The effect of preoperative 18f Fdg-Pet on staging and treatment protocols in breast cancer patients

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The effect of preoperative 18f Fdg-Pet on staging and treatment protocols in breast cancer patients

AIM: *We aimed to evaluate the effect of PET taken before surgery on the treatment protocol in patients diagnosed with BC and whether PET resulted in changes in the disease stage.*
MATERIAL AND METHODS: *BC patients in our hospital who underwent surgery between 2016–2020 were retrospectively analyzed. The effect of preoperative PET on the treatment protocol was evaluated in all. Patients were divided into subgroups depending on whether they underwent direct surgery without CTX or were operated on after CTX initiation. In addition, in the group that did not receive CTX, axillary findings of PET were compared with postoperative histopathological results, and axillary PPV, NPV, sensitivity and specificity of PET were determined. In this subgroup, the preoperative PET stage was compared with the postoperative histopathological stage, and any changes in the disease stage were compared.*
RESULTS: *In our study, PET affected the treatment protocol of 19 patients (20%). PET resulted in staging differences in 57.6% overall, increased staging in four patients (8.8%) who did not receive early-stage CT, and lower staging in 22 (48.8%) patients in the group. In early-stage BC of PET, the PPV for axilla was 81.2%, the NPV was 65.5%, sensitivity was 56.5%, and specificity was 86.3%.*
DISCUSSION: *Although PET has many limitations, the determination of the size of the primary tumor and the multiple foci at different locations according to PET findings helped us to easily determine the treatment protocol for patients planned for BCS.*
CONCLUSION: *The preoperative routine use of PET, which can provide more information about metastasis and stage than other methods in patients undergoing BC surgery, may improve the management of treatment in these patients.*

KEY WORDS: Breast cancer, 18F FDG-PET/CT, Chemotherapy, Staging

Introduction

Breast cancer (BC) is the most common cancer and the second most common cause of cancer death in women in Worldwide; one in eight women will develop BC in the course of their life [1,2]. After BC is diagnosed, determining the scope of the disease is one of the most important points in determining the treatment protocol. While breast ultrasound (USG), mammography (MM) and breast magnetic resonance imaging (MRI) are used to detect the local spread of the disease, imaging techniques such as X-ray examinations, USG, computed tomography (CT), and MRI are used to determine the presence. These imaging methods have an important place in the staging, restaging and planning the treatment for the disease [3]. While the cancer focus detection rate is 30-40% with conventional imaging methods, the primary focus in autopsy series has been determined as 50-75% [4]. In

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ABBREVIATIONS

BC: Breast Cancer
PET/CT: 18F FDG-PET/BT
PPV: Positive predictive value
NPV: Negative predictive value
CTX: Chemotherapy
USG: Ultrasonography
MM: Mammography
MRI: Magnetic Resonance Imaging
CT: Computed Tomography
SLNB: Sentinel Lymph Node Biopsy
FDG: Flurodeoksiglukoz
ER: Estrogen Receptor
PR: Progesterone Receptor
BCS: Breast Conserving Surgery
ALND: Axillary Lymph Node Dissection
MRM: Modified Radical Mastectomy
SM: Simple Mastectomy
SUV: Standardized Uptake Value

cancers where the primary cancer focus has been investigated in cancers with unknown primary, cancer focus is determined by PET at the rate of 23-73% [5].
Determining the status of the axillary lymph node is one of the most important prognostic factors in female breast cancer. The number of metastatic lymph nodes significantly contributes to the decision of adjuvant systemic therapy [6]. Correct staging is very important in BC treatment planning. Among the radiological examinations used for staging, breast MRI and PET are not routinely recommended for the initial staging of BC [7]. The use of PET is less effective in early-stage BC due to lower levels of glycolysis at this stage, and is not routinely recommended for this reason; yet the literature includes studies stating that it may be clinically useful. Compared to sentinel lymph node biopsy (SLNB) and PET for axillary metastasis assessment, the sensitivity of PET is lower, below 70%. The most important reason for this is that the size of the clinically appearing axillary lymph node is generally below 1 cm. Naturally, PET cannot replace a pathological examination, but some publications suggest that PET can be useful in detecting axillary disease in BC [8]. While the sensitivity of PET is 57% for tumors less than 1 cm in diameter, this ratio exceeds 90% above 1 cm. Fluorodeoxyglucose (FDG) uptake in BC depends on tumor receptor status, grade, and histologic type. In grade 3 estrogen receptor (ER)-positive tumors, FDG uptake is higher than in grade 1 tumors that are ER-negative. In the National Comprehensive Cancer Network Guidelines 2019 update, BC is allowed as an option in response to treatment, in detecting regional lymph node and distant metastasis, and in the initial staging of local advanced disease [9]. However, PET may affect the surgical approach due to high PPV (95.8%) in BC patients [10].
In this study, we aimed to evaluate the effect of PET taken before surgery on the treatment protocol of patients diagnosed with BC. In addition, we sought to determine the PPV, NPV, sensitivity and specificity of PET for axillary metastasis in early-stage BC and to evaluate whether PET resulted in changes in disease staging in this subgroup.

