Original Article, PET/CT.

The Correlation between ^{18}F FDG PET/CT Metabolic Parameters and Pathological Prognostic Factors in Early Breast Cancer Patients.

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ABSTRACT:

Objective: correlation between volumetric ^{18}F FDG parameters of primary breast neoplasm and clinico pathological factors in early stage disease. **Methods**: 34 female patients were included in this study that have non-metastatic breast cancer, underwent ^{18}F FDG PET/CT evaluation. The relationship between maximum standardized uptake value (SUVmax), mean standardized uptake value (SUVmean) metabolic tumor volume (MTV), tumor/liver uptake ratio (TLR) and total lesion glycolysis (TLG) and different prognostic factors were evaluated. **Results**: There was significant correlation between primary tumor SUVmax & SUVmean and pathological grade & Ki67. Significant correlations between primary tumor MTV and multi-focality & T stage were also detected. Regarding the TLG, it had multiple relationships with different parameters such as focality, histology, grading, T stage and Ki67 as well as Her2ue positivity. Significant correlation between primary tumor TLR and only Ki67 was elicited. The size of primary tumor was highly positive significantly correlated with SUVmax, MTV and TLG. On the other hand, no significant correlation could be elicited between different volumetric parameters of primary breast neoplasm and age of the patient. **Conclusion**: in early breast cancer we detected significant correlation between F18-FDG derived volumetric parameters and clinico-pathological factors.

Therefore they can reflect aggressiveness of the tumor also may predict prognosis and can greatly help to guide management. SUVmax, SUVmean, and TLG can be integrated with clinic-pathological evaluation for initial risk stratification. We suppose that TLR may be an additional promising tool in evaluating breast cancer.

Key words: Early breast cancer, volumetric ^{18}F FDG PET/CT parameters, clinico-pathological factors.

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INTRODUCTION:

Breast cancer in females is categorized as a second leading cause of cancer mortality in developing counties [(1)], it has many subtypes showing different clinical behavior and therapy responses. Most of breast cancer (85% - 90%) is invasive type and ductal origin. The prognosis is affected by many risk factors such as age, menopausal status, size of tumor, grading of tumor, status of the lymph node, hormonal receptors expression such as estrogen and progesterone receptors (ER ad PR) as well as human epidermal growth factor receptor 2 (c-erbB-2) expressions [(2-3)].

If breast cancer prognosis is predicting, this may be of greatly important for both the patients and their families, through giving important information about the aggressiveness of the neoplasm and may guide therapy strategies [(4)].

Breast cancer patients are commonly classified based on multiple clinical and pathologic variables such as age of the patient, tumor size, axillary nodal staging, hormonal receptors and her2 status and ki67% [(5, 6)].

Four subtypes of breast cancer showing different pattern of prognosis were identified and showing significant correlation with immuno-histochemistry results including ki67, ER , PR and HER2 [(7)].

More over gene expression profile have been used to define the subtypes of breast cancer showing variable prognosis and therapy response [(8, 9)].

In some studies, clinico-pathological factors such as pathology type, grade, stage, ki67, ER, PR and HER2 overexpression show correlation with FDG uptake, while others didn't find such relationship [(10,11)]. ***Kaida et al.,*** documented a statistically significant correlation between TLG and SUVmax with TNM staging and ER, PR, her2 but not found regarding MTV [(12)].

Kajáry et al., showed statistically significant correlation between immune-histochemistry and SUVmax, TLG and MTV [(10)]. In the current study we aim to evaluate the relationship between multiple metabolic PET CT derived parameters and the different clinico-pathological factors to evaluate if they can be added as additional prognostic or predictive factors to guide therapy plan.

PATEINTS AND METHODS:

This prospective study included 34 female patients, pathologically proven breast cancer and referred to our department for staging. The Research Ethics Committee approval was obtained. All the patients were above 18 years old , had non-metastatic breast cancer , while those who had metastatic deposits , another primary malignancy, breast feeding females or who had chronic disease were excluded. A 5 MBq/kg of FDG intravenous was given after at least 6 hours fasting.

All patients had blood glucose level less than 200 mg/dL. They were instructed to rest comfortably during uptake phase about sixty minutes. Non-contrast CT scan from the base of the skull to the upper thigh was acquired followed by PET scans that were obtained using ingenuity TF 64 (Philips Healthcare, Cleveland, OH, USA). About 8 frames with two and half min/frame of emission data were acquired in 3-dimensional mode.

