



Instrumentation for Positron Emission Mammography

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The use of positron emission tomography (PET) to provide images of the glucose metabolism of malignant disease is becoming more and more widespread, and whole body PET (WB-PET) images are now often used to choose appropriate therapy for cancer patients. The first use of F-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) for the study of breast cancer was reported by Wahl and colleagues [1], and since then many other reports have been made [2,3], to cite the first few only. When combined with radiograph CT, PET images provide the equivalent of a “metabolic contrast agent,” which serves to highlight the abnormal glucose metabolism in tumors. Combined PET/CT scanners now outsell conventional PET scanners, and they have become the standard of care in many centers.

PET scanners have a limited spatial resolution compared with structural imaging modalities such as CT and MRI. Because the identification of small tumors leads to earlier diagnosis and treatment, much effort has gone into trying to improve the spatial resolution of PET. There are both instrumental and fundamental factors that degrade spatial resolution in PET. The fundamental limit is caused by the distance positrons move away from

the parent nucleus before they lose energy and annihilate with an electron in tissue. Another limitation is the noncollinearity of the pair of gamma rays that do not travel away from the point of annihilation at exactly 180°, because of the energy of the electron at the time of annihilation. Although this appears as a fundamental limit in conventional PET, it is much less of a problem in an instrument that has its detectors much closer to each other than the separation needed in WB-PET. The major instrumental limitation is the size of the detectors. Making the detectors smaller improves the resolution at the expense of increased complexity and resulting cost; however, if detectors are placed closer, fewer detectors are required, so instruments made especially for breast imaging can be made to provide higher spatial resolution than those from WB-PET. The factors that limit spatial resolution (SR) in PET can be combined as the sum of independent variables in the formula:

$$(SR)^2 = R*[PR^2 + (0.005*DS)^2 + (CW/2)^2 + BE^2]$$

In this equation, R is a factor that relates to the reconstruction method and filter, PR is the effective

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positron range in tissue $0.005 = 1/2 * \tan(\theta/2)$, θ is the mean angle of noncollinearity, DS is the detector separation, CW is the crystal width, and BE combines the effects of light sharing and under-sampling of the image.

One of the design factors in all PET scanners is a trade-off between spatial resolution, sensitivity, and cost. In the equation above, the factor CW is the one that balances the cost versus 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 the patient would no longer fit in the scanner; however, there is an option for doing this in instruments designed exclusively for breast imaging.

The idea of a dedicated PET scanner for breast imaging was first proposed by Weinberg in 1993, in a US patent application [4], and a successful proposal for a small business incentive for research (SBIR) grant from the US National Institutes of Health (NIH).

Feasibility and promise of early instruments

Through a collaboration with Weinberg, the first experiments to examine the concept were published in 1993 [5], and the name "positron emission mammography" (PEM) was coined to represent this technique. The concept was to place two 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 radiograph tube and the compression plate, and another between the lower aspect of the breast and the Radiograph sensor. The two detectors move out of the radiograph field for conventional mammography, and move back over and under the breast for the PEM acquisition [6]. This concept predates PET/CT by several years [7], but the goal was very much the same as that of PET/CT as it has evolved today: to provide a coregistered anatomical and functional image in the same procedure with minimal movement of the patient. The design of the instrument is illustrated in Fig 1.

An important finding of this first PEM paper [5] 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 four tubes of various sizes with either no activity or 9.3 times the background. The images were made over different times, so that each consecutive image contains half the counts of the pre-

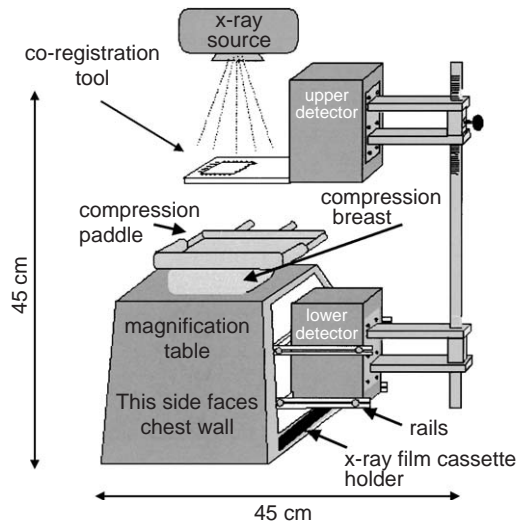


Fig. 1. Layout of PEM-1 breast imaging system. The two detectors, mounted on rails, are moved out of the radiographic field for conventional mammography, and back over and under the breast during the acquisition of a metabolic image.

vious one. This paper provided the basic estimate of both the signal-to-noise ratio and count-rate that could be expected from a clinical PEM instrument.

