The association of axillary lymph node-positive breast cancer with metabolic parameters of 18F-fluorodeoxyglucose PET/CT

Sadiye Altun Tuzcu[1]*, Ayten Gezici[1], Bekir Taşdemir[1], İhsan Kaplan[1], Hüseyin Büyükbayram[2], Feray Altun Çetin[3]

Abstract

Objective: This study aims to examine the association between 18F-fluorodeoxyglucose PET/CT (18F-FDG PET/CT) metabolic parameters of lymph node-positive and lymph node-negative breast carcinomas.

Material and method: We included breast carcinomas patients who underwent 18F-FDG PET/CT imaging at our department between May 2018 and December 2019. A total of 108 female breast cancer patients were included (aged 48.8 ± 13.6years; range, 28-84 years). PET scanning was performed in 3D mode from the skull ceiling to the half of the thigh. According to pathology reports, we divided the patients into two groups: a lymph node-positive group of patients and a lymph node-negative group of patients. We calculated the sensitivity and specificity for determining the PET/CT pathological lymph node. Metabolic parameters like TLG (Total lesion glycolysis), MTV (Metabolic tumor volume), SUVmean, and SUVmax values were calculated.

Result: The lymph node-positive group's body weight and body mass index(BMI) were statistically higher than the lymph node-negative group (p=0,027,p=0,022 respectively). SUV max and SUV mean of the lymph node-positive group were statistically higher than the lymph node-negative group (p=0.008, p=0,009, respectively). Both TLG and MTV of the lymph node-positive group were statistically higher than the lymph node-negative group (p=0.01, P= 0.01, respectively). Ki-67(%) of the lymph node-positive group was not statistically different from the lymph node-negative group. We calculated the PET/CT's sensitivity and specificity as 78,57% and 59,09%, respectively. For the positive predictive value of PET/CT, we found 55%, and for the negative predictive value, it was 81.25%.

Conclusions: PET/CT metabolic parameters of patients with lymph node-positive breast cancer were higher than patients with lymph node-negative. High body weight and BMI appears to increase the possibility of metastases of lymph node. The sensitivity of PET/CT can be considered to be useful in determining the pathological lymph node, but the specificity of PET/CT is not very good.

Keywords: Breast cancer, 18F-FDG PET/CT, Lymph node

Introduction

Breast cancer, as the most deadly cancer for women, is the second most common cancer in the world, after lung cancer, with more than two million cases per year [1, 2].

A precise definition of the extent of the disease after a diagnosis of breast cancer is one of the most important measures to treat it. One of the most important early stages' prognostic factors of breast cancer is the evaluation of lymph node status. Conducting the evaluation by physical examination is not a reliable method for examining axillary lymph nodes' status, as in most cases, it is not possible to touch metastatic lymph nodes, and reactive lymph nodes might be mistakenly diagnosed as them [3,4,5].

About 85% of the breast's quadrants lymphatic drainage reaches the Axillary Lymph Nodes (ALNs), and the rest reaches the internal, supraclavicular and/or infraclavicular lymph nodes. The location and size of the tumor, the presence of lymph node invasion as well as the histologic grade are all associated with the possibility of ALN involvement [6,7].

There are several methods available today to diagnose ALN involvement, including axillary ultrasound, PET/CT, ultrasound-guided needle biopsy, and MRI.

Positron emission tomography/computed tomography (PET/CT) is combined imaging of anatomy and function.

Not only does it show the morphological features of the lesion, but it may also report metabolic information of the lesion, bringing new opportunities for breast cancer's diagnosis, staging, re-staging, and treatment response assessment [8, 9].

The maximum standardized uptake value (SUVmax) and the mean standardized uptake value (SUVmean) measured with FDG PET in breast cancer are sensitive indicators for metabolic activity [10,11], which are usually used for examining the aggressiveness of tumor and is related with prognostic factors, such as the histological grade, histological type, proliferation index, and immunohistochemical factors [10,12-18]. Some parameters mixing volume and FDG intensity can also be used as metabolic parameters such as Total Lesion Glycolysis (TLG) and Metabolic Tumor Volume (MTV). In this study, we seek to find the relationship between 18F-fluorodeoxyglucose PET/CT (18F-FDG PET/CT) metabolic parameters of axillary lymph node-negative and axillary lymph node-positive of breast carcinomas and to determine PET/CT's sensitivity and specificity to evaluate the status of axillary lymph nodes.