The images were then reconstructed by the iterative method (ordered-subsets expectation maximization) and two experienced nuclear medicine physicians interpreted the scans. Region of interest (ROI) was drawn and the Maximum SUV (SUVmax), mean SUV (SUVmean) ,Tumor liver Ratio (TLR) Total lesion glycolysis (TLG) and Metabolic Tumor Volume (MTV) were calculated and normalized by total body weight.

Statistical analysis:

Statistical analyses were done using Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was evaluated using mean, standard deviation, median, minimum and maximum in quantitative data and by frequency (count) and relative frequency (percentage) for categorical data. Comparing quantitative variables were done through non-parametric ***Kruskal-Wallis and Mann-Whitney*** tests. Regarding comparison of categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Relationship between quantitative variables was done using Spearman correlation coefficient. P-values less than 0.05 were considered as statistically significant.

RESULTS:

This prospective study was performed in Nuclear Medicine unit at Kasr Al-Ainy Hospital (NEMROCK), Cairo University. The study included 34 non metastatic breast cancer female patients. The characteristics of the study population are illustrated in ***Table (1)***. Regarding histo-pathological characteristics, most of the patients (32 patients) had IDC and only 2 patients had lobular carcinoma. Regarding the pathological grade, 23 patients were grade II, 8 were grade III and 3 patients were grade I. The other different clinico- histo-pathological factors are shown in details in ***(Table 1***).

Table (1): Clinical and histo-pathological parameters in 34 patients with early breast cancer.

	Minimum	**Maximum**	
Age	30	63	
Size (cm)	0.9	4	
Side	**Right**	21	61.8%
	Left	13	38.2%
Focality	**Unifocal**	20	58.8%
	Multifocal	14	41.2%
T Stage	**1**	15	44.1%
	2	19	55.9%
Histology	**IDC**	32	94.1%
	Lobular	2	5.9%
Grade	**I**	3	8.8%
	II	23	67.7%
	III	8	23.5%
ER	**Negative**	6	17.6%
	Positive	28	82.4%
PR	**Negative**	9	26.5%
	Positive	25	73.5%
Her2ue	**Negative**	23	67.6%
	Positive	11	33.4%
Ki 67 Mean±SD (28.47±16.20)	**<20**	7	20.6%
	±20	27	79.4%

The ^{18}F FDG parameters for primary neoplasm including SUVmax, SUVmean, MTV, TLG and TLR were calculated. There were high statistically significant correlations between SUVmax and grading (p=0.002) & Ki67 (p=0.003) ***(Table 2)***. No significant correlation was detected regarding the rest of the other evaluated parameters including focality (P value 0.418), histology (P value 0.062), ER (P value 0.824), PR (P value 0.293), Her2ue (P value 0.431) and T stage (P value 0.372).

The correlations between SUVmean and different risk factors showed similar findings with significant correlations between SUVmean and pathological grade (p=0.001) & Ki 67 (p=0.009) was found (Table 2) and no significant correlation regarding focality (P value 0.803), histology (P value 0.109), ER (P value 0.911), PR (P value 0.213), Her2ue (P value 0.684) and T stage (P value 0.376).

In view of TLG, it showed significant correlations with multi-focality (p=0.038). Moreover, significant correlations between TLG and histologic type of the tumor (p=0.024), pathologic grade (p=0.043) and Her2ue receptor (p=0.042) was present with a high statistical correlation between TLG and Ki67 (p=0.013) & T stage (p<0.001) (Table 3). No significant correlation was found regarding the remaining parameters including ER (P value 0.182) and PR (P value 0.116) ***(Figure 1&2)***.

There were significant correlations between MTV of the breast tumor and multi-focality (p=0.03) and high statistical correlation with T stage of the tumor (p<0.001) ***(Table 3)***, while no significant correlation was found with grade (P value 0.672), histology (P value 0.171), ER (P value 0.200), PR (P value 0.511), Her2ue (P value 0.115) and Ki 67 (p=0.221).

When correlating TLR of breast tumor and different risk factors, significant correlation was detected only with Ki67 (p=0.014) ***(Table 3)***. No significant correlation was elicited with multi-focality (p=0.799), histological type of the tumor (p=0.071), pathologic grading (p=0.347), Her2ue receptor (p=0.447), ER (P value 0.648), PR (P value 0.451) and T stage (P value 0.809).

