The QIBA FDG-PET/CT Biomarker Committee: Overview and Status Update 2017

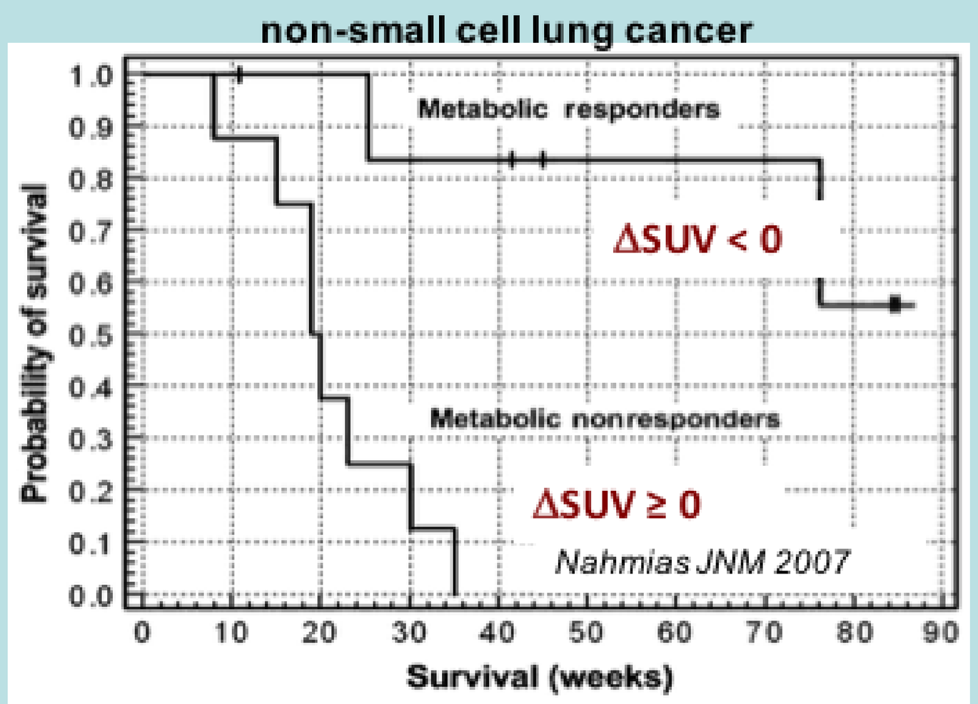
Accelerating the development of new therapies and improving assessment of response

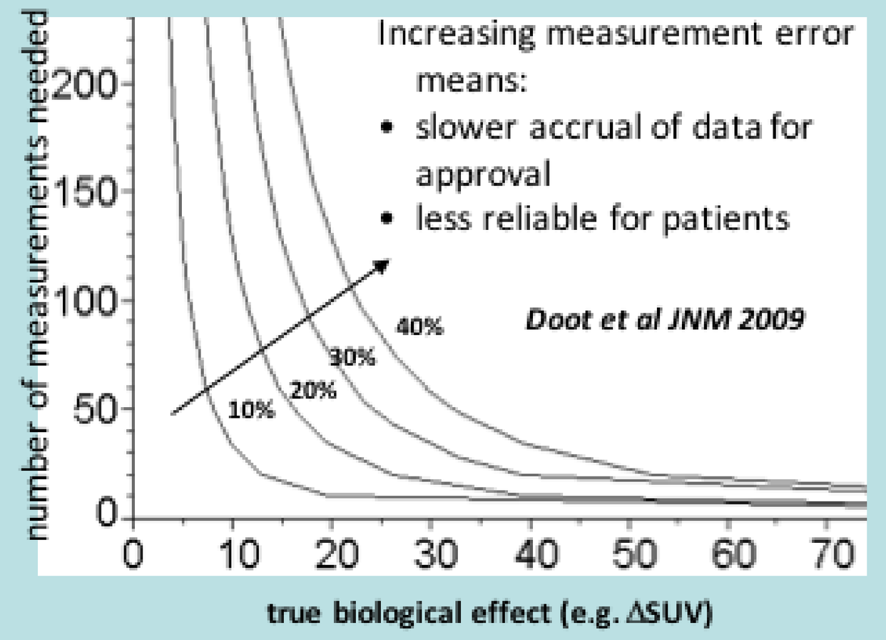
Quantitative Imaging Biomarkers Alliance
RSNA

