Quantitative Medical Imaging for Clinical Research and Practice

Educational Session
ACRIN 2009

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.”

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**

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


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

Reasons for surrogate endpoint failure

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

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
What is QI

- Extracting quantitative measurements from medical imaging

Image is worth a 1000 parameters or measurements

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

Baseline | 1st cycle (7 days) | 4th cycle (5 days) | Before surgery
Apparent Diffusion Coefficient - ADC

value 0.7
L/GT ratio 0.4

DCE – MRI: Kinetic Curve
DCE – MRI: Kinetic Curve

Y-axis represents Percentage enhancement

Time – Intensity Curve

Progressive (I)
Plateau (II)
Washout (III)
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
Baseline  24 hours  1 month  3.5 years
Van den Abbeele et al, Dana-Farber Cancer Institute

Van den Abbeele et al Updated from ASCO 2002
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
- 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
Current Initiatives

• **Key players in QI:**
  – RSNA
  – 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”