OPPORTUNITIES FOR MEDICAL RESEARCH

Advances in Biomedical Imaging

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Diagnosis and Recognition of disease using diagnostic imaging has undergone significant change and development in the past 25 years. This article focuses on 3 major areas of imaging: new techniques, image-guided therapy, and bioinformatics, each of which reflects the dramatic progress in this field.

Clinical Breakthroughs and Current Challenges

Development of magnetic resonance imaging (MRI), computed tomography (CT), and ultrasonography have allowed visualization of different tissue properties than conventional radiography. Many individual tissue properties of the MRI signal, such as MR-proton density, relaxation rates, flow, chemical shift, diffusion, and perfusion, contribute to soft tissue contrast. Computed tomography and ultrasonography each rely on a single characteristic, namely, density and sound reflection, respectively. Four examples illustrate new clinical advances, including cardiac MRI, obstetrical MRI, genitourinary CT, and tumor imaging with positron emission tomography (PET).

Initially, MRI was time-consuming and expensive. While MRI always provided exquisite images of the brain, it did not initially appear likely to be useful for parts of the body where significant motion occurred, such as the heart. However, with different techniques, morphological and even functional cardiac information could be obtained.1,2 Now, due to rapid imaging sequences and technological innovations, exquisite images of the beating heart make possible detailed analysis of cardiac wall motion and perfusion in patients with myocardial ischemia and infarction. Magnetic resonance imaging of the heart during dobutamine stress can evaluate wall motion abnormalities.3 Faster MRI sequences have made direct in utero imaging of the fetus and its development an important addition to obstetrical imaging, particularly in providing opportunities to plan and guide surgical intervention in utero or at birth.4,5

Advances in CT imaging of the urinary tract have resulted in less invasive treatments and more accurate diagnoses. Helical CT is now the criterion standard for detection of renal cell carcinoma and acute ureterolithiasis.7-9 Multidetector CT allows for 3-dimensional reconstruction of the entire urinary tract.10

One major application of PET is tumor imaging. This technique can image tumors noninvasively and detect...
both primary tumors and distant metastases.11-15 The Health Care Financing Administration (HCFA) recently authorized Medicare coverage for 18-fluorodeoxyglucose PET studies for staging and restaging in patients with one of several tumor types if the stage remains in doubt after a standard diagnostic workup and if the resulting information is expected to affect patient treatment or use of PET would be expected to replace a conventional procedure.16 The tumor types are non–small-cell lung, esophageal, and colorectal cancers; lymphoma; melanoma (excluding staging for regional nodes); and cancers of the head and neck (excluding central nervous system and thyroid cancers). In addition, coverage also has been authorized for assessing response to therapy after the course of therapy has been completed for these tumors. HCFA noted in its ruling that “in all of the clinical conditions for which Medicare will now provide coverage, and for the remaining oncologic and other clinical uses, there is still a need for high-quality clinical studies.”16

**Current Scientific Foundation**

Early detection of disease will change dramatically in the future. If the promise of genomics is fulfilled, patients at high risk for disease will be readily identified. New technologies and methods will be required for functional, physiological, and molecular imaging, both for diagnosis and to guide and monitor molecular therapies.

Three areas of research are currently of particular importance: development of new techniques for imaging of physiological and pathophysiological processes and for improvement of anatomic resolution; development of improved imaging for treatment delivery and assessment; and improvement of bioinformatics as it relates to imaging.

**New Technologies.** Technologies in development include molecular imaging, diffusion-weighted MRI, functional MRI, and MR spectroscopy (MRS). Molecular imaging techniques include PET, single-photon emission CT (SPECT), and optical imaging. Positron emission tomography allows direct imaging of biological processes in vivo as well as visualization of the molecular target. Both PET and SPECT can image brain chemistry, neurotransmitter receptors,17 and brain function. Positron emission tomography may provide a means for early diagnosis of Alzheimer disease18 and, by measuring the rate of dopaminergic receptor loss, provides a method to monitor the effects of treatment of Parkinson disease.19 Diffusion-weighted MRI can distinguish healthy brain tissue from brain areas affected by acute stroke20 and provides the ability to separate cytotoxic edema (with acute cerebral infarction) from vasogenic edema (with tumors).21 When applied to the ischemic brain, this technique predicts the amount of infarction and ischemia, thus identifying patients who may benefit from new treatments for reversing ischemia.

Magnetic resonance spectroscopy provides a measure of metabolic differences in various brain areas, as in detecting foci of acute cerebral ischemia and stroke.22 Use of this technique for breast and prostate cancer can help detect foci of tumor involvement. Magnetic resonance imaging is useful for staging and monitoring treatment of prostate cancer and can be enhanced when combined with MRS or demographic data.23-26

The challenge is to increase capability to perform real-time imaging of in vivo molecular and cellular events. For example, among women with the **BRCA1** or **BRCA2** gene, the delay between malignant transformation and development of mammographic findings may be reduced by molecular imaging. In vivo imaging of genetic and molecular markers for disease diagnosis and recognition may be possible with MRI, MRS, or optical imaging. Spatial and temporal image resolution must be refined to allow enhanced detection and visualization of rapid molecular and cellular events. Improved technology includes high-field-strength magnets (up to 7 T), improved MR surface coils, multimodal imaging units (eg, SPECT/CT or PET/CT), and multidetector CT scanners.

