PET/CT imaging for response monitoring in multicenter studies: An update and future challenges

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Disclosures

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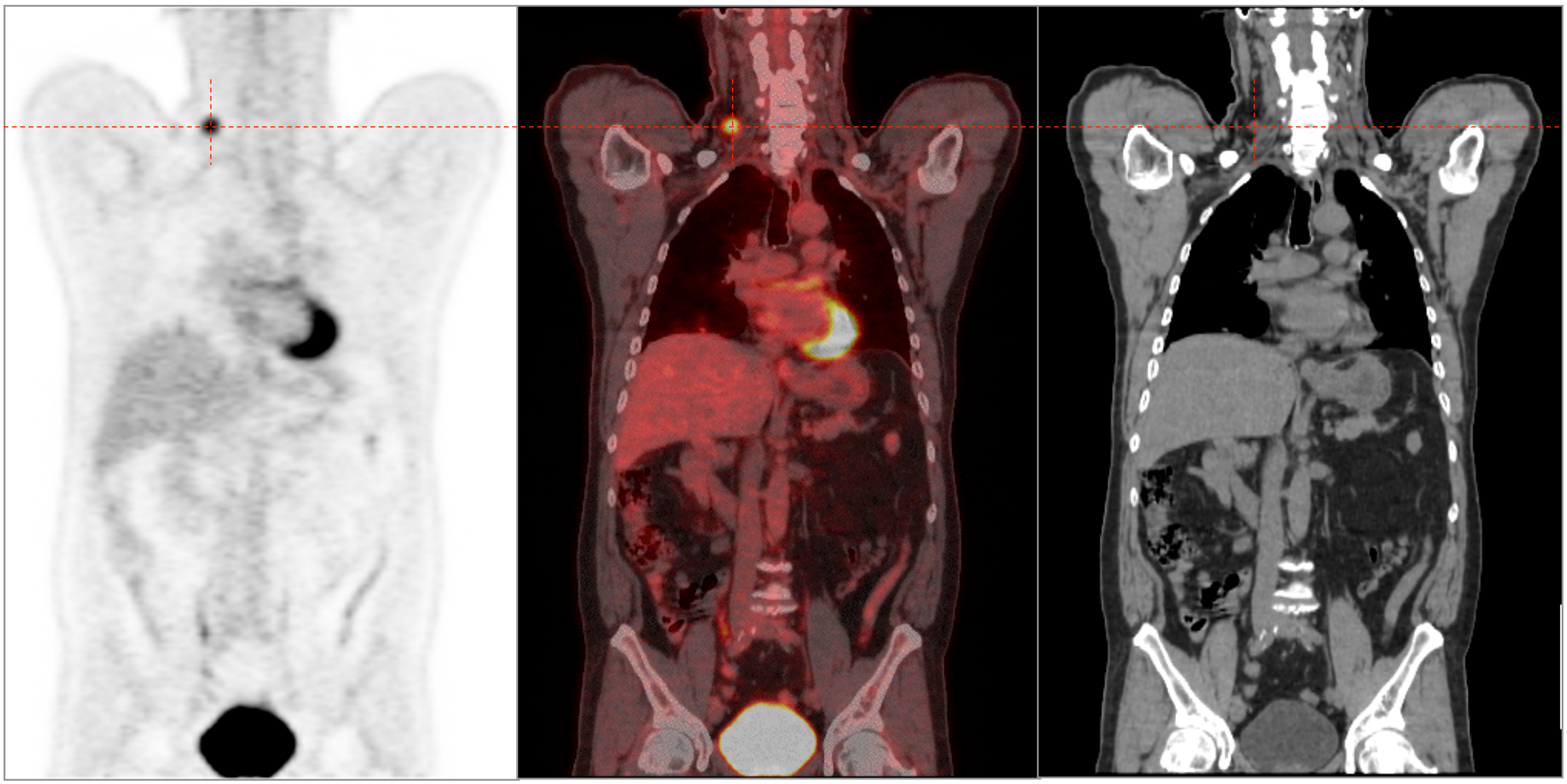
PET/CT Imaging is a powerful tool for detection, diagnosis, and staging of cancer

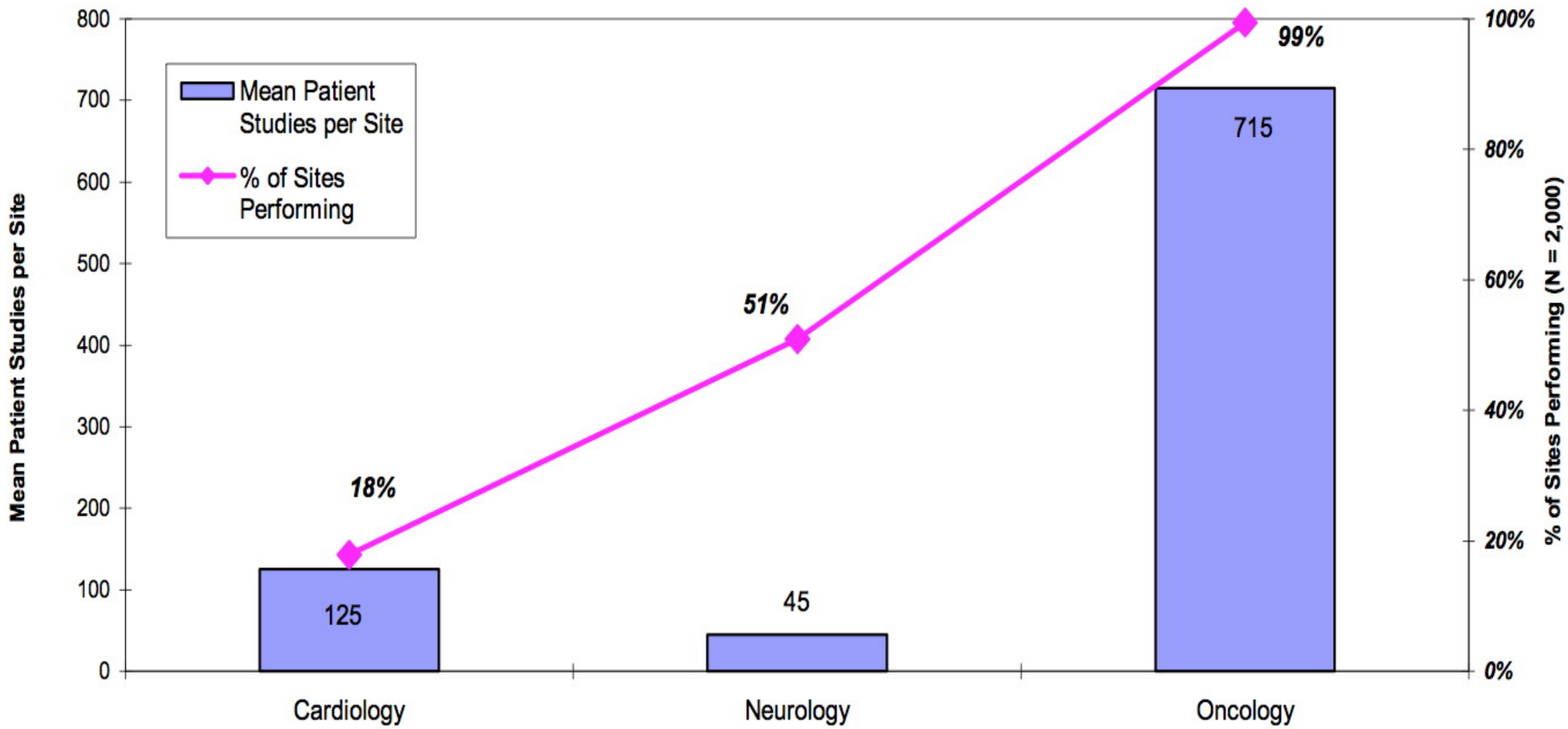


PET Image of Function

Function+Anatomy

CT Image of Anatomy

Clinical Applications



IMV 2008 PET Imaging Market Summary Report

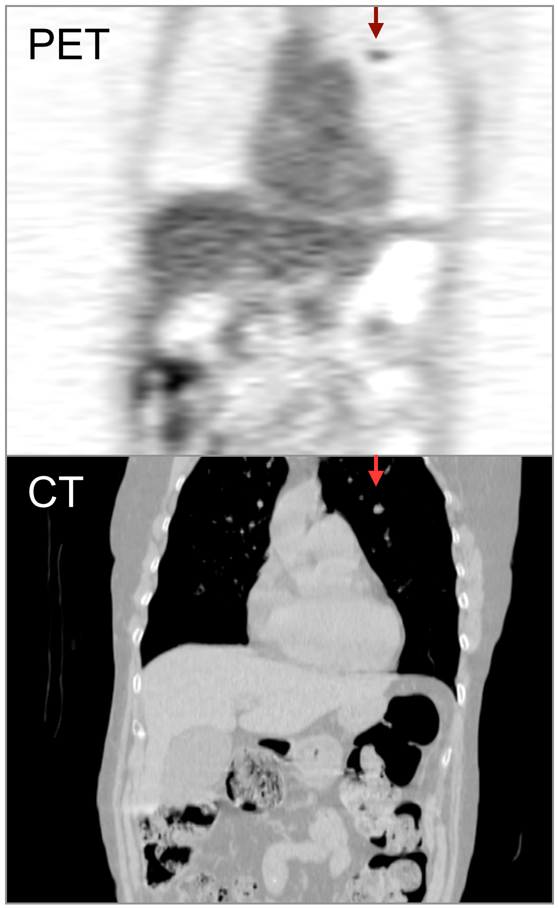
Diagnostic Accuracy of PET/CT exceeds CT or PET only

Tumor entity	References	Purpose of the imaging studies	Number of patients	Accuracy (%)		
				PET/CT	PET	CT
Head and neck	Chen *et al*. (2006)[35]	TNM staging	70	95	83[a]	73[a]
	Schoder *et al*. (2004)[36]	Lesion detection	68	96	90[a]	ND
NSCLC	Lardinois *et al*. (2003)[24]	T stage N stage	40 37	98 84	80[a] 87	78[a] 64
	Shim *et al*. (2005)[37]	T stage N stage	106 106	86 84	ND ND	79 69[a]
Colorectal	Kim *et al*. (2005)[10]	Recurrence	51	88	71[a]	ND
	Votrubova *et al*. (2006)[38]	Recurrence	84	90	75[a]	ND
Lymphoma	Allen-Auerbach *et al*. (2004)[33]	(Re)staging	73	93	84[a]	ND
	la Fougère *et al*. (2006)[39]	(Re)staging	50	99	98	89[a]
Melanoma	Reinhardt *et al*. (2006)[31]	(Re)staging	250	97	93[a]	79[a]
	Mottaghy *et al*. (2007)[40]	(Re)staging	102	91	92	ND

[a]Statistically significant difference when compared with PET/CT. Abbreviations: NSCLC, non-small-cell lung cancer; ND, not determined; TNM, tumor node metastasis.

