Quantification of 3-D PET/CT Imaging

Janet R. Saffer[1,2], Joshua S. Scheuermann[1,2], Joel S. Karp[1,2], Amy Perkins[3]

1. Department of Radiology, University of Pennsylvania
2. PET Core Lab, American College of Radiology Imaging Network (ACRIN)
3. Philips Medical Systems

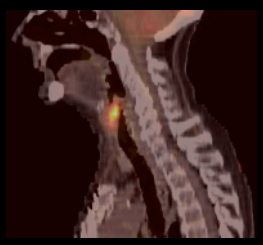
Role of PET/CT Imaging

- In oncology, imaging studies playing an increasingly important role in assessing patient's response to treatment
  - Serial CT scans are evaluated for changes in number and size of tumors
  - Serial PET scans are assessed for changes in metabolic activity of the lesions
- Advent of combined PET/CT systems streamlines the fusion of these anatomic and functional images

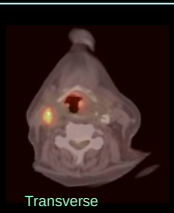
Head and neck cancer **SNM Image of the Year 1999**

CT: 160 mAs; 130 kV_p; pitch 1.6; 5 mm slices

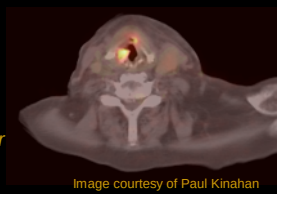
PET: 7 mCi FDG; 2 x 15 min; 3.4 mm slices



Sagittal



Transverse



PET/CT scanner

University of Pittsburgh Medical Center

Image courtesy of Paul Kinahan

UPenn Installation of Gemini TF: November 2005

PET scanner

LYSO : 4 x 4 x 22 mm^3

28,338 crystals, 420 PMTs

70-cm bore, 18-cm axial FOV

CT scanner

Brilliance 16-slice

Spatial resolution: 4.8 mm at 1cm
Sensitivity: 6.1 cps/kcps/Mbq
Energy resolution: 12% FWHM
Scatter fraction at 440 keV:
29% for 20-cm x 70-cm cyl

NEMA Peak NEC:
97 kcps @ 0.42µCi/ml

Confounding effects

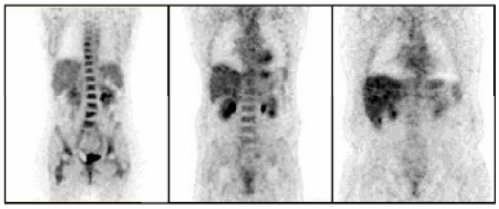
- Trying to glean information about patient's disease state from quantitative measurements of image data
- However, there are many confounding effects that complicate quantification in PET/CT imaging.
- Sources of variability can be grouped into three categories:
  - Patient-related
  - Instrument-related
  - Operator-related

Patient-related factors affecting quantification

Factors we can't control:

- x body habitus (affects attenuation and scatter)
- x patient's flexibility (ability to hold arms over head)
- x patient's ability to hold still (pain, cognitive impairment)
- x patient's individual physiology (affects tracer distribution within patient)
- x for FDG imaging, blood glucose level (4 to 6 hr fast)
  <=200 mg/dL or re-schedule (other thresholds 180 or even 150)

The heavy patient problem



Slim 58 kg "Normal" 89 kg Heavy 127 kg

Object diameter	Equivalent pt. wt.	Relative attenuation	Peak NEC ratio	Peak NEC density ratio
20 cm	41 kg	1	6	18
27 cm	71 kg	2.2	2.7	4.5
35 cm	106 kg	4.3	1	1

Can't compensate simply by increasing scan time!

Patient-related factors affecting quantification

Factors we can't control:

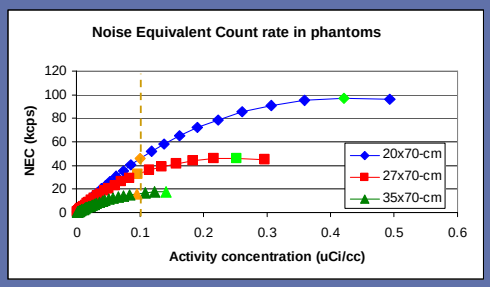
- x body habitus (affects attenuation and scatter)
- x patient's flexibility (ability to hold arms over head)
- x patient's ability to hold still (pain, cognitive impairment)
- x patient's individual physiology (affects tracer distribution within patient)
- x for FDG imaging, blood glucose level (4 to 6 hr fast)
  <=200 mg/dL or re-schedule (other thresholds 180 or even 150)

More patient-related factors

Factors we CAN control:

