Investigating the limit of detectability of a positron emission mammography device: A phantom study

Nicholas A. Shkumat,^{a),b)} Adam Springer,^{c)} and Christopher M. Walker^{d)}

Department of Imaging Physics, UT MD Anderson Cancer Center, 1515 Holcombe Boulevard - Unit 1352, Houston, Texas 77030

Eric M. Rohren^{e)}

Department of Nuclear Medicine, UT MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

Wei T. Yang^{f)}

Department of Diagnostic Radiology, UT MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

Beatriz E. Adrada^{g)}

Department of Diagnostic Radiology, UT MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

Elsa Arribas^{h)} and Selin Carkaciⁱ⁾

Department of Diagnostic Radiology, UT MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

Hubert H. Chuang^{j)}

Department of Nuclear Medicine, UT MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

Lumarie Santiago^{k)}

Department of Diagnostic Radiology, UT MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030

Osama R. Mawlawi^{l)}

Department of Imaging Physics, UT MD Anderson Cancer Center, 1515 Holcombe Boulevard - Unit 1352, Houston, Texas 77030

(Received 26 May 2010; revised 11 July 2011; accepted for publication 3 August 2011; published 24 August 2011)

Purpose: A new positron emission mammography (PEM) device (PEM Flex Solo II, Naviscan Inc., San Diego, CA) has recently been introduced and its performance characteristics have been documented. However, no systematic assessment of its limit of detectability has been evaluated. The aim of this work is to investigate the limit of detectability of this new PEM system using a novel, customized breast phantom.

Methods: Two sets of F-18 infused gelatin breast phantoms of varying thicknesses (2, 4, 6, and 8 cm) were constructed with and without (blank) small, shell-less contrast objects (2 mm thick disks) of varying diameters (3–14.5 mm) [volumes: 0.15–3.3 cc] and activity concentration to background ratio (ACR) (2.7–58). For the phantom set with contrast objects, the disks were placed centrally inside the phantoms and both phantom sets were imaged for a period of 10 min on the PEM device. In addition, scans for the 2 and 6 cm phantoms were repeated at different times (0, 90, and 150 min) post phantom construction to evaluate the impact of total activity concentration (count density) on lesion detectability. Each object from each phantom scan was then segmented and placed randomly in a corresponding blank phantom image. The resulting individual images were presented blindly to seven physician observers (two nuclear medicine and five breast imaging radiologists) and scored in a binary fashion (1—correctly identified object, 0—incorrect). The sensitivity, specificity, and accuracy of lesion detectability were calculated and plots of sensitivity versus ACR and lesion diameters for different phantom thicknesses and count density were generated.

Results: The overall (mean) detection sensitivity across all variables was 0.68 (95% CI: [0.64, 0.72]) with a corresponding specificity of 0.93 [0.87, 0.98], and diagnostic accuracy of 0.72 [0.70, 0.75]. The smallest detectable object varied strongly as a function of ACR, as sensitivity ranged from 0.36 [0.29, 0.44] for the smallest lesion size (3 mm) to 0.80 [0.75, 0.84] for the largest (14.5 mm).

Conclusions: The detectability performance of this PEM system demonstrated its ability to resolve small objects with low activity concentration ratios which may assist in the identification of early stage breast cancer. The results of this investigation can be used to correlate lesion detectability

with tumor size, ACR, count rate, and breast thickness. © 2011 American Association of Physicists in Medicine. [DOI: 10.1118/1.3627149]

Key words: PEM, PET, breast imaging, detectability

I. INTRODUCTION

Breast cancer is the most prevalent malignant cancer among American women, accounting for 27% of all cancer cases and 15% of cancer deaths.¹ In 2009, it was reported that approximately 40,000 women would die as a result of this disease, with an additional 250,000 new cases diagnosed.¹ Like most cancers, early detection of breast cancer is key to survival.

Several imaging modalities are currently used in the early detection of breast cancer; these include mammography, ultrasound, and magnetic resonance imaging. These techniques however, have documented weaknesses either in their sensitivity or specificity particularly in women with dense breasts that have elevated risk of breast cancer.^{2–16} A common attribute amongst these modalities is their primary dependence on morphological features of the underlying tissue to detect breast abnormalities while excluding functional information.

Functional imaging such as scintimammography,^{17,18} breast specific gamma imaging (BSGI),^{19–21} positron emission tomography (PET) Refs. 22–25 and more recently, positron emission mammography (PEM) Refs. 26 and 27 has also been used as a complementary diagnostic modality for the evaluation of breast cancer. In particular, PET using 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (FDG) has been gaining acceptance for the diagnosis, staging, and management of breast cancer.^{23,25} With high sensitivities (84%) and specificities (88%), PET has been shown to influence patient management in over 30% of cases.²⁵ The primary difficulties in using whole-body PET for breast imaging however are twofold. The extrinsic spatial resolution (clinical ~6–9 mm) is insufficient to detect small suspicious regions within the breast, and the scanner's gamma ray detection sensitivity is relatively low (~0.007 cps/Bq). In this regard, whole-body PET is likely able to detect only more advanced disease than small tumors that are in the early stage of development. In addition, negative PET scans would not be able to exclude the presence of small tumors.²²

Dedicated PEM is a new application of positron emission imaging that attempts to address the weaknesses of whole-body PET. Through dedicated geometry and system components, both imaging resolution and gamma ray sensitivity can be dramatically improved. Dedicated breast-PET imag-

ing was initially proposed in 1994,²⁸ but garnered minimal attention in the clinical community. In recent years, numerous groups have invested considerable effort in researching this form of breast imaging,^{29–36} and recently, a clinical PEM system (PEM Flex Solo II, Naviscan Inc., San Diego, CA) has achieved 510(k) clearance. The performance characteristics of this system have been published elsewhere^{37,38} however no systematic evaluation of this system's limit of detectability has been performed.

