

# Impact of preoperative PET/CT for axillary staging in patients with early breast cancer



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Onur Dülgeroğlu<sup>\*\*/\*\*</sup>, Emes Arikan<sup>\*/\*\*</sup>, Halil Kara<sup>\*/\*\*</sup>, Cihan Uras<sup>\*/\*\*</sup>

<sup>\*</sup>Department of General Surgery, School of Medicine, Acibadem Mehmet Ali Aydınlar University, Istanbul, Turkey

<sup>\*\*</sup>Research Institute of Senology, Acibadem Mehmet Ali Aydınlar University, Istanbul, Turkey

<sup>\*\*\*</sup>Vocational School of Health Sciences, Research Institute of Senology, Acibadem Mehmet Ali Aydınlar University, Istanbul, Turkey

## Impact of preoperative PET/CT for axillary staging in patients with early breast cancer

**BACKGROUND:** Preoperative evaluation of axillary lymph node status is very important for the choice of primary treatment in breast cancer. This study assessed predictive properties of positron emission tomography-computerized tomography for axillary lymph node metastasis.

**METHODS:** Patients who were operated between 2014-2019 for early breast cancer and who had preoperative positron emission tomography-computerized tomography images were included. Positron emission tomography-computerized tomography results and histopathologic results were compared retrospectively.

**RESULTS:** Medical records of 223 patients who were operated for early breast cancer and have had positron emission tomography-computerized tomography were evaluated. Positron emission tomography-computerized tomography revealed that axillary lymph node status is positive in 97 patients and negative in 126 patients. In histopathological examination, tumor cells were found in 86 patients, of those 27 were negative while 59 were positive in positron emission tomography-computerized tomography. Furthermore, 137 patients were free from tumor cells, in which 99 were negative and 38 were positive in positron emission tomography-computerized tomography. Positive and negative predictive value of positron emission tomography-computerized tomography for metastatic axillary lymph nodes were found 60.8% and 78.5%, respectively.

**CONCLUSIONS:** Clinically, positron emission tomography-computerized tomography has low negative predictivity for determination of axilla in early stage or operable breast cancer. Even though it is valuable for the systematic scanning, positron emission tomography-computerized tomography can be overlooked for axillary evolution.

**KEY WORDS:** Axilla, Breast Cancer, Cancer Staging, PET-CT

### Introduction

Breast cancer is the most frequently cancer among women in addition to being the leading cause of cancer related deaths in women <sup>1</sup>. Treatment and prognosis of breast cancer related with stage of disease and biologic features of the tumor <sup>2</sup>. One of the most important prognostic factor, in breast cancer is the axillary

lymph node status <sup>3</sup>. Previously, axillary lymph node dissection (ALND) was the standard method for complete axillary staging. But nowadays, sentinel lymph node biopsy (SLNB) is widely accepted as the gold standard method, which is less invasive technique, for axillary staging in early stage breast cancer <sup>4</sup>.

For initial evaluation of early stage breast cancer, many imaging techniques, such as breast ultrasonography (USG), mammography and breast magnetic resonance imaging (MRI) are used <sup>5</sup>. Additionally, 18-fluorodeoxyglucose positron emission tomography combined with computed tomography (PET-CT) has been widely utilized in assessment of locally advanced, recurrent and metastatic breast cancer staging <sup>6</sup>. The use of PET-CT is not recommended in early breast cancer in National Comprehensive Cancer Network (NCCN) guideline. (EBC; i.e.T1-2,N0) <sup>7</sup>.

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Correspondence to: Onur Dülgeroğlu, M.D., Halkalı Merkez, Turgut Özal Bulvarı No:16, 34303 Küçükçekmece, Istanbul, Turkey (e-mail: onur.dulgeroglu@acibadem.edu.tr)

PET-CT imaging has considered to be of valuable in staging, monitoring response to treatment and detection of tumor recurrence for a lot of malignancies<sup>8</sup>. As a result, PET-CT has proven to be powerful in detecting recurrent disease, local and distant metastases<sup>9</sup>. Although, PET-CT has no commonly acceptable imaging method for the assessment of nodal staging due to varied sensitivity and specificity values in the literature. Current study aims to evaluate the clinical efficacy of the PET-CT in the primary workup of EBC.

