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Role of 18 Fluorine-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Imaging in Assessment of Neoadjuvant Chemotherapy Response in Breast Cancer Patients

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ABSTRACT

Background: In cancer, positron emission tomography (PET) using 18 fluorine (18f) fluorodeoxyglucose (FDG) plays an essential role. Its function in breast cancer management is evolving. In most nuclear medicine departments, combined PET and computed tomography (CT) equipment have superseded PET alone in recent years.

Aim: To assess the added value of PET/CT scan in evaluation of pathological response to neoadjuvant chemotherapy in locally advanced or metastatic breast cancer patients before surgery.

Subjects and methods: This study was conducted on forty-four female patients with evidence of proven breast cancer who were referred to PET/CT Unit at Department of Nuclear Medicine in International Medical Center. All clinical and histopathological data were extracted from the patients' clinical sheet. This included the pathological data and the current indication for FDG-PET/CT referral. All patients had a pretreatment PET/CT examination and post chemotherapy PET/CT follow up examination. **Results:** 27 patients (61.3%) showed response after non-adjuvant chemotherapy by pathology. Regarding SUV max, 31 patients (70.4%) showed response (where 6.8% of them revealed complete response and 63.6% revealed partial response). PET CT SUV max revealed that 31 patients as responders and 13 patients as non-responders. Among 31 responders, 27 were TP, 4 were FP. Among 13 non-responders, 13 were TN. The sensitivity, specificity and accuracy were 100%, 76.5% and 90.9% respectively.

Conclusion: PET/CT is a reliable whole body single imaging which can be used in monitoring and evaluation of NAC response in breast cancer patients showing response, high sensitivity, and accuracy compared to CT alone.

Keywords: PET/CT, Fluorine, Fluorodeoxyglucose, Chemotherapy, Breast.

INTRODUCTION

The primary cause of cancer-related mortality in women is breast cancer and the most prevalent cancer that is extremely dangerous to life. In Western Europe and the US, the 40–55 age range has the highest incidence, and this group is becoming more common. It is the second most frequent cause of cancer-related mortality among females in the US and the UK, accounting for 40,000 and 14,000 fatalities, respectively **[1-3].** This study aimed to assess the added value of PET CT scan in evaluation of pathological response to neoadjuvant chemotherapy in locally advanced or metastatic breast cancer patients before surgery.

MATERIAL AND METHODS

This is a prospective study in which forty-four female patients with evidence of proven breast cancer were referred to PET/CT unit at Department of Nuclear Medicine in International Medical Center during the period from March 2020 to October 2022. Patients with age between 30 and 70 years old showed different locally breast and metastatic breast lesions.

Exclusion criteria: Patients having tumors with inflammatory changes, concomitant malignancy, renal insufficiency or who were pregnant were excluded.

All clinical and histopathological data were extracted from the patients' clinical sheet in agreement with the referring physicians. This included the pathological data and the current indication for FDG-PET/CT referral. All patients had a pretreatment PET CT examination and post-chemotherapy PET CT follow up examination. Finally, the results were compared to the histopathological results.

Ethical approval: Written informed consent was obtained from all patients. The protocol of the study was approved by The Ethical Committee of Radiology Department, Faculty of Medicine, Suez Canal University (Number RPNC-6). The Helsinki Declaration was followed throughout the study's conduction.

Statistics analysis: The Shapiro test was used to define the normality of the distribution of the data. Data were analyzed using IBM Statistical Package for Social Sciences software (SPSS), 21st edition, IBM, United States. The predictive values were calculated by obtaining positive predictive values (PPV), negative predictive values (NPV), sensitivity, specificity and total accuracy of PET/CT. Continuous data were expressed as mean ± standard deviation and categorical data as percentage. The t-test was used to compare between two groups' quantitative data normally distributed expressed as mean and standard deviation. For comparisons in between more than 2 groups, analysis of variance (ANOVA) was used. Chi-squared or Fisher's Exact tests were used to compare between the qualitative data expressed as number and percentage, wherever compatible. Correlation (Spearman and Pearson) was used to identify relations between data. Any other kind of test was performed

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when appropriate. Results were considered statistically significant at a p-value of less than or equal to 0.05.

RESULTS

Table (1) showed that the age of the studied participants ranged between 30 and 80 years with a mean of 55.6 ± 13.4 years. More than half of the studied females were in the premenopausal status (65.9%).

