EDITORIALS

Breast Imaging and Computer-Aided Detection

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Breast imaging is the newest, and according to most criteria the weakest, of all radiology subspecialties. Screening mammography in particular often loses money and is subsidized by other sections of the radiology department and occasionally, as in my own case, by direct hospital payments to breast imagers. Screening mammography is also the most common basis for lawsuits in radiology, which is not surprising, since 25 to 50% of cases of breast cancer are identified retrospectively on the previous annual screening mammogram. As the only quasi–public health endeavor in radiology, screening mammography is heavily regulated, with many unfunded mandates. Screening mammography, a particularly stressful task for radiologists, is associated with a relatively high rate of burnout. For all these reasons, residents have avoided this field for decades, leaving a shortfall of fellowship-trained mammographers, many of whom are older and overworked. The problem of workload has recently been exacerbated, since the preferred method of diagnosis for most breast lesions is now imaging-guided core needle biopsy rather than surgery. The low status of breast-imaging experts is ironic, since screening mammography has been a major public health advance, with an estimated cost of only $20,000 per quality life-year saved in the United States.

Mammographers have welcomed two computer-based advances during the past decade: digital mammography and computer-aided detection. A recent study[1] reported that the use of digital mammography improved the accuracy of examination in younger women and in those with dense breasts. Early reports on the use of computer-aided detection showed a 10 to 15% increase in the number of diagnosed cases of breast cancer, with an estimated added cost of only $5,000 per life-year saved. These results are similar to those obtained when a second radiologist "double-reads" the mammogram. This is the practice in Britain and several other European countries, but it is difficult to implement in the United States owing to personnel shortages.

The article concerning computer-aided detection by Fenton et al.[2] in this issue of the *Journal* will surprise and disappoint most mammographers. It is the most comprehensive analysis of computer-aided detection in breast screening to date. The study involved more than 429,000 mammograms and 2351 cases of cancer that were detected at 43 facilities of the Breast Cancer Surveillance Consortium. During 4 years of observation, 7 of the 43 facilities implemented computer-aided detection, allowing for a comparison of the performance at these facilities and their individual radiologists before and after the use of computer-aided detection. The facilities that did not implement computer-aided detection served as controls. Fenton et al. found that the use of computer-aided detection not only failed to increase the cancer-detection rate significantly but also was harmful because of the increased number of false positive mammograms, resulting in significantly more call-backs and biopsies. These downstream costs, which may also include payments to surgeons and pathologists, account for perhaps one third of the total cost of breast-screening programs.

One possible flaw in the study by Fenton et al. was the failure to assess the time it takes to adjust to computer-aided detection. Mammographers initially exposed to computer-aided detection may be unduly influenced by the three to four marks the software places on each mammogram, with the necessity to ignore the 1000 to 2000 false positive marks for every true positive mark. The adjustment to computer-aided detection has been estimated to take weeks to years.

Clustered microcalcifications are the imaging hallmark of ductal carcinoma in situ. Before mammography was introduced, this was a rare and usually incidental diagnosis that now accounts for 25% of the breast cancers diagnosed in the United States. The relationship of ductal carcinoma in situ to invasive breast cancer remains unclear: all invasive breast cancers probably arise from an in situ monoclonal cancer, but many of these lesions may never progress to invasive cancer during a woman's lifetime. Because computer-aided detection is relatively more sensitive in detecting microcalcifications than in detecting masses, it is not surprising that Fenton et al. found that its use was disproportionately associated with the detection of ductal carcinoma in situ. It has been estimated that only 10% of the decrease in mortality linked to screening mammography relates to the diagnosis of ductal carcinoma in situ. Hence, the disproportionate detection of microcalcification and ductal carcinoma in situ by computer-aided detection may not substantially lower mortality from breast cancer.

Computer-aided detection and digital mammography complement each other because both entail a digitized image. Unfortunately, traditional analogue film-based images must be individually digitized before they can be interpreted with the use of computer-aided detection. The start-up costs, $50,000 to $175,000 for computer-aided detection and $500,000 for digital mammography (vs. $125,000 to $150,000 for a conventional analogue unit), are affordable only in relatively high-volume practices. Sales of digital-mammography units (40% of all units sold in the United States in 2003) and computer-aided detection software have been robust in large screening centers, in part because of financial incentives: the Medicare payment per mammogram is increased by approximately $20 for computer-aided detection and $50 for digital mammography. It is noteworthy that reimbursement for computer-aided detection, like that for screening mammography many years earlier, was mandated by a heavily lobbied Congress, despite little evidence-based data in support of its value at the time.