## Methods

Patients who were operated at Acibadem University's Hospitals between June 2014 to January 2019 were assessed. Records of these patients who were operated for EBC were reviewed retrospectively. Although, there were no signs of metastases in axillary lymph nodes in preoperative evaluation with physical examination, breast USG, mammography, and breast MRI in EBC patients who had been referred to PET-CT for various reasons and whose reports were available included in the study. (causes; patients referred from different center patients, patient anxiety, internal mammary lymph node involvement possibility in internal quadrant tumors, etc.)

All patients underwent breast surgery with SLNB and/or ALND.

Histological type of invasive cancer and tumor diameter were determined from the excised specimens. TNM staging was performed appropriate to the American Joint Committee on Cancer (AJCC) 8th edition<sup>10</sup>.

This study is approved by Acibadem University, Medical Researches Evaluation Council (ATADEK) Ethical Board on 13.10.2016 with number 2016-16/8.

## Results

Of the 2125 patients operated for breast cancer between 2014-2019, 1823 were diagnosed as EBC, and 223 of these patients had PET-CT preoperatively. Mean age of these 223 patients was  $50.9 \pm 13$  years (range 25–86 years). Mastectomy performed hundred and fifteen (51,6%) patients and 108 (48,4%) patients underwent breast-conserving surgery. Completion ALND were performed in 85 patients (38.2%), whereas SLNB without ALND were performed in 138 patients (61.8%). Axillary nodal status were presented in Table I.

Hundred and eight patients (48.4%) had T1 and 115 patients (51.6%) had T2 tumor.

Histological types of invasive cancers were as follows; 187 (83.9%) invasive ductal carcinoma (NOS, not other specified), 20 invasive lobular carcinoma (9%), five (0.02%) mixed type (invasive ductal & invasive lobular carcinomas), four (0,01%) mucinous carcinomas, four (0,01%) tubular carcinomas and three (0,01%) metastatic carcinomas.

Hundred and twenty one (54%) PET-CT were requested in other centers and 82 (36%) PET-CT were performed due to patients' anxiety. Twenty (10%) PET-CT, were requested for patients who have deeply located internal quadrant tumors with possibility of metastasis to internal mammary lymph node. PET-CT images of all these patients were re-evaluated.

Of those 223 patients, PET-CT revealed, axillary lymph nodes as positive 97 patients (43.5%), while in 126 patients (56.5%) as negative. In histopathological examination 86 patients (38.6%) were contained tumor cells in which 59 detected positive and 27 negative by PET-CT (Figs. 1, 2).

