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Initial clinical test of a breast-PET scanner

Raymond R Raylman, PhD¹, Jame Abraham, MD², Hannah Hazard, MD³, Courtney Koren, CNMT¹, Shannon Filburn, R.N.⁴, Judith S Schreiman, MD¹, Sobha Kurian, MD², Stan Majewski, PhD¹, and Gary D Marano, MD¹

¹Center for Advanced Imaging, Department of Radiology, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV, USA

²Hematology/Oncology, Department of Medicine, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV, USA

³Surgical Oncology, Department of Surgery, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV, USA

⁴Clinical Trials Research Unit, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV, USA

Summary

Introduction—The goal of this initial clinical study was to test a new positron emission/tomography imager and biopsy system (PEM/PET) in a small group of selected subjects to assess its clinical imaging capabilities. Specifically, the main task of this study is to determine whether the new system can successfully be used to produce images of known breast cancer and compare them to those acquired by standard techniques.

Methods—The PEM/PET system consists of two pairs of rotating radiation detectors located beneath a patient table. The scanner has a spatial resolution of ~2 mm in all three dimensions. The subjects consisted of five patients diagnosed with locally advanced breast cancer ranging in age from 40 to 55 years old scheduled for pre-treatment, conventional whole body PET imaging with F-18 Fluorodeoxyglucose (FDG). The primary lesions were at least 2 cm in diameter.

Results—The images from the PEM/PET system demonstrated that this system is capable of identifying some lesions not visible in standard mammograms. Furthermore, while the relatively large lesions imaged in this study were all visualised by a standard whole body PET/CT scanner, some of the morphology of the tumours (ductal infiltration, for example) was better defined with the PEM/PET system. Significantly, these images were obtained immediately following a standard whole body PET scan.

Conclusions—The initial testing of the new PEM/PET system demonstrated that the new system is capable of producing good quality breast-PET images compared standard methods.

Keywords

breast cancer; clinical test; dedicated imaging; FDG; PET

Introduction

During the past decade, significant advances have been made in the detection and diagnosis of breast cancer with techniques other than standard X-ray mammography. These methods are most often used to examine the breasts of women with inconclusive mammograms due to fibroglandular or multi-cystic breast tissue, and who have an increased risk for cancer. Currently, these women are often examined with dynamic contrast enhanced MRI (DCE-MRI) to determine if an occult lesion is present.¹ A 2008 meta-analysis studying the use of DCE-MRI in the evaluation of suspicious breast lesions reported a sensitivity of 90% and a specificity of 72%.² DCE-MRI relies on the increased vascularity of lesions to distinguish them from surrounding tissues and to aid in assessing the likelihood of malignancy. Since some benign breast diseases (such as fibroadenoma) are hyper-vascular, DCE-MRI is susceptible to false positive findings and, consequently, reduced specificity.³

In addition to these methods, nuclear medicine imaging methods have been proposed for use as an adjunct to X-ray mammography. For example, the single photon-emitting radiopharmaceutical Tc-99m-labelled Sestamibi has been used in combination with specialized imaging systems to detect breast cancer.⁴ This method has reported lesion detection sensitivity similar to DCE-MRI, and a slightly higher specificity.⁵ Furthermore, positron emission tomography (PET) has been applied to breast cancer imaging in women with indeterminate mammograms. The utilisation of tumour avid radiotracers, such as the glucose analogue F-18 Fluorodeoxyglucose (FDG), and high energy of photons produced by positron annihilation (511 keV), result in a potentially powerful method for identifying suspicious breast lesions even in dense, fibroglandular breasts. The utilisation of the radiotracers that depend on biochemical factors, such as glucose metabolism, instead of tumour tissue density or vascularity promise to enhance specificity compared to methods based on non-biochemical characteristics of breast cancers. A 2002 meta-analysis examining the ability of standard whole body PET scanners utilising FDG to detect breast lesions in patients with abnormal mammograms reported a sensitivity of 89% and a specificity of 80%.⁶ The somewhat low sensitivity and specificity found in these studies are due, at least in part, to the use of whole body PET scanners with limited spatial resolution capabilities (~4 mm to ~7 mm). This limitation makes standard FDG-PET imaging of breast cancer most appropriate for staging, instead of detection and diagnosis of most lesions.^{7,8}

Recently, specialised scanners were developed to address the limited capabilities of whole body PET scanners in imaging the breast. The first of these systems, known as the positron emission mammography (PEM) scanner, was proposed in 1994 by Thompson *et al.*⁹ Most PEM systems consist of at least one pair of planar scintillation detectors connected in coincidence. The breast is placed between these devices to permit either limited angle or full three-dimensional tomographic reconstruction if data are acquired from multiple angles. Table 1 shows the current efforts to produce dedicated, PET-based breast scanners, comparing several key capabilities of the systems with each other and with a representative whole body PET/CT scanner.

