# $^{18}$F FDG PET/CT Scan in the Evaluation of Metabolic and Morphologic Change of Breast Cancer after Neoadjuvant Chemotherapy

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## ABSTRACT

***Background:*** Breast cancer remains the most commonly occurring cancer among women across the world and accounts for 69% of cancer deaths. Neoadjuvant chemotherapy (NACT) has been effective in downstaging a primary tumor before surgery. In this study, a fluorine-18, 2-fluoro-2-deoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) scan was used to determine the metabolic and morphological changes of breast cancer after therapy. An $^{18}$F-FDG PET/CT scan was done before and after NACT. The change in maximum standard uptake value (SUVmax) ultimately reflects the metabolic status of tumor cells, and the change in tumor diameter represents the morphology of the tumor.

***Objective:*** To determine the therapeutic response by assessing metabolic and morphologic changes in breast cancer patients using an $^{18}$F-FDG PET/CT scan after NACT.

***Patients and methods:*** The study was conducted at the National Institute of Nuclear Medicine and Allied Sciences (NINMAS), Bangabandhu Sheikh Mujib Medical University (BSMMU) campus, from March 2020 to June 2021, on biopsy-proven female patients diagnosed with breast cancer (stage II to stage IV as defined by the AJCC). A total of nine patients were enrolled in this study. Before and after NACT, a PET/CT scan was performed in accordance with the IAEA CRP guidelines (in a prone posture with breast hanging supported by a breast cushion) and following the NINMAS protocol. Morphological and metabolic data were recorded and analyzed to ascertain the tumor's metabolic and morphologic (as per RECIST 1.1) outcomes.

A follow-up $^{18}$F-FDG PET/CT after NACT was done using the same dose and the same number of beds (1 minute per bed) as done before NACT.

***Results:*** About 89% of patients showed a reduction in tumor size following NACT. The mean tumor size reduction rate was 23.66±22.19 (%) and the difference was statistically significant between prior and after NACT ($P < 0.05$). Only 11% of patients developed higher SUVmax following NACT. According to RECIST 1.1 criteria, 11.11% of patients had progressive disease, 44.44% had a partial response, and 44.44% were stable. In PET/CT scans, approximately 66.67% of patients responded to NACT.

***Conclusion:*** $^{18}$F-FDG PET/CT can be used as a potential state-of-the art imaging approach in breast cancer patients before and after NACT. Following NACT, metabolic and morphological changes are visible in the $^{18}$F-FDG PET/CT scan, distinguishing responder and non-responder, which must be compared with pathologic response.

***Keywords:*** Breast Cancer, Neoadjuvant chemotherapy, 18F-FDG PET/CT, SUVmax.

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## INTRODUCTION

Breast cancer is the most common cancer among Bangladeshi women, accounting for 69% of all cancer fatalities (1). It affects roughly 22.5 per 100,000 women in Bangladesh, with women aged 15 to 44 having the highest occurrence rate (19.3 per 100,000) (2). An estimated 2.1 million women in the world have this disease, with one new case being found every 18 seconds, and 626,679 women dying from it per year (3).

The cornerstone of breast cancer prevention is early detection. Early detection with clinical tests and using conventional imaging modalities followed by timely treatment can reduce the catastrophic implications and significantly improve the survival of breast cancer patients (4). Mammography, ultrasonography (USG), and magnetic resonance imaging (MRI) are the diagnostic imaging modalities used for the initial evaluation of breast cancer, including the local disease, the extent of the lesion, and the stage of the disease. CT, a radionuclide bone scan, and MRI are used to detect distant metastases (5).

The treatment strategy for breast cancer depends on the stage of the disease. Locally advanced breast cancer (LABC) is inoperable and has a poor prognosis; many patients may develop progressive disease, distant metastases, and ultimately die from the disease. NACT is the treatment of choice for LABC (6). In recent years, NACT has gained popularity and become the gold standard for treating LABC, with several major benefits, firstly for downsizing the tumor and secondly for monitoring the therapeutic response and conducting interim evaluations. In the case of poor responders, NACT guides switching to another chemotherapeutic agent, and in some cases, unnecessary and extensive surgery can be avoided (7). In cases of nodal metastases, NACT may also be used to downstage the axillary nodes in patients with early-stage breast cancer. NACT regimens are chosen depending on cancer immunohistochemistry and are indicated for tumors larger than 2 cm in size, triple-negative breast cancer, human epidermal growth factor receptor 2 (HER2) positive carcinoma, and any tumor size with nodal metastasis (6, 7).