Methods and Materials

The population of the study: In this study, we included patients who underwent 18F-FDG PET/CT imaging at our department having breast carcinomas between May 2018 and December 2019. A total of 108 female breast cancer patients were included (aged 48.8 ± 13.6years; range, 28-84 years). Before imaging, breast carcinoma was diagnosed by biopsy of all patients. Height and body weight of the patients were measured. BMI of patients was calculated (BMI=weight(kg)/[height(m)2). Pathological subtypes of breast cancer patients are infiltrative breast carcinoma (n = 83), invasive ductal breast carcinoma (n = 14), invasive lobular carcinoma (n = 6), invasive tubular carcinoma (n = 2), micropapiller carsinoma (n = 2) and cribriform carcinoma (n = 1).

Imaging procedure: After eight hours of fasting, patients were given 18F-FDG intravenously (blood glucose <200 mg / dL) and images of whole-body were taken from PET/CT scanner (Siemens 3D-TOF Siemens Medical Systems) 55 to 75 minutes after injection (19) low-dose CT scan (80mA, 120 kV) was conducted.

An intravenous injection 3,7MBq/Kg 18F-FDG was performed on the arm of the patient opposite to the primary breast tumor location. PET scanning was performed in 3D mode from the skull ceiling to the half of the thigh. Using an SUV of 2.5 as the threshold, MTV (ml) was assigned to the volume of the tumor with SUV $\geq$ 2.5.

In the delineated tumor volume, SUVmean was also defined as a mean SUV. TLG (SUVml) was defined as the product of the MTV multiplied by SUVmean. Metabolic parameters such as Metabolic Tumor Volume (MTV), Total Lesion Glycolysis (TLG), SUVmean, and SUVmax values were calculated.

Statistical Analysis: Via the Kolmogorov-Smirnov test, we tested the data normality. We summarized data for categorical variables as percentages and frequencies, and for continuous variables, we summarized them as mean and standard deviation (SD). For continuous variables, the Student t-test, and for categorical variables, the chi-square test was used to compare two groups. The positive and negative predictive values, sensitivity, and specificity of PET/CT for determination of lymph node positivity were calculated. An alpha level below 0.05 was considered for statistical significance. We conducted analyses by SPSS version 18 (Windows, Chicago, IL, USA).

Results

The body weight and BMI of the lymph node-positive group was statistically higher than the lymph none negative group(p=0,027, p=0,022 respectively). SUV max and SUVmean of the lymph node-positive group were statistically higher than the lymph node-negative group (p=0.008, p=0,009, respectively). Both TLG and MTV of the lymph node-positive group were statistically higher than the lymph node-negative group (p=0.01, P= 0.01, respectively).

The Ki-67(%) of the lymph node-positive group was not statistically different from the lymph node-negative group (figure-1 and table-1). The Sensitivity and specificity of PET/CT were 78.57% and 59.09%, respectively. The negative predictive value of PET/CT and Positive predictive value of PET/CT was 55% and 81.25%, respectively.
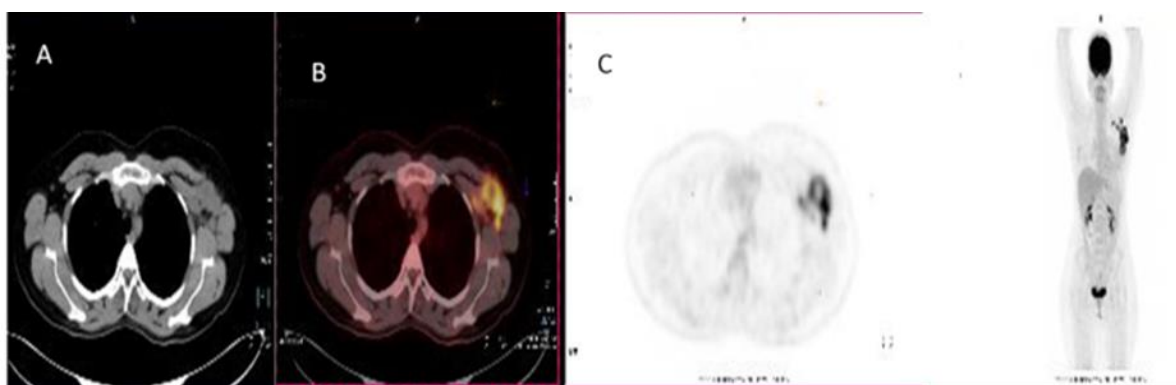

Figure 1: Left axillary lymph node metastasis of forty-five years older women with invasive ductal carcinoma in PET/CT. A= CT, B= PET/CT fusion, C=PET.

