State of the Art in Quantitative Imaging PET/CT

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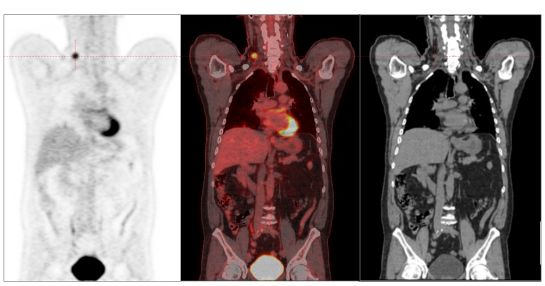
Disclosures

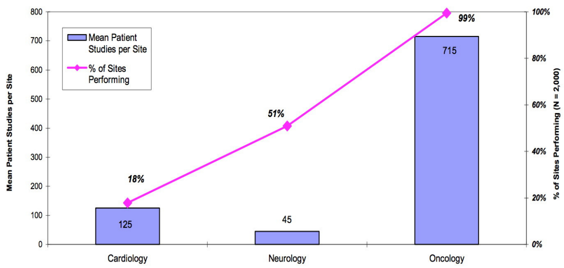
- Research Contract, GE Healthcare

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

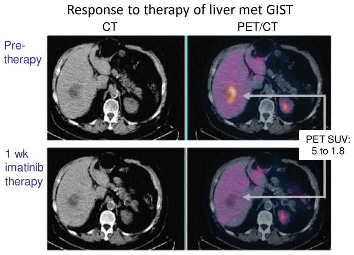
Quantitative imaging can characterize hallmarks of disease and response to therapy

short term drivers

- Clinical research, Clinical trials, and Drug discovery
- New molecular diagnostic agents
- Assessing individual response to therapy
- SUVs are now routinely reported, and are asked for, by referring physicians

increasing volume

Response to therapy of liver met GIST



Castell and Cook, British J Cancer 2008

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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
  - needed for a qualified biomarker

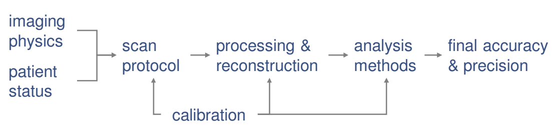
Biomarkers Definitions Working Group. Clin Pharmacol Ther 2001;69(3):89–95.

Quantitative Imaging Requirements

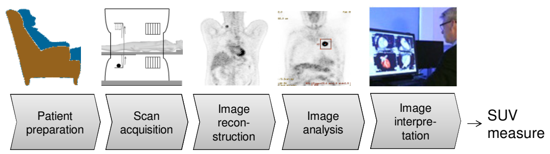
- Prior studies that measure variance
- Defined protocols
- Monitoring of protocols
- Calibration and QA/QC procedures to ensure variance stays within assumed range
- Optional: Techniques and procedures that improve the measurement accuracy

The Imaging Chain

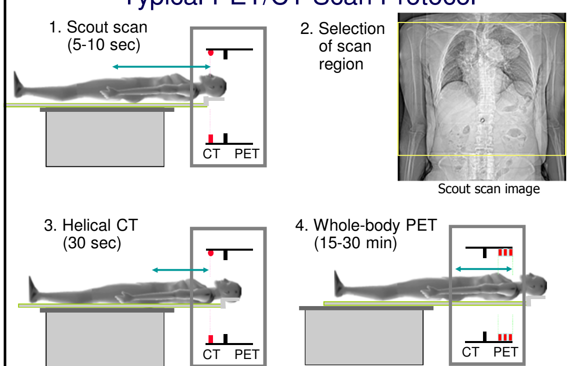
- For quantitative imaging, each component of the imaging chain requires
  - Quality Assurance (i.e protocol)
  - Quality Control (checking what actually happened)
- Outline for all imaging methods:



