The role of ultrasonography and FDG-PET of axillary lymph node staging in breast cancer

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The role of ultrasonography and FDG-PET of axillary lymph node staging in breast cancer

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ABSTRACT

The role of ultrasonography and FDG-PET of axillary lymph node staging in breast cancer

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Background: The presence of axillary lymph node metastasis is the most important prognostic factor and an essential part of staging and prognosis of breast cancer.

Purpose: To elucidate the usefulness and accuracy of the US, FDG-PET and combined analysis for axillary lymph node staging in breast cancer.

Material and Methods: From January 2005 to December 2006, total 250 consecutive breast cancer patients who undertaken US, FDG–PET and sentinel lymph node biopsy (SLNB) before surgery were included. If axillary lymph nodes showed the length to width ratio ≤ 1.5 or cortical thickening ≥ 3mm or compression of the hilum on US, focal hot uptake (maximal standardized uptake value, SUVmax ≥ 2.0) in ipsilateral axilla on FDG-PET, it was considered as metastatic lymph node. In combined analysis of US and FDG-PET, the interpretation was considered positive if at least two of any of the criteria. Each imaging findings were compared with pathologic report that the presence of axillary lymph node metastasis, the number of metastatic lymph nodes and the T stage of breast mass.

Results: Pathologically confirmed axillary lymph node metastasis was noted in

73 cases (29.2%). The mean number of metastatic lymph nodes in pathology was 3.1±3.2, and the size of breast cancer was 2.0±1.04cm. In the detection of lymph node metastasis, diagnostic accuracy of US was 78.8%, and that of FDG-PET was 76.4%. On combined US and FDG-PET, accuracy was improved (91.6%). The number of metastatic lymph nodes on pathology was correlated with the positivity of US and FDG–PET ($p < 0.01$).

Conclusion: Combined evaluation of US and FDG-PET was a sensitive and accurate method for axillary lymph node staging in breast cancer.

Key words: breast cancer, axillary lymph node, ultrasonography, FDG-PET, staging, metastasis

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I. INTRODUCTION

The presence of axillary lymph node metastasis is the most important prognostic factor in breast cancer[1, 2]. Traditionally, axillary lymph node dissection (ALND) has been the standard for axillary nodal assessment; however, this procedure can cause lymphedema, restriction of arm and shoulder movement, and numbness of the upper arm[3, 4]. This has led to the increased necessity of a less invasive procedure. Therefore, sentinel lymph node biopsy (SLNB) has become the new standard in breast cancer patients for axillary lymph node evaluation as a less invasive alternative[5], but this approach has technical and conceptual limits[6, 7]. False-negative results of SLNB can occur in a variable percentage of patients (from 0% to 15%)[2]. Most of these false negative results occur due to massive lymph node metastasis in the first drainage node.

Axillary ultrasonography (US) and fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scan have not been systemically performed in evaluation of axillary lymph node staging in breast cancer patients due to their historically low sensitivity. However, many studies have evaluated the role of US or FDG-PET for axillary lymph node staging as non-invasive alternatives[8-15].

A previous report described the combined evaluation of axillary lymph node staging of US and ^{99m}Tc-sestamibi scintimammography[16]. However, there have not been any reports on the combined use of US and FDG-PET for evaluation of axillary lymph node staging. We performed a study to assess the accuracy of axillary US and FDG-PET both independently and in combination, for axillary lymph node staging, especially in stage Tis, T1 and T2 breast cancer.

II. MATERIALS AND METHODS

1. Inclusion criteria

From January 2005 to December 2006, a total of 320 patients were diagnosed with breast cancer at our institute, and all of these patients underwent breast US, FDG-PET and SLNB before surgery. Among 320 patients, 63 patients with neoadjuvant chemotherapy were excluded due to difficult evaluation of lymph node status. We also excluded 7 cases that failed during SLNB. In total, 250 consecutive patients (median age 48.9 years, range 28-79 years) were enrolled in the study.

2. Imaging procedure

Axillary US were performed by two radiologists (E.J.S and J.A.K) with extensive experience (over 5 years each) in breast radiology. US was performed with 10-12MHz linear transducers (HDI5000, Advanced Technology Laboratories, Bothell, WA, USA). If indeterminate/suspicious/metastatic lymph node were detected in the axilla, transverse and longitudinal scans were taken and longitudinal and the transverse diameters and cortical thicknesses of the nodes were measured. If there were multiple lymph nodes in the axilla, once the images of all visible lymph nodes were obtained, the most suspicious lymph

node was evaluated with the consensus of two radiologists.

