CORRELATION OF SEMIQUANTITATIVE VALUES OF POSITRON EMISSION MAMMOGRAPHY

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ABSTRACT

The objective of this study was to investigate the correlation of semiquantitative values of ^{18}F-FDG positron emission mammography (PEM) images in breast cancer patients. Retrospective ^{18}F-FDG PEM images of 23 patients (32 lesions) were collected. Five semiquantitative values including PUV_{max} and four different lesion-to-background (LTB1, LTB2, LTB3, and LTB4) based on different methods for measuring background PUV_{mean} were measured by two experienced radiological technologists. Two different normal breast areas were selected for measuring background PUV_{mean} including homogenous glandular tissue, and mixed glandular and fatty tissues. By analysing data using SPSS software, for all analysts, the results showed significant positive correlations for all pairs of semiquantitative values. Moreover, PUV_{max} was significantly different from all LTBs and LTB based on glandular tissue was significantly different from LTB based on mixed glandular and fatty tissues. Finally, strong agreement between 2 analysts was found for all semiquantitative values.

Keywords: PEM, ^{18}F-FDG, PUV, LTB, Breast cancer

1. INTRODUCTION

Breast cancer is the most commonly found malignancy in women worldwide. It is growing strongly in South America, Africa, and Asia [1]. In Thailand, breast cancer is the leading cancer in Thai women with mean annual age-standardized incident rate (ASR) of 31.4 per 100,000 populations during 2013-2015 [2]. In addition, the mortality rate reported by Bureau of non-communicable disease in Thailand between 2013 and 2017 was increased from 3.95 to 5.35 per 100,000 [3]. Screening and early detection of breast cancer have an important role in patient care management and mortality rate reduction.

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Several imaging modalities have been introduced for screening and staging breast cancer patients. The most frequently used conventional imaging modality is mammography and the supplementary modality is ultrasound [4]. In nuclear medicine, positron emission mammography (PEM) is a 3D molecular breast imaging system that provides additional information to aid the conventional imaging for diagnosis of breast lesions. Similar to positron emission tomography (PET) imaging, fluorine-18 fluorodeoxyglucose (^{18}F-FDG) is the most frequently used radiotracer for PEM imaging and reflects area of glucose utilization. PEM with ^{18}F-FDG has been shown high sensitivity and specificity for detecting known cases of breast cancer and suspicious lesions [5-6].

Interpretation of PEM images is based on both visually and semiquantitatively assessment. In semiquantitative assessment, maximum PEM uptake value (PUV_{max}) and lesion-to-background (LTB) are commonly used to evaluate the suspected breast lesions. The PUV_{max} is the maximum value within region-of-interest (ROI) of breast lesion and LTB is the ratio of PUV_{max} to the background mean uptake value (PUV_{mean}), which is obtained by drawing ROI in an area of normal breast [7-8]. For LTB measurement, it is noticed that the methods for measuring PUV_{mean} of LTB are different among various studies [4, 7-9]. Based on published studies, either only glandular tissue or mixed area of glandular and fatty tissues can be used to represent normal breast area.

According to a variety of LTB methods, this study aimed to investigate the correlation between semiquantitative values including PUV_{max} and LTBs with different methods for measuring the background PUV_{mean}. In addition, these values were then compared to determine the significant difference.

2. MATERIALS AND METHODS

2.1. Collection of ^{18}F-FDG PEM images

This retrospective study was reviewed and approved by the ethics committee of Rajavithi Hospital. Data of patients who underwent ^{18}F-FDG PEM imaging between 2014 and 2017 were collected. All patients had already been performed mammogram and were diagnosed according to Breast Imaging Reporting and Data System (BI-RADS) categories. Thus a total of 23 patients with 32 suspected breast lesions were included. All patients were female with a mean age of 50.3 $\pm$ 8.73 (in the range of 27 – 66) years.