The West Virginia University (WVU) PEM/PET system used in this study produces high-resolution (~2 mm), three-dimensional tomographic images of the positron-emitting radionuclide distribution in breasts. An image of a mini-Derenzo phantom produced by the system is shown in Figure 1. The mini-Derenzo phantom is a standard tool used to demonstrate the spatial resolution capabilities of nuclear medicine tomographic imaging systems. It consists of a series of hollow rods containing radioactive tracer (the positron-emitting radioisotope F-18 in this case) arranged in sectors around the cylindrical phantom (Fig. 1a). Each sector contains rods of a given diameter with a centre-to-centre separation of twice their diameter.¹⁷ The phantom is placed in the centre of the scanner with its axis co-

linear with the axis of detector rotation. Figure 1b shows a transaxial image of the phantom. The fact that rods with diameters as small as 1.6 mm can be distinguished from one another in the image of the phantom illustrates the sub-2-mm spatial resolution of the system. This capability of the PEM/PET scanner could permit the visualisation of small lesions and features of large lesions not visible with whole body PET scanners. As the first step towards demonstrating the clinical utility of PEM/PET, this initial study was undertaken to assess how well the scanning procedure is tolerated by patients, and how PEM/PET images compare to those acquired by whole body PET scanners.

Methods

PEM/PET imager

The PEM/PET system is shown in Figure 2. It uses two pairs of rotating detector heads consisting of 96×72 arrays of $2 \text{ mm} \times 2 \text{ mm} \times 15 \text{ mm}$ Cerium and Yttrium doped Lutetium Orthosilicate (LYSO) elements coupled to 4×3 arrays of position-sensitive photomultiplier tubes. The detectors are positioned beneath the breast port in the patient bed. The field-of-view of the system is $20 \text{ cm} \times 15 \text{ cm}$. Data are acquired in a step-and-shoot fashion. Details regarding the system's construction and measurements of its intrinsic imaging capabilities are reported elsewhere.¹⁶ The raw data are reconstructed using a three-dimensional, ordered subset, expectation maximisation (3D-OSEM) algorithm¹⁸ optimised for use on a multi-processor computer system. These fully 3D reconstructed image sets can be re-sliced to produce mediolateral oblique (MLO), craniocaudal (CC), transaxial or views from virtually any angle. PEM/PET possesses a reconstructed spatial resolution of approximately 2 mm in all three-dimensions, and very high event detection sensitivity ($489 \text{ kcps}/\mu\text{Ci}/\text{mL}$).¹⁶ It also has the unique capability to guide the biopsy of suspicious lesions observed in the PEM/PET images¹⁹ and accurately quantify radiotracer concentration.²⁰

Patient imaging

In this initial investigation, five patients diagnosed with Stage IIIB locally advanced breast cancer scheduled for whole body FDG-PET/CT scans prior to the initiation of neo-adjuvant chemotherapy were enrolled in the study. The goal of these scans was to assess the metastatic spread of the disease. The subjects ranged in age from 40 to 55 years old. In preparation for the PET scans, the patients fasted at least 4 hours prior to injection of between 10 mCi to 12 mCi of FDG. Whole body PET scanning was performed with a Siemens Medical Solutions Biograph 16 HI-REZ PET/CT scanner (Erlangen, Germany) 1 hour following administration of the radiotracer. Patients voided just prior to the scanning session to reduce the amount of radioactivity in their bladders. The Biograph 16 HI-REZ has a spatial resolution of 4.4 mm at the centre of the field-of-view.¹⁰ The PET/CT scanning protocol consisted of six, 3-minute-long scans, in addition to a contrast-enhanced CT scan. Following the whole body PET/CT scan, the subjects were brought to the PEM/PET imaging room. Imaging of the subjects was performed approximately 2 hours after injection of FDG. The PEM/PET system requires the patients to lay prone on the imaging table and place one breast at a time through the port in the table into the field-of-view of the scanner. The PEM/PET scanner protocol consists of three interval movements of 30° ; the duration of each interval was 1 minute (total scan time was 3 minutes per breast). The breasts were scanned sequentially; so the total scan time was 6 minutes. Informed consent was obtained from the subjects prior to their participation in the study. The protocol was approved by the Institutional Review Board for the protection of human subjects (IRB) at our institution. The study complied with the confidentiality requirements of the United States Health Insurance Portability and Accountability Act of 1996.

