QIBA and Quantitative Imaging in Clinical Trials and Clinical Nuclear Medicine

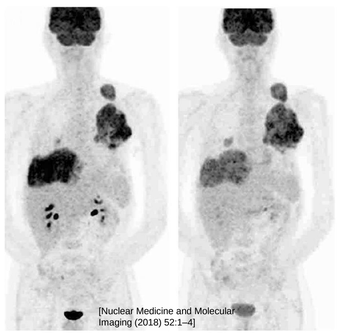
FDG Biomarker Committee, PET Amyloid Biomarker Committee, ^{99m}Tc SPECT Biomarker Committee, I-123 Biomarker Committee

Quantitative Imaging Biomarkers Alliance — RSNA

Quantitative Nuclear Medicine as a Biomarker for Response to Therapy

OVERVIEW

[F-18]FDG PET



[Nuclear Medicine and Molecular Imaging (2018) 52:1–4]

Baseline After therapy

How would you characterize this patient's response to therapy?*

Characterizing a cancer patient's response to therapy is a critical step in determining whether to stay the course or change therapeutic direction.

Quantification of the magnitude of metabolic response with [F-18] FDG PET and using that quantitative information in informing treatment decisions is gaining increasing traction in clinical practice and in the literature.

QIBA has been active in both promoting and characterizing clinical practices to achieve consistent levels of quantitative accuracy through the publication of its "***FDG-PET/CT as an Imaging Biomarker Measuring Response to Cancer Therapy.***"

Recently, several impactful publications and clinical trials have explicitly reported using the QIBA FDG Profile standards as baseline criteria for their study procedures. Two such examples are below…

*By adjusting thresholds, these images could easily be made to visually appear nearly identical suggesting stable metabolic disease. However, quantitative analysis of uptake actually demonstrates a nearly 40% decrease in SUV_{lean}, clearly demonstrating a partial metabolic response. A 40% decrease is considered statistically significant with 95% confidence according to the QIBA FDG Profile.

TBCRC026: Phase II Trial Correlating Standardized Uptake Value With Pathologic Complete Response to Pertuzumab and Trastuzumab in Breast Cancer

Roisin M. Connolly, MD[1]; Jeffrey P. Leal, BA[1]; Lilja Solnes, MD[1]; Chiung-Yu Huang, PhD[1]; Ashley Carpenter, MA[1]; Katy Gaffney, BSN[1]; Vandana Abramson, MD[2]; Lisa A. Carey, MD[3]; Minetta C. Liu, MD[4]; Mothaffar Rimawi, MD[5]; Jennifer Specht, MD[6]; Anna Maria Storniolo, MD[7]; Vicente Valero, MD[8]; Christos Vaklavas, MD[8]; Ian E. Krop, MD, PhD[1,9]; Eric P. Winer, MD[1,9]; Melissa Camp, MD[2]; Robert S. Miller, MD[2]; Antonio C. Wolff, MD[1]; Ashley Cimino-Mathews, MD[1]; Ben H. Park, MD, PhD[1]; Richard L. Wahl, MD[1,5]; and Vered Stearns, MD[1]

QIBA ROLE/RELEVANCE:
QIBA FDG Profile foundational in trial protocol.

FDG Imaging in trial explicitly concordant with QIBA FDG Profile methodology

ROLE OF QUANTIFICATION:

Investigating whether early changes in the SUL_{max} can predict pathological complete response after HER2-directed therapy with Pertuzumab and Trastuzumab alone (no chemotherapy) in early-stage breast cancer.

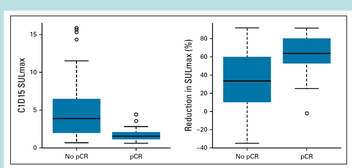


FIG 3. Box plots of 15 days after pertuzumab and trastuzumab initiation (C1D15) and percent reduction in maximum standardized uptake value corrected for lean body mass (SULmax) in patients with pathologic complete response (pCR) vno pCR. The horizontal line inside each box shows the median. The lower and upper hinges of each box represent the 25th and 75th percentiles, respectively. The circles represent actual values of C1D15 and percent reduction in SULmax.

RESULTS A >40% reduction in SUL_{max} yielded a sensitivity of 86% and specificity of 55% for identifying patients who obtained pathologic complete response.

