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Title: The Relationship between 18-FDG-PET/CT and Clinicopathologic Features, Pathologic Response in Patients with Locally Advanced Breast Cancer

Authors: Nilgun Yildirim[1], Melih Simsek[2], Mehmet Naci Aldemir[3], Mehmet Bilici[2], Salim Basol Tekin[2]

Institutions: [1]Department of Medical Oncology, Dr Ersin Arslan Training and Research Hospital, Gaziantep, Turkey

[2]Department of Medical Oncology, Atatürk University School of Medicine, Erzurum, Turkey

[3]Department of Medical Oncology, Erzincan University School of Medicine, Erzincan, Turkey

Correspondence to: Nilgun Yildirim, drnilgunsari@yahoo.com

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ABSTRACT

Objective: We investigated the relation between maximum standardized uptake value (SUV_{max}) of whole body positron emission tomography/computed tomography (PET/CT) performed before treatment and demographical and histopathological features in locally advanced breast cancer(LABC)

and the role of PET/CT in evaluation of pathological complete response (pCR) after neoadjuvant chemotherapy (NAC).

Materials and Methods: 51 LABC patients who have received NAC in our center between 2011 and 2015 were analyzed retrospectively. Basal PET/CT was performed in all patients before NAC. SUV_{max} levels and demographical and histopathological results were compared. The relation between SUV_{max} values after NAC and pathological responses were evaluated.

Results: Mean age of the patients was 49 (32-69). PET/CT performed after NAC showed complete response in 20 patients (39.2%), partial response in 28 patients (54.9%), stable disease in 2 patients (3.9%), and progressive disease in one patient (2%). There was no significant difference between mean SUV_{max} values of the patients according to age (>50, ≤50), menopausal status, tumor localization, clinical stage, and grade. Mean SUV_{max} value was higher in triple negative group than HER2 positive group and luminal group. There was significant difference in SUV_{max} values between the group that pCR achieved after NAC and the group that not pCR (SUV_{max} value for breast 2.92 vs 0.30, p=0.01, SUV_{max} value for axilla 1.5 vs 0.0, p=0.02).

Conclusion: SUV_{max} values are not related to demographical features. There was a significant relationship between pCR and SUV_{max} values after NAC. PET/CT could be useful in evaluation of patients to predict biologic characteristics of tumors.

Keywords: Breast cancer, 18F-FDG, neoadjuvant chemotherapy.

Introduction

Locally advanced breast cancer (LABC) comprises heterogeneous group of patients with slow-growing tumors as well as those with biologically aggressive disease. Because of the high loco-regional recurrence and metastasis risk in these patients, intensive treatment is required in this population [1]. Neoadjuvant chemotherapy (NAC) is accepted as standard treatment in LABC. NAC increases the effective resection rates and breast preserving surgery rates [2, 3]. Furthermore it aims in vivo evaluation of chemotherapy response. [4, 5].

It has been shown that pathological complete response (pCR) after NAC maintains survival advantage in some subtypes of breast cancer. Therefore pCR may be used as a marker to evaluate treatment

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results [6, 7]. Nonetheless breast cancer has different biological features. While recurrence occurs in some patients with pCR, some patients without a pCR have a good prognosis [8]. Therefore, there is a need to search for new predictive and prognostic factors additional to pCR after NAC.

Fluorodeoxyglucose positron emission tomography/computed tomograph (FDG PET/CT) is a valuable instrument in staging, restaging after recurrence, and evaluation of chemotherapy(CT) response of breast cancer patients [9]. Which is expressed as level of F18-FDG uptake, maximum standardized uptake value (SUV_{max}) is reported to be related with aggressive tumor biology in many studies. There are studies showing that histolopathological parameters like tumor size, histological grade or hormone receptor expression status are correlated with FDG uptake in breast cancer [10-12]. . There are also researches suggested that F18-FDG PET/CT is beneficial in preoperative evaluation of prognosis in breast cancer and may be used in decision of CT. [13,14].

FDG PET/CT has advantages against conventional imaging studies. There are studies showing that it is a sensitive method in evaluation of early response to NAC [15]. But there are also studies showing that its sensitivity is not adequate in evaluation of pCR [16]. Therefore use of FDG PET/CT in NAC is controversial. In this study we researched the relationship between demographical and histopathological features of LABC and PET/CT SUV_{max} values before treatment, and the role of PET/CT in evaluation of pCR after NAC.