In FDG-PET imaging, patients received an intravenous injection of 370MBq of fluorine-18 fluorodeoxyglucose (FDG) in the arm contralateral to the primary tumor. Sixty minutes after injection of FDG, whole-body emission scans were obtained using a Philips Allegro PET camera (Philips Medical Systems, Cleveland, Ohio, USA). All patients were studied in the supine position with their arms raised. Attenuation-corrected transaxial images were reconstructed with an interative transmission algorithm called row-action maximum likelihood 3D protocol using a 3D image filter into a 128 × 128 matrix. Quantitative measurement of the single-pixel maximal standardized uptake value (SUV max) was performed for all breast and axillary areas.

3. Image interpretation

US of axillary lymph nodes were evaluated for shape, cortical thickening and the morphology of hilum. A positive finding was given if the lymph node showed: 1) the length-to-width ratio was less than 1.5; 2) the cortex of the nodes was concentrically or eccentrically thickened more than 3mm; or 3) compression of the hilum and especially the absence of the fatty hilum. If the axillary lymph nodes exhibited any of the three findings mentioned above, they were defined as suspicious for axillary lymph node metastasis[8, 9]. Nodes that exhibited none of the three findings mentioned above were defined as negative for axillary lymph node metastasis. In case of multiple axillary lymph nodes on US, we analyzed the most suspicious lymph node.

On evaluation of FDG-PET images, if the SUV max was 2.0 or greater in the ipsilateral axillary lymph node bearing area, it was considered a positive lymph node metastasis. And the SUV max of the main mass was also measured. FDG-PET scans were interpreted by one specialist who had 10 years of experience in nuclear medicine.

In a combined analysis using US and FDG-PET, the interpretation was considered positive if at least two of any of the criteria included was positive.

4. Surgery and pathologic review

All 250 patients underwent SLNB. On the morning of the surgery, 1.0mCi of technetium^{99} sulfur colloid was injected at the subareolar area. Lymphoscintigraphy was routinely performed. Intraoperatively, the sentinel lymph node was identified with a hand-held gamma probe.

Pathologic evaluation was performed by one dedicated pathologist who had over 10 years of experiences of breast pathology. All specimens were submitted in formalin and frozen section for hematoxylin and eosin (HE) and immunohistochemical (cytokeratin) staining. The number and sizes of sentinel lymph nodes were documented. Sentinel lymph nodes >0.5cm in the maximal dimension were serially sectioned transversely; those <0.5cm were bisected. After frozen microscopic examinations, the pathologic result was immediately reported to the surgeon. If there was lymph node metastasis in the sentinels, ALND was performed.

Each imaging finding was compared with the pathologic report on the presence of axillary lymph node metastasis (not include micrometastasis), the number of metastatic lymph nodes, the histologic type of breast cancer, and the T stage of the breast mass.

5. Statistical analysis

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), false positive and false negative rate, and accuracy of axillary US, FDG-PET and SLNB were calculated using SigmaStat 2.03 statistical software (SPSS Inc., Chicago, IL, USA).

Comparisons between groups were performed using the chi-square (χ^2) test when required. Statistical significance was calculated using the t-test, and *p*-values less than 0.05 were considered statistically significant.

III. RESULTS

The histologic diagnoses of breast cancer included invasive ductal carcinoma (n=185), ductal carcinoma in situ (n=32), invasive cribriform carcinoma (n=11), invasive lobular carcinoma (n=8), invasive apocrine carcinoma (n=3), invasive micropapillary carcinoma (n=3), medullary carcinoma (n=3), mucinous carcinoma (n=3), and tubular carcinoma (n=2). The average size of the breast masses was 2.0±1.04cm (range 0.3-5.0cm). The T stages of breast cancer were: Tis (n=32), T1a (n= 7), T1b (n= 37), T1c (n= 86) and T2 (n= 88).

Among 250 patients, 73 (29.2%) were pathologically confirmed with axillary lymph node metastasis. However, there was no lymph node metastasis case in DCIS patients. The pathologic grades of DCIS were: group 1(n=4, 12.5%), group 2(n=9, 28.1%) and group 3(n=19, 59.4%) according to Van-Nuys classification. The mean number of metastatic lymph nodes in pathology was 3.1±3.2 (range 1-15).

