

## Challenges and Opportunities for In Vivo Imaging in Oncology

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Unraveling of the genome and proteome, and advances in biomedical technology are changing the practice of medicine in fundamental ways. In vivo imaging is inextricably caught up in this revolution. Clinical and investigative oncology, in particular, has an expressed need for non-invasive or minimally invasive means to obtain quantitative, serial information about tumors and their milieu, especially molecular information. For the last several years the National Cancer Institute (NCI) has designated cancer imaging as one of its Extraordinary Opportunities for investment. This has translated into a series of programs intended to stimulate and facilitate imaging research as an adjunct to solving the cancer problem. More recently, a new institute has been formed, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) that will further stimulate and increase the NIH support of medical imaging of all kinds.

Advances in in vivo imaging depend on the development of new or improved image acquisition devices (including both hardware and software), on the development of agents to improve contrast (e.g., molecular probes), and on the development of methods to deal with the images after they are acquired. An image is fundamentally a two-dimensional dataset, and much research (e.g., image processing, artificial intelligence, etc.) is needed to fully extract the information available from modern imaging methods.

In oncology, clinical imaging methodologies are essential in the whole spectrum of cancer detection and treatment, including screening, diagnosis, staging, prognosis, monitoring of therapy, and in delivering therapy in a variety of means. In addition to clinical oncology, in vivo imaging has become an indispensable laboratory or research methodology for the study of biology or interventions, particularly in animal models but also in humans. For example, some human imaging methods may be developed for research purposes, such as clinical trials, and may not ever be used clinically. These laboratory or research methods are a form of regional, *in vivo* genomics or proteomics. A research area where in vivo imaging may be particularly important is drug development.

As imaging methods are developed or refined, it is necessary initially to show feasibility and subsequently validation in animals and/or humans. NCI supports Small Animal Imaging Resource Programs (SAIRP's) and the American College of Radiology Imaging Network (ACRIN) to facilitate such studies. These programs are not sufficient in and of themselves to meet the demands for imaging studies, and there is a need for other investigators to perform clinical or preclinical trials as well. However, the paradigms of simple observational studies, or comparisons of one modality against another, are now considered inadequate, and controlled studies with histologic or other independent means of validation are essential.

In investigational and clinical oncology there is a pervasive need for imaging methods that will indicate response to therapy, prior to clinical evidence of response. The traditional imaging approach to this has been anatomic measurements on plain films, CT, MRI, etc. Recently the RECIST criteria have been agreed upon and published as the standard for these types of measurements (Ref. 1). The RECIST criteria are generally considered to be a useful

step forward, but still inadequate for many clinical trial needs. Many investigators think volumetric measurements would be preferable. Such methods have been developed, but they usually involve some operator intervention. There is a need for imaging researchers to develop accurate, reproducible, automatic methods of volume determination.

Therapeutic agents that are highly molecularly targeted tend to induce arrest of cancer cell growth and development, but not necessarily significant tumor shrinkage, at least in the short term. Therefore, anatomic measurements are not useful early indicators of response to these cytostatic agents, in contrast to the situation with more traditional cytotoxic agents where tumor shrinkage occurs early. Thus the demand for functional or molecular imaging methods that would give information about what is happening in the tumor at the molecular level.

A recent analysis of experience with clinical trials of the matrix metalloproteinase inhibitors (MMPI) highlighted the potential value of in vivo imaging agents in improving the testing of new drug therapies (Ref. 2). Despite preclinical evidence that MMPI's should work well, results from clinical trials of a variety of MMPI's have shown poor efficacy. The authors suggest that the poor results are due to the fact that patients in the trials all have advanced disease, and it is not clear how many express the molecular abnormalities that would be best targeted by the MMPI's. Some non-invasive means, such as molecular imaging, is needed to identify which patients are really suitable for the particular targeted therapy, and to indicate whether the drug is reaching its target and in sufficient quantities to block the target or have whatever effect is intended. There is no way currently to get this information in patients. Similarly with current trials of antiangiogenesis drugs, preliminary results are disappointing despite abundant preclinical evidence that the drugs should work. Are these drugs really not effective or are we not selecting the patients appropriately? Are we not giving the drug at the right time? Are we not appropriately assessing the endpoint?