Highly significant positive correlations between size of the primary lesion and SUVmax, MTV & TLG (P value= 0.018, <0.001, <0.001 respectively) was documented and this was not found regarding SUVmean and TLR (with P value= 0.173 and 0.100 respectively).

On the other hand, no significant correlation was established between whole volumetric parameters and the age [SUVmax, SUVmean, MTV and TLG and TLR (P value= 0.464, 0.286, 0.531, 0.897 and 0.330 respectively)].

Table (2): Correlation between SUVmax and SUVmean of early breast neoplasm and clinico-pathological factors.

		SUVmax					p value
		Mean	**SD**	**Median**	**Minimum**	**Maximum**	
Grade	**I**	**3.04**	**.**	**3.04**	**3.04**	**3.04**	**0.002**
	II	**9.34**	**6.23**	**7.58**	**2.25**	**33.66**	
	III	**16.41**	**8.70**	**15.29**	**4.10**	**37.19**	
Ki 67	**<20**	**5.88**	**2.82**	**5.28**	**2.25**	**11.71**	**0.003**
	≥20	**11.37**	**5.94**	**9.55**	**3.42**	**25.33**	
		SUVmean					
		Mean	**SD**	**Median**	**Minimum**	**Maximum**	**p value**
Grade	**I**	1.69	.	1.69	1.69	1.69	0.001
	II	4.86	3.49	4.31	0.92	19.25	
	III	8.99	4.69	8.25	2.12	20.07	
Ki67	**<20**	3.22	1.81	2.90	1.19	7.09	0.009
	≥20	5.96	3.53	4.69	0.92	14.85	

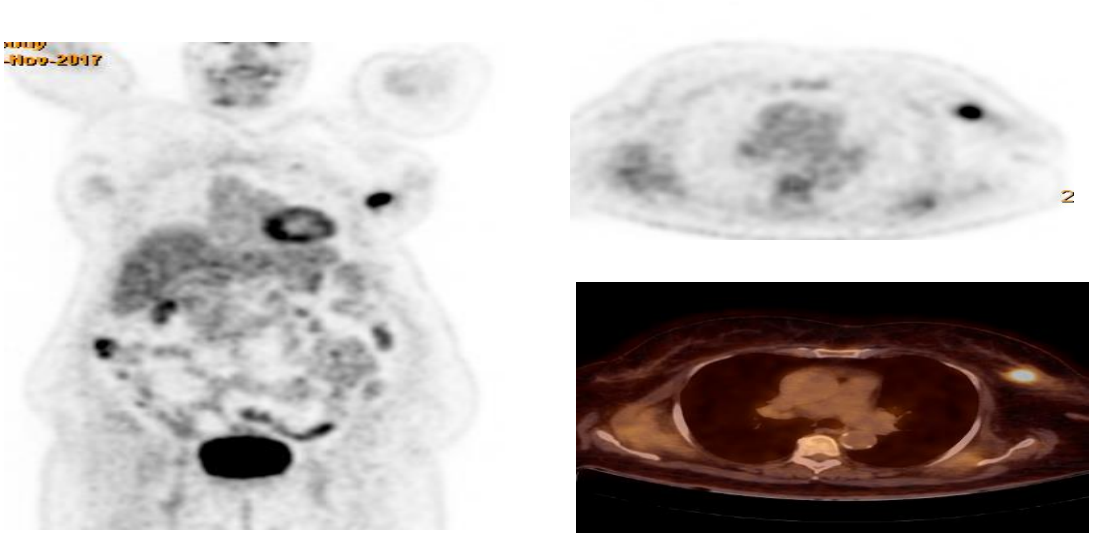

Figure (1): 57 year old female patient with left breast UOQ unifocal mass lesion. Staging: T2N0M0 Stage 2. Pathologically proven IDC grade III, ER positive, PR negative, HER2\neu negative and Ki-67 proliferation index (5%). The PET/CT derived metabolic parameters (SUVmax11.7, SUVmean 7.09, MTV7, TLG47.19, TLR4.11 and size 3.4 cm).

