Quantitative Imaging In Clinical Trials Using PET/CT: Update

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Supported by

RSNA Quantitative Imaging Biomarkers Alliance

American Association of Physicists in Medicine

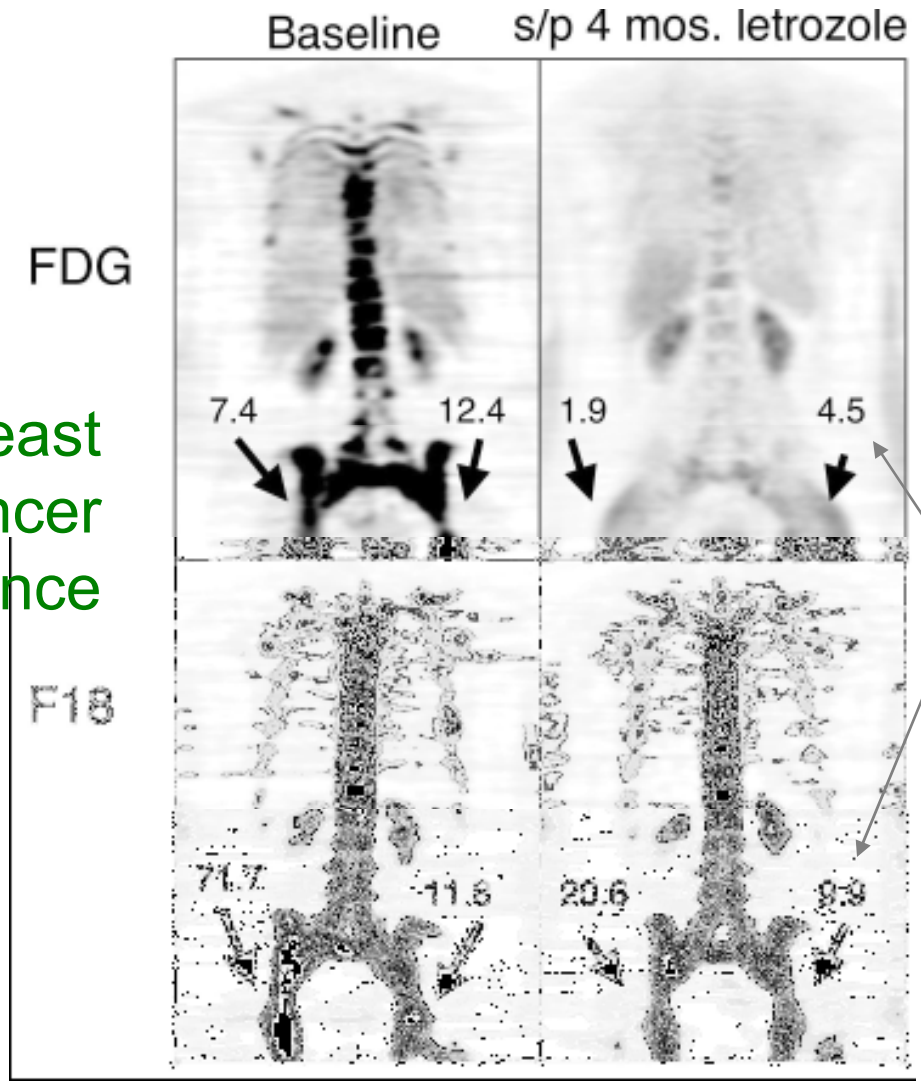
Society of Nuclear Medicine

NCI Cancer Imaging Program contract 24XS036-004 (RIDER)

Seattle Cancer Care Alliance Network

NIH Grant U01-CA148131 (QIN)

Quantitative Assessment of Response to Therapy



Breast cancer recurrence

Qualitatively distinct

SUVs

Quantitatively distinct

Courtesy D Mankoff

Errors in Numbers in PET/CT

- Technical factors
  - Relative calibration between PET scanner and dose calibrator (10%)
  - Time-varying scanner calibration (5%)
  - Residual activity in syringe (5%)
  - Incorrect synchronization of clocks (10%)
  - Injection vs calibration time (10%)
  - Quality of administration (50%)
- Physical factors
  - Scan acquisition parameters (15%)
  - Image reconstruction parameters (30%)
  - Use of contrast agents (10%)
  - ROI (50%)
- Biologic factors
  - Uptake period (15%)
  - Patient motion and breathing (30%)
  - Blood glucose levels (15%)
  - Other factors (5%)

Modified from R. Boellaard and R. Jeraj

PET/CT Quantitation Initiatives

- European Organization for Research and Treatment of Cancer (EORTC)
- American College of Radiology Imaging Network (ACRIN) PET Core Lab
- NIH/NCI
  - Imaging Response Assessment Teams (IRATs)
  - Reference Image Database for Evaluation of Response (RIDER)
- American Association of Physicists in Medicine (AAPM)
  - Quantitative Imaging Initiative Task Group 145 (joint with SNM) PET/CT
- Radiological Society of North America (RSNA):
  - Quantitative Imaging Biomarkers Alliance (QIBA)
- European Association for Nuclear Medicine (EANM)
- Cancer and Leukemia Group B (CALGB) PET Core lab
- Society of Nuclear Medicine (SNM)
  - Validation Task Force
  - Clinical Trials Network

