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Original Articles

Determination of Indication for Sentinel Lymph Node Biopsy in Clinical Node-negative Breast Cancer Using Preoperative ^{18}F-fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography Fusion Imaging

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Objective: Sentinel node biopsy (SNB) is indicated for axillary lymph node metastasis-negative cases (N0), but clarification of the indication may increase treatment efficiency. Fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) may have a high positive predictive value in diagnosis of axillary lymph node metastasis.
Methods: Ninety-two breasts/axillae were analyzed retrospectively in 90 patients (median age 54.6-year old, median primary tumor 1.7 cm). FDG-PET/computed tomography was used to indicate SNB in N0 cases. Axillary lymph node dissection (ALND) was performed in cases that were axillary lymph node metastasis-positive (PET N+) on FDG-PET/CT.
Results: Seventy-four (80.4%) and 18 (19.6%) of the 92 axillae were diagnosed as metastasis-negative (PET N0) and PET N+, respectively, by FDG-PET/CT. SNB was performed in 51 of the 74 PET N0 axillae. ALND was performed in 23 PET N0 axillae (at the patients' request) and in all 18 PET N+ axillae. Of the 74 PET N0 axillae, 14 were metastasis-positive (pN+) and 60 were pN0 pathologically, and of the 18 PET N+ axillae, 13 were pN+ and five were pN0. The sensitivity and specificity of FDG-PET/CT for diagnosis of axillary metastasis were 48.1 and 92.3%, respectively, and the positive and negative predictive values were 72.2 and 81.1%, respectively.
Conclusion: The positive detection rate on FDG-PET/CT was insufficient for determining an indication of SNB. However, use of an appropriate cut-off for SUV_{max} (the positive rate was 90.9% with a cut-off of 2.0) and exclusion of surgically biopsied cases may achieve a clinically applicable positive detection rate.

Key words: breast cancer – sentinel node biopsy – FDG-PET/CT – SUV

INTRODUCTION

The percentage of cases of breast cancer treated at an early stage has risen due to increased breast cancer screening. Since most cases of early breast cancer with a small tumor size are axillary lymph node-negative histologically, the significance of routine performance of axillary lymph node dissection (ALND) in early breast cancer has become questionable, given the low probability of axillary lymph node metastasis. ALND may also induce numbness of the arm, motor disturbance of the upper limb and lymph edema, and decrease long-term quality of life (1). Moreover, the effect of ALND on survival is unclear (2). Therefore, the role of ALND has shifted to an identification

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of prognosis-predictive factors and a less invasive axillary staging procedure is required to replace ALND.

Sentinel node biopsy (SNB) is a less invasive procedure that is now commonly used in axillary staging. SNB is not covered by the health insurance system in Japan, but is increasingly performed at many facilities because of its relative simplicity and its satisfaction of patients' needs. On the other hand, SNB requires more labor and time, compared with ALND. Intraoperative pathological diagnosis requires greater effort and extensive pathological examination of the excised sentinel node is needed, including immunostaining. Therefore, establishment of an appropriate indication for SNB is an important task from the perspective of treatment efficiency. The indication for SNB has not been standardized and clinically apparent metastasis-positive (N+) cases with clinical axillary lymph node enlargement may be excluded from the indication. However, the sensitivity and specificity are low for diagnosis of axillary lymph node metastasis by palpation (3).

Imaging using positron emission tomography (PET) with fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) utilizes enhanced uptake of FDG by cancer cells, compared with normal cells (4,5). Several studies have investigated the significance of preoperative staging of breast cancer by FDG-PET, but the sensitivity has been generally low, and various results have been obtained in the diagnosis of axillary lymph node metastasis by FDG-PET (6). FDG-PET alone cannot substitute for ALND and SNB, but the positive predictive value is high when accumulation of FDG in the axillary lymph node is enhanced (7), and detailed anatomical analysis has recently become possible using PET/computed tomography (CT), in which the lymph node can be evaluated in fused PET and CT images.