2.2. Protocol of ^{18}F-FDG PEM imaging

Commercial available PEM scanner named Naviscan PEM Flex™ Solo II was used to acquire PEM images for all patients. The scanner has two-opposing detectors used to detect annihilation photons and immobilize the breast. Both detectors are motor-controlled compression detectors which can be controlled separately. The distance between the two detectors after breast compression determines the compression thickness. The detectors are constructed from 2 × 2 × 13 mm^3 lutetium yttrium orthosilicate scintillation crystals coupled with positron-sensitive photomultiplier tubes. The detectors can be rotated to allow imaging from different views and scan across the FOV in the direction of 6-cm direction covering up to 24 cm. Thus, the maximum FOV of the system is 24 × 16.4 cm [8, 10].

All patients were instructed to fast for at least 6 hours prior to the scan and only plain water was permitted. In addition, they were advised to avoid caffeine, sugar, tobacco and heavy exercise for 24 hours before scan. On the day of examination, blood glucose level was checked before ^{18}F-FDG administration and the acceptable level was less than 140 mg/dL. Intravenous injection of ^{18}F-FDG with radioactivity of 185-370 MBq (5-10 mCi) was given and the patient rested quietly in a warm room for 45-60 minutes.

PEM imaging was performed in two standard views for both breasts i.e., craniocaudal (CC) and mediolateral oblique (MLO) views. The angle of c-arm for CC was within 0 to 10 degrees and MLO was within 45 to 60 degrees. The energy photopeak was 511 keV and energy window was set from 350 to 750 keV. The data were acquired by continuous mode with scan range of -90 to +90, matrix size of 136 × 200, and FOV of 24 × 16.4 cm. The scan time was 360 and 480 seconds for CC and MLO views, respectively. PEM images were reconstructed by using 3-dimensional (3D) list-mode maximum likelihood expectation maximization (ML-EM) algorithm with 5 iterations. Twelve reconstructed slices paralleled to the detectors were obtained without attenuation and scatter corrections and the slice thickness was equal to the compressed breast thickness divided by twelve.

2.3. Measurement of semiquantitative values

PEM images were sent to a PEM workstation and semiquantitative values (PUV_{max}, LTBs) were measured by two experienced radiological technologists using MIM software™. In this study, analysts were blinded to all clinical and pathological data. PEM images in MLO view was selected and the region of interest (ROI) was drawn around the suspected breast lesion to measure PUV_{max}. In addition, four different LTBs (LTB1, LTB2, LTB3, and LTB4) were calculated with different methods for measuring mean background PEM uptake value (PUV_{mean}). To measure PUV_{mean}, two different normal breast areas were selected for drawing an ROI including homogenous glandular tissue only, and mixed glandular and fatty tissues as shown in Figure 1. For LTB1, the ROI was drawn only glandular tissue on the same slice of lesion used to measure PUV_{max}. The other LTB values were based on mixed glandular and fatty tissues. So, the PUV_{mean} for LTB2, LTB3, and LTB4 was measured on the same slice of PUV_{max}, next one slice of PUV_{max}, and any slices, respectively. The analysts were independently measured semiquantitative values for each breast lesion and a total of 32 breast lesions from 23 patients were studied.

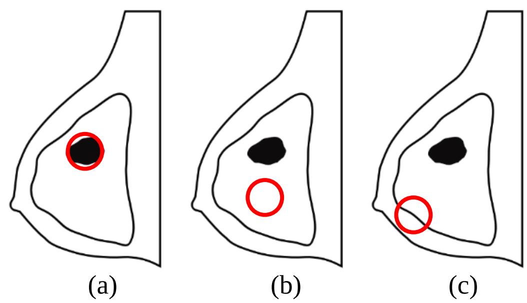

Figure 1. (a) PUV_{max} was measured by drawing an ROI on suspected breast lesion. Two different normal breast areas were selected to measure PUV_{mean} including (b) homogenous glandular tissue, and (c) mixed glandular and fatty tissues.

2.4. Statistical analysis

Statistical analyses were performed using SPSS software for Windows (version 18.0, SPSS Inc, IBM, Chicago, IL, USA). Mean and standard deviation (SD) for all semiquantitative values were reported. Spearman rank correlation was used to investigate relationship among PUV_{max}, LTB1, LTB2, LTB3, and LTB4. The spearman coefficient (spearman's rho) values closer to +1.0 or -1.0 indicate the greater the strength of correlation between 2 observed semiquantitative values and a p-value of less than 0.05 was considered to indicate a significant difference.

