Nuclear imaging of the breast: Translating achievements in instrumentation into clinical use

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Approaches to imaging the breast with nuclear medicine and/or molecular imaging methods have been under investigation since the late 1980s when a technique called scintimammography was first introduced. This review charts the progress of nuclear imaging of the breast over the last 20 years, covering the development of newer techniques such as breast specific gamma imaging, molecular breast imaging, and positron emission mammography. Key issues critical to the adoption of these technologies in the clinical environment are discussed, including the current status of clinical studies, the efforts at reducing the radiation dose from procedures associated with these technologies, and the relevant radiopharmaceuticals that are available or under development. The necessary steps required to move these technologies from bench to bedside are also discussed. © *2013 American Association of Physicists in Medicine*. [http://dx.doi.org/10.1118/1.4802733]

I. INTRODUCTION

Approaches to imaging the breast with nuclear medicine and/or molecular imaging methods have been under investigation since the late 1980s when a technique called scintimammography was first introduced. Nuclear medicine procedures, which detect the preferential uptake of a radiotracer in breast lesions, have the potential to offer valuable functional information that complements conventional anatomical imaging techniques such as mammography and ultrasound. By imaging the biochemical behavior of breast tissue, it was hoped that these techniques could offer improved detection and characterization of breast lesions.

Despite initial enthusiasm for scintimammography and the development of subsequent technologies over the last 20 years, nuclear medicine techniques are only recently finding their niche within the breast imaging community. This slow acceptance is likely attributable to multiple factors, but fundamentally hinges on the relatively poor spatial resolution of conventional Anger gamma cameras and positron emission tomography (PET) scanners that impedes their ability to reliably detect subcentimeter lesions in the breast. Without the ability to detect small lesions indicative of early stage disease, a breast imaging technique has limited clinical utility. The higher radiation burden associated with nuclear medicine procedures, which deliver a systemic dose to the body, relative to mammography is also an important concern, particularly if nuclear medicine tests are considered for use in the screening setting.[1,2] Additionally, previously proposed clinical indications for nuclear breast imaging technologies, such as problem solving of an equivocal mammogram or as an alternative to biopsy, have often been unwise, unclear, or lacking in sufficient evidence to support them.

Key changes in the field of nuclear imaging in recent years warrant a re-evaluation of the role of nuclear medicine in imaging breast cancer. There has been an emergence of several types of dedicated nuclear breast imaging systems (now often referred to as molecular breast imaging systems) that are optimized for breast imaging and offer substantially improved spatial resolution over conventional systems used for whole body SPECT or PET. The collection of dedicated systems currently in clinical use and under development includes a variety of detector designs for both single-photon and coincidence detection systems that are capable of detecting small breast tumors with high sensitivity. These improvements in instrumentation have in turn enabled lower administered doses of radiation to be used, such that the radiation risk from nuclear medicine breast procedures is approaching a level comparable to the extremely low risks associated with radiation exposure from mammography.

Recent clinical studies have demonstrated potential roles of nuclear methods in detecting breast disease that is occult on mammography,[3] in providing a useful evaluation of both the ipsilateral and contralateral breast in the preoperative setting[4–6] and in monitoring the response to neoadjuvant (primary) chemotherapy.[7] These encouraging findings have led to a shift in thinking about nuclear medicine in breast imaging, and dedicated techniques are gradually becoming recognized as valid and beneficial tests for certain subsets of patients that are not served well by currently available modalities.

The purpose of this paper is to review recent developments in dedicated nuclear medicine instrumentation and discuss their potential clinical roles in the diagnosis and management of breast cancer. We also address some of the obstacles that have been encountered during the introduction of a new breast imaging modality into clinical practice and suggest strategies for success.

II. EARLY DEVELOPMENT OF NUCLEAR BREAST IMAGING

Like many scientific developments, the notion of imaging breast cancer with nuclear medicine began as an unanticipated

finding. During the 1970s and the following two decades, a number of radiopharmaceuticals developed for purposes other than tumor imaging were observed to localize in breast disease.[8]

As early as 1973, the bone imaging agent technetium-99m diphosphonate (^{99m}Tc-MDP) was reported to localize in breast tumors of patients having bone scans performed for metastatic evaluation.[9] The perfusion imaging agent thallium-201, developed for nuclear cardiology studies, was also found to concentrate in breast tumors as first reported in 1978.[10] ^{201}Tl was subsequently evaluated in investigations of breast scintigraphy over the next several years until the introduction of a new perfusion agent ^{99m}Tc-methoxyisobutylisonitrile, also known as ^{99m}Tc-sestamibi. The benefits of ^{99m}Tc-sestamibi over ^{201}Tl included shorter half-life (6 h vs 73 h), better radiation dosimetry characteristics, and easier preparation (generator-produced vs cyclotron-produced).[11] Shortly after ^{99m}Tc-sestamibi's effective replacement of ^{201}Tl in nuclear cardiology, it was noted that sestamibi also localized in several types of tumors, primarily parathyroid adenomas, lung cancer, and breast cancer. The first report of avid ^{99m}Tc-sestamibi uptake in breast cancer is by Aktolun et al. in 1992.[12] ^{99m}Tc-tetrofosmin, with properties very similar to ^{99m}Tc-sestamibi, was another technetium-labeled radiopharmaceutical developed for perfusion imaging reported to have avid uptake in breast tumors.[13]

These serendipitous discoveries of radiopharmaceutical uptake in breast cancer led to the development of scintimammography, the name given to nuclear medicine breast imaging performed with scintillating gamma cameras. The gamma cameras utilized for scintimammography were the same large field-of-view conventional gamma cameras used for nuclear cardiology and general nuclear medicine imaging. Both planar and single photon emission computed tomography (SPECT) scintimammographic methods with several options for radiopharmaceuticals were heavily investigated throughout the 1990s.[8,14]

A meta-analysis of scintimammography literature performed prior to 1999 reported an aggregate sensitivity of 85% and specificity of 86% for the technique.[14] However, when analysis was limited to only nonpalpable masses, aggregate sensitivity dropped to 67%.[14] Several large multicenter trials were conducted to evaluate the diagnostic accuracy of ^{99m}Tc-sestamibi planar scintimammography by enrolling women with known breast masses who were scheduled to undergo excisional biopsy or surgery. These trials reported overall sensitivities between 71%–93% and specificities between 69%–87%.[15–17] The sensitivity of scintimammography was substantially lower when only nonpalpable masses were considered: sensitivity for nonpalpable masses was 61% in the trial by Khalkhali et al.[15] and 30% in the trial by Palmedo et al.[16]

The overall conclusion from examination of the numerous studies performed was that scintimammography was not able to provide reliable detection of nonpalpable, small breast tumors.[8,18] This decreased sensitivity for small breast tumors was attributed to the limited resolving power of conventional gamma cameras.[14] At the time, investigators also suspected that ^{99m}Tc-sestamibi had poor uptake in some breast cancers.[19,20]

The primary limitation of conventional gamma cameras for breast imaging is their inability to be easily positioned close to the breast. Conventional gamma camera detectors comprise a large single crystal of sodium iodide (NaI) coupled to an array of photomultiplier tubes (PMTs). Edge effects caused by reflecting scintillation photons at the border of the crystal result in an area of about 7–9 cm at the crystal edge that is unusable for imaging or "dead space." Due to this large dead space at the edge of the detector, the breast cannot be imaged if positioned directly on the detector as in mammography. Anterior views of the breasts could be performed but are limited by activity in the chest and abdomen that is 2–3 orders of magnitude greater than breast activity. Hence, scintimammography was typically performed with the patient prone and with the camera positioned laterally, a technique pioneered by Khalkhali et al. to improve separation of the breast from the chest and abdomen.[21,22] Even with this positioning, the distance between the gamma camera and the pendant, uncompressed breast during planar scintimammography was ∼5 cm. As the average thickness of the pendant breast is ∼16 cm,[23] a tumor in the middle of the breast could be 10–15 cm from the collimator face. Conventional gamma cameras equipped with high resolution collimators typically achieve spatial resolutions of 10–15 mm at this distance. Partial volume effects will diminish the apparent intensity of lesions below this spatial resolution, making their detection difficult.

It was hoped that the use of SPECT rather than planar imaging could improve the sensitivity of scintimammography for small breast tumors. While some studies demonstrated SPECT to offer improved sensitivity and specificity over planar methods,[24–28] others demonstrated similar or better sensitivity with the planar technique.[29,30] Some studies recommended that planar and SPECT imaging in combination would yield the highest sensitivity.[27,29] Like the planar studies examined previously, the studies evaluating SPECT tended to include few patients with small (≤10 mm) lesions and in that subgroup, both methods showed limited sensitivity. The exception to these findings was work by Spanu et al. that demonstrated SPECT with ^{99m}Tc-tetrofosmin to be significantly better than planar scintimammography at detecting sub-cm lesions; in one study SPECT sensitivity for cancers ≤10 mm was 91% versus 45% for planar imaging ($p < 0.0005$), and in another study SPECT sensitivity for T1b cancers (>5 mm but ≤10 mm) was 95% versus 49% for planar ($p < 0.0005$).[24,25]

In addition to the single photon emitting radiopharmaceuticals used for scintimammography, the positron emitter ^{18}F-fluorodeoxyglucose (FDG) as imaged by PET accumulates in both primary breast cancer and metastatic disease. While the spatial resolution of PET is superior to that of conventional gamma cameras, current clinical PET scanners only achieve ∼4–6 mm resolution. Thus, unless uptake in the lesion is very high compared to surrounding tissues, many small, clinically relevant breast lesions are at the limit of detection of current whole body PET/CT systems. In a review of breast cancer

detection with FDG PET, small tumor size (<10 mm) and low tumor grade were significant predictors of a false-negative FDG PET result.[31] Currently, there is widespread agreement that whole-body FDG PET does not have a clinical role in detecting primary breast cancer, nor is it an alternative to histologic sampling to establish or exclude malignancy.[32, 33]

The inability of the nuclear medicine techniques discussed above to detect small breast tumors considerably limited their clinical value, especially in a field that was moving toward adoption of highly sophisticated, high resolution techniques such as breast magnetic resonance imaging. As a result, breast imaging with nuclear medicine was largely abandoned by the late 1990s. At the same time, however, researchers were just beginning to explore the potential of new dedicated nuclear systems to offer improved detection of small breast lesions.[34]

III. DEDICATED NUCLEAR MEDICINE IMAGING SYSTEMS

III.A. Single-photon gamma cameras

Over the last 15 years, several types of compact gamma camera systems have been developed for a variety of dedicated detection tasks, with breast imaging being perhaps the most widely used clinical application. Breast-dedicated gamma detectors have the ability to provide substantially improved spatial resolution compared to conventional gamma cameras due to several factors: use of pixelated arrays of small detector elements; coupling of the detector elements to electronics with better spatial discrimination; isolation of the breast from nearby organs with avid radiopharmaceutical uptake; and reduction in the lesion-to-detector distance through direct contact with the breast and application of mild breast compression.