Table (1): Demographic data of the studied group

Variable		Studied group (n=44)
Age:	Mean ± SD	55.6 ± 13.4
	Range	30 - 80
Menopausal status:	Pre:	29 (65.9%)
	Post:	15 (34.1%)

Table (2) showed that more of the females were of stage II cancer (52.3%), nearly one quarter of them were of stage IV (22.7%). Regarding tumor grade, 61.4% were of grade II, however, grade I was the least frequency (4.5%). About one third of the group (31.8%) had basal cell (BCL) carcinoma and 29.5% had luminal type B tumor. However, HER-2 and luminal type A cancer subtypes showed almost the same frequency.

Table (2): Clinical data of the studied group

	Variable	Studied group (n=44)
Tumor stage:	Stage I:	4 (9.1%)
	Stage II:	23 (52.3%)
	Stage III:	4 (9.1%)
	Stage IV:	10 (22.7%)
	Stage V:	3 (6.8%)
Tumor grade:	Grade I:	2 (4.5%)
	Grade II:	27 (61.4%)
	Grade III:	15 (34.1%)
Tumor subtype:	BCL:	14 (31.8%)
	HER-2:	8 (18.2%)
	Luminal A:	9 (20.5%)
	Luminal B:	13 (29.5%)

Table (3) showed that there was a significant difference between the pre- and post- measurements of SUV, which was found to be significantly decreased (6.7 and 3.2 respectively). The percentage of reduction in SUV post measurement compared to pre- one was 33.27 ± 66.29%.

Table (3): Comparison of SUV measurements for all positive lesions before and after intervention among the studied group

Variable	Before intervention (n=44)	After intervention (n=44)	Sign test	P-value
SUV max: Median Range	6.7 0 –27.1	3.2 0 – 24.7	**-3.166**	**0.002 (S)**
Percent reduction:	33.27 ± 66.29			

Table (4) showed that there was a significant difference between the tumor size before and after intervention. The tumor size was found to be significantly decreased (25*25 to 21*15 respectively). The percentage reduction in tumor size before and after intervention was 16*40%.

Table (4): Comparison of primary tumor size before and after intervention among the studied group

Variable	Before intervention (n=44)	After intervention (n=44)	Sign test	P-value
Tumor size: Median Range	25*25 1 - 66	21*15 0 - 65	**-3.240**	**0.001 (S)**
Percent reduction:	16 ± 77* 40 ± 67			

Table (5) showed the different sites of tumors before intervention and after intervention.

Table (5): Comparison of tumor site before and after intervention among the studied groups

Variable	Before intervention (n=44)
Tumor site before intervention:	
Bones	2 (4.5%)
Both breasts	2 (4.5%)
Breast	16 (36.4%)
Breast, LN, liver and bones	2 (4.5%)
Breast & lung	3 (6.8%)
Breast & LN	11 (25%)
Breast & LN & ovary & bones	2 (4.5%)
Breast, lung, LN	2 (4.5%)
Breast, lung, LN, Bones	2 (4.5%)
LN	2 (4.5%)
Tumor site after intervention:	
Bones	2 (4.5%)
Both breasts	2 (4.5%)
Breast	15 (34.1%)
Breast, LN, Lung liver & bone	2 (4.5%)
Breast & LN	5 (11.4%)
Breast & LN & bone	2 (4.5%)
Breast, lung, LN	2 (4.5%)
Liver	2 (4.5%)
LN	2 (4.5%)
LT Breast	2 (4.5%)
Lung	2 (4.5%)
Nil	2 (4.5%)
RT Breast	4 (9.1%)

Table (6) showed that there was a significant difference between the different stages of the tumor regarding post-measurements of SUV. By comparing the pre- and post-SUV in each stage separately, it was found that there was significant difference between them in patients with stage II and stage IV.

Table (6): Comparison of SUV measurements among the different stages of the tumor

Variable	Stage I (n=4)	Stage II (n=23)	Stage III (n=4)	Stage IV (n=10)	Stage V (n=3)	P-value
Pre SUV max:						
Median	7.7	6.7	9.3	6.2	3.5	0.692
Range	7.2 – 8.2	0 – 27.1	4.6 – 14.1	4.7 – 9.9	3.1 – 7.7	(NS)
Post SUV max:						
Median	2.1	2.8	14.1	4.8	2.1	**0.03 (S)**
Range	1.9 – 2.2	0 – 11.7	3.5 – 24.7	2 – 8.2	2.1 – 11.8	
P-value#	0.06 (NS)	**0.004 (S)**	0.45 (NS)	**0.03 (S)**	1.0 (NS)	

Table (7) showed that there were no significant differences between the different grades of the tumor as regarding both pre- and post-measurements of SUV. By comparing the pre- and post- SUV in each grade separately. It was found that there was significant difference between them in patients with grade II and grade III.