Encouraged by these results, the author's group applied for funding from the Canadian Breast Cancer Research Initiative. We then built and performed a preliminary clinical trial of an instrument known as "PEM-1." Because we had concluded that back-projection images were sufficient to identify regions of higher-than-surrounding uptake, we did not perform any sophisticated reconstruction, preferring to opt for an almost real-time image display of the PEM image. The goal we set was to perform the clinical trial using only 75 MBq (2 mCi) of FDG, and an imaging time of 2 minutes per breast, because this is about the time it takes to develop a radiograph film in an automatic film processor.

Evolution of positron emission mammography instruments

When performing WB-PET scans, it is a simple matter to overscan the regions most likely to harbor metastases, and to overlap the bed positions to compensate for the reduced sensitivity toward the axial ends of each set of slices caused by the fall-off in three dimensional (3D) sensitivity in the scanner. When imaging the breast with PET detectors in a mammographic configuration, this is not possible, as illustrated in Fig. 2. 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 chest wall. PET imaging in the 3D mode is always less sensitive toward the axial ends of the field of view, because fewer detector pairs can be in coincidence in these regions.

A variety of different PEM geometries have been proposed, and several of these are currently in use [Fig. 3]. 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. Fig. 3 shows the detector arrangement in each device. Part A is the classic two-parallel crystal arrays coupled to position-sensitive photo-multipliers (PS-PMTs). One detector is moveable to allow positioning the breast and for variable compression to suit the patient's anatomy. This geometry was first used in the PEM-1 scanner [8–12], and later by Smith and coworkers of the Thomas Jefferson Laboratory [13]. Part B shows a pair of linear arrays of detectors that scan across the breast during the examination [14]. This technique is used in the only commercially available PEM scanner at present, the PEM Flex from Naviscan PET Systems in Rockville, Maryland. Part C is a boxlike detector array that surrounds the breast, and should

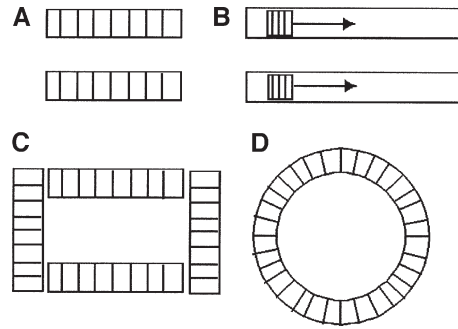


Fig. 3. Four geometries used or proposed for PEM. (A) Two small planar detectors with variable separation. (B) Two multi-element detectors that move inside an enclosure during imaging. (C) Rectangular box structure with moveable detectors. (D) Cylindrical crystal array surrounding pendulous breast.

allow a more complete reconstruction of the activity within the breast. This is the system proposed by Huber and colleagues [15] of the Berkeley National Laboratory in Berkeley, California. A similar concept encloses the breast in a small circular array of detectors with the breast pendant through the hole [16].

All of these instruments use very finely pixilated 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 Huber and coworkers [15], which also encodes the depth at which each gamma ray is detected in the crystal. This allows for a very compact geometry while avoiding the blurring associated with very oblique gamma ray penetration of the detector.

Early clinical findings

In 1999, the author's group published the results of the first clinical trial of any PEM instrument [12]. During the clinical trial of the PEM-1 scanner, we studied 14 patients, 10 of whom had various breast cancers confirmed by pathological 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 on the basis of a significant count-rate asymmetry, after accounting for factors like isotope decay and volume of breast tissue in the field of view, and detector separation.

