▸원 저◂

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The Value of Delayed ^{18}F-FDG PET/CT Imaging for Differentiating Axillary Lymph Nodes in Breast Cancers

- 유방암 환자에서 액와 림프절 진단을 위한 ^{18}F-FDG PET/CT 지연 검사의 유용성 -

Dept. of Nuclear Medicine, Dongnam Institute of Radiological & Medical Sciences Cancer Center
[1)]Dept. of Radiological Technology Dong-Eui Institute of Technology

Young-Sik Ji · Ju-Cheol Son · Cheol-Woo Park[1)]

— **Abstract** —

Positron emission tomography/computed tomography (PET/CT) imaging with fluorodeoxyglucose (FDG) have been used as a powerful fusion modality in nuclear medicine not only for detecting cancer but also for staging and therapy monitoring. Nevertheless, there are various causes of FDG uptake in normal and/or benign tissues. The purpose of present study was to investigate whether additional delayed imaging can improve the diagnosis to differentiate the rates of FDG uptake at axillary lymph nodes (ALN) between malignant and benign in breast cancer patients. 180 PET/CT images were obtained for 27 patients with ALN uptake.

The patients who had radiotherapy and chemotherapy were excluded from the study. ^{18}F-FDG PET/CT scan at 50 min (early phase) and 90 min (delayed phase) after ^{18}F-FDG injection were included in this retrospective study. The staging of cancers was confirmed by final clinical according to radiologic follow-up and pathologic findings. The standardized uptake value (SUV) of ALN was measured at the Syngo Acquisition Workplace by Siemens.

The 27 patients included 18 malignant and 9 ALN benign groups and the 18 malignant groups were classified into the 3 groups according to number of metastatic ALN in each patient. ALNs were categorized less than or equal 3 as N1, between 4 to 9 as N2 and more than 10 as N3 group.

Results are expressed as the mean ± standard deviation (S.D.) and statistically analyzed by SPSS. As a result, Retention index (RI-SUV max) in metastasis was significantly higher than that in non-metastasis about 5 fold increased. On the other hand, RI-SUV max in N group tended to decrease gradually from N1 to N3. However, we could not prove significance statistically in malignant group with ANOVA. As a consequence, RI-SUV max was good indicator for differentiating ALN positive group from node negative group in breast cancer patients. These results show that dual-time-point scan appears to be useful in distinguishing malignant from benign.

Key Words : PET/CT, FDG, ALN and SUV.

Ⅰ. INTRODUCTION

^{18}F-FDG PET/CT is sensitive and specific in the diagnosis and staging of several types of cancers. FDG is a radio-labeled sugar able to detect region

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교신저자: 박철우, (614-715) 부산광역시 부산진구 양지로 54
동의과학대학교 방사선학과
Tel : 051-860-3532, Fax : 051-860-3351
E-mail : cwpark@dit.ac.kr

of abnormal glucose metabolism and localize many cancers[1]. The degree of FDG accumulation is related to the cellular metabolism and the number of glucose transporters. Increased FDG accumulation in cancers is mainly due to an increased number of glucose transporters[2], enzyme levels of hexokinase and phosphofructokinase promoting glycolysis in cancer cells[3].

However, FDG is not specific to cancers. There are many causes of FDG accumulation in benign lesions[4]. Many inflammation and infection have elevated FDG accumulation, leading to false positive results when a patient is managed for a potential malignant disorder. Moreover, there is significant overlap between SUV of metastatic lymph node and benign lymph node, causing difficulty in diagnosing ^{18}F-FDG PET/CT data[5,6].

ALN involvement is the important prognostic factor in breast cancer patients[7]. Therefore, accurate assessment of ALN status is essential not only for predicting outcome but also selecting a therapeutic plan. The most reliable procedure for the examination of ALN is axillary lymph node dissection (ALND). However, the complications related to ALND, such as lymphedema, limitation of shoulder movement and numbness of the skin of the upper arm, lead to decreased quality of life. Therefore, it is important to investigate methods to assess accurate staging of ALNs without unnecessary ALND.

Several researches have shown that FDG accumulation by malignant tumors increase time dependent manner after injection. Thus, we hypothesized that whether delayed ^{18}F-FDG PET/CT may improve the diagnostic accuracy of staging in breast cancer patients.

