Expanding the Use of Magnetic Resonance in the Assessment of Tumor Response to Therapy: Workshop Report

Jeffrey Evelhoch,2 Michael Garwood,3 Daniel Vigneron,4 Michael Knopp,5 Daniel Sullivan,1 Anne Menkens,1 Laurence Clarke,1 and Guoying Liu1

1Cancer Imaging Program, National Cancer Institute, NIH, Rockville, Maryland; 2Amgen, Inc., Thousand Oaks, California; 3University of Minnesota, Minneapolis, Minnesota; University of California San Francisco, San Francisco, California; and 4The Ohio State University, Columbus, Ohio

Abstract
Although dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and magnetic resonance spectroscopy (MRS) have great potential to provide routine assessment of cancer treatment response, their widespread application has been hampered by a lack of standards for use. Thus, the National Cancer Institute convened a workshop to assess developments and applications of these methods, develop standards for methodology, and engage relevant partners (drug and device industries, researchers, clinicians, and government) to encourage sharing of data and methodologies. Consensus recommendations were reached for DCE-MRI methodologies and the focus for initial multicenter trials of MRS. In this meeting report, we outline the presentations, the topics discussed, the ongoing challenges identified, and the recommendations made by workshop participants for the use of DCE-MRI and 1H MRS in the clinical assessment of antitumor therapies. (Cancer Res 2005; 65(16): 7041-4)

Workshop Goals
In the quest to tailor and fine-tune cancer therapies, clinicians may exploit the capacity of magnetic resonance to produce rapid, accurate, in vivo assessment. Two methods in particular, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and magnetic resonance spectroscopy (MRS), have outstanding potential. In recent years, they have been advancing the field of assessment and treatment significantly, despite the fact that issues such as standardization and reliability have limited their broad use.

MRI has served in clinical cancer detection, diagnosis, and intervention and has been employed in the development of drug therapies. There is a need to move beyond the many isolated successes of magnetic resonance applications to widespread routine use of these tools to assess response to cancer treatment. This will require overcoming hurdles that are logistic rather than scientific. It will require the establishment of standards of use, leading to comparable data and reliability.

On November 22-23, 2004 in Bethesda, Maryland, the National Cancer Institute (NCI) convened a workshop on the use of MRI, MRS, and related technologies. Presentations were combined with strategy sessions that focused on ways to assess developments and applications of MRI and MRS, to develop standards for methods of use, and to engage relevant partners (drug and device industries, researchers, clinicians, and government) to encourage the sharing of data and methodologies. The meeting participants also identified ongoing challenges. The main points of discussion from the meeting are given below.

Perspectives from the Field
The oncologist must choose from an array of new drugs, many of which share targets in cancer treatment. MRI and MRS can help identify drug effects within a tumor, revealing which drugs work best, alone or in combination. To the oncologist, some drug effects may be more important than tumor shrinkage, and magnetic resonance can reveal these effects. MRI and MRS can be important tools in new drug development, especially to show biological activity and evaluate pharmacokinetic-pharmacodynamic relationships in early phase trials. Perhaps the best known example of the use of MRI in drug development is the measurement of the exposure-dependent effects of drugs targeting the tumor vasculature (e.g., antiangiogenesis) occurring before tumor shrinkage (1, 2).

MRI and MRS have been used to monitor total choline levels as a marker in functional imaging for adjuvant therapy for cancer, providing information about therapeutic effects within days after treatment. Meissamy et al. (3) described breast cancer research on the use of MRS to reveal the direct relationship of total choline to response to doxorubicin and cyclophosphamide chemotherapy in the neoadjuvant setting. Future applications may detect other molecules or reveal changes in metastatic sites. Ultimately, MRI and MRS could contribute significantly to predicting patient response to therapy and enhance survival.

To minimize costs, pharmaceutical companies must quickly determine the success or failure of a new drug and the potential targeting of the drug to specific types of patients. MRI and MRS may rapidly provide such prognostic information and are being investigated for this use in a variety of tumor types. Critical to the industry researcher's use of magnetic resonance as a biomarker are standards of use and more quantitative procedures.