The aim of this article is to investigate the detectability limits of the PEM Flex Solo II device using a customized phantom developed exclusively for this work. Simulated lesions of varying size, activity concentration ratio (ACR) between lesion and background, total activity (count density), and breast size were evaluated. Using certified radiologists and nuclear medicine physicians as observers, the detectability was determined based on the sensitivity and diagnostic accuracy of lesion identification in a phantom study.

II. MATERIALS AND METHODS

II.A. PEM flex solo II

The PEM Flex Solo II is a commercially available dedicated breast positron emission tomography device [Figs. 1(a) and 1(b)]. Unlike whole-body PET scanners, the PEM Flex Solo II operates using two opposed-head detectors, each contained within a transparent paddle (one support, one “immobilization”). The detectors move synchronously across the field of view during acquisition, and are mounted on a mobile gantry by a rotating, articulating arm. The arm can be repositioned to permit views similar to those encountered in mammography [viz. cranial-caudal (CC), medial-lateral oblique (MLO)], which may potentially assist in side-by-side clinical review.

Image reconstruction is performed using limited angle tomographic methods and a 3D maximum likelihood expectation maximization (MLEM) algorithm^{37,38}. This reconstruction technique offers the ability to create high-resolution in-plane images parallel to the detector faces with significant blurring in the direction perpendicular to the detector face. In its current implementation on the PEM Flex

FIG. 1. (a) Photograph of the PEM Flex Solo II dedicated breast PET imaging device. (b) Magnified view of the immobilization paddles and corresponding coincidence detectors.

Solo II, this reconstruction algorithm does not account for attenuation, scatter, deadtime or random count corrections. The in-plane image size is 200x160 pixels, each measuring 1.2×1.2 mm. Following each acquisition, a total of 12 slices are created, with thickness dependent on paddle separation (viz. slice thickness = paddle separation $\div$ 12). Scanner performance and system characterization can be found elsewhere.^{37,38} In brief, the in-plane spatial resolution is 2.4 ± 0.3 mm and out-of-plane resolution is 8.0 ± 1.0 mm, while the total system sensitivity (NU4 standards) is 0.16 cps/Bq.^{37,38}

II.B. Development of a multimodality PEM phantom:

To test the PEM Flex Solo II limit of lesion detectability requires imaging a phantom that can emulate the female breast, while satisfying the following criteria:

- (i) uniform background activity
- (ii) density similar to tissue
- (iii) ability to create varied thicknesses
- (iv) ability to suspend carapace free objects at varied depths
- (v) free of a container

No existing phantom known to the authors satisfied all of these requirements. Typically, PET phantoms are acrylic containers/shells filled with ^{18}F water, and contrast objects are usually in the form of hollow rods or spheres with shells, filled with a different activity concentration of the radionuclide with respect to the background. In this regard, a gelatin phantom with gelatin inserts was designed and fabricated to satisfy these requirements while being affordable and easy to manufacture. A clear advantage of these inserts over “fillable” objects is that they are free of a carapace and are in direct contact with the background activity. Thus, the detectability of these objects is not enhanced by a cold ring caused by an acrylic shell. Other investigators have previously suggested the use of gelatin based phantoms,^{26,39} however their designs were not specifically suited to satisfy all of the above criteria.

Gelatin (Knox Gelatine, Kraft Foods, Northfield, IL) was used as the base material. It can be thoroughly mixed with any solution (i.e., water), has a density very similar to water, and can be constructed in layers facilitating various phantom thicknesses and suspension of objects at various depths. In addition, while in liquid form, radioactivity can be added

FIG. 2. Schematic of the customizable PEM phantom. The phantom consisted of 25 inserts of different diameters and ACR, sandwiched between two layers of variable thicknesses of gelatin.

and thoroughly and uniformly mixed. This satisfied the first four criteria. The fifth criterion was satisfied once the gelatin mixture was properly cured, (following a short duration in subzero temperatures) as it could be removed from its container and handled while retaining its shape. A schematic of the phantom and its components is shown in Fig. 2.

II.B.1. Phantom formation

Creation of the PEM phantom required approximately 2 h in a multistage process. First, a gelatin mixture was made by combining 1000 ml water with 42 g of gelatin powder. Following complete dissolution, a specified prescription of ^{18}F was added and thoroughly mixed. This solution acted as the uniform background for the phantom, and was calibrated to have an activity concentration of $\leq 0.1 \mu\text{Ci/cc}$ at scan time.

The base layer of the phantom was created by pouring a desired portion of the radioactive gelatin mixture into a lubricated plastic mold ($15.5 \times 15.5 \text{ cm}^2$). It was then placed in a freezer ($\sim -20^\circ\text{C}$) and allowed to harden. This duration of the curing process varied, from 15 to 35 min, depending on the volume of the mixture.

Numerous objects (herein referred to as “inserts”) of varying diameter and contrast were needed to evaluate the detectability performance of the PEM system. Again using gelatin as a base material, several gelatin-water mixtures with varied activity concentrations were inserted into 60 cc syringes. Food coloring was added for uniqueness. After adequate mixing, a fixed volume of each was dispensed into

FIG. 3. (a) Photograph of PEM inserts. (b) Following administration of top gelatin layer and removal of plastic mold. A total of 25 inserts were placed in the phantom.