Histopathological examination detected 137 patients as

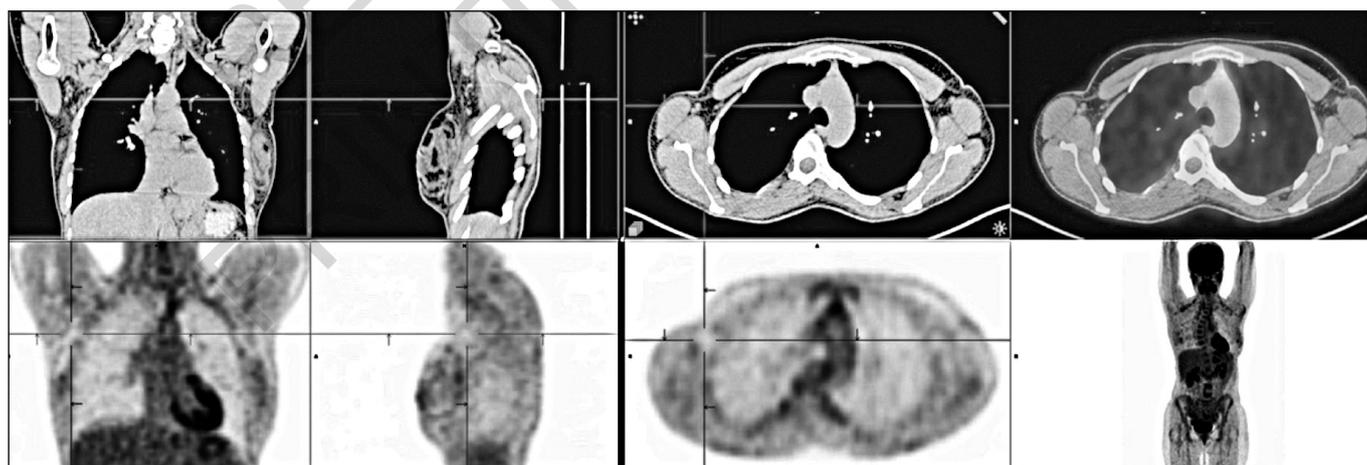


Fig. 1: PET-CT IMAGE Axillary lymph nodes were normal in the preoperative staging PET-CT examination of a 44-year-old patient diagnosed with ER (+), PR (-), Her-2 (-), Grade III Invasive ductal carcinoma detected by routine screening in the left breast. When sentinel lymph node biopsy was positive, axillary dissection was performed and metastasis was detected in three of 18 lymph nodes. (ER; Estrogen receptor expression status, PR; Progesterone receptor expression status, Her-2; Human Epidermal Growth Factor Receptor 2 status, PET-CT; 18-fluorodeoxyglucose positron emission tomography/computed tomography)

