The role of quantitative molecular imaging in therapy development

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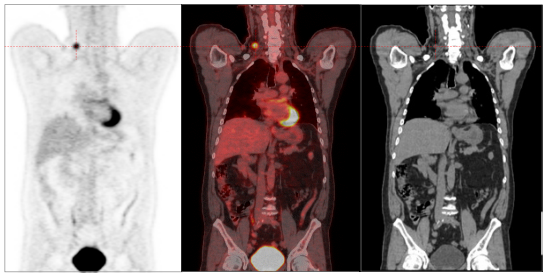
Disclosures

- Research Contract, GE Healthcare

Molecular imaging using PET/CT is a powerful tool for detection, diagnosis, and staging of cancer



PET Image of Function | Function+Anatomy | CT Image of Anatomy

Clinical Realm: 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.

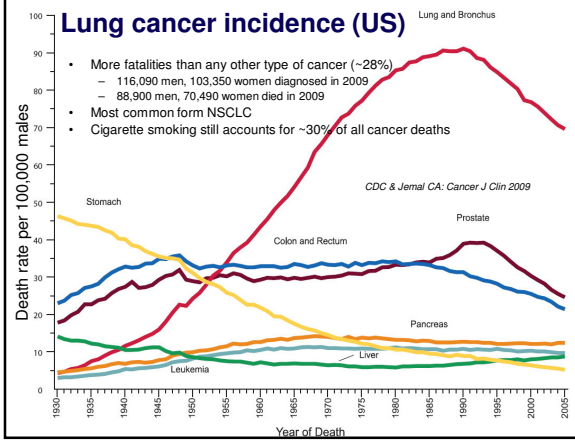
Weber et al. Nature Reviews Clinical Oncology 2008

Expanding the role for molecular imaging to therapy development

We need better therapies

Lung cancer incidence (US)

- More fatalities than any other type of cancer (~28%)
  - 116,090 men, 103,350 women diagnosed in 2009
  - 88,900 men, 70,490 women died in 2009
- Most common form NSCLC
- Cigarette smoking still accounts for ~30% of all cancer deaths



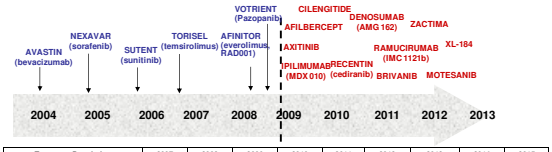
Lung cancer *survival* (US)

Percent survival 5 years after diagnosis

Site	1975-1977	1984-1986	1996-2004
Breast, female	75	79	89
Prostate	69	76	99
Lung	13	13	16

- Therapies
  - Surgery: most potentially curative, but only for very localized disease
  - Radiation: combined with chemo can cure in small number of patients. Can provide palliation in most patients
  - Chemotherapy: offers modest improvements in median survival for advanced stage disease

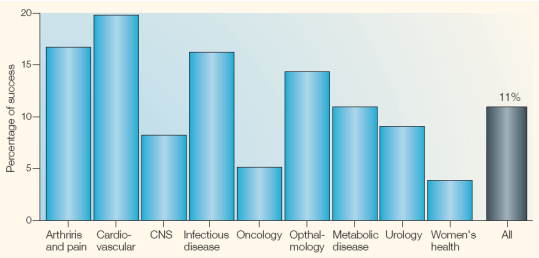
An increasing number of high cost, targeted pharmaceuticals are in research and development for oncology



Treatment Population	2007	2008	2009	2010	2011	2012	2013	2014	2015
Incidence of disease[1]	2,365	2,404	2,445	2,476	2,513	2,554	2,597	2,643	2,677
Patients treated with Anti-angiogenesis treatment[2]	68k	84k	108k(E)	133k(E)	169k(E)	207k(E)	248k(E)	274k(E)	311k(E)
% of cancer patients	2.8%	3.4%	4.4%	5.3%	6.7%	8.1%	9.5%	10.3%	11.6%

Courtesy Richard Frank, GE Healthcare

Success rates from first-in-human to registration



Kola & Landis, Nature Rev Drug Disc 2004

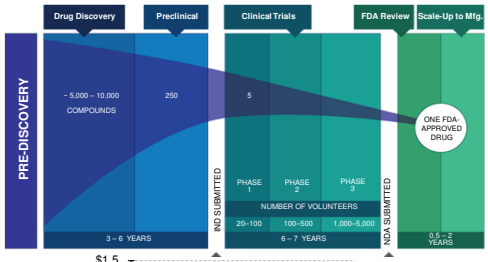
In addition approved drugs are withdrawn (e.g. Bextra, Vioxx, Baycol, Rezulin, Tysabri)

Potential reasons for low success rate

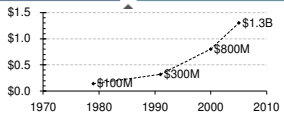
- Easy targets gone
- Wealth of information about targets, little understanding in context of whole organism
- Few animal models translate to humans
- Lengthy clinical trials required to establish efficacy
- Tolerance to risk can be lower with drugs that treat chronic diseases
- Drug development process is inefficient and expensive