In addition, Mann-Whitney U test was performed to determine significant difference between a pair of semiquantitative values and the difference was statistically significant with p-value less than 0.05 at 95% confident interval (CI). Interobserver reliability measuring the agreement between two analysts for all semiquantitative values was tested using intraclass correlation coefficient

(ICC) with two-way random-effect model and 95% CI. The ICC ranges between 0.0 – 1.0 with value closer to 1.0 representing better reliability. The ICC value can be interpreted as follows: the ICC of 0.5 indicated poor reliability; 0.5 – 0.75 indicated moderate reliability; 0.75 – 0.9 indicated good reliability, and greater than 0.9 indicated excellent reliability [11].

3. RESULTS

Five semiquantitative values were measured from 32 suspected breast lesions of 23 patients. The mean±SD of PUV_{max}, LTB1, LTB2, LTB3, and LTB4 was 3.14± 2.03, 5.00±4.59, 7.45±6.65, 7.71±7.60, and 7.81±6.75, respectively, for analyst 1, and 3.10±2.03, 4.67±4.50, 6.80±5.81, 7.20±6.68, and 7.22±7.01, respectively, for analyst 2.

The correlations between pairs of semiquantitative values were investigated for each reader and the results showed that there were significant positive correlations for all pairs of semiquantitative values with ranged from 0.84 to 0.99 for analyst 1 and 0.77 to 0.98 for analyst 2 as shown in Table 1. In addition, strong correlations (spearman's rho > 0.9) was found among the values of LTBs for both analysts.

Table 1. Correlation between semiquantitative values.

Semiquantitative Values	Analyst 1		Analyst 2	
	Rho	p-Val	Rho	p-Val
PUV_{max} Vs. LTB1	0.85	0.00	0.77	0.00
PUV_{max} Vs. LTB2	0.84	0.00	0.78	0.00
PUV_{max} Vs. LTB3	0.84	0.00	0.78	0.00
PUV_{max} Vs. LTB4	0.88	0.00	0.80	0.00
LTB1 Vs. LTB2	0.93	0.00	0.95	0.00
LTB1 Vs. LTB3	0.94	0.00	0.96	0.00
LTB1 Vs. LTB4	0.91	0.00	0.95	0.00
LTB2 Vs. LTB3	0.99	0.00	0.98	0.00
LTB2 Vs. LTB4	0.96	0.00	0.97	0.00
LTB3 Vs. LTB4	0.97	0.00	0.97	0.00

A comparison pair of semiquantitative values was tested by using Mann-Whitney U test for each analyst and found that PUV_{max} was significantly different from all LTBs for both analysts as shown in Table 2. For a comparison among LTBs, there was no statistically significant difference between LTB 2 and LTB3, LTB4, and between LTB3 and LTB4 (p-value > 0.05) for both analysts whereas there was statistically significant difference between LTB 1 and LTB2, LTB3, LTB4 (p-value <0.05).

The agreement between two analysts using ICC for all semiquantitative values was shown in Table 3. As a result, the ICC of PUV_{max}, LTB1, LTB2, LTB3, and LTB4 was 0.99 (95% CI, 0.99 – 1.00), 0.98 (95% CI, 0.96 – 0.99), 0.98 (95% CI, 0.96 – 0.99), 0.99 (95% CI, 0.97 – 0.99), and 0.98 (95% CI, 0.96 – 0.99), respectively. This indicates the strong agreement between 2 analysts for all semiquantitative values.

Table 2. Comparison between semiquantitative values for each analyst using Mann-Whitney U test.

Semiquantitative Values	p-Value	
	Analyst 1	Analyst 2
PUV_{max} Vs. LTB1	0.03	0.05
PUV_{max} Vs. LTB2	0.00	0.00
PUV_{max} Vs. LTB3	0.00	0.00
PUV_{max} Vs. LTB4	0.00	0.00
LTB1 Vs. LTB2	0.01	0.01
LTB1 Vs. LTB3	0.01	0.01
LTB1 Vs. LTB4	0.01	0.00
LTB2 Vs. LTB3	0.95	0.81
LTB2 Vs. LTB4	0.79	0.79
LTB3 Vs. LTB4	0.71	0.96

Table 3. Agreement between two analysts for each semiquantitative value.

