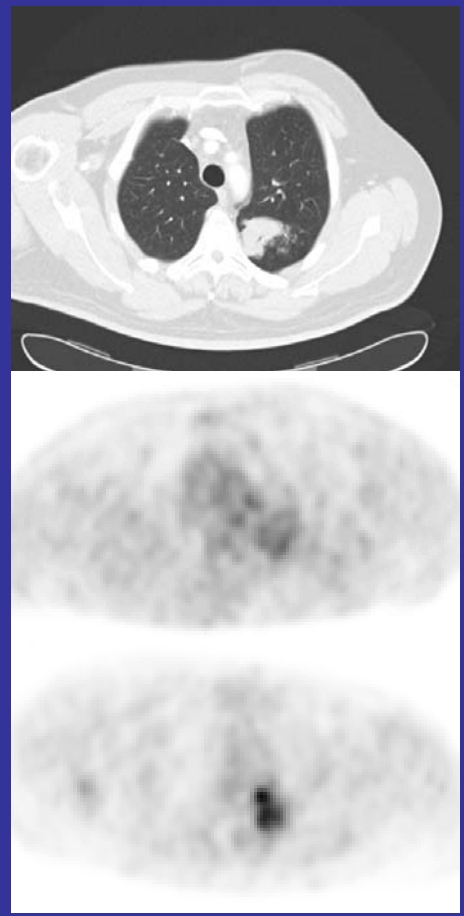
- Additional guidelines for patients suffering from diabetes type I and II

Impact of blood glucose level



Glu 200 mg%

Glu 79 mg%



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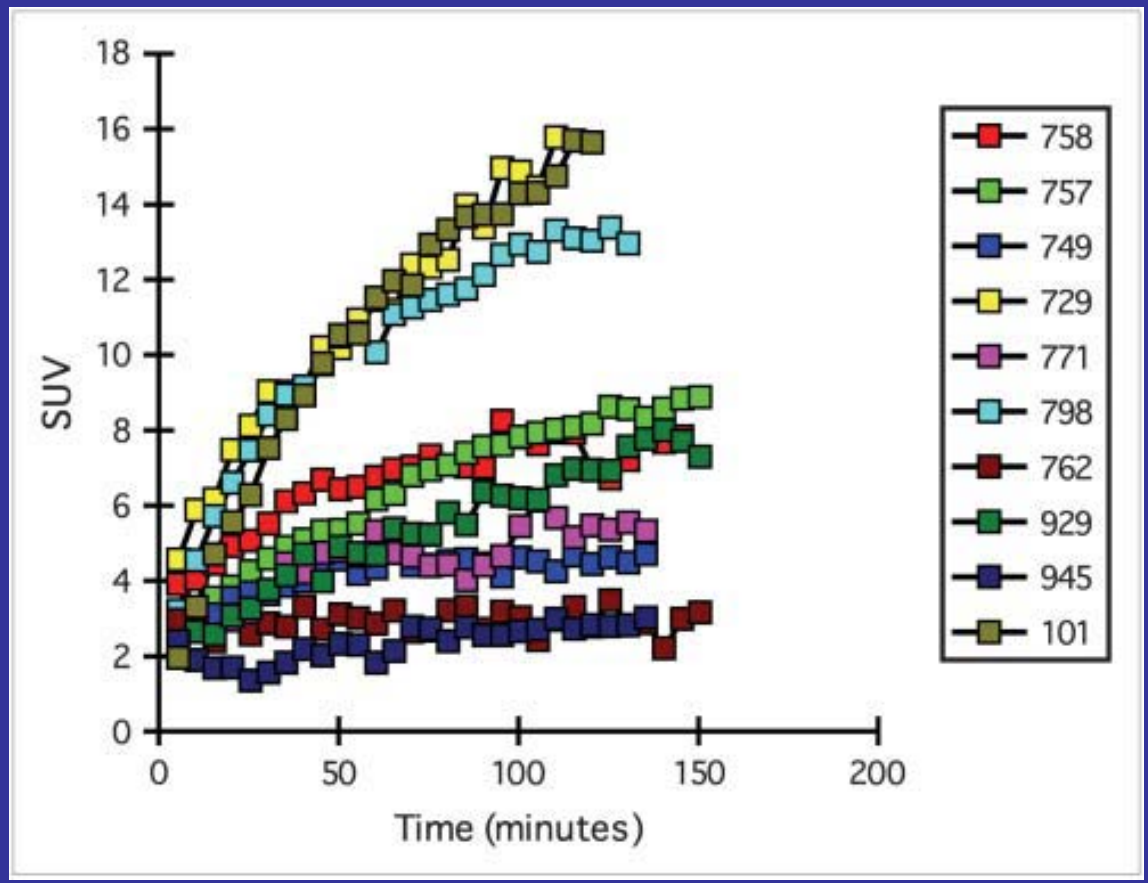
Factors affecting SUV
biological factors – uptake period



Lowe VJ *et al*. Optimum scanning protocol?for FDG-PET evaluation of pulmonary malignancy. J Nucl Med. 1995, image taken from Shankar et al. JNM 2006

FDG dosage and acquisition ‘image quality and quantification’

- Dosage and acquisition definitions aim at matching NEC (statistics, ‘image quality’) across scanners/institutes (to avoid upward bias in SUV)

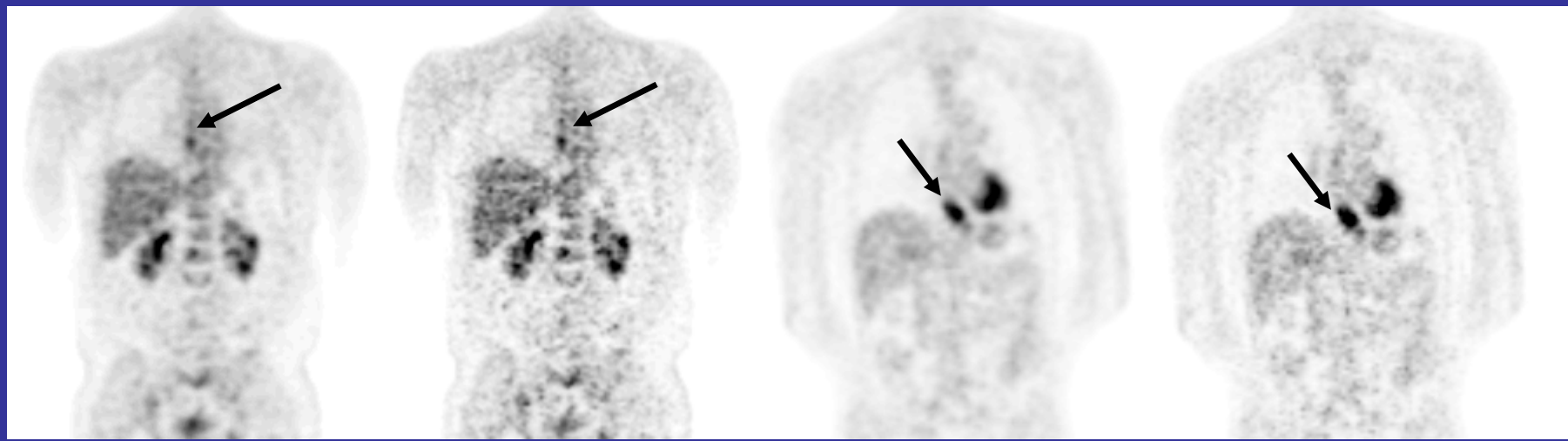
- Dosage is given as function of patient weight, scan mode, bed overlap and scan duration.

Image reconstruction

- Defined reconstruction settings aim at matching final image resolution (~7 mm FWHM=PET/CT) / convergence / contrast recovery across scanners, as this aspect has a large impact on quantification.

