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**Quantitative Medical Imaging for
Clinical Research and Practice**


**Educational Session
ACRIN 2009**



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**Introduction to Quantitative Imaging as
a Biomarker in Clinical Trials**

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Objectives

- **Overview of imaging biomarkers and their use in clinical trials:**
 - What is a biomarker
 - Biomarker's role in clinical trials
 - Quantitative imaging as a biomarker

Biomarker Definition

- **"A characteristic that is **objectively measured** and evaluated as an **indicator** of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."**

** Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95.*

Clinical endpoint

- **A characteristic or variable that reflects how a patient feels, functions, or survives**
- **Used in the assessment of the benefits and risks of a therapeutic intervention in clinical trials**

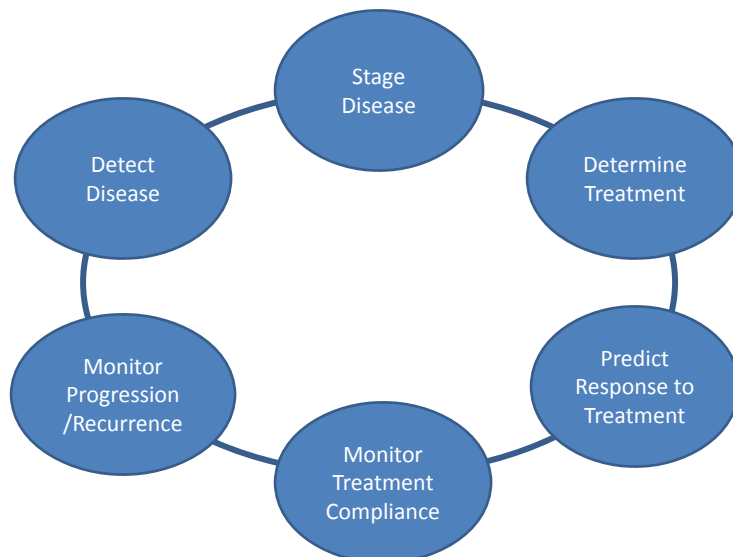
Problem with clinical endpoint

- **Clinical trials which evaluate the effect that new interventions have on clinical outcomes of particular relevance to the patient (morbidity or mortality) need to be large and long**
- **Costly \$\$\$, \$\$\$, \$\$\$**

Surrogate endpoint

- A **biomarker** that is intended to **substitute** for a clinical endpoint (clinical status or outcome)
- It is expected to reliably **predict** clinical benefit (or harm, or lack of benefit or harm)
 - Changes induced by a therapy on a surrogate endpoint are expected to reflect changes on a clinically meaningful endpoint

Biomarkers and the disease process



Why biomarkers are important in clinical trials

- **FDA approval process very rigorous and lengthy**
- **Many years and millions of \$ for new drug approval**
- **New candidate compounds are being constantly developed**
- **Finite \$\$ resources**
- **Surrogate end-points can help with implementation of new medical products by replacing large, long, costly studies of clinical outcomes with **smaller, faster, and cheaper** studies utilizing **surrogate end points** instead of clinical outcomes**

Two questions

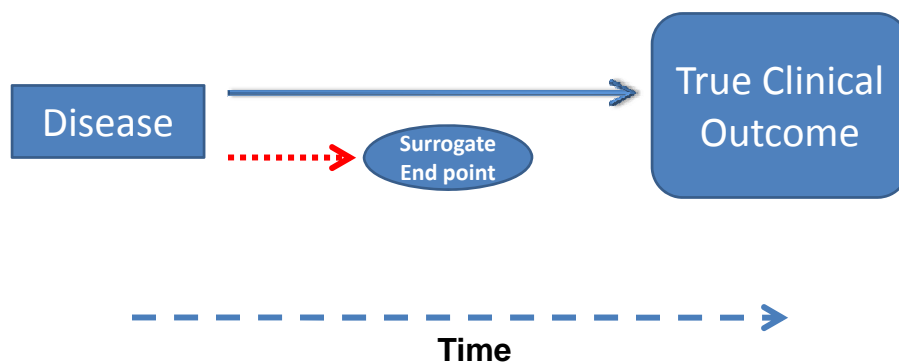
- **Does a biomarker predict disease or state**
 - is it truly on the causal pathway(s) to disease
 - can it help with defining disease mechanisms
- **Can a biomarker be used as surrogate end point for the purpose of the study**