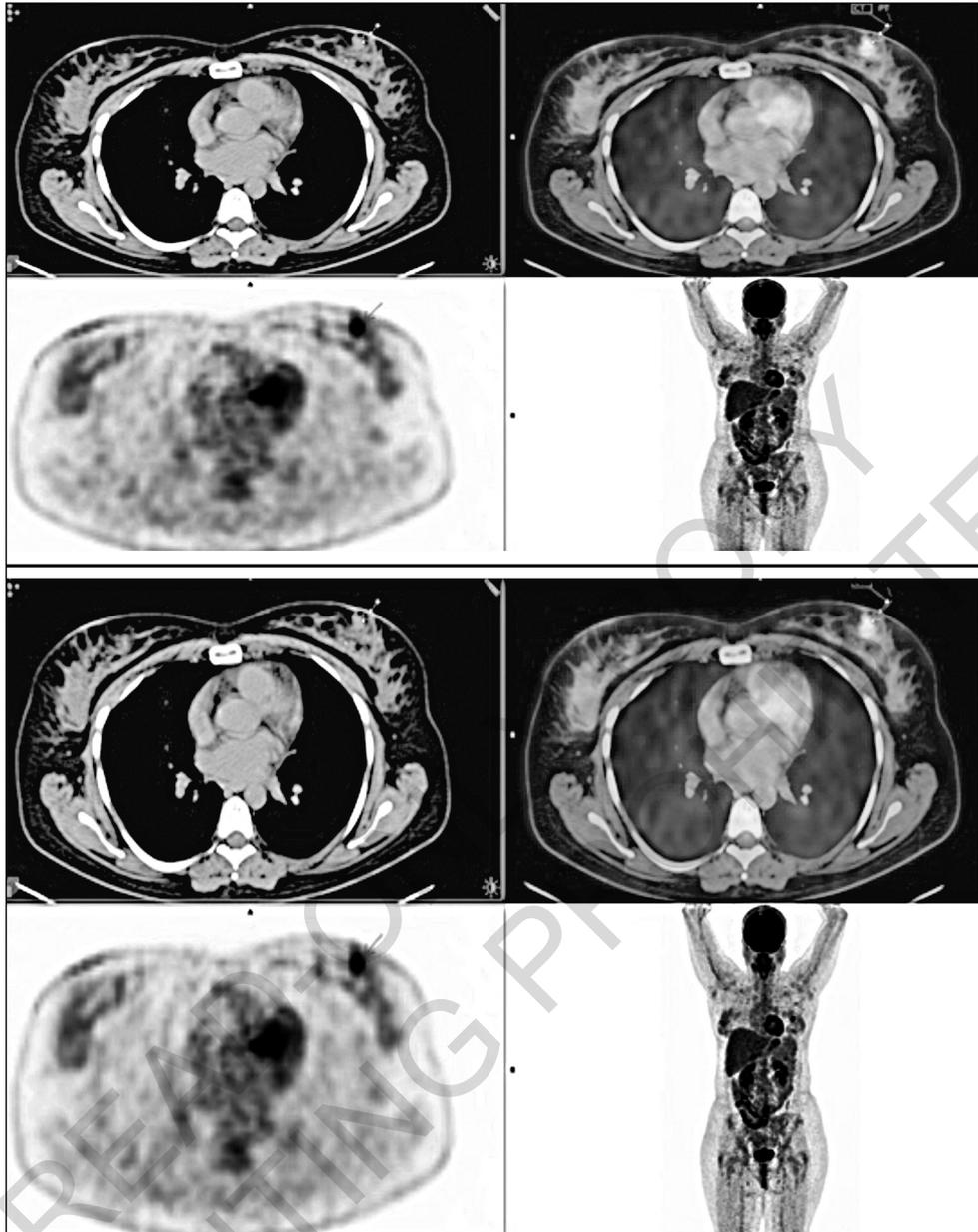


Fig. 2: PET-CT IMAGE A 51-year-old woman with a mass of 24 mm in the right breast, with a mass of ER (+), PR (+), Her-2 (-), Grade II Invasive ductal carcinoma, a suspicious lymph node was visible in the right axilla in preoperative staging PET-CT images (arrow). Metastasis was not detected in 5 lymph nodes in sentinel lymph node biopsy. (ER; Estrogen receptor expression status, PR; Progesterone receptor expression status, Her-2; Human Epidermal Growth Factor Receptor 2 status, PET-CT; 18-fluorodeoxyglucose positron emission tomography/computed tomography).

free from tumor cells, of those, 99 were negative and 38 were positives by PET-CT. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the accuracy of PET-CT for metastatic axillary lymph nodes were 68.6%, 72.26%, 60.82%, 78.57%, and 70,85% respectively in all cases (Table II).

## Discussion

Axillary nodal status is one of the important factor for

reliable staging and treatment planning of breast cancer. ALND or SLNB is the most definitive procedure in evaluation of the axillary status. In addition, SLNB is still the gold standard procedure for axillary nodal staging in EBC. On the other hand, SLNB and ALND has still some comorbidities, such as lymphedema, infection, seroma, pain (acute or chronic), bleeding, paresthesia, and limited shoulder movement<sup>11</sup>. The performance of MRI, axillary USG and PET-CT in axillary staging was compared with SLNB in EBC in recent years. However none of them were as sensitive or specific as SLNB. Recent

TABLE I - Patient characteristics

| Characteristics          | Number (%)   |
|--------------------------|--------------|
| Age (years)              |              |
| Mean +/- SD              | 50.9 +/- 13  |
| Range                    | 25-86        |
| Tumor stage              |              |
| T1 <2 cm                 | 108 (48.4 %) |
| T2 >2 cm <5 cm           | 115 (51.6%)  |
| Axillary Node Metastasis |              |
| Negative                 | 137 (61.9 %) |
| Positive                 | 86 (38.1%)   |
| Histology                |              |
| Ductal                   | 187 (83.9%)  |
| Lobular                  | 20 (9%)      |
| Other                    | 16(7.1%)     |
| Breast Surgery Procedure |              |
| Mastectomy               | 115 (51.6%)  |
| Breast Conserving        | 108 (48.4%)  |

TABLE II - FDG-avid axillary nodes

|                            | Pathologic metastasis exists | Pathologic metastasis free |
|----------------------------|------------------------------|----------------------------|
| PET positive axillary node | 59                           | 38                         |
| PET negative axillary node | 27                           | 99                         |

Sensitivity 68.6%, Specificity 72.2%, Positive Predictive Value 60.8%, Negative Predictive Value 78.5%, Accuracy 70,8%

