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# Discussion on the alteration of 18F-FDG uptake by the breast according to the menstrual cycle in PET imaging

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***Abstract*— 18F-FDG PET/CT is a useful modality for identifying high-glucose-consuming cells, such as cancer cells by the glucose metabolism of FDG. FDG is taken up by cancer and inflammatory cells but occasionally, there is some FDG uptake on normal tissues as a result of their individual physiological characteristics. In particular, in fertile females, unusual FDG uptake in the breast changes according to the stages in the menstrual cycle, which can adversely affect a diagnosis. Therefore, this study examined the change in breast FDG uptake in the menstrual cycle on 18F-FDG PET/CT. One hundred and sixty females (34 ± 3.5 years old), who had not undergone a gynecologic anamnesis and had a regular menstrual cycle over the previous 6 months, were examined from March 2011 to February 2012. The subjects were divided into the following 4 groups (each with 40 patients): flow phase, proliferative phase, ovulatory phase and secretory phase using Pregnancy Calculator 0.14 and history taking. Discovery STE (GE Healthcare, USA) was used as the PET/CT. The SUVs on the accumulated region on the breast were analyzed, and 3 nuclear medicine specialists performed a blind test. The SUVs on the breast were the flow phase (1.64 ± 0.25), proliferative phase (0.93 ± 0.28), ovulatory phase (1.66 ± 0.26) and secretory phase (1.77 ± 0.28). Higher uptake values were observed in the secretory, flow phase and ovulatory phase ($p< 0.05$). The accumulation of the breast was divided into the following 3 grades compared to the lung and liver by gross analysis: the breast uptake was equal to the lung (Grade Ⅰ); between the lung and liver (Grade II); and equal to or greater than the liver (Grade III). These results showed a high uptake value in the secretory, flow phase and ovulatory phase ($p <0.05$). In fertile females, the FDG uptake of the breast showed changes according to the menstrual cycle, which can be used to improve the diagnosis of breast disease. Therefore, the false-negative findings of breast disease can be reduced by performing an examination at the appropriate period through history taking and considering the individual menstrual cycle.**

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## I. Introduction

18F-FDG PET/CT is a useful test for detecting cancer by assessing the abnormal uptake of FDG by cancer cells due to the glucose metabolism [1]. Generally, the high uptake of FDG by cancer cells and in flammatory diseases was observed. Nonetheless, normal cells may show abnormal uptake depending on the physiological characteristic of patients [2]. In particular, the structural changes that occur in the uterine wall according to the menstrual cycle influence the pelvic ultrasonography results. Moreover, the endometrium shows abnormal FDG uptake and influences the PET/CT test due to the change in female hormones [3]. In fertile women, the menstrual cycle is generally 28 days. The menstrual cycle is divided to the Menstrual Flow Phase, Proliferative Phase, Ovulatory Phase, and Secretory Phase according to the changes in the uterus and follicle. The uterus undergoes changes as a regular cycle [4]. During each menstrual cycle, the ovary undergoes changes in two stages, Follicular Phase and Luteal Phase. During this process, the representative female hormones estrogen and progesterone are secreted [5]. After menstruation, the endometrium becomes thick due to the influence of estrogen released from the follicle, and the uterine glands and blood vessels developed simultaneously [6]. The progesterone released from the corpus luteum stimulates the proliferation of endometrium and blood flow in the breast resulting in an increase in the elasticity of breast connective tissues and fat deposition, which induces the development of the lactiferous duct and mammary glands [7]. Therefore, its influence on the result of mammography and PET/CT should not be ruled out.

In Korean women, breast cancer is the second highest cancer next to thyroid cancer, and the importance of PET-CT for determining the stage of breast cancer and assessing the prognosis after the treatments has been emphasized. On the other hand, the abnormal FDG uptake by the breast of women according to the menstrual cycle may be a factor that impairs an accurate diagnosis of breast micro-lesions. Therefore, this study assessed the optimal time for a PET-CT test by comparing the uptake of FDG by the breast according to the menstrual cycle to improve the ability to diagnose micro-lesions in the breast.

## II. Materials and Methods

### A. Patients information

The subjects were 160 female patients (mean age, 34 ± 3.5 years) who visited our hospital from March 2011 to February 2012 without a disease history of gynecological disease, and

with a regular menstrual cycle for longer than 6 months (Figure 1). The subjects were divided into the following phases by history taking and the application of Pregnancy Calculator Ver.0.14: the menstrual flow phase, proliferative phase, ovulatory phase and secretory phase. Information of 40 patients in each phase was collected.

