



# The Relationship between Pathological Features and $^{18}\text{F}$ -FDG PET/CT that Changed the Surgeon's Decision as Neoadjuvant Therapy in Breast Cancer

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## Abstract

**Objective** Patients diagnosed with breast cancer and decided to undergo surgical treatment can undergo neoadjuvant therapy following their 2-deoxy-2-[fluorine-18] fluoro-D-glucose positron emission tomography/computed tomography ( $^{18}\text{F}$ -FDG PET/CT) findings. The present study aims to determine the statistical significance of these patients whose treatment plan was changed and the reasons for the change in the plan.

**Materials and Methods** The demographic features and treatment plans of 151 cases who were diagnosed with any stage of breast cancer were evaluated. These patients consist of those who admitted to Mersin University Hospital Breast Outpatient Clinic between January 2016 and December 2019. All of these patients aged between 41 and 85 years were examined with  $^{18}\text{F}$ -FDG PET/CT after the decision for surgical treatment is made. The analysis included tumor pathology, side, type, subtype, size, and centrality in this study.

**Results** About 18.5% ( $n = 28$ ) of patients' treatment plan was changed after  $^{18}\text{F}$ -FDG PET/CT. They received neoadjuvant therapy. About 81.5% ( $n = 123$ ) of patients did not receive neoadjuvant therapy. Significant differences were observed between patients changed treatment plan and not changed concerning age, lymph node involvement, tumor size, centrality, and subtypes parameters.

**Conclusion** Conventional imaging examinations are used in patients with breast cancer. These examinations may not be sufficient to determine advanced disease requiring neoadjuvant treatment. With  $^{18}\text{F}$ -FDG PET/CT examination, these advanced stage patients are not overlooked. In our study, approximately one in five patients, treatment plan changed after  $^{18}\text{F}$ -FDG PET/CT examination.

## Keywords

- ▶ breast cancer
- ▶ PET
- ▶ subtype
- ▶ neoadjuvant

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## Introduction

Breast cancer is one of the diseases that may cause death in women. In the United States, there are 240,000 new cases per year, and approximately 40,000 patients have breast cancer-related deaths. One in eight women face breast cancer throughout their lifespan.<sup>1</sup> The disease was diagnosed with conventional techniques, such as ultrasonography (USG), mammography, and computerized tomography (CT). <sup>18</sup>F Fluorodeoxyglucose positron emission tomography/computed tomography (<sup>18</sup>F-FDG PET/CT) was mostly used to determine the treatment method of the disease.<sup>2</sup> Studies have revealed that <sup>18</sup>F-FDG PET/CT is effective in breast cancer treatment management and disease staging.<sup>3</sup> <sup>18</sup>F-FDG PET/CT has not been found effective in early-stage breast cancer (stage I–II).<sup>4</sup> In previous studies, <sup>18</sup>F-FDG PET/CT staging and CT and USG staging are compared. <sup>18</sup>F-FDG PET/CT cannot completely replace USG and CT due to inadequate sensitivity.<sup>5</sup> According to the European Society for Medical Oncology (ESMO) guidelines, clinically positive lymph node, tumor size of 5 cm and more, aggressive tumor biology, and clinical findings to suggest metastasis are indications for CT, USG, magnetic resonance, and bone scintigraphy examinations. If sufficient results cannot be obtained from these tests, <sup>18</sup>F-FDG PET/CT is applied, which is a low level of evidence.<sup>6</sup> Patients may not receive appropriate treatment when <sup>18</sup>F-FDG PET/CT is not performed. In our study, we collected data to find out number of these patients. As with all other treatments, it was aimed to provide the patients with the most benefit and do the least harm surgically. The known benefits of preoperative staging for patients enable neoadjuvant therapy and operation to be performed at the most convenient time, preventing possible complications in patients and reducing morbidity. For example, it is challenging to fight lymphedema developing after axillary lymph node dissection. In addition, arm, shoulder pain, nerve damage, hematoma, and shoulder motion limitation deteriorating quality of life and increasing morbidity.<sup>7</sup> <sup>18</sup>F-FDG PET/CT helps make neoadjuvant treatment decisions by medical oncologists, but it is controversial whether <sup>18</sup>F-FDG PET/CT guides for excision width, sentinel lymph node, and the need for axillary dissection for surgical oncologists.<sup>8,9</sup> In locally advanced breast cancer cases, neoadjuvant therapy is administered for breast-conserving surgery and to enable less resection for patients requiring extensive resection. It also aims to control the disease before surgery for hormone receptor-positive patients. It is definitely the primary treatment for advanced-stage patients with distant metastasis.<sup>10</sup>