Quantitation – Why and How

Why Quantitation? Precision Medicine with Imaging

- *Improve individual patient care*
- Clinically proven detection and longitudinal quantitation for follow-up
- Moves imaging from diagnostics and staging to therapy assessment
- *Accelerate adoption of new molecular diagnostics*
- *Make clinical trials of new therapies more effective*
- *All tied to quantitative accuracy*





FDG-PET as a Therapeutic Response Predictor

A joint project between RSNA QIBA and the Foundation for the National Institute of Health

RSNA QIBA and the FNIH Biomarkers Consortium have collaborated in the collection of evidence to demonstrate the clinical utility of quantitative FDG-PET as a therapeutic response predictor. Data generated is being used to inform the FDA imaging biomarker qualification process.[1]

FDG-PET Lymphoma Study[2]
Lymphoma was selected as one of the clinical settings in which to evaluate quantitative FDG-PET performance. An imaging companion study (CALGB/Alliance 580603) within the phase 3 CALGB 50303, *Randomized Study of R-CHOP vs. Dose-Adjusted EPOCH-R in Untreated De Novo Diffuse Large B-Cell Lymphomas* was designed to assess the value of standardized PET imaging acquisition and assessment methods in a multicenter setting (Figure 1).

The imaging sub-study had an enrollment of 169 patients who received a baseline PET/CT scan at >29 separate centers. 158 completed a post-cycle 2 interim PET scan and 151 completed post-cycle 6 end of treatment (EOT) PET scan and were evaluable for three-year and five-year event-free survival (EFS)/overall survival (OS) endpoints.

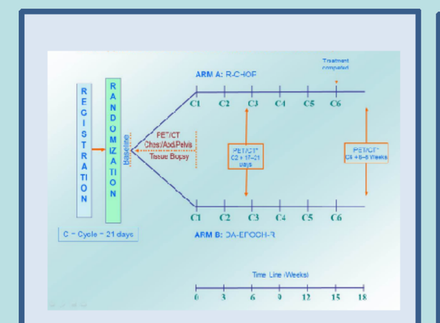


Figure 1

Schema for CALGB 50303 Randomized Study of R-CHOP *vs.* Dose Adjusted EPOCH-R in Untreated *De Novo* Diffuse Large B-Cell Lymphomas

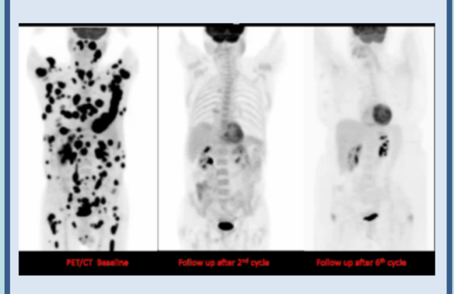


Figure 2

Representative Images from a center demonstrating excellent quality

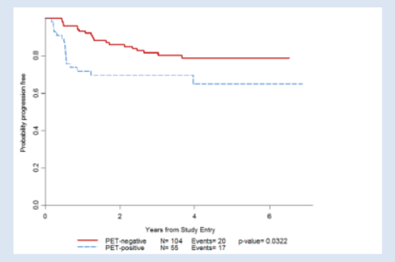


Figure 3

PET scores by Deauville 5-PS at interim post-treatment cycle 2 and EOT cycle 6 scans were grouped into negative (scores 1–3) vs. positive (scores 4–5) response categories for all subjects. With a median follow-up of 3.9 years (maximum 6.9 years) Kaplan-Meier plots of PET- vs PET+ subjects at the interim scan showed significant prolongation of EFS (F p=0.032)