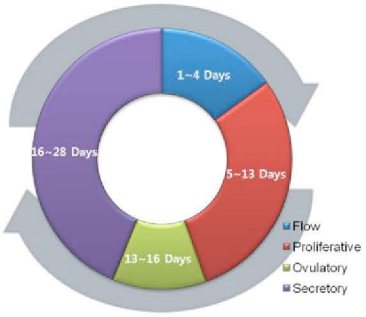


Figure 1. One hundred and sixty females (34 ± 3.5 years old), who did not undergo gynecologic anamnesis and had a regular menstrual cycle (28 days) over the previous 6 months were examined. 1 - 4 days, 5 - 13 days, 13 - 16 days and 16 - 28 days were classified as the flow, proliferative, ovulatory and secretory phase, respectively.

### B. *Equipment and test methods*

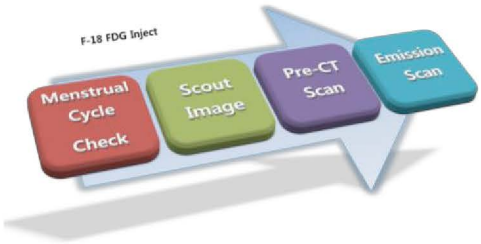


Figure 2. Before the PET/CT procedure, each menstrual cycle was confirmed through history taking, and Whole Body PET/CT was performed.

The Discovery STE scanner (Milwaukee, Wi, GE Healthcare, Co., USA) was used for PET/CT. BGO was used as the crystal. A 6.0 mm full width at half maximum (FWHM) was used as the intrinsic resolution. The display field of view (DFOV) was 70.0 mm, and the Overlap per 1 bed was 9 mm. CT consisted of 8 slices with a 2 mm slice thickness. As the reconstruction method, "subset" was performed 28 times and "iterative" was performed 2 times using the iterative method. As the pretreatment test, the patients were fasted for a minimum of 8 hours, and excessive exercise was prohibited on the day before the test and on the day of the test. The patients took sufficient liquid, more than 100 ~ 500 ml. The blood glucose levels prior to the test were < 6.69 mmol/l (120 mg/dl). For the administration of 18F-FDG, after the patients were allowed to rest for approximately 15 minutes, approximately 5.6 MBq/kg (0.15 mCi) was injected intravenously. Movements were restrained to prevent uptake by the muscles, and a full-body scan was performed after 60 ~ 90 minutes. In a full-body scan, the test range was from the base of the brain to the proximal femoral area in the supine position. Non contrast computed tomography (NCCT) without contrast was performed under the condition of 140 kVp and 30 mAs. Subsequently, an emission scan for 3 minutes per bed was performed (Figure 2).

After the emission scan, contrast enhanced computed tomography (CECT) was performed. OMNIPAQ UE (300 mg iodine/ml, GE Healthcare Co., Ireland) was used as the contrast. At that time, it was injected at a dose of 2 cc per kg of the patient's body weight and a speed of 2 ml per second. A dual shot injector optivantage (Mallinchrodt, LIEBEL FLARSHEIM Co., USA) was used as the automatic injector.

### C. *Image analysis*

Using Pregnancy Calculator Ver. 0.14 and history taking prior to the test, the women were classified according to their menstrual cycle, and in each phase, the changes in SUV in the liver, lung and breast were compared and analyzed (Figure 3).

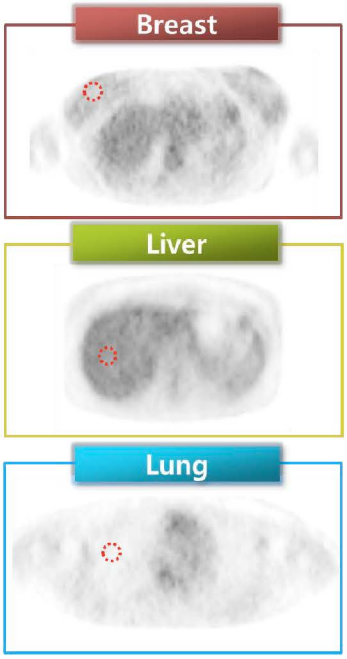


Figure 3. Semi-quantitative analysis was performed using each SUV measured in the breast, liver, and lung to identify the change in SUVs according to the menstrual cycle.