The preoperative evaluation of residual tumors after NACT is fundamental to overall breast cancer management. It may help guide surgical resection to achieve negative margins and avoid unnecessary interventions. However, post-operative histopathologic analysis determines if a pathologic complete response (pCR) is achieved (8). Patients who achieve a pCR after NACT are expected to have better outcomes than those who do not. This emphasizes the need to find the most accurate imaging modality for NACT response prediction. MRI is a reliable imaging modality for assessing NACT response in inoperable breast cancer patients (9). However, MRI may be unable to distinguish viable tumor tissue from fibrotic scar tissue. Several studies have suggested that FDG-PET/CT imaging is useful in assessing early tumor response. It can detect response to therapy earlier than conventional imaging methods, whereas conventional imaging modalities rely on delayed gross morphological changes. The whole-body FDG PET/CT scan has been shown to be extremely useful in monitoring tumor cell activity or the viability of the tumor (10–12). So, PET/CT can be used as an essential tool for oncologists for accurate staging of breast cancer, detecting distant metastases, predicting prognosis, and assessing treatment response (13, 14). There was no prospective study employing the [18]F-FDG PET/CT scan to assess the effectiveness of NACT in breast cancer patients in Bangladesh. Monitoring therapy response is one of the key elements that can help manage breast cancer patients successfully and improve quality of life (QOL).

## PATIENTS AND METHODS

The study was carried out on the biopsy-proven, diagnosed cases of breast cancer patients qualifying for NACT. Patients with inflammatory breast cancer or ulcerating skin lesions, pregnancy, or a previous or present history of other malignancies were excluded. The patients' ages, primary tumor size, tumor size after NACT, SUVmax value of the primary tumor before and after NACT, axillary lymph node size, and nodal SUVmax value all changed.

Image interpretation was performed by measuring the longest diameter of the tumor size and axillary lymph nodes, as well as semi-quantitative data of metabolic activity in the form of an SUVmax value in the region of interest (ROI), which was each patient's tumor and lymph node.A follow-up FDG PET/CT scan was done after at least 4 cycles of NACT, following the NINMAS protocol and using the same dose and the same number of beds (1 minute per bed) as done before NACT.

The metabolic response was evaluated using the study conducted by Rousseau et al., where more than 50% reduction in SUVmax value was considered responder and up to 50% reduction in SUVmax value was considered non-responder (15). Morphologic response evaluation was done considering Response Evaluation Criteria in Solid Tumors (RECIST 1.1) by measuring the longest diameter of the primary tumor and axillary lymph node size and comparing their values (16).

Statistical analyses were carried out using Microsoft Excel 2016 for Windows 10 (Microsoft Corporation, Redmond, Washington, USA). Categorical data were expressed in numbers and percentages. The data results were presented in tables, as necessary. The result of significance has been expressed as a p-value, and statistical analysis was performed by an unpaired t-test using computer-based statistical package for social sciences (SPSS) software (versions are presented in tables as necessary).

The result of significance has been expressed as a p-value, and statistical analysis was performed by an unpaired t-test using computer-based statistical package for social sciences (SPSS) software (Version 23), and a value of $p < 0.05$ was considered statistically significant.

## RESULTS

In this study, it was observed that the majority of the patients (44.45%) belonged to the age group 50 to 59 years, and the mean age was 45.78±12.9 years (Table 1). About 89% of patients showed a reduction in tumor size following NACT. The mean tumor diameter was 36.61±20.16 mm at the baseline scan, and the following NACT was 29.30±19.59 mm. The mean tumor size reduction rate was 23.66±22.19 (%) and the difference was statistically significant between prior and after NACT (P<0.05) (Table 2). The mean SUVmax of the primary tumor was 9.185.14, and the SUVmax of the follow-up was 4.763.45. The mean SUVmax value reduction rate of the primary tumor was 44.44±43.43. Only 11% of patients developed higher SUVmax values following NACT. The difference was statistically significant between prior and after NACT (P < 0.05) (Table 3). The mean metastatic axillary node diameter was 19.68±7.58 mm at the baseline scan, and the following NACT was 13.87±5.38 mm. The mean lymph node size reduction rate was 28.04±14.67 (Table 4). The mean SUVmax value for metastatic axillary lymph nodes was 7.406.06, and the follow-up SUVmax value was 2.982.89. The mean SUVmax value reduction rate of the metastatic lymph node was 52.22±38.49. The difference was statistically significant between prior and after NACT (P < 0.05) (Table 5).

