The Clinical Significance of ^{18}F -Fluorodeoxyglucose Uptake on Axillary Lymph Nodes Metastasis in Breast Cancer

Axillary LN meta가 있는 유방암에서 액와 림프절의 FDG uptake가 가지는 임상적 의미

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Introduction

The axillary lymph node(ALN) status in primary breast cancer is one of the most important predictive factor in tumor recurrence or disease-free survival,¹⁾ and ALN dissection had been recommended a gold standard procedure for decades in ALN staging of breast cancer which providing excellent local control of breast cancer.^{2,3)} But, there is no preoperative screening modality for evaluation of ALN status except ultrasonography-guided biopsy. Thus, sentinel lymph node biopsy(SNB) has become a new standard method for evaluation of ALN status, which is considered a minimally invasive procedure and providing the same information as ALN dissection with less morbidity.⁴⁾

The ^{18}F -Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography(^{18}F -FDG PET/CT) has been suggested for preoperative staging of locally advanced breast cancer such as bigger than 5 cm or spread to other tissues around breast including ALNs metastasis, distant metastasis or for assessment of the chemotherapeutic effects.⁵⁻¹⁰⁾ But, there is rare evidence

that this imaging modality is better than others for preoperative cancer staging, because the ^{18}F -FDG PET/CT shows low sensitivity.¹¹⁻¹⁴⁾ In spite of these results, several studies have shown that false negative rate of breast cancer in ^{18}F -FDG PET/CT is relatively lower when the primary tumor is more aggressive.¹⁵⁻¹⁹⁾ As similar logical reasons, poor prognostic factors of primary tumor might be associated with significant FDG uptake on ALNs in ^{18}F -FDG PET/CT.^{20,21)}

Authors investigated the FDG uptake on ALN in preoperative ^{18}F -FDG PET/CT and tumor characteristics to figure out their association and its clinical significance.

Materials and Methods

Materials

From January to December of 2007, 176 consecutive female patients with invasive ductal carcinoma were performed preoperative ^{18}F -FDG PET/CT. Among 176 cases, 65 of ALN metastasis breast cancer cases were included in this study and they were classified as two groups. The Group A is composed with 31 patients who showed high FDG uptake (maximal standardized uptake value, $\text{SUV}_{\text{max}} > 1.0$) of ALNs in preoperative ^{18}F -FDG PET/CT and the Group B is composed with 34 patients with low FDG uptake ($\text{SUV}_{\text{max}} \leq 1.0$) on ALNs.

We excluded the cases who had received prior breast surgery, excisional biopsy of primary tumor or preoperative chemotherapy before ^{18}F -FDG PET/CT was performed. And

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the patients who had diabetes mellitus previously or distant metastasis at the same time of primary breast cancer diagnosis were also excluded in this study.

Methods

The biologic characteristics of primary tumor (tumor size, tumor differentiation, estrogen receptor (ER), progesterone receptor (PR), p53 gene, c-erbB2 gene, Ki-67 antigen, tumor necrosis, lymphovascular invasion) and metastatic ALN status (number and maximum diameter, N stage) were investigated in each groups. Tumor differentiation and ER/PR/p53/c-erbB2 were confirmed by tissue biopsy before surgery. More than 2+ of ER/PR and 3+ of c-erbB2 in immunohistochemical stain were defined as positive result.

The patients had fasted at least 8 hours before PET imaging acquisition and blood glucose levels were measured to be less than 120 mg/dL. Intravenous injection of 4.5 MBq/Kg of ^{18}F -FDG was performed in opposite arm to the breast cancer. The PET/CT images were acquired after 60 minutes in 3-minute static emission study using PET/CT scanner (Gemini, Philips Medical System, Bothell, WA) and delayed images were not obtained.

