Evolution and Developments in Instrumentation for Positron Emission Mammography

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KEYWORDS

• Positron emission mammography • Molecular imaging
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THE ROLE OF PET WITHIN THE SPECTRUM OF BREAST IMAGING TECHNIQUES

With the advent of advanced medical imaging technologies, clinical diagnosis is rarely made without imaging. Various structural and functional imaging techniques are used nowadays in the clinic for breast imaging. Conventional diagnostic imaging procedures including x-ray mammography and ultrasound imaging have been the work horse for the last 2 decades. Within the spectrum of macroscopic medical imaging, sensitivity ranges from the detection of millimolar to submillimolar concentrations of contrast medium with structural imaging techniques including computed tomography (CT) and magnetic resonance (MR) imaging, respectively, to picomolar concentrations with molecular imaging techniques including single-photon emission computed tomography (SPECT) and PET, a 10^8 to 10^9 difference.[1]

Radiotracer imaging techniques have gained in popularity during the last decade, particularly with the availability of dedicated breast cameras.[2–4] The use of PET to provide images of glucose metabolism or other physiologic functions of malignant disease is becoming more widespread and whole-body PET (WB-PET) images are now widely used to select the most appropriate therapy in clinical oncology. Since the pioneering work of Dr Wahl on the use of PET for breast cancer imaging,[5] many other reports have been published,[6,7] to cite the first few only. When combined with x-ray CT, PET images provide the equivalent of a "metabolic contrast agent," which serves to highlight the abnormal glucose metabolism in tumors. In a few years, combined PET/CT scanners have become the standard of care in many centers.[8]

PET scanners have a limited spatial resolution compared with structural imaging modalities such as CT and MR. Because the detectability of small tumors leads to earlier diagnosis and treatment, much research and development efforts have focused on improving the spatial resolution of PET. There are both instrumentation and physical factors that degrade the spatial resolution in PET. The fundamental limit is due to the distance positrons travel from the parent nucleus before they lose energy and annihilate with an electron in tissue. Another limitation is caused by the noncollinearity of the pair of annihilation photons, which do not travel away from the point of annihilation at exactly 180 degrees because of the energy of the electron at the time of annihilation. Although this seems to be a fundamental limit in WB-PET, it is much less of a problem in dedicated,

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organ-specific, small, transaxial field-of-view scanners where the detectors are much closer to each other compared with the typical separation needed in WB-PET. The major instrumental limitation is the size of the crystals. Making smaller crystals will improve the spatial resolution at the expense of increased complexity and substantially higher cost. However, if the detectors are placed closer, fewer detectors are required; such instruments dedicated for breast imaging can be produced to provide higher spatial resolution images than those from WB-PET. The factors that contribute to the degradation of the spatial resolution (SR) in PET can be combined as the sum of independent variables in the form:

$$SR = a\sqrt{(d/2)^2 + b^2 + (0.0022D)^2 + r^2}$$

where a is a factor related to the reconstruction algorithm and filter used, d is the crystal width, b combines the effects of light sharing and under-sampling of the image, D is the detector ring diameter, and r is the effective positron range in tissue.

Among the common design factors of PET scanners is the trade-off between spatial resolution, sensitivity, and cost. In the equation above, the crystal width (d) is the variable that balances the cost with the spatial resolution, and the one over which scanner manufacturers have the most control. In WB-PET, moving the detectors closer together is not possible, because this will substantially reduce the patient port and some patients will no longer fit in the scanner. However, this option can be fully exploited in dedicated instruments designed exclusively for small-animal or breast imaging.[9,10]

CLINICAL HISTORY OF POSITRON EMISSION MAMMOGRAPHY

The idea of a dedicated PET scanner for breast imaging was first proposed by Weinberg in 1993, in a United States patent application[11] and a successful Small Business Incentive for Research grant from the US National Institutes of Health (NIH). This was followed by publication of the preliminary results of the first experiments carried out to study the feasibility of the concept.[12] The name positron emission mammography (PEM) was coined to represent this technique. The concept consisted of placing 2 planar detectors capable of detecting the 511-keV annihilation photons in a conventional mammography unit. Placing the breast on a magnification table sometimes used in these instruments provides the possibility of having one detector between the x-ray tube and the compression plate, and another between the lower aspect of the breast and the x-ray sensor. The 2 detectors move out of the x-ray field for conventional mammography, and move back over and under the breast for the PEM acquisition.[13] This concept predates PET/CT by several years,[14] but the goal was much the same as that of PET/CT as it has evolved today: to provide a coregistered anatomic and functional image in the same procedure with minimal movement of the patient.[8]