Results

All of the relatively large primary breast lesions (~2 cm in diameter) were visible in the whole body PET/CT scans. These lesions were also seen on the PEM/PET images. Figure 3a shows a digital X-ray mammogram from a 55-year-old subject with extremely dense breasts and a history of fibrocystic changes, who presented with a palpable abnormality in the right breast and enlarged axillary lymph nodes. Ultrasound imaging revealed a 19 mm × 13 mm ovoid lesion at the 9 o'clock position. Following an ultrasound-guided biopsy, the lesion was found to be poorly differentiated infiltrating ductal carcinoma. While the lesion is not clearly discernable on the digital X-ray mammogram, it is visible in the MLO and transaxial views of the PEM/PET images shown in Figures 3b,c. Note that the transaxial view of the breast is only possible with a system such as PEM/PET that produces 3D-tomographic images.

Figure 4 shows representative images from a 51-year-old patient with silicone breast implants, and a biopsy-proven 30 mm × 26 mm infiltrating ductal carcinoma. Figure 4a demonstrates that this relatively large lesion is visible on the whole body PET/CT scan. The PEM/PET image of the lesion in Figure 4b shows the lesion in addition to FDG uptake in a structure that is likely a mammary duct. This enhanced uptake is probably due to either inflammation or FDG-avid cancer cells present in the duct. This determination could change the course of treatment; if ductal infiltration is suspected, then lymph node dissection is often performed. This structure was only visible on the PEM/PET image because of the very good resolution of the system compared to the whole body PET/CT scanner. Since this patient was successfully treated with chemotherapy and did not receive surgical removal of the lesion, we were not able to obtain confirmation of ductal infiltration via pathological analyses.

Figure 5a shows an upper torso FDG-PET/CT image of a 53-year-old woman with a 25 mm × 20 mm infiltrating ductal carcinoma showing FDG uptake in the lesion. Figure 5b is the PEM/PET image from this subject. In addition to FDG uptake in the lesion, increased uptake in a small (~3 mm-diameter) area that is likely an FDG-avid intra-mammary lymph node is visible. While this area was observed on the patient's mammogram, it was not suspected of containing disease and was not seen on the patient's whole body PET/CT scan. The approved study protocol did not permit the biopsy of areas found only with the PEM/PET system, so it was not possible to confirm the presence of disease in this region.

It is important to note that there were no significant artefacts visible in the images attributable to the presence of radioactivity present in the body of the patient out of the scanner's field-of-view. This good result is due, at least in part, to the tungsten shielding incorporated into the patient bed.¹⁶ Finally, the five subjects in this initial trial tolerated the imaging protocol very well. There were no reports of significant discomfort and the amount of time required for the imaging was considered acceptable.

Discussion

The application of specialised PET scanners to the examination of women with breasts that are challenging to effectively image with X-ray mammography has the potential to significantly improve the detection and diagnosis of breast cancer. This initial test was performed to explore the clinical potential of WVU's PEM/PET scanner, and to gain experience with the system in the imaging of humans in preparation for the initiation of a larger clinical trial of the system. Due to the restrictions placed on the study by the IRB, only patients receiving pre-chemotherapy, whole body PET/CT scans were included in the trial (Stage IIIB).

One of the main projected tasks for PEM/PET is detection of lesions not effectively visualised with mammography due to dense, glandular tissue. This capability was demonstrated by the relatively large lesion visible in the PEM/PET images shown in Figure 3. Note that this lesion was challenging to locate in the digital mammogram. The enhanced ability of PET scanners to detect lesions is due in part to its use of metabolic tracer-based imaging compared to structural imaging (such as mammography) that relies on density differences between lesions and surrounding tissue. As illustrated by these images, the difference in glucose metabolism in the tumour relative to surrounding dense breast tissue is significantly greater than the differences in densities between tumours and surrounding tissues. It is also important to note that the PEM/PET MLO and transaxial views could be used to guide biopsy of the lesions with our system.