Utility of a biomarker

- **Surrogate endpoint requires demonstration of its **accuracy****
 - Correlation of the measure with the clinical endpoint
- **And **precision****
 - The reproducibility of the measure
- **Should fully capture the net effect of intervention on the clinical outcome**

Reasons for surrogate endpoint failure

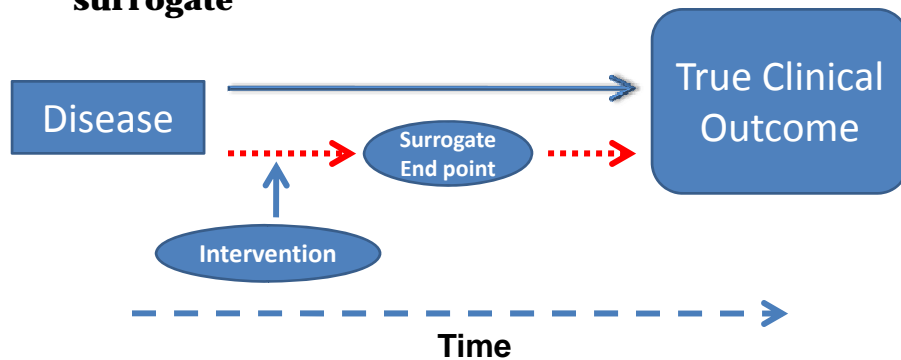
- **Not in the causal pathway of the disease**



Fleming , et al. Ann Intern Med. 1996; 125:605

Reasons for surrogate endpoint failure

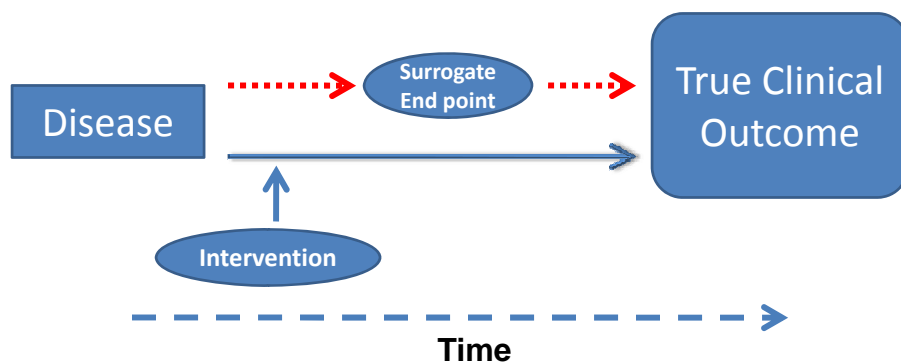
- **Of several causal pathways, the intervention affects only the pathway mediated through the surrogate**



Fleming , et al. Ann Intern Med. 1996; 125:605

Reasons for surrogate endpoint failure

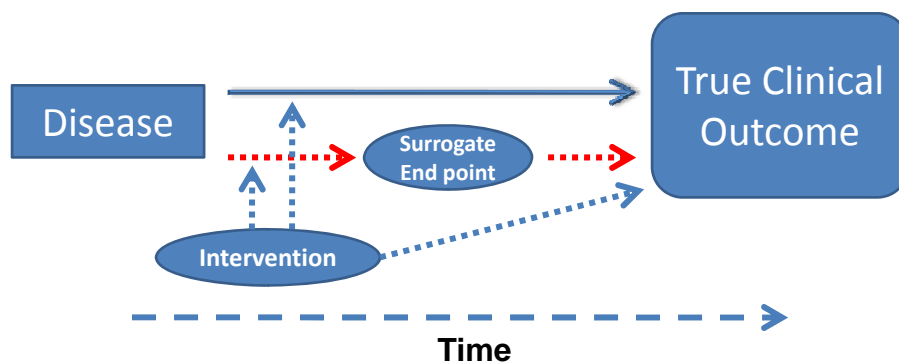
- **The surrogate is not in the pathway of the intervention's effect or is insensitive to its effect**