- Reconstruction settings will be based on MC-QC results

Effects of different number of OSEM iterations, as seen in the Netherlands, on SUV



SUVmax = 4.0	5.9	6.4	8.6
SUV 50%= 3.0	4.1	4.6	5.9

Analysis / VOI definitions

Required:

- Maximum voxel value (always)

Preferable:

- 2D SUV peak based on 1.2 cm diameter circular ROI
- 3D SUV peak based on 1.2 cm diameter spherical VOI

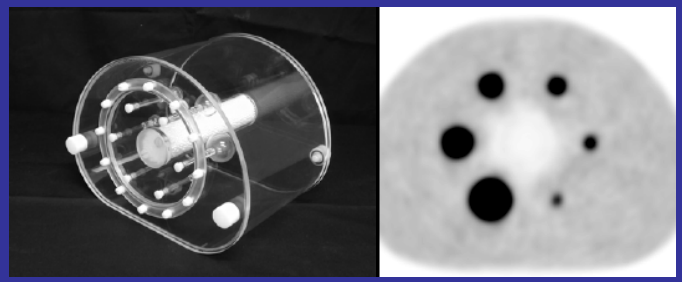
Optional:

- (adaptive) relative threshold 3D VOI
- Any other 3D VOI

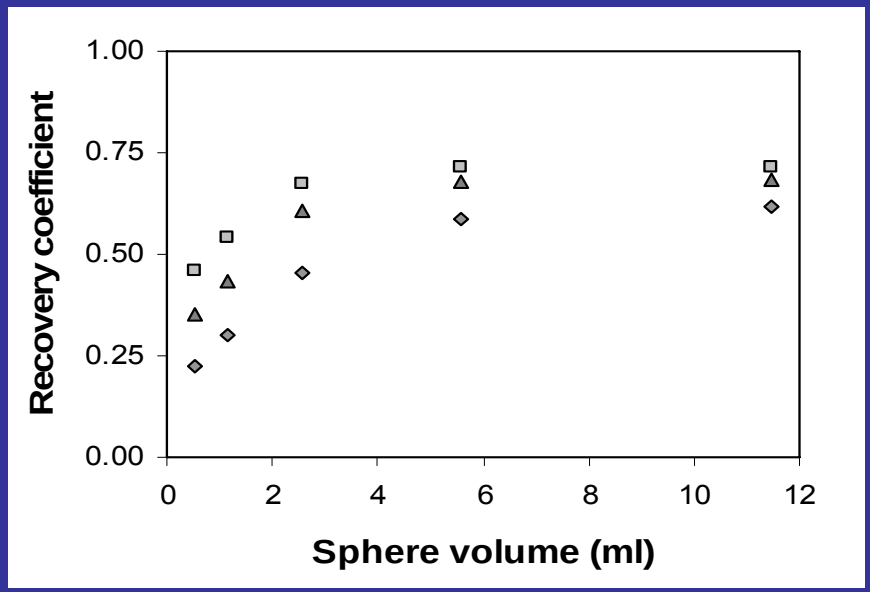
Multi-center QC and calibration

- Daily QC conform standard procedure of system / manufacturer
- Calibration QC using (cylindrical) phantom (15-30cm diameter)
- “Adjusted” NEMA NU 2-2001 Image Quality procedure/measurement to measure recovery coefficients as function of sphere size (= ‘effective image resolution’)
- CT-QC cf recommendations of ESR/national law
- Misc. QC (e.g. for scales, alignment etc)

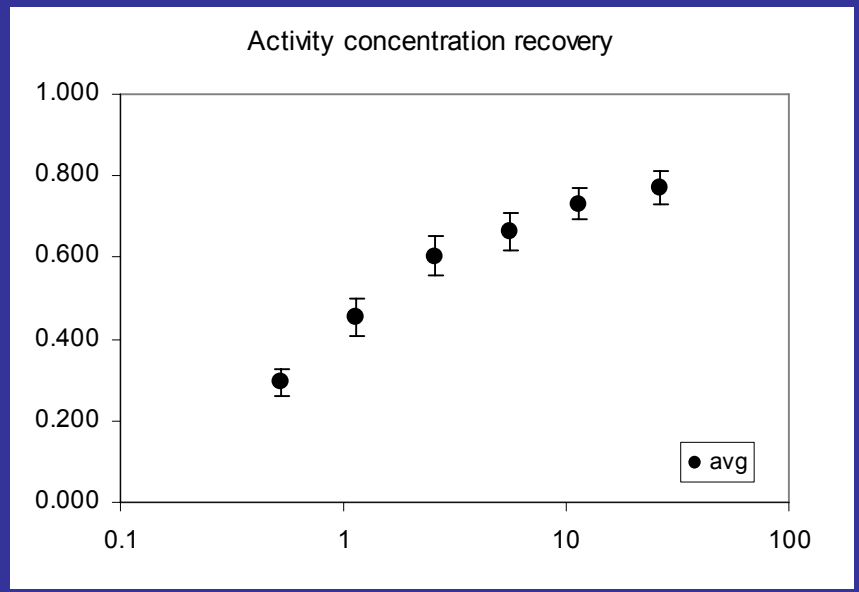
Absolute activity concentration recoveries – NEMA NU 2 2001 IQ Phantom



w/o



with standardisation



Right figure: Average (+/- 1 SD) activity concentration recovery coefficients as function of sphere size observed with image quality quality control measurements at 8 different scanners

UK multi-centre PET clinical trials network

- *Multi-centre trials network operating since 2002*
- Informal network set up by St Thomas' PET Centre
- FDG PET only
- 3 Studies completed / 2 in progress / 2 in preparation
- Accreditation and QC procedures
- Standardised data acquisition / analysis
- Anonymised data transfer
- Centralised or local reporting

- *Future developments*
- Adoption of trials network by UK National Cancer Research Institute (NCRI)
- Develop audit processes
- Improved IT infrastructure
- Introduce new tracers

Courtesy of M. O'Doherty

Currently ~21 accredited sites

Status of multi-center calibration in NL

QC experiments performed in approximately 23 sites

Disapproved

- 3 sites showed deviation > 30% (1 corrected)
- 1 site showed deviation of ~ 15%

Approved:

- 8 sites showed deviation of 5 to 7%
- 11 sites showed deviation < 5%

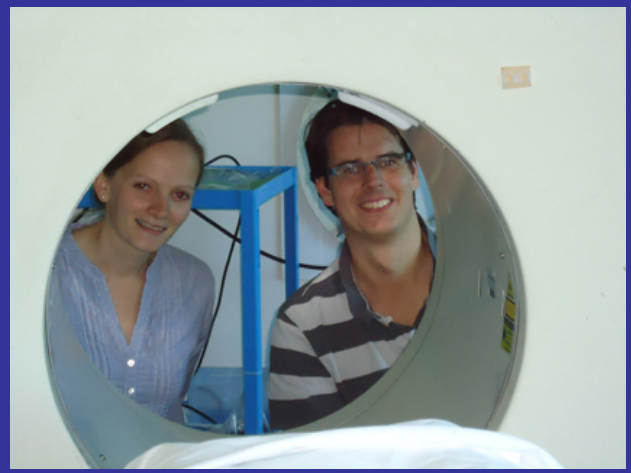
European accreditation program EARL, EANM, EORTC

Based on the QC experiments as described in the EANM guideline published in EJNMMI 2010

Pilot (in collaboration with EORTC) starts in autumn 2010

Manuals, SOPs, online questionnaire finished in august 2010

Training of EARL coordinator (S. Ettinger) dd 3-9-2010



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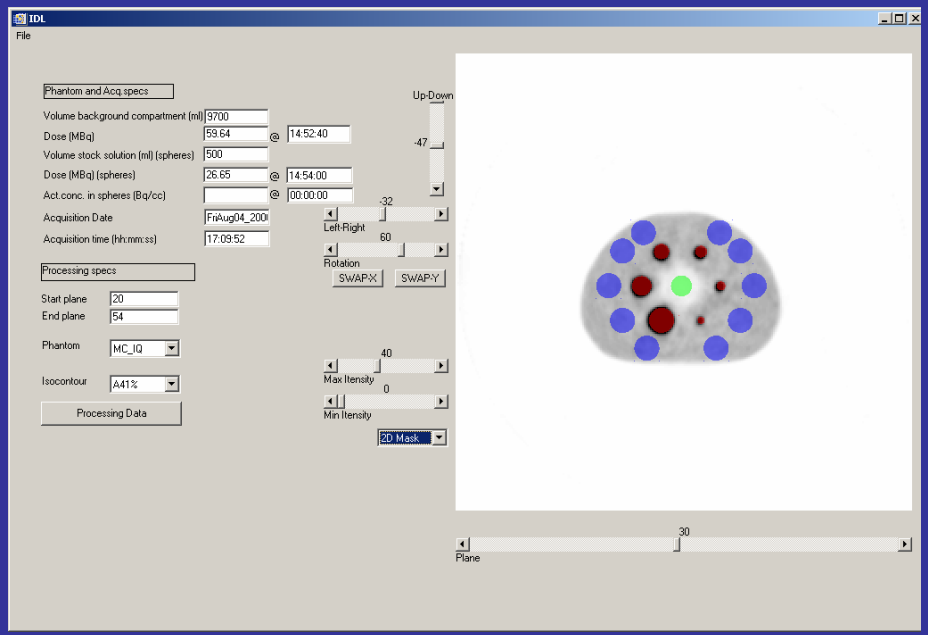
Software tools:



