JBUON 2015; 20(5): 1282-1286
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

# Is there any relation between PET-CT SUVmax value and prognostic factors in locally advanced breast cancer?

Deniz Tural[1], Derya Kivrak Salim[1], Hasan Mutlu[1], Metin Erkilic[2], Seyda Gunduz[1], Melek Karakurt[1], Fatma Musri[1], Savas Tuna[3], Adil Boz[2], Funda Aydin[2], Binnur Karayalcin[2], Hakan Bozcuk[1], Hasan Senol Coskun[1]

[1]Department of Medical Oncology and [2]Department of Nuclear Medicine, Akdeniz University, Medical School, Antalya; [3]Department of Medical Oncology , Bakirkoy Education and Research Hospital, Istanbul, Turkey

## Summary

***Purpose:*** *To investigate the relation between PET-CT SUVmax value and prognostic factors in locally advanced breast cancer.*

***Methods:*** *Data of 73 patients were retrospectively analyzed. Relations between SUVmax value, clinical stage, tumor grade and breast cancer molecular subtypes were analyzed by using one-way ANOVA and $x^2$ tests. Correlations between age, ki-67 scores and SUVmax were evaluated by using Pearson's correlation test. A p value <0.05 was considered statistically significant.*

***Results:*** *Median SUVmax values for clinical stages 1, 2 and 3 were 5 (range 2.1-4.1), 10.6 (range 2.9-19.6), and 12.2 (range 3.2-23.3), respectively. Statistically significant difference was noticed between stage 1 and 2 (p=0.014) and stage 1 and 3 (p=0.001). Median SUVmax values of triple negative, luminal A, luminal B and non-luminal HER2 positive groups were 14.4 (range 6.6-23.3), 8.2 (range 2.1-18.2), 10.1 (range 3.5-19.6), and 14 (range 4.1-22.9), respectively. Statistically significant differences were noticed in SUVmax values between triple-negative and luminal A groups (p=0.005) and between non-luminal HER2 positive and luminal A groups (p=0.02). Median SUVmax values of grade 1, 2 and 3 were 5.7 (range 2.1-18.2), 9.5 (range 2.2-21.3), and 11.6 (range 3.5-23), respectively. Statistically significant difference was noticed only between SUVmax values of grade 1 and 3 (p=0.035). There was negative correlation between age and SUVmax value (r=-0.23, p=0.047) and positive correlation between ki-67 and SUVmax value (r=0.43, p=0.016).*

***Conclusion:*** *There were significant positive relations between PET-CT SUVmax value and clinical stage, tumor grade, and certain breast cancer molecular subtypes (triple-negative and non-luminal HER2 positive groups. Moreover, positive correlation was found between SUVmax value and ki-67 and negative correlation between SUVmax value and age.*

***Key words:*** *breast cancer subtypes, locally advanced breast cancer, PET scan, prognostic factors, SUVmax*

## Introduction

18F-fluorodeoxyglucose positron emission tomography/ computed tomography (18F-FDG PET/CT) is an effective method for evaluating of patients with locally advanced breast cancer. Superiority of 18F-FDG PET/CT over other conventional imaging methods is based on its ability to quantify functional tumor biology. In breast cancer, 18F-FDG PET/CT has been used for tumor detection and staging, monitoring the response of the primary tumor to neoadjuvant chemotherapy and obtaining prognostic information [1,2]. Some previous trials demonstrated that the degree of FDG uptake may provide important clinical and biological information in addition to being a use-

*Correspondence to:* Deniz Tural, MD. Department of Clinical Oncology, Akdeniz University Medical School, Main Campus, Dumlupinar Ave, TR-07985m, Antalya, Turkey. Tel: +90 242 249 60 00, Fax: +90 242 249 69 03, E-mail: deniztural@gmail.com
Received: 04/01/2015; Accepted: 29/01/2015

ful tool for initial detection of primary breast cancer. Therefore, high levels of 18F-FDG uptake are considered to indicate more aggressive potential of the primary tumor than low levels [3-9]. Also, previous trials have demonstrated a correlation between the intensity of 18F-FDG PET/CT uptake and tumor grade, hormonal receptor status, tumor subtype and HER2 status [5,10-14].