Fleming , et al. Ann Intern Med. 1996; 125:605

Reasons for surrogate endpoint failure

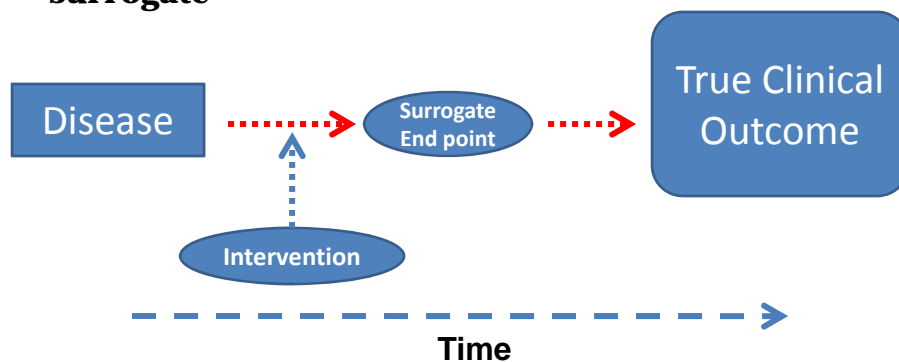
- **The intervention has mechanisms of action independent of the disease process**



Fleming , et al. Ann Intern Med. 1996; 125:605

Surrogate endpoint validity

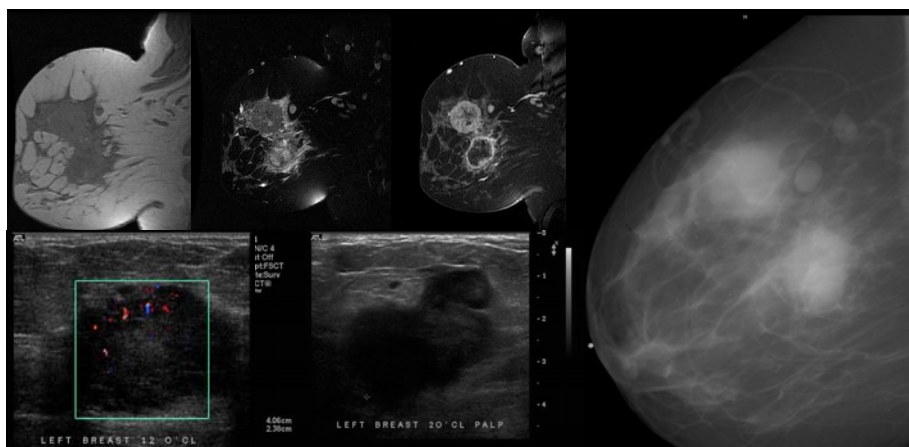
- **Surrogate is in the only causal pathway of disease and intervention's entire effect on true clinical outcome is mediated through its effect on the surrogate**



Fleming , et al. Ann Intern Med. 1996; 125:605

What is QI

- **Extracting quantitative measurements from medical imaging**



What is QI

giggleBites



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Image is worth a 1000 (or 10,000) words



Image is worth a 1000 parameters or measurements

Which imaging parameters are quantitative?