Materials and Methods

Patients

For the period between 2011 and 2015, a file search was performed among 453 patients treated for breast cancer in our unit. 51 breast cancer patients with stage 2 to stage 3 diseases that received NAC evaluated retrospectivelyBasal PET/CT was applied in all patients before NAC. Patients with distant metastasis and bilateral breast cancer were excluded. All the patients were received 4-8 cycles of CT. All the patients were undergone surgery after having a control PET/CT following NAC. Bone metastasis was occurred one patient and this patient was undergone a mastectomy operation . The study was approved by local the ethics committee. As being a retrospective study, inform consent was not received from the patient.

Clinicopathological evaluations

Clinical data and pathological findings of all the patients were recorded by investigation of policlinic follow-up files and hospital archives. Age, menopausal status, clinical stage, and tumor localization of the patients were recorded. All the patients were diagnosed by a tru-cut biopsy. Tumors were graded according to modified Scarf-Bloom-Richardson grading system. Estrojen (ER), progesterone (PR), HER2, and Ki67 expression status were analyzed from the routine pathological evaluation results in our center. Positivity for ER and PR was identified as 1% or more positive stained nuclei in ten high power fields [17]. HER2 was analyzed by immunohistochemistry and the intensity of the staining was reported as 0, 1+, 2+ or 3+. Score of 3+ was determined as HER2 positive, and score of 0 or 1+ was determined as HER2 negative. If the score was 2+, then gene amplification using fluorescence in situ hybridization (FISH) was used. When the ratio of HER2 gene copies to chromosome 17 signals was found to be greater than 2.2, HER2 was considered to be positive [18]. After NAC, modified radical mastectomy (MRM) plus axillary dissection (AD) or breast conserving surgery (BCS) was performed in all patients. Tumor size, histological grade, presence of vascular, lymphatic or perineural invasion, and lymph nodal involvement were assessed from surgical materials. The precise definition of pCR in breast carcinoma is uncertain. We adopted a pCR of yp T0/is ypN0, which means no residual invasive cancer in breast and axillary lymph nodes, but noninvasive breast residuals permitted

Neoadjuvant chemotherapy

Great majority of the patients were received four cycles of antracycline based regimens, and four cycles of taxane regimens. Only one patient was evaluated after receiving three cycles of dose dense antracycline based treatment. There was CR in PET/CT imaging, and after surgery three more cycles were administered. Operation was performed in one patient after 6 cycles of TAC(docetaxel/doxorubicin/cyclophosphamide) regimen. After completion of NAC, BCS or MRM with AD was performed in all patients. All the patients were received anti-HER2 treatment, radiotherapy, and endocrine therapy if necessary according to standard guidelines.

18F-FDG PET/CT imaging

Patients were fasted overnight during at least 12 hours before PET/CT whole body imaging was performed. Patients with a fasting blood sugar level above 120 mg/dl were excluded. After an

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intravenous injection of approximately 12 mCi (444 MBq) 18F-FDG, the patient waited in a silent room for about an hour, and after this period was imaged using an integrated PET/CT camera, which consisted of a 16-slice CT gantry, integrated with an LSO-based fullring PET scanner (Siemens Biograph 16, Siemens, Knoxville, TN, USA). The CT was applied with 120-200 mAs adjusted to the body weight of the patient at a 120 kV. It was scanned proximal to the thigh from the base of his skull. The PET images were reconstructed by a repetitive method (ordered-subset expectation maximization: two iterations, eight subsets) to achieve attenuation correction and image fusion. After reconstruction, PET, CT, and fused images were showed by software which is commercially available (e-soft/VSIM, Siemens Medical Solutions) in axial, coronal, and sagittal planes. Maximum intensity projection (MIP) PET images and co-recorded PET/CT images were appreciated and analyzed by a nuclear medicine practitioner. Which was calculated by the formula as measured activity concentration [Bq/ml] x body weight [kg]/injected activity [Bq], the SUV_{max} was determined by drawing region of interest (ROI) around the primary tumor on the transaxial slices.

Statistical Analysis

Data were presented as mean, standard deviation, median, minimum, maximum, percentage, and number. Normal distribution of constant variables was analyzed with Shapiro Wilk test. While comparing two groups, Independent Samples t test was used if the normal distribution condition was achieved, and Mann Whitney u test if not. While comparing more than two groups, ANOVA test was used if the normal distribution condition was achieved, Kruskal Wallis test if not. Pearson's correlation was used for numerical data. Spearman's correlation was used for ordinal data. To assess the diagnostic accuracy, we performed receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was then estimated. Statistically significance level was determined as $p < 0,05$. SPSS software 20 was used for all statistical analyses that were performed.