Table (7): Comparison of SUV measurements among the different grades of the tumor

Variable	Grade I (n=2)	Grade II (n=27)	Grade III (n=15)	P-value
Pre SUV max:				
Median	4.5	6.7	8.8	0.399
Range	4.5 – 4.5	2.2 – 27.1	0 – 13.5	(NS)
Post SUV max:				
Median	2.1	3.3	3.2	0.576
Range	2.1 – 2.1	0 – 24.7	2 – 11.7	(NS)
P-value#	1.0 (NS)	**0.02 (S)**	**0.03 (S)**	

Table (8) showed that there were no significant differences between the different subtypes of the tumor regarding both pre- and post-measurements of SUV. However, by comparing the pre- and post-SUV in each subtype separately. It was found that there was significant difference between them in basal cell carcinoma patients only.

Table (8): Comparison of SUV measurements among the different subtypes of the tumor

Variable	BCL (n=14)	HER-2 (n=8)	Luminal A (n=9)	Luminal B (n=13)	P-value
Pre SUV max:					
Median	6.9	5.3	9.4	6.7	0.642
Range	2.2 – 27.1	3.5 – 9.9	3.1 – 13.5	0 – 15.1	(NS)
Post SUV max:					
Median	4.1	4.9	3.2	2.2	0.853
Range	0 – 11.8	1.7 – 8.2	0 – 11.7	0.9 – 24.7	(NS)
P-value#	**0.04 (S)**	0.20 (NS)	0.06 (NS)	0.28 (NS)	

Table (9) showed that 27 patients (61.3%) had response after non-adjuvant chemotherapy by pathology. Regarding SUV max, 31 patients (70.4%) showed response (where 6.8% of them revealed complete response and 63.6% revealed partial response).

Table (9): Distribution of the studied group according to response to chemotherapy on SUV max and pathology

Variable	Studied group (n=44)
Pathology:	
Responder	**27 (61.3%)**
Grade 3	16 (36.4%)
Grade 4	6 (13.6%)
Grade 5	5 (11.5%)
Non-responder	**17 (38.7%)**
Grade 1	9 (20.5%)
Grade 2	8 (18.2%)
SUV max:	
Risponder	**31 (70.4%)**
CMR	3 (6.8%)
PR	28 (63.6%)
Non-risponder	**13 (29.6%)**
SD	4 (9.1%)
PD	9 (20.5%)

Table (10) showed that PET CT SUV max revealed that 31 patients as responders and 13 patients as non-responders. Among 31 responders, 27 were TP, 4 were FP. Among 13 non-responders, 13 were TN. Therefore, the sensitivity, specificity and accuracy were 100%, 76.5% and 90.9%.

Table (10): Validity of SUV max as a predictor of response to chemotherapy in comparison to pathology (gold standard):

SUV max	Pathology		Total	p-value
	Responder	Non-responder		
Responder	27 (100%)	4 (23.5%)	31	**<0.001 (HS)**
Non-responder	0 (0%)	13 (76.5%)	13	
Total	27	17	44	
Sensitivity= 100% specificity= 76.5% PVP= 87.1% PVN= 100% Accuracy= 90.9%				

DISCUSSION

Neoadjuvant chemotherapy is one choice for managing breast cancer that has progressed locally. Neoadjuvant chemotherapy aims to reduce the size of the tumour in order to preserve the breast and as a prognostic indicator. The proper measurement of residual tumor following neoadjuvant treatment is a critical prognostic factor in evaluating the patient's fate and likely survival [(4)]**.** Targeting glucose metabolism, which is markedly increased in most malignant tumours, including breast cancer, is what FDG-PET does. FDG is a glucose metabolic marker, hence 18F-FDG PET can monitor treatment response during or after therapy completion by detecting metabolic alterations far earlier than standard imaging methods. Tumour revealed increased 18F-FDG uptake in malignant cells. A semi-quantitative measure is SUVmax statistic that represents 18F-FDG absorption. The density of 18FFDG absorption in tumor cells is associated with the higher proliferative activity in tumor cells [(5)]**.**