TABLE I. PEM insert diameters, volumes, and aspect ratios.

Insert diameter (mm)	Insert Volume (ml)	Aspect ratio (Diameter/Thickness)
3.0	0.14	1.5
4.5	0.32	2.25
6.0	0.57	3
9.0	1.27	4.5
14.5	3.30	7.25

its own Petri dish (viz. 10 cc for a 2 mm thick disk), and allowed to harden in a refrigerator (-3°C). The set volume allowed for a constant disk thickness across numerous FDG concentrations. After curing, individual inserts were “cut” from the Petri dishes using hollow cylinders of various diameters [Fig. 3(a)]. Five insert sizes and one thickness (2 mm) were used, along with five activity concentration ratios, listed in Tables I and II giving a total of 25 different inserts. This process allowed for the creation of inserts with consistent, reproducible thicknesses and diameters. As mentioned before, a clear advantage of these inserts over “fillable” objects is that they are free of a carapace and are in direct contact with the background activity. Thus, the detectability of these objects is not enhanced by a cold ring caused by an acrylic shell.

The activity concentration ratios were chosen to simulate the approximate clinical range of tumor-to-background uptake. From literature,²⁷ the mean tumor to fat ACR is 7.9 (range 1.5–53.8), whereas the tumor to glandular mean ACR is 4.1 (range 1.3–10.2). The inserts were then placed on top of the base layer of gelatin in a known, but randomly established pattern. Following another brief duration within the freezer, the upper layer of the phantom was then carefully poured (so as not to displace the inserts from their preset locations) directly onto the base and inserts. The phantom was then placed within the freezer until completely cured.

After removal from the freezer, the phantom was removed from the plastic shell and placed onto a plastic sheet [Fig. 3(b)]. Four phantoms of different thicknesses (2, 4, 6, and 8 cm) were constructed for this study. In each phantom, the inserts were placed in the center at a thickness of 1, 2, 3, and 4 cm, respectively. In addition, “blank” phantoms (with no inserts) were created with matching background activity concentrations, total thicknesses, and total activities (count density). These phantoms were used for analysis, described later.

II.B.2. Phantom imaging

Each phantom was imaged using the PEM device, immediately following its completion using the default clinical proto-

TABLE II. Insert activity concentration ratios.

Activity concentration ratio
2.7–2.8
5.5–5.8
12.1–12.3
26.3–26.8
57.6–58.0

col (10 min, full field-of-view). Each phantom was centrally placed between the two detector heads (paddles) of the PEM system with a paddle separation set to equal each phantom thickness. The acquired data was then reconstructed using vendor provided software. Currently, this software does not account for attenuation, scatter, deadtime or random count corrections, and the number of iteration, subsets and choice of image smoothing is not user configurable. For the 2 and 6 cm phantom thicknesses with inserts and their corresponding blank phantoms, the imaging was repeated at 90 and 150 min after the initial scan ($t=0$) to produce images with decreasing count density (using the identical protocol). In total, sixteen imaging volumes were collected using the PEM device. Eight volumes with inserts and another eight blank volumes scanned at 0, 90, 150 min for the 2 and 6 cm thicknesses and 0 min for the 4 and 8 cm thick phantoms. The slice thickness for each PEM acquisition depended on the corresponding phantom thickness and varied from 1.67 to 6.7 mm for the 2 and 8 cm phantoms respectively. As each PEM acquisition contained 12 slices, only the central slice intersecting the contrast objects was used in the subsequent analysis.

II.C. Detectability study

To evaluate the performance of the PEM imaging system, a detectability study was performed using seven certified, staff physicians as observers (five radiologists specializing in breast imaging, two nuclear medicine physicians). The diagnostic task was to identify the presence of an object within the image, and its location. Each image was viewed in a reading room on a Planar Dome display workstation (Planar Systems Inc., Beaverton, OR).

To remove any bias from showing images containing all inserts at the same time, each of the 25 inserts in each phantom thickness was manually segmented from the phantom image using custom developed software in the MATLAB (Mathworks, Natick, VA) environment. Following segmentation, each object was individually placed in a random location in the corresponding blank phantom image. Coordinates were chosen using a random number generator and were restricted to the central 11×11 cm region of the phantom (see results section). To ensure that the border between segmented area and the noise image was not detectable, a significant portion of background area around the insert was also segmented, with an irregularly shaped periphery. The significant contribution of background noise within PEM images assisted in ensuring an artifact-free segmentation process. For each phantom acquisition, 30 images were produced; 25 images containing one insert (5 insert sizes $\times$ 5 ACR), and 5 blank images (without inserts). Thus, this observer study contained a total of 240 images (2 and 6 cm thickness imaged at 0, 90, and 150 min; plus 4 and 8 cm thickness imaged at 0 min).

A custom interface was also developed in Matlab to perform the observer study. Each observer was permitted to freely “window” and “level” each image, and, once a decision was made, to click on the location of the insert, if applicable. If no insert was detected, clicking any point outside of the phantom would indicate that decision. The observers

FIG. 4. PEM images of a phantom (4 cm) acquisition. Twelve images correspond to slice thickness of 3.3 mm. The inserts were contained within slice #7.

were notified that the simulated lesions were circular, and were not aware of the total number of noise-only images. As each contrast object was individually segmented from the imaging volume, no bias was introduced as a result of insert and imaging geometry. Prior to the study, each observer participated in a training set, containing three images. The purpose of the training was to ensure that each of the observers was comfortable with the program interface, and that their decisions were accurately recorded.

