Positron Emission Mammography for Breast Cancer in Rajavithi Hospital

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Background: *Positron Emission Mammography (PEM) is a new modality in the investigation of breast cancer in Rajavithi Hospital, and its effectiveness has not yet been evaluated.*

Objective: *To study the effectiveness and characterization of breast images taken with PEM in Rajavithi Hospital.*

Material and Method: *This was a retrospective study in which data were collected and analyzed of patients who were investigated by PEM in Rajavithi Hospital between 18 September 2013 and 31 May 2014. Lesion to background (LTB) ratio of $\geq$2.0 with focal localization was considered to be suggestive of PEM positive for malignancy.*

Results: *Twenty-three female patients were included in the study, and their mean age was 51.7 years. Mean fasting blood glucose (FBS) was 93.64 mg/dl, and mean Fluorodeoxyglucose (FDG) injected dose was 7.76 mCi. The average PUV mean of background of both breasts decreased with advancing age. Fourteen patients were pathologically diagnosed with a total of lesions, of which 12 were malignant and four were benign. The positive predictive value (PPV) was 76.92%, and the mean LTB of true positive lesions was 5.31. Three false positive lesions were found: one mild atypical cell, one papilloma and one fibroadenoma, and the mean LTB was 2.92. The two false negative lesions were both DCIS.*

Conclusion: *There was a moderate PPV in this PEM study for breast cancer in Rajavithi Hospital, and investigators need further experience and training in interpreting PEM. The information of mammographic, ultrasonographic and clinical findings should be used together with PEM to make diagnostic decision. The addition of biopsies could also improve the efficacy of PEM studies.*

Keywords: *Positron emission mammography, PEM, Breast cancer, Breast imaging, F18-FDG*

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Currently, breast cancer is the most common female cancer in Thailand, and the National Cancer Institute reported 10,193 new cases in 2008. The age-standardized incidence rate (ASR) is 26.4 per 100,000 population[1].

Breast cancer can be detected by self-examination. Mammogram and ultrasound are highly efficacious methods of screening for and diagnosing breast cancer and MRI is another useful tool for gaining additional information. However, a new machine is being developed for use in detecting breast cancer through molecular imagery, and this device, the Positron Emission Mammography (PEM) scanner, can provide additional information after the basic study.

In August 2003, the PEM 2400 PET Scanner (PEM Technologies, Inc., Ridgefield, NJ) was cleared for marketing by the US Food and Drug Administration (FDA) through the 510 (k) process. The FDA determined that this device was substantially equivalent to existing devices for "medical purposes to image and measure the distribution of injected positron emitting radiopharmaceuticals in human beings for the purpose of determining various metabolic and physiologic functions within the human body". In March 2009, the Naviscan PEM Flex™ Solo II High Resolution PET Scanner (Naviscan, Inc., San Diego, CA) was cleared for marketing by the FDA through the 510 (k) process for the same indication[2].

Rajavithi Hospital installed the Naviscan PEM Flex™ Solo II (Fig. 1), and started using it on 18 September 2013. However, its effectiveness in the diagnosis of breast cancer has not yet been evaluated in the hospital.

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Material and Method

The protocol of this research was reviewed

and approved by the ethics committee of Rajavithi Hospital (No. 102/2558). It was a descriptive retrospective study in which data were collected and analyzed of 23 patients who were investigated with PEM in Rajavithi Hospital from 18 September 2013 to 31 May 2014. Patients who did not complete the PEM process were excluded from the study.

PEM protocol

Patient pre-scan preparation

Patients with diabetes ate a high-protein and low-carbohydrates diet the day before the test. All patients were advised to fast for 6 hours prior to the test and to refrain from chewing gum or using cough drops. They were directed to drink at least 8 ounces of water before leaving home, and to continue all medications except those for diabetes. They were also advised to avoid caffeine, sugar, tobacco and heavy exercise for 24 hours prior to the exam. Scans were not performed on pregnant women. On the day of examination, blood glucose was measured, and if fasting blood glucose (FBS) was less than 140 mg/dL, radiotracer was injected. An intravenous injection of 5-10 mCi. ^{18}F-FDG (Fluorodeoxyglucose) was given and then flushed with 10 cc saline after that the patients rested quietly in a warm room for 45-90 minutes. Additional hydration in the form of a glass of water was taken 15 minutes before examination, and patients were encouraged to void immediately prior to imaging.

