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Originals

Clinical Relevance of the Standardized Uptake Value (Suv) in Staging Breast Cancer with FDG-PET/CT

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SUMMARY

Purpose : FDG-PET/CT with standardized uptake value (SUV) estimation was applied to breast cancer patients for the purpose of preoperative evaluation of the extent of the disease.

Methods : FDG-PET/CT was performed preoperatively in 71 patients with breast cancer, and the maximum standardized uptake value (SUVmax) of tumors, as well as combination of SUVmax and tumor marker CA 15-3 were investigated for a significant association with lymph node spread and distant metastasis.

Results : Tumor SUVmax high (>3.1) was found to have a reliable predictive value for lymph node spread (sensitivity 82.9%, specificity 75%, $P<0.0001$), while SUVmax-High (>3.8)/CA 15-3-Elevated was found to be superior for the prediction of metastasis (sensitivity ; 75%, specificity ; 92.7%, $P=0.0001$). Moreover, linear regression analysis identified the best correlation was between SUVmax-High (>3.1) with lymph node spread {correlation coefficient (r^2) = 0.580, $P=0.0001$}, and SUVmax-High (>3.8)/CA 15-3-Elevated with distant metastasis {correlation coefficient (r^2) = 0.677, $P<0.0001$}.

Conclusions : SUVmax is a reliable predictor of lymph node spread, and if combined with tumor marker assay (CA 15-3) labeled SUVmax-High/CA 15-3-Elevated is sufficient for the early detection of breast cancer metastasis. This outcome suggests that the FDG-PET/CT findings with SUV calculation could have a strong positive impact on breast cancer patients.

Key Words : FDG-PET/CT-SUVmax-Breast cancer-Lymph node spread-Metastasis

INTRODUCTION

In women, breast cancer has the highest incidence of all types of cancers and is the second leading cause of cancer deaths[1]. Although it is curable when detected early, about one third of women with breast cancer die of the disease[2].

Positron emission tomography with the glucose analog 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG-PET) is increasingly recognized as a powerful tool in evaluating patients with various malignant tumors[3～6]. In patients with breast cancer, FDG-PET has been reported to be useful in the initial tumor evaluation, including locoregional or distant staging, in the evaluation of treatment response, and in the assessment of recurrent disease[7～10]. Positron emission tomography has four main uses in oncology. First, it can be used to determine the presence of malignant tissue within nodules or masses. Second, it is useful for cancer staging. Third, it can be used to evaluate possible residual or recurrent disease. Finally, PET is being studied as a tool for evaluating tumor response to therapy[11].

Recently, combined PET and CT systems (PET/CT) have emerged as promising imaging modalities, and they are being more routinely applied in clinical situations[12～14]. The CT portion of PET/CT provides

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anatomical mapping images for PET as well as attenuation correction data. Exact localization of FDG uptake is possible with this modality, which is sometimes difficult with only PET. PET/CT also allows the demonstration of pathological FDG uptake in small lymph nodes and structures that are negative based on the CT size criteria. Furthermore, PET/CT can clarify the location of physiological FDG uptake[15].

FDG-PET has been shown to be potential in primary breast cancer diagnosis, with sensitivities of 63 % – 96 % and specificities of 75 % – 100 % [8,16]. Schirrmeister et al.[16], compared FDG-PET with conventional staging methods including chest radiographs, ultrasound of the liver and bone scintigraphy for detection of breast cancer metastasis, and it was found that FDG-PET was more accurate than conventional staging procedures, irrespective of the localization of the distant metastases, however, Uematsu et al., concluded from his results that, bone SPECT is superior to FDG-PET in detection of osteoblastic bone metastases in breast cancer[42]. Similar data[17] observed that FDG-PET was superior in the detection of pulmonary metastases and especially of lymph node metastases of the mediastinum in comparison to chest X-ray, whereas the sensitivity of FDG-PET in the detection of bone and liver metastases was of the same magnitude as compared with bone scintigraphy and ultrasound of the abdomen. These results warrant prospective trials with FDG-PET as the single staging procedure in patients with a high risk of distant metastases.

Although the prognosis of breast cancer patients could be evaluated to a considerable extent by clinical staging, a means which can predict the patient prognosis with more accuracy needs to be developed in order to carry out the therapeutic strategy more efficiently. For this purpose, FDG-PET/CT seems to be promising and, therefore, in the present study, we have examined the usefulness of FDG-PET/CT in the preoperative evaluation of the extent of disease in breast cancer patients.

PATIENTS AND METHODS

1. Patient Population

This is a retrospective review of a prospective database. Patients with breast cancer were referred for preoperative FDG-PET/CT to evaluate the extent of disease. Written informed consent was obtained from all patients. Seventy-one patients (all women, age ; average 32 – 78 y, mean 56.7 ± 11.3, median 58 y) with newly diagnosed breast cancer were examined by FDG-PET/CT during the period between April 2005 and March 2007. FDG-PET/CT was performed within 1 – 44 days (mean 15 ± 10, median 14 d) before surgery (breast-conserving surgery or mastectomy). Patient characteristics are shown in (Table 1). Among them, 27 (38 %) breast masses had borderline levels of increased FDG uptake (SUV less than or equal to 2.5). The mean size of the breast cancer was 2.7 ± 2.1 cm (median 2.0, average 0.7 – 12.6 cm) in its greatest dimension. The diagnosis was suggested by clinical examination and mammography. All patients underwent multimodality imaging techniques, such as MRI, ultrasonography, digital mammography, CT, and FDG-PET/CT. Patients who received radiation/chemotherapy before FDG-PET/CT imaging were excluded initially to avoid the confounding influence of concurrent therapy on the FDG-PET/CT outcome and they did not included in the analysis. After surgery, we are able to obtain important information as to patient prognosis which includes axillary lymph node status, histological grade. Surgical histopathological results were considered to provide the definitive diagnosis against which the FDG-PET/CT results were compared. The staging procedure was complemented by other imaging modalities ; chest X-ray, US of the abdomen, CT, MRI and Gallium (Ga) scintigraphy as well as the clinical follow up (CFU) examinations and the follow up FDG-PET/CT for metastatic workup.