An important finding of these first investigations was that a small hyperactive region was just as visible in a superposition of a few near vertical projections as it was in fully reconstructed tomographic images. The experiments were performed in a 15-slice brain scanner on a box phantom containing 4 tubes of various sizes with either no activity or 9.3 times the background. The images were made over different times such that each consecutive image contained half the counts of the previous one. The first paper on PEM provided the basic estimate of the signal-to-noise ratio and the count rate that could be expected from a clinical PEM instrument.[12]

These encouraging results provided the basis for a grant application to the Canadian Breast Cancer Research Initiative. The so-called PEM-1 instrument was built and a preliminary clinical trial was carried out. Because it was concluded that simple back-projection reconstruction provided images with sufficient contrast to identify regions of higher-than-surrounding uptake, the image reconstruction issue was not investigated further as preference was given to providing an almost real-time image display of the PEM image. The goal was to perform the clinical trial using only 75 MBq of [^{18}F]fluorodeoxyglucose (FDG) and an imaging time of 2 minutes per breast (about the time needed to develop an x-ray film in an automatic film processor).

INSTRUMENTATION FOR PEM

Limitations of WB-PET Scanners

An impressive literature exists on the clinical use of large-bore clinical PET scanners in breast imaging for clinical diagnosis, staging and restaging, assessment of response to therapy, and radiation therapy treatment planning.[15–18] A comprehensive overview of the published literature is beyond the scope of this paper.

The detectability of small lesions was affected by the limited spatial resolution of WB-PET systems, reducing the sensitivity and specificity of the technique. Among the various approaches that have been explored to enhance the specificity

of FDG-PET for assessing potential malignant lesions is dual-time point imaging, which has been used in assessing various malignancies including those of breast.[19] The theoretic basis for the role of this approach in this setting is that dephosphorylation in tumor cells is either absent or very slow compared with that in normal cells because of their low glucose-6-phosphatase content. This results in a build up of contrast between malignant lesions and the normal tissues with time, which further increases lesion detectability on delayed images. This approach has been tested by several investigators as a potential way to distinguish malignant and benign lesions.[20,21] **Fig. 1** shows the potential of dual-point imaging for improved discrimination between benign and malignant breast cancer. The increase in standardized uptake value (SUV) between the early PET image acquired 1 hour and the delayed image acquired 2 hours post injection is 25%.

The limited spatial resolution of WB-PET systems relative to the size of small lesions also resulted in substantial loss of signal as a result of the partial volume effect. This problem was tackled in many different ways in the context of breast imaging.[22] However, despite the incremental improvement in image quality and resolution, and the enhanced lesion detectability using the various technical approaches developed to address the limitations of imaging small organs such as the breast on WB-PET scanners, emerging clinical and research applications of molecular breast imaging promise even greater levels of accuracy and precision, and therefore impose more constraints with respect to the intrinsic performance of the PET scanner. Continuous efforts to integrate recent research findings for the design of different geometries and various detector/readout technologies of PET scanners have become the goal of the academic community and nuclear medicine industry. The limited number of studies involving the use of dedicated breast imaging instruments has clearly established the need for PEM to enhance detectability of small tumors.[23] **Fig. 2** compares images of the Derenzo phantom obtained using a general purpose WB-PET system with those obtained using an organ-specific, dedicated, high-resolution PEM scanner. Note the improved spatial resolution on the PEM image, which leads to improved lesion detectability and contrast resolution. **Fig. 3** compares clinical images of a patient with breast cancer obtained using a general-purpose WB-PET system with those obtained using an organ-specific, dedicated, high-resolution PEM scanner showing a mass with increased FDG uptake in the right breast. Similar to the phantom study shown in **Fig. 2**, clinical studies report substantially higher spatial resolution and quantitative accuracy when using the dedicated PEM device. A prospective single-site pilot study designed to evaluate the usefulness of PEM and WB-PET imaging in the surgical management of breast cancer, in which