Ⅱ. MATERIALS AND METHODS

1. Patient population

This retrospective study was performed on 180 breast cancer patients who underwent ^{18}F-FDG PET/CT between August 2010 and December 2012. The patients who had radiotherapy and chemotherapy were excluded from the study.

27 women (mean age 50.6 ± 10.5 years) of them, there were ALN FDG uptake that included 18 metastatic regions and 9 benign regions. The staging of cancers was confirmed from final clinical and radiologic follow-up and pathologic findings.

2. ^{18}F-FDG PET/CT scan

^{18}F-FDG PET/CT images were acquired by Biograph 6 True Point; (Siemens Medical Solution, Knoxville, TN) from breast cancer patients.

All patients had fasted at least 5 hr before ^{18}F-FDG injection and their blood sugar levels were restricted less than 130 mg/dl for PET/CT scan.

We performed PET/CT scan twice with each patient. The early scan was acquired from the upper thigh to the mid cranium at 50 min after injection of 7.03MBq/kg of ^{18}F-FDG and also second scan was acquired from thorax region for delayed PET/CT scan at 90 min. The patients were positioned supine with arm raised and they were recommended drinking water and void during the intervening time between scan.

The early and delayed scan protocols were consisted of 6 to 8 and 2 to 3 beds respectively. The image acquisition time was 2 min per bed. Both of early and delayed scan protocol was the same except for the field of view.

3. Image analysis

All PET/CT images were reviewed in the trans axial, coronal and sagittal planes reconstructed at the Syngo Acquisition Workplace by Siemens.

We evaluated both of early(50 min) and delayed(90 min) PET/CT images by drawing a region of interest (ROI) over the perceptible ^{18}F-FDG uptake at the ALN which included the largest amount of radioactivity for semi-quantitative analysis and then, standardized uptake value (SUV) of ^{18}F-FDG uptake was measured. If the ^{18}F-FDG uptakes

appeared multiply at ALN, the highest SUV max was measured.

The SUV was calculated as following formula:

$$SUV = \frac{mean\,ROI\,activity(MBq/g)}{Injected\ ^{18}F-FDG\ dose\,(MBq/g) - Body\,weight\,(g)}$$

We also estimated the D-SUV max and RI-SUV max for accurate changed SUV max between early SUV max and delayed SUV max at each region.

The D-SUV max and RI-SUV max were calculated as the following formula:

$$D-SUV\max = Delayed\,SUV\max - Early\,SUV\max$$

$$RI-SUV\max = \frac{Delayed\,SUV\max - Early\,SUV\max}{Early\,SUV\max}$$

4. Statistical analysis

We analyzed all semi-quantitative data by using SPSS (V.18 Inc., USA) and those data were divided as 18 malignant and 9 benign groups depending on each patient's final diagnosis.

Furthermore, 18 malignant groups were classified in different 3 groups according to the number of accumulated ^{18}F-FDG uptake in axillary lymph nodes(ALN).

The number of ALN were categorized less than or equal 3 as N1, between 4 to 9 as N2 and more than 10 as N3.

All semi-quantitative data appeared as mean ± standard deviation (S.D.). The independent t-test was used to measure semi-quantitative data (Early SUV max, Delayed SUV max, D-SUV max and RI-SUV max) in between benign and malignant groups respectively. P-values of less than 0.05 were considered statically significant for all analysis.

Furthermore, we performed statistically RI-SUV max in N1, N2 and N3 with ANOVA and compare differences between benign and malignant groups.

Ⅲ. RESULTS

We evaluated 27 breast cancer patients who had perceptible ^{18}F-FDG uptake at ALN between August 2010 and December 2012.

Table.1 shows the mean value of Early SUV max, Delayed SUV max, D-SUV max and RI-SUV max in between benign and malignant group.

The mean values of Early SUV max, Delayed SUV max, D-SUV max and RI-SUV max were 8.77±7.43, 10.32±8.33, 1.55±1.19 and 0.21±0.16 in benign group, and 4.20±2.11, 4.45±2.53, 0.25±1.02 and 0.04±0.23 in malignant group, respectively.