2. FDG-PET/CT Imaging and Assessment

2.1. Image Processing

Patients fasted for at least 6 hours before the PET scan and had blood glucose levels < 140 mg/dl at the time of injection. PET was performed with a dedicated whole-body PET/CT scanner (Biograph Sensation 16 PET-CT Scanner ; Siemens Medical Systems). The FDG-PET/CT scanning was performed as whole-body images from head to thigh, with acquisition of 6 – 7 bed positions ; resulting in a complete axial length of 80 – 100 cm. Scanning began approximately 60 min after injection of ^{18}F-FDG (4.5 MBq/kg of body weight). In all cases, ^{18}F-FDG radiochemical purity was > 95 %

Table 1 Basic Clinical and Pathological Characteristics of the Patients

Sex	all female
Age (years)	
Mean ± SD (median, average)	56.7 ± 11.3 (58, 32 - 78)
Menopausal Status	
Premenopausal/Postmenopausal	21/50*
Histopathology	
DCIS/IDC/ILC	13/55/3*
Tumor Diameter (cm)	
Mean ± SD (median, average)	2.7 ± 2.1 cm (2.0, 0.7 - 12.6)
TNM Classification**	
T1/T2/T3/T4	32/20/3/16*
N0/N1/N2/N3	36/17/13/5*
M0/M1	55/16*
Stage I/II/III/IV	27/19/9/16*
SUVmax	
Mean ± SD (median, average)	4.8 ± 3.9 (3.6, 0.6 - 18.5)
Tumor Marker CA 15-3	
Mean ± SD (median, average)	23 ± 37.2 (13.2, 4.8 - 195)

* Figures express number of patients

** TNM grading according to the histopathological report

DCIS = Ductal carcinoma in-situ, IDC = Invasive ductal carcinoma, ILC = Invasive lobular carcinoma

and specific activity was > 47 GBq/μmol. FDG was infused over 2 min in the antecubital vein contralateral to the affected breast. Transmission scans were performed for all patients to provide attenuation correction with CT. The PET slice thickness was 3.4 mm. Three-dimensional (3D) data acquisition without septa, and image reconstruction with scatter correction using a computer system (e-soft nuclear medicine acquisition, processing, and viewing software).

2.2. Image Analysis

FDG-PET images were reconstructed using measured attenuation correction, dead-time correction and decay correction to the beginning of each scan. Visual assessment, image interpretation and data analysis were performed independently by two nuclear medicine physicians. They were aware of the patients' clinical history, which was provided by the referring physician, but were blinded to the results of other imaging studies if these were performed. The SUVs were identical in 90 % of cases with both of the observers. When there was a difference, a mean was calculated to determine the final SUV. After image reconstruction, a free-hand ROI was carefully drawn on 3 - 6 PET scan slices at the site of the lesion. From these ROIs, the SUV was calculated according to the following formula : (mean ROI activity [MBq/g])/(injected dose [MBq]/body weight [g]), where g = grams. The maximum FDG uptake on the consecutive scans was obtained for quantitative measurement of the metabolic activity of the tracer (SUV). Analysis was based on measuring degree of FDG maximum standardized uptake (SUVmax) at the tumor site as well as determination of tumor stage, lymph node spread and distant metastasis if any.

3. Statistical Analysis

Three levels of statistics were performed using GraphPad Prism for windows, version 4.

3.1. Selection of the best cut-off scores for SUVmax

In order to identify the best cut-off score for SUVmax, receiver operating characteristic (ROC) curve analysis was used [18]. Clinically, relevant cut-off scores were generated such that they maximized both sensitivity and specificity for each outcome under study.

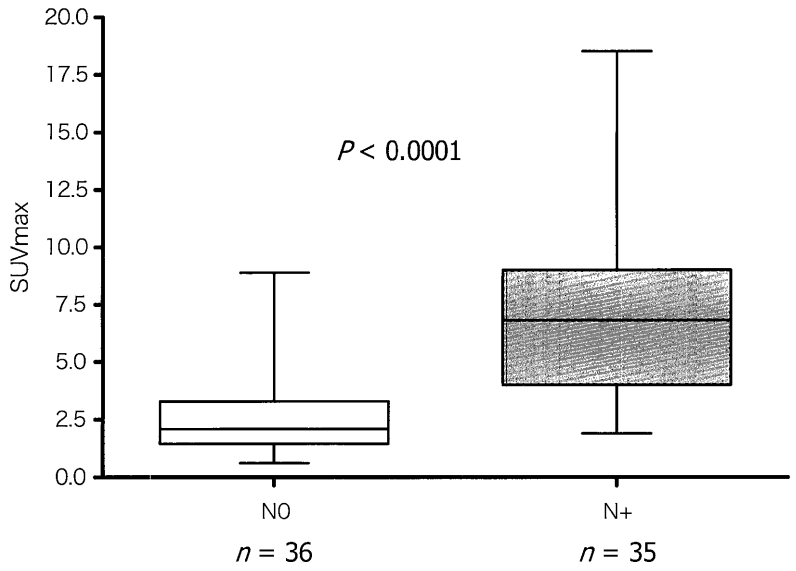


Fig. 1 Box and whiskers, vertical graph. Maximum standardized uptake value (SUVmax) of breast cancers associated with negative and positive lymph node spread. The difference between SUVmax values of both groups was significant ($P<0.0001$). The line shows the median value of SUVmax.

