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Is there an association between immunohistochemical parameters of breast cancer and metabolic parameters obtained with 18F-fluorodeoxyglucose PET / CT?

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Abstract

Introduction: The aim of our study to investigate relationship between 18F -fluorodeoxyglucose PET/CT (18F-FDG PET/CT) metabolic parameters and immunohistochemical factors in breast carcinomas.

Material and method: Patients with breast carcinomas who underwent 18F-FDG PET/CT imaging at our department between May 2018 and November 2019 were included in this study. A total of 146 female patients were included (aged 49.1 ± 13.4years; range, 26-87 years). PET scanning was performed in 3D mode from the skull ceiling to the middle of the thigh. Metabolic parameters such as TLG (Total lesion glycolysis), MTV (Metabolic tumor volume) , SUVmean and SUVmax values were calculated. We obtained the histopathological findings, including the size of invasive cancer, histological type, histological grade, ER and PR status, epidermal growth factor receptor (HER2) and Ki-67 of the primary tumor by reviewing the pathology reports.

Result: SUV max and SUVmean of Oestrogen receptor negative group were statistically higher than Oestrogen receptor positive group (p=0.009). SUVmean of progesterone receptor negative group were statistically higher than progesterone receptor positive group (p=0.05). Ki-67 of the Oestrogen receptor negative group and progesterone receptor negative group were statistically higher than Oestrogen receptor and progesterone receptor positive group (p=0.001, 0,001 respectively). Both SUVmax and SUVmean of Ki-67 positive group were statistically higher than Ki-67negative group (p=0.0001).

*Conclusions: **1**-SUV max, SUVmean and Ki-67 of Oestrogen receptor negative group were statistically higher than Oestrogen receptor positive group.*
***2**-SUVmean and Ki-67 of progesterone receptor negative group were statistically higher than progesteron receptor positive group.*
***3**- HER2 positive and/or triple negative breast cancers were not associated with 18F-FDG PET/CT metabolic parameters*

Keywords: breast cancer, Oestrogen receptor, 18F-FDG PET/CT

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Introduction

Breast cancer is found as one of major health public problems among women which a variety of factors such as genetical and environmental factors could effect on initiation and progression of it (1). Early detection and monitoring of patients in response to various types of therapies are important aspects of breast cancer therapy (2). Oestrogen receptor (ER) and progesterone receptor (PgR) status has been used since the 1970s to describe a subgroup of breast cancer that responds to endocrine therapies representing the initial target treatment for clinics (3). HER2 is one of important proteins involved in breast cancer pathogenesis (4).

The role of fluorodeoxyglucose (FDG) PET in the management of patients with breast cancer (BC) is evolving. Combined PET and computed tomography (CT) systems (PET/CT) have replaced PET alone in most nuclear medicine departments. The CT portion of PET/CT provides the anatomic information useful for accurate interpretation of PET signal. The maximum standardized uptake value (SUVmax) measured with FDG PET is a sensitive indicator for metabolic activity in breast cancer (5,6), which can be used to assess tumor aggressiveness and is associated with prognostic factors, such as the histological type, histological grade, immunohistochemical factors, and proliferation index (5,7,8 , 9-13). Some parameters mixing volume and FDG intensity can also be used to assess the treatment response. The metabolic tumor volume (MTV) is determined as the tumor volume with significant FDG uptake (14). The total lesion glycolysis (TLG) corresponds to the MTV multiplied by the SUV mean. The aim of our study to investigate 18F-fluorodeoxyglucose (18F-FDG) uptake in breast carcinomas by comparing metabolic parameters such as SUVmax, SUVmean MTV and TLG of 18F-FDG PET/computed tomography (CT) images with immunohistochemical factors.

Methods

Patient population:

Patients with breast carcinomas who underwent 18F-FDG PET/CT imaging at our department between May 2018 and November 2019 were included in this study. The diagnosis of breast carcinoma was confirmed by recent biopsy in all patients before imaging. A total of 146 female patients were included (aged 49.1 ± 13.4years; range, 26-87 years) Pathological subtypes of breast cancer patients are infiltrative breast carcinoma (n = 112), invasive ductal breast carcinoma (n = 19), invasive lobular carcinoma (n = 8), invasive tubular carcinoma (n = 3), micropapiller carsinoma (n = 3) and cribriform carcinoma (n = 1).

Imaging procedure:

After eight hours of fasting, patients were given 18F-FDG intravenously (blood glucose <200 mg / dL) and whole body images were taken from PET / CT scanner (Siemens 3D-TOF Siemens Medical Systems) 55 to 75 minutes after injection (15) low-dose CT scan (80mA, 120 kV) was performed. The patients received an intravenous injection 3,7MBq/Kg 18F-FDG

in the arm opposite to the location of the primary breast tumour. PET scanning was performed in 3D mode from the skull ceiling to the middle of the thigh.