CLINICAL IMPLICATIONS:

1) Patients who are unlikely to completely respond to primary dual antibody therapy of breast cancer can be identified with reasonably high certainty within 15 days of the start of treatment (86%) , potentially allowing their treatments to be intensified to include chemotherapy.
2) Exceptionally good responders can be identified early on, potentially allowing their treatment to exclude chemotherapy completely.

Measurement Repeatability of ^{18}F-FDG PET/CT Versus ^{18}F-FDG PET/MRI in Solid Tumors of the Pelvis

Tyler J. Fraum[1], Kathryn J. Fowler[1], John P. Crandall[1], Richard A. Laforest[1], Amber Salter[2], Hongyu An[1], Michael A. Jacobs[3], Perry W. Grigsby[4,5], Farrokh Dehdashti[1,5], and Richard L. Wahl[1,5]

QIBA ROLE/RELEVANCE:
QIBA PET/CT FDG Profile methods extended to PET/MRI

The QIBA FDG Profile statistical claim defines the limits of repeatability for FDG PET/CT in oncology studies, and associated methods. This study extends this approach to PET/MRI.

ROLE OF QUANTIFICATION:

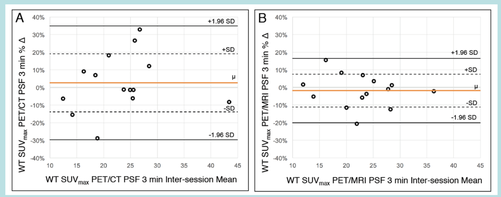
This study measured the reproducibility of SUV measurements in PET/MRI and compared them to PET/CT measures in the same patient.

RESULTS:

Quantitative analysis demonstrated that PET/MRI reproducibility looks at least as good as PET/CT. Repeatability metrics for both modalities were consistent with the QIBA FDG Profile repeatability claim.

CLINICAL IMPLICATIONS:

This study confirms that FDG-PET/MRI can detect comparable treatment effect size as PET/CT using the same number of research subjects. Thus, the QIBA reproducibility claim can be used to perform statistical power calculations in designing clinical trials using both FDG-PET/CT and FDG-PET/MRI.



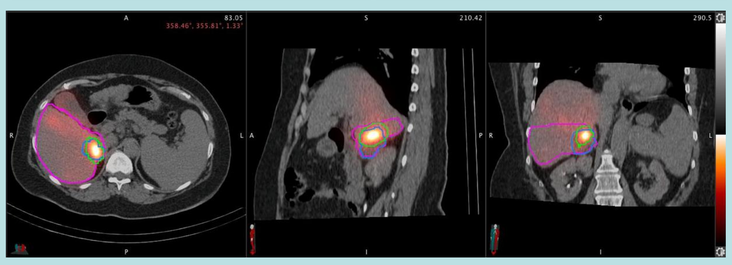
Bland-Altman plots for SUVmax for PET/CT and PET/MRI

Quantitative Nuclear Medicine in Treatment Planning

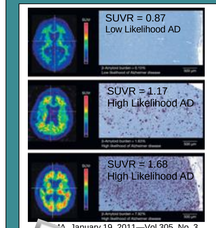
Theranostic pairs include SPECT diagnostics for quantifying the fractions of alpha and beta emitters that will be later deposited in volumes of interest. Localization strategies include specific uptake via cell surface proteins and transarterial administration, as shown below for [Tc-99m]-MAA (macroaggregated albumin). Lesion-to-liver uptake ratio ~ 3:1. Green is the lesion outline from SPECT thresholding (30%).

QIBA ROLE/RELEVANCE: Technetium-99m Profile provides prescriptive methods to achieve accurate and repeatable measurements of the absolute amount of high energy radioactivity that will be deposited in each unit volume of interest.

ROLE OF QUANTIFICATION: To prospectively personalize doses for internal radiotherapy.



Quantitative Nuclear Medicine as Selection Criteria for Clinical Trials

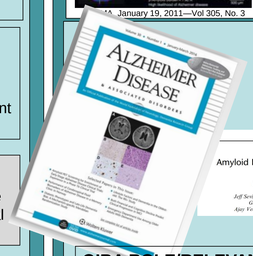


OVERVIEW

Characterization of amyloid burden in patients suffering from dementia with PET is possible using any of the 3 currently FDA approved amyloid PET imaging agents. Quantitative amyloid burden using the cortex to cerebellum Standardized Uptake Value Ratios (SUVR) is the preferred method to characterize a subject as amyloid positive or negative.