III. RESULTS

Images of the entire reconstructed volume (12 images) of the 4 cm PEM phantom are shown in Fig. 4. The 2 mm thick inserts were located completely within the slice thickness of image #7. Noticeable on each of the 12 images are significant artifacts at the phantom periphery, most severe at the chest-wall edge (top). These artifacts were encountered in each image of all phantoms and are presumed to be a result of greater statistical noise due to fewer lines of response (lower sensitivity) at the edge of the field of view.³⁷ For this reason, the placement of each contrast object was restricted to the central 11 × 11 cm region of the phantom. Furthermore, signal contribution from contrast inserts in the central slice of the phantom was visibly apparent in slices both above and below the insert location. Out-of plane spatial blurring in the direction between the detectors was more apparent for inserts with high activity concentration. This is a direct result of the limited angle tomography reconstruction method utilized by the PEM system.

Figure 5 shows image #7 of the reconstruction volume of the 4 and 8 cm thick phantom with all 25 inserts [Figs. 5(a) and 5(c)] alongside corresponding blank images with segmented and randomly placed inserts [ACR = 58.0, diameter = 4.5 mm for Fig. 5(b) and ACR = 58.0, diameter = 14.5 mm in Fig. 5(d)]. Images similar to what is shown in Figs. 5(b) and 5(d) were subsequently evaluated by

the physicians to assess the limit of detectability of the PEM system.

The overall mean sensitivity for lesion detection across all insert sizes, ACR, and phantom thicknesses was 0.68 (95% CI: [0.64, 0.72]) with a corresponding specificity of 0.93 [0.87, 0.98] and diagnostic accuracy of 0.72 [0.70, 0.75]. Separating observers by specialty, the mean sensitivity for breast radiologists was 0.68 [0.59, 0.77], and nuclear medicine physicians was 0.67 [0.65, 0.68]. The difference between observer types was not statistically significant ($p > 0.5$). A summary of the detectability results is shown in Table III.

III.A. Activity concentration ratio

The sensitivity for lesion detection as a function of ACR for all observers across all insert diameters and phantom thicknesses at $t=0$ is shown in Fig. 6(a), with the solid line denoting a curve of best fit for the mean of all observers and error bars denoting the 95% CI. Performance was poor and relatively highly variable at low ACR (mean: 0.22, [0.18, 0.26] for ACR of 2.8), rising sharply to 0.93 [0.91, 0.95] at ACR of 58. The clinical ACR range (mean 4.1 and 7.9)²⁷ corresponds to a mean sensitivity of 0.40 (ACR = 4.1) and 0.63 (ACR = 7.9).

III.B. Lesion diameter

The sensitivity for lesion detection as a function of insert diameters across all phantom thicknesses and insert ACR for all observers at $t=0$ is shown in Fig. 6(b), again with the solid line denoting a curve of best fit and error bars denoting the 95% CI. Sensitivity increased from 0.36 [0.29, 0.44] for the smallest insert size (3 mm) to 0.80 [0.75, 0.84] for the largest insert size (14.5 mm).

III.C. Phantom thickness

The sensitivity of lesion detection as a function of phantom thickness across all ACRs and lesion diameters at $t=0$

FIG. 5. PEM images containing all 25 inserts for the 4 [Fig. 5(a)] and 8 cm [Fig. 5(c)] thick phantoms, (b) Segmented PEM blank image with single, segmented insert [phantom thickness = 4 cm, ACR = 58.0, diameter = 4.5 mm] (d) Segmented PEM blank image with single, segmented insert [phantom thickness = 8 cm, ACR = 58.0, diameter = 14.5 mm].

for all observers is shown in Fig. 6(c) again with the solid line denoting a curve of best fit and error bars denoting the 95% CI. Sensitivity decreased from 0.84 [0.79, 0.89] to 0.47 [0.44, 0.51] for the 2 and 8 cm phantom thicknesses respectively. Overall, sensitivity decreased with increasing phantom thickness due to the increase in attenuation, scattering media, and total background activity. The change in detection sensitivity with phantom thickness across all ACR and lesion diameters for all observers at the initial (time = 0) acquisition was statistically significant (ANOVA test, $p < 0.05$).

III.D. Total activity (count density)

The sensitivity of lesion detection as a function of count density for both phantom thicknesses (2 and 6 cm) across all ACRs and lesion sizes for all observers is shown in Fig. 6(d) with error bars denoting the 95% CI. Sensitivity decreased with decreasing count density ($t = 0$ to $t = 150$ min scan time post phantom construction) from 0.84 [0.79, 0.89] to 0.75 [0.7, 0.8] and 0.63 [0.54, 0.73] to 0.4 [0.35, 0.45] for the 2 and 6 cm thick phantoms, respectively. There was a statistically significant difference in performance between count densities at $t = 0$ and $t = 90$ min, and $t = 0$ and $t = 150$ min ($p < 0.05$ in both cases), regardless of phantom thickness. Images at the lowest count density were clearly noisier and had the lowest observer sensitivity performance. Although the mean detection sensitivity was greater for a count density at $t = 90$ min when compared with $t = 150$ min, the difference was not significant ($p > 0.1$ for both 2 and 6 cm thicknesses). Figure 7 shows the central slice of the 6 cm

phantom imaged at the three different count densities corresponding to $t = 0$, 90, and 150 min.