Materials and Methods

BC patients who underwent surgery at the Gaziantep Dr. Ersin Arslan Education Research Hospital between 2016 and 2020 were retrospectively screened. Patients' age, tumor localization, types of surgery performed (breast-conserving surgery (BCS) / mastectomy ± SLNB ± axillary lymph node dissection (ALND)), tumor markers examined in the preoperative period (carcinoembryonic antigen (CEA), carcinoma antigen (CA) 15-3, or CA 125) and pathology reports, tumor types, tumor sizes, and immunohistochemical parameters (Cerb-B2, estrogen receptor (ER), progesterone receptor (PR), ki-67) were recorded. PETs of the patients in the study were evaluated, and stage, primary tumor diameter and focal number, primary tumor and axillary standard uptake value (SUV) values were recorded.
Patients who underwent PET before surgery were included in the study; those diagnosed with excisional biopsy instead of trucut were excluded from the study, as were patients who received CTX for any reason prior to PET extraction and patients whose data were not fully available. According to the treatment plan, patients who had undergone direct surgery without CTX and had undergone surgery after CTX were re-evaluated.
Comparisons were made between groups in terms of age, tumor localization, types of surgery performed, tumor types, tumor markers, and immunohistochemical parameters. The effect of preoperative PET on the treatment protocol in all patients in the study was evaluated by comparing it with breast USG, MM, and clinical findings . In addition, the axillary PPV, NPV, sensitivity and specificity of PET were determined by comparing the axillary findings of PET with postoperative histopathological results in non-CTX patients. In this subgroup, the preoperative PET stage was compared with the postoperative histopathological stage, and it was evaluated whether there was any change in the disease stage.
In statistical analysis, quantitative variables are expressed as mean ± SD, median, min-max, and interval.
Qualitative variables are reported as numbers and percentages (%). The Shapiro-Wilk test was used to understand homogeneous and heterogeneous distribution. While means and SDs are used for homogenous distributions, median and interval values are given for het-

Table I - *Patient and tumor features*

		CTX not receiving 45 (%47.4)	CTX users 50 (%52.6)		Total 95
The average age		50,6	50,9		50.7 ± 12,9
Tumor localization	Right	21	24		45 (%47.4)
	Left	24	26		50 (%52.6)
Operation					
MRM		13 (%35.5)	38 (%74.5)		51 (%53.6)
BCS + SLNB ± ALND		20 (%100)	-		20 (%21)
SM + SLNB ± ALND		12 (%100)	-		12 (%12.6)
SM			12 (%100)		12 (%12.6)
Pathological diagnosis					
Invasive ductal carcinoma		42	45		87 (%91.6)
Mucinous carcinoma		2	1		3 (%3.1)
Invasive ductal + lobular carcinoma			2		2 (%2.1)
Malign epithelial tumor			2		2 (%2.1
Invasive lobular carcinoma		1			1 (%1)
Immunohistochemical features					
Cerb-B2+		16 (%51.6)	15 (%48.4)	P>0,05	31/91 (%34)
Hormone Receptor ER+		32 (%47)	36 (%53)	P>0,05	68/93 (%73.1)
PR+		33 (%48)	36 (%52)	P>0,05	69/93 (%74.1)
ER and PR+		36 (%54.5)	30 (%45.5)	P<0,05	66/93(%70.9)
Triple-		3 (%33.3)	6 (%66.6)	P<0,05	9/91 (%9,9)
Ki67	<20	15 (%48.4)	16 (%51.6)	P>0,05	31/74 (%41.8)
	20	23 (%43.5)	20 (%46.5)	P>0,05	43/74 (%58)
Tumor Markers					
ca 15-3 (0-25 U/ml)		7 (%27)	19 (%73)	P<0,05	26/85(%30.5)
cea (0-5,5 ng/ml)		1 (%16.7)	5 (%83.3)	P<0,05	6/60 (%10)
ca 125 (0-35 U/ml)		1(%33.3)	2 (%66.7)	P>0,05	3/48 (%6.2)
Spesmen median primary tumor size (cm)		2,5 (1-4,5)			