One of the problems that investigators face in introducing molecularly targeted agents in clinical trials is that the traditional study setting is late stage cancer. The cytostatic effect of these new drugs is difficult to detect in large or disseminated late stage tumors, and the drugs may be ineffective in such a setting. The hope with these cytostatic agents is to use them in patients with earlier stage cancer. However, this requires the ability to carefully select patients who have the particular molecular abnormality and to monitor the cytostatic response in some way.

In molecular imaging there is debate in the research community about whether it would be better to focus on generic, or "downstream", indicators of effects on a biochemical pathway, or on indicators that are specific to an "upstream" target in a particular molecular pathway. The generic approach has the advantages of being applicable to multiple diseases or pathways, and might therefore be more marketable. The molecularly targeted approaches have the advantages of providing more specific information about a therapy's delivery and/or action on its intended target, potentially allowing the therapy to be more individually tailored to a given patient's tumor and metabolism. The disadvantages of the molecularly targeted approaches are that they require devoting resources to multiple parallel developmental efforts and diminish the potential commercial interest. An example of a generic, functional imaging method is the use of FDG-PET to look at the response of gastrointestinal stromal tumor (GIST) to Gleevec. Preliminary studies show marked decrease of FDG uptake in GIST tumors within 24 hours in patients who go on to show clinical response to Gleevec. There are very few examples yet of molecularly

targeted imaging agents that have passed through the stages of feasibility and validation and are being used to monitor response in drug therapy trials. However, several demonstrations have been reported in animal studies. Examples include the use of small molecule ligands or antibody fragments that bind to alpha v beta 3 integrin, for use in monitoring the response to antiangiogenesis therapy.

An alternative to the generic or uniquely targeted approaches is to develop a generic “platform” technology, where targeting and imaging signal moieties can be easily changed or substituted. Polymers, dendrimers, and liposomes, for example, are being investigated for this purpose.

Some functional or molecular information can be determined with spectroscopy such as MR or optical spectroscopy. Preliminary results in breast, prostate, and lymphoma, for example, suggest clinical utility. Wider availability of high-field MR scanners is probably necessary before MR spectroscopy applications mature. Other drawbacks, which suggest research opportunities as well, include the need for hardware and software acquisition tools that are standardized across different manufacturers and are more user-friendly.

Although some molecular information is available from spectroscopy, it is currently assumed that exogenous imaging agents will have to be administered to obtain the specific pathway or target information desired. A wide array of feasibility studies is being performed in laboratories around the world. Approaches involving small molecules and large complexes such as polymers, biologics, and nanoparticles are all being investigated. None is clearly superior to another. Similarly, a variety of imaging modalities show promise, each having relative advantages and disadvantages.

One of the exciting possibilities with targeted agents is the demonstration that imaging probes can be designed to be activatable, giving a signal only in a certain molecular setting or context. Examples using gadolinium for MR contrast and fluorophores for optical contrast have been published (Ref. 3 and 4).

The molecular abnormalities in cancer are complex. One might ask, how could a single imaging agent be useful given the biochemical heterogeneity and chaos in the cancer cell? There are certainly settings where single agents could be useful, but compound or combination imaging techniques would be very useful. Some of the work in genomics and proteomics is directed toward identifying a panel of a small number of gene or protein abnormalities that have diagnostic or prognostic importance. Imaging methodologies that reflect such panels of molecular abnormalities simultaneously or in some integrated way are an important area of investigation. For example, a series of ligands to different receptors that have been identified through genomics or proteomics as having some predictive value could be attached to a polymer. Such a multimeric compound would bind to cells that have this specific combination of abnormalities. Another possibility is tunable optical compounds that can be nanoengineered to give off multiple different wavelengths.