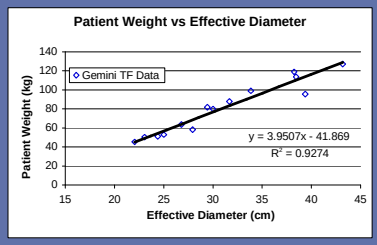
- dose administered
  - weight-based or does one dose fit all?
  - what about CT dose -- adjust mAs for attenuation-correction CT?
- uptake time before imaging
  - standardization for FDG, e.g. 50-70 minute window, then +/- 5 minutes of that on return visit
  - coping with unusual delays – match on return visit?
- imaging time per bed position

Analysis of Weight-based Dose Protocol: Gemini TF PET – Phantom Data



Analysis courtesy of Amy Perkins

Change Protocol to Achieve Optimum NEC



14 Patients

Effective Diameter (cm)	Patient Weight (kg)	Phantom Activity Conc. at NEC Peak (uCi/cc)	Inj. Act.[Scan 60 min PI] to Reach Peak NEC (mCi)
20	36	0.42	22.4
27	64	0.25	23.8
35	96	0.14	19.7

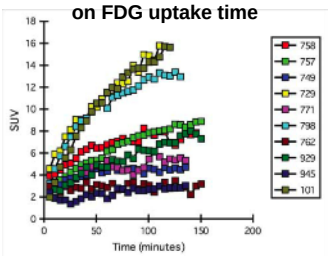
Adopted a 15mCi injection for all adult patients

More patient-related factors

Factors we CAN control:

- dose administered
  - weight-based or does one dose fit all?
  - what about CT dose -- adjust mAs of attenuation-correction CT?
- for FDG, uptake time before imaging
  - standardization, e.g. 50-70 minute window, then +/- 5 minutes of that on return visit
  - coping with unusual delays – match on return visit?
- imaging time per bed position

Dependence of Standardized Uptake Value (SUV) on FDG uptake time



Reference: Lowe VJ, Delong DM, Hoffman JM, Coleman RE. Optimum scanning protocol for FDG-PET evaluation of pulmonary malignancy. J Nucl Med 1995;36:883-87.

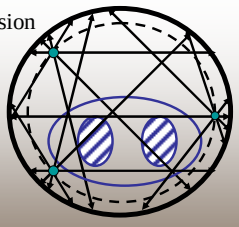
The increase in SUVs with increasing uptake time motivates:
1) Some sites using 90-minute uptake periods instead of 60.
2) Sites performing second timepoint images of lesions to see by how much the SUV has changed.

Instrument-related factors affecting quantification

- spatial and energy resolution
  - partial volume effect
  - discriminate against scattered events
- sensitivity: higher sensitivity => lower Poisson noise
- data acquisition mode for PET (2-D vs 3-D)
  - 2-D reduces scatter and randoms but at cost of sensitivity
- attenuation method
  - using CT for AC vs. measured AC (MAC)

Measured AC: Rotating rod/point source

Transmission Source



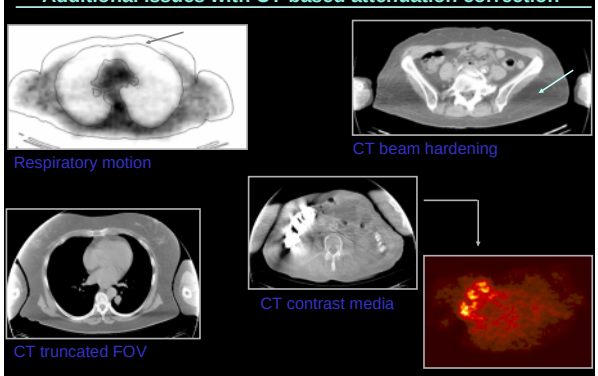
- Source rotates around patient
- Ratio of Transmission to Blank scans gives correction factors: $T/B=\exp(-\mu d)$

Switch to CTAC has effect on quantification

- "…CT-based attenuation correction produced radioactivity concentration values significantly higher than the germanium-based corrected values. These effects, especially in radiodense tissues, should be noted when using and comparing quantitative PET analyses from PET and PET/CT systems."

Nakamoto Y. Osman M. Cohade C. Marshall LT. Links JM. Kohlmyer S. Wahl RL, PET/CT: comparison of quantitative tracer uptake between germanium and CT transmission attenuation-corrected images. *J Nucl Med* 2002;43(9):1137-43.