erogeneous distributions. Fisher's Chi-Square test was used to compare qualitative variables, the Mann-Whitney U test was used for heterogeneous distributions and Student's t test was used for homogeneous distributions. P values below 0.05 were considered statistically significant.

Ethics committee approval is attached.

Results

All 95 patients participating in the study were female, with a mean age of 50.7 ± 12.9 years. All BC cases were unilateral; 45 (47.4%) were on the right and 50 (52.6%) were on the left breast. There were 50 (52.6%) patients in the group who received CTX after PET, and 45 (47.4%) patients in the non-CTX group. Modified radical mastectomy (MRM) was performed in 51 patients (53.6%), BCS + SLNB ± ALND in 20 (21%), simple mastectomy (SM) + SLNB ± ALND in 12 (12.6%), and 12 (12.6%) had SM only. All patients who underwent BCS were in the non-CTX group. SM-only patients were all in the group receiving CTX, and all were performed for palliative/wound control purposes. Tumor markers could not be examined in all patients, and the positivity rates in the patients examined were 30.5% (26/85), 10% (6/60), and 6.2% (3/48) for CA15-3, CEA and CA125, respectively. All of the markers were higher in the group receiving CTX; these elevations were found to be significant (P <0.05) for CA15-3 and CEA. Among the pathological diagnoses, invasive ductal carcinoma was the most common in both groups (N=87, 91.6%). There were very few patients who did not have immunohistochemical parameters evaluated; positivity rates were 34% (31/91), 73.1 (68/93), and 74.1 (69/93) for Cerb-B2, ER, and PR, respectively, and there was no significant difference between the groups. While 70.9% of patients (66/93) had both ER and PR positivity, triple negativity was found in 9.9% (9/91). While ER + PR positivity was higher in the group who did not receive CTX, triple negativity was higher in the group receiving CTX (p <0.05). The Ki-67 value was <20 in 41.8% (31/74) of patients and ≥20 in 58% (43/74); there was no significant difference between groups. The median histopathological tumor diameter in the non-CTX group was 2.5 (1-4.5) cm (Table I).

In preoperative staging performed with PET, the rates of Stage 0, Stage 1, Stage 2, Stage 3 and Stage 4 patients were 2.1%, 18.9%, 30.4%, 30.4%, and 17.8%, respectively. According to the PET findings, primary tumor focus could not be detected in two (2.1%) patients, whereas 66 patients (69.4%) had a single primary and

TABLE II - *18F-FDG PET / CT findings*

		CTX not receiving 45 (%47.4)	CTX users 50 (%52.6)	Total 95
Stage	0	2		2 (%2.1)
Stage	1	18		18 (%18.9)
Stage	2A	13	1	14 (%14.7)
	2B	12	3	15 (%15.7)
Stage	3A		15	15 (%15.7)
	3B		12	12 (%12.6)
	3C		2	2 (%2.1)
Stage	4		17	17 (%17.8)
Median axilla SUV		0 (0-11)	5 (0-30)	2,7 (0-30)
Median primary tumor SUV		6,1 (0-18,1)	10,3 (3,5-54,4)	8,3 (0-54,4)
Median primary tumor size (cm)		2,1 (0-4,7)	3,2 (0,7-10,7)	2,6 (0-10,7)
BC focus count	0	2 (%100)		2 (%2.1)
	1	37 (%56)	29 (%44)	66 (%69.4)
	> 1	6 (%22.2)	21 (%77.8)	27 (%28.5)

27 (28.5%) had more than one. Of the multifocal patients, 21 (77.8%) were in the group receiving CTX, and six (22.2%) were in the other group. The median primary tumor SUV level in PET was 8.3 (0–54.4) in all patients and was 10.3 (3.5–54.4) and 6.1 (0–18.1) in the groups with and without CTX, respectively. The median axilla SUV level was 2.7 (0–30) in all patients, and it was determined to be 5.0 (0–30) and 0 (0–11) in the groups with and without CTX, respectively. According to PET, the median primary tumor diameter was 3.2 (0.7-10.7) and 2.1 (0-4.7) cm, respectively, in the groups with and without CTX (Table II).