Imaging protocol

All images were obtained from the Naviscan PEM Flex™ Solo II High Resolution PET Scanner. We performed the following scans of both sides: 1) Craniocaudal (CC) projection (scan time: 5 to 10 minutes each; angle of c-arm: 0° to 10°); 2) Mediolateral Oblique (MLO) projection (scan time: 5 to 10 minutes each; angle of c-arm: 45° to 60°); 3) Axillary View (scan time: 10 minutes each; angle of c-arm: 45° to 60°). Additional views or delayed scans were obtained at the request of the physician. PEM imaging produces a set 12 tomogram slices in each position (Fig. 2).

Image interpretation

Images were interpreted by a nuclear medicine physician in Rajavithi Hospital, and MIM viewer™ PEM workstation was used in evaluating findings.

Fig. 1 PEM machine in Rajavithi Hospital.

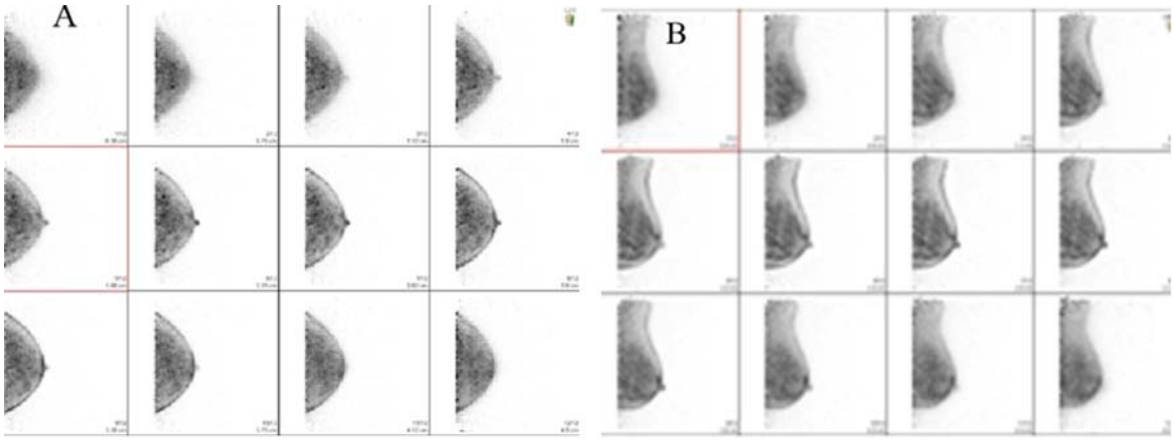

Fig. 2 Tomographic images of PEM (A) left craniocaudal view (B) left mediolateral oblique view.

Quantitative FDG uptake and PEM uptake values (PUV) were recorded, together with PUVmean for background and PUVmax for lesion. PUVmean of background was measured 3 times for each side of the breasts, and their average values were reported. The ratio of the PUVmax of the lesion to the PUVmean of the background (LTB) was also calculated and recorded. We used LTB and the architectural distribution of FDG uptake to determine the diagnosis. LTB ratio of 2.0 and focal localization was considered to be suggestive of malignancy, while LTB ratio of less than 1.5 was considered to be most likely benign, and ratios between 1.5 and 2.0 were rated as suspicious depending on the architecture of FDG uptake.

Results

Twenty-three female patients were included in the research. Their ages ranged from 32 to 66 years old (mean $\pm$ SD = 51.7$\pm$9.94). Range of FBS was 70-128 mg/dl (mean $\pm$ SD = 93.64$\pm$15.05), and the range of FDG injected dose was 4.39-14.65 mCi (mean $\pm$ SD = 7.76$\pm$2.50). Average PUVmean of background of both breasts by age range are shown in Fig. 3.