The Food and Drug Administration (FDA) has targeted imaging as a tool that can help overcome stagnation in drug development. The FDA is interested in using functional and/or molecular imaging—especially MRI and positron emission tomography (PET)—to better delineate the details of responses to therapy.

The NCI Cancer Therapy Evaluation Program serves as an in-house program to develop new cancer treatment agents. J. Abrams noted that future efforts to determine whether a target is being affected by an agent will employ a paradigm different from the old paradigm of determining cell kill. The use of magnetic resonance in the new paradigm began only recently.
Dynamic Contrast-Enhanced Magnetic Resonance Imaging

Characterization of tumor vasculature by DCE-MRI involves acquisition of a series of $T_1$-weighted images before, during, and after bolus i.v. injection of a commonly used contrast agent (gadopentetate dimeglumine). The change in signal over time reflects the exchange of contrast agent between vascular space and, because charged contrast agent does not penetrate cells, extravascular-extracellular space. That exchange depends on the blood flow, vessel permeability surface area, fractional volume of blood, fractional volume of extravascular-extracellular space, and the blood contrast agent concentration as a function of time (4). The tumor (and blood) contrast agent concentration is inferred from the magnitude of the signal change and variables reflecting the underlying vascular physiology are derived using various analytic approaches (1). Generally, treatment-induced changes in these variables reflect changes in blood flow and/or permeability surface area.

M. Knopp stated that morphologic information produced by DCE-MRI can compete with that of PET-computed tomography. DCE-MRI provides functional information as well (5). The number of available contrast agents is growing and expanding the capabilities of DCE-MRI. Changes in enhancement by contrast agents offer clues to tumor heterogeneity (6).

As noted by workshop co-chair J. Evelhoch, MRI has progressed from clinical imaging to quantitative imaging and determining tissue characteristics. However, the algorithms for interpreting readouts need to be standardized. DCE-MRI has advantages over PET in detailing vascular effects. It can image tumors that are smaller than those required for PET and can obtain a wider view than that produced by the transaxial orientation of PET. Yet PET has advantages as well. Early studies of the vascular effects of Combretastatin A-4P found PET superior in revealing perfusion as it related to dosages (7, 8). However, more recent studies have shown clear pharmacokinetic-pharmacodynamic relationships using DCE-MRI (2, 9).

DCE-MRI also is used to monitor responses to radiation therapy. N. Mayr showed cases in which pixel analysis and volume surrogates, based on imaging, allowed researchers to separate out patients susceptible to recurrence. Her work indicated that use of imaging at a point 2 weeks following radiation therapy produced the best predictive value for recurrence.

M. Leach noted that in the United Kingdom, the Cancer Research UK cancer funding agency supported, in 2002, a workshop that developed recommendations for the use of MRI in antiangiogenic research (1). Since then, studies supported by Cancer Research UK have responded to and applied the recommendations, employing quality assurance methods to define effectiveness on instrumentation, assessing reproducibility, increasing supervision of instruments, and more.

Better reproducibility is essential to realize the full potential of DCE-MRI. S. Galbraith said that reproducibility should improve as a result of consensus on methodologies, understanding of the biology underlying contrast transfer between blood and extravascular space, optimization of measurement variables, definition of the region of interest, use of larger cohorts, and understanding of the effects of heterogeneity.

Magnetic Resonance Spectroscopy

Workshop co-chair M. Garwood noted that MRS, after 20 years of use, continues to be considered a novel technology. This suggests that more work is required by the MRI/MRS community, magnetic resonance vendors, and clinical radiology to validate the biomarkers that MRS can detect in vivo and to translate MRS techniques into robust radiological tools.

Proton ($^1$H) MRS is more mature than MRS of other atoms, and it offers the best sensitivity. The MRS signal from the nine $^1$H atoms from the trimethylamine group of choline compounds is a readily detectable biomarker. The concentration of choline-containing compounds is a biomarker for altered membrane-phospholipid metabolism, which is a hallmark of all types of cancers (10–12).