Results

Patient characteristics

Clinicopathological features of the patients were summarized in Table 1. A total of 51 patients were analyzed. Only one patient was male. Mean age of the patients was 49 (32-69). Of the patients 52,9% (n=27) were premenopausal. 92,2% (n=47) had stage 3 disease and the tumor was localized in right breast in 54,9% (n=28). Of the patients 90,2% (n=46) had IDC, 5,9% had ILC, 2% (n=1) had mucinous

carcinoma, and 2% (n=1) had phyllodes tumor as histological subtype. Histologic grades were grade 1 for 1 patients (2%), grade 2 for 22 patients (43%), and grade 3 for 8 patients (15.6%). ER was positive in 43 patients (84.3%), and PR was positive in 39 patients (76.4%). When the estrogen and/ or progesterone receptors were analyzed together, the hormone receptors in 45 patients (88.2%) were found positive. HER2 positivity was observed in 60,8% and 9,8% of the patients had triple negative molecular subtype. Of the patients 39,2% (n=20) achieved complete response, 54,9% (n=28) achieved partial response, 2,9% (n=2) achieved stable disease, and progressive disease was observed in 2% (n=1) in PET/CT which was performed after NAC.

All patients were undergone surgery. One patient had BCS, and one patient who had a negative sentinel lymph node sampling had a simple mastectomy. All of the other patients (96%) had MRM+AD. The patient that bone metastasis was defined was also undergone surgery after NAC, but did not receive radiotherapy to breast, and the patient died at the second year of treatment. In the follow-up period, recurrence was determined in 15,7% (n=8) of the patients with the bone metastasis was the most common site (50%, n=4). The second common site of recurrence was brain. Of the three patients with brain metastasis two died related to disease. Acute leucosis was occurred in one patient that receiving adjuvant endocrine therapy and the patient died because of that. In the follow-up period, 7,8% (n=4) of the patients died. Treatments of the other patients with recurrence are continuing.

The relation between demographical and histopathological features and pre-treatment PET/CT

Mean SUV_{max} of 51 patients was 8,53. There was no statistically significant difference between mean SUV_{max} and age (> 50, ≤ 50), menopausal status (premenopausal, postmenopausal), tumor localization, clinical stage, tumor Ki67 index, and tumor grade of the patients. Mean SUV_{max} is higher in triple negative group than HER2+ and luminal groups. The lowest SUV_{max} was observed in luminal group. Although there was a relation between mean SUV_{max} and molecular subtypes, axillary SUV_{max} were statistically significant (Table 2).

The correlation analysis was made between age, stage, menopausal status, localization, grade, Ki67, subtypes breast/axillary with the after/before CT primary tumor and axillary SUVmax among the all patients but no significant relationship was found.

The role of PET/CT in evaluation of pCR

There was PET/CT FDG uptake after NAC in three of the 15 patients that pCR was achieved. Furthermore pCR could not be achieved in 8 of 20 patients that did not showed abnormal FDG uptake in PET/CT. There was no significant difference between pretreatment mean SUV_{max} of the patients with or without pCR. But there was significant difference between SUV_{max} of these groups after NAC (SUV_{max} breast 2,92 vs 0,30, p=0,01; SUV_{max} axillary 1,5 vs 0,0, p=0.02) (Table 3).
The ROC analysis was performed between after CT primary tumor and axillary SUV_{max} with/without the pathologic complete response. The sensitivity was 75%, specifity was 75% for primary tumor and the sensitivity was 55%, the specifity was 100% for axillary lymph nodes. (Table 4) (Figure 1).

While none of the patients with complete response in PET/CT had recurrence, abnormal FDG uptake in control PET/CT after NAC was continuing in all the patients that metastasis occurred in the follow-up period. DFS and OS analyzes were not performed because of the short follow-up period of the patients.

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Discussion

Which is a noninvasive imaging modality, 18F-FDG PET/CT shows both the metabolism of the tumor and the anatomical details. Higher 18F-FDG uptake in malignant cells makes the tumor visible. SUV_{max} is a semiquantitative value and indicates 18F-FDG uptake. The increased proliferation activity in tumor cells is related to the density of 18F-FDG uptake of the tumor [19]. There was a large space between 18F-FDG uptake values in our study (SUV_{max} 1,13-27,07), and this situation reflects the heterogeneity of glucose metabolism of breast carcinoma.