Calibration QC:
- Automatic VOI placement
- Verification of calibration
- Verification of inter-&intra-plane uniformity

IQ QC
- Recovery coefficients (volume & act.conc.)
- Cold spot recovery using central insert (scatter)
- Verification of calibration using back ground VOI

Now: ready to start pilot

Accreditation results so far… trial EORTC_22071-24071

- 11 sites/12 PET/CT systems

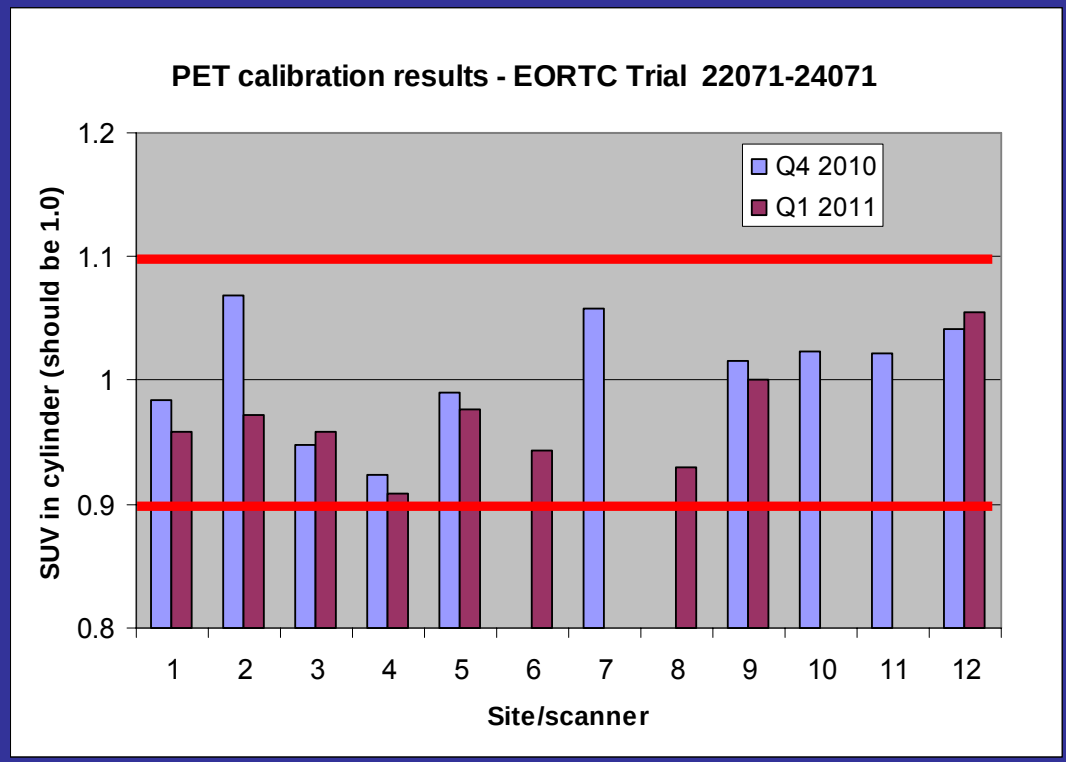
Startup issues:

- Initially some issues reading files: resolved
- For some sites there were some unclarities wrt clocks/reported times
- Phantom availability: resolved, EANM purchased phantom for distribution
- A lot of queries (both parties) and discussions…

- Data entry issues: please enter correct information in submission webpage while uploading data

Accreditation results so far… trial EORTC_22071-2407: basic calibration

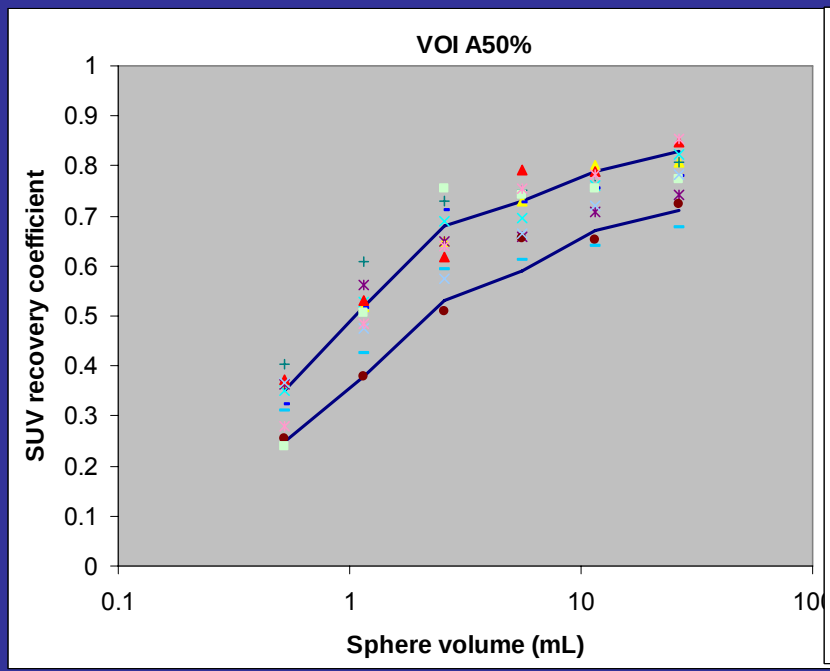
- 11 sites/12 PET/CT systems
- All sites approved since last week

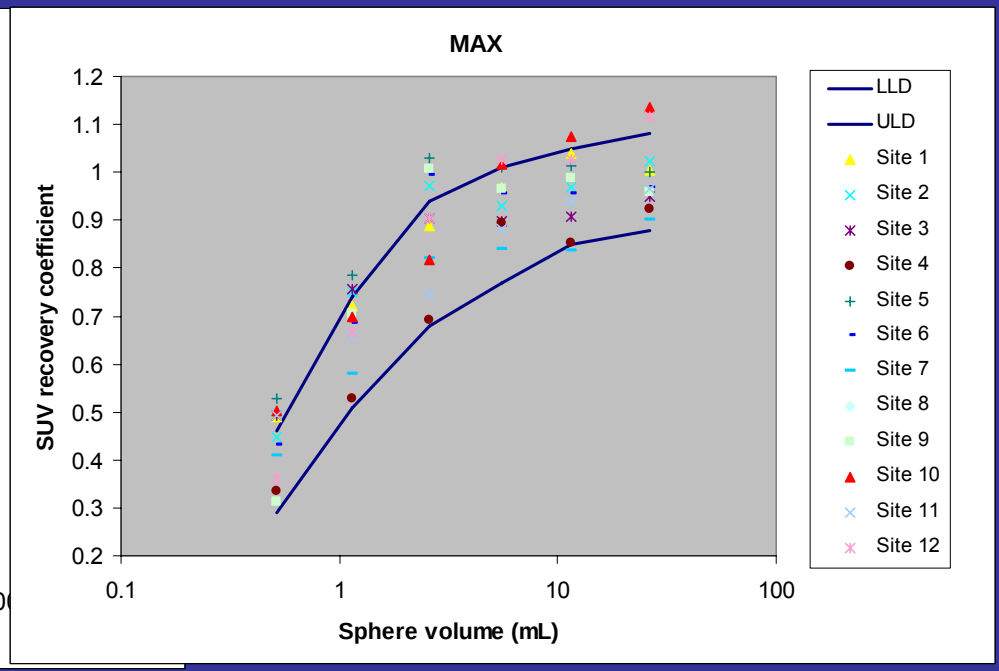


- 2 sites needed re-calibration and/or adjustement of reconstruction settings

Accreditation results so far… trial EORTC_22071-2407: IQ/recovery

- 11 sites/12 PET/CT systems
- All sites approved since last week





Study on test-retest repeatability 'effects of central read and QA'