Based on the potentially high positive predictive value of FDG-PET for diagnosis of axillary lymph node metastasis, we introduced FDG-PET/CT into the judgment criteria for application of SNB as a routine examination, in addition to diagnosis of lymph node metastasis by palpation, in April 2007. As a rule, ALND was performed in cases diagnosed with axillary lymph node metastasis by FDG-PET/CT (PET N+), even though the case was clinically axillary lymph node metastasis-negative (N0). We retrospectively analyzed cases in which breast cancer was evaluated preoperatively by FDG-PET/CT and for which surgical data were available to investigate the significance of performing preoperative FDG-PET/CT in breast cancer.

PATIENTS AND METHODS

FDG-PET/CT

After April 2007, SNB was performed for cases in which no enlargement of the axillary or supraclavicular lymph node was apparent by palpation and axillary lymph node metastasis was negative on FDG-PET/CT (PET N0). ALND was performed in N+ cases and N0/PET N+ cases. Preoperative FDG-PET/CT was performed within 2 weeks before surgery. Patients were fasted for at least 4 h before FDG-PET/CT. [^{18}F]FDG (3 MBq/kg body weight) was administered intravenously into the arm and the patient was then seated on a chair to rest for 60 min. A whole body scan from the upper end of the orbit to the femoral region was performed 60 min after [^{18}F]FDG administration in the supine position with elevation of the bilateral upper limbs. Images were obtained using a PET/CT scanner (Aquiduo™, Toshiba Medical Systems Corporation, Tochigi, Japan). PET/CT images were analyzed visually by two expert radiologists. Images were considered positive if areas in the axillary nodule took up more FDG than surrounding tissue. Quantitative measurement of the single-pixel maximal standardized uptake value (SUV_{max}) normalized using the lean body mass was performed on the main breast lesion and axillary node when abnormal uptake was observed.

SNB and ALND

SNB was performed by the blue dye method (8). After induction of general anesthesia, 3 ml of patent blue dye was injected into the subareolar site (four sites around the excised region when excisional biopsy was performed). After massaging for 5 min, the axilla was incised and the blue node was identified and excised. The excised lymph node was subjected to rapid pathological diagnosis, in which 1−2 frozen sections were prepared from each lymph node and the presence or absence of lymph node metastasis was assessed by hematoxylin and eosin (H&E) staining. After SNB, breast-conserving surgery or mastectomy was performed for the primary tumor. ALND was performed if the pathological diagnosis was positive for metastasis and in N0 cases diagnosed as PET N+ by FDG-PET/CT.

Pathological Examination

In cases in which SNB was performed, the sentinel node was investigated histologically after surgery. The sentinel node was fixed with formalin and embedded in paraffin, and 200-μm whole cross sections were prepared. The sections were subjected to H&E staining and immunostaining using anti-cytokeratin antibody to make a final judgment regarding metastasis. When metastasis was negative in the intraoperative diagnosis but positive in the postoperative histological diagnosis, secondary ALND was performed. For non-N0 sentinel nodes, 1−2 sections were prepared from each lymph node and metastasis was investigated by H&E staining. After formalin fixation, 5-mm whole cross sections of the major tumor were prepared and the tumor diameter and nuclear grade were judged. Nuclear grading of invasive carcinoma was performed following the general rules for clinical and pathological recording of breast cancer established by the Japanese Breast Cancer Society (9), with Nuclear Grade 1 categorized as low grade, and Grades 2 and 3 as high grade.

Estrogen receptor (ER), progesterone receptor (PgR), and HER2 status were analyzed by immunohistochemistry (IHC), using Ventana Confirm ER [6F11], Ventana Confirm PgR [16] and Ventana Confirm C-erbB-2 [CB11], respectively. ER and PgR were regarded as positive when 10% or more of the cells were positive, and HER2 was regarded as positive for immunostaining of 3+ and negative for 0 or 1+. For immunostaining of 2+, the amplification rate of the HER2 gene was analyzed by the HER2 FISH method, and HER2 was judged positive when the amplification rate was ≥2.2 times.