Early dedicated detectors replaced the single NaI scintillating crystal of conventional gamma cameras with pixelated arrays of cesium iodide (CsI) or NaI coupled to position-sensitive photomultiplier tubes (PSPMTs).[35–40] Other designs have comprised multi-crystal arrays of CsI coupled to solid-state silicon photodiodes.[41–43] Small multicrystal gamma cameras have typically been constructed with arrays of individual crystals ~2 or 3 mm in size, in order to optimize detector efficiency and light collection. Loss of light at the sides of the small scintillating crystals can result in average energy resolutions in the range of 12%–17% (of 140 keV photopeak), which is poorer than conventional Anger gamma cameras,[44–46] and results in decreased contrast due to the increased scatter content of events recorded in the energy window.

An alternative to the multicrystal design is a completely solid-state detector that utilizes semiconductor materials such as cadmium zinc telluride (CZT), which can provide better energy resolution and smaller pixel sizes.[47,48] Energy resolution of dedicated CZT detectors is currently in the 4%–6% range.[48,49] In theory, better energy discrimination should provide better ability to separate photopeak (unscattered) and Compton scattered counts and therefore provide better tumor contrast. However, phantom studies and simulations of CZT-
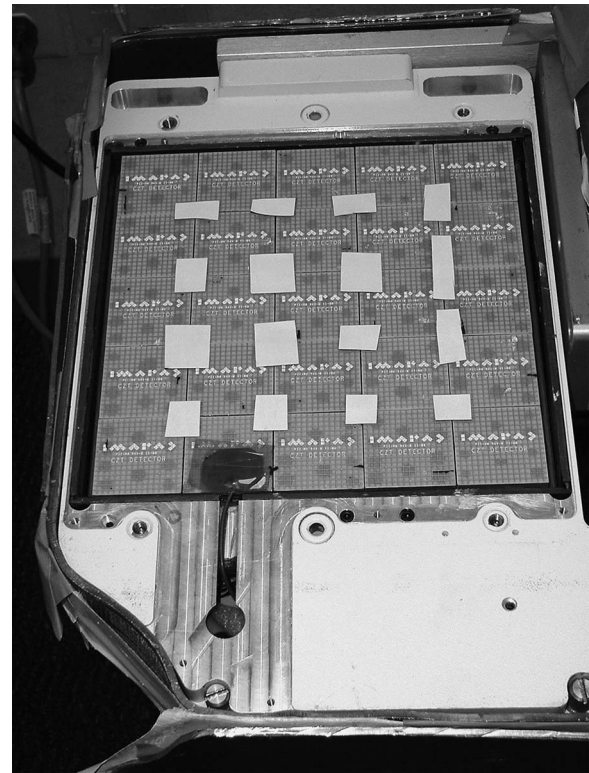

FIG. 1. A cadmium zinc telluride (CZT)-based detector. Collimator and cover plate have been removed to show the 5 × 5 array of CZT modules giving a 20 × 20 cm imaging detector. Each CZT module comprises 16 × 16 array of 2.5 × 2.5 mm pixels.

based gamma cameras have suggested that the proportion of scattered counts in dedicated breast images, in which the breast is largely isolated from the chest, is relatively low.[49,50] Therefore, improvements in energy resolution below about 10% may be a less important factor in determining lesion detection than other factors such as spatial resolution and count sensitivity.

Pixel size in CZT detectors is determined by the placement of electrodes on the material and the design of the application specific integrated circuit card coupled to them. Current CZT detectors are composed of arrays of detector modules (Fig. 1), with each module containing a 16 × 16 array of individual pixels. Current systems have pixel sizes of 1.6 and 2.5 mm, with the possibility of even smaller pixel sizes in the future.[51] The major disadvantage of CZT is that it is still relatively new and substantially more expensive to manufacture compared to NaI and CsI. The development of CZT-based gamma cameras is primarily being driven by the needs of the nuclear cardiology market where the use of unique CZT-based detector designs permits a factor of 3–4 reduction in either imaging time or administered dose of radiopharmaceutical.[52] This new need for CZT in the clinical environment is likely to accelerate its large scale production, which will eventually result in lower costs of the material.

With appropriate collimation, both multicrystal and semiconductor-based gamma cameras are capable of providing a factor of ~2 gain in spatial resolution compared to conventional gamma cameras at distances considered
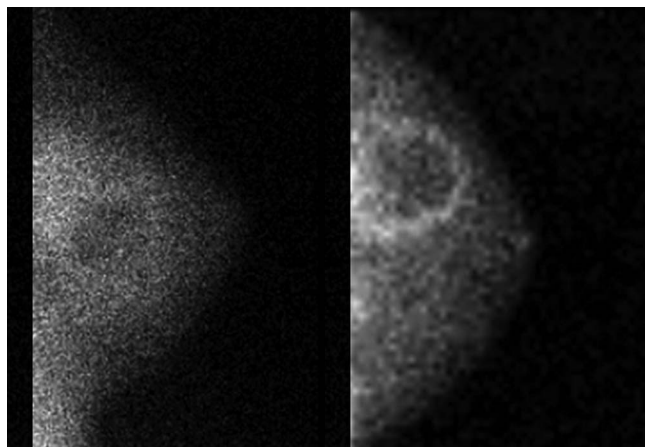
FIG. 2. Lateral view of a benign breast cyst with inflammation. Images were acquired using a conventional gamma camera (scintimammography) (left) and a dedicated breast imaging gamma camera (right).

the "near-field," that is within ∼6 cm from the collimator face.[48,53] While this improvement is of little benefit in conventional nuclear medicine imaging of the body, improved spatial resolution in the near-field has a major impact on image quality in breast imaging, where the breast is in close proximity or in contact with the detector.

Further gains in spatial resolution are realized with dedicated detectors simply because of optimized breast positioning. Dead space at the detector edge of a dedicated detector is only about 5–8 mm, reduced from the 70–90 mm dead space of conventional systems. The compact size and minimal dead space allows the breast to be positioned directly on the camera in geometries similar to those used for mammography (e.g., craniocaudal [CC] and mediolateral oblique [MLO] views). Acquisition of these standard projections has been suggested to increase familiarity and make the study easier to read.[54] Mild breast compression is also possible and is recommended to prevent motion and to further reduce distance between breast lesions and the detector. One study demonstrated that applying mild compression can reduce breast thickness from ∼16 cm for a pendant breast to ∼6 cm for a lightly compressed breast.[23] Because spatial resolution of nuclear medicine detectors degrades with distance from the collimator face, bringing the lesion as close as possible to the camera is essential in improving lesion detection.[34] Figure 2 shows a direct comparison between images acquired using a dedicated CZT detector and a conventional gamma camera (scintimammography) in the same patient.

A number of names have been used to refer to the method of breast imaging with dedicated gamma camera systems, including high resolution scintimammography, single photon emission mammography (SPEM), breast specific gamma imaging (BSGI), molecular breast imaging (MBI), and others. The assignment of a unique name by each research team evaluating a particular technology has created some confusion within and outside of this field of study. The term "scintimammography" was firmly associated with the conventional technique of the 1990s that had unfortunately obtained a poor reputation in breast imaging. Thus, proponents of dedicated systems sought to distinguish the new compact cameras from scintimammography performed with conventional systems. Furthermore, the new semiconductor-based detectors no longer relied on a scintillating crystal detector so the term "scinti" mammography was actually inaccurate.

FIG. 3. Dilon 6800 gamma camera for breast specific gamma imaging (BSGI). (courtesy of Dilon Diagnostics)

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In recent years, developers of breast-dedicated nuclear medicine systems have begun to embrace "molecular breast imaging" or MBI as a collective term to describe compact detectors utilizing either single-photon- or positron-emitting (described next) radiopharmaceuticals. Although several dedicated gamma camera systems are actively undergoing development in the research setting, today three different types of single-photon MBI systems exist in the commercial market.

The dedicated system with the longest history of commercial use is the Dilon 6800 (Dilon Diagnostics, Newport News, VA), most commonly referred to as a breast specific gamma imaging (BSGI) system. The original BSGI system employs a single gamma camera with a 20 × 15 cm field of view (FOV) containing an array of NaI crystals (3 × 3 mm pixel size) coupled to an array of position sensitive photomultiplier tubes (PSPMTs). An initial report from a patient study conducted on this system showed the BSGI system to offer improved detection of smaller and nonpalpable lesions compared to scintimammography performed on a conventional gamma camera.[19] The latest generation BSGI system, the Dilon 6800 Acella (Fig. 3), employs CsI crystals (3.2 × 3.2 mm pixel size) coupled to solid-state photodiodes and has a larger FOV of 25 × 20 cm.

Two dedicated CZT-based detectors for MBI are commercially available: Discovery NM750b (GE Healthcare, Milwaukee, WI) [Fig. 4(a)] and LumaGem 3200s (Gamma Medica, Inc., Northridge, CA) [Fig. 4(b)]. Both of these
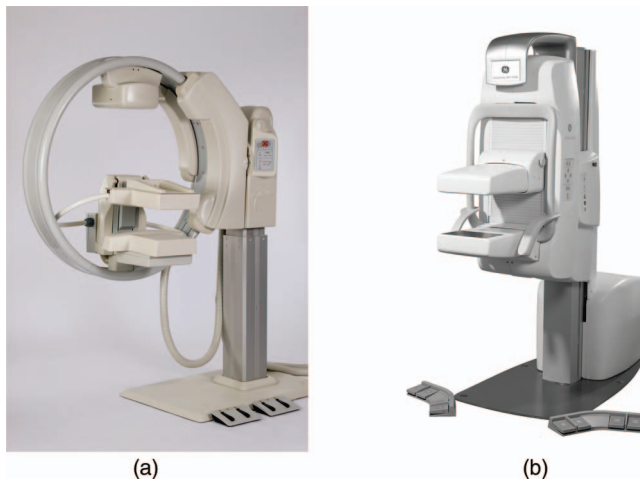
FIG. 4. (a) Gamma Medica Lumagem 3200s system (courtesy of Gamma Medica, Inc.). (b) GE Discovery NM750b system (courtesy of GE Healthcare).

systems employ two opposing CZT detectors in a dual-head configuration, where the breast is positioned between the two detectors. The current Discovery NM 750b has 2.5 mm-pixels and a FOV of 24×16 cm (recently changed from 20×20 cm). The LumaGem has 1.6 mm-pixels and 20×16 cm FOV. Manufacturers of these dedicated systems have recognized the need to increase detector FOV to accommodate larger breasts and in particular to increase detector width such that both the axilla and intramammary fold can be visualized in the MLO position.