- TRT study was part of a pharma initiated phase 1 study
- 61 subjects with advanced gastrointestinal malignancies
- 8 academic sites (5 USA, 2 Canada, 1 Netherlands)
- Double baseline whole body FDG PET studies each within 7 days and both within 14 days prior to treatment

- Data analyzed at local site and at central imaging core lab and central reader (VUMC, Boellaard)

Multi-center study w/o standardisation *effects of QA*

QA performed by image core lab (@ VUMC, Boellaard et al):

- Scans were excluded for technical reasons (corrupted files, incorrect data format, absence of calibration of scaling factors)
- Inconsistencies between CRF and DICOM header information
- High (or absent) plasma glucose levels
- 45 out of 61 scans passed QA

SUV_{max} Relative Absolute Baseline Differences (RelAb_d*) (%)

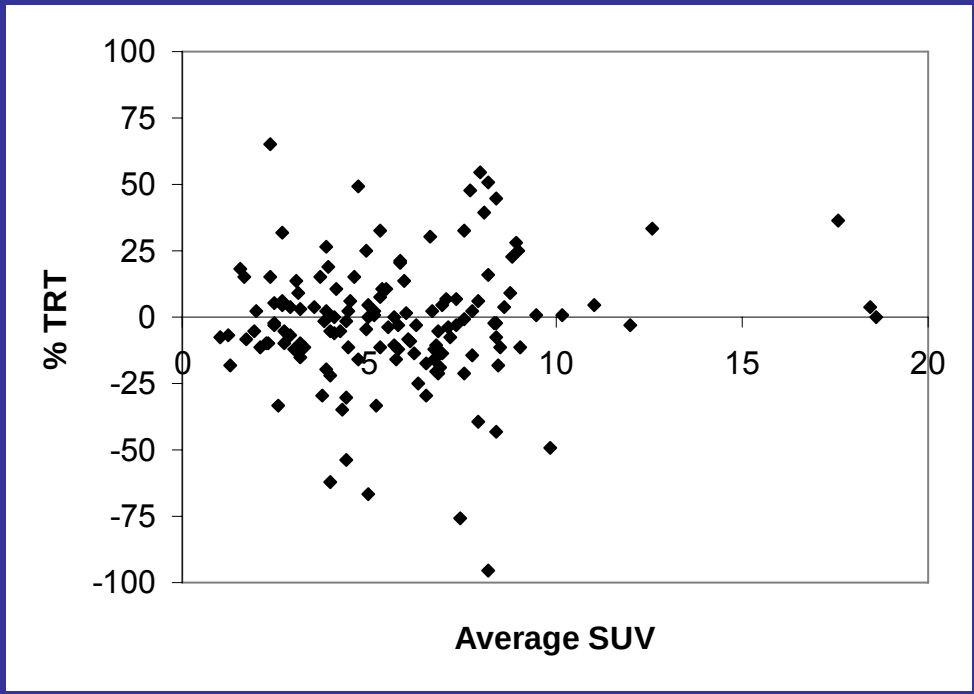
SUV_{max} Value Across Lesions	Full Dataset N=61	QA Dataset N=45	
	Multi-Observer Mean (SD)	Multi-Observer Mean (SD)	Single-Observer Mean (SD)
Average SUV_{max}	14.7 (14.3)	12.2 (9.3)	11.7 (7.9)
Maximum SUV_{max}	14.7 (15.0)	12.1 (9.3)	12.7 (8.7)

*RelAb_d=absolute percent difference at baseline relative to average of two baseline values
SD=Standard Deviation

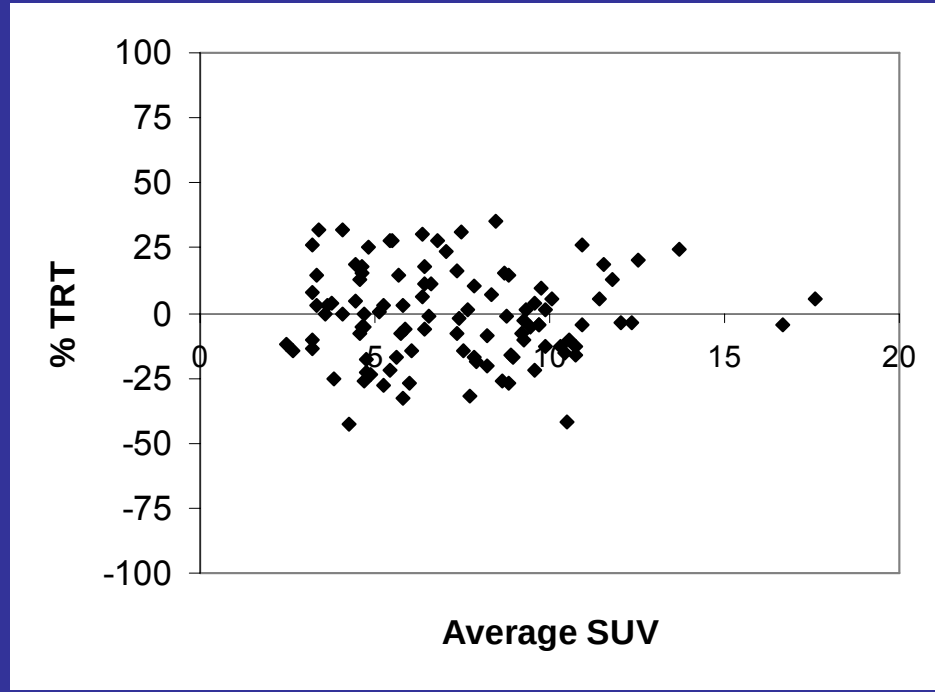
Velasquez, Boellaard et al, JNM 2009

Results: Effects of central QA and data analysis (SUV^{max})