Semiquantitative Values	ICC (95% CI)
PUV_{max}	0.99 (0.99 – 1.00)
LTB1	0.98 (0.96 – 0.99)
LTB2	0.98 (0.96 – 0.99)
LTB3	0.99 (0.97 – 0.99)
LTB4	0.98 (0.96 – 0.99)

4. DISCUSSION

Positron emission mammography (PEM) is an emerging technology of molecular imaging in nuclear medicine that provides high-resolution tomographic images. PEM imaging with ^{18}F-FDG is widely used for diagnosis and staging of patients with breast cancer. Interpretation of high-resolution PEM images can be performed by using semiquantitative analysis. Two semiquantitative values that are recommended by machine manufacturer are PUV_{max} and LTB.

Our results of mean PUV_{max} (3.14±2.03 and 3.10±2.03 for analyst 1 and 2, respectively) are similar to the values reported by several studies. In the study of Muller el al., [4] mean PUV_{max} was 3.78±2.47 for thirty-one malignant tumors. Moreover, mean PUV_{max} reported by Yamamoto et al. [8] for 50 patients was 3.7±2.57 for malignant lesions. For LTB, Yamamoto et al. [8] reported LTB with the value of 4.78±5.29 for malignant lesions using background PUV_{mean} measured from homogeneous glandular tissues of normal breast and their LTB value are in line with our study.

This study also investigated the correlations of all semiquantitative values and found that there were significant positive high correlations between PUV_{max} and

LTBs. Similarly, Soldevilla-Gallardo et al. [12] reported that two PEM semiquantitative parameters including PUV_{max} and LTB showed a statistically significant correlation across different subtypes of breast cancer. Moreover, a strong correlation between PUV_{max} and LTB was also found in the study of Wang et al. [13].

From Table 2, as PUV_{max} was statistically significant different from all LTBs, this indicates that PUV_{max} still plays the main role in PEM study. LTB value will be the additional value for PEM study as it shows a statistically significant correlation with PUV_{max} value for both analysts (Table 1). The ROI of mixed glandular and fatty tissues (LTB2, LTB3, and LTB4) does not make any difference whether it is in the same slice of PUV_{max} or not. But the ROI of glandular only (LTB1) was statistically significant different from other LTBs. This means that the components within the ROIs of LTBs has the effect on the LTB value. In clinical practice, the standard component within the ROI for LTB calculation should be the same for every patient. For this reason, each PEM center should set up the standard protocol for LTB calculation. In addition, it can be suggested that the LTB based on mixed glandular and fatty tissues on the same slice of PUV_{max} calculation may be suitable due to easy measurement and reproducible method.

For each semiquantitative value, agreement between two analysts was very high (ICC > 0.9) representing very good reliability in this study. Similar to the study of Yamamoto et al. [8], interobserver variability for semiquantitative values was also high, especially for PUV_{max} that showed higher agreement than LTB.

Even though the methods for obtaining semiquantitative values are different, several studies showed that PUV_{max} and LTB provided the same diagnostic performance for classifying breast lesions [8, 12]. In addition, it has been suggested that PUV_{max} is a simple and reproducible method for semiquantitative measurement [8].

The results of this study can provide additional information for breast surgeon or oncologist in the patient management. Moreover, semiquantitative values obtained from ^{18}F-FDG PEM images can help to clarify equivocal findings of conventional breast imaging such as mammography and ultrasound resulting in improving patient care and management.

However, a limitation of this study is small numbers of subjects which were depended on several factors such as the cost of the examination, the decision making of the breast surgeon and the appropriate examination period before operation.

In the future, research interests are patient and staff radiation doses for ^{18}F-FDG PEM study in order to optimise protocols and reduce injected activity of the patients. So, the cost of examination, the patient and staff doses can be deducted.