The tumor-to-background (T/B) ratio of ALN was calculated with FDG uptake of ipsilateral to contralateral ALN ratio and ^{18}F -FDG PET/CT scanning images were analyzed by one nuclear medicine physician. The ALN was considered as metastasis when SUVmax was more than 1.0.

Statistical analysis

The statistical analysis was performed by using chi-square test for trend (tumor differentiation, N stage), chi-square test (primary tumor size, ER/PR/p53/c-erbB2 status, tumor necrosis, lymphovascular invasion), Fisher's exact test (triple negative) and t-test (tumor size, incidence of Ki-67 antigen, number and size of metastatic ALNs) by SPSS 11.0 (SPSS, Chicago, USA).

For all of the cases, the cut-off values which provide the highest sensitivity and specificity were generated by Receiver-Operator Characteristic (ROC) curve analysis. The

correlation between significant clinicopathologic factors according to cut-off value and FDG uptake was evaluated also by chi-square test. The statistical significance was defined when $p < 0.05$.

Results

The detection rates of metastatic ALNs in preoperative ^{18}F -FDG PET/CT

Thirty-three cases showed high FDG uptake on ALN in preoperative ^{18}F -FDG PET/CT, but two of them were false positive. Whereas, the false negative result was shown in thirty-four cases. Overall sensitivity, specificity and accuracy of preoperative ^{18}F -FDG PET/CT for detection of ALN metastasis was 47.4%, 98.2% and 79.5%, respectively. Diagnostic performance for evaluation of ALN status (Figure 1)

Fig. 1. Diagnostic performances for evaluation of ALN status in ^{18}F -FDG PET/CT

In group A, metastatic ALNs were confirmed by ultrasonography-guided fine-needle aspiration cytology or biopsy before surgery and ALN dissection were done without SNB. In group B, metastatic ALNs were confirmed by SNB in 31 cases and tissue biopsy had performed before surgery in the rest of three cases. ALN dissection were done, also.

Statistical analysis

Statistical significances were shown between two groups when tumor differentiation was worse than moderate degree ($p=0.005$) and N stage was higher than N2 ($p=0.002$). And negative results of ER ($p=0.028$), PR ($p=0.003$) and p53 gene ($p=0.050$), positive result of c-erbB2 gene ($p=0.027$), presence of tumor necrosis ($p=0.019$) and lymphovascular invasion ($p=0.017$) were associated with high FDG uptake of ALNs in ^{18}F -FDG PET/CT. But, there was no significance in triple negative breast cancer (Table 1).

The mean diameter of primary tumor and metastatic ALNs,

number of metastatic ALNs were higher in group A than that of group B. And all of them showed statistical significance ($p=0.001$, 0.004 , 0.017 , <0.001 , Table 2).

Receiver-Operator Characteristic (ROC) curve analysis

The metastatic ALNs status in preoperative ^{18}F -FDG PET/CT was analyzed with primary tumor size, Ki-67 antigen index, number and size of metastatic ALNs. And the relevant cut-off values were calculated with maximal sensitivity and specificity. The cut-off values were analyzed when the primary tumor size was 1.85 cm (sensitivity=90%;

Table 1. Comparison of primary tumor characteristics between group A and B

Variables	Group A* (n=31)	Group B † (n=34)	p-value	
Histology grade	Well	1	7	0.005
	Moderate	24	26	
Poor		6	1	
Estrogen receptor	Negative	12	5	0.028
	Positive	19	29	
Progesterone receptor	Negative	17	7	0.003
	Positive	14	27	
p53 gene	Negative	19	28	0.050
	Positive	11	6	
c-erbB2 gene	Negative	20	29	0.027
	Positive	11	5	
Triple negative status	No	25	31	0.138
	Yes	6	3	
Presence of necrosis	No	15	26	0.019
	Yes	16	8	
Lymphovascular invasion	No	10	21	0.017
	Yes	21	13	
N stage	1	14	28	0.002
	2	11	5	
	3	6	1	