Weber et al. Nature Reviews Clinical Oncology 2008

“Is quantitation necessary for clinical oncological PET studies interpreted by physicians with experience in interpreting PET images?” - “no.”

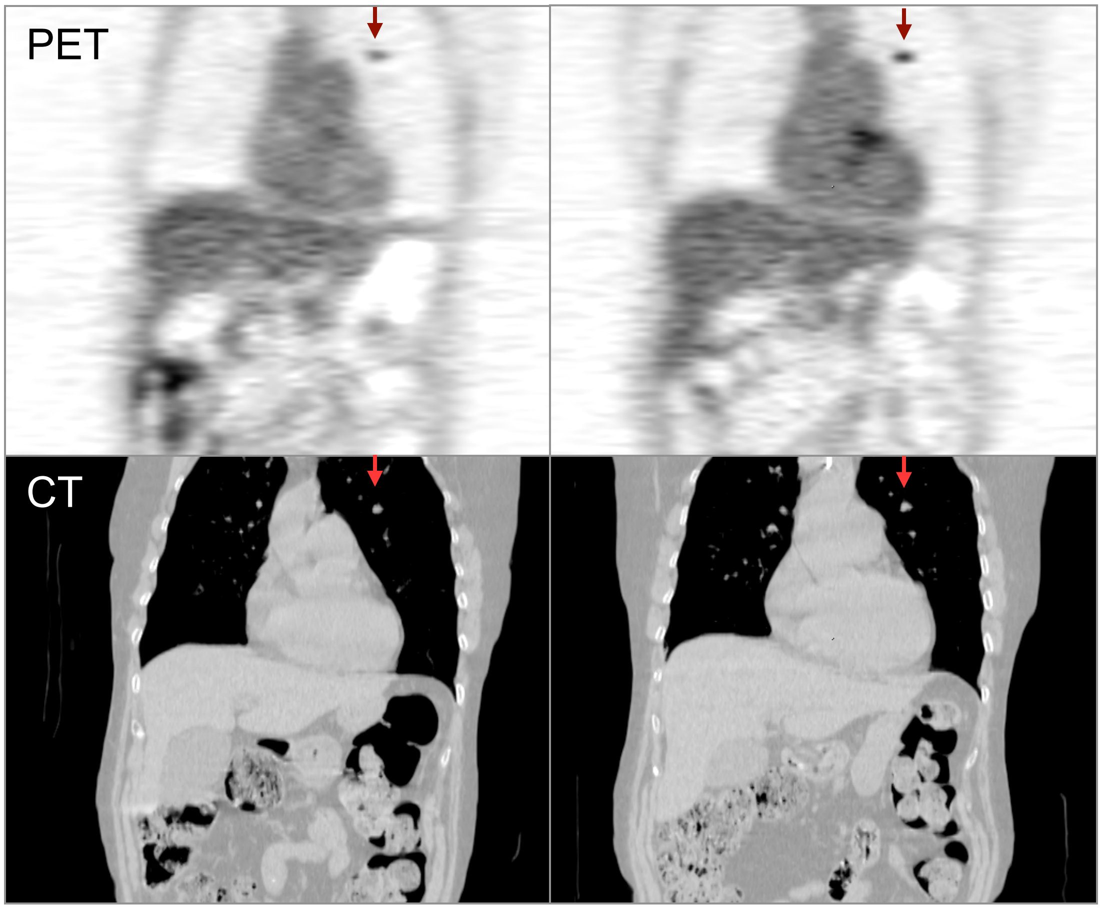


baseline scan

“Is quantitation necessary for clinical oncological PET studies interpreted by physicians with experience in interpreting PET images?” - “no.”

Image quantitation will become increasingly important in determining the effect of therapy in many malignancies.

R Edward Coleman (EJNM 2002)



baseline scan follow-up scan

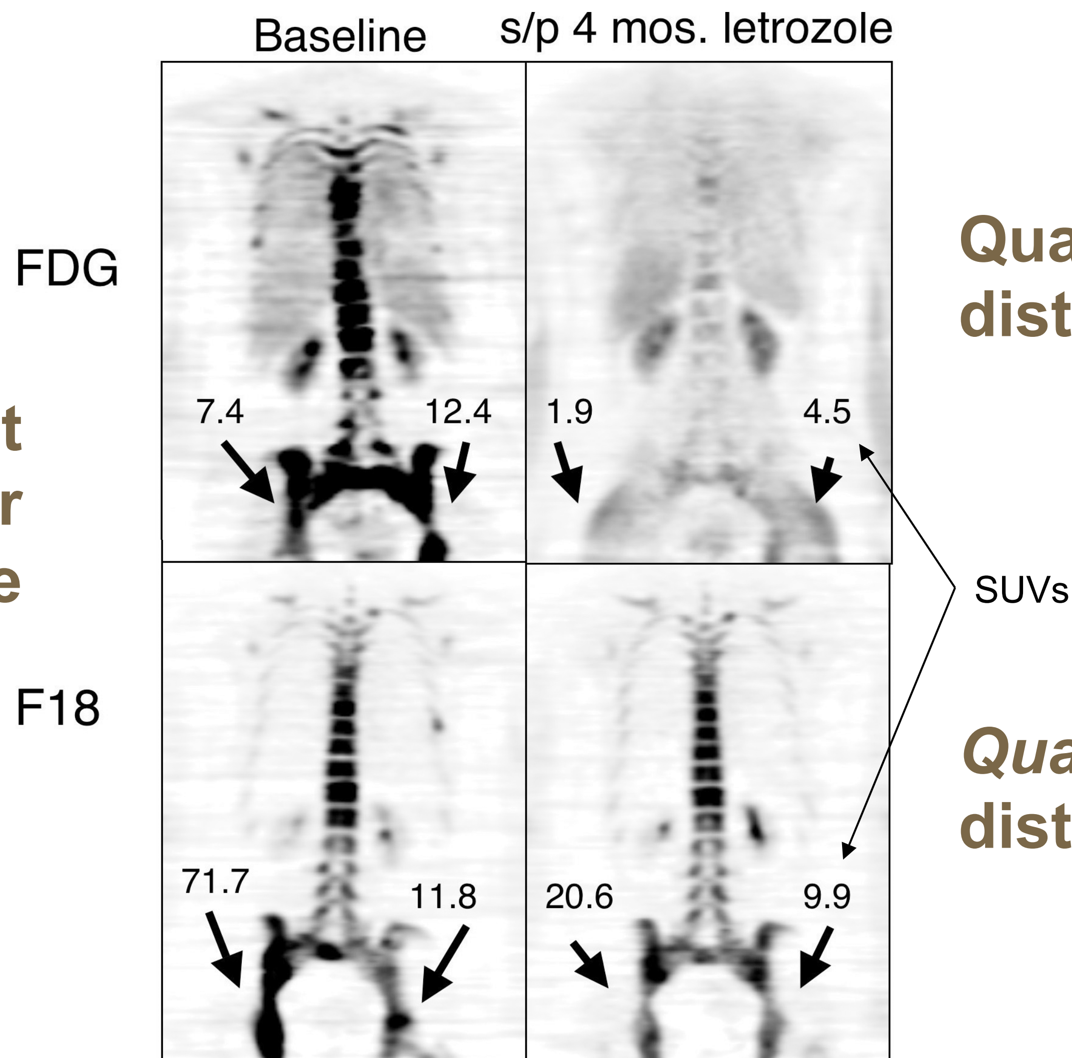
Quantitative PET Imaging

There is a role

- Monitoring patient response or progression
- Treatment planning
- Reporting tracer uptake (for any reason)
- Developing new therapies
- New diagnostic agents