PET Scanning Process



Typical PET/CT Scan Protocol



Sources of Error in SUV Values
SUV = Standardized Uptake Value

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

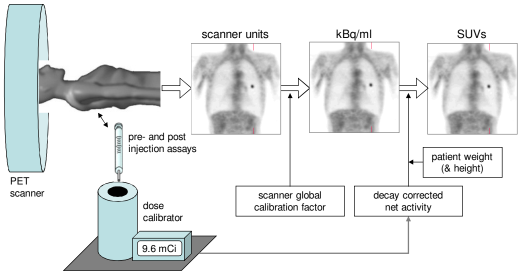
PET = measured PET activity concentration
D' = decay-corrected injected dose
V' = surrogate for volume of distribution

It is important to minimize SUV errors for **serial** (e.g. response to Rx) or **multi-center** studies

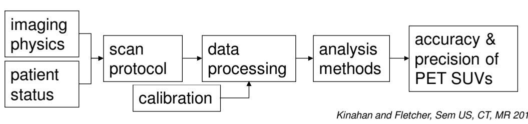
Some potential sources of error are:

- 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

Instrumentation Chain for FDG-PET



Error Propagation in PET Imaging



Kinahan and Fletcher, Sem US, CT, MR 2010

Estimate		Source data
Single-center best case:	10%	e.g. Minn 1999, Weber 2000
Single-center, *typical?*:	10-18%	Velasquez 2009, *(45% Eikman)*
Multi-center, best case:	15-20%	Velasquez 2009
Multi-center, typical:	15-50+%	Fahey 2009, Doot 2010,

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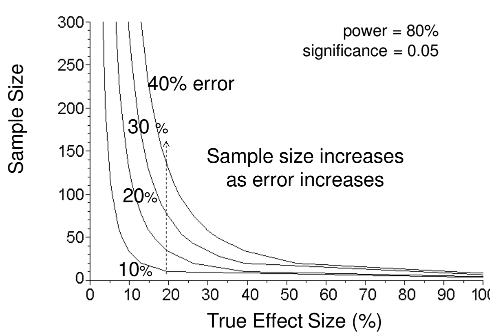
Impact of measurement error on power/sample size



Doot et al., Acad Rad 2012

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

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

effect size = 20%
power = 80%
significance = 0.05

Doot et al., Acad Rad 2012

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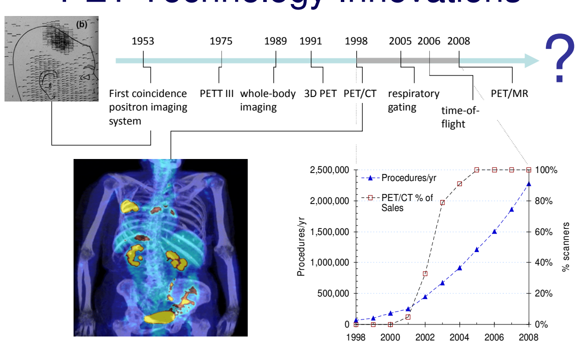
PET Technology Innovations

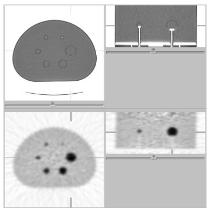


Recent PET Technology Innovations

- 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

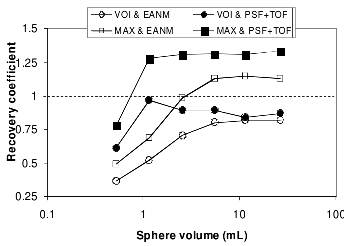
Clinical PET scanners are a moving target

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 19

Challenges with Implementing Quantitative Imaging - Industry

- There is significant variability between manufacturers in allowable scan protocols and trade-offs in image quality
- There are few, if any, tests of the 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
- E.g. when 'standard of care' is requested, any of the following may occur:
  - Blood glucose levels may be ignored or not reported
  - Tracer uptake time may vary
  - PET images may be acquired in 2D or 3D
  - PET images may be reconstructed with different algorithms
  - PET images may be reconstructed with different smoothing
  - SUVs may be measured differently and/or on different platforms
  - May do an MR or CT scan instead

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 PET/CT Standards and/or Accreditation Bodies in the US

- NEMA/MITA
- AAPM
- ANSI (DICOM)

} Standards

- Clinical Research Organizations
- ACR
- IAC

} Clinical (ACR, IAC); } Accreditation (Clinical Research Organizations through PET Core Labs)