1. Ultrasonography

On US, 96 patients (38.4%) showed positive lymph nodes. Of the patients who showed positive findings in US, 88 patients showed concentric or eccentric cortical thickening of more than 3mm, and 23 patients had compression of the hilum or absence of the fatty hilum, 7 patients had the length-to-width ratio less than 1.5. Sixteen patients showed more than two suspicious findings. Among 96 patients, 39 patients showed multiple lymph nodes on US. Overall sensitivity, specificity, PPV, NPV and diagnostic accuracy of US were 79.5%, 78.5%,

60.4%, 90.3% and 78.8%, respectively (Table 1). Among 73 patients who had pathologically confirmed axillary lymph node metastasis, 15 patients were noted negative findings. In other words, among 177 patients who were found to be N0 stage, 38 patients had positive findings, respectively. Therefore, the false negative rate and false positive rate of US were 20.5 % (Fig. 1) and 21.5%, respectively. Among 38 patients who had false positive finding on US, 34 patients showed cortical thickening of more than 3mm (mean 4.54±1.66), 5 patients had compression of the hilum, and 2 patients had the length-to-width ratio less than 1.5. One patient showed all of three suspicious findings. The overall positive predictive values of each finding were: 61.4% (54/88) of cortical thickening, 78.3% (18/23) of hilum changes, and 71.4% (5/7) of length-to-width ratio.

2. FDG-PET

FDG-PET revealed 48 patients (19.2%) revealed focal hot uptake (SUV max≥2.0) in the axillary area. Overall sensitivity, specificity, PPV, NPV and diagnostic accuracy of FDG-PET were 42.5%, 90.4%, 64.6%, 79.2% and 76.4%, respectively (Table 1). In patients with positive lymph node on FDG-PET, the mean SUV max of primary breast cancer was 7.4±5.2 (0.4-43.8). Meanwhile, in patients with negative lymph node on FDG-PET, it was 5.4±4.4. There was a significant correlation between SUV max of primary breast cancer and positivity of axillary lymph nodes on FDG-PET (p=0.033). Among 73 patients who had pathologically confirmed axillary lymph node metastasis, 42 patients were noted to have negative findings on FDG-PET, respectively. In other words, among 177 patients who were found to be N0 stage, 17 patients had positive findings on FDG-PET. Therefore, the false negative rate and false positive rate of FDG-PET were 57.5% and 9.6%, respectively.

The mean SUV of main mass in false negative patients was 6.4. In other

words, the mean SUV max of main mass in false positive cases was 6.2. There was no significant correlation for main mass mean SUV max between these false-negative and false-positive cases (p=0.82).

a b

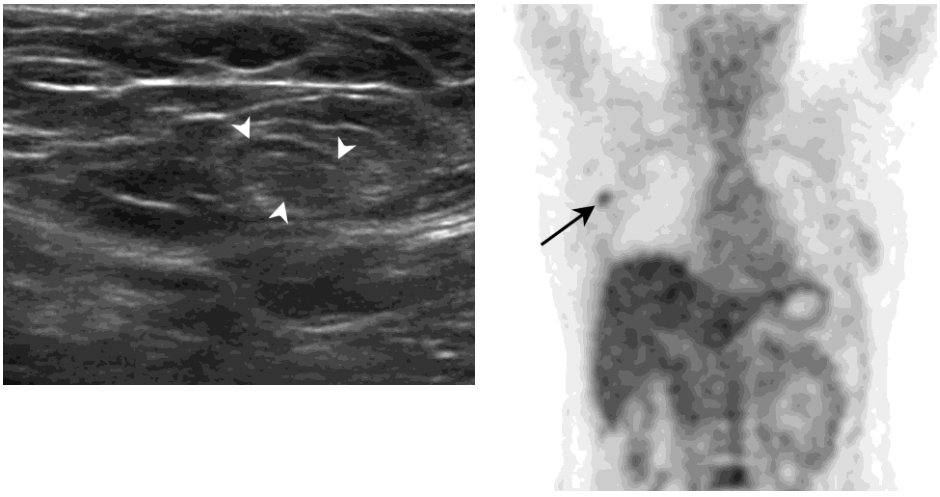

Fig. 1) False negative finding on US for the detection of lymph node metastasis. A 39-year-old woman with infiltrating ductal carcinoma in the right breast. (a) The right axillary lymph node (arrowheads) does not have a length-to-width ratio less than 1.5, a cortical thickening of more 2mm or the loss of hilum on US, so we concluded that it is a negative lymph node. (b) On FDG-PET, hot uptake lesion (SUV max ≥ 2.0) is noted at the right axillary area (arrow), so we decide that it is positive for lymph node metastasis. A pathologically metastatic lymph node is reported, while there is false-negative finding on US.