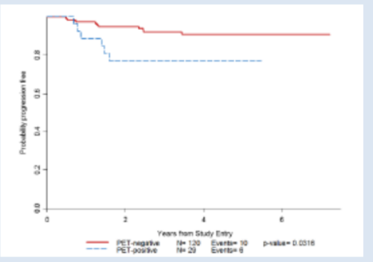


Figure 4

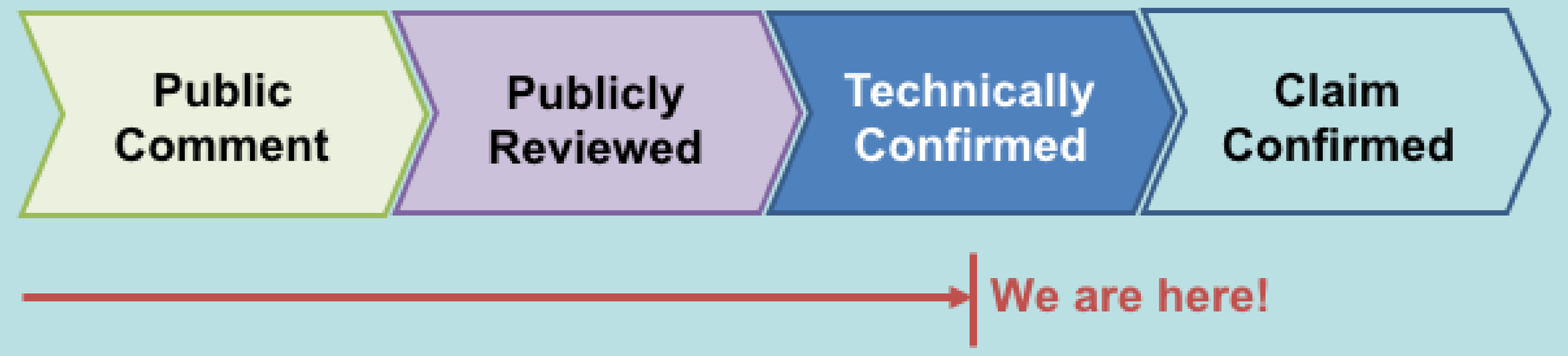
When imaging was performed after cycle 6, there was significant association with survival (p= 0.032) between EOT PET responders and non-responders. Additional follow-up data on progression and overall survival is being collected and therefore these conclusions are intended to be preliminary.

[1] https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/biomarkerqualificationprogram/default.html

[2] Study supported by NCI grants: U10CA031946, U10CA180821 and HHSN261200800001E and a public, private partnership project funded by the Foundation for the National Institutes of Health. made possible through support provided to the FNIH by: Amgen, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Leukemia & Lymphoma Society, Merck, Pfizer, and Wyeth.

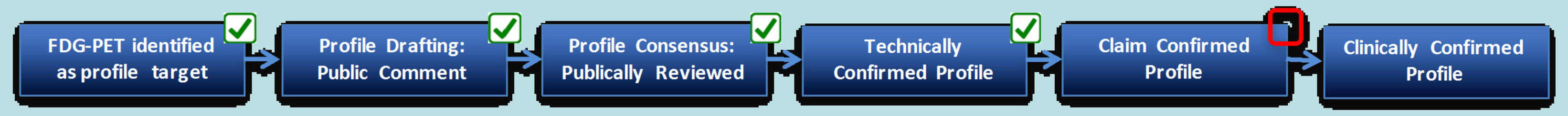
Transition to a Technically Confirmed Profile

Profile Stages



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%

Stage	Description
Public Comment	The Profile describes key factors that affect the claim and has proposed recommended procedures that address the factors
Publicly Reviewed	Each issue raised during Public Comment is formally addressed
Technically Confirmed	Profile details have been implemented in more than one facility using a **Field Test** (described below) and each individual actors (systems and persons) successfully met the specifications
Claim Confirmed	Overall performance was determined and claim was achieved



FDG-PET: Toward "Claim Confirmed" Status:

QIBA Multi-Center FDG PET/CT Clinical Trial: (QIBA-1001)

Purpose of Claim Confirmation:

- To **evaluate** the validity of the statistical assumptions underlying the Profile's Claims
- To **confirm** that the ***actual*** performance is consistent with the Claims, as part of a multi-center clinical trial

GOAL: to confirm the current Profile claim of FDG PET within-subject coefficient of variation (wCV) is $\leq$ 12%.