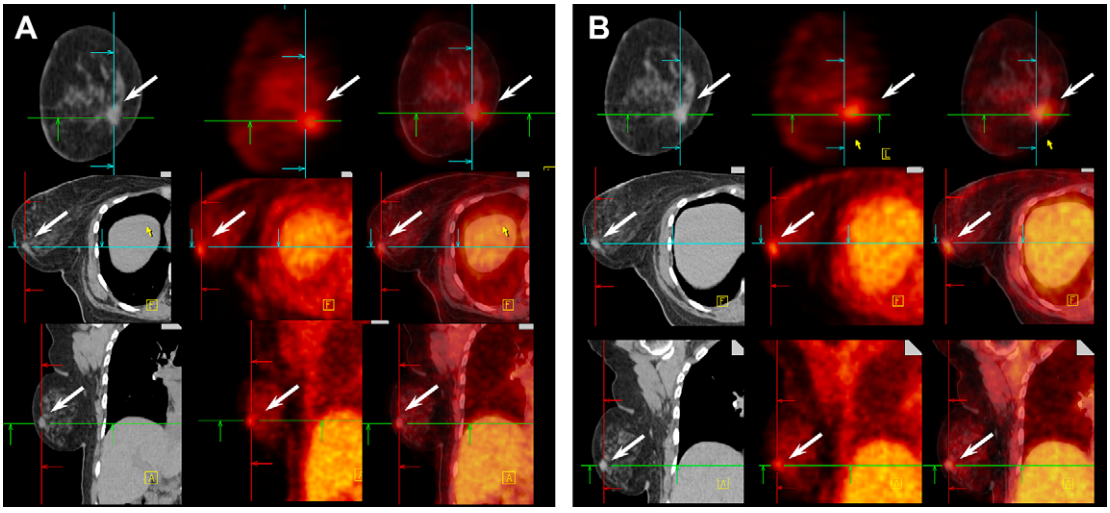

Fig. 1. Illustration of a clinical breast ^{18}F-FDG PET/CT study acquired on a commercial whole-body system showing the potential of dual-point imaging for improved discrimination between benign and malignant breast cancer. The increase in SUV between the early PET image acquired 60 min (*A*) and the delayed image acquired 120 min post-injection (*B*) is 25%. CT, PET, and fused PET/CT images are presented form left to right for axial, sagittal and coronal views.

