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ORIGINAL ARTICLE

Changes in 18F-FDG-PET/CT tumor metabolism are not consistent with pathologic complete response in hormone-positive breast cancer

Serap Kaya[1], Bilge Aktas[2], Eda Tanrikulu[1], Mehmet Akif Ozturk[1], Fuat Dede[3], Handan Kaya[4], Umit Ugurlu[5], Zerrin Ozgen[6], Sinan Koca[1], Suleyman Halil[1], Rahib Hasanov[1], Ozkan Alan[1], Nalan Akgul Babacan[1], Ozlem Ercelep[1], Faysal Dane[1], Mahmut Gumus[2], Fulden Yumuk[1]

[1]Department of Medical Oncology, Marmara University School of Medicine, Istanbul; [2]Department of Medical Oncology, Istanbul Medeniyet University Goztepe Research and Training Hospital, Istanbul; [3]Department of Nuclear Medicine, Marmara University School of Medicine, Istanbul; [4]Department of Pathology, Marmara University School of Medicine, Istanbul; [5]Department of General Surgery, Marmara University School of Medicine, Istanbul; [6]Department of Radiation Oncology, Marmara University School of Medicine, Istanbul Turkey

Summary

Purpose: *Current evaluation of response to neoadjuvant chemotherapy (NAC) shows that it could achieve pathological complete response (pCR). The purpose of this study was to assess the consistency of maximum uptake values (SUVmax) changes and pCR in hormone-positive locally advanced breast cancer (LABC).*

Methods: *Ninety hormone-positive LABC patients treated at Marmara University Medical Oncology Clinic, Istanbul, Turkey, between 2009 and 2015 were retrospectively studied. All eligible patients (n=51) received NAC (4-8 cycles) and were evaluated for pCR. 18F-fluorodeoxyglucose positron emission tomography/ computed tomography (18F-FDG-PET/CT) scan was performed before and after the completion of NAC. The relative changes of SUVmax both in the primary tumor and the axilla were assessed for consistency with pCR.*

Results: *The patient median age was 46 years (range 26-76). The patients 13.7% achieved pCR. Values of >50% (n=40) and <50% (n=11) SUVmax changes were not associated with pCR (15% and 18% respectively) (p=1.00). Patients with >75% SUVmax changes could achieve pCR of 20%. Interestingly, most patients with complete metabolic response did not achieve pCR (81%). The difference of the Ki67 levels before and after NAC, tumor localization, HER-2 positivity, menopausal status, grade of differentiation, lymphovascular and perineural invasion were not associated with pCR.*

Conclusion: *SUVmax changes in later cycles of NAC as commonly practised in oncology clinics were not consistent with pCR (p=1.0). Complete metabolic response may not be associated with pCR in hormone-positive LABC. However, almost 80% of patients had >50% decrease in SUVmax and may still have a chance for conservative surgery and less postoperative morbidity. Therefore, 18F-FDG-PET/CT may still have a role to evaluate the tumor response with a need of larger studies and analysis for cost-effectiveness.*

Key words: *18F-FDG-PET/CT, hormone-positive, locally advanced breast cancer, neoadjuvant chemotherapy, pathologic complete response*

Introduction

The current treatment of breast cancer in clinical practice includes multi-disciplinary therapy with surgery, radiation, chemotherapy, hormonal therapy and targeted therapies. Neoadjuvant treatment has become the standard treatment modality in locally advanced disease that is either inoperable

Correspondence to: Serap Kaya, MD. Marmara University School of Medicine, Department of Internal Medicine, Division of Medical Oncology, University Pendik Training and Research Hospital, Department of Internal Medicine, Division of Medical Oncology, Pendik, Istanbul, Turkey. Tel: +90 505 575 34 11, Fax: +90 216 625 46 09, E-mail: serap.md@hotmail.com
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at presentation or requires extended radical resection [1-5]. Major advantage of neoadjuvant therapy is the reduction of tumor size, resulting in higher percentages of breast-conserving surgery and giving a chance to evaluate chemo-resistance and to predict survival [3,6]. pCR was shown to be strongly associated with improved long-term outcome in different studies [7-10]. On the other hand, anatomical imaging methods (mammography, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) etc.) have roles basically in evaluating changes in tumor size, but their accuracy is limited in predicting response to neoadjuvant treatment [11]. Since 18F-FDG-PET/CT as a functional imaging procedure is able to differentiate viable tumor cells from the changes that are not tumor-associated depending on the glucose metabolism of tumor tissue, it has a role in clinical management of locally advanced and distant metastatic breast cancer, and has been shown to predict accurately pCR to neoadjuvant treatment in different subtypes (HER-2 positive and triple negative) of breast cancer patients in several studies [11-14].