While a dual-head configuration is more expensive than a single head system, this arrangement has the advantage of ensuring that a breast lesion can never be more than $\frac{1}{2}$ the breast thickness from either detector. Use of a dual-head CZT-based design was shown to improve sensitivity for the detection of small breast tumors (≤ 10 mm), particularly those located in the upper inner quadrant of the breast, compared to a single CZT detector: sensitivity was 82% for dual-head versus 68% for single head gamma imaging, $p = 0.004$.[55] Work conducted with phantoms on multicrystal NaI-PSPMT cameras has also advocated for the use of a dual-head configuration to improve lesion detection.[38,56–59]

Besides improving lesion detection, the dual-detector configuration also allows a specialized method for quantitative analysis of tumor uptake to be performed.[60] Both adipose and fibroglandular breast tissue have similar attenuation coefficients at energies of 140 keV. As breast thickness can be readily measured, an absolute estimate can be made of activity in a breast lesion and adjacent normal tissue. As these technologies become better integrated into breast imaging practices, the ability to quantitate tumor uptake may be of particular benefit for certain applications such as monitoring tumor response to neoadjuvant chemotherapy.

III.B. Coincidence detection systems

Just as compact gamma cameras were developed to overcome limitations of conventional scintimammography, sev-

eral compact breast-specific PET systems were concurrently designed to overcome limitations of conventional PET scanners. The introduction of a positron emission mammography (PEM) system was initially met with some skepticism. At the time, only a small number of facilities were offering PET imaging as radiopharmaceutical production of FDG and required personnel were considered too expensive for routine use.[61] Historically, enthusiasm for organ-specific PET devices, such as those specifically created for brain PET, has been low.[62] However, PET has become widely incorporated into clinical practice at major medical centers during the last decade, FDG is now readily available, and dedicated equipment optimized for the breast is expected of breast imaging technologies.

The primary advantage of a breast-dedicated design over conventional PET scanners is substantially improved spatial resolution. Coincidence detectors operate by detecting two 511 keV gamma rays emitted during positron annihilation. To perform reconstruction, it must be assumed that the gamma rays travel in opposite directions 180° apart, which is not always the case if the positron is not entirely at rest when annihilation with an electron occurs. Compared to conventional PET scanners, made up of a ring of detectors about 1 m in diameter, a PEM system with two detectors in direct contact with the breast will have much smaller detector separation (the ~5–6 cm thickness of a lightly compressed breast) and will be less prone to blurring due to angular noncolinearity of the emitted gamma rays. The use of smaller crystals in dedicated devices compared to conventional PET also aids in improved spatial resolution.

In 1994, Thompson et al. provided the earliest proposal of a PEM system by simulating two flat detector arrays of bismuth germinate (BGO) operating in coincidence that could be incorporated within a conventional mammography unit.[61] Experiments of their proposed design suggested that a PEM device could theoretically achieve 2 mm spatial resolution (compared to 4–6 mm in-plane resolution of a conventional PET scanner).[63] Because the compact detector design would subtend a larger solid angle of the emitted gamma rays, this PEM design was expected to achieve approximately 100 times the count sensitivity of conventional PET.[64] The first evaluation of PEM in patients, using this BGO detector as an accessory to a mammography unit, was reported in 1996.[65]

By imaging only the breast rather than the entire chest (as with whole-body PET), the proportion of scattered events is low and tissue attenuation is so minimal that attenuation correction is simple or may not even be required.[61,66] An additional advantage of PEM over dedicated gamma cameras described above was the ability to reconstruct either limited-angle or tomographic 3D slices of the breast rather than only single-projection planar images.

Since that initial feasibility study, numerous other breast-specific PET designs were proposed with arrays of high density scintillating detectors coupled to PSPMTs or more recently, semiconductor photodiodes. The scintillators most commonly used include BGO, lutetium oxyorthosilicate (LSO), lutetium gadolinium oxyorthosilicate (LGSO), and lutetium yttrium oxyorthosilicate (LYSO), but CsI, NaI, and

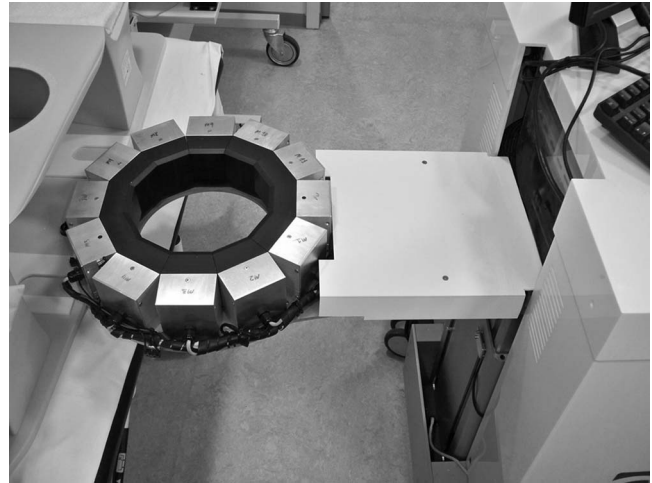FIG. 5.   Naviscan PEM-FLEX Solo II system (courtesy of Naviscan).

FIG. 6.   Oncovision Mammi-PEM system. Cover has been removed to show the 12 detector modules in a ring geometry (courtesy of Oncovision).

CZT have also been proposed.[66–74] These reports have described primarily two types of designs: either two flat detectors placed on opposite sides of the breast that mimic mammographic positioning (typically referred to as PEM systems), or a small ring of detectors within which the breast hangs pendant (often referred to as a dedicated breast PET [DbPET] design). Results from simulations comparing PEM and DbPET designs demonstrated that both offered substantially better lesion visualization than whole-body PET, but showed pros and cons of each type of design.[67] The two detector PEM design offered lower noise, but the DbPET ring design offered better contrast and signal-to-noise ratios. A recognized practical advantage of the PEM design is its flexibility in positioning that can accommodate various breast sizes and provide better visualization of the axilla and lesions near the chest wall.

The first PEM system to become commercially available was the PEM-FLEX (Naviscan Corporation, San Diego, CA). The PEM-FLEX comprises two opposing detectors that are contained within transparent compression plates (Fig. 5). Analogous to mammographic positioning, the patient's breast is placed between the two plates, although only mild compression is applied. The two detectors are both long, narrow configurations of LYSO crystals (dimensions of $2 \times 2 \times 13$ mm) that move in unison across the paddles to scan the entire 24×16.4 cm FOV. Limited-angle tomosynthetic reconstruction is performed to generate 3D slices. Performance evaluations of the PEM-FLEX demonstrated an in-plane spatial resolution of 1.8–2.4 mm, depending on the reconstruction mode used.[75,76] Resolution between planes is degraded due to the limited angle tomography and ranges from 6 to 9 mm.[76] No attenuation correction is applied with this system.

The Mammi-PEM (Oncovision, Valencia, Spain), which is a true tomographic DbPET system, achieved CE certification in Europe in early 2011 and is commercially available. The Mammi-PEM (Fig. 6) comprises a ring of 12 detectors, each with 40×40 mm monolithic crystals of LYSO coupled to PSPMTs. In place of small individual crystals, this design opted for larger crystals to improve count sensitivity and relies on the PSPMT and Anger like electronics to calculate the location of the light pulse within each crystal. Reported intrinsic spatial resolution of the Mammi-PEM is 1.6 mm.[77] For imaging, the patient lies prone on an imaging table and a breast hangs pendant through a table opening into the unit positioned directly beneath. Using an injected dose of ~65 MBq (1.8 mCi) ^{18}F-FDG, a full 3D tomographic dataset can be acquired of each breast in ~5 min, with a resolution of ~2 mm that is relatively isotropic.[78] The system incorporates a calculated (rather than measured) attenuation correction method.[79]

In addition to these commercial systems, there is a substantial amount of research activity focused on improving PEM and DbPET imaging technology. Several types of systems are currently under development by research groups around the world, including University of California-Davis,[80,81] Lawrence Berkeley National Laboratory,[82] Brookhaven National Laboratory,[83] Stanford University,[84] Duke University,[85] Thomas Jefferson National Accelerator Facility and West Virginia University,[86,87] MD Anderson,[88] University of Pisa,[89] the Crystal Clear Collaboration at CERN,[90–92] and Shimadzu Corporation.[93] The developers of these systems are beginning to collect initial patient data and rapidly moving toward clinical trials.

The Clear-PEM design under development by the Crystal Clear Collaboration, is a hybrid type of PEM design in that it comprises two parallel detectors on opposite sides of the breast, but, with the patient lying prone, the detectors can

rotate around the breast during acquisition to allow tomographic reconstruction.[91] The Clear-PEM detector uses LYSO crystals that are coupled to multipixel avalanche photodiodes. By using 2 photodiodes per crystal in the Clear-PEM, a double readout of emitted light is performed, which in turn enables a depth of interaction (DOI) calculation to be done. Using DOI, the Clear-PEM has reported spatial resolution of 1.4 mm at the center of its field of view.[92]

One system that is unique in design compared to other DbPET systems is the C-Shaped detector by Shimadzu that is a partial ring of 4096 LGSO crystals over a 300° arc. The patient is positioned semiprone into the C-shaped ring and a tomographic data set is acquired. The system is expected to achieve a spatial resolution of <1.5 mm.[94] Recent work has shown the clinical feasibility of this system.[95]
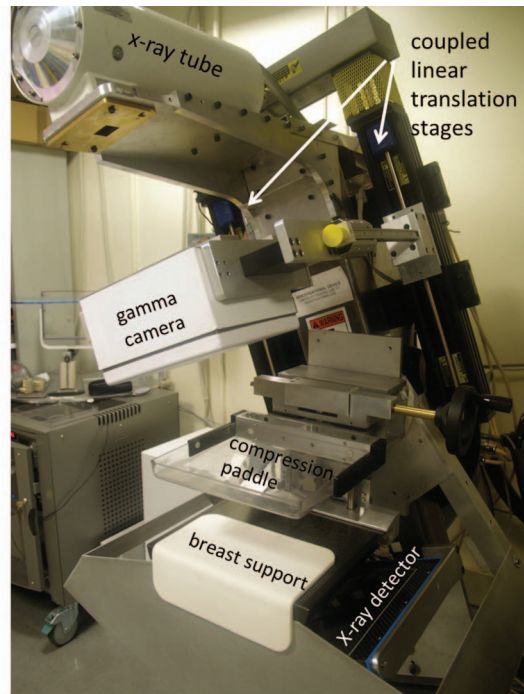
III.C. Multimodality systems

One of the enduring messages learned from the development of PET over the last decade is that fused anatomical and functional information obtained using a combined PET/CT device is more accurate in evaluating patients with known or suspected malignancy than either PET or CT alone or PET and CT acquired separately but interpreted together.[96,97] Translation of that message into breast imaging has spurred the development of multimodality systems capable of providing both anatomical and functional information in a single examination.