Primary Objective

To measure the test – retest repeatability of FDG uptake in human solid tumors and assess the effects of FDG uptake intensity and lesion diameter on the test – retest repeatability.

Secondary Objectives:

- To estimate the effect of point spread function modeling on test – retest repeatability
- To measure the test – retest reader and interpretation system reproducibility
- To measure the test-retest repeatability of SUVpeak
- *Exploratory*: to measure the test-retest repeatability of PET/MRI (*vs. FDG PET/CT Claim*)

STATISTICAL CONSIDERATIONS

Independent Variables:

(SUV_{max}, lesion diameter, +/- PSF modeling, interpretation system)

Derive 95% Confidence Intervals (**CIs**) for the:

- Repeatability coefficient (RC) for lesions with SUV_{max} (< , ≥) 4
- Reproducibility coefficients (RDC) for different (*readers, interpretation systems*)

Bootstrap 95% CI about mean wCV

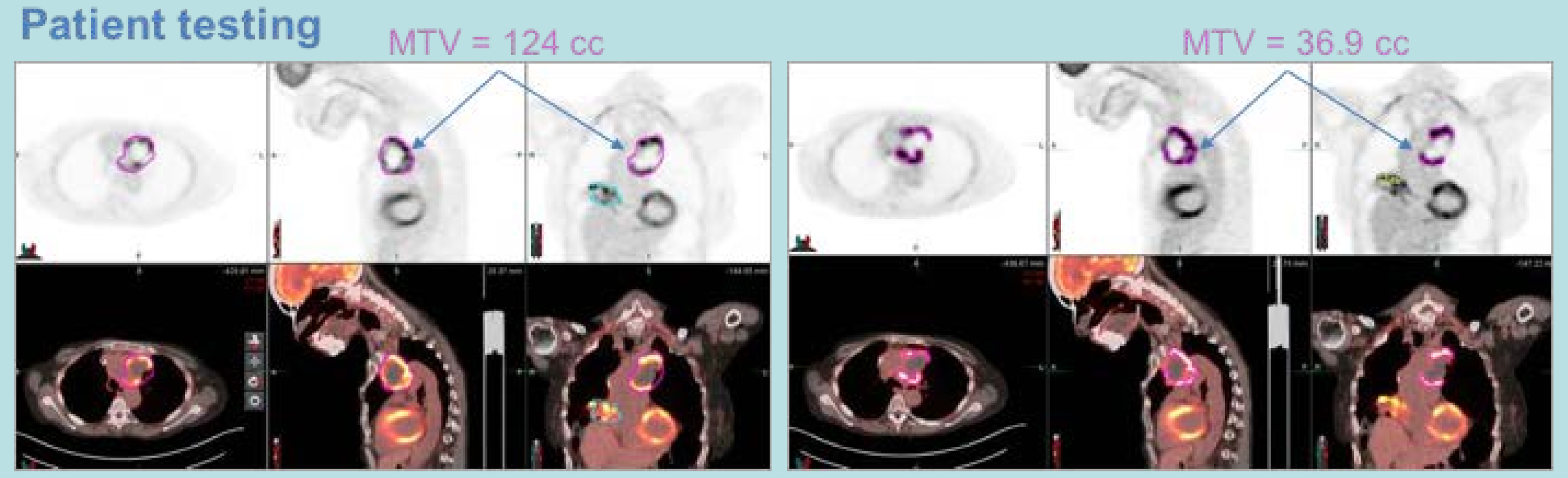
50# (10#per# site)#	75# (15#per# site)#	100# (20#per# site)#	125# (25#per# site)#
[7.4,! 13.6]!	[7.8,! 12.8]!	[8.1,! 12.4]!	[8.2,! 12.1]!