Quantitative PET/CT Accreditation Bodies

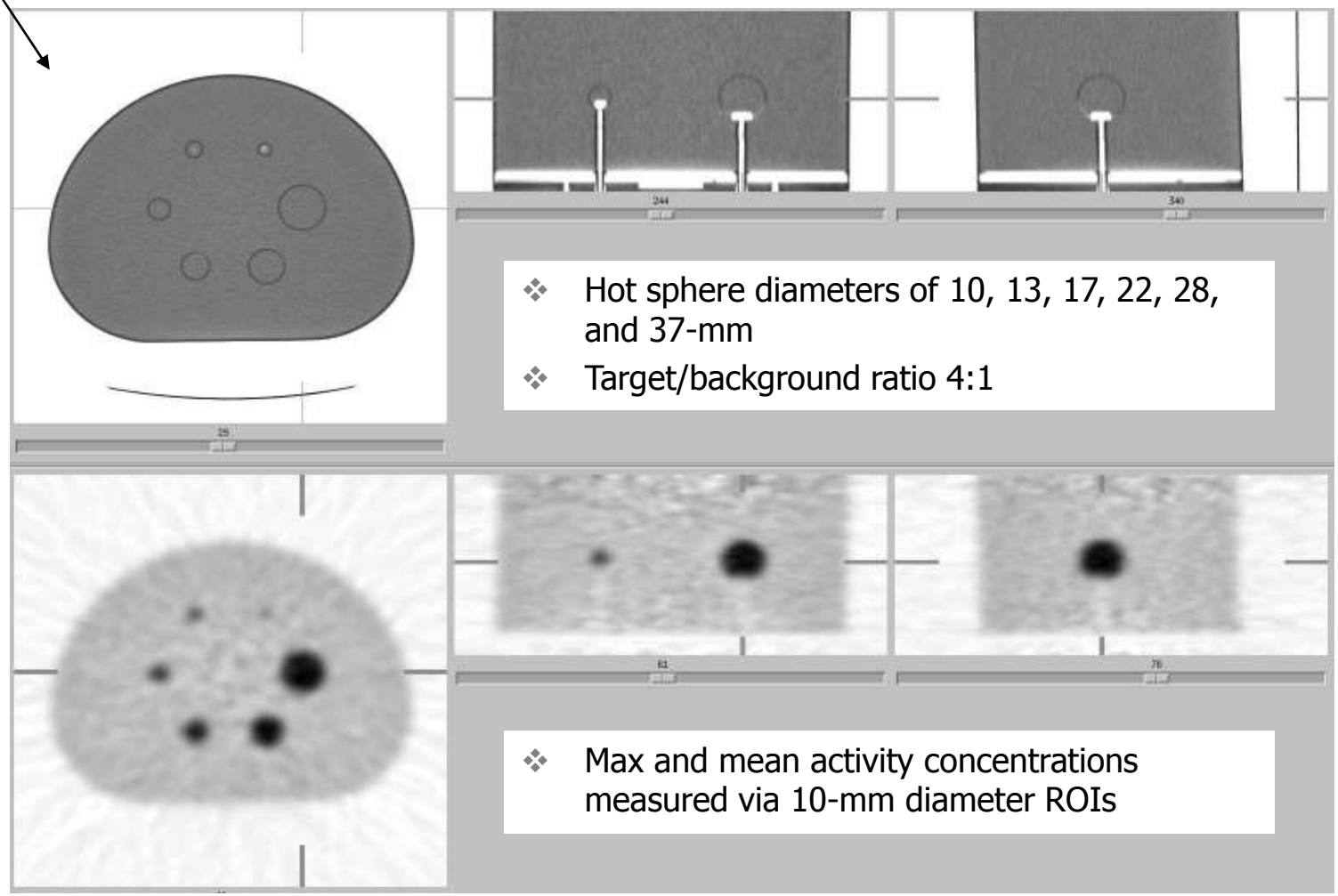
- Medical Imaging Technology Assessment (MITA)
- several Clinical Research Organizations (CROs)
- American College of Radiology (ACR) - 1000 sites!
- PET Core Labs (ACRIN, CALGB, …)
- EANM
- Cancer UK
- SNM
  - Clinical Trials Network

Calibration Phantoms / Methods

- Main Phantoms
  - Uniform cylinder (should get SUV = 1.0 ± 0.1)
  - MITA (NEMA) NU-2 Image Quality
  - ACR PET accreditation
  - AAPM/RIDER modified ACR
  - SNM Clinical Trials Network
  - Cross-calibration kit using NIST ^{68}Ge standard (v2 of modified ACR)
- Dose Calibrator
  - NIST ^{68}Ge standard for ^{18}F dose calibration

Modified NEMA NU-2 IQ Phantom

similar to abdominal x-section



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

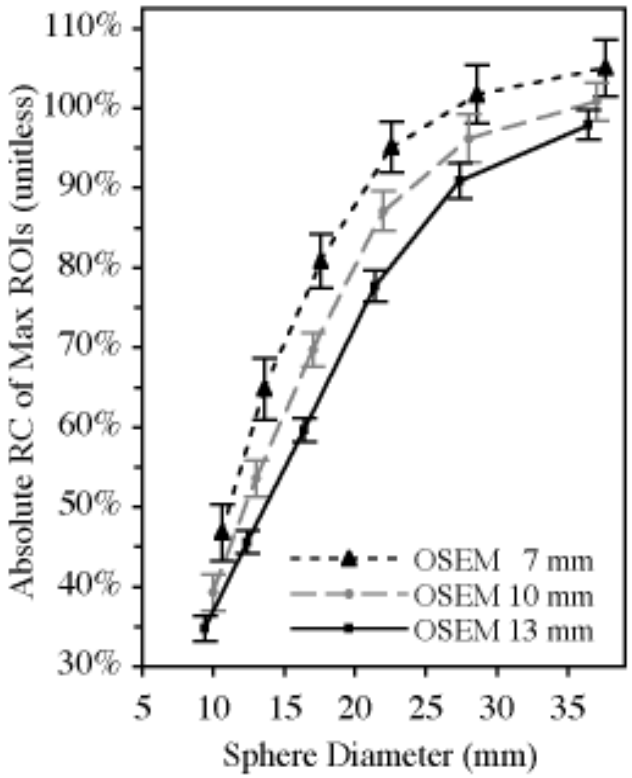
- Max and mean activity concentrations measured via 10-mm diameter ROIs