The aim of this study was to determine if there is an association between SUV changes in 18F-FDG-PET/CT with pCR rates in the breast and/or axilla after NAC (anthracycline and taxane-based) in LABC patients.

Methods

The medical records of 90 patients with LABC, excepting inflammatory breast cancer, who received NAC in the medical oncology clinic of Marmara University Pendik Research and Training Hospital between January 2009 and 2015 were studied. All patients with biopsy-proven diagnosis, completing 4-8 cycles of NAC and having 2 18F-FDG-PET/CT evaluations (before and after NAC) were identified. From 90 patients, 61 were eligible because they had completed full treatments and 18F-FDG-PET/CT scan both before and after NAC. The remaining 29 patients had not completed all the planned treatments or had not PET/CT before or after treatment. Out of 61 eligible patients, 10 patients with hormone-negative disease (5 triple-negative and 5 hormone-negative and HER-2 positive) were excluded from the analysis and finally the remaining 51 patients were included in the study. The majority of the patients received anthracycline-based (anthracycline, cyclophosphamide and/or 5-fluorouracil) and/or taxane-based (3 cycles docetaxel every 21 days or 12 cycles of weekly paclitaxel) as NAC. Trastuzumab was added to taxane regimens in HER-2 positive tumors and completed 1 year post-operatively.

18F-FDG-PET/CT were performed 3-4 weeks after the completion of NAC. Patients were subjected to either lumpectomy or modified radical mastectomy with sentinel node biopsy and/or axillary lymph node dissection after NAC.

Informed consent was waived since the trial included retrospective data analysis. Data on patient demographics, tumor histology, assessment of tumor by metabolic response on 18F-FDG-PET/CT imaging was collected.

The study was approved by the Institutional Review Board at Marmara University School of Medicine in Istanbul (70737436-050.06.04-).

Evaluation of tumor histology

All of the cases were diagnosed by tru-cut biopsy. Estrogen receptor (ER), progesterone receptor (PR), grade of differentiation and Ki67 were determined by immuno-histochemical (IHC) staining. HER-2 status was accepted as 'positive' if strong (3+) membranous staining in IHC was seen. Fluorescence *in situ* hybridization analysis (FISH) was done in samples with moderate (2+) membranous staining in IHC and HER-2 status was accepted as 'positive' if FISH showed amplification [15]. Ki67 cut-off level was accepted as high if ≥15 [16].

A specialized breast pathologist evaluated pathological responses. All specimens of operated breast tissues were assessed microscopically to identify residual tumor. pCR was defined as no residual tumor cells or only a few scattered tumor cells (near pCR) in the breast or axillary nodes regardless of *in situ* carcinoma [17]. Pathological responses other than pCR were defined as incomplete response (non-pCR).

18F-FDG-PET/CT imaging

Patients fasted for at least 6 hrs and blood glucose level had to be <10 mmol/L. 18F-FDG (3.7 MBq/kg) was administered through the arm opposite to breast tumor using a venous line to prevent extravasation. Imaging started approximately 60 min after injection and was performed from mid-thigh level to the base of the skull with arms raised. An integrated PET/CT scanner (Discovery-16 LS, GE Healthcare, Wisconsin, USA) was used for imaging. CT data were acquired first (120 kV;20-120 mAs, determined automatically on the basis of attenuation). Only oral contrast agent was used. PET emission data were acquired in a 3-dimensional mode, with 3 min per bed position, and reconstructed using iterative reconstruction algorithm with 5 mm slice thickness. Attenuation-corrected images were normalized for injected dose and body weight, and subsequently converted into SUV, defined as: [tracer concentration (kBq/mL)]/ [injected activity (kBq)/patient body weight (g)]. 3D volume of interest (VOI) was automatically drawn around the primary tumor and around the axillary lymph nodes when present.