In our study, we aimed to investigate to what extent the treatment plan of these patients has changed after <sup>18</sup>F PET/CT in patients who have been diagnosed with breast cancer and whose surgery decision has been made, and the reasons for this change.

## Materials and Methods

All cases ( $n = 151$ ) with <sup>18</sup>F-FDG PET/CT examination were included in this study. These female patients were between

41 and 85 years of age. Patients were decided to undergo surgery treatment by a surgeon before <sup>18</sup>F-FDG PET/CT examination. These patients were diagnosed with breast cancer and admitted to Mersin University Hospital Breast Outpatient Clinic between January 2016 and December 2019. Our surgical treatment criteria were as follows: patients who were not locally advanced (T1 or T2 lesions), patients who were planned for breast-conserving surgery with a low tumor/breast ratio, patients with T3-T4 lesions, and planned modified radical mastectomy patients without chronic disease for which surgical treatment was contraindicated. Sentinel lymph node biopsy was performed in all patients. Patients with positive lymph nodes underwent axillary dissection, regardless of neoadjuvant therapy. Demographic features of these patients and whether they received neoadjuvant therapy were evaluated. Pathology results of the patients, tumor size, type, subtypes, side of the disease, and centrality were evaluated within the variables. In addition, lesion maximum standard uptake value (SUVmax), axilla <sup>18</sup>F-FDG PET/CT involvement, axilla SUVmax and distant metastasis findings were recorded, sentinel lymph node involvement was also evaluated.

Normality controls of continuous measurements were tested using the Shapiro–Wilk test. Mann–Whitney U test was used for group comparisons of continuous measurements. Minimum, maximum, median, and 25 to 75% were given as descriptive statistics for lesion size and SUVmax level, axilla SUVmax level, and K<sub>i</sub> 67 parameters. Pearson chi-squared and likelihood ratio chi-squared tests were used for the differences between categorical variables. Number and percentage values were given as descriptive statistics. Statistical significance was taken as  $p < 0.05$ .

## Results

The direction, centrality, axillary involvement in <sup>18</sup>F-FDG PET/CT, presence of distant metastasis, and neoadjuvant status in current patients are shown in ►Table 1.

The average age of 151 patients included in this study was calculated as  $57.6 \pm 11.4$ . One-hundred twenty-three (81.5%) of these patients did not receive neoadjuvant therapy and 28 (18.5%) received neoadjuvant therapy. It was determined by <sup>18</sup>F-FDG PET/CT examination. The lymph nodes present in the axilla before neoadjuvant treatment were not seen in 14% of the patients ( $n: 5$ ) during the surgery performed after the treatment. These patients were protected from undesirable effects by axillary dissection. Complete response was seen with neoadjuvant therapy in 10% ( $n: 3$ ) patients and these patients were not operated on. One patient (3.5%) died during the neoadjuvant treatment phase. Accordingly, <sup>18</sup>F-FDG PET/CT was performed on patients who were decided to undergo surgical treatment, and the treatment plan changed to neoadjuvant therapy in 18% of patients. When the groups with and without neoadjuvant treatment were examined concerning average age, there was a statistically significant difference between them ( $p = 0.001$ ). The average age of the treated group was  $51.5 \pm 9.6$ , and the average age of the nontreated group was  $59.0 \pm 11.3$ .

**Table 1** Features of patients

	Feature	n = 151	%
Side of tumor	Right	67	44.4
	Left	75	49.7
	Bilateral	9	6.0
Centricity	Unicentric	103	68.7
	Multicentric	47	31.3
Involvement axilla in PET/CT	No	76	50.3
	Yes	70	46.4
	Uncertain	5	3.3
Distant metastasis	No	128	84.8
	Yes	23	15.2
Neoadjuvant therapy	No	123	81.5
	Yes	28	18.5

Abbreviation: PET/CT, positron emission tomography/computed tomography.