Other Recent and Current Groundwork Projects

Test-Retest Measurements of Metabolic Tumor Volume

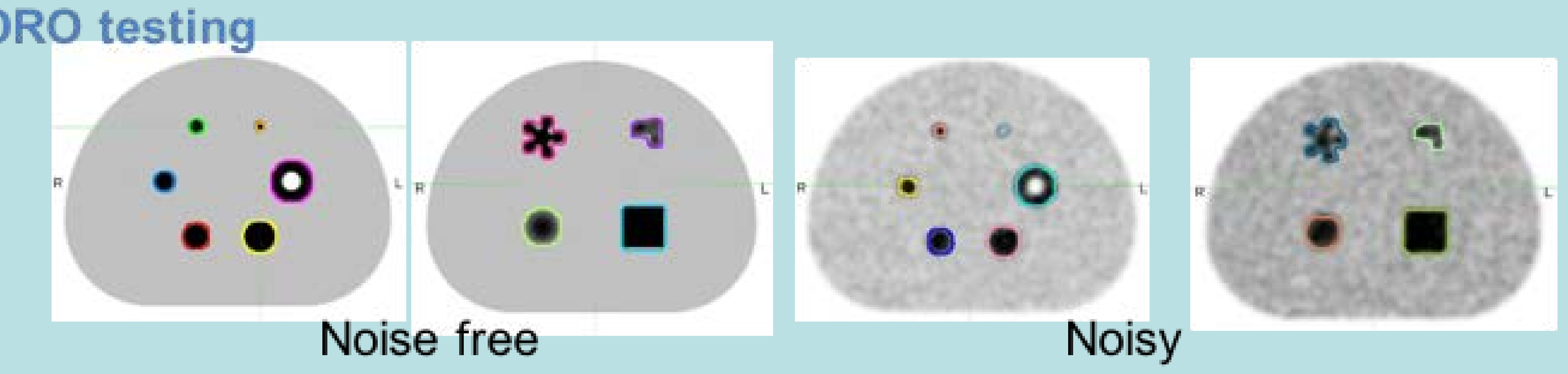
Primary goal: establish the biologic repeatability of FDG PET metabolic tumor volume (MTV) and total lesion glycolysis (TLG) using the arm C data of ACRIN 6678 and MERCK data