Our study objectives were to measure the validity of PET/CT in reaction to patients' neoadjuvant treatment for breast cancer. In the current study, 44 patients were divided into 4 groups based on their molecular subtypes: 9 patients with the luminal A similar subtype, 13 patients with the luminal B subtype, 8 patients with HER2+VE over expression subtype and 14 patients with Basal like subtype. All patients had two separate whole body 18 FDG PET/CT examinations; base line examination was done prior to neoadjuvant chemotherapy, and the follow up examination was carried out following chemotherapy completion. In their investigation, **Vicente *et al.*** [(6)] studied 168 women with advanced breast cancer. In the first staging, both before and after neoadjuvant treatment, PET/CT was requested. Both tests were assessed using a semi-quantitative and qualitative approach, calculating SUVmax and calculating the percentage change in SUVs between PET-1 and PET-2. From initial tumour tissue, biological prognostic factors were ascertained, such as the state of the steroid receptor. Immunohistochemical surrogates were used to classify tumour subtypes in accordance with the recommendations of the 12th International Breast Conference as luminal A, luminal B, HER2(+) or basal. Metabolic semi quantitative parameters and molecular subtypes were correlated. Of the 168 tumors, 151 were classified: 16 were luminal A, 53 were luminal B-HER2 (-), 29 were luminal B, 18 were HER2 (+) and 35 were basal. There were significant differences between SUV-1 and SUV-2 and the different subtypes, with higher SUVs in HER2 (+) such as basal tumours. Among the molecular subtypes of the tumours examined, semi-quantitative metabolic metrics revealed statistically significant differences. Hence, it appears that molecular and glycolytic phenotypes are related [(6)]**.**

Several studies have demonstrated that the 18F-FDG uptake value is associated to tumor biology in various cancers [(4)]**.** There have been studies that compare histological parameters in the absorption of 18F-FDG in breast cancer. The 18F-FDG uptake levels in invasive lobular carcinomas are lower than in invasive ductal carcinomas, according to several studies establishing this connection [(2)]**.** This association, according to the scientists, could characterize the diffuse infiltrative tumour growth patterns of the surrounding tissue, lower proliferation rates, and reduced tumour cell intensity in lobular carcinomas. This study was unable to compare the small number of individuals with invasive lobular cancer (one patient).

There was no discernible correlation found between the patient's SUVmax and menopausal state. Despite the fact that a study found premenopausal patients' 18F-FDG uptake values were 1.3 times higher [(2)], Menopausal status and tumour SUVmax were found to be independent in another investigation [(7)]**.** In breast carcinomas, tumour grade is a major predictor. A strong positive correlation has been revealed between the histological grade and 18F-FDG uptake levels in a study done by **Ekmekcioglu *et al.*** [(8)]**.** Moreover, a study that was carried out revealed a connection between 18F-FDG uptake and nuclear pleomorphisms and mitotic activity. Nonetheless, they discovered no connection to tubular development [(9)]. This could be as a result of the increased significance that nuclear pleomorphism and mitotic count have on the glycolytic pathway and glucose intake. Despite the fact that patients with a grade 2 illness had mean SUVmax values that were greater in our study, no correlation between the grade and SUVmax value was found—possibly as a result of the small patient population.

In order to assess the accuracy of PET CT in NAC response monitoring, we further linked our findings with the pathological outcomes in the current investigation. Following neoadjuvant treatment, PERCIST criteria-based PET CT revealed 31 responders and 13 non-responders. 3 (6.8%) of 31 responder patients showed complete metabolic response and 28 (63.6%) of 31 responders showed partial metabolic response, while 4 cases (9.1 %) of 13

non responders showed stable disease and 9 cases (20.5%) of the non-responders had deteriorating health. There were 31 responses, of whom 27 were TP and 4 FP. Thirteen of the non-respondents were TN. Consequently, following NAC, PET CT's sensitivity, specificity, and accuracy were 100 %, 76.5%, and 90.9%, respectively.

Time and money can be saved, and the patient's health can be maintained, with prompt patient switching to more appropriate therapy types and rapid readings of treatment effect. PET has been used in a number of clinical trials to try and predict, which patients may benefit from treatment for breast cancer. According to earlier studies, PET following a single chemotherapy pulse may be able to accurately predict the full pathologic response of 90% and specificity of 74% **(10).**

In a different trial, early PET assessment after two cycles assisted in identifying non-responders to neoadjuvant therapy, while PET/CT assessments were utilised to detect her positive early responders to docetaxel plus trastuzumab therapy. Noted were pathologically comprehensive replies in 37 (53.6%, 95% CI 41.2-65.7) of the PET predicted responders and 6 (24.0%, 95% CI 9.4-45.1) non-responders. So, PET may be used to predict early select treatment responders **(11).** On the other hand, a study including 98 women with stage II–III breast cancer revealed that the results of neoadjuvant treatment may not be reliably predicted by PET/CT scans **(12).** Furthermore, **Tateishi *et al.* (13)** demonstrated that while PET-CT's specificity was good, its sensitivity for assessing pCR was unacceptable. The specificity (99%–100%) and sensitivity (39–100%) vary widely (74%-100%) of PET-CT in the literature **(13).**

CONCLUSION AND RECOMMENDATIONS

We came to the conclusion that, in comparison with CT alone, PET/CT is a dependable whole body single imaging modality that may be utilised to monitor and assess NAC response in breast cancer patients exhibiting responsiveness, high sensitivity, and accuracy.

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