Table 1) Overall sensitivity, specificity, PPV, NPV and accuracy of US, FDG-PET and SLNB according to T-stage of breast cancer.

		Sensitivity	Specificity	PPV	NPV	Accuracy
US	Tis	0 (0/0)	68.8 (22/32)	0 (0/10)	100.0 (22/22)	68.8 (22/32)
	T1	78.6 (22/28)	85.0 (85/100)	59.5 (22/37)	93.4 (85/91)	83.6 (107/128)
	T2	80.0 (36/45)	71.1 (32/45)	73.5 (36/49)	78.0 (32/41)	75.6 (68/90)
	all	79.5 (58/73)	78.5 (139/177)	60.4 (58/96)	90.3 (139/154)	78.8 (197/250)
FDG-PET	Tis	0 (0/0)	93.8 (30/32)	0 (0/2)	100.0 (30/30)	93.8 (30/32)
	T1	35.7 (10/28)	92.0 (92/100)	55.6 (10/18)	83.6 (92/110)	79.7 (102/128)
	T2	46.7 (21/45)	84.4 (38/45)	75.0 (21/28)	61.3 (38/62)	65.6 (59/90)
	all	42.5 (31/73)	90.4 (160/177)	64.6 (31/48)	79.2 (160/202)	76.4 (191/250)
US+ FDG-PET	Tis	0 (0/0)	90.6 (29/32)	0 (0/3)	100.0 (29/29)	90.6 (29/32)
	T1	82.1 (23/28)	98.0 (98/100)	92.0 (23/25)	95.1 (98/103)	94.5 (121/128)
	T2	84.4 (38/45)	91.1 (41/45)	90.5 (38/42)	85.4 (41/48)	87.8 (79/90)
	all	83.6 (61/73)	94.9 (168/177)	87.1 (61/70)	93.3 (168/180)	91.6 (229/250)
SLNB	Tis	0 (0/0)	100.0 (32/32)	0 (0/0)	100.0 (32/32)	100.0 (32/32)
	T1	75.0 (21/28)	100.0 (100/100)	100.0 (21/21)	93.5 (100/107)	94.5 (121/128)
	T2	97.8 (44/45)	97.8 (44/45)	97.8 (44/45)	97.8 (44/45)	97.8 (88/90)
	all	89.0 (65/73)	99.4 (176/177)	98.5 (65/66)	95.7 (176/184)	96.4 (241/250)

3. US combined FDG-PET

When both imaging modalities were combined, there were 70 (28.0%) cases of positive axillary lymph nodes. Overall sensitivity, specificity, PPV, NPV and diagnostic accuracy were 83.6 %, 94.9%, 87.1%, 93.3% and 91.6%, respectively, on combined US and FDG-PET (Table1). Among 73 patients who had pathologically confirmed axillary lymph node metastasis, 12 patients were noted to have a negative lymph node on FDG-PET and US together, and therefore the false negative rate of combined examinations was 16.4%. On the other hand, among 177 patients who were pathologically confirmed negative for axillary lymph node metastasis, 9 patients were disclosed as having a positive lymph node on combined FDG-PET and US, and therefore the false-positive rate was 5.1% (Fig. 2).

The number of metastatic lymph nodes on pathology was correlated with the positivity of US and FDG–PET ($p < 0.01$). However, suspicious axillary lymph node of FDG-PET and US would have less relevance than the size of the main breast mass and the pathologic type of breast cancer.

4. Sentinel lymph node biopsy

Among 250 patients, 66 patients (26.4%) had metastatic axillary lymph nodes in SLNB. Among 73 patients who had pathologically confirmed axillary lymph node metastasis, 8 patients were noted to have negative findings on SLNB, respectively. Therefore, the false negative rate of SLNB was 11.0%. Diagnostic parameters were listed in table 1.