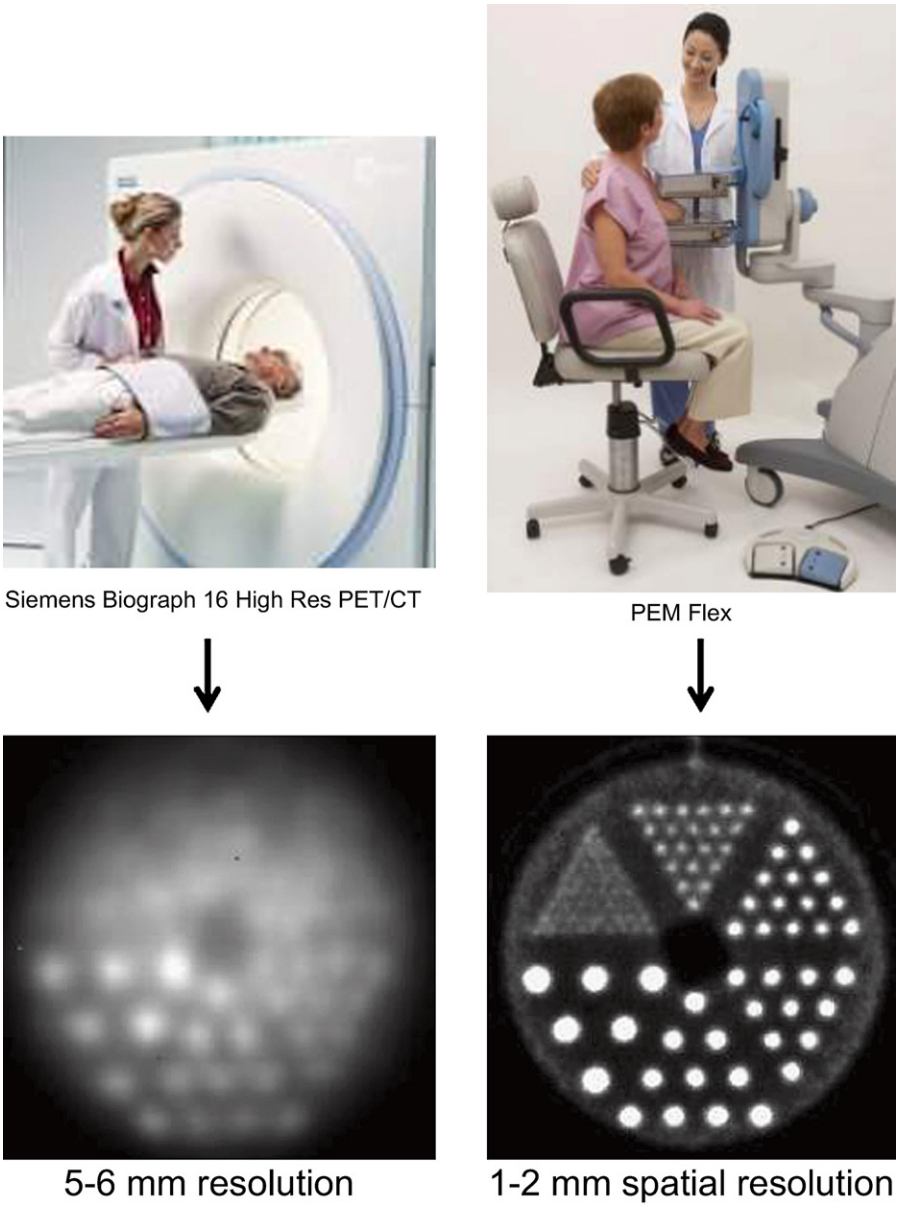

Fig. 2. Comparison of phantom images obtained using a general-purpose whole-body PET system with those obtained using an organ-specific, dedicated, high-resolution PEM scanner. Note the improved spatial resolution on the PEM image of the Derenzo phantom, which leads to improved lesion detectability and contrast resolution. (*Courtesy of* Naviscan PET Systems, San Diego, CA, with permission.)

the results from each modality were compared with final surgical histopathology, concluded that PEM had greater sensitivity than WB-PET (92.3% vs 39%).[24]

The Promise of Dedicated PEM Units

In WB-PET scanning, it is a straightforward to overscan the regions most likely to harbor metastases, and to overlap the bed positions to compensate for the reduced sensitivity towards the axial ends of each set of slices as a result of the fall-off in three-dimensional sensitivity in the scanner. This is not feasible when imaging the breast using PEM detectors. Even when the detectors are placed very close to the chest wall, some shielding is required. This is a serious problem when imaging small breasts, and for investigations close to the

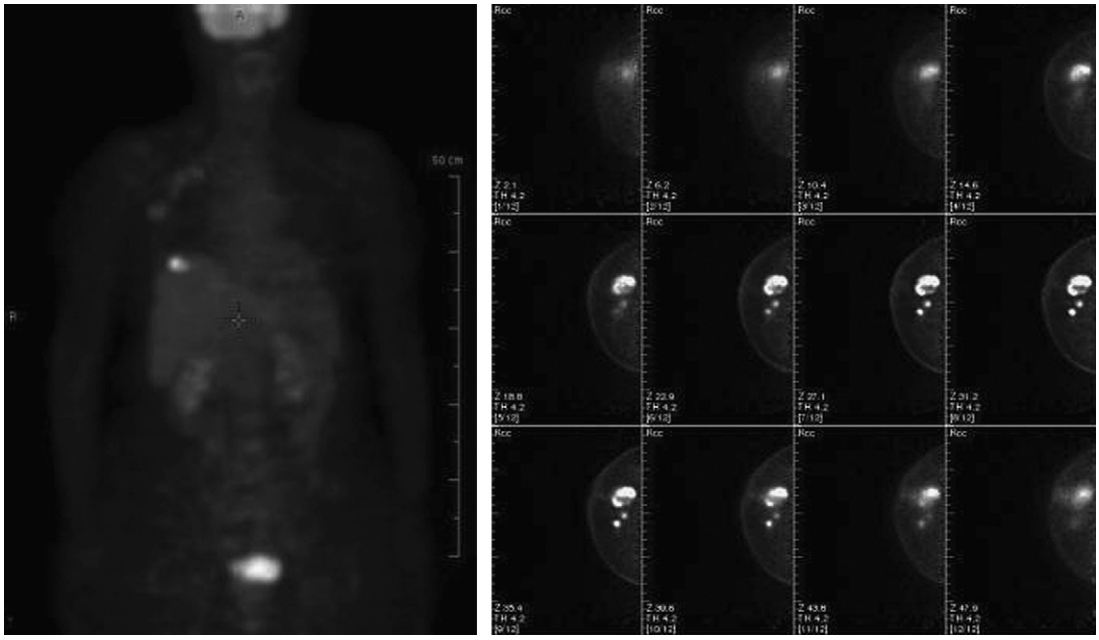

Fig. 3. Comparison of a general purpose whole-body PET scan (*left*) with images obtained using an organ-specific dedicated high resolution PEM scanner (*right*) in a patient with breast cancer. A mass with increased FDG uptake is seen in the right breast. Clinical studies exhibit substantially higher spatial resolution and quantitative accuracy when using the dedicated PEM device. (*Courtesy of* Naviscan PET Systems, San Diego, CA.)

chest wall. Fully three-dimensional PET imaging is always less sensitive towards the axial ends of the field of view because fewer detector pairs can be in coincidence in these regions.

