Early Predictive Value of Non-response to Docetaxel in Neoadjuvant Chemotherapy in Breast Cancer Using ^{18}F-FDG-PET

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Abstract. *Background: The aim of this prospective study of patients with breast cancer was to identify non-responders to docetaxel in neoadjuvant chemotherapy (NCT) using fluorine-18-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG-PET). Patients and Methods: We analyzed the maximum standardized uptake value (SUV_{max}) of ^{18}F-FDG-PET before and after the first course and the reduction rate in tumor size shown by magnetic resonance imaging (MRI) before the first and after the fourth course of docetaxel. Results: None of the eight patients (0%) whose SUV_{max} decrease was less than 18% revealed a clinical partial response or clinical complete response; Seven out of the sixteen patients (44%) with an SUV_{max} decrease over 45% achieved a complete response. Conclusion: An SUV_{max} reduction rate less than 18% is observed in patients with breast cancer after the first course of docetaxel in NCT and may be indicator of non-response to docetaxel.*

Many patients with advanced breast cancer undergo neoadjuvant chemotherapy (NCT). NCT should result in an at least partial response, and if such a response is not obtained, the NCT regimen should be discontinued. It is more important to detect non-responders rather than responders in NCT in order to avoid cytotoxic treatment.

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A patient's clinical response to chemotherapy is usually determined after several courses of chemotherapy, by changes in tumor size shown by imaging modalities such as ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT) (1).

^{18}F-Fluorodeoxyglucose (^{18}F-FDG) is an agent for positron-emission tomographic (PET) imaging agent for both detecting disease and monitoring responses to treatment (1). ^{18}F-FDG-PET was found to be effective for monitoring cancer cell viability of tissues and tumors (2), and it is used to evaluate the glucose metabolic rates of such tissues because most neoplasms have high glycolytic rates. Warburg first described this fundamental aberration of malignant cells in the 1930s (3).

The anaerobic metabolism of glucose is a fundamental property of all tumors, even in the presence of an adequate oxygen supply (4). Several studies have revealed a relationship between changes in tumor glucose metabolism and patients' response to treatment in various types of cancers (5-10). Several groups have also reported the possibility of using ^{18}F-FDG-PET as a parameter of response to NCT in breast cancer (11-20).

The addition of four courses of preoperative docetaxel after four courses of preoperative therapy with adriamycin with cyclophosphamide (AC) significantly increased the clinical and pathologica response rates for operable breast cancer (21, 22). Giordano *et al*. reported a decline in the use of anthracycline for breast cancer, and they noted that the majority of patients were instead receiving taxane-based chemotherapy (23).

The aim of the present prospective study was to evaluate the predictive value of ^{18}F-FDG-PET to detect poor clinical response to preoperative docetaxel monotherapy in patients with breast cancer.

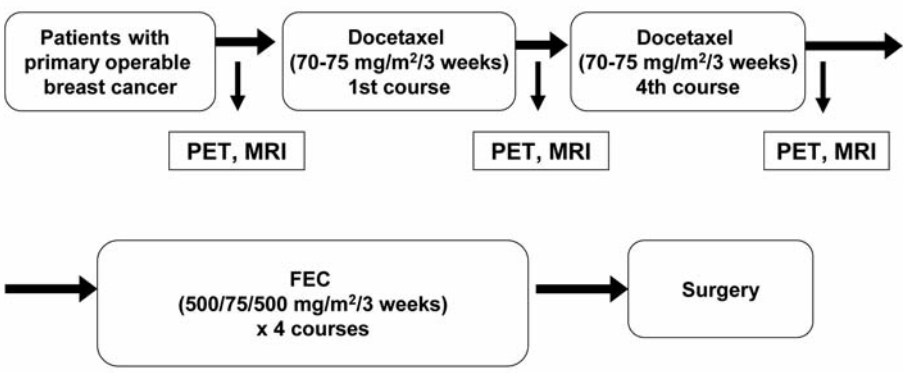

Figure 1. *Study protocol. PET: Positron emission tomography, MRI: magnetic resonance imaging, FEC: fluorouracil/epirubicin/cyclophosphamide.*