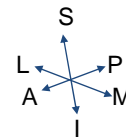
- **Morphology**

- Volume, 3D techniques
- Cellularity/density/composition of tissues

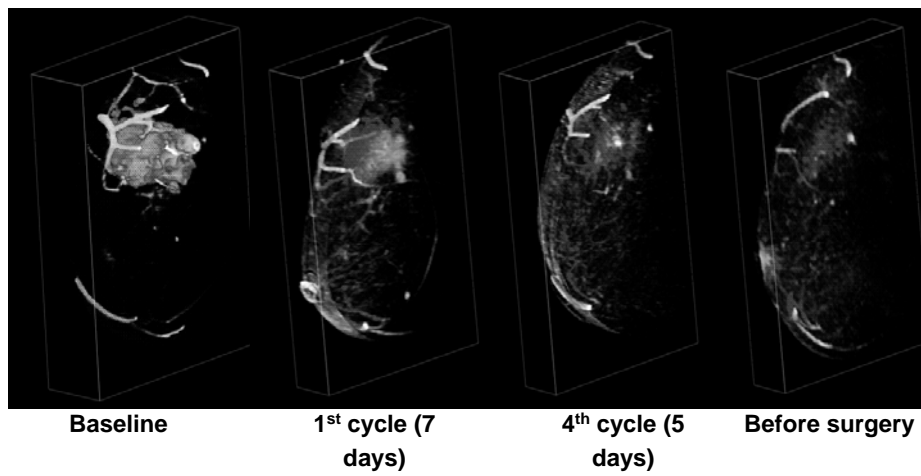
- **Function**

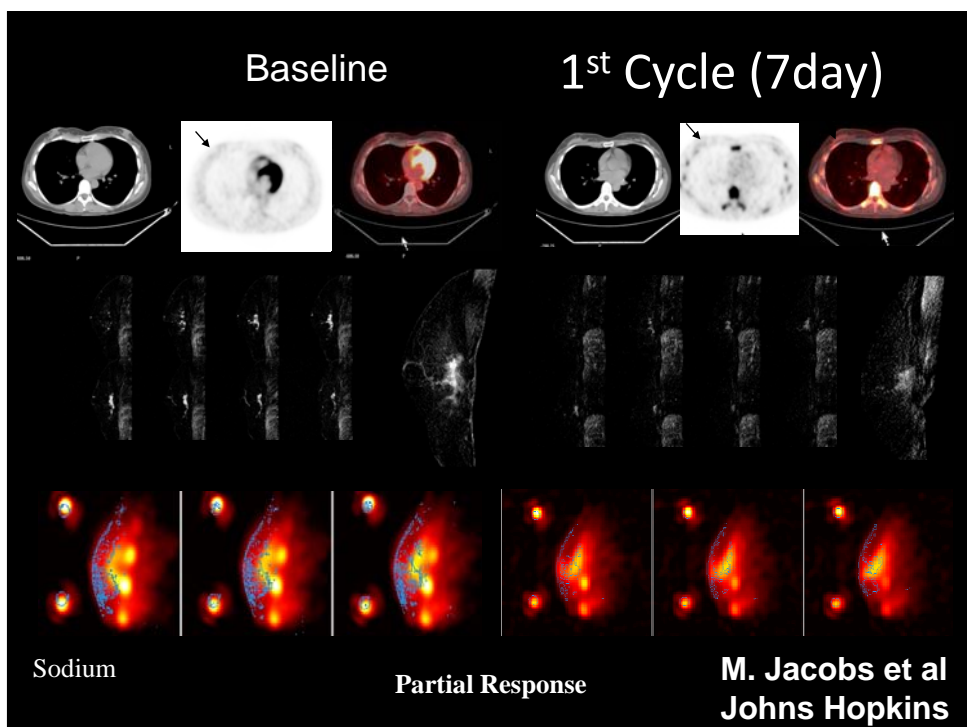
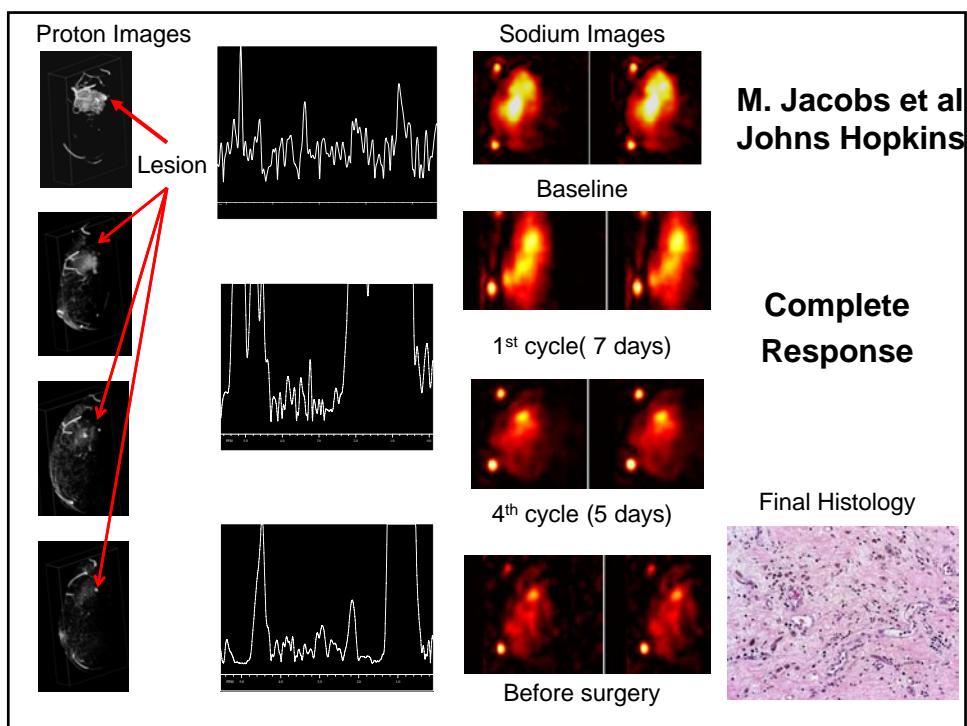
- Perfusion (DCE-MRI)
- Metabolic activity (PET)
- Metabolite concentration (H1 spectroscopy, Na23)
- Molecule movement, e.g. water molecule (DWI)