All, local read

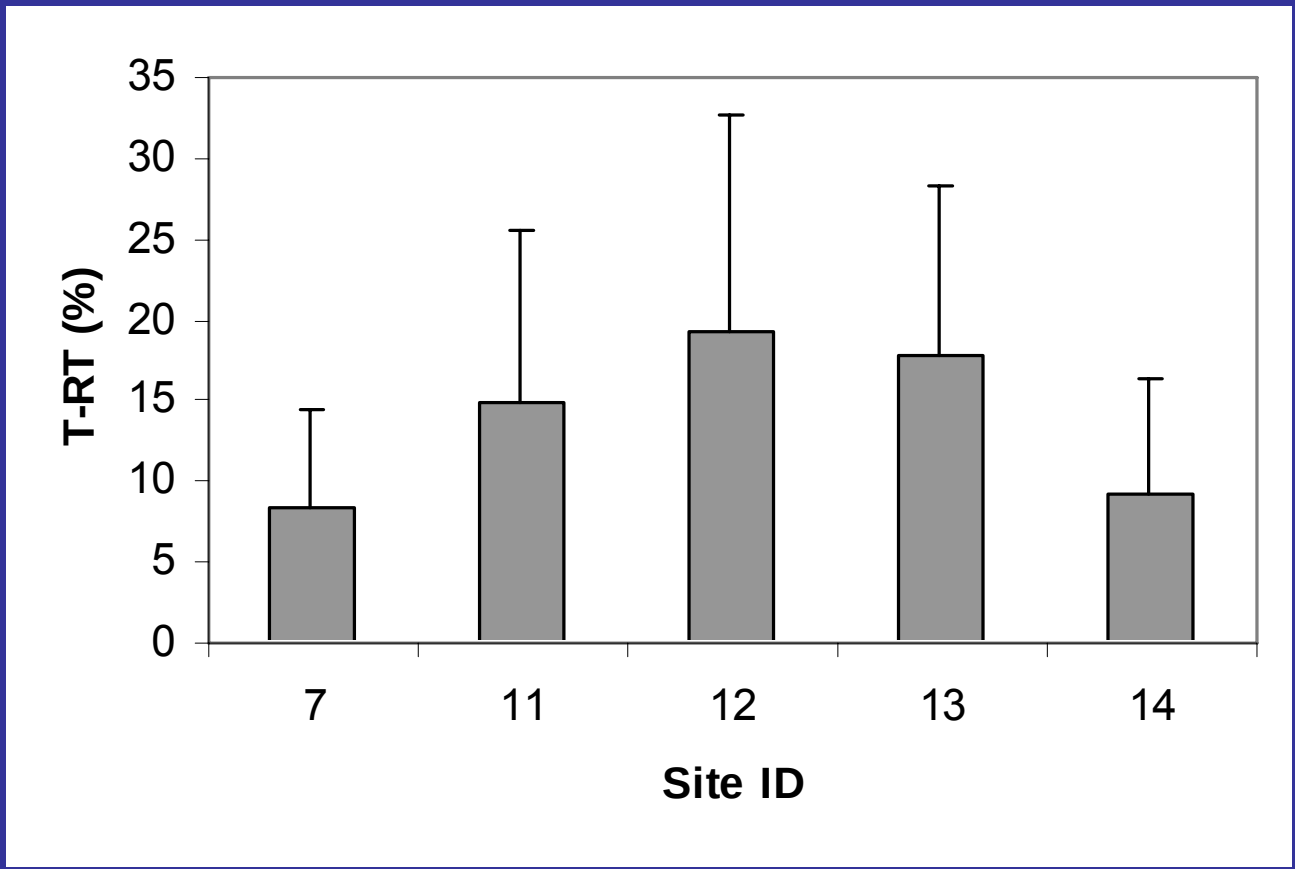


QA, central read

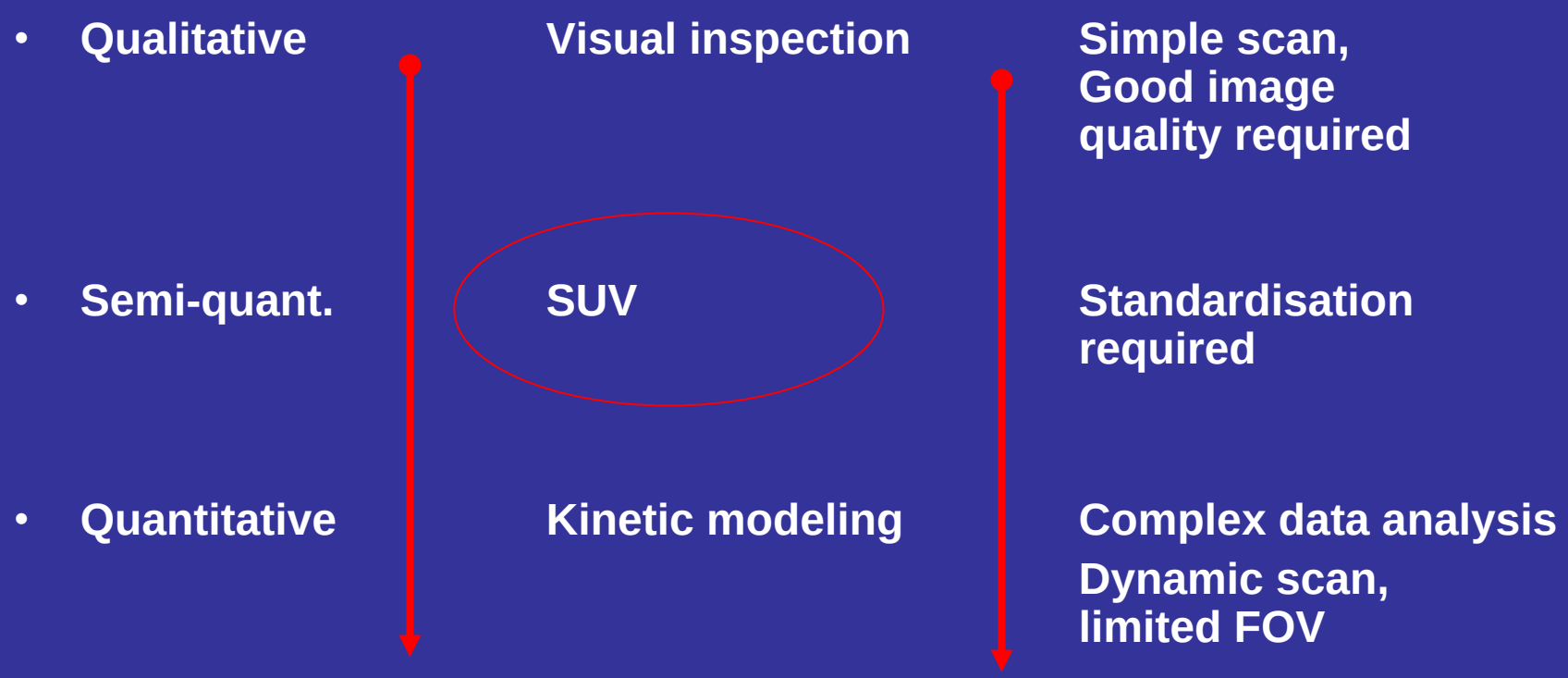


Centralized QA mainly removes outliers

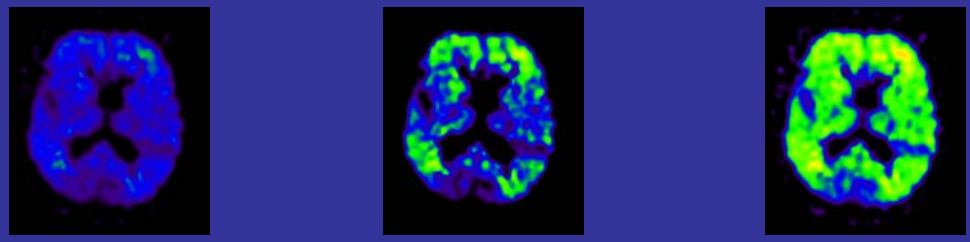
Multi-center study w/o standardisation



Methods of FDG PET quantification in oncology



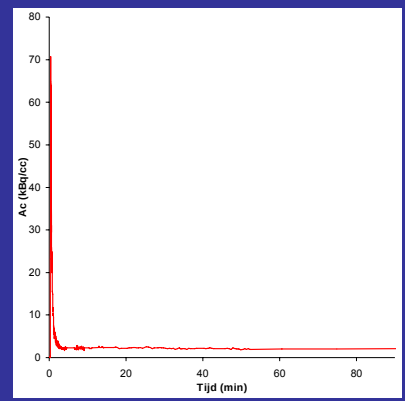
PET pharmacokinetic modeling



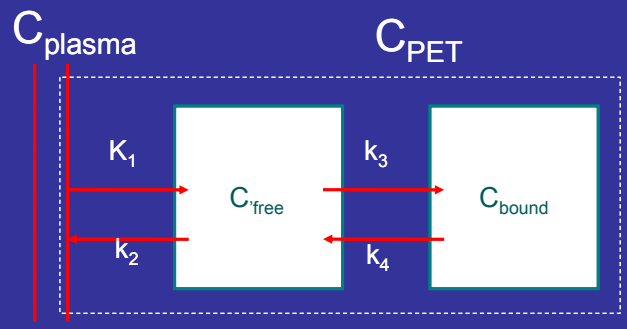
time

Time course and magnitude of uptake depends on:

- Input function (patient and tracer specific)
  - availability of the tracer over time
  - faster clearance = lower uptake in tissue/tumor
  - faster metabolism = lower uptake in tissue/tumor

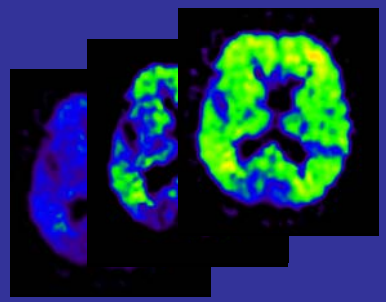


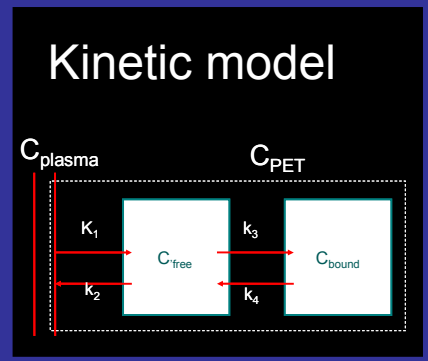
- Kinetic behavior of tissue/tumor (perfusion, binding, washout etc)
  - higher perfusion can result in increased uptake, but also in increased washout
  - more binding sites = increased uptake
  - reversible vs irreversible uptake/binding
  - etc