Patients and Methods

Patients. From August 2007 to December 2010, 41 patients with T1-T4, N0-N3, or M0, with non-metastatic, non-inflammatory breast cancer with performance status 0 or 1 (World Health Organization) were treated at the Gunma Prefectual Cancer Center in Japan. The cases of 37 of these patients were evaluable. The exclusion criteria were: age older than 70 years, inflammatory or bilateral breast cancer, previous treatment for breast cancer, presence of distant metastases, pregnant or breastfeeding at the time of diagnosis, other previous or current malignancies, diabetes mellitus, and severe cardiac hematological, renal, pulmonary or hepatic abnormalities.

The protocol of the study (Figure 1) was approved by the Ethics Committee of the Gunma Prefectual Cancer Center, and all patients gave their written informed consent before enrollment.

Chemotherapy. All 37 patients were treated with chemotherapy consisting of four courses of docetaxel (70-75 mg/m^2) followed by four courses of fluorouracil/epirubicin/cyclophosphamide (FEC) at 500/75/500 mg/m^2 before surgery. Each course was administered every three weeks. Trastuzumab was not concomitantly added to docetaxel in the NCT; it was administered after surgery for epidermal growth factor receptor-2 (HER2)-positive breast cancer for one year. The most efficient way to evaluate patient response to docetaxel is with pathological findings after surgery. However, we did not carry-out surgery until after the fourth course of docetaxel because anthracycline and taxane are sequentially required in NCT for pathological complete response (pCR) (22).

^{18}F-FDG-PET imaging. ^{18}F-FDG-PET imaging was performed with the PET/CT scanner BIOGRAPH 16 (Siemens, Erlangen, Germany). An ^{18}F-FDG-PET scan of a whole body was performed before (baseline), after the first course of docetaxel. The latter scan was performed on day 15 (range −1 to 2 days) after chemotherapy. The ^{18}F-FDG-PET images were analyzed by two radiologists, using the maximum standardized uptake value (SUV_{max}). A region of interest (ROI) was placed manually over the area of maximal activity on slices with the clearest definition of the tumor. Patients fasted at least five hours before the injection of 185 MBq ^{18}F-FDG. For the PET, the patient was positioned prone with hands held over the head on the scanner couch after an uptake period of 60 min.

Blood glucose levels. All patients had a plasma glucose concentration within the reference range, less than 110 mg/dl just before the injection of 185 MBq ^{18}F-FDG at each scan.

Magnetic resonance imaging (MRI). Contrast-enhanced MRI showed a high correlation between measurements of residual disease and those obtained at pathology, validating the sensitivity of MRI of the breast after chemotherapy (24). In the present study, MRI response rate was measured at baseline and after the fourth course of docetaxel. Each approach was performed on day 15 (range −1 to 2 days) after the chemotherapy. The MRI images were evaluated by two radiologists using the Response Evaluation Criteria In Solid Tumors (RECIST) (http://www.eortc.be/recist/documents/RECIST Guidelines.pdf).

Clinical assessment. We assessed the clinical efficacy of the treatment by determining the reduction rate of the primary tumor using two parameters: the SUV_{max} before and after the first course of docetaxel, and the tumor size with MRI before the first and after the fourth course of docetaxel. Each reduction rate was used to consider whether there was a correlation between the early change of SUV_{max} and the later morphological shrinkage of tumor shown by MRI. In cases of multiple cancer in the breast, we set the ROI at the highest SUV_{max} from among the lesions.