Table 1: Comparison of axillary lymph node positive group and axillary lymph node-negative group.. (NS= Non Significant).

	Axillary lymph node negative(n=66)	Axillary lymph node positive(n=42)	p value
Age (year)	49,1 ±13,9	48,4 ±13,3	N.S
Weight (kg)	69,9 ±10,8	75,9± 14,8	0,027
Height(cm)	163±6	164±7	N.S
BMI(kg/m^2)	25,9±4,6	28,4±6,1	0,022
Suvmax	8,8 ±6,0	11,7 ±7,7	0,008
Suvmean	4,5 ±1,9	5,6± 2,4	0,009
TLG	23,8 ±28,3	46,5 ±49,3	0,01
MTV	7,3± 8,3	12,2± 15,5	0,01
Ki-67 (%)	22,2 ±22,8	32,3± 29,2	N.S

Table 2: Distribution of the patients according to pathological and PET/CT findings

		Pathologic findings (number of patients)	
		Positive	**Negative**
PET/CT findings (number of patients)	**Positive**	33	27
	Negative	9	39

Discussion

PET/CT has provided many benefits in developing a treatment plan for breast cancer. It can play an important role for breast cancer patients and identifying distant and occult nodal metastases provide benefits such as surveillance during and after neoadjuvant chemotherapy, preventing non-essential biopsies from a lymph node, and supporting patient treatment planning [20]. Fouster D et al stated that PET/CT have sensitivity (80% -94%) and specificity (86% -90%) in determining axillary lymph node metastases [21]. In a review article, PET/CT sensitivity was reported as 64% (59%-69%) and specificity as 93% (90%-95%) [22]. In contrast, some studies found that it has a 24-82% sensitivity for identifying metastasis of axillary node, and it was also stated that PET/CT has low sensitivity in determining axillary lymph nodes in the early stages of primary breast cancer.

In addition, studies have shown very low effectiveness of PET/CT for detecting micrometastases in breast cancer patients [23, 24]. The differences in results between these studies can be attributed to the population studied, the PET protocol, and the histopathological procedure applied. In our study, the sensitivity and specificity of PET/CT to show axillary lymph nodes in breast cancer cases were 78.57% and 59.09%, respectively. While the sensitivity values of PET/CT in determining the lymph node are compatible, the specificity value of our study is lower than the previous studies. The reason that the specificity values were lower than previous studies may be due to the micrometastases present in our patients. As stated in our study, the PET/CT sensitivity around 80% facilitates the detection of cases with lymph node metastasis.

Despite the fact that in determining ALN staging, the surgical approach reference standard has performed better than all other approaches, the volume-based metabolic PET/CT breast tumor parameters can be used to diagnose patients who do not require invasive procedures. This suggestion can have some clinical benefits for patients.

Volume-based parameters on 18F-FDG PET/CT, such as Total Lesion Glycolysis (TLG) or Metabolic Tumor Volume (MTV), represent total tumor burden as well as tumor metabolic activity. In our study, the SUVmax SUVmean, TLG, and MTV values of the axillary lymph node-positive group were significantly higher than the axillary lymph node-negative group. It was shown that SUVmax of breast tumors on 18F-FDG PET/CT had been associated with ALNM [25]. Young-Sil et al. [26] measured SUVmax SUVmean, MTV, and TLG. On univariate analysis, the authors showed that both SUVmax and SUVmean were associated with ALNM. Because MTV represents the total tumor burden, not merely the metabolic activity, MTV has been suggested as a prognostic factor for breast cancer [27, 28]. Ulaner et al. suggested that MTV may be related to lymph node and liver metastases and TLG associated with bone and lymph node metastases. Another study found TLG of the primary breast tumor as an independent predictor of ALN metastasis in invasive ductal cancer of breast [29]. In conclusion, in light of all findings, it can be said that parameters such as SUVmean, MTV, SUVmax, and TLG were associated with axillary lymph node metastases at specific rates. Especially in cases with very high metabolic parameters, clinicians are more likely to see lymph node metastases.

Considering that Ki-67(%) is one of the indicators of the bad prognosis, our expectation was that the ki-67(%) level was high in cases with positive axillary lymph node, In contrast, in our study, Ki-67 index of axillary lymph node-positive group and axillary lymph node-negative group was not different [30]. According to the results of our study, it can be said that the level of Ki-67(%) is not related to metastases of the axillary lymph node.