The benefits of enhanced capabilities of the dedicated breast-PET scanner compared to the whole body PET/CT scanner is illustrated by the images in Figure 4. Specifically, the presumed infiltration of a mammary duct by FDG-avid cells is detectable only with the PEM/PET imager. The suspicious area was not biopsied, so this finding could not be verified. The capability to assess the extent of ductal infiltration could aid in planning of treatment options. Furthermore, due to the high-energy annihilation photons used in PET, the presence of breast implants in this patient did not compromise PEM/PET image quality. Another potential advantage of dedicated breast-PET systems is illustrated in Figure 5. This image demonstrates the ability of the new system to possibly detect the possible presence of FDG-avid cells in small areas (mammary lymph nodes for example) not discernable with X-ray mammography or whole body PET/CT scanners. This image also gives a glimpse at the potential for detecting small breast lesion with PEM/PET. The lymph node was measured to be 3 mm in diameter with mammography, so this result indicates that FDG-avid lesions at least as small as 3 mm in diameter may be detected with this system. Again, note that this area was not biopsied, so it was not possible to verify that this lymph actually contained tumour cells.

The images produced by our PEM/PET scanner compare well with those reported for the most mature of the other dedicated PET breast scanners. Specifically, our PEM/PET MLO images compare well in quality to those reported for the PEM scanner sold by Naviscan, Inc.¹¹ In contrast to the Naviscan scanner, which produces limited angle tomographic images, PEM/PET produces fully 3D tomographic images. Thus, PEM/PET images can be re-sliced to display virtually any view desired, not just MLO views, which will give radiologists more flexibility in reading the images. Furthermore, radiotracer quantification, often used in the analysis of PET images, is greatly enhanced by the use of the 3D tomographic images produced by PEM/PET.²⁰ This capability could be exploited, for example, to monitor the effectiveness of chemotherapy.

It should be noted that the approved study protocol permitted only the imaging of patients diagnosed with Stage IIIB breast cancer. Thus, the lesions were relatively large, so the task of detecting these tumours was not particularly challenging. Nevertheless, some potentially important capabilities of the scanner were identified, such as the detection of small FDG-avid regions. In addition, these initial results demonstrated that the high event detection sensitivity of the system permits PEM/PET imaging following a clinical whole body PET scan. The high detection sensitivity also means that less radiotracer has to be used to produce a PEM/PET image, thus reducing radiation exposure to the patient.

Conclusion

In conclusion, this initial test demonstrated that the WVU PEM/PET scanner could successfully be used with clinical patients and produce images that showed information not

visible in those produced by a whole body PET/CT scanner or X-ray mammography system. Thus, PEM/PET could be used as a second look method for women with suspicious mammograms with risk factors for breast cancer. Another option is to utilise PEM/PET as an adjunct to breast MRI. Specifically, it may be advantageous to utilise the higher specificity of PET-based imaging to complement the good sensitivity of MRI-based methods. These applications of the PEM/PET will be studied in a future clinical trial. The clinical utility of PEM/PET may be further enhanced by the use of the system to perform biopsies of suspicious regions and quantify radiotracer concentration to assess the effectiveness of therapies.

Acknowledgments

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Fig. 1. Phantom image from the PEM/PET system. (a) Picture of the mini-Derenzo phantom (the numbers shown on the picture are the diameters of the rods in millimetres) (b) PEM/PET image of the phantom.

Fig. 2.
Picture of the PEM/PET system.

Fig. 3. Images from a patient with extremely dense breasts. (a) MLO view of the X-ray mammogram (b) MLO view of the FDG-PET/PET scan of the breast showing the tumour and (c) transaxial PEM/PET view of the breast.

Fig. 4.
(a) Transaxial whole body PET/CT image showing the FDG-avid breast lesion and (b) MLO view of the PEM/PET image of the lesion, radiotracer uptake in an associated mammary duct is highlighted by the arrow.

Fig. 5.
(a) Transaxial view from a whole body PET/CT image showing the FDG-avid breast lesion and (b) MLO PEM/PET image (the arrow shows the likely FDG uptake in an occult lymph node).

Table 1

Comparing dedicated breast-PET imaging scanners

	Biopsy	Breast		Quantitative
	3D tomography	Guidance	Immobilisation	Imaging
Clinical PET/CT ¹⁰	Y	N	N	Y
Naviscan ¹¹	N	Y	Y	N
UC-Davis ¹²	Y	N	N	N [†]
UC-Berkeley ¹³	Y	N	N	N [†]
Clear PEM ¹⁴	N	N	Y	N
Duke PEM ¹⁵	N	N	Y	N
WVU PEM/PET ¹⁶	Y	Y	Y	Y

[†] Capable, but corrections not developed.