**Image-Guided Therapy.** The multidisciplinary field of image-guided therapy and surgery has become increasingly refined with application of techniques such as MRI, CT, and ultrasonography. Image-guided surgery brings powerful technologies into the operating room by applying advances in computer science and engineering. The simultaneous combination of direct vision and imaging is possible with intraoperative MRI.27-32 Open-configuration MRI systems guide, plan, and direct multiple procedures—from biopsies to percutaneous interventions and neurosurgery. Use of MRI to guide biopsies of lesions that cannot otherwise be detected and to direct therapy is a powerful application of this technology.

Functional imaging (functional MRI/SPECT/PET) makes it possible to map brain function directly in the operating room (FIGURE 1).28 Functional MRI allows identification of the brain area by function, such as the speech center or motor cortex, and the surgeon can avoid damage to such critical areas. For certain interventions (eg, biopsies, tumor resection, directed therapies), this im-

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aging information enhances the ability to apply sophisticated imaging techniques to surgery. Intraoperative MR guidance for neurosurgery improves precision of tumor resection, particularly when high-resolution MRI images are combined with functional MRI, SPECT, and MR angiographic data. Further advances in MR-guided interventions, biopsies, ablations, and surgery are needed to expand their capabilities.

**Imaging Treatment Effect.** Improved noninvasive surrogate imaging markers would be useful to monitor drug delivery and effect; for instance, with new imaging techniques that will provide surrogate markers of both treated and untreated disease. Treatment effect monitoring must be both sensitive and accurate. For example, tumor size can be calculated from CT or MRI by direct 1-dimensional or 2-dimensional measurements as proposed in the guidelines of both the Response Evaluation Criteria in Solid Tumors group and the World Health Organization. Although tumor size alone does not provide a full picture of what is happening within the tumor undergoing treatment, tumor shrinkage remains the chief means of assessing response. New methods to measure molecular and cellular effects (eg, tumor regulation, gene therapy, angiogenesis) are essential. More insightful ways to visualize treatment effects directly might include imaging cell death and presence or absence of malignant cells, for example. Likewise, development of antiangiogenesis drugs will require measurement of effects such as the number of vessels or vessel density, vessel permeability, and blood flow to tumors.

**Bioinformatics.** All new medical tools (imaging, drugs, and treatment methods) must undergo lengthy testing and rigorous evaluation before use. As these assessment techniques are increasingly applied to imaging modes, standards are becoming more exacting, and assessments are being applied with much greater frequency to optimize diagnostic imaging modes by using evidence-based approaches. Hospital staff members can now access online guidelines for use of imaging tests by diagnosis. The ability to store and integrate imaging and medical information in 1 system along with tools for management of imaging data contribute to maximizing the benefit of imaging for the patient.

The increasing complexity of information available from image data sets increases demand on the diagnostic skills of radiologists. Two ways to improve diagnostic performance are by improving the radiologist's accuracy and by increasing the utility of diagnostic decisions. The ability to perform multimodal image fusion (eg, combine data sets from PET and CT or SPECT and MRI) increases complexity and also requires innovative methods for increasing diagnostic accuracy, such as feature analysis and computer-aided diagnostic tools. Statistical prediction rules are a form of computer-based decision support that improves diagnostic accuracy. Such rules can enable analysis of more than 20 variables on a mammogram and combine the results to provide an estimate of the probability of cancer. These tools are powerful and can improve the quality and accuracy of diagnostic techniques, as illustrated by application of MRI for staging prostate cancer.

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**Figure 2.** Visualization of In Vivo Gene Expression by Magnetic Resonance Imaging

- **ETR Expression Sequence**
  - 5’ Transfection of Cell With Plasmid Containing Engineered Human Transferrin Receptor (ETR) Sequence
  - 3’ Engineered 3’ Untranslated Region (UTR)
  - stop

- **ETR Coding**
  - 1.7 kB
  - 2.4 kB
  - ~150 nt

- **5’**
  - Stably Transfected Gliosarcoma Cell
  - Compartmentalization

- **4’**
  - Increased Binding and Uptake of Tf-MION

- **6’**
  - MR Imaging
  - Areas of Implanted Cells

Gliosarcoma cells were stably transfected with an expression plasmid containing engineered transferrin receptor (ETR) cDNA (step 1) that overexpresses high levels of the transferrin receptor protein (step 2) and results in a marked increase in the cellular binding and uptake of superparamagnetic monocrystalline iron oxide nanoparticles conjugated to holotransferrin (Tf-MION) (steps 3-5). Nude mice were implanted with transfected ETR+ cells and with control transfected ETR− cells in each flank. Ten to fourteen days after implantation, the mice were injected with Tf-MION. In vivo magnetic resonance imaging of mice (step 6) with ETR+ tumors and control ETR− tumors showed increased uptake of Tf-MION in the ETR+ tumors, suggesting ETR gene expression. kB indicates kilobase; nt, nucleotide.
Cutting-Edge Research Activities