IV. DISCUSSION

This work investigated the limits of detectability of the Naviscan PEM Flex Solo II. An observer study was conducted using five breast radiologists and two nuclear medicine physicians and evaluated the imaging performance of this system as a function of lesion diameter, lesion-to-background activity concentration ratio, phantom thickness, count density, and observer specialty. To evaluate detectability, a novel phantom was designed and developed using inexpensive, readily available components. The result is a disposable medium with a high degree of size and shape customizability, with the ability to suspend objects that varied in both size and contrast. The objects suspended within the phantom were free of a shell, and thus their detection was unbiased by the presence of a cold boundary.

The detectability of an object in this study was quantified using observer sensitivity. The diagnostic accuracy was also used as a supplemental performance measure. As expected, observer performance improved with increased lesion diameter, activity concentration ratio, and count density, in addition to decreased phantom thickness. Also, as indicated by the data presented in Table III, the variability in observer performance between physicians was relatively small (coefficient of variation across observers $< 10\%$ for both sensitivity and specificity).

Thinner phantoms demonstrated a statistically significant (ANOVA test, $p < 0.05$) sensitivity performance benefit over thicker models across all ACRs and lesion diameters for all

TABLE III. Complete detectability study results at full activity concentration ($t = 0$).

	Sensitivity	Specificity	PPV	NPV	Accuracy
Observer 1	0.64	1.00	1.00	0.36	0.70
Observer 2	0.74	0.87	0.96	0.44	0.77
Observer 3	0.76	0.79	0.94	0.45	0.77
Observer 4	0.67	0.95	0.99	0.38	0.72
Observer 5	0.61	1.00	1.00	0.34	0.68
Observer 6	0.68	0.95	0.99	0.38	0.73
Observer 7	0.65	0.91	0.97	0.37	0.70
Study [95% CI]	0.68 [0.638,0.719]	0.93 [0.869,0.981]	0.98 [0.959,0.994]	0.39 [0.357,0.421]	0.72 [0.696,0.747]

observers at the initial acquisition ($t = 0$) [Fig. 6(c)]. Lesion detectability decreased with increasing phantom thicknesses due to an increase in scattering media, attenuation, and total background activity. With regards to count density, phantom thickness did not influence observer performance as the detection sensitivity was consistently greater at count densities of $t = 0$ vs $t = 150$ min as well as $t = 0$ vs $t = 90$ min ($p < 0.05$ for both 2 and 6 cm). The difference between the 2 and 6 cm phantoms at all time points was significant ($p < 0.05$) as shown in Fig. 6(d). These revelations may play an important role in patient management, for the PEM device with its current software implementation may be ideally

suited for smaller breasts, where a patient can be scanned perhaps immediately after a whole body acquisition.

The overall observer performance reinforced many of the potential advantages concerning dedicated breast-PET devices, in particular, a very high specificity and good sensitivity. However, the considerable amount of background noise reduced observer performance of small lesions with low ACR by increasing the number of reported false negatives. For all breast thicknesses, the detectability was poor for the smallest object (3 mm), but improved with increasing object sizes, across all ACRs. This work can then be used to relate tumor size and ACR to detectability performance.

FIG. 6. Detection sensitivity across observers as a function of (a) ACR, (b) lesion diameter, (c) phantom thickness, and (d) count density. Error bars represent the 95% confidence interval for each data point. Figures (a)–(c) correspond to $t = 0$ only.

FIG. 7. Central slice of the 6 cm phantom imaged at the three different count densities corresponding to $t = 0, 90$, and 150 min.

It is difficult to summarize the results of this work using a discrete quantifier. As shown in Fig. 6, the detectability performance of this system is continuous, and whether an object will be detected cannot be predicted with certainty. These results, however, can provide an indicator of the likelihood of detection. For example, given a breast thickness and a lesion ACR at the clinically observed activity concentration ratio²⁷ we can infer the limit of detectability with regards to lesion size. This work specifies that for an insert with an ACR of 5.5 (within the 4.1–7.9 clinical range)²⁷ within a 6 cm breast thickness, the mean detection sensitivity across all observers at the highest investigated count density ($t = 0$) was 0.86 for the largest diameter object (14.5 mm) and dropped to 0 for the smallest object (3 mm).

In addition, the results from this work are similar to those reported in literature³⁷ which indicated that an ACR of 10 was required for visualization of a 4 mm sphere. In this work, the sensitivity for a 4.5 mm disk at an ACR of 12.3 was 0.71 across all phantom thicknesses, reducing to 0.32 at an ACR of 5.5. As reported earlier, these values demonstrate strong phantom thickness dependence.

There are a number of limitations associated with this work. The first is affiliated with the phantom itself. As it was made from gelatin and water, it does not adequately simulate the attenuation characteristics of an average human breast. The impact of this limitation for the PEM detectability study, however, was minimal due to the penetration of 511 keV photons. Its composition was slightly closer to that of a dense, glandular breast, a type of breast that belongs to a member of the target population for this imaging device (due to mammography's reduced performance in this clinical subgroup).