Statistical Analysis

Sensitivity, specificity and positive and negative predictive values of FDG-PET/CT imaging for axillary staging were analyzed using standard statistical analyses. Correlations between SUV values of primary tumors and clinicopathological factors were evaluated using independent *t*-tests. All statistical analyses were performed with Dr SPSS II statistical software (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided and statistical significance was set at the 5% level.

RESULTS

Ninety patients were diagnosed as N0 and underwent surgery after FDG-PET/CT between June 2006 and August 2007. Patients who underwent certain preoperative treatment (chemotherapy, hormone therapy and radiotherapy) and those with ductal carcinoma *in situ* were excluded from the analysis. The clinical background of the 90 patients is shown in Table 1. All patients were female and the median age was 54.6 years (range: 21–82 years old). The affected side was right in 42 (46.7%), left in 46 (51.1%) and bilateral in two (2.2%), and 92 breasts and 92 axillae were examined by FDG-PET/CT. The median size of the primary tumor was 1.7 cm (0.5–5.5 cm), 63 tumors were ≤2 cm (68.5%), 27 were >2 and ≤5 cm (29.3%) and two were >5 cm (2.2%). The surgical procedure for the primary tumor was breast-conserving surgery in 60 cases (65.2%) and mastectomy in 32 (34.8%).

Table 1. Patient characteristics

Item	Number of patients (%) or median (range)
Number of patients	90
Age	54.6 (21–82)
Laterality	
Right	42 (46.7)
Left	46 (51.1)
Bilateral	2 (2.2)
Number of breast	92
Size of primary lesion (cm)	1.7 (0.5–5.5)
Tumor diameter (cm)	
≤2	63 (68.5)
>2 to 5	27 (29.3)
>5	2 (2.2)
Operation	
Breast-conserving surgery	60 (65.2)
Mastectomy	32 (34.8)

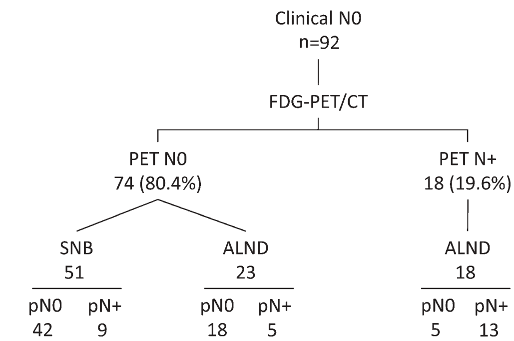

Figure 1. Fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) was used to evaluate 92 breasts/axillae with axillary nodes that were metastasis-negative (N0) clinically. Sentinel node biopsy (SNB) was performed in 51 of the 74 cases found to be axillary metastasis-negative in FDG-PET/CT (PET N0). Axillary lymph node dissection (ALND) was performed in the other 23 PET N0 cases at the request of the patients. ALND was performed in all FDG-PET/CT axillary metastasis-positive cases (PET N+). pN0/+; pathological lymph node negative/positive.

FDG-PET/CT and Pathological Diagnosis of the Axilla

The influence of excisional biopsy on axillary lymph node metastasis detected by FDG-PET/CT has not been examined. Thus, a total of 92 axillae in 92 tumors/breasts were investigated, including six axillae in six cases examined by FDG-PET/CT following excisional biopsy. On preoperative evaluation by FDG-PET/CT, 74 (80.4%) and 18 (19.6%) of the 92 axillae were PET N0 and PET N+, respectively (Fig. 1). The median SUV_{max} of the PET N+ axillary lymph nodes was 2.07 (1.18–6.24). Abnormal accumulation was seen in one lymph node in 13 of the PET N+ axillae and in more than two lymph nodes in the other five PET N+ axillae. SNB was performed in 51 of the 74 PET N0 axillae, and ALND was performed in the remaining 23 axillae at the patients' request. The identification rate by SNB was 100% and the median number of SN was two (1–7). Eight of the 51 axillae for which SNB was performed were diagnosed as metastasis-positive in rapid pathological diagnosis of the sentinel lymph node and subjected to ALND. Forty-three of the 51 axillae were metastasis-negative in the rapid pathological diagnosis, but one axilla was found to be metastasis-positive in postoperative diagnosis and secondary ALND was performed. Lymph node metastasis was noted in five of the 23 axillae subjected to ALND. ALND was also performed in all 18 cases with PET N+ axillae, and pathological diagnosis showed that 13 were metastasis-positive (pN+) and five were metastasis-negative (pN0). For comparison, 14 of the 74 PET N0 axillae were pN+ and 60 were pN0.