18F-FDG uptake value has found to be related to tumor biology in various malignities in many studies [20]. There are studies comparing histopathological parameters in breast cancer with 18F-FDG uptake. Several studies that supported this relation have showed that 18F-FDG uptake values are lower in invasive lobular carcinomas than in invasive ductal carcinomas [11]. The authors were defined that the lower intensity of tumor cells in lobular carcinomas, lower expression of GLUT1, lower proliferation rates and diffuse infiltrative tumor growing patterns to surrounding tissue were responsible from this relationship [21]. A comparison could not be made in this study owing to the low number of patients with invasive lobular carcinoma (three patients).

No relationship was determined between demographical features of the patient and SUV_{max}. No relationship was shown between patient age and SUV_{max} in many studies in the literature like in our study [8, 12]. Also no significant relationship was found between menopausal status of the patient and SUV_{max}. Although the study offered that 18F-FDG uptake was 1.3 times higher in premenopausal patients [11], another study determined no relationship between menopausal status and tumor SUV_{max} [22].

Tumor grade is a significant predictive factor in breast carcinoma. Breast carcinoma is reported by pathologists according to classification system called as modified Bloom Richardson grading system. In this system parameters including nuclear grade, tubule formation, and mitotic rate are scored from one to three. The calculation of the final score gives us the histological grade. A strong positive correlation was shown between histological grade and 18F-FDG uptake in some studies [10, 14]. Also a relationship between 18F-FDG uptake and nuclear pleomorphisms and mitotic activity was reported by Berriolo-Riedinger et al. [23], but they found no relationship with tubular formation. This may be because of the role of mitotic count and nuclear pleomorphism is much more in the glycolytic pathway and glucose consumption. Although mean SUV_{max} values of patients with grade 3 disease was higher in our study, no relationship between grade and SUV_{max} was observed possibly owing to the limited number of patients.

Ki67 is a marker that shows proliferation activity and is used in various cancers. High Ki67 value was found to be releated with poor prognosis in patients [24]. The major disadvantage of Ki67 value is high variability between observers that evaluating this value [25]. There are articles that showed positive correlation between SUV_{max} values and Ki67 proliferation index and lymphovascular invasion [10,12]. But no correlation was shown between Ki67 and SUV_{max} in our study. Because lymphovascular invasion was not defined in pathological reports of some patients it was not evaluated in this study.

Prognosis is better in ER (+) patients than ER (-) ones [26]. Data regarding relationship between 18F-FDG uptake and hormone receptor status is not clear. While no relationship was reported between receptor positivity and FDG uptake in some studies [21], higher SUV_{max} values were determined in ER (-) patients in many studies [11]. Also higher SUV_{max} values were established in receptor negative patients than receptor positive patients in our study.

cerbB2 over expression is associated with aggressiveness of tumor and poor prognosis. Although Ueda et al. [14] reported a correlation between cerbB2 oncogene overexpression and SUV_{max} value, this was not shown in many other studies [23]. Also significant relationship to primary tumor could not be shown in our study. Groheux et al. [11] suggested that there may be a minor role of the HER2 gene in the glycolytic pathway.

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Triple negative breast cancer (TNBC) composes approximately 15% of all invasive breast cancers. It has high recurrence rate and poor OS time [27]. This poor prognosis is a result of aggressive character of the disease and lack of effective targeted therapy options [28]. Because of the high SUV_{max} uptake, PET-CT is found to be more useful in TNBC [29]. 18F-FDG uptake of TNBC patients was found high in our study supporting many other studies [10-12].

PET-CT FDG uptake identifies metabolic changes earlier than conventional imaging methods during or at the end of treatment. It is found to be more sensitive (87%) in evaluation of treatment response than clinical examination (39%) and CT imaging (56%) [1]. Thus it becomes a guide for effectiveness of chemotherapy and treatment process. Wahl et al. [30] showed that PET-CT had a benefit in determining decrease in glucose metabolism in tumor and pathological tumor response after effective treatment of primary breast cancer. Tateishi et al. [16] showed that sensitivity of PET-CT in evaluation of pCR was not acceptable, but its specificity was high. There is a wide range of variation in sensitivity (39-100%) and specificity (74-100%) of PET-CT in the literature. In this study, sensitivity was 75%, specifity was 75% for primary tumor and sensitivity was 55%, specifity was 100% for axillary lymph nodes. False positivity with PET-CT is also established in three of 15 patients that pCR was achieved in our study. Furthermore, of 20 patients that complete response was observed in PET-CT 14 had true positivity and 8 had false positivity. There is no significant difference between mean pre-treatment SUV_{max} values of the patients with or without pCR. But there is a significant difference between SUV_{max} values of these two groups after NAC (SUV_{max} breast 2.92 vs 0.30, p=0.01; SUV_{max} axilla 1.5 vs 0.0, p=0.02).