TABLE III - The studies about predictivity of FDG PET in axillary node metastasis

| Author           | Year | Patient Number | PET-CT Sensitivity (%) | PET-CT Specificity (%) | PET-CT PPV (%) | PET-CT NPV (%) |
|------------------|------|----------------|------------------------|------------------------|----------------|----------------|
| Greco, et al     | 2001 | 167            | 94                     | 86                     | 84             | 95             |
| Lovrics, et al   | 2004 | 98             | 40                     | 97                     | 75             | 60             |
| Wahl, et al      | 2006 | 360            | 61                     | 80                     | 62             | 79             |
| Chung, et al     | 2006 | 462            | 60                     | 100                    | 100            | 60             |
| Veronesi, et al  | 2007 | 236            | 37                     | 96                     | 88             | 66             |
| Ueda, et al      | 2008 | 183            | 58                     | 95                     | 85             | 83             |
| Chae, et al      | 2009 | 108            | 48                     | 84                     | NA             | NA             |
| Heusner, et al   | 2009 | 61             | 58                     | 92                     | 82             | 77             |
| Kim, et al       | 2009 | 137            | 77                     | 100                    | 100            | 94             |
| Groheux, et al   | 2011 | 70             | 63                     | 91                     | 63             | 91             |
| Pritchard, et al | 2012 | 325            | 23                     | 99                     | 95             | 75             |
| Choi, et al      | 2012 | 154            | 37                     | 95                     | NA             | NA             |
| Bernsdorf, et al | 2012 | 103            | 63                     | 97                     | NA             | NA             |
| Jeong, et al     | 2014 | 178            | 20                     | 86                     | 37             | 74             |
| Koolen, et al    | 2014 | 62             | 73                     | 100                    | 100            | 72             |
| Jung et, al      | 2015 | 428            | 67                     | 81                     | 70             | 79             |

PPV: Positive Predictive Value, NPV: Negative Predictive Value

studies in the literature have shown the benefit of PET-CT imaging in patients who were diagnosed with EBC (Table III). Outlines the recent studies about the predictivity of preoperative PET-CT in nodal involvement in breast cancer<sup>3-6,8,12-22</sup>.

Veronesi et al.<sup>6</sup> compared predictability performance of SLNB and PET-CT for axillary involvement in 236 patients. All patients without axillary involvement on clinical examination underwent PET-CT and SLNB. The results showed that PET-CT had high PPV (88%) in axillary evaluation. They even argued that, axillary dissection can be performed without a SLNB in patients with axillary involvement in preoperative PET-CT. In that study, the patient group included also patients with T3 tumor, although it was not classified in early stage breast cancer. Contrary in current study, PET-CT has low PPV (60.8%) for evaluation of axillary lymph node status. In current study, the patient group was consisted of only clinically early breast and patients whose axillary tumor burden was expected to be low. Inconsistency between two studies is due to inclusion of T3 tumors by Veronesi et al.

Wahl et al.<sup>14</sup> compared axillary pathological findings and PET-CT results in 360 patients with early stage breast cancer in a prospective multicenter trial. PET-CT has 80% specificity and 61% sensitivity for detecting axillary involvement with NPV of 79% and PPV of 62%.

They thought that the diagnostic performance of PET-CT was moderate in patients with small size metastatic axillary lymph nodes and numbers. Therefore, they didn't recommend routine use of PET-CT in axillary staging.

There were similar results in terms of axillary predictability in current study.