Patient testing



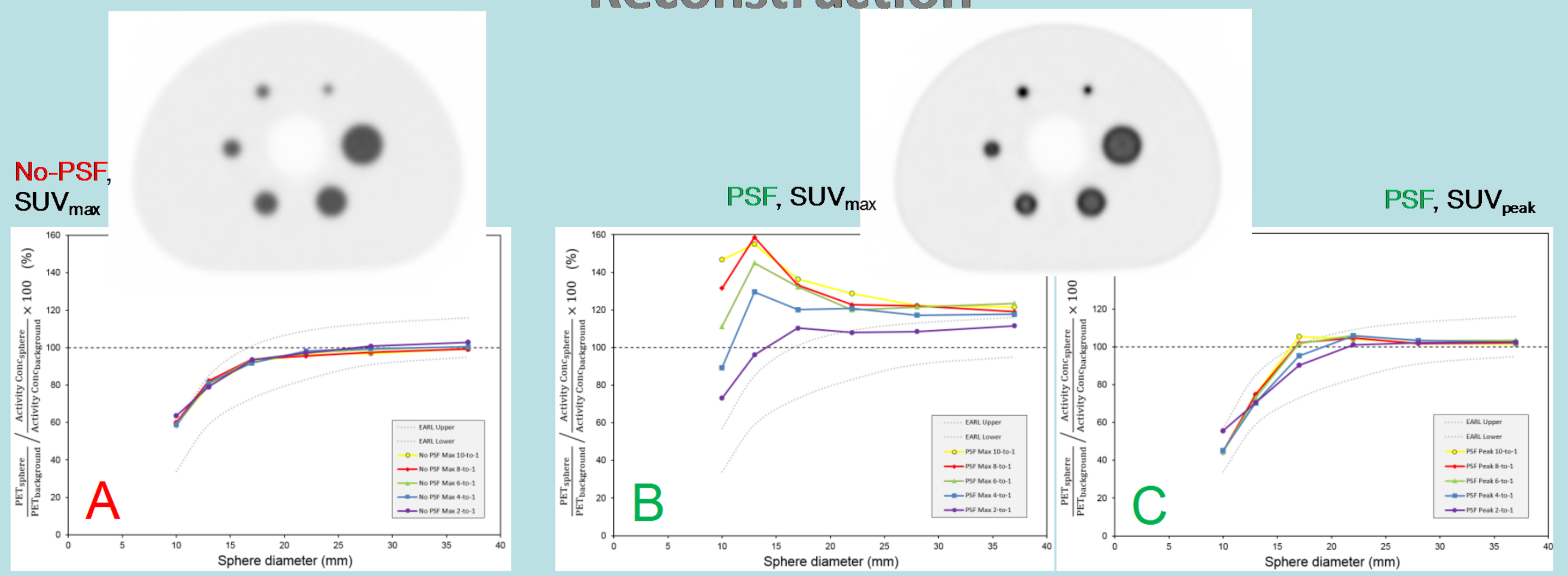
Baseline FDG PET/CT scan　　Re-test FDG PET/CT scan

DRO testing



Noise free　　Noisy

SUV Quantification with Point Spread Function Reconstruction



Key Points

- Tumor SUV_{max} derived from high resolution point spread function (PSF) images is not directly comparable to conventional (No-PSF) images (A & B above).
- Alternative SUV methods (e.g. SUV_{ref}, SUV_{peak}) allow for more consistent SUV quantification from PSF images (A & C above) .

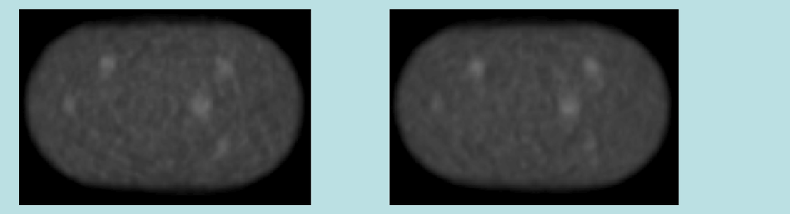
Why this matters

- PSF improves spatial resolution, generally leading to greater lesion contrast.
- There is a need to enable use of PSF while keeping PET quantification capability

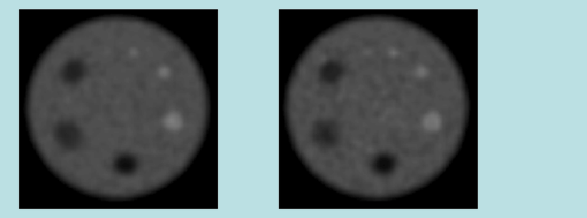
Simple variability estimates in PET

Purpose

- The variability of PET SUV measurements includes multiple sources of error.
- One source of error is the random image noise inherent in obtaining a limited number of counts.
- This noise depends on injected activity, body size, scan protocol, scanner, and image processing.
- To evaluate this noise adequately, a phantom must represent body geometry as well as possible. However, such a large phantom may not be practical to use at all sites to verify proper imaging.
- The purpose of this study is to determine whether images from a routinely used PET phantom can predict variability in lesions in a more realistic patient-sized whole-body (WB) phantom.

