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The Role of ^{18}F-FDG PET/CT in Staging Breast Carcinoma in Hanoi Oncology Hospital, Vietnam

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Abstract

Purpose: This study aimed to evaluate the role of ^{18}F-FDG PET/CT scans in staging breast carcinoma. **Materials and Methods:** A descriptive study on 46 patients who were diagnosed with breast carcinoma in Hanoi Oncology Hospital, Vietnam from June 2019 to June 2021. Those patients underwent ^{18}F-FDG PET/CT scans for pre-treatment staging. **Results:** There was a positive correlation between the size of primary tumors and their SUV ($p < 0.0001$, $r = 0.759$). The mean SUV was reported to be 2.5 for tumors under 2 cm, 5.89 for tumors from 2 - 5 cm, 13.6 for tumors above 5 cm, and 8.23 for skin invasive lesions. In terms of regional lymph node metastasis detection, the sensitivity and specificity of ^{18}F-FDG PET/CT were 75% and 100%, respectively. The rate of distant metastasis detection was 15.2% (7/46 patients). Metastatic lesions were found in bone, lungs, liver, and lymph nodes. There was a significant difference in SUV among organs ($p < 0.001$), with the highest SUV found in bone metastasis. The rates of stage I, II, III and IV diagnosed after PET/CT are 8.7%; 45.7%; 30.4% and 15.2% respectively, compared to 10.9%; 54.3%; 32.6%; 2.2% before taking ^{18}F-FDG PET/CT. After PET/CT, 17.4% patients (8/46) had their treatment plan changed. **Conclusions:** ^{18}F-FDG PET/CT plays an important role in staging breast carcinoma. Determining accurately the breast carcinoma stage by ^{18}F-FDG PET/CT could help alter treatment strategy to best suit with patients, and avoid unnecessary surgery.

Keywords

^{18}F-FDG PET/CT (Positron Emission Tomography with 2-Deoxy-2-[Fluorine-18]Fluoro-D-Glucose Integrated with Computed Tomography), Breast Carcinoma, Staging, SUV (Standardized Uptake Value)

1. Introduction

Breast cancer is the most common cancer in women, and the leading cause of their cancer death. According to GLOBOCAN 2020, globally, there were 2,261,419 new cases of breast cancer identified, and approximately 685,000 women died because of breast cancer [1]. In recent years, many types of diagnosing modalities, including PET/CT, have been used to help with breast cancer diagnosis and staging. PET/CT has an increasingly important role in diagnosing primary tumors, pre-treatment staging, evaluating the effectiveness of treatment, monitoring recurrence and distant metastasis, and in radiation simulation planning.

Fluorodeoxyglucose (**Figure 1**), abbreviated ^{18}F-FDG, is the main radiopharmaceutical used in PET/CT scan. Chemically, it is 2-deoxy-2-fluoro-D-glucose, a [^{18}F]fluorine-labeled glucose analog in which C-2 hydroxyl group has been replaced by a positron-emitting [^{18}F] radioisotope. ^{18}F is a positron-emitting (β+) radionuclide. PET detects the dual-photons emitted in opposite directions following positron annihilation. The half-life of ^{18}F is 110 minutes. Most malignant breast tumors overexpress glucose transporters (especially glucose trans-porter 1 and glucose transporter 3), and show increased hexokinase activity. After being phosphorylated by the hexokinase, FDG no longer goes along the glycolysis pathway, and remains trapped within cancer cells.

Internationally, ^{18}F-FDG PET/CT has been used for early detection, staging, and following up treatment response of many cancers. Authors worldwide have conducted various studies on the role of PET/CT in breast cancer staging and prognosis [2] [3] [4]. However, in Vietnam, there are very few studies on the impact of PET/CT in breast cancer, mostly because PET/CT has only been applied recently and has not been widely used for breast cancer patients. Hanoi Oncology Hospital (HOH) is one of the leading oncology centers in Vietnam where PET/CT has been used since 2017. In our hospital, ^{18}F-FDG PET/CT is used mainly to stage, re-stage, and follow-up the treatment response for patients with lung cancer, colorectal cancer, esophageal cancer, laryngeal cancer, thyroid cancer, lymphoma, and to evaluate solitary pulmonary nodule. Recently, our hospital has conducted studies on the role of ^{18}F-FDG PET/CT on lung cancer, differentiated thyroid cancer with negative I-131 total body scan and high thyroglobulin level, and unknown primary tumors, but this is the first time we evaluated the role of ^{18}F-FDG PET/CT in staging breast carcinoma.