Table 1. Comparison of semi-quantitative analysis as mean ± S.D. in benign and malignant group

Number of Patients	Early SUV_{max}	Delayed SUV_{max}	D-SUV_{max}	RI-SUV_{max}
Malignant 18	8.77±7.43	10.32±8.33	1.55±1.19*	0.21±0.16*
Benign 9	4.20±2.11	4.45±2.53	0.25±1.02*	0.04±0.23*

* $p < 0.05$ (Independent sample t-test)

Early SUV max and Delayed SUV max have no statistical significance (p=0.085 compared with Early SUV max, p=0.051 compared with Delayed SUV max) in the t-test.

There were statistically significant between benign and malignant group in D-SUV max (p=0.009) and RI-SUV max in the t-test. In particular, RI-SUV max (p=0.044) in malignant group was significantly higher than that of benign group of about 5 fold increase (0.21±0.16 versus 0.04±0.23).

Furthermore, we were able to confirm improved visualization through delayed PET/CT images. Figure.1 shows an example of distinguishable

visualization about ^{18}F-FDG uptake in malignant and benign group. Malignant focus became more apparent in later images and SUV max increased from 7.33(a) to 10.82(b) whereas benign focus became faint in later images and SUV max decreased from 2.06(c) to 1.59(d).

And also we could identify even 3 additional lesions through delayed PET/CT images from 2 patients.

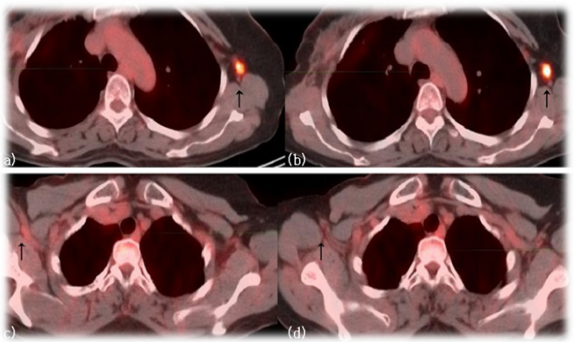

Fig. 1. ^{18}F-FDG uptake left axilla on 50min (a), 90min (b) of malignant ALN and right axilla on 50min (c), 90min (d) of benign ALN in PET/CT

Table. 2 shows the mean value of Early SUV max, Delayed SUV max, D-SUV max and RI-SUV max among N stages.

The mean values of Early SUV max, Delayed SUV max, D-SUV max and RI-SUV max were 7.74±6.43, 9.28±7.21, 1.54±1.21 and 0.21±0.16 in N1, 4.69±3.94, 5.40±4.24, 0.71±0.32 and 0.18±0.06 in N2 and 14.68±9.87, 16.89±11.06, 2.20±1.33 and 0.15±0.05 in N3 respectively.

Table 2. Comparison of semi-quantitative analysis as mean ± S.D. among N stages

Status of N	Number of N	Early SUV_{max}	Delayed SUV_{max}	D-SUV_{max}	RI-SUV_{max}
N1	11	7.74±6.43	9.28±7.21	1.54±1.21	0.23±0.20
N2	3	4.69±3.94	5.40±4.24	0.71±0.32	0.18±0.06
N3	4	14.68±9.87	16.89±11.06	2.20±1.33	0.15±0.05
Total	18	8.77±7.43	10.32±8.33	1.55±1.19	0.21±0.16

In this case, we could not prove statistically significance with One way ANOVA. There are no statistically significant differences in N1, N2 and N3 in ML group for RI-SUV max ($p>0.05$). Despite of that reason, RI-SUV max in N stage tended to decrease gradually from N1 to N3 in ML (Figure.2).

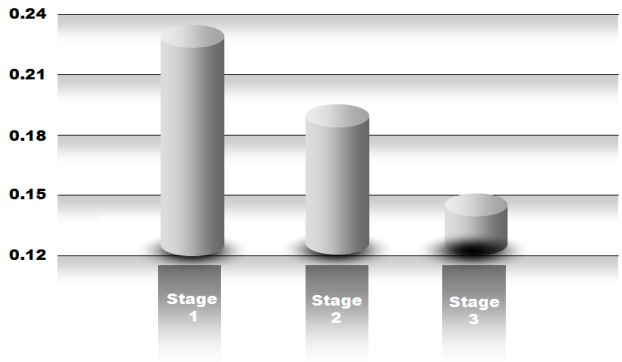

Fig. 2. Correlation between RI-SUV max and stage of ML

Ⅳ. DISCUSSION AND CONCLUSION

Based on our study, it informed that metastatic ALN lesion with large increased SUVs over time seemed to be had a malignancy. In contrast, ALN lesion with decreased or slightly increased SUVs over time was likely to have benign etiology.