As previously mentioned, early developers of breast-dedicated gamma cameras and coincidence detection systems intended for nuclear imaging to be incorporated as an accessory to mammography, rather than an independent device, to allow easy coregistration of anatomical and functional data. This was the case for the initial PEM designs[61,98–100] and for the original Gamma Medica LumaGem MBI detector.[101]

In the breast, coregistration of anatomy and function may be more important than in other organs because breast tissue is so deformable, with few anatomical landmarks. The three most-widely used breast imaging modalities use completely different positioning techniques: the patient is upright with breast tissue compressed during mammography, the patient is supine with breast tissue flat against chest wall during ultrasound, and the patient is prone with breasts hanging pendant during MRI. Even breast radiologists who are accustomed to correlating modalities often find that positioning differences make it difficult to correctly identify the same lesion(s) across modalities.

Researchers at the University of Virginia have worked on the development and evaluation of a hybrid system called dual-modality breast tomosynthesis (DMT) that combines digital x-ray tomosynthesis and limited-angle SPECT.[102,103] The system comprises a small 15 × 20 cm dedicated NaI gamma camera and a mammography system mounted on a tomosynthesis gantry [Fig. 7(a)]. The x-ray tube, x-ray detector, and gamma camera rotate ± 20° around a common axis, producing coregistered x-ray and gamma ray images in three dimensions. A prospective pilot study in 17 patients demonstrated the feasibility of this approach and suggested that the

(a)

(b)

FIG. 7. Multimodality single-photon systems. (a) Dual-modality breast tomosynthesis (DMT) system combining digital x-ray tomosynthesis and limited-angle SPECT. A small high-resolution gamma camera is mounted on a translation stage attached to the gantry arm. The configuration during gamma imaging is shown here. The camera is positioned anteriorly out of the x-ray beam during x-ray imaging. Image courtesy of Dr. Mark Williams, University of Virginia. (b) Combined SPECT/CT system developed at Duke University. Patient is positioned prone and breast is imaged with a small CZT based detector and CT system. Image courtesy of Dr. Martin Tornai, Duke University Medical Center.

addition of unambiguous correlations between the anatomical and functional information could improve specificity.[103]

A breast-dedicated SPECT/CT system has been developed by researchers at Duke University.[104] This system incorporates a small CZT detector mounted on a gantry that is capable of unique, complex acquisition trajectories [Fig. 7(b)]. Phantom work has demonstrated that these trajectories allow a larger volume of breast tissue to be imaged and permit
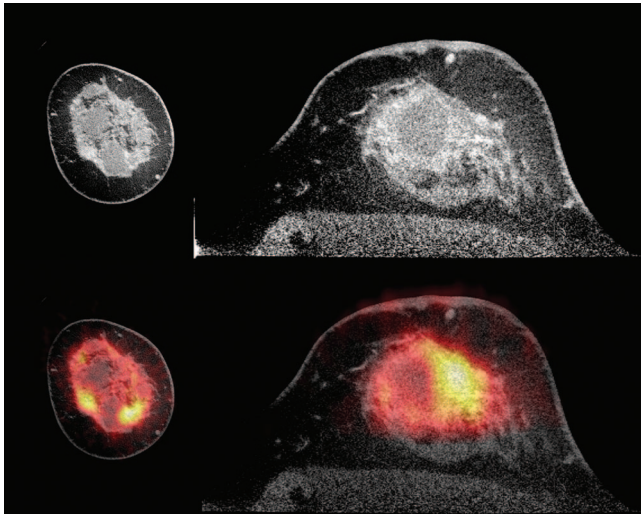
FIG. 8. Images of a patient with an invasive ductal carcinoma with lobular features obtained using a dedicated LYSO PET/CT system. The contrast enhanced CT, shown at top (coronal view at left and axial view at right), has been window to enhance appearance of benign cysts. The fused PET/CT image, at bottom, demonstrates F-18 FDG uptake in the extensive tumor. Image courtesy of Dr. Ramsey Badawi, University of California Davis.

better imaging of breast tissue near the chest wall.[105] Pilot patient data has been reported in patients with this device.[106]

Several of the coincidence detection systems mentioned above are under investigation as multimodality devices. The system developed at University of California-Davis is a combined DbPET/CT system that acquires fully 3D images of the pendant breast using rotating LSO detectors and digital breast CT technology.[80, 81, 107] Figure 8 shows an example of the combined DbPET/CT image of a patient with invasive breast cancer. Researchers at Brookhaven National Laboratory are developing a combined PET/MRI system that uses a DbPET design incorporated into a commercial breast-dedicated MRI system (Aurora Imaging Technology, North Andover, MA).[83] The consortium at CERN that developed the Clear-PEM unit is working on the development of the Clear-PEM-Sonic unit that integrates PEM with an ultrasound system.[108]

IV. CLINICAL EVALUATIONS

IV.A. Establishing diagnostic accuracy

Of the many types of breast-specific detectors described above, few designs have progressed to evaluation with clinical studies. As initially done with conventional scintimammography, the first patient studies to determine clinical performance of dedicated gamma camera systems and PEM systems were conducted in patients with known breast lesions. The primary enrollment criterion was a lesion identified by mammography or clinical exam that was deemed suspicious and scheduled for biopsy. In most studies, the nuclear medicine imaging was performed prior to biopsy and the final surgical pathology findings were used as reference standard to determine the performance of imaging. This type of study design has been heavily utilized to establish baseline values for diagnostic accuracy (sensitivity and specificity) of the techniques and to in-

vestigate the relative advantages and limitations of dedicated nuclear imaging compared to other breast imaging modalities.

The diagnostic accuracy studies performed with independent participants are given in Table I. Although notable differences exist between studies, in general their results demonstrate good sensitivity and specificity for breast cancer with dedicated nuclear medicine systems. In particular, the sensitivity for small breast cancers is respectable and improved for small lesions compared to values previously reported with conventional scintimammography. In the ten studies performed with single photon gamma camera systems in a total of 778 patients, the overall sensitivity was 556 of 605 (92%), the sensitivity for cancers $\leq$10 mm was 199 of 242 (82%), and the specificity was 218 of 294 (74%). In the four studies performed with PEM systems in a total of 130 patients, overall sensitivity was 75 of 86 (87%), sensitivity for cancers $\leq$10 mm was 11 of 15 (73%), and specificity was 53 of 62 (85%).

IV.B. Preoperative evaluation

Accurate evaluation of disease extent is critical for guiding appropriate surgical management of patients diagnosed with breast cancer. The addition of MRI to standard assessment with clinical exam, mammography, and ultrasound is increasingly being incorporated into preoperative planning, but this approach is controversial.[109] Preoperative MRI has been associated with increasing rates of mastectomy over breast conservation therapy,[110, 111] however, to date there is a lack of evidence to demonstrate that use of preoperative MRI can reduce rates of positive margins or local recurrence, or lead to improved survival. Despite this, data from prospective trials have shown that after conventional evaluation, use of preoperative MRI detects additional sites of mammographically-occult cancer in the ipsilateral breast of 7%–12% of women[4, 112] and the contralateral breast of 3%–4% of women.[5, 113] Preoperative measurements of disease extent on MRI have been shown to modestly correlate with pathologic tumor size; reported correlation (r) between tumor size and pathologic size is 0.53–0.81 but a number of studies have noted that MRI measurements tend to over- or underestimate true tumor size.[4, 114–116]

While preoperative MRI has been shown to have very high sensitivity that approaches 100% when combined with mammography and clinical evaluation,[117] its specificity is highly variable, with reported values ranging from 26% to 90%.[4, 5, 118–120] Nuclear medicine techniques have been proposed as useful tests for detection of multifocal, multicentric, or contralateral disease on the basis that they may offer better specificity than MRI, yet still offer better sensitivity than mammography, especially in radiographically dense breasts.

Several studies have been performed to investigate the efficacy of dedicated gamma cameras as an adjunct to conventional diagnostic workup (physical exam, mammography and/or ultrasound) in preoperative evaluation. In patients with newly diagnosed breast cancer, gamma imaging with BSGI identified additional sites of malignancy in 9%–11% of patients, while giving false positive results for additional sites

TABLE I. Findings from independent "diagnostic accuracy" studies of dedicated gamma cameras and PEM in which the primary enrollment criteria for subjects was a suspicious lesion identified by physical exam, mammography, or other imaging.

Author	Year	Camera type	Radio-pharmaceutical	Administered activity (MBq)	Nuclear study interpretation	N	Sensitivity for all cancers[a]	Sensitivity for cancers ≤10 mm[a]	Sensitivity for DCIS[a]	Specificity for benign lesions[a]
De Vincentis (Ref. 35)	1997	Single-head CsI-PSPMT gamma camera	Tc-99m sestamibi	740	Not reported	7	4/4 (100)	3/3 (100)	–	3/3 (100)
Pani (Ref. 44)	1998	Single-head CsI-PSPMT gamma camera	Tc-99m sestamibi	740	Not reported	14	9/11 (82)	5/7 (71)	–	2/3 (67)
Maini (Ref. 211)	1999	Single-head CsI-PSPMT gamma camera	Tc-99m sestamibi	740	Not reported	29	16/19 (84)	6/9 (67)	–	8/10 (80)
Scopinaro (Ref. 23)	1999	Single-head CsI-PSPMT gamma camera	Tc-99m sestamibi	740	Blinded	53	27/31 (87)	13/16 (81)	–	19/22 (86)
Brem (Ref. 19)	2002	Single-head NaI-PSPMT gamma camera	Tc-99m sestamibi	925	Blinded	50	22/28 (79)	10/15 (67)	–	28/30 (93)
O'Connor (Ref. 212)	2007	Single-head CZT gamma camera	Tc-99m sestamibi	740	Access to MG and US findings	99	57/67 (85)	26/35 (74)	8/8 (100)	36/47 (77)
Spanu (Ref. 213)	2007	single-head CZT gamma camera	Tc-99m tetrofosmin	740	Blinded	85	87/90 (97)	28/31 (90)	–	11/12 (92)
Brem (Ref. 214)	2008	Single-head NaI-PSPMT gamma camera	Tc-99m sestamibi	925–1110	In clinical practice, access to available imaging	146	80/83 (96)	17/20 (85)	15/16 (94)	50/84 (60)
Hruska (Ref. 55)	2008	Dual-head CZT gamma camera	Tc-99m sestamibi	740	Blinded	150	115/128 (90)	50/61 (82)	16/17 (94)	42/61 (69)
Spanu (Ref. 215)	2008	Single-head CZT gamma camera	Tc-99m tetrofosmin	740	Blinded	145	139/143 (97)	41/45 (91)	–	19/22 (86)
					Total	**778**	**556/604 (92)**	**199/242 (82)**	**39/41 (95)**	**218/294 (74)**
Murthy (Ref. 216)	2000	Dual-head BGO-PSPMT PEM system	F-18 FDG	75	Access to MG findings	14	8/10 (80)	–	–	4/4 (100)
Levine (Ref. 217)	2003	Dual-head GSO-PSPMT PEM system	F-18 FDG	370	Access to MG findings	16	6/7 (86)	4/4 (100)	2/2 (100)	10/11 (91)
Rosen (Ref. 85)	2005	Dual-head LGSO-PSPMT PEM system	F-18 FDG	74–93	Access to MG findings	23	18/21 (86)	2/3 (67)	2/3 (100)	1/3 (33)
Berg (Ref. 218)	2006	Dual-head LYSO-PSPMT PEM system	F-18 FDG	300–795	Access to MG findings	77	39/42 (93)	5/8 (63)	10/11 (91)	29/35 (83)
					Total	**130**	**75/86 (87)**	**11/15 (73)**	**14/16 (88)**	**53/62 (85)**

Numbers in parentheses are percentages and are rounded.