Quantitative Assessment of Response to Therapy

Breast cancer recurrence

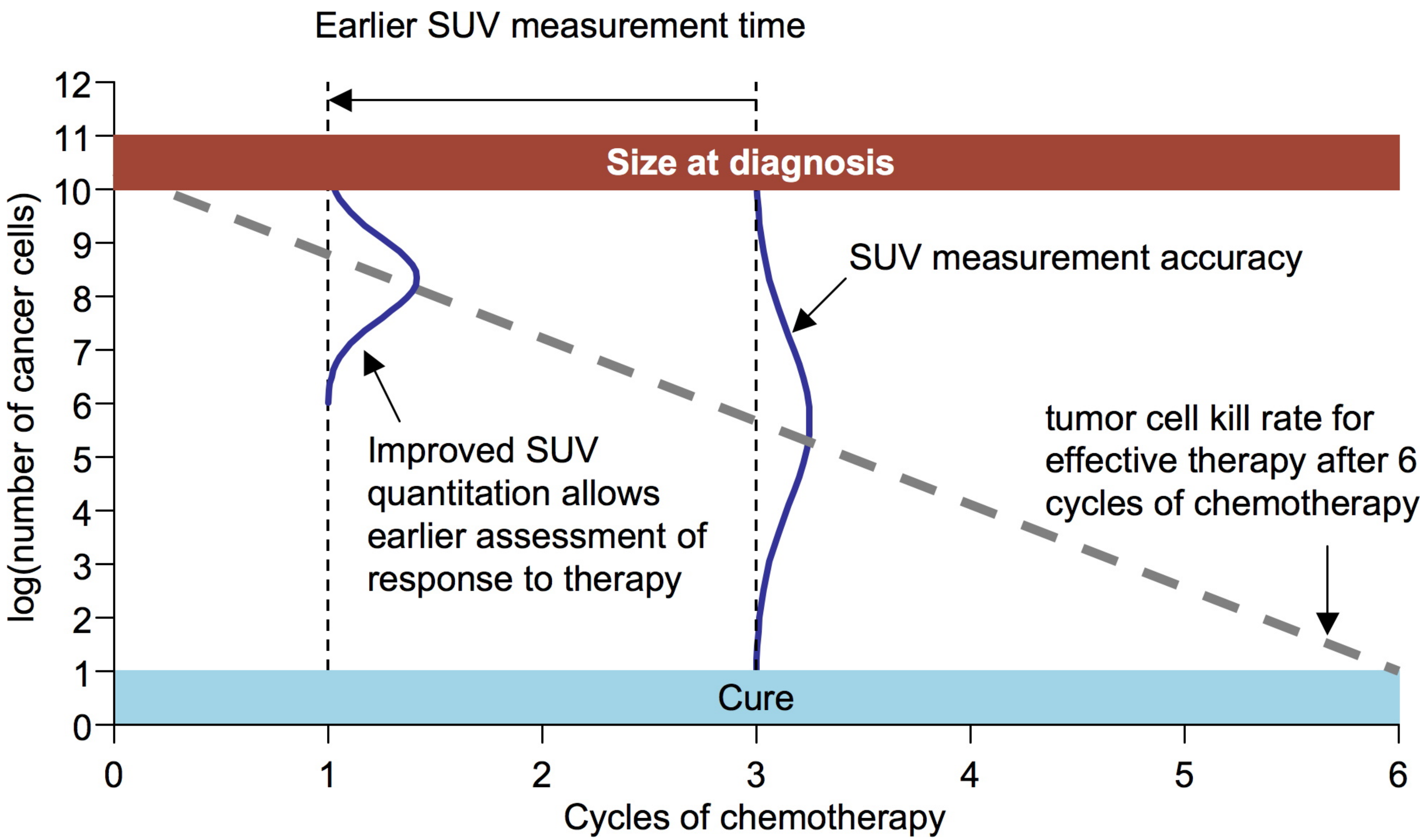


Qualitatively distinct

***Quantitatively* distinct**

Courtesy D Mankoff

Earlier assessment of response to therapy



Drivers for Quantitative PET

increasing volume

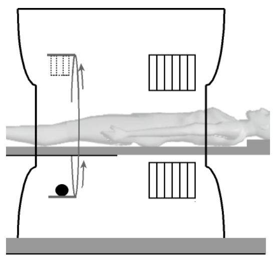
- FDG uptake is now routinely reported, and are asked for, by referring physicians
- Assessing individual response to therapy
- Treatment planning (including RT)
- New molecular diagnostic agents
- Clinical trials and Drug discovery

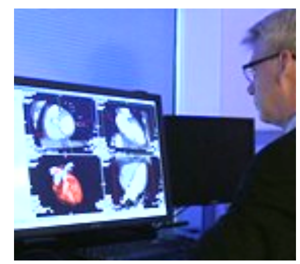
short term drivers

Isn't PET imaging already accurate?

"I'm a victim of my own success. Who should I sue?"

PET Scanning Process

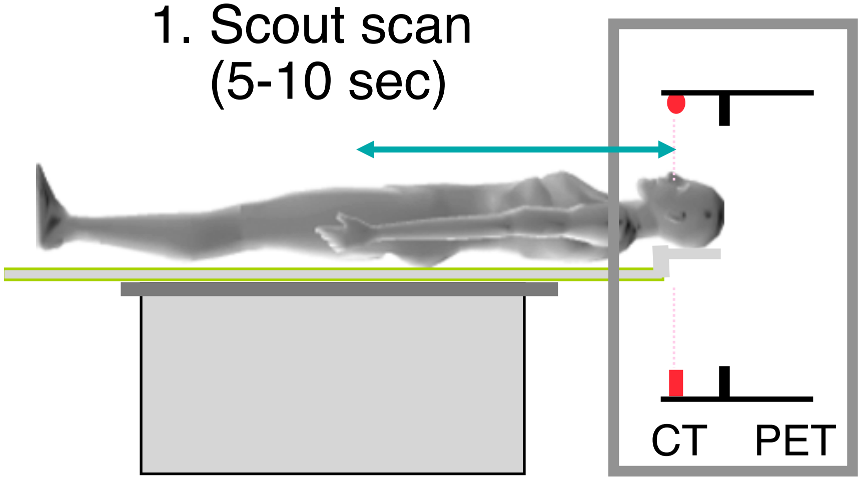




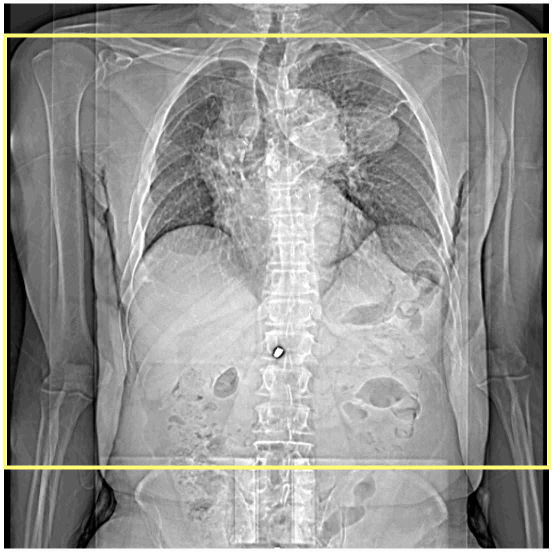
Patient preparation → Scan acquisition → Image recon-struction → Image analysis → Image interpre-tation → uptake measure