3.2. Association of SUVmax and clinico-pathologic features

In order to apply ROC curve analysis, patients were sorted into groups according to the clinico-pathologic features ; as follows : early (T1 + T2) or advanced (T3 + T4) tumor, no (N0) or any (N+) lymph node spread, absence or presence of metastasis. The patients were dichotomized according to the cut-off values of SUVmax. The worth of the predetermined SUVmax cut-off and tumor stage, lymph node spread, and metastasis was analyzed using the Mann-Whitney μ test which was conducted to compare means of SUVmax (as a continuous data) between the different groups.

3.3. Analysis of the relationship between SUVmax and lymph node spread and metastasis

The relationship between SUVmax among other clinicopathological decisive factors with lymph node spread and metastasis was evaluated in univariate analysis using a 2 × 2 contingency tables and Fisher's Exact test. Linear regression analysis was used to determine the correlation coefficient (r^2) for significant clinicopathological risk factors. Sensitivity, specificity, positive predictive value, negative predictive value, and relative risk were obtained with 95 % confidence intervals (CI). All statistical analyses were two sided with significance defined as $P<0.05$.

RESULTS

1. SUVmax and Prognosis

All 71 breast tumors were scanned by FDG-PET/CT. Mean of SUVmax values was 4.8 ± 3.9 (median 3.6, average 0.6 − 18.5). According to tumor staging ; SUVmax of advanced tumor (T3-4), was not significantly ($P = 0.1353$) higher than early ones (T1-2). SUVmax-T1-2 ; $n = 52$ (mean ; 4.3 ± 3.4, 95 % CI ; 3.4 − 5.3, median ; 3.0, average ; 0.6 − 15.3) while SUVmax-T3-4 ; $n = 19$ (mean ; 6.1 ± 4.8, 95 % CI ; 3.8 − 8.4, median ; 4.3, average ; 1.3 − 18.5). According to lymph node spread, SUVmax for tumors associated with lymph node spread (N +), was significantly ($P<0.0001$) higher than those without (N0). SUVmax − N0 ; $n = 36$ (mean ; 2.6 ± 1.8, 95 % CI ; 2.0 − 3.2, median ; 2.1, average ; 0.6 − 8.9) while SUVmax-N + ; $n = 35$ (mean ; 7.0 ± 4.2, 95 % CI ; 5.6 − 8.5, median ; 6.8, average ; 1.9 − 18.5) (Fig. 1). And according to metastasis ; SUVmax for tumors associated with distant metastasis (M1), was significantly ($P = 0.0008$) higher than those without (M0). SUVmax-M0 ; $n = 55$

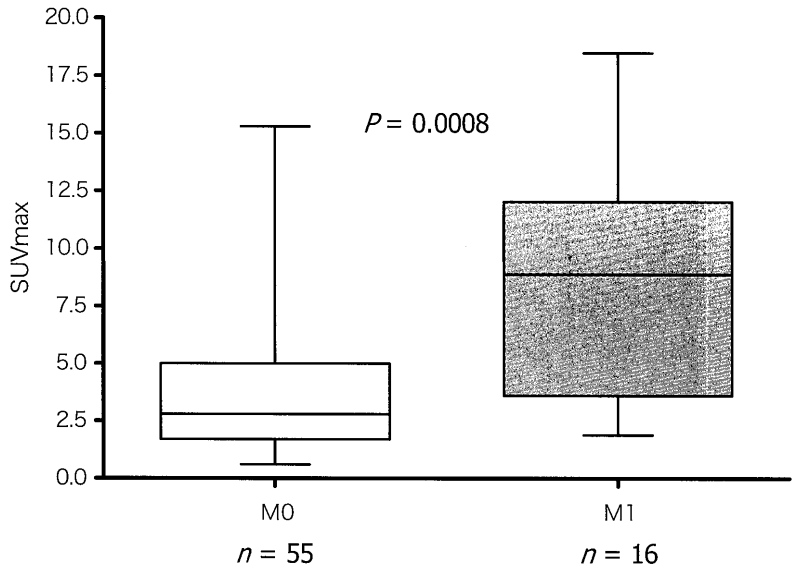


Fig. 2 Box and whiskers, vertical graph. Maximum standardized uptake value (SUVmax) of breast cancers associated with negative and positive distant metastasis. The difference between SUVmax values of both groups was significant ($P = 0.0008$). The line shows the median value of SUVmax.

Table 2 Association between SUVmax and Pathological Criteria in Breast Cancer

	SUVmax Cutoff	Median	SUVmax Low *N*	(%)	SUVmax High *N*	(%)	*p*-Value
Tumor	3.1						0.1353
T1-2		3.0	27	(81.8)	25	(65.8)	
T3-4		4.3	6	(18.2)	13	(34.2)	
Lymph Node Spread	3.1						$< 0.0001^S$
N0		2.1	27	(81.8)	9	(23.7)	
N +		6.8	6	(18.2)	29	(76.3)	
Metastasis	3.8						0.0008^S
M0		2.8	32	(88.9)	23	(65.7)	
M1		8.9	4	(11.1)	12	(34.3)	

N. B. The optimal SUVmax cutoff value for tumor, lymph node spread and metastasis was generated by receiver operating characteristics (ROC) analysis.

(mean ; 3.8 ± 2.8, 95% CI ; 3.0 − 4.5, median ; 2.8, average ; 0.6 − 15.3) while SUVmax-M1 ; $n = 16$ (mean ; 8.3 ± 5.1, 95% CI ; 5.5 − 11.0, median ; 8.9, average ; 1.9 − 18.5) (Fig. 2) (Table 2). The receiver operating characteristic (ROC) analysis suggested tumor SUVmax 3.1 cut-off for differentiating between breast cancer associated with and without lymph node spread (82.9% sensitivity, 75% specificity, 76.3% positive predictive value, 81.8% negative predictive value, Area under the curve 0.8615, 95% CI 78 − 94%, $P <$ 0.0001) and SUVmax 3.8 as a recommended cut-off for differentiating between breast cancer associated with and without distant metastasis (75% sensitivity, 58.2 % specificity, 34.3% positive predictive value, 88.9% negative predictive value, Area under the curve 0.666, 95% CI 54.4 − 77.3%, $P = 0.0420$) .