Using a SUV of 2.5 as the threshold, the volume of tumor with SUV ≥ 2.5 was determined as MTV (ml), and SUVmean was defined as mean SUV in the delineated tumor volume. The product of the MTV multiplied by SUVmean was defined as TLG (SUVml).

Metabolic parameters such as TLG (Total lesion glycolysis), MTV (Metabolic tumor volume) SUVmean and SUVmax values were calculated.

Histopathological analysis:

We obtained the histopathological findings, including the size of invasive cancer, histological type, histological grade, ER and PR status, HER2, epidermal growth factor receptor (EGFR), and Ki-67 of the primary tumor by reviewing the pathology reports. Immunohistochemistry was used to assess the expression of the following molecular markers: ER, PR, HER2, and Ki-67. ER and PR positivity was defined as the presence of 10% or more positively stained nuclei in ten high power fields. The intensity of HER2 immunohistochemical (IHC) staining was scored as 0, 1+, 2+, or 3+. The tumors with ≥1+ were classified as positive.

Statistical Analysis:

Data normality was tested by the Kolmogorov-Smirnov test. Data were summarized as frequencies and percentages for categorical variables or mean and standard deviation (SD) for continuous variables. To compare two groups, we used the student-t test for continuous variables. An alpha level below 0.05 was considered for statistical significance. All analyses were conducted by the statistical package of social sciences (SPSS version 18 for Windows, Chicago, IL, USA).

Results

Age and weight of the Oestrogen receptor positive group were not statistically different from the Oestrogen receptor negative group. SUV max and SUVmean of Oestrogen receptor negative group were statistically higher than Oestrogen receptor positive group (p=0.009). TLG and MTV of the Oestrogen receptor positive group were not statistically different from the Oestrogen receptor negative group. Ki-67 of the Oestrogen receptor negative group was statistically higher than Oestrogen receptor positive group (p=0.001)(Table-1).

Age and weight of the progesterone receptor positive group were not statistically different from the progesterone receptor negative group. SUV max of the progesterone receptor positive group were not statistically different from the progesterone receptor negative group. SUVmean of progesterone receptor negative group were statistically higher than

progesterone receptor positive group (p=0.05). TLG and MTV of the progesterone receptor positive group were not statistically different from the progesterone receptor negative group. Ki-67 of the progesterone receptor positive group was statistically higher than progesterone receptor negative group (p=0.001)(Table-2).

Table-1 Comparison of Oestrogen receptor positive group and Oestrogen receptor negative group.

	Oestrogen receptor	Oestrogen receptor positive(n=95)	p value
Age (year)	46,1 ±14,9	49,4 ±12,9	N.S
Weight (kg)	70,0 ±11,5	72,7± 12,8	N.S
Suvmax	13,8 ±7,8	10,1 ±6,7	0,009
Suvmean	6,0 ±2,3	4,8± 2,3	0,009
TLG	129,6 ±257,7	77,5 ±117,1	N.S
MTV	19,3± 27,6	12,2± 15,5	N.S
Ki-67 (%)	45,7 ±32,2	25,1± 21,5	0,001

Table-2 Comparison of progesterone receptor positive group and progesterone receptor negative group.

	Progesterone receptor negative(n=45)	Progesterone receptor positive(n=82)	p value
Age (year)	46,9 ±13,2	49,5 ±13,7	N.S
Weight (kg)	70,6 ±12,2	72,8± 12,6	N.S
SUVmax	12,6 ±7,2	10,2 ±7,2	N.S
SUVmean	5,6 ±2,1	4,8± 2,1	0,05
TLG	99,1 ±225,7	88,7 ±126,9	N.S
MTV	15,0± 24,4	13,8± 16,7	N.S
Ki-67 (%)	42,7 ±30,1	23,3± 21,2	0,001

Age, SUVmax, SUVmean, TLG, MTV, Ki-67 of the HER-2 receptor positive group were not statistically different from the HER-2 receptor negative group. Body weight of the HER-2 receptor positive group was statistically lower than HER-2 receptor negative group (Table -3).

Age, body weight ,TLG and MTV of Ki-67 positive group(Ki-67>%30) were not statistically different from Ki-67 negative group (Ki-67<%30). Both SUVmax and SUVmean of Ki-67 positive group were statistically higher than Ki-67 negative group (Table-4)

Body weight, age , SUVmax , SUVmean ,TLG and MTV of Triple negative group were not significantly different from non-triple negative group. Ki-67 values of triple negative group was statisticaly higher than non-triple negative group (Table-5).