- PET Core Labs (CALGB, DFCI, ...)
- ACRIN
- SNM

} Clinical Trials

- FDA
- NRC (DOE), DOT

} Regulatory

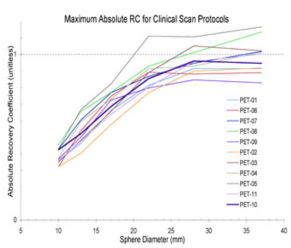
Quantitative Imaging Initiatives

- ACRIN Centers of Quantitative Imaging Excellence (CQIE)
- Quantitative Imaging Biomarkers Alliance (QIBA)
  - Now includes the Uniform Protocols for Imaging in Clinical Trials (UPICT)
- Quantitative Imaging Network (QIN)
- American Association of Physicists in Medicine Task Group 145 (Quantitative Imaging for PET)
- Reconstruction Harmonization Project (ACRIN / SNM-CTN / QIN / QIBA)
- EANM and EORTC initiatives

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

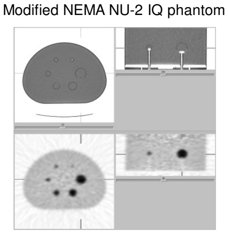
- Uniform Cylinder (used by ACRIN and many others)
- ACR PET phantom
- NEMA NU-2 Image Quality (IQ) phantom
- Modified NEMA Image Quality (IQ) phantom
- SNM CTN phantom
- Cross Calibration Phantom with NIST-traceable ^{68}Ge standard for Dose Calibrator
- Digital reference object

Multi-center repeated PET/CT scans



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

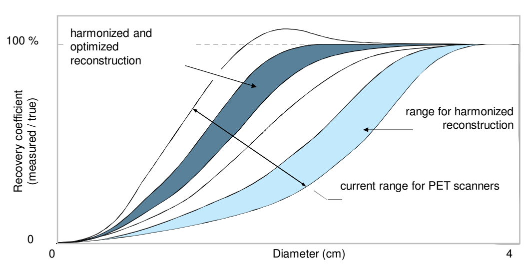
Modified NEMA NU-2 IQ phantom



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

Doot PhD Thesis 2008, Kinahan et al 2008 SNM

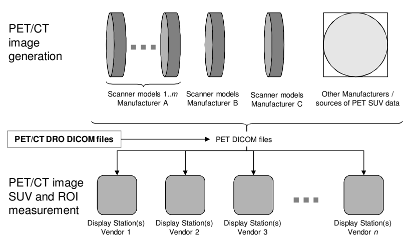
PET image reconstruction harmonization



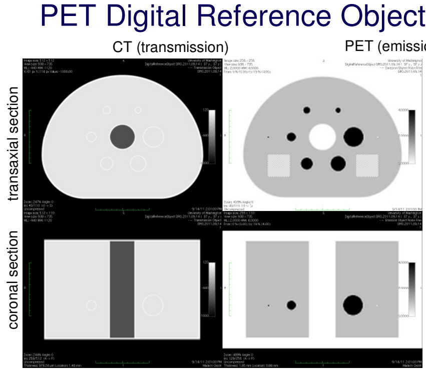
PET Digital Reference Object (DRO)

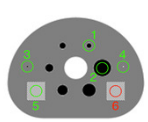
- The DRO is a synthetically generated set of DICOM image files of known voxel values for PET and CT
- Intended to test computation of SUVs and ROIs
- Version 1 released 10/31/2011
- More info at depts.washington.edu/petctdro

PET Digital Reference Object (DRO)



PET Digital Reference Object (DRO)