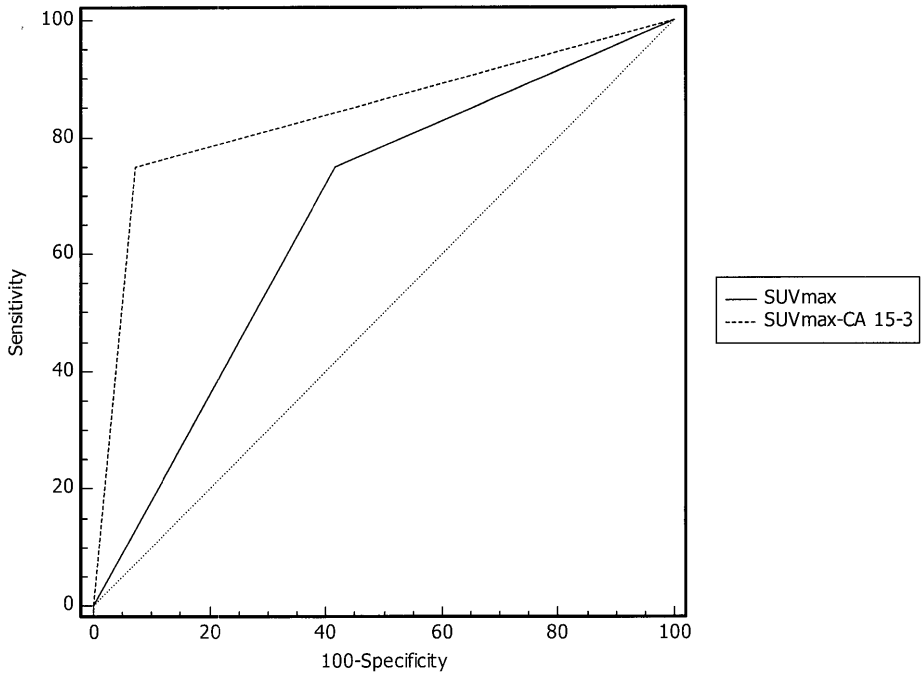


Fig. 3 Receiver operating characteristic analysis of SUVmax, and SUVmax-CA 15-3 in differentiation between breast cancer with (M1) and without (M0) distant metastasis. Area under curve (Az) ± SE for SUVmax = 0.666 ± 0.082, and for SUVmax-CA 15-3 = 0.839 ± 0.065. Comparative ROC analysis revealed significant differences among the performances of SUVmax and SUVmax-CA 15-3 for correlation with distant metastasis ($P = 0.008$)

Table 3 Analysis of the Relationship between Tumor stage, SUVmax, SUVmax/CA 15-3 and Lymph Node Spread

	Cutoff value	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Relative Risk	p-Value
Tumor stage	T3-4	42.9 % (26.3 - 60.7 %)	91.7 % (77.5 - 98.3 %)	83.3 % (58.6 - 96.4 %)	62.3 % (47.9 - 75.2 %)	2.2 (1.5 - 3.3)	0.0010^S
SUVmax	3.1	82.9 % (66.4 - 93.4 %)	75.0 % (57.8 - 87.8 %)	76.3 % (59.8 - 88.6 %)	81.8 % (64.5 - 93 %)	4.2 (2 - 8.8)	< 0.0001^S
SUVmax/CA 15-3	3.1/Elevated	40.0 % (23.9 - 57.9 %)	97.2 % (85.5 - 99.9 %)	93.3 % (68.1 - 99.8 %)	62.5 % (48.6 - 75.1 %)	2.5 (1.7 - 3.6)	0.0001^S

N. B. The optimal Cutoff value for SUVmax was generated by receiver operating characteristics (ROC) analysis.
S = Significant, Parentheses means 95 % confidence interval (95 % CI).

2. Prediction of Distant Metastasis by Combination of SUVmax, and Tumor Marker CA 15-3

Combination of SUVmax (>3.8) and tumor marker CA 15-3 (CA 15-3-elevated) was supposed to be more useful in the prediction of distant metastasis. ROC analysis for SUVmax-High/CA 15-3-Elevated was (75 % sensitivity, 92.7 % specificity, 75 % positive predictive value, 92.7 % negative predictive value, Area under the curve 0.839, 95 % CI 73.2 - 91.5 %, $P = 0.0001$). SUVmax/CA 15-3 has higher specificity than SUVmax, with similar sensitivity. Comparative ROC analysis for SUVmax and SUVmax/CA 15-3, revealed significant differences among the performances of SUVmax and SUVmax/CA 15-3 for correlation with distant metastasis ($P = 0.008$) (Fig. 3).

Then, the patients were divided into groups concern-

Table 4 Analysis of the Relationship between Tumor stage, SUVmax, Lymph Node Spread, SUVmax/CA 15-3 and Metastasis

	Cutoff value	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Relative Risk	*p*-Value
Tumor stage	T3-4	56.3 % (29.9 - 80.3 %)	83.6 % (71.2 - 92.2 %)	50.0 % (26 - 74 %)	86.8 % (74.7 - 94.5 %)	3.8 (1.7 - 8.7)	0.0027^S
SUVmax	3.8	75.0 % (47.6 - 92.7 %)	58.2 % (44.1 - 71.4 %)	34.3 % (19.1 - 52.2 %)	88.9 % (73.9 - 96.9 %)	3.1 (1.1 - 8.7)	0.0008^S
Lymph node spread	N +	93.8 % (69.8 - 99.8 %)	63.6 % (49.6 - 76.2 %)	42.9 % (26.3 - 60.7 %)	97.2 % (85.5 - 99.9 %)	15.4 (2.2 - 110.7)	< 0.0001^S
SUVmax/CA 15-3	3.8/Elevated	75.0 % (47.6 - 92.7 %)	92.7 % (82.4 - 98 %)	75.0 % (47.6 - 92.7)	92.7 % (82.4 - 98 %)	10.3 (3.9 - 27.6)	0.0001^S

N. B. The optimal cut-off value for SUVmax was generated by receiver operating characteristics (ROC) analysis.
S = Significant, Parentheses means 95 % confidence interval (95 % CI).