In our study, distant metastases of 17 patients in the group receiving CTX were determined by PET. In this group, four patients who were at an early stage compared to PET; MM, breast USG and clinical findings were accepted as local advanced stage. In four of our patients, high FDG involvement was observed in thyroid, obturator muscle, mediastinum, and false pelvis. PET could not detect the tumor in two patients in the group who did not receive CTX.

In our study, treatment management of 19 (20%) patients changed on the occasion of PET. Since the presence of axillary metastasis in eight patients in the non-CTX group was also supported by clinical observation , direct ALND was performed; as four patients showed multifocal involvement in different quadrants, SM + SLNB ± ALND was planned instead of BCS, for a total of changes in treatment in 12 non-CTX patients. Seven of the 33 locally advanced patients in the group receiving CTX had changes in treatment due to findings that were not detected in USG and MM (skin involvement in two patients and N2 lymph node in five patients); these patients underwent surgery after neoadjuvant CTX.

In the comparison of PET axilla findings and postoperative histopathological findings of patients in the group who did not receive CTX, in the pathological evaluation, it was found that while the axillary lymph node was positive in 23 patients, PET was able to detect 13, it was false positive in three patients, and false negative in 10 patients. In this group, PET's PPV for axilla was 81.2%, NPV was 65.5%, sensitivity was 56.5% and specificity was 86.3%. Again, when comparing histopathological stage with PET in this group, a staging difference was found in 57.6% of the patients, namely overstaging in four (8.8%) patients and understaging in 22 (48.8%) patients.

Discussion

The incidence and death rates of BC increase with age, and about 95% of new cases occur in women aged 40 years and over [11]. The average age of our patients was 50.7 ± 12.9 years. Invasive ductal carcinoma constitutes 75–80% of primary breast malignancies and invasive lobular carcinoma 10–15% [9]; invasive ductal carcinoma was detected in 91.6% of our patients and was the most common histological subtype in both groups. The determination of ER, PR, CA15-3, CA125 and CEA levels can guide diagnosis and treatment while evaluating the prognosis of BC [12,13]. A study conducted in 743,623 women of reproductive age investigated the relationship between immunohistochemical parameters and BC cases, and reported that 8203 and 645 patients with ER-positive and triple-negative BC were detected, respectively [11]. In our study, the incidence rate among patients whose tumor markers were examined was 30.5%, 10%, and 6.2% for CA15-3, CEA and CA125, respectively, and 68 patients were ER+, while 9 patients had triple-negative BC.

MM, breast USG, and breast MRI are frequently used in the diagnosis of primary lesions and in detecting possible metastases in the axillary region in patients with

BC. According to the guidelines, bone scintigraphy, abdominal and/or pelvic CT, USG, and MRI are used in the staging of the disease [14]. Because PET has a low sensitivity for micrometastases, it is not yet recommended for detection of primary BC or for use as a standard tool in the evaluation of axillary lymph nodes in early-stage BC [15]. FDG uptake level in BC may vary depending on tumor type, location, phenotype, grade, and Ki-67 proliferation index [16]. Evaluation of the axillary lymph node status is very important to determining additional treatment after surgery [17]. A review has reported that positive axillary PET is a good indicator for evaluating axillary propagation [18], and some publications postulate that PET may replace SLNB in the future [19-21]. When PET detect metastatic axillary lymph node, it is said that direct axillary dissection can be performed without SLNB[22]. The accuracy rate of USG in detecting axillary metastasis is 78.8% while that of PET is 76.4%; this rate increases to 91.6% when the two methods are combined [23]. In a study comparing clinical examination and PET, there was up-staging in 35 patients and down-staging in 5 patients, and this was detected with a positive accuracy of 86% by pathological examination [24]. Another study reported that PET may result in upstaging by 9-30% of patients with BC [25]. Another study in 61 patients found the high specificity and positive prediction accuracy of PET/CT to be 79% [26]. In a review on PET sensitivity and specificity, these rates were found to be 63% (20–100%) and 94% (75–100%), respectively. The high value range obtained from different studies may be attributable to the differences in PET imaging methods and interpretation variables in study populations [27]. In our study, the sensitivity of PET/CT for the axilla was 56.5%, the specificity was 86.3%, the PPV was 81.2%, and the NPV was 65.5% in patients who did not receive CTX.

