Integration of Biomarkers and Imaging

Edward F. Patz, Jr., MD

Abstract: Imaging studies provide essential diagnostic information in the care of cancer patients. Unfortunately, radiographic findings are not always diagnostic and thus an alternative approach with biomarkers has been suggested as part of the diagnostic evaluation. This discussion focuses on integration of biomarkers with imaging in the effort to guide patient management.

Key Words: Biomarkers, Molecular-Diagnostics, Imaging.

The primary goal of radiographic evaluation is to provide diagnostic information. Although imaging offers exquisite anatomic, morphologic and, more recently with positron emission tomography, biochemical and metabolic information, the findings are not always sufficient to establish a definitive diagnosis. Thus, interventional procedures are often required for tissue sampling before treatment is initiated. Even after a pathologic diagnosis is confirmed, characterization of lesions is often inadequate, as therapeutic options and prognosis are frequently based on sequential follow-up imaging studies.

As an alternative and complementary approach to imaging, biomarkers have been suggested as part of the diagnostic strategy. Biomarkers could theoretically provide the necessary detail to address issues that conventional imaging and pathologic evaluation have not been able to offer.

Discovery of Biomarkers

Biomarkers in medical practice have been defined as indicators of normal biological processes, pathologic processes, or response to a therapeutic intervention. They are intended to substitute for a clinical endpoint and can be expected to suggest a diagnosis, characterize a disease, predict responsiveness to treatment, or suggest outcome. Thus, by definition, many imaging and specimen features can be considered biomarkers, but there remain a number of unresolved issues because of the lack of sensitivity and specificity of these findings. If biomarkers are to be effective in clinical practice, they should be easily obtainable with noninvasive or minimally invasive procedures, they should be accurate, and the assay must be reproducible and cost effective.

The search for tumor biomarkers begins with an understanding that the fundamental property of cancer is that it is a disease of the genes. Many investigators have explored a variety of biological biomarkers, including DNA, mRNA, and proteins, which can differentiate cancer from normal or other diseases. Some have attempted to develop biomarkers by elucidating the spectrum of genetic changes using gene or oligonucleotide microarrays. Although this has resulted in a large amount of data and the elucidation of links between biological pathways involved in oncogenesis, integration of this information for clinical purposes has been difficult to achieve. This is not only because tumors are heterogeneous but also because minimal genetic changes often have a large spectrum of downstream consequences. It is often difficult to sort out which are meaningful markers for clinical practice.

In addition, given the disparity between gene transcription, protein expression, and posttranslational modifications, it is possible that relevant phenotypic characteristics of disease may be overlooked by investigations of gene expression or the transcriptome alone. Because of this, an interest in directly studying disease-specific changes in protein expression is becoming an attractive alternative strategy. The ability of proteomic analysis to complement transcript level–based microarray studies has been well documented. It is postulated that the phenotype of a cell is a reflection of its proteome. Thus elucidation of comprehensive protein profiles will permit investigators to gain more insight into tumor biology.

Proteomic technology, however, is just beginning to be engaged in translational applications, and more basic research into protein separation, amplification, and differential expression would clearly lead to advances in protein biomarker discovery.

Clinical Utility of Biomarkers

Regardless of the platform or type of biomarkers discovered, appropriate incorporation of tumor biomarkers into clinical practice could dramatically alter diagnostic strategies, affect treatment options, and eventually improve patient outcomes. There are a number of specific management issues that would undoubtedly benefit from more accurate lesion characterization. A clear understanding of the relevant diagnostic problems and translation into clinical practice, however, is a complex process. Integration of biomarkers with imaging requires knowledge of not only the specific clinical question but the current limitations of radiologic studies. The
most common challenges in tumor diagnostics can be divided into four general categories. These include the following:

1. Defining a high-risk population.
2. Determining the cause of an indeterminate abnormality identified on imaging studies and establishing a diagnosis (Figure 1).
3. Characterizing disease (prognostics/therapeutics).
4. Predict disease progression.

The first three issues help in the identification of patients with disease, diagnosis of disease, and characterization of lesions so that appropriate treatment is administered, and suggest outcomes. The last category, following disease progression, has traditionally been an essential element in patient management, but one could argue that as tumor characteriza-

**FIGURE 1.** Two patients with indeterminate nodules. Both had their blood tested for biomarkers MUC1 and CK19 (epithelial cell markers) to differentiate benign from malignant lesions. (A) A 68-year-old man underwent computed tomographic scanning for emphysema. Axial computed tomographic image demonstrates an 8-mm left lower lobe nodule. Several other small nodules were also identified. Follow-up radiographic studies over the next year showed these to be stable, suggestive of a benign abnormality. The patient has had 2-year clinical follow-up and is without evidence of a malignancy. (B) Reverse-transcriptase polymerase chain reaction was negative for both MUC1 and CK19, suggesting a benign lesion. Lanes: L, ladder; 1, CK19; 2, MUC1; 3, positive control; 4, negative control. Lane 3 was added to this image for direct comparison. (C) A 71-year-old woman with an enlarging nodule on chest radiography. Axial computed tomographic image confirms the 1.5-cm nodule. This proved to be non–small-cell lung cancer. (D) Reverse-transcriptase polymerase chain reaction was positive for both MUC1 and CK19, suggesting malignancy. Lanes: L, ladder; 1, CK19; 2, MUC1; 3, positive control; 4, negative control. Lane 3 was added to this image for direct comparison.
tion at the time of diagnosis becomes more sophisticated and tailored therapy becomes a reality, the need to follow these patients with anything more than a routine imaging study will be unnecessary.

SUMMARY

Once diagnostic issues are defined and biomarkers discovered, specific hypothesis-driven clinical trials can be performed. As the field of molecular diagnostics evolves, it will be essential to integrate a spectrum of noninvasive techniques into the choice of diagnostic methods if improvements in patient outcomes are to be realized.

REFERENCES


