QIBA Quarterly

Quantitative Imaging Biomarkers Alliance RSNA

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QIBA MISSION
Improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients and time.

QIBA CONNECTIONS

Quantitative Imaging Biomarkers Alliance (QIBA)

QIBA Wiki

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Comments & suggestions welcome

Daniel C. Sullivan, MD
RSNA Science Advisor

IN MY OPINION

Quantitative Imaging Speaks Volumes about Biomarker Response

By P. DAVID MOZLEY, MD, and ANDREW J. BUCKLER, MS

Because all stakeholders are seeking the most sensitive biomarkers for response, quantitative imaging is almost completely aligned with the needs of both biopharmaceutical companies and individual patients.

For a patient in an ordinary medical setting, beginning a new therapy is analogous to starting a personal clinical trial. Patients want to know as soon as possible whether a new treatment is working, and if not, they want to search for alternatives as soon as possible. Although informed patients understand that almost no treatment is without risks, they

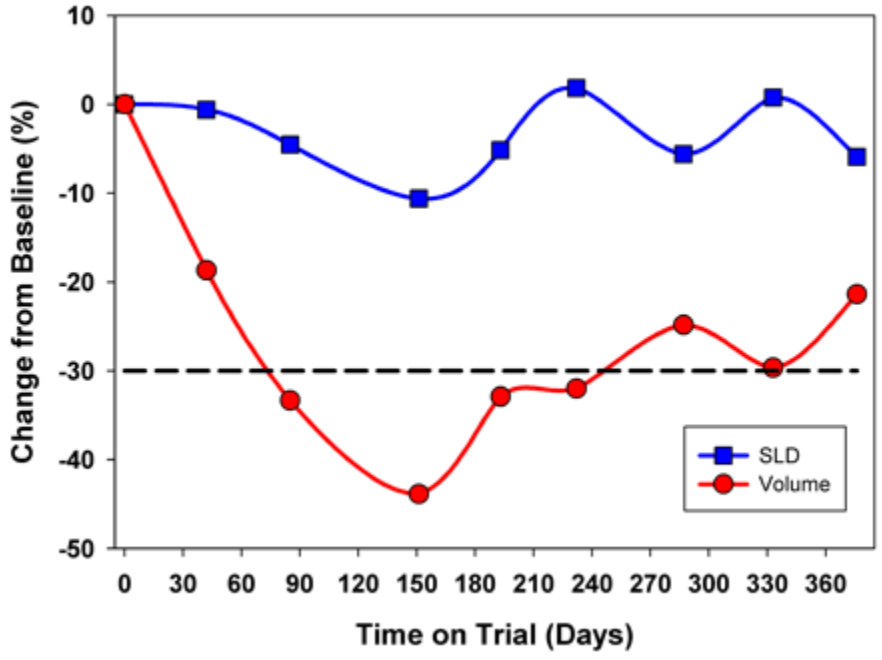
don't want to endure those risks longer than necessary if the therapy is not working. Bottom line: No one wants to waste time, effort, and money on ineffective treatments.