Assessment of tumor by metabolic response

A lesion with the highest initial uptake (either primary tumor or axillary lymph node) was considered as the target. SUVmax (maximum SUV value within the -VOI) was used for study analysis. Metabolic responses were evaluated by calculating relative changes [ΔSUVmax (%)] in SUVmax of the PET/CT before and after

NAC including both pCR and non-pCR patients [ΔSUV= relative value (%) in SUVmax = (post NAC SUVmax-pre NAC SUV)/ pre NAC SUVmax x100] [18].

Statistics

The statistical methods used were chi-square test for comparison of the categorical groups, with p values accepted as significant at p<0.05. Since there was no specific data on hormone-positive breast cancer regarding the consistency of SUVmax changes after completion of NAC and pCR rates, the cut-off point for SUVmax was accepted as 50%, depending on the previous data on triple-negative breast cancer [19].

All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software.

Results

Out of 51 patients, 48 had clinical disease stage III and 3 stage II. Their median age was 46 years (range 26-76). All patients were ER-positive, while 48 (94.1%) were PR-positive. HER-2 overexpression/amplification was positive in 20 (39.2%) patients (Table 1). The median follow-up time was 24 months (range 7-70). During this period, only one patient died and 7 patients relapsed (2 in the lung, 1 in the liver, 1 in the other breast, 1 in the bone, 1 with local and 1 both with local and bone disease). Median progression free survival (PFS) and overall survival (OS) have not been reached.

Only 7 (13.7%) patients had pCR among all eligible patients. More than 50% decrease in PET/CT evaluations has been observed in 40 (78.4%)

Table 1. Clinical and pathological characteristics of the patients (n=51)

Characteristics	*n*	*%*
Median age (years), n (range)	46 (26-76)	
Clinical stage		
II	3	5.8
III	48	94.2
Menopausal status		
Pre	28	54.9
Post	23	45.1
Localization		
Left	33	64.7
Right	18	35.3
Hormonal status		
ER +/-	51/0	100/0
PR +/-	48/3	94.1/5.9
HER-2neu +/-	20/31	39.2/60.8
Grade		
I	2	3.9
II	19	37.2
III	22	43.1
N/A	8	15.6
Ki67 (<15% / ≥15%/ NA) (at diagnosis)	8/39/4	15.6/ 76.4/ 7.8
Lymphatic/vascular/perineural invasion (L/V/P)	26/11/13	50.9/ 21.5/ 25.4
pCR		
(+)	8	15.7
(-)	43	84.3

n:number, ER:estrogen receptor, PR:progesterone receptor, NA: not applicable, pCR:pathological complete response

Table 2. Axilla-negative patients at baseline 18F-FDG-PET/CT evaluation (n=10)

Primary tumor(+) Axilla(-)		*Metabolic response in 18F-FDG-PET/CT*					
		>50%			*<50%*		
		pCR(+) (n=0)	*pCR(-) (n=6)*	*p*	*pCR(+) (n=1)*	*pCR(-) (n=3)*	*p*
Stage	II	0	2	NA	1	0	0.250
Stage	III	0	4		0	3	
HER-2	Positive	0	2	NA	1	0	0.500
HER-2	Negative	0	4		0	3	

HER-2: human epidermal growth factor receptor, pCR: pathological complete response, NA: not applicable

Table 3. Axilla and primary tumor positive patients at baseline 18F-FDG-PET/CT evaluation (n=40)

Primary tumor (+) Axilla (+)		*Metabolic response in 18F-FDG-PET/CT*					
		>50%			*<50%*		
		pCR(+) (n=6)	*pCR(-) (n=27)*	*p*	*pCR(+) (n=1)*	*pCR(-) (n=6)*	*p*
Stage	II	0	0	NA	0	0	NA
Stage	III	6	27		1	6	
HER-2	Positive	3	12	0.674	0	2	NA
HER-2	Negative	3	15		1	4	