There is general recognition that computer-aided detection is less useful for experienced mammographers than for inexperienced ones. In many high-volume settings, computer-aided detection is introduced primarily as a public-relations tool and because of the increased reimbursement, with recovery of initial costs in about 3 years. Computer-aided detection is less popular in Europe, partly for economic reasons and partly because most examinations are interpreted in high-volume settings by more experienced mammographers. Britain, for example, requires screening mammographers, not all of whom are physicians, to read 5000 examinations per year; in the United States, the requirement is only 480 per year.

A potential advantage of digital mammography is the possibility of teleradiology, which permits the digitized images to be interpreted remotely by more experienced mammographers in large specialized facilities. This relieves general radiologists, often in small rural practices, of the task of interpretation, which virtually always loses money in low-volume settings. Unfortunately, in the United States, mammographers in low-volume practices, who could potentially benefit the most from computer-aided detection — and the teleradiology that digital mammography offers — are least able to afford it.

There are legal implications of the use of computer-aided detection in breast imaging. Both plaintiff and defense lawyers have applied computer-aided detection to mammograms, a practice that could become routine. However, the findings of computer-aided detection are not entirely reproducible, and sensitivity thresholds differ for calcifications and masses, among various brands of the software, and with each new version of a given brand of software.

Will the results of Fenton et al. end the use of computer-aided detection in screening mammography? Of course not, but they constitute a substantial hit to this technology. As is the habit of editorialists, I recommend the conduct of larger, controlled studies of computer-aided detection that assess not only cancer diagnosis but also the gold standard: mortality. But such studies will be expensive, controversial, indeterminate, or quickly passé owing to the emergence of new technology. It took two to three decades of controversy before it was proved that screening mammography saves lives.

What is the future of breast imaging? I find it hard to believe that we will continue to use mammography to screen up to one quarter of the adult population of the world annually. Mammography is an inherently poor, two-dimensional projectional method being used to diagnose small, three-dimensional cancers. It is least effective in the screening of dense breasts, which, as emphasized in another recent study,[3] are a substantial risk factor for breast cancer. If genetic and other tests can eventually identify women who are at risk for breast cancer, these women could be selectively screened with methods that have higher sensitivity than routine mammography. Which brings us to magnetic resonance imaging (MRI) of the breast.

MRI of the breast does not involve exposure to radiation and has a very high sensitivity, albeit a low specificity. Many studies have confirmed that screening MRI performed in high-risk women diagnoses 4 to 5 occult cancers (those not identified by mammography or palpation) per 100 examinations, whereas routine screening mammography diagnoses 4 to 5 cancers per 1000 examinations. The morphologic characteristics and kinetics after contrast enhancement in MRI involve hundreds of images and data sets, making computer-aided detection indispensable for expeditious assessment. The major problems with MRI of the breast and related magnetic resonance spectroscopy are cost and interpretive expertise. These same problems were involved with the acceptance of mammography as a screening method three decades ago. Here we go again.

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Natural Killer T Cells in Asthma — Toward Increased Understanding

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This issue of the *Journal* contains the second report within about a year on the presence of natural killer T cells in the lungs of patients with asthma. The two reports represent an intersection of two complex entities — asthma, because its pathogenesis is genetically and environmentally heterogeneous, and natural killer T cells, because their functions and mechanisms of action remain unclear. Natural killer T cells make up a unique family of cells with immunoregulatory properties. They express an invariant T-cell receptor that recognizes glycolipids rather than peptides. Natural killer T cells are known to modulate the activity of disease-causing T cells in animal models of type 1 diabetes mellitus and multiple sclerosis[1] and can control the expansion of antigen-specific T cells.[2] Their role in asthma is not known.

During the past few years, investigators studying natural killer T cells in mouse models of allergic airway inflammation — a surrogate for asthma — concluded that these cells may be important in the biology of the murine response[3,4] and have begun to question whether the cells might have a role in the pathogenesis of asthma in humans. Data from the first study in humans, were dramatic: Akbari and colleagues[5] reported that about 60% of the CD4+ T cells in bronchoalveolar-lavage fluid obtained from 14 patients with moderate-to-severe persistent asthma met the criteria for natural killer T cells that also expressed the CD4 molecule. Natural killer T cells usually make up only 0.5 to 1% of peripheral-blood mononuclear cells, although they compensate for this by being able to produce far more of the cytokines interleukin-4 and interferon-γ than do conventional CD4+ and CD8+ T cells. Natural killer T cells act quickly, releasing cytokines within half an hour after activation by high-avidity antigens such as the synthetic glycolipid α-galactosylceramide. Activated natural killer T cells have potent and far-reaching effects on other immune cells; they trigger a cascade of chemokine and cytokine release, enhance natural killer cell function, and promote the maturation of dendritic cells and