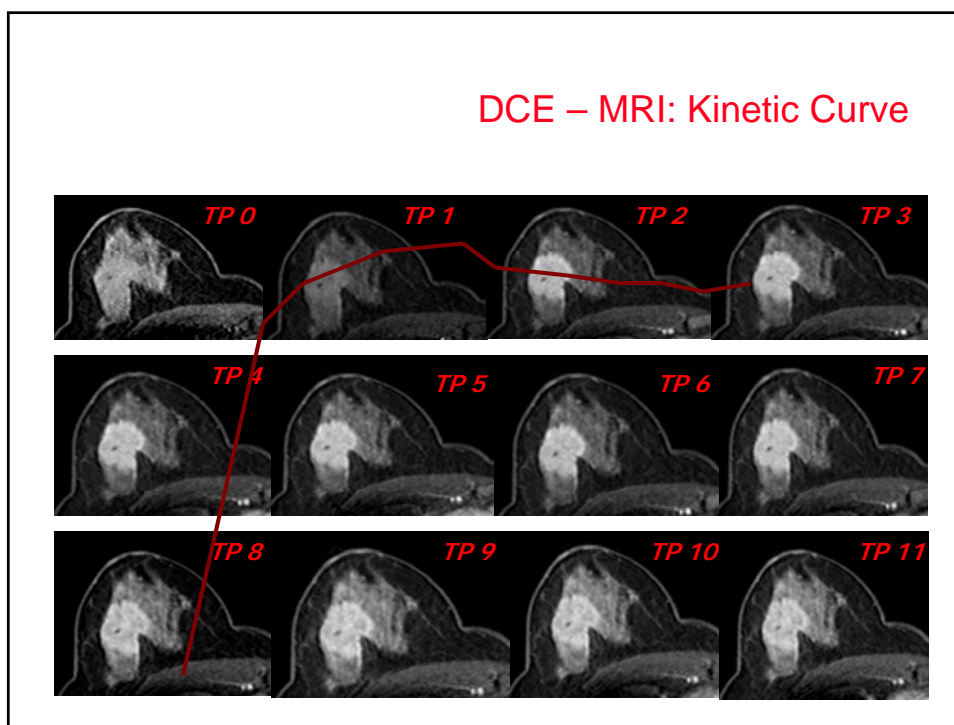
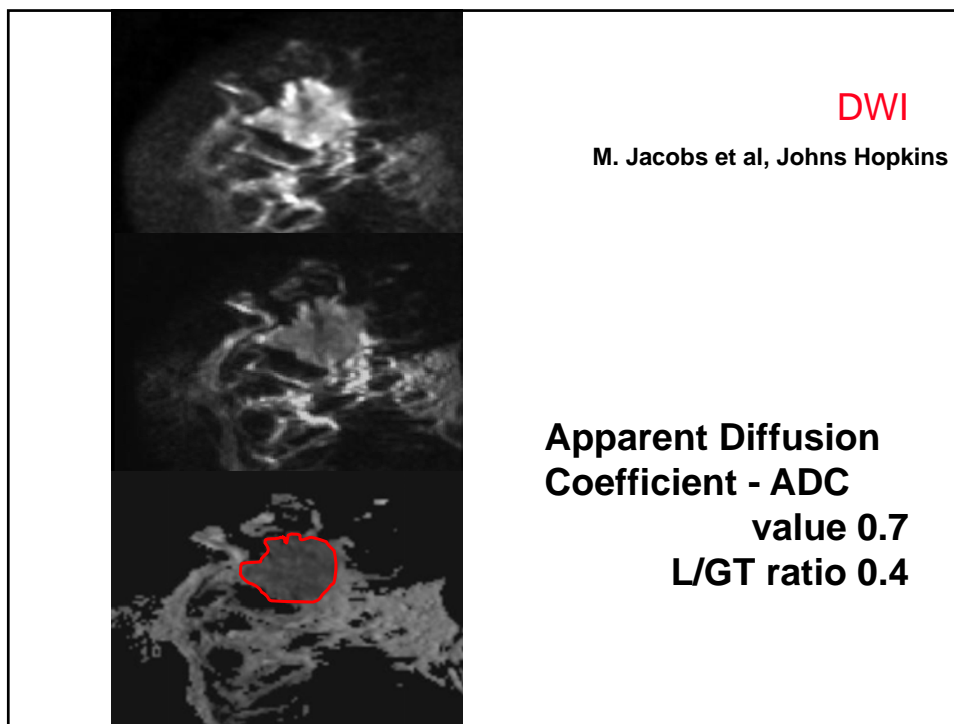
Volumetrics



