Commentary

Noninvasive Imaging of Anticancer Therapy

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The paper by Blasberg (1) in this issue represents the first of a series of manuscripts that represent the breadth of functional and molecular imaging approaches to interrogate cancers with nondestructive and noninvasive imaging methods. This body of work illustrates the culmination of effort over the past 2 decades that is revolutionizing the practice of diagnostic radiology, changing it from a discipline that was based on anatomy to one that is increasingly based on tissue function and gene expression profiles (1–5). A future article by Chenevert et al. (2) will discuss an MRI method to interrogate the endogenous apparent diffusion coefficient of water in living tissues. Available evidence in animals and humans indicates that apparent diffusion coefficient of water increases in response to effective radio-, chemo-, or gene therapies. This response is becoming defined in biological and cellular terms, and may provide a noninvasive measure of cell death via apoptosis or necrosis. A future article by Nelson (3) will describe the use of endogenous MR spectroscopic signatures that can be exquisitely localized to extremely small volumes in the brain. These spectra reveal alterations in cellular metabolites that can be pathodiagnostic for different cancerous lesions and are being used to monitor the effects of therapy. Knopp et al. (4) have pioneered the development of DCE methods to diagnose, predict, and monitor tumor perfusion in the resting state, and in response to therapy. DCE methods measure the time-dependent changes in image signal intensities after bolus injection of a contrast agent. Although the relationship between these complex kinetics and actual physiological parameters is the subject of much debate, it is clear from these studies that DCE imaging is a powerful tool in the armamentarium of the oncologist. Exquisite molecular specificity will be demonstrated in the future article by Mahmood and Weissleder (5), who describe the use of near-infrared fluorescence to monitor the activity of proteases in vivo. This approach uses “molecular beacon” technology, which was developed for in vitro applications, illustrating the importance of translation between basic and preclinical sciences. Proteases play important roles in metastatic progression, and noninvasive imaging probes can be molecularly specific for distinct enzymes. The Weissleder group (Massachusetts General Hospital, Boston, MA) and others are developing novel imaging platforms to translate this work to the clinic. Finally, the article by Blasberg (1) in the current issue describes the development and application of noninvasive reporter gene imaging. This author presents a balanced description of this powerful approach. The article is primarily concerned with PET reporter genes, yet also illustrates the power of using multiple imaging platforms. Reporter gene imaging technology has also been successfully implemented on MR, optical, and other radioisotope imaging platforms. It is proving to be an outstanding approach to define and understand the causes and consequences of gene expression, as well as being a practical indicator for the efficacy of gene therapy in vivo. To fully exploit all of the above techniques for the treatment of human health and disease, modern radiology departments are being transformed by partnerships with biochemists, molecular biologists, and cellular biologists.

As illustrated by this body of work, techniques are being developed on a regular basis to assess tissue metabolism, and physiology and biochemical expression patterns with higher and higher precision and information density (1–5). Because the same imaging platforms can be used in both animals and humans, these developments have the potential of rapid translation from the bench to the clinic. In the area of patient care and treatment, noninvasive imaging has significant potential to aid in the development and application of new drugs. Applications impacted by imaging include: (a) the assessment of response; (b) the diagnosis and segmentation of patients; and (c) elucidating mechanisms of therapy response and resistance.

Assessment of Response. The use of noninvasive imaging to monitor therapy response is a powerful application of this technology, as it allows individual patients to serve as their own controls through the acquisition of images both pre- and post-therapy. There are two major types of applications in this arena: (a) detection of surrogate response during preclinical and Phase I trials; and (b) early detection of response during Phase II and beyond. The need for imaging surrogates in Phase I studies is becoming more acute with the advent of targeted drugs with fewer dose-limiting toxicities. Thus, dose determination can be aided by noninvasive measures of response.