In recent years, microarrays technology has allowed the identification and characterization of distinct breast cancer subtypes such as luminal A, luminal B, HER2 overexpressing and triple-negative tumors [15]. The molecular diversity in cell biology is associated with significant differences in clinical outcomes and immunohistochemical techniques give more details in the characterization of breast cancer subtypes [16-18]. Several trials have demonstrated association between the intensity of 18F-FDG uptake and histological and biological characteristics such as hormonal receptor status, HER2 status, grade and tumor type. However, the relation between the prognostic value of SUVmax and the molecular subtypes of breast cancer has not been assessed. Therefore, the purpose of this study was to evaluate the relation between SUVmax and molecular subtypes of breast cancer, such as luminal A, luminal B, HER2 overexpressing and triple-negative tumors. If such a relation could exist it would have serious implications in the treatment of locally advanced breast cancer.

## Methods

*Inclusion criteria*

Between 2009 and 2013, patients with locally advanced breast cancer who underwent PET/CT in our hospital were evaluated. We identified 98 patients, 73 of whom had available clinical and radiological information and were included in this study. Patients with biopsy (tru-cat) proven breast cancer who underwent PET/CT before surgery, and chemo/radiochemotherapy were included in this study. Patients who had excisional biopsy were excluded. Primary tumors' clinical stage was assessed by clinical examination, mammogram, ultrasonography and magnetic resonance imaging (MRI) in all of the patients.

*Imaging protocol*

The patients fasted for at least 4 hrs prior to PET/CT imaging and their blood glucose levels were obtained prior to tracer injection. The blood glucose levels of all patients were below 200 mg/dl at the time of FDG injection. Each patient received intravenously 7-10 mCi (260-370MBq) of FDG as tracer. Following this, the patients rested on a comfortable chair in a silent room for 1 hr to allow FDG biodistribution. For optimal delineation of bowel structures, 400-600 ml of contrast material diluted in water was ingested 1 hr before CT imaging. No urinary bladder catheterization was performed, and no diuretics were administered at this time. Whole body imaging was performed 1 hr after radiotracer injection using a Siemens Biograph PET/CT scanner with lutetium orthosilicate (LSO) detectors (Siemens Biograph 6, IL, Chicago, USA). First, low dose CT was performed with 140 kV, 50 mA, a table speed of 22.5 mm/s and without any specific breath holding instructions. Scanning from the top of the skull down to the upper thighs was performed in a single step with the patient in supine position. CT data were used for attenuation correction (5 mm contiguous axial cuts). Immediately afterwards, a PET emission scan was obtained without changing the patient's position. Six to eight bed positions were used with an acquisition time of 3 min for each bed position. The PET scan was acquired in a three dimensional mode over the same anatomical regions, starting at the level of the mid thigh. The PET image data sets were reconstructed iteratively using the CT data for attenuation correction and co-registered images were displayed on a workstation.

*Image analysis*

All PET/CT images were analyzed by an expert nuclear medicine physician who had no information about the diagnostic CT findings. Attenuation corrected PET images, CT scans, and co-registered PET/CT images were interpreted using a dedicated image fusion workstation and a final consensus was reached for all patients. Any foci with increased FDG uptake, except for areas of physiologically increased FDG uptake, corresponding to a CT abnormality (tissue or lymph node) were considered positive for breast lesions. Suspicious findings on CT were considered negative if they did not correspond to an area of increased FDG uptake. In this study we used SUVmax value because it is less variable than mean SUV in terms of measurements [6].

*Immunohistochemistry*

Immunohistochemistry was used in the examination of estrogen (ER) and pro¬gesterone receptors (PR) in 73 patientx with locally advanced breast cancer. Intranuclear staining in the cells was expressed as the percentage of stained cells; ≥1% staining was defined as positive. The evaluation of HER2 positivity was based on the guidelines of American Society of Clinical Oncology (College of American Pathologists).