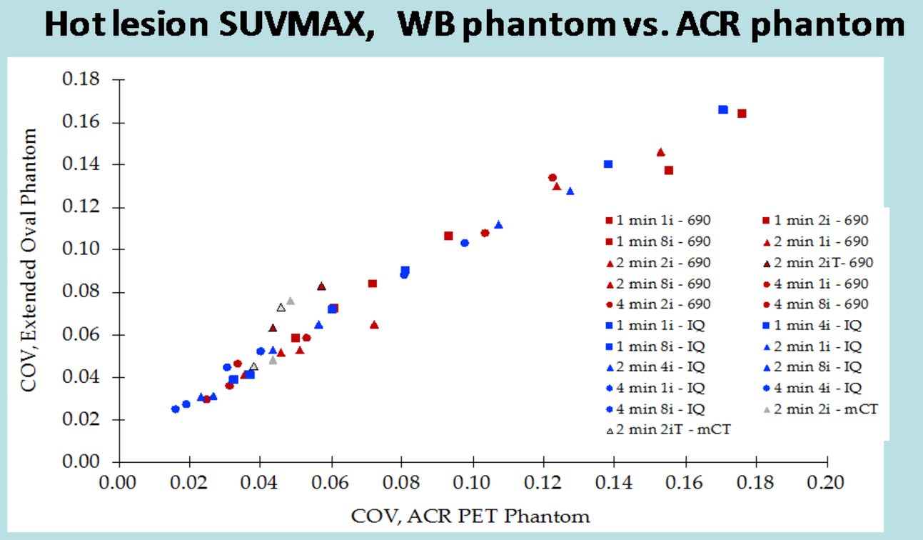


Images from two subsequent scans of whole-body phantom (22 cm x 36 cm x 40 cm), with spherical hot lesions of multiple sizes in warm background.



Images from the ACR PET phantom (20 cm dia, 20 cm long) demonstrate less variability than whole-body, even though scanned and processed the same way.

Hot lesion SUVMAX, WB phantom vs. ACR phantom


COV, Extended Oval Phantom
COV, ACR PET Phantom
1 min 1i - 690
1 min 2i - 690
1 min 8i - 690
2 min 1i - 690
2 min 2i - 690
2 min 2iT- 690
2 min 8i - 690
4 min 1i - 690
4 min 2i - 690
4 min 8i - 690
1 min 1i - IQ
1 min 4i - IQ
1 min 8i - IQ
2 min 1i - IQ
2 min 4i - IQ
2 min 8i - IQ
4 min 1i - IQ
4 min 4i - IQ
4 min 8i - IQ
2 min 2i - mCT
2 min 2iT - mCT

These results show WB vs ACR phantom SUV_{max} measurements for 3 scanners and 3 scan durations and demonstrate that whole-body noise can be predicted from repeated scans of a commonly used phantom

What We're Doing
and How You Can Participate

Specific accomplishments and plan

- ✓ Collection of recommendations for quantitative PET
- ✓ Presentation (joint with FNIH) to FDA for Biomarker Status
- ✓ NIBIB grant applications to fund operations
- ✓ Year 1 -4 research projects accomplished
- ✓ Year 5 research project funding- progress
- ✓ FDG-PET/CT Profile published and publically reviewed
- ✓ Collaboration with UPICT on Protocols
- ✓ Amyloid Writing Group established, Draft profile approaching completion
- ✓ PET Amyloid Profile Writing Group working for 2 years and became an Affiliate of Global Alzheimer's Association Interactive Network
- ✓ SPECT Profile Writing Group initiated
- ✓ Completed Phase II Profile testing of PET/CT FDG profile.
- ✓ Implementation of Profiles
- ✓ Clinical use of Profile

Organization Standing Activities

- ✓ QIBA Monthly Steering Committee meeting
- ✓ Profile telephone conferences: Alternating weekly for FDG profile, Amyloid profile, and SPECT profile writing groups
- ✓ Bi-annual QIBA meetings, and updates at RSNA
- ✓ Working visits with vendors
- ✓ Special task force meetings – as necessary
- ✓ Profile testing
- ✓ Profile Implementation (by QIBA and vendors)

For more information, visit http://qibawiki.rsna.org

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