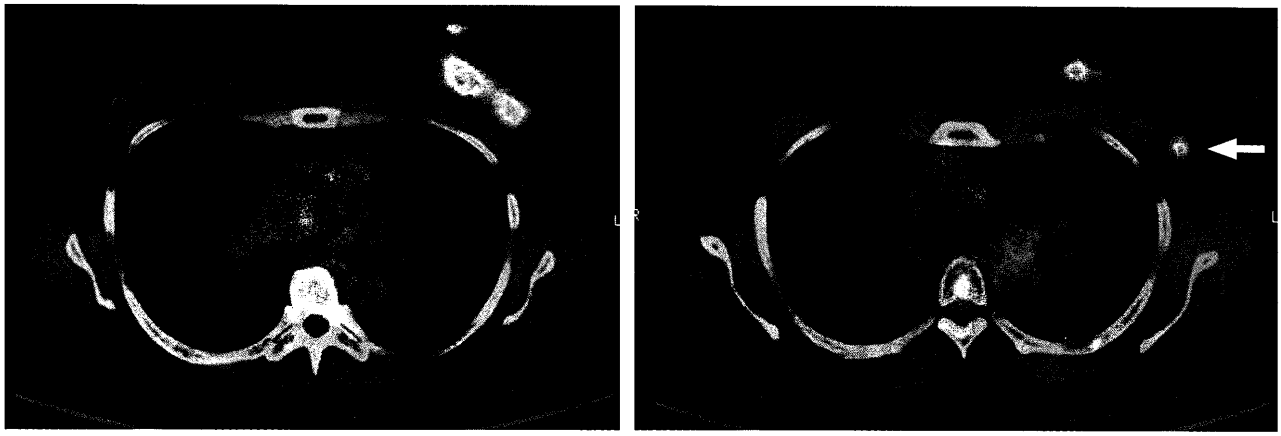
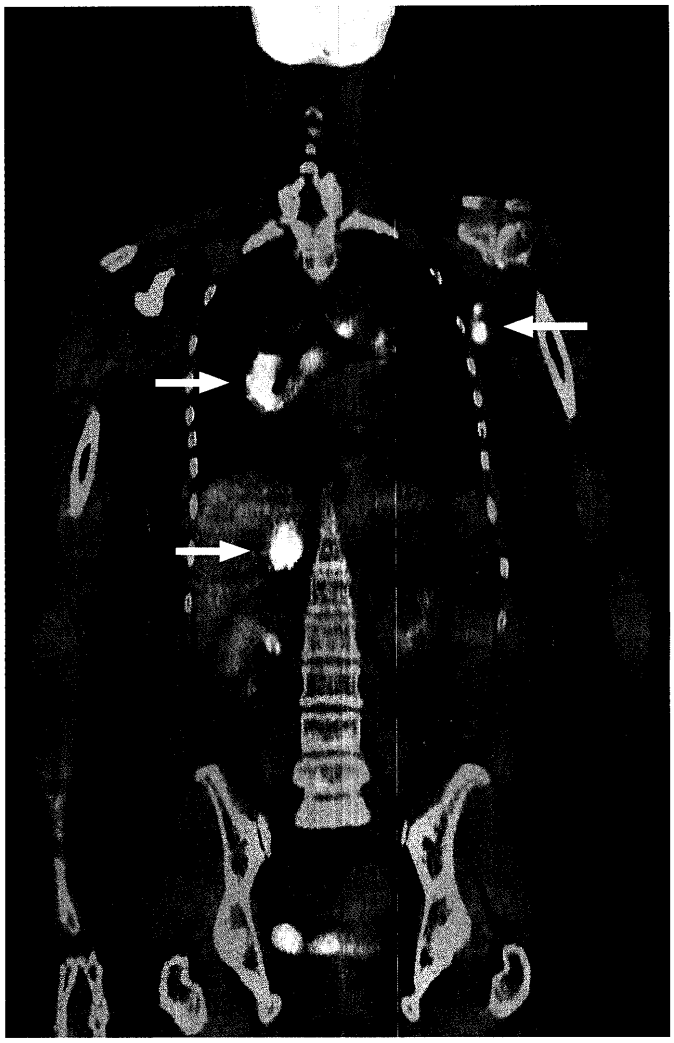


Fig. 4 A 51-years-old patient with left breast cancer and left axillary lymph node spread N + (arrow). T3,N1,M0 ... Stage IIIA. Surgical histopathological report confirmed Invasive Ductal Carcinoma (papillotubular). Prognostic risk factors for lymph node spread were SUVmax 4.9 and tumor grade 3 (T3).

ing the lymph node spread (N0, N +) and distant metastasis (M0, M1). We analyzed the relationship between SUVmax among other clinicopathological factors with lymph node and distant metastasis. Statistical analysis could identify three significant clinicopathological risk factors associated with lymph node spread {tumor stage T3-4 ; $P = 0.0010$, SUVmax > 3.1 ; $P < 0.0001$, and SUVmax-high/CA 15-3-elevated ; $P = 0.0001$} (Table 3), and four associated with distant metastasis {tumor stage T3-4 ; $P = 0.0027$, SUVmax > 3.8 ; $P = 0.0008$, lymph node spread (N +) ; $P < 0.0001$, and SUVmax-high/CA 15-3-elevated ; $P = 0.0001$} (Table 4). Amongst those clinicopathological factors ; SUVmax > 3.1 recorded the highest risk ratio (4.2) for correspondence with lymph node spread, while lymph node spread (N +) and SUVmax-High/CA 15-3-Elevated recorded the highest risk ratios (15.4 and 10.3, respectively) for correspondence with distant metastasis.