Drug development process

Developing a new medicine takes an average of 10–15 years



cost for a new drug is increasing



www.innovation.org

Role for Imaging in Drug Development

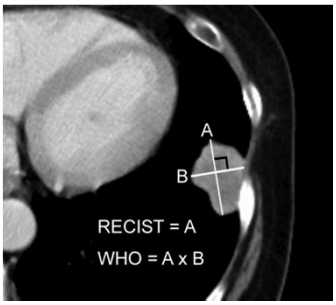
- Drug development is costly and inefficient
- New tools are needed to *identify losers early*
  - Rule out unsuccessful methods earlier (before phase III)
  - Improving phase III 'hit rate' from 1 in 5 to 1 in 3 could reduce development costs by ~50% [DiMasi 2002]
- Imaging biomarkers can help
- Quantitative PET imaging has enormous potential to boost efficiency of clinical trials evaluating new therapies [Frank 2003]

Imaging biomarker examples

Biomarker	Assay
Tumor volume	CT, MRI
β-amyloid	PET
Tumor proliferation	PET
Bone mineral density	DXA, CT
Receptor occupancy	PET
Plaque composition	US, IR, MRI, PET

Courtesy Jeff Evelhoch, Merck

Anatomical imaging biomarker: Response Evaluation Criteria in Solid Tumors (RECIST)

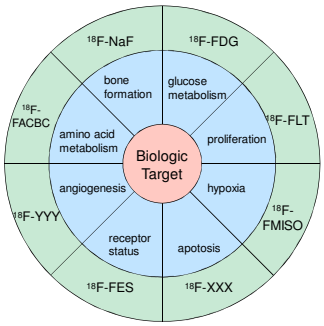


Response: δελταA < -30% after 4 weeks
Progression: δελταA > +20%

Suzuki, RadioGraphics 2008

The case for *molecular* imaging biomarkers

Biomarkers To Quantify Hallmarks of Disease

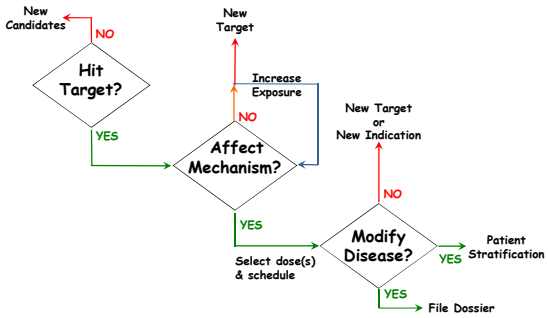


New uses for existing PET agents

New molecular diagnostic agents

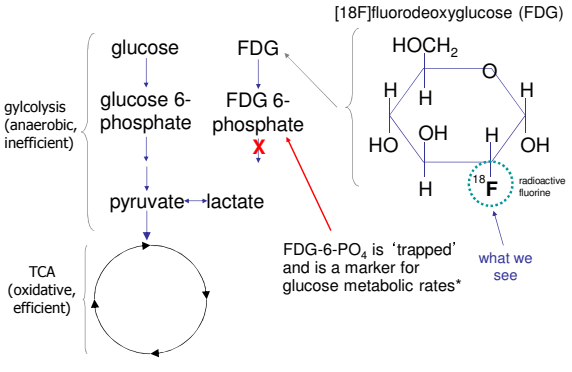
Many different types of PET 'measurements' are needed

Molecular imaging can evaluate primary points of impact in therapy development



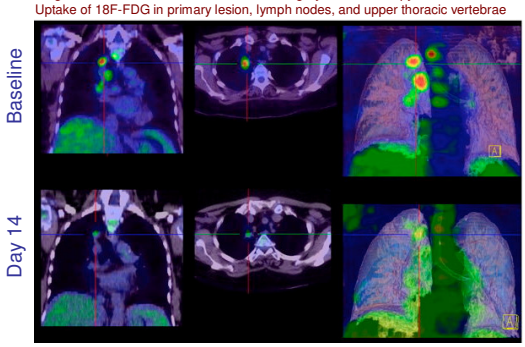
Courtesy Jeff Evelhoch, Merck

Molecular Imaging: Glu Metabolism



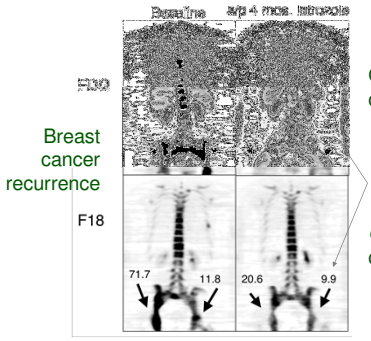
Cytostatic effects of EGGF Inhibitors

Stage IV disease not suitable for curative surgery or radiotherapy
Uptake of 18F-FDG in primary lesion, lymph nodes, and upper thoracic vertebrae