We also evaluated the overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy according to T stage: Tis and T1(1a, 1b, and 1c) vs. T2 (Table 1). There was higher sensitivity in diagnosing

the axilla LN state in T2 stage breast cancer. Otherwise, the specificities were high in Tis and T1 stage breast cancer (Table 1).

a b

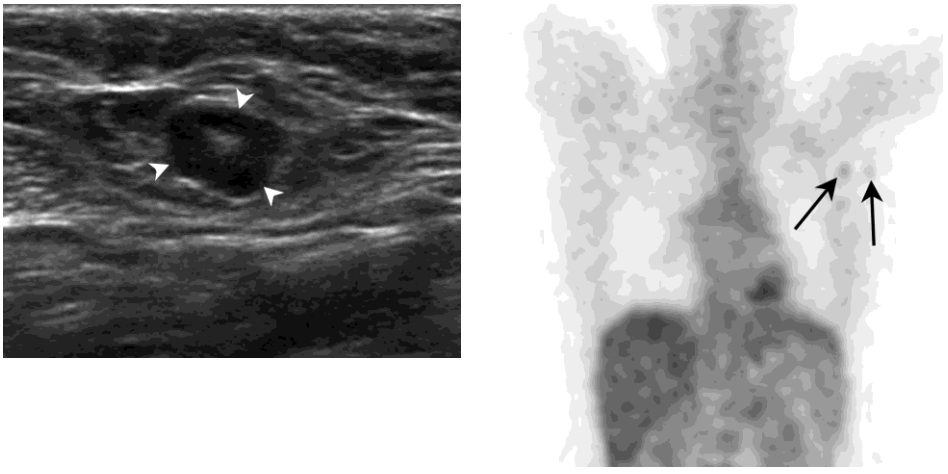

Fig. 2) False positive finding on both US and FDG-PET for the detection of lymph node metastasis. A 41-year-old woman with infiltrating ductal carcinoma at the left breast. (a) Left axillary lymph node (arrowheads) shows a globular shape and cortical thickening of more 2mm on US. (b) And hot uptake lesions (SUV max ≥ 2.0) are noted at the left axillary area (arrows) on FDG-PET. We concluded that the lymph node was positive on both US and FDG-PET. However, a pathologically negative lymph node was reported, with a false-positive finding on both US and FDG-PET.

IV. DISCUSSION

The reported sensitivity and specificity of axillary US range between 50% and 90%, and between 70% and 100%, respectively[8, 10, 11, 17]. F. Lumachi et al.[16] reported that the sensitivity and specificity of US alone are 68% and 80%, respectively, in patients with T1-2 stage breast cancer. According to Alvarez [18], axillary US is moderately sensitive and quite specific in the diagnosis of axillary metastatic involvement in patients with breast cancer. Therefore, axillary US cannot be used in isolation as a method for deciding whether to perform ALND. In our study, sensitivity, specificity, positive predictive value and negative predictive value of US were 79.5%, 78.5%, 60.4% and 90.3%, respectively, so metastatic axillary lymph node cannot be determined using axillary US alone, even though US is acceptable for the detection of metastatic axillary lymph node. In addition, PPV of cortical thickening in US finding is lower (61.4%) than other criteria in our study. Even though cortical thickening is important and widely used criteria for assessment of lymph node status[8, 9, 16, 18, 19], it cannot be used alone for deciding whether the lymph node was metastatic or not.

FDG-PET is increasingly being used to stage patients with breast cancer. Prior studies have revealed the capability to detect axillary metastases in patients with large primary breast tumors, with sensitivities ranging from 90% to 100% and specificities of 75% to 100%. However, higher false-negative rates were noted in patients with smaller tumors[15-17]. Several studies about FDG-PET for axillary metastases have reported a relationship between sensitivity and primary tumor size. In addition, some studies relate the diagnostic accuracy of FDG-PET to primary tumor characteristics. Utech et al.[13] explored a variety of variables, including tumor size, type, grader, estrogen receptor/progesterone receptor status, and number of dissected nodes. They found weak correlations between axillary uptake and tumor size and the number of cells in S-phase.

Greco et al.[20] reported a higher sensitivity for T2 tumors, but a higher specificity for T1 tumors. Chung et al.[21] noted that larger axillary metastatic lymph nodes were more likely to be positive in FDG-PET. The size of the primary tumor may weakly affect the SUVs of axillary lymph nodes, but other tumor characteristics were not correlated with FDG-PET activity of the axillary lymph node[21]. Sensitivity has been reported to vary with tumor type[22] and is in general higher in cases of invasive ductal carcinoma than in invasive lobular carcinoma[23]. In our study, however, no significant correlation between the positivity of FDG-PET and the size or tumor type of primary breast cancer. In addition, there is no significant correlation for main mass SUV max between the false-negative case and true-positive case.

In our study, the SUV max of primary breast cancer was found to vary, and to reflect the degree of tumor metabolism. In addition, we observed a significant correlation between mean SUV max of primary breast cancer and positivity of axillary lymph nodes on FDG-PET. Therefore, a false-negative axillary lymph node on FDG-PET may result from metastatic axillary lymph nodes derived from primary breast cancer with a low SUV max.