To clearly visualize and accurately quantify the biodistribution of a PET tracer in small structures within the breast requires dedicated high-resolution PET units.[25] In the last 2 decades, much worthwhile research and development efforts have been devoted to the development of dedicated PET scanners for breast imaging. This work has resulted in the development of numerous research prototypes[26–35] and commercially available PEM systems.[36]

Overview of Current PEM Systems

The ultimate performance in spatial resolution, sensitivity, and signal-to-noise ratio of dedicated PEM units can be achieved through careful selection of the design geometry, detector assembly, readout electronics, optimized data acquisition protocols, and image reconstruction algorithms. The rationale in designing dedicated breast versus multipurpose WB-PET scanners is that unlike whole-body imaging where a larger detector ring diameter is needed to accommodate large patients, the size of the female breast is relatively small thus allowing the scanner's diameter to be reduced and the solid-angle coverage to be increased, leading to higher sensitivity per unit detector volume. A small field-of-view design has the advantage of improving the inherent spatial resolution degradation caused by noncollinearity of the annihilation photons in addition to reducing the overall cost of the PET scanner at the expense of a higher parallax error, hence an image degradation depending on the emission point in the transaxial plane and/or the angle of incidence of the lines of responses. This effect becomes worse when reducing the diameter of the scanner or the size of the crystal's cross-sectional area. This inherent limitation could be coped with by keeping the radial length of the crystal small, typically at values around the attenuation length at 511 keV, which however would strongly compromise the detection efficiency.

Various PEM geometries have been proposed and some of these are currently in use. However, only 1 commercial device has been approved by the Food and Drug Administration (FDA) for clinical use.[37] Almost all have a larger field of view than the first prototype. Complete coverage of the breast while the breast remains in place has become the norm. Various detector arrangements have been proposed, including the classic 2 parallel crystal arrays coupled to position-sensitive photomultipliers (PS-PMTs). One detector is moveable to

allow positioning of the breast and for variable compression to suit the patient's anatomy. This geometry was first used in the PEM-1 scanner,[38–40] and later by Smith and colleagues.[41,42] The technique used on the only commercially available PEM Flex Solo scanner (Naviscan PET Systems, San Diego, CA) exploits a pair of linear arrays of detectors that scan across the breast during the examination.[25,36] Another design consists of a boxlike detector array that surrounds the breast, which should allow a more complete reconstruction of the activity within the breast.[43] A similar concept, not yet reduced to practice or implemented in either an experimental or a clinical setting, encloses the breast in a small cylindrical array of detectors with the breast pendant through the hole.[44]

All of these instruments use finely pixelated detectors and a compact geometry designed to reduce the blurring associated with the noncollinearity of the annihilation photons. Of special interest is the proposal by the Lawrence Berkeley National Laboratory group[45] in which the depth at which each annihilation photon is detected in the crystal is also encoded, allowing for a very compact geometry while avoiding the blurring associated with very oblique annihilation photons penetrating the detector. Another PEM prototype consisting of 2 opposing detectors and an array of pixelated (2×2 mm^2) YAP (yttrium aluminum perovskit):Ce crystals coupled to position-sensitive photomultiplier tubes was also developed.[31] The Clear-PEM developed by the Crystal Clear Collaboration at CERN consists of 2 compact and planar detector heads with dimensions 16.5×14.5 cm^2 for breast and axilla imaging.[29] This design is based on a fast, segmented, high atomic number detector with depth-of-interaction measurement capabilities.

An alternative design has been developed consisting of a dual-plate PET camera with the 2 plates (10×15 cm^2) constructed from arrays of $1 \times 1 \times 3$ mm^3 lutetium oxyorthosilicate (LSO) crystals coupled to silicon position-sensitive avalanche photodiodes (PSAPD).[33] Experimental measurements demonstrated close to 1 mm^3 volumetric spatial resolution, less than 12% energy resolution, and approximately 2 ns coincidence time resolution, whereas Monte Carlo simulations predict a 10% to 15% sensitivity for an 8- to 4-cm panel separation. The same group also investigated the advantages of semiconductor detectors comprising cadmium zinc telluride (CZT) crystal slabs with thin anode and cathode strips deposited in orthogonal directions on either side of each slab, which allows narrower energy window settings.[32] Recently, Raylman and colleagues[34] have developed a high-resolution PEM/tomography imaging and biopsy device (PEM/PET) to detect and guide the biopsy of suspicious breast lesions. The idea is to acquire PET images to detect abnormal focal tracer uptake and limited-angle PEM images that could be used to corroborate the biopsy needle position before tissue sampling. A spatial resolution of 2.01 mm at the center of the field of view was reported.