For abbreviations see footnote of Table 2

patients [decrease in primary tumor (n=6), axillary nodes (n=1) and both primary tumor and axillary nodes (n=33)]. Of these 40 patients, 5 (12.5%) patients had pCR. The remaining 11 patients had <50% decrease in 18F-FDG-PET/CT SUVmax [decrease in primary tumor (n=4), both in the primary tumor and axillary nodes (n=7)] and 1 of these patients (9%) was found to have pCR (Tables 2 nad 3). No significant difference was noticed in achieving pCR between patients with >50% and <50% changes in SUVmax (p=1.00).

Among all eligible patients, 10 with no axillary disease (breast-only disease) at diagnosis achieved 10% pCR rate (6 had >50% decrease in SUVmax with no pCR, 4 had <50% decrease in SUVmax, but 1 achieved pCR) (Table 2). One patient had only axillary nodal disease at diagnosis and did not also achieve pCR. Forty patients had both primary tumor and axillary nodes at baseline with a pCR rate of 15% (Figure 1).

Thirty-nine percent of the patients (n=20) had >75% SUVmax changes and only 20% (n=4) of them achieved pCR. Similarly, 81% with complete metabolic response did not achieve pCR.

Lastly, the difference of the Ki67 levels before and after NAC, tumor localization (axilla and/or breast), menopausal status, grade of differentiation, HER-2 positivity, lymphovascular and perineural invasion were not found to be associated with pCR.

Discussion

NAC is the current treatment method in LABC, contributing to increased breast-conserving surgery rates, decreasing post-operative complications and facilitating radical postoperative radiotherapy [5,20,21]. The most appealing potential effect of NAC is to treat possible occult micrometastases earlier and to test for chemotherapy resistance post-operatively with pathological response evaluation [22,23]. Although pCR is not accepted as a surrogate endpoint of long-term outcomes, promising data exists on strong association of pCR with improved outcomes in more aggressive subtypes [24]. Despite the unsatisfactory pCR rates in hormone-positive LABC with current treatment modalities, imaging methods are emerging into clinical practice with the advantage of being non-invasive and offering early detection of the chemotherapy response. Predicting chemotherapy response with MRI evaluation