Another potential limitation with the phantom was that the inserts themselves may not effectively simulate the true shape of a breast lesion. Each insert was 2 mm thick, and was initially chosen as it was a reproducible thickness in manufacturing and was able to fit precisely within a single PEM slice with 4, 6, and 8 cm paddle separation. With the considerable amount of out-of-plane blurring caused by the reconstruction method, it is conceivable that lesions larger than a single slice would demonstrate an increase in signal, potentially increasing the detectability performance. Thus, this study can be considered a scenario where detectability is most difficult, and would likely increase with spherical-shaped lesions. Fabrication of spherical lesions was investigated (stacking multiple disks), but they were difficult and

unfeasible to construct. The variable slice thickness between different phantom sizes may also have influenced the results. For phantom thicknesses greater than 2 cm, the PEM slice thickness was larger than the insert height (2 mm), and thus the influence of partial volume effects were not present. For the 2 cm phantom thickness, however, PEM slices were 1.67 mm, thus the entire insert volume was not contained within the slice. This may have resulted in a slight reduction in observer performance, however the more significant out-of-plane blurring likely minimized this effect. Differences caused by partial volume effects were not investigated in this work.

Another possible limitation of the study was the process of segmenting inserts and adding them to the blank image for observer evaluation. Such an approach could potentially result in artifacts or noise texture at the periphery of the segmented insert, thereby biasing image interpretation. However, since we had no access to the reconstruction engine to embed each individual lesion in the sinogram data and later reconstruct the image, nor was it feasible to construct a phantom for each lesion size and ACR, we felt this approach is the best possible solution. In an effort to reduce the impact of this process, care was taken to segment each lesion with a non-uniform boundary and ample background material to provide a seamless boarder when inserted into the blank phantom image. Moreover, the segmented inserts were placed within the central 11×11 cm of the phantom (the most uniform and artifact-free area of the reconstructed image) to aid in this process. Furthermore, the considerable contribution of background noise within the resulting PEM images also assisted in suppressing any border artifacts between the segmented region and the background.

Finally, the use of a homogeneous background and the absence of activity outside of the imaging volume are two other limitations of this work. Both of these limitations likely caused a slight improvement in the detectability performance across the entire study due to a reduction in background variability in FDG uptake and scattered and random events, respectively. Future work will investigate the effects of an activity-filled phantom (i.e., torso phantom) placed at the chest-wall edge of the system on the performance of the PEM Flex Solo II.

Additional future work includes extending the use of the phantom to new applications (routine quality assurance, system performance verification), and research developments. The current configuration, however, was not viable for an

extended period of time (the gelatin concentration was low to minimize the overall density), causing the phantom to lose shape and stability after a number of hours at room temperature. Long-lived phantoms may be created using more permanent materials (i.e., epoxy), and longer-lived radionuclides (i.e., Ge-68). Additional phantom improvements include: developing lesions that better represent true tumor size and shape (spheres, fibers), and creation of larger phantoms. In particular, evaluating thicker phantoms can present a number of interesting investigations, as it would change the effective slice thickness, introducing partial volume effects.

V. CONCLUSIONS

This study provided a quantitative analysis of the detectability performance of the Naviscan PEM Flex Solo II. Through use of a customized breast phantom, the detectability was investigated in the most technically difficult task (viz. in-plane visualization). Although the observers were unable to detect the smallest objects consistently across ACR, it was evident that PEM can image lesions that are relatively small in size and that have low activity-to-background concentrations. The true potential of this system, however, remains to be established with an extensive clinical study. The detectability performance of PEM would indicate a potential use in applications where tumors are small, with low FDG uptake, potentially in screening populations.

ACKNOWLEDGMENTS

The authors would like to thank the Imaging Physics Residency Program (University of Texas M.D. Anderson Cancer Center), and its director, Dr. Charles Willis. The authors would also like to thank Naviscan Inc. for providing the PEM system on loan to the UT MD Anderson Cancer Center throughout the duration of this project. The authors declare that they have no conflict of interest.

^{a)}Present address: The first author has joined The Cleveland Clinic since the first submission of this paper.

^{b)}Electronic mail: Nick.shkumat@gmail.com

^{c)}Electronic mail: Adam.srpinger@gmail.com

^{d)}Electronic mail: cmwalker@mdanderson.org

^{e)}Electronic mail: eric.rohren@mdanderson.org

^{f)}Electronic mail: wyang@mdanderson.org

^{g)}Electronic mail: beatriz.adrada@mdanderson.org

^{h)}Electronic mail: earribas@mdanderson.org

ⁱ⁾Electronic mail: selin.carkaci@mdanderson.org

^{j)}Electronic mail: hhchuang@mdanderson.org

^{k)}Electronic mail: lumarie.santiago@mdanderson.org

^{l)}Current address: Dept. of Imaging Physics Unit 1352 MD Anderson Cancer Center 1515 Holcombe Boulevard Houston TX 77030. Author to whom correspondence should be addressed. Electronic mail: omawlawi@mdanderson.org

¹⁾American Cancer Society, *Facts and Figures* (American Cancer Society, Atlanta, 2009).

²⁾L. Humphrey, M. Helfand, B. Chan, and S. Woolf, "Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force," *Ann. Intern. Med.* **137**(5 Part 1), 347–360 (2002).

³⁾F. Sardanelli, F. Podo, G. D'Agnolo, A. Verdecchia, M. Santaquilani, R. Musumeci, G. Trecate, S. Manoukian, S. Morassut, C. Giacomini, M. Federico, L. Cortesi, S. Corcione, S. Cirillo, V. Marra, and for the High Breast Cancer Risk Italian Trial (HIBCRI), "Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRI study): interim results," *Radiology* **242**(3), 698–715 (2007).