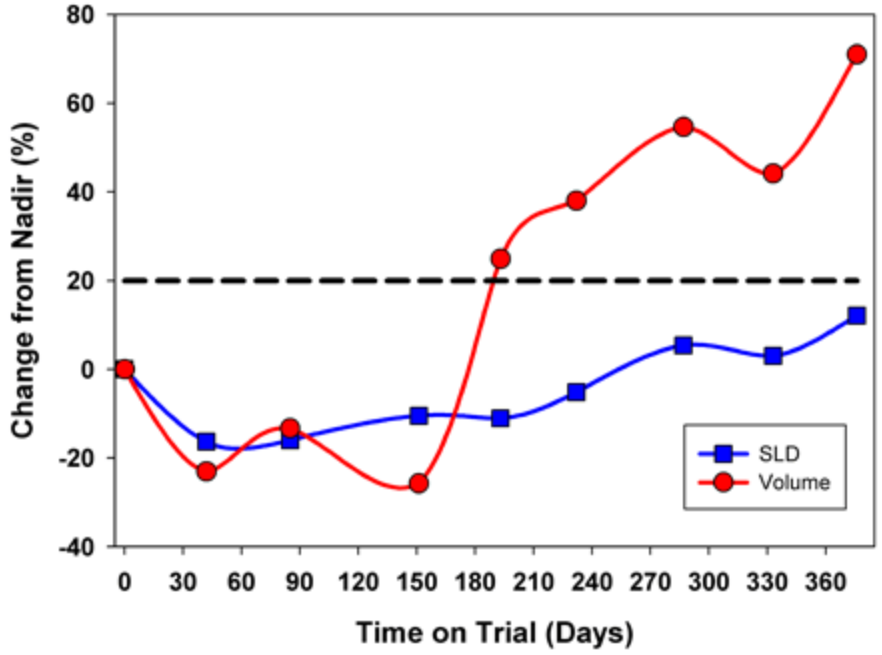
Biopharmaceutical enterprises view clinical trials of products in much the same way. Like patients, those companies want their products to alleviate suffering, succeed, and produce a return on investment. Sensitive biomarkers for response allow industry to reduce the number of patients required to test new products as well as decrease the time patients remain in the study. The net effect would increase the number of new treatments for unmet medical needs.

Quantification Underutilized in Oncology

Although quantification is routinely used in medical imaging to make critical decisions about a number of major health problems, it has often been rather rudimentary in oncology. This is ironic, because innovations in instrumentation and signal processing have long made it possible to visualize large portions of many whole-body tumors with exquisite resolution.

Consider the case below. The original Response Evaluation Criteria in Solid Tumors (RECIST) analysis suggested that the patient remain in a prolonged state of stable disease; consequently, the subject added little of the analytical power needed to distinguish between the two arms of the trial. In retrospect, volumetric image analysis suggests that this patient had an initial response to treatment but could have switched therapies several months before changes in unidimensional line lengths met criteria for progressive disease. All stakeholders lose when there is a delay in diagnosing progressive disease.





CT scans were acquired every 6 weeks in a patient with lung cancer enrolled in a trial of a novel drug or placebo plus the standard of care. RECIST line lengths were placed by radiologists working for a central laboratory. Tumor volumes were measured by another image analysis laboratory.

Legend:
• Baseline: The CT scan acquired immediately before starting a new treatment regimen
• SLD: Sum of longest diameters placed on a single slice of a tumor according to the RECIST formalism
• Tumor volume: The whole volume of the corresponding tumor
• Dashed lines represent categorical response thresholds

In the top panel, all values are normalized for the measurements at baseline immediately prior to the initiation of treatment. RECIST suggests the patient remained in a state of stable disease for the duration of the trial.

In the bottom panel, all values are normalized for the smallest measurement that preceded the time point, referred to as the "prior nadir." All negative values reflect a decrease in size, while all positive values represent an increase in size. An increase in 20% from the prior nadir is categorized as progressive disease. This patient showed clinical signs of progression before the longest diameters ever reached RECIST threshold values for progressive disease. In contrast, volumetric image analysis revealed clear signs of progression more than 5 months before the patient came off the trial.

QIBA Advances Quantitative Imaging in Oncology

QIBA is one of the few places where imaging device manufacturers, software developers, academicians, officers in

regulatory agencies, representatives of biopharmaceutical enterprises, and other stakeholders can collaborate to create strategies for advancing quantitative imaging in oncology.

The QIBA Quantitative CT Committee has now produced a systematic research program to determine whether volumetric image analysis is practical, reproducible, and valuable to all of the stakeholders. So far, results have been extremely encouraging. Delivering more sensitive biomarkers for responses to treatments for cancer will be a win-win for everyone involved.

P. David Mozley, MD, is a senior director of clinical research for Merck Research Laboratories and represents the Extended PhRMA Imaging Group on the QIBA Quantitative CT Committee. Andrew J. Buckler, MS, is an imaging analytics specialist who has worked in the medical device manufacturing sector for more than 20 years. Dr. Mozley and Mr. Buckler co-chair the QIBA Quantitative CT Committee along with Dr. Lawrence Schwartz.