Used ^{68}Ge in epoxy to remove filling variations at sites

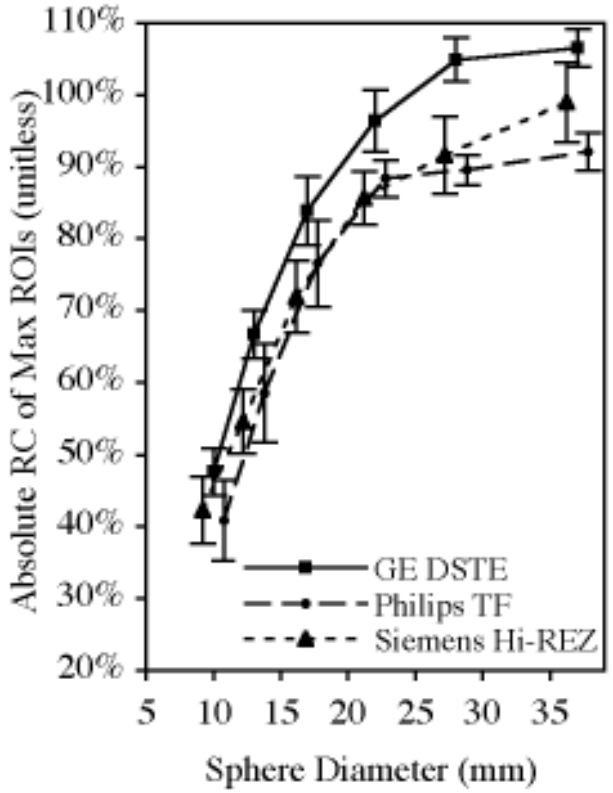
Single-site repeat PET/CT scans

Plots of recovery coefficient (RC) = measured in ROI/true

SUVs from 20 3D-OSEM scans with 7-mm smoothing



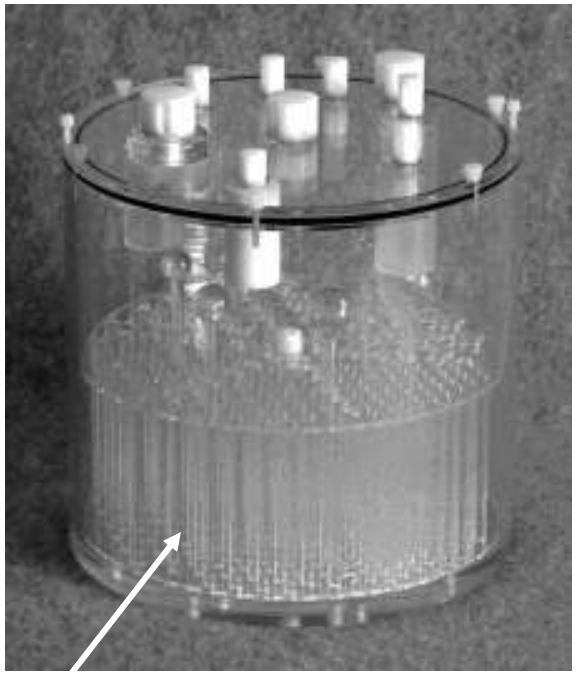
Absolute recovery coefficients from 3D-OSEM reconstructions using 7, 10, and 13 mm smoothing.



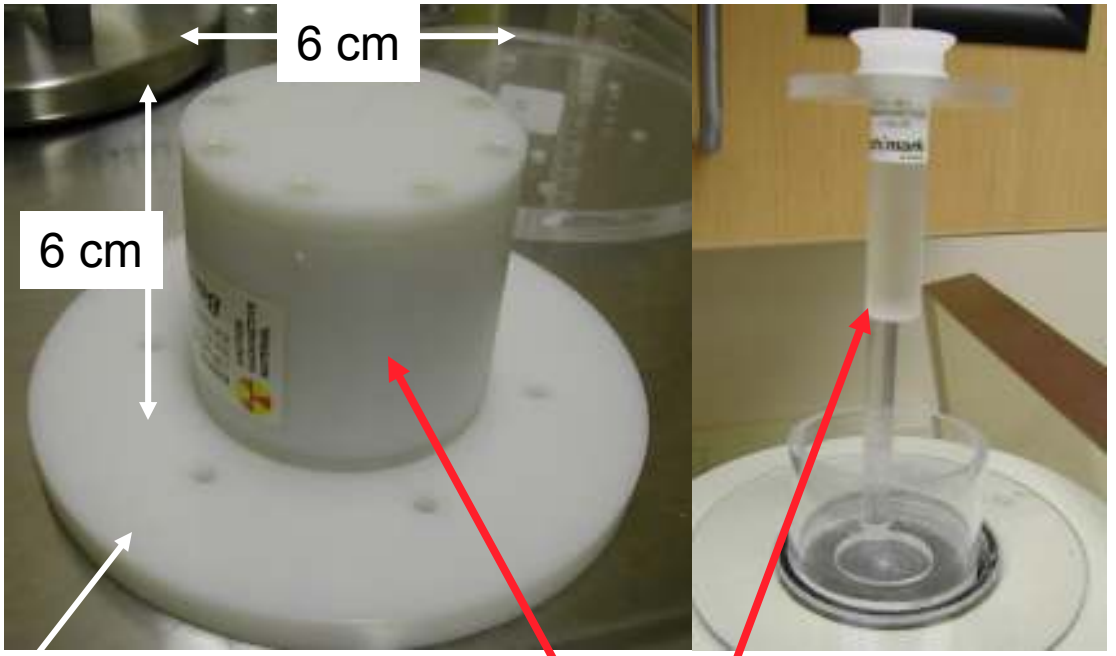
Maximum ROI recovery coefficients versus sphere diameter for the same phantom repositioned and imaged 20 times using PET/CTs from three vendors

Doot et al. 2010

Version 2 Modified ACR phantom with long half-life source matched to NIST standard



removable resolution insert



adapter base plate

^{68}Ge in epoxy sources from same batch using NIST traceable methods (1.3% error)

Preliminary results: Multi-site repeated scans

- All units in kBq/ml
- (number) in brackets is value from repeat scan after > 3 months
- True activity 217 kBq/ml (All activity measures decay corrected to 9/2/09)