*significant FDG uptake on ALN in preoperative ^{18}F -FDG PET/CT; † low FDG uptake on ALN in preoperative ^{18}F -FDG PET/CT

Table 2. Comparison of mean tumor size, Ki-67 antigen and axillary lymph nodes status between group A and B

Variables	Group A* (n=31)	Group B † (n=34)	p-value
Mean tumor size (cm)	3.5	2.0	0.001
Incidence of Ki-67 antigen (%)	25.6	13.5	0.004
Mean number of metastatic ALNs ††	5.7	2.7	0.017
Mean size of metastatic ALN (cm)	1.8	0.7	< 0.001

*High FDG uptake on ALN in preoperative ^{18}F -FDG PET/CT; † Low FDG uptake on ALN in preoperative ^{18}F -FDG PET/CT;

†† Axillary lymph node

Fig. 2. ROC curve of tumor size; the cut-off value of tumor size is 1.85cm which shows the most relevant sensitivity(90%) and specificity(59%)

Fig. 3. ROC curve of Ki-67; the cut-off value of Ki-67 is 17.5% which shows the most relevant sensitivity(63%) and specificity(68%).

Fig. 4. ROC curve for number of metastatic lymph node; the cut-off value is 2.5 which shows the most relevant sensitivity(65%) and specificity(79%).

Fig. 5. ROC curve of metastatic lymph node size; the cut-off value of metastatic lymph node size is 0.95cm which shows the most relevant sensitivity(88%) and specificity(74%).

Table 3. Clinicopathological factors correlated with SUVmax*

		High FDG uptake (SUVmax>1.0)	Low FDG uptake (SUVmax≤1.0)	p-value
Tumor size	≤1.8 cm	3 (4.6%)	20 (30.8%)	<0.001
	>1.8 cm	28 (43.1%)	14 (21.5%)	
Size of metastatic LN [†]	≤0.95 cm	5 (7.7%)	25 (38.5%)	<0.001
	>0.95 cm	26 (40.0%)	9 (13.9%)	
No. of metastatic LNs	≤3	14 (21.5%)	28 (43.1%)	0.002
	>3	17 (26.2%)	6 (9.2%)	

*Maximum standardized uptake value; [†] Lymph node

specificity=59%, Figure 2), Ki-67 antigen index was 17.5% (sensitivity=63%; specificity=68%, Figure 3), number of ALNs was 2.5 (sensitivity=65%; specificity=79%, Figure 4) and the size of ALNs was 0.95 cm (sensitivity=88%; specificity=74%, Figure 5). The tumor size ($p<0.001$), size and number of metastatic LNs ($p<0.001$, <0.05) showed significance with FDG uptake in PET/CT when the patients were divided based on cut-off value (Table 3).

Discussion

Although many physicians have reported the role of preoperative ^{18}F -FDG PET/CT for metastatic ALNs or preoperative staging, it still shows poor results compared with ultrasonography or other imaging modalities.¹¹⁻¹⁴ To improve the low sensitivity or detection rates, physicians should figure out the characteristics of metastatic ALN in ^{18}F -FDG PET/CT.

Because ^{18}F -FDG PET/CT is not superior to ultrasonography for evaluation of ALN status, the SNB has been done even though the FDG uptake of ALNs was shown in PET/CT.²⁰ But high FDG uptake of ALNs in preoperative PET/CT would be a predictive factor for aggressiveness of breast cancer.²³ In our results, the FDG uptake on ALNs in preoperative ^{18}F -FDG PET/CT was associated with poor histologic grade and negative results of ER or PR, positive result of c-erbB2 gene which are commonly available before surgery by tissue biopsy.

Although the FDG uptake of primary tumor focus in ^{18}F -FDG PET/CT reflects tumor aggressiveness, long-term survival rates does not affect and the clinical usefulness has not been verified yet. However, the clinical significance of ^{18}F -FDG PET/CT for preoperative tumor staging might be expected with the association between high FDG uptake on ALN and primary tumor characteristics.