Body weight, age, SUVmax, SUVmean, TLG, MTV and Ki-67 index of age<45 year group were not significantly different from age ≥ 45 group(Table-6).

Table-3 Comparison of HER-2 receptor positive group and HER-2 receptor negative group.

	HER-2 receptor negative(n=45)	HER-2 receptor positive(n=82)	p value
Age (year)	51,3 ±14,2	47,0 ±12,6	N.S
Weight (kg)	75,1 ±13,8	69,6± 10,9	0,01
SUVmax	10,8 ±8,3	11,2 ±6,2	N.S
SUVmean	4,9 ±2,3	5,3± 2,0	N.S
TLG	92,6 ±208,6	81,9 ±117,1	N.S
MTV	13,5± 21,8	13,9± 17,1	N.S
Ki-67 (%)	31,0±28,0	31,1± 25,3	N.S

Table-4 Comparison of group with Ki-67<%30 and group with Ki-67>%30.

	Ki-67<%30 Ki-67negative (n=45)	Ki-67>%30 Ki-67positive(n=82)	p value
Age (year)	49,8 ±13,7	47,9 ±12,4	N.S
Weight (kg)	71,5 ±6,42	72,8± 10,9	N.S
SUVmax	9,5 ±8,3	14,7 ±8,00	0,0001
SUVmean	4,7 ±2,09	6,17± 2,20	0,0001
TLG	80 ±124,08	131,9 ±240,58	N.S
MTV	13,6± 17,9	17,2± 23,9	N.S

Table-5 Comparison of triple negative group and non-triple negative group.

	Triple negative(n=11)	Non-triple negative (n=135)	p value
Age (year)	49,8 ±13,7	47,9 ±12,4	N.S
Weight (kg)	73,2 ±10,8	72,1± 12,3	N.S
SUVmax	13,9±11,6	10,8 ±6,7	N.S
SUVmean	5,7 ±2,9	5,1± 2,1	N.S
TLG	180 ±428	98,3 ±203,2	N.S
MTV	20,7± 39,6	15,4± 30,2	N.S
Ki-67	60,3± 31,1	28,1± 24,4	0,0001

Table-6 Comparison of Age <45 group and Age>45 group .

	Age <45(n=69)	Age≥45(n=77)	p value
Weight (kg)	70,7 ±11,02	73,5± 13,05	N.S
SUVmax	10,3 ±7,1	11,7 ±7,32	N.S
SUVmean	4,9 ±2,0	5,3± 2,3	N.S
TLG	120,9 ±302,5	89,8 ±124,2	N.S
MTV	17,4± 40,9	14,3± 17,8	N.S
Ki-67 (%)	30,8±27,0	31,0± 26,4	N.S

Discussion

According to gene-expression profiles, the first breast cancer subtypes were defined by Perou et al. (16). The presence of both ER, PR hormone receptors (HR) and human epidermal growth factor receptor (HER)-2 is a principal factor determining the clinical management. Subtypes identified based on hormone receptors, HER2 status, and Ki-67 proliferative index give information on tumour biology and clinical behaviour (17, 18).

Estrogen and progesterone receptors hold a crucial place in determining prognosis for patients with breast cancer. In our study, the SUVmax and SUVmean values of the estrogen receptor negative group were significantly higher than the estrogen receptor positive group. Conflicting results have been reported as regards the relationship between 18F-FDG uptake and hormone receptor status. In many studies, the SUVmax and SUVmean values of the estrogen receptor negative group were shown to be high (10, 11, 19-21). On the contrary some studies have claimed no association between oestrogen receptor negativity and PET/CT parameters (22, 23).

Various studies have compared 18F-FDG uptake with histopathological prognostic factors in patients with breast carcinoma. A study reported that tumours with high 18F-FDG uptake levels were more aggressive than those with low 18F-FDG uptake levels (24). Another study showed that disease-free survival rates were better in patients with lower SUVmax than in those with higher SUVmax in breast carcinoma (25). In addition, Avril et al. (26) found that 18F-FDG PET/CT is useful as a prognostic factor for breast carcinoma risk classification and for taking decisions on adjuvant chemotherapy.

In our study, Ki-67 index was higher in oestrogen receptor negative group than estrogen receptor positive group. Considering Ki-67 index is an indicator of poor prognosis in some studies (27). SUVmax and SUVmean values, which are indirect indicators of tumor activity, can be expected to be high.