Based on the above findings, the sensitivity and specificity of the diagnosis of axillary metastasis by FDG-PET/CT were 48.1 and 92.3%, respectively, and the positive and negative predictive values were 72.2 and 81.1%, respectively (Table 2). In an analysis using a SUV_{max} cut-off value of 2.0 for the axillary lymph node, the sensitivity and specificity were 37.0 and 98.5%, respectively, and the positive and negative predictive values were 90.9 and 79.0%, respectively, showing a high positive predictive value. False positive results from FDG-PET/CT were noted in five axillae, and two of these were evaluated by FDG-PET/CT after excisional biopsy of the primary tumor. Excluding six axillae evaluated by FDG-PET/CT after excisional biopsy, the performance of FDG-PET/CT in the diagnosis of axillary metastasis showed a sensitivity of 46.2%, a specificity of 95%, a positive predictive value of 80% and a negative predictive value of 80.3%.

Correlation Between SUV_{MAX} of the Primary Tumor and Clinicopathological Parameters

The clinicopathological background of the 92 excised tumors was as follows: tumor diameter ≤2 cm in 63 (68.5%) cases, 2.1−5 cm in 27 (29.3%) and ≥5 cm in two (2.2%), and the nuclear grade was low-grade in 39 (42.4%) and high-grade in 53 (57.6%). Regarding hormone receptor expression, the tumors were ER+, PgR+ in 55 (59.8%) cases, ER+, PgR− in 20 (21.7%) and ER−, PgR− in 17 (18.5%). HER2 was negative in 85 (92.4%) cases and positive in seven (7.6%). Sixty-five axillae were pN0 (70.7%) and 27 were pN+ (29.3%) and the median number of axillary metastatic lymph nodes was 2 (1-21).

SUV_{max} of the primary tumor on FDG-PET/CT could be measured in 86 of the 92 tumors (excluding six excisionally biopsied tumors) and the median SUV_{max} value was 4.11 (0.76−16.56). No significant relationship was noted between SUV_{max} of the primary tumor and the presence or absence of pathological axillary lymph node metastasis (Table 3), whereas SUV_{max} of the primary tumor was significantly correlated with the nuclear grade, HER2 status and tumor size.

Table 2. Axillary node staging by FDG-PET CT and pathological diagnosis ($N = 92$)

Pathological diagnosis	FDG-PET/CT diagnosis		
	N+	N0	Total
pN+	13	14	27
pN0	5	60	65
Total	18	74	92

FDG-PET, fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose positron emission tomography; CT, computed tomography; pN+, metastasis-positive; pN0, metastasis-negative.

Table 3. Correlation of clinicopathologic factors and SUV_{max} of breast tumors ($n = 86$)

	Number of tumors (%)	SUV_{max} average	SUV_{max} SD	*P* value
Nuclear grade				
Low	38 (44.2)	2.74	1.34	<0.001
High	48 (55.8)	5.14	3.82	
ER				
Postitive	71 (82.6)	4.06	3.18	0.903
Negative	15 (17.4)	4.17	3.47	
PgR				
Positive	53 (61.6)	3.85	3.02	0.397
Negative	33 (38.4)	4.46	3.51	
HER2				
Positive	7 (8.1)	7.61	5.27	0.002
Negative	79 (91.9)	3.77	2.8	
pN				
Positive	26 (30.2)	4.61	3.4	0.318
Negative	60 (69.8)	3.85	3.13	
T				
*T*1	62 (72.1)	2.95	1.94	<0.0001
*T*2,*T*3	24 (27.9)	6.99	3.98	

SUV, standardized uptake value; SD, standard deviation; ER, estrogen receptor; PgR, progesterone receptor.