			Measure errors	
Site	Dose calibrator	PET mean	Dose calibrator	PET (mean)
1	237	213	9.2%	- 1.8%
2	236 (235)	256 (219)	8.6% (8.2%)	18.0% (1.2%)
3	235 (236)	204 (231)	8.3% (9.0%)	- 5.8% (6.4%)
4	216 (212)	200 (185)	- 0.6% (-2.3%)	- 7.7% (-14.8%)
5	217 (209)	200 (182)	- 0.1% (-3.6%)	- 7.6% (-16.0%)
	1st 2nd	1st 2nd	1st 2nd	1st 2nd

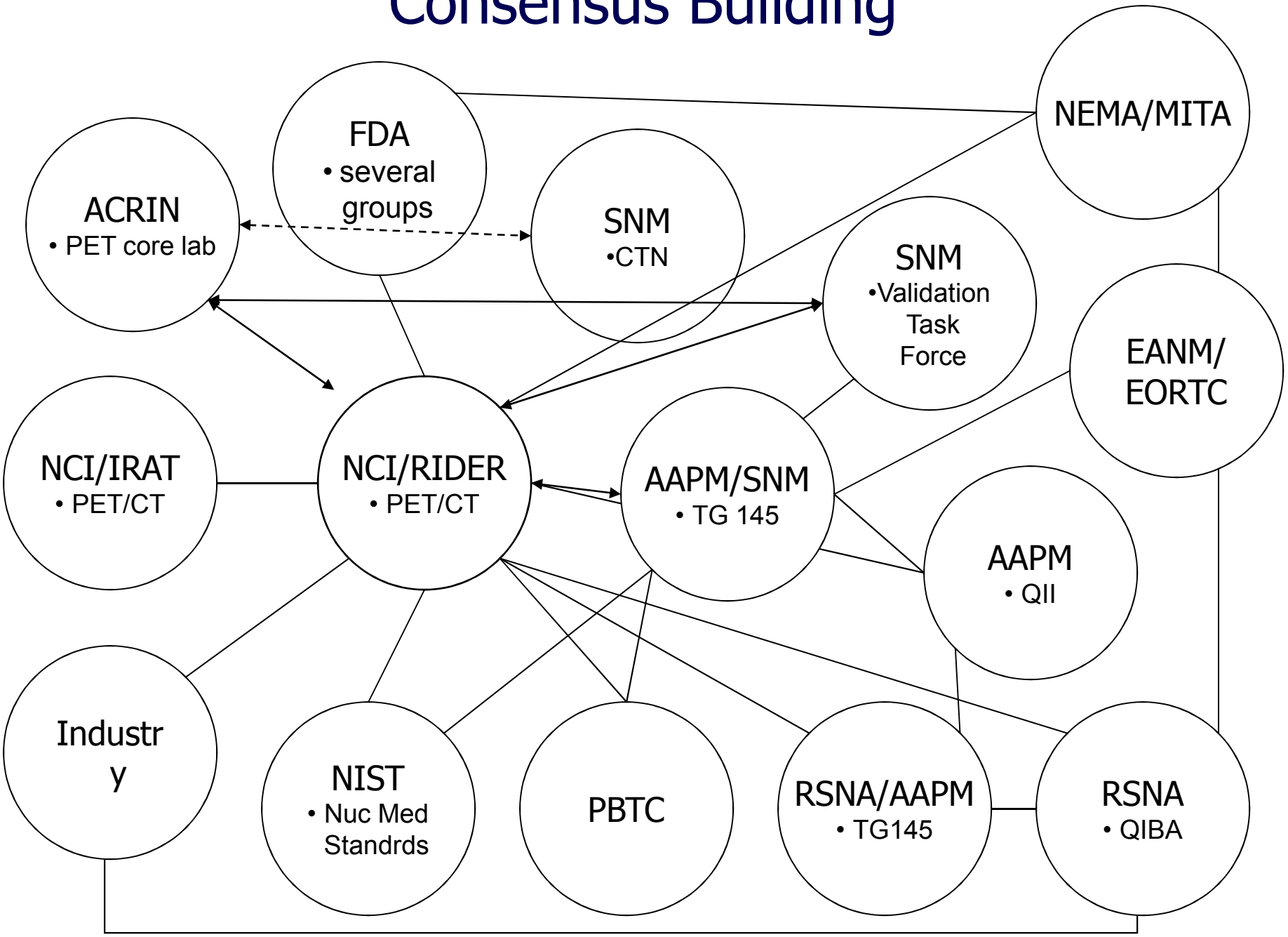
Next steps

- PET/CT is evolving from a valid *qualitative* clinical tool with excellent image fidelity to a *quantitative* clinical research tool
- Imaging results are quantitative if we pay attention to all aspects of image acquisition processing and analysis (scanner QA/QC ≠ quantitation)
- Reducing/controlling variability may be more important (and feasible) than reducing bias
- There are, however, simple changes that can reduce bias
- Paying attention means reporting *what was done*, not just what was specified, for the protocol: acquisition, processing, and analysis
- Through collaboration we can:
  - Determine impact of image bias/variance on clinical trials
  - Minimize impact across multiple sites by adhering to standards
- Quantitative imaging results can be used as disease response or stratification markers if:
  - We adhere to standards to *quantitatively validate* imaging
  - Acquire sufficient number of quantitatively validated studies with outcomes

Numbers Do Matter

- "The favorable experience to date is beginning to support the use of PET as a surrogate end point in trials that are aimed at testing or comparing the efficacy of new drugs or treatments" *[Juweid & Cheson NEJM 2006]*
- Evaluation of new therapies requires multicenter studies for patient recruitment
  - Pooling results between different PET/CT scanners requires knowledge of biases between scanners to improve the statistical power of studies
- Until recently, there have been few systematic efforts to understand or improve quantitative accuracy, precision, and stability between multiple sites.