Courtesy of Yaqub *et al.*

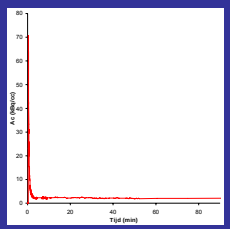
PET pharmacokinetic modeling

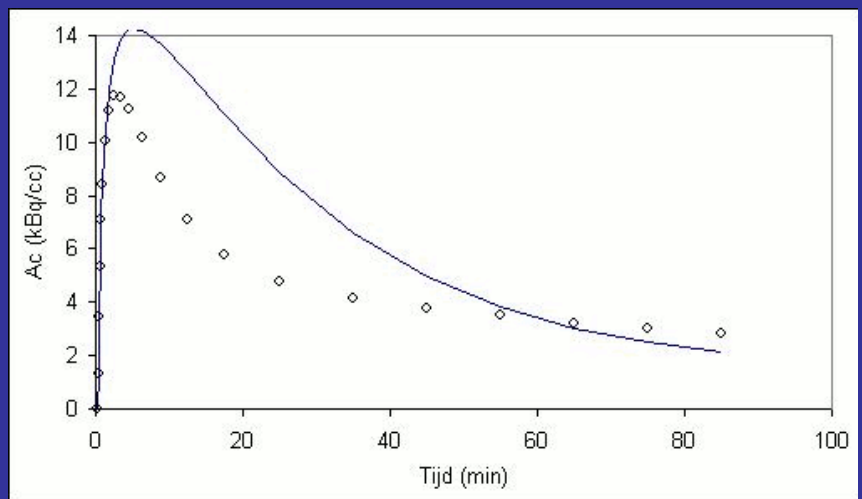




Fit routine

Input function

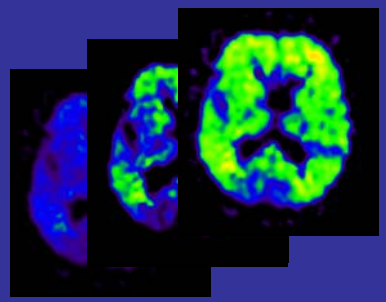




K1,k2,k3 = ??

Ki, MRGlu = ??