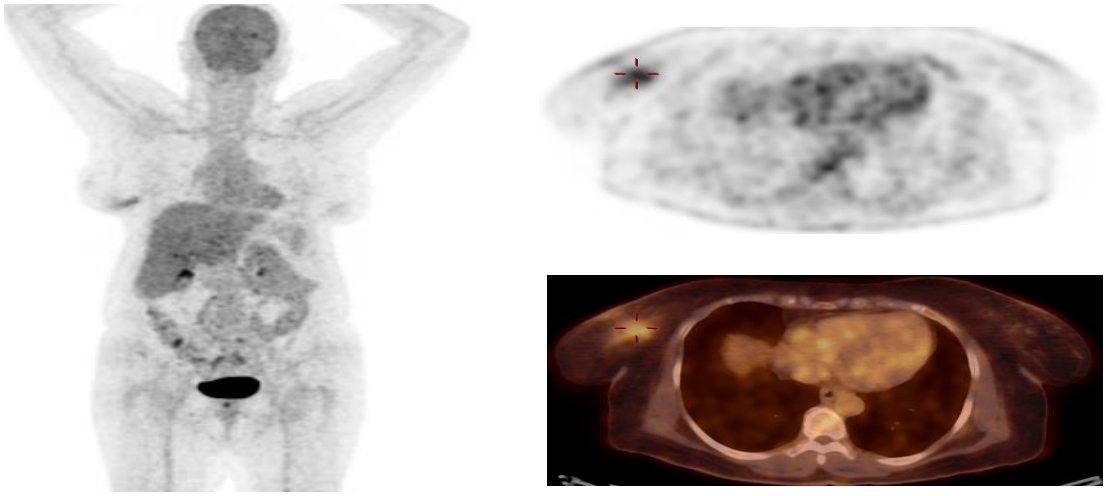

Figure (2): A 64-year-old female patient with right unifocal retroareolar breast mass lesion. Staging: T2N0M0 Stage 2. The histopathology was IDC grade II, ER positive, PR positive, HER2\neu negative and Ki-67 proliferation index (5%). PET/CT parameters (SUVmax4.63, SUVmean4.41, MTV17, TLG41.06, TLR1.37 and size 2.9 cm).

Table (3): Correlation between TLG, MTV and TLR, of primary breast neoplasm and clinico-pathological factors**.**

		TLG (SUVmax breast/SUVmean liver)					
		Mean	**SD**	**Median**	**Minimum**	**Maximum**	**P value**
Focality	**Unifocal**	132.95	196.77	61.91	8.80	1079.61	0.038
	multifocal	440.58	821.19	188.81	7.09	4331.11	
histology	**IDC**	299.13	623.54	91.70	7.38	4331.11	0.024
	lobular	44.69	47.58	28.45	7.09	127.98	
Grade	**I**	35.15	.	35.15	35.15	35.15	0.043
	II	211.07	387.34	81.08	7.09	2660.90	
	III	595.89	1111.71	212.39	39.18	4331.11	
Her2ue	**positive**	224.94	225.49	152.83	28.99	713.10	0.042
	negative	191.21	458.79	55.16	7.38	2660.90	
Ki67	**<20**	48.98	49.13	35.15	7.38	180.41	0.013
	≥20	291.26	512.72	111.03	8.80	2660.90	
T Stage	**1**	64.45	53.15	41.69	7.38	185.04	< 0.001
	2	125.08	145.82	58.73	7.09	600.75	
		MTV (Cm3)					
		Mean	**SD**	**Median**	**Minimum**	**Maximum**	**p value**
Focality	**Unifocal**	32.05	51.49	15.56	3.00	294.00	0.030
	multifocal	74.45	94.00	32.50	2.00	434.82	
T Stage	**1**	30.74	40.15	12.61	2.00	142.00	< 0.001
	2	22.72	30.27	12.00	3.00	142.00	
		TLR (Breast Tumor)					
		Mean	**SD**	**Median**	**Minimum**	**Maximum**	**P value**
Ki67	**<20**	2.68	1.51	2.08	1.17	5.75	0.014
	≥20	4.51	2.41	4.04	0.85	10.02	

DISCUSSION:

The ^{18}F-FDG PET/CT are known to have an important role in breast cancer management. Many studies evaluate the relationship between the clino- pathological factors and breast cancer subtypes with metabolic PET CT parameter **(10-12-13)**. In the current study, and according to T staging, T2 group included the highest number 19 (55.9%) of the patients. This is comparable to those reported by ***Chiacchio et al***. 52 (72%), ***Önner et al***. 52 (55.3%), ***Im et al.*** 12 (50%) and ***Kim et al.*** 30 (57%) **(14-9-15-16)**, this similarity may be due to the palpable breast mass in the T2 stage. Many studies reported low avidity of ILC to ^{18}F-FDG uptake compared to IDC.