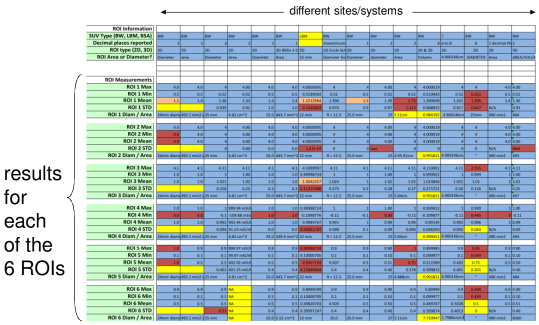




ROI based analysis

Results: 13 sites, 20 different display systems

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



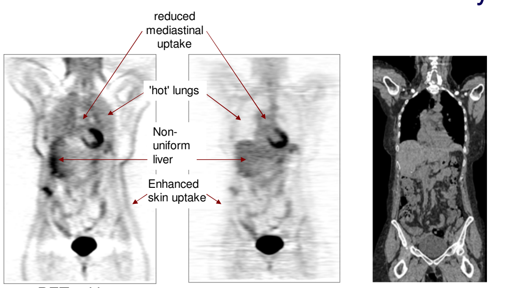
CONCLUSION

State of the art: Quantitative imaging requirements

- Test-retest studies in the literature demonstrate that quantitative image acquisition protocols are possible
- To enable quantitative image acquisition protocols we need
  - Standards by which users can assure compliance
  - The above standards can be provided by standardized methods, e.g. QIBA Profiles and UPICT Protocols
  - Education for (and adoption by) radiologists, if they are to remain in the image processing chain

Extra slides

Effects of Attenuation: Patient Study



PET: without attenuation correction | PET: with attenuation correction (accurate) | CT image (accurate)

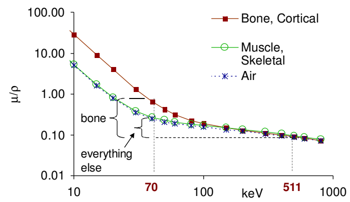
Attenuation, and errors in attenuation correction, can dominate image quality

Typical Radiation Doses

Type	Techniques	Effective Dose (mSv)
PET	Administration 190-370 MBq (5-10 mCi) of ^{18}F-FDG	3.6 - 7 (1.9E-02 mSv/MBq)
Dx Helical CT	Wide range of settings reported. Coverage: C+A+P	7 – 43
PET + Low dose Helical CT	110 - 120 kVp, 30 - 60 mAs, 0.75 - 6.5 mm slice collimation, 1.25 - 2.0 pitch. Scan axial coverage: 851 - 910 mm	1.3 – 4.5 Geometrical mean 2.4 Total for PET/CT: **6 - 10**

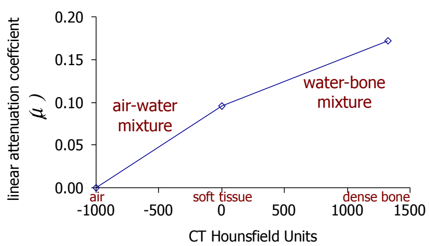
CT-based Attenuation Correction

- The mass-attenuation coefficient (μ/ρ) is similar for all non-bone materials since Compton scatter dominates for these materials
- Bone has a higher photoelectric absorption cross-section due to presence of calcium
- Can use two different scaling factors: one for bone and one for everything else

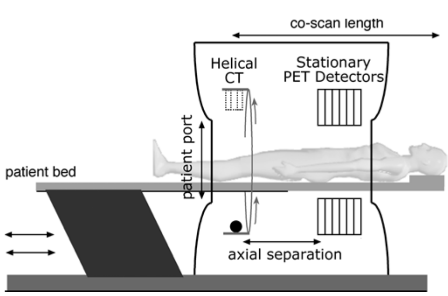


CT-based Attenuation Correction

- Bi-linear scaling methods apply different scale factors for bone and non-bone materials
- Should be calibrated for every kVp and/or contrast agent



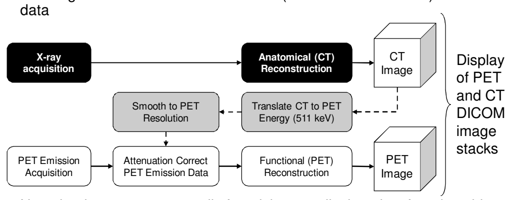
PET/CT Anatomy



All 3 (couch, CT and PET) must be in accurate alignment

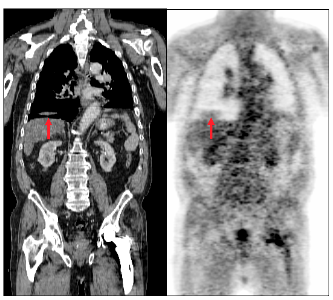
Data Flow and Processing

- CT images are also used for calibration (attenuation correction) of the PET data