Molecular Imaging. Molecular imaging, the next frontier in diagnostic imaging, involves noninvasive mapping of cellular and subcellular molecular events. Several methods are used to facilitate this imaging, including PET, MRI, and optical imaging, which enable assessment of gene expression in vivo. Optical imaging uses either near-infrared fluorescence or optical coherence tomography. Near-infrared fluorescence uses probes that allow in vivo imaging of enzyme pathways, such as activity of cathepsin D, an enzyme overexpressed in many tumors. In rodent cell lines, that enzyme can be visualized with a 350-fold amplification of signal in vitro. Figure 2 shows MRI of transgene expression.

Image-Guided Therapy. The ultimate goal of treatment is to identify the target of treatment and to deliver the maximum therapy to that target. The 3 critical components of image-guided therapy are navigation, control, and monitoring of therapy delivery. Precise navigation requires clear identification of the target. To assess treatment delivery, the target lesion and all adjacent tissues must be identified accurately while controlling the intervention or procedure.

Open MR systems are useful to guide treatment and assess follow-up effects in brain and spinal cord surgery, cryoablation of liver tumors, breast cancer, and laser interventions. Magnetic resonance imaging is sensitive for detection of breast masses and lesions but not specific in breast cancer diagnosis. To understand and use MRI in early detection of breast cancer (eg, in BRCA1-positive or high-risk women), MR-guided breast biopsy must be performed on all suspicious lesions and compared with mammography and histology. In addition, several ablative techniques will allow physicians to halt the disease process using thermal methods. For example, MR-guided cryotheray allows clear visualization of the “freezing” of the diseased tissue with argon, and is used in several disease processes, such as liver metastases, uterine leiomyomas, renal tumors, and prostate cancer.

Image-guided therapy for prostate cancer has improved local treatment and reduced the complication rate. In local therapy, introduction of ultrasonographic guidance for brachytherapy has led to increased use of this treatment method. Radioactive seeds also can be placed into the prostate with MR guidance (Figure 3). This approach allows direct visualization of the target to be treated, the treatment delivery, and the resulting radiation dose. The approach also has been adopted for performing MR-guided prostate biopsies when transrectal ultrasonography has failed or is not possible. Integration of image information from high-field-strength MRI and MRS into the biopsy guidance tool will improve the precision and accuracy of the procedure.

Research Priorities and Critical Issues

Priorities for imaging research can be grouped into 2 categories. The first is increased recognition by the international research community of the need for biomedical imaging research and increased infrastructure support and funding. Second, integration and trans...
lution of basic imaging research to the bedside and direct patient care should be increased.

Biomedical imaging is an interdisciplinary field that requires collaboration among biologists, chemists, physicists, pharmacologists, computer scientists, bioengineers, and clinicians of all specialties. Skills and tools provided by radiologists are at the core of many clinical research programs. In interventional cardiology, for example, the tools and techniques introduced by radiologists have radically altered treatment of heart disease. Continued development of new interventional techniques will emerge from imaging research laboratories.

Integration of these multiple fields to improve patient care will be difficult because these groups have not traditionally worked together. Given the current health care environment, time and effort dedicated to research is declining, even in the largest academic health care centers. However, the trend to integrate research and clinical care centered on disease groups, such as cancer centers or women’s health centers, will enhance integration of the interdisciplinary fields.

**Forecast of Major Research Advances**

Just as major breakthroughs such as CT, MRI, and image-guided therapy could not have been predicted, future developments are difficult, if not impossible, to predict.

If sequencing of the human genome provides as much knowledge as is predicted, the focus of imaging will change from diagnosis and recognition of disease to prediction and prevention. In vivo markers and maps will allow stratification of high-risk individuals. Realization of the promise of molecular imaging with PET and other modes will provide unique insights into the extent of disease and allow for improved staging and better treatment. The combination of molecular imaging and image-guided therapy systems will make it possible to direct treatment to a disease at the time of recognition. For instance, for a 30-year-old man with a family history of prostate cancer, it may be possible to perform a “prostate scan” and detect a small focus of aggressive cancer confined to the gland using, for instance, a prostate-specific antigen optical imaging probe or improved MRI with simultaneous MRS. The patient could be treated immediately using an image-guided ablative method with direct injection of radioactive seeds, a direct injection of gene therapy, cryotherapy, or even noninvasive focused ultrasonic ablation.

Early diagnosis of disease must be accompanied by effective treatments. As technological advances occur in identifying diseases and disorders early in their development, increasingly innovative, well validated by outcome studies, are also required. The continued quest for improvement in health care undoubtedly will produce many unimaginable, innovative new diagnostic imaging techniques.

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