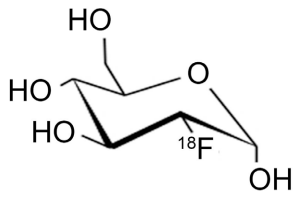

Figure 1. Chemical formula of fluorodeoxyglucose-$C_6H_{11}{}^{18}FO_5$.

2. Materials and Methods

2.1. Materials

Inclusion criteria: Patients whose histopathology results were breast carcinoma. They were diagnosed in HOH from June 2019 to June 2021. Their stage was evaluated by standard modalities: breast MRI; breast, neck and abdominal ultrasound, mammography, and bone scan. All of these patients then underwent ^{18}F-FDG PET/CT and were re-evaluated post-scan. Patients officially agreed to participate in the study.

Exclusion criteria: Pregnant women; patients with severe comorbidities (heart failure, kidney failure); Patients whose medical records were incomplete; patients already underwent chemotherapy and/or radiotherapy; Patients who refused to participate the study.

Radiopharmaceutical: ^{18}F-FDG (^{18}F-fluoro-2-deoxyglucose).

Equipment: Whole-body PET/CT imaging was performed using PET/CT scanner system (GE Discovery Light Speed).

2.2. Methods

Study design: descriptive study using retrospective and prospective data.

Sampling: convenient sampling—all patients who satisfied inclusion criteria and did not have any exclusion criterion were selected.

Procedure:

- All diagnostic data were collected, including breast MRI; breast, neck and abdominal ultrasound, mammography, bone scan.
- ^{18}F-FDG PET/CT imaging performance: Patients were fasting for at least 6 hours before being injected with ^{18}F-FDG, 0.15 mCi/kg. All patients took contrast agents orally, and no IV contrast agent was used. PET/CT scan was performed 60 minutes after ^{18}F-FDG injection, from the vertex of the skull to the mid femoral region, with extra scans on focused areas when necessary. PET/CT images were evaluated by at least 2 nuclear medicine specialists.

Image processing and result evaluation: the quantity, location, size of the primary tumor, metastatic regional lymph node(s), distant metastatic lesion(s), images of ^{18}F-FDG uptake and distribution, and SUV were evaluated. SUV of detected lesions were compared to the radioactivity of the mediastinal blood pool (SUV mean value = 2.5). If the lesion had SUV from 2 to 2.5, it was suspected between benign and malignant. If its SUV was above 2.5, its malignancy was confirmed.

Data analysis: Data were processed by SPSS 20.0.

3. Results

3.1. Characteristics of Research Objects

Among 51 patients qualified for the study, there were 46 agreed to participate in. All were females, with the average age of 56.6 years old (range 33 - 85 years old). Results showed that the majority of patients were from 40 to 60 years old, ac-

counted for 58.7%, whereas the young age group (less than 40 years old) had the lowest proportion.

3.2. Primary Tumor Location

The most common location of the primary tumor was the upper outer quadrant of the breast (61%). The tumors in the upper inner quadrant accounted for 28%, and those in the lower outer accounted for 7%. The least common location of the primary tumors was the lower inner quadrant, appearing in only 4% of patients.

3.3. Characteristics of Primary Tumors on ^{18}F-FDG PET/CT

According to Table 1 and Figure 2, SUVmax mean value of primary tumors was 6.39, with standard deviation (SD) = 4.02. There was a positive correlation between tumor size and SUVmax with r = 0.759. That means, the larger the tumor size was, the higher the SUV was, with p value = 0.0001.

3.4. Characteristics of Regional Lymph Nodes on ^{18}F-FDG PET/CT

According to Table 2, there were 18 patients underwent surgery. Those patients had taken pre-operative PET/CT and histopathology after PET/CT. Eight of them had malignant lymph node(s) on their histopathology results, while the rest (10) had benign result. Conventionally, if the SUVmax is above 2.5, the lymph node is considered malignant. Among 8 patients in the malignant group confirmed by histopathology, 6 cases had SUVmax above 2.5, thus, the sensitivity of ^{18}F-FDG-PET/CT in lymph node evaluation was 75% (6/8). Among 10 patients having the benign result confirmed by histopathology, all of them had SUVmax below 2.5, so the specificity ^{18}F-FDG-PET/CT in lymph node evaluation was 100% (10/10) in our study.

Table 1. Correlation between SUVmax and tumor size.