The mean age of the patients who received neoadjuvant therapy by changing the treatment plan was significantly lower (→ **Table 2**).

The differences between those who received and did not receive neoadjuvant therapy concerning continuous parameters are given in → **Table 3**. When → **Table 3** was examined, differences were found significant regarding lesion size and axilla SUVmax parameters ( $p < 0.0001$  and  $p = 0.010$ , respectively). In patients who were decided to receive neoadjuvant therapy by changing the treatment plan after  $^{18}\text{F}$ -FDG PET/CT, SUVmax values of the lymph nodes involved in the axilla of these patients were significantly higher in  $^{18}\text{F}$ -FDG PET/CT. There was no significant difference in  $K_i$ -67 percentages (→ **Table 3**).

No significant relationship was found between the disease on the right, left or bilateral breast and patients whose treatment plan was changed. There was no significant difference concerning the pathological type of the tumor. In most cases, the pathology was reported as nonspecific type invasive ductal carcinoma (82.1%). Four percent were lobular carcinomas. There was no difference in terms of the tumor as ductal or lobular and other types of ductal carcinoma as papillary, medullary, mucinous, tubular, and cribriform. However, a difference was found regarding subtypes.

When the subtypes of luminal A, luminal B, Her 2 Neu, and triple negative were compared among themselves, the subtype of the lesion was significantly higher as luminal A and B in patients who were decided to treat using neoadjuvant therapy. The breast lesions of these patients, which were decided to have an operation, were multicentric. While breast-conserving surgery and sentinel lymph node excision

were planned for other patients, mastectomy was recommended for these patients (31.3%), whose mass was multicentric. Treatment plan changes were significantly associated with being multicentric. In  $^{18}\text{F}$ -FDG PET/CT, lymph node involvement in the axilla or out of axilla was significantly higher in cases where neoadjuvant treatment decision was taken. There was also a significant correlation with sentinel lymph node positivity. Distant metastasis in patients was significantly higher in cases where neoadjuvant treatment decision was taken. There was no significant relationship between E-cadherin or pancreatin staining in tumor cells and treatment change (→ **Table 4**).

### Discussion

With  $^{18}\text{F}$ -FDG PET/CT examination important advantages are provided concerning treatment planning in breast cancer patients. Distant metastases and axillary involvement are some of them. In the review of Bahl et al, it was emphasized that patients were saved from many invasive procedures with the measurements obtained with  $^{18}\text{F}$ -FDG PET/CT. An example of this is determining the stage of the patient more clearly with the detection of axillary involvement or distant metastasis and changing the treatment plan accordingly.<sup>11</sup> In our study, distant metastasis and axillary involvement were more common in patients whose treatment plan was changed after  $^{18}\text{F}$ -FDG PET/CT examination, as a significant difference. SUVmax values of the lymph nodes involved in the axilla were significantly higher in patients who had a neoadjuvant treatment decision.  $^{18}\text{F}$ -FDG PET/CT also shows

**Table 2** Age of patients

	Neoadjuvant	n	Mean	SD	SE	p-Value
Age	No	123	58.99	11.311	1.020	< 0.01
	Yes	28	51.46	9.617	1.817	

Abbreviations: SD, standard deviation; SE, standard error.

**Table 3** Characteristics of lesions of those who received and did not receive neoadjuvant therapy

	Not neoadjuvant (n = 123)		Neoadjuvant (n = 28)		p-Value
	Min–Max	Median (% 25–75)	Min–Max	Median (% 25–75)	
Size (mm)	5–100	20 (15–27)	7–98	35 (20–50)	< 0.001
Lesion SUVmax	1–275	7 (4.68–11.02)	1.8–34	8 (4.9–14.3)	0.300
Axilla SUVmax	0–27	4 (2.29–9.62)	2.29–23	7 (5–12.3)	0.010
Ki67 PI (%)	4–80	20 (15–40)	5–70	30 (15–50)	0.185

Abbreviation: SUVmax, maximum standard uptake value.