Typical PET/CT Scan Protocol

1. Scout scan
(5-10 sec)

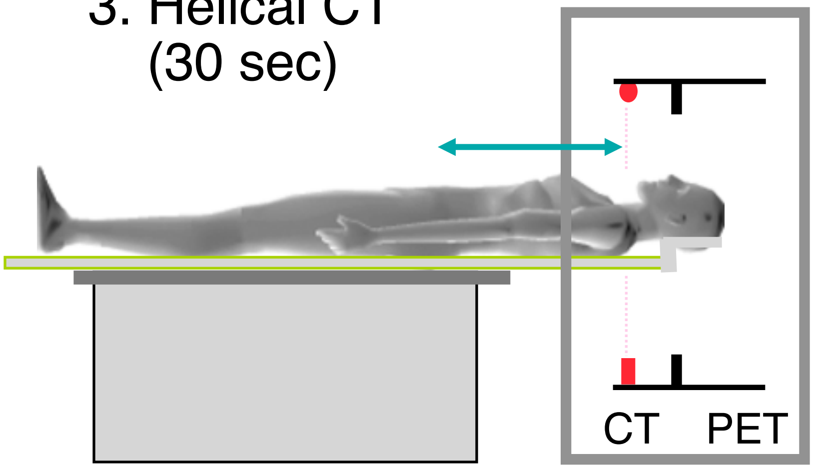


2. Selection
of scan
region

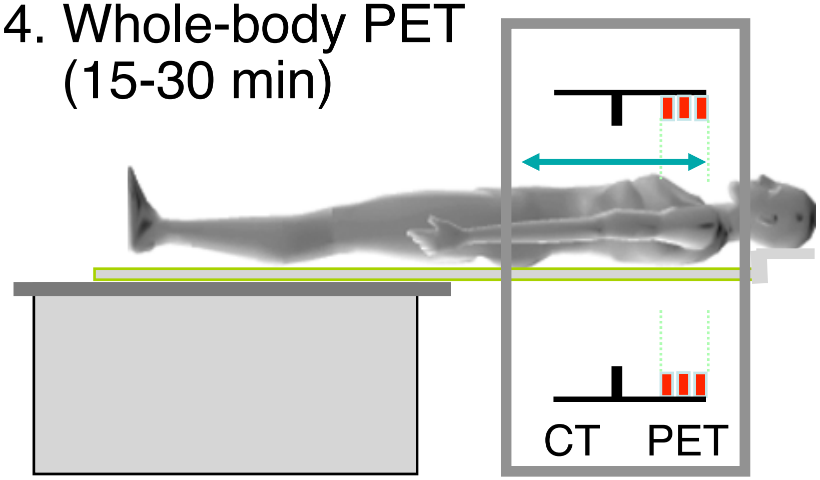


Scout scan image

3. Helical CT
(30 sec)

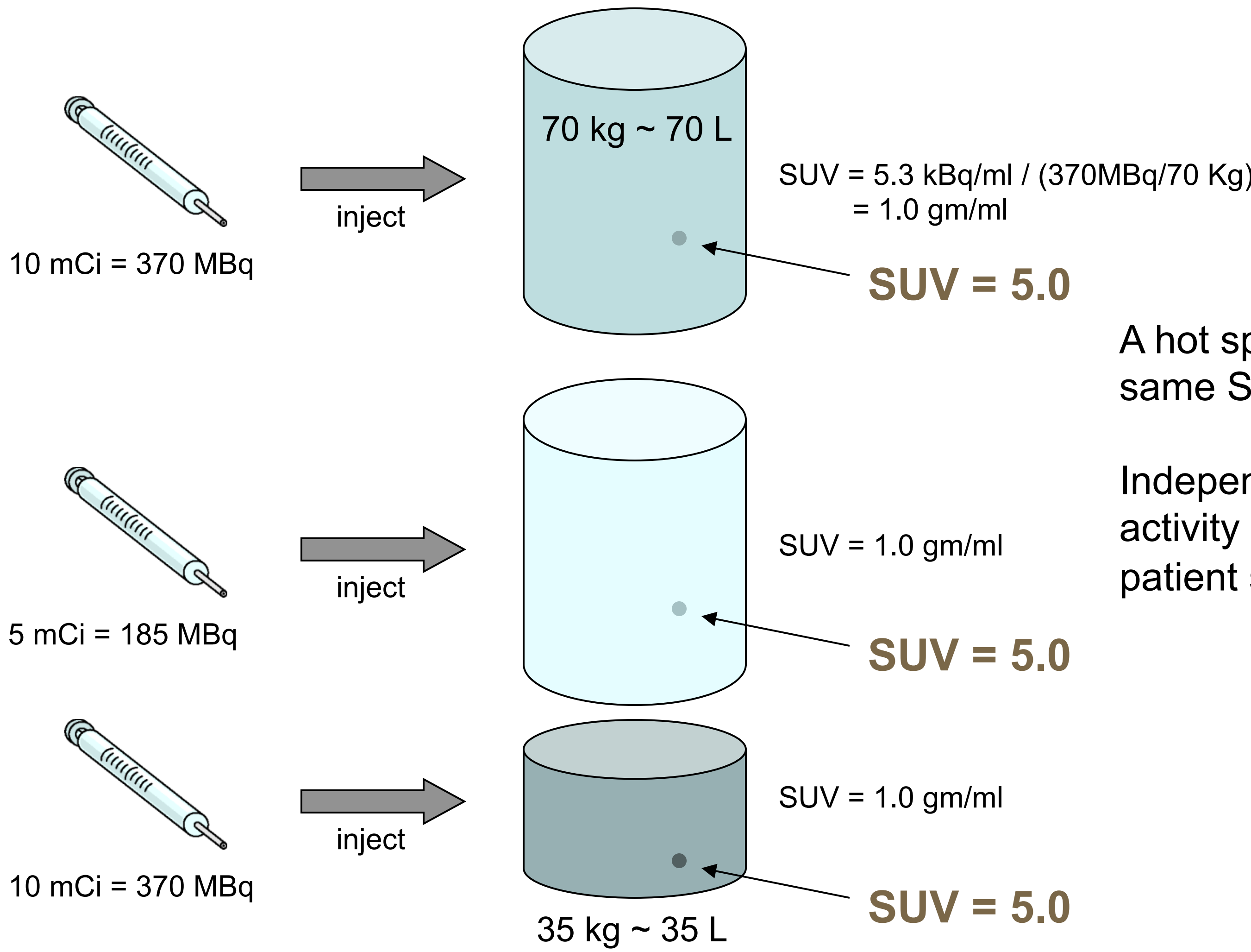


4. Whole-body PET
(15-30 min)



Standardized uptake value (SUV) in PET

- Normalize by amounts injected and weight to get the same relative distribution



A hot spot has the same SUV

Independent of activity injected or patient size

Sources of Error in SUV Values
SUV = Standardized Uptake Value

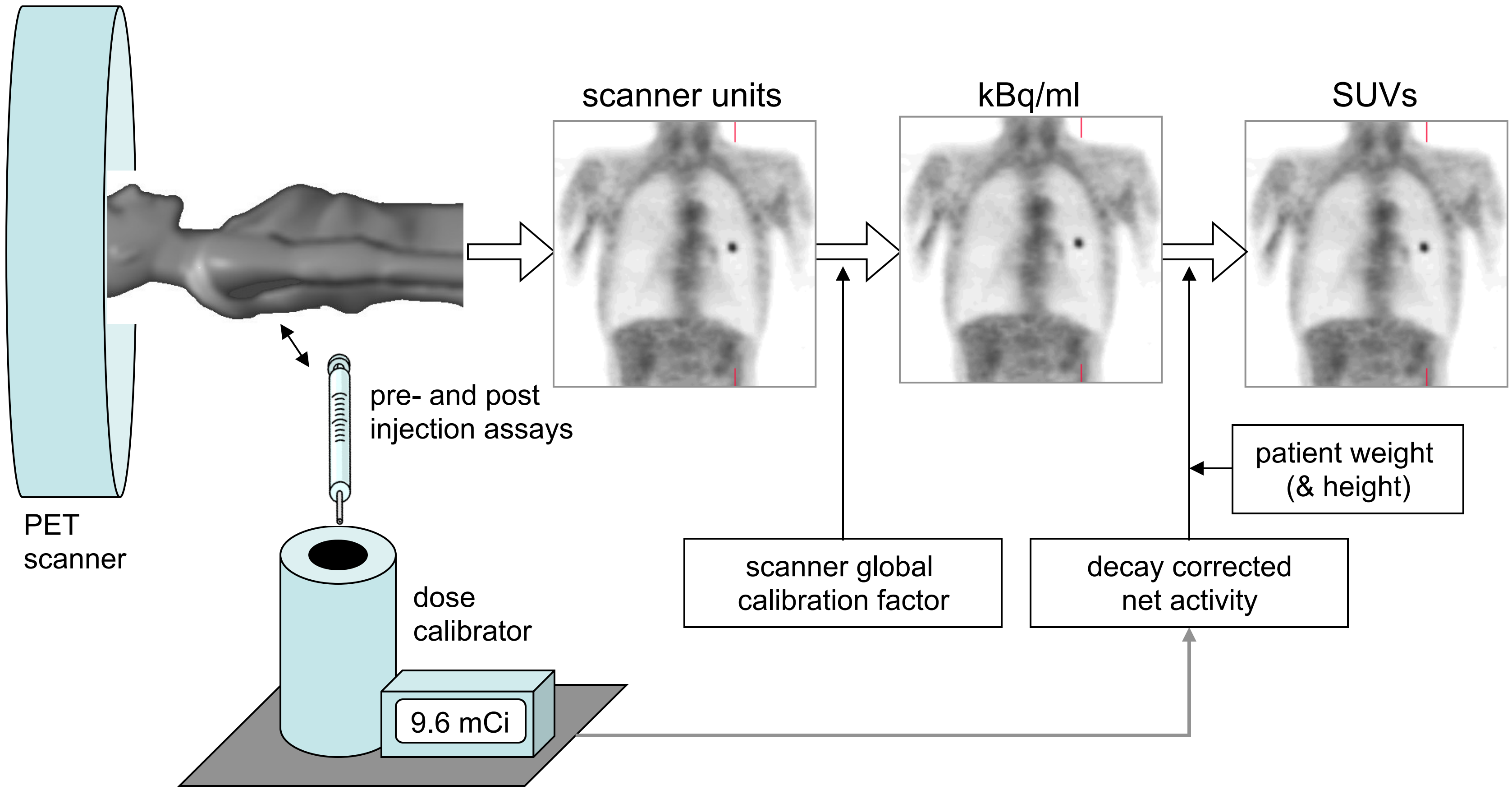
$$\mathrm{SUV} = \frac{\mathrm{PET}_{\mathrm{ROI}}}{D'_{\mathrm{INJ}} \,/\, V'}$$

PET = measured PET activity concentration
D′ = decay-corrected injected dose
V′ = surrogate for volume of distribution

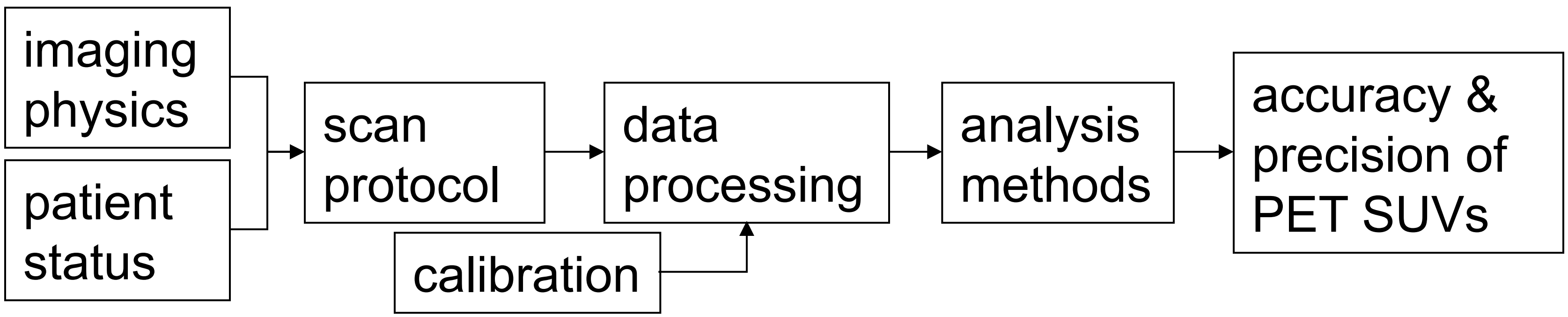
Some potential sources of error are:

- High blood glucose levels
- Variations in dose uptake time
- Uncalibrated clocks (including scanner) and cross calibration of scanner with dose calibrator
- Errors in radioactive dose assay
- Variations in image reconstruction and other processing protocols and parameters
- Variations in images analysis methods: E.g. how ROIs are drawn and whether max or mean SUV values are reported
- Scanner calibration