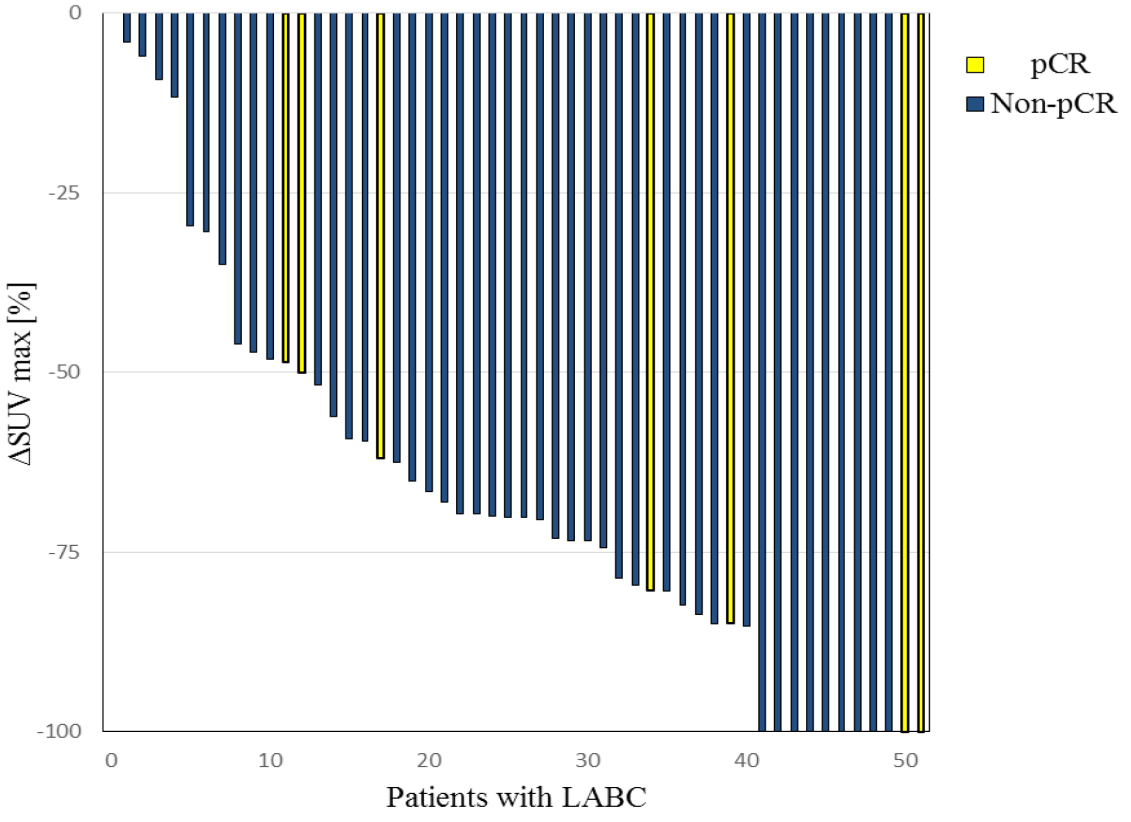

Figure 1. Changes in metabolic response in patients who achieved pathological complete response (pCR). Every single column represents one patient with hormone-positive LABC. Patients have been divided into 5 groups representing 0, 25, 50, 75 and 100% SUVmax changes in y-axis. Of 51 eligible patients 13.7% achieved pCR. There was no significant difference in pCR rates between the patients who had <50% and >50% SUVmax changes (p=1.00). Four patients (20%) who had >75% SUVmax change achieved pCR and this rate was similar to patients who had complete metabolic response (19%).

in breast cancer has been shown in previous studies [25,26]. However, conventional imaging modalities (mammography, ultrasound or MRI) were not shown to be effective in predicting pCR [27,28]. The reliability of 18F-FDG-PET/CT to detect the functional behavior of a tumor after NAC is superior to conventional imaging methods by measuring SUV values. On the other hand, higher baseline SUV values have been shown to have higher response rates to NAC compared to lower SUV values, aside from being a criterion to predict response to NAC [29]. Functional early response to NAC has been a popular research interest lately to take advantage of managing treatment earlier. Difference in 18F-FDG uptake of tumor between baseline and after 1 to 2 cycles of NAC has been calculated to understand if early response of tumor detected in 18F-FDG-PET/CT is predictive for pCR and found to be significant in most studies [18,30,31]. However, response evaluation after the first cycle of NAC resulted in lower accuracy for predicting tumor response than after several cycles of treatment. Since response to NAC in 18F-FDG-PET/CT investigated in previous studies had different inclusion criteria, imaging time and frequency, chemotherapeutic modalities and pathological scoring systems, the overall data is not clear for the emergence of early imaging by 18F-FDG-PET/CT to clinical practice yet [11-13, 29,30,32-34]. Given the fact that, evaluation at later cycles by imaging methods is occurring mostly in current clinical practice, there is a disadvantage of an increased toxicity and economic burden of chemotherapy for the non-responding subgroup [32,33].

Based on these data, this is the first study in hormone-positive LABC to evaluate the 18F-FDG-PET/CT response and pCR consistency by detecting the difference between SUV values measured at baseline and after completion of chemotherapy at later cycles (4-8 cycles) instead of early cycles [35,36]. Although pCR rates to NAC are known to be lower in hormone-positive LABC (2-10%) compared to other subtypes [37], our study included a homogeneous group treated with current chemotherapy regimens to evaluate NAC response by 18F-FDG-PET/CT.