Table 6 shows, partial response was achieved by 44.44% of patients according to RECIST 1.1 criteria, 44.44% of patients remained in a stable diseased condition, and only 11.11% of patients developed progressive disease. No one achieved a complete response to NACT. According to Rousseau C. et al. about 66.67% of patients were responders to NACT (considering > 50% reduction as responders and <50% reduction as non-responders) (Table 7).

**Table 1: Distribution of the study patients according to age (n=9)**

| Age range (years) | Number | Percentage % |
|---|---|---|
| 20 - 29 | 2 | 22.22 |
| 30 - 39 | 1 | 11.11 |
| 40 - 49 | 1 | 11.11 |
| 50 - 59 | 4 | 44.45 |
| 60 - 69 | 1 | 11.11 |
| Mean±SD | | 45.78±12.90 |
| Range (min-max) | | (26 - 62) Years |

**Table 2: Comparison of primary tumor size on CT scan**

| | Prior NACT (mm) | After NACT (mm) | Tumor reduction rate (%) | p-value |
|---|---|---|---|---|
| Primary tumor size | 36.61±20.16 | 29.30±19.59 | 23.66±22.19 | 0.026 |

The p-value reached an unpaired t-test

**Table 3: Comparison of primary tumor SUVmax prior to NACT and after NACT with percent change**

| Variables | Prior NACT | After NACT | Reduction rate (%) | p-value |
|---|---|---|---|---|
| **SUVmax** | 9.18±5.14 | 4.76±3.45 | 44.44±43.43 | 0.009 |

The p-value reached an unpaired t-test

**Table 4: Comparison of lymph node size prior NACT, after NACT and percent change**

| Variables | Prior NACT (mm) | After NACT (mm) | Reduction rate (%) | p value |
|---|---|---|---|---|
| **Axillary Lymph node size** | 19.68±7.58 | 13.87±5.38 | 28.04±14.67 | 0.002 |

The p-value reached an unpaired t-test

**Table 5: Comparison of SUVmax of axillary lymph node prior and after NACT with percent change**

| Variables | Prior NACT | After NACT | Reduction rate (%) | p value |
|---|---|---|---|---|
| LN SUVmax | 7.40±6.06 | 2.98±2.89 | 52.22±38.49 | 0.001 |

The p-value reached an unpaired t-test

**Table 6: NACT response evaluation according to RECIST 1.1 criteria**

| RECIST 1.1 Criteria | Complete Response (CR) | Partial Response (PR) | Progressive Disease (PD) | Stable Disease (SD) |
|---|---|---|---|---|
| Characteristics | Disappearance of tumor | ≥30% decreased size of the tumor | ≥20% increased size of the tumor | not classified as PR or PD |
| Percentage (%) | 0 | 44.44 | 11.11 | 44.44 |

**Table 7: Responder and non-responder patients according to SUVmax reduction rate**

| | >50% reduction of tumor SUVmax (Responder to NACT) | Up to 50% reduction of tumor SUVmax (non-responder to NACT) |
|---|---|---|
| Percentage (%) | 66.67% | 33.33% |

## DISCUSSION

This study showed alteration of the primary breast tumor diameter, changes in SUVmax value or metabolic activity after NACT, and alteration of the diameter and SUVmax value of the axillary lymph nodes. In this study, it was observed that the majority of the patients belonged to the age group between 50 and 59 years, and the mean age was 45.78 years, with an age range of 26 to 62 years (Table 1). Koolen et al. and Ogino et al. found similar mean ages in their studies: 47 and 48.6 years, respectively (17, 18).

A study with 25 patients by Ogino et al reported the mean primary tumor diameter and SUVmax value at baseline scanning to be 30.7 mm and 7.9 mm, respectively (18). In another study of 23 patients, Kumar et al reported that the mean size of the primary tumor in their population at baseline before NACT was 46.7 mm and the mean SUVmax was 11.7 (19). In this study, the baseline mean primary tumor diameter was 36.61 mm (Table 2) and the mean SUVmax value was 9.18 mm (Table 3). The current study and Kumar et al. found comparatively higher tumor size and SUVmax than Ogino et al., possibly due to delayed diagnosis in a similar middle-income socio-economic condition (18, 19).

On follow-up scan after NACT, there is a morphological and metabolic reduction of the mean tumor diameter of 29.30 mm (Table 2) and the mean SUVmax value of 4.76 (Table 3); which is almost identical to Kumar et al's findings (19). On the contrary, Ogino et al. reported a greater reduction of the mean tumor diameter and the mean SUVmax value (the mean diameter was 6.8 mm and the mean SUVmax value was 1.6) compared to this study (18). The dissimilarity with Ogino et al. might be due to geographical variations and socio-economic factors.