Additional issues with CT-based attenuation correction



Slide courtesy of Paul Kinahan

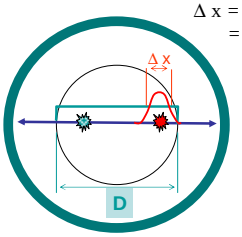
Instrument-related factors continued

- scatter correction method
  - background subtraction method
  - single-scatter simulation (model-based)
- additional instrument capabilities
  - Time of Flight (TOF)
  - respiratory motion-correction
  - cardiac gating

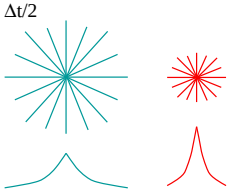
Time of Flight PET - Basic Concept

Localize source along line of response - *depends on timing resolution Δt*

Δx = uncertainty in position along LOR $= c \cdot \Delta t/2$



Greatest potential benefit is for largest patients



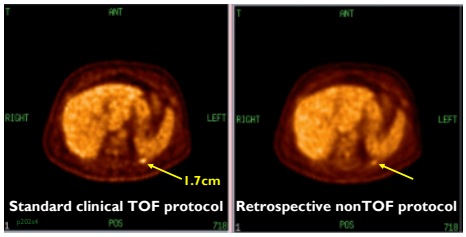
Conventional Back-projection

TOF weighted

PHILIPS Penn

Comparison of TOF and nonTOF images: heavy patient

56 year old male with a history of NHL
237 lbs, 37.2 BMI , 15 mCi FDG, 1 hr post-injection
TOF lesion uptake to nonTOF = 1.6



Same patient data reconstructed differently.

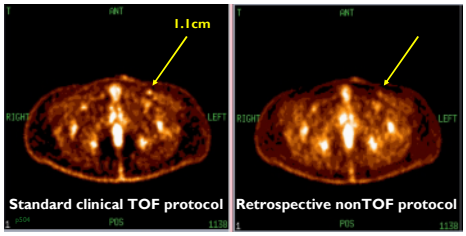
A. Perkins et al, "Clinical optimization of the acquisition time of FDG time-of-flight PET", SNM 2007.

20

PHILIPS Penn

Comparison of TOF and nonTOF images: heavy patient

20 year old male recently diagnosed with Hodgkin's lymphoma
255 lbs, 38.9 BMI, 15 mCi FDG, 2 hr post-injection
TOF lesion uptake to nonTOF = 2.1



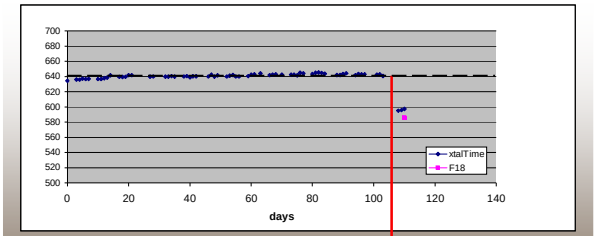
Same patient data reconstructed differently.

21

Operator-related factors affecting quantification

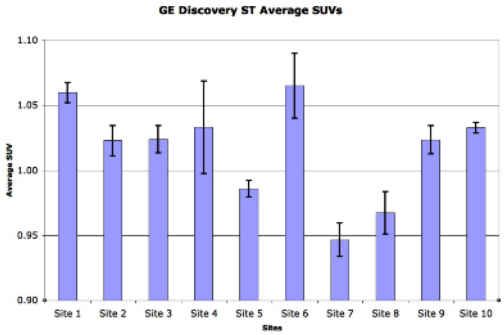
- acquisition and reconstruction protocols
  - arms up/down, imaging time per bed position
  - reconstruction protocol can make a difference in SUVs
    - Westerterp, M et al. Quantification of FDG PET studies using standardized uptake values in multicentre trials: effects of image reconstruction, resolution and ROI definition parameters, *Eur J Nucl Med Mol Imaging* (2007) 34:392-404.
- instrument quality control
  - daily QC, air cals, PMT gains, energy resolution, timing resolution checks
- instrument calibrations
  - normalization, SUV cal, timing cal
    - slow drifts over time characteristic of PMT-based systems

Timing resolution (FWHM) vs. time



12/05 1/06 2/06 3/06

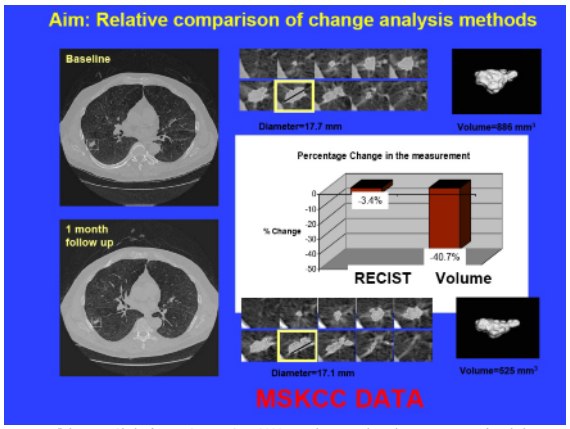
3/20/06 re-calibration ->595 ps



Data from cylinders submitted to ACRIN for PET credentialing which indicate that can't assume interchangeability even between cameras of same make and model.