Consensus Building

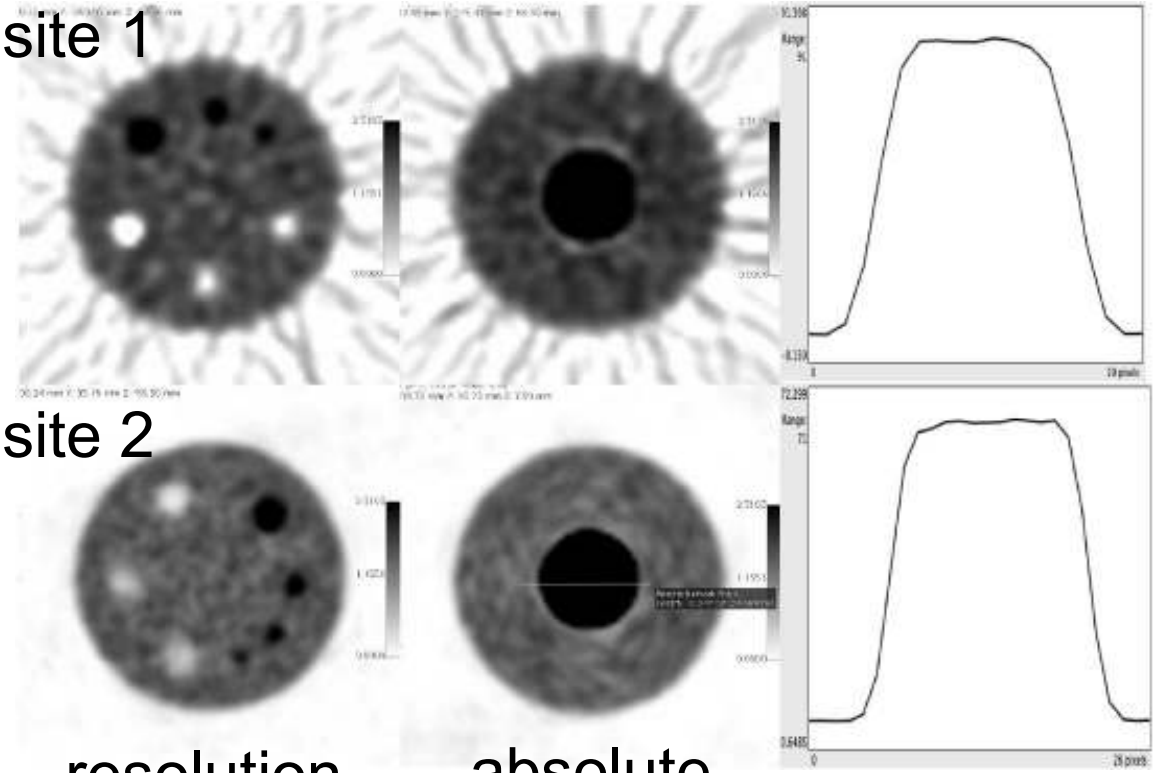


Version 2 Modified ACR phantom with long half-life source using NIST standard

assembled

site 1

site 2



resolution effects

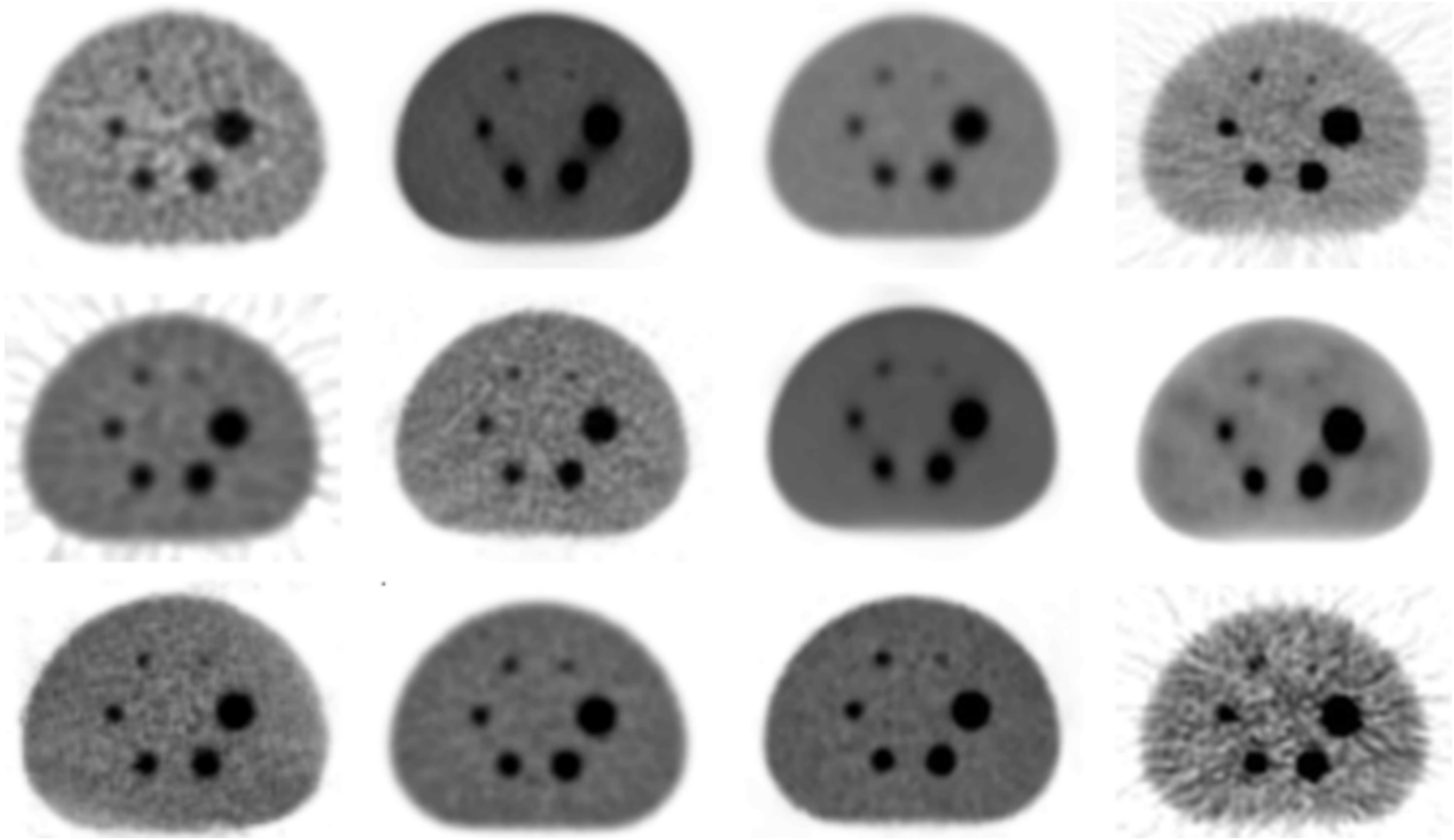
absolute quantitation

(also measure uniform region in between to check for SUV=1)