- Note that images are not really fused, but are displayed as fused or side-by-side with linked cursors
- Note also that the CT is used for attenuation correction, thus a significant potential for error

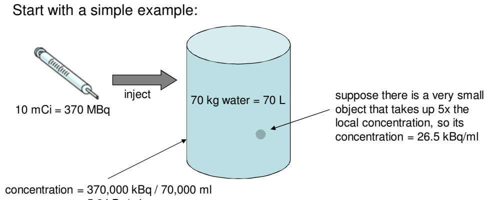
Respiratory Artifacts: Propagation of CT breathing artifacts via CT-based attenuation correction



Attenuation artifacts can dominate true tracer uptake values

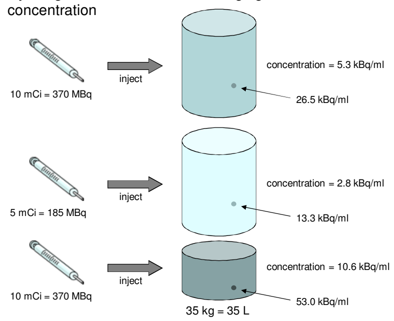
What Do PET Scans Measure?

- If everything goes well, the role of the PET scanner is to measure the radioactivity per unit volume
- Typically measured as kBq/ml or υCi/ml
- Start with a simple example:



What if there are different activities or distribution volumes?

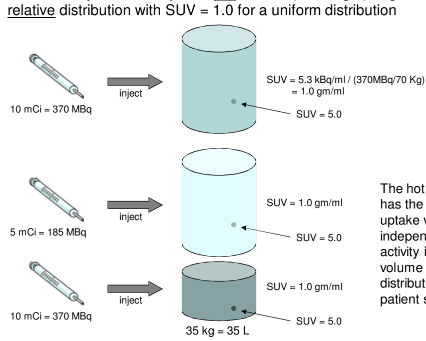
- Injecting different amounts or changing the volume will change the concentration



The hot spot has different uptake values in kBq/ml even though it has the same relative uptake compared to background

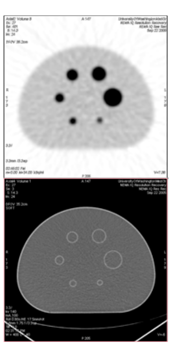
Standardized uptake values (SUVs)

- Normalize by amounts injected per volume (i.e. weight) to get the same relative distribution with SUV = 1.0 for a uniform distribution

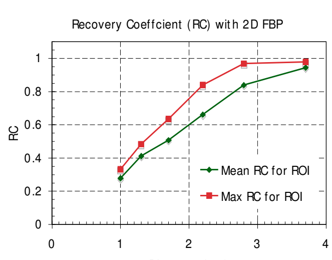


The hot spot now has the same SUV uptake values independent in activity injected or volume of distribution (i.e. patient size)

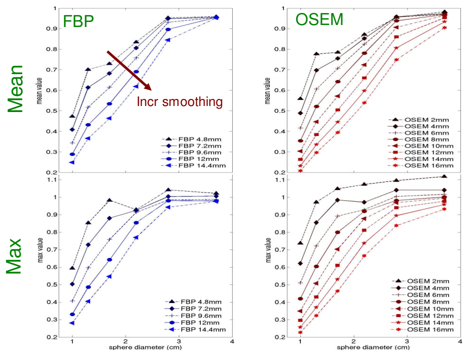
Resolution Effects



- Modified NEMA NU-2 Image Quality Phantom (30 cm x 23 cm cross section)
- Sphere diameters:1.0, 1.3, 1.7, 2.2, 2.8, 3.7 cm
- 4:1 target:background ratio and typical patient activity
- RC = measured / true



Variations in resolution loss vs. size and smoothing



Question

What is the goal of a combined PET/CT scanner?

1. Accurate attenuation correction
2. Accurate image alignment
3. Revitalize nuclear medicine
4. Job security for physicists

PET Technology Innovations