Linear regression analysis was applied to identify the correlation coefficient for the clinicopathological criteria associated with lymph node spread and distant metastasis. SUVmax was found to have the best correlation with lymph node spread {correlation coefficient (r^2) = 0.580, $P = 0.0001$}, while SUVmax-High/CA 15-3-Elevated {correlation coefficient (r^2) = 0.677, $P < 0.0001$}, and lymph node spread (N +) {correlation coefficient (r^2) = 0.480, $P = 0.0001$} were found to have



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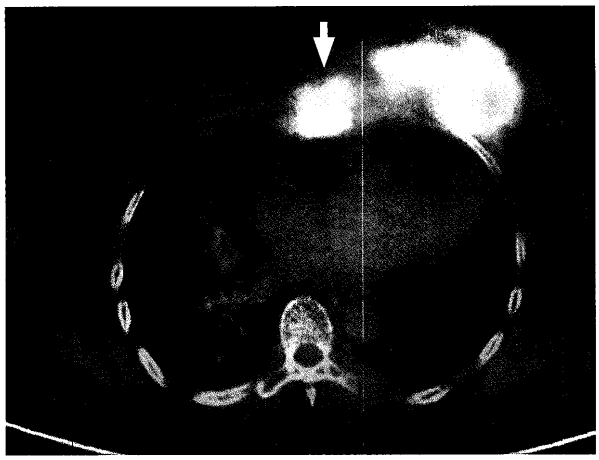

A

Fig. 5 A 59-years-old patient with Invasive Ductal Carcinoma (solid tubular) of left breast with axillary lymph node spread N+, distant metastasis M1 (bone, adrenal). (A) Axial image FDG-PET/CT confirmed disease in left breast with metastasis to manubrium (arrow). (B) Coronal image FDG-PET/CT ; left axillary, mediastinal lymph nodes and right adrenal metastasis was verified (arrows). Prognostic risk factors for distant metastasis were tumor grade 4 (T4), SUVmax 10.2, lymph node spread (N+), SUVmax (High)/CA 15-3 (Elevated).

the best correlation with distant metastasis.

DISCUSSION

The cancer patient posed a complex set of issues to the managing oncologic team in terms of evaluating the extent of disease and deciding the most appropriate form of treatment. Previous reports had suggested the significance of the degree of uptake of FDG by tumor can be as an important prognostic factor for breast cancer [19,20], esophageal cancer [21,22], lung cancer [23~25], and head and neck cancer [26]. In addition, several lines of research have demonstrated the superiority of FDG-PET compared to physical examination in the diagnosis of axillary lymph node metastases [20, 27]. In line with these reports, we have been able to show that, high SUVmax is significantly correlated with lymph node spread and distant metastasis in breast cancer patients. Since SUVmax (>3.1) had been found to be a significant prognostic factor of lymph node spread with 82.9% sensitivity and 75% specificity ($P<0.0001$), then SUVmax is suggested to be useful in the preoperative evaluation of patient prognosis with more accuracy.

In a large study by Pecking et al.[28], 132 patients treated for breast cancer were enrolled. Positive PET scans were obtained in 106 patients, including 89 with a single lesion and 17 with two or more lesions, resulting in an overall sensitivity of 93.6% and a positive predictive value of 96.2%. The smallest detected lesion was a lymph node metastasis with a diameter of 6 mm. Equivalent to these results, is our series which showed that the smallest lesion could be detected by FDG-PET/CT primary tumor, lymph node or distant metastasis is 6 mm.

In addition to the axillary lymph node status, the presence of distant metastases is the main prognostic factor in patients with primary breast cancer. This presence has a significant influence on the choice of therapy. So far, only limited data exist on the value of FDG-PET/CT for initial staging of distant metastases in primary breast cancer.

According to Gion et al.[29,30], the patient-based sensitivity of CA 15-3 in different studies ranged between 33% and 78% with a specificity of between 60% and 93%. Ravaioli et al.[31], divided breast cancer patients into two groups, suggesting that complete imaging tools and tumor markers CEA and CA 15-3 are necessary in the follow-up of patients with advanced primary tumor (pT4, N2). The prognostic implications of CA 15-3 concerning metastatic disease were evaluated by De La Lande et al.[32]. For this purpose, CA 15-3 values before and at first metastasis were examined. It was concluded that the CA 15-3 value before the first metastasis is of prognostic value. FDG-PET is reported to be more sensitive in detecting relapse. Taking these results together, it is suggested that the combination of SUVmax and CA 15-3 could be more useful than conventional clinical staging and than SUVmax or CA 15-3 investigated individually in the preoperative evaluation of patient prognosis. In fact, we have been able to show that the combination of SUVmax-High (>3.8)/CA 15-3-Elevated has been found to be a significant prognostic factor for distant metastasis, with sensitivity 75% and specificity 92.7% (P = 0.0001), and furthermore, the prognostic value of such a combination has been proven in the subset analysis of breast cancer staging as it was found to have positive correlation with TNM classification {$P < 0.0001$, correlation coefficient (r^2) = 0.629}. These results seem to suggest that the prognosis of breast cancer patients can be evaluated preoperatively with more accuracy by FDG-PET/CT, and consequently, therapeutic approach can be decided more precisely.