Tumor size	<2 cm	2 - 5 cm	>5 cm	Breast skin invasion	
N	5	31	3	7	
SUVmax ($\bar{X} \pm SD$)	2.5 ± 0.1	5.89 ± 3.31	13.6 ± 5.33	8.23 ± 3.62	**p = 0.0001 (Anova test)**
mean SUVmax ($\bar{X} \pm SD$)	6.39 ± 4.02				

Table 2. Comparison of lymph node result between PET/CT and histopathology.

SUVmax (cm)	Histopathology		Total	
	Benign	*Malignant*	(*n*)	(*%*)
SUVmax < 2.5	10	2	12	66.7
SUVmax > 2.5	0	6	6	33.3
Total	10	8	18	100

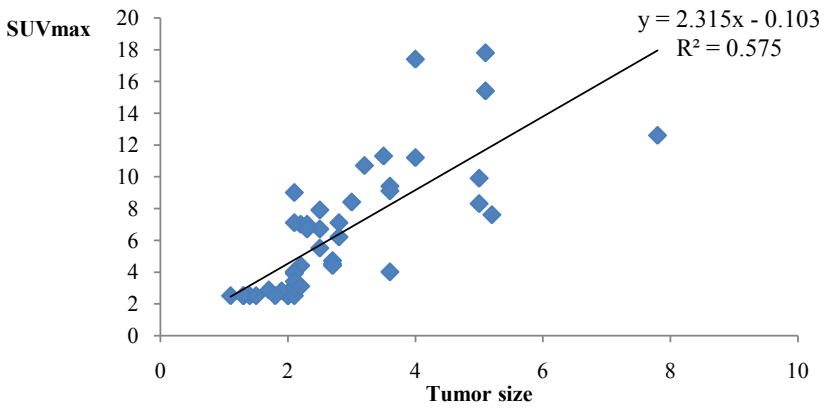

Figure 2. Correlation between SUVmax and tumor size.

3.5. Characteristics of Distant Metastases on ^{18}F-FDG PET/CT

^{18}F-FDG PET/CT detected distant metastases on 7/46 breast carcinoma patients (15.2%), which consisted of 2 bone metastasis cases, 1 lung metastasis case, 1 liver and bone metastasis case, 1 bone and distant lymph node metastasis case, and 1 distant lymph node metastasis case.

As presented in **Table 3**, four patients had bone metastasis, in which there was a total of 11 metastatic lesions, found in spinal bone, pelvis bone, scapula, and femur. Totally, there were 26 distant metastatic lesions detected on ^{18}F-FDG PET/CT. There was a statistically significant difference among ^{18}F-FDG SUVmax mean values of metastatic sites, with the highest mean value of SUVmax found in bone metastasis.

3.6. Impact of ^{18}F-FDG PET/CT in Staging Breast Cancer

According to **Table 4**, there were 21/46 patients (45.6%) had their TNM stages changed. Especially, distant metastases were detected in 7 patients, whereas the TNM stage of 1 patient was changed from end stage to operable stage. Consequently, the initial treatment strategies of these 8 patients (17.4%) have been altered.

Table 3. Metastactic organs and number of metastatic lesions with their average ^{18}F-FDG SUVmax.

Metastatic site	No. of patients (N = 7**)	No. of metastatic lesions (N = 26)	mean SUVmax
Bone	4	11	9.26 ± 3.49*
Distant metastatic lymph nodes	2	7	7.54 ± 2.87*
Liver	2	4	7.37 ± 0.93*
Lung	1	4	1.4 ± 0.18*

* $p < 0.001$; ** There were 2 patients having multiple-site metastases.

Table 4. Alterations of TNM stages after taking ^{18}F-FDG PET/CT.

Before ^{18}F-FDG PET/CT		After ^{18}F-FDG PET/CT						
Stage	**No. of cases**	**I**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IIIC**	**IV**
I	5	4	1[a]	-	-	-	-	-
IIA	14	-	10	3[a]	-	-	-	1[ac]
IIB	11	-	2[b]	4	3[a]	-	1[a]	1[ac]
IIIA	6	-	-	-	2	-	1[a]	3[ac]
IIIB	7	-	-	-	-	4	2[a]	1[ac]
IIIC	2	-	-	-	-	-	1	1[ac]
IV	1	-	1[bd]	-	-	-	-	-
No. of cases with changed stage/Total	21/46	0/4	4/14	3/7	3/5	0/4	4/5	**7/7**

[a]Changed from lower stage to higher stage; [b]Changed from higher stage to lower stage; [c]Distant metastasis detected by ^{18}F-FDG PET/CT; [d]Changed from end stage to earlier, operable stage.