SUV_{max} of the primary tumor was significantly higher in high-nuclear grade tumors ($P < 0.001$), HER2-positive tumors ($P = 0.002$) and tumors of size >2 cm ($P < 0.0001$). SUV_{max} was not significantly correlated with the ER or PgR status.

DISCUSSION

In previous comparisons of diagnosis of axillary metastasis by pathological examination with ALND and FDG-PET, the sensitivity of diagnosis by FDG-PET has ranged from 46 to 95%, the specificity from 66 to 100%, the positive predictive value from 62 to 100% and the negative predictive value from 73 to 99%, indicating a generally low sensitivity (7,10−16). Compared with the evaluation of the axilla by SNB, the sensitivity is still lower (0−79%), suggesting that micrometastasis detected by extensive pathological examination of SNB is undetectable by FDG-PET (15−20). Based on these findings, FDG-PET cannot substitute for ALND or SNB in staging of axillae.

Among previous studies that reported by Wahl et al. (7) was performed on the largest scale and showed that diagnosis of micro lymph node metastasis by FDG-PET was difficult. Routine use of FDG-PET was not recommended, but the positive predictive value of FDG-PET was shown to be high when many abnormal accumulations of FDG were detected in the axillary lymph node. Based on these results, it was concluded that ALND should be performed without initial SNB in such cases, and that FDG-PET may be useful for selecting cases in which SNB should be performed.

SNB is a less invasive axillary staging technique compared with ALND and has become the standard procedure. However, SNB requires more labor and time than ALND, with increased work for intraoperative rapid diagnosis and extensive pathological examination of the excised sentinel node, including immunostaining. Veronesi et al. (20) showed a high positive predictive value of FDG-PET and emphasized that ALND should be performed without SNB in FDG-PET N+ cases. This led us to include PET N0 cases among the indications for SNB, in addition to N0 cases. As a result, the sensitivity and specificity were 48.1 and 92.3%, respectively, and the positive and negative predictive values were 72.2 and 81.1%, respectively. Gil-Rendo et al. (21) used a similar method in a prospective investigation of 125 patients and found a sensitivity and specificity of 78.9 and 98.1%, respectively, and positive and negative predictive values of 98.2 and 77.9%, respectively, showing a high positive predictive value. However, these results cannot be compared with our data directly because both N0 and PET N0 subjects underwent SNB. Gil-Rendo et al. also indicated that cases with abnormal accumulation of FDG in the axilla should undergo ALND.

The positive detection rate was 72.2% in N0 patients on FDG-PET/CT, which is not high enough for routine clinical practice. The low rate may partly be due to the positive metastasis criteria being unclear because this was a retrospective study. SUV_{max} may be an important index for objective evaluation of metastasis, since setting the SUV_{max} cut-off value for the axillary lymph node at 2.0 gave a high positive predictive value of 90.9% that is sufficient for use in routine clinical practice. A second reason for the low positive detection rate may be the inclusion of surgically biopsied cases in the study. Our results also suggest that excisional biopsy of the primary tumor affects the false positive rate in FDG-PET/CT, since excisional biopsy of the primary tumor had been performed in two of the five false-positive axillae. Excluding six axillae evaluated by FDG-PET/CT after excisional biopsy, the performance of FDG-PET/CT in diagnosis of axillary metastasis showed a positive predictive value of 80%. Inflammatory reactions to surgical excision of the primary lesion may have disseminated to the regional axillary lymph node and led to the false positive findings, suggesting that diagnosis of axillae by FDG-PET/CT after excisional biopsy is not recommended.

The economical effect and efficiency of the use of FDG-PET to determine application of SNB also requires discussion, in addition to the clinical issues described above. Since FDG-PET is a very extensive examination, its application should be limited to the cases for which it is highly beneficial (20). The axillary metastasis rate of small tumors is generally low and the probability of avoiding SNB based on FDG-PET/CT findings may be correspondingly low, suggesting that the benefit of FDG-PET is limited in such cases. In contrast, the latent axillary metastasis rate increases in large N0 tumors and the benefit of FDG-PET also increases. Therefore, FDG-PET/CT may be very useful to determine an indication for SNB in large N0 tumors.