N = number of analyzable participants. MG = mammography. US = ultrasound. DCIS = ductal carcinoma *in situ*.

[a]Sensitivity and specificity are reported on the per lesion level and some patients had more than one lesion.

in 7%–20% of patients.[6,121,122] In a comparison of BSGI with MRI used in preoperative evaluation, the sensitivities of the two techniques were similar (89% and 92%) but BSGI demonstrated significantly better specificity of 90% compared to 39% for MRI ($p < 0.0001$).[123]

A study performed using a dedicated CZT-based MBI system and ^{99m}Tc-tetrofosmin in 264 patients showed gamma imaging to significantly improve detection of multifocal or multicentric disease compared to that detected with mammography (88% vs 48% of cases, $p < 0.0005$) and to

correctly alter surgical management in 16% of patients.[124] Preliminary results from a similar study using a dual-head version of the CZT-based MBI system and reduced doses of ~300 MBq ^{99m}Tc-sestamibi were reported: gamma imaging detected additional disease not appreciated by mammography and ultrasound in 12 of 98 patients (12%), which altered surgical management.[125] A comparison of measured tumor size on MBI and pathological size showed good correlation of $r = 0.681$.[7]

Preoperative evaluation has been one of the primary proposed indications for PEM technology and a number of studies have been performed to investigate the efficacy of PEM in this setting.[4,5,126–128] Findings from a large multicenter trial comparing PEM to MRI in preoperative planning were recently reported by Berg *et al.*[4,5] In preoperative evaluation of the ipsilateral breast in 388 patients,[4] the addition of either PEM or MRI to conventional imaging (mammography and/or ultrasound) improved sensitivity for additional malignancies compared to conventional imaging alone. PEM and MRI were found to be complementary: adding MRI to conventional imaging detected additional disease in 13% of patients, adding PEM to conventional imaging detected additional disease in 11% of patients, and the combination of conventional imaging with both MRI and PEM detected additional disease in 18% of patients. MRI demonstrated greater lesion-level sensitivity and more accurately depicted the need for mastectomy compared to PEM, but PEM had greater specificity at the breast and lesion levels and therefore prompted fewer biopsies that proved benign. Tumor size measured on imaging was better correlated with pathological size using MRI measurements ($r = 0.81$) compared to PEM measurements ($r = 0.55$, $p < 0.001$).

In a separate report of preoperative evaluation of the contralateral breast in 367 women with breast cancer,[5] the sensitivity of MRI for contralateral malignancies was significantly higher than PEM (14 of 15 [93%] vs 3 of 15 [20%], $p < 0.001$). However, a subsequent retrospective blinded interpretation of PEM imaging by experienced readers detected 11 of 15 (73%) contralateral malignancies, citing interpretive errors or assignment of a probably benign assessment as factors for false negative results.

IV.C. Monitoring neoadjuvant therapy

Closely tied with the need for accurate imaging in preoperative evaluation is the need for accurate imaging in monitoring response to neoadjuvant therapy. Neoadjuvant therapy, which is chemotherapy or hormonal therapy administered prior to surgical treatment, is increasingly being used as evidence suggests that it can improve patient outcomes by reducing cancer burden and potentially allowing less extensive surgery. Early assessment of the tumor's response to therapy can indicate if treatment should be altered or prolonged in order to achieve optimal response prior to surgery. Measurement of the residual disease at the completion of neoadjuvant therapy can also be used to guide surgical options. Thus, accurate assessment of response to neoadjuvant therapy through diagnostic imaging is critical to fully utilize the benefits of neoadjuvant therapy.

Similar to the setting of preoperative evaluation, there is no standard protocol that dictates which imaging tools should be used in monitoring neoadjuvant therapy. Physical exam, mammography, ultrasound have been shown to only moderately correlate with pathologic size and often over- or underestimate disease extent.[129] All diagnostic imaging tests are inherently unable to identify with certainty the absence of all malignant cells and therefore have been demonstrated to unreliably predict pathologic complete response (pCR).[130,131] However, it has been proposed that functional imaging with nuclear medicine techniques may be able to better characterize residual tumor viability and reflect response at an earlier stage through its ability to depict a decrease in tumor function that precedes a decrease in anatomical size.

Initial studies performed with conventional gamma cameras in patients with locally advanced breast cancer provided evidence that ^{99m}Tc-sestamibi uptake could accurately differentiate responders from nonresponders to neoadjuvant chemotherapy.[132–134] ^{99m}Tc-sestamibi uptake was also demonstrated to have prognostic significance: in a series of 62 patients, residual uptake observed on scintimammography studies performed after completion of neoadjuvant therapy was significantly associated with poorer disease free survival and poorer overall survival.[135] It must be noted, however, that sestamibi has reduced uptake in tumors that express the P-glycoprotein-mediate multidrug resistance gene[136] and therefore lack of uptake may in some patients reflect drug resistance rather than reduced tumor function. Conventional PET with ^{18}F-FDG has also demonstrated potential for predicting response to neoadjuvant therapy.[137,138] Ultimately, because conventional scintimammography and PET lack the necessary spatial resolution to visualize very small residual tumor foci, they are limited in their ability to accurately determine whether residual disease is present.

Dedicated systems with improved spatial resolution have thus allowed for a renewed consideration of using functional radiotracer uptake in assessing response. Spanu *et al.* demonstrated in a small series of patients that a dedicated MBI gamma camera could visualize uptake of ^{99m}Tc-tetrofosmin in multifocal, sub-cm scattered cancers remaining after neoadjuvant therapy when findings on a conventional gamma camera incorrectly demonstrated no residual disease.[139] Pilot data from the Mayo Clinic has shown that MBI performed with ^{99m}Tc-sestamibi is capable of indicating response as early as 3 weeks following initiation of chemotherapy (Fig. 9).[140] Additionally, measurements of tumor size have correlated well with pathology size, indicating that MBI could be useful in guiding surgical choices.[7,140]

Encouraging findings showing the ability of PEM systems to monitor neoadjuvant chemotherapy have been reported. In trials underway at MD Anderson using the Naviscan PEM system, quantitative measurements of uptake on PEM were performed at baseline and 14 days into chemotherapy. Both higher baseline uptake and a decrease in uptake from baseline to 14 days into chemotherapy were significantly associated with pCR.[141] The group at UC Davis is also performing a trial
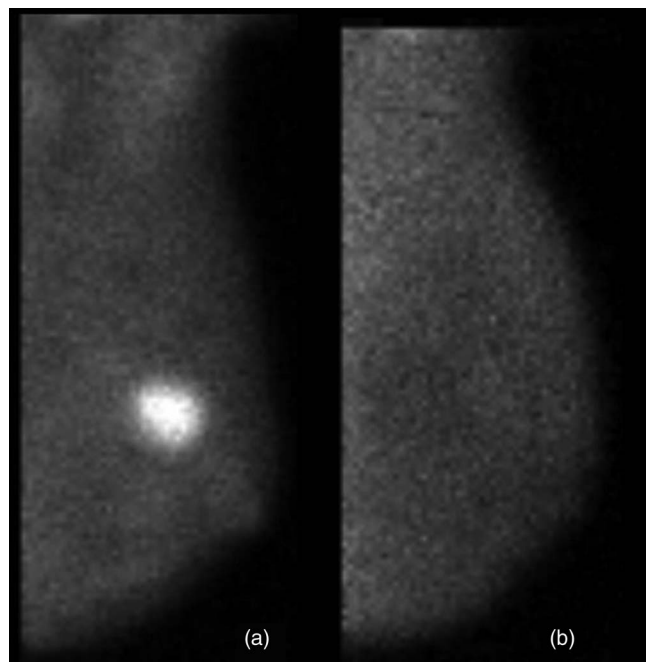
FIG. 9. A patient with a 2.2 cm invasive breast cancer was imaged with MBI prior to initiation of neoadjuvant chemotherapy (panel a) and again at 3 weeks after initiation (panel b). MBI performed at 3 weeks showed nearly complete resolution of the tumor, indicating a functional response to neoadjuvant chemotherapy. Surgery performed after four months of therapy showed complete pathological response (pCR), i.e., no residual *in situ* or invasive disease.

in neoadjuvant chemotherapy patients using their dedicated PET/CT system.[142]

IV.D. Comparisons with MRI

The design and implementation of a research study that compares diagnostic accuracy of nuclear techniques and MRI in detection of breast cancer is challenging. Because MRI is capable of detecting very small lesions that may never be found at surgery or never reported by the pathologist, determining a reference standard for every diagnosed lesion is sometimes not possible, especially when analysis is performed retrospectively.

Most reports comparing performance of nuclear techniques to that of MRI have been done retrospectively and have noteworthy limitations such as small numbers of patients and unblinded interpretations of the imaging studies. In reviews comparing performance of dedicated gamma camera systems and MRI, findings have indicated that gamma imaging and MRI correlate well and have similar sensitivities for cancer, and gamma imaging demonstrated better specificity in a limited number of patients.[123,143–147] The only prospective trials yet performed to compare performance of a dedicated nuclear technology with MRI are the studies investigating preoperative evaluation with PEM compared to that with MRI that were previously discussed.[4,5,127] Based on complementary findings between PEM and MRI, the authors concluded that PEM could be a useful option for patients who could not tolerate MRI.