Instrumentation Chain for FDG-PET

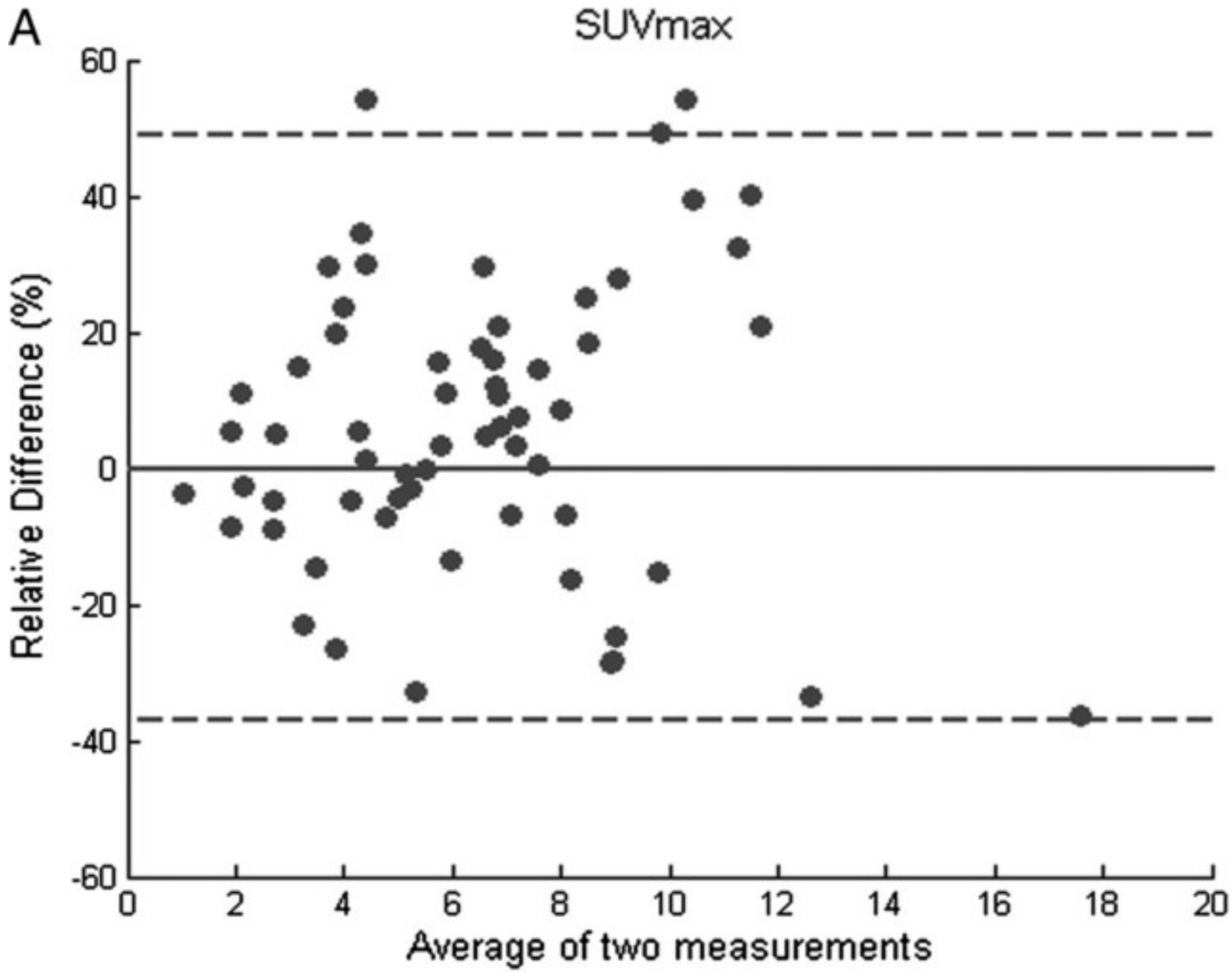


Error Propagation in PET Imaging



Estimate		Source data
Single-center best case:	10-12%	Minn 1999, Weber 2000, etc
Single-center, typical:	10-18%	Velasquez 2009
Multi-center, best case:	15-20%	Velasquez 2009
Multi-center, typical:	15-50%	Fahey 2009, Doot 2010, Kumar 2013

Kinahan and Fletcher, Sem US, CT, MR 2010



Kumar et al. Clin nuc med 2013

Impact of measurement error and sensitivity to true change on sample size

effect size (e.g. ΔSUV) = 20%
power = 80%
significance = 0.05

Trial Scenario	error	# of patients
Single site	10%	12
Multi-center (good calibration)	20%	42
Multi-center (poor calibration)	40%	158

Doot et al., Acad Rad 2012

Quantitative Imaging Definitions

- A biomarker is an objectively measured indicator of biological/pathobiological process or pharmacologic response to treatment
- Qualified biomarker: A disease-related biomarker linked by graded evidence to biological and clinical endpoints <u>and</u> dependent upon the intended use
- Imaging biomarker: a number, set of numbers, or classification derived from an image (in general imaging biomarkers are not surrogate endpoints)
- Validated assay: An assay (i.e. quantitative imaging) that has documented performance characteristics showing suitability for the intended applications

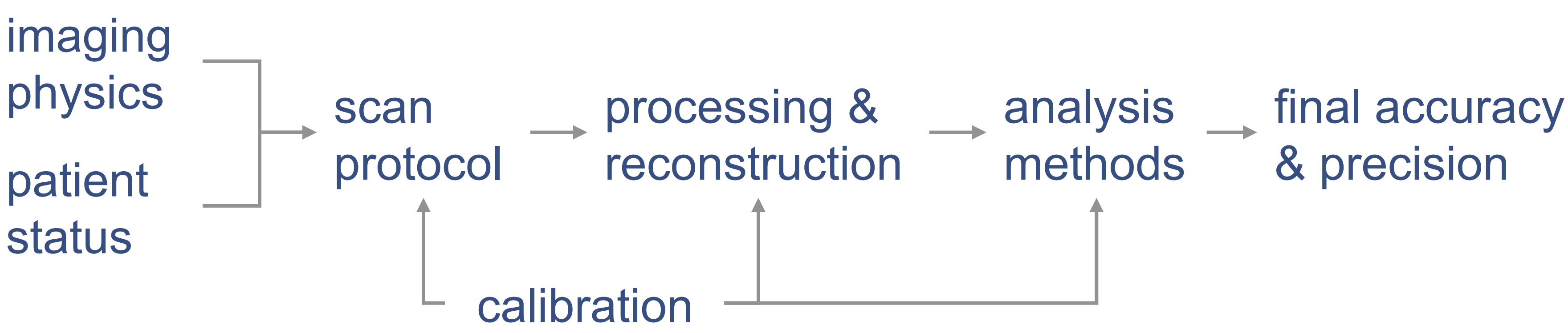
Biomarkers Definitions Working Group. Clin Pharmacol Ther 2001;69(3):89–95.

Quantitative Imaging Requirements

- Prior studies that measure bias and/or variance
- Defined protocols
- Monitoring of protocols
- Calibration and QA/QC procedures to ensure variance stays within assumed range
- *Optional*: Techniques and procedures that improve measurement accuracy

The Imaging Chain

- Quantitative measurements have known a measurement error, e.g. SUV = $x \pm y$
- For quantitative imaging each component of the imaging chain requires:
  - Quality Assurance (i.e protocol saying what to do)
  - Quality Control (checking what actually happened)
- Outline of propagation of errors through main components for all imaging methods:

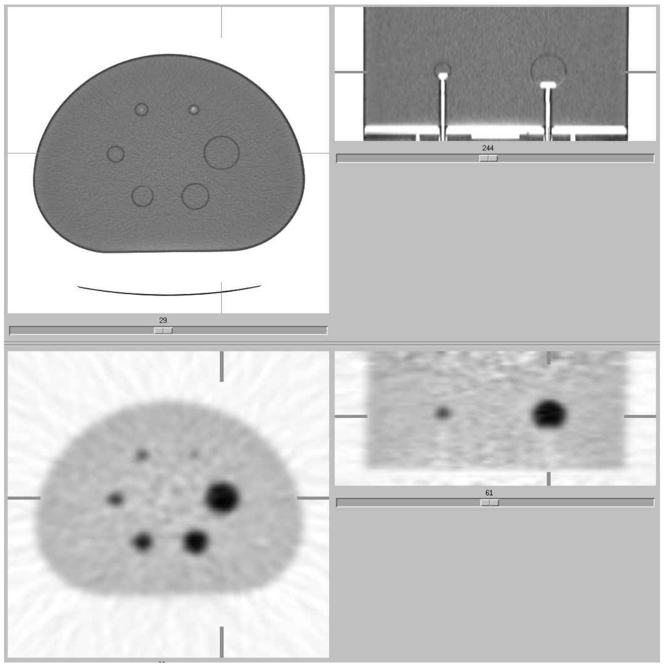


Recent PET Technology Innovations

- Respiratory motion compensation
- Time of flight imaging
- Advanced modeling of PET physics in image reconstruction
- Extended axial field of view
- Cost effective PET/CT scanners
- New detector systems
- PET/MR scanners
- CT dose reduction methods

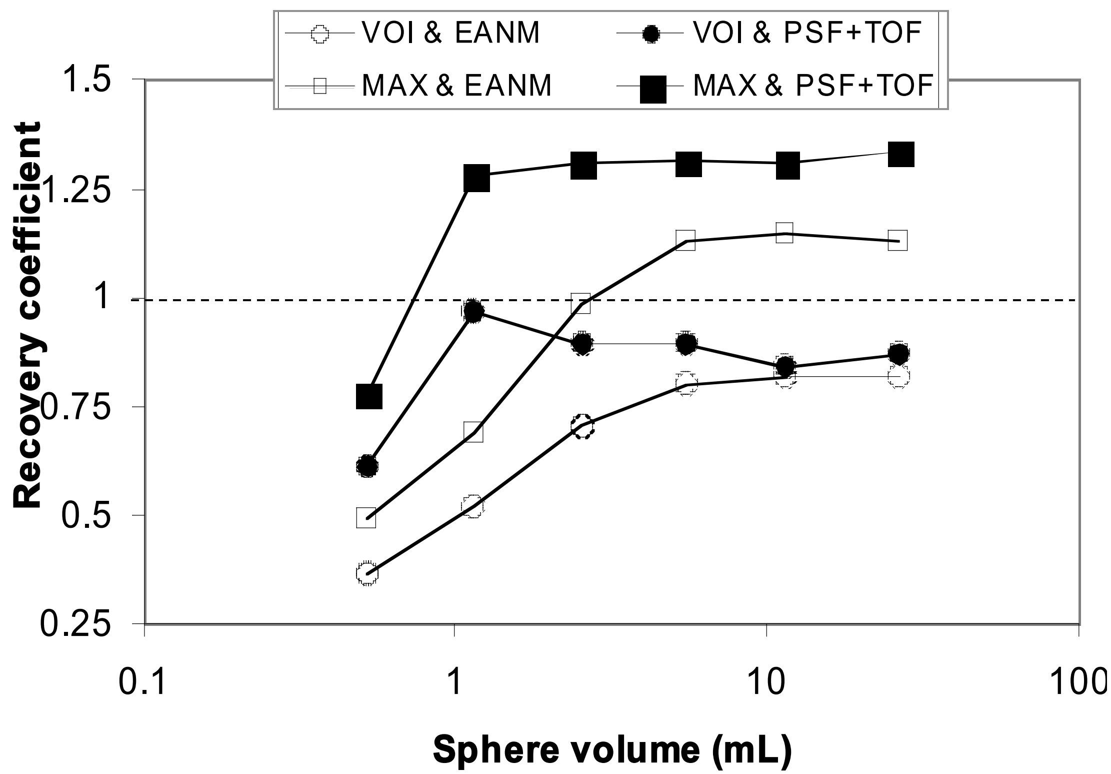
Clinical PET scanners are a moving target

Modified NEMA NU-2 IQ phantom



- Hot sphere diameters of 10, 13, 17, 22, 28, and 37-mm
- Target/background ratio 4:1

Different reconstruction methods on the same PET/CT scanner



Courtesy Ronald Boellaard

Challenges with Implementing Quantitative Imaging - Industry

- Significant variability between manufacturers in scan protocols and image quality
- No tests of quantitative accuracy of images transferred between display/analysis systems
- Due to several reasons:
  - Lack of standards by which vendors can assure compliance of acquisition/processing algorithms
  - Lack of convincing (to vendors) evidence of a market for quantitative imaging

Challenges with Implementing Quantitative Imaging - Imaging Sites

- There is a tension with imaging protocols suitable for current clinical practice
- Often there is no standard clinical practice

Guidance for Industry

Standards for Clinical Trial Imaging Endpoints

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Dr. Rafel Rieves at 301-796-2050 or (CBER) Office of Communication, Outreach, and Development at 301-827-1800 or 800-835-4709.