Pathology. The pathological diagnosis of invasive breast cancer was performed by ultrasound-guided core needle biopsy (CNB) before treatment in all 37 patients, and estrogen receptor (ER), progesterone receptor (PgR), and HER2 were measured by immunohistochemistry (IHC). ER and PgR were each considered negative if the Allred total score was 0-2 and positive if the score was 3-8 (25). HER2 protein overexpression was negative if 0 and 1+ by IHC. When the IHC was a score of 2+ or 3+, we performed *HER2* gene amplification by fluorescence *in situ* hybridization (FISH). HER2 ≥2.2 shown by FISH was considered positive in accordance with the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guideline recommendations (26). We evaluated the patients' response by pathology with another CNB after the fourth course of docetaxel in patients who submitted written informed consent for this procedure before enrollment. All patients also underwent surgery after the fourth course of FEC.

Table I. *Characteristics of patients*.

Number of patients	37	Tumor	n (%)	Histology	n (%)
Median age, years	56	Tl	5 (14)	Ductal	34 (92)
range	31-70	T2	29 (78)	Lobular	2 (5)
		T3	1 (3)	Other	1 (3)
		T4	2 (5)		
		Nodal status	n (%)	ER/HER2 status	n (%)
Menopausal status	n (%)	N0	10 (27)	$ER^+/HER2^-$	17 (46)
		Nl	22 (59)	$ER^+/HER2^+$	6 (16)
		N2	2 (5)	$ER^-/HER2^+$	4 (11)
Pre-menopausal	12(32)	N3	3 (8)	$ER^-/HER2^-$	10 (27)
Post-menopausal	25(68)				

Statistical analysis. Continuous variables were analyzed with the Kolmogorov-Smirnov test. The relationships between quantitative variables were analyzed with the Pearson rank correlation coefficient. Multiple comparisons between groups were performed with the Scheffe test. All statistical analyses were performed using SPSS software (version 16.0) (IBM, Armonk, New York, USA).

Results

The characteristics of the 37 patients with breast cancer are given in Table I. Their age range was 31 to 70 (mean 56) years 12 patients were pre-menopausal and 25 were post-menopausal. The tumor sizes were T1-T4 (median=3.0 cm, range=1.7-5.0 cm) and nodal status was N0–N3. Invasive ductal carcinoma was diagnosed in 34 (92%) of the patients, and invasive lobular carcinoma was diagnosed in two (5%). ER/HER2 status is shown in Table II.

The ^{18}F-FDG-PET SUV_{max} reduction rate after the first course of docetaxel was significantly correlated with the tumor size reduction rate, as shown by MRI after the fourth course of docetaxel (r=0.746, $p<0.001$; Figure 2). The SUV_{max} decrease at two weeks after the first course of docetaxel were divided into three groups: <18% (low) [95% confidence interval (CI)=3%-14%], range=19%-44% (intermediate) [95% CI=26%-35%], and >45% (high) [95% CI=51%-61%] ($p<0.001$) (Figure 3).

The <18% SUV_{max} change group were non-responders; that is, none of the eight patients in this group achieved a clinical partial response (cPR) or clinical complete response (cCR), with only clinical stable disease (cSD) on MRI ($p<0.001$) (Figure 4). In the non-responder group, the number of $ER^+/HER2^-$ cases was five (29%) and that of $ER^-/HER2^-$ was three (30%). This group consisted of only $ER^+/HER2^-$ and $ER^-/HER2^-$ cases. The high-responder group had five $ER^+/HER2^-$ patients (29%), five $ER^+/HER2^+$ patients (83%), three $ER^-/HER2^+$ patients (75%), and three $ER^-/HER2^-$ patients (30%). $HER2^+$ groups had good response regardless of ER status (Table II).

Table II. *SUV_{max} reduction rates. SUV_{max} reduction rates were divided into three groups low, intermediate and high response*.