IV.E. Screening

Screening mammography has a long history as the best available screening test for the general population of women due to several important factors: wide accessibility; relatively low cost to patients and reimbursement by insurance carriers; low radiation risks; fast patient throughput; highly regulated systems for quality control of equipment and images (such as the American College of Radiology (ACR) Mammography Accreditation Program and the Mammography Quality and Standards Act [MQSA]); and an established and validated system for radiologist interpretation [ACR Breast Imaging Reporting and Data System (BI-RADS)[148]]. Mammography is also the only screening modality yet to demonstrate a breast cancer mortality benefit.[149,150] Thus, any new technology trying to gain the same widespread acceptance as mammography in the screening setting is at a distinct disadvantage, as many years and many patients studied are required to build up the necessary evidence and infrastructure to support its clinical implementation.

Despite widespread implementation of mammographic screening, it is well recognized that mammographic sensitivity is considerably limited in certain subsets of patients, such as women with radiographically dense breasts,[151–155] those with a personal history of breast cancer,[156] and those who are carriers of the breast cancer gene BRCA-1 or -2.[157] The subset of women with dense breasts is particularly interesting due to current increases in public awareness and discussion about the topic of breast density.

It is estimated that over 30% of women age 40 and older have breast tissue considered dense on mammography—that is, their mammograms are classified as one of the BI-RADS density categories of heterogeneously dense or extremely dense.[158] Density is not only associated with reduced sensitivity (reported sensitivity in extremely dense breasts is between 29% and 62% (Refs. 151, 152, and 154), but epidemiological evidence also demonstrates that density is a strong independent risk factor for development of breast cancer. In a study by Boyd *et al.*, women with the densest breasts on mammography (>75% fibroglandular tissue) were up to five times more likely to develop breast cancer than those with almost no density (<10% fibroglandular tissue).[159] Due to efforts by patient advocate groups, legislation in several U.S. states now requires medical centers to notify patients if their screening mammogram demonstrates dense tissue and to recommend considering additional screening with another imaging modality. Digital tomosynthesis, whole-breast ultrasound (automated or hand-held), MRI, and nuclear medicine techniques have all been under study as supplemental screening tests to mammography for women with dense breasts. A major criticism of this legislation, however, is that there is not yet enough evidence to support recommendation of any of these particular modalities for adjunct screening of dense breasts.

Recent reader studies conducted in cancer-enriched populations indicate that adding tomosynthesis to mammography can significantly reduce the recall rate of noncancer cases by an average of 39% in one reader study and 17% in another.[160]

To date, there is little published on the performance of tomosynthesis in the screening setting and no evidence yet that it can lead to improved sensitivity specifically in the dense breast population. Interim results from the 12 600 examinations studied in the Oslo Tomosynthesis Screening trial demonstrated a significantly improved diagnostic yield with addition of digital tomosynthesis to mammography (6.1 for mammography alone vs 8.0 for mammography plus digital tomosynthesis, $p = 0.001$) and a 15% decrease in recall rate for the combined technologies ($p < 0.001$).[161] The improvement in cancer detection with tomosynthesis was noted to be in invasive cancers but not ductal carcinoma *in situ*, and was across all breast densities, even fatty breasts.[161]

Results from the ACRIN 6666 clinical trial showed that adding physician-performed whole-breast screening ultrasound to screening mammography significantly increased diagnostic yield (number of cancers detected per 1000 women screened) from 8.1 for mammography alone to 11.8 for mammography and ultrasound combined in women with dense breasts and other risk factors. However, the addition of whole breast ultrasound to mammography also significantly increased the number of false positive findings. At the first year of screening with the combined modalities over one-quarter (27%) of women were recalled for additional workup and 10% were biopsied, and after three years of annual screening 17% of women were recalled and 7% were biopsied.[162] The malignancy rate per biopsy (positive predictive value [PPV]3) for combined mammography and ultrasound (16%) was significantly worse than that of screening mammography alone (38%) after three years of screening.[162] Other multicenter trial results from Italy demonstrated that physician-performed screening ultrasound in women with dense breasts who had negative screening mammograms increased diagnostic yield from 2.8 with mammography alone to 7.2 with combined ultrasound and mammography.[163]

A multicenter study of automated breast ultrasound (ABUS) in over 4000 women also showed a significant increase in cancers detected in dense breast tissue with only a small decrease in specificity.[164] However, a number of obstacles need to be addressed with regard to the use of ABUS in clinical practice, including the time to read a study (3–12 min), increased recall rate and increased biopsy rate.

MRI is currently recommended by the American Cancer Society (ACS) as an annual screening method for women in the highest risk categories, such as those at greater than 20% lifetime risk by risk prediction models or those who carry a pathologic mutation in BRCA-1 or -2 genes. However, the ACS has stated that there is insufficient evidence to recommend for or against MRI screening for women in intermediate risk categories, such as those with dense breasts or personal history of breast cancer, when the high risk criteria are not met.[165] The ACS also recognized the variable specificity of this modality, which can range from 50% to 90%. The addition of MRI to screening mammography in women with dense breasts in a cohort of 612 participants of the ACRIN 6666 trial resulted in significantly improved diagnostic yield (26.1 for combined MRI and mammography vs 8.2 for mammography alone, normalized per 1000 women screened) but significantly worse specificity (71% for combined modalities vs 92% for mammography alone).[162] In the current economic climate, the high cost of breast MRI is likely to be a limiting factor in the widespread adoption of this imaging technique.

Nuclear medicine techniques have been considered as an option for those women with dense breasts who do not qualify for, do not have access to, or cannot afford MRI screening. The primary barrier to implementation of nuclear techniques in the screening setting has been concern that their radiation dose is too high for annual or biennial use in an asymptomatic population.[1] However, more recent data showing that lowered activities of radiopharmaceuticals can be administered and still achieve acceptable diagnostic accuracy support further investigation into whether nuclear techniques could have a role in the screening setting.

Several patient studies have demonstrated the ability of dedicated gamma cameras to detect mammographically occult breast cancer in the screening setting.[3,101,166,167] The largest trial of screening with dedicated gamma imaging yet performed was a single-center trial that compared the efficacy of MBI performed with a dual-head CZT-based gamma camera and screening mammography in 936 asymptomatic women with dense breasts.[3] Results showed that the addition of a one-time or prevalence screen MBI, performed using 740 MBq (20 mCi) ^{99m}Tc-sestamibi, to incident screening mammography in women with dense breasts significantly increased diagnostic yield from 3.2 with mammography alone to 10.7 with the combination of tests ($p = 0.016$). Although the recall rates of incident mammography and prevalent MBI used independently were similar (9% vs 8%, respectively), recall rate of the combination of techniques was increased to 15% ($p < 0.001$ when compared with mammography alone). The addition of MBI to mammography also increased the biopsy rate from 1.8% to 3.9%; absolute PPV3 was consequently raised from 18% with mammography alone to 24% with the combination of MBI and mammography, but this increase was not statistically significant ($p = 0.516$). It is expected that with repeated rounds of MBI screening (incidence screening), recall and biopsy rates of MBI would improve, as has been observed with all other breast imaging screening modalities, including mammography,[162,168] ultrasound,[162] and MRI.[169]

Recent improvements in the CZT-based MBI technology used in this screening MBI trial have resulted in a ∼3 fold reduction in the administered dose of ^{99m}Tc-sestamibi required for MBI.[170,171] Preliminary results from 600 patients screened with low-dose MBI performed with 300 MBq (8 mCi) ^{99m}Tc-sestamibi and mammography confirmed the findings of improved sensitivity of MBI relative to mammography in dense breasts at reduced administered dose.[172] Early findings from trials underway at Mayo Clinic indicate feasibility of performing screening MBI using administered doses as low as 150 MBq (4 mCi) ^{99m}Tc-sestamibi. Figure 10 shows an example of a breast cancer detected on separate MBI studies performed following injections of 150 MBq ^{99m}Tc-sestamibi and 300 MBq ^{99m}Tc-sestamibi in the same patient.

PEM has not been evaluated as a screening tool. The patient preparation requirements for PEM dictated by the
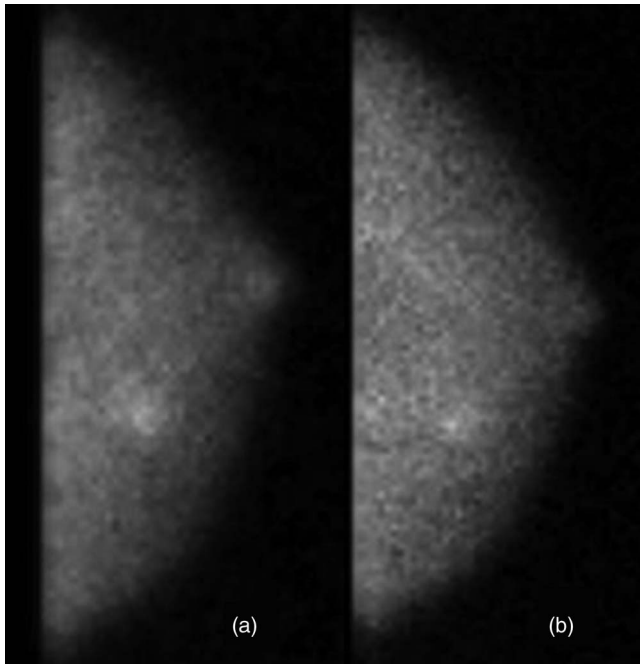
FIG. 10. Two separate MBI studies performed in the same patient with a 10-mm invasive ductal carcinoma. MBI was performed using 150 MBq with a resolution recovery algorithm applied (panel a) and 300 MBq (panel b) Tc-99m sestamibi on a dual-head CZT-based gamma camera.

use of ^{18}F-FDG, including fasting for 4–6 h, blood glucose monitoring, and a 40–60 min wait time postinjection, reduce the likelihood of its adoption in the screening setting in the near future.

V. NECESSARY FACTORS FOR ADOPTION OF NUCLEAR MEDICINE BREAST IMAGING

V.A. Clear indications

After over 20 years of investigation and the development of a number of high-resolution dedicated detectors for nuclear medicine breast imaging, a vital question stills plagues the modality—where do these technologies fit within a clinical breast imaging practice?

The primary goal of any new modality is to perform better than existing techniques. Nuclear medicine breast imaging has been shown to offer improved detection of certain cancers within mammographically dense breast tissue compared to mammography. It promises to be better tolerated by patients, easier to interpret, less costly, and possibly more specific than breast MRI. The possible indications for nuclear medicine breast imaging are thus very broad.[173] Some have suggested that a general indication for nuclear techniques for the breast is any patient in whom MRI is indicated, but cannot be performed due to lack of availability, inability to pay, or contraindications such as an implanted device, allergy to gadolinium, large body habitus, or inability to tolerate the exam.[174]

Based on current evidence presented above, three key patient groups have emerged as the most likely to benefit from imaging with new dedicated nuclear medicine techniques.