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ANALYSIS TOOLS & TECHNIQUES

MR-Based Functional Assessment of Tumors: Challenges and Opportunities

By EDWARD F. JACKSON, PhD

One key advantage of MR is the wide range of intrinsic tissue properties that can be assessed by the appropriate choice of parameters defining the associated measurement technique.

In neuroimaging applications, for example, routine MR imaging provides a qualitative means of assessing the breakdown of the blood brain barrier as reflected by the extent of gadolinium contrast agent extravasation (T1-weighted sequences), the extent of vasogenic edema (T2-weighted and T2-weighted fluid attenuated inversion recovery sequences), the presence of blood products such as hemosiderin, methemoglobin (T1-weighted and T2* susceptibility-weighted images), and the ability to assess brain atrophy and regional white/gray matter abnormalities (using proton density-weighted and/or magnetization prepared gradient-echo sequences).

Neurovascular anatomy can be evaluated with or without the injection of exogenous contrast agents (using time-of-flight and/or phase-contrast MR angiography techniques). Such wide-ranging contrast mechanisms and acquisition techniques

have frequently led to MR as the modality of choice for soft tissue neuroimaging. Recent improvements in acquisition rates and contrast agent-enhanced MR angiographic techniques have expanded such applications throughout the body.

Use of Functional MR Measures Increasing

In addition to such morphological, qualitative assessments, there is increasing interest in MR-based assessments of the functional status of tissue.

A partial, but not comprehensive, list of such functional MR measures includes those used to detect changes in cellular volume/density due to disease process or response to therapy as reflected by the degree of restriction of water diffusion (diffusion-weighted MR imaging); changes in the microvascular environment (microvascular volume, flow, and permeability assessment using dynamic contrast-enhanced and/or dynamic susceptibility change MR imaging); and biochemical changes (in vivo MR spectroscopy).

Such functional measures are now being used as secondary or exploratory endpoints in several Phase I/II clinical trials of targeted therapies or combinations of such therapies with conventional treatment regimens [1-3].

However, to fully realize the power of such a broad range of anatomical and functional techniques and to use them in a quantitative manner in clinical trials—and ultimately in clinical patient management—several challenges must be overcome, including:

1) Characterization of the sources of bias and variance and mitigation of such effects at the instrument, acquisition protocol, and data analysis levels.
2) Standardization, or at least harmonization, of signal response for a given protocol across instruments from a single vendor and, ultimately, across instruments from multiple vendors.
3) Standardization of acquisition and processing protocols used to obtain quantitative anatomical and/or functional measures.
4) Validation of such quantitative measures using accepted outcome-based comparison measures.

Various groups are now addressing each of these areas.
• QIBA Quantitative MRI Committee—issues pertaining to areas 1–3.
• National Cancer Institute (NCI) Cancer Imaging Program Reference Image Database to Evaluate Response MR Subcommittee—areas 1 and 2.
• International Society for Magnetic Resonance in Medicine (ISMRM) Ad Hoc Committee on Standards for Quantitative MR

(with the National Institute of Standards and Technology) —developing a system phantom that can be used to address areas 1 and 2.
• American Association of Physicists in Medicine (AAPM) Quantitative Imaging Initiative MR-related task and working groups—areas 1 and 2.
• Uniform Protocols in Clinical Trials—area 3, acquisition protocols.
• NCI-funded Imaging Response Assessment Teams and Quantitative Imaging Network—areas 1–4.

Finally, the RSNA Imaging Biomarker Roundtable, comprising representatives from these and other groups, seeks to harmonize and enhance each of these efforts. The RSNA Toward Quantitative Imaging (TQI) initiative, which offered education exhibits at RSNA 2009, aims to educate radiologists and other physicians about the challenges and potential rewards of quantitative imaging.

Other groups—too many to mention by name—are also involved in many of these efforts or are poised to become involved.