In a prospective study examining 160 BC patients, PET changed the clinical stage in 36% of patients (28% lower staging; 8% upper staging), and 58% had changed treatment [28]. In another study conducted with patients with BC of stages 2-4, 21% of patients have been found stage increased and 16% have been found stage lower due to PET; It has been reported that PET affects the treatment plan to a moderate or high degree in 13% of patients [29]. In our study, 45 early-stage patients (57.6%) had different staging (8.8% higher staging, 48.8% lower staging) resulting from PET. Treatment management of a total of 19 patients (20%) was altered by PET (12 in the group without CTX, 7 in the group receiving CTX).

PET is reported to be highly specific and sensitive compared to other methods in detecting extra axillary metastases [30]. PET / CT contributes to the detection of not only axillary but also internal mammarial and mediastinal lymph nodes [22]. In our study, distant metastases were determined by PET in 17 patients in the CTX group. There are various limitations in the use of PET. One of them is that FDG, which has proven superiority in marking cancer tissue, is also retained by other tissues with high metabolic activity, including those that show active and chronic active inflammation. On the other hand, FDG uptake by cancers that do not have very high metabolic activity may not be sufficient [31]. In four of our patients, high FDG involvement was observed in thyroid, obturator muscle, mediastinal and pelvic tissue, which were confirmed to be benign via MRI, CT and biopsies, having caused unnecessary further examination. Four patients who were at an early stage compared to PET in the CTX group but were detected by MM, breast USG and clinical findings (skin involvement and N2 axillary lymph node) were accepted locally and underwent surgery after neoadjuvant CTX. Some publications have reported that T1 tumors are below the sensitivity/resolution threshold of current PET technology [31]. In our study, PET could not detect T1 (1 and 1.5 cm) tumors in two patients in the group who did not receive CT. Despite these limitations, the determination of the size of the primary tumor and the multiple foci at different locations according to PET findings helped us to easily determine the treatment protocol for patients planned for BCS.

Conclusion

Surgery remains the most effective treatment in breast cancer, but the surgeon must know about the patient's stage in the preoperative period. Routine preoperative use of PET, which can provide more information about metastasis and stage than other methods in patients undergoing breast cancer surgery, may positively affect treatment management.

Riassunto

Lo studio è finalizzato a valutare l'effetto della PET preoperatoria sul protocollo di trattamento nelle pazienti affetta da cancro mammario e se la PET ha comportato variazioni nell'evoluzione della malattia. Sono state analizzate retrospettivamente le pazienti affetta da cancro della mammella e trattate chirurgicamente nel nostro ospedale tra il 2016-2020, valutando in tutte l'effetto degli esiti della PET sul protocollo di trattamento. Le pazienti sono state divise in due sottogruppi a seconda che fossero state sottoposte a intervento chirurgico senza preliminare CTX o dopo essere state sottoposte a questa indagine.

Inoltre nel gruppo senza CTX preoperatoria i risultati della PET a livello ascellare sono stati confrontati con i reperti istopatologici postoperatori, determinando PPV e NPV, sensibilità e specificità della PET.

In questo sottogruppo, il referto della PET preoperatoria è stata confrontata con quello istopatologico postop-

eratorio e sono stati confrontati eventuali cambiamenti nello sviluppo della malattia.
In questo nostro studio, la PET ha influenzato il protocollo di trattamento di 19 pazienti (20%). La PET ha portato a differenze di stadiazione complessive del 57,6%, con un incremento di stadio in quattro pazienti (8,8%) non sottoposte a TC in fase iniziale e una riduzione di stadio in 22 (48,8%) pazienti del gruppo.
In early-stage BC of PET, the PPV for axilla was 81.2%, the NPV was 65.5%, sensitivity was 56.5%, and specificity was 86.3%.
Sebbene la PET abbia molte limitazioni, la determinazione della dimensione del tumore primario e dei focolai multipli in diverse posizioni in base ai risultati della PET ci ha aiutato a determinare facilmente il protocollo di trattamento per le pazienti destinate alla chirurgia conservativa. L'uso preoperatorio di routine della PET, può fornire più informazioni sulle metastasi e sullo stadio rispetto ad altri metodi nei pazienti sottoposti a chirurgia BC, può migliorare la gestione del trattamento in questi pazienti..

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