A primary use of this technology is to enrich clinical trial populations with true AD patients, rather than a population with mixed dementia etiology.

The **QIBA Amyloid Profile** details practices necessary to achieve the most highly reproducible amyloid SUVR measurements.

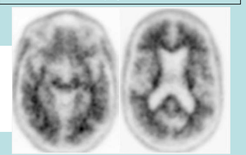


ORIGINAL ARTICLE

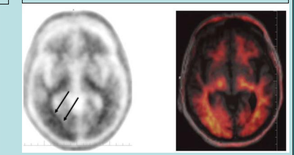
Amyloid PET Screening for Enrichment of Early-Stage Alzheimer Disease Clinical Trials
Experience in a Phase 1b Clinical Trial

Jeff Sevigny, MD*; Joyce Suhy, PhD†; Ping Chiao, PhD*; Tianle Chen, PhD*; Gregory Klein, PhD†; Derk Purcell, MD,‡§; Jeremi Oh, PhD†; Ajay Verma, MD, PhD*; Mehul Sampat, PhD†; and Jerome Barakos, MD‡§

A. Read as negative. Quantitation suggests strongly positive. Mismatch between visual and quantitative results possibly attributable to level of brain atrophy. SUVR = 1.30



B. Read as positive. Quantitation suggests negative. Mismatch between visual and quantitative results possibly due to differences in area sampled. SUVR = 1.09



QIBA ROLE/RELEVANCE:
QIBA Amyloid Profile provides methods to achieve reproducible SUVR measures.

The QIBA Amyloid Profile is designed to guide single or multi-center studies towards practices that guarantee high reproducibility of SUVR. This will aid in higher statistical powering of amyloid trials.

ROLE OF QUANTIFICATION:

To characterize subjects as either amyloid positive or amyloid negative for enrichment of subjects for clinical trial. Threshold SUVR = 1.1

RESULTS:

Amyloid quantitation ***corrected*** the visual reads for amyloid positive/negative classification in 10-15% of cases.

CLINICAL IMPLICATIONS:

SUVR thresholds are used for consistent quantitatively-based classification of amyloid positive/negative. Visual interpretation can be confounded by non-standard amyloid distributions masking global disease. This has major clinical implications. It also provides a tool to enhance clinical trial statistical power.

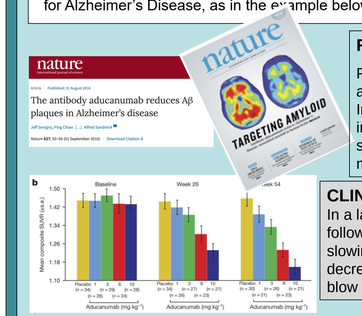
Quantitative Nuclear Medicine as an Endpoint for Clinical Trials

OVERVIEW

Another primary use of Quantitative PET imaging is as an endpoint in a clinical trial. Numerous applications exist in neurologic, cardiac, and oncology literature. Examples of quantitative endpoints in oncology include reduction in FDG SUV_{max}, SUV_{Lean} or Metabolic Tumor Volume to assess response to therapy. Examples in cardiology include measurement of changes in myocardial blood flow or coronary flow reserve. Examples in neurology include quantitative measurement of SUVR for Alzheimer's Disease, as in the example below.

QIBA ROLE/RELEVANCE:
QIBA Amyloid Profile provides methods to achieve reproducible SUVR measures.

The QIBA Amyloid Profile is designed to help guide single or multi-center studies towards practices that guarantee a high level of reproducibility of SUVR. SUVR is a common endpoint in AD therapy trials.



ROLE OF QUANTITATION:

PET SUVR measures were used to track aducanumab induced reduction of amyloid burden. In patients with mild AD, one year of monthly IV infusions of aducanumab reduced brain Aβ in a statistically significant dose and time-dependent manner.

CLINICAL IMPLICATIONS:

In a large multi-center study with aducanumab, clinical follow-up of these patients demonstrated no significant slowing of clinical decline, despite dramatic quantitative decreases in amyloid burden, resulting in a significant blow to the amyloid hypothesis.