Our study has several limitations. Firstly, since this was a retrospective designed and the number of patients was low, the results of should be interpreted with caution. In some studies it was determined that the ΔSUV_{max} measurements used to evaluate the metabolic response after NAC correlated with pCR. In our study, ΔSUV_{max} measurements were not performed. The association between histological subtypes and pCR was not assessed because of the low number of patients in the subgroups. Finally, we did not attempt to analyze the relationship between SUV_{max} values and survival as the follow-up period of the study population was relatively short.

Consequently, no relationship between PET-CT SUV_{max} values and demographical features of the patients is established in LABC. But is seems that there may be a relation with some histopathological

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prognostic factors. Besides there is a significant relationship between post-treatment SUV_{max} value and pCR. PET / CT may be useful in predicting prognosis in NAC received patients with local advanced breast cancer because none of the patients with complete response in PET/CT had recurrence. In order to support these results, there is a need for randomized prospective studies including large number of patients, long-follow up period.

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Table 1: Clinical and Pathologic Characteristics of the Patients

	Number	%
Age		
Median	49	
Range	32-69	
Tumor localisation		
Right	28	54.9
Left	23	45.1
Menapousal status		
Premenapous	27	52.9
Postmenapous	23	47.1
Histologıcal Type		
IDC	46	90.1
ILC	3	5.9
Musinous carcinoma	1	2
Phyloides tumor	1	2
Stage before NAC		
Stage II	4	7.8
Stage III	47	92.2
Type of surgery		
Breast-conserving surgery	1	2
Mastectomy	50	98
Type of axial surgery		
Sentinel lymph node biopsy	1	2
Axial dissection after sentinel lymph node biopsy	0	
Axial dissection	49	96
Subtype		
Luminal A and luminal B	15	29.4

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Luminal HER2	30	58.8
HER2 positive	1	2
Triple negative	5	9.8
Nuclear grade		
I	1	2
II	22	43.1
III	8	15.6
Unknown	20	39.2
Ki67		
High(>20)	35	68.6
Low(≤20)	5	9.8
Pathologic complete response,positive	15	29.4

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, NAC: Neoadjuvant chemotherapy

Table 2: Metabolic characteristics of the primary tumor according to the clinical and histopathological status

Feature		N	Mean	SD	Median	Min	Max	p-value
Age (years)	<50	30	8,42	6,40		1,61	27,07	,882
	≥50	20	7,61	5,23		1,13	19,85	

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Menopausal status	premenopausal	26	8,52	6,78		1,61	27,07	,802
	postmenopausal	23	7,85	4,90		1,13	19,85	
Localisation	right	27	7,04	4,43		1,13	19,20	,436
	left	23	9,33	7,19		1,61	27,07	
Grade*	grade 2	22	7,81	5,09	6,82	2,13	17,22	,639
	grade 3	8	9,25	6,04	6,57	1,80	19,20	
Ki67*	High(>20)	34	7,18	4,36	7,63	1,13	17,10	,943
	Low(≤20)	5	7,03	6,16	7,31	2,63	17,22	
Subtypes(breast)*	Luminal A, B	14	5,78	4,97	5,85	1,13	19,20	,134
	Luminal HER2	31	8,41	6,30	8,32	1,61	27,07	
	Triple Negatif	5	11,43	4,09	8,11	6,05	17,10	
Subtypes(axiller)*	Luminal A, B	10	3,82	1,60	4,02	2,22	7,32	,02
	Luminal HER2	25	6,95	4,37	6,87	1,93	14,87	
	Triple Negatif	5	9,08	4,27	7,80	4,30	17,50	

*used the non-parametric tests (Mann Whitney U test or Kruskal Wallis test)

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Table 3: Tumor metabolic characteristics according to achievement of pCR

		N	Mean	St.Dev	Min	Max	p
Before CT primary tumor	No-pCR	35	7,82	5,12	1,80	19,20	,751
SUVmax	pCR	15	8,73	7,62	1,13	27,07	
Before CT axillar SUVmax	No-pCR	30	6,16	4,20	1,93	17,50	,316
	pCR	12	7,57	4,11	2,94	14,74	
After CT primary tumor	No-pCR	36	2,92	4,10	0,00	20,95	,001
SUVmax	pCR	15	0,30	0,72	0,00	2,60	
After CT axillar SUVmax	No-pCR	36	1,5	2,4	0,00	12,6	,002
	pCR	15	0,00	0,00	0,00	0,00	