(FDA, August 2011)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2011
Clinical/Medical

I:\9676dft.doc
08/08/11

Defines:

- medical practice standard
- clinical trial standard

"… clinical trial standard[s] for image acquisition and interpretation… exceed those typically used in medical practice."

What do we do?

There are three main routes of action

1. Accreditation authorities
2. Standards definitions and harmonization initiatives
3. Calibration methods and/or phantoms

Quantitative Imaging Initiatives

- ACRIN Centers of Quantitative Imaging Excellence (CQIE)
- RSNA Quantitative Imaging Biomarkers Alliance (QIBA)
- NCI Quantitative Imaging Network (QIN)
- AAPM Task Group 145: Quantitative Imaging for PET
- Reconstruction Harmonization Project (ACRIN / SNM-CTN / QIN / QIBA)
- EANM and EORTC initiatives

National Cancer Institute

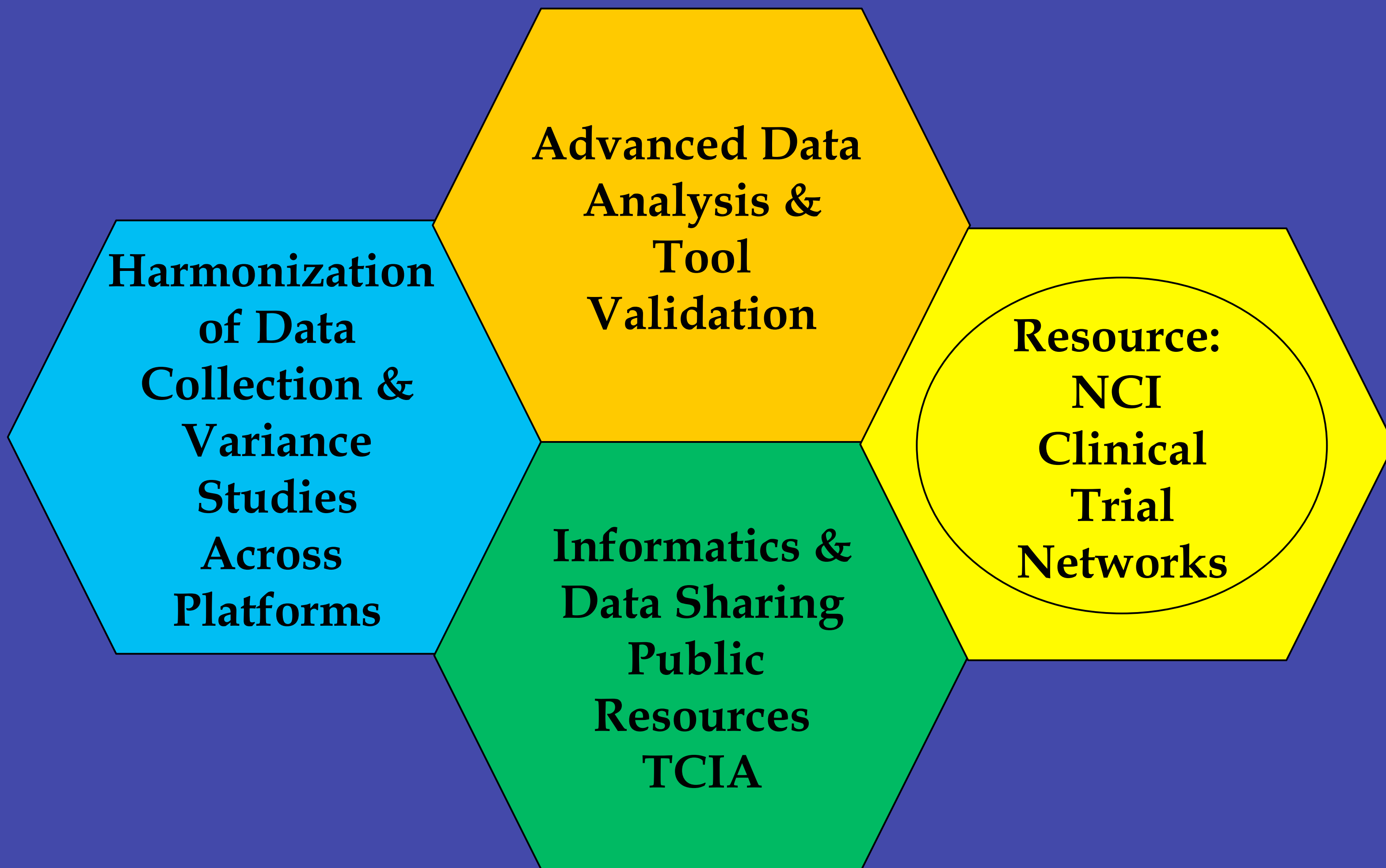
Quantitative Imaging Network (QIN)

Laurence Clarke PhD, Science Officer
Robert Nordstrom PhD: Lead Program Director
Gary Kelloff MD: Science Officer
CIP and RRP Program Staff

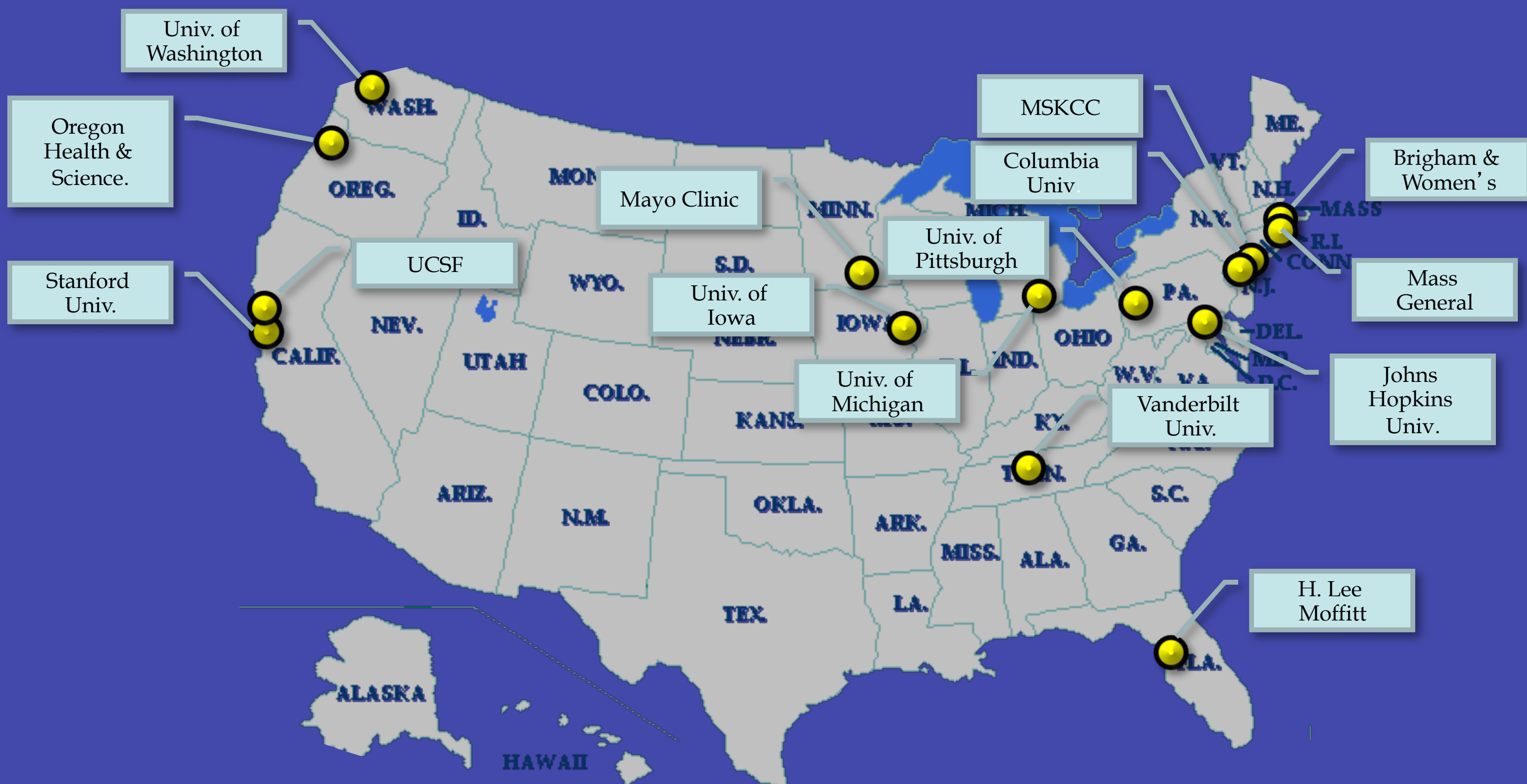
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