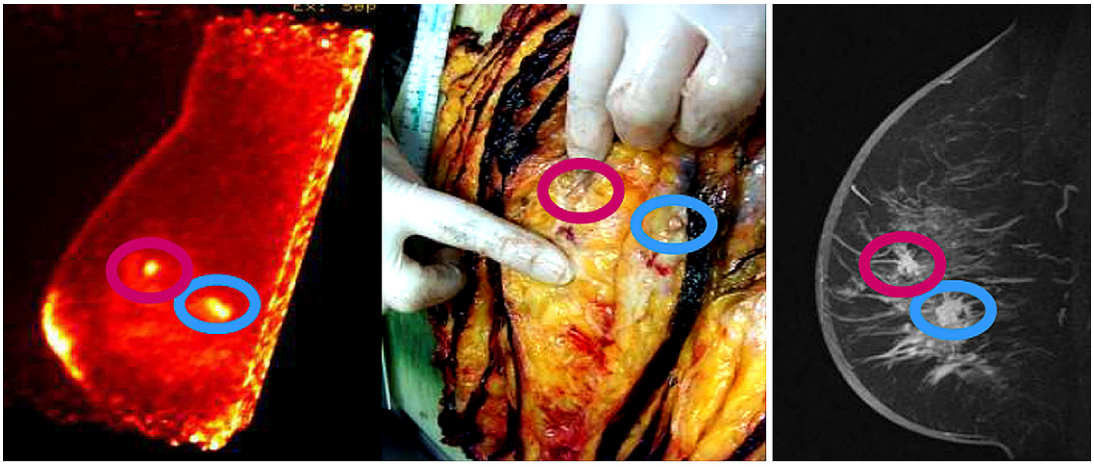

Fig. 4. A mass with increased FDG uptake in the left breast of a patient with breast cancer. MRI and PEM found 2 IDC lesions not seen by conventional mammography. Ultrasound identified lesion at 10 o'clock. PEM gave a closer estimate of lesion size. More importantly, PEM interpretation time was significantly faster than MRI acquired at 0.6-mm slice thickness which is an important issue for busy diagnostic imaging facilities. (*Courtesy of* Naviscan PET Systems, San Diego, CA.)

The availability of faster scintillation crystals and electronics that made time-of-flight (TOF) PET feasible opened new avenues to partial-ring dedicated PEM scanners without rotation of the detectors.[35] Simulation studies have shown that the contrast recovery coefficient for small hot lesions in a partial-ring scanner is similar to a full-ring non-TOF scanner. In addition, timing resolutions of 600 picoseconds and 300 picoseconds are needed for a two-thirds ring and a half ring scanner, respectively.

CLINICAL RELEVANCE OF PEM

The clinical relevance of this technology and its high diagnostic accuracy for the detection of breast lesions including ductal carcinoma in situ was demonstrated in the recent literature.[25,46,47] A PubMed search (in December 2009) using the term "PEM" resulted in 38 publications ranging from bench studies to large, independent, prospective clinical trials.

The results of the first clinical trial characterizing the clinical performance of PEM was published as early as 1999.[40] During the clinical trial of the PEM-1 scanner, 14 patients were studied including 10 patients who had various breast cancers confirmed by pathologic investigation of the surgically excised specimens. Only 5 of these had a clearly focal uptake (with a mean contrast of 5.8:1 with respect to the surrounding breast tissue). Three other patients were considered PEM-positive based on a significant count-rate asymmetry after accounting for factors such as isotope decay and volume of breast tissue in the field of view and detector separation.[10]

The first report of clinical results from a commercial PEM instrument, the PEM-Flex, were published by Weinberg and colleagues[25] in 2005. They reported on 94 cases performed at 4 different sites during the first year of use of the instrument. Analysis of these cases showed a sensitivity of 93% and a specificity of 83%. Unlike the PEM-1 scanner, the field of view of the commercial device is much larger, 24 × 18 cm versus 5.5 × 6.0 cm. A more sophisticated limited-angle reconstruction algorithm, which produces much clearer three-dimensional images, is also implemented on this system. It also has the ability to scan closer to the chest wall.

A more recent study presented at the 2008 Radiological Society of North America (RSNA) meeting including 208 patients reported that PEM imaging has a similar sensitivity to MR imaging but greater specificity (93% vs 79%).[47] This is consistent with the results reported earlier.[46] In addition, PEM was reported to provide valuable surgical information for cancer detection and surgical planning.[48] **Fig. 4** demonstrates the good correlation PEM has with both pathology and MRI. In addition, another argument in favour of PEM is the fact that it takes on average only one fourth of the time to interpret the PEM images compared to the time it takes to review the huge number of slices of a breast MRI.

In addition to the improvement in lesion detectability, a substantial improvement of the quantitative accuracy when using PEM compared with WB-PET was reported.[36,49,50] This is an important asset for metabolic characterization of lesions where more accurate estimates of the SUV may assist in discriminating benign and malignant lesions and also improve confidence in assessing response to treatment.