MRS can detect and quantitate other metabolites besides choline compounds. It can discriminate between kinetic patterns of drugs and drug metabolites and can measure outcome in the same patient in which it measures pharmacokinetics, thereby relating tumor response to pharmacology. In pharmacologic applications, MRS can measure perfusion, tissue changes, and biochemical modulation. Fluorine ($^{19}$F) MRS seems to be a potential candidate for predicting early response to $^{19}$F-labeled drug therapy.

MRS is used for prostate cancer staging and increasingly for assisting therapeutic selection, treatment planning, and response. Kurhanewicz et al. (13) noted that MRS can identify prostate cancer by measuring low levels of citrate as well as high levels of choline-containing compounds. He described a scoring system based on citrate, creatine, and other variables. One study showed a sensitivity of 87%, specificity of 72%, and overall accuracy of 81%. The use of diffusion MRI in combination with MRS may lead to better assessment of volumes within the prostate.

For brain tumors, MRS can distinguish different metabolic levels within the cancer and has been used clinically for several years. Both single-voxel and multivoxel MRS acquisitions are supported by most magnetic resonance manufacturers for brain tumor applications. Studies have correlated MRS variables, therapeutic response, and brain tumor survival (14, 15).

The American College of Radiology Imaging Network prostate trial is currently employing MRI and MRS to evaluate accuracy of their use at multiple institutions—in this case, 7 sites and 134 laboratories—where researchers evaluate the robustness and reproducibility of acquired data, standardize the interpretation of data, and explore issues of validation.

Issues for Discussion

N. Mayr noted that choosing methods of evaluation depends on the specific tumor under study and the response sought (e.g., palliation or full outcome). The rapid progression of lung cancer makes it a good candidate for validation studies. Many members of the pharmaceutical industry are currently using DCE-MRI in the development of antiangiogenic drugs.

Heterogeneity within a tumor and across individuals remains a key issue to be resolved in the effort to achieve validity and reliability. Issues of heterogeneity extend to study design and image reading. Because of the complexity of issues, researchers should consider multidimensional indices. N. Mayr encouraged the community to develop simpler ways to acquire and interpret data (16). One way to bring imaging into more clinical trials would be to collect imaging data in a repository that could be used to perform assessments using different methodologies.

The issue of population differences also remains. A. Wolff suggested that study designs might better identify populations, leading to robustness in the imaging results.
Device and Pharmaceutical Manufacturers

L. Clarke called on the MRI/MRS community to develop software standards that would allow it to interact better with device and drug manufacturers. One possible strategy would be to leverage ongoing clinical trials to develop standards. The establishment of a clearinghouse of reference protocols might lead to protocols that researchers and vendors would endorse. The imaging community might develop specific demonstration sequences that adhere to certain standards and that which industry could support and address.

Recommendations for Dynamic Contrast
Enhancement-magnetic Resonance Imaging

Building on the recommendations of earlier workshops on this topic (1, 17), the attendees developed consensus recommendations for magnetic resonance measurement methods at 1.5 T and end points for use in phase 1/2a trials of anticancer therapeutics affecting tumor vascular function. Specific recommendations were made for the type of measurement, images to be acquired before contrast injection, requirements for contrast agent injection, the dynamic acquisition protocol, primary end points, measurement requirements for the primary end points, secondary end points, trial design, nomenclature, image analysis, data reduction, and the region of interest. These recommendations are available at the NCI Cancer Imaging Program website and will be published in greater detail in magnetic resonance literature in the near future. Although these should provide guidelines for the use of DCE-MRI in drug development, it was recognized that the potential applications are much broader and a need for considerable research in this area remains.