CANCER IMAGING PROGRAM

QIN can deliver next generation of QI methods for data collection and analysis

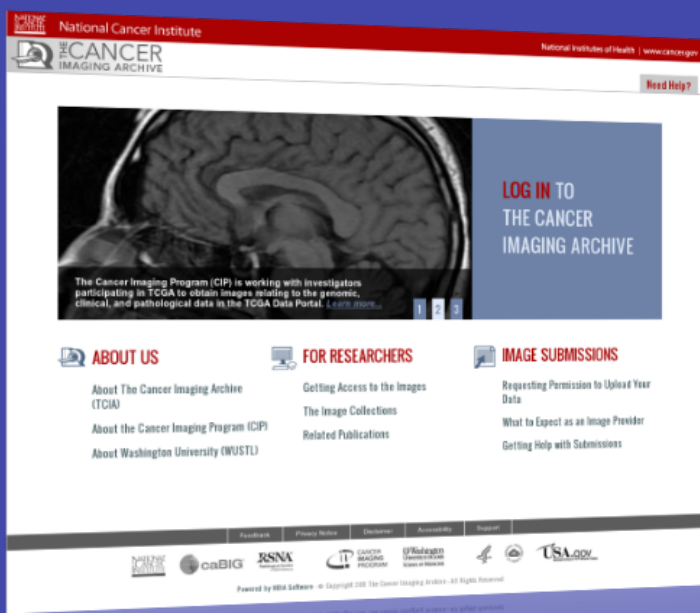


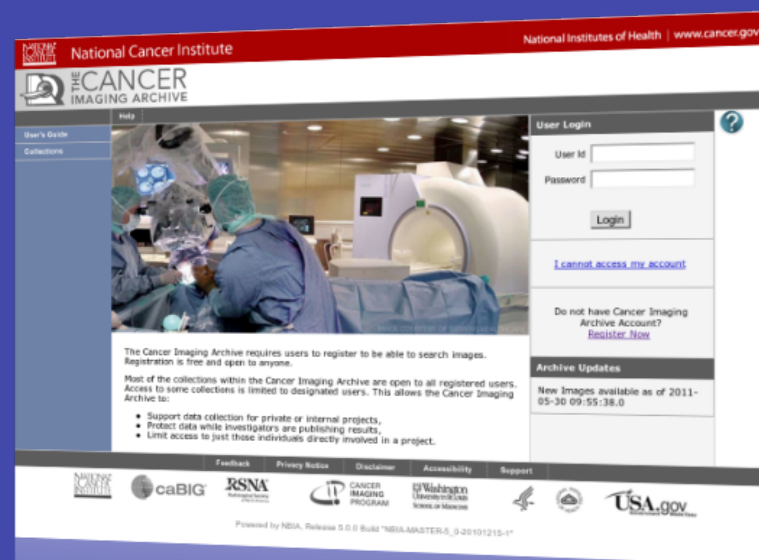
The QIN Network of 16 Teams



Network teams are tasked to develop a consensus on how to compare the performance of software tools for data collection and analysis.

THE CANCER IMAGING ARCHIVE





QIN is an early user of the public archive

http://cancerimagingarchive.net

CANCER IMAGING PROGRAM

Quantitative Imaging Biomarkers Alliance (QIBA)

- Basic premise for the RSNA:

  Extracting objective, quantitative results from imaging studies will improve the value of imaging in clinical practice

- Mission:

  Improve value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time.

  - Build 'measuring devices' rather than imaging devices
  - 'Industrialize' imaging biomarkers

QIBA Protocols & Profiles

- **QIBA Profile**

  Describes a specific performance Claim and how it can be achieved

  Establishes a written standard procedure for all parties to obtain an accurate and reproducible measurement that reflects an imaging biomarker of clinical interest

- **UPICT Protocol**

  (Uniform Protocol for Imaging in Clinical Trials)

  Consensus-derived description of a process to create quantitative medical images

FDG-PET/CT Profile Claim

If Profile criteria are met, then tumor glycolytic activity as reflected by the maximum standardized uptake value (SUVmax) should be measurable from FDG-PET/CT with a within-subject coefficient of variation of 10-12%.

Profile specified for use with: patients with malignancy, for the following indicated biology: primary or metastatic, and to serve the following purpose: therapeutic response.

FDG-PET Technical Committee. FDG-PET/CT as an Imaging Biomarker Measuring Response to Cancer Therapy, Quantitative Imaging Biomarkers Alliance. Version 1.03. Version for Public Comment. QIBA, March 9, 2013

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QIBA Profiles

QIBA Profile

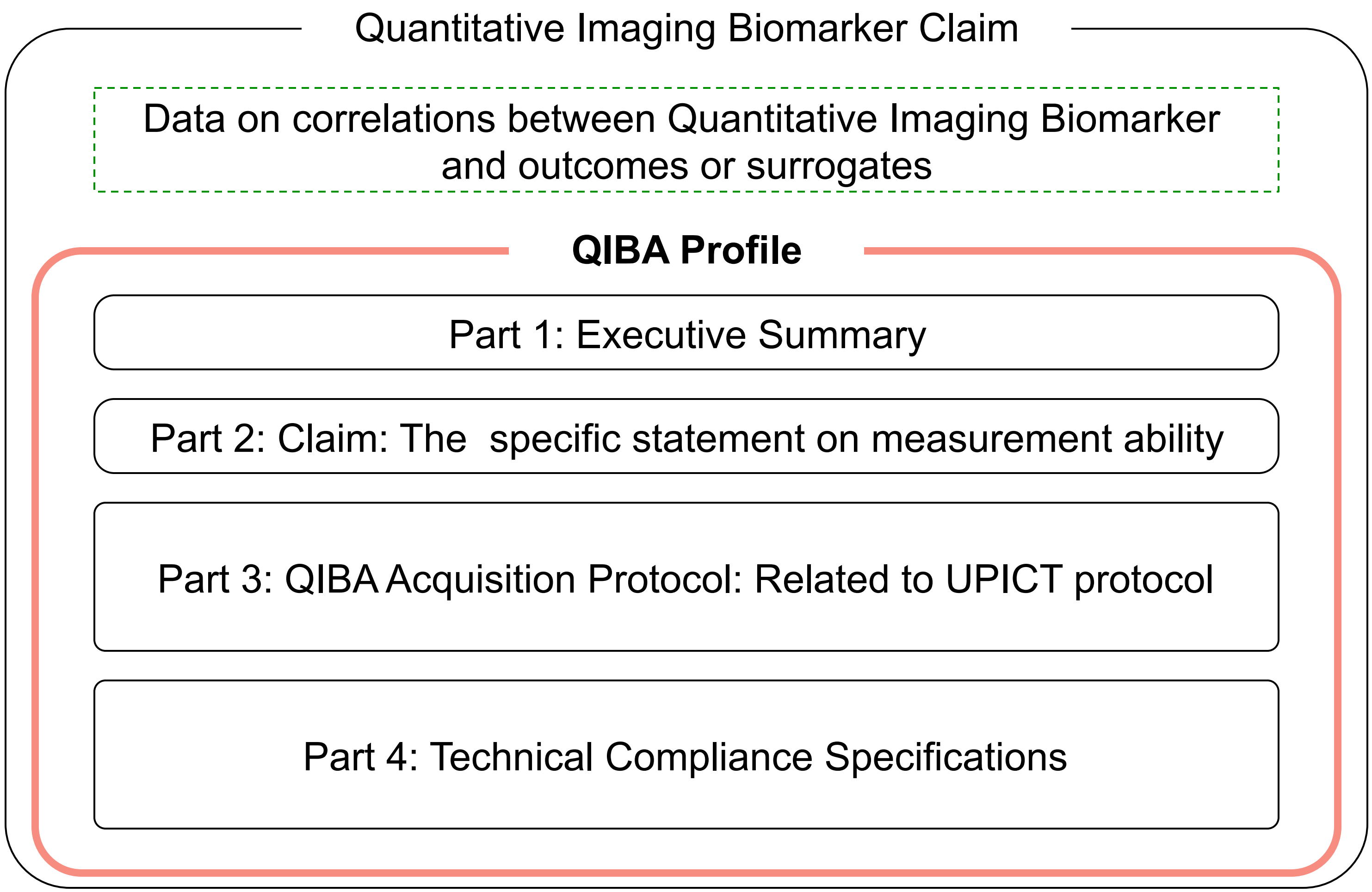
Part 1: Executive Summary

Part 2: Claim: The specific statement on measurement ability

Part 3: QIBA Acquisition Protocol: Related to UPICT protocol

Part 4: Technical Compliance Specifications

QIBA Profiles



Other QIBA Activities

Developing metrology standards for quantitative imaging biomarkers

Five papers submitted:

- Terminology
- Technical Performance
- Algorithm Comparisons
- Meta-analysis
- Application to Pulmonary Nodule Volume

Calibration phantoms for Quantitative PET/CT Standards and/or Accreditation

- Uniform Cylinder (used by ACRIN and many others)
- ACR PET phantom
- NEMA NU-2 Image Quality (IQ) phantom
- Modified NEMA Image Quality (IQ) phantom
- SNM CTN phantom
- Cross Calibration Phantom with NIST-traceable ^{68}Ge standard for Dose Calibrator
- Digital reference object

PET Digital Reference Object (DRO)