4. Discussion

4.1. Primary Tumor Location

In our study, primary tumors were found in the left breast more frequently than in the right breast (54.3% vs. 45.7%). This finding was similar to that of other national studies. In Vu Kien's study on 116 breast cancer patients, the rate of left breast cancer was higher than that of the right one (54% vs. 46%) [5]. Our study also revealed that the most common primary tumor location was the upper outer quadrant of the breast (61%), which is also similar to the result of other studies. According to Le Hong Quang (2012), the rate of tumors detected in the upper outer quadrant was the highest, accounted for 51.2% cases [6]. Nguyen Thi Sang *et al.* (2016) also found that the upper outer quadrant of the breast is the most common location of primary tumors (39.9%), followed by the lower outer quadrant (26.5%) [7].

Internationally, McMasters *et al.* studied 2148 patients and detected 51.0% of primary tumors on the upper outer quadrant [8]. This finding could be explained by the anatomic structure of the breast. Mammary glands tend to extend towards the axillary fossa, therefore the quantity of glands and the volume of breast tissues in the upper outer quadrant is the largest among all locations. Hence, the rate of breast carcinoma occurring in this location is highest.

4.2. The Role of ^{18}F-FDG PET/CT in Determining Characteristics of Primary Tumors

The size of the primary tumor and that of axillary lymph node(s) are the most important prognostic factors, which significantly impact the five-year survival rate of breast cancer patients. In our study, the average tumor size was 2.8 cm,

ranging from 1.1 cm to 7.8 cm. Most of our research subjects were at early stages and under pre-operative evaluation, therefore the majority have tumor size at the T2 stage.

According to the study of Sang Kyu Yang *et al.*, the ability to evaluate breast tumors on PET/CT depends on the tumor size and its histopathological characteristics. Tumor sensitivity was recorded at 68% for tumors under 2 cm, and at 92% for tumors from 2 - 5 cm. In case of tumor in situ (Tis) with low sensitivity (2% - 25%), the ability of PET/CT to detect breast tumors is low if tumors are small or if they are non-invasive breast cancer [9].

^{18}FDG uptake level and tumor metabolism varied among patients. In our study, the mean ^{18}FDG SUVmax was 6.39 ± 4.02, with the highest value recorded being 17.8. Comparing SUVmax among tumors, there was a statistically significant difference in tumor size corresponding to tumor stage (<2 cm, 2 - 5 cm, and >5 cm). There was a positive correlation between tumor size and SUVmax. This is a relatively strong correlation, with r = 0.759. That means, the larger the tumor size was, the higher the SUV value was, with p = 0.0001.

This finding is similar to that of Song's study on 55 patients, with the mean SUVmax being 6.3 ± 4.8. SUVmax of primary tumors varied among stages, and the difference was statistically significant, which means that SUVmax increased along with tumor size. Patients with high SUVmax had their disease advanced faster, compared to those with lower SUVmax [10]. Hence, assessing ^{18}F-FDG uptake level on PET/CT could help prognose for patients.

4.3. The Role of ^{18}F-FDG PET/CT in Lymph Node Evaluation

In breast cancer, determining axillary lymph node metastasis is crucial for treatment planning and prognosis. Axillary lymph node dissection for histopathology is the most accurate method to detect lymph node metastasis. However, its complications such as lymphedema, swollen axillary skin, or reduced movement of the shoulder would eventually lead to a decrease in patient's quality of life. Thus, accurately staging lymph nodes by non-invasive methods is necessary to help patients avoid unnecessary axillary node dissection.

In our study, the sensitivity of ^{18}F-FDG-PET/CT in lymph node evaluation was 75% (6/8), and its specificity was 100% (10/10). Wahl *et al.* studied 360 breast cancer patients who underwent ^{18}F-FDG PET/CT and concluded that the sensitivity of ^{18}F-FDG-PET/CT in axillary lymph node evaluation was 61% and the specificity was 81% [11]. Furthermore, ^{18}F-FDG PET/CT was proven to be more efficient in evaluating supraclavicular, infraclavicular, and mediastinal lymph nodes. According to Schirrmeister *et al.*, the sensitivity and specificity of ^{18}F-FDG-PET/CT in axillary lymph node detection were 79% and 92% respectively [12]. PET/CT could accurately detect the anatomic location and distinguish metastatic and non-metastatic lymph nodes when visible on CT [9]. ^{18}F-FDG PET/CT shows superiority in lymph node evaluation over conventional diagnostic imaging modalities.