There is highly significant association between SUVmax and histological grade. FDG uptake reflects the glucose metabolic activity in tumors. Since tumors with high glucose metabolism actively proliferate and tumors with high proliferation activity usually show high histological grade[33~35], it is reasonable that high SUVmax is associated with high histological grade. Matching with these series, we have been able to show the statistical significance of SUVmax as a prognostic factor correlated well with TNM staging ; principally N-factor and M-factor. Accordingly, like other studies[36~41], our study showed the significant incremental worth of SUVmax on FDG-PET/CT to define the extent of disease and can differentiate well between early (N0, M0) and advanced (N+, M1) disease (P = < 0.0001 and 0.0008 respectively) (Fig. 1 and 2).

There are strengths and limitations to every study. Strengths of this study include the prospective database used, all the FDG-PET/CT images were performed by the same PET/CT scanner and were analyzed by the same nuclear medicine radiologists, which limit confounders, Standerized Uptake Value maximum (SUVmax) was calculated for all the patients, the use of pathologic instead of clinical staging, the accessibility to histolopathological reports of the primary tumors and regional lymph node spread as well as clinical and imaging follow-up proof of distant metastasis. Limitations to this study include ; no further analysis was performed to identify to which extent the FDG-PET/CT results could affect the clinical staging and/or alter the treatment plan.

There are many possible clinical imperatives of these data. Perhaps a patient with a negative lymph node at FDG-PET/CT and low SUVmax (<3.1) of the primary cancer may be spared from sentinel node biopsy (SNB) and further axillary lymph node dissection (ALND). Perhaps a patient with a breast cancer that has a SUVmax-High (>3.8)/CA 15-3-Elevated may benefit from radiation/chemotherapy. Perhaps a patient with a SUVmax-High (>3.8)/CA 15-3-Elevated, is more likely to recur systemically and deserves more careful follow-up or even adjuvant chemotherapy. The SUVmax from a FDG-PET/CT scan may provide clues of undiscovered oncogenic, molecular, or biological factors that affect survival. Further studies are needed to answer these provocative questions.

CONCLUSION

FDG-PET/CT, as a metabolic and morphological diagnostic tool, can complement the information provided by other morphological imaging techniques and thereby increase the sensitivity and specificity in the evaluation of potential disease sites. We can show that

the quantitative FDG uptake expressed through SUVmax is a significant predictor of lymph node spread. Furthermore, the combination of SUVmax and tumor marker assay (CA 15-3) is sufficient for the early detection of breast cancer metastasis. Since both tests are based on metabolic changes due to tumor activity, they provide information on disease progression in a different way than conventional imaging. This outcome suggests that the FDG-PET/CT findings with SUV calculation could have a strong positive impact on breast cancer patients.

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REFERENCES

1) Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. : Cancer statistics, 2003. CA Cancer J Clin., **53** : 5-26, 2003.
2) Scheidhauer K, Walter C, Seemann MD. : FDG PET and other imaging modalities in the primary diagnosis of suspicious breast lesions. Eur J Nucl Med Mol Imaging, **31**(suppl 1) : S70-S79, 2004.
3) Delbeke D. : Oncological applications of FDG PET imaging : brain tumors, colorectal cancer, lymphoma and melanoma. J Nucl Med, **40** : 591-603, 1999.
4) Coleman RE. : PET in lung cancer. J Nucl Med, **40** : 814-820, 1999.
5) Delbeke D. : Oncological applications of FDG PET imaging. J Nucl Med, **40** : 1706-1715, 1999.
6) Gambhir SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME. : A tabulated summary of the FDG PET literature. J Nucl Med, **42** Suppl 1 : 1S-93S, 2001.
7) Wahl RL. : Current status of PET in breast cancer imaging, staging, and therapy. Semin Roentgenol, **36** : 250-260, 2001.
8) Rose C, Dose J, Avril N. : Positron emission tomography for the diagnosis of breast cancer. Nucl Med Commun, **23** : 613-618, 2002.
9) Dehdashti F, Siegel BA. : Evaluation of breast and gynecologic cancers by positron emission tomography. Semin Roentgenol, **37** : 151-168, 2002.
10) Kostakoglu L, Goldsmith SJ. : ^{18}F-FDG PET evaluation of the response to therapy for lymphoma and for breast, lung, and colorectal carcinoma. J Nucl Med, **44** : 224-239, 2003.
11) Lorna Weir, Daniel Worsley, Vanessa Bernstein. : The value of FDG positron emission tomography in the management of patients with breast cancer. The Breast Journal, **11** : 204-209, 2005.
12) Beyer T, Townsend DW, Brun T, Kinahan PE, Charron M, Roddy R, et al. : A combined PET/CT scanner for clinical oncology. J Nucl Med, **41** : 1369-1379, 2000.
13) Ell PJ, Von Schulthess GK. : PET/CT : a new road map [editorial]. Eur J Nucl Med Mol Imaging, **29** : 719-720, 2002.
14) Cohade C, Wahl RL. : Applications of positron emission tomography/computed tomography image fusion in clinical positron emission tomography—clinical use, interpretation methods, diagnostic improvements. Semin Nucl Med, **33** : 228-237, 2003.
15) Mitsuaki Tatsumi, Christian Cohade, Karen A. Mourtzikos, et al. : Initial experience with FDG-PET/CT in the evaluation of breast cancer. Eur J Nucl Med Mol Imaging, **33** : 254-262, 2006.
16) Schirrmeister H, Kuhn T, Guhlmann A, et al. : Fluorine-18 2-deoxy-2-fluoro-Dglucose PET in the preoperative staging of breast cancer : Comparison with the standard staging procedures. Eur J Nucl Med, **28** : 351-358, 2001.
17) Dose J, Bleckmann C, Bachmann S, et al. : Comparison of fluorodeoxyglucose positron emission tomography and conventional diagnostic procedures for the detection of distant metastases in breast cancer patients. Nucl Med Commun, **23** : 857-864, 2002.
18) Nancy A. : Obuchowski. Receiver Operating Characteristic Curves and Their Use in Radiology. Radiology, **229** : 3-8, 2003.
19) Oshida M, Uno K, Suzuki M, et al. : Predicting the prognosis of breast carcinoma patients with positron emission tomography using 2-deoxy-2-fluoro [^{18}F]-D-glucose. Cancer, **82** : 2227-2234, 1998.
20) Tomoo Inoue, Kenji Yutani, Tetsuya Taguchi, et al. : 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, **130** : 273-278, 2004.