In our study, all metabolic parameters were lower in ILC as compared to IDC. However, this difference was not statistically valid because of the low number of ILC included in our study; 2 out of 34 patients had ILC. Similarly, Higuchi et al showed no statistical difference between different breast cancer subtypes **(17)**.

The most commonly used FDG parameter is SUVmax, however their value does not show the total actual tumor glucose metabolism, the MTV and TLG considered better in the assessment of the

Volume, shape, and heterogeneity of the tumor **(10)**. In the present study, there were significant correlations between primary breast neoplasm FDG uptake intensity (SUVmax and SUVmean) and tumor grade & tumor proliferation index Ki67, where higher tumor grade and Ki67 ≥20% had a significantly higher SUVs than lower tumor grade and Ki67 <20, respectively. Similarly, many studies showed that FDG uptake intensity correlates with breast cancer grade & tumor proliferation index Ki67 **(13-18-19-20)**.

Regarding TLG of the primary neoplasm, we found its significant correlations with multi-focality of the tumor, histology, grading, Ki67 expression and T stage with higher values in females who had multi-focal disease, IDC, grade III, Ki67 expression ≥20 and T2.

Our findings are concordant with results of ***Qu et al*** and ***Önner et al*** regarding grade and T stage and ***Erol, et al*** regarding tumor grade also **(20 , 9 and 21)**.

The relationship between ER, PR receptors expression and PET CT volumetric parameters showed contradicting results **(13-20-21-22-23-24-25)**.

Our results matched the studies that showed no correlation between hormone receptor status and SUVs values such as those reported by ***Kumar et al., Shimoda et al, and Buck et al,.*** [24-27-28]. Also ***Ueda et al,.*** reported no correlation between them [25]. On the other hand ***Erol*** found correlation between SUVmax [21], TLG and MTV and hormone-receptor, where they were higher in hormone receptor negative patients compared with the positive patients, but the differences were insignificant [13-22]. However, ***Ikenaga et al,*** and ***Gil-Rendo et al,.*** showed higher SUVs in estrogen receptor negative tumor. The contradicting results may be due to different number of the studied patients where the latter studies included a large number of the patients.

In our study, MTV significantly correlated with the focality of the tumor and T stage, however, it showed non-significant correlation with hormonal receptor status, and Ki-67 index. Similarly, ***Önner et al***. and ***Qu, et al*** [9-20] documented significant correlation between MTV and T stage, which sound reasonable as it is mainly a measurement of volume rather than activity. In ***Chang et al.*** study MTV was only significantly correlated with the tumor grade and no

Significant association was elicited regarding hormonal receptor status, and Ki-67 index [26].

Many authors found no correlation between FDG uptake and HER2 expression [21-13-22-24].

In our study we also didn't found significant correlation between SUVmax, SUVmean and MTV and HER2 expression while only significant correlation between TLG and HER2 expression was found with higher values in patients with HER2 negative expression. Our findings regarding Her2 receptor are concordant with results of ***Önner et al*** [9].

The most commonly used parameters for calculating background activity are mediastinal vessels and liver. ***Paquet et al,.*** reported that regardless of which correction method was used, the SUV liver is relatively constant [29]. In the current study, we used the SUV liver to represent individual normal uptake. Normalization of the SUVmax value using normal liver uptake may reduce the effect of individual bias.

Some studies have evaluated the TLR as an alternative different parameter to evaluate prognosis & treatment response [19-30]. The TLR value was associated with regional nodal and distant deposits [13].

In our study we didn't included patients with metastatic disease; however we found that there is a significant correlation between TLR of the primary breast neoplasm and Ki67 percentage expression.

Tumor size is a well-established prognostic factor in breast cancer [31]. Although several studies reported a positive correlation between ^{18}F FDG uptake intensity and tumor size [12], others did not found such relationship [10]. This discrepancy may be due to what is called partial volume effect. ***Groheux et al***,. Included only patients with tumors more than two centimeters to minimize this effect and reported that SUVmax value was not associated with the tumor size [32]. In the present study we found significant correlations between SUVmax, MTV and TLG with tumor size.

Conclusions:

In early breast cancer we detected significant correlation between ^{18}F-FDG derived volumetric parameters and clinico-pathological factors. Therefore they can reflect aggressiveness of the tumor also may predict prognosis and can greatly help to guide management. SUVmax, SUVmean, and TLG can be integrated with clinic-pathological evaluation for initial risk stratification. We suppose that TLR may be an additional promising tool in evaluating breast cancer.

Declaration of competing interest: Authors declares that there is no conflict of Interest.

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