4.4. The Role of ^{18}F-FDG PET/CT in Detecting Metastatic Lesions

In our study, distant metastasis was found in 7/46 patients (15.2%), with a total of 26 distant metastasis lesions detected on ^{18}F-FDG-PET/CT including 2 bone metastasis cases, 1 lung metastasis case, 1 liver and bone metastasis case, 1 bone and distant lymph node metastasis case, and 1 distant lymph node metastasis case. All of these patients were diagnosed with stage II-III breast cancer before PET/CT.

Groheux *et al.* took PET/CT on 117 breast cancer patients, and compared PET/CT staging with staging by other, conventional modalities including bone scan, abdominal ultrasound, chest X-ray, and chest CT. On PET/CT, authors detected distant metastases in 43 patients, whereas other diagnostic imaging modalities detected metastases in only 28 cases [13].

In comparison, PET/CT is a better modality for detecting metastases in bone, liver, and lymph nodes than other conventional diagnostic imaging modalities. PET could effectively detect mediastinal lymph nodes, even those under 1 cm. When both PET and CT of ^{18}F-FDG PET/CT have detected bone metastases, the bone scan is no longer necessary. An advantage of PET/CT compared to other diagnostic imaging methods such as chest X-ray, bone scan, or abdominal ultrasound, is the ability to identify distant metastatic lesions in various organs in only one examination [9].

Among 26 metastatic lesions (4 lung lesions, 11 bone lesions, 4 liver lesions, and 7 distant lymph node lesions) in our study, the mean value of ^{18}F-FDG SUVmax of metastatic bone was the highest (9.26 ± 3.49), followed by that of distant metastasis lymph node and liver, which were 7.54 ± 2.87 and 7.37 ± 0.93 respectively, whereas metastatic lesions in lung has the lowest mean value of ^{18}F-FDG SUVmax. There was a statistically significant difference among ^{18}F-FDG SUVmax of different metastatic lesion groups by site ($p < 0.001$). Cokmert *et al.* performed pre-treatment ^{18}F-FDG PET/CT on 176 breast cancer patients with distant metastasis. Regression analysis results showed that SUVmax below 7.55 could be an independent indicator having prognostic value for survival rate in all stage IV cancer patients [14]. Hence, our study and previous studies have shown the superior ability of ^{18}F-FDG PET/CT in detecting distant metastases, compared to other conventional diagnostic imaging modalities.

4.5. The Role of ^{18}F-FDG PET/CT in Staging Breast Cancer

Staging plays the key role in planning treatment strategies for most cancer patients. Based on domestic and international studies, Ministry of Health of Vietnam has established "Guidelines for breast cancer diagnosis and treatment". Specifically, for stage I and II breast cancer, the initial treatment method is surgery, followed by chemotherapy, radiotherapy, or hormone therapy. Stage III breast cancer is divided into two groups: instantly operable and uninstantly operable diseases. In case of instantly operable diseases, the recommended approach is surgery first, followed by chemotherapy, WBRT (Whole Breast

Radiotherapy), RNI (Regional Nodal Irradiation), and hormone therapy when HR (Hormone Receptor) is positive. In case of tumors adhesive to the chess wall, and/or adhesive and immobile axillary lymph nodes, the recommended indications would be chemotherapy first with 6 - 8 circles (depends on the regimen), then surgery. If the disease responds to chemotherapy and downstages to be operable, surgery would be performed, followed by radiotherapy, and hormone therapy if HR is positive. If the disease does not respond to chemotherapy, a different regimen of radiotherapy could be considered to reduce the tumor's size and invasive level. In case of overexposed HER-2/neu receptor disease, trastuzumab—a monoclonal antibody—could be used. For stage IV patients, the treatment plan would include chemotherapy, hormone therapy, and molecular biology therapy [15].

Comparing stages before and after ^{18}F-FDG PET/CT, we found that ^{18}F-FDG PET/CT could detect meaningful lesions, which alter completely the disease stage, such as metastatic lesions in supraclavicular lymph nodes, internal mammary lymph nodes, bone, lung, liver, and distant lymph nodes. Among 46 patients, there were 7 patients had their stages changed to stage IV because distant metastases were detected on their PET/CT scan, whereas in another patient, the stage was down from IV to II (operable disease). Consequently, these 8 patients had their treatment strategy changed after PET/CT, accounted for 17.5% cases.