Profiles:
No partial volume effects in center

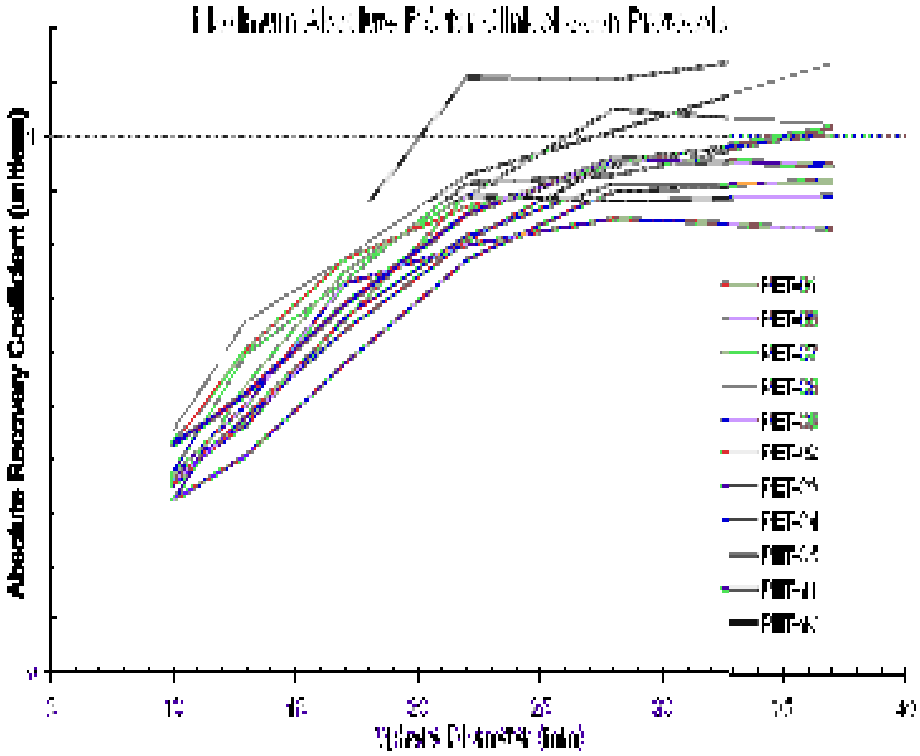
SNM Validation Phantom Study

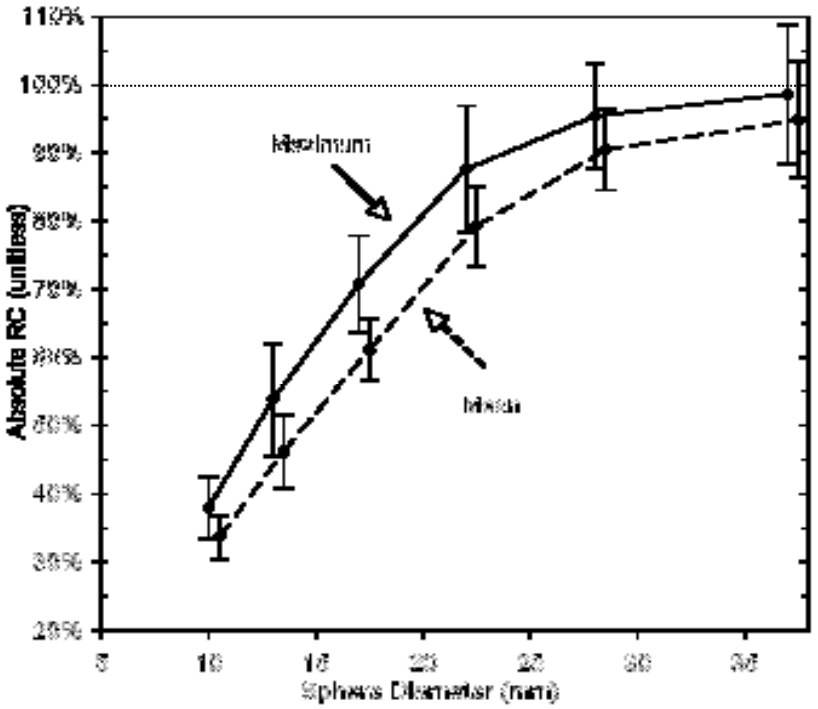
- Sample images of the IDENTICAL object from 12 different PET and PET/CT scanners



Not meant as a "Consumer's Report" evaluation, but rather to facilitate multi-center comparisons

Multi-center repeated PET/CT scans





- Values for 11 scanners at at 8 academic imaging centers.
- Results should be independent of sphere diameter.