SUV reduction rate	Less than 18% (low) (n=8)	19 to 44% (intermediate) (n=13)	More than 45% (high) (n=16)
Median age	58	54	51
range	33-69	34-69	31-70
$ER^+/HER2^-$, % (n=17)	29% (n=5)	42% (n=7)	29% (n=5)
$ER^+/HER2^+$, % (n=6)	0% (n=0)	17% (n=l)	83% (n=5)
$ER^-/HER2^+$, % (n=4)	0% (n=0)	25% (n=l)	75% (n=3)
$ER^-/HER2^-$, % (n=10)	30% (n=3)	40% (n=4)	30% (n=3)

Discussion

Several studies have shown that ^{18}F-FDG-PET is a good parameter for predicting the response of breast cancer to NCT (13-20). A meta-analysis by Wang *et al*. revealed that performing ^{18}F-FDG-PET earlier, after the first or second course of chemotherapy, can gain significantly better parameters of accuracy than ^{18}F-FDG-PET performed later, after the third course or beyond (27). Kolesnikov-Gauthier *et al*. reported the predictive value of NCT failure in breast cancer using ^{18}F-FDG-PET after the first course of FEC at 500/100/500 mg/m^2. They found that a decrease in SUV_{max} of less than 15% after the first course was a very potent predictor of NCT failure, especially of pCR, even when the chemotherapy regimen was changed after the third course (16).

In addition to these findings obtained with breast cancer, Wieder *et al*.'s study of esophageal squamous cell carcinoma

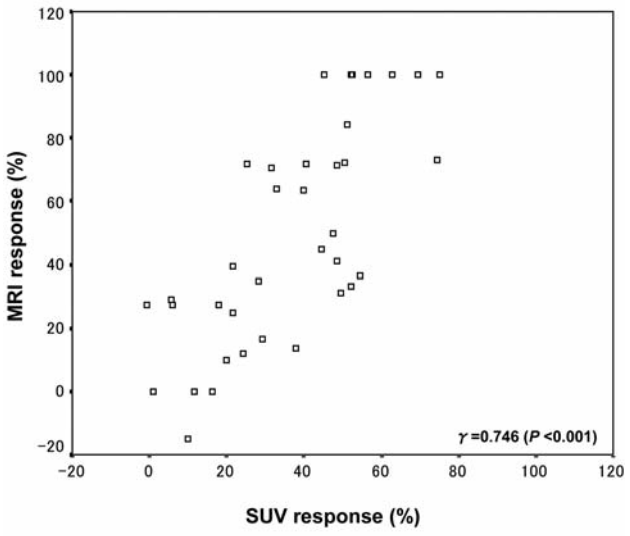

Figure 2. *Correlation between SUV_{max} response rate at two weeks after the first course of docetaxel and tumor size reduction rate with (MRI) after the fourth course of docetaxel.*

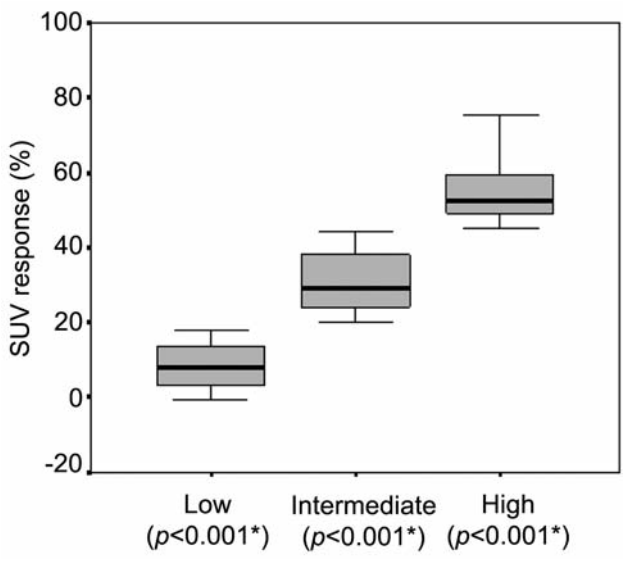

Figure 3. *^{18}F-FDG-PET) (SUV_{max} reduction rate at two weeks after the first course of docetaxel in three groups: <18% (low) [95% confidence interval (CI)=3%-14%], range=19%-44% (intermediate) [95% CI=26%-35%], and >45% (high) [95% CI=51%–61%] (p<0.001).*