Obesity and low physical activity are related to a higher risk of breast cancer, and weight gain after diagnosis of breast cancer is related to a higher risk of recurrence. The mechanism between "energy excess" states and breast

cancer is likely multifactorial, including inflammatory cytokines and immune cells, adipocytokines, and excess hormones. Obese postmenopausal women have a higher risk of breast cancer with a relative risk of about 1.3 compared with the normal weight ones [31]. The Women's Intervention Nutrition Study (WINS) found that a dietary intervention associated with weight loss could decrease the risk of breast cancer recurrence by 24% at five years [32]. In the present study, the bodyweight and BMI of the patients with an axillary lymph node metastasis was higher than those without a lymph node metastasis. In many studies, it seems that this issue has not been clarified since the body weights of breast cancer cases are not specified. Bodyweight gain may indeed cause recurrences and lymph node metastases in breast cancers.

Conclusions

PET/CT metabolic parameters of axillary lymph node-positive breast cancer patients were higher than axillary lymph node-negative patients. High body weight and increased BMI levels appears to increase the possibility of axillary lymph node metastases. The sensitivity of PET/CT can be considered to be useful in determining the pathological axillary lymph node, but the specificity of PET/CT is not very good

Acknowledgments: None

Author Contributions: SAT, AG, BT, İK, HB, FAÇ: Design of project, Patient examination, image analyzes and statistic **SAT:** Revisions

Conflict of Interest: The authors declare that they have no conflict of interest

References

1. World Health Organization International Agency for Research on Cancer. The Global Cancer Observatory. 2018 statistics. http://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf (Accessed on January 17, 2019).

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70:7.

3. de Freitas R Jr, Costa MV, Schneider SV, Nicolau MA, Marussi E. Accuracy of ultrasound and clinical examination in the diagnosis of axillary lymph node metastases in breast cancer. Eur J Surg Oncol 1991; 17:240.

4. Lanng C, Hoffmann J, Galatius H, Engel U. Assessment of clinical palpation of the axilla as a criterion for performing the sentinel node procedure in breast cancer. Eur J Surg Oncol 2007; 33:281.

5. Vaidya JS, Vyas JJ, Thakur MH, Khandelwal KC, Mittra I. Role of ultrasonography to detect axillary node involvement in operable breast cancer. Eur J Surg Oncol 1996; 22:140.

6. Fein DA, Fowble BL, Hanlon AL, Hooks MA, Hoffman JP, Sigurdson ER et al. Identification of women with T1-T2 breast cancer at low risk of positive axillary nodes. J Surg Oncol 1997; 65:34.

7. McGee JM, Youmans R, Clingan F, Malnar K, Bellefeuille C, Berry B. The value of axillary dissection in T1a breast cancer. Am J Surg 1996; 172:501.

8. S. Shin, K. Pak, D.Y. Park, Kim SJ. Tumor heterogeneity assessed by 18F-FDG-PET/CT is not significantly associated with nodal metastasis in breast cancer patients, Oncol Res Treat 39(1-2) (2016), 61–66.

9. B.B. Koolen, K.E. Pengel, J. Wesseling, et al. Sequential (18) F-FDG PET/CT for early prediction of complete pathological response in breast and axilla during neoadjuvant chemotherapy, Eur J Nucl Med Mol Imaging 2014 41(1);32–40.

10. Koolen BB, Vrancken Peeters MJ, Wesseling J, Lips EH, Vogel WV, Aukema TS, et al. Association of primary tumour FDG uptake with clinical, histopathological and molecular characteristics in breast cancer patients scheduled for neoadjuvant chemotherapy. Eur J Nucl Med Mol Imaging. 2012;39:1830–8.

11. Flanagan FL, Dehdashti F, Siegel BA. PET in breast cancer. Semin Nucl Med. 1998;28:290–302.

12. Choi BB, KimSH, Kang BJ, Lee JH, Song BJ, Jeong SH, et al. Diffusion-weighted imaging and FDG PET/CT: predicting the prognoses with apparent diffusion coefficient values and maximum standardized uptake values in patients with invasive ductal carcinoma. World J Surg Oncol. 2012;10:126.

13. Bos R, van Der Hoeven JJ, van Der Wall E, van Der Groep P, van Diest PJ, Comans EF. Biologic correlates of (18)fluorodeoxyglucose uptake in human breast cancer measured by positron emission tomography. J Clin Oncol. 2002;20:379–87.

14. Ekmekcioglu O, Aliyev A, Yilmaz S, Arslan E, Kaya R, Kocael P. Correlation of 18F fluorodeoxyglucose uptake with histopathological prognostic factors in breast carcinoma. Nucl Med Commun. 2013;34:1055–67.