*Microarrays*

In recent years, microarrays have allowed the identification and characterization of distinct breast cancer subtypes such as luminal A, luminal B, HER2 overexpressing and triple-negative tumors [16]. Breast cancer

based on the expression of ER, PR, HER2 was classified into 4 molecular subtypes in 73 patients as follows: luminal A tumors (ER positive or PR positive and HER2 negative), luminal B tumors (ER positive or PR positive and HER2 positive), non-luminal HER2 positive tumors (ER negative or PR negative and HER2 positive), triple-negative tumors (ER negative or PR negative and HER2 negative).

*Statistics*

Relations between SUVmax value of the primary tumor and ER, PR, HER2 receptors, clinical stage, tumor grade, ki-67 scores and age were investigated. Relations between SUVmax value and clinical stage, tumor grade and breast cancer molecular subtypes were analyzed by using one-way ANOVA and $x^2$ tests. Correlations between age, ki-67 scores and SUVmax were evaluated by using Pearson's correlation test. A p value <0.05 was considered statistically significant.

## Results

Seventy-three patients with locally advanced invasive breast carcinoma were included before neoadjuvant chemotherapy. Their median age was 50 years (range 30-72) and median SUV max value was 10.3 (range 2.1-23.3). Thirty-four patients (47%) were premenopausal and 39 (53%) menopausal at the time of diagnosis. Patient clinical characteristics are shown in Table 1.

The relationship between SUVmax and prognostic factors, such as stage, grade, hormone receptor status and ki-67 index was evaluated. A negative correlation between age and SUVmax value (r=-0.23, p=0.047) and a positive correlation between ki-67 score and SUVmax value (r=0.43, p=0.016) were noticed.

Median SUVmax values for clinical stages 1, 2 and 3 were 5 (range 2.1-4.1), 10.6 (range 2.9-19.6) and 12.2 (range 3.2-23.3), respectively. Statistically significant differences were noticed between stage 1 and 2 (p=0.014) and stage 1 and 3 (p=0.001), while there was no statistically significant difference between stages 2 and 3 with respect to SUVmax value. Median SUVmax values of triple-negative, luminal A, luminal B and non-luminal HER2 positive groups were 14.4 (range 6.6-23.3), 8.2 (range 2.1-18.2), 10.1 (range 3.5-19.6) and 14 (range 4.1-22.9), respectively. Statistically significant differences in SUVmax values were registered between triple-negative and luminal A groups (p=0.005) and between non-luminal HER2 positive and luminal A groups (p=0.02). Median SUVmax values of grade 1, 2 and 3 were 5.7 (range 2.1-18.2), 9.5 (range 2.2-21.3) and 11.6 (range 3.5-23), respectively (one way ANOVA, p=0.034). Statistically significant difference in SUVmax values was found only between grade 1 and grade 3 (p=0.035). The relationship between clinicopathological features and SUV max value are shown in detail in Table 2.

**Table 1.** Patient and disease characteristics

| *Characterisitics* | *N* | *%* |
|---|---|---|
| Age, years, median (range) | 50 | (30-72) |
| SUVmax, median (range) | 10.3 | (2.1-23.3) |
| Menopausal status | | |
| Premenopausal | 34 | 47 |
| Postmenopausal | 39 | 53 |
| Histology | | |
| Invasive ductal carcinoma | 63 | 86 |
| Invasive lobular carcinoma | 4 | 6 |
| Mixed histology* | 6 | 8 |
| T stage | | |
| T1 | 16 | 22 |
| T2 | 35 | 48 |
| T3 | 11 | 15 |
| T4 | 11 | 15 |
| Nodal status | | |
| Positive | 31 | 43 |
| Negative | 42 | 57 |
| Grade | | |
| I | 6 | 8 |
| II | 35 | 48 |
| III | 26 | 36 |
| Unknown | 6 | 8 |
| Estrogen receptor status | | |
| Positive | 51 | 70 |
| Negative | 22 | 30 |
| Progesterone receptor status | | |
| Positive | 42 | 58 |
| Negative | 31 | 42 |
| HER2 receptor status | | |
| Positive | 30 | 41 |
| Negative | 43 | 59 |
| Triple-negative status | | |
| Positive | 12 | 16 |
| Negative | 61 | 84 |
| Ki-67 mean (range)** | 40 | 1-80 |