There are many challenges facing MR-based quantitative imaging biomarkers—some of them considerable. However, given the broad range of anatomical and functional information potentially available in a quantitative fashion using such techniques, the potential rewards are clearly sufficient to continue and, hopefully, accelerate our efforts to address such challenges.

References:
[1] Dynamic Contrast-Enhanced Magnetic Resonance Imaging as an Imaging Biomarker. J Clin Oncol 2006 July; 24:3293-98. Hylton N.

[2] Quantitative Imaging Biomarkers in the Clinical Development of Targeted Therapeutics: Current and Future Perspectives. Lancet Oncol 2008 August; 9:766-76. O'Connor J.P., et al.

[3] Diffusion-Weighted Magnetic Resonance Imaging as a Cancer Biomarker: Consensus and Recommendations. Neoplasia 2009 February; 11:102-25. Padhani A.R., et al.

Edward F. Jackson, PhD, is section chief for MR and ultrasound physics and professor and deputy chair of the Department of Imaging Physics at the University of Texas M.D. Anderson Cancer Center in Houston. He is co-chair of the QIBA Quantitative MR Committee, a member of the RSNA TQI Steering Committee, chair of the ISMRM Ad Hoc Committee on Standards for Quantitative MR, and chair of the AAPM Working Group on Standards for Quantitative MR Measures.

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FOCUS ON

RSNA 2009: Quantitative Imaging/Imaging Biomarkers

Quantitative imaging and imaging biomarkers were well represented at RSNA 2009.

At an open informational meeting held November 30, RSNA Science Advisor Daniel C. Sullivan, MD, offered an overview of imaging biomarkers and the QIBA process. The meeting marked the 2 year anniversary of an RSNA 2007 meeting of quantitative imaging stakeholders.

Since then, the Quantitative Imaging Biomarkers Alliance —comprising representatives from the pharmaceutical industry, imaging equipment manufacturers, imaging informatics companies, government agencies, imaging societies, the clinical community and RSNA leadership—has progressed from discussion to action. The QIBA Committees and the Uniform Protocols for Imaging in Clinical Trials (UPICT) subgroup of the CTSA Imaging Working Group reported on the past year's activities.

The QIBA Committees noted their experimental groundwork with phantoms and human data as well as the development of documentation in the form of QIBA Profiles. The UPICT subgroup has developed a template for a uniform imaging protocol and is engaged in extracting and reviewing proffered protocols into the UPICT template.

Lakeside Learning Center at RSNA 2009
On the exhibit floor at the RSNA annual meeting, the QIBA Committees and UPICT presented educational posters and held Meet the Expert sessions and question/answer segments throughout the week.

The *Toward Quantitative Imaging: Reading Room of the Future* area focused on quantitative imaging and analysis. An educational showcase offered visual and experiential exposure to quantitative imaging and biomarkers through 15 exhibitor products integrating quantitative analysis into the image interpretation process. The *Reading Room of the Future* also featured hands-on exhibits and informational posters, computer-based demonstrations, and Meet the Expert presentations throughout the week.

In his December 1 Annual Oration in Diagnostic Radiology (see *Daily Bulletin* article), Dr Sullivan emphasized the

importance of extracting quantitative information from scans and noted that quantification is attainable with current imaging modalities. He also highlighted the work of RSNA initiatives such as QIBA, the Imaging Biomarkers Roundtable and Toward Quantitative Imaging that aid the transition toward quantitative imaging.

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QI/IMAGING BIOMARKERS IN THE LITERATURE

PubMed Search on Imaging and Treatment Response in Oncology

Each issue of *QIBA Quarterly* will feature a link to a dynamic search in PubMed, the National Library of Medicine's interface to its MEDLINE database. Click here to view a PubMed search on imaging and treatment response in oncology.

Take advantage of the My NCBI feature of PubMed that allows you to save searches and results and includes an option to automatically update and e-mail search results from your saved searches. My NCBI includes additional features for highlighting search terms, storing an e-mail address, filtering search results and setting LinkOut, a document delivery service.

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