M. Jacobs et al, Johns Hopkins

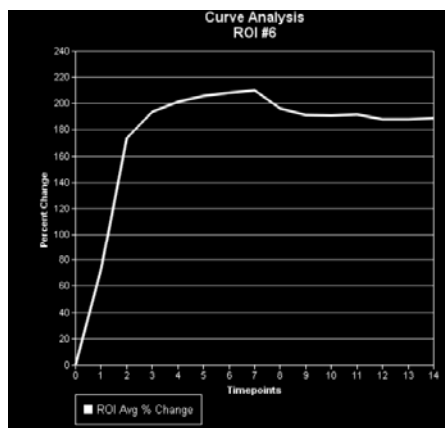




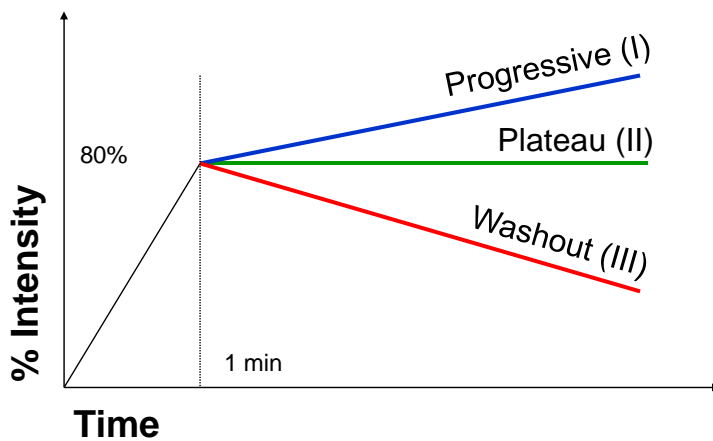


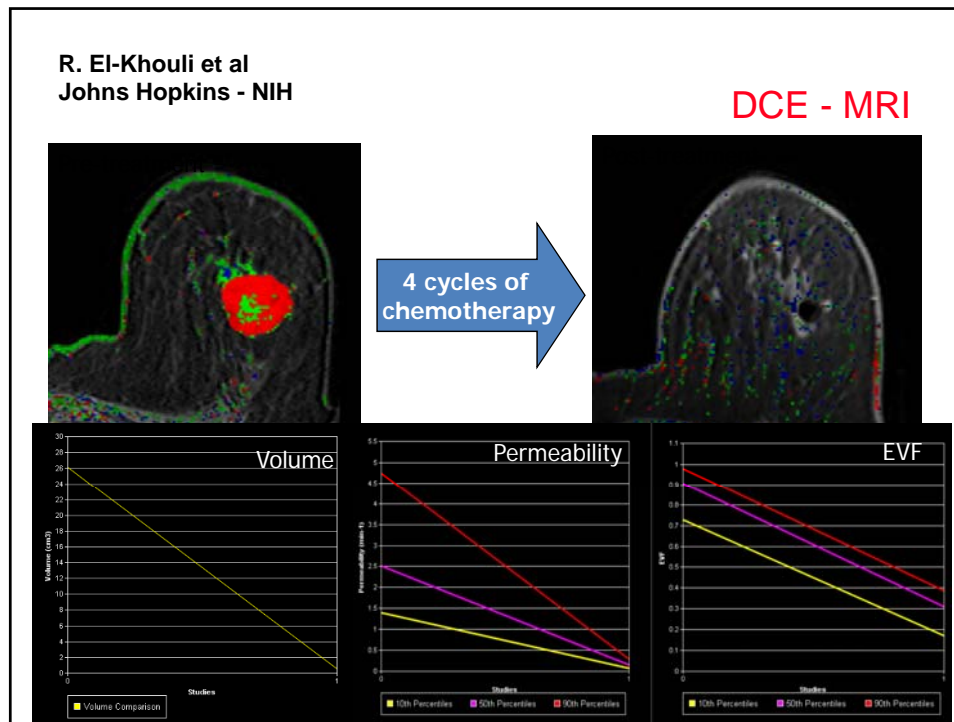