In this study SUVmean of progesterone receptor negative group were statistically higher than progesterone receptor positive group but there was no difference between SUVmax of two groups. Some studies have demonstrated higher SUVmax levels in patient groups with a PR-negative receptor status (11,12), whereas another study did not find any association between PR-receptor negativity and PR-positivity (20). Our study revealed that the negative of the progesterone receptor in breast cancer cases is less important than the negative estrogen receptor. In addition, our study suggests that negative progesterone receptor affects more SUVmean levels and may not be more effective on SUVmax.

HER2 status is an important predictive factor that determines whether the patients can start goal-directed therapy . Age, SUVmax, SUVmean, TLG, MTV, Ki-67 of the HER-2 receptor positive group were not statistically different from the HER-2 receptor negative group. Body weight of the HER-2 receptor positive group was statistically lower than HER-2 receptor negative group. In the current study, SUVmax tended to be higher in HER-2 (+) tumors than HER-2 (−) tumors; however, the trend did not reach statistical significance. Other

previous studies are consistent with our result (28, 26, 29, 30). We found no correlation between FDG uptake and hormone receptor status or Her2 overexpression. This is consistent with the results reported by Dehdashti et al(28), who were unable to demonstrate any significant differences in FDG uptake recently, it was shown that hormone receptor status and the combination of the over expression of the HER2 correlated with molecular behavior and malignancy(30), however, hormone Her2 did not influence SUVs in our examination.

In recent years, a high Ki-67 proliferation index has been investigated as a prognostic factor for breast carcinoma and aggressiveness of tumours (31-33). In our study, if patients were grouped according to Ki-67 levels, < 30% and ≥30%, the latter group showed significantly higher SUVmax ratios. Nishimura et al. (27) showed a correlation between a high Ki-67 index and poor prognosis with early recurrence (<2 years). Several studies have demonstrated that the Ki-67 index is positively correlated with 18F-FDG uptake in primary tumours (30,34,35). Similarly, our study showed a positive correlation between Ki-67 levels and tumour SUVmax and tumour-to-background SUVmax ratios. Ki-67 is an indicator of the proliferation of cancer cells; however, its measurement and limit values change in different centres. In a study by Ito et al. (36) with 138 patients with invasive ductal breast cancer, the authors compared patients with Ki-67 values >14% and ≤14% and reported statistically significantly higher FDG involvement in patients with high Ki-67 values. In their comparison by number of mitosis, Ueda et al. (37) found the mean SUV values statistically significantly increased as the number of mitosis increased. In our study, no statistical comparison was performed because there were only a small number of patients whose number of mitosis and Ki-67 index were reported. One of the limitations in our study is that the effects of SUVmax value on treatment results, local control, and survival were not investigated.

Triple negativity is a poor prognostic factor for aggressive disease progression (38). Koolen et al.(5) suggested that 18F-FDG PET/CT imaging is more useful in breast carcinomas with triple negativity that show higher 18F-FDG uptake values. The present study, body weight, age, SUVmax, SUVmean ,TLG and MTV of Triple negative group were not significantly different from non-triple negative group. Kİ-67 values of triple negative group was statistically higher than non-triple negative group. In contrast to the findings of our study, patients with triple-negative breast carcinomas have been shown to have higher tumour 18F-FDG uptake levels than any other receptor group (10,39). In our study, although the SUVmax and SUVmean values of the triple negative group were slightly higher, this difference did not reach statistical significance. In addition, the triple negative group in our research is a relatively small group. Studies in larger patient groups may better reveal whether the PET / CT parameters of the triple negative group will differ from the non-triple negative group.

As in the our study, most of the studies have shown no association between age groups and 18F-FDG uptake in tumours (27,34,5). In our study, there was also no correlation between age status and tumour SUVmax. There was no difference in PET / CT parameters of breast cancer patients older than 45 years and breast cancer patients younger than 45 years

and Ki-67 levels of these two groups were not different. Taken together, all these data reveal that age is not an important entity in determining the metabolic activity of breast cancer.

In conclusion our study demonstrates that SUVmax and SUVmean values are related to the recognized immunohistochemical prognostic factors in breast cancer.

1- SUV max, SUVmean and Ki-67 of Oestrogen receptor negative group were statistically higher than Oestrogen receptor positive group .
2- SUVmean of progesterone receptor negative group were statistically higher than progesteron receptor positive group
3- The effect of HER-2 positivity on SUVmax and SUVmean was not observed.
4- SUVmax and SUVmean values of breast cancer patients whose Ki-67 level is above 30% positive were higher than those with Ki-67 level below 30%.
5- There was no difference in PET / CT parameters between breast cancer patients over 45 years and patients under 45 years.
6- According to these results, PET/CT scanning is beneficial in displaying the biologic characteristics and behaviour of the tumours in breast cancer patients.

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