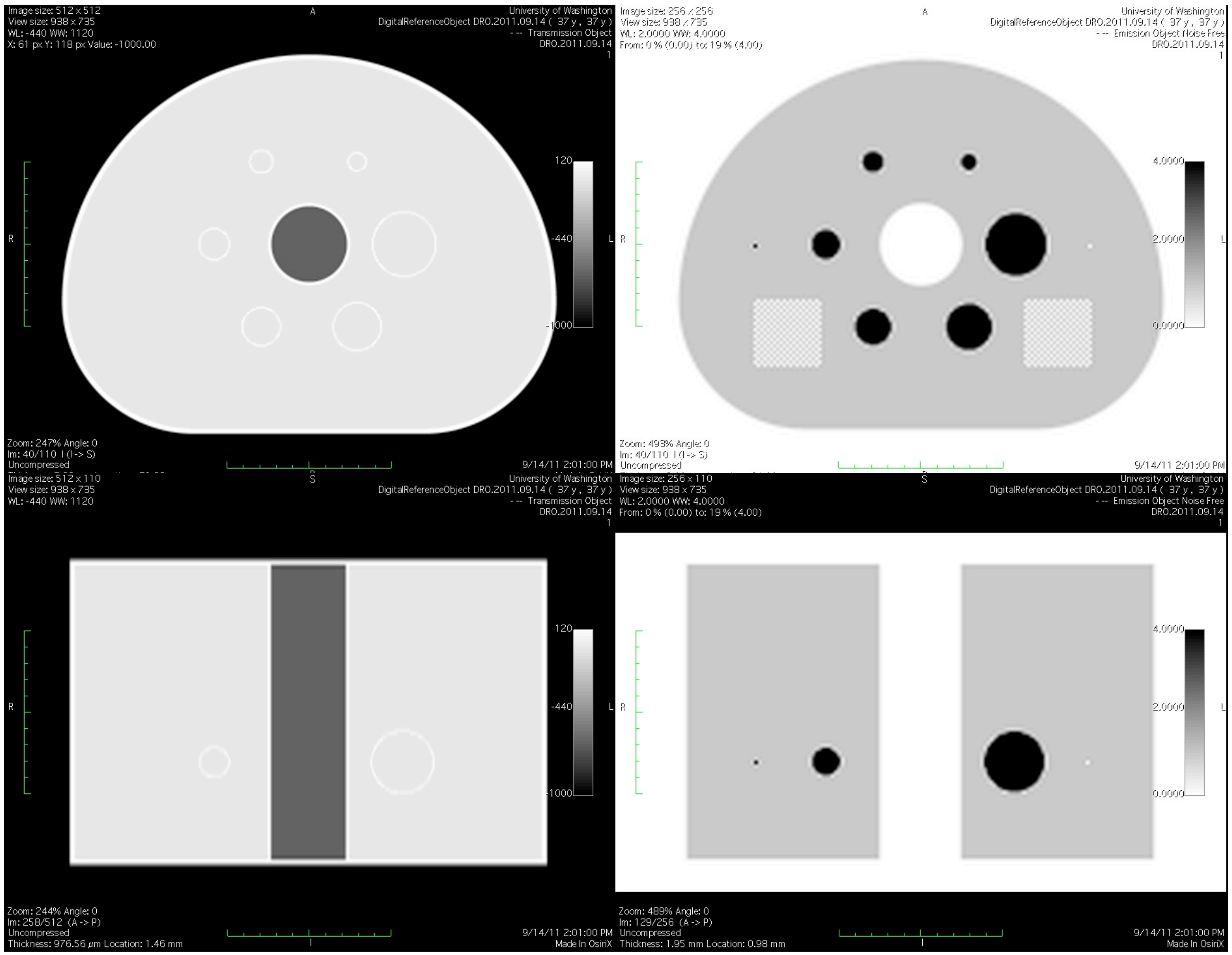
- The DRO is a synthetically generated set of DICOM image files of known voxel values for PET and CT
- Intended to test computation of SUVs and ROIs
- Version 1 released 10/31/2011
- More info at depts.washington.edu/petctdro

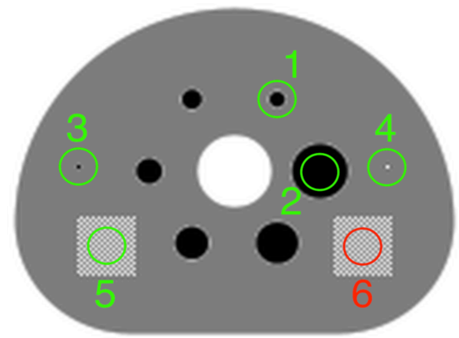
PET Digital Reference Object (DRO)

CT (transmission) PET (emission)

transaxial section

coronal section





ROI based analysis

Results: 13 sites, 20 different display systems

blue = okay, **yellow** = ?, **pink** = borderline, **red** = wrong

different sites/systems

results for each of the 6 ROIs

ROI Information																
SUV Type (BW, LBM, BSA)	BW	BW	BW	BW	BW	BW	LBM	BW	BW	BW	BW	BW	?	BW	BW	BW
Decimal places reported	1	1	3	2	1	1		maximimum	1	2	2	6	6 to 8	6	1 decimal Pla	2
ROI type (2D, 3D)	3D	2D	2D	2D	2D	2D (ROIs 1-5	3D	2D Circle SU\	2D	2D	2D	2D & 3D	2D	2D	2D	3D
ROI Area or Diameter?	Diameter	area	Diameter	Area	Diameter	Area	22 mm	Diameter for	Diameter	diameter	Area	Volume	4.900146cm	DIAMETER	Area	AREA/VOLUM
ROI Measurements																
ROI 1 Max	4.0	4.0	4	4.00	4.0	4.0	4.0000095	4	4	4.00	4	4.000019	4	4	4.0	4.00
ROI 1 Min	0.5	0.5	0.52	0.52	0.5	0.5	0.5199092	0.52	0.5	0.52	0.52	0.519943	0.52	0.622	0.5	0.52
ROI 1 Mean	1.1	1.4	1.36	1.33	1.4	1.4	1.2212964	1.396	1.3	1.39	1.73	1.390698	1.341	1.296	1.4	1.36
ROI 1 STD			0.939	0.91	1.0	1.0	0.7435832	0.974	0.9	0.97	1.223	0.968925	0.917	0.847	N/A	0.93
ROI 1 Diam / Area	24mm diame	492.1 mm2 a	25 mm	4.82 cm^2	25.0	443.7 mm^2	22 mm	R = 12.3	25.0 mm	25	5.11cm	0.984192	4.900146cm	25mm	490 mm2	484
ROI 2 Max	4.0	4.0	4	4.00	4.0	4.0	4.0000095	4	4	4.00	4	4.000019	4	4	4.0	4.00
ROI 2 Min	0.6	4.0	4	4.00	4.0	4.0	4.0000095	4	4	4.00	4	4.000019	4	4	4.0	4.00
ROI 2 Mean	3.9	4.0	4	4.00	4.0	4.0	4.0000095	4	4	4.00	4	4.000019	4	4	4.0	4.00
ROI 2 STD			0	0.00	0.0	0.0	2.61E-07	0	0	nan	0	0	0	0	N/A	NaN
ROI 2 Diam / Area	24mm diame	492.1 mm2 a	25 mm	4.82 cm^2	25.0	443.7 mm^2	22 mm	R = 12.3	25.0 mm	25	4.95.91cm	0.991821	4.900146cm	"	490 mm2	493
ROI 3 Max	4.1	4.1	4.11	4.11	4.1	4.1	4.1099997	4.11	4.1	4.11	4.11	4.110001	4.11	2.555	4.1	4.11
ROI 3 Min	1.0	1.0	1	1.00	1.0	1.0	0.99998724	1	1	1.00	1	0.999922	1	0.999	1	1.00
ROI 3 Mean	1.0	1.0	1.021	1.02	1.0	1.0	1.0042257	1.024	1	1.02	1.02	1.023846	1.022	1.01	1	1.02
ROI 3 STD			0.256	0.25	0.3	0.3	0.11473396	0.275	0.3	0.28	0.27	0.271721	0.26	0.126	N/A	0.25
ROI 3 Diam / Area	24mm diame	492.1 mm2 a	25 mm	4.81 cm^2	25.0	443.7 mm^2	22 mm	R = 12.3	25.0 mm	25	5.04cm	0.991821	4.900146cm	"	490 mm2	497
ROI 4 Max	1.0	1.0	1	999.94 mSU\	1.0	1.0	0.99998724	1	1	1.00	1	0.999922	1	0.999	1	1.00
ROI 4 Min	0.0	0.0	-0.1	-109.88 mSU	1.0	1.0	-0.1098776	-0.11	-0.1	0.00	-0.11	-0.109877	-0.11	0.445	0	-0.11
ROI 4 Mean	1.0	1.0	0.992	992.44 mSU\	1.0	1.0	0.9984767	0.991	1	0.99	0.99	0.99145	0.992	0.996	1	0.99
ROI 4 STD			0.094	91.23 mSUVI	0.0	0.0	0.04091707	0.098	0.1	0.09	0.096	0.096593	0.092	0.044	N/A	0.09
ROI 4 Diam / Area	24mm diame	492.1 mm2 a	25 mm	4.82 cm^2	25.0	439.9 mm^2	22 mm	R = 12.3	25.0 mm	25	5.04cm	0.999451	4.900146cm	"	490 mm2	494
ROI 5 Max	1.0	0.9	0.9	899.97 mSU\	0.9	0.9	0.99998724	0.9	0.9	0.90	1	0.899985	0.9	0.95	0.9	0.90
ROI 5 Min	0.1	0.1	0.1	99.97 mSUVI	0.1	0.1	0.10000705	0.1	0.1	0.10	0.1	0.099977	0.1	0.549	0.1	0.10
ROI 5 Mean	1.0	0.5	0.5	492.02 mSU\	0.5	0.5	0.9307193	0.507	0.5	0.51	0.75	0.512289	0.492	0.75	0.5	0.50
ROI 5 STD			0.401	401.25 mSU\	0.4	0.4	0.22840944	0.4	0.4	0.40	0.378	0.399815	0.401	0.201	N/A	0.40
ROI 5 Diam / Area	24mm diame	492.1 mm2 a	25 mm	4.81 cm^2	25.0	443.7 mm^2	22 mm	R = 12.3	25.0 mm	25	4.888cm	0.991821	4.900146cm	"	490 mm2	484
ROI 6 Max	0.9	0.9	0.9	NA	0.9	0.9	0.8999599	0.9	0.9	0.90	0.9	0.89999	0.9	0.499	0.9	0.90
ROI 6 Min	0.1	0.1	0.1	NA	0.1	0.1	0.10000705	0.1	0.1	0.10	0.1	0.099977	0.1	0.499	0.1	0.10
ROI 6 Mean	0.5	0.5	0.5	NA	0.5	0.5	0.49820703	0.505	0.5	0.50	0.5	0.489707	0.5026	0.5	0.5	0.51
ROI 6 STD			0.53	NA	0.4	0.4	0.39997247	0.4	0.4	0.40	0.4	0.399874	0.4013	0	N/A	0.40
ROI 6 Diam / Area	24mm diame	492.1 mm2 a	25 mm	NA	25.0	5.52 cm^3	22 mm	25.0	25.0 mm	27	5.11cm	7.720947	1.7986cm^3	"	490 mm2	8360

CONCLUSION

State of the art for FDG-PET/CT: Quantitative imaging requirements

- Test-retest studies in the literature demonstrate that quantitative image acquisition protocols are definable and possible
- To enable quantitative image acquisition protocols we need
  - Standards by which users can assure compliance, e.g. QIBA Profile
  - Methods to collectively agree on data transfer and analysis, e.g. QIN/ACRIN methods
  - Education for (and adoption by) radiologists, if they are to remain in the image processing chain

PET image reconstruction harmonization