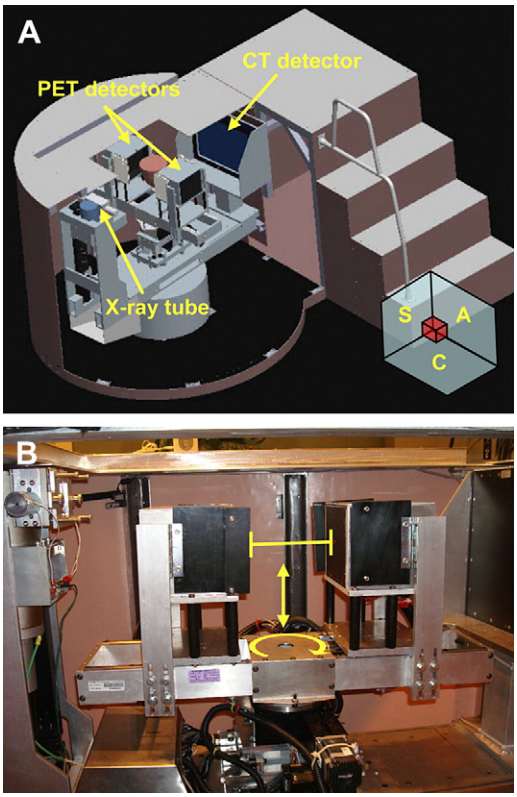

Fig. 5. (*A*) The dedicated breast PET/CT. The object between the PET detectors shows the approximate position of the patient's breast during scanning. Orientation of positioned patient's coronal (C), sagittal (S), and axial plane (A) are shown in the bottom-right-hand corner. (*B*) PET gantry allows for control of detector height (*vertical arrow*), separation distance (*horizontal line with end markers*), and rotation (*curved arrow*). (*Reprinted from* Bowen SL, Wu Y, Chaudhari AJ, et al. Initial characterization of a dedicated breast PET/CT scanner during human imaging. J Nucl Med 2009;50:1402; with permission.)

MULTIMODALITY BREAST IMAGING

Software Fusion of Multimodality Breast Imaging

The demand for multimodality imaging arose as a clinical prerequisite given the many positive features it can provide for improving diagnostic and therapeutic procedures. Software-based image registration can be challenging to perform on a routine basis in a clinical setting because it requires compatibility between scanning protocols used by various imaging modalities and outstanding collaboration between various clinical departments. These challenges may be overcome by the use of dual-modality systems described in the following section, however, software-based coregistration offers greater flexibility and might in some cases offer some complementary advantages to hardware-based approaches.[51,52]

Various techniques have been developed to coregister clinical multimodality medical imaging data.[53,54] The coregistration problem in the breast is quite different from the situation in brain imaging. In brain imaging, rigid-body registration involving simple geometric transformations such as translation and rotation to match the 2 image data sets is sufficient in most cases and has been used routinely in clinical settings worldwide since the 1990s. The solution to the image registration problem becomes more complicated particularly when the functional (SPECT or PET) and anatomic (CT or MR imaging) images are acquired in separate sessions on standalone systems, often in different locations and on different days. In this case, geometric relationships between different anatomic regions might be affected by various factors that render the solution difficult to achieve.

Deformable registration (warping) has been introduced as a technique to improve registration accuracy over a larger region of the patient's body. Various deformable image registration techniques have been suggested and used in the context of multimodality breast imaging. However, software-based image registration is still challenging and time consuming in most cases, which limits its use to academic institutions with advanced technical support that can also accommodate the requirements of these procedures (scanning on both modalities on the same day using carefully matched anatomic positioning and respiration protocols).[55,56] Moreover, clinical validation of deformable image registration in the context of breast imaging remains challenging and requires further research and development efforts.[57–60]

Dedicated Breast PET/CT Scanners

The introduction of WB-PET/CT systems in the clinic has revolutionized clinical practice in different ways, particularly in oncology. The use of this technology in the management of patients with breast cancer provides the possibility of correlating metabolic abnormalities observed on PET with patient anatomy, thus improving the