averaged coefficients of variation

mean SUV: 8.6%, max SUV: 11.1%

Doot PhD Thesis 2008, Kinahan et al 2008 SNM

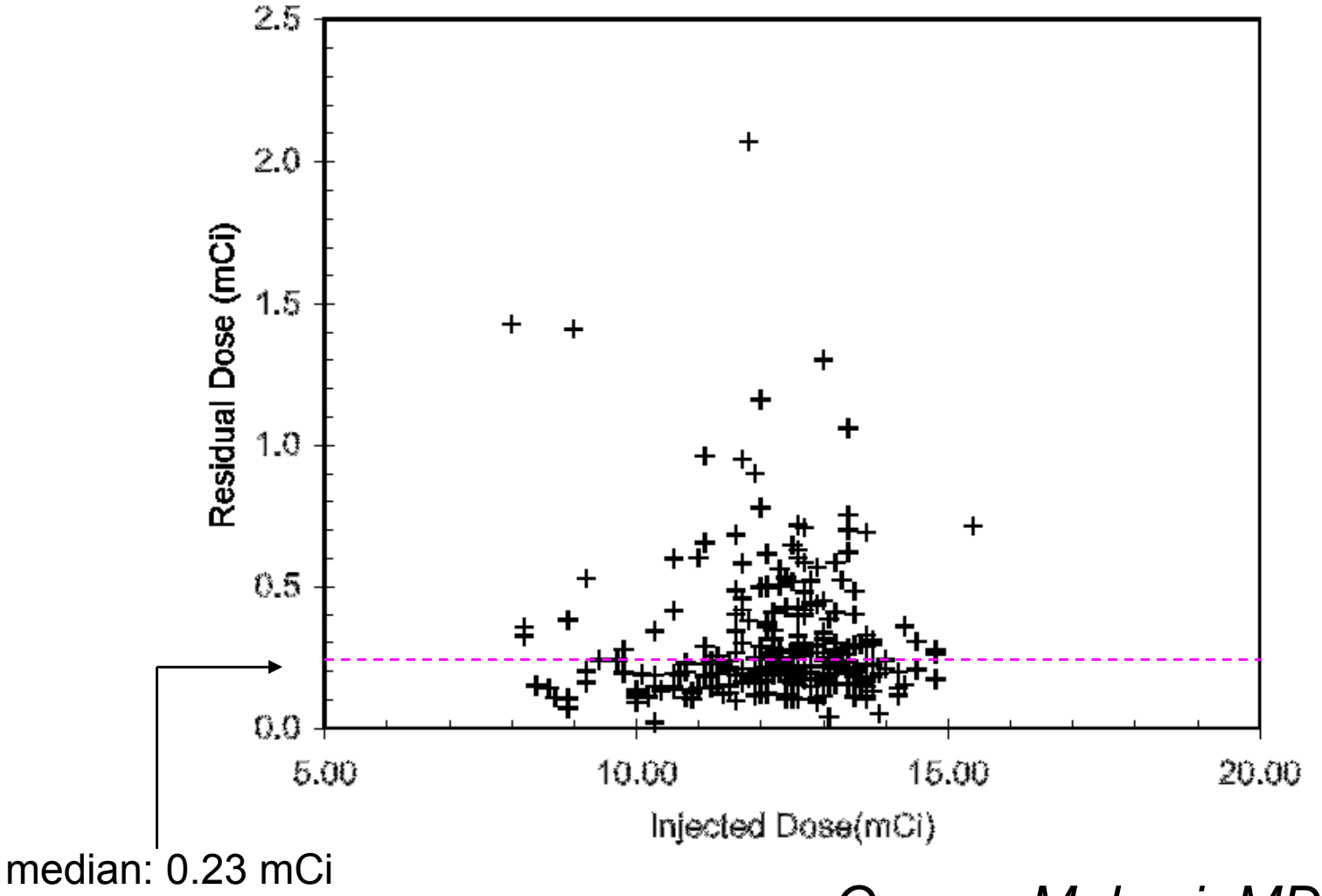
With Current Clinical Practice, do Numbers Matter in PET Images?

- *R Edward Coleman Eur J Nucl Med (2002)*
  - The answer to the question "Is quantitation necessary for clinical oncological PET studies interpreted by physicians with experience in interpreting PET images?" is "no."
  - Image quantitation will become increasingly important in determining the effect of therapy in many malignancies

- What do we need accurate SUVs for?
  - Clinical research, Clinical trails, and Drug discovery
  - Individual response to therapy
  - SUVs are now routinely reported, and asked for by referring physicians