Nanoengineering is the creation of functional materials, devices and systems through control of matter at the nanometer scale. It means that humans can now individually manipulate atoms and electrons and create new materials that do not occur in nature. These materials have properties that are completely unique and unfamiliar. They introduce lots of exciting opportunities for imaging devices (signal sensors) and imaging agents.

To assist with the testing and integration of these new imaging methods into cancer

clinical trials, many of the therapy cooperative groups funded by NCI are forming imaging committees or imaging groups of various kinds. Similarly, Cancer Centers are realizing the need to incorporate imaging expertise into the planning and implementation of their studies, and imaging cores in cancer centers are increasing. To support the preclinical studies that have to be done to obtain an FDA IND for new imaging agents, NCI funds the Development of Clinical Imaging Drugs and Enhancers (DCIDE) program which provides contract resources to developers of promising imaging agents (<http://www3.cancer.gov/bip/dcide.htm>).

Using imaging to actively guide the delivery of drugs or other interventions is another important area for research and development. Image-guided interventions require development of devices to carry out the procedure, image-processing techniques to guide tracking and navigation, methods to integrate data from multiple sources, such as combining anatomic and molecular information, and methods to monitor the therapeutic agent delivery and monitor cellular response in real time.

One way to deal with the problems of combining or fusing imaging data from different sources is to acquire the images simultaneously. The combination PET/CT scanner quickly became accepted and commercially available from multiple companies. Other combinations, such as combining MRI with optical techniques, are under development and show similar promise.

Whole body screening, although controversial, is likely to increase rather than decrease. In the United States now whole body CT screening is relatively common and available. In Europe whole body MR scanning is being promoted in several countries. In Japan, some companies offer whole body FDG PET scans to their employees as a benefit. In the future, when sub-four-minute CT/PET scanners become available, combined CT/PET scanning will probably become available in the U.S. Depending on the success of MRI in Europe we may also see that here as well. *In vitro* technologies, such as blood tests screening for panels of tumor-associated proteins, may also become widely available. The concern with these whole-body screening methods is overdiagnosis and false positives, and the cost and treatment implications of these false results.

The relative importance of overdiagnosis and false positive results is inversely proportional to the cost and morbidity of the options available for managing them. Consider the example of skin cancer screening. Essentially it is a whole body screening method using the optical techniques of room light and the retina. A dermatologist identifies abnormalities by their look and feel. Based on these criteria he decides that some could be actinic keratoses, which have approximately a two percent chance of progressing to skin cancer. Without doing any definitive diagnostic procedures, such as a biopsy and histologic evaluation, the dermatologist treats all of these lesions with a local ablative technique, such as spraying them with liquid nitrogen. This amounts to massive overdiagnosis and over-treatment because many of these lesions will not be actinic keratoses at all, and the majority of those that are will never progress to skin cancer. However, we accept this massive overdiagnosis because the treatment is cheap, easy and relatively benign. It targets only those abnormal cells (whatever they are) and spares the normal cells. This is the paradigm that we need to develop for abnormal cells detected by whole body screening in other organs. This challenge creates a huge need for developments in very directed therapies to diminish the overdiagnosis problem.

One example of a method to deal with these abnormal cells is focused ultrasound, which

is completely noninvasive. At present it is not as inexpensive or technologically easy to administer as the therapies in the skin cancer model, but it has potential for such applications in many solid organ tumors. Other possibilities exist as well.

NCI has a program to facilitate research on this problem, called the unconventional innovations program (UIP). The UIP was not created to facilitate imaging research, but rather is open to any technology that has long-term promise. Nevertheless, the projects that have been funded in this program since its inception in 1999 all involve either imaging or nanotechnologies. This tells us that applicants and reviewers see imaging and nanotechnology as high among the most important, exciting areas of opportunity and challenge for cancer research in the next few years.

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