Pathological reports were obtained for 14 patients. Of the other nine patients, six were PEM negative, one underwent surgery in another hospital, one was lost to follow-up, and one patient died. In the 14 patients for whom pathological reports were received, 16 breast lesions were found of which 12 were malignant and four were benign. In the 12 malignant lesions, PEM were positive for 10 and negative for 2. In the 10 PEM positive malignant lesions, the mean LTB was 5.31. Data of pathohistology and LTB are shown in Table 1, and example images of positive PEM are shown in Fig. 4-6. Both malignant lesions that PEM failed to detect were DCIS, and an example is shown in Fig. 7. Data for the 4 benign lesions are presented in Table 2, and examples of benign lesions images are

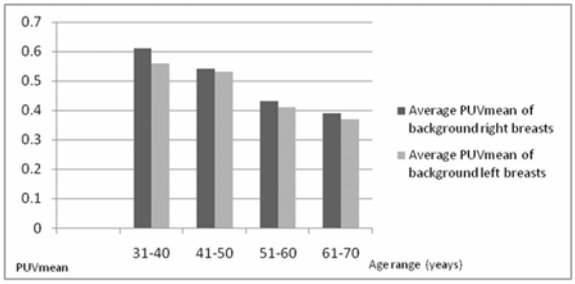

Fig. 3 Average PUVmean of background of both breasts by age range.

Table 1. Pathohistology and LTB of cases of true positive PEM

Type	N	Range LTB	Mean LTB
Invasive ductal carcinoma	7	2.46-9.13	5.77
Ductal carcinoma in situ	2	2.78-5.67	4.23
Paget	1	4.31	4.31

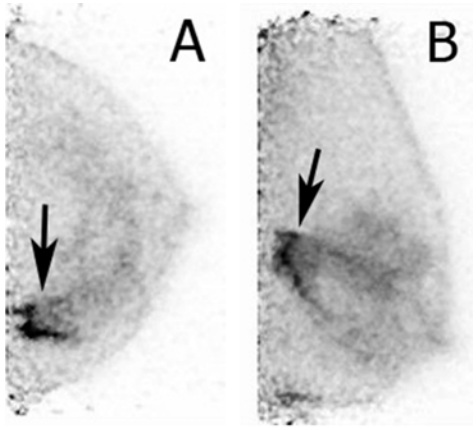

Fig. 4 PEM images of a 63 year-old female (A) left CC view (B) left MLO view, show area of high FDG uptake at 9-10 o'clock of left breast (arrow), LTB 9.13, pathological diagnosis (left MRM) is infiltrating ductal carcinoma.

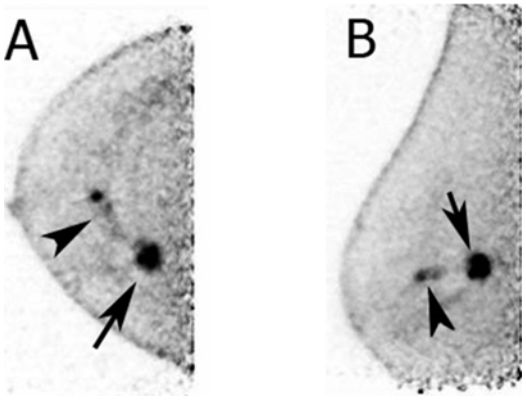

Fig. 5 PEM images of a 63 year-old female (A) right CC view (B) right MLO view, show area of high FDG uptake at 2 o'clock of right breast (arrow), LTB 9.12, pathological diagnosis (right MRM) is invasive ductal carcinoma, grade 3.
Note: FDG uptake along biopsy tract (arrow head).

shown in Fig. 8, 9. At one-year clinical FU of the 6 PEM negative patients who did not undergo biopsy, none had developed breast cancer. The calculated positive predictive value (PPV) of PEM in this study was 76.92%

Discussion

PEM is a high-resolution tomographic method for molecular imaging of positron-emitting isotopes. F18-FDG was injected into the patient's vein. Uptake of FDG in the cells is proportional to glucose metabolic activity. In the cells FDG becomes phosphorylated and cannot be transported back out, leading to its accumulation. On the basis that cancer cells demonstrate increased utilization of glucose, FDG will accumulate in cancer cells more than in adjacent normal tissue. Fluorine-18 attached to FDG is a radioisotope, and as it decays, a positron is emitted. The collision of the positron with an electron results in the production of two 511 keV gamma rays, which are emitted at 180 degrees from each other. In PEM, these gamma rays are detected by striking a pair of dedicated gamma radiation detectors placed above and below the breast. Once the gamma rays are detected, they are amplified by photon-sensitive photomultipliers and translated into an electrical signal that becomes digitized and is stored in computer memory[3,4]. PEM is optimized for small body parts and utilizes gentle immobilization of the breast to attain high spatial resolution (1-2 mm) and minimize the radiation dose by reducing breast thickness[5]. Even in very small tumors measuring <1 cm, the imaging sensitivity of PEM has been reported to be 60% to 70%[6]. Direct comparisons have shown the sensitivity of PEM to be comparable to that of MRI and