Choi et al.<sup>21</sup> reported that PET-CT has a similar specificity and sensitivity to conventional techniques in axillary mapping for nodal status. In that study, 144 patients who has invasive breast cancer and had preoperative PET-CT and classical image modalities were included. The sensitivity and specificity of PET-CT to identify positive axilla were 37.3% and 95.8%, respectively. They compared PET-CT separately with radiological imaging methods such as breast USG and MRI. Considering the results of the study group which was composed of patients at all breast cancer stages, it was observed that PET-CT has a high specificity in diagnosing of axillary disease, while sensitivity is low. In current study, the sensitivity of PET-CT in detecting axillary lymph node involvement in EBC was found as 68.6% and specificity as 72.2%. In recent studies, axillary ultrasonography has been shown to have high sensitivity and specificity for evaluating lymph node involvement<sup>23</sup>. Since the number of patients who underwent axilla-specific USG in current study group was 19, we didn't compare with PET-CT considering that it would not have statistical value. In fact, it was shown that the possibility of predicting axillary lymph node involvement increases in all stage breast cancers with the use of axillary USG and PET-CT in combination. Ueda et al.<sup>15</sup> compared PET-CT to PET-CT in combination with axillary USG for assessment of axillary area in 183 EBC patients. In that study, only PET-CT showed 58% sensitivity and 95% specificity. At the same time, in the combination of PET-CT and axillary USG specificity and accuracy were 94% and 85%. In a retrospective 95 patients study, in which Gündoğdu et al.<sup>24</sup> examined the effect of PET-CT on staging and treatment in breast cancer, the patients were divided into two groups. In the first group of 47 patients with early stage breast cancer who did not receive neoadjuvant chemotherapy; PET-CT's axillary lymph node evaluation was found to be PPV 81.2%, NPV 65.5%, sensitivity 56.5%, and specificity 86.3%. In a prospective study of 236 patients, Güney et al.<sup>(25)</sup> was compared axillary ultrasound, contrast-enhanced MRI, and PET-CT to detect axillary involvement in patients with breast cancer, the sensitivity of PET-CT in early stage (Stage 1-2) patients was 74%, specificity 96%, PPV 93%, NPV 82% and accuracy 86%. The reason why it is higher than our rates; as stated in the limitation of their study, it is a prospective study and the PET-CT's readers had knowledge of the axillary USG results of patients. Current study has some limitations. First, current study was retrospective which may cause bias on patient selection. Second, the preoperative PET-CT of the patients we included in the study belonged to different centers with different shooting techniques. Third, even in the same stage, the ability of PET-CT to predict immunohistochemically can be different among subtypes of breast cancer (HER-2 (+), Triple (-), Luminal etc.).

## Conclusion

In patients with early stage breast cancer via physical examination and/or conventional imaging modalities, PET-CT is commonly utilized to assess distant organ metastasis. In early stage of breast cancer, axillary USG and SLNB are thought to be adequate methods for preoperative evaluation.

In current study, the predictability of PET-CT for axillary nodal involvement in EBC was evaluated. In addition to conventional imaging methods such as breast USG, mammography and breast MRI in preoperative initial evaluation phase of these patients, if PET-CT was used for various reasons; we believe it has low predictive sensitivity in the axillary region.

## Riassunto

**CONTESTO:** La valutazione preoperatoria dello stato dei linfonodi ascellari è molto importante per la scelta del trattamento primario nel carcinoma mammario. Questo studio ha valutato le proprietà predittive della tomografia computerizzata a emissione di positroni per le metastasi dei linfonodi ascellari.

**METODI:** Sono stati inclusi i pazienti che sono stati operati tra il 2014-2019 per carcinoma mammario in fase iniziale e con immagini di tomografia computerizzata a emissione di positroni preoperatoria. I risultati della tomografia a emissione di positroni-tomografia computerizzata e i risultati istopatologici sono stati confrontati retrospettivamente.

**RISULTATI:** Sono state valutate le cartelle cliniche di 223 pazienti operate per carcinoma mammario in fase iniziale e che sono state sottoposte a tomografia a emissione di positroni-tomografia computerizzata. La tomografia computerizzata a emissione di positroni ha rivelato che lo stato dei linfonodi ascellari è positivo in 97 pazienti e negativo in 126 pazienti. All'esame istopatologico, le cellule tumorali sono state trovate in 86 pazienti, di questi 27 erano negativi mentre 59 erano positivi alla tomografia computerizzata a emissione di positroni. Inoltre, 137 pazienti erano privi di cellule tumorali, di cui 99 negativi e 38 positivi alla tomografia computerizzata a emissione di positroni. Il valore predittivo positivo e negativo della tomografia a emissione di positroni-tomografia computerizzata per i linfonodi ascellari metastatici è stato trovato rispettivamente del 60,8% e del 78,5%.

**CONCLUSIONI:** Dal punto di vista clinico, la tomografia computerizzata a emissione di positroni ha una bassa predittività negativa per la determinazione dell'ascella nel carcinoma mammario in fase iniziale o operabile. Anche se è utile per la scansione sistematica, la tomografia computerizzata a emissione di positroni può essere trascurata per l'evoluzione ascellare.

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