This finding is consistent with that of the study of Koolen *et al.* (2012). In that study, they took ^{18}F-FDG PET/CT on 154 stage IIB - III breast cancer patients. Distant metastatic lesions were found in 13% of patients, which changed their stages to stage IV [16]. In another study conducted by Groheux *et al.*, during a period of 71 months, they performed ^{18}F-FDG PET/CT scan for 254 stage II - III breast cancer patients (their definitive diagnosis determined by clinical examination, mammography, breast MRI and ultrasound). Results showed that there were 77 patients had stage changed (30.3%, $p = 0.05$). N3 nodes were detected in 40 patients, and distant metastases were found in 53 cases. ^{18}F-FDG PET/CT detected distant metastases in 1/44 stage IIa patients (2.3%), 6/56 stage IIb patients (10.7%), 11/63 IIIa patients (17.5%), and 27/74 stage IIIb patients (36.5%) [13].

In another study, Garami *et al.* performed ^{18}F-FDG PET/CT scan on 115 breast cancer patients, in whom no regional lymph node, distant metastasis, or primary tumor size below 4 cm were detected by other diagnostic imaging modalities. The sensitivity in detecting primary tumors of ^{18}F-FDG PET/CT was 93%. The sensitivity and specificity of lymph node ultrasound were 30% and 95% respectively, while those of ^{18}F-FDG PET/CT were 72% and 96%. ^{18}F-FDG PET/CT also detected distant metastases in 8 patients, changed the stage of 54 patients (47%), and altered the treatment plan of 18 patients (15.6%). Thus, ^{18}F-FDG PET/CT could detect distant metastases in 7% - 8% of patients whose metastatic lesions were previously unable to be detected by any other diagnostic imaging modalities [17].

Overall, our findings are consistent with and confirm the findings of other in-

ternational studies on the advantages of ^{18}F-FDG PET/CT over other, conventional diagnostic imaging modalities in evaluating accurately the breast carcinoma stage before treatment, which help determine most suitable treatment strategies for patients.

However, our study still has limitations. First, our small sample size and convenient sampling could lead to not very high representative value of the data. It is because in a developing country as Vietnam, the accessibility to PET/CT is still limited due to unavailability of equipment and its high expense that makes it unaffordable for many patients. Second, we couldn't conduct further analysis because patients came from different provinces where the database was separated, which made collecting data and monitoring patients more difficult. To overcome these limitations, it is recommended to conduct further studies with larger sample size and more comprehensive methodology and analysis. Additionally, an upgrade in the database is necessary, and a radiopharmaceutical manufacturing system needs to be developed to lower the cost of PET/CT to make it more accessible with majority of cancer patients.

5. Conclusions

Our study generated the following findings:

- The average age of breast cancer patients in the study was 56.6 years old. Breast tumor was more commonly found in the left breast, and the most frequent location of the primary tumor was the upper outer quadrant of the breast.
- There was a relatively strong positive correlation between primary tumor size and SUVmax (r = 0.759). The uptake level of ^{18}F-FDG of the tumor not only helped distinguish between benign and malignant diseases but also represented the tumor's biological characteristics. Therefore, in many cases, beside diagnostic value, SUV also provides prognostic value for survival rate and tumor's responsiveness to chemotherapy and radiotherapy.
- The sensitivity and specificity of ^{18}F-FDG PET/CT in detecting metastatic axillary lymph nodes were 75% and 100%, respectively.
- Distant metastasis was detected in 7/46 (15.2%) patients, with the most common metastatic sites were bone, liver, lung, and distant lymph nodes. All of those patients had no distant metastatic lesions found before taking PET/CT.
- 21 patients (45.6%) had their disease stages changed after taking ^{18}F-FDG PET/CT. ^{18}F-FDG PET/CT results led to altering treatment plans of 8/46 patients (17.4%).

These findings are consistent with those of studies in other countries, therefore contributing to prove advantages of ^{18}F-FDG PET/CT in staging breast carcinoma. Accurately staging by ^{18}F-FDG PET/CT could help alter treatment strategy to better suit patients' stage and avoid unnecessary surgery. Hence, PET/CT should be used for staging breast carcinoma patients in Hanoi Oncology Hospit-

al and other cancer centers in order to enhance quality and effectiveness of breast cancer treatment.

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Availability of Data and Materials

All data related to this manuscript are presented within the text.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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