Residual dose

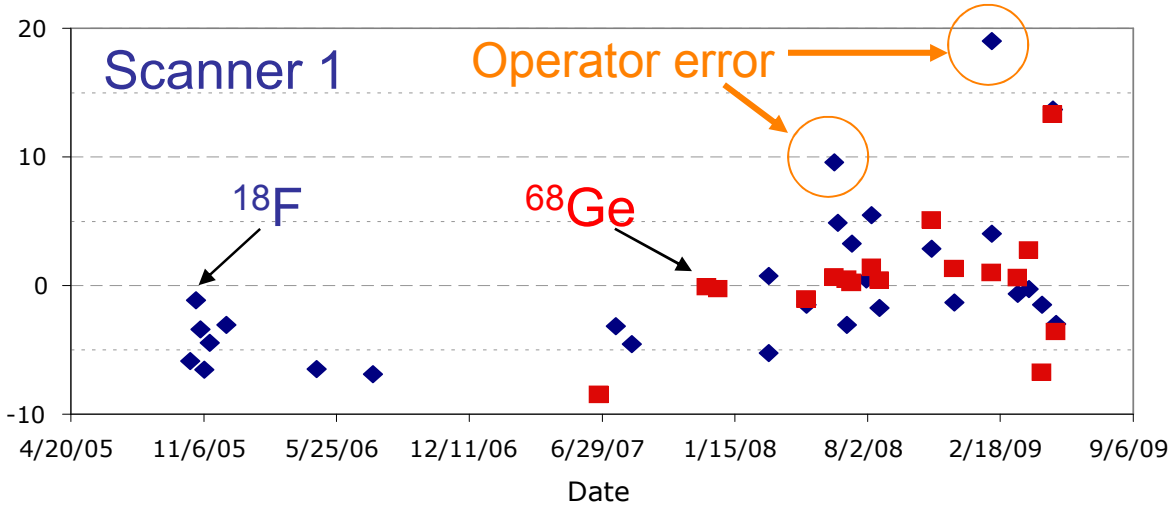
- *n* = 250 patients



Osama Malawi, MD Anderson

We know short term variability, but not long term variability

Activity Correction Factors



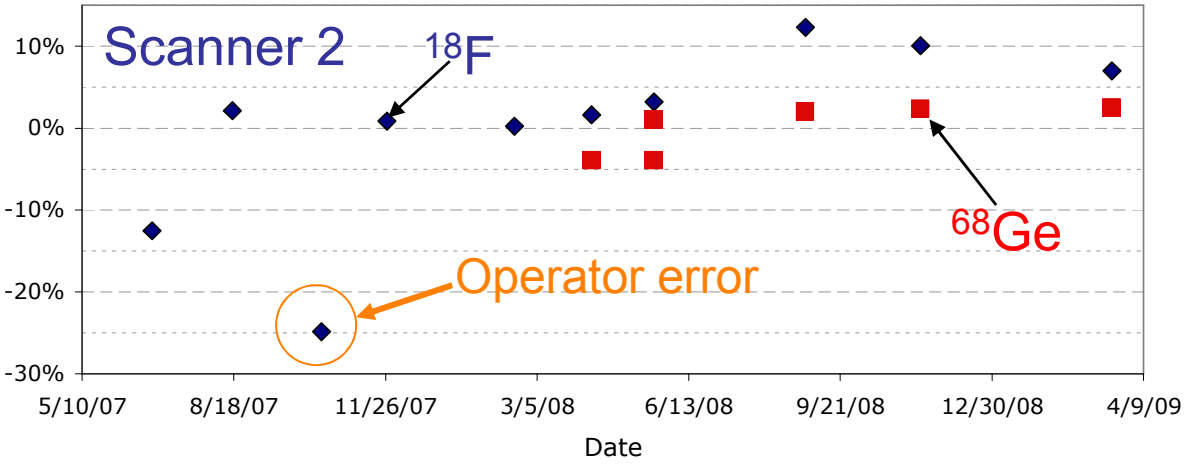
Standard Deviation

^{68}Ge= 3.2%

^{18}F = 6.1%

Outliers Removed

^{18}F = 4.1%



Standard Deviation

^{68}Ge= 3.1%

^{18}F = 11.0%

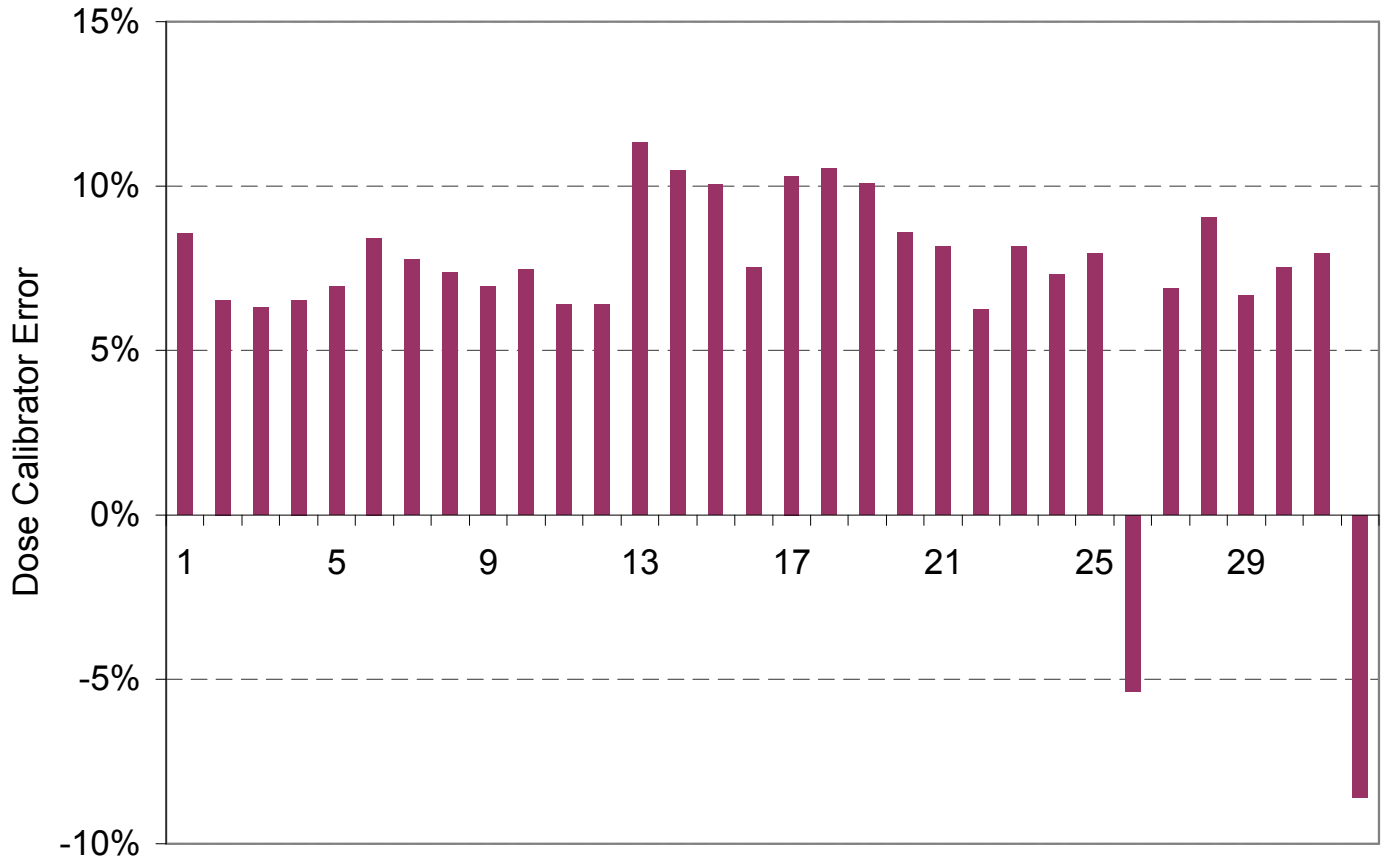
Outliers Removed

^{18}F = 7.0%

Lockhart SNM 2009

Dose Calibrators have significant variability, and not all scanners calibrate against a dose calibrator

Sample of 32 dose calibrators at 3 sites using RadQual/NIST Ge-68 standard



Zimmerman SNM 2009