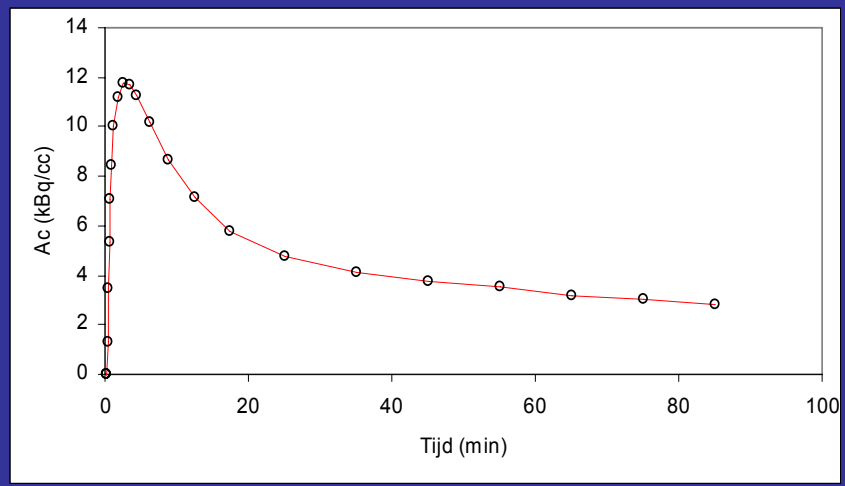
PET research studies



Kinetic model

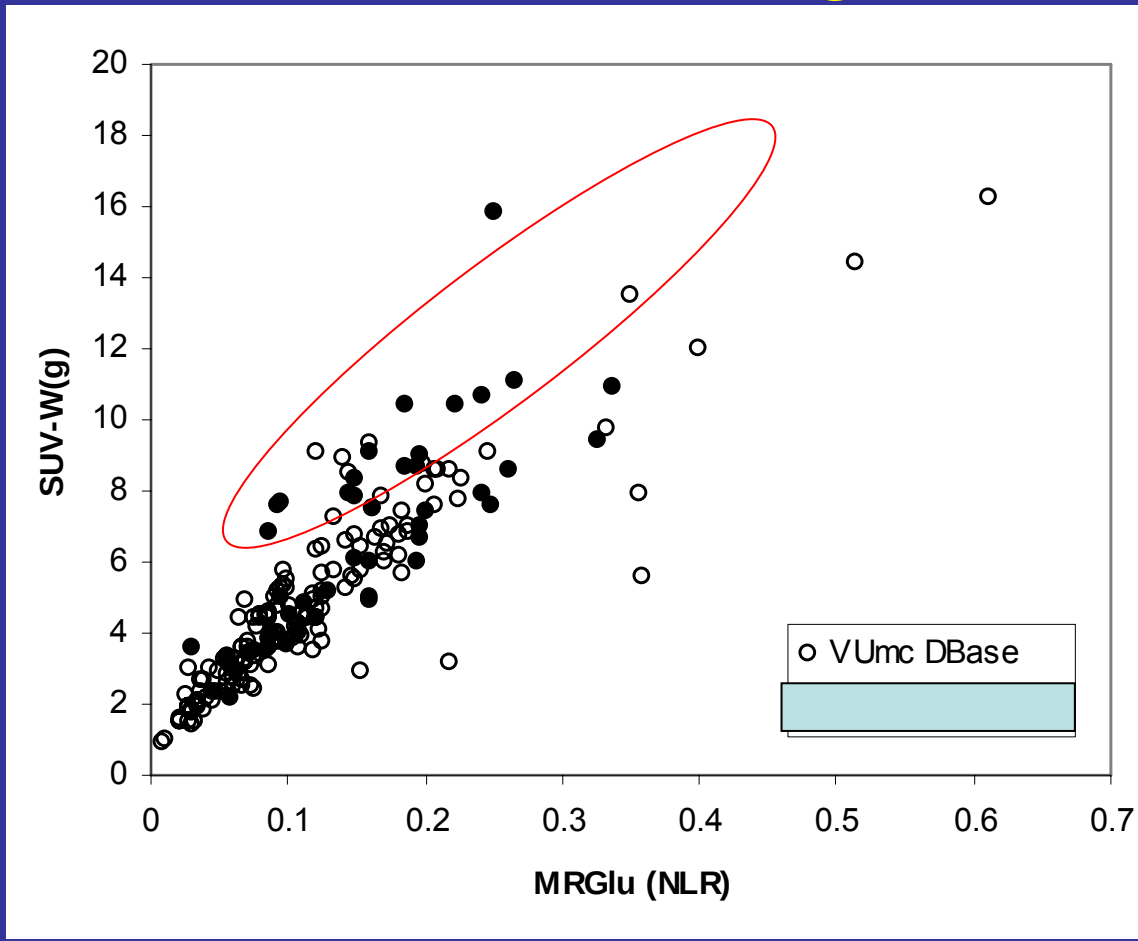
Fit routine

Input function

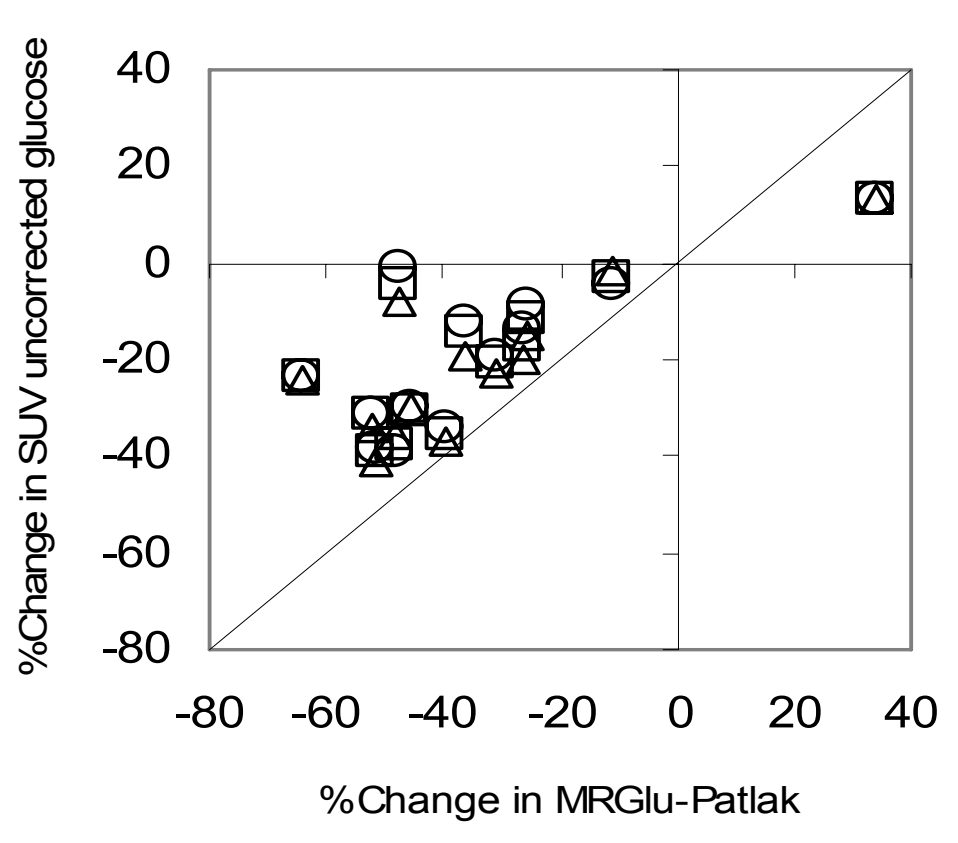


MRGlu assessed

Change in SUV vs change in MRGlu:
need for validating SUV ?



Change in SUV vs change in MRGlu: *need for validating SUV ?*



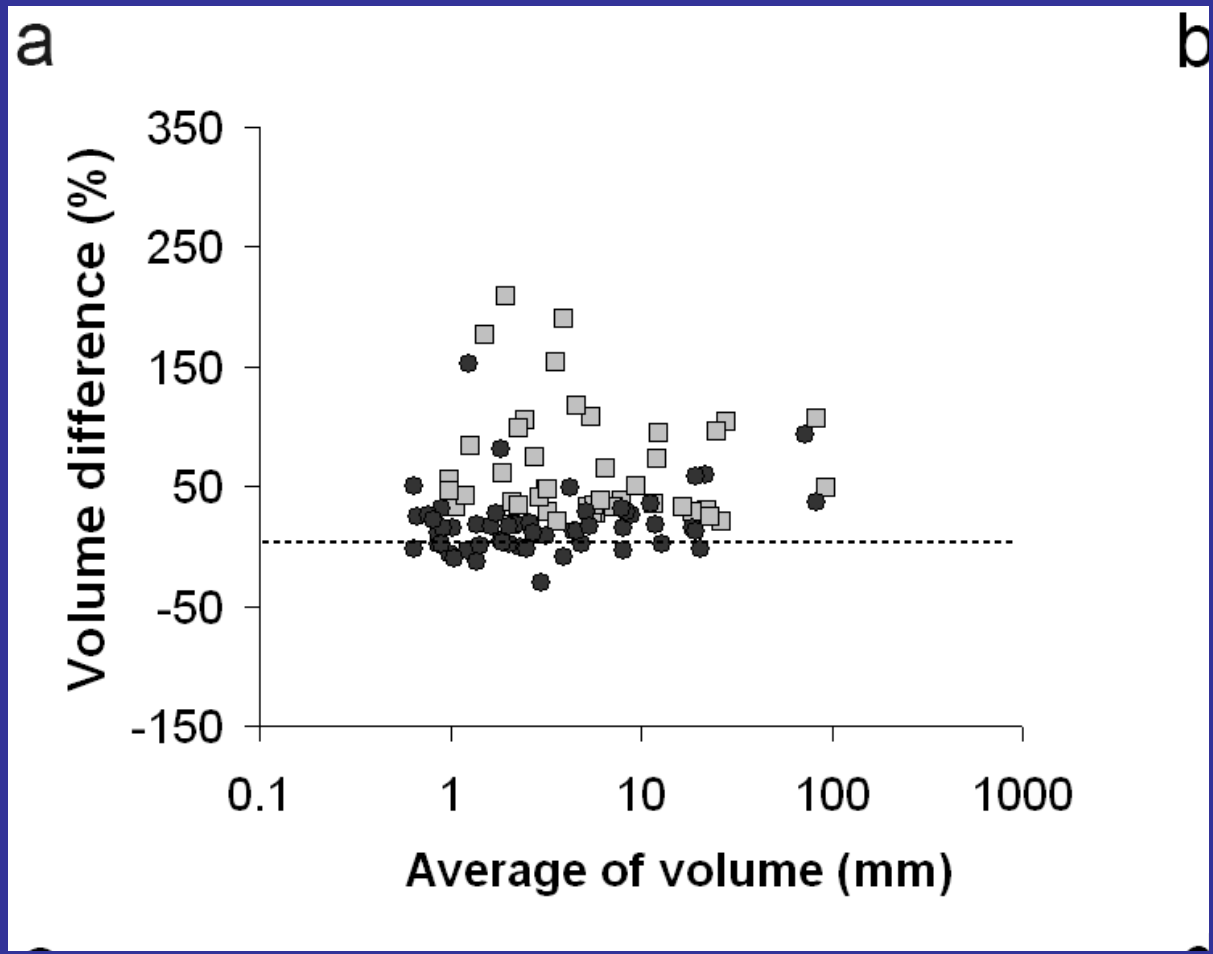
Drug affected clearance of FDG from blood

SUV may underestimate efficacy of a new drug/therapy

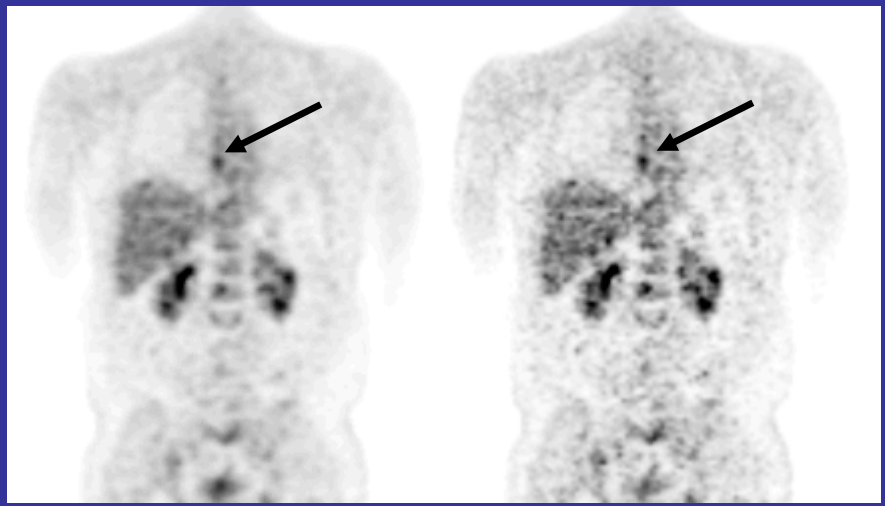
Use of PET in for response monitoring

1. Phase I, IIA: Validation of SUV response
   - SUV versus Ki, MRGlu (dynamic scans, kinetic analysis)
   - % Δ SUV versus % Δ Ki, MRGlu
2. Larger multi-center studies:
   - Standardisation
   - QA/QC procedures specific for multi-center quantitative FDG PET studies = scanner validation & site accreditation
   - Data analysis/QA performed by image core lab