CT: Chemotherapy, PCR: Pathologic complete response

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Table 4. Sensitivity, specificity, AUC, cut-off and asymptotic significance of ROC analysis of parameters

	Sensitivity (%)	Specificity (%)	AUC	Cut-off	PPV	NPV	P value	Confidence Interval	
								Lower Bound	Upper Bound
SUV2T	75.9	75	0.815	0.185	**75.2**	**75.7**	**0.002**	0.685	0.944
SUV2N	55.2	100	0.776	0.525	**100**	**69.1**	**0.006**	0.638	0.914

To assess the diagnostic accuracy, we performed receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was then estimated. AUC: area under curve; NPV: negative predictive value; PPV: positive predictive value;SUV2T: SUV_{max} in the primary tumor after chemotherapy ; SUV2N: SUV_{max} in the lymph nodes after chemotherapy.

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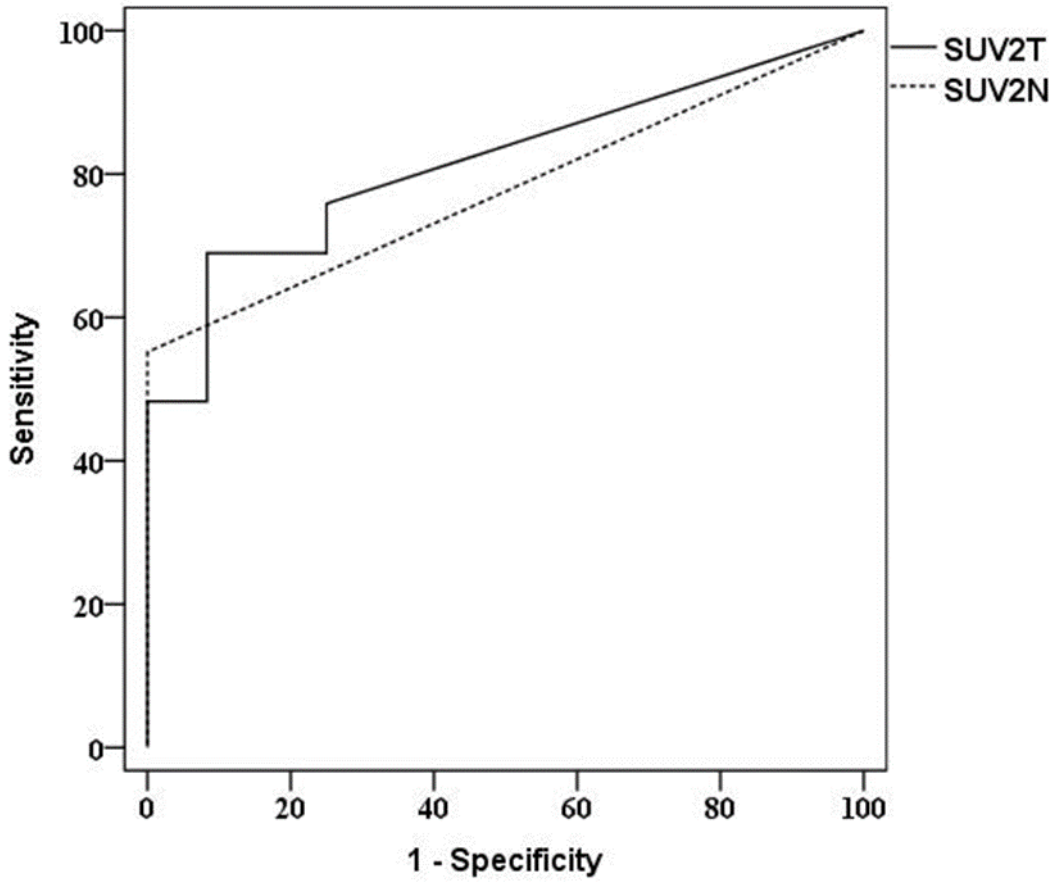
Figure Legend

Figure 1. ROC curve analysis of PET2 SUV_{max} for prediction of pCR. SUV2T: SUV_{max} in the primary tumour after chemotherapy; SUV2N: SUV_{max} in the lymph nodes after chemotherapy.



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