In addition, a macroscopic evaluation was performed by 3 radiologists as a Blind Tests. The level of FDG uptake by the lung, liver and breast was measured in each menstrual phase. Cases in whom the FDG uptake by the breast was comparable to the lung were classified as Grade I. Cases in whom the FDG uptake of the breast was between the lung and liver were Grade II. Cases in whom the FDG uptake of the breast was comparable to the liver or higher than the liver were Grade III (Figure 4).

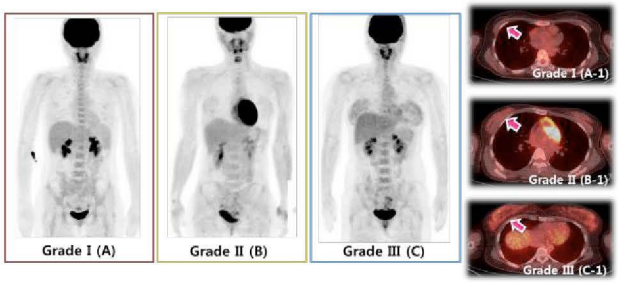


Figure 4. Three nuclear medicine specialists performed the blind test. (A), (B), (C) were PET whole body images, and (A-1, B-1, C-1) were the fusion image of each grade. The unusually Breast FDG uptake increased with increasing grade.

## III. Results

The $SUV_{max}$ of the menstrual, proliferative, ovulatory and secretory phases was 1.64 ± 0.25 g/ml, 0.93 ± 0.28 g/ml, 1.66 ± 0.26 g/ml and 1.77 ± 0.28 g/ml, respectively (Table I).

The SUV was highest in the secretory phase followed in order by the menstrual flow phase and the ovulatory phase ($p < 0.05$). In addition, the change in SUV in each menstrual phase was drawn as a Box Plot, which revealed an increased in the secretory phase, menstrual flow phase and ovulatory phase. The SUV was lower in the proliferative phase (Figure 5). On the other hand, the SUV in the lung and the liver showed no change according to the menstrual cycle (Figure 6).

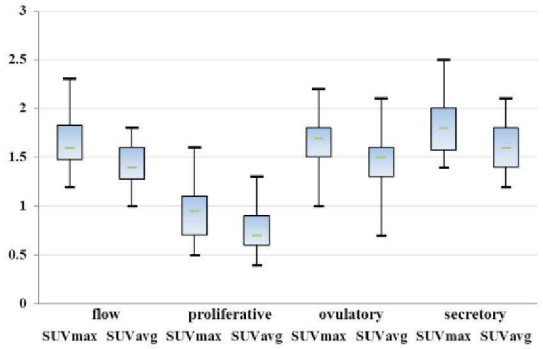


Figure 5. The breast uptake values increased in the order of secretory, flow, and ovulatory phase. The proliferative phase showed comparative low SUVs.

Three radiologists evaluated the uptake of the 160 patients by macroscopic analysis as a blind test. The results revealed, Grade I in 34 patients (21.2 %). Among them, 2 and 34 cases were in the menstrual flow and proliferative phases, respectively. No cases were observed in the ovulatory and secretory phases. Most of the patients who underwent the test during the proliferative phase corresponded to Grade I. Forty six (28.8 %) patients were in Grade II; 13 and 16 cases were in the menstrual flow and ovulatory phase, respectively.

Eighty cases (50 %) were Grade III, of which the FDG uptake was highest. Thirty one patients were in the secretory phase, and their ratio was highest (Table II).

In particular, all images of the secretory phase corresponded to Grades II or III, and the FDG uptake by the breast was noticeably higher than the proliferative phase (Figure 7).

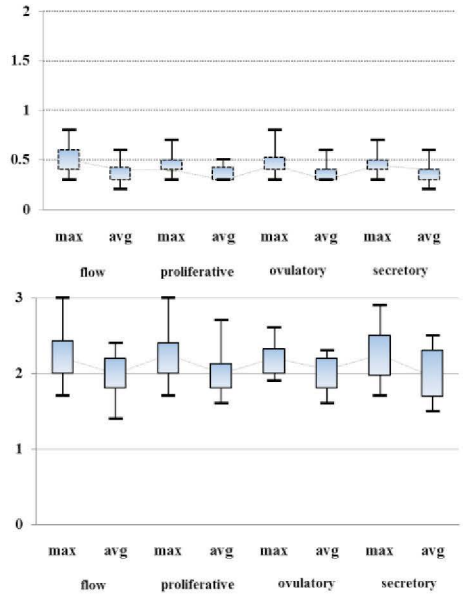


Figure 6. The uptake values of the lung and liver had almost no variation over menstrual cycle. This suggests that the breast's SUVs are affected by the menstrual cycle.