The pharmaceutical industry has gained confidence in the use of DCE-MRI in drug development studies to assess vascular effects (18). However, the oncology community has less confidence in its value as a therapy-response marker because there are insufficient data showing a correlation with clinical outcome. Hence, there is a need to evaluate the relationship of DCE-MRI measurements to clinical response (both pretreatment and early after treatment). The attendees suggested an initial evaluation in colorectal cancer and renal cell cancer. Also, there should be an evaluation of both the effect of prior/concurrent treatment on the ability of DCE-MRI to detect vascular response and the potential for DCE-MRI to detect and/or predict normal tissue toxicity.

The need to explore DCE-MRI at 3 T was noted, together with the need to compare 3 T results with 1.5 T results in settings with established vascular effects. New macromolecular contrast agents should be explored as they become available. Comparison of DCE-MRI with other contrast mechanisms, functional/molecular imaging techniques, and other bioassays (e.g., growth factor assays) should advance our understanding of the biological underpinnings of this method. Intra- and intertumor heterogeneity questions also need to be addressed to realize the full potential of DCE-MRI.

The workshop attendees suggested that public domain analysis software should be made available and/or standard analysis capabilities built into magnetic resonance systems. Other data analysis related issues requiring further exploration include the following: automation, normalization function (e.g., blood, muscle, and spleen), effect of region of interest definition on variability, consensus on acceptable statistical measures of reproducibility, and information content of alternate (both simple and complex) analysis approaches. It was noted that data sets with known outcome available in a public database and an improved T1 phantom could help evaluate analysis methods. Technical improvements that could be implanted to substantially improve the performance of DCE-MRI include parallel imaging, motion robustness (e.g., navigator echoes), robust registration algorithms, pulse sequences providing greater coverage, and quantitative pulse sequences. It was noted that a "standard" tissue (e.g., benign prostatic hyperplasia and meningioma) might be useful to evaluate method variability independent of biological variability.

Recommendations for Magnetic Resonance Spectroscopy

With a goal of standardizing the application of MRS, the workshop members agreed to focus on prostate, brain, and breast cancers. D. Vigneron proposed conducting multisite trials with a single protocol to verify the MRS techniques. For this to occur, certain issues must be resolved, including the use of many vendors, models, and methodologies. In fact, researchers possibly must bring MRS to a higher level of maturity before using it in multicenter trials. This would include development of quality assurance criteria.

Researchers need to develop resources, such as links with industry, define metrics and software to produce data, and interface with industry about them. Metric standards should be incorporated into the scanners. Funding of an academia-industry project might be useful.

The group agreed to recommend the methods being used in the American College of Radiology Imaging Network trial, including the use of signal-to-noise requirements, quality assurance, and a central data-processing site. Rescanning patients to test reliability is not practical. Researchers should consider incorporating the use of 3 T instruments.

Main conclusions and recommendations for MRS were as follows:

- Breast, prostate, and brain tumors are ready for multicenter multivendor clinical trials.
- There is a need to study proton MRS for metastatic disease.
- Trials should move toward the use of 3 T instruments with quality assurance.
- Application-dependent, post-processing, and analysis software must be developed. This must include uniform spectral processing on vendors’ scanners and centralized processing and database development for clinical trials. The database should contain raw data.

The workshop participants agreed to further develop the recommendations for the two main technologies, DCE-MRI and MRS, in the form of proposed protocol variables, to be published. They recognized topics that will require future discussion and consensus, such as the physiologic bases for variables, the use of other nuclei (for MRS), assessment of metastatic sites, and diffusion MRI.

Acknowledgments

Received 2/28/2005; revised 6/2/2005; accepted 6/14/2005.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
References


Expanding the Use of Magnetic Resonance in the Assessment of Tumor Response to Therapy: Workshop Report

Jeffrey Evelhoch, Michael Garwood, Daniel Vigneron, et al.


Updated version  Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/65/16/7041

Cited articles  This article cites 16 articles, 6 of which you can access for free at: http://cancerres.aacrjournals.org/content/65/16/7041.full#ref-list-1

Citing articles  This article has been cited by 6 HighWire-hosted articles. Access the articles at: http://cancerres.aacrjournals.org/content/65/16/7041.full#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.