We obtained interesting findings for FDG-PET/CT of primary lesions. The SUV_{max} of the primary breast cancer lesions was significantly correlated with the histological grade, size and HER2 status of the tumor, suggesting that SUV_{max} of the primary lesion may be useful as a prognostic factor. Significant correlations of SUV_{max} of primary lesions with known prognostic factors and biological characteristics of breast cancer (tumor size, histological grade, nuclear grade, nuclear atypia, mitosis counts, lymph node metastasis, Ki-67 labeling index, hormone receptor status and HER2 status) have been reported (22–24). Inoue et al. (25) showed that the 5-year disease-free survival rate was significantly lower in patients with high SUV_{max} of the primary tumor compared with those having low SUV_{max}. However, SUV_{max} was not found to be independent in multivariate analysis including well-known prognostic factors. Nonetheless, since SUV_{max} reflects the FDG requirement of tumors in vivo, i.e. tumor activity, it differs completely from other prognostic factors and is worth investigating as a new prognostic factor.

In conclusion, FDG-PET/CT in N0 cases provides useful information to determine an indication for sentinel lymph node biopsy. The positive predictive value for diagnosis of axillary lymph node metastasis by FDG-PET/CT was ~72.2% in N0 cases, which is insufficient. However, a high positive detection rate can be obtained by setting an appropriate SUV_{max} cut-off value and excluding surgically biopsied cases, thereby enabling an objective evaluation.

We suggest that SNB should be performed in cases with a low probability of histological axillary lymph node metastasis, and that PET N+ cases differ from these cases and may be indicated for ALND, rather than SNB. Since FDG-PET/CT is expensive and false positive cases will be subjected to unnecessary ALND, proper selection of cases in which the highest benefit of FDG-PET/CT can be expected is the most important task.

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Conflict of interest statement

None declared.

References

1. Kwan W, Jackson J, Weir LM, Dingee C, McGregor G, Olivotto IA. Chronic arm morbidity after curative breast cancer treatment: prevalence and impact on quality of life. *J Clin Oncol* 2002;20:4242–8.
2. Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL, et al. Ten-year results of a randomized clinical trial comparing radical