TABLE I. In, $SUV_{MAX}$ was highest at 1.77 ± 0.28 g/ml in the secretory phase, and lowest at 0.93 ± 0.28 g/ml in the proliferative phase.

| Cycle Phase | No. of Patients | $SUV_{max}$ | $SUV_{avg}$ |
|---|---|---|---|
| Menstrual Flow Phase | 40 | 1.64 ± 0.25 g/ml | 1.40 ± 0.22 g/ml |
| Proliferative Phase | 40 | 0.93 ± 0.28 g/ml | 0.74 ± 0.22 g/ml |
| Ovulatory Phase | 40 | 1.66 ± 0.26 g/ml | 1.46 ± 0.29 g/ml |
| Secretory Phase | 40 | 1.77 ± 0.28 g/ml | 1.60 ± 0.24 g/ml |

TABLE II. The FDG uptake in the breast regions showed Grades I, II and III in 34 (21.2 %), 46(28.8 %) and 80 women (50.0 %), respectively. The FDG uptake of breast was the lowest in the proliferative phase and highest in the secretory phase.

| FDG Uptake in Breast | Flow | Proliferative | Ovulatory | Secretory | Total No. |
|---|---|---|---|---|---|
| Grade I | 2 | 32 | 0 | 0 | 34 |
| Grade II | 13 | 8 | 16 | 9 | 46 |
| Grade III | 25 | 0 | 24 | 31 | 80 |
| Total No. | 40 | 40 | 40 | 40 | 160 |

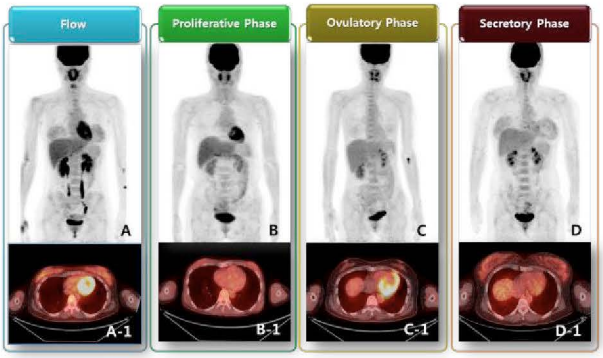


Figure 7. PET Whole Body images of Secretory phase (D) and flow phase (A) were the highest FDG uptake of breast, and each fusion images (D-1, A-1) showed increases remarkably. (B) and (B-1) were proliferative phase, and breast uptake was almost no increase. (C) and (C-1) were ovulatory phase that breast FDG uptake was increased more than proliferative.

## IV. Discussion And Conclusion

In a PET/CT full-body scan, hormonal changes according to the menstrual cycle increase the FDG uptake by the breast [8]. The change in FDG uptake was largest in the secretory phase, and its effect was lowest in the proliferative phase [9-10]. Based on this study, the SUV changes in the breast according to the menstrual cycle and the macroscopic changes in uptake by the breast could be detected by a full-body PET/CT scan [11-13]. If a PET/CT test is performed during the proliferative phase in collaboration with the diagnosis department, it can provide an accurate test that could detect even micro lesions in the breast. Nonetheless, in the present study, the subjects were patients with a regular menstrual cycle [14-16]. Patients with an irregular menstrual cycle were excluded [17]. Accordingly, many studies will be needed before this can be applied to patients with an irregular menstrual cycle.

The level of the FDG uptake by the breast in fertile women varies according to the menstrual cycle. In particular, information on the menstrual cycle can be applied widely for a diagnosis of breast micro-lesions. Through this study, the uptake of FDG by the breast in each phase was compared. In fertile women, the FDG uptake by the breast was highest during the secretory phase and lowest in the proliferative phase. Therefore, it is believed that false negative results of micro breast lesions may be reduced by assessing the accurate menstrual cycle through history taking before the test and by performing the test at the appropriate phase.

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