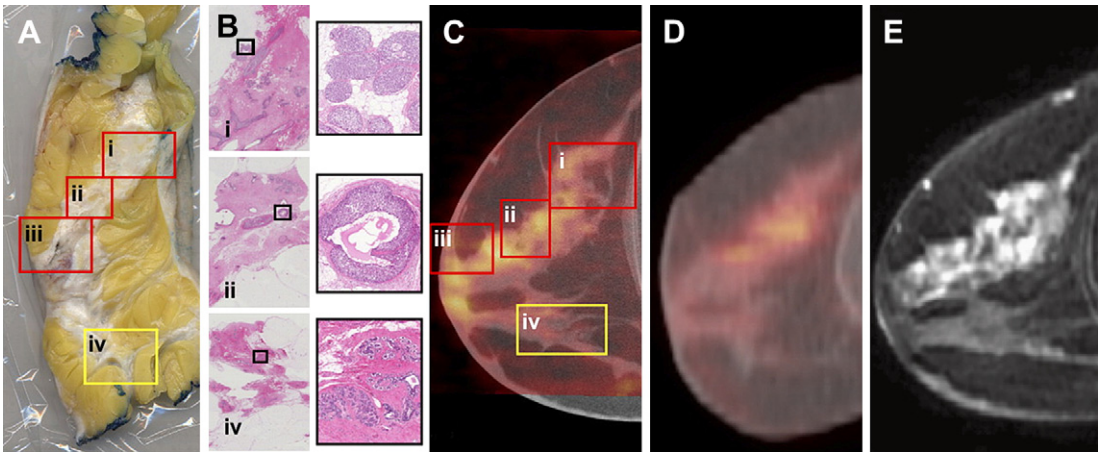

Fig. 6. (*A*) Sagittal tissue section excised from a mastectomy sample of a clinical study affected breast with 4 areas (*boxes*) of histology performed. (*B*) Histology tissue slides with magnified regions (*right*, corresponding to black boxes) revealed ductal carcinoma in situ, alone (i, ii) or with intralymphatic invasion (iii, not shown) and benign tissue (iv). Dedicated breast PET/CT (*C*), WB PET/CT (*D*), and delayed contrast enhancement MR imaging (*E*) sagittal image slices corresponding to tissue section (*A*). Boxes in dedicated breast PET/CT image (*C*) are at locations approximating those in tissue section (*A*). PET images (*C*, *D*) were windowed between 0% and 60% maximum image intensity. (*Reprinted from* Bowen SL, Wu Y, Chaudhari AJ, et al. Initial characterization of a dedicated breast PET/CT scanner during human imaging. J Nucl Med 2009;50:1406; with permission.)

accuracy of clinical diagnosis with respect to preoperative staging and primary diagnosis, disease restaging, treatment monitoring, and radiation therapy treatment planning.[61,62]

The development of dedicated breast CT units[63,64] paved the way for the introduction of high-resolution PET/CT systems dedicated for the breast with the aim of achieving improved spatial resolution and sensitivity compared with WB-PET systems. One such prototype consisting of an LSO-based dual-planar head PET camera (crystal size, $3 \times 3 \times 20$ mm^3) and 768-slice cone-beam CT was designed, fabricated, and tested at the University of California, Davis, CA, USA (**Fig. 5**).[65] The average spatial resolution obtained using a line source in warm background using maximum a posteriori (MAP) reconstruction was 2.5 mm; a peak sensitivity of 1.6% was measured at the center of the field of view. Preliminary results from a clinical trial demonstrate the potential of this technology, which clearly visualized the three-dimensional extent of suspected lesions in patients with cancer confirmed by biopsy.[66] **Fig. 6** shows a clinical study highlighting the improvement in image quality and contrast resolution when using dedicated breast PET/CT compared with WB-PET/CT.

Other combinations of imaging modalities for breast imaging have also been explored in academic settings including ultrasound (US)-MR,[67] US-mammography,[68] and PET-MR.[69,70] It is not clear if these technologies will find their way to the clinic in the near future and gain popularity as PET/CT did, but the future of multimodality breast imaging is certainly bright and novel emerging hybrid imaging technologies will certainly influence clinical care.

SUMMARY AND FUTURE PERSPECTIVES

Although WB-PET has the potential to detect distant spread of breast cancer, dedicated PEM systems offer a higher spatial resolution and sensitivity, and as such enhance the detectability of small-sized lesions. Following approval of PEM technology by the FDA, many facilities acquired this technology and are now gathering clinical experience through clinical trials.

The major limitation of early PEM instruments was their small field of view and reduced sensitivity near the chest wall. The field of view was limited by the PS-PMTs available in the early 1990s. Recent demands for these devices and their deployment in small-animal PET scanners, has led to much improvement in uniformity and the ability to image much closer to the edge without serious distortion. Now instruments like the PEM Flex Solo are able to capitalize on the advances in photon sensors. The problem of sensitivity loss near the edges of the field of view is intrinsic to three-dimensional PET acquisitions. During the early stages of PEM development this was not considered seriously enough. Now that it has been widely recognized, the situation has been improved using higher density, thinner shielding, better PMTs, and improved geometry. The effective field of view is at least 3 cm closer to the chest in the latest instruments than in the first prototype.

It is expected that PEM will play a pivotal role for screening high-risk patients and in preoperative surgical staging of patients with recent cancer diagnosis. This technology is not intended to replace conventional mammography as a screening tool, but will likely operate as a complementary molecular imaging tool similar to breast MR imaging.

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