⁴⁾E. Pisano, C. Gatsonis, E. Hendrick, M. Yaffe, J. Baum, S. Acharyya, E. Conant, L. Fajardo, L. Bassett, C. D'Orsi, R. Jong, M. Rebner, and Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group, "Diagnostic performance of digital versus film mammography for breast-cancer screening," *N. Engl. J. Med.* **353**(17), 1773–1783 (2005).

⁵⁾W. Berg, L. Gutierrez, M. NessAiver, W. Carter, M. Bhargavan, R. Lewis, and O. Loffe, "Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer," *Radiology* **233**(3), 830–849 (2004).

⁶⁾T. Kolb, J. Lichy, and J. Newhouse, "Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: An analysis of 27,825 patient evaluations," *Radiology* **225**(1), 165–175 (2002).

⁷⁾W. Berg, "Supplemental screening sonography in dense breasts," *Radiol. Clin. North Am.* **42**(5), 845–851 (2004).

⁸⁾P. Crystal, S. Strano, S. Shcharynski, and M. Koretz, "Using sonography to screen women with mammographically dense breasts," *AJR, Am. J. Roentgenol.* **181**(1), 177–182 (2003).

⁹⁾W. Berg, J. Blume, J. Cormack, E. Mendelson, D. Lehrer, M. Böhm-Vélez, E. Pisano, R. Jong, W. Phil Evans, M. Morton, M. Mahoney, L. Larsen, R. Barr, D. Farria, H. Marques, K. Boparai, and for the ACRIN 6666 Investigators, "Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer," *JAMA*. **299**(18), 2151–2163 (2008). Erratum in: *JAMA*. **303**(15), 1482 (2010).

¹⁰⁾D. Farria, M. Schmidt, B. Monsees, R. Smith, C. Hildebolt, R. Yoffre, D. Monticciolo, S. Feig, and L. Bassett, "Professional and economic factors affecting access to mammography: a crisis today, or tomorrow? Results from a national survey," *Cancer* **104**(3), 491–498 (2005).

¹¹⁾C. Boetes, S. Strijk, R. Holland, J. Barentsz, R. Van Der Sluis, and J. Ruijs, "False-negative MR imaging of malignant breast tumors," *Eur. Radiol.* **7**(8), 1231–1234 (1997).

¹²⁾C. Lee, R. Smith, J. Levine, R. Troiano, and I. Tocino, "Clinical usefulness of MR imaging of the breast in the evaluation of the problematic mammogram," *AJR, Am. J. Roentgenol.* **173**(5), 1323–1329 (1999).

¹³⁾C. Kuhl, H. Bieling, J. Gieseke, B. Kreft, T. Sommer, G. Lutterbey, and H. Schild, "Healthy premenopausal breast parenchyma in dynamic contrast-enhanced MR imaging of the breast: normal contrast medium enhancement and cyclical-phase dependency," *Radiology* **203**, 137–144 (1997).

¹⁴⁾D. Saslow, C. Boetes, W. Burke, S. Harms, M. Leach, C. Lehman, E. Morris, E. Pisano, M. Schnall, S. Sener, R. Smith, E. Warner, M. Yaffe, K. Andrews, C. Russell, and for the American Cancer Society Breast Cancer Advisory Group, "American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography," *Ca-Cancer J. Clin.* **57**(2), 75–89 (2007); Erratum in: *Ca-Cancer J. Clin.* **57**(3), 185 (2007).

¹⁵⁾C. Lehman, "Role of MRI in screening women at high risk for breast cancer," *J. Magn. Reson. Imaging* **24**(5), 964–970 (2006).

¹⁶⁾W. Berg, J. Blume, A. Adams, R. Jong, R. Barr, D. Lehrer, E. Pisano, W. Evans, M. Mahoney, L. Larson, G. Gabrielli, and E. Mendelson, "Reasons women at elevated risk of breast cancer refuse breast MR imaging screening: ACRIN 6666," *Radiology* **254**(1), 79–87 (2010).

¹⁷⁾R. Hussain and J. Buscombe, "A meta-analysis of scintimammography: an evidence-based approach to its clinical utility," *Nucl. Med. Commun.* **27**(7), 589–594 (2006).

¹⁸⁾O. Schillaci, R. Danieli, P. Romano, R. Santoni, and G. Simonetti, "Scintimammography for the detection of breast cancer," *Expert Rev. Med. Devices* **2**(2), 191–196 (2005).

¹⁹⁾R. Brem, M. Ioffe, J. Rapelyea, K. Yost, J. Weigert, M. Bertrand, and L. Stern, "Invasive lobular carcinoma: detection with mammography, sonography, MRI, and breast-specific gamma imaging," *AJR, Am. J. Roentgenol.* **192**(2), 379–383 (2009).

²⁰⁾R. Brem, A. Floerke, J. Rapelyea, C. Teal, T. Kelly, and V. Mathur, "Breast-specific gamma imaging as an adjunct imaging modality for the diagnosis of breast cancer," *Radiology* **247**(3), 651–657 (2008).

²¹⁾R. Brem, I. Petrovitch, J. Rapelyea, H. Young, C. Teal, and T. Kelly, "Breast-specific gamma imaging with 99mTc-Sestamibi and magnetic resonance imaging in the diagnosis of breast cancer—a comparative study," *Breast J.* **13**(5), 465–469 (2007).