DCE – MRI: Kinetic Curve

Y-axis represents Percentage enhancement



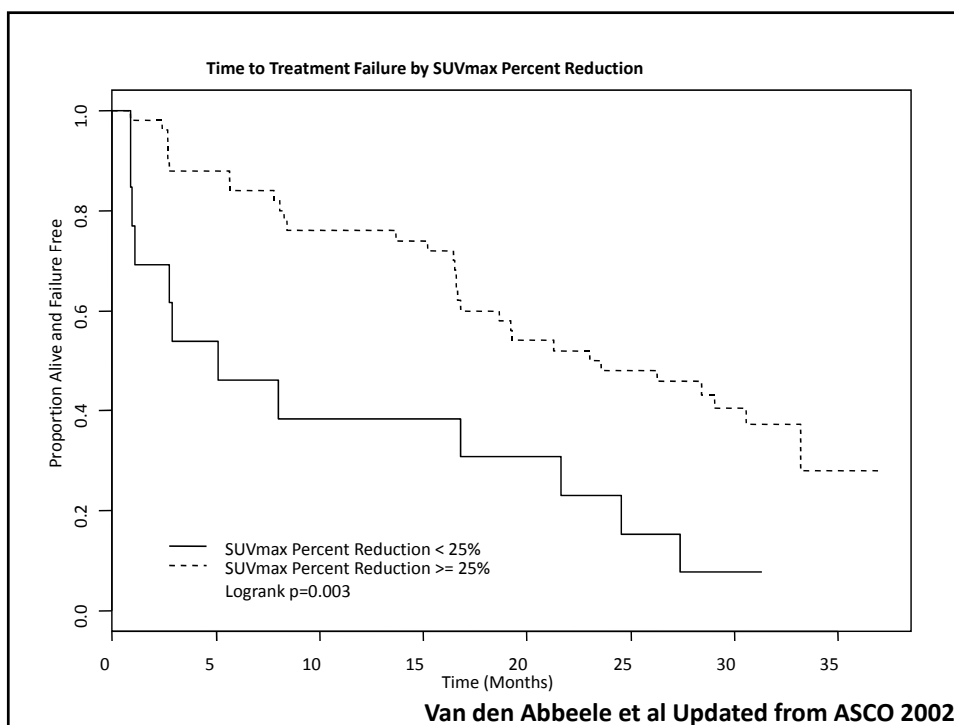
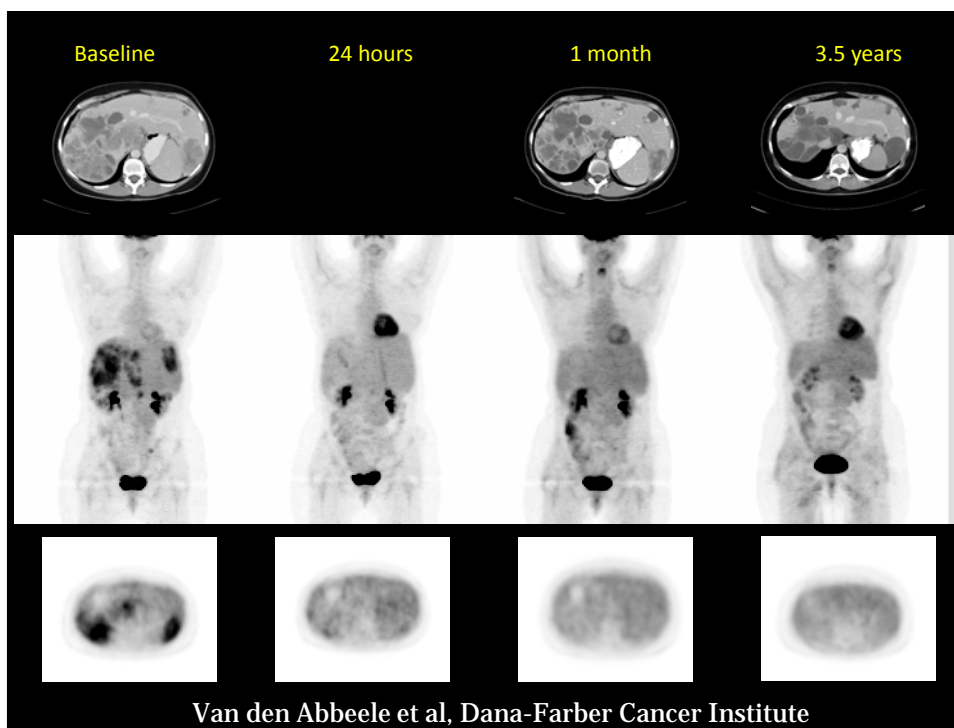
Time – Intensity Curve