15. Gil-Rendo A, Martinez-Regueira F, Zornoza G, García-Velloso MJ, Beorlegui C, Rodriguez-Spiteri N. Association between [18F]fluorodeoxyglucose uptake and prognostic parameters in breast cancer. Br J Surg. 2009;96:166–70.

16. Groheux D, Giacchetti S, Moretti JL, Porcher R, Espié M, Lehmann-Che J, et al. Correlation of high 18F-FDG uptake to clinical, pathological and biological prognostic factors in breast cancer. Eur J Nucl Med Mol Imaging. 2011;38:426–35.

17. Heudel P, Cimarelli S, Montella A, Bouteille C, Mognetti T. Value of PET-FDG in primary breast cancer based on histopathological and immunohistochemical prognostic factors. Int J Clin Oncol. 2010;15:588–93.

18. Sanli Y, Kuyumcu S, Ozkan ZG, Isik G, Karanlik H, Guzelbey B. Increased FDG uptake in breast cancer is associated with prognostic factors. Ann Nucl Med. 2012;26:345–50.

19. Boellaard R, Delgado-Bolton R, Oyen WJ Giammarile F, Tatsch K, Eschner W et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0.European Association of Nuclear Medicine (EANM). Eur J Nucl Med Mol Imaging. 2015;42(2):328-354.

20. Koolen BB, Valdés Olmos RA, Elkhuizen PHM, Vogel WV, Vrancken Peeters MJ, Rodenhuis S. Locoregional lymph node involvement on 18F-FDG PET/CT in breast cancer patients scheduled for neoadjuvant chemotherapy. Breast Cancer Res Treat 2012; 135: 231– 240.

21. Fuster D, Duch J, Paredes P elasco M, Muñoz M, Santamaría G, et al. Preoperative staging of large primary breast cancer with [18F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. J Clin Oncol 2008; 26: 4746– 4751.

22. Marino MA, Avendano D, Zapata P, Riedl CC, Pinker K. Lymph Node Imaging in Patients with Primary Breast Cancer: Concurrent Diagnostic Tools. Oncologist. 2020 Feb;25(2):e231-e242.

23. Liu, Y. Role of FDG PET-CT in evaluation of locoregional nodal disease for initial staging of breast cancer. World. J. Clin. Oncol. 2014, 5:982-989.

24. Avril N, Rosé CA, Schelling M Dose J, Kuhn W, Bense S, et al. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: Use and limitations. J Clin Oncol Off J Am Soc Clin Oncol 2000; 18: 3495– 3502.

25. Kim JY, Lee SH, Kim S , Kang T, Bae YT. Tumour 18 F-FDG Uptake on preoperative PET/CT may predict axillary lymph node metastasis in ER-positive/HER2-negative and HER2-positive breast cancer subtypes. Eur Radiol 2015;25:1172-81.

26. An, Young-Sil, Kang, Doo Kyoung, Jung, Yongsik , Kim, Tae Hee . Volume-based metabolic parameter of breast cancer on preoperative 18F-FDG PET/CT could predict axillary lymph node metastasis Section Editor(s): Zhuang., Hongming

27. Marinelli B, Espinet-Col C, Ulaner GA, McArthur HL, Gonen M, Jochelson M et al. Prognostic value of FDG PET/CT-based metabolic tumor volumes in metastatic triple negative breast cancer patients. Am J Nucl Med Mol Imaging 2016;6:120-7. Bibliographic Links 28-Ulaner GA, Eaton A, Morris PG, Lilienstein J, Jhaveri K, Patil S et al. Prognostic value of quantitative fluorodeoxyglucose measurements in newly diagnosed metastatic breast cancer. Cancer Med 2013;2:725-33.

28. Yoo J, Kim BS, Yoon HJ. Predictive value of primary tumor parameters using 18F-FDG PET/CT for occult lymph node metastasis in breast cancer with clinically negative axillary lymph node. Ann Nucl Med. 2018 Nov;32(9):642-648.

29. Nishimura R, Osako T, Okumura Y, Hayashi M, Toyozumi Y, Arima N. Ki-67 as a prognostic marker according to breast cancer subtype and a predictor of recurrence time in primary breast cancer. Exp Ther Med 2010;1:747-754.

30. Lahmann PH ,Hughes MC, Williams GM, Green AC.: Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). Int J Cancer. 2004 111(5):762-71,

31. Blackburn GL, Wang KA. Dietary fat reduction and breast cancer outcome: results from the Women's Intervention Nutrition Study (WINS). Am J Clin Nutr. 2007 86(3):s878-81