

Are We Ready for Dedicated Breast Imaging Approaches?

Breast cancer is the most common non-skin cancer and the second leading cause of mortality in women, accounting for an estimated 40,000 deaths per year in the United States (1). Early detection has been one of the keys to recent declines in breast cancer mortality. Thus far only mammography has been established as an effective tool for breast cancer screening and for reducing deaths resulting from breast cancer (2). However, the limitations of mammography (e.g., reduced accuracy in younger women or women with dense breasts) have led to a search for new approaches to breast cancer imaging. Newer breast imaging modalities include ultrasound, MRI, and radiotracer methods using both single-photon and positron-emitting radiopharmaceuticals. These imaging approaches have been tested mainly as adjuncts to mammography. They may help to characterize suspicious lesions detected by mammography or physical examination, to direct tissue sampling, or to determine the extent of disease in the breast once a cancer has been diagnosed. Thus far only ultrasound has become part of routine clinical practice (3). However, MRI is rapidly emerging as an important clinical tool, especially for determining the extent of disease in the breast (4). None of these newer breast imaging methods has been established as a method of breast cancer screening. Trials of ultrasound and MRI in women who are asymptomatic and at high risk are underway.

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The ability to exploit biochemical differences between breast cancers and normal breast tissue makes radiotracer imaging an attractive complement to anatomically based breast cancer imaging. Radiotracer breast cancer imaging has been tested using a variety of radiopharmaceuticals. The largest clinical experience to date lies with ^{18}F -FDG for PET imaging and $^{99\text{m}}\text{Tc}$ -sestamibi (MIBI) or related compounds for single-photon imaging. These tracers have high uptake in most invasive breast cancers and low background uptake in most nonmalignant tissues, including the normal breast. This underlies their expanding use in breast cancer staging (i.e., determining the extent of disease outside the breast) and in monitoring breast cancer response to treatment (5,6). Although early studies (7–10) were promising, radiotracer imaging has seen only limited clinical use for primary breast cancer detection. This is in large part because subsequent experience showed limited sensitivity for smaller or nonpalpable breast cancers, the cancers most important to detect to reduce breast cancer mortality (11–14). The hypothesis that reduced sensitivity for smaller breast lesions results from the limitations of general-purpose radiotracer imaging devices spurred the development of dedicated breast imaging approaches. Devices more tailored to breast imaging might be able to improve spatial resolution without sacrifices in count sensitivity and might also be able to eliminate the image-degrading effects of high tracer uptake in some nearby background tissues, such as the heart and the liver.

The preliminary results presented in this issue of *The Journal of Nuclear Medicine* by Tornai et al. (15) demonstrate how dedicated breast imaging

approaches might be able to improve detection of breast lesions. Using limited-angle pinhole SPECT and adaptation of existing imaging equipment in a technique termed “PICO-SPECT,” the authors achieved higher image contrast for small lesions and were able to visualize lesions not seen on planar $^{99\text{m}}\text{Tc}$ phantom imaging studies. A single patient imaging study showed higher contrast and more spatial detail of the tumor tracer uptake with PICO-SPECT than with planar imaging. There were some limitations to the approach. For example, the tomographic phantom image shown appears to have less uniformity in normal breast background than corresponding planar images. Also, although the images presented suggest improvements for PICO-SPECT over planar imaging, anecdotal images alone do not prove the superiority of one approach to another. Future studies should include quantitative analyses of the relevant task performance determined from repeated studies and accounting for true noise and object variability (16). The relative performances of PICO-SPECT and planar imaging for lesion detection can be assessed quantitatively, although, as the authors point out, the planar and SPECT imaging modalities are only semiquantitative. Overall, however, this study demonstrates the potential of dedicated breast imaging methods to detect smaller lesions when they have sufficiently higher uptake than the surrounding normal breast and illustrates a successful and necessary first step in the development of a new imaging approach. Other promising approaches for both PET and SPECT breast instrumentation were highlighted in a recent Workshop on the Nuclear Radiology of Breast Cancer held in conjunction with the 2002 Institute of Electrical

and Electronics Engineers Medical Imaging Conference (Norfolk, VA).

There are several reasons to believe, however, that the limited sensitivity of FDG and MIBI imaging in detecting early breast cancer is not simply the result of limitations in instrumentation. Studies in several laboratories, including ours, have shown that the uptake of both FDG and MIBI tends to be higher in breast tumors exhibiting more aggressive features, including higher nuclear grade, higher indices of proliferation, greater microvessel density, and higher tumor blood flow (13,17–20). On the other hand, early, nonpalpable breast lesions may have more indolent, less aggressive features than lesions that are larger at the time of detection (21). Some early forms of breast cancer, such as ductal carcinoma in situ, have been shown, even when large, to have lower FDG and MIBI uptake than more invasive cancers (13,19,22). This suggests that the failure to detect smaller lesions by FDG and MIBI may be the result, in part, of a mismatch between these tracers and early breast cancer biology. In other words, reduced FDG and MIBI sensitivity for early breast cancers may not be remedied fully by improved instrumentation. An examination of several of the large studies of MIBI and FDG primary breast tumor detection supports this concept. In the North American study of MIBI imaging (12), sensitivity was better for nonpalpable lesions >1 cm than for those <1 cm (74% and 48%, respectively) but was still not adequate for most clinical primary breast cancer detection tasks. The studies of FDG primary breast tumor imaging by Avril et al. (13) showed similar results and very low uptake in certain histologic subtypes, for example, invasive lobular carcinoma. Studies in our center have shown low FDG uptake in low-grade invasive lobular carcinoma, even when the disease is locally advanced (T3 or greater tumors) (20).

Radiotracer imaging of cancer works best when it takes advantage of its ability to image tumor biology. Radiotracer imaging already plays an im-

portant role in the management of more advanced breast cancer, in which existing tracers match the biology of the disease. The use of radiotracer imaging to help direct breast cancer treatment is likely to expand as therapy becomes more targeted and as we continue to develop and use tracers to characterize biologic features that are therapeutic targets for individual patients with breast cancer. These applications generally do not require specialized imaging instrumentation. To better detect early primary breast cancer lesions, we will need a more detailed understanding of early molecular events in breast cancer oncogenesis, accompanied by the development of radiopharmaceuticals designed to match the biology of early breast cancer. These tasks are equally if not more daunting than the development of improved instrumentation for radiotracer breast imaging. To have an impact on early breast cancer detection, radiotracer breast imaging will require the combined efforts of tumor biologists, radiopharmaceutical chemists, and instrumentation physicists. The studies of Tornai et al. (15) represent a promising effort on the physics front. Similar successes in biology and chemistry are necessary before radiotracer imaging will gain widespread clinical use in early breast cancer detection.

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