mastectomy and total mastectomy with or without radiation. *N Engl J Med* 1985;312:674–81.
3. Cserni G. The impact of axillary lymphadenopathy on further treatment in breast cancer? A model for clinical staging. *Pathol Oncol Res* 1998; 4:301–3.
4. Brown RS, Wahl RL. Overexpression of Glut-1 glucose transporter in human breast cancer. An immunohistochemical study. *Cancer* 1993;72:2979–85.
5. Wahl RL, Cody RL, Hutchins GD, Mudgett EE. Primary and metastatic breast carcinoma: initial clinical evaluation with PET with the radiolabeled glucose analogue 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1991;179:765–70.
6. Quon A, Gambhir SS. FDG-PET and beyond: molecular breast cancer imaging. *J Clin Oncol* 2005;23:1664–73.
7. Wahl RL, Siegel BA, Coleman RE, Gatsonis CG. Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the staging breast cancer with PET Study Group. *J Clin Oncol* 2004;22:277–85.
8. Reitsamer R, Peintinger F, Rettenbacher L, Prokop E, Sedlmayer F. Subareolar subcutaneous injection of blue dye versus peritumoral injection of technetium-labeled human albumin to identify sentinel lymph nodes in breast cancer patients. *World J Surg* 2003;27:1291–4.
9. The Japanese Breast Cancer Society. General Rules for Clinical and Pathological Recording of Breast Cancer. 15th edn. Tokyo: Kanehara & Co., Ltd 2004.
10. Schirrmeister H, Kühn T, Guhlmann A, Santjohanser C, Hörster T, Nüssle K, et al. Fluorine-18 2-deoxy-2-fluoro-D-glucose PET in the preoperative staging of breast cancer: comparison with the standard staging procedures. *Eur J Nucl Med* 2001;28:351–8.
11. Yutani K, Shiba E, Kusuoka H, Tatsumi M, Uehara T, Taguchi T, et al. Comparison of FDG-PET with MIBI-SPECT in the detection of breast cancer and axillary lymph node metastasis. *J Comput Assist Tomogr* 2000;24:274–80.
12. Adler LP, Faulhaber PF, Schnur KC, Al-Kasi NL, Shenk RR. Axillary lymph node metastases: screening with [F-18]2-deoxy-2-fluoro-D-glucose (FDG) PET. *Radiology* 1997;203:323–7.
13. Smith IC, Ogston KN, Whitford P, Smith FW, Sharp P, Norton M, et al. Staging of the axilla in breast cancer: accurate in vivo assessment using positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose. *Ann Surg* 1998;228:220–7.
14. Greco M, Crippa F, Agresti R, Seregni E, Gerali A, Giovanazzi R, et al. Axillary lymph node staging in breast cancer by 2-fluoro-2-deoxy-D-glucose-positron emission tomography: clinical evaluation and alternative management. *J Natl Cancer Inst* 2001;93:630–5.
15. Gil-Rendo A, Zornoza G, García-Velloso MJ, Regueira FM, Beorlegui C, Cervera M. Fluorodeoxyglucose positron emission tomography with sentinel lymph node biopsy for evaluation of axillary involvement in breast cancer. *Br J Surg* 2006;93:707–12.
16. van der Hoeven JJ, Hoekstra OS, Comans EF, Pijpers R, Boom RP, van Geldere D, et al. Determinants of diagnostic performance of [F-18]fluorodeoxyglucose positron emission tomography for axillary staging in breast cancer. *Ann Surg* 2002;236:619–24.
17. Lovrics PJ, Chen V, Coates G, Cornacchi SD, Goldsmith CH, Law C, et al. A prospective evaluation of positron emission tomography scanning, sentinel lymph node biopsy, and standard axillary dissection for axillary staging in patients with early stage breast cancer. *Ann Surg Oncol* 2004;11:846–53.
18. Guller U, Nitzsche EU, Schirp U, Viehl CT, Torhorst J, Moch H, et al. Selective axillary surgery in breast cancer patients based on positron emission tomography with 18F-fluoro-2-deoxy-D-glucose: not yet!. *Breast Cancer Res Treat* 2002;71:171–3.
19. Kelemen PR, Lowe V, Phillips N. Positron emission tomography and sentinel lymph node dissection in breast cancer. *Clin Breast Cancer* 2002;3:73–7.
20. Veronesi U, De Cicco C, Galimberti VE, Fernandez JR, Rotmensz N, Viale G, et al. A comparative study on the value of FDG-PET and sentinel node biopsy to identify occult axillary metastases. *Ann Oncol* 2007;18:473–8.
21. Gil-Rendo A, Zornoza G, García-Velloso MJ, Regueira FM, Beorlegui C, Cervera M. Fluorodeoxyglucose positron emission tomography with sentinel lymph node biopsy for evaluation of axillary involvement in breast cancer. *Br J Surg* 2006;3:707–12.
22. Oshida M, Uno K, Suzuki M, Nagashima T, Hashimoto H, Yagata H, et al. Predicting the prognoses of breast carcinoma patients with positron emission tomography using 2-deoxy-2-fluoro[18F]-D-glucose. *Cancer* 1998;82:2227–34.
23. Buck A, Schirrmeister H, Kühn T, Shen C, Kalker T, Kotzerke J, et al. FDG uptake in breast cancer: correlation with biological and clinical prognostic parameters. *Eur J Nucl Med Mol Imaging* 2002;29:1317–23.
24. Ueda S, Tsuda H, Asakawa H, Shigekawa T, Fukatsu K, Kondo N, et al. Clinicopathological and prognostic relevance of uptake level using 18F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in primary breast cancer. *Jpn J Clin Oncol* 2008;38:250–8.
25. Inoue T, Yutani K, Taguchi T, Tamaki Y, Shiba E, Noguchi S. Preoperative evaluation of prognosis in breast cancer patients by [(18)F]2-Deoxy-2-fluoro-D-glucose-positron emission tomography. *J Cancer Res Clin Oncol* 2004;130:273–8.