FDG - PET success story

- **FDG-PET as an imaging biomarker of metabolic response to imatinib in GIST**
 - Integration of anatomic and functional imaging in molecularly targeted therapy
 - Metabolic response closely related to clinical benefit (alive and failure free)
 - Metabolic changes precede by weeks/months significant decrease in tumor size on CT
 - Lack of metabolic response indicates primary resistance of tumor to the drug



FDG-PET vs. RECIST

- **ACRIN 6665/RTOG 0132 phase II trial of neoadjuvant imatinib mesylate for primary and recurrent operable malignant GIST: Imaging findings and correlation with genotype and GLUT4 expression**
 - A. D. Van den Abbeele, C. Gatsonis, D. J. de Vries, Y. Melenevsky, A. Szot Barnes, J. T. Yap, A. K. Godwin, M. Blevins, B. Eisenberg and B. A. Siegel
- **Conclusion: After imatinib initiation, metabolic response by FDG-PET was documented earlier (1–7 days), and was of much greater magnitude than that documented by RECIST**

Why QI qualifies as a biomarker ?

- **An ideal biomarker should give a specific and continuous indication of the disease and be quantifiable by using a readily obtainable matrix**
- **Imaging provides quantifiable parameters noninvasively**

Needs of QI

- **Accuracy**
- **Reproducibility across patients, time-points, instruments, hardware, software**
- **Standardization of imaging protocols during image acquisition**
- **Standardization of analysis, post-processing**
- **“Suite” of qualified and validated biomarkers**
- **“Suite” of validated processing tools**

Compliance in QI

- **Acquisition modality**
 - System calibration, QA
 - Image acquisition
 - Image reconstruction
 - Image distribution
- **Measurement system**
 - Measurement
 - Measurement distribution
- **Reader**
 - Measurement
 - Interpretation
- **Reporting**
 - Measurement distribution
 - Image distribution

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• **Key players in QI:**

- RSNA
 - QIBA Quantitative Imaging Biomarkers Alliance, chaired by Dr. Dan Sullivan, e-newsletter *QIBA Quarterly*, <http://qibawiki.rsna.org/>
- ACRIN
 - Imaging core laboratory
- CTSA
 - UPICT, Uniform Protocols for Imaging Clinical Trials



RSNA TQI (Toward Quantitative Imaging) Committee

- **Quantitative imaging: the extraction of quantifiable features from medical images for the assessment of normal (or the severity, degree of change or status of a disease, injury, or chronic condition relative to normal).**
- **Development, standardization, and optimization of anatomical, functional, and molecular imaging acquisition protocols, data analyses, display methods, and reporting structures**
- **Validation of accurately and precisely obtained image-derived metrics with anatomically and physiologically relevant parameters, e.g. treatment response and outcome**

Benefits of QI

- **Clinical trials of new therapeutics need quantitative input**
- **Quantitative results are needed for personalized medicine of the future**
- **Evidence-based medicine depends on quantitative data**
- **Decision support tools need quantitative input**

RSNA-sponsored Imaging Biomarkers Roundtable

- **Developing a roadmap for biomarker evaluation**
- **A national repository of validated imaging biomarkers**
- **An infrastructure to support creation, optimization, validation, and qualification of imaging biomarkers**

“Radiology Reading Room of the Future”