As an example of a typical patient from that study, consider the case of a 75-year-old lady who presented with a suspicious mammogram of her right breast, and was a candidate for lumpectomy. She had a cranio-caudal (CC) PEM scan of her right breast starting 60 minutes after the admin-

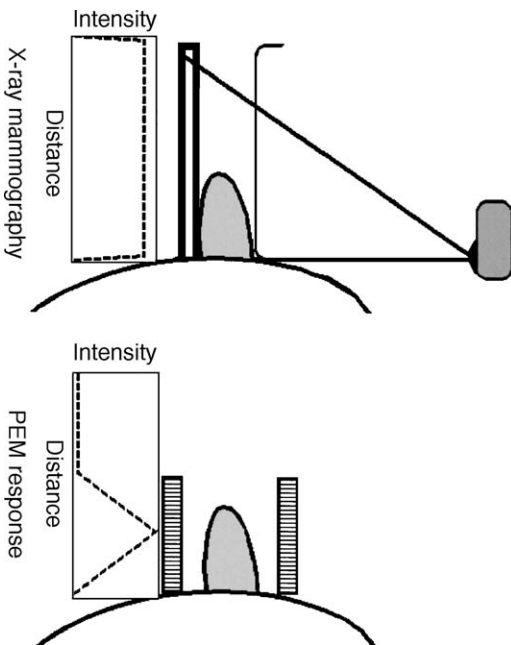


Fig. 2. Geometry for conventional radiographic mammography and PEM using two planar detectors. The radiograph beam is centered over the edge of the image sensor near the chest wall, and collimated to expose only the compressed breast. The response of the sensor to the radiograph beam (plotted below the geometry) is essentially constant over the entire surface. In contrast, the response of the PEM detectors is triangular, with its peak in the geometric center of the detector pair.

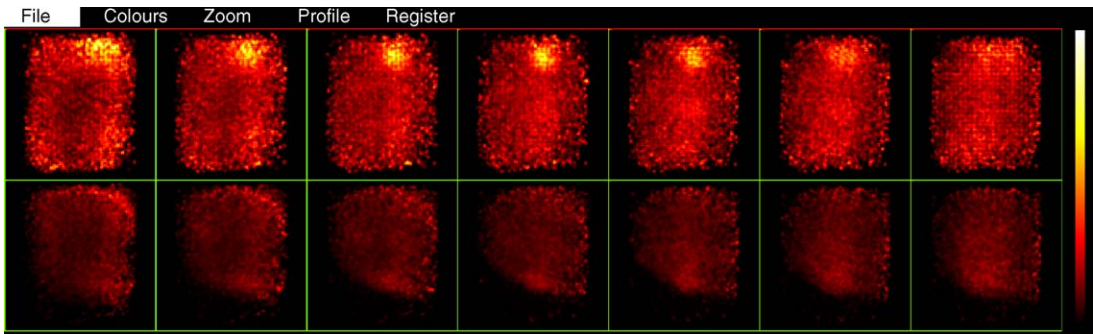


Fig. 4. PEM-1 images showing focal uptake in a 1.5 cm inter-ductal carcinoma (*upper row*) compared with normal uptake in the contra-lateral breast (*lower row*). These images were scaled to the equivalent counting time and isotope decay, showing an asymmetry in the overall uptake.

istration of 75 MBq of ^{18}F -FDG. A CC scan of the left breast was then acquired starting 70 minutes postinjection. She underwent a right-breast segmental mastectomy 4 days after the PEM study. The pathologist's report described a $1.5 \times 1.5 \times 1.3$ cm intraductal carcinoma and infiltrating ductal carcinoma, with a histological grade of 3 on the Bloom and Richardson scale. The appearance of the PEM images is shown in **Fig. 4**. Seven images are presented for each breast, with the right breast displayed as if the breast were pendant, so that the chest wall would be above the images presented. The left-most image corresponds with the upper aspect of the breast on the CC mammogram. The focal activity visible near the top (chest wall) in the upper row is most intense in image 4, but extends further toward the upper breast surface. The lower row of images from the normal breast is more uniform, and was read as normal.

The correlation between the PEM and mammogram is illustrated in **Fig. 5**. The PEM image is first "windowed" such that only the suspicious region is visible. The mammogram, following digitization with a video frame digitizer, is then displayed. The images are rescaled and fused by aligning the top-right and bottom-left corners of a digital representation of a wire grid with its image, which is visible on the mammogram. A fused image is made by displaying alternate pixels from the mammogram and scaled PEM image in differing color scales. This technique is now used to display PET/CT images, although the image fusion software of the author's group predates PET/CT.