*invasive ductal and invasive lobular carcinoma
**Ki-67 values were avaible in 40 patients

## Discussion

To our knowledge, there are only few published data about the findings from PET-CT SU-

**Table 2.** Relationship between clinicopathologic features and SUV max value

| *Variables* | *N* | *%* | *SUVmax median (range)* | *Statistical test* | *p value* |
|---|---|---|---|---|---|
| Age, years, median (range) | 50 | (30-72) | r=-0.23 | Pearson's correlation test | 0.047 |
| Clinical stage | | | | ANOVA | 0.001 |
| I | 15 | 20.8 | 4.1 (2.1-14) | | |
| II | 12 | 16.7 | 8.25 (2.9-19.6) | | |
| III | 46 | 62.5 | 12 (3.2-23.3) | | |
| Grade | | | | ANOVA | 0.034 |
| I | 6 | 8.2 | 5.7 (2.1-18.2) | | |
| II | 35 | 47.9 | 9.5 (2.2-21.3) | | |
| III | 26 | 35.6 | 11.6 (3.5-23) | | |
| Unknown | 6 | 8.2 | | | |
| Molecular subtypes | | | | ANOVA | 0.002 |
| Luminal A | 34 | 46.6 | 8.2 (2.1-18.2) | | |
| Luminal B | 19 | 26 | 10.1 (3.5-19.69 | | |
| No Luminal A and B, HER 2 positive | 9 | 12.3 | 14 (4.1-22.9) | | |
| Triple-negative | 11 | 15.1 | 14,4 (6.6-23.3) | | |
| Ki-67 median (range) | 40 | (1-85) | r=0.43 | Pearson's correlation test | 0.016 |

Vmax value in the four molecular subtypes of breast cancer. In our study we elucidated the relationship between 4 molecular subtypes of breast cancer and PET-CT and our patients have shown significant relationship between PET-CT SUVmax value and the parameters that have prognostic significance in breast cancer. Basu et al. [19] assessed the FDG PET-CT imaging characteristics in 29 patients with triple-negative breast cancer and compared these results with the imaging characteristics of 59 patients with ER positive/ PR positive/ HER2 negative breast cancer, which usually carry a favorable prognosis. The authors demonstrated that triple-negative breast cancers were associated with enhanced FDG uptake which revealed their aggressive biology when compared ER positive/ PR positive/ HER2 negative breast carcinoma.

Our study is consistent with the Basu et al. findings in which triple-negative and non-luminal HER2 breast cancer, which have more aggressive clinical course than others, had significantly higher SUVmax values than the other types of breast cancer with favorable prognosis (e.g. luminal A).

In the literature, several trials have demonstrated the usefulness of PET-CT imaging for assessing patients with breast cancer. Some previous trials elucidated that the degree of FDG uptake may provide information in addition to being a useful approach for detection of primary breast cancer [8-14].

Kadoya et al. have evaluated the relationship between prognostic factors and PET-CT SUVmax value in 344 patients with clinical stage I-III who did not receive surgical intervention and induction therapy [8]. The authors have demonstrated that there was a relationship between high value of PET-CT SUVmax and HER2 receptor positivity, and high tumor grade.

Ohara et al. evaluated the significance of PET-CT SUVmax value as prognostic factor for operable breast cancer [9]. They reported that high SUVmax was significantly associated with large tumor size, lymph node metastasis, high nuclear grade, lymphovascular invasion, hormone receptor status, positive HER2 status and poor prognosis. Our results by which we demonstrated the relationship between SUVmax values and prognostic factors such as clinical stage, tumor grade, hormone receptor status and HER2 receptor status, are consistent with the findings of Ohara et al. study.

In their study, Gil-Rendo et al. Demonstrated that there was a relationhip between SUVmax and ki-67 proliferative index [14]. The results of our study coincide with the results of Gil-Rendo et al. study.

In conclusion, the current study suggests that FDG PET-CT SUVmax values may reflect the mo-

lecular subtypes of locally advanced breast cancer, and also a relationship between FDG PET-CT SUVmax value and aggressive clinical disease course.

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