revealed that changes in tumor metabolic activity of SUV_{max} after 14 days of preoperative chemoradiotherapy were significantly correlated with tumor response and patient survival (8). We set the evaluation time point at two weeks after the first course of chemotherapy for non-responders, who should be identified as early as possible to avoid ineffective and potentially harmful treatment. We used the SUV_{max} reduction rate as the measure of the clinical response because a cut-off value has not been established in SUV_{max} as a measure of the metabolic response in prior studies. We analyzed our patients' MRI images after their fourth course of docetaxel as a surrogate clinical measure in the place of a pathological analysis.

After 2005, a sharp increase in the use of taxane-based chemotherapy and a decline in anthracycline-based chemotherapy for breast cancer was seen. In a Medicare breast cancer cohort in the U.S. in 2008, 51% of the patients received taxane-based chemotherapy and 32% received anthracycline-based chemotherapy (23).

Our study has several limitations. The pathological response to docetaxel was evaluated with ultrasound-guided CNB. CNB was performed after the fourth course of docetaxel and before the first course of FEC. There were no relative data between the ^{18}F-FDG-PET response rate after the first course of docetaxel and the pathological response obtained by CNB after the fourth course of docetaxel. It was difficult to obtain the appropriate part of the malignant lesion by CNB, especially the highly responsive part after chemotherapy, because ultrasound cannot differentiate viable tissue from fibrotic changes in tumors (28, 29). We also did not present the patients' pathological responses after surgery, because the efficacy of the FEC was included in the final pathological result.

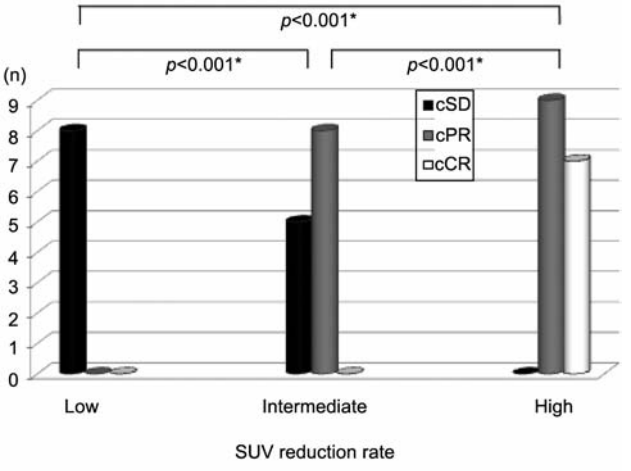

Figure 4. *The low SUV_{max} reduction group were non-responders with only cSD with MRI. cCR was only found in the high-response group.*

Concomitant trastuzumab chemotherapy was required to increase the pCR rate in an HER2-positive breast cancer population (30). In Japan, however, trastuzumab was not available as an NCT regimen until November 2011, which is later than our study's enrollment period.

A clear tumor shown by morphology is adequate for the determination of the ROI, whereas the ROI in a diffused, expansive or inflammatory lesion is not reliable for defining the tumor boundaries. In the present study, 41 patients with invasive carcinoma were eligible but only 37 were assessable. Krak *et al*. showed that the method used to define the ROI was of crucial importance in the monitoring of tumor FDG uptake during therapy, but no consensus has been reached on the optimal type of ROI for monitoring response during therapy (31). Shankar *et al*. showed consensus recommendations for the use of ^{18}F-FDG-PET as an indicator of therapeutic response; that is, that threshold-determination or edge-finding algorithms could be applied with less subjective interaction in the determination of ROIs by a technician or physician (1). In the present study, two radiologists determined the ROIs or range of lesion.

Greater numbers of patients and further observations are necessary to further determine the utility of 18F-FDG-PET in predicting response to docetaxel in NCT.

Conclusion

An SUV_{max} decrease of less than 18% after the first course of docetaxel appears to indicate potential failure of docetaxel in NCT.

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