The first is women with a diagnosis of breast cancer requiring preoperative evaluation, especially for women in whom MRI is contraindicated. PEM has been demonstrated to be particularly useful in this group.[4] The second is women undergoing neoadjuvant therapy, although the true potential of functional nuclear medicine imaging to accurately show response and aid in tailoring treatment may not be realized until targeted radiopharmaceuticals are implemented in this setting.[7] The third group, and by far the largest, is women with mammographically dense breasts who either do not meet the risk eligibility criteria for screening MRI or who decline MRI screening for a number of reasons.[175] Women with additional risk factors (personal history of breast cancer, strong family history) in this subgroup may be the most likely to benefit from additional screening with nuclear medicine. Low-dose gamma imaging with dedicated CZT-based MBI systems has already shown promise in this setting.[3,171,172]

As discussed above, numerous studies investigating nuclear breast imaging systems have had the inclusion criteria bias of enrolling women with suspicious lesions that were scheduled to be biopsied. Although the intention of such a study design was to establish diagnostic accuracy of the specific technique using an enriched population, some have erroneously used such studies to infer that a negative nuclear study could prevent "unnecessary biopsies."[176–178]

Indeterminate imaging findings (BIRADS 3) on mammography and/or ultrasound where biopsy is not indicated or a persistent clinical concern have also been proposed indications for nuclear medicine breast imaging. Little evidence supports this use other than knowledge that the nuclear techniques have a high probability of finding cancer (greater than 5 mm) if it exists and a negative study can offer additional reassurance to patients.

V.B. Biopsy capability

Precisely because nuclear techniques can visualize lesions that are occult on conventional imaging with mammography and directed ultrasound, a direct localization method is essential for widespread clinical acceptance. Several designs for direct biopsy have been introduced and evaluated with simulations and phantoms, however only two commercial systems offer an accessory biopsy unit.

Early approaches to localization for biopsy using needle localization and surgical removal were proposed for scintimammography and dedicated gamma cameras.[101,179,180] Approaches of integrating a dedicated gamma camera detector or PEM detector into a mammographic stereotactic biopsy unit have been explored.[86,181,182]

The only commercial, Food and Drug Administration (FDA)-approved biopsy scheme for dedicated gamma cameras is the system developed by Dilon Technologies for BSGI.[183] This system uses a sliding slant-hole collimator to acquire two separate gamma images and allow stereotactic localization the lesion. Biopsy is performed with the patient positioned upright at the BSGI imaging system and the needle is inserted through a grid-support and needle positioning block that also acts as a compression paddle. Preliminary findings

demonstrated successful BSGI-guided biopsy performed in 17 patients, with a reported procedure time of 86 min.[184]

Direct biopsy capability has also been developed and FDA-approved for the Naviscan PEM system. Like the BSGI biopsy scheme, PEM-guided biopsy is performed with the patient upright while positioned at the imaging system. Because both detectors of the PEM system are required for coincidence imaging, the needle is inserted from the lateral side of the compressed breast. A prospective multicenter clinical trial showed successful biopsy of lesions in 22 patients, with an average procedure time of ~30 min.[185] Currently, there are no biopsy schemes available for the dedicated ring-based breast PET designs, and there is some concern that access to the breast for biopsy may be limited with such designs that utilize a ring of detectors.

In the Mayo Clinic practice and in other institutions that are exploring the use of MBI performed with dual-head CZT-based gamma cameras, the standard protocol for evaluation of newly detected lesions on nuclear studies is evaluation with diagnostic mammography and/or targeted ultrasound, and biopsy is typically performed under stereotactic or ultrasound guidance if warranted. If diagnostic workup by conventional imaging is negative, further evaluation is determined by the level of suspicion of the MBI-detected lesion: indeterminate lesions (MBI assessment = 3) are followed by MBI performed at six month intervals, suspicious lesions (MBI assessment = 4 or 5) are evaluated with MRI. A review of the diagnostic workup generated by adding screening MBI to mammography in women with dense breasts was recently presented.[186] In 1640 women, 109 (6.6%) had newly detected lesions on MBI, of which 13 (0.8%) necessitated MRI evaluation, and 8 (0.5%) underwent MRI-guided biopsy. These findings suggest a limited role for direct MBI-guided biopsy capability, but such a device may have been useful for obviating the need to perform MRI in a small number of patients.

Although there is a FDA-approved method of imaging the obturator with PEM to verify its position after placement, a limitation of direct biopsy techniques for nuclear systems developed thus far is the lack of real-time feedback (as in ultrasound-guided biopsy) on the location of the biopsy needle or obturator. A recently proposed approach of using a high sensitivity focused ring-shaped collimator for dedicated gamma imaging may allow monitoring of the obturator that approaches real time (frames updated every 1 min), a substantial improvement over the current acquisition of 5–10 min frames during imaging.[187] Use of a multimodality system could also overcome the real-time monitoring problem by providing anatomical localization of the functional abnormality along with real-time visualization of needle location. Systems such as the combined Clear-PEM Sonic system may allow the option of performing biopsy under ultrasound guidance.

V.C. Radiation dose considerations

Concern about radiation risk associated with nuclear medicine breast imaging techniques is one of the primary factors that have limited their clinical adoption. The breast is considered one of the most radiosensitive organs in the body.[188] Hence there will always be considerable scrutiny of any breast imaging procedure that involves ionizing radiation. Numerous reports have documented the very low risk of any harmful effects associated with radiation received from mammography, and that risk is even lower with today's digital mammography detectors.[189] Hence, researchers are striving to implement dose reduction strategies that allow the nuclear techniques to be performed at radiation doses comparable to that used in mammography.

Initial studies with dedicated gamma cameras employed doses of ^{99m}Tc-sestamibi that were comparable to those originally employed by conventional scintimammography.[19] Doses usually ranged from 740 MBq up to 1110 MBq ^{99m}Tc-sestamibi resulting in an estimated absorbed dose to breast tissue of up to 2 mGy. Initial PEM studies typically used administered doses up to 370 MBq ^{18}F-FDG, resulting in dose to the breast of 3.4 mGy. By comparison, the mean glandular dose (to the breast) from digital mammography is ~4 mGy.[1]

However, with nuclear medicine techniques, the administered radiotracer delivers a systemic dose and most of the radiation burden is to organs other than the breast, mainly the upper and lower intestines for ^{99m}Tc-sestamibi, and the spleen, heart and bladder for ^{18}F-FDG. The effective (whole-body) dose from administration of 740–1100 MBq ^{99m}Tc-sestamibi is 5.9–9.4 mSv and the effective dose from administration of 370 MBq ^{18}F-FDG is 6.2–7.1 mSv.[1] These effective doses are a factor of 10–20 times greater than the average effective dose of 0.5 mSv for digital mammography.[1]

The higher effective radiation doses from these nuclear medicine breast imaging techniques compared to mammography have raised concerns about the cumulative radiation burden to patients, particularly if these procedures become widely adopted and their use is expanded into screening. An analysis by O'Connor et al.,[2] which calculated the lifetime attributable risk (LAR) of cancer incidence and mortality from annual mammography and annual nuclear medicine procedures, concluded that in order for the radiation-induced cancer risks from nuclear medicine techniques to be comparable to that of mammography, the injected radiotracer activities need to be reduced to 150 MBq or less of ^{99m}Tc-sestamibi and 70 MBq or less of ^{18}F-FDG. These administered activities both correspond to an effective radiation dose of ~1.2 mSv, which is comparable to the effective dose from combined mammography and breast tomosynthesis.

The low doses received from annual screening mammography programs have been determined to be of low risk compared with expected mortality reductions achievable through mammographic screening. Hence, it is reasonable to assume that a more sensitive screening technique would likewise be considered to be low risk relative to the potential mortality reduction. Recent efforts at optimization of current CZT-based MBI gamma camera technology have yielded a reduction in the administered dose of ^{99m}Tc-sestamibi to 300 MBq as currently routinely used at our institution and 150 MBq in the research setting.[170,171] Further work with some of the newer radiopharmaceuticals may yield an additional factor of 2–3 reduction, which would bring the effective dose down below

that of mammography. At these dose levels, it is now reasonable to consider the incorporation of MBI into a screening regime: this could be accomplished by alternating annually between mammography and MBI or the addition of MBI as an adjunct screening tool on a biennial basis.

Clinical studies with the Naviscan PEM unit have typically employed a 370 MBq dose of ^{18}F-FDG but some recent data suggest that adequate diagnostic image quality can be obtained using 185 MBq ^{18}F-FDG.[190] The next generation of PEM systems that incorporate either fully populated detector plates such as the ClearPEM unit, or dedicated breast PET systems full ring detectors such as the MammiPEM system, are likely to be considerably more sensitive than the current PEM-Flex system and should permit a corresponding reduction in the administered dose of ^{18}F-FDG required for clinical studies.[191,192] An evaluation of several types of dedicated PET configurations recently demonstrated the sensitivity to true coincidence events at the center of a box-shaped or polygon-shaped ring detector to be 33%–35% compared to 8% for a dual-detector PEM system.[192]

V.D. Targeted radiopharmaceuticals

In nuclear medicine, the successful creation of a useful imaging test requires two components; the right instrumentation, which is now available, and the appropriate radiopharmaceuticals that can target and characterize breast cancer while delivering a low radiation burden to the patient. The lack of suitable instrumentation over the last 10–15 years has effectively undercut any major attempts to develop better radiopharmaceuticals for breast imaging. Consider that ^{99m}Tc-sestamibi became the first radiopharmaceutical specifically approved for breast imaging as a second-line diagnostic test by the FDA as far back as 1997. ^{99m}Tc-tetrofosmin was FDA approved in 1999, but never received specific approval for breast imaging in the U.S. ^{99m}Tc-tetrofosmin did, however, receive European approval as a breast imaging agent in 2002. Since then no other radiopharmaceuticals have been approved for breast imaging in either the U.S. or Europe.

As discussed earlier, from the studies performed in the 1990s in both scintimammography and PET, it was assumed that the failure of both techniques to detect small breast tumors was partly due to variable uptake of ^{99m}Tc-sestamibi and ^{18}F-FDG by some tumors. As is now apparent from more recent clinical results with dedicated systems, both radiopharmaceuticals appear to demonstrate good to excellent uptake in small breast lesions, and the problem was not with the radiopharmaceutical, but with the limitations of the imaging technology.

Quantitative measurements from our laboratory in breast tumors with ^{99m}Tc-sestamibi have indicated that tumor to background concentration ratio are in the range of 10:1–40:1,[60,193] considerably higher than reported in prior scintimammography studies,[194] and more in-line with *in vitro* studies of the uptake of ^{99m}Tc-sestamibi in carcinoma cell lines.[195] This is good news for both single photon and positron emitting technologies as the development and regulatory approval of new radiopharmaceuticals is a long and expensive process and one that few manufacturers would be willing to undertake in the absence of a proven clinical market.