The detection rate of metastatic ALNs in imaging modality is very important for determining preoperative staging in locally advanced breast cancer. Although ^{18}F -FDG PET/CT has provided information for preoperative staging and response to chemotherapy,⁷⁻¹⁰ the ^{18}F -FDG PET/CT cannot

be recommended for evaluation of ALN metastasis because of lower detection rate and sensitivity than other previous imaging methods. Generally, more than 2.0 of SUVmax is accepted as the cut-off level for malignancy in PET/CT, but the recent literature showed that SUVmax has a wide variety of malignancies including breast cancer.²⁴ In our study, the significant FDG uptake of ALN is defined when T/B ratio is more than 1.0, and the sensitivity, specificity and accuracy were similar as prior reports for metastatic ALNs in ^{18}F -FDG PET/CT.^{1,22}

The FDG uptake of ALNs in ^{18}F -FDG PET/CT has been known as relatively lower in small and few metastatic ALNs.²⁵ According to our results, the cut-off values of FDG uptake on ALNs were 0.95 cm diameter and 3 of them. More than 0.95 cm or 3 of metastatic ALNs would be detected on ultrasonography for biopsy and the SNB could be skipped when the metastasis is confirmed.

Conclusion

The high FDG uptake of ALNs in preoperative ^{18}F -FDG PET/CT is associated with aggressiveness of primary tumor. And the most valuable sensitivity and specificity were shown in 3 or 0.95cm sized metastatic ALN which is large enough to performing biopsy. We suggest preoperative ALN biopsy for cases of high FDG uptake on ALN in preoperative ^{18}F -FDG PET/CT and the SNB would be skipped if metastasis is confirmed.

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Abstract

Purpose: ^{18}F -Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (^{18}F -FDG PET/CT) has been recommended as a diagnostic modality for preoperative staging of breast cancer. But, the information for FDG uptake on axillary lymph node (ALN) is not sufficient. Authors investigated the FDG uptake on ALN in preoperative ^{18}F -FDG PET/CT and tumor characteristics to figure out their association and its clinical significance. **Materials and Methods:** From Jan. to Dec. 2007, 176 patients had been performed preoperative ^{18}F -FDG PET/CT. Only sixty-five cases were confirmed as ALN metastasis in pathologic report. Thirty-one patients with high FDG uptake of ALN ($\text{SUV}_{\text{max}} > 1.0$) and thirty-four with low FDG uptake ($\text{SUV}_{\text{max}} \leq 1.0$) in ^{18}F -FDG PET/CT were classified as group A and B, respectively. **Results:** The FDG uptake of ALN showed significant relationship with poor prognostic factors of primary tumor (worse histologic grade, negativity of estrogen and progesterone receptor, positivity of p53 and c-erbB2 gene, tumor necrosis, lymphovascular invasion) and ALN metastasis. In multivariate analysis, FDG uptake of ALN showed larger tumor size ($p=0.001$), higher Ki-67 ($p=0.004$), bigger and more metastatic ALN ($p=0.017$, <0.001) compared to low FDG uptake of ALN. The cut-off values of high FDG uptake were 1.85 cm of primary tumor size, 17.5% of Ki-67, 2.5 and 0.95 cm of number and size of metastatic ALN. **Conclusion:** The most valuable sensitivity and specificity of FDG uptake in metastatic ALN were shown when the number and size of ALN was more than 3 or 0.95 cm and they would be large enough to perform ultrasonography-guided biopsy. We recommend preoperative ALN biopsy for the cases of FDG uptake on ALN in preoperative ^{18}F -FDG PET/CT and the sentinel lymph node biopsy might be skipped if metastasis is confirmed on biopsy.

Key Words : ^{18}F -Fluorodeoxyglucose uptake, Axillary lymph nodes, Breast cancer, Primary tumor characteristics

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