Patients with breast-only disease might be assumed to have less aggressive tumor, with lower response to NAC and lower pCR rate expectations in hormone-positive LABC [38]. Similar to previous reports, none of our patients with breast-only disease achieved pCR. Sixty percent of breast-only disease patients had higher (≥50%) metabolic response rate in the functional imaging that was not associated with pCR. In addition, having higher stages (40%) didn't affect this result. This data still may guide further studies to select better candidates for breast-conserving surgery in hormone-positive breast cancer since they have higher metabolic response. The remaining 40% of the patients with breast-only disease had <50% metabolic response and achieved 25% pCR rate. In contrast to higher metabolic response rates, patients with lower response rates achieved better pCR rates (25%) and this raises the question if a subgroup of patients may still benefit from metabolic response imaging regardless of SUVmax changes. In this study, patients who had >50% (n=40) and <50% (n=11) SUVmax changes were not associated with pCR rates (15% and 18% respectively) (p=1.00). Interestingly, almost 40% of the patients had >75% SUVmax changes, but out of these only 20% could achieve pCR. Moreover, patients with complete metabolic response (100%) achieved only 19% pCR rates, questioning if higher magnitude of SUVmax changes may not reflect the pCR rates in hormone-positive LABC. This discordance in metabolic and pathological response rates may be due to decreased or loss of FDG avidity as tumor size decreases. However, the lesion may still have activity that cannot be detected by FDG-PET/CT and result in non-pCR at the end.

In this study, out of 51 patients, 7 (13.7%) had pCR which is higher than the rates reported in the previous studies [37]. This discordance may be related to the addition of trastuzumab in the last years in our country, resulting in a higher percentage of pCR in our study. In addition, previous studies are either heterogeneous or lack data for reliable comparisons to clarify the increased rate of response to therapy in HER-2 positive tumors [39]. In this study, out of 40 patients who had both positive axilla and primary tumor at baseline imaging, 17.6% achieved pCR in the HER-2 positive subgroup and 13% achieved pCR in the HER-2 negative subgroup supporting the fact that the HER-2 positivity managed with current treatment modalities including trastuzumab may not affect the pCR rate in hormone-positive breast cancer. However, the low number of patients limits the reliability of the data. This foresight may be a backbone for future studies that will explore the predictability of 18F-FDG-PET/CT response rates for pCR in HER-2 positive subgroup of hormone-positive LABC and detect if these tumors are more sensitive to NAC than HER-2 negative hormone-positive group.

In conclusion, this was the first study to show the discordance between metabolic response and pCR in hormone-positive LABC patients in the later cycles of chemotherapy (as commonly practised in

medical oncology clinics) rather than in the earlier cycles. Furthermore, complete response rates detected by 18F-FDG-PET/CT may not result in pCR in patients who received NAC. However, if higher metabolic response on imaging is due to shrinkage of the tumor after NAC, 18F-FDG-PET/CT may still have an impact on increasing conservative surgery rates with less morbidity advantage, resulting in a need for cost-effective analysis. The low number of patients limited reaching statistically significant results in this pilot study, but this data may lead to larger studies investigating the predictability of pCR by 18F-FDG-PET/CT studies in different LABC subgroups. Given the fact that chemotherapy is less effective in this subgroup, anti-hormonal and/or novel targeted therapy approaches for neoadjuvant treatment for higher stages are needed [37,40]. Recently, endocrine treatment has been shown to be effective, especially in low-risk hormone-positive tumors [41]. Endocrine treatment in the neoadjuvant setting may be a standard treatment option in particular groups of patients, like low-risk hormone-sensitive, that may affect the results of both 18F-FDG-PET/CT responses and pCR rates in future studies.

Ethics approval and consent to participate

Institutional Review Board at Marmara University School of Medicine in Istanbul, Turkey (70737436-050.06.04-). Informed consent was waived since the trial included retrospective data analysis.

Authors' contributions

Conceived the study, participated in the design, and drafted the manuscript: PFY,SK, BA and **FD. *Performed the research:* SK, ETS, MAO, HK, UU, ZO, SH, RH, OA, NAB, OE. *Analyzed the data:* MG, BA, SK and FD*. All authors played a significant role in the acquisition and interpretation of data, and revised the manuscript critically for important intellectual content. All authors played a role in study design or acquisition of data, and all participated in manuscript composition or revision. All authors read and approved the final manuscript (*Dane F, **Dede F).

Disclosure

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Conflict of interests

The authors declare no confict of interests.

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