Although there are no significant differences between N stage and RI-SUV max, the changed ^{18}F-FDG uptake value in malignant group was very distinguishable from that in benign group.

We regarded that the reason we could not find out the correlation among N stages was small subjects included in this study. However, despite this limitation, this result showed that using delayed PET/CT scan was potentially useful to distinguish metastatic lymphadenopathy (LAP) from benign LAP in breast cancer patients.

The usefulness of delayed PET/CT has already been proven by several studies. A study with ^{18}F-FDG PET that showed promising results reported sensitivity and specificity of over 90% in

detection of ALN metastasis from breast cancer[8]. Kumar et al[9] also reported that the change of SUVs over time was helpful in differentiating even inflammatory lesions from malignant lesions.

However, we have to consider additional radiation exposure from delayed ^{18}F-FDG PET/CT scan. Even if the radiation exposure cause low radiation dose, meticulous care is required depending on comprehensive state of patients to reduce radiation dose. In the case of children and patients who are undergoing frequent follow-up radiation scan, more invasive test such as biopsy will be helpful for the evaluation of breast pathologies.

^{18}F-FDG has been used widely throughout the world for diagnosis and staging of several types of cancers. However, ^{18}F-FDG uptake can accumulate not only in tumors but also in inflammatory site, so distinguishing metastatic lymph node by ^{18}F-FDG PET/CT is difficult.

To resolve this problem, delayed ^{18}F-FDG PET/CT imaging with conventional imaging would be useful. In addition, further research on it is needed.

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•국문초록

유방암 환자에서 액와 림프절 진단을 위한 ^{18}F-FDG PET/CT 지연 검사의 유용성

지영식 · 손주철 · 박철우[1)]

동남권 원자력의학원 핵의학과 · 동의과학대학교 방사선과[1)]

핵의학과에서 ^{18}F-FDG PET/CT 검사는 종양의 진단 뿐 아니라 치료병기를 설정하는데 중요한 역할을 하고 있다. 하지만 정상 조직이나 양성 종양 간의 FDG 섭취를 초래하는 다양한 요인이 있어 정확한 진단에 혼란을 초래할 수 있다. 본 연구의 목적은 유방암환자에서 ^{18}F-FDG PET/CT 지연 검사가 악성 종양과 양성 종양을 구별 하는데 있어 유용성을 가지고 있는지에 관하여 알아보고자 함에 있다.

본원을 내원하여 ^{18}F-FDG PET/CT 검사를 받은 환자 중 방사선 치료나 화학 치료를 받은 환자를 제외한 액와림프절에 FDG섭취를 보인 27명의 환자를 대상으로 하였으며, ^{18}F-FDG 투여 후 50분 후에 검사를 시행하였고 90분 후에 지연상을 획득했다.

종양의 병기 설정은 방사선 검사나 병리학적 검사를 바탕으로 확정된 결과를 바탕으로 분류 하였으며, 액와림프절의 SUV는 Siemens사의 Syngo Aquisition Workplace로 측정하였다. 27명의 환자는 18명의 악성종양 군과 9명의 양성종양 군으로 분류하였고 악성종양 군은 액와림프절의 개수에 따라 1-3개는 N1, 4-9개는 N2, 10개 이상은 N3로 분류 하였다. 실험 결과는 평균 ± 표준편차로 표현하였고, SPSS (V.18 Inc., USA)를 사용하여 통계분석을 실행하였다.

50분 검사와 90분 검사 간의 비교 시, 악성종양 군의 RI-SUVmax는 양성종양 군에 비해 5배 이상의 증가를 보였다. N그룹에서의 RI-SUVmax는 N1에서 N3로 갈수록 점점 감소되는 경향을 보였지만 통계적 유의성을 확인 할 수 없었다. 그럼에도 불구하고 유방암 환자에서 RI-SUVmax는 액와림프절의 악성과 양성을 판단하는 좋은 지표가 되었고 이를 구별하는데 유용할 것으로 사료된다.

중심 단어 : 액와림프절, PET/CT, SUV.