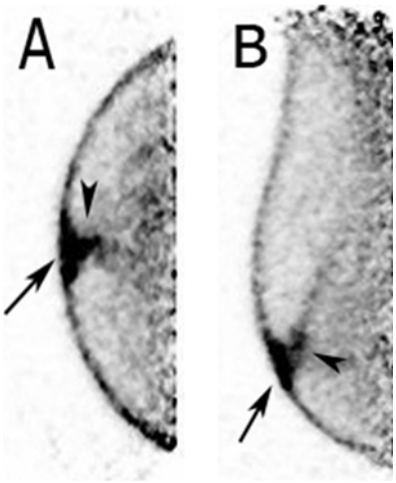

Fig. 6 PEM images of a 62 year-old female (A) right CC view (B) right MLO view, show high FDG uptake at right nipple (arrow) & subareolar area (arrow head), LTB at nipple = 4.31, subareolar area = 2.78, pathological diagnosis (right MRM) is invasive Paget's disease of nipple, 0.1 cm depth of invasion into dermis and high grade DCIS with focal microinvasion of breast tissue (1.5 cm beneath the nipple).

Fig. 7 The left CC view PEM image of a 46 year-old female shows no area of significant abnormal FDG uptake; however, she underwent simple mastectomy due to microcalcifications detected by mammogram, and pathological diagnosis was DCIS.

Table 2. Data of benign lesions

Pathology	Site	Size (mm)	LTB
Fibrocystic disease	2 o'clock left breast	-	-
Mild atypical cell	12 o'clock left breast	7	2.10
Papilloma	2 o'clock right breast	4	3.27
Fibroadenoma	Central area of left breast	5	3.39

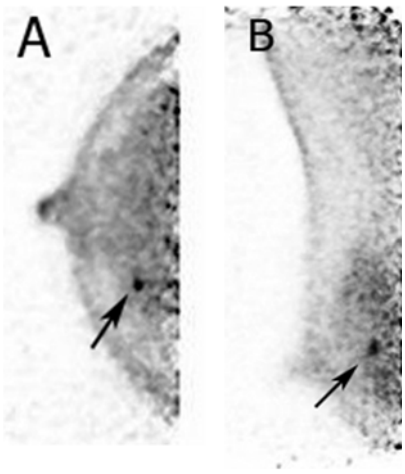

Fig. 8 PEM images of a 46 year-old female (A) right CC view (B) right MLO view, show a spot of high FDG uptake at 2 o'clock of right breast (arrow), LTB 3.27; pathological diagnosis (right simple mastectomy) was papilloma.

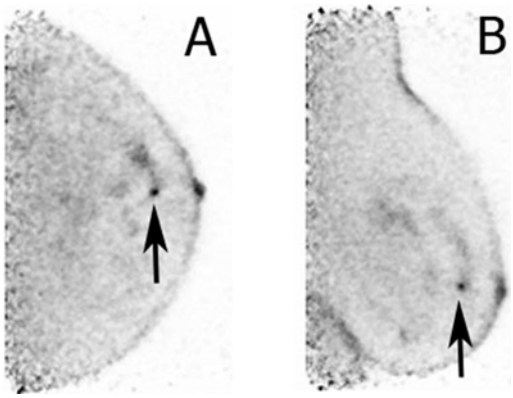

Fig. 9 PEM images of a 64 year-old female (A) left CC view (B) left MLO view, show a spot of high FDG uptake at central area of left breast, LTB 3.39; pathological diagnosis (core needle biopsy) was fibroadenoma.

significantly higher than that of PET, particularly in small tumors[7]. PEM and MRI have both been shown to have index lesion sensitivity of 92.8%. In another study, whole-body PET demonstrated a sensitivity of only 67.9%[8]. The specificity for detecting carcinoma ranges from 85% to 92% for MRI and from 92% to 97% for PEM[9]. PEM sensitivity was 91%, specificity 93%, PPV 95%, NPV 88%, accuracy 92%, and Az 0.949 when interpreted with mammographic and clinical findings. FDG-PEM has been shown to have high diagnostic accuracy for breast lesions, including DCIS[10].