**Table 4** Pathologic features of cases

	Neoadjuvant (%)		Not neoadjuvant (%)		p-Value
	+	–	+	–	
Axillary lymph node involvement (%)	34.3	10.7	37.4	59.3	< 0.001
Extraaxillary lymph node	69.2	30.8	25.4	74.6	< 0.001
Sentinel lymph node	76.9	23.1	47.5	52.5	0.006
Multicentric	53.6	46.4	26.2%	73.8	0.005
Distant metastasis	50	50	7.3	92.7	< 0.001
E-cadherin	83.3	16.7	93.4	6.6	0.147
Pancreatin	33.3	66.7	29.7	70.3	0.897
Luminal A	32		59.5		0.015
Luminal B	56		23.4		0.021
Her 2 Neu	4		5.4		0.393
Triple negative	8		11.7		0.256

axilla involvement and provides an advantage in staging the patient. Robertson et al in their review stated that there are not enough data for the opinion of using  $^{18}\text{F}$ -FDG PET/CT instead of sentinel lymph node sampling.<sup>12</sup> In our study, most patients receiving neoadjuvant therapy had extraaxillary lymph node involvement, and this difference was found significant. Bernsdorf et al compared  $^{18}\text{F}$ -FDG PET/CT with conventional diagnostic methods in 103 patients with a breast cancer mass of 2 cm or more. Extraaxillary lymph node involvement was significantly higher with  $^{18}\text{F}$ -FDG PET/CT.<sup>13</sup> Axilla SUVmax was significantly higher in our patients planned to be administered neoadjuvant therapy. Although valuable information for preoperative staging is obtained with this examination, which is very sensitive for axillary macrometastases, Guller et al in their study concluded that  $^{18}\text{F}$ -FDG PET/CT misses micrometastases and is not yet fully sufficient for preoperative staging.<sup>14</sup> In the study in which Senkus et al examined the ESMO guideline, it was stated that the preexisting sentinel lymph node could not be

found after neoadjuvant therapy and this would result in false negativity. Thus, it has been emphasized that sentinel lymph node biopsy is still the gold standard.<sup>15</sup> Some of the subtypes of breast cancer have been associated with SUVmax in  $^{18}\text{F}$ -FDG PET/CT. However, it has been shown that there is a correlation between SUVmax and tumor size and it is also associated with axillary lymph node metastasis.<sup>16</sup> The lesion SUVmax of our patients for whom neoadjuvant treatment decision was made after  $^{18}\text{F}$ -FDG PET/CT examination did not differ from those who did not decide on neoadjuvant treatment. However, it was found that there was a correlation between the neoadjuvant treatment decision and the lesion size. In their study, Kajáry et al examined the subtypes, proliferation rate, and FDG uptake rate of the tumor. Uptake was also high in cases with high grade and high proliferation rate with negative hormone receptors. They even showed that Her2+ subtype was more aggressive.<sup>17</sup> In contrast, in our study, patients with neoadjuvant therapy decisions were shown to have more luminal A and B. Also, no relation could

be shown with the proliferation rate. In our study, while there was a significant relationship between the decision of neoadjuvant treatment and low age, no relation was found between the pathological type of the tumor. There was no significant relationship between whether the tumor was on the right or the left. In a study evaluating the effects of <sup>18</sup>F-FDG PET/CT findings on treatment, tumor side, age, and pathological type did not affect treatment.<sup>18</sup>

## Conclusion

Conventional imaging examinations are used in patients with breast cancer. These examinations may not be sufficient to determine advanced disease requiring neoadjuvant treatment. With <sup>18</sup>F-FDG PET/CT examination, these advanced stage patients are not overlooked. In our study, approximately one in five patients, treatment plan changed after <sup>18</sup>F-FDG PET/CT examination. Further clinical studies are needed for <sup>18</sup>F-FDG PET/CT to be accepted as the standard in breast cancer staging.

**Conflict of Interest**  
None declared.

### Acknowledgment

The informed consent form was obtained from all patients, allowing their medical data to be used. This study was approved by Mersin University Local Ethics Committee with decision number 670 dated 30.09.2020.

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