21) Henderik L. van Westreenen, John T. M. Plukker, David C. P. Cobben et al. : Prognostic Value of the Standardized Uptake Value in Esophageal Cancer. AJR, **185** : 436-440, 2005.

22) Robert J. Cerfolio, and Ayesha S. Bryant. : Maximum Standardized Uptake Values on Positron Emission Tomography of Esophageal Cancer Predicts Stage, Tumor Biology, and Survival. Ann Thorac Surg, **82** : 391-395, 2006.

23) Johan F. Vansteenkiste, Sigrid G. Stroobants, Patrick J. Dupont, Paul R. De Leyn, Erik K. Verbeken, Georges J. Deneffe. : Prognostic Importance of the Standardized Uptake Value on ^{18}F-Fluoro-2-Deoxy-Glucose-Positron Emission Tomography Scan in Non-Small-Cell Lung Cancer : An Analysis of 125 Cases. J Clin Oncol, **17** : 3201-3206, 1999.

24) Robert J. Cerfolio, Ayesha S. Bryant, Buddhiwardhan Ohja, Alfred A. Bartolucci. : The maximum standardized uptake values on positron emission tomography of a non-small cell lung cancer predict stage, recurrence, and survival. J Thorac Cardiovasc Surg, **130** : 151-159, 2005.

25) Dirk Hellwig, Andreas Gröschel, Thomas P. Graeter, et al. : Diagnostic performance and prognostic impact of FDG-PET in suspected recurrence of surgically treated non-small cell lung cancer. Eur J Nucl Med Mol Imaging, **33** : 13-21, 2006.

26) Allal AS, Dulguerov P, Allaoua M, Haenggeli CA. Standardized uptake value of 2-[(18)F] fluoro-2-deoxy-D-glucose in predicting outcome in head and neck carcinomas treated by radiotherapy with or without chemotherapy. J Clin Oncol, **20** : 1398-1404, 2002.

27) Greco M, Crippa F, Agresti R. : 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, **93** : 630-635, 2001.

28) Pecking AP, Mechelany-Corone C, Bertrand-Kermorgant F. : Detection of occult disease in breast cancer using fluorodeoxyglucose camera-based positron emission tomography. Clin Breast Cancer, **2** : 229-234, 2001.

29) Gion M, Boracchi P, Dittadi R, et al. : Prognostic role of serum CA 15.3 in 362 node-negative breast cancers. An old player for a new game. Eur J Cancer, **38** : 1181-1188, 2002.

30) Gion M, Barioli P, Mione R, et al. : Tumor markers in breast cancer follow-up : a potentially useful parameter still awaiting definitive assessment. Ann Oncol, **6** Suppl 2 : 31-35, 1995.

31) Ravaioli A, Pasini G, Polselli A, Papi M, Tassinari D, Arcangeli V, Milandri C, Amadori D, Bravi M, Rossi D, Fattori PP, Pasquini E, Panzini I. : Staging of breast cancer : new recommended standard procedure. Breast Cancer Res Treat, **72** : 53-60, 2002.

32) De La Lande B, Hacene K, Floiras JL, Alatrakchi N, Pichon MF. Prognostic value of CA 15.3 kinetics for metastatic breast cancer. Int J Biol Markers, **17** : 231-238, 2002.

33) Avril N, Menzel M, Dose J, et al. : Glucose metabolism of breast cancer assessed by ^{18}F-FDG PET : histologic and immunohistochemical tissue analysis. J Nucl Med, **42** : 9-16, 2001.

34) Bombardieri E, Crippa F. : PET imaging in breast cancer. J Nucl Med, **45** : 245-256, 2001.

35) Bombardieri E, Crippa F, Baio SM, Peeters BA, Greco M, Pauwels EK : Nuclear medicine advances in breast cancer imaging. Tumori, **87** : 277-287, 2001.

36) William B. Eubank David Mankoff Mallar Bhattacharya, et al. : Impact of FDG PET on Defining the Extent of Disease and on the Treatment of Patients with Recurrent or Metastatic Breast Cancer. AJR, **183** : 479-486, 2004.

37) Moon DH, Maddahi J, Silverman DHS, et al. : Accuracy of whole-body [fluorine-18]-FDG PET for the detection of recurrent or metastatic breast carcinoma. J Nucl Med, **39** : 431-435, 1998.

38) Eubank WB, Mankoff DA, Takasugi J, et al. : ^{18}Fluorodeoxyglucose positron emission tomography to detect mediastinal or internal mammary metastases in breast cancer. J Clin Oncol, **19** : 3516-3523, 2001.

39) Bender H, Kirst J, Palmedo H, et al. : Value of ^{18}fluoro-deoxyglucose positron emission tomography in the staging of recurrent breast carcinoma. Anticancer Res, **17** : 1687-1692, 1997.

40) Dose J, Bleckmann C, Bachmann S, et al. : Comparison of fluorodeoxyglucose positron emission tomography and "conventional diagnostic procedures" for the

detection of distant metastases in breast cancer patients. Nucl Med Commun, **23** : 857-864, 2002.

41) Siggelkow W, Zimny M, Faridi A, Petzold K, Buell U, Rath W. : The value of positron emission tomography in the follow-up for breast cancer. Anticancer Res, **23** : 1859-1868, 2003.

42) Takayoshi Uematsu, Sachiko Yuen, Seigo Yukisawa, et al. : Comparison of FDG PET and SPECT for Detection of Bone Metastases in Breast Cancer. AJR, **184** : 1266-1273, 2005.