5. CONCLUSION

Five semiquantitative values (PUV_{max} and the 4 different LTBs) were measured from ^{18}F-FDG PEM images by two experienced radiological technologists. High correlations for all semiquantitative values were obtained. Moreover, there were a significant difference between PUV_{max} and LTBs, and LTB based on glandular tissue was significant differed from LTB based on mixed glandular and fatty tissues. Finally, agreement between 2 analysts was very high for all semiquantitative values representing very good reliability among interoberver.

6. ACKNOWLEDGEMENT

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REFERENCES

[1] M. Ghoncheh, Z. Pournamdar, H. Salehiniya, “Incidence and mortality and epidemiology of breast cancer in the world,” *Asian Pac J Cancer Prev*, vol. 17, pp. 43-46, 2016.

[2] W. Imsamran, A. Chaiwerawattana, S. Wiangnon, D. Pongnikorn, K. Suwanrungrung, S. Sangrajrang, R. Buasom, “Cancer in Thailand,” *Ministry of Public Health, Ministry of Education*, vol. 8, 2015.

[3] Division of non-communicable diseases, “Annual report 2015,” BKK, Thailand: WVO Thai Printing, 2015. [online]. Available: http://thaincd.com/document/file/download/paper-manual/Annual-report-2015.pdf.

[4] F.H.H. Muller, J. Farahati, A.G. Muller, E. Gillman, M. Hentschel, “Positron emission mammography in the diagnosis of breast cancer. Is maximum PEM uptake value a valuable threshold for malignant breast cancer detection?,” *Nuklearmedizin*, vol. 55, pp. 1-6, 2016.

[5] W.A. Berg, I.N. Weinberg, D. Narayanan, M.E. Lobrano, E. Ross, L. Amodei, et al., “High-resolution fluorodeoxyglucose positron emission tomography with compression (“positron emission mammography”) is highly accurate in depicting primary breast cancer,” *The Breast Journal*, vol. 12, pp. 309-323, 2006.

[6] C. Caldarella, G. Treglia, A. Giordano, “Diagnostic performance of dedicated positron emission mammography using fluorine-18-fluorodeoxyglucose in women with suspicious breast lesions: a meta-analysis,” *Clinical Breast Cancer*, Vol. 14, pp. 241-248, 2014.

[7] D. Narayanan, K.S. Madsen, J.E. Kalinyak, W.A. Berg, “Interpretation of positron emission

mammography: feature analysis and rates of malignancy," *AJR*, Vol. 196, pp. 956-970, 2011.

[8] Y. Yamamoto, Y. Tasaki, Y. Kuwada, Y. Ozawa, A. Katayama, Y. Kanemaki, et al., "Positron emission mammography (PEM): reviewing standardized semiquantitative method," *Ann Nucl Med*, Vol. 27, pp. 795-801, 2013.

[9] A. Boonyaleepan, "Positron emission mammography for breast cancer in Rajavithi hospital," *J Med Assoc Thai*, Vol. 99 (Suppl. 2), pp. S130-S-135, 2016.

[10] L. MacDonald, J. Edwards, T. Lewellen, D. Haseley, J. Rogers, P. Kinahan, "Clinical imaging characteristics of the positron emission mammography camera: PEM Flex Solo II," *J Nucl Med*, Vol. 50(10), pp. 1666-1675, 2009.

[11] T.K. Koo, M.Y. Li, "A guideline of selecting and reporting intraclass correlation coefficients for reliability research," *Journal of Chiropractic Medicine*, Vol. 15, pp. 155-163, 2016.

[12] I. Soldevilla-Gallardo, S.S. Medina-Ornelas, C. Villarreal-Garza, E. Bargallo-Rocha, C.H.S. Caro-Sanchez, R. Hernandez-Ramirez, E. Estrada-Lobato, "Usefulness of positron emission mammography in the evaluation of response to neoadjuvant chemotherapy in patients with breast cancer," *Am J Nucl Med Mol Imaging*, Vol. 8(5), pp. 341-350, 2018.

[13] C.L. Wang, L.R. MacDonald, J.V. Rogers, A. Aravkin, D.R. Haseley, J.D. Beatty, "Positron emission mammography: correlation of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status and ^{18}F-FDG," *AJR*, Vol. 197, pp. W247-W255, 2011.

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