When US and FDG-PET are combined, the accuracy of detection of axillary lymph node metastasis was improved relative to the accuracy of each modality alone. In addition, the false-negative rate and false-positive rate also decreased with the combined use of US and FDG-PET. Therefore, US and FDG–PET might have complementary roles in the evaluation of axillary lymph node metastasis in breast cancer patients.

SLNB is an invasive modality for axillary assessment, but it is a highly sensitive and specific method for detecting metastatic axillary lymph nodes in breast cancer patients. However, a variable percentage of false-negative axillary results have been reported for SLNB[2]. In our study, SLNB also showed a high sensitivity, specificity and accuracy, but the false-negative rate of SLNB was 11.0%. In addition, SLNB has a possibility of failure. Therefore, the combined

use of US and FDG-PET can improve the detection of axillary lymph node metastasis, especially in SLNB failed cases.

This study has several limitations. First, there is the issue of objectivity in detection of suspicious axillary lymph node on US, since US is an operator-dependent imaging modality. However, axillary lymph nodes were evaluated by two radiologists and we used morphologic criteria to promote objectivity. Second, the SUV is affected by various conditions such as lesion size, acquisition and processing protocol, and the time after fluorine 18-FDG injection[24, 25].

V. CONCLUSION

In conclusion, US revealed high sensitivity and acceptable specificity for detecting axillary lymph node metastasis in breast cancer patients. On the other hand, FDG–PET was highly specific in diagnosing lymph node metastasis in breast cancer. However, the combination of axillary US and FDG-PET is a sensitive and accurate procedure for preoperative evaluation of the axillary lymph node status in breast cancer patients. Therefore, the evaluation of axillary lymph nodes by a combination of US and FDG-PET can be used as a supplement for axillary lymph node staging.

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국문요약

유방암 환자에서 겨드랑이 림프절의 병기 결정에 있어 초음파와 양전자 방출 단층 촬영술의 역할

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안 지 현

배경: 유방암 환자에서 겨드랑이 림프절 전이 존재 유무는 유방암의 병기 결정과 예후에 있어 가장 중요한 예후 인자이다.
목적: 유방암에서 겨드랑이 림프절의 병기 결정에 있어 초음파와 양전자 방출 단층 촬영술의 유용성과 정확도에 대해 알아보고자 한다.
재료 및 방법: 2005년 1월부터 2006년 12월까지 유방암 수술 전에 초음파, 양전자 방출 단층 촬영술 및 감시 림프절 생검을 시행한 총 250명의 환자를 대상으로 하였다. 만일 초음파상에서 겨드랑이 림프절의 장폭비가 1.5 이하이거나, 피질 두께가 3㎜ 이상이거나 또는 림프절 문이 압박되는 소견이 있을 때 림프절 전이로 판단하였다. 또한 양전자 방출 단층 촬영술상, 유방암과 동측의 겨드랑이에 최대 표준화 섭취계수(SUV max)가 2.0 이상인 국소 열소가 있는 경우 림프절 전이로 여겼다. 초음파와 양전자 방출 단층 촬영술을 병합하여 분석함에 있어, 한 가지 이상의 조건을 만족하는 경우 양성 결과로 해석하였다. 각각의 영상 소견들은 겨드랑이 림프절 전이 존재 유무, 전이 림프절의 수, 그리고 유방 병변의 T 병기 등에 대해 병리 결과와 비교하였다.
결과: 73명의 환자(29.2%)에서 겨드랑이 림프절 전이가 조직학적으로 확인되었다. 병리 조직상, 전이 림프절의 평균 개수는 3.1±3.2개였으며, 유방암의 크기는 2.0±1.04 ㎝였다. 전이 림프절 발견에 있어서 초음파의 진단 정확도는 78.8%였고, 양전자 방출 단층

촬영술의 진단 정확도는 76.4%였다. 두 검사를 병합하여 판단하였을 때 진단 정확도는 향상되었다 (91.6%). 조직학적으로 전이 림프절의 수는 초음파 및 양전자 방출 단층 촬영술에서의 양성도와 연관이 있었다 ($p < 0.01$).
결론: 초음파와 양전자 방출 단층 촬영술을 병합하여 평가하는 것이 유방암에서 겨드랑이 림프절의 병기 결정에 있어 보다 민감하고 정확한 방법이다.

핵심되는 말 : 유방암, 겨드랑이 림프절, 초음파, 양전자 방출 단층 촬영술, 병기 결정, 전이