Operator-related factors continued

- method of image analysis - How to characterize patient's disease?
  - What to measure? How to measure?
    - size of lesion? (2-D or 3-D)?
    - max SUV? average SUV within a region?
  - Vendor-specific SUVs
- non-uniform uptake within tumor (e.g. necrotic center)
  - Important if using image for treatment planning
  - CT not as helpful in determining size of PET lesion as you might think
- image interpretation
  - Setting a semi-quantitative threshold for malignancy is difficult (e.g. SUV =>2.5)
  - Image display/analysis tools not optimized for measurement of change over time
  - Intra- and Inter-Reader variability



From talk by Larry Clark of NIH's CIP at RSNA 2006 "Imaging as a Biomarker: Importance of Technique."

Operator-related factors continued

- method of image analysis - How to characterize patient's disease?
  - What to measure? How to measure?
    - size of lesion? (2-D or 3-D)?
    - max SUV? average SUV within a region?
  - Vendor-specific SUVs due to limitations in current DICOM standard
- non-uniform uptake within tumor (e.g. necrotic center)
  - Important if using image for treatment planning
  - CT not as helpful in determining size of PET lesion as you might think
- image interpretation
  - Setting a semi-quantitative threshold for malignancy is difficult (e.g. SUV =>2.5)
  - Image display/analysis tools not optimized for measurement of change over time
  - Intra- and Inter-Reader variability

Take Home Messages

1) Reduce variability in factors you can control by standardizing everything as much as possible
2) Ensure consistency by creating Standard Operating Procedures (SOPs)
   - ACRIN PET SOPs online: http://www.acrin.org
   - Shankar et al, Consensus Recommendations for the Use of 18F-FDG PET as an Indicator of Therapeutic Response in NCI Trials. *J Nucl Med* (2006);47(6):1059-1006.
3) If make changes in acquisition and processing protocols, characterize the effect on quantification and communicate info to clinicians
4) Clearly label images to denote any differences in acquisition and/or processing
5) Communication is vital: between technologist and reader of study, also with referring physicians, other sections within Radiology and other departments within your institution.

Future Challenges

- Increasing pressure for earlier feedback on treatment efficacy
- Expansion from diagnosis/staging to individualized treatment
- New tracers: hypoxia tracers like EF5, new applications of existing tracers – FDOPA for infant hyperinsulinism

Questions? Email: saffer@mail.med.upenn.edu

Complexities inherent in multicenter trials

- Multiple instruments: Difference in performance characteristics (resolution, sensitivity, scatter fraction, count rate performance)
  - ACRIN – PET credentialing program
    - 11% failure rate in first 53 applications
  - SNM Validation Phantom exercise
    - IEC phantom (without lung insert) made of Ge-68
  - AAPM Task Group 145
    - What phantom would help in quantification of multicenter trials?

Additional complexities in multicenter trials

- Multiple readers
  - Core lab "over"-reads
- Multiple analysis tools
  - Makes it difficult to specify a uniform measurement that all participants can accomplish
    - Westerterp et al (2007): "Small unavoidable differences in methodology can be accommodated by performing a phantom study to assess inter-institute correction factors."
  - RIDER initiative (Reference Image Database to Evaluate Response)
    - Standardized, open-source tools

References

1) Lowe VJ ,Delong DM, Hoffman JM, Coleman RE. Optimum scanning protocol for FDG-PET evaluation of pulmonary malignancy. *J Nucl Med* 1995;36:883-87.
2) Nakamoto Y, Osman M, Cohade C Marshall LT, Links JM, Kohlmyer S, Wahl RL. PET/CT: comparison of quantitative tracer uptake between germanium and CT transmission attenuation-corrected images. *J Nucl Med* 2002;43(9):1137-43.
3) Shankar LK, Hoffman JM, Bacharach S, Graham MM, Karp JS, Lammertsma AA, Larson S, Mankoff DA, Siegel BA, Van den Abbeele A, Yap J, Sullivan D. Consensus Recommendations for the Use of 18F-FDG PET as an Indicator of Therapeutic Response in NCI Trials. J Nucl Med (2006);47(6):1059-1006.
4) Westerterp, M et al. Quantification of FDG PET studies using standardized uptake values in multicentre trials: effects of image reconstruction, resolution and ROI definition parameters, *Eur J Nucl Med Mol Imaging* (2007) 34:392-404.