Kumar et al reported on axillary lymph node size and SUVmax, and they found the mean axillary lymph node size at baseline was 18.71 mm, and this current study found nearly a similar result of about 19.68 mm (Table 4). In a follow-up study, Kumar et al found the mean axillary lymph node size to be 11.45 mm, whereas the current study found the mean diameter to be about 13.87 mm (Table 4). The mean nodal SUVmax in the baseline study described by Kumar et al was 4.67, whereas this study described 7.40 (Table 5), which is higher than Kumar et al's finding. They reported complete resolution of the axillary lymph node in their follow-up study, but this study found no axillary lymph node resolution. On follow-up, they reported the mean SUVmax of the metastatic axillary lymph node was 0.71, while this study found 2.98 (Table 5), which is much higher than their findings and could be the outcome of performing PET/CT at different cycles of NACT (19).

Rousseau et al. conducted a study with 64 patients and evaluated the metabolic and morphologic changes of breast cancer by doing an [18]F-FDG PET/CT scan before and after NACT. All 64 patients underwent surgical resection after the completion of six cycles of chemotherapy and were histopathologically evaluated. Among 64 patients, 36 showed minimal residual disease and 28 showed gross residual disease. They also reported that the [18]F-FDG PET/CT scan could distinguish microscopic and macroscopic residual disease after the second cycle of NACT with a sensitivity and specificity of 89% and 95%, and after the first cycle with a sensitivity and specificity of 61% and 96%, respectively. The 36 patients with minimal residual disease had a reduction in SUVmax of more than 50% on PET/CT and

were considered responders. In contrast, 28 patients with gross residual disease had a reduction in SUVmax value of up to 50% after NACT and were classified as non-responders (15). In this current study, according to Rousseau et al., a 50% reduction of SUVmax was used as a cut-off value to determine responder and non-responder status for the evaluation of NACT. Kumar et al. also conducted almost a similar study and evaluated the role of the $^{18}$F-FDG PET/CT scan for the assessment of response after two cycles of NACT in breast cancer patients and also used the same cut-off value of 50% reduction of SUVmax to differentiate responders and non-responders, referencing Rousseau et al. (15, 19). Kumar et al. studied a total of 23 patients and reported that 16 patients (69.57%) were responders and seven patients (30.43%) were non-responders, which was histologically proven. In this study, of the nine patients, six (66.67%) showed more than 50% reduction in SUVmax and were considered responders, while three (33.33%) showed less than 50% reduction in SUVmax and were considered non-responders (Table 7), which was similar to the study conducted by Kumar et al.

According to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (16) definition, we found four patients (44.44%) who achieved 30% or more regression of primary tumor diameter and were considered to have a partial response, four cases (44.44%) who showed none of the criteria for a partial response or progressive disease and were considered to have stable disease, and only one patient who showed a 20% increase of tumor diameter after NACT and was classified as having progressive disease (11.11%). Neither one showed a complete response (Table 6). Kitajima et al. notified 78.1% of partial responses, 6.3% of stable disease, 15.6% of complete responses, and 0% of progressive disease. The achievement of a complete response in 15.6% of patients by Kitajima et al might be due to early diagnosis, early intervention, and early commencement of NACT based on tumor immunohistochemistry. It may be due to the availability of newer-generation drugs from their socioeconomic perspective (20).

The timing of response evaluation after NACT varies greatly. The majority of studies looked at treatment response after one chemotherapy cycle and found promising outcomes (21–26). However, Rousseau et al reported that the best time to evaluate therapy response is after two cycles of NACT using a PET/CT scan, which was the biggest sample (15). Kumar et al also evaluated the response to NACT in 23 patients after 2 cycles of NACT (19). In this study, follow-up PET/CT was done in six patients after receiving eight cycles of NACT, two patients after four cycles of NACT, and one patient after six cycles of NACT. Based on Rousseau et al. and Kumar et al., this study showed that after completion of NACT, an $^{18}$F-FDG PET/CT scan could distinguish between responders and non-responders (15, 19). According to studies, a PET/CT scan is a simple imaging protocol that can detect metabolic and morphological changes, ultimately indicating a response to NACT, and is extremely useful in determining the best therapeutic approach (10, 15, 19, 20).

## CONCLUSION

Metabolic and morphological changes are evident in the $^{18}$F-FDG PET/CT scan after NACT distinguishing responder and non-responder, which is a relatively accurate predictor of pathologic response. However, a small patient population and lack of pathological response evaluation are inconclusive and need further study with a large population and a comparison of multimodality imaging with pathological response evaluation.

## CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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