Recent clinical findings

The first report of clinical results from PEM Flex was published by Weinberg and coworkers earlier this year [14]. They reported on 94 cases performed at

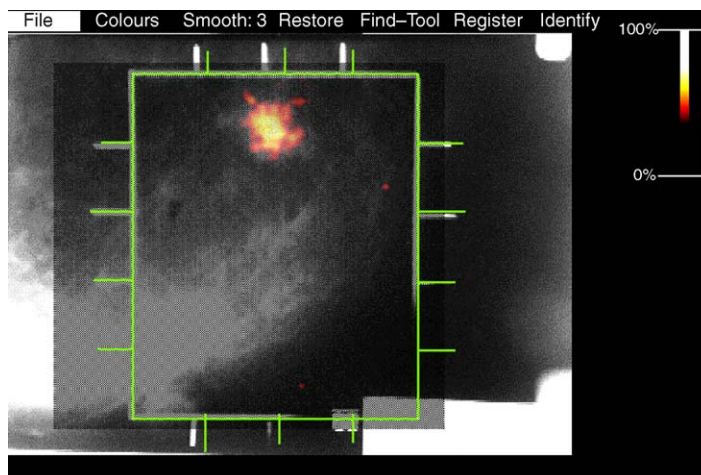


Fig. 5. Correlation of the intensity-thresholded PEM-1 image and a hyperdense region of the mammogram using the coregistration technique developed for this instrument. The field of view of the mammogram is bigger than that of the PEM-1 detectors, and in the active PEM region, alternate pixels are assigned to PEM and radiograph images in a manner identical to that commonly used for PET/CT image display.

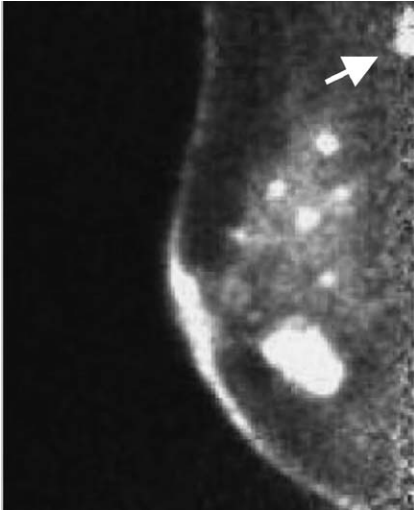


Fig. 6. PEM image from the Naviscan imager. In addition to one large and four smaller interductal lesions in the outer aspect of the breast, there is another hypermetabolic region at the posterior wall (arrow), suggestive of axillary node involvement. (From Weinberg IN, Beylin D, Zavarzin V, et al. Positron emission mammography: high-resolution biochemical breast imaging. *Technol Cancer Res Treat* 2005;4:55–60; with permission.)

four 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%.

Fig. 6 is an example of a PEM image from this instrument. Unlike the PEM-1 scanner, the field of view is much larger, 24×18 cm rather than 5.5×6.0 cm. The device also employs a sophisticated limited-angle reconstruction algorithm, which produces much clearer 3D images. The five smaller lesions would not have been visible on a conventional PET scan, or on the PEM-1 instrument. The PEM Flex also has the ability of scanning closer to the chest wall.

Future prospects for positron emission mammography

In the United States, Medicare approval for use of PET imaging of breast cancer was given in late 2003 [17]. Unlike the approvals granted for PET in other forms of malignant disease, the approval document refers to three specific areas: initial staging of axillary lymph nodes, detection of loco-regional recurrence or distant metastasis/recurrence, and evaluating response to treatment. Although this is intended for the use of conventional WB-PET scanners, there is an opportunity for the assessment of dedicated PEM imaging instruments within the guidelines of these new regulations. The “response to treatments” aspect of the approval document is

perhaps the most relevant to PEM. The technology assessment report from the Blue Cross and Blue Shield Association [17], which forms the basis of the review of the utility of FDG-PET in breast cancer, contains over 70 references on the use of PET and single photon imaging agents such as ^{99m}Tc sestamibi in the detection and staging of breast cancer.

The major limitations of early PEM instruments were 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, both in uniformity and in ability to image much closer to the edge without serious distortion. Now instruments such as the PEM Flex 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 3D PET acquisitions. During early PEM development, this was not considered seriously enough. Now that it has been widely recognized, the situation has been improved through the use of higher density, thinner shielding, better PMTs, and improved geometry. This results in the effective field of view being at least 3 cm closer to the chest in the latest instruments than in the prototype developed by the author’s group.

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