In the present study, the mean background uptake decreased with age. We were unable to calculate sensitivity or specificity because we did not perform biopsies in the cases of patients who were PEM negative. The PPV was 76.92% (10/13), which is quite low in comparison with that found in Wendie A. Berg's study[10], and this could be the result of lack of experience of the readers and the information of mammographic, ultrasonographic and clinical findings should be used together with PEM to make diagnostic decision. The false positives found were of mild atypical cell, papilloma and fibroadenoma. The two false negatives were both DCIS, and this failure could be due to the low metabolic activity of this type of breast cancer.

Conclusion

A moderate PPV was found in this PEM study in Rajavithi Hospital. PEM could be another useful diagnostic adjunct for evaluating breast cancer when the basic study does not yield enough information; however, investigators need training and should become familiar with mammographic and ultrasonographic information,and clinical findings together with PEM to make diagnosis. Additional biopsies can also help to improve the efficacy of PEM studies. The PEM technique is quite expensive and further research into its cost effectiveness should be performed.

What is already known on this topic ?

Efficacy of PEM in diagnosis breast cancer, study mainly in USA.

What this study adds ?

First report PEM cases from ASEAN.

Acknowledgement

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Potential conflicts of interest

None.

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การตรวจวินิจฉัยมะเร็งเต้านมด้วยเครื่องถ่ายภาพเต้านมอนุภาคโพสิตรอนในโรงพยาบาลราชวิถี

อารยา บุญยะลีพรรณ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพในการตรวจวินิจฉัยมะเร็งเต้านมและศึกษาลักษณะทั่วไปของภาพเต้านมที่ถ่ายจากเครื่องถ่ายภาพเต้านมอนุภาคโพสิตรอนในผู้ป่วยโรงพยาบาลราชวิถี*

วัสดุและวิธีการ: *เป็นการศึกษาย้อนหลังถึงผลการตรวจวินิจฉัยมะเร็งเต้านมด้วยเครื่องถ่ายภาพเต้านมอนุภาคโพสิตรอนของหน่วยงานเวชศาสตร์นิวเคลียร์ โรงพยาบาลราชวิถีตั้งแต่วันที่ 18 กันยายน พ.ศ. 2556 ถึง วันที่ 31 พฤษภาคม พ.ศ. 2557 รอยโรคที่มีลักษณะเป็นก้อนและค่า LTB ตั้งแต่ 2.0 ขึ้นไปถือว่าเป็นลักษณะของมะเร็ง*

ผลการศึกษา: *ผู้ป่วย 23 ราย เป็นเพศหญิงทั้งหมดอายุเฉลี่ย 51.7 ปี ค่าเฉลี่ยระดับน้ำตาลในเลือดก่อนฉีดสารเภสัชรังสี 93.64 mg/dl ค่าเฉลี่ยปริมาณสารเภสัชรังสีที่ฉีดให้ผู้ป่วย 7.76 mCi ค่าเฉลี่ย PUV mean of background ของเต้านมทั้ง 2 ข้าง ลดลงตามอายุ มีผู้ป่วยที่ได้ผลชิ้นเนื้อยืนยันการวินิจฉัยจำนวน 14 ราย 16 รอยโรค เป็นมะเร็งเต้านม 12 รอยโรค ไม่ใช่มะเร็ง 4 รอยโรค พบว่าค่า positive predictive value (PPV) = 76.92% ค่าเฉลี่ย LTB ของรอยโรคที่ได้ผลบวกจริงคือ 5.31 ผลบวกลวงเกิดในผู้ป่วย 3 ราย ผลชิ้นเนื้อ mild atypical cell, papilloma และ fibroadenoma ค่าเฉลี่ย LTB 2.92 ส่วนผลลบลวงเกิดในผู้ป่วย DCIS 2 ราย*

สรุป: *การวินิจฉัยมะเร็งเต้านมด้วยเครื่องถ่ายภาพเต้านมอนุภาคโพสิตรอนในผู้ป่วยโรงพยาบาลราชวิถี มีประสิทธิภาพปานกลาง ซึ่งสามารถพัฒนาให้ดีขึ้นได้จากประสบการณ์ รวมถึงการแปลผลร่วมกับแมมโมแกรม อัลตราซาวน์ และอาการทางคลินิกของผู้ป่วย รวมทั้งการเจาะชิ้นเนื้อตรวจ ซึ่งสามารถทำร่วมกับการถ่ายภาพได้*