Hicks, JNM 2009

Quantitative Assessment of Response to Therapy



Qualitatively distinct

SUVs

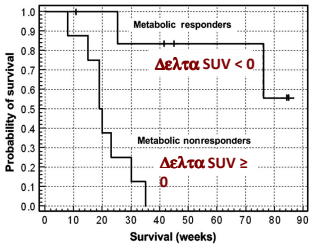
Quantitatively distinct

Courtesy D Mankoff

Quantitation Improves Characterization of Response

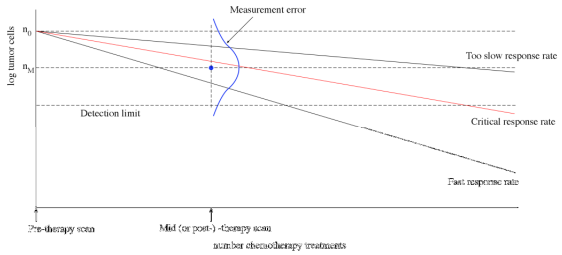
- *Make clinical trials of new therapies more effective*
- *Accelerate adoption of new molecular diagnostics*
- *Improve individual patient care*

All tied to quantitative accuracy



Nahmias JNM 2007

Why *quantitative* imaging matters



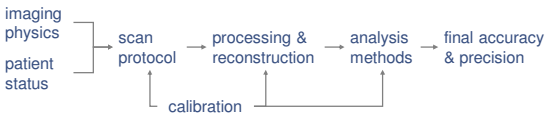
quantitative = known measurement error

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:



Sources of Error in SUV Values
SUV = Standardized Uptake Value

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

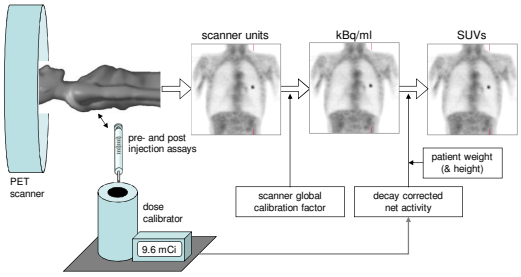
PET = measured PET activity concentration
D' = decay-corrected injected dose
V' = surrogate for volume of distribution

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

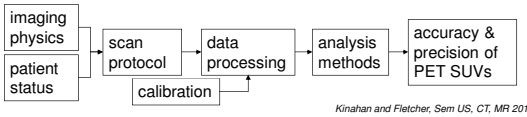
Some potential sources of error are:

- 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

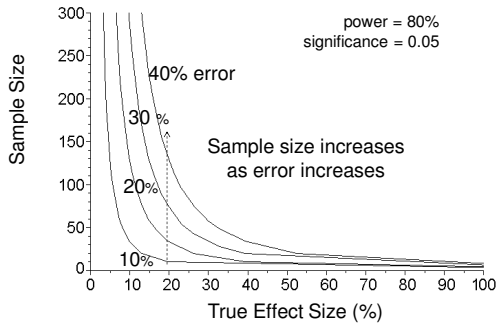


Kinahan and Fletcher, Sem US, CT, MR 2010

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,

27

Impact of measurement error on power/sample size



Doot et al., Acad Rad 2012

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

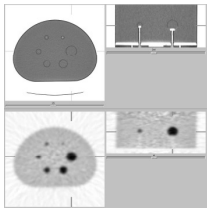
Doot et al., Acad Rad 2012

PET/CT scanners are a moving target: 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

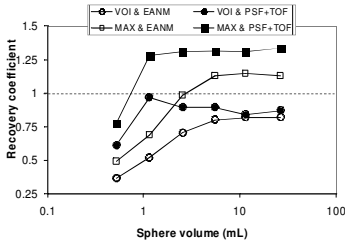
PET/CT scanners are a moving target

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

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

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

→ Clinical Trials

→ Accreditation

- 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

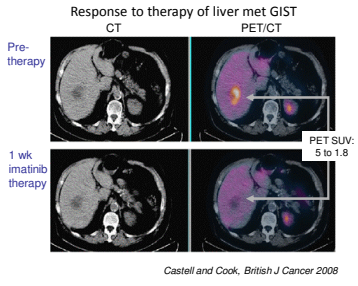
- Uniform Cylinder (used by ACRIN and many others)
- ACR PET phantom
- NEMA NU-2 Image Quality (IQ) phantom
- Modified NEMA Image Quality (IQ) phantom
- SNM CTN phantom
- Cross Calibration Phantom with NIST-traceable ^{68}Ge standard for Dose Calibrator
- Digital reference object

Quantitative imaging can characterize individual 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



Castell and Cook, British J Cancer 2008

CONCLUSION

The role of quantitative PET/CT imaging in therapy development

- There is a need for improved
  - cancer therapies
  - Individualized assessment of therapies
- Quantitative PET imaging can help if we
  - determine the bias and variance
  - constrain (and optionally reduce) the variance
- To enable quantitative PET we need to
  - educate and link together groups in the different areas of responsibility (i.e. big picture)
  - develop standards by which manufacturers and users can assure compliance

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