^{99m}Tc-sestamibi and ^{18}F-FDG serve the role as generic markers of increased metabolic function, and hence surrogates of breast cancer, but are relatively nonspecific in their uptake and are often unable to distinguish between benign and malignant processes. Several alternative radiopharmaceuticals may provide more specific information on the functional aspects of breast cancers. While a full review of other potential radiotracers for breast imaging is outside the scope of this paper, Table II presents a partial list of the radiolabeled compounds that have been used to detect breast cancer in humans (adapted from Kong *et al.*).[196]

The development of new blood vessels (angiogenesis) around tumors is essential for tumor growth. Protein-based receptors known as integrins play a key role in the process of angiogenesis. The expression of the integrin $\alpha v \beta 3$ on vascular endothelium has a key role in this process. This integrin has been successfully labeled with both ^{99m}Tc and ^{18}F,[197,198] and initial studies have shown uptake of radiolabeled integrin in primary breast cancer and metastases.[199,200] Figure 11 compares images of a breast cancer obtained in the same patient with ^{99m}Tc-sestamibi and ^{99m}Tc-radiolabeled integrin (^{99m}Tc-NC100692) on a CZT-based MBI system. Compared to the ^{99m}Tc-sestamibi images, the ^{99m}Tc-radiolabeled integrin images demonstrated higher uptake of the radiopharmaceutical in both the normal breast tissue and in the tumor. ^{99m}Tc-NC100692 imparts an effective dose of 7.8 μSv/MBq,[201] which is slightly lower than the effective dose of sestamibi (8.1–8.5 μSv/MBq).[1] The higher relative uptake in breast tissue obtained with ^{99m}Tc-radiolabeled integrin may allow for a reduction in the administered dose required for acceptable image quality.

Estrogen exerts an important effect in breast tissue, causing growth and enhancing many metabolic pathways cells while inhibiting others. One of the earliest changes of breast cancer is the inability of a breast cell to maintain the appropriate estrogen receptor levels. Excess levels of estrogen receptor cause sustained, prolonged, and unopposed estrogen stimulation of the breast cell. A large percentage of breast cancers express the estrogen receptor (ER). Knowledge of a patient's ER status has important consequences for treatment decision making, because patients with ER-positive tumors are likely to benefit from antiestrogen therapy. Several groups have developed radiolabeled derivatives of estradiol using either ^{123}I or ^{18}F.[202,203] Early work by Preston *et al.*[204] and Bennink *et al.*[205] indicated that ^{123}I estradiol may be able to detect current disease and be a sensitive tool for the detection of estrogen receptors in patients with breast cancer. Also, several studies showed that ^{18}F fluoroestradiol (FES) PET could assess the *in vivo* pharmacodynamics of ER-targeted agents and may give insight into the activity of established therapeutic agents.[206]

Radiopharmaceuticals targeting angiogenesis and estrogen receptor status are just two of the myriad of new radiolabeled compounds that offer the promise of providing better functional and metabolic information on breast cancer. Other potential compounds include F-18

TABLE II. Radiotracers that have been used in human studies to detect breast cancer. Listed by tumor-specific target humans [adapted from Kong *et al.* (Ref. 196)].

Target	Single-photon (MBI/BSGI)	Positron-emitter (PET or PEM)
Perfusion	Tl-201 Thallous Chloride	O-15 Water
	Tc-99m Sestamibi	
	Tc-99m tetrofosmin	
Glucose metabolism	Tc-99m EC-glucosamine	F-18 FDG
Hormone receptor	I-123 estradiol	F-18 FES
		F-18 fluoro-tamoxifen
		F-18 fluoro-norprogesterone
		F-18 fluoromoxestol
HER2	In-111 trastuzumab	Zr-89 trastuzumab
Cell proliferation/angiogenesis	Tc-99m maraciclatide	F-18 flucuclatide
	In-111 bevacizumab	F-18 galacto-RGD
		F-18 fluorothymidine
		Zr-80 bevacizumab
Amino acid transporters & protein synthesis	Tc-99m methionine	C-11 methionine
	I-123 methyltyrosine	C-11 tyrosine
		F-18 fluoro-ethyl-tyrosine
Epidermal growth factor receptor		C-11 Iressa
Cell surface receptor (VPAC1)	Tc-99m VPAC1	Cu-64 VPAC1
Hypoxia		F-18 fluoromisonidazole
		F-18 fluoroetanidazole
		F-18 fluoroazomycin-arabinoside
		Cu-64 diacetyl-bis-N4-methylthiosemicarbazone
Apoptosis	Tc-99m EC-annexin V	F-18 annexin V
Somatostatin receptors	In-111 octreotide	
Membrane synthesis		C-11 choline

fluorodeoxythymidine and ^{99m}Tc-(V) dimercaptosuccinic acid (DMSA), both with uptake in the breast that appears to mirror cell proliferation,[207,208] and ^{99m}Tc-Annexin V which mimics tumor cell death.[209] In a recent review of novel genomic biomarkers for molecular imaging of cancer, Thakur[210] discussed the numerous biomarkers that are under development and that have the potential promise to better identify and characterize breast cancer.

The promise of all of these radiolabeled compounds can only be realized with high resolution SPECT and PET instrumentation. This is a symbiotic relationship that can only succeed if developments in instrumentation are matched by developments in new radiopharmaceuticals. With the developments in coincidence and single-photon detector instrumentation over the last 5–10 years, the time is now right for a renaissance in radiopharmaceuticals optimized for both the detection of breast cancer and the evaluation of breast function.

VI. CONCLUSION

A number of single-photon and coincidence-detection nuclear breast imaging technologies and their potential clinical roles were discussed. A summary of these technologies is given in Table III.

The future of nuclear breast imaging technologies is dependent upon several key factors. The primary factor is clinical relevance: these technologies need to establish a place as cost-effective tools in either the screening environment or the diagnostic work-up of patients with breast concerns. Failure to establish a role for these technologies in the routine care of breast cancer and in the minds of the breast radiologists and ordering physicians will be a critical obstacle to their future development.
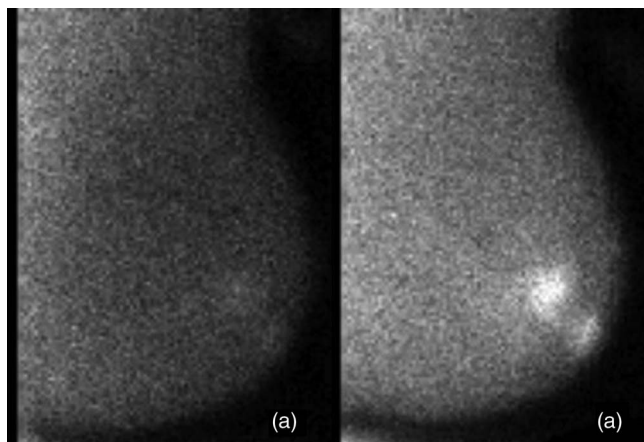

FIG. 11. Images from a patient with two areas of confirmed ductal carcinoma *in situ* who had MBI performed with 300 MBq Tc-99m sestamibi (panel a) and 300 MBq Tc-99m alphaV beta 3 integrin (panel b).

TABLE III. Comparison of single-photon and coincidence-detection nuclear medicine technologies as applied to breast imaging.

	MBI (Dual-head CZT-based)	MBI (BSGI)	PEM	DbPET
Primary proposed clinical indications	Preoperative evaluation Monitoring response to neoadjuvant therapy Patients with contraindications to MRI Screening in dense breasts (at low radiation dose)		Preoperative evaluation Monitoring response to neoadjuvant therapy Patients with contraindications to MRI	
Radiopharmaceutical	Tc-99m sestamibi or Tc-99m tetrofosmin		F-18 FDG	
Administered activity	300 MBq	740–1110 MBq	370 MBq	370 MBq
Fasting period prior to imaging	None	None	4–6 h	4–6 h
Wait period between injection and imaging	5 min	5 min	40–60 min	40–60 min
Acquisition duration	10 min/view × 4 views	10 min/view × 4 views	10 min/view × 4 views	Variable
Biopsy guidance	In development	FDA-approved	FDA-approved	Not available
FOV	20 × 16 cm or 24 × 16 cm	20 cm by 15 cm or 25 cm × 20 cm	24 × 16 cm	Variable
Standardized interpretive criteria	Yes (Refs. 219 and 220)	Yes (Ref. 173)	Yes (Ref. 221)	No

[a] Although a range of values are used in clinical and research settings, typical administered doses used in clinical exams are given.

Over the last ten years our research group at Mayo Clinic has worked on the development of MBI with dedicated CZT-based gamma cameras. An enduring lesson from those ten years has been that development of the technical aspects of a new procedure is only the tip of the iceberg. Technical journals are rife with excellent papers on new techniques and technologies that demonstrate notable improvements in image quality. Few of these advancements ever progress from a physics project to a clinical tool. Unfortunately having a great technology is no guarantee that it will ever go from the research work bench into routine clinical use.

Many of us working in the field of medical physics naively assume that our job is finished once we complete the technical aspects, but as the people who best understand the technology, we also need to stay deeply involved in all the additional steps that are required to translate it into clinical use. These steps include active participation in the initial patient studies, development of clinical trials, and education of the end users to the strengths and limitations of the technology. As physicists and engineers we also need to understand where a new technology fits with competing technologies, and to recognize that a new technology, particularly if it is disruptive, may not be welcomed, even if it is demonstrably superior to current technologies. Much of the above discussion requires us to move out of our comfort zone into a world where decisions are influenced by economic pressures and bias toward the status quo. However, participation in translating the new technology from bench to bedside is equally as important as the physics work that went into the original design.

Nuclear techniques have already been evaluated in breast imaging and found wanting. The emergence of dedicated nuclear breast imaging systems in recent years presents a second chance to demonstrate that these technologies have an important role to play in the detection and understanding of breast cancer. The continued involvement of physicists and engineers beyond the workbench and into the clinical studies is important to ensure good science and that the capabilities of the technologies are appropriately represented. Failure to understand how our clinical colleagues employ these technologies and failure to adequately realize the technologies' strengths and weaknesses may lead to a repeat of what occurred with scintimammography in the 1990s. The strength of molecular imaging is its ability to detect pathophysiological changes at the onset of disease. While molecular imaging technology is commonly used for imaging many disease processes today, it has lagged behind in clinical use for imaging of breast cancer. We believe that with the latest generation of PET and SPECT imaging technologies dedicated to breast imaging, we can now begin to explore how molecular imaging can improve our understanding and treatment of this disease.

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