It is commonly believed that markers that are at the site of drug action or are immediately downstream will be most robust indicators, as in the case of perfusion measurements for monitoring angiogenic therapies. In limited cases, transgenes may be also useful in Phase I studies to directly assess the actions of targeted therapies. As discussed by Blasberg (1), transgene probes have been developed to assess gene expression and protein–protein interactions. However, it might also be the case that markers that are farther

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2 The abbreviations used are: MRI, magnetic resonance imaging; MR, magnetic resonance; DCE, dynamic contrast enhanced; PET, positron emission tomography; BIP, Biomedical Imaging Program.
downstream from the site of drug action may be more robust or have a larger dynamic range. This might be the case for diffusion MRI and fluorodeoxyglucose (FDG)-PET, which both report downstream sequelae related to chemotherapy responses. A major consideration in these studies is timing, as the imaging pharmacodynamics may show up at any time after the pharmacokinetics. In response to this, generic protocols have been developed that first assess timing of response to high-dose therapy, followed by dose escalation at a single time point. Whereas this may lead to prolongation of Phase I, it does promise to provide more quantitative data on targeted responses.

The second important application of this technology is the early detection of response in patients undergoing treatments in Phase II and beyond. The rationale for these studies is to monitor individual patients with the expectation that their therapy choices and dosing schedules can be iteratively adjusted in midcourse. Because of the need for multiple follow-up imaging sessions, this approach is more amenable to noninvasive and nonionizing approaches, such as MRI and ultrasound. A number of possible endpoints exist, which will require many comparisons and clinical trials to assess the different imaging paradigms for efficacy. However, because these approaches are early in development it is advisable to make conclusive comparisons between different techniques. At this time, effort may be better spent on ad hoc empirical and mechanistic validation of the individual markers for clinical use. Comparisons between approaches should only be made after validation, and this will require multicenter trials to determine the relationship between the imaging endpoint and patient outcomes.

**Diagnosis and Segmentation of Patients.** The use of noninvasive imaging has a home in diagnostic radiology. Hence, many of these molecularly based imaging approaches will continue to assist in the diagnosis of disease. As biochemical markers of disease become more available, it is inevitable that molecular and imaging phenotypes will be compared. For example, in the case of PET imaging, FDG uptake values can be correlated with expression patterns of specific glucose transporters and hexokinases. Additionally, leakage of MR contrast agents from blood vessels can be correlated with vascular endothelial growth factor expression. It is likely that more and more sophisticated comparisons will be forthcoming in the ensuing years. A natural consequence of such approaches will be the use of imaging to predict patient outcomes to specific therapies, as an adjunct to pharmacogenomics. A relatively few clinical trials involving a variety of cancers have shown the utility of imaging in predicting therapy outcomes. Hence, functional and molecular imaging are likely to begin affecting therapeutic choices in the near future, especially at certain leading centers. This aspect of therapy imaging will be discussed in later papers of this series by Nelson (3) and Knopp et al. (4).

One of the major strengths of imaging approaches is the rapid and relatively seamless translation between preclinical and clinical studies. As indicated above, imaging can provide important data for drug development in Phase I and beyond. This is recognized at the federal level, where the NIH has sponsored a number of significant initiatives to improve the visibility of imaging in the drug development pipeline. Foremost among these is the BIP, which has been instrumental in helping the research community translate imaging approaches to the clinic. This program has long recognized the need for basic research in this area, and has developed two successful programs to support preclinical small animal imaging centers and in vivo cell and molecular imaging centers. In these programs, there is a strong emphasis on the use of transgenic animals, through the mouse models of human cancer consortia. The BIP has established the Development of Clinical Imaging Drugs and Enhancers (DCIDE) program to expedite and facilitate the development of promising investigational contrast agents or molecular probes from the laboratory to Investigational New Drug (IND) status. Furthermore, the National Cancer Institute/NIH funds the American College of Radiology Imaging Network (ACRIN) to support large, multicenter clinical trials for the characterization of novel clinical imaging applications. To further the use of imaging endpoints to clinical drug trials, the BIP has been proactive in providing informed opinions to the Cancer Therapy Evaluation Program (CTEP) and to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for clinical trials. The Food and Drug Administration has been active in documenting the need to validate imaging endpoints in clinical trials for new drugs. Pharmaceutical companies are increasingly including imaging in their protocols to develop new anticancer agents, and the general sense is that this will provide the most benefit early in drug development, to allow more rapid dose determinations and separation of ineffective compounds from those with more promise.

**References**


3 Internet address: http://www3.cancer.gov/bip.
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