- ²²E. Rosen, W. Eubank, and D. Mankoff, "FDG PET, PET/CT, and breast cancer imaging," *Radiographics* **27**(Suppl 1), 215–229 (2007).
- ²³W. Eubank, and D. Mankoff, "Current and future uses of positron emission tomography in breast cancer imaging," *Semin. Nucl. Med.* **34**(3), 224–240 (2004).
- ²⁴C. Rosé, J. Dose, and N. Avril, "Positron emission tomography for the diagnosis of breast cancer," *Nucl. Med. Commun.* **23**(7), 613–618 (2002).
- ²⁵D. Wu and S. Gambhir, "Positron emission tomography in diagnosis and management of invasive breast cancer: current status and future perspectives," *Clin. Breast Cancer* **4**(Suppl 1), 55–63 (2003).
- ²⁶R. Raylman, S. Majewski, R. Wojcik, A. Weisenberger, B. Kross, and H. Bishop, "The potential role of positron emission mammography for detection of breast cancer. A phantom study," *Med. Phys.* **27**(8), 1943–1954 (2000).
- ²⁷W. Berg, I. Weinberg, D. Narayanan, M. Loblano, E. Ross, L. Amodi, L. Tafra, L. Adler, J. Uddo, W. Stein, E. Levine, and the Positron Emission Mammography Working Group, "High-resolution fluorodeoxyglucose positron emission tomography with compression (positron emission mammography) is highly accurate in depicting primary breast cancer," *Breast J.* **12**(4), 309–323 (2006).
- ²⁸C. Thompson, K. Murthy, I. Weinberg, and F. Mako, "Feasibility study for positron emission mammography," *Med. Phys.* **21**(4), 529–538 (1994).
- ²⁹E. Rosen, T. Turkington, M. Soo, J. Baker, and R. Coleman, "Detection of primary breast carcinoma with a dedicated, large-field-of-view FDG PET mammography device: initial experience," *Radiology* **234**, 527–534 (2005).
- ³⁰S. Bowen, Y. Wu, A. Chaudhari, L. Fu, N. Packard, G. Burkett, K. Yang, K. Lindfors, D. Shelton, R. Hagge, A. Borowsky, S. Martinez, J. Qi, J. Boone, S. Cherry, and R. Badawi, "Initial characterization of a dedicated breast PET/CT scanner during human imaging," *J. Nucl. Med.* **50**(9), 1401–1408 (2009).
- ³¹M. Abreu, J. Aguiar, F. Almeida, P. Almeida, P. Bento, B. Carrico, M. Ferreira, N. Ferreira, F. Goncalves, C. Leong, F. Lopes, P. Lousa, M. Martins, N. Matela, P. Mendes, R. Moura, J. Nobre, N. Oliveira, C. Ortigao, L. Peralta, R. Pereira, J. Rego, R. Ribeiro, P. Rodrigues, J. Sampaio, A. Santos, L. Silva, J. Silva, P. Sousa, I. Teixeira, J. Teixeira, A. Trindade, and J. Varela, "Design and evaluation of the Clear-PEM scanner for positron emission mammography," *IEEE Trans. Nucl. Sci.* **53**(1), 71–77 (2006).
- ³²K. Murthy, M. Aznar, C. Thompson, A. Loutfi, R. Lisbona, and J. Gagnon, "Results of preliminary clinical trials of the positron emission mammography system PEM-I: a dedicated breast imaging system producing glucose metabolic images using FDG," *J. Nucl. Med.* **41**(11), 1851–1858 (2000).
- ³³R. Freifelder, C. Cardi, I. Grigoras, J. Saffer, and J. Karp, "First results of a dedicated breast PET imager, BPET, using NaI(Tl) curve plate detectors," *IEEE Nucl. Sci. Symp. Conf. Rec.* **3**, 1241–1245 (2001).
- ³⁴G. Wang, J. Huber, W. Moses, J. Qi, and W. Choong, "Characterization of the LBNL PEM camera," *IEEE Trans. Nucl. Sci.* **53**(3), 1129–1135 (2006).
- ³⁵R. Raylman, S. Majewski, M. Smith, J. Proffitt, W. Hammond, A. Srinivasan, J. McKisson, V. Popov, A. Weisenberger, C. Judy, B. Kross, S. Ramasubramanian, L. Banta, P. Kinahan, and K. Champey, "The positron emission mammography/tomography breast imaging and biopsy system (PEM/PET): design, construction and phantom-based measurements," *Phys. Med. Biol.* **53**(3), 637–653 (2008).
- ³⁶Y. Wu, S. Bowen, K. Yang, N. Packard, L. Fu, G. Burkett, J. Qi, J. Boone, S. Cherry, and R. Badawi, "PET characteristics of a dedicated breast PET/CT scanner prototype," *Phys. Med. Biol.* **54**, 4273–4287 (2009).
- ³⁷L. MacDonald, J. Edwards, T. Lewellen, D. Haseley, J. Rogers, and P. Kinahan, "Clinical imaging characteristics of the positron emission mammography camera: PEM FLEX Solo II," *J. Nucl. Med.* **50**(10), 1666–1675 (2009).
- ³⁸W. Luo, E. Anashkin, and C. Matthews, "First test results of a commercially available clinical PET scanner using the NEMA NU 4-2008 small animal PET standards," *IEEE Nucl. Sci. Symp. Conf. Rec.* M10-94, 4718–4723 (2008).
- ³⁹J. Huber, Q. Peng, and W. Moses, "Multimodality phantom development," *IEEE Nucl. Sci. Symp. Conf. Rec.* **56**(5), 2944–2948 (2007).