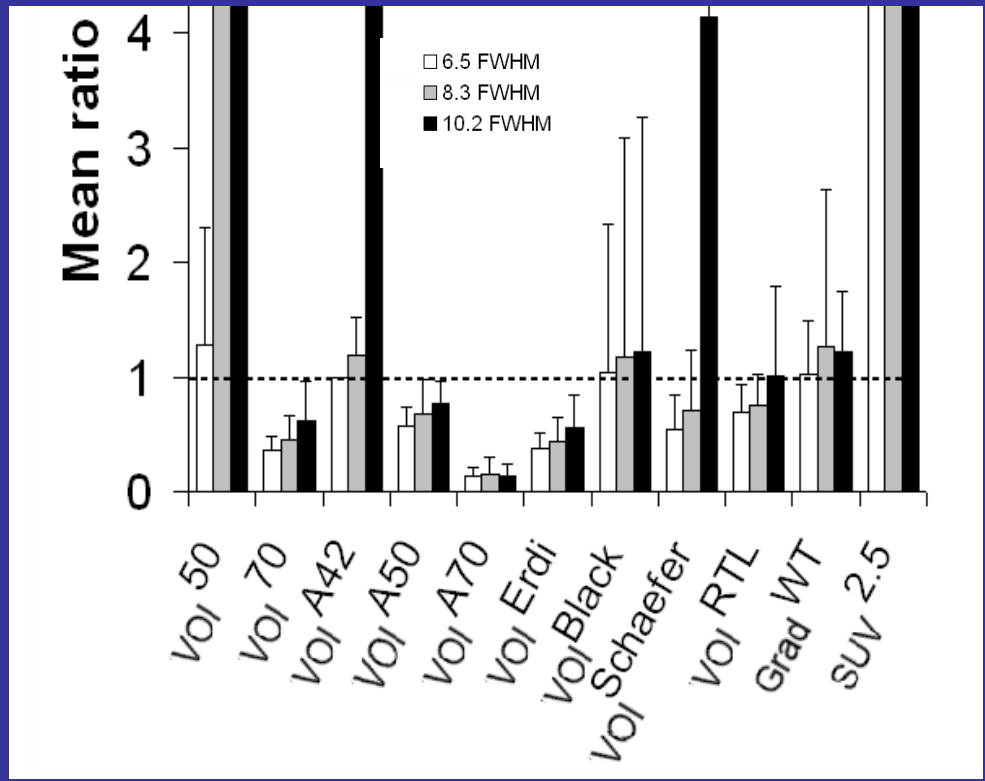
Dynamic vs static imaging impact on VOI performance



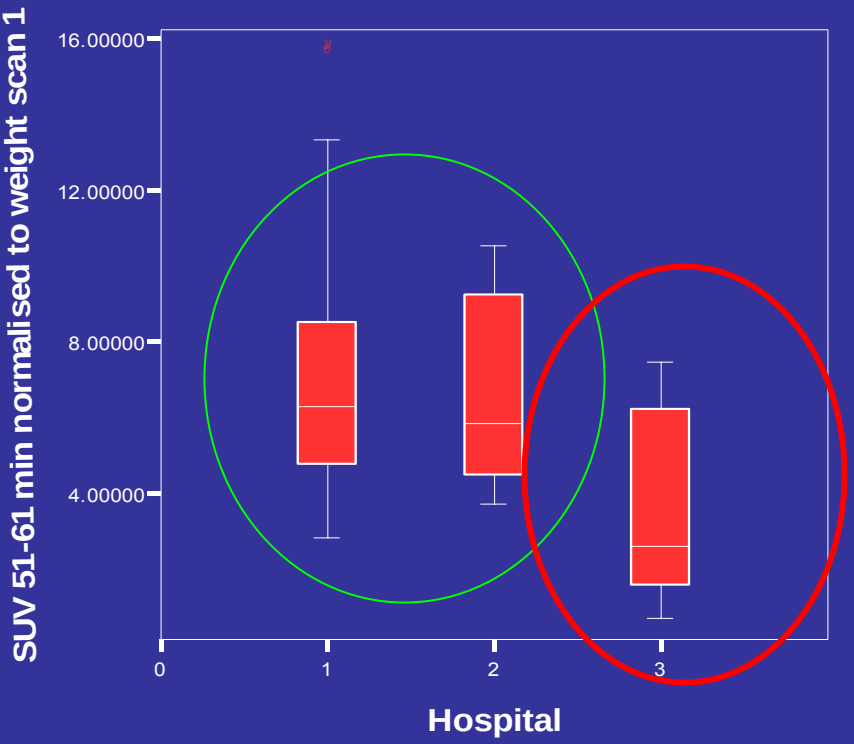
Impact of image characteristics on SUV (left) and metabolic active volume assessment (right)



SUVmax = 4.0 5.9
SUV 50%= 3.0 4.1



Why do we need a guideline for quantitative FDG PET ?



Recent (2009) observation on site differences in SUV
-Site 1 & 2 closely followed NL standardized protocol
-Site 3 did not – almost factor 2 lower SUV on average

The SUV (and BTV!) does not exist and cannot be used in clinical trials/research studies……unless it is …….

- validated
- standardized
- QC'd
- QA'd

FDG PET and PET/CT: EANM Procedure Guidelines for Tumour PET Imaging: version 1.0

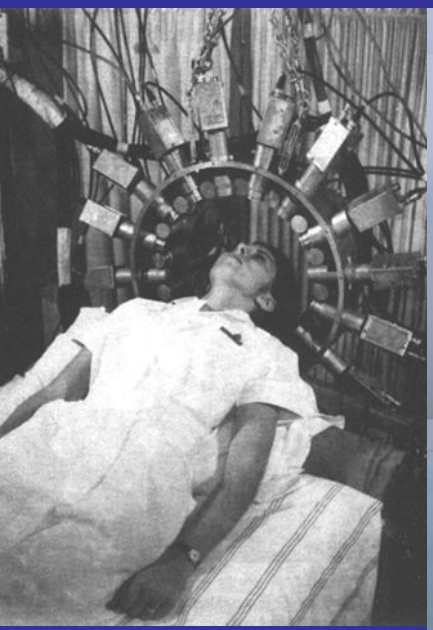
FDG PET and PET/CT: EANM Procedure Guidelines for Tumour PET Imaging: version 1.0

Ronald Boellaard, Mike O'Doherty, Wolfgang A. Weber, Felix M. Mottaghy, Markus N. Lonsdale, Sigrid G. Stroobants, Wim J.G. Oyen, Joerg Kotzerke, Otto S. Hoekstra, Jan Pruim, Paul K. Marsden, Klaus Tatsch, Corneline J. Hoekstra, Eric.P. Visser, Bertjan Arends, Fred J. Verzijlbergen, Josee M. Zijlstra, Emile FI Comans, Adriaan A. Lammertsma, Anne M. Paans, Antoon T. Willemsen, Thomas Beyer, Andreas Bockisch, Cornelia Schaefer-Prokop, Dominique Delbeke, Richard P. Baum, Arturo Chiti, Bernd J. Krause.

Eur.J.Nucl.Med.Mol.Imag. 2010

Thank you for your attention!

PET

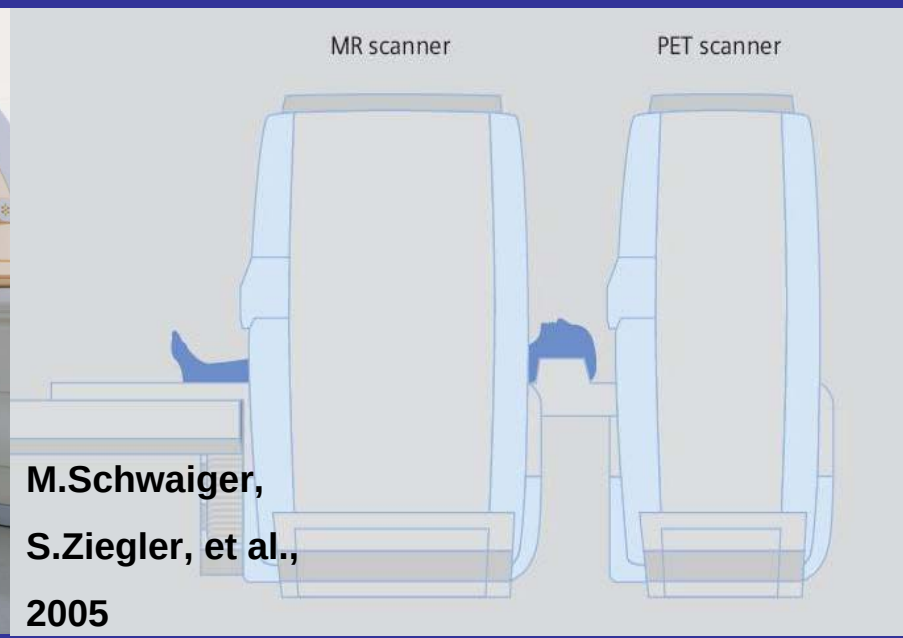


1975

PET-CT

Today

PET-MRI



M.Schwaiger, S.Ziegler, et al., 2005

Today/tomorow